Biostatistics

A Methodology for the Health Sciences

Second Edition

GERALD VAN BELLE
LLOYD D. FISHER
PATRICK J. HEAGERTY
THOMAS LUMLEY

Department of Biostatistics and
Department of Environmental and
Occupational Health Sciences
University of Washington
Seattle, Washington

A JOHN WILEY & SONS, INC., PUBLICATION

Published by John Wiley & Sons, Inc., Hoboken, New Jersey.
Published simultaneously in Canada.

Library of Congress Cataloging-in-Publication Data:

Biostatistics: a methodology for the health sciences / Gerald van Belle ... [et al.]– 2nd ed.
p. cm. – (Wiley series in probability and statistics)
First ed. published in 1993, entered under Fisher, Lloyd.
Includes bibliographical references and index.
ISBN 0-471-03185-2 (cloth)
1. Biometry. I. Van Belle, Gerald. II. Fisher, Lloyd, 1939– Biostatistics. III. Series.

QH323.5.B562 2004
610′.1′5195–dc22

2004040491

Printed in the United States of America.

10 9 8 7 6 5 4 3 2 1

Ad majorem Dei gloriam

Contents

Preface to the First Edition

The purpose of this book is for readers to learn how to apply statistical methods to the biomedical sciences. The book is written so that those with no prior training in statistics and a mathematical knowledge through algebra can follow the text—although the more mathematical training one has, the easier the learning. The book is written for people in a wide variety of biomedical fields, including (alphabetically) biologists, biostatisticians, dentists, epidemiologists, health services researchers, health administrators, nurses, and physicians. The text appears to have a daunting amount of material. Indeed, there is a great deal of material, but most students will not cover it all. Also, over 30% of the text is devoted to notes, problems, and references, so that there is not as much material as there seems to be at first sight. In addition to not covering entire chapters, the following are optional materials: asterisks (*) preceding a section number or problem denote more advanced material that the instructor may want to skip; the notes at the end of each chapter contain material for extending and enriching the primary material of the chapter, but this may be skipped.

Although the order of authorship may appear alphabetical, in fact it is random (we tossed a fair coin to determine the sequence) and the book is an equal collaborative effort of the authors. We have many people to thank. Our families have been helpful and long-suffering during the writing of the book: for LF, Ginny, Brad, and Laura; for GvB, Johanna, Loeske, William John, Gerard, Christine, Louis, and Bud and Stacy. The many students who were taught with various versions of portions of this material were very helpful. We are also grateful to the many collaborating investigators, who taught us much about science as well as the joys of collaborative research. Among those deserving thanks are for LF: Ed Alderman, Christer Allgulander, Fred Applebaum, Michele Battie, Tom Bigger, Stan Bigos, Jeff Borer, Martial Bourassa, Raleigh Bowden, Bob Bruce, Bernie Chaitman, Reg Clift, Rollie Dickson, Kris Doney, Eric Foster, Bob Frye, Bernard Gersh, Karl Hammermeister, Dave Holmes, Mel Judkins, George Kaiser, Ward Kennedy, Tom Killip, Ray Lipicky, Paul Martin, George McDonald, Joel Meyers, Bill Myers, Michael Mock, Gene Passamani, Don Peterson, Bill Rogers, Tom Ryan, Jean Sanders, Lester Sauvage, Rainer Storb, Keith Sullivan, Bob Temple, Don Thomas, Don Weiner, Bob Witherspoon, and a large number of others. For GvB: Ralph Bradley, Richard Cornell, Polly Feigl, Pat Friel, Al Heyman, Myles Hollander, Jim Hughes, Dave Kalman, Jane Koenig, Tom Koepsell, Bud Kukull, Eric Larson, Will Longstreth, Dave Luthy, Lorene Nelson, Don Martin, Duane Meeter, Gil Omenn, Don Peterson, Gordon Pledger, Richard Savage, Kirk Shy, Nancy Temkin, and many others. In addition, GvB acknowledges the secretarial and moral support of Sue Goleeke. There were many excellent and able typists over the years; special thanks to Myrna Kramer, Pat Coley, and Jan Alcorn. We owe special thanks to Amy Plummer for superb work in tracking down authors and publishers for permission to cite their work. We thank Robert Fisher for help with numerous figures. Rob Christ did an excellent job of using LaTeX for the final version of the text. Finally, several people assisted with running particular examples and creating the tables; we thank Barry Storer, Margie Jones, and Gary Schoch.

Our initial contact with Wiley was the indefatigable Beatrice Shube. Her enthusiasm for our effort carried over to her successor, Kate Roach. The associate managing editor, Rose Ann Campise, was of great help during the final preparation of this manuscript.

With a work this size there are bound to be some errors, inaccuracies, and ambiguous statements. We would appreciate receiving your comments. We have set up a special electronic-mail account for your feedback:

http://www.biostat-text.info

LLOYD D. FISHER
GERALD VAN BELLE

Preface to the Second Edition

Biostatistics did not spring fully formed from the brow of R. A. Fisher, but evolved over many years. This process is continuing, although it may not be obvious from the outside. It has been ten years since the first edition of this book appeared (and rather longer since it was begun). Over this time, new areas of biostatistics have been developed and emphases and interpretations have changed.

The original authors, faced with the daunting task of updating a 1000-page text, decided to invite two colleagues to take the lead in this task. These colleagues, experts in longitudinal data analysis, survival analysis, computing, and all things modern and statistical, have given a twenty-first-century thrust to the book.

The author sequence for the first edition was determined by the toss of a coin (see the Preface to the First Edition). For the second edition it was decided to switch the sequence of the first two authors and add the new authors in alphabetical sequence.

This second edition adds a chapter on randomized trials and another on longitudinal data analysis. Substantial changes have been made in discussing robust statistics, model building, survival analysis, and discrimination. Notes have been added, throughout, and many graphs redrawn. We have tried to eliminate errata found in the first edition, and while more have undoubtedly been added, we hope there has been a net improvement. When you find mistakes we would appreciate hearing about them at *http://www.vanbelle.org/biostatistics/*.

Another major change over the past decade or so has been technological. Statistical software and the computers to run it have become much more widely available—many of the graphs and new analyses in this book were produced on a laptop that weighs only slightly more than a copy of the first edition—and the Internet provides ready access to information that used to be available only in university libraries. In order to accommodate the new sections and to attempt to keep up with future changes, we have shifted some material to a set of Web appendices. These may be found at *http://www.biostat-text.info*. The Web appendices include notes, data sets and sample analyses, links to other online resources, all but a bare minimum of the statistical tables from the first edition, and other material for which ink on paper is a less suitable medium.

These advances in technology have not solved the problem of deadlines, and we would particularly like to thank Steve Quigley at Wiley for his equanimity in the face of schedule slippage.

GERALD VAN BELLE
LLOYD FISHER
PATRICK HEAGERTY
THOMAS LUMLEY

Seattle, June 15, 2003

CHAPTER 1

Introduction to Biostatistics

1.1 INTRODUCTION

We welcome the reader who wishes to learn biostatistics. In this chapter we introduce you to the subject. We define statistics and biostatistics. Then examples are given where biostatistical techniques are useful. These examples show that biostatistics is an important tool in advancing our biological knowledge; biostatistics helps evaluate many life-and-death issues in medicine.

We urge you to read the examples carefully. Ask yourself, "what can be inferred from the information presented?" How would you design a study or experiment to investigate the problem at hand? What would you do with the data after they are collected? We want you to realize that biostatistics is a tool that can be used to benefit you and society.

The chapter closes with a description of what you may accomplish through use of this book. To paraphrase Pythagoras, there is no royal road to biostatistics. You need to be involved. You need to work hard. You need to think. You need to analyze actual data. The end result will be a tool that has immediate practical uses. As you thoughtfully consider the material presented here, you will develop thought patterns that are useful in evaluating information in all areas of your life.

1.2 WHAT IS THE FIELD OF STATISTICS?

Much of the joy and grief in life arises in situations that involve considerable uncertainty. Here are a few such situations:

1. Parents of a child with a genetic defect consider whether or not they should have another child. They will base their decision on the chance that the next child will have the same defect.
2. To choose the best therapy, a physician must compare the *prognosis*, or future course, of a patient under several therapies. A therapy may be a success, a failure, or somewhere in between; the evaluation of the chance of each occurrence necessarily enters into the decision.
3. In an experiment to investigate whether a food additive is *carcinogenic* (i.e., causes or at least enhances the possibility of having cancer), the U.S. Food and Drug Administration has animals treated with and without the additive. Often, cancer will develop in both the treated and untreated groups of animals. In both groups there will be animals that do

Biostatistics: A Methodology for the Health Sciences, Second Edition, by Gerald van Belle, Lloyd D. Fisher, Patrick J. Heagerty, and Thomas S. Lumley
ISBN 0-471-03185-2

not develop cancer. There is a need for some method of determining whether the group treated with the additive has "too much" cancer.

4. It is well known that "smoking causes cancer." Smoking does not cause cancer in the same manner that striking a billiard ball with another causes the second billiard ball to move. Many people smoke heavily for long periods of time and do not develop cancer. The formation of cancer subsequent to smoking is not an invariable consequence but occurs only a fraction of the time. Data collected to examine the association between smoking and cancer must be analyzed with recognition of an uncertain and variable outcome.
5. In designing and planning medical care facilities, planners take into account differing needs for medical care. Needs change because there are new modes of therapy, as well as demographic shifts, that may increase or decrease the need for facilities. All of the uncertainty associated with the future health of a population and its future geographic and demographic patterns should be taken into account.

Inherent in all of these examples is the idea of uncertainty. Similar situations do not always result in the same outcome. Statistics deals with this variability. This somewhat vague formulation will become clearer in this book. Many definitions of statistics explicitly bring in the idea of variability. Some definitions of statistics are given in the Notes at the end of the chapter.

1.3 WHY BIOSTATISTICS?

Biostatistics is the study of statistics as applied to biological areas. Biological laboratory experiments, medical research (including clinical research), and health services research all use statistical methods. Many other biological disciplines rely on statistical methodology.

Why should one study biostatistics rather than statistics, since the methods have wide applicability? There are three reasons for focusing on biostatistics:

1. Some statistical methods are used more heavily in biostatistics than in other fields. For example, a general statistical textbook would not discuss the life-table method of analyzing survival data—of importance in many biostatistical applications. The topics in this book are tailored to the applications in mind.
2. Examples are drawn from the biological, medical, and health care areas; this helps you maintain motivation. It also helps you understand how to apply statistical methods.
3. A third reason for a biostatistical text is to teach the material to an audience of health professionals. In this case, the interaction between students and teacher, but especially among the students themselves, is of great value in learning and applying the subject matter.

1.4 GOALS OF THIS BOOK

Suppose that we wanted to learn something about drugs; we can think of four different levels of knowledge. At the first level, a person may merely know that drugs act chemically when introduced into the body and produce many different effects. A second, higher level of knowledge is to know that a specific drug is given in certain situations, but we have no idea why the particular drug works. We do not know whether a drug might be useful in a situation that we have not yet seen. At the next, third level, we have a good idea why things work and also know how to administer drugs. At this level we do not have complete knowledge of all the biochemical principles involved, but we do have considerable knowledge about the activity and workings of the drug.

Finally, at the fourth and highest level, we have detailed knowledge of all of the interactions of the drug; we know the current research. This level is appropriate for researchers: those seeking

to develop new drugs and to understand further the mechanisms of existing drugs. Think of the field of biostatistics in analogy to the drug field discussed above. It is our goal that those who complete the material in this book should be on the third level. This book is written to enable you to do more than apply statistical techniques mindlessly.

The greatest danger is in statistical analysis untouched by the human mind. We have the following objectives:

1. You should understand specified statistical concepts and procedures.
2. You should be able to identify procedures appropriate (and inappropriate) to a given situation. You should also have the knowledge to recognize when you do not know of an appropriate technique.
3. You should be able to carry out appropriate specified statistical procedures.

These are high goals for you, the reader of the book. But experience has shown that professionals in a wide variety of biological and medical areas can and do attain this level of expertise. The material presented in the book is often difficult and challenging; time and effort will, however, result in the acquisition of a valuable and indispensable tool that is useful in our daily lives as well as in scientific work.

1.5 STATISTICAL PROBLEMS IN BIOMEDICAL RESEARCH

We conclude this chapter with several examples of situations in which biostatistical design and analysis have been or could have been of use. The examples are placed here to introduce you to the subject, to provide motivation for you if you have not thought about such matters before, and to encourage thought about the need for methods of approaching variability and uncertainty in data.

The examples below deal with clinical medicine, an area that has general interest. Other examples can be found in Tanur et al. [1989].

1.5.1 Example 1: Treatment of King Charles II

This first example deals with the treatment of King Charles II during his terminal illness. The following quote is taken from Haggard [1929]:

> Some idea of the nature and number of the drug substances used in the medicine of the past may be obtained from the records of the treatment given King Charles II at the time of his death. These records are extant in the writings of a Dr. Scarburgh, one of the twelve or fourteen physicians called in to treat the king. At eight o'clock on Monday morning of February 2, 1685, King Charles was being shaved in his bedroom. With a sudden cry he fell backward and had a violent convulsion. He became unconscious, rallied once or twice, and after a few days died. Seventeenth-century autopsy records are far from complete, but one could hazard a guess that the king suffered with an embolism—that is, a floating blood clot which has plugged up an artery and deprived some portion of his brain of blood—or else his kidneys were diseased. As the first step in treatment the king was bled to the extent of a pint from a vein in his right arm. Next his shoulder was cut into and the incised area "cupped" to suck out an additional eight ounces of blood. After this homicidal onslaught the drugging began. An emetic and purgative were administered, and soon after a second purgative. This was followed by an enema containing antimony, sacred bitters, rock salt, mallow leaves, violets, beet root, camomile flowers, fennel seeds, linseed, cinnamon, cardamom seed, saphron, cochineal, and aloes. The enema was repeated in two hours and a purgative given. The king's head was shaved and a blister raised on his scalp. A sneezing powder of hellebore root was administered, and also a powder of cowslip flowers "to strengthen his brain." The cathartics were repeated at frequent intervals and interspersed with a soothing drink composed of barley water, licorice and sweet almond. Likewise

white wine, absinthe and anise were given, as also were extracts of thistle leaves, mint, rue, and angelica. For external treatment a plaster of Burgundy pitch and pigeon dung was applied to the king's feet. The bleeding and purging continued, and to the medicaments were added melon seeds, manna, slippery elm, black cherry water, an extract of flowers of lime, lily-of-the-valley, peony, lavender, and dissolved pearls. Later came gentian root, nutmeg, quinine, and cloves. The king's condition did not improve, indeed it grew worse, and in the emergency forty drops of extract of human skull were administered to allay convulsions. A rallying dose of Raleigh's antidote was forced down the king's throat; this antidote contained an enormous number of herbs and animal extracts. Finally bezoar stone was given. Then says Scarburgh: "Alas! after an ill-fated night his serene majesty's strength seemed exhausted to such a degree that the whole assembly of physicians lost all hope and became despondent: still so as not to appear to fail in doing their duty in any detail, they brought into play the most active cordial." As a sort of grand summary to this pharmaceutical debauch a mixture of Raleigh's antidote, pearl julep, and ammonia was forced down the throat of the dying king.

From this time and distance there are comical aspects about this observational study describing the "treatment" given to King Charles. It should be remembered that his physicians were doing their best according to the state of their knowledge. Our knowledge has advanced considerably, but it would be intellectual pride to assume that all modes of medical treatment in use today are necessarily beneficial. This example illustrates that there is a need for sound scientific development and verification in the biomedical sciences.

1.5.2 Example 2: Relationship between the Use of Oral Contraceptives and Thromboembolic Disease

In 1967 in Great Britain, there was concern about higher rates of thromboembolic disease (disease from blood clots) among women using oral contraceptives than among women not using oral contraceptives. To investigate the possibility of a relationship, Vessey and Doll [1969] studied existing cases with thromboembolic disease. Such a study is called a *retrospective study* because retrospectively, or after the fact, the cases were identified and data accumulated for analysis. The study began by identifying women aged 16 to 40 years who had been discharged from one of 19 hospitals with a diagnosis of deep vein thrombosis, pulmonary embolism, cerebral thrombosis, or coronary thrombosis.

The idea of the study was to interview the cases to see if more of them were using oral contraceptives than one would "expect." The investigators needed to know how much oral contraceptive us to expect assuming that such us does not predispose people to thromboembolic disease. This is done by identifying a group of women "comparable" to the cases. The amount of oral contraceptive use in this *control*, or *comparison*, *group* is used as a standard of comparison for the cases. In this study, two control women were selected for each case: The control women had suffered an acute surgical or medical condition, or had been admitted for elective surgery. The controls had the same age, date of hospital admission, and parity (number of live births) as the cases. The controls were selected to have the absence of any predisposing cause of thromboembolic disease.

If there is no relationship between oral contraception and thromboembolic disease, the cases with thromboembolic disease would be no more likely than the controls to use oral contraceptives. In this study, 42 of 84 cases, or 50%, used oral contraceptives. Twenty-three of the 168 controls, or 14%, of the controls used oral contraceptives. After deciding that such a difference is unlikely to occur by chance, the authors concluded that there is a relationship between oral contraceptive use and thromboembolic disease.

This study is an example of a case–control study. The aim of such a study is to examine potential risk factors (i.e., factors that may dispose a person to have the disease) for a disease. The study begins with the identification of cases with the disease specified. A control group is then selected. The control group is a group of subjects comparable to the cases except for the presence of the disease and the possible presence of the risk factor(s). The case and control

groups are then examined to see if a risk factor occurs more often than would be expected by chance in the cases than in the controls.

1.5.3 Example 3: Use of Laboratory Tests and the Relation to Quality of Care

An important feature of medical care are laboratory tests. These tests affect both the quality and the cost of care. The frequency with which such tests are ordered varies with the physician. It is not clear how the frequency of such tests influences the quality of medical care. Laboratory tests are sometimes ordered as part of "defensive" medical practice. Some of the variation is due to training. Studies investigating the relationship between use of tests and quality of care need to be designed carefully to measure the quantities of interest reliably, without bias. Given the expense of laboratory tests and limited time and resources, there clearly is a need for evaluation of the relationship between the use of laboratory tests and the quality of care.

The study discussed here consisted of 21 physicians serving medical internships as reported by Schroeder et al. [1974]. The interns were ranked independently on overall clinical capability (i.e., quality of care) by five faculty internists who had interacted with them during their medical training. Only patients admitted with uncomplicated acute myocardial infarction or uncomplicated chest pain were considered for the study. "Medical records of all patients hospitalized on the coronary care unit between July 1, 1971 and June 20, 1972, were analyzed and all patients meeting the eligibility criteria were included in the study. . . . " The frequency of laboratory utilization ordered during the first three days of hospitalization was translated into cost. Since daily EKGs and enzyme determinations (SGOT, LDH, and CPK) were ordered on all patients, the costs of these tests were excluded. Mean costs of laboratory use were calculated for each intern's subset of patients, and the interns were ranked in order of increasing costs on a per-patient basis.

Ranking by the five faculty internists and by cost are given in Table 1.1. There is considerable variation in the evaluations of the five internists; for example, intern K is ranked seventeenth in clinical competence by internists I and III, but first by internist II. This table still does not clearly answer the question of whether there is a relationship between clinical competence and the frequency of use of laboratory tests and their cost. Figure 1.1 shows the relationship between cost and one measure of clinical competence; on the basis of this graph and some statistical calculations, the authors conclude that "at least in the setting measured, no overall correlation existed between cost of medical care and competence of medical care."

This study contains good examples of the types of (basically statistical) problems facing a researcher in the health administration area. First, what is the population of interest? In other words, what population do the 21 interns represent? Second, there are difficult measurement problems: Is level of clinical competence, as evaluated by an internist, equivalent to the level of quality of care? How reliable are the internists? The variation in their assessments has already been noted. Is cost of laboratory use synonymous with cost of medical care as the authors seem to imply in their conclusion?

1.5.4 Example 4: Internal Mammary Artery Ligation

One of the greatest health problems in the world, especially in industrialized nations, is coronary artery disease. The coronary arteries are the arteries around the outside of the heart. These arteries bring blood to the heart muscle (myocardium). Coronary artery disease brings a narrowing of the coronary arteries. Such narrowing often results in chest, neck, and arm pain (angina pectoris) precipitated by exertion. When arteries block off completely or *occlude*, a portion of the heart muscle is deprived of its blood supply, with life-giving oxygen and nutrients. A myocardial infarction, or heart attack, is the death of a portion of the heart muscle.

As the coronary arteries narrow, the body often compensates by building *collateral circulation*, circulation that involves branches from existing coronary arteries that develop to bring blood to an area of restricted blood flow. The internal mammary arteries are arteries that bring

Table 1.1 Independent Assessment of Clinical Competence of 21 Medical Interns by Five Faculty Internists and Ranking of Cost of Laboratory Procedures Ordered, George Washington University Hospital, 1971–1972

Intern	Clinical Competence[a]							Rank of Costs of Procedures Ordered[b]
	I	II	III	IV	V	Total	Rank	
A	1	2	1	2	1	7	1	10
B	2	6	2	1	2	13	2	5
C	5	4	11	5	3	28	3	7
D	4	5	3	12	7	31	4	8
E	3	9	8	9	8	37	5	16
F	13	11	7	3	5	39	7	9
G	7	12	5	4	11	39	7	13
H	11	3	9	10	6	39	7	18
I	9	15	6	8	4	42	9	12
J	16	8	4	7	14	49	10	1
K	17	1	17	11	9	55	11	20
L	6	7	21	16	10	60	12	19
M	8	20	14	6	17	65	13	21
N	18	10	13	13	13	67	14	14
O	12	14	12	18	15	71	15	17
P	19	13	10	17	16	75	16	11
Q	20	16	16	15	12	77	17	4
R	14	18	19	14	19	84	18	15
S	10	19	18	20	20	87	19	3
T	15	17	20	21	21	94	20.5	2
U	21	21	15	19	18	94	20.5	5

Source: Data from Schroeder et al. [1974]; by permission of Medical Care.
[a] 1 = most competent.
[b] 1 = least expensive.

blood to the chest. The tributaries of the internal mammary arteries develop collateral circulation to the coronary arteries. It was thus reasoned that by tying off, or *ligating*, the internal mammary arteries, a larger blood supply would be forced to the heart. An operation, internal mammary artery ligation, was developed to implement this procedure.

Early results of the operation were most promising. Battezzati et al. [1959] reported on 304 patients who underwent internal mammary artery ligation: 94.8% of the patients reported improvement; 4.9% reported no appreciable change. It would seem that the surgery gave great improvement [Ratcliff, 1957; Time, 1959]. Still, the possibility remained that the improvement resulted from a placebo effect. A *placebo effect* is a change, or perceived change, resulting from the psychological benefits of having undergone treatment. It is well known that inert tablets will cure a substantial portion of headaches and stomach aches and afford pain relief. The placebo effect of surgery might be even more substantial.

Two studies of internal mammary artery ligation were performed using a sham operation as a control. Both studies were *double blind*: Neither the patients nor physicians evaluating the effect of surgery knew whether the ligation had taken place. In each study, incisions were made in the patient's chest and the internal mammary arteries exposed. In the sham operation, nothing further was done. For the other patients, the arteries were ligated. Both studies selected patients having the ligation or sham operation by random assignment [Hitchcock et al., 1966; Ruffin et al., 1969].

Cobb et al. [1959] reported on the subjective patient estimates of "significant" improvement. Patients were asked to estimate the percent improvement after the surgery. Another indication

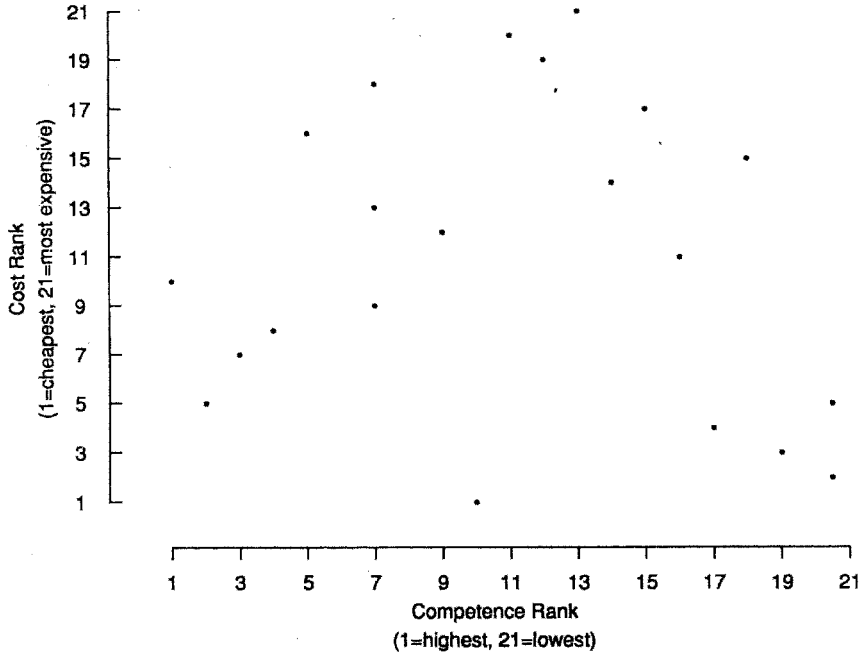


Figure 1.1 Rank order of clinical competence vs. rank order of cost of laboratory tests orders for 21 interns, George Washington University Hospital, 1971–1972. (Data from Schroeder et al. [1974].)

of the amount of pain experienced is the number of nitroglycerin tablets taken for anginal pain. Table 1.2 reports these data.

Dimond et al. [1960] reported a study of 18 patients, of whom five received the sham operation and 13 received surgery. Table 1.3 presents the patients' opinion of the percentage benefit of surgery.

Both papers conclude that it is unlikely that the internal mammary artery ligation has benefit, beyond the placebo effect, in the treatment of coronary artery disease. Note that 12 of the 14, or 86%, of those receiving the sham operation reported improvement in the two studies. These studies point to the need for appropriate comparison groups when making scientific inferences.

Table 1.2 Subjective Improvement as Measured by Patient Reporting and Number of Nitroglycerin Tablets

	Ligated	Nonligated
Number of patients	8	9
Average percent improvement reported	32	43
Subjects reporting 40% or more improvement	5	5
Subjects reporting no improvement	3	2
Nitroglycerin tablets taken		
Average before operation (no./week)	43	30
Average after operation (no./week)	25	17
Average percent decrease (no./week)	34	43

Source: Cobb et al. [1959].

Table 1.3 Patients' Opinions of Surgical Benefit

Patients' Opinions of the Benefit of Surgery	Patient Number[a]
Cured (90–100%)	4, 10, 11, 12*, 14*
Definite benefit (50–90%)	2, 3*, 6, 8, 9*, 13*, 15, 17, 18
Improved but disappointed (25–50%)	7
Improved for two weeks, now same or worse	1, 5, 16

Source: Dimond et al. [1960].
[a]The numbers 1–18 refer to the individual patients as they occurred in the series, grouped according to their own evaluation of their benefit, expressed as a percentage. Those numbers followed by an asterisk indicate a patient on whom a sham operation was performed.

The use of clinical trials has greatly enhanced medical progress. Examples are given throughout the book, but this is not the primary emphasis of the text. Good references for learning much about clinical trials are Meinert [1986], Friedman et al. [1981], Tanur et al. [1989], and Fleiss [1986].

NOTES

1.1 Some Definitions of Statistics

- "The science of statistics is essentially a branch of Applied Mathematics, and may be regarded as mathematics applied to observational data. ... Statistics may be regarded (i) as the study of populations, (ii) as the study of variation, (iii) as the study of methods of the reduction of data." Fisher [1950]
- "Statistics is the branch of the scientific method which deals with the data obtained by counting or measuring the properties of populations of natural phenomena." Kendall and Stuart [1963]
- "The science and art of dealing with variation in such a way as to obtain reliable results." Mainland [1963]
- "Statistics is concerned with the inferential process, in particular with the planning and analysis of experiments or surveys, with the nature of observational errors and sources of variability that obscure underlying patterns, and with the efficient summarizing of sets of data." Kruskal [1968]
- "Statistics = Uncertainty and Behavior." Savage [1968]
- "... the principal object of statistics [is] to make inference on the probability of events from their observed frequencies." von Mises [1957]
- "The technology of the scientific method." Mood [1950]
- "The statement, still frequently made, that statistics is a branch of mathematics is no more true than would be a similar claim in respect of engineering ... [G]ood statistical practice is equally demanding of appreciation of factors outside the formal mathematical structure, essential though that structure is." Finney [1975]

There is clearly no complete consensus in the definitions of statistics. But certain elements reappear in all the definitions: variation, uncertainty, inference, science. In previous sections we have illustrated how the concepts occur in some typical biomedical studies. The need for biostatistics has thus been shown.

REFERENCES

Battezzati, M., Tagliaferro, A., and Cattaneo, A. D. [1959]. Clinical evaluation of bilateral internal mammary artery ligation as treatment of coronary heart disease. *American Journal of Cardiology*, **4**: 180–183.

Cobb, L. A., Thomas, G. I., Dillard, D. H., Merendino, K. A., and Bruce, R. A. [1959]. An evaluation of internal-mammary-artery ligation by a double blind technique. *New England Journal of Medicine*, **260**: 1115–1118.

Dimond, E. G., Kittle, C. F., and Crockett, J. E. [1960]. Comparison of internal mammary artery ligation and sham operation for angina pectoris. *American Journal of Cardiology*, **5**: 483–486.

Finney, D. J. [1975]. Numbers and data. *Biometrics*, **31**: 375–386.

Fisher, R. A. [1950]. *Statistical Methods for Research Workers*, 11th ed. Hafner, New York.

Fleiss, J. L. [1986]. *The Design and Analysis of Clinical Experiments*. Wiley, New York.

Friedman, L. M., Furberg, C. D., and DeMets, D. L. [1981]. *Fundamentals of Clinical Trials*. John Wright, Boston.

Haggard, H. W. [1929]. *Devils, Drugs, and Doctors*. Blue Ribbon Books, New York.

Hitchcock, C. R., Ruiz, E., Sutherland, R. D., and Bitter, J. E. [1966]. Eighteen-month follow-up of gastric freezing in 173 patients with duodenal ulcer. *Journal of the American Medical Association*, **195**: 115–119.

Kendall, M. G., and Stuart, A. [1963]. *The Advanced Theory of Statistics*, Vol. 1, 2nd ed. Charles Griffin, London.

Kruskal, W. [1968]. In *International Encyclopedia of the Social Sciences*, D. L. Sills (ed). Macmillan, New York.

Mainland, D. [1963]. *Elementary Medical Statistics*, 2nd ed. Saunders, Philadelphia.

Meinert, C. L. [1986]. *Clinical Trials: Design, Conduct and Analysis*. Oxford University Press, New York.

Mood, A. M. [1950]. *Introduction to the Theory of Statistics*. McGraw-Hill, New York.

Ratcliff, J. D. [1957]. New surgery for ailing hearts. *Reader's Digest*, **71**: 70–73.

Ruffin, J. M., Grizzle, J. E., Hightower, N. C., McHarcy, G., Shull, H., and Kirsner, J. B. [1969]. A cooperative double-blind evaluation of gastric "freezing" in the treatment of duodenal ulcer. *New England Journal of Medicine*, **281**: 16–19.

Savage, I. R. [1968]. *Statistics: Uncertainty and Behavior*. Houghton Mifflin, Boston.

Schroeder, S. A., Schliftman, A., and Piemme, T. E. [1974]. Variation among physicians in use of laboratory tests: relation to quality of care. *Medical Care*, **12**: 709–713.

Tanur, J. M., Mosteller, F., Kruskal, W. H., Link, R. F., Pieters, R. S., and Rising, G. R. (eds.) [1989]. *Statistics: A Guide to the Unknown*, 3rd ed. Wadsworth & Brooks/Cole Advanced Books & Software, Pacific Grove, CA.

Time [1962]. Frozen ulcers. *Time*, May 18: 45–47.

Vessey, M. P., and Doll, R. [1969]. Investigation of the relation between use of oral contraceptives and thromboembolic disease: a further report. *British Medical Journal*, **2**: 651–657.

von Mises, R. [1957]. *Probability, Statistics and Truth*, 2nd ed. Macmillan, New York.

CHAPTER 2

Biostatistical Design of Medical Studies

2.1 INTRODUCTION

In this chapter we introduce some of the principles of biostatistical design. Many of the ideas are expanded in later chapters. This chapter also serves as a reminder that statistics is not an end in itself but a tool to be used in investigating the world around us. The study of statistics should serve to develop critical, analytical thought and common sense as well as to introduce specific tools and methods of processing data.

2.2 PROBLEMS TO BE INVESTIGATED

Biomedical studies arise in many ways. A particular study may result from a sequence of experiments, each one leading naturally to the next. The study may be triggered by observation of an interesting case, or observation of a mold (e.g., penicillin in a petri dish). The study may be instigated by a governmental agency in response to a question of national importance. The basic ideas of the study may be defined by an advisory panel. Many of the critical studies and experiments in biomedical science have come from one person with an idea for a radical interpretation of past data.

Formulation of the problem to be studied lies outside the realm of statistics per se. Statistical considerations may suggest that an experiment is too expensive to conduct, or may suggest an approach that differs from that planned. The need to evaluate data from a study statistically forces an investigator to sharpen the focus of the study. It makes one translate intuitive ideas into an analytical model capable of generating data that may be evaluated statistically.

To answer a given scientific question, many different studies may be considered. Possible studies may range from small laboratory experiments, to large and expensive experiments involving humans, to observational studies. It is worth spending a considerable amount of time thinking about alternatives. In most cases your first idea for a study will not be your best—unless it is your only idea.

In laboratory research, many different experiments may shed light on a given hypothesis or question. Sometimes, less-than-optimal execution of a well-conceived experiment sheds more light than arduous and excellent experimentation unimaginatively designed. One mark of a good scientist is that he or she attacks important problems in a clever manner.

Biostatistics: A Methodology for the Health Sciences, Second Edition, by Gerald van Belle, Lloyd D. Fisher, Patrick J. Heagerty, and Thomas S. Lumley
ISBN 0-471-03185-2

2.3 VARIOUS TYPES OF STUDIES

A problem may be investigated in a variety of ways. To decide on your method of approach, it is necessary to understand the types of studies that might be done. To facilitate the discussion of design, we introduce definitions of commonly used types of studies.

Definition 2.1. An *observational study* collects data from an existing situation. The data collection does not intentionally interfere with the running of the system.

There are subtleties associated with observational studies. The act of observation may introduce change into a system. For example, if physicians know that their behavior is being monitored and charted for study purposes, they may tend to adhere more strictly to procedures than would be the case otherwise. Pathologists performing autopsies guided by a study form may invariably look for a certain finding not routinely sought. The act of sending out questionnaires about health care may sensitize people to the need for health care; this might result in more demand. Asking constantly about a person's health can introduce hypochondria.

A side effect introduced by the act of observation is the *Hawthorne effect*, named after a famous experiment carried out at the Hawthorne works of the Western Electric Company. Employees were engaged in the production of electrical relays. The study was designed to investigate the effect of better working conditions, including increased pay, shorter hours, better lighting and ventilation, and pauses for rest and refreshment. All were introduced, with "resulting" increased output. As a control, working conditions were returned to original conditions. Production continued to rise! The investigators concluded that increased morale due to the attention and resulting *esprit de corps* among workers resulted in better production. Humans and animals are not machines or passive experimental units [Roethlisberger, 1941].

Definition 2.2. An *experiment* is a study in which an investigator deliberately sets one or more factors to a specific level.

Experiments lead to stronger scientific inferences than do observational studies. The "cleanest" experiments exist in the physical sciences; nevertheless, in the biological sciences, particularly with the use of randomization (a topic discussed below), strong scientific inferences can be obtained. Experiments are superior to observational studies in part because in an observational study one may not be observing one or more variables that are of crucial importance to interpreting the observations. Observational studies are always open to misinterpretation due to a lack of knowledge in a given field. In an experiment, by seeing the change that results when a factor is varied, the causal inference is much stronger.

Definition 2.3. A *laboratory experiment* is an experiment that takes place in an environment (called a *laboratory*) where experimental manipulation is facilitated.

Although this definition is loose, the connotation of the term *laboratory experiment* is that the experiment is run under conditions where most of the variables of interest can be controlled very closely (e.g., temperature, air quality). In laboratory experiments involving animals, the aim is that animals be treated in the same manner in all respects except with regard to the factors varied by the investigator.

Definition 2.4. A *comparative experiment* is an experiment that compares two or more techniques, treatments, or levels of a variable.

There are many examples of comparative experiments in biomedical areas. For example, it is common in nutrition to compare laboratory animals on different diets. There are many

experiments comparing different drugs. Experiments may compare the effect of a given treatment with that of no treatment. (From a strictly logical point of view, "no treatment" is in itself a type of treatment.) There are also comparative observational studies. In a comparative *study* one might, for example, observe women using and women not using birth control pills and examine the incidence of complications such as thrombophlebitis. The women themselves would decide whether or not to use birth control pills. The user and nonuser groups would probably differ in a great many other ways. In a comparative *experiment*, one might have women selected by chance to receive birth control pills, with the control group using some other method.

Definition 2.5. An *experimental unit* or *study unit* is the smallest unit on which an experiment or study is performed.

In a clinical study, the experimental units are usually humans. (In other cases, it may be an eye; for example, one eye may receive treatment, the other being a control.) In animal experiments, the experimental unit is usually an animal. With a study on teaching, the experimental unit may be a class—as the teaching method will usually be given to an entire class. Study units are the object of consideration when one discusses sample size.

Definition 2.6. An experiment is a *crossover experiment* if the same experimental unit receives more than one treatment or is investigated under more than one condition of the experiment. The different treatments are given during nonoverlapping time periods.

An example of a crossover experiment is one in which laboratory animals are treated sequentially with more than one drug and blood levels of certain metabolites are measured for each drug. A major benefit of a crossover experiment is that each experimental unit serves as its own control (the term *control* is explained in more detail below), eliminating subject-to-subject variability in response to the treatment or experimental conditions being considered. Major disadvantages of a crossover experiment are that (1) there may be a carryover effect of the first treatment continuing into the next treatment period; (2) the experimental unit may change over time; (3) in animal or human experiments, the treatment introduces permanent physiological changes; (4) the experiment may take longer so that investigator and subject enthusiasm wanes; and (5) the chance of dropping out increases.

Definition 2.7. A *clinical study* is one that takes place in the setting of clinical medicine.

A study that takes place in an organizational unit dispensing health care—such as a hospital, psychiatric clinic, well-child clinic, or group practice clinic—is a clinical study.

We now turn to the concepts of prospective studies and retrospective studies, usually involving human populations.

Definition 2.8. A *cohort* of people is a group of people whose membership is clearly defined.

Examples of cohorts are all persons enrolling in the Graduate School at the University of Washington for the fall quarter of 2003; all females between the ages of 30 and 35 (as of a certain date) whose residence is within the New York City limits; all smokers in the United States as of January 1, 1953, where a person is defined to be a smoker if he or she smoked one or more cigarettes during the preceding calendar year. Often, cohorts are followed over some time interval.

Definition 2.9. An *endpoint* is a clearly defined outcome or event associated with an experimental or study unit.

An endpoint may be the presence of a particular disease or five-year survival after, say, a radical mastectomy. An important characteristic of an endpoint is that it can be clearly defined and observed.

Definition 2.10. A *prospective study* is one in which a cohort of people is followed for the occurrence or nonoccurrence of specified endpoints or events or measurements.

In the analysis of data from a prospective study, the occurrence of the endpoints is often related to characteristics of the cohort measured at the beginning of the study.

Definition 2.11. *Baseline characteristics* or *baseline variables* are values collected at the time of entry into the study.

The Salk polio vaccine trial is an example of a prospective study, in fact, a prospective experiment. On occasion, you may be able to conduct a prospective study from existing data; that is, some unit of government or other agency may have collected data for other purposes, which allows you to analyze the data as a prospective study. In other words, there is a well-defined cohort for which records have already been collected (for some other purpose) which can be used for your study. Such studies are sometimes called *historical prospective studies*.

One drawback associated with prospective studies is that the endpoint of interest may occur infrequently. In this case, extremely large numbers of people need to be followed in order that the study will have enough endpoints for statistical analysis. As discussed below, other designs, help get around this problem.

Definition 2.12. A *retrospective study* is one in which people having a particular outcome or endpoint are identified and studied.

These subjects are usually compared to others without the endpoint. The groups are compared to see whether the people with the given endpoint have a higher fraction with one or more of the factors that are conjectured to increase the risk of endpoints.

Subjects with particular characteristics of interest are often collected into registries. Such a registry usually covers a well-defined population. In Sweden, for example, there is a twin registry. In the United States there are cancer registries, often defined for a specified metropolitan area. Registries can be used for retrospective as well as prospective studies. A cancer registry can be used retrospectively to compare the presence or absence of possible causal factors of cancer after generating appropriate controls—either randomly from the same population or by some matching mechanism. Alternatively, a cancer registry can be used prospectively by comparing survival times of cancer patients having various therapies.

One way of avoiding the large sample sizes needed to collect enough cases prospectively is to use the case–control study, discussed in Chapter 1.

Definition 2.13. A *case–control study* selects all cases, usually of a disease, that meet fixed criteria. A group, called *controls*, that serve as a comparison for the cases is also selected. The cases and controls are compared with respect to various characteristics.

Controls are sometimes selected to match the individual case; in other situations, an entire group of controls is selected for comparison with an entire group of cases.

Definition 2.14. In a *matched case–control study*, controls are selected to match characteristics of individual cases. The cases and control(s) are associated with each other. There may be more than one control for each case.

Definition 2.15. In a *frequency-matched case–control study*, controls are selected to match characteristics of the entire case sample (e.g., age, gender, year of event). The cases and controls are not otherwise associated. There may be more than one control for each case.

Suppose that we want to study characteristics of cases of a disease. One way to do this would be to identify new cases appearing during some time interval. A second possibility would be to identify all known cases at some fixed time. The first approach is *longitudinal*; the second approach is *cross-sectional*.

Definition 2.16. A *longitudinal study* collects information on study units over a specified time period. A *cross-sectional study* collects data on study units at a fixed time.

Figure 2.1 illustrates the difference. The longitudinal study might collect information on the six new cases appearing over the interval specified. The cross-sectional study would identify the nine cases available at the fixed time point. The cross-sectional study will have proportionately more cases with a long duration. (Why?) For completeness, we repeat the definitions given informally in Chapter 1.

Definition 2.17. A *placebo treatment* is designed to appear exactly like a comparison treatment but to be devoid of the active part of the treatment.

Definition 2.18. The *placebo effect* results from the belief that one has been treated rather than having experienced actual changes due to physical, physiological, and chemical activities of a treatment.

Definition 2.19. A study is *single blind* if subjects being treated are unaware of which treatment (including any control) they are receiving. A study is *double blind* if it is single blind

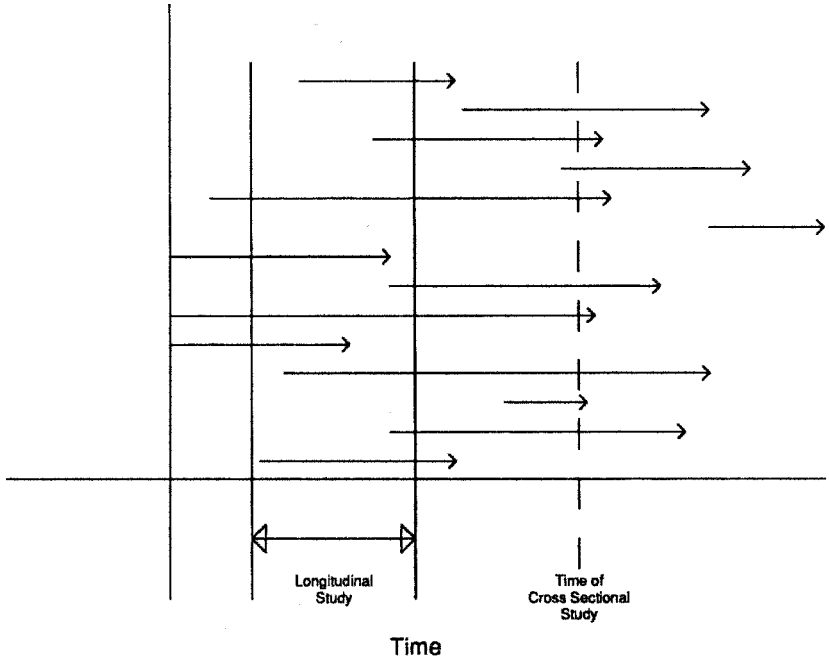


Figure 2.1 Longitudinal and cross-sectional study of cases of a disease.

and the people who are evaluating the outcome variables are also unaware of which treatment the subjects are receiving.

2.4 STEPS NECESSARY TO PERFORM A STUDY

In this section we outline briefly the steps involved in conducting a study. The steps are interrelated and are oversimplified here in order to isolate various elements of scientific research and to discuss the statistical issues involved:

1. A question or problem area of interest is considered. This does not involve biostatistics per se.
2. A study is to be designed to answer the question. The design of the study must consider at least the following elements:
   a. Identify the data to be collected. This includes the variables to be measured as well as the number of experimental units, that is, the size of the study or experiment.
   b. An appropriate analytical model needs to be developed for describing and processing data.
   c. What inferences does one hope to make from the study? What conclusions might one draw from the study? To what population(s) is the conclusion applicable?
3. The study is carried out and the data are collected.
4. The data are analyzed and conclusions and inferences are drawn.
5. The results are used. This may involve changing operating procedures, publishing results, or planning a subsequent study.

2.5 ETHICS

Many studies and experiments in the biomedical field involve animal and/or human participants. Moral and legal issues are involved in both areas. Ethics must be of primary concern. In particular, we mention five points relevant to experimentation with humans:

1. It is our opinion that all investigators involved in a study are responsible for the conduct of an ethical study to the extent that they may be expected to know what is involved in the study. For example, we think that it is unethical to be involved in the analysis of data that have been collected in an unethical manner.
2. Investigators are close to a study and often excited about its potential benefits and advances. It is difficult for them to consider all ethical issues objectively. For this reason, in proposed studies involving humans (or animals), there should be review by people not concerned or connected with the study or the investigators. The reviewers should not profit directly in any way if the study is carried out. Implementation of the study should be contingent on such a review.
3. People participating in an experiment should understand and sign an informed consent form. The *principle of informed consent* says that a participant should know about the conduct of a study and about any possible harm and/or benefits that may result from participation in the study. For those unable to give informed consent, appropriate representatives may give the consent.
4. Subjects should be free to withdraw at any time, or to refuse initial participation, without being penalized or jeopardized with respect to current and future care and activities.
5. Both the Nuremberg Code and the Helsinki Accord recommend that, when possible, animal studies be done prior to human experimentation.

References relevant to ethical issues include the U.S. Department of Health, Education, and Welfare's (HEW's) statement on *Protection of Human Subjects* [1975], Papworth's book, *Human Guinea Pigs* [1967], and Spicker et al. [1988]; Papworth is extremely critical of the conduct of modern biological experimentation. There are also guidelines for studies involving animals. See, for example, *Guide for the Care and Use of Laboratory Animals* [HEW, 1985] and *Animal Welfare* [USDA, 1989]. Ethical issues in randomized trials are discussed further in Chapter 19.

2.6 DATA COLLECTION: DESIGN OF FORMS

2.6.1 What Data Are to Be Collected?

In studies involving only one or two investigators, there is often almost complete agreement as to what data are to be collected. In this case it is very important that good laboratory records be maintained. It is especially important that variations in the experimental procedure (e.g., loss of power during a time period, unexpected change in temperature in a room containing laboratory animals) be recorded. If there are peculiar patterns in the data, detailed notes may point to possible causes. The necessity for keeping detailed notes is even more crucial in large studies or experiments involving many investigators; it is difficult for one person to have complete knowledge of a study.

In a large collaborative study involving a human population, it is not always easy to decide what data to collect. For example, often there is interest in getting prognostic information. How many potentially prognostic variables should you record?

Suppose that you are measuring pain relief or quality of life; how many questions do you need to characterize these abstract ideas reasonably? In looking for complications of drugs, should you instruct investigators to enter all complications? This may be an unreliable procedure if you are dependent on a large, diverse group of observers. In studies with many investigators, each investigator will want to collect data relating to her or his special interests. You can arrive rapidly at large, complex forms. If too many data are collected, there are various "prices" to be paid. One obvious price is the expense of collecting and handling large and complex data sets. Another is reluctance (especially by volunteer subjects) to fill out long, complicated forms, leading to possible biases in subject recruitment. If a study lasts a long time, the investigators may become fatigued by the onerous task of data collection. Fatigue and lack of enthusiasm can affect the quality of data through a lack of care and effort in its collection.

On the other hand, there are many examples where too few data were collected. One of the most difficult tasks in designing forms is to remember to include all necessary items. The more complex the situation, the more difficult the task. It is easy to look at existing questions and to respond to them. If a question is missing, how is one alerted to the fact? One of the authors was involved in the design of a follow-up form where mortality could not be recorded. There was an explanation for this: The patients were to fill out the forms. Nevertheless, it was necessary to include forms that would allow those responsible for follow-up to record mortality, the primary endpoint of the study.

To assure that all necessary data are on the form, you are advised to follow four steps:

1. Perform a thorough review of all forms *with a written response* by all participating investigators.
2. Decide on the statistical analyses beforehand. Check that *specific* analyses involving *specific* variables can be run. Often, the analysis is changed during processing of the data or in the course of "interactive" data analysis. This preliminary step is still necessary to ensure that data are available to answer the primary questions.
3. Look at other studies and papers in the area being studied. It may be useful to mimic analyses in the most outstanding of these papers. If they contain variables not recorded

in the new study, find out why. The usual reason for excluding variables is that they are not needed to answer the problems addressed.

4. If the study includes a pilot phase, as suggested below, analyze the data of the pilot phase to see if you can answer the questions of interest when more data become available.

2.6.2 Clarity of Questions

The task of designing clear and unambiguous questions is much greater than is generally realized. The following points are of help in designing such questions:

1. Who is filling out the forms? Forms to be filled out by many people should, as much as possible, be self-explanatory. There should not be another source to which people are required to go for explanation—often, they would not take the trouble. This need not be done if trained technicians or interviewers are being used in certain phases of the study.
2. The degree of accuracy and the units required should be specified where possible. For example, data on heights should not be recorded in both inches and centimeters in the same place. It may be useful to allow both entries and to have a computer adjust to a common unit. In this case have two possible entries, one designated as centimeters and the other designated as inches.
3. A response should be required on all sections of a form. Then if a portion of the form has no response, this would indicate that the answer was missing. (If an answer is required only under certain circumstances, you cannot determine whether a question was missed or a correct "no answer" response was given; a blank would be a valid answer. For example, in pathology, traditionally the pathologist reports only "positive" findings. If a finding is absent in the data, was the particular finding not considered, and missed, or was a positive outcome not there?)
4. There are many alternatives when collecting data about humans: forms filled out by a subject, an in-person interview by a trained interviewer, a telephone interview, forms filled out by medical personnel after a general discussion with the subject, or forms filled out by direct observation. It is an eye-opening experience to collect the "same" data in several different ways. This leads to a healthy respect for the amount of variability in the data. It may also lead to clarification of the data being collected. In collecting subjective opinions, there is usually interaction between a subject and the method of data collection. This may greatly influence, albeit unconsciously, a subject's response.

The following points should also be noted. A high level of formal education of subjects and/or interviewer is not necessarily associated with greater accuracy or reproducibility of data collected. The personality of a subject and/or interviewer can be more important than the level of education. The effort and attention given to a particular part of a complex data set should be proportional to its importance. Prompt editing of data for mistakes produces higher-quality data than when there is considerable delay between collecting, editing, and correction of forms.

2.6.3 Pretesting of Forms and Pilot Studies

If it is extremely difficult, indeed almost impossible, to design a satisfactory form, how is one to proceed? It is necessary to have a pretest of the forms, except in the simplest of experiments and studies. In a *pretest*, forms are filled out by one or more people prior to beginning an actual study and data collection. In this case, several points should be considered. People filling out forms should be representative of the people who will be filling them out during the study. You can be misled by having health professionals fill out forms that are designed for the "average" patient. You should ask the people filling out the pretest forms if they have any questions or are not sure about parts of the forms. However, it is important not to interfere while the

forms are being used but to let them be used in the same context as will pertain in the study; then ask the questions. Preliminary data should be analyzed; you should look for differences in responses from different clinics or individuals. Such analyses may indicate that a variable is being interpreted differently by different groups. The pretest forms should be edited by those responsible for the design. Comments written on the forms or answers that are not legitimate can be important in improving the forms. During this phase of the study, one should pursue vigorously the causes of missing data.

A more complete approach is to have a *pilot study*, which consists of going through the actual mechanics of a proposed study. Thus, a pilot study works out both the "bugs" from forms used in data collection and operational problems within the study. Where possible, data collected in a pilot study should be compared with examples of the "same" data collected in other studies. Suppose that there is recording of data that are not quantitative but categorical (e.g., the amount of impairment of an animal, whether an animal is losing its hair, whether a patient has improved morale). There is a danger that the investigator(s) may use a convention that would not readily be understood by others. To evaluate the extent to which the data collected are understood, it is good procedure to ask others to examine some of the same study units and to record their opinion without first discussing what is meant by the categories being recorded. If there is great variability, this should lead to a need for appropriate caution in the interpretation of the data. This problem may be most severe when only one person is involved in data collection.

2.6.4 Layout and Appearance

The physical appearance of forms is important if many people are to fill them out. People attach more importance to a printed page than to a mimeographed page, even though the layout is the same. If one is depending on voluntary reporting of data, it may be worthwhile to spend a bit more to have forms printed in several colors with an attractive logo and appearance.

2.7 DATA EDITING AND VERIFICATION

If a study involves many people filling out forms, it will be necessary to have a manual and/or computer review of the content of the forms before beginning analysis. In most studies there are inexplicably large numbers of mistakes and missing data. If missing and miscoded data can be attacked vigorously *from the beginning* of a study, the quality of data can be vastly improved. Among checks that go into data editing are the following:

1. *Validity checks*. Check that only allowable values or codes are given for answers to the questions. For example, a negative weight is not allowed. A simple extension of this idea is to require that most of the data fall within a given range; range checks are set so that a small fraction of the valid data will be outside the range and will be "flagged"; for example, the height of a professional basketball team center (who happens to be a subject in the study) may fall outside the allowed range even though the height is correct. By checking out-of-range values, many incorrectly recorded values can be detected.
2. *Consistency checks*. There should be internal consistency of the data. Following are some examples:
   - **a.** If more than one form is involved, the dates on these forms should be consistent with each other (e.g., a date of surgery should precede the date of discharge for that surgery).
   - **b.** Consistency checks can be built into the study by collecting crucial data in two different ways (e.g., ask for both date of birth and age).
   - **c.** If the data are collected sequentially, it is useful to examine unexpected changes between forms (e.g., changes in height, or drastic changes such as changes of weight by 70%). Occasionally, such changes are correct, but they should be investigated.

d. In some cases there are certain combinations of replies that are mutually inconsistent; checks for these should be incorporated into the editing and verification procedures.

3. *Missing forms*. In some case–control studies, a particular control may refuse to participate in a study. Some preliminary data on this control may already have been collected. Some mechanism should be set up so that it is clear that no further information will be obtained for that control. (It will be useful to keep the preliminary information so that possible selection bias can be detected.) If forms are entered sequentially, it will be useful to decide when missing forms will be labeled "overdue" or "missing."

2.8 DATA HANDLING

All except the smallest experiments involve data that are eventually processed or analyzed by computer. Forms should be designed with this fact in mind. It should be easy to enter the form by keyboard. Some forms are called *self-coding*: Columns are given next to each variable for data entry. Except in cases where the forms are to be entered by a variety of people at different sites, the added cluttering of the form by the self-coding system is not worth the potential ease in data entry. Experienced persons entering the same type of form over and over soon know which columns to use. Alternatively, it is possible to overlay plastic sheets that give the columns for data entry.

For very large studies, the logistics of collecting data, putting the data on a computer system, and linking records may hinder a study more than any other factor. Although it is not appropriate to discuss these issues in detail here, the reader should be aware of this problem. In any large study, people with expertise in data handling and computer management of data should be consulted during the design phase. Inappropriately constructed data files result in unnecessary expense and delay during the analytic phase. In projects extending over a long period of time and requiring periodic reports, it is important that the timing and management of data collection and management be specified. Experience has shown that even with the best plans there will be inevitable delays. It is useful to allow some slack time between required submission of forms and reports, between final submission and data analysis.

Computer files or tapes will occasionally be erased accidentally. In the event of such a disaster it is necessary to have backup computer tapes and documentation. If information on individual subject participants is required, there are confidentiality laws to be considered as well as the investigator's ethical responsibility to protect subject interests. During the design of any study, everyone will underestimate the amount of work involved in accomplishing the task. Experience shows that caution is necessary in estimating time schedules. During a long study, constant vigilance is required to maintain the quality of data collection and flow. In laboratory experimentation, technicians may tend to become bored and slack off unless monitored. Clinical study personnel will tire of collecting the data and may try to accomplish this too rapidly unless monitored.

Data collection and handling usually involves almost all participants of the study and should not be underestimated. It is a common experience for research studies to be planned without allowing sufficient time or money for data processing and analysis. It is difficult to give a rule of thumb, but in a wide variety of studies, 15% of the expense has been in data handling, processing, and analysis.

2.9 AMOUNT OF DATA COLLECTED: SAMPLE SIZE

It is part of scientific folklore that one of the tasks of a statistician is to determine an appropriate sample size for a study. Statistical considerations do have a large bearing on the selection of a sample size. However, there is other scientific input that must be considered in order to arrive at the number of experimental units needed. If the purpose of an experiment is to estimate

some quantity, there is a need to know how precise an estimate is desired and how confident the investigator wishes to be that the estimate is within a specified degree of precision. If the purpose of an experiment is to compare several treatments, it is necessary to know what difference is considered important and how certain the investigator wishes to be of detecting such a difference. Statistical calculation of sample size requires that all these considerations be quantified. (This topic is discussed in subsequent chapters.) In a descriptive observational study, the size of the study is determined by specifying the needed accuracy of estimates of population characteristics.

2.10 INFERENCES FROM A STUDY

2.10.1 Bias

The statistical term *bias* refers to a situation in which the statistical method used does not estimate the quantity thought to be estimated or test the hypothesis thought to be tested. This definition will be made more precise later. In this section the term is used on a intuitive level. Consider some examples of biased statistical procedures:

1. A proposal is made to measure the average amount of health care in the United States by means of a personal health questionnaire that is to be passed out at an American Medical Association convention. In this case, the AMA respondents constitute a biased sample of the overall population.
2. A famous historical example involves a telephone poll made during the Dewey–Truman presidential contest. At that time—and to some extent today—a large section of the population could not afford a telephone. Consequently, the poll was conducted among more well-to-do citizens, who constituted a biased sample with respect to presidential preference.
3. In a laboratory experiment, animals receiving one treatment are kept on one side of the room and animals receiving a second treatment are kept on another side. If there is a large differential in lighting and heat between the two sides of the room, one could find "treatment effects" that were in fact ascribable to differences in light and/or heat. Work by Riley [1975] suggests that level of stress (e.g., bottom cage vs. top cage) affects the resistance of animals to carcinogens.

In the examples of Section 1.5, methods of minimizing bias were considered. Single- and double-blind experiments reduce bias.

2.10.2 Similarity in a Comparative Study

If physicists at Berkeley perform an experiment in electron physics, it is expected that the same experiment could be performed successfully (given the appropriate equipment) in Moscow or London. One expects the same results because the current physical model is that all electrons are precisely the same (i.e., they are identical) and the experiments are truly similar experiments. In a comparative experiment, we would like to try out experiments on similar units.

We now discuss similarity where it is assumed for the sake of discussion that the experimental units are humans. The ideas and results, however, can be extended to animals and other types of experimental units. The experimental situations being compared will be called *treatments*. To get a fair comparison, it is necessary that the treatments be given to similar units. For example, if cancer patients whose disease had not progressed much receive a new treatment and their survival is compared to the standard treatment administered to all types of patients, the comparison would not be justified; the treatments were not given to similar groups.

Of all human beings, *identical twins* are the most alike, by having identical genetic background. Often, they are raised together, so they share the same environment. Even in an observational twin study, a strong scientific inference can be made if enough appropriate pairs of identical twins can be found. For example, suppose that the two "treatments" are smoking and nonsmoking. If one had identical twins raised together where one of the pair smoked and the other did not, the incidence of lung cancer, the general health, and the survival experience could provide quite strong scientific inferences as to the health effect of smoking. (In Sweden there is a twin registry to aid public health and medical studies.) It is difficult to conduct twin studies because sufficient numbers of identical twins need to be located, such that one member of the pair has one treatment and the other twin, another treatment. It is expensive to identify and find them. Since they have the same environment, in a smoking study it is most likely, that either both would smoke or both would not smoke. Such studies are logistically not possible in most circumstances.

A second approach is that of matching or pairing individuals. The rationale behind *matched* or *matched pair studies* is to find two persons who are identical with regard to all "pertinent" variables under consideration except the treatment. This may be thought of as an attempt to find a surrogate identical twin. In many studies, people are matched with regard to age, gender, race, and some indicator of socioeconomic status. In a prospective study, the two matched individuals receive differing treatments. In a retrospective study, the person with the endpoint is identified first (the person usually has some disease); as we have seen, such studies are called case–control studies. One weakness of such studies is that there may not be a sufficient number of subjects to make "good" matches. Matching on too many variables makes it virtually impossible to find a sufficient number of control subjects. No matter how well the matching is done, there is the possibility that the groups receiving the two treatments (the case and control groups) are not sufficiently similar because of unrecognized variables.

A third approach is not to match on specific variables but to try to select the subjects on an intuitive basis. For example, such procedures often select the next person entering the clinic, or have the patient select a friend of the same gender. The rationale here is that a friend will tend to belong to the same socioeconomic environment and have the same ethnic characteristics.

Still another approach, even farther removed from the "identical twins" approach, is to select a group receiving a given treatment and then to select in its entirety a second group as a control. The hope is that by careful consideration of the problem and good intuition, the control group will, in some sense, mirror the first treatment group with regard to "all pertinent characteristics" except the treatment and endpoint. In a retrospective study, the first group usually consists of cases and a control group selected from the remaining population.

The final approach is to select the two groups in some manner realizing that they will not be similar, and to measure pertinent variables, such as the variables that one had considered matching upon, as well as the appropriate endpoint variables. The idea is to make statistical adjustments to find out what would have happened had the two groups been comparable. Such adjustments are done in a variety of ways. The techniques are discussed in following chapters.

None of the foregoing methods of obtaining "valid" comparisons are totally satisfactory. In the 1920s, Sir Ronald A. Fisher and others made one of the great advances in scientific methodology—they assigned treatments to patients by chance; that is, they assigned treatments *randomly*. The technique is called *randomization*. The statistical or chance rule of assignment will satisfy certain properties that are best expressed by the concepts of probability theory. These concepts are described in Chapter 4. For assignment to two therapies, a coin toss could be used. A head would mean assignment to therapy 1; a tail would result in assignment to therapy 2. Each patient would have an equal chance of getting each therapy. Assignments to past patients would not have any effect on the therapy assigned to the next patient. By the laws of probability, on the average, treatment groups will be similar. *The groups will even be similar with respect to variables not measured or even thought about!* The mathematics of probability allow us to estimate whether differences in the outcome might be due to the chance assignment to the two

groups or whether the differences should be ascribed to true differences between treatments. These points are discussed in more detail later.

2.10.3 Inference to a Larger Population

Usually, it is desired to apply the results of a study to a population beyond the experimental units. In an experiment with guinea pigs, the assumption is that if other guinea pigs had been used, the "same" results would have been found. In reporting good results with a new surgical procedure, it is implicit that this new procedure is probably good for a wide variety of patients in a wide variety of clinical settings. To extend results to a larger population, experimental units should be *representative* of the larger population. The best way to assure this is to select the experimental units *at random*, or by chance, from the larger population. The mechanics and interpretation of such random sampling are discussed in Chapter 4. Random sampling assures, on the average, a representative sample. In other instances, if one is willing to make assumptions, the extension may be valid. There is an implicit assumption in much clinical research that a treatment is good for almost everyone or almost no one. Many techniques are used initially on the subjects available at a given clinic. It is assumed that a result is true for all clinics if it works in one setting.

Sometimes, the results of a technique are compared with "historical" controls; that is, a new treatment is compared with the results of previous patients using an older technique. The use of historical controls can be hazardous; patient populations change with time, often in ways that have much more importance than is generally realized. Another approach with weaker inference is the use of an animal model. The term *animal model* indicates that the particular animal is susceptible to, or suffers from, a disease similar to that experienced by humans. If a treatment works on the animal, it may be useful for humans. There would then be an investigation in the human population to see whether the assumption is valid.

The results of an observational study carried out in one country may be extended to other countries. This is not always appropriate. Much of the "bread and butter" of epidemiology consists of noting that the same risk factor seems to produce different results in different populations, or in noting that the particular endpoint of a disease occurs with differing rates in different countries. There has been considerable advance in medical science by noting different responses among different populations. This is a broadening of the topic of this section: extending inferences in one population to another population.

2.10.4 Precision and Validity of Measurements

Statistical theory leads to the examination of variation in a method of measurement. The variation may be estimated by making repeated measurements on the same experimental unit. If instrumentation is involved, multiple measurements may be taken using more than one of the instruments to note the variation between instruments. If different observers, interviewers, or technicians take measurements, a quantification of the variability between observers may be made. It is necessary to have information on the precision of a method of measurement in calculating the sample size for a study. This information is also used in considering whether or not variables deserve repeated measurements to gain increased precision about the true response of an experimental unit.

Statistics helps in thinking about alternative methods of measuring a quantity. When introducing a new apparatus or new technique to measure a quantity of interest, validation against the old method is useful. In considering subjective ratings by different people (even when the subjective rating is given as a numerical scale), it often turns out that a quantity is not measured in the same fashion if the measurement method is changed. A new laboratory apparatus may measure consistently higher than an old one. In two methods of evaluating pain relief, one way of phrasing a question may tend to give a higher percentage of improvement. Methodologic statistical studies are helpful in placing interpretations and inferences in the proper context.

2.10.5 Quantification and Reduction of Uncertainty

Because of variability, there is uncertainty associated with the interpretation of study results. Statistical theory allows quantification of the uncertainty. If a quantity is being estimated, the amount of uncertainty in the estimate must be assessed. In considering a hypothesis, one may give numerical assessment of the chance of occurrence of the results observed when the hypothesis is true.

Appreciation of statistical methodology often leads to the design of a study with increased precision and consequently, a smaller sample size. An example of an efficient technique is the statistical idea of blocking. Blocks are subsets of relatively homogeneous experimental units. The strategy is to apply all treatments randomly to the units within a particular block. Such a design is called a *randomized block design*. The advantage of the technique is that comparisons of treatments are intrablock comparisons (i.e., comparisons within blocks) and are more precise because of the homogeneity of the experimental units within the blocks, so that it is easier to detect treatment differences. As discussed earlier, simple randomization does ensure similar groups, but the variability within the treatment groups will be greater if no blocking of experimental units has been done. For example, if age is important prognostically in the outcome of a comparative trial of two therapies, there are two approaches that one may take. If one ignores age and randomizes the two therapies, the therapies will be tested on similar groups, but the variability in outcome due to age will tend to mask the effects of the two treatments. Suppose that you place people whose ages are close into blocks and assign each treatment by a chance mechanism within each block. If you then compare the treatments within the blocks, the effect of age on the outcome of the two therapies will be largely eliminated. A more precise comparison of the therapeutic effects can be gained. This increased precision due to statistical design leads to a study that requires a smaller sample size than does a completely randomized design. However, see Meier et al. [1968] for some cautions.

A good statistical design allows the investigation of several factors at one time with little added cost (Sir R. A. Fisher as quoted by Yates [1964]):

> No aphorism is more frequently repeated with field trials than we must ask Nature a few questions, or ideally, one question at a time. The writer is convinced that this view is wholly mistaken. Nature, he suggests, will best respond to a logical and carefully thought out questionnaire; indeed if we ask her a single question, she will often refuse to answer until some other topic has been discussed.

PROBLEMS

2.1 Consider the following terms defined in Chapters 1 and 2: single blind, double blind, placebo, observational study, experiment, laboratory experiment, comparative experiment, crossover experiment, clinical study, cohort, prospective study, retrospective study, case–control study, and matched case–control study. In the examples of section 1.5, which terms apply to which parts of these examples?

2.2 List possible advantages and disadvantages of a double-blind study. Give some examples where a double-blind study clearly cannot be carried out; suggest how virtues of "blinding" can still be retained.

2.3 Discuss the ethical aspects of a randomized placebo-controlled experiment. Can you think of situations where it would be extremely difficult to carry out such an experiment?

2.4 Discuss the advantages of randomization in a randomized placebo-controlled experiment. Can you think of alternative, possibly better, designs? Consider (at least) the aspects of bias and efficiency.

2.5 This problem involves the design of two questions on "stress" to be used on a data collection form for the population of a group practice health maintenance organization. After a few years of follow-up, it is desired to assess the effect of physical and psychological stress.

(a) Design a question that classifies jobs by the amount of physical work involved. Use eight or fewer categories. Assume that the answer to the question is to be based on job title. That is, someone will code the answer given a job title.

(b) Same as part (a), but now the classification should pertain to the amount of psychological stress.

(c) Have yourself and (independently) a friend answer your two questions for the following occupational categories: student, college professor, plumber, waitress, homemaker, salesperson, unemployed, retired, unable to work (due to illness), physician, hospital administrator, grocery clerk, prisoner.

(d) What other types of questions would you need to design to capture the total amount of stress in the person's life?

2.6 In designing a form, careful distinction must be made between the following categories of nonresponse to a question: (1) not applicable, (2) not noted, (3) don't know, (4) none, and (5) normal. If nothing is filled in, someone has to determine which of the five categories applies—and often this cannot be done after the interview or the records have been destroyed. This is particularly troublesome when medical records are abstracted. Suppose that you are checking medical records to record the number of pregnancies (*gravidity*) of a patient. Unless the gravidity is specifically given, you have a problem. If no number is given, any one of the four categories above could apply. Give two other examples of questions with ambiguous interpretation of "blank" responses. Devise a scheme for interview data that is unambiguous and does not require further editing.

REFERENCES

Meier, P., Free, S. M., Jr., and Jackson, G. L. [1968]. Reconsideration of methodology in studies of pain relief. *Biometrics*, **14**: 330–342.

Papworth, M. H. [1967]. *Human Guinea Pigs*. Beacon Press, Boston.

Riley, V. [1975]. Mouse mammary tumors: alteration of incidence as apparent function of stress. *Science*, **189**: 465–467.

Roethlisberger, F. S. [1941]. *Management and Morals*. Harvard University Press, Cambridge, MA.

Spicker, S. F., et al. (eds.) [1988]. *The Use of Human Beings in Research, with Special Reference to Clinical Trials*. Kluwer Academic, Boston.

U.S. Department of Agriculture [1989]. Animal welfare: proposed rules, part III. *Federal Register*, Mar. 15, 1989.

U.S. Department of Health, Education, and Welfare [1975]. Protection of human subjects, part III. *Federal Register*, Aug. 8, 1975, **40**: 11854.

U.S. Department of Health, Education, and Welfare [1985]. *Guide for the Care and Use of Laboratory Animals*. DHEW Publication (NIH) 86–23. U.S. Government Printing Office, Washington, DC.

Yates, F. [1964]. Sir Ronald Fisher and the design of experiments. *Biometrics*, **20**: 307–321. Used with permission from the Biometric Society.

CHAPTER 3

Descriptive Statistics

3.1 INTRODUCTION

The beginning of an introductory statistics textbook usually contains a few paragraphs placing the subject matter in encyclopedic order, discussing the limitations or wide ramifications of the topic, and tends to the more philosophical rather than the substantive–scientific. Briefly, we consider science to be a study of the world emphasizing qualities of permanence, order, and structure. Such a study involves a drastic reduction of the real world, and often, numerical aspects only are considered. If there is no obvious numerical aspect or ordering, an attempt is made to impose it. For example, quality of medical care is not an immediately numerically scaled phenomenon but a scale is often induced or imposed. Statistics is concerned with the estimation, summarization, and obtaining of reliable numerical characteristics of the world. It will be seen that this is in line with some of the definitions given in the Notes in Chapter 1.

It may be objected that a characteristic such as the gender of a newborn baby is not numerical, but it can be coded (arbitrarily) in a numerical way; for example, 0 = male and 1 = female. Many such characteristics can be *labeled* numerically, and as long as the code, or the dictionary, is known, it is possible to go back and forth.

Consider a set of measurements of head circumferences of term infants born in a particular hospital. We have a quantity of interest—head circumference—which varies from baby to baby, and a collection of actual values of head circumferences.

Definition 3.1. A *variable* is a quantity that may vary from object to object.

Definition 3.2. A *sample* (or data set) is a collection of values of one or more variables. A member of the sample is called an *element*.

We distinguish between a variable and the value of a variable in the same way that the label "title of a book in the library" is distinguished from the title *Gray's Anatomy*. A variable will usually be represented by a capital letter, say, Y, and a value of the variable by a lowercase letter, say, y.

In this chapter we discuss briefly the types of variables typically dealt with in statistics. We then go on to discuss ways of *describing* samples of values of variables, both numerically and graphically. A key concept is that of a *frequency distribution*. Such presentations can be considered part of *descriptive statistics*. Finally, we discuss one of the earliest challenges to statistics, how to *reduce* samples to a few summarizing numbers. This will be considered under the heading of descriptive statistics.

Biostatistics: A Methodology for the Health Sciences, Second Edition, by Gerald van Belle, Lloyd D. Fisher, Patrick J. Heagerty, and Thomas S. Lumley
ISBN 0-471-03185-2

3.2 TYPES OF VARIABLES

3.2.1 Qualitative (Categorical) Variables

Some examples of qualitative (or categorical) variables and their values are:

1. Color of a person's hair (black, gray, red, . . . , brown)
2. Gender of child (male, female)
3. Province of residence of a Canadian citizen (Newfoundland, Nova Scotia, . . . , British Columbia)
4. Cause of death of newborn (congenital malformation, asphyxia, . . .)

Definition 3.3. A *qualitative variable* has values that are intrinsically nonnumerical (categorical).

As suggested earlier, the values of a qualitative variable can always be put into numerical form. The simplest numerical form is consecutive labeling of the values of the variable. The values of a qualitative variable are also referred to as *outcomes* or *states*.

Note that examples 3 and 4 above are ambiguous. In example 3, what shall we do with Canadian citizens living outside Canada? We could arbitrarily add another "province" with the label "Outside Canada." Example 4 is ambiguous because there may be more than one cause of death. Both of these examples show that it is not always easy to anticipate all the values of a variable. Either the list of values must be changed or the variable must be redefined.

The arithmetic operation associated with the values of qualitative variables is usually that of counting. Counting is perhaps the most elementary—but not necessarily simple—operation that organizes or abstracts characteristics. A *count* is an answer to the question: How many? (Counting assumes that whatever is counted shares some characteristics with the other "objects." Hence it disregards what is unique and reduces the objects under consideration to a common category or class.) Counting leads to statements such as "the number of births in Ontario in 1979 was 121,655."

Qualitative variables can often be ordered or ranked. *Ranking* or *ordering* places a set of objects in a sequence according to a specified scale. In Chapter 2, clinicians ranked interns according to the quality of medical care delivered. The "objects" were the interns and the scale was "quality of medical care delivered." The interns could also be ranked according to their height, from shortest to tallest—the "objects" are again the interns and the scale is "height." The provinces of Canada could be ordered by their population sizes from lowest to highest. Another possible ordering is by the latitudes of, say, the capitals of each province. Even hair color could be ordered by the wavelength of the dominant color. Two points should be noted in connection with ordering or qualitative variables. First, as indicated by the example of the provinces, there is more than one ordering that can be imposed on the outcomes of a variable (i.e., there is no natural ordering); the type of ordering imposed will depend on the nature of the variable and the purpose for which it is studied—if we wanted to study the impact of crowding or pollution in Canadian provinces, we might want to rank them by population size. If we wanted to study rates of melanoma as related to amount of ultraviolet radiation, we might want to rank them by the latitude of the provinces as summarized, say by the latitudes of the capitals or most populous areas. Second, the ordering need not be complete; that is, we may not be able to rank each outcome above or below another. For example, two of the Canadian provinces may have virtually identical populations, so that it is not possible to order them. Such orderings are called *partial*.

3.2.2 Quantitative Variables

Some examples of quantitative variables (with scale of measurement; values) are the following:

1. Height of father ($\frac{1}{2}$ inch units; 0.0, 0.5, 1.0, 1.5, . . . , 99.0, 99.5, 100.0)

2. Number of particles emitted by a radioactive source (counts per minute; 0, 1, 2, 3, . . .)
3. Total body calcium of a patient with osteoporosis (nearest gram; 0, 1, 2, . . . , 9999, 10,000)
4. Survival time of a patient diagnosed with lung cancer (nearest day; 0, 1, 2, . . . , 19,999, 20,000)
5. Apgar score of infant 60 seconds after birth (counts; 0, 1, 2, . . . , 8, 9, 10)
6. Number of children in a family (counts; 0, 1, 2, 3, . . .)

Definition 3.4. A *quantitative variable* has values that are intrinsically numerical.

As illustrated by the examples above, we must specify two aspects of a variable: the scale of measurement and the values the variable can take on. Some quantitative variables have numerical values that are integers, or discrete. Such variables are referred to as *discrete variables*. The variable "number of particles emitted by a radioactive source" is such an example; there are "gaps" between the successive values of this variable. It is not possible to observe 3.5 particles. (It is sometimes a source of amusement when discrete numbers are manipulated to produce values that cannot occur—for example, "the average American family" has 2.125 children). Other quantitative variables have values that are potentially associated with real numbers—such variables are called *continuous variables*. For example, the survival time of a patient diagnosed with lung cancer may be expressed to the nearest day, but this phrase implies that there has been rounding. We could refine the measurement to, say, hours, or even more precisely, to minutes or seconds. The exactness of the values of such a variable is determined by the precision of the measuring instrument as well as the usefulness of extending the value. Usually, a reasonable unit is assumed and it is considered *pedantic* to have a unit that is too refined, or *rough* to have a unit that does not permit distinction between the objects on which the variable is measured. Examples 1, 3, and 4 above deal with continuous variables; those in the other examples are discrete. Note that with quantitative variables there is a natural ordering (e.g., from lowest to highest value) (see Note 3.7 for another taxonomy of data).

In each illustration of qualitative and quantitative variables, we listed all the possible values of a variable. (Sometimes the values could not be listed, usually indicated by inserting three dots ". . . " into the sequence.) This leads to:

Definition 3.5. The *sample space* or *population* is the set of all possible values of a variable.

The definition or listing of the sample space is not a trivial task. In the examples of qualitative variables, we already discussed some ambiguities associated with the definitions of a variable and the sample space associated with the variable. Your definition must be reasonably precise without being "picky." Consider again the variable "province of residence of a Canadian citizen" and the sample space (Newfoundland, Nova Scotia, . . . , British Columbia). Some questions that can be raised include:

1. What about citizens living in the Northwest Territories? (Reasonable question)
2. Are landed immigrants who are not yet citizens to be excluded? (Reasonable question)
3. What time point is intended? Today? January 1, 2000? (Reasonable question)
4. If January 1, 2000 is used, what about citizens who died on that day? Are they to be included? (Becoming somewhat "picky")

3.3 *DESCRIPTIVE* STATISTICS

3.3.1 Tabulations and Frequency Distributions

One of the simplest ways to summarize data is by tabulation. John Graunt, in 1662, published his observations on bills of mortality, excerpts of which can be found in Newman [1956].

Table 3.1 Diseases and Casualties in the City of London 1632

Disease	Casualties
Abortive and stillborn	445
Affrighted	1
Aged	628
Ague	43
⋮	
Crisomes and infants	2268
⋮	
Tissick	34
Vomiting	1
Worms	27
In all	9535

Source: A selection from Graunt's tables; from Newman [1956].

Table 3.1 is a condensation of Graunt's list of 63 diseases and casualties. Several things should be noted about the table. To make up the table, three ingredients are needed: (1) a *collection* of objects (in this case, humans), (2) a *variable* of interest (the cause of death), and (3) the *frequency* of occurrence of each category. These are defined more precisely later. Second, we note that the disease categories are arranged alphabetically (ordering number 1). This may not be too helpful if we want to look at the most common causes of death. Let us rearrange Graunt's table by listing disease categories by greatest frequencies (ordering number 2).

Table 3.2 lists the 10 most common disease categories in Graunt's table and summarizes $8274/9535 = 87\%$ of the data in Table 3.1. From Table 3.2 we see at once that "crisomes" is the most frequent cause of death. (A *crisome* is an infant dying within one month of birth. Gaunt lists the number of "christenings" [births] as 9584, so a crude estimate of neonatal mortality is $2268/9584 \doteq 24\%$. The symbol "$\doteq$" means "approximately equal to.") Finally, we note that data for 1633 almost certainly would not have been identical to that of 1632. However, the number in the category "crisomes" probably would have remained the largest. An example of a statistical question is whether this predominance of "crisomes and infants" has a quality of permanence from one year to the next.

A second example of a tabulation involves keypunching errors made by a data-entry operator. To be entered were 156 lines of data, each line containing data on the number of crib deaths for a particular month in King County, Washington, for the years 1965–1977. Other data on

Table 3.2 Rearrangement of Graunt's Data (Table 3.1) by the 10 Most Common Causes of Death

Disease	Casualties	Disease	Casualties
Crisomes and infants	2268	Bloody flux, scowring, and flux	348
Consumption	1797	Dropsy and swelling	267
Fever	1108	Convulsion	241
Aged	628	Childbed	171
Flocks and smallpox	531		
Teeth	470	Total	8274
Abortive and stillborn	445		

Table 3.3 Number of Keypunching Errors per Line for 156 Consecutive Lines of Data Entered[a]

0	0	1	0	2	0	0	0	1	0	0	0
0	0	0	0	1	0	0	1	2	0	0	1
1	0	0	2	0	0	0	0	0	0	0	0
0	1	0	0	0	0	0	0	0	0	0	0
1	0	0	0	0	0	0	0	0	0	0	0
0	0	0	0	0	0	0	0	1	0	0	0
0	1	1	1	1	0	0	0	0	0	0	1
0	1	0	0	1	0	0	0	0	2	0	0
1	0	0	0	2	0	0	0	0	0	0	0
1	0	0	0	1	0	1	0	0	0	0	0
1	1	1	0	0	0	0	0	0	0	0	0
0	1	0	1	1	0	0	0	0	0	0	0
0	0	0	0	0	0	1	0	0	0	0	0

[a]Each digit represents the number of errors in a line.

a line consisted of meteorological data as well as the total number of births for that month in King County. Each line required the punching of 47 characters, excluding the spaces. The numbers of errors per line starting with January 1965 and ending with December 1977 are listed in Table 3.3.

One of the problems with this table is its bulk. It is difficult to grasp its significance. You would not transmit this table over the phone to explain to someone the number of errors made. One way to summarize this table is to specify how many times a particular combination of errors occurred. One possibility is the following:

Number of Errors per Line	Number of Lines
0	124
1	27
2	5
3 or more	0

This list is again based on three ingredients: a *collection* of lines of data, a *variable* (the number of errors per line), and the *frequency* with which values of the variable occur. Have we lost something in going to this summary? Yes, we have lost the order in which the observations occurred. That could be important if we wanted to find out whether errors came "in bunches" or whether there was a learning process, so that fewer errors occurred as practice was gained. The original data are already a condensation. The "number of errors per line" does not give information about the location of the errors in the line or the type of error. (For educational purposes, the latter might be very important.)

A difference between the variables of Tables 3.2 and 3.3 is that the variable in the second example was *numerically valued* (i.e., took on numerical values), in contrast with the *categorically valued* variable of the first example. Statisticians typically mean the former when *variable* is used by itself, and we will specify *categorical variable* when appropriate. [As discussed before, a categorical variable can always be made numerical by (as in Table 3.1) arranging the values alphabetically and numbering the observed categories 1, 2, 3, ... This is not biologically meaningful because the ordering is a function of the language used.]

The data of the two examples above were discrete. A different type of variable is represented by the age at death of crib death, or SIDS (sudden infant death syndrome), cases. Table 3.4

Table 3.4 Age at Death (in Days) of 78 Cases of SIDS Occurring in King County, Washington, 1976–1977

225	174	274	164	130	96	102	80	81	148	130	48
68	64	234	24	187	117	42	38	28	53	120	66
176	120	77	79	108	117	96	80	87	85	61	65
68	139	307	185	150	88	108	60	108	95	25	80
143	57	53	90	76	99	29	110	113	67	22	118
47	34	206	104	90	157	80	171	23	92	115	87
42	77	65	45	32	44						

Table 3.5 Frequency Distribution of Age at Death of 78 SIDS Cases Occurring in King County, Washington, 1976–1977

Age Interval (days)	Number of Deaths	Age Interval (days)	Number of Deaths
1–30	6	211–240	1
31–60	13	241–270	0
61–90	23	271–300	1
91–120	18	301–330	1
121–150	7		
151–180	5	Total	78
181–210	3		

displays ages at death in days of 78 cases of SIDS in King County, Washington, during the years 1976–1977. The variable, age at death, is continuous. However, there is rounding to the nearest whole day. Thus, "68 days" could represent 68.438 . . . or 67.8873 . . . , where the three dots indicate an unending decimal sequence.

Again, the table staggers us by its bulk. Unlike the preceding example, it will not be too helpful to list the number of times that a particular value occurs: There are just too many different ages. One way to reduce the bulk is to define intervals of days and count the number of observations that fall in each interval. Table 3.5 displays the data grouped into 30-day intervals (months). Now the data make more sense. We note, for example, that many deaths occur between the ages of 61 and 90 days (two to three months) and that very few deaths occur after 180 days (six months). Somewhat surprisingly, there are relatively few deaths in the first month of life. This age distribution pattern is unique to SIDS.

We again note the three characteristics on which Table 3.5 is based: (1) a *collection* of 78 objects—SIDS cases, (2) a *variable* of interest—age at death, and (3) the *frequency* of occurrence of values falling in specified intervals. We are now ready to define these three characteristics more explicitly.

Definition 3.6. An *empirical frequency distribution* (EFD) of a variable is a listing of the values or ranges of values of the variable together with the frequencies with which these values or ranges of values occur.

The adjective *empirical* emphasizes that an *observed* set of values of a variable is being discussed; if this is obvious, we may use just "frequency distribution" (as in the heading of Table 3.5).

The choice of interval width and interval endpoint is somewhat arbitrary. They are usually chosen for convenience. In Table 3.5, a "natural" width is 30 days (one month) and convenient endpoints are 1 day, 31 days, 61 days, and so on. A good rule is to try to produce between

seven and 10 intervals. To do this, divide the range of the values (*largest to smallest*) by 7, and then adjust to make a simple interval. For example, suppose that the variable is "weight of adult male" (expressed to the nearest kilogram) and the values vary from 54 to 115 kg. The range is $115 - 54 = 61$ kg, suggesting intervals of width $61/7 \doteq 8.7$ kg. This is clearly not a very good width; the closest "natural" width is 10 kg (producing a slightly coarser grid). A reasonable starting point is 50 kg, so that the intervals have endpoints 50 kg, 60 kg, 70 kg, and so on.

To compare several EFDs it is useful to make them comparable with respect to the total number of subjects. To make them comparable, we need:

Definition 3.7. The *size* of a sample is the number of elements in the sample.

Definition 3.8. An *empirical relative frequency distribution* (ERFD) is an empirical frequency distribution where the frequencies have been divided by the sample size.

Equivalently, the relative frequency of the value of a variable is the proportion of times that the value of the variable occurs. (The context often makes it clear that an *empirical* frequency distribution is involved. Similarly, many authors omit the adjective *relative* so that "frequency distribution" is shorthand for "empirical relative frequency distribution.")

To illustrate ERFDs, consider the data in Table 3.6, consisting of systolic blood pressures of three groups of Japanese men: native Japanese, first-generation immigrants to the United States (Issei), and second-generation Japanese in the United States (Nisei). The sample sizes are 2232, 263, and 1561, respectively.

It is difficult to compare these distributions because the sample sizes differ. The *relative* frequencies (proportions) are obtained by dividing each frequency by the corresponding sample size. The ERFD is presented in Table 3.7. For example, the (empirical) relative frequency of native Japanese with systolic blood pressure less than 106 mmHg is $218/2232 = 0.098$.

It is still difficult to make comparisons. One of the purposes of the study was to determine how much variables such as blood pressure were affected by environmental conditions. To see if there is a *shift* in the blood pressures, we could consider the proportion of men with blood pressures less than a specified value and compare the groups that way. Consider, for example, the proportion of men with systolic blood pressures less than or equal to 134 mmHg. For the native Japanese this is (Table 3.7) $0.098 + 0.122 + 0.151 + 0.162 = 0.533$, or 53.3%. For the Issei and Nisei these figures are 0.413 and 0.508, respectively. The latter two figures are somewhat lower than the first, suggesting that there has been a shift to higher systolic

Table 3.6 Empirical Frequency Distribution of Systolic Blood Pressure of Native Japanese and First- and Second-Generation Immigrants to the United States, Males Aged 45–69 Years

Blood Pressure (mmHg)	Native Japanese	Issei	California Nisei
<106	218	4	23
106–114	272	23	132
116–124	337	49	290
126–134	362	33	347
136–144	302	41	346
146–154	261	38	202
156–164	166	23	109
>166	314	52	112
Total	2232	263	1561

Source: Data from Winkelstein et al. [1975].

Table 3.7 Empirical Relative Frequency Distribution of Systolic Blood Pressure of Native Japanese and First- and Second-Generation Immigrants to the United States, Males Aged 45–69 Years

Blood Pressure (mmHg)	Native Japanese	Issei	California Nisei
<106	0.098	0.015	0.015
106–114	0.122	0.087	0.085
116–124	0.151	0.186	0.186
126–134	0.162	0.125	0.222
136–144	0.135	0.156	0.222
146–154	0.117	0.144	0.129
156–164	0.074	0.087	0.070
>166	0.141	0.198	0.072
Total	1.000	0.998	1.001
Sample size	(2232)	(263)	(1561)

Source: Data from Winkelstein et al. [1975].

blood pressure among the immigrants. Whether this shift represents sampling variability or a genuine shift in these groups can be determined by methods developed in the next three chapters.

The concept discussed above is formalized in the empirical cumulative distribution.

Definition 3.9. The *empirical cumulative distribution* (ECD) of a variable is a listing of values of the variable together with the *proportion* of observations less than or equal to that value (cumulative proportion).

Before we construct the ECD for a sample, we need to clear up one problem associated with rounding of values of continuous variables. Consider the age of death of the SIDS cases of Table 3.4. The first age listed is 225 days. Any value between 224.5+ and 225.5− is rounded off to 225 (224.5+ indicates a value greater than 224.5 by some arbitrarily small amount, and similarly, 225.5− indicates a value less than 225.5). Thus, the upper endpoint of the interval 1–30 days in Table 3.5 is $30.4\overline{9}$, or 30.5.

The ECD associated with the data of Table 3.5 is presented in Table 3.8, which contains (1) the age intervals, (2) endpoints of the intervals, (3) EFD, (4) ERFD, and (5) ECD.

Two comments are in order: (1) there is a slight rounding error in the last column because the relative frequencies are rounded to three decimal places—if we had calculated from the frequencies rather than the relative frequencies, this problem would not have occurred; and (2) given the cumulative proportions, the original proportions can be recovered. For example, consider the following endpoints and their cumulative frequencies:

150.5	0.860
180.5	0.924

Subtracting, $0.924 - 0.860 = 0.064$ produces the proportion in the interval 151–180. Mathematically, the ERFD and the ECD are equivalent.

Table 3.8 Frequency Distribution of Age at Death of 78 SIDS Cases Occurring in King County, Washington, 1976–1977

Age Interval (days)	Endpoint of Interval (days)	Number of Deaths	Relative Frequency (Proportion)	Cumulative Proportion
1–30	30.5	6	0.077	0.077
31–60	60.5	13	0.167	0.244
61–90	90.5	23	0.295	0.539
91–120	120.5	18	0.231	0.770
121–150	150.5	7	0.090	0.860
151–180	180.5	5	0.064	0.924
181–210	210.5	3	0.038	0.962
211–240	240.5	1	0.013	0.975
241–270	270.5	0	0.000	0.975
271–300	300.5	1	0.013	0.988
301–330	330.5	1	0.013	1.001
Total		78	1.001	

3.3.2 Graphs

Graphical displays frequently provide very effective descriptions of samples. In this section we discuss some very common ways of doing this and close with some examples that are innovative. Graphs can also be used to enhance certain features of data as well as to distort them. A good discussion can be found in Huff [1993].

One of the most common ways of describing a sample pictorially is to plot on one axis values of the variable and on another axis the frequency of occurrence of a value or a measure related to it. In constructing a *histogram* a number of cut points are chosen and the data are tabulated. The relative frequency of observations in each category is divided by the width of the category to obtain the *probability density*, and a bar is drawn with this height. The area of a bar is proportional to the frequency of occurrence of values in the interval.

The most important choice in drawing a histogram is the number of categories, as quite different visual impressions can be conveyed by different choices. Figure 3.1 shows measurements of albumin, a blood protein, in 418 patients with the liver disease *primary biliary cirrhosis*, using

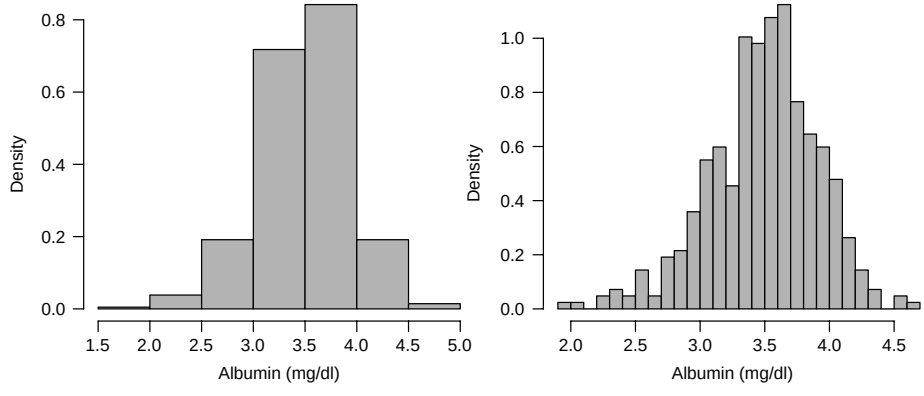


Figure 3.1 Histograms of serum albumin concentration in 418 PBC patients, using two different sets of categories.

data made available on the Web by T. M. Therneau of the Mayo Clinic. With five categories the distribution appears fairly symmetric, with a single peak. With 30 categories there is a definite suggestion of a second, lower peak. Statistical software will usually choose a sensible default number of categories, but it may be worth examining other choices.

The values of a variable are usually plotted on the abscissa (x-axis), the frequencies on the ordinate (y-axis). The ordinate on the left-hand side of Figure 3.1 contains the probability densities for each category. Note that the use of probability density means that the two histograms have similar vertical scales despite having different category widths: As the categories become narrower, the numerator and denominator of the probability density decrease together.

Histograms are sometimes defined so that the y-axis measures absolute or relative frequency rather than the apparently more complicated probability density. Two advantages arise from the use of a probability density rather than a simple count. The first is that the categories need not have the same width: It is possible to use wider categories in parts of the distribution where the data are relatively sparse. The second advantage is that the height of the bars does not depend systematically on the sample size: It is possible to compare on the same graph histograms from two samples of different sizes. It is also possible to compare the histogram to a hypothesized mathematical distribution by drawing the mathematical density function on the same graph (an example is shown in Figure 4.7.

Figure 3.2 displays the empirical cumulative distribution (ECD). This is a *step function* with jumps at the endpoints of the interval. The height of the jump is equal to the relative frequency of the observations in the interval. The ECD is nondecreasing and is bounded above by 1. Figure 3.2 emphasizes the discreteness of data. A *frequency polygon* and *cumulative frequency polygon* are often used with continuous variables to emphasize the continuity of the data. A frequency polygon is obtained by joining the heights of the bars of the histogram at their midpoints. The frequency polygon for the data of Table 3.8 is displayed in Figure 3.3. A question arises: Where is the midpoint of the interval? To calculate the midpoint for the interval 31–60 days, we note

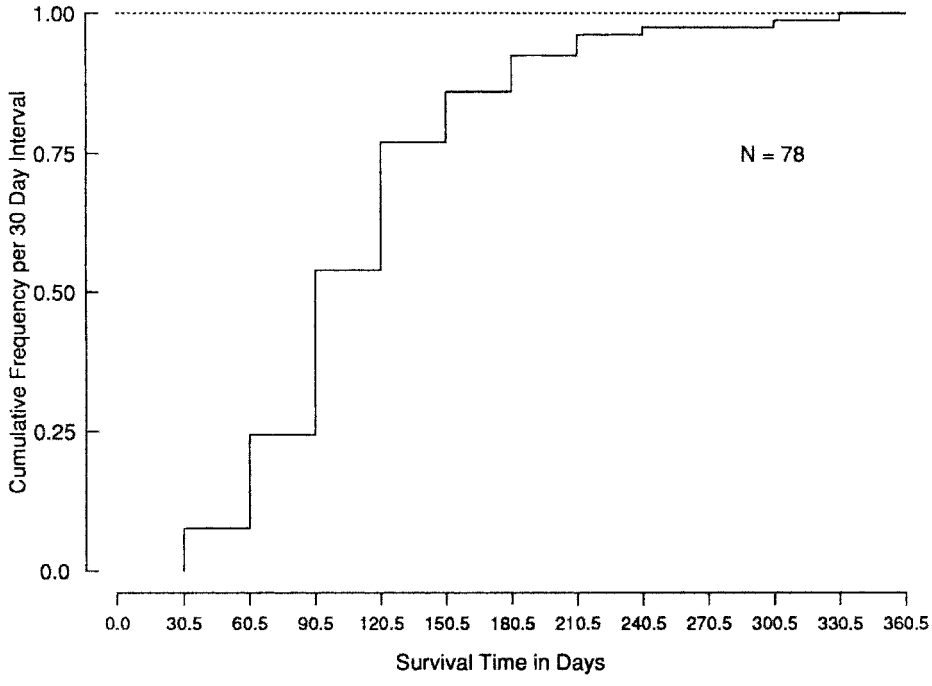


Figure 3.2 Empirical cumulative distribution of SIDS deaths.

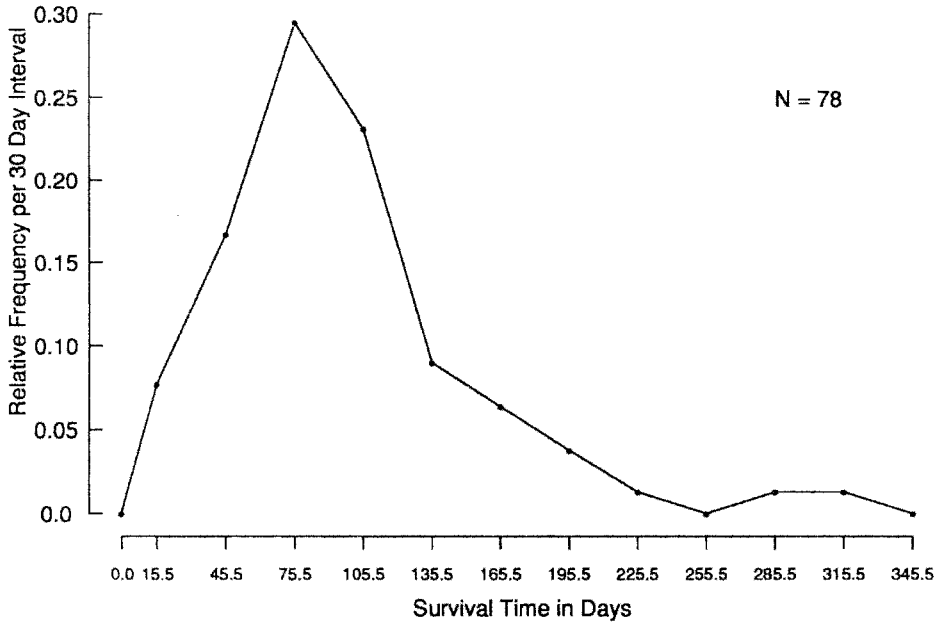


Figure 3.3 Frequency polygon of SIDS deaths.

that the limits of this interval are 30.5–60.5. The midpoint is halfway between these endpoints; hence, $midpoint = (30.5 + 60.5)/2 = 45.5$ days.

All midpoints are spaced in intervals of 30 days, so that the midpoints are 15.5, 45.5, 75.5, and so on. To close the polygon, the midpoints of two additional intervals are needed: one to the left of the first interval (1–30) and one to the right of the last interval observed (301–330), both of these with zero observed frequencies.

A cumulative frequency polygon is constructed by joining the cumulative relative frequencies observed at the endpoints of their respective intervals. Figure 3.4 displays the cumulative relative frequency of the SIDS data of Table 3.8. The curve has the value 0.0 below 0.5 and the value 1.0 to the right of 330.5. Both the histograms and the cumulative frequency graphs implicitly assume that the observations in our interval are evenly distributed over that interval.

One advantage of a cumulative frequency polygon is that the proportion (or percentage) of observations less than a specified value can be read off easily from the graph. For example, from Figure 3.4 it can be seen that 50% of the observations have a value of less than 88 days (this is the median of the sample). See Section 3.4.1 for further discussion.

EFDs can often be graphed in an innovative way to illustrate a point. Consider the data in Figure 3.5, which contains the frequency of births per day as related to phases of the moon. Data were collected by Schwab [1975] on the number of births for two years, grouped by each day of the 29-day lunar cycle, presented here as a circular distribution where the lengths of the sectors are proportional to the frequencies. (There is clearly no evidence supporting the hypothesis that the cycle of the moon influences birth rate.)

Sometimes more than one variable is associated with each of the objects under study. Data arising from such situations are called *multivariate data*. A moment's reflection will convince you that most biomedical data are multivariate in nature. For example, the variable "blood pressure of a patient" is usually expressed by two numbers, systolic and diastolic blood pressure. We often specify age and gender of patients to characterize blood pressure more accurately.

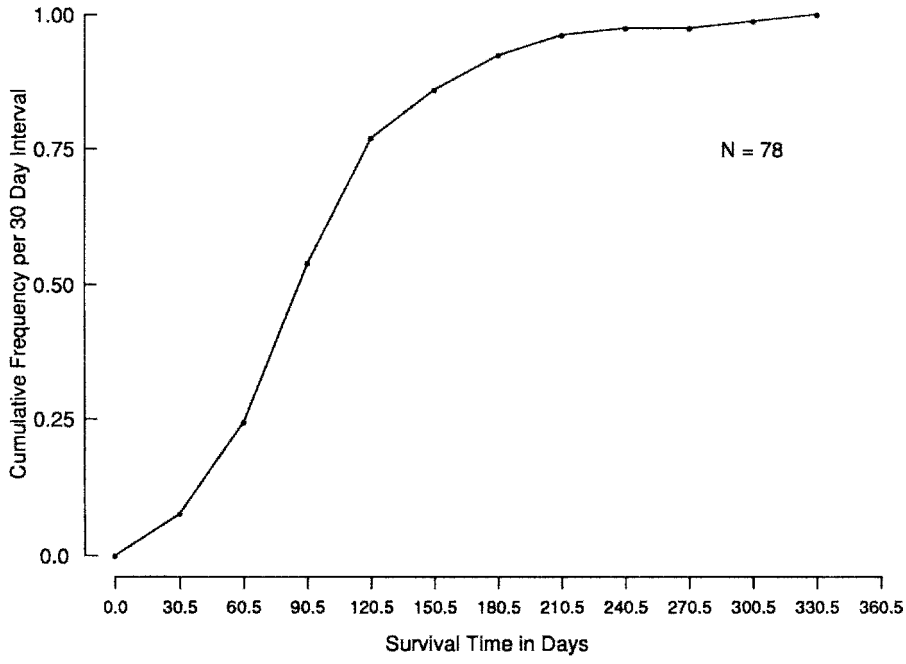


Figure 3.4 Cumulative frequency polygon of SIDS deaths.

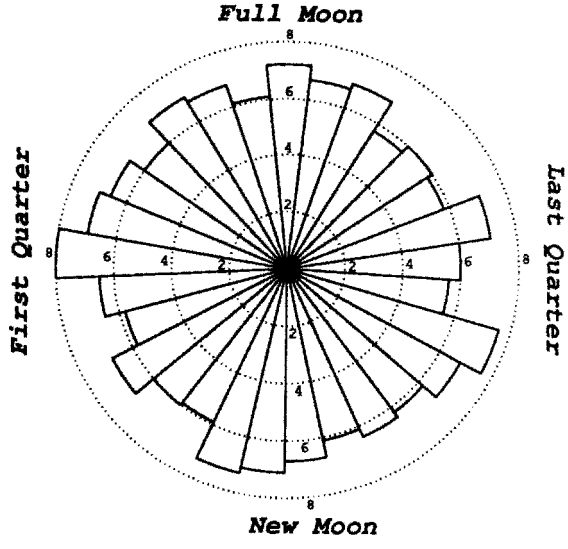


Figure 3.5 Average number of births per day over a 29-day lunar cycle. (Data from Schwab [1975].)

In the multivariate situation, in addition to describing the frequency with which each value of each variable occurs, we may want to study the relationships among the variables. For example, Table 1.2 and Figure 1.1 attempt to assess the relationship between the variables "clinical competence" and "cost of laboratory procedures ordered" of interns. Graphs of multivariate data will be found throughout the book.

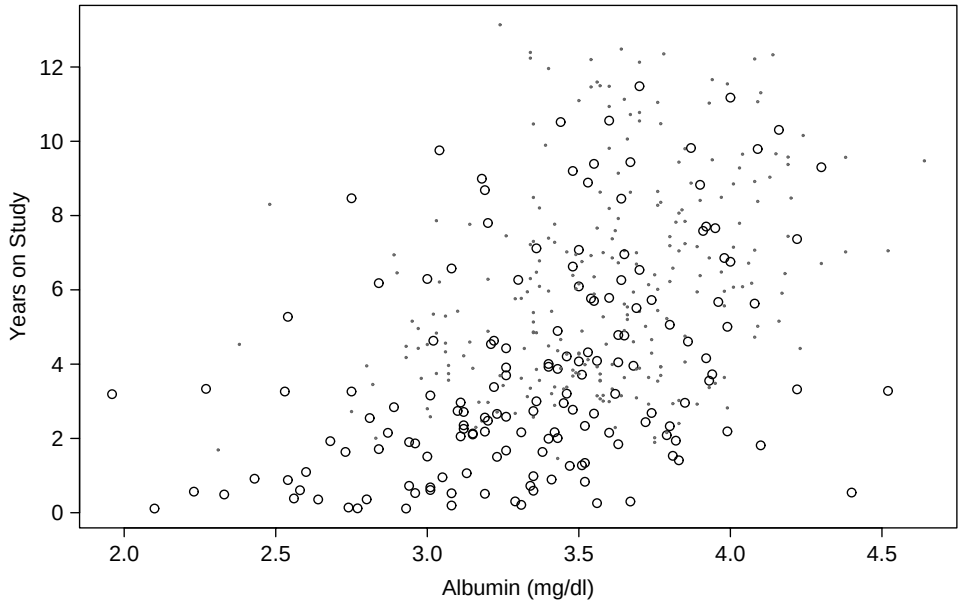


Figure 3.6 Survival time in primary biliary cirrhosis by serum albumin concentrations. Large circles are deaths, small circles are patients alive at last contact. (Data from Fleming and Harrington [1991].)

Here we present a few examples of visually displaying values of several variables at the same time. A simple one relates the serum albumin values from Figure 3.1 to survival time in the 418 patients. We do not know the survival times for everyone, as some were still alive at the end of the study. The statistical analysis of such data occupies an entire chapter of this book, but a simple descriptive graph is possible. Figure 3.6 shows large circles at survival time for patients who died. For those still alive it shows small circles at the last time known alive. For exploratory analysis and presentation these could be indicated by different colors, something that is unfortunately still not feasible for this book.

Another simple multivariate example can be found in our discussion of factor analysis. Figure 14.7 shows a matrix of correlations between variables using shaded circles whose size shows the strength of the relationship and whose shading indicates whether the relationship is positive or negative. Figure 14.7 is particularly interesting, as the graphical display helped us find an error that we missed in the first edition.

A more sophisticated example of multivariate data graphics is the *conditioning plot* [Cleveland, 1993]. This helps you examine how the relationship between two variables depends on a third. Figure 3.7 shows daily data on ozone concentration and sunlight in New York, during the summer of 1973. These should be related monotonically; ozone is produced from other pollutants by chemical reactions driven by sunlight. The four panels show four plots of ozone concentration vs. solar radiation for various ranges of temperature. The shaded bar in the title of each plot indicates the range of temperatures. These ranges overlap, which allows more panels to be shown without the data becoming too sparse. Not every statistical package will produce these coplots with a single function, but it is straightforward to draw them by taking appropriate subsets of your data.

The relationship clearly varies with temperature. At low temperatures there is little relationship, and as the temperature increases the relationship becomes stronger. Ignoring the effect of temperature and simply graphing ozone and solar radiation results in a more confusing relationship (examined in Figure 3.9). In Problem 10 we ask you to explore these data further.

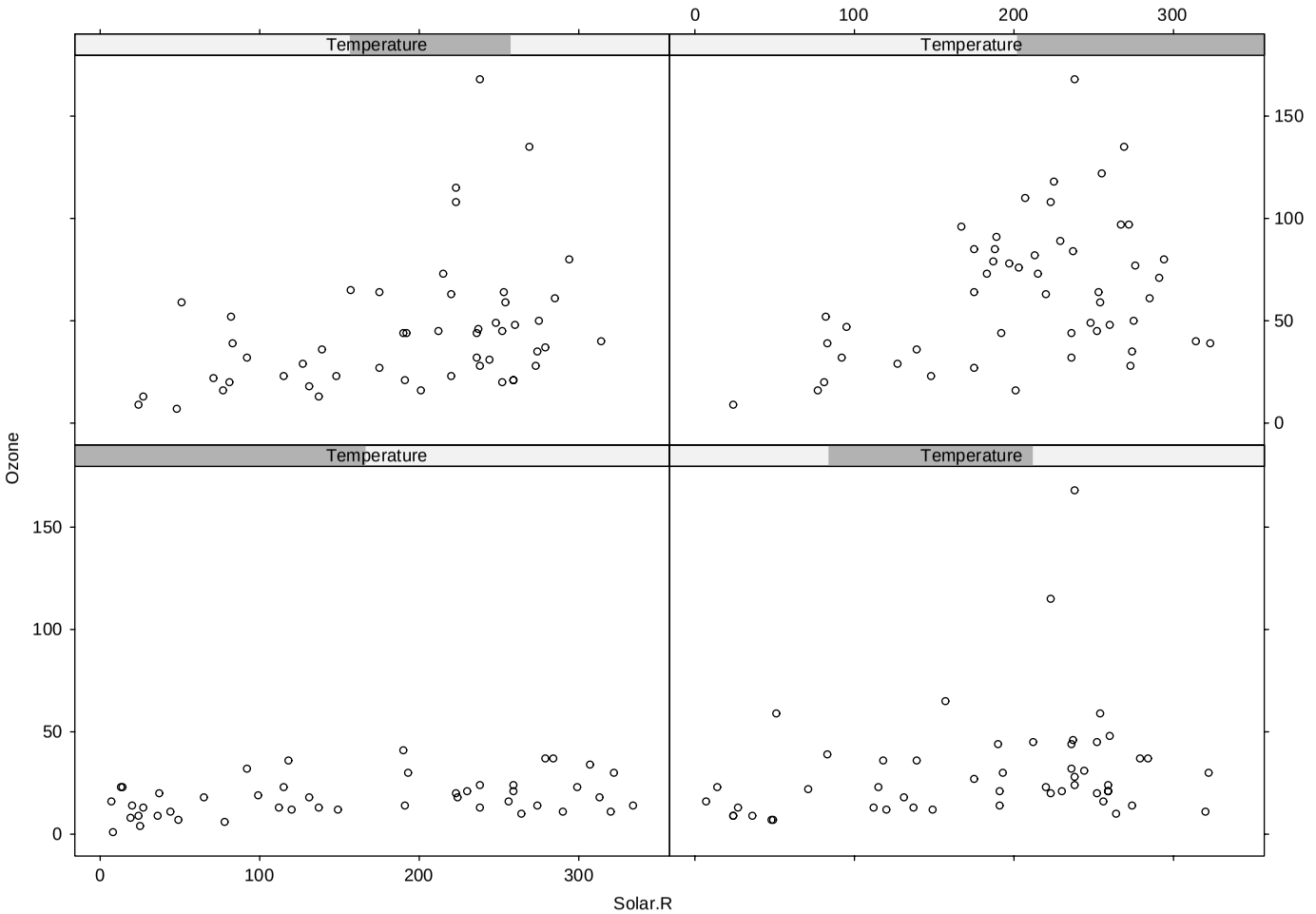


Figure 3.7 Ozone concentration by solar radiation intensity in New York, May–September 1973, conditioned on temperature. (From R Foundation [2002].)

For beautiful books on the visual display of data, see Tufte [1990, 1997, 2001]. A very readable compendium of graphical methods is contained in Moses [1987], and more recent methods are described by Cleveland [1994]. Wilkinson [1999] discusses the structure and taxonomy of graphs.

3.4 DESCRIPTIVE *STATISTICS*

In Section 3.3 our emphasis was on tabular and visual display of data. It is clear that these techniques can be used to great advantage when summarizing and highlighting data. However, even a table or a graph takes up quite a bit of space, cannot be summarized in the mind too easily, and particularly for a graph, represents data with some imprecision. For these and other reasons, numerical characteristics of data are calculated routinely.

Definition 3.10. A *statistic* is a numerical characteristic of a sample.

One of the functions of statistics as a field of study is to describe samples by as few numerical characteristics as possible. Most numerical characteristics can be classified broadly into statistics derived from percentiles of a frequency distribution and statistics derived from moments of a frequency distribution (both approaches are explained below). Roughly speaking, the former approach tends to be associated with a statistical methodology usually termed *nonparametric*, the latter with *parametric* methods. The two classes are used, contrasted, and evaluated throughout the book.

3.4.1 Statistics Derived from Percentiles

A *percentile* has an intuitively simple meaning—for example, the 25th percentile is that value of a variable such that 25% of the observations are less than that value and 75% of the observations are greater. You can supply a similar definition for, say, the 75th percentile. However, when we apply these definitions to a particular sample, we may run into three problems: (1) small sample size, (2) tied values, or (3) nonuniqueness of a percentile. Consider the following sample of four observations:

$$22, 22, 24, 27$$

How can we define the 25th percentile for this sample? There is no value of the variable with this property. But for the 75th percentile, there is an infinite number of values—for example, 24.5, 25, and 26.9378 all satisfy the definition of the 75th percentile. For large samples, these problems disappear and we will define percentiles for small samples in a way that is consistent with the intuitive definition. To find a particular percentile in practice, we would rank the observations from smallest to largest and count until the proportion specified had been reached. For example, to find the 50th percentile of the four numbers above, we want to be somewhere between the second- and third-largest observation (between the values for ranks 2 and 3). Usually, this value is taken to be halfway between the two values. This could be thought of as the value with rank 2.5—call this a *half rank*. Note that

$$2.5 = \left(\frac{50}{100}\right)(1 + \text{sample size})$$

You can verify that the following definition is consistent with your intuitive understanding of percentiles:

Definition 3.11. The Pth *percentile* of a sample of n observations is that value of the variable with rank $(P/100)(1 + n)$. If this rank is not an integer, it is rounded to the nearest half rank.

The following data deal with the aflatoxin levels of raw peanut kernels as described by Quesenberry et al. [1976]. Approximately 560 g of ground meal was divided among 16 centrifuge bottles and analyzed. One sample was lost, so that only 15 readings are available (measurement units are not given). The values were

$$30, 26, 26, 36, 48, 50, 16, 31, 22, 27, 23, 35, 52, 28, 37$$

The 50th percentile is that value with rank $(50/100)(1 + 15) = 8$. The eighth largest (or smallest) observation is 30. The 25th percentile is the observation with rank $(25/100)(1+15) = 4$, and this is 26. Similarly, the 75th percentile is 37. The 10th percentile (or decile) is that value with rank $(10/100)(1 + 15) = 1.6$, so we take the value halfway between the smallest and second-smallest observation, which is $(1/2)(16 + 22) = 19$. The 90th percentile is the value with rank $(90/100)(1 + 15) = 14.4$; this is rounded to the nearest half rank of 14.5. The value with this half rank is $(1/2)(50 + 52) = 51$.

Certain percentile or functions of percentiles have specific names:

Percentile	Name
50	Median
25	Lower quartile
75	Upper quartile

All these statistics tell something about the location of the data. If we want to describe how spread out the values of a sample are, we can use the range of values (largest minus smallest), but a problem is that this statistic is very dependent on the sample size. A better statistic is given by:

Definition 3.12. The *interquartile range* (IQR) is the difference between the 75th and 25th percentiles.

For the aflatoxin example, the interquartile range is $37 - 26 = 11$. Recall the *range* of a set of numbers is the largest value minus the smallest value. The data can be summarized as follows:

Median	30	Measures of location
Minimum	16	
Maximum	52	
Interquartile range	11	Measures of spread
Range	36	

The first three measures describe the location of the data; the last two give a description of their spread. If we were to add 100 to each of the observations, the median, minimum, and maximum would be shifted by 100, but the interquartile range and range would be unaffected.

These data can be summarized graphically by means of a *box plot* (also called a *box-and-whisker plot*). A rectangle with upper and lower edges at the 25th and 75th percentiles is drawn with a line in the rectangle at the median (50th percentile). Lines (whiskers) are drawn from the rectangle (box) to the highest and lowest values that are within $1.5 \times$ IQR of the median; any points more extreme than this are plotted individually. This is Tukey's [1977] definition of the box plot; an alternative definition draws the whiskers from the quartiles to the maximum and minimum.

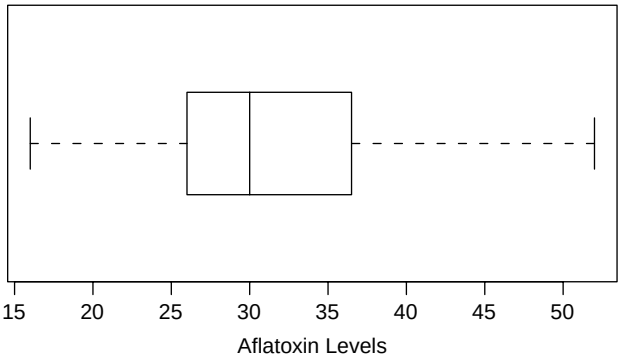


Figure 3.8 Box plot.

The box plot for these data (Figure 3.8) indicates that 50% of the data between the lower and upper quartiles is distributed over a much narrower range than the remaining 50% of the data. There are no extreme values outside the "fences" at median $\pm$ 1.5 $\times$ IQR.

3.4.2 Statistics Derived from Moments

The statistics discussed in Section 3.4.1 dealt primarily with describing the location and the variation of a sample of values of a variable. In this section we introduce another class of statistics, which have a similar purpose. In this class are the ordinary average, or arithmetic mean, and standard deviation. The reason these statistics are said to be derived from *moments* is that they are based on powers or moments of the observations.

Definition 3.13. The *arithmetic mean* of a sample of values of a variable is the average of all the observations.

Consider the aflatoxin data mentioned in Section 3.4.1. The arithmetic mean of the data is

$$\frac{30 + 26 + 26 + \cdots + 28 + 37}{15} = \frac{487}{15} = 32.4\overline{6} \doteq 32.5$$

A reasonable rule is to express the mean with one more significant digit than the observations, hence we round $32.4\overline{6}$—a nonterminating decimal—to 32.5. (See also Note 3.2 on significant digits and rounding.)

Notation. The specification of some of the statistics to be calculated can be simplified by the use of notation. We use a capital letter for the name of a variable and the corresponding lowercase letter for a value. For example, $Y =$ *aflatoxin level* (the name of the variable); $y = 30$ (the value of aflatoxin level for a particular specimen). We use the Greek symbol $\sum$ to mean "sum all the observations." Thus, for the aflatoxin example, $\sum y$ is shorthand for the statement "sum all the aflatoxin levels." Finally, we use the symbol $\overline{y}$ to denote the arithmetic mean of the sample. The arithmetic mean of a sample of n values of a variable can now be written as

$$\overline{y} = \frac{\sum y}{n}$$

For example, $\sum y = 487, n = 15$, and $\overline{y} = 487/15 \doteq 32.5$. Consider now the variable of Table 3.3: the number of keypunching errors per line. Suppose that we want the average

Table 3.9 Calculation of Arithmetic Average from Empirical Frequency and Empirical Relative Frequency Distribution[a]

Number of Errors per Line, y	Number of Lines, f	Proportion of Lines, p	$p \times y$
0	124	0.79487	0.00000
1	27	0.17308	0.17308
2	5	0.03205	0.06410
3	0	0.00000	0.00000
Total	156	1.00000	0.23718

[a]Data from Table 3.3.

number of errors per line. By definition, this is $(0+0+1+0+2+\cdots+0+0+0+0)/156 = 37/156 \doteq 0.2$ error per line. But this is a tedious way to calculate the average. A simpler way utilizes the frequency distribution or relative frequency distribution.

The total number of errors is $(124 \times 0) + (27 \times 1) + (5 \times 2) + (0 \times 3) = 37$; that is, there are 124 lines without errors; 27 lines each of which contains one error, for a total of 27 errors for these types of lines; and 5 lines with two errors, for a total of 10 errors for these types of lines; and finally, no lines with 3 errors (or more). So the arithmetic mean is

$$\overline{y} = \frac{\sum fy}{\sum f} = \frac{\sum fy}{n}$$

since the frequencies, f, add up to n, the sample size. Here, the sum $\sum fy$ is over observed values of y, each value appearing once.

The arithmetic mean can also be calculated from the empirical relative frequencies. We use the following algebraic property:

$$\overline{y} = \frac{\sum fy}{n} = \sum \frac{fy}{n} = \sum \frac{f}{n} y = \sum py$$

The *f/n* are precisely the empirical relative frequencies or proportions, p. The calculations using proportions are given in Table 3.9. The value obtained for the sample mean is the same as before. The formula $\overline{y} = \sum py$ will be used extensively in Chapter 4 when we come to probability distributions. If the values y represent the midpoints of intervals in an empirical frequency distribution, the mean of the grouped data can be calculated in the same way.

Analogous to the interquartile range there is a measure of spread based on sample moments.

Definition 3.14. The *standard deviation* of a sample of n values of a variable Y is

$$s = \sqrt{\frac{\sum (y - \overline{y})^2}{n - 1}}$$

Roughly, the standard deviation is the square root of the average of the square of the deviations from the sample mean. The reason for dividing by $n - 1$ is explained in Note 3.5. Before giving an example, we note the following properties of the standard deviation:

1. The standard deviation has the same units of measurement as the variable. If the observations are expressed in centimeters, the standard deviation is expressed in centimeters.

Cartoon 3.1 Variation is important: statistician drowning in a river of average depth 10.634 inches.

2. If a constant value is added to each of the observations, the value of the standard deviation is unchanged.
3. If the observations are multiplied by a positive constant value, the standard deviation is multiplied by the same constant value.
4. The following two formulas are sometimes computationally more convenient in calculating the standard deviation by hand:

$$s = \sqrt{\frac{\sum y^2 - n\overline{y}^2}{n-1}} = \sqrt{\frac{\sum y^2 - (\sum y)^2/n}{n-1}}$$

   Rounding errors accumulate more rapidly using these formulas; care should be taken to carry enough significant digits in the computation.
5. The square of the standard deviation is called the *variance*.
6. In many situations the standard deviation can be approximated by

$$s \doteq \frac{\text{interquartile range}}{1.35}$$

7. In many cases it is true that approximately 68% of the observations fall within one standard deviation of the mean; approximately 95% within two standard deviations.

3.4.3 Graphs Based on Estimated Moments

One purpose for drawing a graph of two variables X and Y is to decide how Y changes as X changes. Just as statistics such as the mean help summarize the location of one or two samples,

they can be used to summarize how the location of Y changes with X. A simple way to do this is to divide the data into *bins* and compute the mean or median for each bin.

Example 3.1. Consider the New York air quality data in Figure 3.7. When we plot ozone concentrations against solar radiation without conditioning variables, there is an apparent triangular relationship. We might want a summary of this relationship rather than trying to assess it purely by eye. One simple summary is to compute the mean ozone concentration for various ranges of solar radiation. We compute the mean ozone for days with solar radiation 0–50 langleys, 50–150, 100–200, 150–250, and so on. Plotting these means at the midpoint of the interval and joining the dots gives the dotted line shown in Figure 3.9.

Modern statistical software provides a variety of different *scatter plot smoothers* that perform more sophisticated versions of this calculation. The technical details of these are complicated, but they are conceptually very similar to the local means that we used above. The solid line in Figure 3.9 is a popular scatter plot smoother called *lowess* [Cleveland, 1981].

3.4.4 Other Measures of Location and Spread

There are many other measures of location and spread. In the former category we mention the mode and the geometric mean.

Definition 3.15. The *mode* of a sample of values of a variable Y is that value that occurs most frequently.

The mode is usually calculated for large sets of discrete data. Consider the data in Table 3.10, the distribution of the number of boys per family of eight children. The most frequently occurring value of the variable Y, the number of boys per family of eight children, is 4. There are more families with that number of boys than any other specified number of boys. For data arranged in histograms, the mode is usually associated with the midpoint of the interval having the highest frequency. For example, the mode of the systolic blood pressure of the native Japanese men listed in Table 3.6 is 130 mmHg; the modal value for Issei is 120 mmHg.

Definition 3.16. The *geometric mean* of a sample of nonnegative values of a variable Y is the nth root of the product of the n values, where n is the sample size.

Equivalently, it is the antilogarithm of the arithmetic mean of the logarithms of the values. (See Note 3.1 for a brief discussion of logarithms.)

Consider the following four observations of systolic blood pressure in mmHg:

$$118, 120, 122, 160$$

The arithmetic mean is 130 mmHg, which is larger than the first three values because the 160 mmHg value "pulls" the mean to the right. The geometric mean is $(118 \times 120 \times 122 \times 160)^{1/4} \doteq 128.9$ mmHg. The geometric mean is less affected by the extreme value of 160 mmHg. The median is 121 mmHg. If the value of 160 mmHg is changed to a more extreme value, the mean will be affected the most, the geometric mean somewhat less, and the median not at all.

Two other measures of spread are the average deviation and median absolute deviation (MAD). These are related to the standard deviation in that they are based on a location measure applied to deviations. Where the standard deviation squares the deviations to make them all positive, the average deviation takes the absolute value of the deviations (just drops any minus signs).

Definition 3.17. The *average deviation* of a sample of values of a variable is the arithmetic average of the absolute values of the deviations about the sample mean.

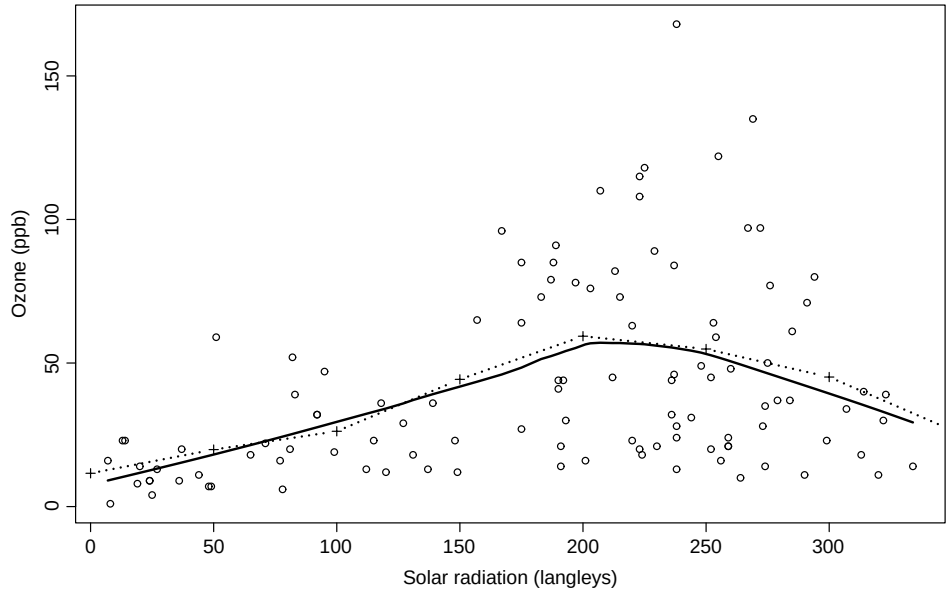


Figure 3.9 Ozone and solar radiation in New York during the summer of 1973, with scatter plot smoothers.

Table 3.10 Number of Boys in Families of Eight Children

Number of Boys per Family of Eight Children	Empirical Frequency (Number of Families)	Empirical Relative Frequency of Families
0	215	0.0040
1	1, 485	0.0277
2	5, 331	0.0993
3	10, 649	0.1984
4	14, 959	0.2787
5	11, 929	0.2222
6	6, 678	0.1244
7	2, 092	0.0390
8	342	0.0064
Total	53, 680	1.0000

Source: Geissler's data reprinted in Fisher [1958].

Using symbols, the average deviation can be written as

$$\text{average deviation} = \frac{\sum |y - \overline{y}|}{n}$$

The median absolute deviation takes the deviations from the median rather than the mean, and takes the median of the absolute values of these deviations.

Definition 3.18. The *median absolute deviation* of a sample of values of a variable is the median of the absolute values of the deviations about the sample median.

Using symbols, the median absolute deviation can be written as

$$\text{MAD} = \text{median}\,\{|y - \text{median}\{y\}|\}$$

The average deviation and the MAD are substantially less affected by extreme values than is the standard deviation.

3.4.5 Which Statistics?

Table 3.11 lists the statistics that have been defined so far, categorized by their use. The question arises: Which statistic should be used for a particular situation? There is no simple answer because the choice depends on the data and the needs of the investigator. Statistics derived from percentiles and those derived from moments can be compared with respect to:

1. *Scientific relevance*. In some cases the scientific question dictates or at least restricts the choice of statistic. Consider a study conducted by the Medicare program being on the effects of exercise on the amount of money expended on medical care. Their interest is in whether exercise affects total costs, or equivalently, whether it affects the arithmetic mean. A researcher studying serum cholesterol levels and the risk of heart disease might be more interested in the proportions of subjects whose cholesterol levels fell in the various categories defined by the National Cholesterol Education Program. In a completely different field, Gould [1996] discusses the absence of batting averages over 0.400 in baseball in recent years and shows that considering a measure of spread rather than a measure of location provides a much clearer explanation

2. *Robustness*. The robustness of a statistic is related to its resistance to being affected by extreme values. In Section 3.4.4 it was shown that the mean—as compared to the median and geometric mean—is most affected by extreme values. The median is said to be more robust. Robustness may be beneficial or harmful, depending on the application: In sampling pollution levels at an industrial site one would be interested in a statistic that was very much affected by extreme values. In comparing cholesterol levels between people on different diets, one might care more about the typical value and not want the results affected by an occasional extreme.

3. *Mathematical simplicity*. The arithmetic mean is more appropriate if the data can be described by a particular mathematical model: the normal or Gaussian frequency distribution, which is the basis for a large part of the theory of statistics. This is described in Chapter 4.

4. *Computational Ease*. Historically, means were easier to compute by hand for moderately large data sets. Concerns such as this vanished with the widespread availability of computers but may reappear with the very large data sets produced by remote sensing or high-throughput genomics. Unfortunately, it is not possible to give general guidelines as to which statistics

Table 3.11 Statistics Defined in This Chapter

Location	Spread
Median	Interquartile range
Percentile	Range
Arithmetic mean	Standard deviation
Geometric mean	Average deviation
Mode	Median absolute deviation

will impose less computational burden. You may need to experiment with your hardware and software if speed or memory limitations become important.

5. *Similarity*. In many samples, the mean and median are not too different. If the empirical frequency distribution of the data is almost symmetrical, the mean and the median tend to be close to each other.

In the absence of specific reasons to chose another statistic, it is suggested that the median and mean be calculated as measures of location and the interquartile range and standard deviation as measures of spread. The other statistics have limited or specialized use. We discuss robustness further in Chapter 8.

NOTES

3.1 Logarithms

A *logarithm* is an exponent on a base. The base is usually 10 or e (2.71828183 . . .). Logarithms with base 10 are called *common logarithms*; logarithms with base e are called *natural logarithms*. To illustrate these concepts, consider

$$100 = 10^2 = (2.71828183\ldots)^{4.605170\ldots} = e^{4.605170\ldots}$$

That is, the logarithm to the base 10 of 100 is 2, usually written

$$\log_{10}(100) = 2$$

and the logarithm of 100 to the base e is

$$\log_e(100) = 4.605170\ldots$$

The three dots indicate that the number is an unending decimal expansion. Unless otherwise stated, logarithms herein will always be natural logarithms. Other bases are sometimes useful—in particular, the base 2. In determining hemagglutination levels, a series of dilutions of serum are set, each dilution being half of the preceding one. The dilution series may be 1 : 1, 1 : 2, 1 : 4, 1 : 8, 1 : 16, 1 : 32, and so on. The logarithm of the dilution factor using the base 2 is then simply

$$\log_2(1) = 0$$
$$\log_2(2) = 1$$
$$\log_2(4) = 2$$
$$\log_2(8) = 3$$
$$\log_2(16) = 4 \qquad \text{etc.}$$

The following properties of logarithms are the only ones needed in this book. For simplicity, we use the base e, but the operations are valid for any base.

1. Multiplication of numbers is equivalent to adding logarithms ($e^a \times e^b = e^{a+b}$).

2. The logarithm of the reciprocal of a number is the negative of the logarithm of the number ($1/e^a = e^{-a}$).

3. Rule 2 is a special case of this rule: Division of numbers is equivalent to subtracting logarithms ($e^a/e^b = e^{a-b}$).

Most pocket calculators permit rapid calculations of logarithms and antilogarithms. Tables are also available. You should verify that you can still use logarithms by working a few problems both ways.

3.2 Stem-and-Leaf Diagrams

An elegant way of describing data by hand consists of *stem-and-leaf diagrams* (a phrase coined by J. W. Tukey [1977]; see his book for some additional innovative methods of describing data). Consider the aflatoxin data from Section 3.4.1. We can tabulate these data according to their first digit (the "stem") as follows:

Stem (tens)	Leaf (units)	Stem (tens)	Leaf (units)
1	6	4	8
2	6 6 2 7 3 8	5	0 2
3	0 6 1 5 7		

For example, the row 3|06157 is a description of the observations 30, 36, 31, 35, and 37. The most frequently occurring category is the 20s. The smallest value is 16, the largest value, 52.

A nice feature of the stem-and-leaf diagram is that all the values can be recovered (but not in the sequence in which the observations were made). Another useful feature is that a quick ordering of the observations can be obtained by use of a stem-and-leaf diagram. Many statistical packages produce stem-and-leaf plots, but there appears to be little point to this, as the advantages over histograms or empirical frequency distributions apply only to hand computation.

3.3 Color and Graphics

With the wide availability of digital projectors and inexpensive color inkjet printers, there are many more opportunities for statisticians to use color to annotate and extend graphs. Differences in color are processed "preattentively" by the brain—they "pop out" visually without a conscious search. It is still important to choose colors wisely, and many of the reference books we list discuss this issue. Colored points and lines can be bright, intense colors, but large areas should use paler, less intense shades. Choosing colors to represent a quantitative variable is quite difficult, and it is advisable to make use of color schemes chosen by experts, such as those at *http://colorbrewer.org*.

Particular attention should be paid to limitations on the available color range. Color graphs may be photocopied in black and white, and might need to remain legible. LCD projectors may have disappointing color saturation. Ideas and emotions associated with a particular color might vary in different societies. Finally, it is important to remember that about 7% of men (and almost no women) cannot distinguish red and green. The Web appendix contains a number of links on color choice for graphics.

3.4 Significant Digits: Rounding and Approximation

In working with numbers that are used to estimate some quantity, we are soon faced with the question of the number of significant digits to carry or to report. A typical rule is to report the mean of a set of observations to one more place and the standard deviation to two more places than the original observation. But this is merely a guideline—which may be wrong. Following DeLury [1958], we can think of two ways in which approximation to the value of a quantity can arise: (1) through arithmetical operations only, or (2) through measurement. If we express the

mean of the three numbers 140, 150, and 152 as 147.3, we have approximated the exact mean, $147\frac{1}{3}$, so that there is *rounding error*. This error arises purely as the result of the arithmetical operation of division. The rounding error can be calculated exactly: $147.\overline{3} - 147.3 = 0.0\overline{3}$.

But this is not the complete story. If the above three observations are the weights of three teenage boys measured to the nearest pound, the true average weight can vary all the way from $146.8\overline{3}$ to $147.8\overline{3}$ pounds; that is, the recorded weights (140, 150, 152) could vary from the three lowest values (139.5, 149.5, 151.5) to the three highest values (140.5, 150.5, 152.5), producing the two averages above. This type of rounding can be called *measurement rounding*. Knowledge of the measurement operation is required to assess the extent of the measurement rounding error: If the three numbers above represent systolic blood pressure readings in mmHg expressed to the nearest *even* number, you can verify that the actual arithmetic mean of these three observations can vary from 146.33 to 148.33, so that even the third "significant" digit could be in error.

Unfortunately, we are not quite done yet with assessing the extent of an approximation. If the weights of the three boys are a sample from populations of boys and the population mean is to be estimated, we will also have to deal with *sampling variability* (a second aspect of the measurement process), and the effect of sampling variability is likely to be much larger than the effect of rounding error and measurement roundings. Assessing the extent of sampling variability is discussed in Chapter 4.

For the present time, we give you the following guidelines: When calculating by hand, minimize the number of rounding errors in intermediate arithmetical calculations. So, for example, instead of calculating

$$\sum (y - \overline{y})^2$$

in the process of calculating the standard deviation, use the equivalent relationship

$$\sum y^2 - \frac{(\sum y)^2}{n}$$

You should also note that we are more likely to use approximations with the arithmetical operations of division and the taking of square roots, less likely with addition, multiplication, and subtraction. So if you can sequence the calculations with division and square root being last, rounding errors due to arithmetical calculations will have been minimized. Note that the guidelines for a computer would be quite different. Computers will keep a large number of digits for all intermediate results, and guidelines for minimizing errors depend on keeping the size of the rounding errors small rather than the number of occasions of rounding.

The rule stated above is reasonable. In Chapter 4 you will learn a better way of assessing the extent of approximation in measuring a quantity of interest.

3.5 Degrees of Freedom

The concept of degrees of freedom appears again and again in this book. To make the concept clear, we need the idea of a linear constraint on a set of numbers; this is illustrated by several examples. Consider the numbers of girls, X, and the number of boys, Y, in a family. (Note that X and Y are variables.) The numbers X and Y are free to vary and we say that there are two degrees of freedom associated with these variables. However, suppose that the total number of children in a family, as in the example, is specified to be precisely 8. Then, given that the number of girls is 3, the number of boys is fixed—namely, $8 - 3 = 5$. Given the constraint on the total number of children, the two variables X and Y are no longer both free to vary, but fixing one determines the other. That is, now there is only one degree of freedom. The constraint can be expressed as

$$X + Y = 8 \qquad \text{so that} \quad Y = 8 - X$$

Constraints of this type are called *linear constraints*.

Table 3.12 Frequency Distribution of Form and Color of 556 Garden Peas

	Variable 1: Form		
Variable 2: Color	Round	Wrinkled	Total
Yellow	315	101	416
Green	108	32	140
Total	423	133	556

Source: Data from Mendel [1911].

A second example is based on Mendel's work in plant propagation. Mendel [1911] reported the results of many genetic experiments. One data set related two variables: form and color. Table 3.12 summarizes these characteristics for 556 garden peas. Let A, B, C, and D be the numbers of peas as follows:

	Form	
Color	**Round**	**Wrinkled**
Yellow	A	B
Green	C	D

For example, A is the number of peas that are round and yellow. Without restrictions, the numbers A, B, C and D can be any nonnegative integers: There are four degrees of freedom. Suppose now that the total number of peas is fixed at 556 (as in Table 3.12). That is, $A + B + C + D = 556$. Now only three of the numbers are free to vary. Suppose, in addition, that the number of yellows peas is fixed at 416. Now only two numbers can vary; for example, fixing A determines B, and fixing C determines D. Finally, if the numbers of round peas is also fixed, only one number in the table can be chosen. If, instead of the last constraint on the number of round peas, the number of green peas had been fixed, two degrees would have remained since the constraints "number of yellow peas fixed" and "number of green peas fixed" are not independent, given that the total number of peas is fixed.

These results can be summarized in the following rule: Given a set of N quantities and $M(\leq N)$ linear, independent constraints, the number of degrees of freedom associated with the N quantities is $N - M$. It is often, but not always, the case that degrees of freedom can be defined in the same way for nonlinear constraints.

Calculations of averages will almost always involve the number of degrees of freedom associated with a statistic rather than its number of components. For example, the quantity $\sum(y - \overline{y})^2$ used in calculating the standard deviation of a sample of, say, n values of a variable Y has $n - 1$ degrees of freedom associated with it because $\sum(y - \overline{y}) = 0$. That is, the sum of the deviations about the mean is zero.

3.6 Moments

Given a sample of observations $y_1, y_2, \ldots, y_n$ of a variable Y, the rth sample moment about zero, m_r^*, is defined to be

$$m_r^* = \frac{\sum y^r}{n} \qquad \text{for } r = 1, 2, 3, \ldots$$

For example, $m_1^* = \sum y^1/n = \sum y/n = \overline{y}$ is just the arithmetic mean.

The rth sample moment about the mean, m_r, is defined to be

$$m_r = \frac{\sum(y - \overline{y})^r}{n} \qquad \text{for } r = 1, 2, 3, \ldots$$

The value of m_1 is zero (see Problem 3.15). It is clear that m_2 and s^2 (the sample variance) are closely connected. For a large number of observations, m_2 will be approximately equal to s^2. One of the earliest statistical procedures (about 1900) was the *method of moments* of Karl Pearson. The method specified that all estimates derived from a sample should be based on sample moments. Some properties of moments are:

- $m_1 = 0$.
- Odd-numbered moments about the mean of symmetric frequency distributions are equal to zero.
- A unimodal frequency distribution is skewed to the right if the mean is greater than the mode; it is skewed to the left if the mean is less than the mode. For distributions skewed to the right, $m_3 > 0$; for distributions skewed to the left, $m_3 < 0$.

The latter property is used to characterize the *skewness of a distribution*, defined by

$$a_3 = \frac{\sum(y - \overline{y})^3}{[\sum(y - \overline{y})^2]^{3/2}} = \frac{m_3}{(m_2)^{3/2}}$$

The division by $(m_2)^{3/2}$ is to standardize the statistic, which now is unitless. Thus, a set of observations expressed in degrees Fahrenheit will have the same value of a_3 when expressed in degrees Celsius. Values of $a_3 > 0$ indicate positive skewness, skewness to the right, whereas values of $a_3 < 0$ indicate negative skewness. Some typical curves and corresponding values for the skewness statistics are illustrated in Figure 3.10. Note that all but the last two frequency distributions are symmetric; the last figure, with skewness $a_3 = -2.71$, is a mirror image of the penultimate figure, with skewness $a_3 = 2.71$.

The fourth moment about the mean is involved in the characterization of the flatness or peakedness of a distribution, labeled *kurtosis* (degree of archedness); a measure of kurtosis is defined by

$$a_4 = \frac{\sum(y - \overline{y})^4}{[\sum(y - \overline{y})^2]^2} = \frac{m_4}{(m_2)^2}$$

Again, as in the case of a_3, the statistic is unitless. The following terms are used to characterize values of a_4.

$a_4 = 3$	*mesokurtic*: the value for a bell-shaped distribution (Gaussian or normal distribution)
$a_4 < 3$	*leptokurtic*: thin or peaked shape (or "light tails")
$a_4 > 3$	*platykurtic*: flat shape (or "heavy tails")

Values of this statistic associated with particular frequency distribution configurations are illustrated in Figure 3.10. The first figure is similar to a bell-shaped curve and has a value $a_4 = 3.03$, very close to 3. Other frequency distributions have values as indicated. It is meaningful to speak of kurtosis only for symmetric distributions.

3.7 Taxonomy of Data

Social scientists have thought hard about types of data. Table 3.13 summarizes a fairly standard taxonomy of data based on the four scales nominal, ordinal, interval, and ratio. This table is to

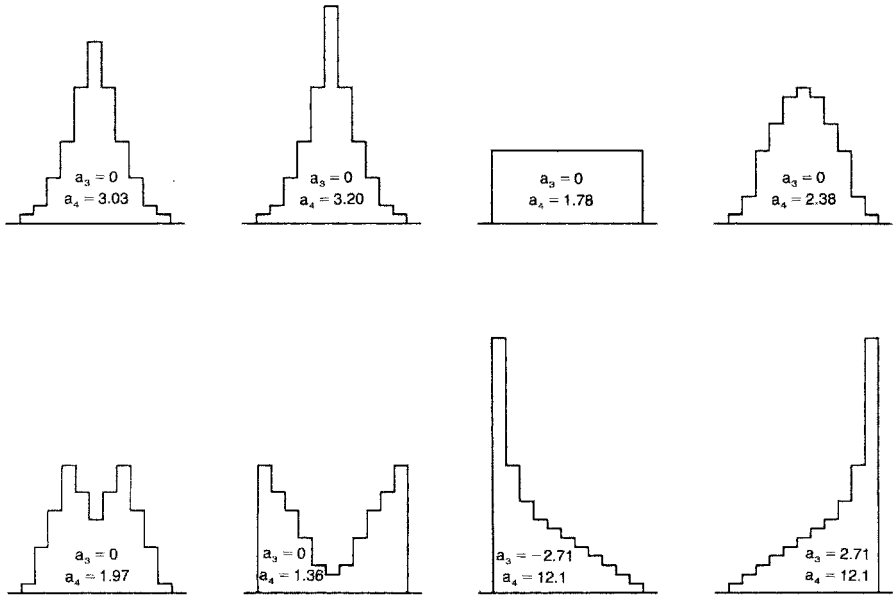


Figure 3.10 Values of skewness (a_3) and kurtosis (a_4) for selected data configurations.

Table 3.13 Standard Taxonomy of Data

Scale	Characteristic Question	Statistic	Statistic to Be Used
Nominal	Do A and B differ?	List of diseases; marital status	Mode
Ordinal	Is A bigger (better) than B?	Quality of teaching (unacceptable/acceptable)	Median
Interval	How much do A and B differ?	Temperatures; dates of birth	Mean
Ratio	How many times is A bigger than B?	Distances; ages; heights	Mean

be used as a guide only. You can be too rigid in applying this scheme (as unfortunately, some academic journals are). Frequently, ordinal data are coded in increasing numerical order and averages are taken. Or, interval and ratio measurements are ranked (i.e., reduced to ordinal status) and averages taken at that point. Even with nominal data, we sometimes calculate averages. For example: coding male $= 0$, female $= 1$ in a class of 100 students, the average is the proportion of females in the class. Most statistical procedures for ordinal data implicitly use a numerical coding scheme, even if this is not made clear to the user. For further discussion, see Luce and Narens [1987], van Belle [2002], and Velleman and Wilkinson [1993].

PROBLEMS

3.1 Characterize the following variables and classify them as qualitative or quantitative. If qualitative, can the variable be ordered? If quantitative, is the variable discrete or continuous? In each case define the values of the variable: (1) race, (2) date of birth, (3) systolic blood pressure, (4) intelligence quotient, (5) Apgar score, (6) white blood count, (7) weight, and (8) quality of medical care.

3.2 For each variable listed in Problem 3.1, define a suitable sample space. For two of the sample spaces so defined, explain how you would draw a sample. What statistics could be used to summarize such a sample?

3.3 Many variables of medical interest are derived from (functions of) several other variables. For example, as a measure of obesity there is the body mass index (BMI), which is given by weight/height^2. Another example is the dose of an anticonvulsant to be administered, usually calculated on the basis of milligram of medicine per kilogram of body weight. What are some assumptions when these types of variables are used? Give two additional examples.

3.4 Every row of 12 observations in Table 3.3 can be summed to form the number of keypunching errors per year of data. Calculate the 13 values for this variable. Make a stem-and-leaf diagram. Calculate the (sample) mean and standard deviation. How do this mean and standard deviation compare with the mean and standard deviation for the number of keypunching errors per line of data?

3.5 The precise specification of the value of a variable is not always easy. Consider the data dealing with keypunching errors in Table 3.3. How is an error defined? A fairly frequent occurrence was the transposition of two digits—for example, a value of "63" might have been entered as "36." Does this represent one or two errors? Sometimes a zero was omitted, changing, for example, 0.0317 to 0.317. Does this represent four errors or one? Consider the list of qualitative variables at the beginning of Section 3.2, and name some problems that you might encounter in defining the values of some of the variables.

3.6 Give three examples of frequency distributions from areas of your own research interest. Be sure to specify (1) what constitutes the sample, (2) the variable of interest, and (3) the frequencies of values or ranges of values of the variables.

3.7 A constant is added to each observation in a set of data (relocation). Describe the effect on the median, lower quartile, range, interquartile range, minimum, mean, variance, and standard deviation. What is the effect on these statistics if each observation is multiplied by a constant (rescaling)? Relocation and rescaling, called linear *transformations*, are frequently used: for example, converting from °C to °F, defined by $°\mathrm{F} = 1.8 \times °\mathrm{C} + 32$. What is the rescaling constant? Give two more examples of rescaling and relocation. An example of nonlinear transformation is going from the radius of a circle to its area: $A = \pi r^2$. Give two more examples of nonlinear transformations.

3.8 Show that the geometric mean is always smaller than the arithmetic mean (unless all the observations are identical). This implies that the mean of the logarithms is not the same as the logarithm of the mean. Is the median of the logarithms equal to the logarithm of the median? What about the interquartile range? How do these results generalize to other nonlinear transformations?

3.9 The data in Table 3.14 deal with the treatment of essential hypertension (*essential* is a technical term meaning that the cause is unknown; a synonym is *idiopathic*). Seventeen patients received treatments *C, A*, and *B*, where C = control period, A = propranolol + phenoxybenzamine, and B = propranolol + phenoxybenzamine + hydrochlorothiazide. Each patient received C first, then either A or B, and finally, B or A. The data consist of the systolic blood pressure in the recumbent position. (Note that in this example blood pressures are not always even-numbered.)

Table 3.14 Treatment Data for Hypertension

	C	*A*	*B*		*C*	*A*	*B*
1	185	148	132	10	180	132	136
2	160	128	120	11	176	140	135
3	190	144	118	12	200	165	144
4	192	158	115	13	188	140	115
5	218	152	148	14	200	140	126
6	200	135	134	15	178	135	140
7	210	150	128	16	180	130	130
8	225	165	140	17	150	122	132
9	190	155	138				

Source: Vlachakis and Mendlowitz [1976].

(a) Construct stem-and-leaf diagrams for each of the three treatments. Can you think of some innovative way of displaying the three diagrams together to highlight the data?

(b) Graph as a single graph the ECDFs for each of treatments *C, A*, and *B*.

(c) Construct box plots for each of treatments *C, A*, and *B*. State your conclusions with respect to the systolic blood pressures associated with the three treatments.

(d) Consider the difference between treatments *A* and *B* for each patient. Construct a box plot for the difference. Compare this result with that of part (b).

(e) Calculate the mean and standard deviation for each of the treatments *C, A*, and *B*.

(f) Consider, again, the difference between treatments *A* and *B* for each patient. Calculate the mean and standard deviation for the difference. Relate the mean to the means obtained in part (d). How many standard deviations is the mean away from zero?

3.10 The New York air quality data used in Figure 3.7 are given in the Web appendix to this chapter. Using these data, draw a simple plot of ozone vs. Solar radiation and compare it to conditioning plots where the subsets are defined by temperature, by wind speed, and by both variables together (i.e., one panel would be high temperature and high wind speed). How does the visual impression depend on the number of panels and the conditioning variables?

3.11 Table 3.15 is a frequency distribution of fasting serum insulin (μU/mL) of males and females in a rural population of Jamaican adults. (Serum insulin levels are expressed as whole numbers, so that "7-" represents the values 7 and 8.) The last frequencies are associated with levels greater than 45. Assume that these represent the levels 45 and 46.

(a) Plot both frequency distributions as histograms.

(b) Plot the relative frequency distributions.

(c) Calculate the ECDF.

(d) Construct box plots for males and females. State your conclusions.

(e) Assume that all the observations are concentrated at the midpoints of the intervals. Calculate the mean and standard deviation for males and females.

(f) The distribution is obviously skewed. Transform the levels for males to logarithms and calculate the mean and standard deviation. The transformation can be carried in at least two ways: (1) consider the observations to be centered at the midpoints,

Table 3.15 Frequency Distribution of Fasting Serum Insulin

Fasting Serum Insulin ($\mu U/mL$)	Males	Females	Fasting Serum Insulin ($\mu U/mL$)	Males	Females
7–	1	3	29–	8	14
9–	9	3	31–	8	11
11–	20	9	33–	4	10
13–	32	21	35–	4	8
15–	32	23	37–	3	7
17–	22	39	39–	1	2
19–	23	39	41–	1	3
21–	19	23	43–	1	1
23–	20	27	≥ 45	6	11
25–	13	23			
27–	8	19	Total	235	296

Source: Data from Florey et al. [1977].

transform the midpoints to logarithms, and group into six to eight intervals; and (2) set up six to eight intervals on the logarithmic scale, transform to the original scale, and estimate by interpolation the number of observations in the interval. What type of mean is the antilogarithm of the logarithmic mean? Compare it with the median and arithmetic mean.

3.12 There has been a long-held belief that births occur more frequently in the "small hours of the morning" than at any other time of day. Sutton [1945] collected the time of birth at the King George V Memorial Hospital, Sydney, for 2654 consecutive births. (*Note:* The total number of observations listed is 2650, not 2654 as stated by Sutton.) The frequency of births by hour in a 24-hour day is listed in Table 3.16.

(a) Sutton states that the data "confirmed the belief ... that more births occur in the small hours of the morning than at any other time in the 24 hours." Develop a graphical display that illustrates this point.

(b) Is there evidence of Sutton's statement: "An interesting point emerging was the relatively small number of births during the meal hours of the staff; this suggested either hastening or holding back of the second stage during meal hours"?

Table 3.16 Frequency of Birth by Hour of Birth

Time	Births	Time	Births	Time	Births
6–7 pm	92	2 am	151	10 am	101
7 pm	102	3 am	110	11 am	107
8 pm	100	4 am	144	12 pm	97
9 pm	101	5–6 am	136	1 pm	93
10 pm	127	6–7 am	117	2 pm	100
11 pm	118	7 am	80	3 pm	93
12 am	97	8 am	125	4 pm	131
1 am	136	9 am	87	5–6 pm	105

(c) The data points in fact represent frequencies of values of a variable that has been divided into intervals. What is the variable?

3.13 At the International Health Exhibition in Britain, in 1884, Francis Galton, a scientist with strong statistical interests, obtained data on the strength of pull. His data for 519 males aged 23 to 26 are listed in Table 3.17. Assume that the smallest and largest categories are spread uniformly over a 10-pound interval.

Table 3.17 Strength of Pull

Pull Strength (lb)	Cases Observed	Pull Strength (lb)	Cases Observed
Under 50	10	Under 90	113
Under 60	42	Under 100	22
Under 70	140	Above 100	24
Under 80	168		
		Total	519

(a) The description of the data is exactly as in Galton [1889]. What are the intervals, assuming that strength of pull is measured to the nearest pound?

(b) Calculate the median and 25th and 75th percentiles.

(c) Graph the ECDF.

(d) Calculate the mean and standard deviation assuming that the observations are centered at the midpoints of the intervals.

(e) Calculate the proportion of observations within one standard deviation of the mean.

3.14 The aflatoxin data cited at the beginning of Section 3.2 were taken from a larger set in the paper by Quesenberry et al. [1976]. The authors state:

> Aflatoxin is a toxic material that can be produced in peanuts by the fungus *Aspergillus flavus*. As a precautionary measure all commercial lots of peanuts in the United States (approximately 20,000 each crop year) are tested for aflatoxin.... Because aflatoxin is often highly concentrated in a small percentage of the kernels, variation among aflatoxin determinations is large.... Estimation of the distribution (of levels) is important. ... About 6200g of raw peanut kernels contaminated with aflatoxin were comminuted (ground up). The ground meal was then divided into 11 subsamples (lots) weighing approximately 560g each. Each subsample was blended with 2800ml methanol-water-hexane solution for two minutes, and the homogenate divided equally among 16 centrifuge bottles. One observation was lost from each of three subsamples leaving eight subsamples with 16 determinations and three subsamples with 15 determinations.

The original data were given to two decimal places; they are shown in Table 3.18 rounded off to the nearest whole number. The data are listed by lot number, with asterisks indicating lost observations.

(a) Make stem-and-leaf diagrams of the data of lots 1, 2, and 10. Make box plots and histograms for these three lots, and discuss differences among these lots with respect to location and spread.

(b) The data are analyzed by means of a MINITAB computer program. The data are entered by columns and the command DESCRIBE is used to give standard

Table 3.18 Aflatoxin Data by Lot Number

1	2	3	4	5	6	7	8	9	10	11
121	95	20	22	30	11	29	34	17	8	53
72	56	20	33	26	19	33	28	18	6	113
118	72	25	23	26	13	37	35	11	7	70
91	59	22	68	36	13	25	33	12	5	100
105	115	25	28	48	12	25	32	25	7	87
151	42	21	27	50	17	36	29	20	7	83
125	99	19	29	16	13	49	32	17	12	83
84	54	24	29	31	18	38	33	9	8	65
138	90	24	52	22	18	29	31	15	9	74
83	92	20	29	27	17	29	32	21	14	112
117	67	12	22	23	16	32	29	17	13	98
91	92	24	29	35	14	40	26	19	11	85
101	100	15	37	52	11	36	37	23	5	82
75	77	15	41	28	15	31	28	17	7	95
137	92	23	24	37	16	32	31	15	4	60
146	66	22	36	*	12	*	32	17	12	*

Table 3.19 MINITAB Analysis of Aflatoxin Data[a]

MTB > desc c1–c11

	N	N*	MEAN	MEDIAN	STDEV	MIN	MAX	Q1	Q3
C1	16	0	109.69	111.00	25.62	72	151	85.75	134.00
C2	16	0	79.25	83.50	20.51	42	115	60.75	94.25
C3	16	0	20.687	21.500	3.860	12	25	19.25	24.00
C4	16	0	33.06	29.00	12.17	22	68	24.75	36.75
C5	15	1	32.47	30.00	10.63	16	52	26.00	37.00
C6	16	0	14.688	14.500	2.651	11	19	12.25	17.00
C7	15	1	33.40	32.00	6.23	25	49	29.00	37.00
C8	16	0	31.375	32.000	2.849	26	37	29.00	33.00
C9	16	0	17.06	17.00	4.19	9	25	15.00	19.75
C10	16	0	8.438	7.500	3.076	4	14	6.25	11.75
C11	15	1	84.00	83.00	17.74	53	113	70.00	98.00

[a]N*, number of missing observations; Q1 and Q3, 25th and 75th percentiles, respectively.

descriptive statistics for each lot. The output from the program (slightly modified) is given in Table 3.19.

(c) Verify that the statistics for lot 1 are correct in the printout.

(d) There is an interesting pattern between the means and their standard deviations. Make a plot of the means vs. standard deviation. Describe the pattern.

(e) One way of describing the pattern between means and standard deviations is to calculate the ratio of the standard deviation to the mean. This ratio is called the *coefficient of variation*. It is usually multiplied by 100 and expressed as the percent coefficient of variation. Calculate the coefficients of variation in percentages for each of the 11 lots, and make a plot of their value with the associated means. Do you see any pattern now? Verify that the average of the coefficients of variation is about 24%. A reasonable number to keep in mind for many biological measurements is that the variability as measured by the standard deviation is about 30% of the mean.

Table 3.20 Plasma Prostaglandin E Levels

Patient Number	Mean Plasma iPGE (pg/mL)	Mean Serum Calcium (ml/dL)
	Patients with Hypercalcemia	
1	500	13.3
2	500	11.2
3	301	13.4
4	272	11.5
5	226	11.4
6	183	11.6
7	183	11.7
8	177	12.1
9	136	12.5
10	118	12.2
11	60	18.0
	Patients without Hypercalcemia	
12	254	10.1
13	172	9.4
14	168	9.3
15	150	8.6
16	148	10.5
17	144	10.3
18	130	10.5
19	121	10.2
20	100	9.7
21	88	9.2

3.15 A paper by Robertson et al. [1976] discusses the level of plasma prostaglandin E (iPGE) in patients with cancer with and without hypercalcemia. The data are given in Table 3.20. Note that the variables are the mean plasma iPGE and mean serum Ca levels—presumably, more than one assay was carried out for each patient's level. The number of such tests for each patient is not indicated, nor is the criterion for the number.

(a) Calculate the mean and standard deviation of plasma iPGE level for patients with hypercalcemia; do the same for patients without hypercalcemia.

(b) Make box plots for plasma iPGE levels for each group. Can you draw any conclusions from these plots? Do they suggest that the two groups differ in plasma iPGE levels?

(c) The article states that normal limits for serum calcium levels are 8.5 to 10.5 mg/dL. It is clear that patients were classified as hypercalcemic if their serum calcium levels exceeded 10.5 mg/dL. Without classifying patients it may be postulated that high plasma iPGE levels tend to be associated with high serum calcium levels. Make a plot of the plasma iPGE and serum calcium levels to determine if there is a suggestion of a pattern relating these two variables.

3.16 Prove or verify the following for the observations $y_1, y_2, \ldots, y_n$.

(a) $\sum 2y = 2\sum y$.

(b) $\sum(y - \overline{y}) = 0$.

(c) By means of an example, show that $\sum y^2 \neq (\sum y)^2$.

(d) If a is a constant, $\sum ay = a \sum y$.
(e) If a is a constant, $\sum (a + y) = na + \sum y$.
(f) $\sum (y/n) = (1/n) \sum y$.
(g) $\sum (a + y)^2 = na^2 + 2a \sum y + \sum y^2$.
(h) $\sum (y - \overline{y})^2 = \sum y^2 - (\sum y)^2/n$.
(i) $\sum (y - \overline{y})^2 = \sum y^2 - n\overline{y}^2$.

3.17 A variable Y is grouped into intervals of width h and represented by the midpoint of the interval. What is the maximum error possible in calculating the mean of all the observations?

3.18 Prove that the two definitions of the geometric mean are equivalent.

3.19 Calculate the average number of boys per family of eight children for the data given in Table 3.10.

3.20 The formula $\overline{Y} = \sum py$ is also valid for observations not arranged in a frequency distribution as follows: If we let $1/N = p$, we get back to the formula $\overline{Y} = \sum py$. Show that this is so for the following four observations: 3, 9, 1, 7.

3.21 Calculate the average systolic blood pressure of native Japanese men using the frequency data of Table 3.6. Verify that the same value is obtained using the relative frequency data of Table 3.7.

3.22 Using the taxonomy of data described in Note 3.6, classify each of the variables in Problem 3.1 according to the scheme described in the note.

REFERENCES

Cleveland, W. S. [1981]. LOWESS: a program for smoothing scatterplots by robust locally weighted regression. *American Statistician*, **35**: 54.

Cleveland, W. S. [1993]. *Visualizing Data*. Hobart Press, Summit, NJ.

Cleveland, W. S. [1994]. *The Elements of Graphing Data*. Hobart Press, Summit, NJ.

DeLury, D. B. [1958]. Computations with approximate numbers. *Mathematics Teacher*, **51**: 521–530. Reprinted in Ku, H. H. (ed.) [1969]. *Precision Measurement and Calibration*. NBS Special Publication 300. U.S. Government Printing Office, Washington, DC.

Fisher, R. A. [1958]. *Statistical Methods for Research Workers*, 13th ed. Oliver & Boyd, London.

Fleming, T. R. and Harrington, D. P. [1991]. *Counting Processes and Survival Analysis*. John Wiley & Sons, New York.

Florey, C. du V., Milner, R. D. G., and Miall, W. E. [1977]. Serum insulin and blood sugar levels in a rural population of Jamaican adults. *Journal of Chronic Diseases*, **30**: 49–60. Used with permission from Pergamon Press, Inc.

Galton, F. [1889]. *Natural Inheritance*. Macmillan, London.

Gould, S. J. [1996]. *Full House: The Spread of Excellence from Plato to Darwin*. Harmony Books, New York.

Graunt, J. [1662]. Natural and political observations mentioned in a following index and made upon the Bills of Mortality. In Newman, J. R. (ed.) [1956]. *The World of Mathematics*, Vol. 3. Simon & Schuster, New York, pp. 1421–1435.

Huff, D. [1993]. *How to Lie with Statistics*. W. W. Norton, New York.

Luce, R. D. and Narens, L. [1987]. Measurement scales on the continuum. *Science*, **236**: 1527–1532.

Mendel, G. [1911]. *Versuche über Pflanzenhybriden*. Wilhelm Engelmann, Leipzig, p. 18.

Moses, L. E. [1987]. Graphical methods in statistical analysis. *Annual Reviews of Public Health*, **8**: 309–353.

Newman, J. R. (ed.) [1956]. *The World of Mathematics*, Vol. 3. Simon & Schuster, New York, pp. 1421–1435.

Quesenberry, P. D., Whitaker, T. B., and Dickens, J. W. [1976]. On testing normality using several samples: an analysis of peanut aflatoxin data. *Biometrics*, **32**: 753–759. With permission of the Biometric Society.

R Foundation for Statistical Computing [2002]. *R, Version 1.7.0*, Air quality data set. *http://cran.r-project.org*.

Robertson, R. P., Baylink, D. J., Metz, S. A., and Cummings, K. B. [1976]. Plasma prostaglandin E in patients with cancer with and without hypercalcemia. *Journal of Clinical Endocrinology and Metabolism*, **43**: 1330–1335.

Schwab, B. [1975]. Delivery of babies and full moon (letter to the editor). *Canadian Medical Association Journal*, **113**: 489, 493.

Sutton, D. H. [1945]. Gestation period. *Medical Journal of Australia*, Vol. I, **32**: 611–613. Used with permission.

Tufte, E. R. [1990]. *Envisioning Information*. Graphics Press, Cheshire, CT.

Tufte, E. R. [1997]. *Visual Explanations*. Graphics Press, Cheshire, CT.

Tufte, E. R. [2001]. *The Visual Display of Quantitative Information*. 2nd ed. Graphics Press, Cheshire, CT.

Tukey, J. W. [1977]. *Exploratory Data Analysis*. Addison-Wesley, Reading, MA.

van Belle, G. [2002]. *Statistical Rules of Thumb*. Wiley, New York.

Velleman, P. F. and Wilkinson, L. [1993]. Nominal, ordinal, interval, and ratio typologies are misleading. *American Statistician* **46**: 193–197.

Vlachakis, N. D. and Mendlowitz, M. [1976]. Alpha- and beta-adrenergic receptor blocking agents combined with a diuretic in the treatment of essential hypertension. *Journal of Clinical Pharmacology*, **16**: 352–360.

Wilkinson, L. [1999]. *The Grammar of Graphics*. Springer, New York.

Winkelstein, W., Jr., Kagan, A., Kato, H., and Sacks, S. T. [1975]. Epidemiological studies of coronary heart disease and stroke in Japanese men living in Japan, Hawaii and California: blood pressure distributions. *American Journal of Epidemiology*, **102**: 502–513.

CHAPTER 4

Statistical Inference: Populations and Samples

4.1 INTRODUCTION

Statistical inference has been defined as "the attempt to reach a conclusion concerning all members of a class from observations of only some of them" [Runes, 1959]. In statistics, "all members of a class" form the *population* or *sample space*, and the subset observed forms a *sample*; we discussed this in Sections 3.1 and 3.2. We now discuss the *process* of obtaining a valid sample from a population; specifically, when is it valid to make a statement about a population on the basis of a sample? One of the assumptions in any scientific investigation is that valid inferences can be made—that the results of a study can apply to a larger population. For example, we can assume that a new therapy developed at the Memorial Sloan–Kettering Cancer Center in New York is applicable to cancer patients in Great Britain. You can easily supply additional examples.

In the next section we note which characteristics of a population are of interest and illustrate this with two examples. In Section 4.3 we introduce probability theory as a way by which we can define valid sampling procedures. In Section 4.4 we apply the theory to a well-known statistical model for a population, the normal frequency distribution, which has practical as well as theoretical interest. One reason for the importance of the normal distribution is given in Section 4.5, which discusses the concept of sampling distribution. In the next three sections we discuss inferences about population means and variances on the basis of a single sample.

4.2 POPULATION AND SAMPLE

4.2.1 Definition and Examples

You should review Chapter 3 for the concepts of *variable*, *sample space* or *population*, and *statistic*.

Definition 4.1. A *parameter* is a numerical characteristic of a population.

Analogous to numerical characteristics of a sample (statistics), we will be interested in numerical characteristics of populations (parameters). The population characteristics are usually unknown because the entire population cannot be enumerated or studied. The problem of

Biostatistics: A Methodology for the Health Sciences, Second Edition, by Gerald van Belle, Lloyd D. Fisher, Patrick J. Heagerty, and Thomas S. Lumley
ISBN 0-471-03185-2

statistical inference can then be stated as follows: On the basis of a sample from a population, what can be said about the population from which the sample came? In this section we illustrate the four concepts of population and its corresponding parameters, and sample and its corresponding statistics.

Example 4.1. We illustrate those four concepts with an example from Chapter 3, systolic blood pressure for Japanese men, aged 45–69, living in Japan. The "population" can be considered to be the collection of blood pressures of all Japanese men. The blood pressures are assumed to have been taken under standardized conditions. Clearly, Winkelstein et al. [1975] could not possibly measure all Japanese men, but a subset of 2232 eligible men were chosen. This is the sample. A numerical quantity of interest could be the average systolic blood pressure. This average for the population is a *parameter*; the average for the sample is the *statistic*. Since the total population cannot be measured, the parameter value is unknown. The statistic, the average for the sample, can be calculated. You are probably assuming now that the sample average is a good estimate of the population average. You may be correct. Later in this chapter we specify under what conditions this is true, but note for now that all the elements of inference are present.

Example 4.2. Consider this experimental situation. We want to assess the effectiveness of a new special diet for children with phenylketonuria (PKU). One effect of this condition is that untreated children become mentally retarded. The diet is used with a set of PKU children and their IQs are measured when they reach 4 years of age. What is the population? It is hypothetical in this case: all PKU children who could potentially be treated with the new diet. The variable of interest is the IQ associated with each child. The sample is the set of children actually treated. A parameter could be the median IQ of the hypothetical population; a statistic might be the median IQ of the children in the sample. The question to be answered is whether the median IQ of this treated hypothetical population is the same or comparable to that of non-PKU children.

A sampling situation has the following components: A population of measurement is specified, a sample is taken from the population, and measurements are made. A statistic is calculated which—in some way—makes a statement about the corresponding population parameter. Some practical questions that come up are:

1. Is the population defined unambiguously?
2. Is the variable clearly observable?
3. Is the sample "valid"?
4. Is the sample "big enough"?

The first two questions have been discussed in previous chapters. In this chapter we begin to answer the last two.

Conventionally, parameters are indicated by Greek letters and the estimate of the parameter by the corresponding Roman letter. For example, μ is the population mean, and m is the sample mean. Similarly, the population standard deviation will be indicated by σ and the corresponding sample estimate by s.

4.2.2 Estimation and Hypothesis Testing

Two approaches are commonly used in making statements about population parameters: estimation and hypothesis testing. *Estimation*, as the name suggests, attempts to estimate values of parameters. As discussed before, the sample mean is thought to estimate, in some way, the mean of the population from which the sample was drawn. In Example 4.1 the mean of

the blood pressures is considered an estimate of the corresponding population value. *Hypothesis testing* makes inferences about (population) parameters by supposing that they have certain values, and then testing whether the data observed are consistent with the hypothesis. Example 4.2 illustrates this framework: Is the mean IQ of the population of PKU children treated with the special diet the same as that of the population of non-PKU children? We could hypothesize that it is and determine, in some way, whether the data are inconsistent with this hypothesis.

You could argue that in the second example we are also dealing with estimation. If one could estimate the mean IQ of the treated population, the hypothesis could be dealt with. This is quite true. In Section 4.7 we will see that in many instances hypothesis testing and estimation are but two sides of the same coin.

One additional comment about estimation: A distinction is usually made between point estimate and interval estimate. A sample mean is a *point estimate*. An *interval estimate* is a range of values that is reasonably certain to straddle the value of the parameter of interest.

4.3 VALID INFERENCE THROUGH PROBABILITY THEORY

4.3.1 Precise Specification of Our Ignorance

Everyone "knows" that the probability of heads coming up in the toss of a coin is 1/2 and that the probability of a 3 in the toss of a die is 1/6. More subtly, the probability that a randomly selected patient has systolic blood pressure less than the population median is 1/2, although some may claim, after the measurement is made, that it is either 0 or 1—that is, the systolic blood pressure of the patient is either below the median or greater than or equal to the median.

What do we mean by the phrase "the probability of"? Consider one more situation. We toss a thumbtack on a hard, smooth surface such as a table, if the outcome is $\perp$, we call it "up"; if the outcome is $\top$, we call it "down." What is the probability of "up"? It is clear that in this example we do not know, a priori, the probability of "up"—it depends on the physical characteristics of the thumbtack. How would you *estimate* the probability of "up"? Intuitively, you would toss the thumbtack a large number of times and observe the proportion of times the thumbtack landed "up"—and that is the way we define probability. Mathematically, we define the probability of "up" as the relative frequency of the occurrence of "up" as the number of tosses become indefinitely large. This is an illustration of the *relative frequency* concept of probability. Some of its ingredients are: (1) a trial or experiment has a set of specified outcomes; (2) the outcome of one trial does not influence the outcome of another trial; (3) the trials are identical; and (4) the probability of a specified outcome is the limit of its relative frequency of occurrence as the number of trials becomes indefinitely large.

Probabilities provide a link between a population and samples. A *probability* can be thought of as a numerical statement about what we know and do not know: a precise specification of our ignorance [Fisher, 1956]. In the thumbtack-tossing experiment, we know that the relative frequency of occurrences of "up" will approach some number: the probability of "up." What we do not know is what the outcome will be on the next toss. A probability, then, is a characteristic of a population of outcomes. When we say that the probability of a head in a coin toss is 1/2, we are making a statement about a population of tosses. For alternative interpretations of probability, see Note 4.1. On the basis of the relative frequency interpretation of probability, we deduce that probabilities are numbers between zero and 1 (including zero and 1).

The outcome of a trial such as a coin toss will be denoted by a capital letter; for example, H = "coin toss results in head" and T = "coin toss results in tail." Frequently, the letter can be chosen as a mnemonic for the outcome. The probability of an outcome, O, in a trial will be denoted by $P[O]$. Thus, in the coin-tossing experiment, we have $P[H]$ and $P[T]$ for the probabilities of "head" and "tail," respectively.

4.3.2 Working with Probabilities

Outcomes of trials can be categorized by two criteria: statistical independence and mutual exclusiveness.

Definition 4.2. Two outcomes are *statistically independent* if the probability of their joint occurrence is the product of the probabilities of occurrence of each outcome.

Using notation, let C be one outcome and D be another outcome; $P[C]$ is the probability of occurrence of C, and $P[D]$ is the probability of occurrence of D. Then C and D are statistically independent if

$$P[CD] = P[C]P[D]$$

where $[CD]$ means that both C and D occur.

Statistically independent events are the model for events that "have nothing to do with each other." In other words, the occurrence of one event does not change the probability of the other occurring. Later this is explained in more detail.

Models of independent outcomes are the outcomes of successive tosses of a coin, die, or the spinning of a roulette wheel. For example, suppose that the outcomes of two tosses of a coin are statistically independent. Then the probability of two heads, $P[HH]$, by statistical independence is

$$P[HH] = P[H]P[H] = \frac{1}{2} \times \frac{1}{2} = \frac{1}{4}$$

Similarly,

$$P[HT] = \frac{1}{2} \times \frac{1}{2} = \frac{1}{4}$$

$$P[TH] = \frac{1}{2} \times \frac{1}{2} = \frac{1}{4}$$

and

$$P[TT] = \frac{1}{2} \times \frac{1}{2} = \frac{1}{4}$$

Note that the outcome HT means "head on toss 1 and tail on toss 2."

You may wonder why we refer to coin tossing and dice throws so much. One reason has been given already: These activities form patterns of probabilistic situations. Second, they can be models for many experimental situations. Suppose that we consider the Winkelstein et al. [1975] study dealing with blood pressures of Japanese men. What is the probability that each of two men has a blood pressure less than the median of the population? We can use the coin-toss model: By definition, half of the population has blood pressure less than the median. The populations can then be thought of as a very large collection of trials each of which has two outcomes: less than the median, and greater than or equal to the median. If the selection of two men can be modeled by the coin-tossing experiment, the probability that both men have blood pressures less than the median is $1/2 \times 1/2 = 1/4$. We now formalize this:

Definition 4.3. Outcomes of a series of repetitions of a trial are a *random sample* of outcomes if the probability of their joint occurrence is the product of the probabilities of each occurring separately. If every possible sample of k outcomes has the same probability of occurrence, the sample is called a *simple random sample*. This is the most common type of random sample.

Suppose that we are dealing with the outcomes of trials. We label the outcomes O_k, where the subscript is used to denote the order in the sequence; O_1 is the outcome specified for the first trial, O_2 is the outcome for the second trial, and so on. Then the outcomes form a random sample if

$$P[O_1 O_2 O_3 \cdots O_k] = P[O_1]P[O_2]P[O_3] \cdots P[O_k].$$

The phrase "a random sample" is therefore not so much a statement about the sample as a statement about the method that produced the sample. The randomness of the sample allows us to make valid statements about the population from which it came. It also allows us to quantify what we know and do not know. (See Note 4.6 for another type of random sampling.)

How can we draw a random sample? For the coin tosses and dice throws, this is fairly obvious. But how do we draw a random sample of Japanese men? Theoretically, we could have their names on slips of paper in a very large barrel. The contents are stirred and slips of paper drawn out—a random sample. Clearly, this is not done in practice. In fact, often, a sample is claimed to be random by default: "There is no reason to believe that it is not random." Thus, college students taking part in a experiment are implicitly assumed to be a "random sample of people." Sometimes this is reasonable; as mentioned earlier, cancer patients treated in New York are considered very similar with respect to cancer to cancer patients in California. There is a gradation in the seriousness of nonrandomness of samples: "Red blood cells from healthy adult volunteers" are apt to be similar in many respects the world over (and dissimilar in others); "diets of teenagers," on the other hand, will vary from region to region.

Obtaining a truly random sample is a difficult task that is rarely carried out successfully. A standard criticism of any study is that the sample of data is not a random sample, so that the inference is not valid. Some problems in sampling were discussed in Chapter 2; here we list a few additional problems:

1. The population or sample space is not defined.
2. Part of the population of interest is not available for study.
3. The population is not identifiable or it changes with time.
4. The sampling procedure is faulty, due to limitations in time, money, and effort.
5. Random allocation of members of a group to two or more treatments does not imply that the group itself is necessarily a random sample.

Most of these problems are present in any study, sometimes in an unexpected way. For example, in an experiment involving rats, the animals were "haphazardly" drawn from a cage for assignment to one treatment, and the remaining rats were given another treatment. "Differences" between the treatments were due to the fact that the more agile and larger animals evaded "haphazard" selection and wound up in the second treatment. For some practical ways of drawing random samples, see Note 4.9.

Now we consider probabilities of mutually exclusive events:

Definition 4.4. Two outcomes are *mutually exclusive* if at most one of them can occur at a time; that is, the outcomes do not overlap.

Using notation, let C be one outcome and D another; then it can be shown (using the relative frequency definition) that $P[C \text{ or } D] = P[C] + P[D]$ if the outcomes are mutually exclusive. Here, the connective "or" is used in its inclusive sense, "either/or, or both."

Some examples of mutually exclusive outcomes are H and T on a coin toss; the race of a person for purposes of a study can be defined as "black," "white," or "other," and each subject can belong to only one category; the method of delivery can be either "vaginal" or by means of a "cesarean section."

Example 4.3. We now illustrate outcomes that are not mutually exclusive. Suppose that the Japanese men in the Winkelstein data are categorized by weight: "reasonable weight" or "overweight," and their blood pressures by "normal" or "high." Suppose that we have the following table:

	Blood Pressure		
Weight	**Normal (N)**	**High (H)**	
Reasonable (R)	0.6	0.1	0.7
Overweight (O)	0.2	0.1	0.3
Total	0.8	0.2	1.0

The entries in the table are the probabilities of outcomes for a person selected randomly from the population, so that, for example, 20% of Japanese men are considered overweight and have normal blood pressure. Consider the outcomes "overweight" and "high blood pressure." What is the probability of the outcome [O or H] (overweight, high blood pressure, or both)? This corresponds to the following data in boldface type:

	N	H	
R	0.6	**0.1**	0.7
O	**0.2**	**0.1**	0.3
Total	0.8	0.2	1.0

$$P[O \text{ or } H] = 0.2 + 0.1 + 0.1 = 0.4$$

But $P[O] + P[H] = 0.2 + 0.3 = 0.5$. Hence, O and H are not mutually exclusive. In terms of calculation, we see that we have added in the outcome $P[OH]$ twice:

	N	H	
R		0.1	
O	0.2	0.1	0.3
Total		0.2	

The correct value is obtained if we subtract $P[OH]$ as follows:

$$\begin{aligned} P[O \text{ or } H] &= P[O] + P[H] - P[OH] \\ &= 0.3 + 0.2 - 0.1 \\ &= 0.4 \end{aligned}$$

This example is an illustration of the addition rule of probabilities.

Definition 4.5. By the *addition rule*, for any two outcomes, the probability of occurrence of either outcome or both is the sum of the probabilities of each occurring minus the probability of their joint occurrence.

Using notation, for any two outcomes C and D,

$$P[C \text{ or } D] = P[C] + [D] - P[CD]$$

Two outcomes, C and D, are mutually exclusive if they cannot occur together. In this case, $P[CD] = 0$ and $P[C \text{ or } D] = P[C] + P[D]$, as stated previously.

We conclude this section by briefly discussing dependent outcomes. The outcomes O and H in Example 4.3 were not mutually exclusive. Were they independent? By Definition 4.2, O and H are statistically independent if $P[OH] = P[O]P[H]$.

From the table, we get $P[OH] = 0.1$, $P[O] = 0.3$, and $P[H] = 0.2$, so that

$$0.1 \neq (0.3)(0.2)$$

Of subjects with reasonable weight, only 1 in 7 has high blood pressure, but among overweight persons, 1 in 3 has high blood pressure. Thus, the probability of high blood pressure in overweight subjects is greater than the probability of high blood pressure in subjects of normal weight. The reverse statement can also be made: 2 of 8 persons with normal blood pressure are overweight; 1 of 2 persons with high blood pressure is overweight.

The statement "of subjects with reasonable weight, only 1 in 7 has high blood pressure" can be stated as a probability: "The probability that a person with reasonable weight has high blood pressure is 1/7." Formally, this is written as

$$P[H|R] = \frac{1}{7}$$

or P[high blood pressure *given* a reasonable weight] $= 1/7$. The probability $P[H|R]$ is called a *conditional* probability. You can verify that $P[H|R] = P[HR]/P[R]$.

Definition 4.6. For any two outcomes C and D, the *conditional probability* of the occurrence of C *given* the occurrence of D, $P[C|D]$, is given by

$$P[C|D] = \frac{P[CD]}{P[D]}$$

For completeness we now state the multiplication rule of probability (which is discussed in more detail in Chapter 6).

Definition 4.7. By the *multiplication rule*, for any two outcomes C and D, the probability of the joint occurrence of C and D, $P[CD]$, is given by

$$P[CD] = P[C]P[D|C]$$

or equivalently,

$$P[CD] = P[D]P[C|D]$$

Example 4.3. [continued] What is the probability that a randomly selected person is overweight and has high blood pressure? In our notation we want $P[OH]$. By the multiplication rule, this probability is

$$P[OH] = P[O]P[H|O]$$

Using Definition 4.6 gives us

$$P[H|O] = \frac{P[OH]}{P[O]} = \frac{0.1}{0.3} = \frac{1}{3}$$

so that

$$P[OH] = 0.3\left(\frac{1}{3}\right) = 0.1$$

Alternatively, we could have calculated $P[OH]$ by

$$P[OH] = P[H]P[O|H]$$

which becomes

$$P[OH] = 0.2\left(\frac{0.1}{0.2}\right) = 0.1$$

We can also state the criterion for statistical independence in terms of conditional probabilities. From Definition 4.2, two outcomes C and D are statistically independent if $P[CD] = P[C]P[D]$ (i.e., the probability of the joint occurrence of C and D is the product of the probability of C and the probability of D). The multiplication rule states that for *any* two outcomes C and D,

$$P[CD] = P[C]P[D|C]$$

Under independence,

$$P[CD] = P[C]P[D]$$

Combining the two, we see that C and D are independent if (and only if) $P[D|C] = P[D]$. In other words, the probability of occurrence of D is not altered by the occurrence of C. This has intuitive appeal.

When do we use the addition rule; when the multiplication rule? Use the addition rule to calculate the probability that either one or both events occur. Use the multiplication rule to calculate the probability of the joint occurrence of two events.

4.3.3 Random Variables and Distributions

Basic to the field of statistics is the concept of a random variable:

Definition 4.8. A *random variable* is a variable associated with a random sample.

The only difference between a *variable* defined in Chapter 3 and a *random variable* is the process that generates the value of the variable. If this process is random, we speak of a random variable. All the examples of variables in Chapter 3 can be interpreted in terms of random variables if the samples are random samples. The empirical relative frequency of occurrence of a value of the variable becomes an estimate of the probability of occurrence of that value. For example, the relative frequencies of the values of the variable "number of boys in families with eight children" in Table 3.12 become estimates of the probabilities of occurrence of these values.

The distinction between discrete and continuous variables carries over to random variables. Also, as with variables, we denote the label of a random variable by capital letters (say $X, Y, V, \ldots$) and a value of the random variable by the corresponding lowercase letter ($x, y, v, \ldots$).

We are interested in describing the probabilities with which values of a random variable occur. For discrete random variables, this is straightforward. For example, let Y be the outcome of the toss of a die. Then Y can take on the values 1, 2, 3, 4, 5, 6, and we write

$$P[Y = 1] = \frac{1}{6}, \quad P[Y = 2] = \frac{1}{6}, \ldots, \quad P[Y = 6] = \frac{1}{6}$$

This leads to the following definition:

Definition 4.9. A *probability function* is a function that for each possible value of a discrete random variable takes on the probability of that value occurring. The function is usually presented as a listing of the values with the probabilities of occurrence of the values.

Consider again the data of Table 3.12, the number of boys in families with eight children. The observed empirical relative frequencies can be considered estimates of probabilities if the 53,680 families are a random sample. The probability distribution is then estimated as shown in Table 4.1. The estimated probability of observing precisely two boys in a family of eight children is 0.0993 or, approximately, 1 in 10. Since the sample is very large, we will treat—in this discussion—the estimated probabilities as if they were the actual probabilities. If Y represents the number of boys in a family with eight children, we write

$$P[Y = 2] = 0.0993$$

What is the probability of two boys or fewer? This can be expressed as

$$P[Y \leq 2] = P[Y = 2 \text{ or } Y = 1 \text{ or } Y = 0]$$

Since these are mutually exclusive outcomes,

$$\begin{aligned} P[Y \leq 2] &= P[Y = 2] + P[Y = 1] + P[Y = 0] \\ &= 0.0993 + 0.0277 + 0.0040 \\ &= 0.1310 \end{aligned}$$

Approximately 13% of families with eight children will have two or fewer boys. A probability function can be represented graphically by a plot of the values of the variable against the probability of the value. The probability function for the Geissler data is presented in Figure 4.1.

How can we describe probabilities associated with continuous random variables? Somewhat paradoxically, the probability of a specified value for a continuous random variable is zero! For example, the probability of finding anyone with height 63.141592654 inches—and not 63.141592653 inches—is virtually zero. If we were to continue the decimal expansion, the probability becomes smaller yet. But we do find people with height, say, 63 inches. When we write 63 inches, however, we do not mean 63.000... inches (and we are almost certain not to find anybody with that height), but we have in mind *an interval* of values of height, anyone with height between 62.500... and 63.500... inches. We could then divide the values of the continuous random variable into intervals, treat the midpoints of the intervals as the values of a discrete variable, and list the probabilities associated with these values. Table 3.7 illustrates this approach with the division of the systolic blood pressure of Japanese men into discrete intervals.

We start with the histogram and the relative frequencies associated with the intervals of values in the histogram. The area under the "curve" is equal to 1 if the width of each interval

Table 4.1 Number of Boys in Eight-Child Families

Number of Boys	Probability	Number of Boys	Probability
0	0.0040	6	0.1244
1	0.0277	7	0.0390
2	0.0993	8	0.0064
3	0.1984		
4	0.2787		
5	0.2222	Total	1.0000

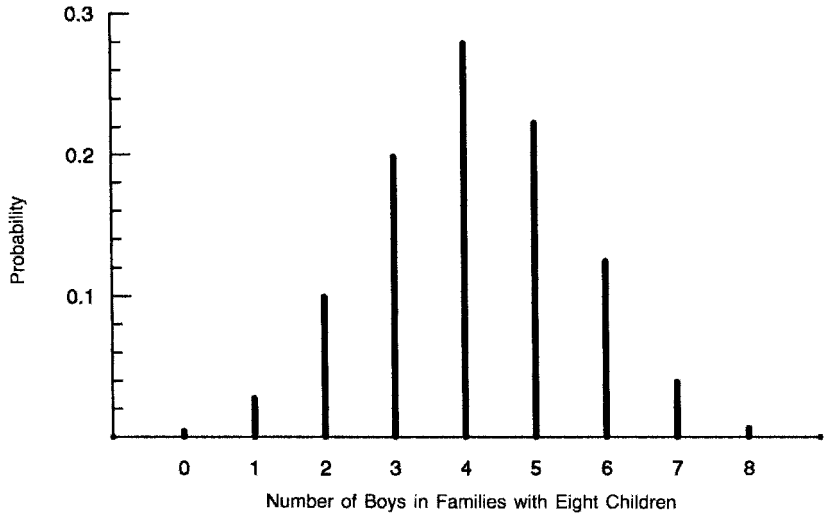


Figure 4.1 Probability function of the random variable "number of boys in families with eight children." (Geissler's date; reprinted in Fisher [1958]; see Table 3.10.)

is 1; or if we normalize (i.e., multiply by a constant so that the area is equal to 1). Suppose now that the interval widths are made smaller and smaller, and simultaneously, the number of cases increased. Normalize so that the area under the curve remains equal to 1; then the curve is assumed to take on a smooth shape. Such shapes are called *probability density functions* or, more briefly, *densities*:

Definition 4.10. *A probability density function* is a curve that specifies, by means of the area under the curve over an interval, the probability that a continuous random variable falls within the interval. The total area under the curve is 1.

Some simple densities are illustrated in Figure 4.2. Figure 4.2(a) and (b) represent uniform densities on the intervals $(-1, 1)$ and $(0, 1)$, respectively. Figure 4.2(c) illustrates a triangular

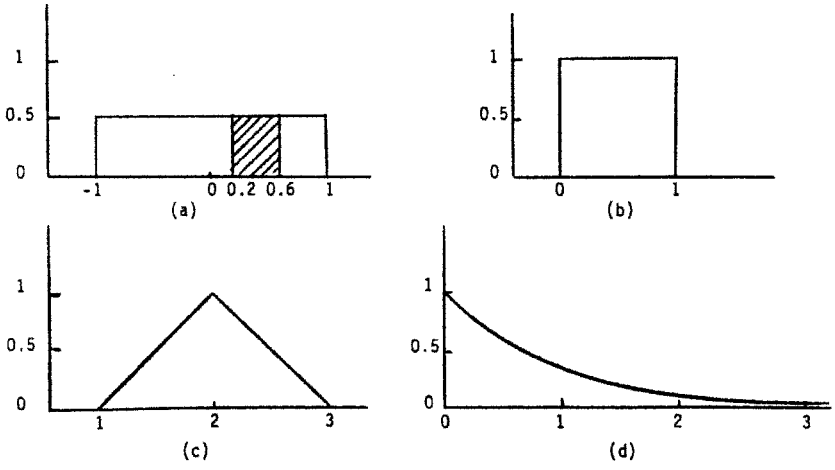


Figure 4.2 Examples of probability density functions. In each case, the area under the curve is equal to 1.

density, and Figure 4.2(d) an exponential density. The latter curve is defined over the entire positive axis. (It requires calculus to show that the area under this curve is 1.) The probability that a continuous random variable takes on a value in a specified interval is equal to the area over the interval. For example, the probability that the random variable in Figure 4.2(a) falls in the interval 0.2–0.6 is equal to the area over the interval. This is, $(0.6 - 0.2)(0.5) = 0.20$, so that we expect 20% of values of this random variable to fall in this interval. One of the most important probability density function is the normal distribution; it is discussed in detail in Section 4.4.

How can we talk about a random sample of observations of a continuous variable? The simplest way is to consider the drawing of an observation as a trial and the probability of observing an arbitrary (but specified) value or smaller of the random variable. Definition 4.3 can then be applied.

Before turning to the normal distribution, we introduce the concept of averages of random variables. In Section 3.4.2, we discussed the average of a discrete variable based on the empirical relative frequency distribution. The average of a discrete variable Y with values $y_1, y_2, \ldots, y_k$ occurring with relative frequencies $p_1, p_2, \ldots, p_k$, respectively, was shown to be

$$\overline{y} = \sum py$$

(We omit the subscripts since it is clear that we are summing over all the values.) Now, if Y is a *random* variable and $p_1, p_2, \ldots, p_k$ are the *probabilities* of occurrence of the values $y_1, y_2, \ldots, y_k$, we give the quantity $\sum py$ a special name:

Definition 4.11. The *expected value of a discrete random variable* Y, denoted by $E(Y)$, is

$$E(Y) = \sum py$$

where $p_1, \ldots, p_k$ are the probabilities of occurrence of the k possible values $y_1, \ldots, y_k$ of Y. The quantity $E(Y)$ is usually denoted by μ.

To calculate the expected value for the data of Table 3.12, the number of boys in families with eight children, we proceed as follows. Let $p_1, p_2, \ldots, p_k$ represent the probabilities $P[Y = 0], P[Y = 1], \ldots, P[Y = 8]$. Then the expected value is

$$\begin{aligned} E(Y) &= p_0 \times 0 + p_1 \times 1 + \cdots + p_8 \times 8 \\ &= (0.0040)(0) + (0.0277)(1) + (0.0993)(2) + \cdots + (0.0064)(8) \\ &= 4.1179 \\ &= 4.12 \text{ boys} \end{aligned}$$

This leads to the statement: "A family with eight children will have an average of 4.12 boys."

Corresponding to the sample variance, s^2, is the variance associated with a discrete random variable:

Definition 4.12. The *variance of a discrete random variable* Y is

$$E(Y - \mu)^2 = \sum p(y - \mu)^2$$

where $p_1, \ldots, p_k$ are the probabilities of occurrence of the k possible values $y_1, \ldots, y_k$ of Y.

The quantity $E(Y-\mu)^2$ is usually denoted by σ^2, where σ is the Greek lowercase letter *sigma*. For the example above, we calculate

$$\sigma^2 = (0.0040)(0-4.1179)^2 + (0.0277)(1-4.1179)^2 + \cdots + (0.0064)(1-4.1179)^2$$
$$= 2.0666$$

Several comments about $E(Y-\mu)^2$ can be made:

1. Computationally, it is equivalent to calculating the sample variance using a divisor of n rather than $n-1$, and probabilities rather than relative frequencies.
2. The square root of $\sigma^2(\sigma)$ is called the (population) *standard deviation* of the random variable.
3. It can be shown that $\sum p(y-\mu)^2 = \sum py^2 - \mu^2$. The quantity $\sum py^2$ is called the *second moment about the origin* and can be defined as the average value of the squares of Y or the expected value of Y^2. This can then be written as $E(Y^2)$, so that $E(Y-\mu)^2 = E(Y^2) - E^2(Y) = E(Y^2) - \mu^2$. See Note 4.9 for further development of the algebra of expectations.

What about the mean and variance of a continuous random variable? As before, we could divide the range of the continuous random variable into a number of intervals, calculate the associated probabilities of the variable, assume that the values are concentrated at the midpoints of the intervals, and proceed with Definitions 4.8 and 4.9. This is precisely what is done with one additional step: The intervals are made narrower and narrower. The mean is then the limit of a sequence of means calculated in this way, and similarly the variance. In these few sentences we have crudely summarized the mathematical process known as *integration*. We will only state the results of such processes but will not actually derive or demonstrate them. For the densities presented in Figure 4.2, the following results can be stated:

Figure	Name	μ	σ^2
4.2(a)	Uniform on $(-1, 1)$	0	1/3
4.2(b)	Uniform on (0, 1)	1/2	1/12
4.2(c)	Triangular on (1, 3)	2	1/6
4.2(d)	Exponential	1	1

The first three densities in Figure 4.2 are examples of *symmetric* densities. A symmetric density always has equality of mean and median. The exponential density is not symmetric; it is "skewed to the right." Such a density has a mean that is larger than the median; for Figure 4.2(d), the median is about 0.69.

It is useful at times to state the functional form for the density. If Y is the random variable, then for a value $Y = y$, the height of the density is given by $f(y)$. The densities in Figure 4.2 have the functional forms shown in Table 4.2. The letter e in $f(y) = e^{-y}$ is the base of the natural logarithms. The symbol ∞ stands for positive infinity.

4.4 NORMAL DISTRIBUTIONS

Statistically, a *population* is the set of all possible values of a variable; random selection of objects of the population makes the variable a random variable and the population is described completely (*modeled*) if the probability function or the probability density function is specified.

Table 4.2 Densities in Figure 4.2

Figure	Name of Density	Function	Range of Y
4.2(a)	Uniform on $(-1, 1)$	$f(y) = 0.5$	$(-1, 1)$
		$f(y) = 0$	elsewhere
4.2(b)	Uniform on (0, 1)	$f(y) = 1$	(0, 1)
		$f(y) = 0$	elsewhere
4.2(c)	Triangular on (1,3)	$f(y) = y - 1$	(1, 2)
		$f(y) = 3 - y$	(2, 3)
		$f(y) = 0$	elsewhere
4.2(d)	Exponential	$f(y) = e^{-y}$	$(0, \infty)$
		$f(y) = 0$	elsewhere

A statistical challenge is to find models of populations that use a few parameters (say, two or three), yet have wide applicability to real data. The *normal* or *Gaussian distribution* is one such statistical model.

The term *Gaussian* refers to Carl Friedrich Gauss, who developed and applied this model. The term *normal* appears to have been coined by Francis Galton. It is important to remember that there is nothing normal or abnormal about the normal distribution! A given data set may or may not be modeled adequately by the normal distribution. However, the normal distribution often proves to be a satisfactory model for data sets. The first and most important reason is that it "works," as will be indicated below. Second, there is a mathematical reason suggesting that a Gaussian distribution may adequately represent many data sets—the famous central limit theorem discussed in Section 4.5. Finally, there is a matter of practicality. The statistical theory and methods associated with the normal distribution work in a nice fashion and have many desirable mathematical properties. But no matter how convenient the theory, the assumptions that a data set is modeled adequately by a normal curve should be verified when looking at a particular data set. One such method is presented in Section 4.4.3.

4.4.1 Examples of Data That Might Be Modeled by a Normal Distribution

The first example is taken from a paper by Golubjatnikov et al. [1972]. Figure 4.3 shows serum cholesterol levels of Mexican and Wisconsin children in two different age groups. In each case

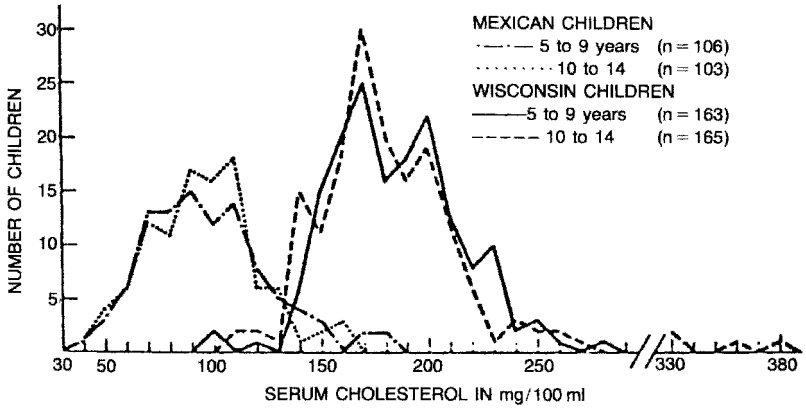


Figure 4.3 Distribution of serum cholesterol levels in Mexican and Wisconsin school children. (Data from Golubjatnikov et al. [1972].)

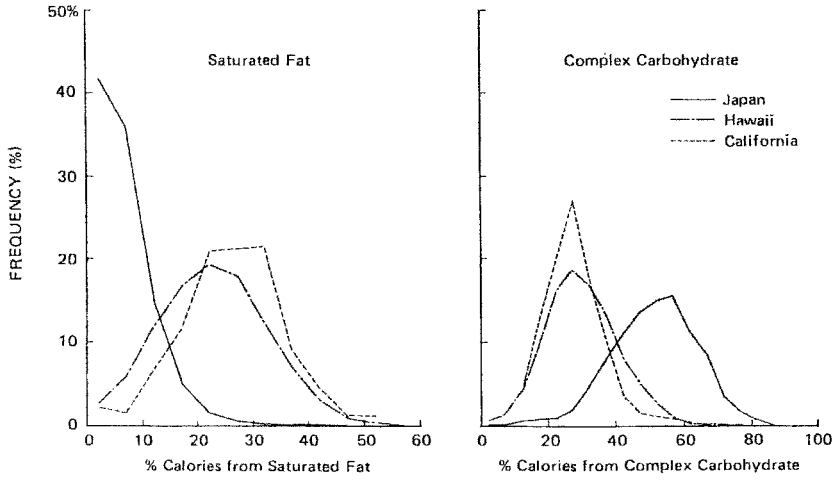


Figure 4.4 Frequency distribution of dietary saturated fat and dietary complex carbohydrate intake. (Data from Kato et al. [1973].)

there is considerable fluctuation in the graphs, probably due to the small numbers of people considered. However, it might be possible to model such data with a normal curve. Note that there seem to be possibly too many values in the right tail to model the data by a normal curve since normal curves are symmetric about their center point.

Figure 4.4 deals with epidemiologic studies of coronary heart disease and stroke in Japanese men living in Japan, Hawaii, and California. The curves present the frequency distribution of the percentage of calories from saturated fat and from complex carbohydrate in the three groups of men. Such percentages necessarily lie on the interval from 0 to 100. For the Hawaiian and Californian men with regard to saturated fat, the bell-shaped curve might be a reasonable model. Note, however, that for Japanese men, with a very low percentage of the diet from saturated fat, a bell-shaped curve would obviously be inappropriate.

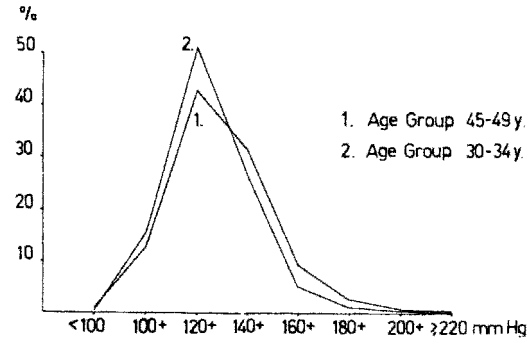
A third example from Kesteloot and van Houte [1973] examines blood pressure measurements on 42,000 members of the Belgian army and territorial police. Figure 4.5 gives two different age groups. Again, particularly in the graphs of the diastolic pressures, it appears that a bell-shaped curve might not be a bad model.

Another example of data that do not appear to be modeled very well by a symmetric bell-shaped curve is from a paper by Hagerup et al. [1972] dealing with serum cholesterol, serum triglyceride, and ABO blood groups in a population of 50-year-old Danish men and women. Figure 4.6 shows the distribution of serum triglycerides. There is a notable asymmetry to the distribution, there being too many values to the right of the peak of the distribution as opposed to the left.

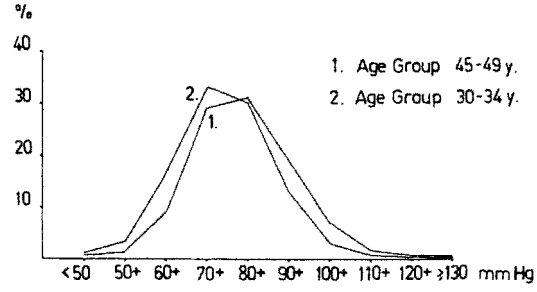
A final example of data that are not normally distributed are the 2-hour plasma glucose levels (mg per 100 mL) in Pima Indians. The data in Figure 4.7 are the plasma glucose levels for male Pima Indians for each decade of age. The data become clearly bimodal (two modes) with increasing decade of age. Note also that the overall curve is shifting to the right with increasing decade: The first mode shifts from approximately 100 mg per 100 mL in the 5- to 14-year decade to about 170 mg per 100 mL in the 65- to 74-year decade.

4.4.2 Calculating Areas under the Normal Curve

A normal distribution is specified completely by its mean, μ, and standard deviation, σ. Figure 4.8 illustrates some normal distributions with specific means and standard deviations. Note that two



Distribution of SBP according to age. (Distribution is slightly skewed towards the higher values.)



Distribution of DBP according to age. (Distribution is slightly skewed towards the higher values.)

Figure 4.5 Distributions of systolic and diastolic blood pressures according to age. (Data from Kesteloot and van Houte [1973].)

normal distributions with the same standard deviation but different means have the same shape and are merely shifted; similarly, two normal distributions with the same means but different standard deviations are centered in the same place but have different shapes. Consequently, μ is called a *location parameter* and σ a *shape parameter*.

The *standard deviation* is the distance from the mean to the point of inflection of the curve. This is the point where a tangent to the curve switches from being over the curve to under the curve.

As with any density, the probability that a normally distributed random variable takes on a value in a specified interval is equal to the area over the interval. So we need to be able to calculate these areas in order to know the desired probabilities. Unfortunately, there is no simple algebraic formula that gives these areas, so tables must be used (see Note 4.15). Fortunately, we need only one table. For any normal distribution, we can calculate areas under its curve using a table for a normal distribution with mean $\mu = 0$ and standard deviation $\sigma = 1$ by expressing the variable in the number of standard deviations from the mean. Using algebraic notation, we get the following:

Definition 4.13. For a random variable Y with mean μ and standard deviation σ, the associated *standard score, Z*, is

$$Z = \frac{Y - \mu}{\sigma}$$

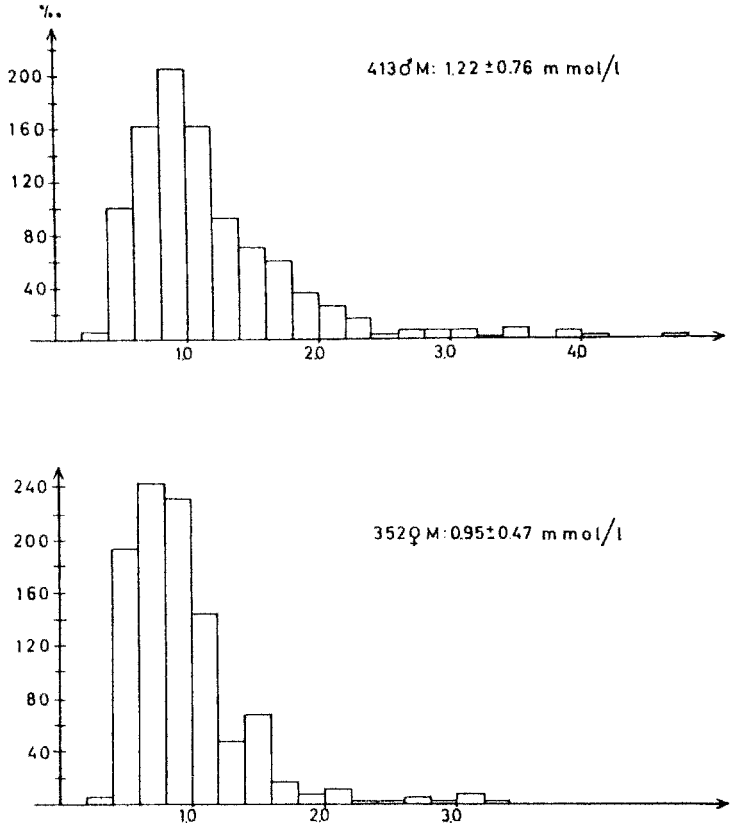


Figure 4.6 Serum triglycerides: 50-year survey in Glostrup. Fasting blood samples were drawn for determination of serum triglyceride by the method of Laurell. (Data from Hagerup et al. [1972].)

Given values for μ and σ, we can go from the "Y scale" to the "Z scale," and vice versa. Algebraically, we can solve for Y and get $Y = \mu + \sigma Z$. This is also the procedure that is used to get from degrees Celsius (°C) to degrees Fahrenheit (°F). The relationship is

$$^{\circ}\text{C} = \frac{^{\circ}\text{F} - 32}{1.8}$$

Similarly,

$$^{\circ}\text{F} = 32 + 1.8 \times {}^{\circ}\text{C}$$

Definition 4.14. A *standard normal distribution* is a normal distribution with mean $\mu = 0$ and standard deviation $\sigma = 1$.

Table A.1 in the Appendix gives standard normal probabilities. The table lists the area to the left of the stated value of the standard normal deviate under the columns headed "cum. dist." For example, the area to the left of $Z = 0.10$ is 0.5398, as shown in Figure 4.9.

In words, 53.98% of normally distributed observations have values less than 0.10 standard deviation above the mean. We use the notation $P[Z \leq 0.10] = 0.5398$, or in general, $P[Z \leq z]$. To indicate a value of Z associated with a specified area, p, to its left, we will use a subscript on the value Z_p. For example, $P[Z \leq z_{0.1}] = 0.10$; that is, we want that value of Z such that

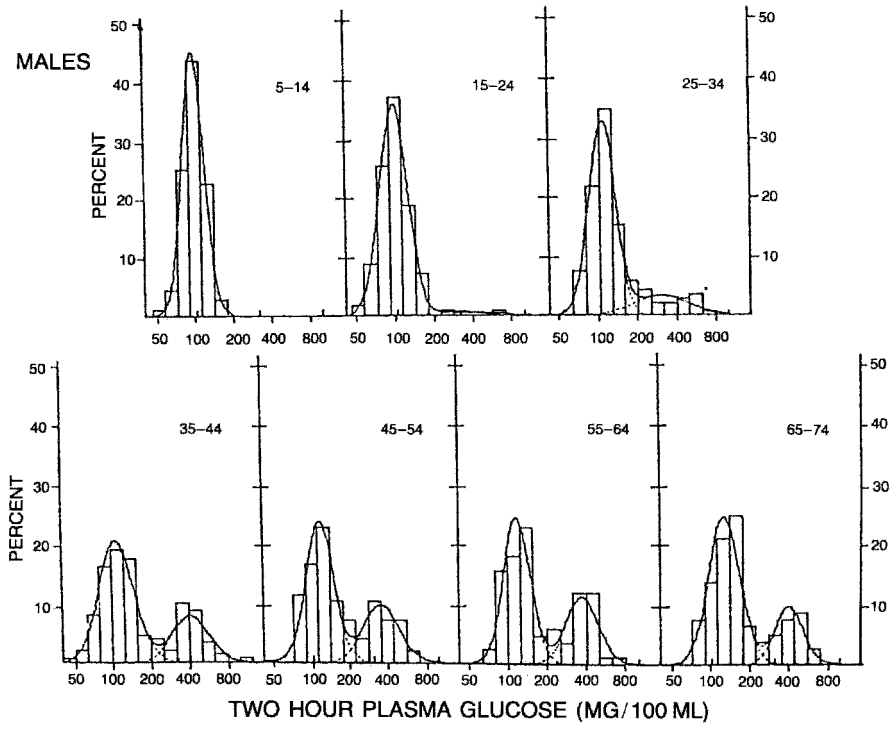


Figure 4.7 Distribution of 2-hour plasma glucose levels (mg/100 mL) in male Pima Indians by decade. (Data from Rushforth et al. [1971].)

0.1 of the area is to its left (call it $z_{0.1}$), or equivalently, such that a proportion 0.1 of Z values are less than or equal to $z_{0.1}$. By symmetry, we note that $z_{1-p} = -z_p$.

Since the total area under the curve is 1, we can get areas in the right-hand tail by subtraction. Formally,

$$P[Z > z] = 1 - P[Z \leq z]$$

In terms of the example above, $P[Z > 0.10] = 1 - 0.5398 = 0.4602$. By symmetry, areas to the left of $Z = 0$ can also be obtained. For example, $P[Z \leq -0.10] = P[Z > 0.10] = 0.4602$. These values are indicated in Figure 4.10.

We now illustrate use of the standard normal table with two word problems. When calculating areas under the normal curve, you will find it helpful to draw a rough normal curve and shade in the required area.

Example 4.4. Suppose that IQ is normally distributed with mean $\mu = 100$ and standard deviation $\sigma = 15$. A person with IQ > 115 has a *high IQ*. What proportion of the population has high IQs? The area required is shown in Figure 4.11. It is clear that IQ = 115 is one standard deviation above the mean, so the statement $P[IQ > 115]$ is equivalent to $P[Z > 1]$. This can be obtained from Table A.1 using the relationship $P[Z > 1] = 1 - P[Z \leq 1] = 1 - 0.8413 = 0.1587$. Thus, 15.87% of the population has a high IQ. By the same token, if an IQ below 85 is labeled *low IQ*, 15.87% of the population has a low IQ.

Example 4.5. Consider the serum cholesterol levels of Wisconsin children as pictured in Figure 4.3. Suppose that the population mean is 175 mg per 100 mL and the population standard

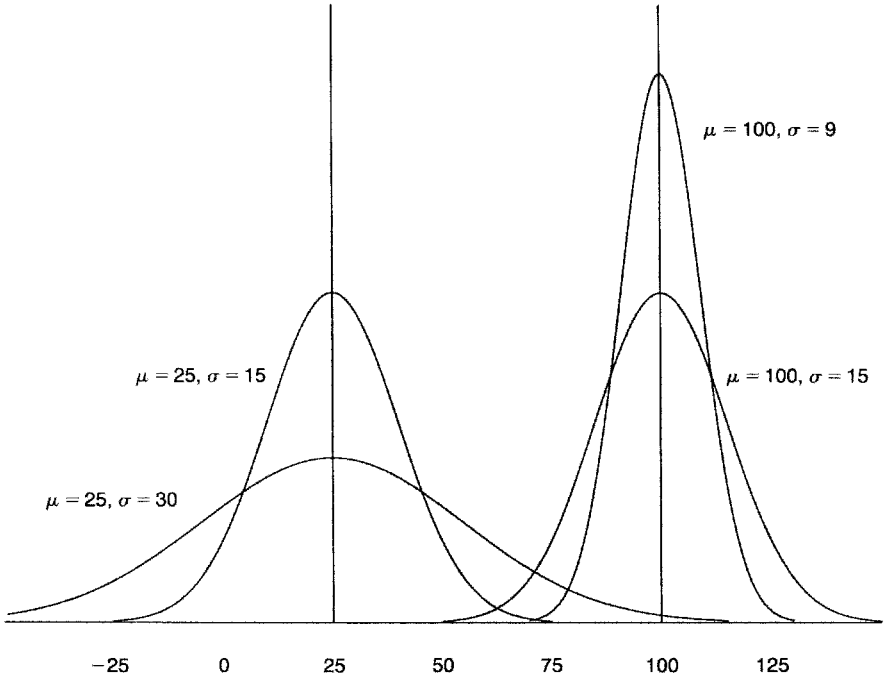


Figure 4.8 Examples of normal distributions.

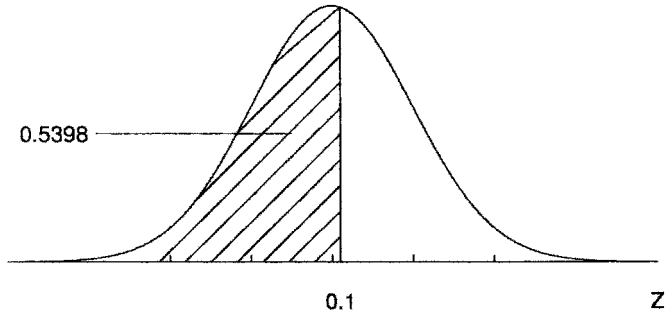


Figure 4.9 Area to the left of $Z = 0.10$ is 0.5398.

deviation is 30 mg per 100 mL. Suppose that a "normal cholesterol value" is taken to be a value within two standard deviations of the mean. What are the *normal limits*, and what proportion of Wisconsin children will be within normal limits?

We want the area within ± 2 standard deviations of the mean (Figure 4.12). This can be expressed as $P[-2 \leq Z \leq +2]$. By symmetry and the property that the area under the normal curve is 1.0, we can express this as

$$P[-2 \leq Z \leq 2] = 1 - 2P[Z > 2]$$

(You should sketch this situation, to convince yourself.) From Table A.1, $P[Z \leq 2] = 0.9772$, so that $P[Z > 2] = 1 - 0.9772 = 0.0228$. (Note that this value is computed for you in the

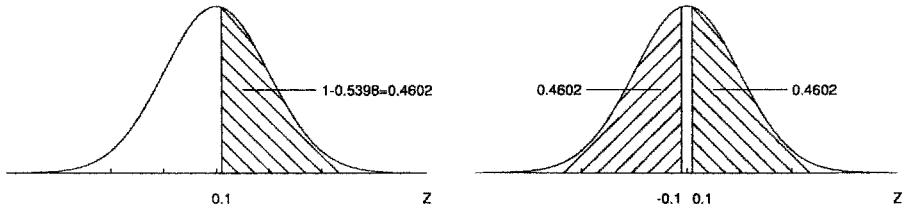


Figure 4.10 $P[Z \leq -0.10] = P[Z > 0.10] = 0.4602$.

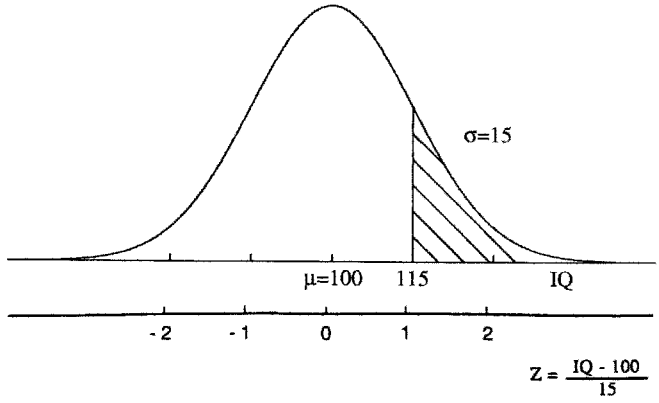


Figure 4.11 Proportion of the population with high IQs.

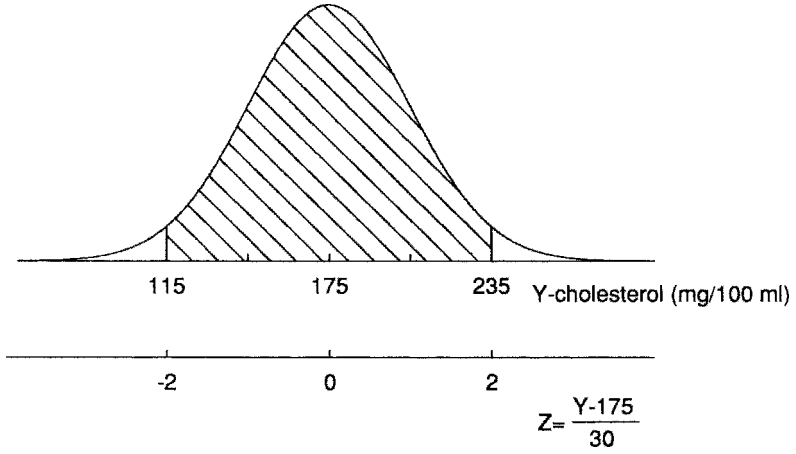


Figure 4.12 Area with ±2 standard deviations of the mean.

column labeled "one-sided.") The desired probability is

$$P[-2 \leq Z \leq 2] = 1 - 2(0.0228)$$
$$= 0.9544$$

In words, 95.44% of the population of Wisconsin schoolchildren have cholesterol values within normal limits.

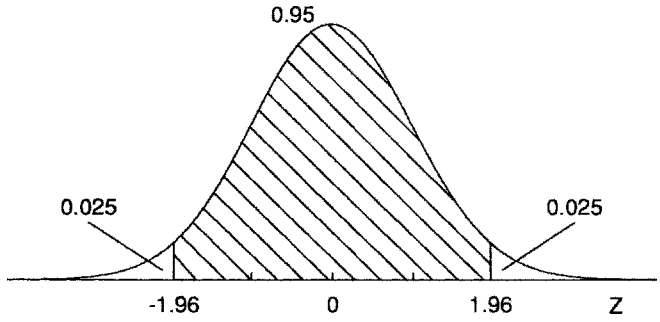


Figure 4.13 Ninety-five percent of normally distributed observations are within ±1.96 standard deviations of the mean.

Suppose that we change the question: Instead of defining normal limits and calculating the proportion within these limits, we define the limits such that, say, 95% of the population has cholesterol values within the stated limits. Before, we went from cholesterol level to Z-value to area; now we want to go from area to Z-value to cholesterol values. In this case, Table A.2 will be useful. Again, we begin with an illustration, Figure 4.13. From Table A.2 we get $P[Z > 1.96] = 0.025$, so that $P[-1.96 \leq Z \leq 1.96] = 0.95$; in words, 95% of normally distributed observations are within ±1.96 standard deviations of the mean. Or, translated to cholesterol values by the formula, $Y = 175 + 30Z$. For $Z = 1.96$, $Y = 175 + (30)(1.96) = 233.8 \doteq 234$, and for $Z = -1.96$, $Y = 175 + (30)(-1.96) = 116.2 \doteq 116$. On the basis of the model, 95% of cholesterol values of Wisconsin children are between 116 and 234 mg per 100 mL. If the mean and standard deviation of cholesterol values of Wisconsin children are 175 and 30 mg per 100 mL, respectively, the 95% limits (116, 234) are called 95% *tolerance limits*.

Often, it is useful to know the range of normal values of a substance (variable) in a normal population. A laboratory test can then be carried out to determine whether a subject's values are high, low, or within normal limits.

Example 4.6. An article by Zervas et al. [1970] provides a list of normal values for more than 150 substances ranging from ammonia to vitamin B_{12}. These values have been reprinted in *The Merck Manual of Diagnosis and Therapy* [Berkow, 1999]. The term *normal values* does not imply that variables are normally distributed (i.e., follow a Gaussian or bell-shaped curve). A paper by Elveback et al. [1970] already indicated that of seven common substances (calcium, phosphate, total protein, albumin, urea, magnesium, and alkaline phosphatase), only albumin values can be summarized adequately by a normal distribution. All the other substances had distributions of values that were skewed. The authors (correctly) conclude that "the distributions of values in healthy persons *cannot* be assumed to be normal." Admittedly, this leaves an unsatisfactory situation: What, then, do we mean by *normal limits*? What proportion of normal values will fall outside the normal limits as the result of random variation? None of these—and other—critical questions can now be answered, because a statistical model is not available. But that appears to be the best we can do at this point; as the authors point out, "good limits are hard to get, and bad limits hard to change."

4.4.3 Quantile–Quantile Plots

How can we know whether the normal distribution model fits a particular set of data? There are many tests for normality, some graphical, some numerical. In this section we discuss a simple graphical test, the *quantile–quantile* (QQ) *plot*. In this approach we plot the quantiles of the data distribution observed against the expected quantiles for the normal distribution. The resulting graph is a version of the cumulative frequency distribution but with distorted axes

chosen so that a normal distribution would give a straight line. In precomputer days, quantile–quantile plots for the normal distribution were obtained by drawing the empirical cumulative frequency distribution on special *normal probability paper*, but it is now possible to obtain quantile–quantile plots for many different distributions from the computer.

A famous book by Galton [1889] contains data on the stature of parents and their adult children. Table 4.3 gives the frequency distributions of heights of 928 adult children. The

Table 4.3 Frequency Distribution of Stature of 928 Adult Children

Endpoint (in.)	Frequency	Cumulative Frequency	Cumulative Percentage
61.7[a]	5	5	0.5
62.2	7	12	1.3
63.2	32	44	4.7
64.2	59	103	11.1
65.2	48	151	16.3
66.2	117	268	28.9
67.2	138	406	43.8
68.2	120	526	56.7
69.2	167	693	74.7
70.2	99	792	85.3
71.2	64	856	92.2
72.2	41	897	96.7
73.2	17	914	98.5
73.7[a]	14	928	100

Source: Galton [1889].

[a] Assumed endpoint.

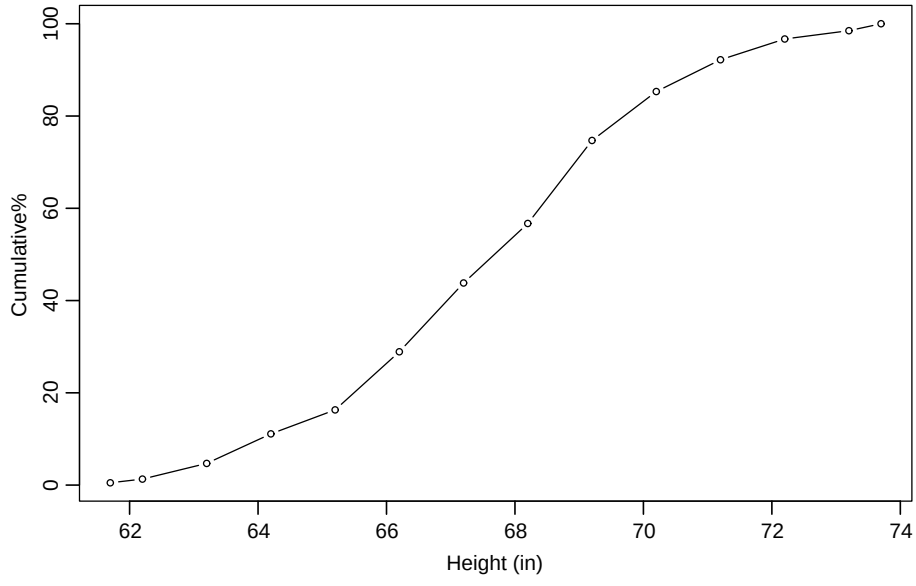


Figure 4.14 Empirical cumulative frequency polygon of heights of 928 adult children. (Data from Galton [1889].)

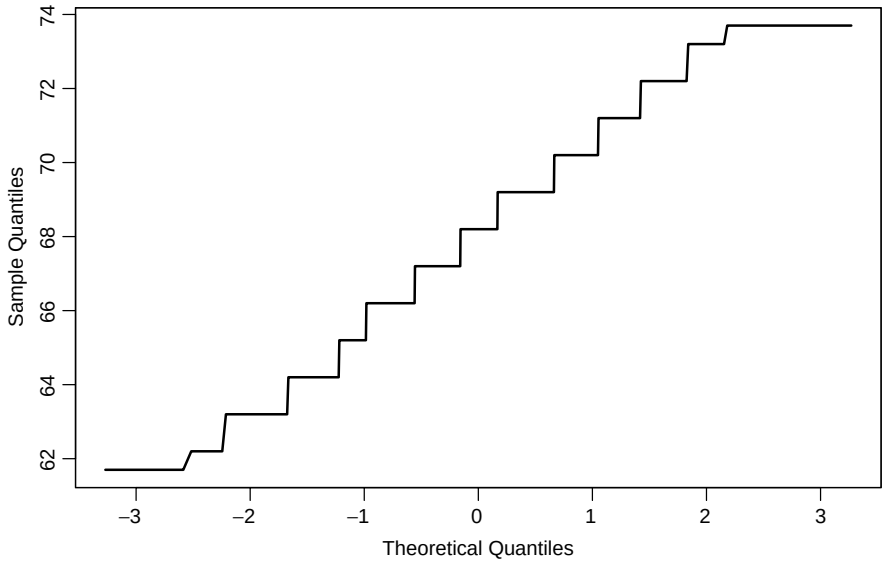


Figure 4.15 Quantile–quantile plot of heights of 928 adult children. (Data from Galton [1889].)

cumulative percentages plotted against the endpoints of the intervals in Figure 4.14 produce the usual sigmoid-shaped curve.

These data are now plotted on normal probability paper in Figure 4.15. The vertical scale has been stretched near 0% and 100% in such a way that data from a normal distribution should fall on a straight line. Clearly, the data are consistent with a normal distribution model.

4.5 SAMPLING DISTRIBUTIONS

4.5.1 Statistics Are Random Variables

Consider a large multicenter collaborative study of the effectiveness of a new cancer therapy. A great deal of care is taken to standardize the treatment from center to center, but it is obvious that the average survival time on the new therapy (or increased survival time if compared to a standard treatment) will vary from center to center. This is an illustration of a basic statistical fact: Sample statistics vary from sample to sample. The key idea is that a statistic associated with a random sample is a random variable. What we want to do in this section is to relate the variability of a statistic based on a random sample to the variability of the random variable on which the sample is based.

Definition 4.15. The probability (density) function of a statistic is called the *sampling distribution of the statistic*.

What are some of the characteristics of the sampling distribution? In this section we state some results about the sample mean. In Section 4.8 some properties of the sampling distribution of the sample variance are discussed.

4.5.2 Properties of Sampling Distribution

Result 4.1. If a random variable Y has population mean μ and population variance σ^2, the sampling distribution of sample means (of samples of size n) has population mean μ and

population variance σ^2/n. Note that this result does not assume normality of the "parent" population.

Definition 4.16. The standard deviation of the sampling distribution is called the *standard error*.

Example 4.7. Suppose that IQ is a random variable with mean $\mu = 100$ and standard deviation $\sigma = 15$. Now consider the average IQ of classes of 25 students. What are the population mean and variance of these class averages? By Result 4.1, the class averages have population mean $\mu = 100$ and population variance $\sigma^2/n = 15^2/25 = 9$. Or, the standard error is $\sqrt{\sigma^2/n} = \sqrt{15^2/25} = \sqrt{9} = 3$.

To summarize:

	Population		
	Mean	**Variance**	**$\sqrt{\text{Variance}}$**
Single observation, Y	100	$15^2 = 225$	$15 = \sigma$
Mean of 25 observations, $\overline{Y}$	100	$15^2/25 = 9$	$3 = \sigma/\sqrt{n}$

The standard error of the sampling distribution of the sample mean $\overline{Y}$ is indicated by $\sigma_{\overline{Y}}$ to distinguish it from the standard deviation, σ, associated with the random variable Y. It is instructive to contemplate the formula for the standard error, $\sigma/\sqrt{n}$. This formula makes clear that a reduction in variability by, say, a factor of 2 requires a fourfold increase in sample size. Consider Example 4.7. How large must a class be to reduce the standard error from 3 to 1.5? We want $\sigma/\sqrt{n} = 1.5$. Given that $\sigma = 15$ and solving for n, we get $n = 100$. This is a fourfold increase in class size, from 25 to 100. In general, if we want to reduce the standard error by a factor of k, we must increase the sample size by a factor of k^2. This suggests that if a study consists of, say, 100 observations and with a great deal of additional effort (out of proportion to the effort of getting the 100 observations) another 10 observations can be obtained, the additional 10 may not be worth the effort.

The standard error based on 100 observations is $\sigma/\sqrt{100}$. The ratio of these standard errors is

$$\frac{\sigma/\sqrt{100}}{\sigma/\sqrt{110}} = \frac{\sqrt{100}}{\sqrt{110}} = 0.95$$

Hence a 10% increase in sample size produces only a 5% increase in precision. Of course, precision is not the only criterion we are interested in; if the 110 observations are randomly selected persons to be interviewed, it may be that the last 10 are very hard to locate or difficult to persuade to take part in the study, and not including them may introduce a serious *bias*. But with respect to *precision* there is not much difference between means based on 100 observations and means based on 110 observations (see Note 4.11).

4.5.3 Central Limit Theorem

Although Result 4.1 gives some characteristics of the sampling distribution, it does not permit us to calculate probabilities, because we do not know the form of the sampling distribution. To be able to do this, we need the following:

Result 4.2. If Y is normally distributed with mean μ and variance σ^2, then $\overline{Y}$, based on a random sample of n observations, is *normally distributed* with mean μ and variance σ^2/n.

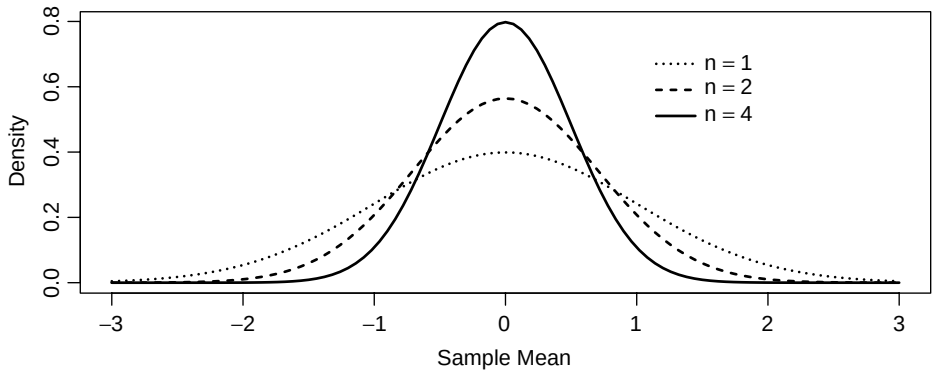


Figure 4.16 Three sampling distributions for means of random samples of size 1, 2, and 4 from a $N(0, 1)$ population.

Result 4.2 basically states that if Y is normally distributed, then $\overline{Y}$, the mean of a random sample, is normally distributed. Result 4.1 then specifies the mean and variance of the sampling distribution. Result 4.2 implies that as the sample size increases, the (normal) distribution of the sample mean becomes more and more "pinched." Figure 4.16 shows three sampling distributions for means of random samples of size 1, 2, and 4.

What is the probability that the average IQ of a class of 25 students exceeds 106? By Result 4.2, $\overline{Y}$, the average of 25 IQs, is normally distributed with mean $\mu = 100$ and standard error $\sigma/\sqrt{n} = 15/\sqrt{25} = 3$. Hence the probability that $\overline{Y} > 106$ can be calculated as

$$\begin{aligned} P[\overline{Y} \geq 106] &= P\left[Z \geq \frac{106 - 100}{3}\right] \\ &= P[Z \geq 2] \\ &= 1 - 0.9772 \\ &= 0.0228 \end{aligned}$$

So approximately 2% of average IQs of classes of 25 students will exceed 106. This can be compared with the probability that a single person's IQ exceeds 106:

$$P[Y > 106] = P\left[Z > \frac{6}{15}\right] = P[Z > 0.4] = 0.3446$$

The final result we want to state is known as the *central limit theorem.*

Result 4.3. If a random variable Y has population mean μ and population variance σ^2, the sample mean $\overline{Y}$, based on n observations, is approximately normally distributed with mean μ and variance σ^2/n, for sufficiently large n.

This is a remarkable result and the most important reason for the central role of the normal distribution in statistics. What this states basically is that means of random samples from *any* distribution (with mean and variance) will tend to be normally distributed as the sample size becomes sufficiently large. How large is "large"? Consider the distributions of Figure 4.2. Samples of six or more from the first three distributions will have means that are virtually normally

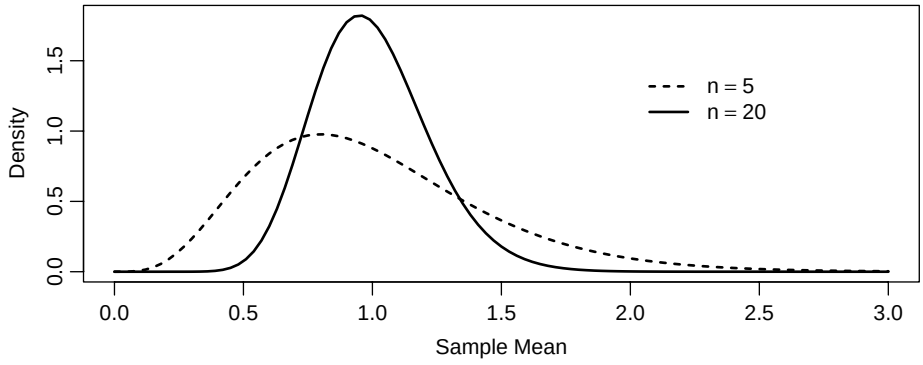


Figure 4.17 Sampling distributions of means of 5 and 20 observations when the parent distribution is exponential.

distributed. The fourth distribution will take somewhat larger samples before approximate normality is obtained; n must be around 25 or 30. Figure 4.17 is a more skewed figure that shows the sampling distributions of means of samples of various sizes drawn from Figure 4.2(d).

The central limit theorem provides some reassurance when we are not certain whether observations are normally distributed. The means of reasonably sized samples will have a distribution that is approximately normal. So inference procedures based on the sample means can often use the normal distribution. But you must be careful not to impute normality to the original observations.

4.6 INFERENCE ABOUT THE MEAN OF A POPULATION

4.6.1 Point and Interval Estimates

In this section we discuss inference about the mean of a population when the population variance is known. The assumption may seem artificial, but sometimes this situation will occur. For example, it may be that a new treatment alters the level of a response variable but not its variability, so that the variability can be assumed to be known from previous experiments. (In Section 4.8 we discuss a method for comparing the variability of an experiment with previous established variability; in Chapter 5 the problem of inference when both population mean and variance are unknown is considered.)

To put the problem more formally, we have a random variable Y with unknown population mean μ. A random sample of size n is taken and inferences about μ are to be made on the basis of the sample. We assume that the population variance is known; denote it by σ^2. Normality will also be assumed; even when the population is not normal, we may be able to appeal to the central limit theorem.

A "natural" estimate of the population mean μ is the sample mean $\overline{Y}$. It is a natural estimate of μ because we know that $\overline{Y}$ is normally distributed with the same mean, μ, and variance σ^2/n. Even if Y is not normal, $\overline{Y}$ is approximately normal on the basis of the central limit theorem. The statistic $\overline{Y}$ is called a *point estimate* since we estimate the parameter μ by a single value or point.

Now the question arises: How precise is the estimate? How can we distinguish between two samples of, say, 25 and 100 observations? Both may give the same—or approximately the same—sample mean, but we know that the mean based on the 100 observations is more accurate, that is, has a smaller standard error. One possible way of summarizing this information is to give the sample mean and its standard error. This would be useful for *comparing* two samples. But this does not seem to be a useful approach in considering one sample and its information about

the parameter. To use the information in the sample, we set up an *interval* estimate as follows: Consider the quantity $\mu \pm (1.96)\sigma/\sqrt{n}$. It describes the spread of sample means; in particular, 95% of means of samples of size n will fall in the interval $[\mu - 1.96\sigma/\sqrt{n}, \mu + 1.96\sigma/\sqrt{n}]$. The interval has the property that as n increases, the width decreases (refer to Section 4.5 for further discussion). Suppose that we now replace μ by its point estimate, $\overline{Y}$. How can we interpret the resulting interval? Since the sample mean, $\overline{Y}$, varies from sample to sample, it cannot mean that 95% of the sample means will fall in the interval for a specific sample mean. The interpretation is that the probability is 0.95 that the interval *straddles* the population mean. Such an interval is referred to as a *95% confidence interval* for the population mean, μ. We now formalize this definition.

Definition 4.17. A $100(1-\alpha)\%$ *confidence interval* for the mean μ of a normal population (with variance known) based on a random sample of size n is

$$\overline{Y} \pm z_{1-\alpha/2}\frac{\sigma}{\sqrt{n}}$$

where $z_{1-\alpha/2}$ is the value of the standard normal deviate such that $100(1-\alpha)\%$ of the area falls within $\pm z_{1-\alpha/2}$.

Strictly speaking, we should write

$$\left(\overline{Y} + z_{\alpha/2}\frac{\sigma}{\sqrt{n}}, \overline{Y} + z_{1-\alpha/2}\frac{\sigma}{\sqrt{n}}\right)$$

but by symmetry, $z_{\alpha/2} = -z_{1-\alpha/2}$, so that it is quicker to use the expression above.

Example 4.8. In Section 3.3.1 we discussed the age at death of 78 cases of crib death (SIDS) occurring in King County, Washington, in 1976–1977. Birth certificates were obtained for these cases and birthweights were tabulated. Let Y = birthweight in grams. Then, for these 78 cases, $\overline{Y} = 2993.6 = 2994$ g. From a listing of all the birthweights, it is known that the standard deviation of birthweight is about 800 g (i.e., $\sigma = 800$ g). A 95% confidence interval for the mean birthweight of SIDS cases is calculated to be

$$2994 \pm (1.96)\left(\frac{800}{\sqrt{78}}\right) \quad \text{or} \quad 2994 \pm (1.96)(90.6) \quad \text{or} \quad 2994 \pm 178$$

producing a lower limit of 2816 g and an upper limit of 3172 g. Thus, on the basis of these data, we are 95% confident that we have straddled the population mean, μ, of birthweight of SIDS infants by the interval (2816, 3172).

Suppose that we had wanted to be more confident: say, a level of 99%. The value of Z now becomes 2.58 (from Table A.2), and the corresponding limits are $2994 \pm (2.58)(800/\sqrt{78})$, or (2760, 3228). The width of the 99% confidence interval is greater than that of the 95% confidence interval (468 g vs. 356 g), the price we paid for being more sure that we have straddled the population mean.

Several comments should be made about confidence intervals:

1. Since the population mean μ is fixed, it is not correct to say that the probability is $1-\alpha$ that μ is in the confidence interval *once it is computed*; that probability is zero or 1. Either the mean is in the interval and the probability is equal to 1, or the mean is not in the interval and the probability is zero.

2. We can increase our confidence that the interval straddles the population mean by decreasing α, hence increasing $Z_{1-\alpha/2}$. We can take values from Table A.2 to construct the following confidence levels:

Confidence Level	Z-Value
90%	1.64
95%	1.96
99%	2.58
99.9%	3.29

The effect of increasing the confidence level will be to increase the width of the confidence interval.

3. To decrease the width of the confidence interval, we can either decrease the confidence level or increase the sample size. The width of the interval is $2z_{1-\alpha/2}\sigma/\sqrt{n}$. For a fixed confidence level the width is essentially a function of $\sigma/\sqrt{n}$, the standard error of the mean. To decrease the width by a factor of, say, 2, the sample size must be increased by a factor of 4, analogous to the discussion in Section 4.5.2.
4. Confidence levels are usually taken to be 95% or 99%. These levels are a matter of convention; there are no theoretical reasons for choosing these values. A rough rule to keep in mind is that a 95% confidence interval is defined by the sample mean ± 2 standard errors (*not* standard deviations).

4.6.2 Hypothesis Testing

In estimation, we start with a sample statistic and make a statement about the population parameter: A confidence interval makes a probabilistic statement about straddling the population parameter. In hypothesis testing, we start by assuming a value for a parameter, and a probability statement is made about the value of the corresponding statistic. In this section, as in Section 4.6.1, we assume that the population variance is known and that we want to make inferences about the mean of a normal population on the basis of a sample mean. The basic strategy in hypothesis testing is to measure how far an observed statistic is from a hypothesized value of the parameter. If the distance is "great" (Figure 4.18) we would argue that the hypothesized parameter value is inconsistent with the data and we would be inclined to reject the hypothesis (we could be wrong, of course; rare events do happen).

To interpret the distance, we must take into account the basic variability (σ^2) of the observations and the size of the sample (n) on which the statistic is based. As a rough rule of thumb that is explained below, if the observed value of the statistic is more than two standard errors from the hypothesized parameter value, we question the truth of the hypothesis.

To continue Example 4.8, the mean birthweight of the 78 SIDS cases was 2994 g. The standard deviation σ_0 was assumed to be 800 g, and the standard error $\sigma/\sqrt{n} = 800/\sqrt{78} = 90.6$ g. One question that comes up in the study of SIDS is whether SIDS cases tend to have a different birthweight than the general population. For the general population, the average birthweight is about 3300 g. Is the *sample* mean value of 2994 g consistent with this value? Figure 4.19 shows that the distance between the two values is 306 g. The standard error is 90.6,

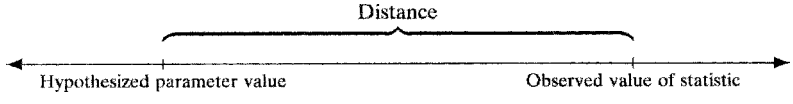


Figure 4.18 Great distance from a hypothesized value of a parameter.

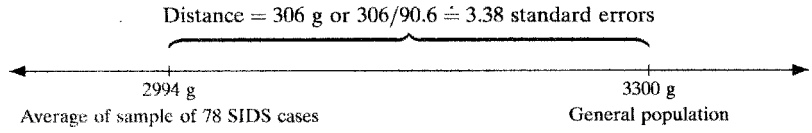


Figure 4.19 Distance between the two values is 306 g.

so the observed value is 306/90.6 = 3.38 standard errors from the hypothesized population mean. By the rule we stated, the distance is so great that we would conclude that the mean of the *sample* of SIDS births is inconsistent with the mean value in the general population. Hence, we would conclude that the SIDS births come from a population with mean birthweight somewhat less than that of the general population. (This raises more questions, of course: Are the gestational ages comparable? What about the racial composition? and so on.) The best estimate we have of the mean birthweight of the population of SIDS cases is the sample mean: in this case, 2994 g, about 300 g lower than that for the normal population.

Before introducing some standard hypothesis testing terminology, two additional points should be made:

1. We have expressed "distance" in terms of number of standard errors from the hypothesized parameter value. Equivalently, we can associate a tail probability with the observed value of the statistic. For the sampling situation described above, we know that the sample mean $\overline{Y}$ is normally distributed with standard error $\sigma/\sqrt{n}$. As Figure 4.20 indicates, the farther away the observed value of the statistic is from the hypothesized parameter value, the smaller the area (probability) in the tail. This tail probability is usually called the *p-value*. For example (using Table A.2), the area to the right of 1.96 standard errors is 0.025; the area to the right of 2.58 standard errors is 0.005. Conversely, if we specify the area, the number of standard errors will be determined.
2. Suppose that we planned before doing the statistical test that we would not question the hypothesized parameter value if the observed value of the statistic fell within, say, two standard errors of the parameter value. We could divide the sample space for the statistic (i.e., the real line) into three regions as shown in Figure 4.21. These regions could have been set up before the value of the statistic was observed. All that needs to be determined then is in which region the observed value of the statistic falls to determine if it is consistent with the hypothesized value.

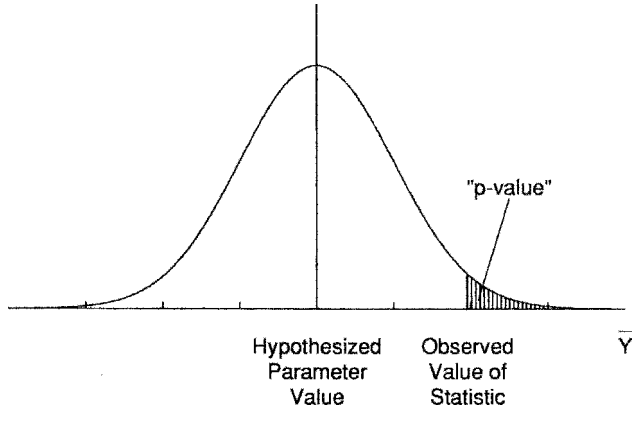


Figure 4.20 The farther away the observed value of a statistic from the hypothesized value of a parameter, the smaller the area in the tail.

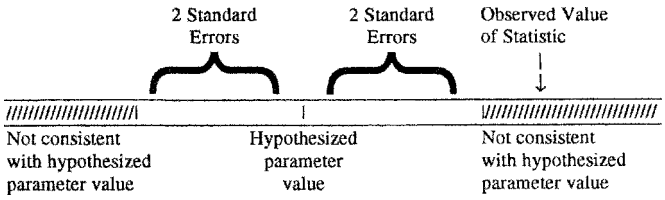


Figure 4.21 Sample space for the statistic.

We now formalize some of these concepts:

Definition 4.18. A *null hypothesis* specifies a hypothesized real value, or values, for a parameter (see Note 4.15 for further discussion).

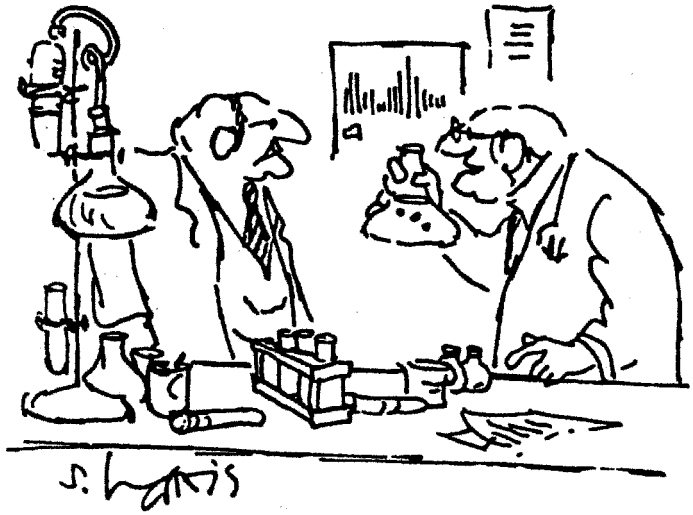
Definition 4.19. The *rejection region* consists of the set of values of a statistic for which the null hypothesis is rejected. The values of the boundaries of the region are called the *critical values*.

Definition 4.20. A *Type I error* occurs when the null hypothesis is rejected when, in fact, it is true. The *significance level* is the probability of a Type I error when the null hypothesis is true.

Definition 4.21. An *alternative hypothesis* specifies a real value or range of values for a parameter that will be considered when the null hypothesis is rejected.

Definition 4.22. A *Type II error* occurs when the null hypothesis is not rejected when it is false.

Definition 4.23. The *power of a test* is the probability of rejecting the null hypothesis when it is false.



"It may very well bring about immortality, but it will take forever to test it."

© 1976 by Sidney Harris — *American Scientist* Magazine

Cartoon 4.1 Testing some hypotheses can be tricky. (From *American Scientist*, March–April 1976.)

Definition 4.24. The *p-value* in a hypothesis testing situation is that value of p, $0 \leq p \leq 1$, such that for $\alpha > p$ the test rejects the null hypothesis at significance level α, and for $\alpha < p$ the test does not reject the null hypothesis. Intuitively, the p-value is the probability under the null hypothesis of observing a value as unlikely or more unlikely than the value of the test statistic. The p-value is a measure of the distance from the observed statistic to the value of the parameter specified by the null hypothesis.

Notation

1. The null hypothesis is denoted by H_0 the alternative hypothesis by H_A.
2. The probability of a Type I error is denoted by α, the probability of a Type II error by β. The power is then

$$\begin{aligned} \text{power} &= 1 - \text{probability of Type II error} \\ &= 1 - \beta \end{aligned}$$

Continuing Example 4.8, we can think of our assessment of the birthweight of SIDS babies as a type of decision problem illustrated in the following layout:

	State of Nature SIDS Birthweights	
Decision SIDS Birthweights	**Same as Normal**	**Not the Same**
Same as normal	Correct $(1 - \alpha)$	Type II error (β)
Not the same	Type I error (α)	Correct $(1 - \beta)$

This illustrates the two types of errors that can be made depending on our decision and the *state of nature*. The null hypothesis for this example can be written as

$$H_0 : \mu = 3300 \text{ g}$$

and the alternative hypothesis written as

$$H_A : \mu \neq 3300 \text{ g}$$

Suppose that we want to reject the null hypothesis when the sample mean $\overline{Y}$ is more than two standard errors from the H_0 value of 3300 g. The standard error is 90.6 g. The rejection region is then determined by $3300 \pm (2)(90.6)$ or 3300 ± 181.

We can then set up the hypothesis-testing framework as indicated in Figure 4.22. The rejection region consists of values to the left of 3119 g (i.e., $\mu - 2\sigma/\sqrt{n}$) and to the right of 3481 g (i.e., $\mu + 2\sigma/\sqrt{n}$). The observed value of the statistic, $\overline{Y} = 2994$ g, falls in the rejection region, and we therefore reject the null hypothesis that SIDS cases have the same mean birthweight as normal children. On the basis of the sample value observed, we conclude that SIDS babies tend to weigh less than normal babies.

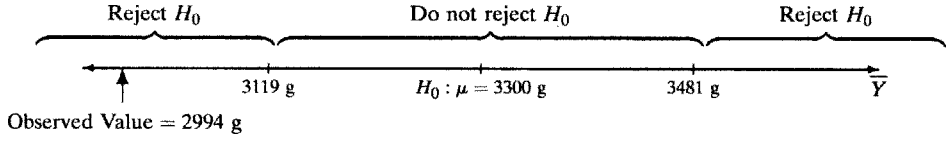


Figure 4.22 Hypothesis-testing framework for birthweight assessment.

The probability of a Type I error is the probability that the mean of a sample of 78 observations from a population with mean 3300 g is less than 3119 g or greater than 3481 g:

$$P[3119 \le \overline{Y} \le 3481] = P\left[\frac{3119 - 3300}{90.6} \le Z \le \frac{3481 - 3300}{90.6}\right]$$
$$= P[-2 \le Z \le +2]$$

where Z is a standard normal deviate.
From Table A.1,

$$P[Z \le 2] = 0.9772$$

so that

$$1 - P[-2 \le Z \le 2] = (2)(0.0228) = 0.0456$$

the probability of a Type I error. The probability is 0.0455 from the two-sided p-value of Table A.1. The difference relates to rounding.

The probability of a Type II error can be computed when a value for the parameter under the alternative hypothesis is specified. Suppose that for these data the alternative hypothesis is

$$H_A : \mu = 3000 \text{ g}$$

this value being suggested from previous studies. To calculate the probability of a Type II error—and the power—we assume that $\overline{Y}$, the mean of the 78 observations, comes from a normal distribution with mean 3000 g and standard error as before, 90.6 g. As Figure 4.23 indicates, the probability of a Type II error is the area over the interval (3119, 3481). This can be calculated as

$$P[\text{Type II error}] = P[3119 \le \overline{Y} \le 3481]$$
$$= P\left[\frac{3119 - 3000}{90.6} \le Z \le \frac{3481 - 3000}{90.6}\right]$$
$$\doteq P[1.31 \le Z \le 5.31]$$
$$\doteq 1 - 0.905$$
$$\doteq 0.095$$

So $\beta = 0.095$ and the power is $1 - \beta = 0.905$. Again, these calculations can be made before any data are collected, and they say that if the SIDS population mean birthweight were 3000 g and the normal population birthweight 3300 g, the probability is 0.905 that a mean from a sample of 78 observations will be declared significantly different from 3300 g.

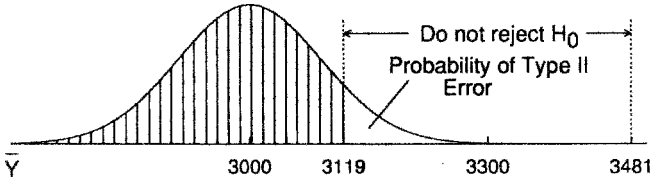


Figure 4.23 Probability of a Type II error.

Let us summarize the analysis of this example:

Hypothesis-testing setup (no data taken)

- $H_0 : \mu = 3300$ g
- $H_A : \mu = 3000$ g
- $\sigma = 800$ g (known)
- $n = 78$
- rejection region: ± 2 standard errors from 3000 g
- $\alpha = 0.0456$
- $\beta = 0.095$
- $1 - \beta = 0.905$

Observe: $\overline{Y} = 2994$

Conclusion: Reject H_0

The value of α is usually specified beforehand: The most common value is 0.05, somewhat less common values are 0.01 or 0.001. Corresponding to the confidence level in interval estimation, we have the *significance level* in hypothesis testing. The significance level is often expressed as a percentage and defined to be $100\alpha\%$. Thus, for $\alpha = 0.05$, the hypothesis test is carried out at the 5%, or 0.05, significance level.

The use of a single symbol β for the probability of a Type II error is standard but a bit misleading. We expect β to stand for one number in the same way that α stands for one number. In fact, β is a function whose argument is the assumed true value of the parameter being tested. For example, in the context of $H_A : \mu = 3000$ g, β is a function of μ and could be written $\beta(\mu)$. It follows that the power is also a function of the true parameter: power $= 1 - \beta(\mu)$. Thus one must specify a value of μ to compute the power.

We finish this introduction to hypothesis testing with a discussion of the one- and two-tailed test. These are related to the choice of the rejection region. Even if α is specified, there is an infinity of rejection regions such that the area over the region is equal to α. Usually, only two types of regions are considered as shown in Figure 4.24. A *two-tailed test* is associated with a

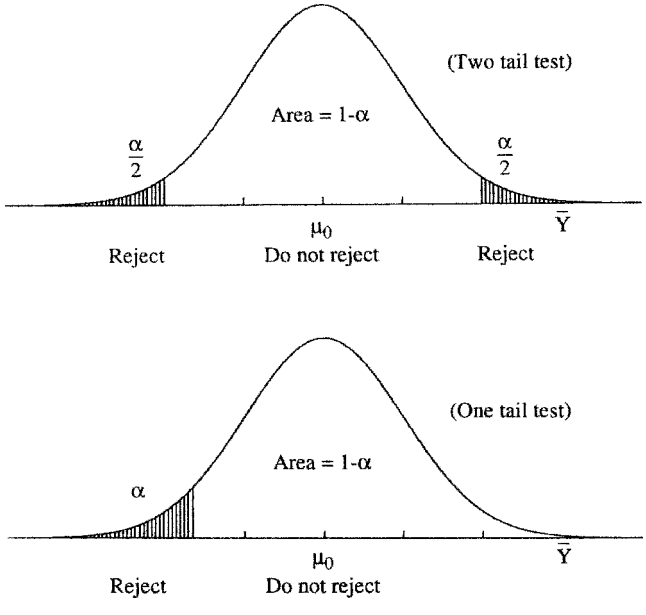


Figure 4.24 Two types of regions considered in hypothesis testing.

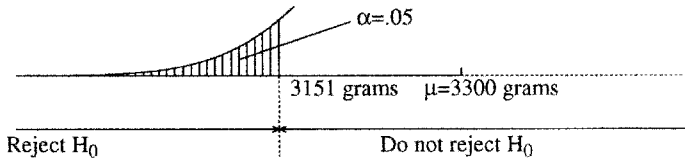


Figure 4.25 Start of the rejection region in a one-tailed test.

rejection region that extends both to the left and to the right of the hypothesized parameter value. A *one-tailed test* is associated with a region to one side of the parameter value. The alternative hypothesis determines the type of test to be carried out. Consider again the birthweight of SIDS cases. Suppose we know that if the mean birthweight of these cases is not the same as that of normal infants (3300 g), it must be less; it is not possible for it to be more. In that case, if the null hypothesis is false, we would expect the sample mean to be below 3300 g, and we would reject the null hypothesis for values of $\overline{Y}$ below 3300 g. We could then write the null hypothesis and alternative hypothesis as follows:

$$H_0 : \mu = 3300 \text{ g}$$
$$H_A : \mu < 3300 \text{ g}$$

We would want to carry out a one-tailed test in this case by setting up a rejection region to the left of the parameter value. Suppose that we want to test at the 0.05 level, and we only want to reject for values of $\overline{Y}$ below 3300 g. From Table A.2 we see that we must locate the start of the rejection region 1.64 standard errors to the left of $\mu = 3300$ g, as shown in Figure 4.25. The value is $3300 - (1.64)(800/\sqrt{78})$ or $3300 - (1.64)(90.6) = 3151$ g.

Suppose that we want a two-tailed test at the 0.05 level. The Z-value (Table A.2) is now 1.96, which distributes 0.025 in the left tail and 0.025 in the right tail. The corresponding values for the critical region are $3300 \pm (1.96)(90.6)$ or (3122, 3478), producing a region very similar to the region calculated earlier.

The question is: When should you do a one-tailed test and when a two-tailed test? As was stated, the alternative hypothesis determines this. An alternative hypothesis of the form $H_A : \mu \neq \mu_0$ is called *two-sided* and will require a two-tailed test. Similarly, the alternative $H_A : \mu < \mu_0$ is called one-sided and will lead to a one-tailed test. So should the alternative hypothesis be one- or two-sided? The experimental situation will determine this. For example, if nothing is known about the effect of a proposed therapy, the alternative hypothesis should be made two-sided. However, if it is suspected that a new therapy will do nothing or increase a response level, and if there is no reason to distinguish between no effect and a decrease in the response level, the test should be one-tailed. The general rule is: The more specific you can make the experiment, the greater the power of the test (see Fleiss et al. [2003, Sec. 2.4]). (See Problem 4.33 to convince yourself that the power of a one-tailed test is greater *if* the alternative hypothesis specifies the situation correctly.)

4.7 CONFIDENCE INTERVALS VS. TESTS OF HYPOTHESES

You may have noticed that there is a very close connection between the confidence intervals and the tests of hypotheses that we have constructed. In both approaches we have used the standard normal distribution and the quantity α.

In *confidence intervals* we:

1. Specify the confidence level $(1 - \alpha)$.

2. Read $z_{1-\alpha/2}$ from a standard normal table.
3. Calculate $\overline{Y} \pm z_{1-\alpha/2}\sigma/\sqrt{n}$.

In *hypothesis testing* we:

1. Specify the null hypothesis ($H_0 : \mu = \mu_0$).
2. Specify α, the probability of a Type I error.
3. Read $z_{1-\alpha/2}$ from a standard normal table.
4. Calculate $\mu_0 \pm z_{1-\alpha/2}\sigma/\sqrt{n}$.
5. Observe $\overline{Y}$; reject or accept H_0.

The two approaches can be represented pictorially as shown in Figure 4.26. It is easy to verify that if the confidence interval does not straddle μ_0 (as is the case in the figure), $\overline{Y}$ will fall in the rejection region, and vice versa. Will this always be the case? The answer is "yes." When we are dealing with inference about the value of a parameter, the two approaches will give the same answer. To show the equivalence algebraically, we start with the key inequality

$$P\left[-z_{1-\alpha/2} \leq \frac{\overline{Y} - \mu}{\sigma/\sqrt{n}} \leq z_{1-\alpha/2}\right] = 1 - \alpha$$

If we solve the inequality for $\overline{Y}$, we get

$$P\left[\mu - \frac{z_{1-\alpha/2}\sigma}{\sqrt{n}} \leq \overline{Y} \leq \mu + \frac{z_{1-\alpha/2}}{\sqrt{n}}\right] = 1 - \alpha$$

Given a value $\mu = \mu_0$, the statement produces a region ($\mu_0 \pm z_{1-\alpha/2}\sigma/\sqrt{n}$) within which $100(1-\alpha)\%$ of sample means fall. If we solve the inequality for μ, we get

$$P\left[\overline{Y} - \frac{z_{1-\alpha/2}\sigma}{\sqrt{n}} \leq \mu \leq \overline{Y} + \frac{z_{1-\alpha/2}\sigma}{\sqrt{n}}\right] = 1 - \alpha$$

This is a confidence interval for the population mean μ. In Chapter 5 we examine this approach in more detail and present a general methodology.

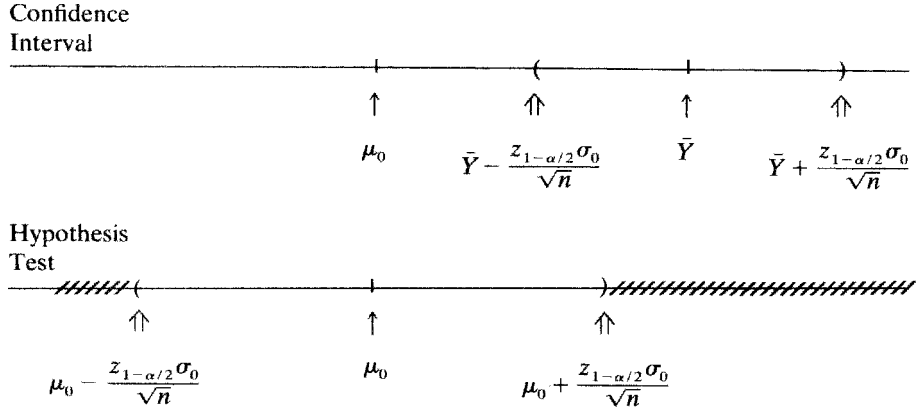


Figure 4.26 Confidence intervals vs. tests of hypothesis.

If confidence intervals and hypothesis testing are but two sides of the same coin, why bother with both? The answer is (to continue the analogy) that the two sides of the coin are not the same; there is different information. The confidence interval approach emphasizes the precision of the estimate by means of the width of the interval and provides a point estimate for the parameter, regardless of any hypothesis. The hypothesis-testing approach deals with the consistency of observed (new) data with the hypothesized parameter value. It gives a probability of observing the value of the statistic or a more extreme value. In addition, it will provide a method for estimating sample sizes. Finally, by means of power calculations, we can decide beforehand whether a proposed study is feasible; that is, what is the probability that the study will demonstrate a difference if a (specified) difference exists?

You should become familiar with both approaches to statistical inference. Do not use one to the exclusion of another. In some research fields, hypothesis testing has been elevated to the only "proper" way of doing inference; all scientific questions have to be put into a hypothesis-testing framework. This is absurd and stultifying, particularly in pilot studies or investigations into uncharted fields. On the other hand, not to consider *possible* outcomes of an experiment and the chance of picking up differences is also unbalanced. Many times it will be useful to specify very carefully what is known about the parameter(s) of interest *and* to specify, in perhaps a crude way, alternative values or ranges of values for these parameters. If it is a matter of emphasis, you should stress hypothesis testing before carrying out a study and estimation after the study has been done.

4.8 INFERENCE ABOUT THE VARIANCE OF A POPULATION

4.8.1 Distribution of the Sample Variance

In previous sections we assumed that the population variance of a normal distribution was known. In this section we want to make inferences about the population variance on the basis of a sample variance. In making inferences about the population mean, we needed to know the sampling distribution of the sample mean. Similarly, we need to know the sampling distribution of the sample variance in order to make inferences about the population variance; analogous to the statement that for a normal random variable, Y, with sample mean $\overline{Y}$, the quantity

$$\frac{\overline{Y} - \mu}{\sigma/\sqrt{n}}$$

has a normal distribution with mean 0 and variance 1. We now state a result about the quantity $(n-1)s^2/\sigma^2$. The basic information is contained in the following statement:

Result 4.4. If a random variable Y is normally distributed with mean μ and variance σ^2, then for a random sample of size n the quantity $(n-1)s^2/\sigma^2$ has a chi-square distribution with $n-1$ degrees of freedom.

Each distribution is indexed by $n-1$ degrees of freedom. Recall that the sample variance is calculated by dividing $\sum(y-\overline{y})^2$ by $n-1$, the degrees of freedom.

The chi-square distribution is skewed; the amount of skewness decreases as the degrees of freedom increases. Since $(n-1)s^2/\sigma^2$ can never be negative, the sample space for the chi-square distribution is the nonnegative part of the real line. Several chi-square distributions are shown in Figure 4.27. The mean of a chi-square distribution is equal to the degrees of freedom, and

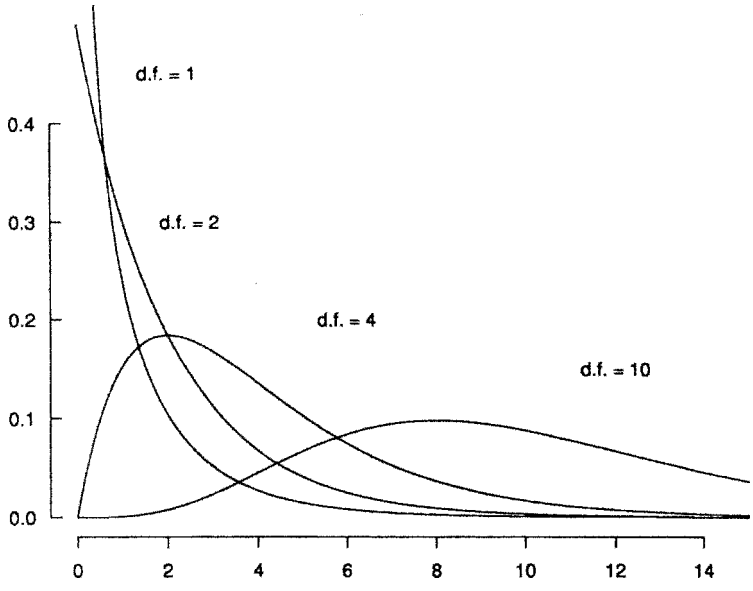


Figure 4.27 Chi-square distributions.

the variance is twice the degrees of the freedom. Formally,

$$E\left[\frac{(n-1)s^2}{\sigma^2}\right] = n - 1 \tag{1}$$

$$\text{var}\left[\frac{(n-1)s^2}{\sigma^2}\right] = 2(n-1) \tag{2}$$

It may seem somewhat strange to talk about the variance of the sample variance, but under repeated sampling the sample variance will vary from sample to sample, and the chi-square distribution describes this variation if the observations are from a normal distribution.

Unlike the normal distribution, a tabulation of the chi-square distribution requires a separate listing for each degree of freedom. In Table A.3, a tabulation is presented of percentiles of the chi-square distribution. For example, 95% of chi-square random variables with 10 degrees of freedom have values less than or equal to 18.31. Note that the median (50th percentile) is very close to the degrees of freedom when the number of the degrees of freedom is 10 or more.

The symbol for a chi-square random variable is χ^2, the Greek lowercase letter chi, to the power of 2. So we usually write $\chi^2 = (n-1)s^2/\sigma^2$. The degrees of freedom are usually indicated by the Greek lowercase letter ν (nu). Hence, χ^2_ν is a symbol for a chi-square random variable with ν degrees of freedom. It is not possible to maintain the notation of using a capital letter for a variable and the corresponding lowercase letter for the value of the variable.

4.8.2 Inference about a Population Variance

We begin with hypothesis testing. We have a sample of size n from a normal distribution, the sample variance s^2 has been calculated, and we want to know whether the value of s^2 observed is consistent with a hypothesized population value σ_0^2, perhaps known from previous research. Consider the quantity

$$\chi^2 = \frac{(n-1)s^2}{\sigma^2}$$

If s^2 is very close to σ^2, the ratio s^2/σ^2 is close to 1; if s^2 differs very much from σ^2, the ratio is either very large or very close to 0: This implies that $\chi^2 = (n-1)s^2/\sigma^2$ is either very large or very small, and we would want to reject the null hypothesis. This procedure is analogous to a hypothesis test about a population mean; we measured the distance of the observed sample mean from the hypothesized value in units of standard errors; in this case we measure the "distance" in units of the hypothesized variance.

Example 4.9. The SIDS cases discussed in Section 3.3.1 were assumed to come from a normal population with variance $\sigma^2 = (800)^2$. To check this assumption, the variance, s^2, is calculated for the first 11 cases occurring in 1969. The birthweights (in grams) were

3374, 3515, 3572, 2977, 4111, 1899, 3544, 3912, 3515, 3232, 3289

The sample variance is calculated to be

$$s^2 = (574.3126 \text{ g})^2$$

The observed value of the chi-square quantity is

$$\chi^2 = \frac{(11-1)(574.3126)^2}{(800)^2}$$
$$= 5.15 \text{ with 10 degrees of freedom}$$

Figure 4.14 illustrates the chi-square distribution with 10 degrees of freedom. The 2.5th and 97.5th percentiles are 3.25 and 20.48 (see Table A.3). Hence, 95% of chi-square values will fall between 3.25 and 20.48.

If we follow the usual procedure of setting our significance level at $\alpha = 0.05$, we will not reject the null hypothesis that $\sigma^2 = (800 \text{ g})^2$, since the observed value $\chi^2 = 5.15$ is less extreme than 3.25. Hence, there is not sufficient evidence for using a value of σ^2 not equal to 800 g.

As an alternative to setting up the rejection regions formally, we could have noted, using Table A.3, that the observed value of $\chi^2 = 5.15$ is between the 5th and 50th percentiles, and therefore the corresponding two-sided p-value is greater than 0.10.

A $100(1-\alpha)\%$ confidence interval is constructed using the approach of Section 4.7. The key inequality is

$$P[\chi^2_{\alpha/2} \le \chi^2 \le \chi^2_{1-\alpha/2}] = 1-\alpha$$

The degrees of freedom are not indicated but assumed to be $n-1$. The values $\chi^2_{\alpha/2}$ and $\chi^2_{1-\alpha/2}$ are chi-square values such that $1-\alpha$ of the area is between them. (In Figure 4.14, these values are 3.25 and 20.48 for $1-\alpha = 0.95$.)

The quantity χ^2 is now replaced by its equivalent, $(n-1)s^2/\sigma^2$, so that

$$P\left[\chi^2_{\alpha/2} \le \frac{(n-1)s^2}{\sigma^2} \le \chi^2_{1-\alpha/2}\right] = 1-\alpha$$

If we solve for σ^2, we obtain a $100(1-\alpha)\%$ confidence interval for the population variance. A little algebra shows that this is

$$P\left[\frac{(n-1)s^2}{\chi^2_{1-\alpha/2}} \le \sigma^2 \le \frac{(n-1)s^2}{\chi^2_{\alpha/2}}\right] = 1-\alpha$$

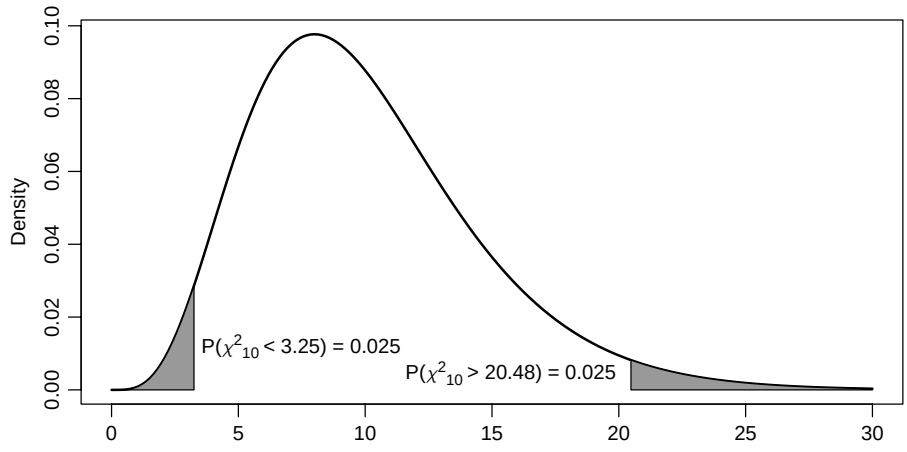


Figure 4.28 Chi-square distribution with 10 degrees of freedom.

Given an observed value of s^2, the confidence interval required can now be calculated.

To continue our example, the variance for the 11 SIDS cases above is $s^2 = (574.3126 \text{ g})^2$. For $1 - \alpha = 0.95$, the values of χ^2 are (see Figure 4.28)

$$\chi^2_{0.025} = 3.25, \qquad \chi^2_{0.975} = 20.48$$

We can write the key inequality then as

$$P[3.25 \leq \chi^2 \leq 20.48] = 0.95$$

The 95% confidence interval for σ^2 can then be calculated:

$$\frac{(10)(574.3126)^2}{20.48} \leq \sigma^2 \leq \frac{(10)(574.3126)^2}{3.25}$$

and simplifying yields

$$161{,}052 \leq \sigma^2 \leq 1{,}014{,}877$$

The corresponding values for the population standard deviation are

$$\text{lower 95\% limit for } \sigma = \sqrt{161,052} = 401 \text{ g}$$

$$\text{upper 95\% limit for } \sigma = \sqrt{1{,}014{,}877} = 1007 \text{ g}$$

These are rather wide limits. Note that they include the null hypothesis value of $\sigma = 800$ g. Thus, the confidence interval approach leads to the same conclusion as the hypothesis-testing approach.

NOTES

4.1 Definition of Probability

The relative frequency definition of probability was advanced by von Mises, Fisher, and others (see Hacking [1965]). A radically different view is held by the *personal* or *subjective school*,

exemplified in the work of De Finetti, Savage, and Savage. According to this school, probability reflects subjective belief and knowledge that can be quantified in terms of betting behavior. Savage [1968] states: "My probability for the event A under circumstances H is the amount of money I am indifferent to betting on A in an elementary gambling situation." What does Savage mean? Consider the thumbtack experiment discussed in Section 4.3.1. Let the event A be that the thumbtack in a single toss falls $\perp$. The other possible outcome is $\top$; call this event B. You are to bet a dollars on A and b dollars on B, such that you are indifferent to betting either on A or on B (you must bet). You clearly would not want to put all your money on A; then you would prefer outcome A. There is a split, then, in the total amount, $a + b$, to be bet so that you are indifferent to either outcome A or B. Then *your* probability of A, $P[A]$, is

$$P[A] = \frac{b}{a+b}$$

If the total amount to be bet is 1 unit, you would split it $1 - P$, P, where $0 \leq P \leq 1$, so that

$$P[A] = \frac{P}{1-P+P} = P$$

The bet is a device to link quantitative preferences for amounts b and a of money, which are assumed to be well understood, to preferences for degrees of certainty, which we are trying to quantify. Note that Savage is very careful to require the estimate of the probability to be made under as specified circumstances. (If the thumbtack could land, say, $\top$ on a soft surface, you would clearly want to modify your probability.) Note also that betting behavior is a *definition* of personal probability rather than a guide for action. In practice, one would typically work out personal probabilities by comparison to events for which the probabilities were already established (Do I think this event is more or less likely than a coin falling heads?) rather than by considering sequences of bets.

This definition of probability is also called *personal probability*. An advantage of this view is that it can discuss more situations than the relative frequency definition, for example: the probability (rather, *my* probability) of life on Mars, or my probability that a cure for cancer will be found. You should not identify personal probability with the irrational or whimsical. Personal probabilities do utilize empirical evidence, such as the behavior of a tossed coin. In particular, if you have good reason to believe that the relative frequency of an event is P, your personal probability will also be P. It is possible to show that any self-consistent system for choosing between uncertain outcomes corresponds to a set of personal probabilities.

Although different individuals will have different personal probabilities for an event, the way in which those probabilities are updated by evidence is the same. It is possible to develop statistical analyses that summarize data in terms of how it should change one's personal probabilities. In simple analyses these *Bayesian methods* are more difficult to use than those based on relative frequencies, but the situation is reversed for some complex models. The use of Bayesian statistics is growing in scientific and clinical research, but it is still not supported by most standard software. An introductory discussion of Bayesian statistics is given by Berry [1996], and more advanced books on practical data analysis include Gelman et al. [1995] and Carlin and Louis [2000]. There are other views of probability. For a survey, see the books by Hacking [1965] and Barnett [1999] and references therein.

4.2 Probability Inequalities

For the normal distribution, approximately 68% of observations are within one standard deviation of the mean, and 95% of observations are within two standard deviations of the mean. If the distribution is not normal, a weaker statement can be made: The proportion of observations

within K standard deviations of the mean is greater than or equal to $(1 - 1/K^2)$; notationally, for a variable Y,

$$P\left[-K \leq \frac{Y - E(Y)}{\sigma} \leq K\right] \leq 1 - \frac{1}{K^2}$$

where K is the number of standard deviations from the mean. This is a version of *Chebyshev's inequality*. For example, this inequality states that at least 75% of the observations fall within two standard deviations of the mean (compared to 95% for the normal distribution). This is not nearly as stringent as the first result stated, but it is more general. If the variable Y can take on only positive values and the mean of Y is μ, the following inequality holds:

$$P[Y \leq y] \leq 1 - \frac{\mu}{y}$$

This inequality is known as the *Markov inequality*.

4.3 Inference vs. Decision

The hypothesis tests discussed in Sections 4.6 and 4.7 can be thought of as decisions that are made with respect to a value of a parameter (or *state of nature*). There is a controversy in statistics as to whether the process of inference is equivalent to a decision process. It seems that a "decision" is sometimes not possible in a field of science. For example, it is not possible at this point to decide whether better control of insulin levels will reduce the risk of neuropathy in diabetes mellitus. In this case and others, the types of inferences we can make are more tenuous and cannot really be called decisions. For an interesting discussion, see Moore [2001]. This is an excellent book covering a variety of statistical topics ranging from ethical issues in experimentation to formal statistical reasoning.

4.4 Representative Samples

A random sample from a population was defined in terms of repeated independent trials or drawings of observations. We want to make a distinction between a random and a representative sample. A random sample has been defined in terms of repeated independent sampling from a population. However (see Section 4.3.2), cancer patients treated in New York are clearly not a random sample of all cancer patients in the world or even in the United States. They will differ from cancer patients in, for instance, Great Britain in many ways. Yet we do frequently make the assumption that if a cancer treatment worked in New York, patients in Great Britain can also benefit. The experiment in New York has wider applicability. We consider that with respect to the outcome of interest in the New York cancer study (e.g., increased survival time), the New York patients, although not a random sample, constitute a representative sample. That is, the survival times are a random sample from the population of survival times.

It is easier to disprove randomness than representativeness. A measure of scientific judgment is involved in determining the latter. For an interesting discussion of the use of the word *representative*, see the papers by Kruskal and Mosteller [1979a–c].

4.5 Multivariate Populations

Usually, we study more than one variable. The Winkelstein et al. [1975] study (see Example 4.1) measured diastolic and systolic blood pressures, height, weight, and cholesterol levels. In the study suggested in Example 4.2, in addition to IQ, we would measure physiological and psychological variables to obtain a more complete picture of the effect of the diet. For completeness we therefore define a *multivariate population* as the set of all possible values of a specified set of variables (measured on the objects of interest). A second category of topics then comes up:

relationships among the variables. Words such as *association* and *correlation* come up in this context. A discussion of these topics begins in Chapter 9.

4.6 Sampling without Replacement

We want to select two patients *at random* from a group of four patients. The same patient cannot be chosen twice. How can this be done? One procedure is to write each name on a slip of paper, put the four slips of paper in a hat, stir the slips of paper, and—without looking—draw out two slips. The patients whose names are on the two slips are then selected. This is known as *sampling without replacement*. (For the procedure to be *fair*, we require that the slips of paper be indistinguishable and well mixed.) The events "outcome on first draw" and "outcome on second draw" are clearly not independent. If patient A is selected in the first draw, she is no longer available for the second draw. Let the patients be labeled *A, B, C*, and *D*. Let the symbol *AB* mean "patient A is selected in the first draw and patient B in the second draw." Write down all the possible outcomes; there are 12 of them as follows:

$$\begin{array}{cccc} AB & BA & CA & DA \\ AC & BC & CB & DB \\ AD & BD & CD & DC \end{array}$$

We define the selection of two patients to be random if each of the 12 outcomes is equally likely, that is, the probability that a particular pair is chosen is 1/12. This definition has intuitive appeal: We could have prepared 12 slips of paper each with one of the 12 pairs recorded and drawnout one slip of paper. If the slip of paper is drawn randomly, the probability is 1/12 that a particular slip will be selected.

One further comment. Suppose that we only want to know which two patients have been selected (i.e., we are not interested in the order). For example, what is the probability that patients C and D are selected? This can happen in two ways: CD or DC. These events are mutually exclusive, so that the required probability is $P[CD \text{ or } DC] = P[CD] + P[DC] = 1/12 + 1/12 = 1/6$.

4.7 Pitfalls in Sampling

It is very important to define the population of interest carefully. Two illustrations of rather subtle pitfalls are Berkson's fallacy and length-biased sampling. *Berkson's fallacy* is discussed in Murphy [1979] as follows: In many studies, hospital records are reviewed or sampled to determine relationships between diseases and/or exposures. Suppose that a review of hospital records is made with respect to two diseases, A and B, which are so severe that they always lead to hospitalization. Let their frequencies in the population at large be p_1 and p_2. Then, assuming independence, the probability of the joint occurrence of the two diseases is $p_1 p_2$. Suppose now that a healthy proportion p_3 of subjects (H) never go to the hospital; that is, $P[H] = p_3$. Now write $\overline{H}$ as that part of the population that will enter a hospital at some time; then $P[\overline{H}] = 1 - p_3$. By the rule of conditional probability, $P[A|\overline{H}] = P[A\overline{H}]/P[\overline{H}] = p_1/(1-p_3)$. Similarly, $P[B|\overline{H}] = p_2/(1-p_3)$ and $P[AB|\overline{H}] = p_1 p_2/(1-p_3)$, and this is not equal to $P[A|\overline{H}]P[B|\overline{H}] = [p_1/(1-p_3)][p_2/(1-p_3)]$, which must be true in order for the two diseases to be unrelated in the hospital population. Now, you can show that $P[AB|\overline{H}] < P[AB]$, and, quoting Murphy:

> The hospital observer will find that they occur together less commonly than would be expected if they were independent. This is known as Berkson's fallacy. It has been a source of embarrassment to many an elegant theory. Thus, cirrhosis of the liver and common cancer are both reasons for admission to the hospital. *A priori*, we would expect them to be less commonly associated in the hospital than in the population at large. In fact, they have been found to be negatively correlated.

Table 4.4 Expected Composition of Visit-Based Sample in a Hypothetical Population

	Type of Patient		
Variable	Hypertensive	Other	Total
Number of patients	200	800	1000
Visits per patient per year	12	1	13
Visits contributed	2400	800	3200
Expected number of patients in a 3% sample of visits	72	24	96
Expected percent of sample	75	25	100

Source: Shepard and Neutra [1977].

(Murphy's book contains an elegant, readable exposition of probability in medicine; it will be worth your while to read it.)

A second pitfall deals with the area of *length-biased sampling*. This means that for a particular sampling scheme, some objects in the population may be more likely to be selected than others. A paper by Shepard and Neutra [1977] illustrates this phenomenon in sampling medical visits. Our discussion is based on that paper. The problem arises when we want to make a statement about a population of patients that can only be identified by a sample of patient visits. Therefore, frequent visitors will be more likely to be selected. Consider the data in Table 4.4, which illustrates that although hypertensive patients make up 20% of the total patient population, a sample based on visits would consist of 75% hypertensive patients and 25% other.

There are other areas, particularly screening procedures in chronic diseases, that are at risk for this type of problem. See Shepard and Neutra [1977] for suggested solutions as well as references to other papers.

4.8 Other Sampling Schemes

In this chapter (and almost all the remainder of the book) we are assuming *simple random sampling*, that is, sampling where every unit in the population is equally likely to end up in the sample, and sampling of different units is independent. A sufficiently large simple random sample will always be representative of the population. This intuitively plausible result is made precise in the mathematical result that the empirical cumulative distribution of the sample approaches the true cumulative distribution of the population as the sample size increases.

There are some important cases where other random sampling strategies are used, trading increased mathematical complexity for lower costs in obtaining the sample. The main techniques are as follows:

1. *Stratified sampling*. Suppose that we sampled 100 births to study low birthweight. We would expect to see about one set of twins on average, but might be unlucky and not sample any. As twins are much more likely to have low birthweight, we would prefer a sampling scheme that fixed the number of twins we observed.
2. *Unequal probability sampling*. In conjunction with stratified sampling, we might want to increase the number of twin births that we examined to more than the 1/90 in the population. We might decide to sample 10 twin births rather than just one.
3. *Cluster sampling*. In a large national survey requiring face-to-face interviews or clinical tests, it is not feasible to use a simple random sample, as this would mean that nearly every person sampled would live in a different town or city. Instead, a number of cities or counties might be sampled and simple random sampling used within the selected geographic regions.

4. *Two-phase sampling*. It is sometimes useful to take a large initial sample and then take a smaller subsample to measure more expensive or difficult variables. The probability of being included in the subsample can then depend on the values of variables measured at the first stage. For example, consider a study of genetic influences on lung cancer. Lung cancer is rare, so it would be sensible to use a stratified (case–control) sampling scheme where an equal number of people with and without lung cancer was sampled. In addition, lung cancer is extremely rare in nonsmokers. If a first-stage sample asked about smoking status it would be possible to ensure that the more expensive genetic information was obtained for a sufficient number of nonsmoker cancer cases as well as smokers with cancer.

These sampling schemes have two important features in common. The sampling scheme is fully known in advance, and the sampling is random (even if not with equal probabilities). These features mean that a valid statistical analysis of the results is possible. Although the sample is not representative of the population, it is unrepresentative in ways that are fully under the control of the analyst. Complex probability samples such as these require different analyses from simple random samples, and not all statistical software will analyze them correctly. The section on Survey Methods of the American Statistical Association maintains a list of statistical software that analyzes complex probability samples. It is linked from the Web appendix to this chapter. There are many books discussing both the statistical analysis of complex surveys and practical considerations involved in sampling, including Levy and Lemeshow [1999], Lehtonen and Pahkinen [1995], and Lohr [1999]. Similar, but more complex issues arise in environmental and ecological sampling, where measurement locations are sampled from a region.

4.9 How to Draw a Random Sample

In Note 4.6 we discussed drawing a random sample without replacement. How can we draw samples with replacement? Simply, of course, the slips could be put back in the hat. However, in some situations we cannot collect the total population to be sampled from, due to its size, for example. One way to sample populations is to use a table of random numbers. Often, these numbers are really *pseudorandom*: They have been generated by a computer. Use of such a table can be illustrated by the following problem: A random sample of 100 patient charts is to be drawn from a hospital record room containing 45,850 charts. Assume that the charts are numbered in some fashion from 1 to 45,850. (It is not necessary that they be numbered consecutively or that the numbers start with 1 and end with 45,850. All that is required is that there is some unique way of numbering each chart.) We enter the random number table randomly by selecting a page and a column on the page at random. Suppose that the first five-digit numbers are

$$06812, \quad 16134, \quad 15195, \quad 84169, \quad \text{and} \quad 41316$$

The first three charts chosen would be chart 06812, 16134, and 15195, in that order. Now what do we do with the 84169? We can skip it and simply go to 41316, realizing that if we follow this procedure, we will have to throw out approximately half of the numbers selected.

A second example: A group of 40 animals is to be assigned at random to one of four treatments A, B, C, and D, with an equal number in each of the treatments. Again, enter the random number table randomly. The first 10-digit numbers between 1 and 40 will be the numbers of the animals assigned to treatment A, the second set of 10-digit numbers to treatment B, the third set to treatment C, and the remaining animals are assigned to treatment D. If a random number reappears in a subsequent treatment, it can simply be omitted. (Why is this reasonable?)

4.10 Algebra of Expectations

In Section 4.3.3 we discuss random variables, distributions, and expectations of random variables. We defined $E(Y) = \sum py$ for a discrete random variable. A similar definition, involving

integrals rather than sums, can be made for continuous random variables. We will now state some rules for working with expectations.

1. If a is a constant, $E(aY) = aE(Y)$.
2. If a and b are constants, $E(aY + b) = aE(Y) + b$.
3. If X and Y are two random variables, $E(X + Y) = E(X) + E(Y)$.
4. If a and b are constants, $E(aX + bY) = E(aX) + E(bY) = aE(X) + bE(Y)$.

You can demonstrate the first three rules by using some simple numbers and calculating their average. For example, let $y_1 = 2$, $y_2 = 4$, and $y_3 = 12$. The average is

$$E(Y) = \frac{1}{3} \times 2 + \frac{1}{3} \times 4 + \frac{1}{3} \times 12 = 6$$

Two additional comments:

1. The second formula makes sense. Suppose that we measure temperature in °C. The average is calculated for a series of readings. The average can be transformed to °F by the formula

$$\text{average in } ^\circ\text{F} = \frac{9}{5} \times \text{average in } ^\circ\text{C} + 32$$

   An alternative approach consists of transforming each original reading to °F and then taking the average. It is intuitive that the two approaches should provide the same answer.
2. It is not true that $E(Y^2) = [E(Y)]^2$. Again, a small example will verify this. Use the same three values ($y_1 = 2$, $y_2 = 4$, and $y_3 = 12$). By definition,

$$E(Y^2) = \frac{2^2 + 4^2 + 12^2}{3} = \frac{4 + 16 + 144}{3} = \frac{164}{3} = 54.\overline{6}$$

   but

$$[E(Y)]^2 = 6^2 = 36$$

   Can you think of a special case where the equation $E(Y^2) = [E(Y)]^2$ is true?

4.11 Bias, Precision, and Accuracy

Using the algebra of expectations, we define a statistic T to be a biased estimate of a parameter τ if $E(T) \neq \tau$. Two typical types of bias are $E(T) = \tau + a$, where a is a constant, called *location bias*; and $E(T) = b\tau$, where b is a positive constant, called *scale bias*. A simple example involves the sample variance, s^2. A more "natural" estimate of σ^2 might be

$$s_*^2 = \frac{\sum (y - \overline{y})^2}{n}$$

This statistic differs from the usual sample variance in division by n rather than $n - 1$. It can be shown (you can try it) that

$$E(s_*^2) = \frac{n - 1}{n}\sigma^2$$

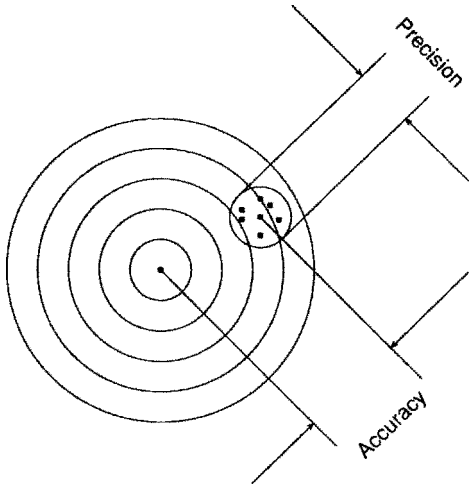


Figure 4.29 Accuracy involves the concept of bias.

Hence, s_*^2 is a biased estimate of σ^2. The statistic s_*^2 can be made unbiased by multiplying s_*^2 by $n/(n-1)$ (see rule 1 in Note 4.10); that is,

$$E\left[\frac{n}{n-1}s_*^2\right] = \frac{n}{n-1}\frac{n-1}{n}\sigma^2 = \sigma^2$$

But $n/(n-1)s_*^2 = s^2$, so s^2 rather than s_*^2 is an unbiased estimate of σ^2. We can now discuss precision and accuracy. *Precision* refers to the degree of closeness to each other of a set of values of a variable; *accuracy* refers to the degree of closeness of these values to the quantity (parameter) being measured. Thus, precision is an internal characteristic of a set of data, while accuracy relates the set to an external standard. For example, a thermometer that consistently reads a temperature 5 degrees too high may be very precise but will not be very accurate. A second example of the distribution of hits on a target illustrates these two concepts. Figure 4.29 shows that accuracy involves the concept of bias. Together with Note 4.10, we can now make these concepts more precise. For simplicity we will refer only to location bias.

Suppose that a statistic T estimates a quantity τ in a biased way; $E[T] = \tau + a$. The variance in this case is defined to be $E[T - E(T)]^2$. What is the quantity $E[T-\tau]^2$? This can be written as

$$E[T-\tau]^2 = E[T-(\tau+a)+a]^2 = E[T-E[T]+a]^2$$

$$\underset{\text{(mean square error)}}{E[T-\tau]^2} = \underset{\text{(variance)}}{E[T-E[T]]^2} + \underset{\text{(bias)}}{a^2}$$

The quantity $E[T-\tau]^2$ is called the *mean square error*. If the statistic is unbiased (i.e., $a = 0$), the mean square error is equal to the variance (σ^2).

4.12 Use of the Word Parameter

We have defined *parameter* as a numerical characteristic of a population of values of a variable. One of the basic tasks of statistics is to estimate values of the unknown parameter on the basis of a sample of values of a variable. There are two other uses of this word. Many clinical scientists use *parameter* for *variable*, as in: "We measured the following three parameters: blood pressure,

amount of plaque, and degree of patient satisfaction." You should be aware of this pernicious use and strive valiantly to eradicate it from scientific writing. However, we are not sanguine about its ultimate success. A second incorrect use confuses *parameter* and *perimeter*, as in: "The parameters of the study did not allow us to include patients under 12 years of age." A better choice would have been to use the word *limitations*.

4.13 Significant Digits (continued)

This note continues the discussion of significant digits in Note 3.4. We discussed approximations to a quantity due to arithmetical operations, measurement rounding, and finally, sampling variability. Consider the data on SIDS cases of Example 4.11. The mean birthweight of the 78 cases was 2994 g. The probability was 95% that the interval 2994 ± 178 straddles the unknown quantity of interest: the mean birthweight of the population of SIDS cases. This interval turned out to be 2816–3172 g, although the last digits in the two numbers are not very useful. In this case we have carried enough places so that the rule mentioned in Note 3.4 is not applicable. The biggest source of approximation turns out to be due to sampling. The approximations introduced by the arithmetical operation is minimal; you can verify that if we had carried more places in the intermediate calculations, the final confidence interval would have been 2816–3171 g.

4.14 A Matter of Notation

What do we mean by 18 ± 2.6? In many journals you will find this notation. What does it mean? Is it mean plus or minus the standard deviation, or mean plus or minus the standard error? You may have to read a paper carefully to find out. Both meanings are used and thus need to be specified clearly.

4.15 Formula for the Normal Distribution

The formula for the normal probability density function for a normal random variable Y with mean μ and variance σ^2 is

$$f(y) = \frac{1}{\sqrt{2\pi}\sigma} \exp\left[-\frac{1}{2}\left(\frac{y-\mu}{\sigma}\right)^2\right]$$

Here, $\pi = 3.14159\ldots$, and e is the base of the natural logarithm, $e = 2.71828\ldots$. A standard normal distribution has $\mu = 0$ and $\sigma = 1$. The formula for the standard normal random variable, Z, is

$$f(z) = \frac{1}{\sqrt{2\pi}} \exp\left(-\frac{1}{2}z^2\right)$$

Although most statistical packages will do this for you, the heights of the curve can easily be calculated using a hand calculator. By symmetry, only one half of the range of values has to be computed [i.e., $f(z) = f(-z)$]. For completeness in Table 4.5 we give enough points to enable you to graph $f(z)$. Given any normal variable y with mean μ and variance σ^2, you can calculate $f(y)$ by using the relationships

$$Z = \frac{Y-\mu}{\sigma}$$

and plotting the corresponding heights:

$$f(y) = \frac{1}{\sigma} f(z)$$

where Z is defined by the relationship above. For example, suppose that we want to graph the curve for IQ, where we assume that IQ is normal with mean $\mu = 100$ and standard deviation

Table 4.5 Heights of the Standard Normal Curve

z	f(z)	z	f(z)	z	f(z)	z	f(z)	z	f(z)
0.0	0.3989	0.5	0.3521	1.0	0.2420	1.5	0.1295	2.0	0.0540
0.1	0.3970	0.6	0.3332	1.1	0.2179	1.6	0.1109	2.1	0.0440
0.2	0.3910	0.7	0.3123	1.2	0.1942	1.7	0.0940	2.2	0.0355
0.3	0.3814	0.8	0.2897	1.3	0.1714	1.8	0.0790	2.3	0.0283
0.4	0.3683	0.9	0.2661	1.4	0.1497	1.9	0.0656	2.4	0.0224

$\sigma = 15$. What is the height of the curve for an IQ of 109? In this case, $Z = (109-100)/15 = 0.60$ and $f(\text{IQ}) = (1/15)f(z) = (1/15)(0.3332) = 0.0222$. The height for an IQ of 91 is the same.

4.16 Null Hypothesis and Alternative Hypothesis

How do you decide which of two hypotheses is the null and which is the alternative? Sometimes the advice is to make the null hypothesis the hypothesis of "indifference." This is not helpful; indifference is a poor scientific attitude. We have three suggestions: (1) In many situations there is a prevailing view of the science that is accepted; it will continue to be accepted unless "definitive" evidence to the contrary is produced. In this instance the prevailing view would be made operational in the null hypothesis. The null hypothesis is often the "straw man" that we wish to reject. (Philosophers of science tell us that we never prove things conclusively; we can only disprove theories.) (2) An excellent guide is *Occam's razor*, which states: Do not multiply hypotheses beyond necessity. Thus, in comparing a new treatment with a standard treatment, the simpler hypothesis is that the treatments have the same effect. To postulate that the treatments are different requires an additional operation. (3) Frequently, the null hypothesis is one that allows you to calculate the p-value. Thus, if two treatments are assumed the same, we can calculate a p-value for the result observed. If we hypothesize that they are not the same, then we cannot compute a p-value without further specification.

PROBLEMS

4.1 Give examples of populations with the number of elements finite, virtually infinite, potentially infinite, and infinite. Define a sample from each population.

4.2 Give an example from a study in a research area of interest to you that clearly assumes that results are applicable to, as yet, untested subjects.

4.3 Illustrate the concepts of *population, sample, parameter*, and *statistic* by two examples from a research area of your choice.

4.4 In light of the material discussed in this chapter, now review the definitions of statistics presented at the end of Chapter 1, especially the definition by Fisher.

4.5 In Section 4.3.1, probabilities are defined as long-run relative frequencies. How would you interpret the probabilities in the following situations?

(a) The probability of a genetic defect in a child born to a mother over 40 years of age.
(b) The probability of you, the reader, dying of leukemia.
(c) The probability of life on Mars.
(d) The probability of rain tomorrow. What does the meteorologist mean?

4.6 Take a thumbtack and throw it onto a hard surface such as a tabletop. It can come to rest in two ways; label them as follows:

$$\perp = \text{up} = U$$

$$\top = \text{down} = D$$

(a) Guess the probability of U. Record your answer.

(b) Now toss the thumbtack 100 times and calculate the proportion of times the outcome is U. How does this agree with your guess? The observed proportion is an estimate of the probability of U. (Note the implied distinction between *guess* and *estimate*.)

(c) In a class situation, split the class in half. Let each member of the first half of the class toss a thumbtack 10 times and record the outcomes as a histogram: (i) the number of times that U occurs in 10 tosses; and (ii) the proportion of times that U occurs in 10 tosses. Each member of the second half of the class will toss a thumbtack 50 times. Record the outcomes in the same way. Compare the histograms. What conclusions do you draw?

4.7 The estimation of probabilities and the proper combination of probabilities present great difficulties, even to experts. The best we can do in this book is warn you and point you to some references. A good starting point is the paper by Tversky and Kahneman [1974] reprinted in Kahneman et al. [1982]. They categorize the various errors that people make in assessing and working with probabilities. Two examples from this book will test your intuition:

(a) In tossing a coin six times, is the sequence HTHHTT more likely than the sequence HHHHHH? Give your "first impression" answer, then calculate the probability of occurrence of each of the two sequences using the rules stated in the chapter.

(b) The following is taken directly from the book:

> A certain town is served by two hospitals. In the larger hospital, about 45 babies are born each day, and in the smaller hospital about 15 babies are born each day. As you know, about 50% of all babies are boys. However, the exact percentage varies from day to day. Sometimes it may be higher than 50%, sometimes lower. For a period of one year, each hospital recorded the days on which more than 60% of the babies born were boys. Which hospital do you think recorded more such days? The larger hospital, the smaller hospital, [or were they] about the same (that is, within 5% of each other)?

Which of the rules and results stated in this chapter have guided your answer?

4.8 This problem deals with the *gambler's fallacy*, which states, roughly, that if an event has not happened for a long time, it is "bound to come up." For example, the probability of a head on the fifth toss of a coin is assumed to be greater if the preceding four tosses all resulted in tails than if the preceding four tosses were all heads. This is incorrect.

(a) What statistical property associated with coin tosses is violated by the fallacy?

(b) Give some examples of the occurrence of the fallacy from your own area of research.

(c) Why do you suppose that the fallacy is so ingrained in people?

4.9 Human blood can be classified by the ABO blood grouping system. The four groups are A, B, AB, or O, depending on whether antigens labeled *A* and *B* are present on red blood cells. Hence, the AB blood group is one where both *A* and *B* antigens are present; the O group has none of the antigens present. For three U.S. populations, the following distributions exist:

	Blood Group				
	A	**B**	**AB**	**O**	**Total**
Caucasian	0.44	0.08	0.03	0.45	1.00
American black	0.27	0.20	0.04	0.49	1.00
Chinese	0.22	0.25	0.06	0.47	1.00

For simplicity, consider only the population of American blacks in the following question. The table shows that for a person selected randomly from this population, $P[\text{A}] = 0.27$, $P[\text{B}] = 0.20$, $P[\text{AB}] = 0.04$, and $P[\text{O}] = 0.49$.

(a) Calculate the probability that a person is *not* of blood group A.

(b) Calculate the probability that a person is either A *or* O. Are these mutually exclusive events?

(c) What is the probability that a person carries *A* antigens?

(d) What is the probability that in a marriage both husband and wife are of blood group O? What rule of probability did you use? (What assumption did you need to make?)

4.10 This problem continues with the discussion of ABO blood groups of Problem 4.9. We now consider the black and Caucasian population of the United States. Approximately 20% of the U.S. population is black. This produces the following two-way classification of race and blood type:

	Blood Group				
	A	**B**	**AB**	**O**	**Total**
Caucasian	0.352	0.064	0.024	0.360	0.80
American black	0.054	0.040	0.008	0.098	0.20
Total	0.406	0.104	0.032	0.458	1.00

This table specifies, for example, that the probability is 0.352 that a person selected at random is both Caucasian and blood group A.

(a) Are the events "blood group A" and "Caucasian race" statistically independent?

(b) Are the events "blood group A" and "Caucasian race" mutually exclusive?

(c) Assuming statistical independence, what is the expected probability of the event "blood group A and Caucasian race"?

(d) What is the conditional probability of "blood group A" given that the race is Caucasian?

4.11 The distribution of the Rh factor in a Caucasian population is as follows:

Rh Positive (Rh^+, Rh^+)	Rh Positive (Rh^+, Rh^-)	Rh Negative
0.35	0.48	0.17

Rh^- subjects have two Rh^- genes, while Rh^+ subjects have two Rh^+ genes or one Rh^+ gene and one Rh^- gene. A potential problem occurs when a Rh^+ male mates with an Rh^- female.

(a) Assuming random mating with respect to the Rh factor, what is the probability of an Rh^- female mating with an Rh^+ male?

(b) Since each person contributes one gene to an offspring, what is the probability of Rh incompatibility given such a mating? (Incompatibility occurs when the fetus is Rh^+ and the mother is Rh^-.)

(c) What is the probability of incompatibility in a population of such matings?

4.12 The following data for 20- to 25-year-old white males list four primary causes of death together with a catchall fifth category, and the probability of death within five years:

Cause	Probability
Suicide	0.00126
Homicide	0.00063
Auto accident	0.00581
Leukemia	0.00023
All other causes	0.00788

(a) What is the probability of a white male aged 20 to 25 years dying from *any* cause of death? Which rule did you use to determine this?

(b) Out of 10,000 white males in the 20 to 25 age group, how many deaths would you expect in the next five years? How many for each cause?

(c) Suppose that an insurance company sells insurance to 10,000 white male drivers in the 20 to 25 age bracket. Suppose also that each driver is insured for $100,000 for accidental death. What annual rate would the insurance company have to charge to break even? (Assume a fatal accident rate of 0.00581.) List some reasons why your estimate will be too low or too high.

(d) Given that a white male aged 20 to 25 years has died, what is the most likely cause of death? Assume nothing else is known. Can you explain your statement?

4.13 If $Y \sim N(0,1)$, find

(a) $P[Y \leq 2]$

(b) $P[Y \leq -1]$

(c) $P[Y > 1.645]$

(d) $P[0.4 < Y \leq 1]$

(e) $P[Y \leq -1.96 \text{ or } Y \geq 1.96] = P[|Y| \geq 1.96]$

4.14 If $Y \sim N$ (2,4), find

(a) $P[Y \leq 2]$
(b) $P[Y \leq 0]$
(c) $P[1 \leq Y < 3]$
(d) $P[0.66 < Y \leq 2.54]$

4.15 From the paper by Winkelstein et al. [1975], glucose data for the 45 to 49 age group of California Nisei as presented by percentile are:

Percentile	90	80	70	60	50	40	30	20	10
Glucose (mg/100 mL)	218	193	176	161	148	138	128	116	104

(a) Plot these data on normal probability paper connecting the data points by straight lines. Do the data seem normal?
(b) Estimate the mean and standard deviation from the plot.
(c) Calculate the median and the interquartile range.

4.16 In a sample of size 1000 from a normal distribution, the sample mean $\overline{Y}$ was 15, and the sample variance s^2 was 100.

(a) How many values do you expect to find between 5 and 45?
(b) How many values less than 5 or greater than 45 do you expect to find?

4.17 Plot the data of Table 3.8 on probability paper. Do you think that age at death for these SIDS cases is normally distributed? Can you think of an a priori reason why this variable, age at death, is not likely to be normally distributed? Also make a QQ plot.

4.18 Plot the aflatoxin data of Section 3.2 on normal probability paper by graphing the cumulative proportions against the individual ordered values. Ignoring the last two points on the graph, draw a straight line through the remaining points and estimate the median. On the basis of the graph, would you consider the last three points in the data set *outliers*? Do you expect the arithmetic mean to be larger or smaller than the median? Why?

4.19 Plot the data of Table 3.12 (number of boys per family of eight children) on normal probability paper. Consider the endpoints of the intervals to be 0.5, 1.5, . . . , 8.5. What is your conclusion about the normality of this variable? Estimate the mean and the standard deviation from the graph and compare it with the calculated values of 4.12 and 1.44, respectively.

4.20 The random variable Y has a normal distribution with mean 1.0 and variance 9.0. Samples of size 9 are taken and the sample means, $\overline{Y}$, are calculated.

(a) What is the sampling distribution of $\overline{Y}$?
(b) Calculate $P[1 < \overline{Y} \leq 2.85]$.
(c) Let $W = 4\overline{Y}$. What is the sampling distribution of W?

4.21 The sample mean and standard deviation of a set of temperature observations are 6.1°F and 3.0°F, respectively.

(a) What will be the sample mean and standard deviation of the observations expressed in °C?

(b) Suppose that the original observations are distributed with population mean μ°F and standard deviation σ°F. Suppose also that the sample mean of 6.1°F is based on 25 observations. What is the approximate sampling distribution of the mean? What are its parameters?

4.22 The frequency distributions in Figure 3.10 were based on the following eight sets of frequencies in Table 4.6.

Table 4.6 Sets of Frequencies for Figure 3.10

	Graph Number							
Y	1	2	3	4	5	6	7	8
−1	1	1	8	1	1	14	28	10
−2	2	2	8	3	5	11	14	24
−3	5	5	8	8	9	9	10	14
−4	10	9	8	11	14	6	8	10
−5	16	15	8	14	11	3	7	9
−6	20	24	8	15	8	2	6	7
−7	16	15	8	14	11	3	5	6
−8	10	9	8	11	14	6	4	4
−9	5	5	8	8	9	9	3	2
−10	2	2	8	3	5	11	2	1
−11	1	1	8	1	1	14	1	1
Total	88	88	88	88	88	88	88	88
a_4	3.03	3.20	1.78	2.38	1.97	1.36	12.1	5.78

(The numbers are used to label the graph for purposes of this exercise.) Obtain the probability plots associated with graphs 1 and 6.

4.23 Suppose that the height of male freshmen is normally distributed with mean 69 inches and standard deviation 3 inches. Suppose also (contrary to fact) that such subjects apply and are accepted at a college without regard to their physical stature.

(a) What is the probability that a randomly selected (male) freshman is 6 feet 6 inches (78 inches) or more?

(b) How many such men do you expect to see in a college freshman class of 1000 men?

(c) What is the probability that this class has at least one man who is 78 inches or more tall?

4.24 A normal distribution (e.g., IQ) has mean $\mu = 100$ and standard deviation $\sigma = 15$. Give limits within which 95% of the following would lie:

(a) Individual observations

(b) Means of 4 observations

(c) Means of 16 observations

(d) Means of 100 observations

(e) Plot the width of the interval as a function of the sample size. Join the points with an appropriate freehand line.

(f) Using the graph constructed for part (e), estimate the width of the 95% interval for means of 36 observations.

4.25 If the standard error is the measure of the precision of a sample mean, how many observations must be taken to double the precision of a mean of 10 observations?

4.26 The duration of gestation in healthy humans is approximately 280 days with a standard deviation of 10 days.

(a) What proportion of (healthy) pregnant women will be more than one week "overdue"? Two weeks?

(b) The gestation periods for a set of four women suffering from a particular condition are 240, 250, 265, and 280 days. Is this evidence that a shorter gestation period is associated with the condition?

(c) Is the sample variance consistent with the population variance of $10^2 = 100$? (We assume normality.)

(d) In view of part (c), do you want to reconsider the answer to part (b)? Why or why not?

4.27 The mean height of adult men is approximately 69 inches; the mean height of adult women is approximately 65 inches. The variance of height for both is 4^2 inches. Assume that husband–wife pairs occur without relation to height, and that heights are approximately normally distributed.

(a) What is the sampling distribution of the mean height of a couple? What are its parameters? (The variance of two statistically independent variables is the sum of the variances.)

(b) What proportion of couples is expected to have a mean height that exceeds 70 inches?

(c) In a collection of 200 couples, how many average heights would be expected to exceed 70 inches?

***(d)** In what proportion of couples do you expect the wife to be taller than the husband?

4.28 A pharmaceutical firm claims that a new analgesic drug relieves mild pain under standard conditions for 3 hours, with a standard deviation 1 hour. Sixteen patients are tested under the same conditions and have an average pain relief time of 2.5 hours. The hypothesis that the population mean of this sample is actually 3 hours is to be tested against the hypothesis that the population mean is in fact less than 3 hours; $\alpha = 0.05$.

(a) What is an appropriate test?

(b) Set up the appropriate critical region.

(c) State your conclusion.

(d) Suppose that the sample size is doubled. State precisely how the region where the null hypothesis is not rejected is changed.

***4.29** For Y, from a normal distribution with mean μ and variance σ^2, the variance of $\overline{Y}$, based on n observations, is σ^2/n. It can be shown that the sample median $\tilde{Y}$ in this situation has a variance of approximately $1.57\sigma^2/n$. Assume that the standard error of $\tilde{Y}$ equal to the standard error of $\overline{Y}$ is desired, based on $n = 10$; 20, 50, and 100 observations. Calculate the corresponding sample sizes needed for the median.

***4.30** To determine the strength of a digitalis preparation, a continuous intrajugular perfusion of a tincture is made and the dose required to kill an animal is observed. The lethal dose varies from animal to animal such that its logarithm is normally distributed. One cubic centimeter of the tincture kills 10% of all animals, 2 cm^3 kills 75%. Determine the mean and standard deviation of the distribution of the logarithm of the lethal dose.

4.31 There were 48 SIDS cases in King County, Washington, during the years 1974 and 1975. The birthweights (in grams) of these 48 cases were:

2466	3941	2807	3118	2098	3175	3515
3317	3742	3062	3033	2353	2013	3515
3260	2892	1616	4423	3572	2750	2807
2807	3005	3374	2722	2495	3459	3374
1984	2495	3062	3005	2608	2353	4394
3232	2013	2551	2977	3118	2637	1503
2438	2722	2863	2013	3232	2863	

(a) Calculate the sample mean and standard deviation for this set.

(b) Construct a 95% confidence interval for the population mean birthweight assuming that the population standard deviation is 800 g. Does this confidence interval include the mean birthweight of 3300 g for normal children?

(c) Calculate the p-value of the sample mean observed, assuming that the population mean is 3300 g and the population standard deviation is 800 g. Do the results of this part and part (b) agree?

(d) Is the sample standard deviation consistent with a population standard deviation of 800? Carry out a hypothesis test comparing the sample variance with population variance $(800)^2$. The critical values for a chi-square variable with 47 degrees of freedom are as follows:

$$\chi^2_{0.025} = 29.96, \qquad \chi^2_{0.975} = 67.82$$

(e) Set up a 95% confidence interval for the population standard deviation. Do this by first constructing a 95% confidence interval for the population variance and then taking square roots.

4.32 In a sample of 100 patients who had been hospitalized recently, the average cost of hospitalization was \$5000, the median cost was \$4000, and the modal cost was \$2500.

(a) What was the total cost of hospitalization for all 100 patients? Which statistic did you use? Why?

(b) List one practical use for *each* of the three statistics.

(c) Considering the ordering of the values of the statistics, what can you say about the distribution of the raw data? Will it be skewed or symmetric? If skewed, which way will the skewness be?

4.33 For Example 4.8, as discussed in Section 4.6.2:

(a) Calculate the probability of a Type II error and the power if α is fixed at 0.05.

(b) Calculate the power associated with a one-tailed test.

(c) What is the price paid for the increased power in part (b)?

4.34 The theory of hypothesis testing can be used to determine statistical characteristics of laboratory tests, keeping in mind the provision mentioned in connection with Example 4.6. Suppose that albumin has a normal (Gaussian) distribution in a healthy population with mean $\mu = 3.75$ mg per 100 mL and $\sigma = 0.50$ mg per 100 mL. The normal range of values will be defined as $\mu \pm 1.96\sigma$, so that values outside these limits will be classified as "abnormal." Patients with advanced chronic liver disease have reduced albumin levels; suppose that the mean for patients from this population is 2.5 mg per 100 mL and the standard deviation is the same as that of the normal population.

(a) What are the critical values for the rejection region? (Here we work with an individual patient, $n = 1$.)

(b) What proportion of patients with advanced chronic liver disease (ACLD) will have "normal" albumin test levels?

(c) What is the probability that a patient with ACLD will be classified correctly on a test of albumin level?

(d) Give an interpretation of Type I error, Type II error, and power for this example.

(e) Suppose we consider only low albumin levels to be "abnormal." We want the same Type I error as above. What is the critical value now?

(f) In part (e), what is the associated power?

4.35 This problem illustrates the power of probability theory.

(a) Two SIDS infants are selected at random from a population of SIDS infants. We note their birthweights. What is the probability that both birthweights are (1) below the population median; (2) above the population median; (3) straddle the population median? The last interval is a nonparametric confidence interval.

(b) Do the same as in part (a) for four SIDS infants. Do you see the pattern?

(c) How many infants are needed to have interval 3 in part (a) have probability greater than 0.95?

REFERENCES

Barnett, V. [1999]. *Comparative Statistical Inference*. Wiley, Chichester, West Sussex, England.

Berkow, R. (ed.) [1999]. *The Merck Manual of Diagnosis and Therapy*, 17th ed. Merck, Rahway, NJ.

Berry, D. A. [1996]. *Statistics: A Bayesian Perspective*. Duxbury Press, North Scituate, MA.

Carlin, B. P., and Louis, T. A. [2000]. *Bayes and Empirical Bayes Methods for Data Analysis*, 2nd ed. CRC Press, Boca Raton, FL.

Elveback, L. R., Guillier, L., and Keating, F. R., Jr. [1970]. Health, normality and the ghost of Gauss. *Journal of the American Medical Association*, **211**: 69–75.

Fisher, R. A. [1956]. *Statistical Methods and Scientific Inference*. Oliver & Boyd, London.

Fleiss, J. L., Levin, B., and Park, M. C. [2003]. *Statistical Methods for Rates and Proportions*, 3rd ed. Wiley, New York.

Galton, F. [1889]. *Natural Inheritance*. Macmillan, London.

Gelman, A., Carlin, J. B., Stern, H. S., and Rubin, D. A. [1995]. *Bayesian Data Analysis.* CRC Press, Boca Raton, FL.

Golubjatnikov, R., Paskey, T., and Inhorn, S. L. [1972]. Serum cholesterol levels of Mexican and Wisconsin school children. *American Journal of Epidemiology*, **96**: 36–39.

Hacking, I. [1965]. *Logic of Statistical Inference*. Cambridge University Press, London.

Hagerup, L., Hansen, P. F., and Skov, F. [1972]. Serum cholesterol, serum-triglyceride and ABO blood groups in a population of 50-year-old Danish men and women. *American Journal of Epidemiology*, **95**: 99–103.

Kahneman, D., Slovic, P., and Tversky, A. (eds.) [1982]. *Judgement under Uncertainty: Heuristics and Biases*. Cambridge University Press, Cambridge.

Kato, H., Tillotson, J., Nichaman, M. Z., Rhoads, G. G., and Hamilton, H. B. [1973]. Epidemiologic studies of coronary heart disease and stroke in Japanese men living in Japan, Hawaii and California: serum lipids and diet. *American Journal of Epidemiology*, **97**: 372–385.

Kesteloot, H., and van Houte, O. [1973]. An epidemiologic study of blood pressure in a large male population. *American Journal of Epidemiology*, **99**: 14–29.

Kruskal, W., and Mosteller, F. [1979a]. Representative sampling I: non-scientific literature. *International Statistical Review*, **47**: 13–24.

Kruskal, W., and Mosteller, F. [1979b]. Representative sampling II: scientific literature excluding statistics. *International Statistical Review*, **47**: 111–127.

Kruskal, W., and Mosteller, F. [1979c]. Representative sampling III: the current statistical literature. *International Statistical Review*, **47**: 245–265.

Lehtonen, R., and Pahkinen, E. J. [1995]. *Practical Methods for Design and Analysis of Complex Surveys*. Wiley, New York.

Levy, P. S., and Lemeshow S. [1999]. *Sampling of Populations: Methods and Applications*, 3rd Ed. Wiley, New York.

Lohr, S. [1999]. *Sample: Design and Analysis*. Duxbury Press, Pacific Grove, CA.

Moore, D. S. [2001]. *Statistics: Concepts and Controversies*, 5th ed. W. H. Freeman, New York.

Murphy, E. A. [1979]. *Biostatistics in Medicine*. Johns Hopkins University Press, Baltimore.

Runes, D. D. [1959]. *Dictionary of Philosophy*. Littlefield, Adams, Ames, IA.

Rushforth, N. B., Bennet, P. H., Steinberg, A. G., Burch, T. A., and Miller, M. [1971]. Diabetes in the Pima Indians: evidence of bimodality in glucose tolerance distribution. *Diabetes*, **20**: 756–765. Copyright © 1971 by the American Diabetic Association.

Savage, I. R. [1968]. *Statistics: Uncertainty and Behavior*. Houghton Mifflin, Boston.

Shepard, D. S., and Neutra, R. [1977]. Pitfalls in sampling medical visits. *American Journal of Public Health*, **67**: 743–750. Copyright © by the American Public Health Association.

Tversky, A., and Kahneman, D. [1974]. Judgment under uncertainty: heuristics and biases. *Science*, **185**: 1124–1131. Copyright © by the AAAS.

Winkelstein, W. Jr., Kazan, A., Kato, H., and Sachs, S. T. [1975]. Epidemiologic studies of coronary heart disease and stroke in Japanese men living in Japan, Hawaii and California: blood pressure distributions. *American Journal of Epidemiology*, **102**: 502–513.

Zervas, M., Hamacher, H., Holmes, O., and Rieder, S. V. [1970]. Normal laboratory values. *New England Journal of Medicine*, **283**: 1276–1285.

CHAPTER 5

One- and Two-Sample Inference

5.1 INTRODUCTION

In Chapter 4 we laid the groundwork for statistical inference. The following steps were involved:

1. Define the population of interest.
2. Specify the parameter(s) of interest.
3. Take a random sample from the population.
4. Make statistical inferences about the parameter(s): (a) estimation; and (b) hypothesis testing.

A good deal of "behind-the-scenes" work was necessary, such as specifying what is meant by a *random* sample, but you will recognize that the four steps above summarize the process. In this chapter we (1) formalize the inferential process by defining pivotal quantities and their uses (Section 5.2); (2) consider normal distributions for which *both* the mean and variance are unknown, which will involve the use of the famous Student t-distribution (Sections 5.3 and 5.4); (3) extend the inferential process to a comparison of two normal populations, including comparison of the variances (Sections 5.5 to 5.7); and (4) finally begin to answer the question frequently asked of statisticians: "How many observations should I take?" (Section 5.9).

5.2 PIVOTAL VARIABLES

In Chapter 4, confidence intervals and tests of hypotheses were introduced in a somewhat ad hoc fashion as inference procedures about population parameters. To be able to make inferences, we needed the sampling distributions of the statistics that estimated the parameters. To make inferences about the mean of a normal distribution (with variance known), we needed to know that the sample mean of a random sample was normally distributed; to make inferences about the variance of a normal distribution, we used the chi-square distribution. A pattern also emerged in the development of estimation and hypothesis testing procedures. We discuss next the unifying scheme. This will greatly simplify our understanding of the statistical procedures, so that attention can be focused on the assumptions and appropriateness of such procedures rather than on understanding the mechanics.

Biostatistics: A Methodology for the Health Sciences, Second Edition, by Gerald van Belle, Lloyd D. Fisher, Patrick J. Heagerty, and Thomas S. Lumley
ISBN 0-471-03185-2

In Chapter 4, we used basically two quantities in making inferences:

$$Z = \frac{\overline{Y} - \mu}{\sigma/\sqrt{n}} \quad \text{and} \quad \chi^2 = \frac{(n-1)s^2}{\sigma^2}$$

What are some of their common features?

1. Each of these expressions involves *at least* a statistic *and* a parameter for the statistic estimated: for example, s^2 and σ^2 in the second formula.
2. The distribution of the quantity was tabulated in a standard normal table or chi-square table.
3. Distribution of the quantity was not dependent on a value of the parameter. Such a distribution is called a *fixed distribution*.
4. Both confidence intervals and tests of hypotheses were derived from a probability inequality involving either Z or χ^2.

Formally, we define:

Definition 5.1. A *pivotal variable* is a function of statistic(s) and parameter(s) having the same fixed distribution (usually tabulated) for all values of the parameter(s).

The quantities Z and χ^2 are pivotal variables. One of the objectives of theoretical statistics is to develop appropriate pivotal variables for experimental situations that cannot be modeled adequately by existing variables.

In Table 5.1 are listed eight pivotal variables and their use in statistical inference. In this chapter we introduce pivotal variables 2, 5, 6, and 8. Pivotal variables 3 and 4 are introduced in Chapter 6. For each variable, the fixed or tabulated distribution is given as well as the formula for a $100(1-\alpha)\%$ confidence interval. The corresponding test of hypothesis is obtained by replacing the statistic(s) by the hypothesized parameter value(s). The table also lists the assumptions underlying the test. Most of the time, the minimal assumption is that of normality of the underlying observations, or appeal is made to the central limit theorem.

Pivotal variables are used primarily in inferences based on the normal distribution. They provide a methodology for estimation and hypothesis testing. The aim of estimation and hypothesis testing is to make probabilistic statements about parameters. For example, confidence intervals and p-values make statements about parameters that have probabilistic aspects. In Chapters 6 to 8 we discuss inferences that do not depend as explicitly on pivotal variables; however, even in these procedures, the methodology associated with pivotal variables is used; see Figure 5.1.

5.3 WORKING WITH PIVOTAL VARIABLES

We have already introduced the manipulation of pivotal variables in Section 4.7. Table 5.1 summarizes the end result of the manipulations. In this section we again outline the process for the case of one sample from a normal population with the variance known. We have a random sample of size n from a normal population with mean μ and variance σ^2 (known). We start with the basic probabilistic inequality

$$P[z_{\alpha/2} \le Z \le z_{1-\alpha/2}] = 1 - \alpha$$

Table 5.1 Pivotal Variables and Their Use in Statistical Inference

	Pivotal Variable	Assumptions: Model	Assumptions: Other[a]	$100(1-\alpha)\%$ Confidence Interval[b]	Inference/Comments
1.	$\dfrac{\overline{Y}-\mu}{\sigma/\sqrt{n}} = Z$	$N(0, 1)$	(i) and (iii); or (ii)	$\overline{Y} \pm \dfrac{z_*\sigma}{\sqrt{n}}$	μ or $\mu = \mu_1 - \mu_2$ based on paired data $z_* = z_{1-\alpha/2}$
2.	$\dfrac{(\overline{Y}_1-\overline{Y}_2)-(\mu_1-\mu_2)}{\sqrt{\sigma_1^2/n_1+\sigma_2^2/n_2}} = Z$	$N(0, 1)$	(i) and (iii); or (ii)	$(\overline{Y}_1-\overline{Y}_2) \pm z_*\sqrt{\dfrac{\sigma_1^2}{n_1}+\dfrac{\sigma_2^2}{n_2}}$	$\mu_1 - \mu_2$ based on independent data $z_* = z_{1-\alpha/2}$
3.	$\dfrac{p-\pi}{\sqrt{p(1-p)/n}} = Z$	$N(0, 1)$	(ii)	$p \pm z_*\sqrt{\dfrac{p(1-p)}{n}}$	π $z_* = z_{1-\alpha/2}$
4.	$\dfrac{(p_1-p_2)-(\pi_1-\pi_2)}{\sqrt{p_1q_1/n_1+p_2q_2/n_2}} = Z$	$N(0, 1)$	(ii)	$(p_1-p_2) \pm z_*\sqrt{\dfrac{p_1q_1}{n_1}+\dfrac{p_2q_2}{n_2}}$	$\pi_1 - \pi_2$ based on independent data $z_* = z_{1-\alpha/2}$ $q_1 = 1-p_1$; $q_2 = 1-p_2$
5.	$\dfrac{\overline{Y}-\mu}{s/\sqrt{n}} = t$	t_{n-1}	(i)	$\overline{Y} \pm \dfrac{t_*s}{\sqrt{n}}$	μ or $\mu = \mu_1 - \mu_2$ based on paired data $t_* = t_{n-1,1-\alpha/2}$
6.	$\dfrac{(\overline{Y}_1-\overline{Y}_2)-(\mu_1-\mu_2)}{s_p\sqrt{1/n_1+1/n_2}} = t$	$t_{n_1+n_2-2}$	(i) and (iv)	$(\overline{Y}_1-\overline{Y}_2) \pm t_*s_p\sqrt{\dfrac{1}{n_1}+\dfrac{1}{n_2}}$	$\mu_1 - \mu_2$ based on independent data $t_* = t_{n_1+n_2-2,1-\alpha/2}$ $s_p^2 = \dfrac{(n_1-1)s_1^2+(n_2-1)s_2^2}{n_1+n_2-2}$
7.	$\dfrac{(n-1)s^2}{\sigma^2} = \chi^2$	χ^2_{n-1}	(i)	$\dfrac{(n-1)s^2}{\chi_*^2}, \dfrac{(n-1)s^2}{\chi_{**}^2}$	σ^2 $\chi_*^2 = \chi^2_{n-1,1-\alpha/2}$ $\chi_{**}^2 = \chi^2_{n-1,\alpha/2}$
8.	$\dfrac{s_1^2/\sigma_1^2}{s_2^2/\sigma_2^2} = F$	F_{n_1-1,n_2-1}	(i)	$\dfrac{s_1^2/s_2^2}{F_*}, \dfrac{s_1^2/s_2^2}{F_{**}}$	$\dfrac{\sigma_1^2}{\sigma_2^2}$ $F_* = F_{n_1-1,n_2-1,1-\alpha/2}$ $F_{**} = F_{n_1-1,n_2-1,\alpha/2}$

[a] Assumptions (other): (i) Observations (for paired data, the differences) are independent, normally distributed; (ii) large-sample result; (iii) variance(s) known; (iv) population variances equal.

[b] To determine the appropriate critical region in a test of hypothesis, replace statistic(s) by hypothesized values of parameter(s).

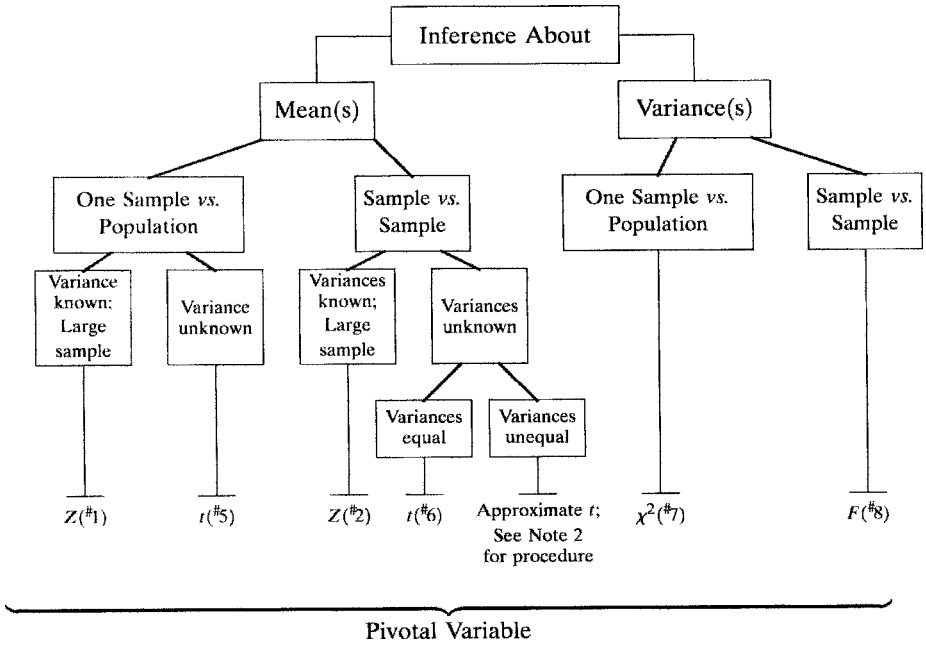


Figure 5.1 Methodology associated with pivotal variables.

We substitute $Z = (\overline{Y} - \mu)/(\sigma_0/\sqrt{n})$, writing σ_0 to indicate that the population variance is assumed to be known:

$$P\left[z_{\alpha/2} \leq \frac{\overline{Y} - \mu}{\sigma_0/\sqrt{n}} \leq z_{1-\alpha/2}\right] = 1 - \alpha$$

Solving for μ produces a $100(1-\alpha)\%$ confidence interval for μ; solving for $\overline{Y}$ and substituting a hypothesized value, μ_0, for μ produces the nonrejection region for a $100(\alpha)\%$ test of the hypothesis:

$100(1 - \alpha)\%$ confidence interval for μ:

$$[\overline{Y} + z_{\alpha/2}\sigma_0/\sqrt{n}, \quad \overline{Y} + z_{1-\alpha/2}\sigma_0/\sqrt{n}]$$

$100(\alpha)\%$ hypothesis test of $\mu = \mu_0$; reject if $\overline{Y}$ is not in

$$[\mu_0 + z_{\alpha/2}\sigma_0/\sqrt{n}, \quad \mu_0 + z_{1-\alpha/2}\sigma_0/\sqrt{n}]$$

Notice again the similarity between the two intervals. These intervals can be written in an abbreviated form using the fact that $z_{\alpha/2} = -z_{1-\alpha/2}$,

$$\overline{Y} \pm \frac{z_{1-\alpha/2}\sigma_0}{\sqrt{n}} \quad \text{and} \quad \mu_0 \pm \frac{z_{1-\alpha/2}\sigma_0}{\sqrt{n}}$$

for the confidence intervals and tests of hypothesis, respectively.

To calculate the p-value associated with a test statistic, again use is made of the pivotal variable. The null hypothesis value of the parameter is used to calculate the probability of the observed value of the statistic or an observation more extreme. As an illustration, suppose that a population variance is claimed to be $100(\sigma_0^2 = 100)$ vs. a larger value $(\sigma_0^2 > 100)$. From

a random sample of size 11, we are given $s^2 = 220$. What is the p-value for this value (or more extreme)? We use the pivotal quantity $(n-1)s^2/\sigma_0^2$, which under the null hypothesis is chi-square with 10 degrees of freedom.

The one-sided p-value is the probability of a value of $s^2 \geq 220$. Using the pivotal variable, we get

$$P\left[\chi^2 \geq \frac{(11-1)(220)}{100}\right] = P[\chi^2 \geq 22.0]$$

where χ^2 has $11 - 1 = 10$ degrees of freedom, giving a one-sided p-value of 0.0151.

Additional examples in the use of pivotal variables will occur throughout this and later chapters. See Note 5.1 for some additional comments on the pivotal variable approach.

5.4 t-DISTRIBUTION

For a random sample from a normal distribution with mean μ and variance σ^2 (known), the quantity $Z = (\overline{Y} - \mu)/(\sigma/\sqrt{n})$ is a pivotal quantity that has a normal (0,1) distribution. What if the variance is unknown? Suppose that we replace the variance σ^2 by its estimate s^2 and consider the quantity $(\overline{Y} - \mu)/(s/\sqrt{n})$. What is its sampling distribution?

This problem was solved by the statistician W. S. Gossett, in 1908, who published the result under the pseudonym "Student" using the notation

$$t = \frac{\overline{Y} - \mu}{s/\sqrt{n}}$$

The distribution of this variable is now called *Student's t-distribution*. Gossett showed that the distribution of t was similar to that of the normal distribution, but somewhat more "heavy-tailed" (see below), and that for each sample size there is a different distribution. The distributions are indexed by $n - 1$, the degrees of freedom identical to that of the chi-square distribution. The t-distribution is symmetrical, and as the degrees of freedom become infinite, the standard normal distribution is reached.

A picture of the t-distribution for various degrees of freedom, as well as the limiting case of the normal distribution, is given in Figure 5.2. Note that like the standard normal distribution, the t-distribution is bell-shaped and symmetrical about zero. The t-distribution is *heavy-tailed*: The area to the right of a specified positive value is greater than for the normal distribution; in other words, the t-distribution is less "pinched." This is reasonable; unlike a standard normal deviate where only the mean $(\overline{Y})$ can vary (μ and σ are fixed), the t statistic can vary with *both* $\overline{Y}$ and s, so that t will vary even if $\overline{Y}$ is fixed.

Percentiles of the t-distribution are denoted by the symbol $t_{v,\alpha}$, where v indicates the degrees of freedom and α the 100αth percentile. This is indicated in Figure 5.3. In Table 5.1, rather than writing all the subscripts on the t variate, an asterisk is used and explained in the comment part of the table.

Table A.4 lists the percentiles of the t-distribution for each degree of freedom to 30, by fives to 100, and values for 200, 500, and ∞ degrees of freedom. This table lists the t-values such that the percent to the left is as specified by the column heading. For example, for an area of 0.975 (97.5%), the t-value for six degrees of freedom is 2.45. The last row in this column corresponds to a t with an infinite number of degrees of freedom, and the value of 1.96 is identical to the corresponding value of Z; that is, $P[Z \leq 1.96] = 0.975$. You should verify that the last row in this table corresponds precisely to the normal distribution values (i.e., $t_\infty = Z$) and that for practical purposes, t_n and Z are equivalent for $n > 30$. What are the mean and the variance of the t-distribution? The mean will be zero, and the variance is $v/(v-2)$. In the symbols used in Chapter 4, $E(t) = 0$ and $\text{Var}(t) = v/(v-2)$.

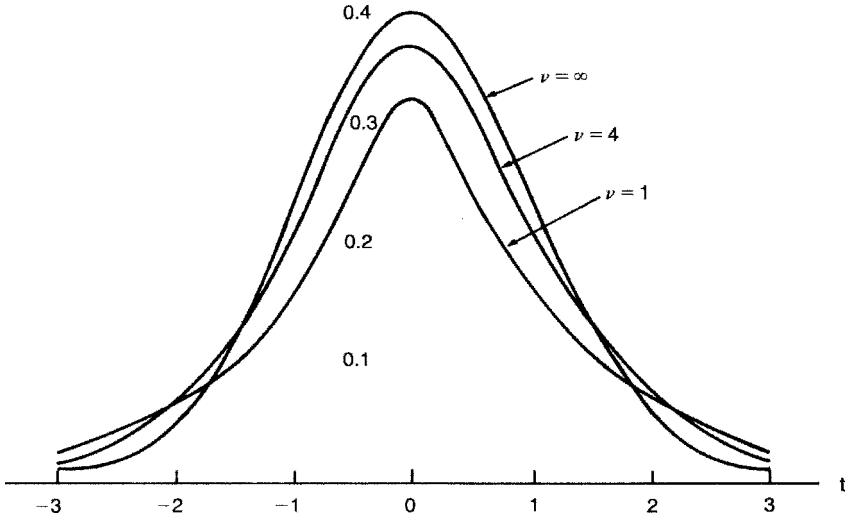


Figure 5.2 Student t-distribution with one, four, and ∞ degrees of freedom.

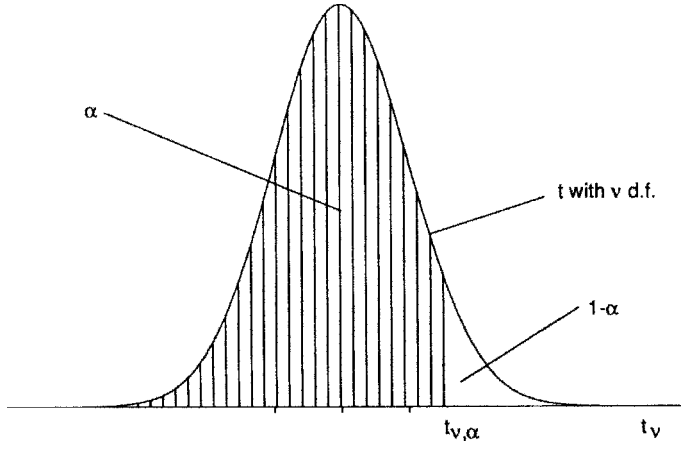


Figure 5.3 Percentiles of the t-distribution.

The converse table of percentiles for a given absolute t-value is given in the Web appendix, and most statistical software will calculate it. We find that the probability of a t-value greater than 1 in absolute value for one degree of freedom is 0.500; the corresponding areas for 7, 30, and ∞ degrees of freedom are 0.351, 0.325, and 0.317, respectively. Thus, at 30 degrees of freedom, the t-distribution is for most practical purposes, indistinguishable from a normal distribution. The term *heavy-tailed* can now be made precise: For a specified value (e.g., with an abscissa value of 1), $P[t_1 \geq 1] > P[t_7 \geq 1] > P[t_{10} \geq 1] > P[Z \geq 1]$.

5.5 ONE-SAMPLE INFERENCE: LOCATION

5.5.1 Estimation and Testing

We begin this section with an example.

Example 5.1. In Example 4.9 we considered the birthweight in grams of the first 11 SIDS cases occurring in King Country in 1969. In this example, we consider the birthweights of the first 15 cases born in 1977. The birthweights for the latter group are

2013	3827	3090	3260	4309	3374	3544	2835
3487	3289	3714	2240	2041	3629	3345	

The mean and standard deviation of this sample are 3199.8 g and 663.00 g, respectively. Without assuming that the population standard deviation is known, can we obtain an interval estimate for the population mean or test the null hypothesis that the population birthweight average of SIDS cases is 3300 g (the same as the general population)?

We can now use the t-distribution. Assuming that birthweights are normally distributed, the quantity

$$\frac{\overline{Y} - \mu}{s/\sqrt{15}}$$

has a t-distribution with $15 - 1 = 14$ degrees of freedom.

Using the estimation procedure, the point estimate of the population mean birthweight of SIDS cases is $3199.8 \doteq 3200$ g. A 95% confidence interval can be constructed on the basis of the t-distribution. For a t-distribution with $15 - 1 = 14$ degrees of freedom, the critical values are ± 2.14, that is, $P[-2.14 \leq t_{14} \leq 2.14] = 0.95$. Using Table 5.1, a 95% confidence interval is constructed using pivotal variable 5:

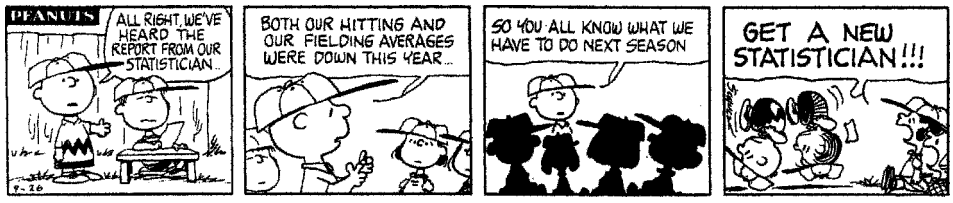
$$3200 \pm \frac{(2.14)(663.0)}{\sqrt{15}} = 3200 \pm 366, \qquad \text{lower limit : 2834 g, upper limit : 3566 g}$$

Several comments are in order:

1. This interval includes 3300 g, the average birthweight in the non-SIDS population. If the analysis had followed a hypothesis-testing procedure, we could not have rejected the null hypothesis on the basis of a two-tailed test.
2. The standard error, $633.0/\sqrt{15}$, is multiplied by 2.14 rather than the critical value 1.96 using a normal distribution. Thus, the confidence interval is wider by approximately 9%. This is the price paid for our ignorance about the value of the population standard deviation. Even in this fairly small sample, the price is modest.

5.5.2 t-Tests for Paired Data

A second example of the one-sample t-test involves its application to paired data. What are *paired data*? Typically, the term refers to repeated or multiple measurements on the same subjects. For example, we may have a measurement of the level of pain before and after administration of an analgesic drug. A somewhat different experiment might consider the level of pain in response to each of *two* drugs. One of these could be a placebo. The first experiment has the weakness that there may be a spontaneous reduction in level of pain (e.g., postoperative pain level), and thus the difference in the responses (after/before) may be made up of two effects: an effect of the drug as well as the spontaneous reduction. Some experimental design considerations are discussed further in Chapter 10. The point we want to make with these two examples is that the basic data consist of pairs, and what we want to look at is the differences within the pairs. If, in the second example, the treatments are to be compared, a common null hypothesis is that the effects are the same and therefore the differences in the treatments should be centered around zero. A natural approach then tests whether the mean of the *sample differences* could have come from a population of differences with mean zero. If we assume that the means of the sample differences are normally distributed, we can apply the t-test (under the null hypothesis),



Cartoon 5.1 PEANUTS. (Reprinted by permission of UFS, Inc.)

Table 5.2 Response of 13 Patients to Aminophylline Treatment at 16 Hours Compared with 24 Hours before Treatment (Apneic Episodes per Hour)

Patient	24 h Before	16 h After	Before–After (Difference)
1	1.71	0.13	1.58
2	1.25	0.88	0.37
3	2.13	1.38	0.75
4	1.29	0.13	1.16
5	1.58	0.25	1.33
6	4.00	2.63	1.37
7	1.42	1.38	0.04
8	1.08	0.50	0.58
9	1.83	1.25	0.58
10	0.67	0.75	−0.08
11	1.13	0.00	1.13
12	2.71	2.38	0.33
13	1.96	1.13	0.83
Total	22.76	12.79	9.97
Mean	1.751	0.984	0.767
Variance	0.7316	0.6941	0.2747
Standard deviation	0.855	0.833	0.524

Source: Data from Bednarek and Roloff [1976].

and estimate the variance of the population of differences σ^2, by the variance of the *sample differences*, s^2.

Example 5.2. The procedure is illustrated with data from Bednarek and Roloff [1976] dealing with the treatment of apnea (a transient cessation of respiration) using a drug, aminophylline, in premature infants. The variable of interest, "average number of apneic episodes per hour," was measured before and after treatment with the drug. An episode was defined as the absence of spontaneous breathing for more than 20 seconds or less if associated with bradycardia or cyanosis.

Patients who had "six or more apneic episodes on each of two consecutive 8 h shifts were admitted to the study." For purposes of the study, consider only the difference between the average number of episodes 24 hours before treatment and 16 hours after. This difference is given in the fourth column of Table 5.2. The average difference for the 13 patients is 0.767 episode per hour. That is, there is a change from 1.751 episodes per hour before treatment to 0.984 episode per hour at 16 hours after treatment.

The standard deviation of the differences is $s = 0.524$. The pivotal quantity to be used is variable 5 from Table 5.1. The argument is as follows: The basic statement about the pivotal variable t with $13 - 1 = 12$ degrees of freedom is $P[-2.18 \leq t_{12} \leq 2.18] = 0.95$ using Table A.4. The form taken for this example is

$$P\left[-2.18 \leq \frac{\overline{Y} - \mu}{0.524/\sqrt{13}} \leq 2.18\right] = 0.95$$

To set up the region to test some hypothesis, we solve for $\overline{Y}$ as before. The region then is

$$P[\mu - 0.317 \leq \overline{Y} \leq \mu + 0.317] = 0.95$$

What is a "reasonable" value to hypothesize for μ? The usual procedure in this type of situation is to assume that the treatment has "no effect." That is, the average difference in the number of apneic episodes from before to after treatment represents random variation. If there is no difference in the population average number of episodes before and after treatment, we can write this as

$$H_0\colon\ \mu = 0$$

We can now set up the hypothesis-testing region as illustrated in Figures 5.4 and 5.5. Figure 5.4 indicates that the sample space can be partitioned without knowing the observed value of $\overline{Y}$. Figure 5.5 indicates the observed value of $\overline{Y} = 0.767$ episode per hour; it clearly falls into the rejection region. Note that the scale has been changed from Figure 5.4 to accommodate the value observed. Hence the null hypothesis is rejected and it is concluded that the average number of apneic episodes observed 16 hours after treatment differs significantly from the average number of apneic episodes observed 24 hours before treatment.

This kind of test is often used when two treatments are applied to the same experimental unit or when the experimental unit is observed over time and a treatment is administered so that it

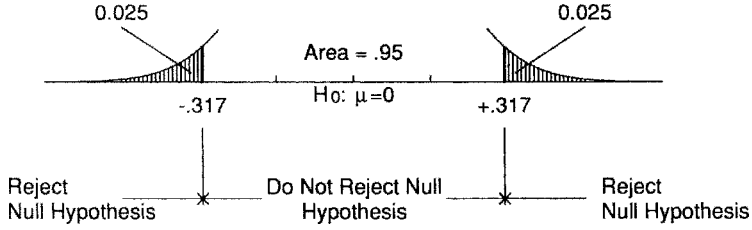


Figure 5.4 Partitioning of sample space of $\overline{Y}$ into two regions: (*a*) region where the null hypothesis is not rejected, and (*b*) region where it is rejected. (Data from Bednarek and Roloff [1976]; see Table 5.2.)

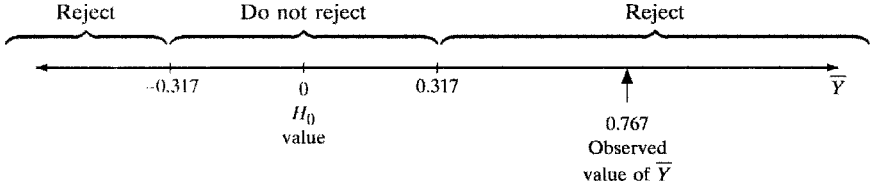


Figure 5.5 Observed value of $\overline{Y}$ and location on the sample space. (Data from Bednarek and Roloff [1976]; see Table 5.2.)

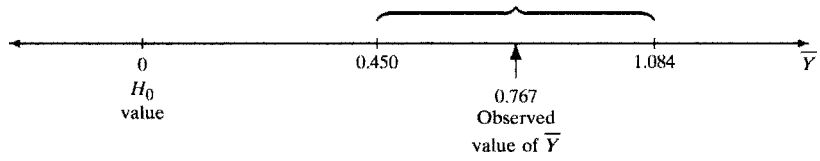


Figure 5.6 A 95% confidence interval for the difference in number of apneic episodes per hour. (Data from Bednarek and Roloff [1976]; see Table 5.2.)

is meaningful to speak of pretreatment and posttreatment situations. As mentioned before, there is the possibility that changes, if observed, are in fact due to changes over time and not related to the treatment.

To construct a confidence interval, we solve the inequality for μ so that we get

$$P[\overline{Y} - 0.317 \leq \mu \leq \overline{Y} + 0.317] = 0.95$$

Again, this interval can be set up to this point without knowing the value of $\overline{Y}$. The value of $\overline{Y}$ is observed to be 0.767 episode per hour, so that the 95% confidence interval becomes

$$[0.767 - 0.317 \leq \mu \leq 0.767 + 0.317] \text{ or } [0.450 \leq \mu \leq 1.084]$$

This interval is displayed in Figure 5.6. Two things should be noted:

1. The width of the confidence interval is the same as the width of the region where the null hypothesis is not rejected (cf. Figure 5.5).
2. The 95% confidence interval does not include zero, the null hypothesis value of μ.

5.6 TWO-SAMPLE STATISTICAL INFERENCE: LOCATION

5.6.1 Independent Random Variables

A great deal of research activity involves the comparison of two or more groups. For example, two cancer therapies may be investigated: one group of patients receives one treatment and a second group the other. The experimental situation can be thought of in two ways: (1) there is one population of subjects, and the treatments induce two subpopulations; or (2) we have two populations that are identical except in their responses to their respective treatments. If the assignment of treatment is random, the two situations are equivalent.

Before exploring this situation, we need to state a definition and a statistical result:

Definition 5.2. Two random variables Y_1 and Y_2 are *statistically independent* if for all fixed values of numbers (say, y_1 and y_2),

$$P[Y_1 \leq y_1, Y_2 \leq y_2] = P[Y_1 \leq y_1]P[Y_2 \leq y_2]$$

The notation $[Y_1 \leq y_1, Y_2 \leq y_2]$ means that Y_1 takes on a value less than or equal to y_1, and Y_2 takes on a value less than or equal to y_2. If we define an event A to have occurred when Y_1 takes on a value less than or equal to y_1, and an event B when Y_2 takes on a value less than or equal to y_2, Definition 5.2 is equivalent to the statistical independence of events $P[AB] = P[A]P[B]$ as defined in Chapter 4. So the difference between statistical independence of random variables and statistical independence of events is that the former in effect describes a relationship between many events (since the definition has to be true for *any* set of values of y_1 and y_2). A basic result can now be stated:

Result 5.1. If Y_1 and Y_2 are statistically independent random variables, then for any two constants a_1 and a_2, the random variable $W = a_1Y_1 + a_2Y_2$ has mean and variance

$$E(W) = a_1E(Y_1) + a_2E(Y_2)$$
$$\text{Var}(W) = a_1^2\text{Var}(Y_1) + a_2^2\text{Var}(Y_2)$$

The only new aspect of this result is that of the variance. In Note 4.10, the expectation of W was already derived. Before giving an example, we also state:

Result 5.2. If Y_1 and Y_2 are statistically independent random variables that are normally distributed, $W = a_1Y_1 + a_2Y_2$ is normally distributed with mean and variance given by Result 5.1.

Example 5.3. Let Y_1 be normally distributed with mean $\mu_1 = 100$ and variance $\sigma_1^2 = 225$; let Y_2 be normally distributed with mean $\mu_2 = 50$ and variance $\sigma_2^2 = 175$. If Y_1 and Y_2 are statistically independent, $W = Y_1 + Y_2$ is normally distributed with mean $100 + 50 = 150$ and variance $225 + 175 = 400$. This and additional examples are given in the following summary:

$$Y_1 \sim N(100, 225),\ Y_2 \sim N(50, 175)$$

W	Mean of W	Variance of W
$Y_1 + Y_2$	150	400
$Y_1 - Y_2$	50	400
$2Y_1 + Y_2$	250	1075
$2Y_1 - 2Y_2$	100	1600

Note that the variance of $Y_1 - Y_2$ is the same as the variance of $Y_1 + Y_2$; this is because the coefficient of Y_1, -1, is squared in the variance formula and $(-1)^2 = (+1)^2 = 1$. In words, the variance of a sum of independent random variables is the same as the variance of a difference of independent random variables.

Example 5.4. Now we look at an example that is more interesting and indicates the usefulness of the two results stated. Heights of females and males are normally distributed with means 162 cm and 178 cm and variances $(6.4\text{ cm})^2$ and $(7.5\text{ cm})^2$, respectively. Let Y_1 = height of female; let Y_2 = height of male. Then we can write

$$Y_1 \sim N(162, (6.4)^2) \quad \text{and} \quad Y_2 \sim N(178, (7.5)^2)$$

Now consider husband–wife pairs. Suppose (probably somewhat contrary to societal *mores*) that husband–wife pairs are formed independent of stature. That is, we interpret this statement to mean that Y_1 and Y_2 are statistically independent. The question is: On the basis of this model, what is the probability that the wife is taller than the husband? We formulate the problem as follows: Construct the new variable $W = Y_1 - Y_2$. From Result 5.2 it follows that

$$W \sim N(-16, (6.4)^2 + (7.5)^2)$$

Now the question can be translated into a question about W; namely, if the wife is taller than the husband, $Y_1 > Y_2$, or $Y_1 - Y_2 > 0$, or $W > 0$. Thus, the question is reformulated as $P[W > 0]$.

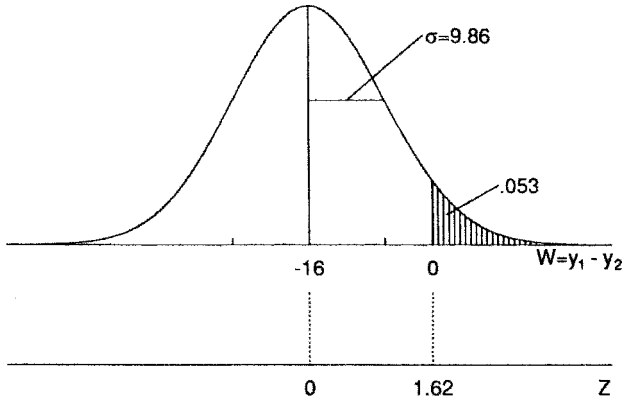


Figure 5.7 Heights of husband–wife pairs.

Hence,

$$\begin{aligned} P[W > 0] &= P\left[Z > \frac{0-(-16)}{\sqrt{(6.4)^2+(7.5)^2}}\right] \\ &\doteq P\left[Z > \frac{16}{9.86}\right] \\ &\doteq P[Z > 1.62] \\ &\doteq 0.053 \end{aligned}$$

so that under the model, in 5.3% of husband–wife pairs the wife will be taller than the husband. Figure 5.7 indicates the area of interest.

5.6.2 Estimation and Testing

The most important application of Result 5.1 involves distribution of the difference of two sample means. If $\overline{Y}_1$ and $\overline{Y}_2$ are the means from two random samples of size n_1 and n_2, respectively, and Y_1 and Y_2 are normally distributed with means μ_1 and μ_2 and variances σ_1^2 and σ_2^2, then by Result 5.2,

$$\overline{Y}_1 - \overline{Y}_2 \sim N\left(\mu_1 - \mu_2, \frac{\sigma_1^2}{n_1} + \frac{\sigma_2^2}{n_2}\right)$$

so that

$$\frac{(\overline{Y}_1 - \overline{Y}_2) - (\mu_1 - \mu_2)}{\sqrt{\sigma_1^2/n_1 + \sigma_2^2/n_2}} = Z$$

has a standard normal distribution. This, again, is a pivotal variable, number 2 in Table 5.1. We are now in a position to construct confidence intervals for the quantity $\mu_1 - \mu_2$ or to do hypothesis testing. In many situations, it will be reasonable to assume (null hypothesis) that $\mu_1 = \mu_2$, so that $\mu_1 - \mu_2 = 0$; although the values of the two parameters are unknown, it is reasonable for testing purposes to assume that they are equal, and hence, the difference will be zero. For example, in a study involving two treatments, we could assume that the treatments were equally effective (or ineffective) and that differences between the treatments should be centered at zero.

How do we determine whether or not random variables are statistically independent? The most common way is to note that they are causally independent in the population. That is, the value of Y for one person does not affect the value for another. As long as the observations are sampled independently (e.g., by simple random sampling), they will remain statistically independent. In some situations it is not clear a priori whether variables are independent and there are statistical procedures for testing this assumption. They are discussed in Chapter 9. For the present we will assume that the variables we are dealing with are either statistically independent or if not (as in the case of the paired t-test discussed in Section 5.5.2), use aspects of the data that can be considered statistically independent.

Example 5.5. Zelazo et al. [1972] studied the age at which children walked as related to "walking exercises" given newborn infants. They state that "if a newborn infant is held under his arms and his bare feet are permitted to touch a flat surface, he will perform well-coordinated walking movements similar to those of an adult." This reflex disappears by about eight weeks. They placed 24 white male infants into one of four "treatment" groups. For purposes of this example, we consider only two of the four groups: "active exercise group" and "eight-week control group." The active group received daily stimulation of the walking reflex for eight weeks. The control group was tested at the end of the eight-week treatment period, but there was no intervention. The age at which the child subsequently began to walk was then reported by the mother. The data and basic calculations are shown in Table 5.3.

For purposes of this example, we assume that the sample standard deviations are, in fact, population standard deviations, so that Result 5.2 can be applied. In Example 5.6 we reconsider this example using the two-sample t-test. For this example, we have

$n_1 = 6$	$n_2 = 5$
$\overline{Y}_1 = 10.125$ months	$\overline{Y}_2 = 12.350$ months
$\sigma_1 = 1.4470$ months (assumed)	$\sigma_2 = 0.9618$ month (assumed)

For purposes of this example, the quantity

$$Z = \frac{(\overline{Y}_1 - \overline{Y}_2) - (\mu_1 - \mu_2)}{\sqrt{(1.4470)^2/6 + (0.9618)^2/5}} = \frac{(\overline{Y}_1 - \overline{Y}_2) - (\mu_1 - \mu_2)}{0.7307}$$

has a standard normal distribution and is based on pivotal variable 2 of Table 5.1. Let us first set up a 95% confidence interval on the difference $(\mu_1 - \mu_2)$ in the population means. The 95% confidence interval is

$$(\overline{Y}_1 - \overline{Y}_2) \pm 1.96(0.7307)$$

with

$$\text{upper limit} = (10.125 - 12.350) + 1.4322 = -0.79 \text{ month}$$

$$\text{lower limit} = (10.125 - 12.350) - 1.4322 = -3.66 \text{ months}$$

The time line is shown in Figure 5.8.

The 95% confidence interval does not straddle zero, so we would conclude that there is a real difference in age in months when the baby first walked in the exercise group compared to the control group. The best estimate of the difference is $10.125 - 12.350 = -2.22$ months; that is, the age at first walking is about two months earlier than the control group.

Note the flow of the argument: The babies were a homogeneous group before treatment. Allocation to the various groups was on a random basis (assumed but not stated explicitly in the article); the only subsequent differences between the groups were the treatments, so significant differences between the groups must be attributable to the treatments. (Can you think of some reservations that you may want checked before accepting the conclusion?)

Table 5.3 Distribution of Ages (in Months) in Infants for Walking Alone

	Age for Walking Alone	
	Active Exercise Group	Eight-Week Control Group
	9.00	13.25
	9.50	11.50
	9.75	12.00
	10.00	13.50
	13.00	11.50
	9.50	[a]
n	6	5
Mean	10.125	12.350
Standard deviation	1.4470	0.9618

Source: Data from Zelazo et al. [1972].

[a] One observation is missing from the paper.

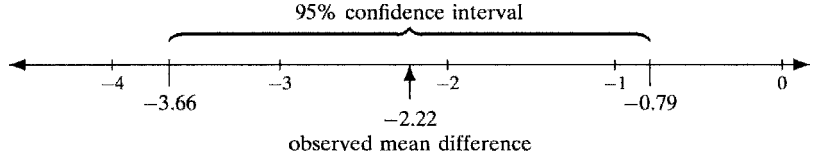


Figure 5.8 Time line for difference in time to infants walking alone.

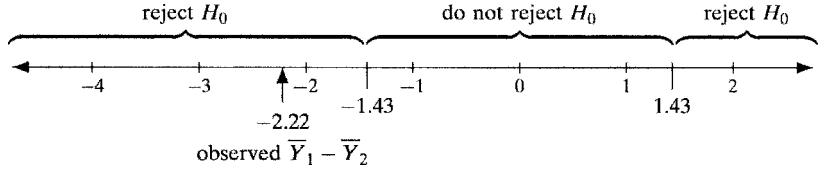


Figure 5.9 Plot showing the nonrejection region.

Formulating the problem as a hypothesis-testing problem is done as follows: A reasonable null hypothesis is that $\mu_1 - \mu_2 = 0$; in this case, the hypothesis of no effect. Comparable to the 95% confidence interval, a test at the 5% level will be carried out. Conveniently, $\mu_1 - \mu_2 = 0$, so that the nonrejection region is simply $0 \pm 1.96(0.7307)$ or 0 ± 1.4322. Plotting this on a line, we get Figure 5.9.

We would reject the null hypothesis, $H_0 : \mu_1 - \mu_2 = 0$, and accept the alternative hypothesis, $H_A : \mu_1 \neq \mu_2$; in fact, on the basis of the data, we conclude that $\mu_1 < \mu_2$.

To calculate the (one-sided) p-value associated with the difference observed, we again use the pivotal variable

$$P\left[[\overline{Y}_1 - \overline{Y}_2] \leq -2.225\right] \doteq P\left[Z \leq \frac{-2.225 - 0}{0.7307}\right]$$

$$\doteq P[Z \leq -3.05]$$

$$\doteq 0.0011$$

The p-value is 0.0011, much less than 0.05, and again, we would reject the null hypothesis. To make the p-value comparable to the two-sided confidence and hypothesis testing procedure, we must multiply it by 2, to give a p-value

$$p\text{-value} = 2(0.0011) = 0.0022$$

We conclude this section by considering the two sample location problem when the population variances are not known. For this we need:

Result 5.3. If $\overline{Y}_1$ and $\overline{Y}_2$ are based on two independent random samples of size n_1 and n_2 from two normal distributions with means μ_1 and μ_2 and the same variances $\sigma_1^2 = \sigma_2^2 = \sigma^2$, then

$$\frac{(\overline{Y}_1 - \overline{Y}_2) - (\mu_1 - \mu_2)}{s_p\sqrt{1/n_1 + 1/n_2}}$$

has a t-distribution with $n_1 + n_2 - 2$ degrees of freedom. Here s_p^2 is "the pooled estimate of common variance σ^2," as defined below.

This result is summarized by pivotal variable 6 in Table 5.1. Result 5.3 assumes that the population variances are the same, $\sigma_1^2 = \sigma_2^2 = \sigma^2$. There are then two estimates of σ^2 : s_1^2 from the first sample and s_2^2 from the second sample. How can these estimates be combined to provide the best possible estimate of σ^2? If the sample sizes, n_1 and n_2, differ, the variance based on the larger sample should be given more weight; the pooled estimate of σ^2 provides this. It is defined by

$$s_p^2 = \frac{(n_1 - 1)s_1^2 + (n_2 - 1)s_2^2}{n_1 + n_2 - 2}$$

If $n_1 = n_2$, then $s_p^2 = \frac{1}{2}(s_1^2 + s_2^2)$, just the arithmetic average of the variances. For $n_1 \neq n_2$, the variance with the larger sample size receives more weight. See Note 5.2 for a further discussion.

Example 5.5. (*continued*) Consider again the data in Table 5.3 on the age at which children first walk. We will now take the more realistic approach by treating the standard deviations as sample standard deviations, as they should be.

The pooled estimate of the (assumed) common variance is

$$s_p^2 \doteq \frac{(6-1)(1.4470)^2 + (5-1)(0.9618)^2}{6+5-2} \doteq \frac{14.1693}{9} \doteq 1.5744$$

$$s_p \doteq 1.2547 \text{ months}$$

A 95% confidence interval for the difference $\mu_1 - \mu_2$ is constructed first. From Table A.4, the critical t-value for nine degrees of freedom is $t_{9,0.975} = 2.26$. The 95% confidence interval is calculated to be

$$(10.125 - 12.350) \pm (2.26)(1.2547)\sqrt{1/6 + 1/5} \doteq -2.225 \pm 1.717$$

$$\text{lower limit} = -3.94 \text{ months and upper limit} = -0.51 \text{ month}$$

Notice that these limits are wider than the limits $(-3.66, -0.79)$ calculated on the assumption that the variances are known. The wider limits are the price for the additional uncertainty.

The same effect is observed in testing the null hypothesis that $\mu_1 - \mu_2 = 0$. The rejection region (Figure 5.10), using a 5% significance level, is outside

$$0 \pm (2.26)(2.2547)\sqrt{1/6 + 1/5} \doteq 0 \pm 1.72$$

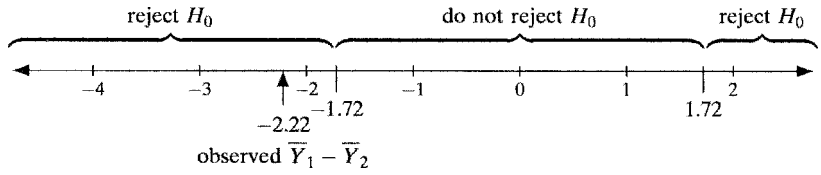


Figure 5.10 Plot showing the rejection region.

The observed value of −2.22 months also falls in the rejection region. Compared to the regions constructed when the variances were assumed known, the region where the null hypothesis is *not* rejected in this case is wider.

5.7 TWO-SAMPLE INFERENCE: SCALE

5.7.1 *F*-Distribution

The final inference procedure to be discussed in this chapter deals with the equality of variances of two normal populations.

Result 5.4. Given two random samples of size n_1 and n_2, with sample variances s_1^2 and s_2^2, from two normal populations with variances σ_1^2 and σ_2^2, the variable

$$F = \frac{s_1^2/\sigma_1^2}{s_2^2/\sigma_2^2}$$

has an F-distribution with $n_1 - 1$ and $n_2 - 1$ degrees of freedom.

The F-distribution (named in honor of Sir R. A. Fisher) does not have a simple mathematical formula, but most statistical packages can compute tables of the distribution. The F-distribution is indexed by the degrees of freedom associated with s_1^2 (the numerator degrees of freedom) and the degrees of freedom associated with s_2^2 (the denominator degrees of freedom). A picture of the F-distribution is presented in Figure 5.11. The distribution is skewed; the extent of skewness depends on the degrees of freedom. As *both* increase, the distribution becomes more symmetric.

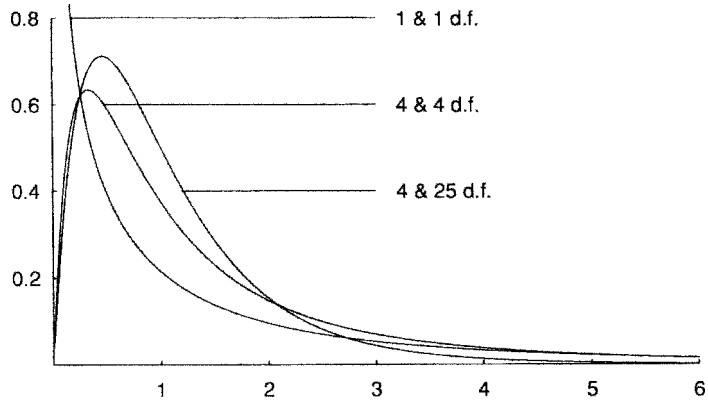


Figure 5.11 F-distribution for three sets of degrees of freedom.

We write $F_{v_1,v_2,\alpha}$ to indicate the 100αth percentile value of an F-statistic with v_1 and v_2 degrees of freedom. The mean of an F-distribution is $v_2/(v_2-2)$, for $v_2 > 2$; the variance is given in Note 5.3. In this note you will also find a brief discussion of the relationship between the four distributions we have now discussed: normal, chi-square, Student t, and F.

It is clear that

$$F = \frac{s_1^2/\sigma_1^2}{s_2^2/\sigma_2^2}$$

is a pivotal variable, listed as number 8 in Table 5.1. Inferences can be made on the *ratio* σ_1^2/σ_2^2. [To make inferences about σ_1^2 (or σ_2^2) by itself, we would use the chi-square distribution and the procedure outlined in Chapter 4.] Conveniently, if we want to test whether the variances are equal, that is, $\sigma_1^2 = \sigma_2^2$, the ratio σ_1^2/σ_2^2 is equal to 1 and "drops out" of the pivotal variable, which can then be written

$$F = \frac{s_1^2/\sigma_1^2}{s_2^2/\sigma_2^2} = \frac{s_1^2}{s_2^2}$$

We would reject the null hypothesis of equality of variances if the observed ratio s_1^2/s_1^2 is "very large" or "very small," how large or small to be determined by the F-distribution.

5.7.2 Testing and Estimation

Continuing Example 5.5, the sample variances in Table 5.3 were $s_1^2 = (1.4470)^2 = 2.0938$ and $s_2^2 = (0.9618)^2 = 0.9251$. Associated with s_1^2 are $6-1=5$ degrees of freedom, and with s_2^2, $5-1=4$ degrees of freedom. Under the null hypothesis of equality of population variances, the ratio s_1^2/s_2^2 has an F-distribution with (5, 4) degrees of freedom. For a two-tailed test at the 10% level, we need $F_{5,4,0.05}$ and $F_{5,4,0.95}$. From Table A.7, the value for $F_{5,4,0.95}$ is 6.26. Using the relationship $F_{v_1,v_2,\alpha} = 1/F_{v_2,v_1,1-\alpha}$, we obtain $F_{5,4,0.05} = 1/F_{4,5,0.95} = 0.19$. The value of F observed is $F_{5,4} = s_1^2/s_2^2 = 2.0938/0.9251 \doteq 2.26$.

From Figure 5.12 it is clear that the null hypothesis of equality of variances is not rejected. Notice that the rejection region is not symmetric about 1, due to the zero bound on the left-hand side. It is instructive to consider F-ratios for which the null hypothesis would have been rejected. On the right-hand side, $F_{5,4,0.95} = 6.26$; this implies that s_1^2 must be 6.26 times as large as s_2^2 before the 10% significance level is reached. On the left-hand side, $F_{5,4,0.05} = 0.19$, so that s_1^2 must be 0.19 times as small as s_2^2 before the 10% significance level is reached. These are reasonably wide limits (even at the 10% level).

At one time statisticians recommended performing an F-test for equality of variances before going on to the t-test. This is no longer thought to be useful. In small samples the F-test cannot reliably detect even quite large differences in variance; in large samples it will reject the hypothesis of equality of variances for differences that are completely unimportant. In addition, the F-test is extremely sensitive to the assumption of normality, even in large samples. The modern solution is to use an approximate version of the t-test that does not assume equal variances (see Note 5.2). This test can be used in all cases or only in cases where the sample variances appear substantially different. In large samples it reduces to the Z-test based on pivotal variable 2 in Table 5.1. The F-test should be restricted to the case where there is a genuine scientific interest in whether two variances are equal.

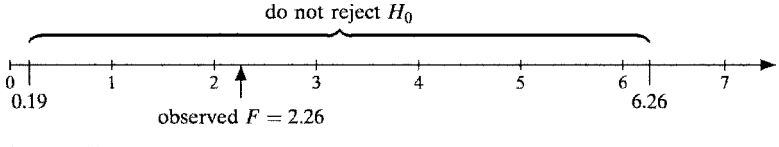


Figure 5.12 Plot showing nonrejection of the null hypothesis of equality of variances.

A few comments about terminology: Sample variances that are (effectively) the same are called *homogeneous*, and those that are not are called *heterogeneous*. A test for equality of population variances, then, is a test for homogeneity or heterogeneity. In the more technical statistical literature, you will find the equivalent terms *homoscedasticity* and *heteroscedasticity tests*.

A confidence interval on the ratios of the population variances σ_1^2/σ_2^2 can be constructed using the pivotal variable approach once more. To set up a $100(1-\alpha)\%$ confidence interval, we need the $100(\alpha/2)$ percentile and $100(1-\alpha/2)$ percentile of the F-distribution.

Continuing with Example 5.5, suppose that we want to construct a 90% confidence interval on σ_1^2/σ_2^2 on the basis of the observed sample. Values for the 5th and 95th percentiles have already been obtained: $F_{5,4,0.05} = 0.19$ and $F_{5,4,0.95} = 6.26$. A 90% confidence interval on σ_1^2/σ_2^2 is then determined by

$$\left(\frac{s_1^2/s_2^2}{F_{5,4,0.95}}, \frac{s_1^2/s_2^2}{F_{5,4,0.05}} \right)$$

For the data observed, this is

$$\left(\frac{2.0938/0.9251}{6.26}, \frac{2.0938/0.9251}{0.19} \right) = (0.36, 11.9)$$

Thus, on the basis of the data observed, we can be 90% confident that the interval (0.36, 11.9) straddles or covers the ratio σ_1^2/σ_2^2 of the population variances. This interval includes 1.0. So, also on the basis of the estimation procedure, we conclude that $\sigma_1^2/\sigma_2^2 = 1$ is not unreasonable.

A 90% confidence interval on the ratio of the standard deviations, σ_1/σ_2, can be obtained by taking square roots of the points (0.36, 11.9), producing (0.60, 3.45) for the interval.

5.8 SAMPLE-SIZE CALCULATIONS

One of the questions most frequently asked of a statistician is: How big must my n be? Stripped of its pseudojargon, a valid question is being asked: How many observations are needed in this study? Unfortunately, the question cannot be answered before additional information is supplied. We first put the requirements in words in the context of a study comparing two treatments; then we introduce the appropriate statistical terminology. To determine sample size, you need to specify or know:

1. How variable the data are
2. The chance that you are willing to tolerate concluding incorrectly that there is an effect when the treatments are equivalent
3. The magnitude of the effect to be detected
4. The certainty with which you wish to detect the effect

Each of these considerations is clearly relevant. The more variation in the data, the more observations are needed to pin down a treatment effect; when there is no difference, there is a chance that a difference will be observed, which due to sampling variability is declared significant. The more certain you want to be of detecting an effect, the more observations you will need, everything else remaining equal. Finally, if the difference in the treatments is very large, a rather economical experiment can be run; conversely, a very small difference in the treatments will require very large sample sizes to detect.

We now phrase the problem in statistical terms: The model we want to consider involves two normal populations with equal variances σ^2, differing at most in their means, μ_1 and μ_2. To determine the sample size, we must specify:

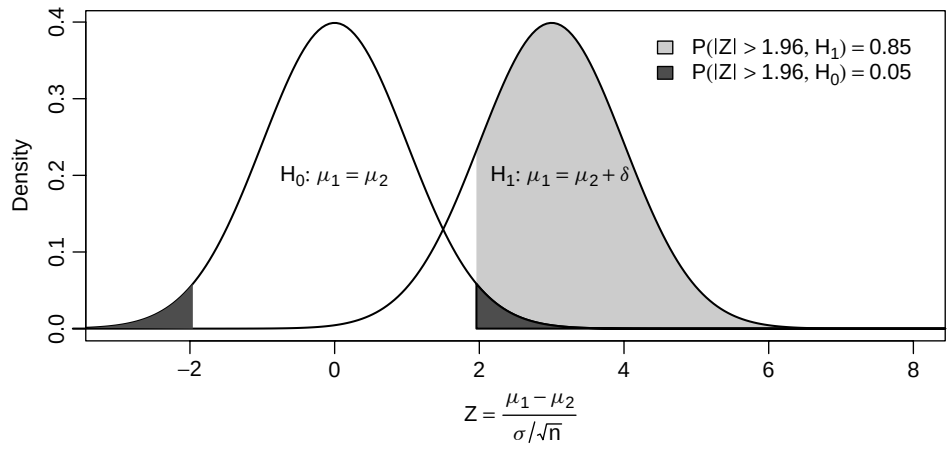


Figure 5.13 Distributions of the Z-statistic under the null and an alternative hypothesis. The probability of $Z < -1.96$ or $Z > 1.96$ under the null hypothesis (the level) is dark gray. The probability under the alternative hypothesis (the power) is light gray.

1. σ^2
2. The probability, α, of a Type I error
3. The magnitude of the difference $\mu_1 - \mu_2$ to be detected
4. The power, $1 - \beta$, or equivalently, the probability of a Type II error, β

Figure 5.13 shows an example of these quantities visually. There are two normal distributions, corresponding to the distribution of the two-sample Z-statistic under the null hypothesis that two means are equal and under the alternative hypothesis that the mean of the first sample is greater than the mean of the second. In the picture, $(\mu_1 - \mu_2)/(\sigma/\sqrt{n}) = 3$, for example, a difference in means of $\mu_1 - \mu_2 = 3$ with a standard deviation $\sigma = 10$ and a sample size of $n = 100$.

The level, or Type I error rate, is the probability of rejecting the null hypothesis if it is true. We are using a 0.05-level two-sided test. The darkly shaded regions are where $Z < -1.96$ or $Z > 1.96$ if $\mu_1 = \mu_2$, adding up to a probability (area under the curve) of 0.05. The power is the probability of rejecting the null hypothesis if it is not true. The lightly shaded region is where $Z > 1.96$ if the alternative hypothesis is true. In theory there is a second lightly shaded region where $Z < -1.96$, but this is invisibly small: There is effectively no chance of rejecting the null hypothesis "in the wrong direction." In this example the lightly shaded region adds up to a probability of 0.85, meaning that we would have 85% power.

Sample sizes are calculated as a function of

$$\Delta = \frac{|\mu_1 - \mu_2|}{\sigma}$$

which is defined to be the standardized distance between the two populations. For a two-sided test, the formula for the required sample size *per group* is

$$n = \frac{2(z_{1-\alpha/2} + z_{1-\beta})^2}{\Delta^2}$$

It is instructive to contemplate this formula. The standardized difference enters as a square. Thus, to detect a treatment different *half* as small as perhaps considered initially will require

four times as many observations per group. Decreasing the probabilities of Type I and Type II errors has the same effect on the sample size; it increases it. However, the increment is not as drastic as it is with Δ. For example, to reduce the probability of a Type I error from 0.05 to 0.025 changes the Z-value from $Z_{0.975} = 1.96$ to $Z_{0.9875} = 2.24$; even though $Z_{1-\alpha/2}$ is squared, the effect will not even be close to doubling the sample size. Finally, the formula assumes that the difference $\mu_1 - \mu_2$ can either be positive or negative. If the direction of the difference can be specified beforehand, a one-tailed value for Z can be used. This will result in a reduction of the sample sizes required for each of the groups, since $z_{1-\alpha}$ would be used.

Example 5.6. At a significance level of $1 - \alpha = 0.95$ (one tail) and power $1 - \beta = 0.80$, a difference $\Delta = 0.3$ is to be detected. The appropriate Z-values are

$$Z_{0.95} = 1.645 \text{ (a more accurate value than given in Table A.2)}$$
$$Z_{0.80} = 0.84$$

The sample size required per group is

$$n = \frac{2(1.645 + 0.84)^2}{(0.3)^2} = 137.2$$

The value is rounded up to 138, so that at least 138 observations *per group* are needed to detect the specified difference at the specified significant level and power.

Suppose that the variance σ^2 is not known, how can we estimate the sample size needed to detect a standardized difference Δ? One possibility is to have an estimate of the variance σ^2 based on a previous study or sample. Unfortunately, no explicit formulas can be given when the variance is estimated; many statistical texts suggest adding between two and four observations per group to get a reasonable approximation to the sample size (see below).

Finally, suppose that *one group*—as in a paired experiment—is to be used to determine whether a populations mean μ differs from a hypothesized mean μ_0. Using the same standardized difference $\Delta = |\mu - \mu_0|/\sigma$, it can be shown that the appropriate number in the group is

$$n = \frac{(z_{1-\alpha/2} + z_{1-\beta})^2}{\Delta^2}$$

or one-half the number needed in one group in the two-sample case. This is why tables for sample sizes in the one-sample case tell you, in order to apply the table to the two-sample case, to (1) double the number in the table, and (2) use that number *for each group*.

Example 5.7. Consider data involving PKU children. Assume that IQ in the general population has mean $\mu = 100$ and standard deviation $= 15$. Suppose that a sample of eight PKU children whose diet has been terminated has an average IQ of 94, which is not significantly different from 100. How large would the sample have to be to detect a difference of six IQ points (i.e., the population mean is 94)? The question cannot be answered yet. (Before reading on: What else must be specified?) Additionally, we need to specify the Type I and Type II errors. Suppose that $\alpha = 0.05$ and $\beta = 0.10$. We make the test one-tailed because the alternative hypothesis is that the IQ for PKU children is less than that of children in the general population. A value of $\beta = 0.10$ implies that the power is $1 - \beta = 0.90$. We first calculate the standardized distance

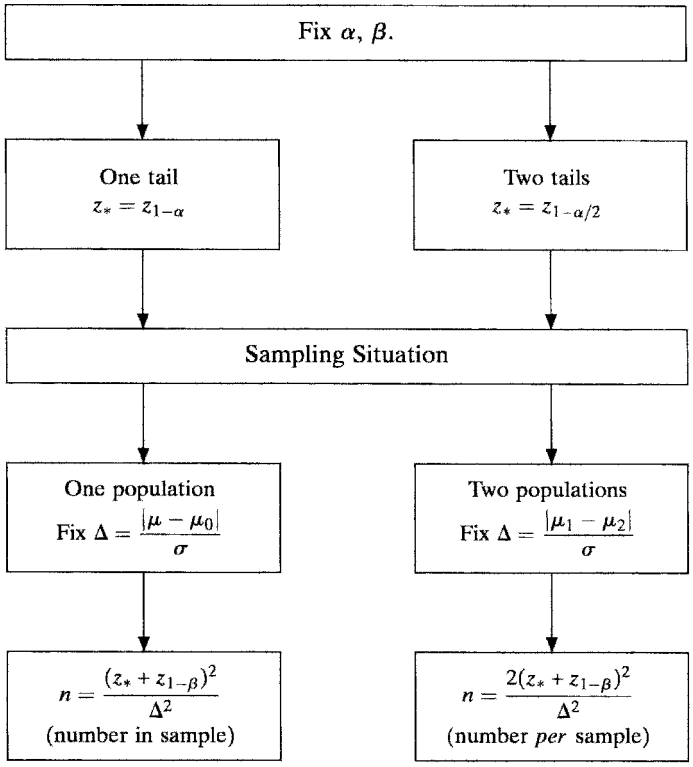
$$\Delta = \frac{|94 - 100|}{15} = \frac{6}{15} = 0.40$$

Then $z_{1-0.05} = z_{0.95} = 1.645$ and $z_{1-0.10} = z_{0.90} = 1.28$. Hence,

$$n = \frac{(1.645 + 1.28)^2}{(0.40)^2} = 53.5$$

Rounding up, we estimate that it will take a sample of 54 observations to detect a difference of $100 - 94 = 6$ IQ points (or greater) with probabilities of Type I and Type II errors as specified.

If the variance is not known, and estimated by s^2, say $s^2 = 15^2$, then statistical tables (not included in this book) indicate that the sample size is 55, not much higher than the 54 we calculated. A summary outline for calculating sample sizes is given in Figure 5.14.



Comments:

1. In the case of two populations, if $\sigma_1^2 \neq \sigma_2^2$, define $\sigma^2 = (\sigma_1^2 + \sigma_2^2)/2$ and proceed as before.
2. If σ is to be estimated from the data, add to the calculated values the following values for an approximate sample size:

		One population	Two populations
One tail	$\alpha = 0.05$	Add 2	Add 1
	$\alpha = 0.01$	Add 4	Add 2
Two tails	$\alpha = 0.05$	Add 2	Add 1
	$\alpha = 0.01$	Add 3	Add 2

Figure 5.14 Sample-size calculations for measurement data.

There is something artificial and circular about all of these calculations. If the difference Δ is known, there is no need to perform an experiment to estimate the difference. Calculations of this type are used primarily to make the researcher aware of the kinds of differences that can be detected. Often, a calculation of this type will convince a researcher *not* to carry out a piece of research, or at least to think very carefully about the possible ways of increasing precision, perhaps even contemplating a radically different attack on the problem. In addition, the size of a sample may be limited by considerations such as cost, recruitment rate, or time constraints beyond control of the investigations. In Chapter 6 we consider questions of sample size for discrete variables.

NOTES

5.1 Inference by Means of Pivotal Variables: Some Comments

1. The problem of finding pivotal variables is a task for statisticians. Part of the problem is that such variables are not always unique. For example, when working with the normal distribution, why not use the sample median rather than the sample mean? After all, the median is admittedly more robust. However, the variance of the sample median is larger than that of the sample mean, so that a less precise probabilistic statement would result.

2. In many situations there is no exactly pivotal variable available in small samples, although a pivotal variable can typically be found in large samples.

3. The principal advantage of using the pivotal variable approach is that it gives you a unified picture of a great number of procedures that you will need.

4. There is a philosophical problem about the interpretation of a confidence interval. For example, consider the probability inequality

$$P[-1.96 \leq Z \leq 1.96] = 0.95$$

which leads to a 95% confidence interval for the mean of a normal population on the basis of a random sample of size n:

$$P\left[\overline{Y} - \frac{1.96\sigma}{\sqrt{n}} \leq \mu \leq \overline{Y} + \frac{1.96\sigma}{\sqrt{n}}\right] = 0.95$$

It is argued that once $\overline{Y}$ is observed, *this* interval either covers the mean or not; that is, P is either 0 or 1. One answer is that probabilities are not associated with a particular event—whether they have occurred or may occur at some future time—but with a population of events. For this reason we say *after the fact* that we are 95% confident that the mean is in the interval, *not* that the probability is 0.95 that the mean is in the interval.

5. Given two possible values for a parameter, which one will be designated as the null hypothesis value and which one as the alternative hypothesis value in a hypothesis testing situation? If nothing else is given, the designation will be arbitrary. Usually, there are at least four considerations in designating the *null value* of a parameter:

- **a.** Often, the null value of the parameter permits calculation of a p-value. For example, if there are two hypotheses, $\mu = \mu_0$ and $\mu \neq \mu_0$, only under $\mu = \mu_0$ can we calculate the probability of an occurrence of the observed value or a more extreme value.
- **b.** Past experience or previous work may suggest a specified value. The new experimentation or treatment then has a purpose: rejection of the value established previously, or assessment of the magnitude of the change.

c. Occam's razor can be appealed to. It states: "Do not multiply hypotheses beyond necessity," meaning in this context that we usually start from the value of a parameter that we would assume if no new data were available or to be produced.

d. Often, the null hypothesis is a "straw man" we hope to reject, for example, that a new drug has the same effect as a placebo.

6. Sometimes it is argued that the smaller the p-value, the stronger the treatment effect. You now will recognize that this cannot be asserted baldly. Consider the two-sample t-test. A p-value associated with this test will depend on the quantities $\mu_1 - \mu_2, s_p, n_1$, and n_2. Thus, differences in p-values between two experiments may simply reflect differences in sample size or differences in background variability (as measured by s_p).

5.2 Additional Notes on the t-Test

1. *Heterogeneous variances in the two-sample*. t-*test*. Suppose that the assumption of homogeneity of variances in the two-sample t-test is not tenable. What can be done? At least three avenues are open:

a. Use an approximation to the t procedure.

b. Transform the data.

c. Use another test, such as a nonparametric test.

With respect to the last point, alternative approaches are discussed in Chapter 8. With respect to the first point, one possibility is to rank the observations from smallest to largest (disregarding group membership) and then carry out the t-test on the ranks. This is a surprisingly good *test* but does not allow us to estimate the magnitude of the difference between the two groups. See Conover and Iman [1981] for an interesting discussion and Thompson [1991] for some precautions. Another approach adjusts the degrees of freedom of the two-sample t-test. The procedure is as follows: Let $Y_1 \sim N(\mu_1, \sigma_1^2)$ and $Y_2 \sim N(\mu_2, \sigma_2^2)$, and samples of size n_1 and n_2 are taken, respectively. The variable

$$\frac{(\overline{Y}_1 - \overline{Y}_2) - (\mu_1 - \mu_2)}{\sqrt{\sigma_1^2/n_1 + \sigma_2^2/n_2}}$$

has a standard normal distribution. However, the analogous quantity with the population variances σ_1^2 and σ_2^2 replaced by the sample variances s_1^2 and s_2^2 does not have a t-distribution. The problem of finding the distribution of this quantity is known as the *Behrens–Fisher problem*. It is of theoretical interest in statistics because there is no exact solution to such an apparently simple problem. There are, however, perfectly satisfactory practical solutions. One approach adjusts the degrees of freedom of this statistic in relation to the extent of dissimilarity of the two sample variances. The t-table is entered not with $n_1 + n_2 - 2$ degrees of freedom, but with

$$\text{degrees of freedom} = \frac{(s_1^2/n_1 + s_2^2/n_2)^2}{(s_1^2/n_1)^2/(n_1 + 1) + (s_2^2/n_2)^2/(n_2 + 1)} - 2$$

This value need not be an integer; if you are working from tables of the t-distribution rather than software, it may be necessary to round down this number. The error in this approximation is very small and is likely to be negligible compared to the errors caused by nonnormality. For

large samples (e.g., $n_1, n_2 > 30$), the statistic

$$\frac{(\overline{Y}_1 - \overline{Y}_2) - (\mu_1 - \mu_2)}{\sqrt{s_1^2/n_1 + s_2^2/n_2}}$$

can be treated as a standard normal deviate even if the distribution of Y is not a normal distribution.

2. *The two-sample* t*-test and design of experiments*. Given that a group has to be divided into two subgroups, the arrangement that minimizes the standard error of the difference is that of equal sample sizes in each group when there is a common σ^2. To illustrate, suppose that 10 objects are to be partitioned into two groups; consider the multiplier $\sqrt{1/n_1 + 1/n_2}$, which determines the relative size of the standard errors.

n_1	n_2	$\sqrt{1/n_1 + 1/n_2}$
5	5	0.63
6	4	0.65
7	3	0.69
8	2	0.79

This list indicates that small deviations from a 5 : 5 ratio do not affect the multiplier very much. It is sometimes claimed that sample sizes must be equal for a valid t-test: Except for giving the smallest standard error of the difference, there is no such constraint.

3. *The "wrong"* t*-test*. What is the effect of carrying out a two-sample t-test on paired data, that is, data that should have been analyzed by a paired t-test? Usually, the level of significance is reduced. On the one hand, the degrees of freedom are *increased* from $(n - 1)$, assuming n pairs of observations, to $2(n - 1)$, but at the same time, additional variation is introduced, so that the standard error of the difference is now larger. In any event the assumption of statistical independence between "groups" is usually inappropriate.

4. *Robustness of the* t*-test*. The t-test tends to be sensitive to *outliers*, unusually small or large values of a variable. We discuss other methods of analysis in Chapter 8. As a matter of routine, you should always graph the data in some way. A simple box plot or histogram will reveal much about the structure of the data. An outlier may be a perfectly legitimate value and its influence on the t-test entirely appropriate, but it is still useful to know that this influence is present.

5.3 Relationships and Characteristics of the Fixed Distributions in This Chapter

We have already suggested some relationships between the fixed distributions. The connection is more remarkable yet and illustrates the fundamental role of the normal distribution. The basic connection is between the standard normal and the chi-square distribution. Suppose that we draw randomly 10 independent values from a standard normal distribution, square each value, and sum them. This sum is a random variable. What is its sampling distribution? It turns out to be chi-square with 10 degrees of freedom. Using notation, let $Z_1, Z_2, \ldots, Z_{10}$ be the values of Z obtained in drawings 1 to 10. Then, $Z_1^2 + \cdots + Z_{10}^2$ has a chi-square distribution with 10 degrees of freedom: $\chi_{10}^2 = Z_1^2 + \cdots + Z_{10}^2$. This generalizes the special case $\chi_1^2 = Z^2$.

The second connection is between the F-distribution and the chi-square distribution. Suppose that we have two independent chi-square random variables with v_1 and v_2 degrees of freedom. The ratio

$$\frac{\chi_{v_1}^2/v_1}{\chi_{v_2}^2/v_2} = F_{v_1, v_2}$$

has an F-distribution with v_1 and v_2 degrees of freedom. Finally, the square of a t-variable with v degrees of freedom is $F_{1,v}$. Summarizing yields

$$\chi_v^2 = \sum_{i=1}^{v} Z_i^2, \qquad t_v^2 = F_{1,v} = \frac{\chi_1^2/1}{\chi_v^2/v}$$

A special case connects all four pivotal variables:

$$Z^2 = t_\infty^2 = \chi_1^2 = F_{1,\infty}$$

Thus, given the F-table, all the other tables can be generated from it. For completeness, we summarize the mean and variance of the four fixed distributions:

Distribution	Symbol	Mean	Variance	
Normal	Z	0	1	
Student t	t_v	0	$\frac{v}{v-2}$	$(v > 2)$
Chi-square	χ_v^2	v	$2v$	
Fisher's F	F_{v_1,v_2}	$\dfrac{v_2}{v_2-2}$	$\dfrac{2v_2^2(v_1+v_2-2)}{v_1(v_2-2)^2(v_2-4)}$	$(v_2 > 4)$

5.4 One-Sided Tests and One-Sided Confidence Intervals

Corresponding to one-sided (one-tailed) tests are one-sided confidence intervals. A one-sided confidence interval is derived from a pivotal quantity in the same was as a two-sided confidence interval. For example, in the case of a one-sample t-test, a pivotal equation is

$$P\left[-\infty \le \frac{\overline{x}-\mu}{s/\sqrt{n}} \le t_{n-1,1-\alpha}\right] = 1-\alpha$$

Solving for μ produces a $100(1-\alpha)\%$ *upper* one-sided confidence interval for μ : $(\overline{x} - t_{n-1,1-\alpha}s/\sqrt{n}, \infty)$. Similar intervals can be constructed for all the pivotal variables.

PROBLEMS

5.1 Rickman et al. [1974] made a study of changes in serum cholesterol and triglyceride levels of subjects following the Stillman diet. The diet consists primarily of protein and animal fats, restricting carbohydrate intake. The subjects followed the diet with length of time varying from 3 to 17 days. (Table 5.4). The mean cholesterol level increased significantly from 215 mg per/100 mL at baseline to 248 mg per/100 mL at the end of the diet. In this problem, we deal with the triglyceride level.

(a) Make a histogram or stem-and-leaf diagram of the *changes* in triglyceride levels.

(b) Calculate the average change in triglyceride level. Calculate the standard error of the difference.

(c) Test the significance of the average change.

(d) Construct a 90% confidence interval on the difference.

(e) The authors indicate that subjects (5,6), (7,8), (9,10), and (15,16) were "repeaters," that is, subjects who followed the diet for two sequences. Do you think it is

Table 5.4 Diet Data for Problem 5.1

Subject	Days on Diet	Weight (kg)		Triglyceride (mg/100 ml)	
		Initial	Final	Baseline	Final
1	10	54.6	49.6	159	194
2	11	56.4	52.8	93	122
3	17	58.6	55.9	130	158
4	4	55.9	54.6	174	154
5	9	60.0	56.7	148	93
6	6	57.3	55.5	148	90
7	3	62.7	59.6	85	101
8	6	63.6	59.6	180	99
9	4	71.4	69.1	92	183
10	4	72.7	70.5	89	82
11	4	49.6	47.1	204	100
12	7	78.2	75.0	182	104
13	8	55.9	53.2	110	72
14	7	71.8	68.6	88	108
15	7	71.8	66.8	134	110
16	14	70.5	66.8	84	81

reasonable to include their data the "second time around" with that of the other subjects? Supposing not, how would you now analyze the data? Carry out the analysis. Does it change your conclusions?

5.2 In data of Dobson et al. [1976], 36 patients with a confirmed diagnosis of phenylketonuria (PKU) were identified and placed on dietary therapy before reaching 121 days of age. The children were tested for IQ (Stanford–Binet test) between the ages of 4 and 6; subsequently, their normal siblings of closest age were also tested with the Stanford–Binet. The following are the first 15 pairs listed in the paper:

Pair	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**
IQ of PKU case	89	98	116	67	128	81	96	116	110	90	76	71	100	108	74
IQ of sibling	77	110	94	91	122	94	121	114	88	91	99	93	104	102	82

(a) State a suitable null and an alternative hypotheses with regard to these data.

(b) Test the null hypothesis.

(c) State your conclusions.

(d) What are your assumptions?

(e) Discuss the concept of power with respect to this set of data using the fact that PKU invariably led to mental retardation until the cause was found and treatment comprising a restricted diet was instituted.

(f) The mean difference (PKU case − sibling) in IQ for the full 36 pairs was −5.25; the standard deviation of the difference was 13.18. Test the hypothesis of no difference in IQ for this entire set of data.

5.3 Data by Mazze et al. [1971] deal with the preoperative and postoperative creatinine clearance (ml/min) of six patients anesthetized by halothane:

	Patient					
	1	2	3	4	5	6
Preoperative	110	101	61	73	143	118
Postoperative	149	105	162	93	143	100

(a) Why is the paired t-test preferable to the two-sample t-test in this case?

(b) Carry out the paired t-test and test the significance of the difference.

(c) What is the model for your analysis?

(d) Set up a 99% confidence interval on the difference.

(e) Graph the data by plotting the pairs of values for each patient.

5.4 Some of the physiological effects of alcohol are well known. A paper by Squires et al. [1978] assessed the acute effects of alcohol on auditory brainstem potentials in humans. Six volunteers (including the three authors) participated in the study. The latency (delay) in response to an auditory stimulus was measured before and after an intoxicating dose of alcohol. Seven different peak responses were identified. In this exercise, we discuss only latency peak 3. Measurements of the latency of peak (in milliseconds after the stimulus onset) in the six subjects were as follows:

	Latency of Peak					
	1	2	3	4	5	6
Before alcohol	3.85	3.81	3.60	3.68	3.78	3.83
After alcohol	3.82	3.95	3.80	3.87	3.88	3.94

(a) Test the significance of the difference at the 0.05 level.

(b) Calculate the p-value associated with the result observed.

(c) Is your p-value based on a one- or two-tailed test? Why?

(d) As in Problem 5.3, graph these data and state your conclusion.

(e) Carry out an (incorrect) two-sample test and state your conclusions.

(f) Using the sample variances s_1^2 and s_2^2 associated with the set of readings observed before and after, calculate the variance of the difference, *assuming* independence (call this variance 1). How does this value compare with the variance of the difference calculated in part (a)? (Call this variance 2.) Why do you suppose variance 1 is so much bigger than variance 2? The *average* of the differences is the same as the difference in the averages. Show this. Hence, the two-sample t-test differed from the paired t-test only in the divisor. Which of the two tests in more powerful in this case, that is, declares a difference significant when in fact there is one?

5.5 The following data from Schechter et al. [1973] deal with sodium chloride preference as related to hypertension. Two groups, 12 normal and 10 hypertensive subjects, were isolated for a week and compared with respect to Na^+ intake. The following are the average daily Na^+ intakes (in milligrams):

Normal	10.2	2.2	0.0	2.6	0.0	43.1	45.8	63.6	1.8	0.0	3.7	0.0
Hypertensive	92.8	54.8	51.6	61.7	250.8	84.5	34.7	62.2	11.0	39.1		

(a) Compare the average daily Na^+ intake of the hypertensive subjects with that of the normal volunteers by means of an appropriate t-test.

(b) State your assumptions.

(c) Assuming that the population variances are not homogeneous, carry out an appropriate t-test (see Note 5.2).

5.6 Kapitulnik et al. [1976] compared the metabolism of a drug, zoxazolamine, in placentas from 13 women who smoked during pregnancy and 11 who did not. The purpose of the study was to investigate the presence of the drug as a possible proxy for the rate at which benzo[a]pyrene (a by-product of cigarette smoke) is metabolized. The following data were obtained in the measurement of zoxazolamine hydroxylase production (nmol $3H_2O$ formed/g per hour):

Nonsmoker	0.18	0.36	0.24	0.50	0.42	0.36	0.50	0.60	0.56	0.36	0.68		
Smoker	0.66	0.60	0.96	1.37	1.51	3.56	3.36	4.86	7.50	9.00	10.08	14.76	16.50

(a) Calculate the sample mean and standard deviation for each group.

(b) Test the assumption that the two sample variances came from a population with the same variance.

(c) Carry out the t-test using the approximation to the t-procedure discussed in Note 5.2. What are your conclusions?

(d) Suppose we agree that the variability (as measured by the standard deviations) is proportional to the level of the response. Statistical theory then suggests that the logarithms of the responses should have roughly the same variability. Take logarithms of the data and test, once more, the homogeneity of the variances.

5.7 Sometime you may be asked to do a two-sample t-test knowing only the mean, standard deviation, and sample sizes. A paper by Holtzman et al. [1975] dealing with terminating a phenylalanine-restricted diet in 4-year-old children with phenylketonuria (PKU) illustrates the problem. The purpose of the diet is to reduce the phenylalanine level. A high level is associated with mental retardation. After obtaining informed consent, eligible children of 4 years of age were randomly divided into two groups. Children in one group had their restricted diet terminated while children in the other group were continued on the restricted diet. At 6 years of age, the phenylalanine levels were tested in all children and the following data reported:

	Diet Terminated	**Diet Continued**
Number of children	5	4
Mean phenylalanine level (mg/dl)	26.9	16.7
Standard deviation	4.1	7.3

(a) State a reasonable null hypothesis and alternative hypothesis.

(b) Calculate the pooled estimate of the variance s_p^2.

(c) Test the null hypothesis of part (a). Is your test one-tailed, or two? Why?

(d) Test the hypothesis that the sample variances came from two populations with the same variance.

(e) Construct a 95% confidence interval on the difference in the population phenylalanine levels.

(f) Interpret the interval constructed in part (e).

(g) "This set of data has little power," someone says. What does this statement mean? Interpret the implications of a Type II error in this example.

(h) What is the interpretation of a Type I error in this example? Which, in your opinion, is more serious in this example: a Type I error or a Type II error?

(i) On the basis of these data, what would you recommend to a parent with a 4-year-old PKU child?

(j) Can you think of some additional information that would make the analysis more precise?

5.8 Several population studies have demonstrated an inverse correlation of sudden infant death syndrome (SIDS) rate with birthweight. The occurrence of SIDS in one of a pair of twins provides an opportunity to test the hypothesis that birthweight is a major determinant of SIDS. The data shown in Table 5.5 consist of the birthweights (in grams) of each of 22 dizygous twins and each of 19 monozygous twins.

(a) With respect to the dizygous twins, test the hypothesis given above. State the null hypothesis.

(b) Make a similar test on the monozygous twins.

(c) Discuss your conclusions.

Table 5.5 Birthweight Data for Problem 5.8

Dizygous Twins		Monozygous Twins	
SID	Non-SID	SID	Non-SID
1474	2098	1701	1956
3657	3119	2580	2438
3005	3515	2750	2807
2041	2126	1956	1843
2325	2211	1871	2041
2296	2750	2296	2183
3430	3402	2268	2495
3515	3232	2070	1673
1956	1701	1786	1843
2098	2410	3175	3572
3204	2892	2495	2778
2381	2608	1956	1588
2892	2693	2296	2183
2920	3232	3232	2778
3005	3005	1446	2268
2268	2325	1559	1304
3260	3686	2835	2892
3260	2778	2495	2353
2155	2552	1559	2466
2835	2693		
2466	1899		
3232	3714		

Source: D. R. Peterson, Department of Epidemiology, University of Washington.

5.9 A pharmaceutical firm claims that a new analgesic drug relieves mild pain under standard conditions for 3 hours with a standard deviation of 1 hour. Sixteen patients are tested under the same conditions and have an average pain relief of 2.5 hours. The hypothesis that the population mean of this sample is also 3 hours is to be tested against the hypothesis that the population mean is in fact less than 3 hours; $\alpha = 0.5$.

(a) What is an appropriate test?

(b) Set up the appropriate critical region.

(c) State your conclusion.

(d) Suppose that the sample size is doubled. State precisely how the nonrejection region for the null hypothesis is changed.

5.10 Consider Problem 3.9, dealing with the treatment of essential hypertension. Compare treatments A and B by means of an appropriate t-test. Set up a 99% confidence interval on the reduction of blood pressure under treatment B as compared to treatment A.

5.11 During July and August 1976, a large number of Legionnaires attending a convention died of mysterious and unknown cause. Epidemiologists talked of "an outbreak of Legionnaires' disease." One possible cause was thought to be toxins: nickel, in particular. Chen et al. [1977] examined the nickel levels in the lungs of nine of the cases, and selected nine controls. All specimens were coded by the Centers for Disease Control in Atlanta before being examined by the investigators. The data are as follows (μg per 100 g dry weight):

Legionnaire cases	65	24	52	86	120	82	399	87	139
Control cases	12	10	31	6	5	5	29	9	12

Note that there was no attempt to match cases and controls.

(a) State a suitable null hypothesis and test it.

(b) We now know that Legionnaires' disease is caused by a bacterium, genus *Legionella*, of which there are several species. How would you explain the "significant" results obtained in part (a)? (Chen et al. [1977] consider various explanations also.)

5.12 Review Note 5.3. Generate a few values for the normal, t, and chi-square tables from the F-table.

5.13 It is claimed that a new drug treatment can substantially reduce blood pressure. For purposes of this exercise, assume that only diastolic blood pressure is considered. A certain population of hypertensive patients has a mean blood pressure of 96 mmHg. The standard deviation of diastolic blood pressure (variability from subject to subject) is 12 mmHg. To be biologically meaningful, the new drug treatment should lower the blood pressure to at least 90 mmHg. A random sample of patients from the hypertensive population will be treated with the new drug.

(a) Assuming that $\alpha = 0.05$ and $\beta = 0.05$, calculate the sample size required to demonstrate the effect specified.

(b) Considering the labile nature of blood pressure, it might be argued that any "treatment effect" will merely be a "put-on-study effect." So the experiment is redesigned to consider two random samples from the hypertensive population, one of which will receive the new treatment, and the other, a placebo. Assuming the same specifications as above, what is the required sample size per group?

(c) Blood pressure readings are notoriously variable. Suppose that a subject's diastolic blood pressure varies randomly from measurement period to measurement period with a standard deviation of 4 mmHg. Assuming that measurement variability is independent of subject-to-subject variability, what is the overall variance or the total variability in the population? Recalculate the sample sizes for the situation described in parts (a) and (b).

(d) Suppose that the *change* in blood pressure from baseline is used. Suppose that the standard deviation of the change is 6 mmHg. How will this change the sample sizes of parts (a) and (b)?

5.14 In a paper in the *New England Journal of Medicine*, Rodeheffer et al. [1983] assessed the effect of a medication, nifedipine, on the number of painful attacks in patients with Raynaud's phenomenon. This phenomenon causes severe digital pain and functional disability, particularly in patients with underlying connective tissue disease. The drug causes "vascular smooth-muscle relaxation and relief of arterial vasospasm." In this study, 15 patients were selected and randomly assigned to one of two treatment sequences: placebo–nifedipine, or nifedipine–placebo. The data in Table 5.6 were obtained.

(a) Why were patients *randomly* assigned to one of the two sequences? What are the advantages?

(b) The data of interest are in the columns marked "placebo" and "nifedipine." State a suitable null hypothesis and alternative hypothesis for these data. Justify your choices. Test the significance of the difference in total number of attacks in two weeks on placebo with that of treatment. Use a t-test on the differences in the response. Calculate the p-value.

(c) Construct a 95% confidence interval for the difference. State your conclusions.

(d) Make a scatter plot of the placebo response (x-axis) vs. the nifedipine response (y-axis). If there was no significant difference between the treatments, about what line should the observations be scattered?

(e) Suppose that a statistician considers only the placebo readings and calculates a 95% confidence interval on the population mean. Similarly, the statistician calculates a 95% confidence interval on the nifedipine mean. A graph is made to see if the intervals overlap. Do this for these data. Compare your results with that of part (c). Is there a contradiction? Explain.

(f) One way to get rid of outliers is to carry out the following procedure: Take the differences of the data in columns 7 (placebo) and 9 (nifedipine), and rank them disregarding the signs of the differences. Put the sign of the difference on the rank. Now, carry out a paired t-test on the signed ranks. What would be an appropriate null hypothesis? What would be an appropriate alternative hypothesis? Name one advantage and one disadvantage of this procedure. (It is one form of a nonparametric test discussed in detail in Chapter 8.)

5.15 Rush et al. [1973] reported the design of a randomized controlled trial of nutritional supplementation in pregnancy. The trial was to be conducted in a poor American black population. The variable of interest was the birthweight of infants born to study participants; study design called for the random allocation of participants to one of three treatment groups. The authors then state: "The required size of the treatment groups was calculated from the following statistics: the standard deviation of birthweight ... is of the order of 500 g. An increment of 120 g in birthweight was arbitrarily taken to constitute a biologically meaningful gain. Given an expected difference between subjects and controls of 120 g, the required sample size for each group, in order to have a 5% risk of falsely rejecting, and a 20% risk of falsely accepting the null hypothesis, is about 320."

Table 5.6 Effect of Nifedipine on Patients with Raynaud's Phenomenon

Case	Age (yr)/ Gender	Diagnosis[a]	History of Digital Ulcer	ANA[b]	Duration of Raynaud's Phenomenon (yr)	Placebo		Nifedipine	
						Total Number of Attacks in 2 Weeks	Patient Assessment of Therapy[c]	Total Number of Attacks in 2 Weeks	Patient Assessment of Therapy[c]
1	49/F	R[d]	No	20	4	15	0	0	3+
2	20/F	R	No	Neg	3	3	1+	5	0
3	23/F	R	No	Neg	8	14	2+	6	2+
4	33/F	R	No	640	5	6	0	0	3+
5	31/F	R[d]	No	2560	2	12	0	2	3+
6	52/F	PSS	No	320	3	6	1+	1	0
7	45/M	PSS[d]	Yes	320	4	3	1+	2	2+
8	49/F	PSS	Yes	320	4	22	0	30	1+
9	29/M	PSS	Yes	1280	7	15	0	14	1+
10	33/F	PSS[d]	No	2560	9	11	1+	5	1+
11	36/F	PSS	Yes	2560	13	7	2+	2	3+
12	33/F	PSS[d]	Yes	2560	11	12	0	4	2+
13	39/F	PSS	No	320	6	45	0	45	0
14	39/M	PSS	Yes	80	6	14	1+	15	2+
15	32/F	SLE[d]	Yes	1280	5	35	1+	31	2+

Source: Data from Rodeheffer et al. [1983].

[a]R Raynaud's phenomenon without systemic disease; PSS, Raynaud's phenomenon with progressive systemic sclerosis; SLE, Raynaud's phenomenon with systemic lupus erythematosus (in addition, this patient had cryoglobulinemia).

[b]Reciprocal of antinuclear antibody titers.

[c]The Wilcoxon signed rank test, two-tailed, was performed on the patient assessment of placebo vs. nifedipine therapy: $p = 0.02$. Global assessment scale: 1− = worse; 0 = no change; 1+ = minimal improvement; 2+ = moderate improvement; and 3+ = marked improvement.

[d]Previous unsuccessful treatment with prazosin.

(a) What are the values for α and β?

(b) What is the estimate of Δ, the standardized difference?

(c) The wording in the paper suggests that sample size calculations are based on a two-sample test. Is the test one-tailed or two?

(d) Using a one-tailed test, verify that the sample size per group is $n = 215$. The number 320 reflects adjustments for losses and, perhaps, "multiple comparisons" since there are three groups (see Chapter 12).

5.16 This problem deals with the data of Problem 5.14. In column 4 of Table 5.6, patients are divided into those with a history of digital ulcers and those without. We want to compare these two groups. There are seven patients with a history and eight without.

(a) Consider the total number of attacks (in column 9) on the active drug. Carry out a two-sample t-test. Compare the group with a digital ulcer history with the group without this history. State your assumptions and conclusions.

(b) Rank all the observations in column 9, then separate the ranks into the two groups defined in part (a). Now carry out a two-sample t-test on the ranks. Compare your conclusions with those of part (b). Name an advantage to this approach. Name a disadvantage to this approach.

(c) We now do the following: Take the difference between the "placebo" and "nifedipine" columns and repeat the procedures of parts (a) and (b). Supposing that the conclusions of part (a) are not the same as those in this part, how would you interpret such discrepancies?

(d) The test carried out in part (c) is often called a *test for interaction*. Why do you suppose that this is so?

REFERENCES

Bednarek, F. J., and Roloff, D. W. [1976]. Treatment of apnea of prematurity with aminophylline. *Pediatrics*, **58**: 335–339. Used with permission.

Chen, J. R., Francisco, R. B., and Miller, T. E. [1977]. Legionnaires' disease: nickel levels. *Science*, **196**: 906–908. Copyright © 1977 by the AAAS.

Conover, W. J., and Iman, R. L. [1981]. Rank transformations as a bridge between parametric and nonparametric statistics. *American Statistician*, **35**: 124–129.

Dobson, J. C., Kushida, E., Williamson, M., and Friedman, E. G. [1976]. Intellectual performance of 36 phenylketonuria patients and their non-affected siblings. *Pediatrics*, **58**: 53–58. Used with permission.

Holtzman, N. A., Welcher, D. M., and Mellits, E. D. [1975]. Termination of restricted diet in children with phenylketonuria: a randomized controlled study. *New England Journal of Medicine*, **293**: 1121–1124.

Kapitulnik, J., Levin, W., Poppers, J., Tomaszewski, J. E., Jerina, D. M., and Conney, A. H. [1976]. Comparison of the hydroxylation of zoxazolamine and benzo[a]pyrene in human placenta: effect of cigarette smoking. *Clinical Pharmaceuticals and Therapeutics*, **20**: 557–564.

Mazze, R. I., Shue, G. L., and Jackson, S. H. [1971]. Renal dysfunction associated with methoxyflurane anesthesia. *Journal of the American Medical Association*, **216**: 278–288. Copyright © 1971 by the American Medical Association.

Rickman, R., Mitchell, N., Dingman, J., and Dalen, J. E. [1974]. Changes in serum cholesterol during the Stillman diet. *Journal of the American Medical Association*, **228**: 54–58. Copyright © 1974 by the American Medical Association.

Rodeheffer, R. J., Romner, J. A., Wigley, F., and Smith, C. R. [1983]. Controlled double-blind trial of Nifedipine in the treatment of Raynaud's phenomenon. *New England Journal of Medicine*, **308**: 880–883.

Rush, D., Stein, Z., and Susser, M. [1973]. The rationale for, and design of, a randomized controlled trial of nutritional supplementation in pregnancy. *Nutritional Reports International*, **7**: 547–553. Used with permission of the publisher, Butterworth-Heinemann.

Schechter, P. J., Horwitz, D., and Henkin, R. I. [1973]. Sodium chloride preference in essential hypertension. *Journal of the American Medical Association*, **225**: 1311–1315. Copyright © 1973 by The American Medical Association.

Squires, K. C., Chen, N. S., and Starr, A. [1978]. Acute effects of alcohol on auditory brainstem potentials in humans. *Science*, **201**: 174–176.

Thompson, G. L. [1991]. A unified approach to rank tests for multivariate and repeated measures designs. *Journal of the American Statistical Association*, **86**: 410–419.

Zelazo, P. R., Zelazo, N. A., and Kolb, S. [1972]. "Walking" in the newborn. *Science*, **176**: 314–315.

CHAPTER 6

Counting Data

6.1 INTRODUCTION

From previous chapters, recall the basic ideas of statistics. *Descriptive statistics* present data, usually in summary form. Appropriate *models* describe data concisely. The model *parameters* are *estimated* from the data. *Standard errors* and *confidence intervals* quantify the precision of estimates. Scientific hypotheses may be tested. A *formal hypothesis test* involves four things: (1) planning an experiment, or recognizing an opportunity, to collect appropriate data; (2) selecting a *significance level* and *critical region*; (3) collecting the data; and (4) rejecting the *null hypothesis* being tested if the value of the test statistic falls into the critical region. A less formal approach is to compute the *p-value*, a measure of how plausibly the data agree with the null hypothesis under study. The remainder of this book shows you how to apply these concepts in different situations, starting with the most basic of all data: counts.

Throughout recorded history people have been able to count. The word *statistics* comes from the Latin word for "state"; early statistics were counts used for the purposes of the state. Censuses were conducted for military and taxation purposes. Modern statistics is often dated from the 1662 comments on the Bills of Mortality in London. The Bills of Mortality counted the number of deaths due to each cause. John Graunt [1662] noticed patterns of regularity in the Bills of Mortality (see Section 3.3.1). Such vital statistics are important today for assessing the public health. In this chapter we return to the origin of statistics by dealing with data that arise by counting the number of occurrences of some event.

Count data lead to many different models. The following sections present examples of count data. The different types of count data will each be presented in three steps. First, you learn to recognize count data that fit a particular model. (This is the diagnosis phase.) Second, you examine the model to be used. (You learn about the illness.) Third, you learn the methods of analyzing data using the model. (At this stage you learn how to treat the disease.)

6.2 BINOMIAL RANDOM VARIABLES

6.2.1 Recognizing Binomial Random Variables

Four conditions characterize binomial data:

1. A response or trait takes on one and only one of two possibilities. Such a response is called a *binary response*. Examples are:

Biostatistics: A Methodology for the Health Sciences, Second Edition, by Gerald van Belle, Lloyd D. Fisher, Patrick J. Heagerty, and Thomas S. Lumley
ISBN 0-471-03185-2

a. In a survey of the health system, people are asked whether or not they have hospitalization insurance.

b. Blood samples are tested for the presence or absence of an antigen.

c. Rats fed a potential carcinogen are examined for tumors.

d. People are classified as having or not having cleft lip.

e. Injection of a compound does or does not cause cardiac arrhythmia in dogs.

f. Newborn children are classified as having or not having Down syndrome.

2. The response is observed a known number of times. Each observation of the response is sometimes called a *Bernoulli trial*. In condition 1(a) the number of trials is the number of people questioned. In 1(b), each blood sample is a trial. Each newborn child constitutes a trial in 1(f).

3. The chance, or probability, that a particular outcome occurs is the same for each trial. In a survey such as 1(a), people are sampled at random from the population. Since each person has the same chance of being interviewed, the probability that the person has hospitalization insurance is the same in each case. In a laboratory receiving blood samples, the samples could be considered to have the same probability of having an antigen *if* the samples arise from members of a population who submit tests when "randomly" seeking medical care. The samples would not have the same probability if batches of samples arrive from different environments: for example, from schoolchildren, a military base, and a retirement home.

4. The outcome of one trial must not be influenced by the outcome of other trials. Using the terminology of Chapter 5, the trials outcomes are independent random variables. In 1(b), the trials would not be independent if there was contamination between separate blood samples. The newborn children of 1(f) might be considered independent trials for the occurrence of Down syndrome if each child has different parents. If multiple births are in the data set, the assumption of independence would not be appropriate.

We illustrate and reinforce these ideas by examples that may be modeled by the binomial distribution.

Example 6.1. Weber et al. [1976] studied the irritating effects of cigarette smoke. Sixty subjects sat, in groups of five to six, in a 30-m^2 climatic chamber. Tobacco smoke was produced by a smoking machine. After 10 cigarettes had been smoked, 47 of the 60 subjects reported that they wished to leave the room.

Let us consider the appropriateness of the binomial model for these data. Condition 1 is satisfied. Each subject was to report whether or not he or she desired to leave the room. The answer gives one of two possibilities: yes or no. Sixty trials are observed to take place (i.e., condition 2 is satisfied).

The third condition requires that each subject have the same probability of "wishing to leave the room." The paper does not explain how the subjects were selected. Perhaps the authors advertised for volunteers. In this case, the subjects might be considered "representative" of a larger population who would volunteer. The probability would be the *unknown* probability that a person selected at random from this larger population would wish to leave the room.

As we will see below, the binomial model is often used to make inferences about the unknown probability of an outcome in the "true population." Many would say that an experiment such as this shows that cigarette smoke irritates people. The extension from the ill-defined population of this experiment to humankind in general does *not* rest on this experiment. It must be based on other formal or informal evidence that humans do have much in common; in particular, one would need to assume that if one portion of humankind is irritated by cigarette smoke, so will other segments. Do you think such inferences are reasonable?

The fourth condition needed is that the trials are independent variables. The authors report in detail that the room was cleared of all smoke between uses of the climatic chamber. There should not be a carryover effect here. Recall that subjects were tested in groups of five or six. How do you think that one person's response would be changed if another person were coughing? Rubbing the eyes? Complaining? It seems possible that condition 4 is not fulfilled; that is, it seems possible that the responses were not independent.

In summary, a binomial model might be used for these data, but with some reservation. The overwhelming majority of data collected on human populations is collected under less than ideal conditions; a subjective evaluation of the worth of an experiment often enters in.

Example 6.2. Karlowski et al. [1975] reported on a controlled clinical trial of the use of ascorbic acid (vitamin C) for the common cold. Placebo and vitamin C were randomly assigned to the subjects; the experiment was to be a double-blind trial. It turned out that some subjects were testing their capsules and claimed to know the medication. Of 64 subjects who tested the capsule and guessed at the treatment, 55 were correct. Could such a split arise by chance if testing did not help one to guess correctly?

One thinks of using a binomial model for these data since there is a binary response (correct or incorrect guess) observed on a known number of people. Assuming that people tested only their own capsules, the guesses should be statistically independent. Finally, if the guesses are "at random," each subject should have the same probability—one-half—of making a correct guess since half the participants receive vitamin C and half a placebo. This binomial model would lead to a test of the hypothesis that the probability of a correct guess was 1/2.

Example 6.3. Bucher et al. [1976] studied the occurrence of hemolytic disease in newborns resulting from ABO incompatibility between the parents. Parents are said to be incompatible if the father has antigens that the mother lacks. This provides the opportunity for production of maternal antibodies from fetal–maternal stimulation. Low-weight immune antibodies that cross the placental barrier apparently cause the disease [Cavalli-Sforza and Bodmer, 1999]. The authors reviewed 7464 consecutive infants born at North Carolina Hospital. Of 3584 "black births," 43 had ABO hemolytic disease. What can be said about the true probability that a black birth has ABO hemolytic disease?

It seems reasonable to consider the number of ABO hemolytic disease cases to be binomial. The presence of disease among the 3584 trials should be independent (assuming that no parents had more than one birth during the period of case recruitment—October 1965 to March 1973—and little or no effect from kinship of parents). The births may conceptually be thought of as a sample of the population of "potential" black births during the given time period at the hospital.

6.2.2 Binomial Model

In speaking about a Bernoulli trial, without reference to a particular example, it is customary to label one outcome as a "success" and the other outcome as a "failure." The mathematical model for the binomial distribution depends on two parameters: n, the number of trials, and π, the probability of a success in one trial. A binomial random variable, say Y, is the count of the number of successes in the n trials. Of course, Y can only take on the values $0, 1, 2, \ldots, n$. If π, the probability of a success, is large (close to 1), then Y, the number of successes, will tend to be large. Conversely, if the probability of success is small (near zero), Y will tend to be small.

To do statistical analysis with binomial variables, we need the probability distribution of Y. Let k be an integer between 0 and n inclusive. We need to know $P[Y = k]$. In other words, we want the probability of k successes in n independent trials when π is the probability of success. The symbol $b(k; n, \pi)$ will be used to denote this probability. The answer involves the *binomial coefficient*. The binomial coefficient $\binom{n}{k}$ is the number of different ways that

k objects may be selected from n objects. (Problem 6.24 helps you to derive the value of $\binom{n}{k}$.) For each positive integer n, n factorial (written $n!$) is defined to be $1 \times 2 \times \cdots \times n$. So $6! = 1 \times 2 \times 3 \times 4 \times 5 \times 6 = 720$. 0!, zero factorial, is defined to be 1. With this notation the binomial coefficient may be written

$$\binom{n}{k} = \frac{n!}{(n-k)!\,k!} = \frac{n(n-1)\cdots(k+1)}{(n-k)(n-k-1)\cdots 1} \tag{1}$$

Example 6.4. This is illustrated with the following two cases:

1. Of 10 residents, three are to be chosen to cover a hospital service on a holiday. In how many ways may the residents be chosen? The answer is

$$\binom{10}{3} = \frac{10!}{7!\,3!} = \frac{1 \times 2 \times 3 \times 4 \times 5 \times 6 \times 7 \times 8 \times 9 \times 10}{(1 \times 2 \times 3 \times 4 \times 5 \times 6 \times 7)(1 \times 2 \times 3)} = 120$$

2. Of eight consecutive patients, four are to be assigned to drug A and four to drug B. In how many ways may the assignments be made? Think of the eight positions as eight objects; we need to choose four for the drug A patients. The answer is

$$\binom{8}{4} = \frac{8!}{4!\,4!} = \frac{1 \times 2 \times 3 \times 4 \times 5 \times 6 \times 7 \times 8}{(1 \times 2 \times 3 \times 4)(1 \times 2 \times 3 \times 4)} = 70$$

The binomial probability, $b(k; n, \pi)$, may be written

$$b(k; n, \pi) = \binom{n}{k} \pi^k (1-\pi)^{n-k} \tag{2}$$

Example 6.5. Ten patients are treated surgically. For each person there is a 70% chance of successful surgery (i.e., $\pi = 0.7$). What is the probability of only five or fewer successful surgeries?

$$\begin{aligned} P[\text{five or fewer successful cases}] &= P[\text{five successful cases}] + P[\text{four successful cases}] \\ &\quad + P[\text{three successful cases}] + P[\text{two successful cases}] \\ &\quad + P[\text{one successful case}] + P[\text{no successful case}] \\ &= b(5; 10, 0.7) + b(4; 10, 0.7) + b(3; 10, 0.7) + b(2; 10, 0.7) \\ &\quad + b(1; 10, 0.7) + b(0; 10, 0.7) \\ &= 0.1029 + 0.0368 + 0.0090 + 0.0014 + 0.0001 + 0.0000 \\ &= 0.1502 \end{aligned}$$

(*Note*: The actual value is 0.1503; the answer 0.1502 is due to round-off error.)

The binomial probabilities may be calculated directly or found by a computer program. The mean and variance of a binomial random variable with parameters π and n are given by

$$\begin{aligned} E(Y) &= n\pi \\ \text{var}(Y) &= n\pi(1-\pi) \end{aligned} \tag{3}$$

From equation (3) it follows that Y/n has the expected value π:

$$E\left(\frac{Y}{n}\right) = \pi \tag{4}$$

In other words, the proportion of successes in n binomial trials is an unbiased estimate of the probability of success.

6.2.3 Hypothesis Testing for Binomial Variables

The hypothesis-testing framework established in Chapter 4 may be used for the binomial distribution. There is one minor complication. The binomial random variable can take on only a finite number of values. Because of this, it may not be possible to find hypothesis tests such that the significance level is precisely some fixed value. If this is the case, we construct regions so that the significance level is close to the desired significance level.

In most situations involving the binomial distribution, the number of trials (n) is known. We consider statistical tests about the true value of π. Let $p = Y/n$. If π is hypothesized to be π_0, an observed value of p close to π_0 reinforces the hypothesis; a value of p differing greatly from π_0 makes the hypothesis seem unlikely.

Procedure 1. To construct a significance test of H_0: $\pi = \pi_0$ against H_A: $\pi \neq \pi_0$, at significance level α:

1. Find the smallest c such that $P\ [|p - \pi_0| \geq c] \leq \alpha$ when H_0 is true.
2. Compute the *actual* significance level of the test; the actual significance level is $P[|p - \pi_0| \geq c]$.
3. Observe p, call it $\widehat{p}$; reject H_0 if $|\widehat{p} - \pi_0| \geq c$.

The quantity c is used to determine the critical value (see Definition 4.19); that is, determine the bounds of the rejection region, which will be $\pi_0 \pm c$. Equivalently, working in the Y scale, the region is defined by $n\pi_0 \pm nc$.

Example 6.6. For $n = 10$, we want to construct a test of the null hypothesis H_0: $\pi = 0.4$ vs. the alternative hypothesis H_A: $\pi \neq 0.4$. Thus, we want a two-sided test. The significance level is to be as close to $\alpha = 0.05$ as possible. We work in the $Y = np$ scale. Under H_0, Y has mean $n\pi = (10)(0.4) = 4$. We want to find a value C such that $P[|Y - 4| \geq C]$ is as close to $\alpha = 0.05$ (and less than α) as possible. The quantity C is the distance Y is from the null hypothesis value 4. Using the definition of the binomial distribution, we construct Table 6.1.

The closest α-value to 0.05 is $\alpha = 0.0183$; the next value is 0.1012. Hence we choose $C = 4$; we reject the null hypothesis H_0: $n\pi = 4$ if $Y = 0$ or $Y \geq 8$; equivalently, if $p = 0$ or $p \geq 0.8$, or in the original formulation, if $|p - 0.4| \geq 0.4$ since $C = 10c$.

Table 6.1 C-Values for Example 6.6

C	$4 - C$	$C + 4$	$P[\|Y - 4\| \geq C] = \alpha$
6	—	10	$0.0001 = P[Y = 10]$
5	—	9	$0.0017 = P[Y \geq 9]$
4	0	8	$0.0183 = P[Y = 0] + P[Y \geq 8]$
3	1	7	$0.1012 = P[Y \leq 1] + P[Y \geq 7]$
2	2	6	$0.3335 = P[Y \leq 2] + P[Y \geq 6]$
1	3	5	$0.7492 = P[Y \leq 3] + P[Y \geq 5]$

Procedure 2. To find the *p-value* for testing the hypothesis H_0: $\pi = \pi_0$ vs. H_A: $\pi \neq \pi_0$:

1. Observe $p : \widehat{p}$ is now fixed, where $\widehat{p} = y/n$.
2. Let $\widetilde{p}$ be a binomial random variable with parameters n and π_0. The p-value is $P[|\widetilde{p} - \pi_0| \geq |\widehat{p} - \pi_0|]$.

Example 6.7. Find the p-value for testing $\pi = 0.5$ if $n = 10$ and we observe that $p = 0.2$. $|\widetilde{p} - 0.5| \geq |0.2 - 0.5| = 0.3$ only if $\widetilde{p} = 0.0, 0.1, 0.2, 0.8, 0.9$, or 1.0. The p-value can be computed by software or by adding up the probabilities of the "more extreme" values: $0.0010 + 0.0098 + 0.0439 + 0.0439 + 0.0098 + 0.0010 = 0.1094$. Tables for this calculation are provided in the Web appendix. The appropriate one-sided hypothesis test and calculation of a one-sided p-value is given in Problem 6.25.

6.2.4 Confidence Intervals

Confidence intervals for a binomial proportion can be found by computer or by looking up the confidence limits in a table. Such tables are not included in this book, but are available in any standard handbook of statistical tables, for example, Odeh et al. [1977], Owen [1962], and Beyer [1968].

6.2.5 Large-Sample Hypothesis Testing

The central limit theorem holds for binomial random variables. If Y is binomial with parameters n and π, then for "large n,"

$$\frac{Y - E(Y)}{\sqrt{\text{var}(Y)}} = \frac{Y - n\pi}{\sqrt{n\pi(1-\pi)}}$$

has approximately the same probability distribution as an $N(0, 1)$ random variable. Equivalently, since $Y = np$, the quantity $(p - \pi)/\sqrt{\pi(1-\pi)/n}$ approaches a normal distribution. We will work interchangeably in the p scale or the Y scale. For large n, hypothesis tests and confidence intervals may be formed by using critical values of the standard normal distribution.

The closer π is to 1/2, the better the normal approximation will be. If $n \leq 50$, it is preferable to use tables for the binomial distribution and hypothesis tests as outlined above. A reasonable rule of thumb is that n is "large" if $n\pi(1-\pi) \geq 10$.

In using the central limit theorem, we are approximating the distribution of a discrete random variable by the continuous normal distribution. The approximation can be improved by using a *continuity correction*. The normal random variable with continuity correction is given by

$$Z_c = \begin{cases} \dfrac{Y - n\pi - 1/2}{\sqrt{n\pi(1-\pi)}} & \text{if } Y - n\pi > 1/2 \\ \dfrac{Y - n\pi}{\sqrt{n\pi(1-\pi)}} & \text{if } |Y - n\pi| \leq 1/2 \\ \dfrac{Y - n\pi + 1/2}{\sqrt{n\pi(1-\pi)}} & \text{if } Y - n\pi < -1/2 \end{cases}$$

For $n\pi(1-\pi) \geq 100$, or quite large, the factor of 1/2 is usually ignored.

Procedure 3. Let Y be binomial n, π, with a large n. A hypothesis test of H_0: $\pi = \pi_0$ vs. H_A: $\pi \neq \pi_0$ at significance level α is given by computing Z_c with $\pi = \pi_0$. The null hypothesis is rejected if $|Z_c| \geq z_{1-\alpha/2}$.

Example 6.8. In Example 6.2, of the 64 persons who tested their capsules, 55 guessed the treatment correctly. Could so many people have guessed the correct treatment "by chance"? In Example 6.2 we saw that chance guessing would correspond to $\pi_0 = 1/2$. At a 5% significance level, is it plausible that $\pi_0 = 1/2$?

As $n\pi_0(1 - \pi_0) = 64 \times 1/2 \times 1/2 = 16$, a large-sample approximation is reasonable. $y - n\pi_0 = 55 - 64 \times 1/2 = 23$, so that

$$Z_c = \frac{Y - n\pi_0 - 1/2}{\sqrt{n\pi_0(1-\pi_0)}} = \frac{22.5}{\sqrt{64 \times 1/2 \times 1/2}} = 5.625$$

As $|Z_c| = 5.625 > 1.96 = z_{0.975}$, the null hypothesis that the correct guessing occurs purely by chance must be rejected.

Procedure 4. The large-sample two-sided p-value for testing H_0: $\pi = \pi_0$ vs. H_A: $\pi \neq \pi_0$ is given by $2(1 - \Phi(|Z_c|))$. $\Phi(x)$ is the probability that an $N(0, 1)$ random variable is less than x. $|Z_c|$ is the absolute value of Z_c.

6.2.6 Large-Sample Confidence Intervals

Procedure 5. For large n, say $n\widehat{p}(l-\widehat{p}) \geq 10$, an approximate $100(1-\alpha)\%$ confidence interval for π is given by

$$\left(\widehat{p} - z_{1-\alpha/2}\sqrt{\frac{\widehat{p}(1-\widehat{p})}{n}}, \quad \widehat{p} + z_{1-\alpha/2}\sqrt{\frac{\widehat{p}(1-\widehat{p})}{n}}\right) \tag{5}$$

where $\widehat{p} = y/n$ is the observed proportion of successes.

Example 6.9. Find a 95% confidence interval for the true fraction of black children having ABO hemolytic disease in the population represented by the data of Example 6.3. Using formula (5) the confidence interval is

$$\frac{43}{3584} \pm 1.96\sqrt{\frac{(43/3584)(1-43/3584)}{3584}} \quad \text{or} \quad (0.0084, 0.0156)$$

6.3 COMPARING TWO PROPORTIONS

Often, one is not interested in only one proportion but wants to compare two proportions. A health services researcher may want to see whether one of two races has a higher percentage of prenatal care. A clinician may wish to discover which of two drugs has a higher proportion of cures. An epidemiologist may be interested in discovering whether women on oral contraceptives have a higher incidence of thrombophlebitis than those not on oral contraceptives. In this section we consider the statistical methods appropriate for comparing two proportions.

6.3.1 Fisher's Exact Test

Data to estimate two different proportions will arise from observations on two populations. Call the two sets of observations sample 1 and sample 2. Often, the data are presented in 2×2 (verbally, "two by two") tables as follows:

	Success	Failure
Sample 1	n_{11}	n_{12}
Sample 2	n_{21}	n_{22}

The first sample has n_{11} successes in $n_{11} + n_{12}$ trials; the second sample has n_{21} successes in $n_{21} + n_{22}$ trials. Often, the null hypothesis of interest is that the probability of success in the two populations is the same. *Fisher's exact test* is a test of this hypothesis for small samples.

The test uses the row and column totals. Let $n_{1\cdot}$ denote summation over the second index; that is, $n_{1\cdot} = n_{11} + n_{12}$. Similarly define $n_{2\cdot}$, $n_{\cdot 1}$, and $n_{\cdot 2}$. Let $n_{\cdot\cdot}$ denote summation over both indices; that is, $n_{\cdot\cdot} = n_{11} + n_{12} + n_{21} + n_{22}$. Writing the table with row and column totals gives:

	Success	**Failure**	
Sample 1	n_{11}	n_{12}	$n_{1\cdot}$
Sample 2	n_{21}	n_{22}	$n_{2\cdot}$
	$n_{\cdot 1}$	$n_{\cdot 2}$	$n_{\cdot\cdot}$

Suppose that the probabilities of success in the two populations are the same. Suppose further that we are given the row and column totals but *not* n_{11}, n_{12}, n_{21}, and n_{22}. What is the probability distribution of n_{11}?

Consider the $n_{\cdot\cdot}$ trials as $n_{\cdot\cdot}$ objects; for example, $n_{1\cdot}$ purple balls and $n_{2\cdot}$ gold balls. Since each trial has the same probability of success, any subset of $n_{\cdot 1}$ trials (balls) has the same probability of being chosen as any other. Thus, the probability that n_{11} has the value k is the same as the probability that there are k purple balls among $n_{\cdot 1}$ balls chosen without replacement from an urn with $n_{1\cdot}$ purple balls and $n_{2\cdot}$ gold balls. The probability distribution of n_{11} is called the *hypergeometric distribution*.

The mathematical form of the hypergeometric probability distribution is derived in Problem 6.26.

Example 6.10. Kennedy et al. [1981] consider patients who have undergone coronary artery bypass graft surgery (CABG). CABG takes a saphenous vein from the leg and connects the vein to the aorta, where blood is pumped from the heart, and to a coronary artery, an artery that supplies the heart muscle with blood. The vein is placed beyond a narrowing, or stenosis, in the coronary artery. If the artery would close at the narrowing, the heart muscle would still receive blood. There is, however, some risk to this open heart surgery. Among patients with moderate narrowing (50 to 74%) of the left main coronary artery emergency cases have a high surgical mortality rate. The question is whether emergency cases have a surgical mortality different from that of nonemergency cases. The in-hospital mortality figures for emergency surgery and other surgery were:

	Discharge Status	
Surgical Priority	**Dead**	**Alive**
Emergency	1	19
Other	7	369

From the hypergeometric distribution, the probability of an observation this extreme is $0.3419 = P[n_{11} \geq 1] = P[n_{11} = 1] + \cdots + P[n_{11} = 8]$. (Values for $n_{\cdot\cdot}$ this large are not tabulated and need to be computed directly.) These data do not show any difference beyond that expected by chance.

Example 6.11. Sudden infant death syndrome (SIDS), or crib death, results in the unexplained death of approximately two of every 1000 infants during their first year of life. To study the genetic component of such deaths, Peterson et al. [1980] examined sets of twins with at least one SIDS child. If there is a large genetic component, the probability of both twins dying will

be larger for identical twin sets than for fraternal twin sets. If there is no genetic component, but only an environmental component, the probabilities should be the same. The following table gives the data:

	SIDS Children	
Type of Twin	**One**	**Both**
Monozygous (identical)	23	1
Dizygous (fraternal)	35	2

The Fisher's exact test one-sided p-value for testing that the probability is higher for monozygous twins is $p = 0.784$. Thus, there is no evidence for a genetic component in these data.

6.3.2 Large-Sample Tests and Confidence Intervals

As mentioned above, in many situations one wishes to compare proportions as estimated by samples from two populations to see if the true population parameters might be equal or if one is larger than the other. Examples of such situations are a drug and placebo trial comparing the percentage of patients experiencing pain relief; the percentage of rats developing tumors under diets involving different doses of a food additive; and an epidemiologic study comparing the percentage of infants suffering from malnutrition in two countries.

Suppose that the first binomial variable (the sample from the first population) is of size n_1 with probability π_1, estimated by the sample proportion p_1. The second sample estimates π_2 by p_2 from a sample of size n_2.

It is natural to compare the proportions by the difference $p_1 - p_2$. The mean and variance are given by

$$E(p_1 - p_2) = \pi_1 - \pi_2,$$

$$\text{var}(p_1 - p_2) = \frac{\pi_1(1-\pi_1)}{n_1} + \frac{\pi_2(1-\pi_2)}{n_2}$$

A version of the central limit theorem shows that for large n_1 and n_2 [say, both $n_1\pi_1(1-\pi_1)$ and $n_2\pi_2(1-\pi_2)$ greater than 10],

$$\frac{p_1 - p_2 - (\pi_1 - \pi_2)}{\sqrt{p_1(1-p_1)/n_1 + p_2(1-p_2)/n_2}} = Z$$

is an approximately normal pivotal variable. From this, hypothesis tests and confidence intervals develop in the usual manner, as illustrated below.

Example 6.12. The paper by Bucher et al. [1976] discussed in Example 6.3 examines racial differences in the incidence of ABO hemolytic disease by examining records for infants born at North Carolina Memorial Hospital. In this paper a variety of possible ways of defining hemolytic disease are considered. Using their class I definition, the samples of black and white infants have the following proportions with hemolytic disease:

$$\text{black infants, } n_1 = 3584, \qquad p_1 = \frac{43}{3584}$$

$$\text{white infants, } n_2 = 3831, \qquad p_2 = \frac{17}{3831}$$

It is desired to perform a two-sided test of the hypothesis $\pi_1 = \pi_2$ at the $\alpha = 0.05$ significance level. The test statistic is

$$Z = \frac{(43/3584) - (17/3831)}{\sqrt{[(43/3584)(1 - 43/3584)]/3584 + [(17/3831)(1 - 17/3831)]/3831}} \doteq 3.58$$

The two-sided p-value is $P[|Z| \geq 3.58] = 0.0003$ from Table A.1. As $0.0003 < 0.05$, the null hypothesis of equal rates, $\pi_1 = \pi_2$, is rejected at the significance level 0.05.

The pivotal variable may also be used to construct a confidence interval for $\pi_1 - \pi_2$. Algebraic manipulation shows that the endpoints of a symmetric (about $p_1 - p_2$) confidence interval are given by

$$p_1 - p_2 \pm z_{1-\alpha/2}\sqrt{\frac{p_1(1 - p_1)}{n_1} + \frac{p_2(1 - p_2)}{n_2}}$$

For a 95% confidence interval $z_{1-\alpha/2} = 1.96$ and the interval for this example is

$$0.00756 \pm 0.00414 \quad \text{or} \quad (0.00342, 0.01170)$$

A second statistic for testing for equality in two proportions is the χ^2 (chi-square) statistic. This statistic is considered in more general situations in Chapter 7. Suppose that the data are as follows:

	Sample 1	**Sample 2**	
Success	$n_1 p_1 = n_{11}$	$n_2 p_2 = n_{12}$	$n_{1\cdot}$
Failure	$n_1(1 - p_1) = n_{21}$	$n_2(1 - p_2) = n_{22}$	$n_{2\cdot}$
	$n_1 = n_{\cdot 1}$	$n_2 = n_{\cdot 2}$	$n_{\cdot\cdot}$

A statistic for testing H_0: $\pi_1 = \pi_2$ is the χ^2 statistic with one degree of freedom. It is calculated by

$$X^2 = \frac{n_{\cdot\cdot}(n_{11}n_{22} - n_{12}n_{21})^2}{n_{1\cdot}n_{2\cdot}n_{\cdot 1}n_{\cdot 2}}$$

For technical reasons (Note 6.2) the chi-square distribution with continuity correction, designated by X_c^2, is used by some people. The formula for X_c^2 is

$$X_c^2 = \frac{n_{\cdot\cdot}(|n_{11}n_{22} - n_{12}n_{21}| - \frac{1}{2}n_{\cdot\cdot})^2}{n_{1\cdot}n_{2\cdot}n_{\cdot 1}n_{\cdot 2}}$$

For the Bucher et al. [1976] data, the values are as follows:

	Race		
ABO Hemolytic Disease	**Black**	**White**	**Total**
Yes	43	17	60
No	3541	3814	7355
Total	3584	3831	7415

$$X^2 = \frac{7415(43 \times 3814 - 17 \times 3541)^2}{60(7355)(3584)(3831)} = 13.19$$

$$X_c^2 = \frac{7415(|43 \times 3814 - 17 \times 3541| - 7415/2)^2}{60(7355)(3584)(3831)} = 12.26$$

These statistics, for large n, have a chi-square (χ^2) distribution with one degree of freedom under the null hypothesis of equal proportions. If the null hypothesis is not true, X^2 or X_c^2 will tend to be large. The null hypothesis is rejected for large values of X^2 or X_c^2. Table A.3 has χ^2 critical values. The Bucher data have $p < 0.001$ since the 0.001 critical value is 10.83 and require rejection of the null hypothesis of equal proportions.

From Note 5.3 we know that $\chi_1^2 = Z^2$. For this example the value of $Z^2 = 3.58^2 = 12.82$ is close to the value $X^2 = 13.19$. The two values would have been identical (except for rounding) if we had used in the calculation of Z an estimate of the standard error of $\sqrt{pq(1/n_1 + 1/n_2)}$, where $p = 60/7415$ is the pooled estimate of π under the null hypothesis $\pi_1 = \pi_2 = \pi$.

6.3.3 Finding Sample Sizes Needed for Testing the Difference between Proportions

Consider a study planned to test the equality of the proportions π_1 and π_2. Only studies in which both populations are sampled the same number of times, $n = n_1 = n_2$, will be considered here. There are five quantities that characterize the performance and design of the test:

1. π_1, the proportion in the first population.
2. π_2, the proportion in the second population under the alternative hypothesis.
3. n, the number of observations to be obtained from *each* of the two populations.
4. The significance level α at which the statistical test will be made. α is the probability of rejecting the null hypothesis when it is true. The null hypothesis is that $\pi_1 = \pi_2$.
5. The probability, β, of accepting the null hypothesis when it is not true, but the alternative is true. Here we will have $\pi_1 \neq \pi_2$ under the alternative hypothesis (π_1 and π_2 as specified in quantities 1 and 2 above).

These quantities are interrelated. It is not possible to change one of them without changing at least one of the others. The actual determination of sample size is usually an iterative process; the usual state of affairs is that the desire for precision and the practicality of obtaining an appropriate sample size are in conflict. In practice, one usually considers various possible combinations and arrives at a "reasonable" sample size or decides that it is not possible to perform an adequate experiment within the constraints involved.

The "classical" approach is to specify π_1, π_2 (for the alternative hypothesis), α, and β. These parameters determine the sample size n. Table A.8 gives some sample sizes for such binomial studies using one-sided hypothesis tests (see Problem 6.27). An approximation for n is

$$n = 2\left\{\frac{z_{1-\alpha} + z_{1-\beta}}{\pi_1 - \pi_2}\sqrt{\frac{1}{2}[\pi_1(1-\pi_1) + \pi_2(1-\pi_2)]}\right\}^2$$

where $\alpha = 1 - \Phi(z_{1-\alpha})$; that is, $z_{1-\alpha}$ is the value such that a $N(0, 1)$ variable Z has $P[Z > z_{1-\alpha}] = \alpha$. In words, $z_{1-\alpha}$ is the one-sided normal α critical value. Similarly, $z_{1-\beta}$ is the one-sided normal β critical value.

Figure 6.1 is a flow diagram for calculating sample sizes for discrete (binomial) as well as continuous variables. It illustrates that the format is the same for both: first, values of α and β are selected. A one- or two-sided test determines $z_{1-\alpha}$ or $z_{1-\alpha/2}$ and the quantity NUM, respectively. For discrete data, the quantities π_1 and π_2 are specified, and

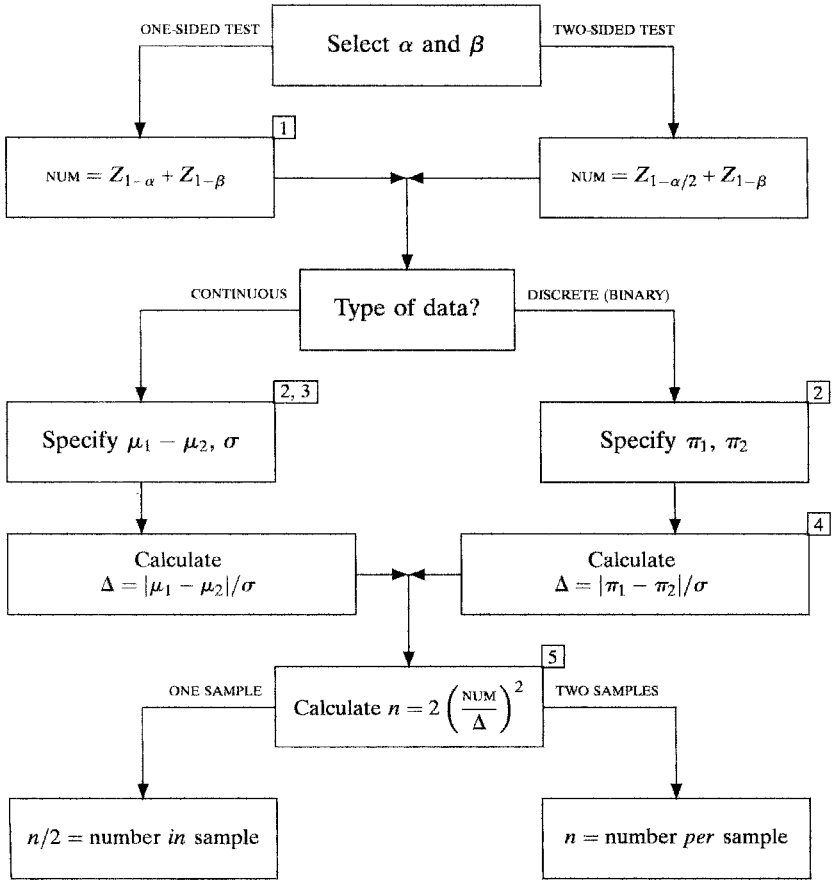


Figure 6.1 Flowchart for sample-size calculations (continuous and discrete variables).

1 Values of Z_c for various values of c are:

c	0.500	0.800	0.900	0.950	0.975	0.990	0.995
Z_c	0.000	0.842	1.282	1.645	1.960	2.326	2.576

2 If one sample, μ_2 and π_2 are null hypothesis values.

3 If $\sigma_1^2 \neq \sigma_2^2$, calculate $\sigma^2 = \frac{1}{2}(\sigma_1^2 + \sigma_2^2)$.

4 $\sigma = \sqrt{\frac{1}{2}(\pi_1(1-\pi_1) + \pi_2(1-\pi_2))}$.

5 Sample size for discrete case is an approximation. For an improved estimate, use $n^* = n + 2/\Delta$.

Note: Two sample case, unequal sample sizes. Let n_1 and kn_1 be the required sample sizes. Calculate n as before. Then calculate $n_1 = n(k+1)/2k$ and $n_2 = kn_1$. (Total sample size will be larger.) If also, $\sigma_1^2 \neq \sigma_2^2$ calculate n using σ_1; then calculate $n_1 = (n/2)[1 + \sigma_2^2/(k\sigma_1^2)]$ and $n_2 = kn_1$.

$\Delta = |\pi_1 - \pi_2|/\sqrt{\frac{1}{2}(\pi_1(1-\pi_1) + \pi_2(1-\pi_2))}$ is calculated. This corresponds to the standardized differences $\Delta = |\mu_1 - \mu_2|/\sigma$ associated with normal or continuous data. The quantity $n = 2(\text{NUM}/\Delta)^2$ then produces the sample size needed for a two-sample procedure. For a one-sample procedure, the sample size is $n/2$. Hence a two-sample procedure requires a total of *four* times the number of observations of the one-sample procedure. Various refinements are available

in Figure 6.1. A list of the most common Z-values is provided. If a one-sample test is wanted, the values of μ_2 and π_2 can be considered the null hypothesis values. Finally, the equation for the sample size in the discrete case is an approximation, and a more precise estimate, n^*, can be obtained from

$$n^* = n + \frac{2}{\Delta}$$

This formula is reasonably accurate.

Other approaches are possible. For example, one might specify the largest feasible sample size n, α, π_1, and π_2 and then determine the power $1 - \beta$. Figure 6.2 relates π_1, $\Delta = \pi_2 - \pi_1$, and n for two-sided tests for $\alpha = 0.05$ and $\beta = 0.10$.

Finally, we note that in certain situations where sample size is necessarily limited, for example, a rare cancer site with several competing therapies, trials with $\alpha = 0.10$ and $\beta = 0.50$ have been run.

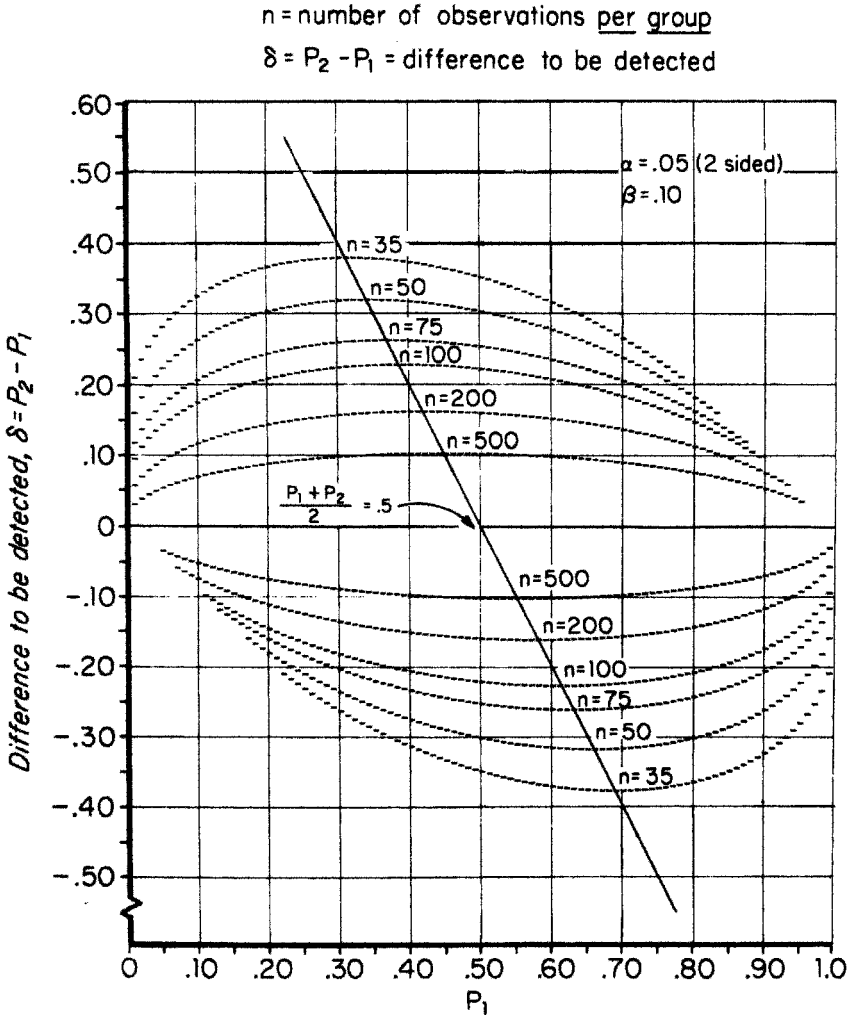


Figure 6.2 Sample sizes required for testing two proportions, π_1 and π_2 with 90% probability of obtaining a significant result at the 5% (two-sided) level. (From Feigl [1978].)

In practice, it is difficult to arrive at a sample size. To one unacquainted with statistical ideas, there is a natural tendency to expect too much from an experiment. In answer to the question, "What difference would you like to detect?" the novice will often reply, "any difference," leading to an infinite sample size!

6.3.4 Relative Risk and the Odds Ratio

In this section we consider studies looking for an association between two binary variables, that is, variables that take on only two outcomes. For definiteness we speak of the two variables as disease and exposure, since the following techniques are often used in epidemiologic and public health studies. In effect we are comparing two proportions (the proportions with disease) in two populations: those with and without exposure. In this section we consider methods of summarizing the association.

Suppose that one had a complete enumeration of the population at hand and the true proportions in the population. The probabilities may be presented in a 2×2 table:

	Disease	
Exposure	**+ (Yes)**	**− (No)**
+ (Yes)	π_{11}	π_{12}
− (No)	π_{21}	π_{22}

where $\pi_{11} + \pi_{12} + \pi_{21} + \pi_{22} = 1$.

There are subtleties glossed over here. For example, by disease (for a human population), does one mean that the person develops the disease at some time before death, has the disease at a particular point in time, or develops it by some age? This ignores the problems of accurate diagnosis, a notoriously difficult problem. Similarly, exposure needs to be defined carefully as to time of exposure, length of exposure, and so on.

What might be a reasonable measure of the effect of exposure? A plausible comparison is $P[\text{disease}+|\text{exposure}+]$ with $P[\text{disease}+|\text{exposure}-]$. In words, it makes sense to compare the probability of having disease among those exposed with the probability of having the disease among those not exposed.

Definition 6.1. A standard measure of the strength of the exposure effect is the *relative risk*. The relative risk is defined to be

$$\rho = \frac{P[\text{disease} + |\text{exposure}+]}{P[\text{disease} + |\text{exposure}-]} = \frac{\pi_{11}/(\pi_{11} + \pi_{12})}{\pi_{21}/(\pi_{21} + \pi_{22})} = \frac{\pi_{11}(\pi_{21} + \pi_{22})}{\pi_{21}(\pi_{11} + \pi_{12})}$$

Thus, a relative risk of 5 means that an exposed person is five times as likely to have the disease. The following tables of proportions or probabilities each has a relative risk of 2:

	Disease		**Disease**		**Disease**		**Disease**	
Exposure	**+**	**−**	**+**	**−**	**+**	**−**	**+**	**−**
+	0.50	0.00	0.25	0.25	0.10	0.40	0.00010	0.49990
−	0.25	0.25	0.125	0.375	0.05	0.45	0.0005	0.49995

We see that many patterns may give rise to the same relative risk. This is not surprising, as one number is being used to summarize four numbers. In particular, information on the amount of disease and/or exposure is missing.

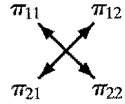
Definition 6.2. Given that one has the exposure, the *odds* (or betting odds) of getting the disease are

$$\frac{P[\text{disease} + \mid \text{exposure}+]}{P[\text{disease} - \mid \text{exposure}+]}$$

Similarly, one may define the odds of getting the disease given no exposure. Another measure of the amount of association between the disease and exposure is the *odds ratio* defined to be

$$\begin{aligned}\omega &= \frac{P[\text{disease} + \mid \text{exposure}+]/P[\text{disease} - \mid \text{exposure}+]}{P[\text{disease} + \mid \text{exposure}-]/P[\text{disease} - \mid \text{exposure}-]} \\ &= \frac{(\pi_{11}/(\pi_{11}+\pi_{12}))/(\pi_{12}/(\pi_{11}+\pi_{12}))}{(\pi_{21}/(\pi_{21}+\pi_{22}))/(\pi_{22}/(\pi_{21}+\pi_{22}))} \\ &= \frac{\pi_{11}\pi_{22}}{\pi_{12}\pi_{21}}\end{aligned}$$

The odds ratio is also called the *cross-product ratio* on occasion; this name is suggested by the following scheme:



Consider now how much the relative risk and odds ratio may differ by looking at the ratio of the two terms, ρ and ω,

$$\frac{\rho}{\omega} = \left(\frac{\pi_{21}+\pi_{22}}{\pi_{22}}\right)\left(\frac{\pi_{12}}{\pi_{11}+\pi_{12}}\right)$$

Suppose that the disease affects a small segment of the population. Then π_{11} is small compared to π_{12}, so that $\pi_{12}/(\pi_{11}+\pi_{12})$ is approximately equal to 1. Also, π_{21} will be small compared to π_{22}, so that $(\pi_{21}+\pi_{22})/\pi_{22}$ is approximately 1. Thus, in this case, $\rho/\omega = 1$. Restating this: If the disease affects a small fraction of the population (in both exposed and unexposed groups), the odds ratio and the relative risk are approximately equal. For this reason the odds ratio is often called the *approximate relative risk*. If the disease affects less than 5% in each group, the two quantities can be considered approximately equal.

The data for looking at the relative risk or the odds ratio usually arise in one of three ways, each of which is illustrated below. The numbers observed in each of the four cells will be denoted as follows:

	Disease	
Exposure	**+**	**−**
+	n_{11}	n_{12}
−	n_{21}	n_{22}

As before, a dot will replace a subscript when the entries for that subscript are summed. For example,

$$\begin{aligned}n_{1\cdot} &= n_{11} + n_{12} \\ n_{\cdot 2} &= n_{12} + n_{22} \\ n_{\cdot\cdot} &= n_{11} + n_{12} + n_{21} + n_{22}\end{aligned}$$

Pattern 1. (Cross-Sectional Studies: Prospective Studies of a Sample of the Population) There is a sample of size $n..$ from the population; both traits (exposure and disease) are measured on each subject. This is called *cross-sectional data* when the status of the two traits is measured at some fixed cross section in time. In this case the expected number in each cell is the expectation:

$n..\pi_{11}$	$n..\pi_{12}$	
$n..\pi_{21}$	$n..\pi_{22}$	
		$n..$

Example 6.13. The following data are from Meyer et al. [1976]. This study collected information on all births in 10 Ontario (Canada) teaching hospitals during 1960–1961. A total of 51,490 births was involved, including fetal deaths and neonatal deaths (perinatal mortality). The paper considers the association of perinatal events and maternal smoking during pregnancy. Data relating perinatal mortality and smoking are as follows:

	Perinatal Mortality		
Maternal Smoking	**Yes**	**No**	**Total**
Yes	619	20,443	21,062
No	634	26,682	27,316
Total	1,253	47,125	48,378

Estimation of the relative risk and odds ratio is discussed below.

Pattern 2. (Prospective Study: Groups Based on Exposure) In a prospective study of exposure, fixed numbers—say $n_1.$ and $n_2.$—of people with and without the exposure are followed. The endpoints are then noted. In this case the expected number of observations in the cells are:

$n_1 . \dfrac{\pi_{11}}{\pi_{11}+\pi_{12}}$	$n_1 . \dfrac{\pi_{12}}{\pi_{11}+\pi_{12}}$	$n_1.$
$n_2 . \dfrac{\pi_{21}}{\pi_{21}+\pi_{22}}$	$n_2 . \dfrac{\pi_{22}}{\pi_{21}+\pi_{22}}$	$n_2.$

Note that as the sample sizes of the exposure and nonexposure groups are determined by the experimenter, the data will not allow estimates of the proportion exposed, only the conditional probability of disease given exposure or nonexposure.

Example 6.14. As an example, consider a paper by Shapiro et al. [1974] in which they state that "by the end of this [five-year] period, there were 40 deaths in the [screened] study group of about 31,000 women as compared with 63 such deaths in a comparable group of women." Placing this in a 2×2 table and considering the screening to be the exposure, the data are:

	Breast Cancer Death		
On Study (Screened)	**Yes**	**No**	**Total**
Yes	40	30,960	31,000
No	63	30,937	31,000

Pattern 3. (Retrospective Studies) The third way of commonly collecting the data is the retrospective study. Usually, cases and an appropriate control group are identified. (Matched or paired data are *not* being discussed here.) In this case, the sizes of the disease and control groups,

$n_{\cdot 1}$ and $n_{\cdot 2}$, are specified. From such data one cannot estimate the probability of disease but rather, the probability of being exposed given that a person has the disease and the probability of exposure given that a person does not have the disease. The expected number of observations in each cell is

$$\begin{array}{cc} n_{\cdot 1}\dfrac{\pi_{11}}{\pi_{11}+\pi_{21}} & n_{\cdot 2}\dfrac{\pi_{12}}{\pi_{12}+\pi_{22}} \\ n_{\cdot 1}\dfrac{\pi_{21}}{\pi_{11}+\pi_{21}} & n_{\cdot 2}\dfrac{\pi_{22}}{\pi_{12}+\pi_{22}} \\ \hline n_{\cdot 1} & n_{\cdot 2} \end{array}$$

Example 6.15. Kelsey and Hardy [1975] studied the driving of motor vehicles as a risk factor for acute herniated lumbar intervertebral disk. Their cases were people between the ages of 20 and 64; the studies were conducted in the New Haven metropolitan area at three hospitals or in the office of two private radiologists. The cases had low-back x-rays and were interviewed and given a few simple diagnostic tests. A control group was composed of those with low-back x-rays who were not classified as surgical probable or possible cases of herniated disk and who had not had their symptoms for more than one year. The in-patients, cases, and controls, of the Yale–New Haven hospital were asked if their job involved driving a motor vehicle. The data were:

	Herniated Disk?	
Motor Vehicle Job?	**Yes (Cases)**	**No (Controls)**
Yes	8	1
No	47	26
Total	55	27

Consider a two-way layout of disease and exposure to an agent thought to influence the disease:

	Disease	
Exposure	**+**	**−**
+	n_{11}	n_{12}
−	n_{21}	n_{22}

The three types of studies discussed above can be thought of as involving conditions on the marginal totals indicated in Table 6.2.

Table 6.2 Characterization of Cross-Sectional, Prospective, and Retrospective Studies and Relationship to Possible Estimation of Relative Risk and Odds Ratio

	Totals for:		Can One Estimate the:	
Type of Study	Column	Row	Relative Risk?	Odds Ratio?
Cross-sectional or prospective sample	Random	Random	Yes	Yes
Prospective on exposure	Random	Fixed	Yes	Yes
Retrospective	Fixed	Random	No	Yes

For example, a prospective study can be thought of as a situation where the totals for "exposure+" and "exposure−" are fixed by the experimenter, and the column totals will vary randomly depending on the association between the disease and the exposure.

For each of these three types of table, how might one estimate the relative risk and/or the odds ratio? From our tables of expected numbers of observations, it is seen that for tables of types 1 and 2,

$$\frac{E(n_{11})/(E(n_{11})+E(n_{12}))}{E(n_{21})/(E(n_{21})+E(n_{22}))} = \frac{E(n_{11})/E(n_{1\cdot})}{E(n_{21})/E(n_{2\cdot})} = \frac{\pi_{11}/(\pi_{11}+\pi_{12})}{\pi_{21}/(\pi_{21}+\pi_{22})} = \rho$$

Thus, one estimates the relative risk ρ by replacing the expected value of n_{11} by the observed value of n_{11}, etc., giving

$$\widehat{\rho} = \frac{n_{11}/n_{1\cdot}}{n_{21}/n_{2\cdot}}$$

For retrospective studies of type 3 it is not possible to estimate ρ unless the disease is rare, in which case the estimate of the odds ratio gives a reasonable estimate of the relative risk.

For all three types of tables, one sees that

$$\frac{E(n_{11})E(n_{22})}{E(n_{12})E(n_{21})} = \frac{\pi_{11}\pi_{22}}{\pi_{12}\pi_{21}} = \omega$$

Therefore, we estimate the odds ratio by

$$\widehat{\omega} = \frac{n_{11}n_{22}}{n_{12}n_{21}}$$

It is clear from the definition of relative risk that if exposure has no association with the disease, $\rho = 1$. That is, both "exposed" and "nonexposed" have the same probability of disease. We verify this mathematically, and also that under the null hypothesis of no association, the odds ratio ω is also 1. Under H_0:

$$\pi_{ij} = \pi_{i\cdot}\pi_{\cdot j} \qquad \text{for} \quad i = 1,2 \quad \text{and} \quad j = 1,2$$

Thus,

$$\rho = \frac{\pi_{11}/\pi_{1\cdot}}{\pi_{21}/\pi_{2\cdot}} = \frac{\pi_{1\cdot}\pi_{\cdot 1}/\pi_{1\cdot}}{\pi_{2\cdot}\pi_{\cdot 1}/\pi_{2\cdot}} = 1 \quad \text{and} \quad \omega = \frac{\pi_{11}\pi_{22}}{\pi_{12}\pi_{21}} = \frac{\pi_{1\cdot}\pi_{\cdot 1}\pi_{2\cdot}\pi_{\cdot 2}}{\pi_{1\cdot}\pi_{\cdot 2}\pi_{2\cdot}\pi_{\cdot 1}} = 1$$

If ρ or ω are greater than 1, the exposed group has an increased risk of the disease. If ρ or ω are less than 1, the group not exposed has an increased risk of the disease. Note that an increased or decreased risk may, or may not, be due to a causal mechanism.

For the three examples above, let us calculate the estimated relative risk and odds ratio where appropriate. For the smoking and perinatal mortality data,

$$\widehat{\rho} = \frac{619/21{,}062}{634/27{,}316} \doteq 1.27, \qquad \widehat{\omega} = \frac{619(26{,}682)}{634(20{,}443)} \doteq 1.27$$

From these data we estimate that smoking during pregnancy is associated with an increased risk of perinatal mortality that is 1.27 times as large. (*Note*: We have not concluded that smoking causes the mortality, only that there is an association.)

The data relating screening for early detection of breast cancer and five-year breast cancer mortality gives estimates

$$\widehat{\rho} = \frac{40/31{,}000}{63/31{,}000} \doteq 0.63, \qquad \widehat{\omega} = \frac{40(30{,}937)}{63(30{,}960)} \doteq 0.63$$

Thus, in this study, screening was associated with a risk of dying of breast cancer within five years only 0.63 times as great as the risk among those not screened.

In the unmatched case–control study, only ω can be estimated:

$$\widehat{\omega} = \frac{8 \times 26}{1 \times 47} \doteq 4.43$$

It is estimated that driving jobs increase the risk of a herniated lumbar intervertebral disk by a factor of 4.43.

Might there really be no association in the tables above and the estimated $\widehat{\rho}$'s and $\widehat{\omega}$'s differ from 1 merely by chance? You may test the hypothesis of no association by using Fisher's exact test (for small samples) or the chi-squared test (for large samples).

For the three examples, using the table of χ^2 critical values with one degree of freedom, we test the statistical significance of the association by using the chi-square statistic with continuity correction.

Smoking–perinatal mortality:

$$X_c^2 = \frac{48{,}378[|619 \times 26{,}682 - 634 \times 20{,}443| - \frac{1}{2}(48{,}378)]^2}{21{,}062(27{,}316)(1253)(47{,}125)} = 17.76$$

From Table A.3, $p < 0.001$, and there is significant association. (Equivalently, for one degree of freedom, $Z = \sqrt{\chi_c^2} = 4.21$ and Table A.3 shows $p < 0.0001$.)

Breast cancer and screening:

$$X_c^2 = \frac{62{,}000[|40 \times 30{,}937 - 63 \times 30{,}960| - \frac{1}{2}(62{,}000)]^2}{31{,}000(31{,}000)(103)(61{,}897)} = 4.71$$

From the table, $0.01 < p < 0.05$ and the association is statistically significant at the 0.05 level.

Motor-vehicle job and herniated disk: $X_c^2 = 1.21$. From the χ^2 table, $p > 0.25$, and there is *not* a statistical association using only the Yale–New Haven data. In the next section we return to this data set.

If there is association, what can one say about the accuracy of the estimates? For the first two examples, where there is a statistically significant association, we turn to the construction of confidence intervals for ω. The procedure is to construct a confidence interval for $\ln \omega$, the natural log of ω, and to "exponentiate" the endpoints to find the confidence interval for ω. Our logarithms are natural logarithms, that is, to the base e. Recall e is a number; $e = 2.71828\ldots$.

The estimate of $\ln \omega$ is $\ln \widehat{\omega}$. The standard error of $\ln \widehat{\omega}$ is estimated by

$$\sqrt{\frac{1}{n_{11}} + \frac{1}{n_{12}} + \frac{1}{n_{21}} + \frac{1}{n_{22}}}$$

The estimate is approximately normally distributed; thus, normal critical values are used in constructing the confidence intervals. A $100(1-\alpha)\%$ confidence interval for $\ln \omega$ is given by

$$\ln \widehat{\omega} \pm z_{1-\alpha/2} \sqrt{\frac{1}{n_{11}} + \frac{1}{n_{12}} + \frac{1}{n_{21}} + \frac{1}{n_{22}}}$$

where an $N(0, 1)$ variable has probability $\alpha/2$ of exceeding $z_{1-\alpha/2}$.

Upon finding the endpoints of this confidence interval, we exponentiate the values of the endpoints to find the confidence interval for ω. We find a 99% confidence interval for ω with the smoking and perinatal mortality data. First we construct the confidence interval for $\ln \omega$:

$$\ln(1.27) \pm 2.576\sqrt{\frac{1}{619} + \frac{1}{20{,}443} + \frac{1}{26{,}682} + \frac{1}{634}}$$

or 0.2390 ± 0.1475 or (0.0915, 0.3865). The confidence interval for ω is

$$(e^{0.0915}, e^{0.3865}) = (1.10, 1.47)$$

To find a 95% confidence interval for the breast cancer–screening data,

$$\ln(0.63) \pm 1.96\sqrt{\frac{1}{40} + \frac{1}{30{,}960} + \frac{1}{30{,}937} + \frac{1}{63}}$$

or -0.4620 ± 0.3966 or $(-0.8586, -0.0654)$. The 95% confidence interval for the odds ratio, ω, is (0.424, 0.937).

The reason for using logarithms in constructing the confidence intervals is that $\ln \widehat{\omega}$ is more normally distributed than ω. The standard error of ω may be estimated directly by

$$\widehat{\omega}\sqrt{\frac{1}{n_{11}} + \frac{1}{n_{12}} + \frac{1}{n_{21}} + \frac{1}{n_{22}}}$$

(see Note 6.2 for the rationale). However, confidence intervals should be constructed as illustrated above.

6.3.5 Combination of 2 × 2 Tables

In this section we consider methods of combining 2×2 tables. The tables arise in one of two ways. In the first situation, we are interested in investigating an association between disease and exposure. There is, however, a third variable taking a finite number of values. We wish to "adjust" for the effect of the third variable. The values of the "confounding" third variable sometimes arise by taking a continuous variable and grouping by intervals; thus, the values are sometimes called *strata*. A second situation in which we will deal with several 2×2 tables is when the study of association and disease is made in more than one group. In some reasonable way, one would like to consider the combination of the 2×2 tables from each group.

Why Combine 2 × 2 *Tables?*

To see why one needs to worry about such things, suppose that there are two strata. In our first example there is no association between exposure and disease in each stratum, but if we ignore strata and "pool" our data (i.e., add it all together), an association appears. For stratum 1,

	Disease	
Exposure	+	−
+	5	50
−	10	100

$$\widehat{\omega}_1 = \frac{5(100)}{10(50)} = 1$$

and for stratum 2,

	Disease	
Exposure	**+**	**−**
+	40	60
−	40	60

$$\widehat{\omega}_2 = \frac{40(60)}{40(60)} = 1$$

In both tables the odds ratio is 1 and there is no association. Combining tables, the combined table and its odds ratio are:

	Disease	
Exposure	**+**	**−**
+	45	110
−	50	160

$$\widehat{\omega}_{\text{combined}} = \frac{45(160)}{50(110)} \doteq 1.31$$

When combining tables with no association, or odds ratios of 1, the combination may show association. For example, one would expect to find a positive relationship between breast cancer and being a homemaker. Possibly tables given separately for each gender would not show such an association. If the inference to be derived were that homemaking might be related causally to breast cancer, it is clear that one would need to adjust for gender.

On the other hand, there can be an association within each stratum that disappears in the pooled data set. The following numbers illustrate this:

Stratum 1:

	Disease	
Exposure	**+**	**−**
+	60	100
−	10	50

$$\widehat{\omega}_1 = \frac{60(50)}{10(100)} = 3$$

Stratum 2:

	Disease	
Exposure	**+**	**−**
+	50	10
−	100	60

$$\widehat{\omega}_2 = \frac{50(60)}{100(10)} = 3$$

Combined data:

	Disease	
Exposure	**+**	**−**
+	110	110
−	110	110

$$\widehat{\omega}_{\text{combined}} = 1$$

Thus, ignoring a confounding variable may "hide" an association that exists within each stratum but is not observed in the combined data.

Formally, our two situations are the same if we identify the stratum with differing groups. Also, note that there may be more than one confounding variable, that each strata of the "third" variable could correspond to a different combination of several other variables.

Questions of Interest in Multiple 2 × 2 *Tables*

In examining more than one 2×2 table, one or more of three questions is usually asked. This is illustrated by using the data of the study involving cases of acute herniated lumbar disk and controls (not matched) in Example 6.15, which compares the proportions with jobs driving motor vehicles. Seven different hospital services are involved, although only one of them was presented in Example 6.15. Numbering the sources from 1 to 7 and giving the data as 2×2 tables, the tables and the seven odds ratios are:

Source 1:

	Herniated Disk	
Motor Vehicle Job	**+**	**−**
+	8	1
−	47	26

$\widehat{\omega} = 4.43$

Source 2:

	+	−
+	5	0
−	17	21

$\widehat{\omega} = \infty$

Source 3:

	+	−
+	4	4
−	13	77

$\widehat{\omega} = 5.92$

Source 4:

	+	−
+	2	10
−	12	65

$\widehat{\omega} = 1.08$

Source 5:

	+	−
+	1	3
−	5	10

$\widehat{\omega} = 0.67$

Source 6:

	+	−
+	1	2
−	3	11

$\widehat{\omega} = 1.83$

Source 7:

	+	−
+	2	2
−	12	37

$\widehat{\omega} = 3.08$

The seven odds ratios are 4.43, ∞, 5.92, 1.08, 0.67, 1.83, and 3.08. The ratios vary so much that one might wonder whether each hospital service has the same degree of association (question 1). If they do not have the same degree of association, one might question whether the controls are appropriate, the patient populations are different, and so on.

One would also like an estimate of the overall or average association (question 2). From the previous examples it is seen that it might not be wise to sum all the tables and compute the association based on the pooled tables.

Finally, another question, related to the first two, is whether there is any evidence of any association, either overall or in some of the groups (question 3).

Two Approaches to Estimating an Overall Odds Ratio

If the seven different tables come from populations with the same odds ratio, how do we estimate the common or overall odds ratio? We will consider two approaches.

The first technique is to work with the natural logarithm, log to the base e, of the estimated odds ratio, $\widehat{\omega}$. Let $a_i = \ln \widehat{\omega}_i$, where $\widehat{\omega}_i$ is the estimated odds ratio in the ith of k 2×2 tables. The standard error of a_i is estimated by

$$s_i = \sqrt{\frac{1}{n_{11}} + \frac{1}{n_{12}} + \frac{1}{n_{21}} + \frac{1}{n_{22}}}$$

where n_{11}, n_{12}, n_{21}, and n_{22} are the values from the ith 2×2 table. How do we investigate the problems mentioned above? To do this, one needs to understand a little of how the χ^2 distribution arises. The square of a standard normal variable has a chi-square distribution with one degree of freedom. If independent chi-square variables are added, the result is a chi-square variable whose degrees of freedom comprises the sum of the degrees of freedom of the variables that were added (see Note 5.3 also).

We now apply this to the problem at hand. Under the null hypothesis of no association in any of the tables, each a_i/s_i is approximately a standard normal value. If there is no association, $\omega = 1$ and $\ln \omega = 0$. Thus, $\log \widehat{\omega}_i$ has a mean of approximately zero. Its square, $(a_i/s_i)^2$, is approximately a χ^2 variable with one degree of freedom. The sum of all k of these independent, approximately chi-square variables is approximately a chi-square variable with k degrees of freedom. The sum is

$$X^2 = \sum_{i=1}^{k} \left(\frac{a_i}{s_i}\right)^2$$

and under the null hypothesis it has approximately a χ^2-distribution with k degrees of freedom.

It is possible to partition this sum into two parts. One part tests whether the association might be the same in all k tables (i.e., it tests for homogeneity). The second part will test to see whether on the basis of all the tables there is any association.

Suppose that one wants to "average" the association from all of the 2×2 tables. It seems reasonable to give more weight to the better estimates of association; that is, one wants the estimates with higher variances to get less weight. An appropriate weighted average is

$$\overline{a} = \sum_{i=1}^{k} \frac{a_i}{s_i^2} \Big/ \sum_{i=1}^{k} \frac{1}{s_i^2}$$

The χ^2-statistic then is partitioned, or broken down, into two parts:

$$X^2 = \sum_{i=1}^{k} \left(\frac{a_i}{s_i}\right)^2 = \sum_{i=1}^{k} \frac{1}{s_i^2}(a_i - \overline{a})^2 + \sum_{i=1}^{k} \frac{1}{s_i^2}\overline{a}^2$$

On the right-hand side, the first sum is approximately a χ^2 random variable with $k-1$ degrees of freedom if all k groups have the same degree of association. It tests for the homogeneity of the association in the different groups. That is, if χ^2 for homogeneity is too large, we reject the null hypothesis that the degree of association (whatever it is) is the same in each group. The second term tests whether there is association on the average. This has approximately a χ^2-distribution with one degree of freedom if there is no association in each group. Thus, define

$$\chi_H^2 = \sum_{i=1}^{k} \frac{1}{s_i^2}(a_i - \overline{a})^2 = \sum_{i=1}^{k} \frac{a_i^2}{s_i^2} - \overline{a}^2 \sum_{i=1}^{k} \frac{1}{s_i^2}$$

and

$$\chi_A^2 = \overline{a}^2 \sum_{i=1}^{k} \frac{1}{s_i^2}$$

Of course, if we decide that there are different degrees of association in different groups, this means that at least one of the groups must have some association.

Consider now the data given above. A few additional points are introduced. We use the log of the odds ratio, but the second group has $\widehat{\omega} = \infty$. What shall we do about this?

With small numbers, this may happen due to a zero in a cell. The bias of the method is reduced by adding 0.5 to each cell in each table:

[1]	+	−
+	8.5	1.5
−	47.5	26.5

[2]	+	−
+	5.5	0.5
−	17.5	21.5

[3]	+	−
+	4.5	4.5
−	13.5	77.5

[4]	+	−
+	2.5	10.5
−	12.5	65.5

[5]	+	−
+	1.5	3.5
−	5.5	10.5

[6]	+	−
+	1.5	2.5
−	3.5	11.5

[7]	+	−
+	2.5	2.5
−	12.5	37.5

Now

$$\widehat{\omega}_i = \frac{(n_{11} + 0.5)(n_{22} + 0.5)}{(n_{12} + 0.5)(n_{21} + 0.5)}, \qquad s_i = \sqrt{\frac{1}{n_{11} + 0.5} + \frac{1}{n_{22} + 0.5} + \frac{1}{n_{12} + 0.5} + \frac{1}{n_{21} + 0.5}}$$

The calculations above are shown in Table 6.3.

Table 6.3 Calculations for the Seven Tables

Table i	$\widehat{\omega}_i$	$a_i = \log \widehat{\omega}_i$	s_i^2	$1/s_i^2$	a_i^2/s_i^2	a_i/s_i^2
1	3.16	1.15	0.843	1.186	1.571	1.365
2	13.51	2.60	2.285	0.438	2.966	1.139
3	5.74	1.75	0.531	1.882	5.747	3.289
4	1.25	0.22	0.591	1.693	0.083	0.375
5	0.82	−0.20	1.229	0.813	0.033	−0.163
6	1.97	0.68	1.439	0.695	0.320	0.472
7	3.00	1.10	0.907	1.103	1.331	1.212
Total				7.810	12.051	7.689

Then

$$\overline{a} = \sum_{i=1}^{k} \frac{a_i}{s_i^2} \Big/ \sum_{i=1}^{k} \frac{1}{s_i^2} = \frac{7.689}{7.810} \doteq 0.985$$

$$X_A^2 = (0.985)^2(7.810) \doteq 7.57$$

$$X_H^2 = \sum \frac{a_i^2}{s_i^2} - \chi_A^2 = 12.05 - 7.57 = 4.48$$

X_H^2 with $7 - 1 = 6$ degrees of freedom has an $\alpha = 0.05$ critical value of 12.59 from Table A.3. We do *not* conclude that the association differs between groups.

Moving to the X_A^2, we find that $7.57 > 6.63$, the χ^2 critical value with one degree of freedom at the 0.010 level. We conclude that there *is* some overall association.

The odds ratio is estimated by $\widehat{\omega} = e^{\overline{a}} = e^{0.985} = 2.68$. The standard error of $\overline{a}$ is estimated by

$$\frac{1}{\sqrt{\sum_{i=1}^{k} (1/s_i^2)}}$$

To find a confidence interval for ω, first find one for $\ln \omega$ and "exponentiate" back. To find a 95% confidence interval, the calculation is

$$\overline{a} \pm \frac{z_{0.975}}{\sqrt{\sum (1/s_i^2)}} = 0.985 \pm \frac{1.96}{\sqrt{7.810}} \quad \text{or} \quad 0.985 \pm 0.701 \quad \text{or} \quad (0.284, 1.696)$$

Taking exponentials, the confidence interval for the overall odds ratio is (1.33, 5.45).

The second method of estimation is due to Mantel and Haenszel [1959]. Their estimate of the odds ratio is

$$\widehat{\omega} = \sum_{i=1}^{k} \frac{n_{11}(i)n_{22}(i)}{n_{..}(i)} \Big/ \sum_{i=1}^{k} \frac{n_{12}(i)n_{21}(i)}{n_{..}(i)}$$

where $n_{11}(i), n_{22}(i), n_{12}(i), n_{21}(i)$, and $n_{..}(i)$ are $n_{11}, n_{22}, n_{12}, n_{21}$, and $n_{..}$ for the ith table.

In this problem,

$$\widehat{\omega} = \frac{\dfrac{8 \times 26}{82} + \dfrac{5 \times 21}{43} + \dfrac{4 \times 77}{98} + \dfrac{2 \times 65}{89} + \dfrac{1 \times 10}{19} + \dfrac{1 \times 11}{17} + \dfrac{2 \times 37}{53}}{\dfrac{47 \times 1}{82} + \dfrac{17 \times 10}{43} + \dfrac{13 \times 4}{98} + \dfrac{12 \times 10}{89} + \dfrac{5 \times 3}{19} + \dfrac{3 \times 2}{17} + \dfrac{12 \times 12}{53}}$$

$$\doteq \frac{12.1516}{4.0473} \doteq 3.00$$

A test of association is given by the following statistic, X_A^2, which is approximately a chi-square random variable with one degree of freedom:

$$X_A^2 = \frac{\left[\left|\sum_{i=1}^{k} n_{11}(i) - \sum_{i=1}^{k} n_{1\cdot}(i)n_{\cdot 1}(i)/n_{..}(i)\right| - \frac{1}{2}\right]^2}{\sum_{i=1}^{k} n_{1\cdot}(i)n_{2\cdot}(i)n_{\cdot 1}(i)n_{\cdot 2}(i)/n_{..}(i)^2[n_{..}(i) - 1]}$$

The herniated disk data yield $X_A^2 = 7.92$, so that, as above, there is a significant ($p < 0.01$) association between an acute herniated lumbar intervertebral disk and whether or not a job

requires driving a motor vehicle. See Schlesselman [1982] and Breslow and Day [1980] for methods of setting confidence intervals for ω using the Mantel–Haenszel estimate.

In most circumstances, combining 2×2 tables will be used to adjust for other variables that define the strata (i.e., that define the different tables). The homogeneity of the odds ratio is usually of less interest unless the odds ratio differs widely among tables. Before testing for homogeneity of the odds ratio, one should be certain that this is what is desired (see Note 6.3).

6.3.6 Screening and Diagnosis: Sensitivity, Specificity, and Bayes' Theorem

In clinical medicine, and also in epidemiology, tests are often used to screen for the presence or absence of a disease. In the simplest case the test will simply be classified as having a positive (disease likely) or negative (disease unlikely) finding. Further, suppose that there is a "gold standard" that tells us whether or not a subject actually has the disease. The definitive classification might be based on data from follow-up, invasive radiographic or surgical procedures, or autopsy results. In many cases the gold standard itself will only be relatively correct, but nevertheless the best classification available. In this section we discuss summarization of the prediction of disease (as measured by our gold standard) by the test being considered. Ideally, those with the disease should all be classified as having disease, and those without disease should be classified as nondiseased. For this reason, two indices of the performance of a test consider how often such correct classification occurs.

Definition 6.3. The *sensitivity* of a test is the percentage of people with disease who are classified as having disease. A test is sensitive to the disease if it is positive for most people having the disease. The *specificity* of a test is the percentage of people without the disease who are classified as not having the disease. A test is specific if it is positive for a small percentage of those without the disease.

Further terminology associated with screening and diagnostic tests are true positive, true negative, false positive, and false negative tests.

Definition 6.4. A test is a *true positive test* if it is positive and the subject has the disease. A test is a *true negative test* if the test is negative and the subject does not have the disease. A *false positive test* is a positive test of a person without the disease. A *false negative test* is a negative test of a person with the disease.

Definition 6.5. The *predictive value of a positive test* is the percentage of subjects with a positive test who have the disease; the *predictive value of a negative test* is the percentage of subjects with a negative test who do not have the disease.

Suppose that data are collected on a test and presented in a 2×2 table as follows:

	Disease Category	
Screening Test Result	**Disease (+)**	**Nondiseased (−)**
Positive (+) test	a (true $+'$ s)	b (false $+'$ s)
Negative (−) test	c (false $-'$ s)	d (true $-'$ s)

The sensitivity is estimated by $100a/(a+c)$, the specificity by $100d/(b+d)$. If the subjects are representative of a population, the predictive value of positive and negative tests are estimated

by $100a/(a+b)$ and $100d/(c+d)$, respectively. These predictive values are useful only when the proportions with and without the disease in the study group are approximately the same as in the population where the test will be used to predict or classify (see below).

Example 6.16. Remein and Wilkerson [1961] considered a number of screening tests for diabetes. They had a group of consultants establish criteria, their gold standard, for diabetes. On each of a number of days, they recruited patients being seen in the outpatient department of the Boston City Hospital for reasons other than suspected diabetes. The table below presents results on the Folin–Wu blood test used 1 hour after a test meal and using a blood sugar level of 150 mg per 100 mL of blood sugar as a positive test.

Test	Diabetic	Nondiabetic	Total
+	56	49	105
−	14	461	475
Total	70	510	580

From this table note that there are 56 true positive tests compared to 14 false negative tests. The sensitivity is $100(56)/(56+14) = 80.0\%$. The 49 false positive tests and 461 true negative tests give a specificity of $100(461)/(49+461) = 90.4\%$. The predictive value of a positive test is $100(56)/(56+49) = 53.3\%$. The predictive value of a negative test is $100(461)/(14+461) = 97.1\%$.

If a test has a fixed value for its sensitivity and specificity, the predictive values will change depending on the prevalence of the disease in the population being tested. The values are related by *Bayes' theorem*. This theorem tells us how to update the probability of an event A: for example, the event of a subject having disease. If the subject is selected at random from some population, the probability of A is the fraction of people having the disease. Suppose that additional information becomes available; for example, the results of a diagnostic test might become available. In the light of this new information we would like to update or change our assessment of the probability that A occurs (that the subject has disease). The probability of A before receiving additional information is called the *a priori* or *prior probability*. The updated probability of A after receiving new information is called the *a posteriori* or *posterior probability*. Bayes' theorem is an explanation of how to find the posterior probability.

Bayes' theorem uses the concept of a conditional probability. We review this concept in Example 6.17.

Example 6.17. Comstock and Partridge [1972] conducted an informal census of Washington County, Maryland, in 1963. There were 127 arteriosclerotic heart disease deaths in the follow-up period. Of the deaths, 38 occurred among people whose usual frequency of church attendance was once or more per week. There were 24,245 such people as compared to 30,603 people whose usual attendance was less than once weekly. What is the probability of an arteriosclerotic heart disease death (event A) in three years given church attendance usually once or more per week (event B)?

From the data

$$P[A] = \frac{127}{24{,}245 + 30{,}603} = 0.0023$$

$$P[B] = \frac{24{,}245}{24{,}245 + 30{,}603} = 0.4420$$

$$P[A \ \& \ B] = \frac{38}{24{,}245 + 30{,}603} = 0.0007$$

$$P[A \mid B] = \frac{P[A \text{ and } B]}{P[B]} = \frac{0.0007}{0.4420} = 0.0016$$

If you knew that someone attended church once or more per week, the prior estimate of 0.0023 of the probability of an arteriosclerotic heart disease death in three years would be changed to a posterior estimate of 0.0016.

Using the conditional probability concept, Bayes' theorem may be stated.

Fact 1. (Bayes' Theorem) Let $B_1, \ldots, B_k$ be events such that one and only one of them must occur. Then for each i,

$$P[B_i|A] = \frac{P[A|B_i]P[B_i]}{P[A|B_1]P[B_1] + \cdots + P[A|B_k]P[B_k]}$$

Example 6.18. We use the data of Example 6.16 and Bayes' theorem to show that the predictive power of the test is related to the prevalence of the disease in the population. Suppose that the prevalence of the disease were not 70/580 (as in the data given), but rather, 6%. Also suppose that the sensitivity and specificity of the test were 80.0% and 90.4%, as in the example. What is the predictive value of a positive test?

We want $P[\text{disease}+|\text{test}+]$. Let B_1 be the event that the patient has disease and B_2 be the event of no disease. Let A be the occurrence of a positive test. A sensitivity of 80.0% is the same as $P[A|B_1] = 0.800$. A specificity of 90.4% is equivalent to $P[\text{not}A|B_2] = 0.904$. It is easy to see that

$$P[\text{not } A|B] + P[A|B] = 1$$

for any A and B. Thus, $P[A|B_2] = 1 - 0.904 = 0.096$. By assumption, $P[\text{disease}+] = P[B_1] = 0.06$, and $P[\text{disease}-] = P[B_2] = 0.94$. By Bayes' theorem,

$$P[\text{disease}+|\text{test}+] = \frac{P[\text{test} + |\text{disease}+]P[\text{disease}+]}{P[\text{test} + |\text{disease}+]P[\text{disease}+] + P[\text{test} + |\text{disease}-]P[\text{disease}-]}$$

Using our definitions of A, B_1, and B_2, this is

$$\begin{aligned} P[B_1|A] &= \frac{P[A|B_1]P[B_1]}{P[A|B_1]P[B_1] + P[A|B_2]P[B_2]} \\ &= \frac{0.800 \times 0.06}{0.800 \times 0.06 + 0.096 \times 0.94} \\ &= 0.347 \end{aligned}$$

If the disease prevalence is 6%, the predictive value of a positive test is 34.7% rather than 53.3% when the disease prevalence is 70/580 (12.1%).

Problems 6.15 and 6.28 illustrate the importance of disease prevalence in assessing the results of a test. See Note 6.8 for relationships among sensitivity, specificity, prevalence, and predictive values of a positive test. Sensitivity and specificity are discussed further in Chapter 13. See also Pepe [2003] for an excellent overview.

6.4 MATCHED OR PAIRED OBSERVATIONS

The comparisons among proportions in the preceding sections dealt with samples from different populations or from different subsets of a specified population. In many situations, the estimates of the proportions are based on the same objects or come from closely related, matched, or paired observations. You have seen matched or paired data used with a one-sample t-test.

A standard epidemiological tool is the retrospective paired case–control study. An example was given in Chapter 1. Let us recall the rationale for such studies. Suppose that one wants to see whether or not there is an association between a risk factor (say, use of oral contraceptives), and a disease (say, thromboembolism). Because the incidence of the disease is low, an extremely large prospective study would be needed to collect an adequate number of cases. One strategy is to *start* with the cases. The question then becomes one of finding appropriate controls for the cases. In a matched pair study, one control is identified for each case. The control, not having the disease, should be identical to the case in all relevant ways except, possibly, for the risk factor (see Note 6.6).

Example 6.19. This example is a retrospective matched pair case–control study by Sartwell et al. [1969] to study thromboembolism and oral contraceptive use. The cases were 175 women of reproductive age (15 to 44), discharged alive from 43 hospitals in five cities after initial attacks of idiopathic (i.e., of unknown cause) thrombophlebitis (blood clots in the veins with inflammation in the vessel walls), pulmonary embolism (a clot carried through the blood and obstructing lung blood flow), or cerebral thrombosis or embolism. The controls were matched with their cases for hospital, residence, time of hospitalization, race, age, marital status, parity, and pay status. More specifically, the controls were female patients from the same hospital during the same six-month interval. The controls were within five years of age and matched on parity (0, 1, 2, 3, or more prior pregnancies). The hospital pay status (ward, semiprivate, or private) was the same. The data for oral contraceptive use are:

	Control Use?	
Case Use?	**Yes**	**No**
Yes	10	57
No	13	95

The question of interest: Are cases more likely than controls to use oral contraceptives?

6.4.1 Matched Pair Data: McNemar's Test and Estimation of the Odds Ratio

The 2×2 table of Example 6.19 does not satisfy the assumptions of previous sections. The proportions using oral contraceptives among cases and controls cannot be considered samples from two populations since the cases and controls are paired; that is, they come together. Once a case is selected, the control for the case is constrained to be one of a small subset of people who match the case in various ways.

Suppose that there is no association between oral contraceptive use and thromboembolism after taking into account relevant factors. Suppose a case and control are such that only one of the pair uses oral contraceptives. Which one is more likely to use oral contraceptives? They may both be likely or unlikely to use oral contraceptives, depending on a variety of factors. Since the pair have the same values of such factors, neither member of the pair is more likely to have the risk factor! That is, in the case of disagreement, or discordant pairs, the probability that the case has the risk factor is 1/2. More generally, suppose that the data are

	Control Has Risk Factor?	
Case Has Risk Factor?	**Yes**	**No**
Yes	a	b
No	c	d

If there is no association between disease (i.e., case or control) and the presence or absence of the risk factor, the number b is binomial with $\pi = 1/2$ and $n = b + c$. To test for association we test $\pi = 1/2$, as shown previously. For large n, say $n \geq 30$,

$$X^2 = \frac{(b-c)^2}{b+c}$$

has a chi-square distribution with one degree of freedom if $\pi = 1/2$. For Example 6.19,

$$X^2 = \frac{(57-13)^2}{57+13} = 27.66$$

From the chi-square table, $p < 0.001$, so that there is a statistically significant association between thromboembolism and oral contraceptive use. This statistical test is called *McNemar's test*.

Procedure 6. For retrospective matched pair data, the odds ratio is estimated by

$$\widehat{\omega}_{\text{paired}} = \frac{b}{c}$$

The standard error of the estimate is estimated by

$$(1 + \widehat{\omega}_{\text{paired}})\sqrt{\frac{\widehat{\omega}_{\text{paired}}}{b+c}}$$

In Example 6.19, we estimate the odds ratio by

$$\widehat{\omega} = \frac{57}{13} \doteq 4.38$$

The standard error is estimated by

$$(1 + 4.38)\sqrt{\frac{4.38}{70}} \doteq 1.35$$

An approximate 95% confidence interval is given by

$$4.38 \pm (1.96)(1.35) \quad \text{or} \quad (1.74, 7.02)$$

More precise intervals may be based on the use of confidence intervals for a binomial proportion and the fact that $\widehat{\omega}_{\text{paired}}/(\widehat{\omega}_{\text{paired}} + 1) = b/(b+c)$ is a binomial proportion (see Fleiss [1981]). See Note 6.5 for further discussion of the chi-square analysis of paired data.

6.5 POISSON RANDOM VARIABLES

The Poisson distribution occurs primarily in two closely related situations. The first is a situation in which one counts discrete events in space or time, or some other continuous situation. For example, one might note the time of arrival (considered as a particular point in time) at an emergency medical service over a fixed time period. One may count the number of discrete occurrences of arrivals over this continuum of time. Conceptually, we may get any nonnegative integer, no matter how large, as our answer. A second example occurs when counting numbers of red blood cells that occur in a specified rectangular area marked off in the field of view. In a diluted blood sample where the distance between cells is such that they do not tend to "bump into each other," we may idealize the cells as being represented by points in the plane. Thus, within the particular area of interest, we are counting the number of points observed. A third example where one would expect to model the number of counts by a Poisson distribution would be a situation in which one is counting the number of particle emissions from a radioactive source. If the time period of observation is such that the radioactivity of the source does not decrease significantly (i.e., the time period is small compared to the half-life of a particle), the counts (which may be considered as coming at discrete time points) would again be modeled appropriately by a Poisson distribution.

The second major use of the Poisson distribution is as an approximation to the binomial distribution. If n is large and π is small in a binomial situation, the number of successes is very closely modeled by the Poisson distribution. The closeness of the approximation is specified by a mathematical theorem. As a rough rule of thumb, for most purposes the Poisson approximation will be adequate if π is less than or equal to 0.1 and n is greater than or equal to 20.

For the Poisson distribution to be an appropriate model for counting discrete points occurring in some sort of a continuum, the following two assumptions must hold:

1. The number of events occurring in one part of the continuum should be statistically independent of the number of events occurring in another part of the continuum. For example, in the emergency room, if we measure the number of arrivals during the first half hour, this event could reasonably be considered statistically independent of the number of arrivals during the second half hour. If there has been some cataclysmic event such as an earthquake, the assumption will not be valid. Similarly, in counting red blood cells in a diluted blood solution, the number of red cells in one square might reasonably be modeled as statistically independent of the number of red cells in another square.
2. The expected number of counts in a given part of the continuum should approach zero as its size approaches zero. Thus, in observing blood cells, one does not expect to find any in a very small area of a diluted specimen.

6.5.1 Examples of Poisson Data

Example 6.3 [Bucher et al., 1976] examines racial differences in the incidence of ABO hemolytic disease by examining records for infants born at the North Carolina Memorial Hospital. The samples of black and white infants gave the following estimated proportions with hemolytic disease:

$$\text{black infants}, \quad n_1 = 3584, \quad p_1 = 43/3584$$

$$\text{white infants}, \quad n_2 = 3831, \quad p_2 = 17/3831$$

The observed number of cases might reasonably be modeled by the Poisson distribution. (*Note:* The n is large and π is small in a binomial situation.) In this paper, studying the incidence of ABO hemolytic disease in black and white infants, the observed fractions for black and white infants of having the disease were 43/3584 and 17/3831. The 43 and 17 cases may be considered values of Poisson random variables.

A second example that would be modeled appropriately by the Poisson distribution is the number of deaths resulting from a large-scale vaccination program. In this case, n will be very large and π will be quite small. One might use the Poisson distribution in investigating the simultaneous occurrence of a disease and its association within a vaccination program. How likely is it that the particular "chance occurrence" might actually occur by chance?

Example 6.20. As a further example, a paper by Fisher et al. [1922] considers the accuracy of the plating method of estimating the density of bacterial populations. The process we are speaking about consists in making a suspension of a known mass of soil in a known volume of salt solution, and then diluting the suspension to a known degree. The bacterial numbers in the diluted suspension are estimated by plating a known volume in a nutrient gel medium and counting the number of colonies that develop from the plate. The estimate was made by a calculation that takes into account the mass of the soil taken and the degree of dilution. If we consider the colonies to be points occurring in the volume of gel, a Poisson model for the number of counts would be appropriate. Table 6.4 provides counts from seven different plates with portions of soil taken from a sample of Barnfield soil assayed in four parallel dilutions:

Example 6.21. A famous example of the Poisson distribution is data by von Bortkiewicz [1898] showing the chance of a cavalryman being killed by a horse kick in the course of a year (Table 6.5). The data are from recordings of 10 corps over a period of 20 years supplying 200 readings. A question of interest here might be whether a Poisson model is appropriate. Was the corps with four deaths an "unlucky" accident, or might there have been negligence of some kind?

Table 6.4 Counts for Seven Soil Samples

	Dilution			
Plate	I	II	III	IV
1	72	74	78	69
2	69	72	74	67
3	63	70	70	66
4	59	69	58	64
5	59	66	58	62
6	53	58	56	58
7	51	52	56	54
Mean	60.86	65.86	64.29	62.86

Table 6.5 Horse-kick Fatality Data

Number of Deaths per Corps per Year	Frequency
0	109
1	65
2	22
3	3
4	1
5	0
6	0

6.5.2 Poisson Model

The Poisson probability distribution is characterized by one parameter, λ. For each nonnegative integer k, if Y is a variable with the Poisson distribution with parameter λ,

$$P[Y = k] = \frac{e^{-\lambda}\lambda^k}{k!}$$

The parameter λ is both the mean and variance of the Poisson distribution,

$$E(Y) = \text{var}(Y) = \lambda$$

Bar graphs of the Poisson probabilities are given in Figure 6.3 for selected values of λ. As the mean (equal to the variance) increases, the distribution moves to the right and becomes more spread out and more symmetrical.

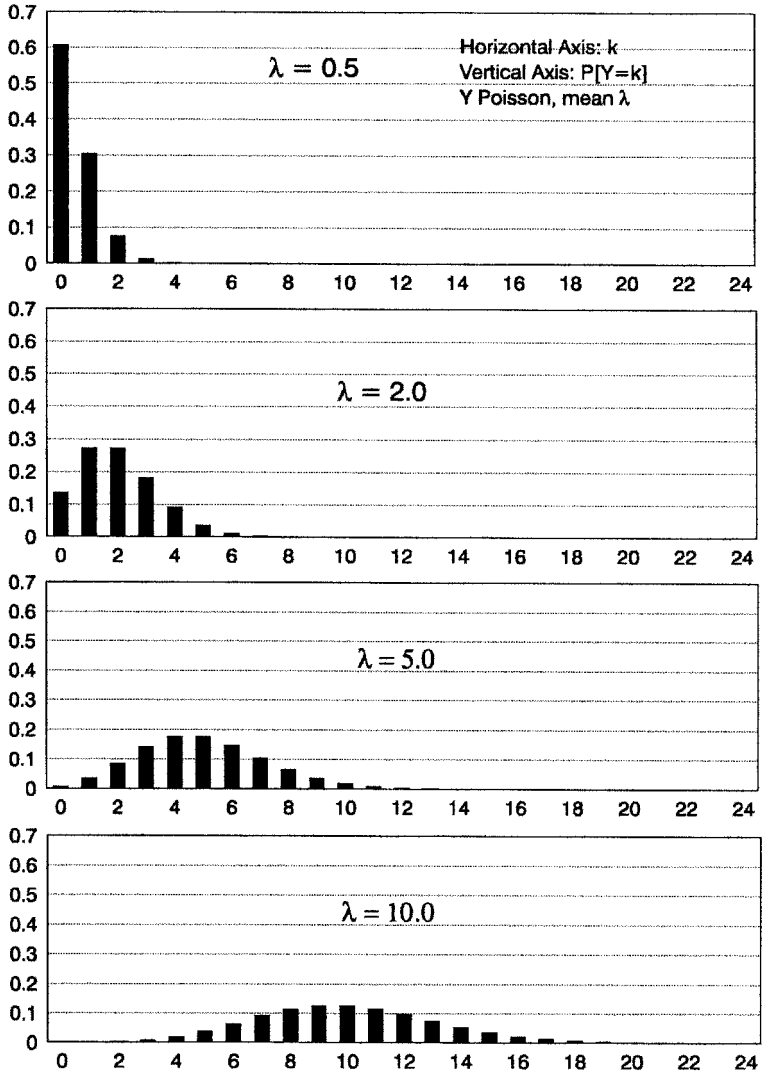


Figure 6.3 Poisson distribution.

Table 6.6 Binomial and Poisson Probabilities

	Binomial Probabilities			
k	$n = 10$ $\pi = 0.20$	$n = 20$ $\pi = 0.10$	$n = 40$ $\pi = 0.05$	Probabilities Poisson
0	0.1074	0.1216	0.1285	0.1353
1	0.2684	0.2702	0.2706	0.2707
2	0.3020	0.2852	0.2777	0.2707
3	0.2013	0.1901	0.1851	0.1804
4	0.0881	0.0898	0.0901	0.0902
5	0.0264	0.0319	0.0342	0.0361
6	0.0055	0.0089	0.0105	0.0120

In using the Poisson distribution to approximate the binomial distribution, the parameter λ is chosen to equal $n\pi$, the expected value of the binomial distribution. Poisson and binomial probabilities are given in Table 6.6 for comparison. This table gives an idea of the accuracy of the approximation (table entry is $P[Y = k], \lambda = 2 = n\pi$) for the first seven values of three distributions.

A fact that is often useful is that a sum of independent Poisson variables is itself a Poisson variable. The parameter for the sum is the sum of the individual parameter values. The parameter λ of the Poisson distribution is estimated by the sample mean when a sample is available. For example, the horse-kick data leads to an estimate of λ—say l—given by

$$l = \frac{0 \times 109 + 1 \times 65 + 2 \times 22 + 3 \times 3 + 4 \times 1}{109 + 65 + 22 + 3 + 1} = 0.61$$

Now, we consider the construction of confidence intervals for a Poisson parameter. Consider the case of one observation, Y, and a small result, say, $Y \leq 100$. Note 6.8 describes how confidence intervals are calculated and there is a table in the Web appendix to this chapter. From this we find a 95% confidence interval for the proportion of black infants having ABO hemolytic disease, in the Bucher et al. [1976] study. The approximate Poisson variable is the binomial variable, which in this case is equal to 43; thus, a 95% confidence interval for $\lambda = n\pi$ is (31.12, 57.92). The equation $\lambda = n\pi$ equates the mean values for the Poisson and binomial models. Now $n\pi$ is in (31.12, 57.92) if and only if π is in the interval

$$\left(\frac{31.12}{n}, \frac{57.92}{n}\right)$$

In this case, $n = 3584$, so the confidence interval is

$$\left(\frac{31.12}{3584}, \frac{57.92}{3584}\right) \quad \text{or} \quad (0.0087, 0.0162)$$

These results are comparable with the 95% binomial limits obtained in Example 6.9: (0.0084, 0.0156).

6.5.3 Large-Sample Statistical Inference for the Poisson Distribution

Normal Approximation to the Poisson Distribution

The Poisson distribution has the property that the mean and variance are equal. For the mean large, say ≥ 100, the normal approximation can be used. That is, let $Y \sim$ Poisson(λ) and $\lambda \geq 100$. Then, approximately, $Y \sim N(\lambda, \lambda)$. An approximate $100(1 - \alpha)\%$ confidence interval

for λ can be formed from

$$Y \pm z_{1-\alpha/2}\sqrt{Y}$$

where $z_{1-\alpha/2}$ is a standard normal deviate at two-sided significance level α. This formula is based on the fact that Y estimates the mean as well as the variance. Consider, again, the data of Bucher et al. [1976] (Example 6.3) dealing with the incidence of ABO hemolytic disease. The observed value of Y, the number of black infants with ABO hemolytic disease, was 43. A 95% confidence interval for the mean, λ, is (31.12, 57.92). Even though $Y \leq 100$, let us use the normal approximation. The estimate of the variance, σ^2, of the normal distribution is $Y = 43$, so that the standard deviation is 6.56. An approximate 95% confidence interval is $43 \pm (1.96)(6.56)$, producing (30.1, 55.9), which is close to the values (31.12, 57.92) tabled.

Suppose that instead of one Poisson value, there is a random sample of size n, $Y_1, Y_2, \ldots, Y_n$ from a Poisson distribution with mean λ. How should one construct a confidence interval for λ based on these data? The sum $Y = Y_1 + Y_2 + \cdots + Y_n$ is Poisson with mean $n\lambda$. Construct a confidence interval for $n\lambda$ as above, say (L, U). Then, an appropriate confidence interval for λ is $(L/n, U/n)$. Consider Example 6.20, which deals with estimating the bacterial density of soil suspensions. The results for sample I were 72, 69, 63, 59, 59, 53, and 51. We want to set up a 95% confidence interval for the mean density using the seven observations. For this example, $n = 7$.

$$Y = Y_1 + Y_2 + \cdots + Y_7 = 72 + 69 + \cdots + 51 = 426$$

A 95% confidence interval for 7λ is $426 \pm 1.96\sqrt{426}$.

$$L = 385.55, \qquad \frac{L}{7} = 55.1$$

$$U = 466.45, \qquad \frac{U}{7} = 66.6$$

$$\overline{Y} = 60.9$$

The 95% confidence interval is (55.1, 66.6).

Square Root Transformation

It is often considered a disadvantage to have a distribution with a variance not "stable" but dependent on the mean in some way, as, for example, the Poisson distribution. The question is whether there is a transformation, $g(Y)$, of the variable such that the variance is no longer dependent on the mean. The answer is "yes." For the Poisson distribution, it is the square root transformation. It can be shown for "reasonably large" λ, say $\lambda \geq 30$, that if $Y \sim \text{Poisson}(\lambda)$, then $\text{var}(\sqrt{Y}) \doteq 0.25$.

A side benefit is that the distribution of $\sqrt{Y}$ is more "nearly normal," that is, for specified λ, the difference between the sampling distribution of $\sqrt{Y}$ and the normal distribution is smaller for most values than the difference between the distribution of Y and the normal distribution.

For the situation above, it is approximately true that

$$\sqrt{Y} \sim N(\sqrt{\lambda}, 0.25)$$

Consider Example 6.20 again. A confidence interval for $\sqrt{\lambda}$ will be constructed and then converted to an interval for λ. Let $X = \sqrt{Y}$.

Y	72	69	63	59	59	53	51
$X = \sqrt{Y}$	8.49	8.31	7.94	7.68	7.68	7.28	7.14

The sample mean and variance of X are $\overline{X} = 7.7886$ and $s_x^2 = 0.2483$. The sample variance is very close to the variance predicted by the theory $\sigma_x^2 = 0.2500$. A 95% confidence interval on $\sqrt{\lambda}$ can be set up from

$$\overline{X} \pm 1.96\frac{s_x}{\sqrt{7}} \quad \text{or} \quad 7.7886 \pm (1.96)\sqrt{\frac{0.2483}{7}}$$

producing lower and upper limits in the X scale.

$$L_x = 7.4195, \quad U_x = 8.1577$$
$$L_x^2 = 55.0, \quad U_x^2 = 66.5$$

which are remarkably close to the values given previously.

Poisson Homogeneity Test

In Chapter 4 the question of a test of normality was discussed and a graphical procedure was suggested. Fisher et al. [1922], in the paper described in Example 6.20, derived an approximate test for determining whether or not a sample of observations could have come from a Poisson distribution with the same mean. The test does not determine "Poissonness," but rather, equality of means. If the experimental situations are identical (i.e., we have a random sample), the test is a test for Poissonness.

The test, the *Poisson homogeneity test*, is based on the property that for the Poisson distribution, the mean equals the variance. The test is the following: Suppose that $Y_1, Y_2, \ldots, Y_n$ are a random sample from a Poisson distribution with mean λ. Then, for a large λ—say, $\lambda \geq 50$—the quantity

$$X^2 = \frac{(n-1)s^2}{\overline{Y}}$$

has approximately a chi-square distribution with $n - 1$ degrees of freedom, where s^2 is the sample variance.

Consider again the data in Example 6.20. The mean and standard deviation of the seven observations are

$$n = 7, \qquad \overline{Y} = 60.86, \qquad s_y = 7.7552$$
$$X^2 = \frac{(7-1)(7.7552)^2}{60.86} = 5.93$$

Under the null hypothesis that all the observations are from a Poisson distribution with the same mean, the statistic $X^2 = 5.93$ can be referred to a chi-square distribution with six degrees of freedom. What will the rejection region be? This is determined by the alternative hypothesis. In this case it is reasonable to suppose that the sample variance will be greater than expected if the null hypothesis is not true. Hence, we want to reject the null hypothesis when χ^2 is "large"; "large" in this case means $P[X^2 \geq \chi_{1-\alpha}^2] = \alpha$.

Suppose that $\alpha = 0.05$; the critical value for $\chi_{1-\alpha}^2$ with 6 degrees of freedom is 12.59. The observed value $X^2 = 5.93$ is much less than that and the null hypothesis is not rejected.

6.6 GOODNESS-OF-FIT TESTS

The use of appropriate mathematical models has made possible advances in biomedical science; the key word is *appropriate*. An inappropriate model can lead to false or inappropriate ideas.

In some situations the appropriateness of a model is clear. A random sample of a population will lead to a binomial variable for the response to a yes or no question. In other situations the issue may be in doubt. In such cases one would like to examine the data to see if the model used seems to fit the data. Tests of this type are called *goodness-of-fit tests*. In this section we examine some tests where the tests are based on count data. The count data may arise from continuous data. One may count the number of observations in different intervals of the real line; examples are given in Sections 6.6.2 and 6.6.4.

6.6.1 Multinomial Random Variables

Binomial random variables count the number of successes in n independent trials where one and only one of two possibilities must occur. *Multinomial random variables* generalize this to allow more than two possible outcomes. In a multinomial situation, outcomes are observed that take one and only one of two or more, say k, possibilities. There are n independent trials, each with the same probability of a particular outcome. Multinomial random variables count the number of occurrences of a particular outcome. Let n_i be the number of occurrences of outcome i. Thus, n_i is an integer taking a value among $0, 1, 2, \ldots, n$. There are k different n_i, which add up to n since one and only one outcome occurs on each trial:

$$n_1 + n_2 + \cdots + n_k = n$$

Let us focus on a particular outcome, say the ith. What are the mean and variance of n_i? We may classify each outcome into one of two possibilities, the ith outcome or anything else. There are then n independent trials with two outcomes. We see that n_i is a binomial random variable when considered alone. Let π_i, where $i = 1, \ldots, k$, be the probability that the ith outcome occurs. Then

$$E(n_i) = n\pi_i, \qquad \text{var}(n_i) = n\pi_i(1 - \pi_i) \tag{6}$$

for $i = 1, 2, \ldots, k$.

Often, multinomial outcomes are visualized as placing the outcome of each of the n trials into a separate *cell* or box. The probability π_i is then the probability that an outcome lands in the ith cell.

The remainder of this section deals with multinomial observations. Tests are presented to see if a specified multinomial model holds.

6.6.2 Known Cell Probabilities

In this section, the cell probabilities $\pi_1, \ldots, \pi_k$ are specified. We use the specified values as a null hypothesis to be compared with the data $n_1, \ldots, n_k$. Since $E(n_i) = n\pi_i$, it is reasonable to examine the differences $n_i - n\pi_i$. The statistical test is given by the following fact.

Fact 2. Let n_i, where $i = 1, \ldots, k$, be multinomial. Under $H_0 : \pi_i = \pi_i^0$,

$$X^2 = \sum_{i=1}^{k} \frac{(n_i - n\pi_i^0)^2}{n\pi_i^0}$$

has approximately a chi-square distribution with $k - 1$ degrees of freedom. If some π_i are not equal to π_i^0, X^2 will tend to be too large.

The distribution of X^2 is well approximated by the chi-square distribution if all of the expected values, $n\pi_i^0$, are at least five, except possibly for one or two of the values. When the null hypothesis is not true, the null hypothesis is rejected for X^2 too large. At significance level

α, reject H_0 if $X^2 \geq \chi^2_{1-\alpha,k-1}$, where $\chi^2_{1-\alpha,k-1}$ is the $1-\alpha$ percentage point for a χ^2 random variable with $k-1$ degrees of freedom.

Since there are k cells, one might expect the labeling of the degrees of freedom to be k instead of $k-1$. However, since the n_i add up to n we only need to know $k-1$ of them to know all k values. There are really only $k-1$ quantities that may vary at a time; the last quantity is specified by the other $k-1$ values.

The form of X^2 may be kept in mind by noting that we are comparing the observed values, n_i, and expected values, $n\pi_i^0$. Thus,

$$X^2 = \sum \frac{(\text{observed} - \text{expected})^2}{\text{expected}}$$

Example 6.22. Are births spread uniformly throughout the year? The data in Table 6.7 give the number of births in King County, Washington, from 1968 through 1979 by month. The estimated probability of a birth in a given month is found by taking the number of days in that month and dividing by the total number of days (leap years are included in Table 6.7).

Testing the null hypothesis using Table A.3, we see that $163.15 > 31.26 = \chi^2_{0.001,11}$, so that $p < 0.001$. We reject the null hypothesis that births occur uniformly throughout the year. With this large sample size ($n = 160{,}654$) it is not surprising that the null hypothesis can be rejected. We can examine the magnitude of the effect by comparing the ratio of observed to expected numbers of births, with the results shown in Table 6.8. There is an excess of births in the spring (March and April) and a deficit in the late fall and winter (October through January). Note that the difference from expected values is small. The maximum "excess" of births occurred

Table 6.7 Births in King County, Washington, 1968–1979

Month	Births	Days	π_i^0	$n\pi_i^0$	$(n_i - n\pi_i^0)^2/n\pi_i^0$
January	13,016	310	0.08486	13,633	27.92
February	12,398	283	0.07747	12,446	0.19
March	14,341	310	0.08486	13,633	36.77
April	13,744	300	0.08212	13,193	23.01
May	13,894	310	0.08486	13,633	5.00
June	13,433	300	0.08212	13,193	4.37
July	13,787	310	0.08486	13,633	1.74
August	13,537	310	0.08486	13,633	0.68
September	13,459	300	0.08212	13,193	5.36
October	13,144	310	0.08486	13,633	17.54
November	12,497	300	0.08212	13,193	36.72
December	13,404	310	0.08486	13,633	3.85
Total	160,654 (n)	3653	0.99997		$163.15 = X^2$

Table 6.8 Ratios of Observed to Expected Births

Month	Observed/Expected Births	Month	Observed/Expected Births
January	0.955	July	1.011
February	0.996	August	0.993
March	1.052	September	1.020
April	1.042	October	0.964
May	1.019	November	0.947
June	1.018	December	0.983

in March and was only 5.2% above the number expected. A plot of the ratio vs. month would show a distinct sinusoidal pattern.

Example 6.23. Mendel [1866] is justly famous for his theory and experiments on the principles of heredity. Sir R. A. Fisher [1936] reviewed Mendel's work and found a surprisingly good fit to the data. Consider two parents heterozygous for a dominant–recessive trait. That is, each parent has one dominant gene and one recessive gene. Mendel hypothesized that all four combinations of genes would be equally likely in the offspring. Let A denote the dominant gene and a denote the recessive gene. The two parents are Aa. The offspring should be

Genotype	Probability
AA	1/4
Aa	1/2
aa	1/4

The Aa combination has probability 1/2 since one cannot distinguish between the two cases where the dominant gene comes from one parent and the recessive gene from the other parent. In one of Mendel's experiments he examined whether a seed was wrinkled, denoted by a, or smooth, denoted by A. By looking at offspring of these seeds, Mendel classified the seeds as aa, Aa, or AA. The results were

	AA	Aa	aa	Total
Number	159	321	159	639

as presented in Table II of Fisher [1936]. Do these data support the hypothesized $1:2:1$ ratio? The chi-square statistic is

$$X^2 = \frac{(159-159.75)^2}{159.75} + \frac{(321-319.5)^2}{319.5} + \frac{(159-159.75)^2}{159.75} = 0.014$$

For the χ^2 distribution with two degrees of freedom, $p > 0.95$ from Table A.3 (in fact $p = 0.993$), so that the result has more agreement than would be expected by chance. We return to these data in Example 6.24.

6.6.3 Addition of Independent Chi-Square Variables: Mean and Variance of the Chi-Square Distribution

Chi-square random variables occur so often in statistical analysis that it will be useful to know more facts about chi-square variables. In this section facts are presented and then applied to an example (see also Note 5.3).

Fact 3. Chi-square variables have the following properties:

1. Let X^2 be a chi-square random variable with m degrees of freedom. Then

$$E(X^2) = m \quad \text{and} \quad \text{var}(X^2) = 2m$$

2. Let $X_1^2, \ldots, X_n^2$ be independent chi-square variables with $m_1, \ldots, m_n$ degrees of freedom. Then $X^2 = X_1^2 + \cdots + X_n^2$ is a chi-square random variable with $m = m_1 + m_2 + \cdots + m_n$ degrees of freedom.

Table 6.9 Chi-Square Values for Mendel's Experiments

Experiments	X^2	Degrees of Freedom
3 : 1 Ratios	2.14	7
2 : 1 Ratios	5.17	8
Bifactorial experiments	2.81	8
Gametic ratios	3.67	15
Trifactorial experiments	15.32	26
Total	29.11	64

3. Let X^2 be a chi-square random variable with m degrees of freedom. If m is large, say $m \geq 30$,

$$\frac{X^2 - m}{\sqrt{2m}}$$

is approximately a $N(0, 1)$ random variable.

Example 6.24. We considered Mendel's data, reported by Fisher [1936], in Example 6.23. As Fisher examined the data, he became convinced that the data fit the hypothesis too well [Box, 1978, pp. 195, 300]. Fisher comments: "Although no explanation can be expected to be satisfactory, it remains a possibility among others that Mendel was deceived by some assistant who knew too well what was expected."

One reason Fisher arrived at his conclusion was by combining χ^2 values from different experiments by Mendel. Table 6.9 presents the data.

If all the null hypotheses are true, by the facts above, $X^2 = 29.11$ should look like a χ^2 with 64 degrees of freedom. An approximate normal variable,

$$Z = \frac{29.11 - 64}{\sqrt{128}} = -3.08$$

has less than 1 chance in 1000 of being this small ($p = 0.99995$). One can only conclude that something peculiar occurred in the collection and reporting of Mendel's data.

6.6.4 Chi-Square Tests for Unknown Cell Probabilities

Above, we considered tests of the goodness of fit of multinomial data when the probability of being in an individual cell was specified precisely: for example, by a genetic model of how traits are inherited. In other situations, the cell probabilities are not known but may be estimated. First, we motivate the techniques by presenting a possible use; next, we present the techniques, and finally, we illustrate the use of the techniques by example.

Consider a sample of n numbers that may come from a normal distribution. How might we check the assumption of normality? One approach is to divide the real number line into a finite number of intervals. The number of points observed in each interval may then be counted. The numbers in the various intervals or cells are multinomial random variables. If the sample were normal with known mean μ and known standard deviation σ, the probability, π_i, that a point falls between the endpoints of the ith interval—say Y_1 and Y_2—is known to be

$$\pi_i = \Phi\left(\frac{Y_2 - \mu}{\sigma}\right) - \Phi\left(\frac{Y_1 - \mu}{\sigma}\right)$$

where Φ is the distribution function of a standard normal random variable. In most cases, μ and σ are not known, so μ and σ, and thus π_i, must be estimated. Now π_i depends on two variables, μ and σ : $\pi_i = \pi_i(\mu, \sigma)$ where the notation $\pi_i(\mu, \sigma)$ means that π_i is a function of μ and σ. It is natural if we estimate μ and σ by, say, $\widehat{\mu}$ and $\widehat{\sigma}$, to estimate π_i by $p_i(\widehat{\mu}, \widehat{\omega})$. That is,

$$p_i(\widehat{\mu}, \widehat{\sigma}) = \Phi\left(\frac{Y_2 - \widehat{\mu}}{\widehat{\sigma}}\right) - \Phi\left(\frac{Y_1 - \widehat{\mu}}{\widehat{\sigma}}\right)$$

From this, a statistic (X^2) can be formed as above. If there are k cells,

$$X^2 = \sum \frac{(\text{observed} - \text{expected})^2}{\text{expected}} = \sum_{i=1}^{k} \frac{[n_i - np_i(\widehat{\mu}, \widehat{\sigma})]^2}{np_i(\widehat{\mu}, \widehat{\sigma})}$$

Does X^2 now have a chi-square distribution? The following facts describe the situation.

Fact 4. Suppose that n observations are grouped or placed into k categories or cells such that the probability of being in cell i is $\pi_i = \pi_i(\Theta_1, \ldots, \Theta_s)$, where π_i depends on s parameters Θ_j and where $s < k-1$. Suppose that none of the s parameters are determined by the remaining $s - 1$ parameters. Then:

1. If $\widehat{\Theta}_1, \ldots, \widehat{\Theta}_s$, the parameter estimates, are chosen to minimize X^2, the distribution of X^2 is approximately a chi-square random variable with $k - s - 1$ degrees of freedom for large n. Estimates chosen to minimize the value of X^2 are called *minimum chi-square estimates*.
2. If estimates of $\Theta_1, \ldots, \Theta_s$ other than the minimum chi-square estimates are used, then for large n the distribution function of X^2 lies between the distribution functions of chi-square variables with $k - s - 1$ degrees of freedom and $k - 1$ degrees of freedom. More specifically, let $X^2_{1-\alpha,m}$ denote the α-significance-level critical value for a chi-square distribution with m degrees of freedom. The significance-level-α critical value of X^2 is less than or equal to $X^2_{1-\alpha,k-1}$. A conservative test of the multinomial model is to reject the null hypothesis that the model is correct if $X^2 \geq \chi^2_{1-\alpha,k-1}$.

These complex statements are best understood by applying them to an example.

Example 6.25. Table 3.4 in Section 3.3.1 gives the age in days at death of 78 SIDS cases. Test for normality at the 5% significance level using a χ^2-test.

Before performing the test, we need to divide the real number line into intervals or cells. The usual approach is to:

1. Estimate the parameters involved. In this case the unknown parameters are μ and σ. We estimate by $\overline{Y}$ and s.
2. Decide on k, the number of intervals. Let there be n observations. A good approach is to choose k as follows:
   - **a.** For $20 \leq n \leq 100, k \doteq n/5$.
   - **b.** For $n > 300, k \doteq 3.5n^{2/5}$ (here, $n^{2/5}$ is n raised to the 2/5 power).

3. Find the endpoints of the k intervals so that each interval has probability $1/k$. The k intervals are

$$\begin{array}{cc} (-\infty, a_1] & \text{interval 1} \\ (a_1, a_2] & \text{interval 2} \\ \vdots & \vdots \\ (a_{k-2}, a_{k-1}] & \text{interval } (k-1) \\ (a_{k-1}, \infty) & \text{interval k} \end{array}$$

Let Z_i be a value such that a standard normal random variable takes a value less than Z_i with probability i/k. Then

$$a_i = \overline{X} + sZ_i$$

(In testing for a distribution other than the normal distribution, other methods of finding cells of approximately equal probability need to be used.)

4. Compute the statistic

$$X^2 = \sum_{i=1}^{k} \frac{(n_i - n/k)^2}{n/k}$$

where n_i is the number of data points in cell i.

To apply steps 1 to 4 to the data at hand, one computes $n = 78$, $\overline{X} = 97.85$, and $s = 55.66$. As $78/5 = 15.6$, we will use $k = 15$ intervals. From tables of the normal distribution, we find Z_i, $i = 1, 2, \ldots, 14$, so that a standard normal random variable has probability $i/15$ of being less than Z_i. The values of Z_i and a_i are given in Table 6.10.

The number of observations observed in the 15 cells, from left to right, are 0, 8, 7, 5, 7, 9, 7, 5, 6, 6, 2, 2, 3, 5, and 6. In each cell, the number of observations expected is $np_i = n/k$ or $78/15 = 5.2$. Then

$$X^2 = \frac{(0-5.2)^2}{5.2} + \frac{(8-5.2)^2}{5.2} + \cdots + \frac{(6-5.2)^2}{5.2} = 16.62$$

We know that the 0.05 critical values are between the chi-square critical values with 12 and 14 degrees of freedom. The two values are 21.03 and 23.68. Thus, we do not reject the hypothesis of normality. (If the X^2 value had been greater than 23.68, we would have rejected the null hypothesis of normality. If X^2 were between 21.03 and 23.68, the answer would be in doubt. In that case, it would be advisable to compute the minimum chi-square estimates so that a known distribution results.)

Note that the largest observation, 307, is $(307 - 97.85)/55.6 = 3.76$ sample standard deviations from the sample mean. In using a chi-square goodness-of-fit test, all large observations are placed into a single cell. The magnitude of the value is lost. If one is worried about large outlying values, there are better tests of the fit to normality.

Table 6.10 Z_i and a_i Values

i	Z_i	a_i	i	Z_i	a_i	i	Z_i	a_i
1	−1.50	12.8	6	−0.25	84.9	11	0.62	135.0
2	−1.11	35.3	7	−0.08	94.7	12	0.84	147.7
3	−0.84	50.9	8	0.08	103.9	13	1.11	163.3
4	−0.62	63.5	9	0.25	113.7	14	1.50	185.8
5	−0.43	74.5	10	0.43	124.1			

NOTES

6.1 *Continuity Correction for* 2 × 2 *Table Chi-Square Values*

There has been controversy about the appropriateness of the continuity correction for 2×2 tables [Conover, 1974]. The continuity correction makes the *actual* significance levels under the null hypothesis closer to the hypergeometric (Fisher's exact test) actual significance levels. When compared to the chi-square distribution, the *actual* significance levels are too low [Conover, 1974; Starmer et al., 1974; Grizzle, 1967]. The *uncorrected* "chi-square" value referred to chi-square critical values gives actual and nominal significance levels that are close. For this reason, the authors recommend that the continuity correction *not* be used. Use of the continuity correction would be correct but overconservative. For arguments on the opposite side, see Mantel and Greenhouse [1968]. A good summary can be found in Little [1989].

6.2 *Standard Error of* $\widehat{\omega}$ *as Related to the Standard Error of* $\log \widehat{\omega}$

Let X be a positive variate with mean μ_x and standard deviation σ_x. Let $Y = \log_e X$. Let the mean and standard deviation of Y be μ_y and σ_y, respectively. It can be shown that under certain conditions

$$\frac{\sigma_x}{\mu_x} \doteq \sigma_y$$

The quantity σ_x/μ_x is known as the *coefficient of variation*. Another way of writing this is

$$\sigma_x \doteq \mu_x \sigma_y$$

If the parameters are replaced by the appropriate statistics, the expression becomes

$$s_x \doteq \overline{x} s_y$$

and the standard deviation of $\widehat{\omega}$ then follows from this relationship.

6.3 *Some Limitations of the Odds Ratio*

The odds ratio uses one number to summarize four numbers, and some information about the relationship is necessarily lost. The following example shows one of the limitations. Fleiss [1981] discusses the limitations of the odds ratio as a measure for public health. He presents the mortality rates per 100,000 person-years from lung cancer and coronary artery disease for smokers and nonsmokers of cigarettes [U.S. Department of Health, Education and Welfare, 1964]:

	Smokers	Nonsmokers	Odds Ratio	Difference
Cancer of the lung	48.33	4.49	10.8	43.84
Coronary artery disease	294.67	169.54	1.7	125.13

The point is that although the risk ω is increased much more for cancer, the added number dying of coronary artery disease is higher, and in some sense smoking has a greater effect in this case.

6.4 *Mantel–Haenszel Test for Association*

The chi-square test of association given in conjunction with the Mantel–Haenszel test discussed in Section 6.3.5 arises from the approach of the section by choosing a_i and s_i appropriately

[Fleiss, 1981]. The corresponding chi-square test for homogeneity does *not* make sense and should not be used. Mantel et al. [1977] give the problems associated with using this approach to look at homogeneity.

6.5 Matched Pair Studies

One of the difficult aspects in the design and execution of matched pair studies is to decide on the matching variables, and then to find matches to the degree desired. In practice, many decisions are made for logistic and monetary reasons; these factors are not discussed here. The primary purpose of matching is to have a *valid* comparison. Variables are matched to increase the validity of the comparison. Inappropriate matching can hurt the statistical power of the comparison. Breslow and Day [1980] and Miettinen [1970] give some fundamental background. Fisher and Patil [1974] further elucidate the matter (see also Problem 6.30).

6.6 More on the Chi-Square Goodness-of-Fit Test

The goodness-of-fit test as presented in this chapter did not mention some of the subtleties associated with the subject. A few arcane points, with appropriate references, are given in this note.

1. In Fact 4, the estimate used should be maximum likelihood estimates or equivalent estimates [Chernoff and Lehmann, 1954].
2. The initial chi-square limit theorems were proved for fixed cell boundaries. Limiting theorems where the boundaries were random (depending on the data) were proved later [Kendall and Stuart, 1967, Secs. 30.20 and 30.21].
3. The number of cells to be used (as a function of the sample size) has its own literature. More detail is given in Kendall and Stuart [1967, Secs. 30.28 to 30.30]. The recommendations for k in the present book are based on this material.

6.7 Predictive Value of a Positive Test

The predictive value of a positive test, PV^+, is related to the prevalence (PREV), sensitivity (SENS), and specificity (SPEC) of a test by the following equation:

$$\text{PV}^+ = \frac{1}{1 + \left[(1 - \text{SPEC})/\text{SENS}\right]\left[(1 - \text{PREV})/\text{PREV}\right]}$$

Here PREV, SENS, and SPEC, are on a scale of 0 to 1 of proportions instead of percentages.

If we define $\text{logit}(p) = \log[p/(1-p)]$, the predictive value of a positive test is related very simply to the prevalence as follows:

$$\text{logit}[\text{PV}^+] = \log\left(\frac{\text{SENS}}{1 - \text{SPEC}}\right) + \text{logit}(\text{PREV})$$

This is a very informative formula. For rare diseases (i.e., low prevalence), the term "logit (PREV)" will dominate the predictive value of a positive test. So no matter what the sensitivity or specificity of a test, the predictive value will be low.

6.8 Confidence Intervals for a Poisson Mean

Many software packages now provide confidence intervals for the mean of a Poisson distribution. There are two formulas: an approximate one that can be done by hand, and a more complex exact formula. The approximate formula uses the following steps. Given a Poisson variable Y:

1. Take $\sqrt{Y}$.
2. Add and subtract 1.
3. Square the result $[(\sqrt{Y}-1)^2,\ (\sqrt{Y}+1)^2]$.

This formula is reasonably accurate for $Y \geq 5$. See also Note 6.9 for a simple confidence interval when $Y = 0$. The exact formula uses the relationship between the Poisson and χ^2 distributions to give the confidence interval

$$\left[\frac{1}{2}\chi^2_{\alpha/2}(2x),\ \frac{1}{2}\chi^2_{1-\alpha/2}(2x+2)\right]$$

where $\chi^2_{\alpha/2}(2x)$ is the $\alpha/2$ percentile of the χ^2 distribution with $2x$ degrees of freedom.

6.9 Rule of Threes

An upper 90% confidence bound for a Poisson random variable with observed values 0 is, to a very good approximation, 3. This has led to the *rule of threes*, which states that if in n trials zero events of interest are observed, a 95% confidence bound on the underlying rate is $3/n$. For a fuller discussion, see Hanley and Lippman-Hard [1983]. See also Problem 6.29.

PROBLEMS

6.1 In a randomized trial of surgical and medical treatment a clinic finds eight of nine patients randomized to medicine. They complain that the randomization must not be working; that is, π cannot be 1/2.

(a) Is their argument reasonable from their point of view?

***(b)** With 15 clinics in the trial, what is the probability that *all* 15 clinics have fewer than eight people randomized to each treatment, of the first nine people randomized? Assume independent binomial distributions with $\pi = 1/2$ at each site.

6.2 In a dietary study, 14 of 20 subjects lost weight. If weight is assumed to fluctuate by chance, with probability 1/2 of losing weight, what is the exact two-sided p-value for testing the null hypothesis $\pi = 1/2$?

6.3 Edwards and Fraccaro [1960] present Swedish data about the gender of a child and the parity. These data are:

	Order of Birth							
Gender	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**Total**
Males	2846	2554	2162	1667	1341	987	666	12,223
Females	2631	2361	1996	1676	1230	914	668	11,476
Total	5477	4915	4158	3343	2571	1901	1334	23,699

(a) Find the p-value for testing the hypothesis that a birth is equally likely to be of either gender using the combined data and binomial assumptions.

(b) Construct a 90% confidence interval for the probability that a birth is a female child.

(c) Repeat parts (a) and (b) using only the data for birth order 6.

6.4 Ounsted [1953] presents data about cases with convulsive disorders. Among the cases there were 82 females and 118 males. At the 5% significance level, test the hypothesis that a case is equally likely to be of either gender. The siblings of the cases were 121 females and 156 males. Test at the 10% significance level the hypothesis that the siblings represent 53% or more male births.

6.5 Smith et al. [1976] report data on ovarian carcinoma (cancer of the ovaries). People had different numbers of courses of chemotherapy. The five-year survival data for those with 1–4 and 10 or more courses of chemotherapy are:

	Five-Year Status	
Courses	**Dead**	**Alive**
1–4	21	2
$\geq$10	2	8

Using Fisher's exact test, is there a statistically significant association ($p \leq 0.05$) in this table? (In this problem and the next, you will need to compute the hypergeometric probabilities using the results of Problem 6.26.)

6.6 Borer et al. [1980] study 45 patients following an acute myocardial infarction (heart attack). They measure the *ejection fraction* (EF), the percent of the blood pumped from the left ventricle (the pumping chamber of the heart) during a heart beat. A low EF indicates damaged or dead heart muscle (myocardium). During follow-up, four patients died. Dividing EF into low (<35%) and high ($\geq$35%) EF groups gave the following table:

	Vital Status	
EF	**Dead**	**Alive**
<35%	4	9
$\geq$35%	0	32

Is there reason to suspect, at a 0.05 significance level, that death is more likely in the low EF group? Use a one-sided p-value for your answer, since biological plausibility (and prior literature) indicates that low EF is a risk factor for mortality.

6.7 Using the data of Problem 6.4, test the hypothesis that the proportions of male births among those with convulsive disorders and among their siblings are the same.

6.8 Lawson and Jick [1976] compare drug prescription in the United States and Scotland.

(a) In patients with congestive heart failure, two or more drugs were prescribed in 257 of 437 U.S. patients. In Scotland, 39 of 179 patients had two or more drugs prescribed. Test the null hypothesis of equal proportions giving the resulting p-value. Construct a 95% confidence interval for the difference in proportions.

(b) Patients with dehydration received two or more drugs in 55 of 74 Scottish cases as compared to 255 of 536 in the United States. Answer the questions of part (a).

6.9 A randomized study among patients with angina (heart chest pain) is to be conducted with five-year follow-up. Patients are to be randomized to medical and surgical treatment. Suppose that the estimated five-year medical mortality is 10% and it is hoped that the surgical mortality will be only half as much (5%) or less. If a test of binomial proportions at the 5% significance level is to be performed, and we want to be 90% certain of detecting a difference of 5% or more, what sample sizes are needed for the two (equal-sized) groups?

6.10 A cancer with poor prognosis, a three-year mortality of 85%, is studied. A new mode of chemotherapy is to be evaluated. Suppose that when testing at the 0.10 significance level, one wishes to be 95% certain of detecting a difference if survival has been increased to 50% or more. The randomized clinical trial will have equal numbers of people in each group. How many patients should be randomized?

6.11 Comstock and Partridge [1972] show data giving an association between church attendance and health. From the data of Example 6.17, which were collected from a prospective study:

(a) Compute the relative risk of an arteriosclerotic death in the three-year follow-up period if one usually attends church less than once a week as compared to once a week or more.

(b) Compute the odds ratio and a 95% confidence interval.

(c) Find the percent error of the odds ratio as an approximation to the relative risk; that is, compute $100(\text{OR} - \text{RR})/\text{RR}$.

(d) The data in this population on deaths from cirrhosis of the liver are:

Usual Church Attendance	Cirrhosis Fatality?	
	Yes	No
$\geq$1 per week	5	24,240
$<$1 per week	25	30,578

Repeat parts (a), (b), and (c) for these data.

6.12 Peterson et al. [1979] studied the patterns of infant deaths (especially SIDS) in King County, Washington during the years 1969–1977. They compared the SIDS deaths with a 1% sample of all births during the time period specified. Tables relating the occurrence of SIDS with maternal age less than or equal to 19 years of age, and to birth order greater than 1, follow for those with single births.

	Child			Child	
Birth Order	SIDS	Control	Maternal Age	SIDS	Control
$>$1	201	689	$\leq$19	76	164
$=$1	92	626	$>$19	217	1151

	Child	
	SIDS	**Control**
Birth order >1 *and* maternal age ≤ 19	26	17
Birth order $=1$ *or* maternal age >19	267	1298
Birth order >1 *and* maternal age ≤ 19	26	17
Birth order $=1$ *and* maternal age >19	42	479

(a) Compute the odds ratios and 95% confidence intervals for the data in these tables.

(b) Which pair of entries in the second table do you think best reflects the risk of both risk factors at once? Why? (There is not a definitely correct answer.)

***(c)** The control data represent a 1% sample of the population data. Knowing this, how would you estimate the relative risk directly?

6.13 Rosenberg et al. [1980] studied the relationship between coffee drinking and myocardial infarction in young women aged 30–49 years. This retrospective study included 487 cases hospitalized for the occurrence of a myocardial infarction (MI). Nine hundred eighty controls hospitalized for an acute condition (trauma, acute cholecystitis, acute respiratory diseases, and appendicitis) were selected. Data for consumption of five or more cups of coffee containing caffeine were:

Cups per Day	**MI**	**Control**
≥ 5	152	183
<5	335	797

Compute the odds ratio of a MI for heavy (≥ 5 cups per day) coffee drinkers vs. nonheavy coffee drinkers. Find the 90% confidence interval for the odds ratio.

6.14 The data of Problem 6.13 were considered to be possibly confounded with smoking. The 2×2 tables by smoking status, in cigarettes per day, are displayed in Table 6.11.

(a) Compute the Mantel–Haenszel estimate of the odds ratio and the chi-square statistic for association. Would you reject the null hypothesis of no association between coffee drinking and myocardial infarction at the 5% significance level?

(b) Using the log odds ratio as the measure of association in each table, compute the chi-square statistic for association. Find the estimated overall odds ratio and a 95% confidence interval for this quantity.

6.15 The paper of Remein and Wilkerson [1961] considers screening tests for diabetes. The Somogyi–Nelson (venous) blood test (data at 1 hour after a test meal and using 130 mg per 100 mL as the blood sugar cutoff level) gives the following table:

Test	**Diabetic**	**Nondiabetic**	**Total**
+	59	48	107
−	11	462	473
Total	70	510	580

Table 6.11 2 × 2 Tables for Problem 6.14

Cups per Day	MI	Control
Never smoked		
≥5	7	31
<5	55	269
Former smoker		
≥5	7	18
<5	20	112
1–14 cigarettes per day		
≥5	7	24
<5	33	114
15–24 cigarettes per day		
≥5	40	45
<5	88	172
25–34 cigarettes per day		
≥5	34	24
<5	50	55
35–44 cigarettes per day		
≥5	27	24
<5	55	58
45+ cigarettes per day		
≥5	30	17
<5	34	17

(a) Compute the sensitivity, specificity, predictive value of a positive test, and predictive value of a negative test.

(b) Using the sensitivity and specificity of the test as given in part (a), plot curves of the predictive values of the test vs. the percent of the population with diabetes (0 to 100%). The first curve will give the probability of diabetes given a positive test. The second curve will give the probability of diabetes given a negative test.

6.16 Remein and Wilkerson [1961] present tables showing the trade-off between sensitivity and specificity that arises by changing the cutoff value for a positive test. For blood samples collected 1 hour after a test meal, three different blood tests gave the data given in Table 6.12.

(a) Plot three curves, one for each testing method, on the same graph. Let the vertical axis be the sensitivity and the horizontal axis be (1 − specificity) of the test. The curves are generated by the changing cutoff values.

(b) Which test, if any, looks most promising? Why? (See also Note 6.7)

6.17 Data of Sartwell et al. [1969] that examine the relationship between thromboembolism and oral contraceptive use are presented below for several subsets of the population. For each subset:

(a) Perform McNemar's test for a case–control difference (5% significance level).

(b) Estimate the relative risk.

(c) Find an appropriate 90% confidence interval for the relative risk.

Table 6.12 Blood Sugar Data for Problem 6.16

Blood Sugar (mg/100 mL)	Type of Test					
	Somogyi–Nelson		Folin–Wu		Anthrone	
	SENS	SPEC	SENS	SPEC	SENS	SPEC
70	—	—	100.0	8.2	100.0	2.7
80	—	1.6	97.1	22.4	100.0	9.4
90	100.0	8.8	97.1	39.0	100.0	22.4
100	98.6	21.4	95.7	57.3	98.6	37.3
110	98.6	38.4	92.9	70.6	94.3	54.3
120	97.1	55.9	88.6	83.3	88.6	67.1
130	92.9	70.2	78.6	90.6	81.4	80.6
140	85.7	81.4	68.6	95.1	74.3	88.2
150	80.0	90.4	57.1	97.8	64.3	92.7
160	74.3	94.3	52.9	99.4	58.6	96.3
170	61.4	97.8	47.1	99.6	51.4	98.6
180	52.9	99.0	40.0	99.8	45.7	99.2
190	44.3	99.8	34.3	100.0	40.0	99.8
200	40.0	99.8	28.6	100.0	35.7	99.8

For nonwhites:

	Case	
Control	**Yes**	**No**
Yes	3	3
No	11	9

For married:

	Case	
Control	**Yes**	**No**
Yes	8	10
No	41	46

and for ages 15–29:

	Case	
Control	**Yes**	**No**
Yes	5	33
No	7	57

6.18 Janerich et al. [1980] compared oral contraceptive use among mothers of malformed infants and matched controls who gave birth to healthy children. The controls were matched for maternal age and race of the mother. For each of the following, estimate the odds ratio and form a 90% confidence interval for the odds ratio.

(a) Women who conceived while using the pill or immediately following pill use.

	Case	
Control	**Yes**	**No**
Yes	1	33
No	49	632

(b) Women who experienced at least one complete pill-free menstrual period prior to conception.

	Case	
Control	**Yes**	**No**
Yes	38	105
No	105	467

(c) Cases restricted to major structural anatomical malformations; use of oral contraceptives after the last menstrual period or in the menstrual cycle prior to conception.

	Case	
Control	**Yes**	**No**
Yes	0	21
No	45	470

(d) As in part (c) but restricted to mothers of age 30 or older.

	Case	
Control	**Yes**	**No**
Yes	0	1
No	6	103

6.19 Robinette et al. [1980] studied the effects on health of occupational exposure to microwave radiation (radar). The study looked at groups of enlisted naval personnel who were enrolled during the Korean War period. Find 95% confidence intervals for the percent of men dying of various causes, as given in the data below. Deaths were recorded that occurred during 1950–1974.

(a) Eight of 1412 aviation electronics technicians died of malignant neoplasms.

(b) Six of the 1412 aviation electronics technicians died of suicide, homicide, or other trauma.

(c) Nineteen of 10,116 radarmen died by suicide.

(d) Sixteen of 3298 fire control technicians died of malignant neoplasms.

(e) Three of 9253 radiomen died of infective and parasitic disease.

(f) None of 1412 aviation electronics technicians died of infective and parasitic disease.

6.20 The following data are also from Robinette et al. [1980]. Find 95% confidence intervals for the population percent dying based on these data: (1) 199 of 13,078 electronics technicians died of disease; (2) 100 of 13,078 electronics technicians died of circulatory disease; (3) 308 of 10,116 radarmen died (of any cause); (4) 441 of 13,078 electronics technicians died (of any cause); (5) 103 of 10,116 radarmen died of an accidental death.

(a) Use the normal approximation to the Poisson distribution (which is approximating a binomial distribution).

(b) Use the large-sample binomial confidence intervals (of Section 6.2.6). Do you think the intervals are similar to those calculated in part (a)?

6.21 Infant deaths in King County, Washington were grouped by season of the year. The number of deaths by season, for selected causes of death, are listed in Table 6.13.

Table 6.13 Death Data for Problem 6.21

	Season			
	Winter	Spring	Summer	Autumn
Asphyxia	50	48	46	34
Immaturity	30	40	36	35
Congenital malformations	95	93	88	83
Infection	40	19	40	43
Sudden infant death syndrome	78	71	87	86

(a) At the 5% significance level, test the hypothesis that SIDS deaths are uniformly ($p = 1/4$) spread among the seasons.

(b) At the 10% significance level, test the hypothesis that the deaths due to infection are uniformly spread among the seasons.

(c) What can you say about the p-value for testing that asphyxia deaths are spread uniformly among seasons? Immaturity deaths?

6.22 Fisher [1958] (after [Carver, 1927]) provided the following data on 3839 seedlings that were progeny of self-fertilized heterozygotes (each seedling can be classified as either starchy or sugary and as either green or white):

Number of Seedlings	Green	White	Total
Starchy	1997	906	2903
Surgary	904	32	936
Total	2901	938	3839

(a) On the assumption that the green and starchy genes are dominant and that the factors are independent, show that by Mendel's law that the ratio of expected frequencies (starchy green, starchy white, sugary green, sugary white) should be 9 : 3 : 3 : 1.

(b) Calculate the expected frequencies under the hypothesis that Mendel's law holds and assuming 3839 seedlings.

(c) The data are multinomial with parameters π_1, π_2, π_3, and π_4, say. What does Mendel's law imply about the relationships among the parameters?

(d) Test the goodness of fit.

6.23 Fisher [1958] presented data of Geissler [1889] on the number of male births in German families with eight offspring. One model that might be considered for these data is the binomial distribution. This problem requires a goodness-of-fit test.

(a) Estimate π, the probability that a birth is male. This is done by using the estimate $p =$ (total number of male births)/(total number of births). The data are given in Table 3.10.

(b) Using the p of part (a), find the binomial probabilities for number of boys $= 0$, 1, 2, 3, 4, 5, 6, 7, and 8. Estimate the expected number of observations in each cell if the binomial distribution is correct.

(c) Compute the X^2 value.

(d) The X^2 distribution lies between chi-square distributions with what two degrees of freedom? (Refer to Section 6.6.4)

***(e)** Test the goodness of fit by finding the two critical values of part (d). What can you say about the p-value for the goodness-of-fit test?

***6.24** **(a)** Let $R(n)$ be the number of ways to arrange n distinct objects in a row. Show that $R(n) = n! = 1 \cdot 2 \cdot 3 \cdot \ldots \cdot n$. By definition, $R(0) = 1$. *Hint:* Clearly, $R(1) = 1$. Use *mathematical induction*. That is, show that if $R(n-1) = (n-1)!$, then $R(n) = n!$. This would show that for all positive integers n, $R(n) = n!$. Why? [To show that $R(n) = n!$, suppose that $R(n-1) = (n-1)!$. Argue that you may choose any of the n objects for the first position. For each such choice, the remaining $n-1$ objects may be arranged in $R(n-1) = (n-1)!$ different ways.]

(b) Show that the number of ways to select k objects from n objects, denoted by $\binom{n}{k}$ (the binomial coefficient), is $n!/((n-k)!\,k!)$. *Hint*: We will choose the k objects by arranging the n objects in a row; the first k objects will be the ones we select. There are $R(n)$ ways to do this. When we do this, we get the *same* k objects many times. There are $R(k)$ ways to arrange the *same* k objects in the first k positions. For each such arrangement, the other $n-k$ objects may be arranged in $R(n-k)$ ways. The number of ways to arrange these objects is $R(k)R(n-k)$. Since each of the k objects is counted $R(k)R(n-k)$ times in the $R(n)$ arrangements, the number of different ways to select k objects is

$$\frac{R(n)}{R(k)R(n-k)} = \frac{n!}{k!\,(n-k)!}$$

from part (a). Then check that

$$\binom{n}{n} = \binom{n}{0} = 1$$

(c) Consider the binomial situation: n independent trials each with probability π of success. Show that the probability of k successes

$$b(k; n, \pi) = \binom{n}{k} \pi^k (1-\pi)^{n-k}$$

Hint: Think of the n trials as ordered. There are $\binom{n}{k}$ ways to choose the k trials that give a success. Using the independence of the trials, argue that the probability of the k trials being a success is $\pi^k(1-\pi)^{n-k}$.

(d) Compute from the definition of $b(k; n, \pi)$: (i) $b(3; 5, 0.5)$; (ii) $b(3; 3, 0.3)$; (iii) $b(2; 4, 0.2)$; (iv) $b(1; 3, 0.7)$; (v) $b(4; 6, 0.1)$.

6.25 In Section 6.2.3 we presented procedures for two-sided hypothesis tests with the binomial distribution. This problem deals with one-sided tests. We present the procedures for a test of $H_0 : \pi \geq \pi_0$ vs. $H_A : \pi < \pi_0$. [The same procedures would be used for $H_0 : \pi = \pi_0$ vs. $H_A : \pi < \pi_0$. For $H_0 : \pi \leq \pi_0$ vs. $H_A : \pi > \pi_0$, the procedure would be modified (see below).]

Procedure A: To construct a significance test of $H_0 : \pi \geq \pi_0$ vs. $H_a : \pi < \pi_0$ at significance level α:

(a) Let Y be binomial n, π_0, and $p = Y/n$. Find the largest c such that $P[p \leq c] \leq \alpha$.

(b) Compute the actual significance level of the test as $P[p \leq c]$.

(c) Observe p. Reject H_0 if $p \leq c$.

Procedure B: The p-value for the test if we observe p is $P[\widetilde{p} \leq p]$, where p is the *fixed* observed value and $\widetilde{p}$ equals $\widetilde{Y}/n$, where $\widetilde{Y}$ is binomial n, π_0.

(a) In Problem 6.2, let π be the probability of losing weight. (i) Find the critical value c for testing $H_0 : \pi \geq 1/2$ vs. $H_A : \pi < 1/2$ at the 10% significance level. (ii) Find the one-sided p-value for the data of Problem 6.2.

(b) Modify procedures A and B for the hypotheses $H_0 : \pi \leq \pi_0$ vs. $H_A : \pi > \pi_0$.

***6.26** Using the terminology and notation of Section 6.3.1, we consider proportions of success from two samples of size $n_{1\cdot}$ and $n_{2\cdot}$. Suppose that we are told that there are $n_{\cdot 1}$ total successes. That is, we observe the following:

	Success	**Failures**	
Sample 1	?		$n_{1\cdot}$
Sample 2			$n_{2\cdot}$
	$n_{\cdot 1}$	$n_{\cdot 2}$	$n_{\cdot\cdot}$

If both populations are equally likely to have a success, what can we say about n_{11}, the number of successes in population 1, which goes in the cell with the question mark?

Show that

$$P[n_{11} = k] = \binom{n_{1\cdot}}{k} \binom{n_{2\cdot}}{n_{\cdot 1} - k} \Big/ \binom{n_{\cdot\cdot}}{n_{\cdot 1}}$$

for $k \leq n_{1\cdot}$, $k \leq n_{\cdot 1}$, and $n_{\cdot 1} - k \leq n_{2\cdot}$. *Note*: $P[n_{11} = k]$, which has the parameters $n_{1\cdot}, n_{2\cdot}$, and $n_{\cdot 1}$, is called a *hypergeometric probability*. *Hint*: As suggested in Section 6.3.1, think of each trial (in sample 1 or 2) as a ball [purple ($n_{1\cdot}$) or gold ($n_{2\cdot}$)].

Since successes are equally likely in either population, any ball is as likely as any other to be drawn in the $n_{\cdot 1}$ successes. All subsets of size $n_{\cdot 1}$ are equally likely, so the probability of k successes is the number of subsets with k purple balls divided by the total number of subsets of size $n_{\cdot 1}$. Argue that the first number is $\binom{n_{1\cdot}}{k}\binom{n_{2\cdot}}{n_{\cdot 1}-k}$ and the second is $\binom{n_{\cdot\cdot}}{n_{\cdot 1}}$.

6.27 This problem gives more practice in finding the sample sizes needed to test for a difference in two binomial populations.

(a) Use Figure 6.2 to find *approximate* two-sided sample sizes *per group* for $\alpha = 0.05$ and $\beta = 0.10$ when (i) $P_1 = 0.5, P_2 = 0.6$; (ii) $P_1 = 0.20, P_2 = 0.10$; (iii) $P_1 = 0.70, P_2 = 0.90$.

(b) For each of the following, find one-sided sample sizes *per group* as needed from the formula of Section 6.3.3. (i) $\alpha = 0.05, \beta = 0.10, P_1 = 0.25, P_2 = 0.10$; (ii) $\alpha = 0.05, \beta = 0.05, P_1 = 0.60, P_2 = 0.50$; (iii) $\alpha = 0.01, \beta = 0.01, P_1 = 0.15, P_2 = 0.05$; (iv) $\alpha = 0.01, \beta = 0.05, P_1 = 0.85, P_2 = 0.75$. To test π_1 vs. π_2, we need the same sample size as we would to test $1 - \pi_1$ vs. $1 - \pi_2$. Why?

6.28 You are examined by an excellent screening test (sensitivity and specificity of 99%) for a rare disease (0.1% or 1/1000 of the population). Unfortunately, the test is positive. What is the probability that you have the disease?

***6.29** **(a)** Derive the rule of threes defined in Note 6.9.

(b) Can you find a similar constant to set up a 99% confidence interval?

***6.30** Consider the matched pair data of Problem 6.17: What null hypothesis does the usual chi-square test for a 2×2 table test on these data? What would you decide about the matching if this chi-square was not significant (e.g., the "married" table)?

REFERENCES

Beyer, W. H. (ed.) [1968]. *CRC Handbook of Tables for Probability and Statistics*. CRC Press, Cleveland, OH.

Borer, J. S., Rosing, D. R., Miller, R. H., Stark, R. M., Kent, K. M., Bacharach, S. L., Green, M. V., Lake, C. R., Cohen, H., Holmes, D., Donahue, D., Baker, W., and Epstein, S. E. [1980]. Natural history of left ventricular function during 1 year after acute myocardial infarction: comparison with clinical, electrocardiographic and biochemical determinations. *American Journal of Cardiology*, **46**: 1–12.

Box, J. F. [1978]. *R. A. Fisher: The Life of a Scientist*. Wiley, New York.

Breslow, N. E., and Day, N. E. [1980]. *Statistical Methods in Cancer Research*, Vol. 1, *The Analysis of Case–Control Studies*, IARC Publication 32. International Agency for Research in Cancer, Lyon, France.

Bucher, K. A., Patterson, A. M., Elston, R. C., Jones, C. A., and Kirkman, H. N., Jr. [1976]. Racial difference in incidence of ABO hemolytic disease. *American Journal of Public Health*, **66**: 854–858. Copyright © 1976 by the American Public Health Association.

Carver, W. A. [1927]. A genetic study of certain chlorophyll deficiencies in maize. *Genetics*, **12**: 415–440.

Cavalli-Sforza, L. L., and Bodmer, W. F. [1999]. *The Genetics of Human Populations*. Dover Publications, New York.

Chernoff, H., and Lehmann, E. L. [1954]. The use of maximum likelihood estimates in χ^2 tests for goodness of fit. *Annals of Mathematical Statistics*, **25**: 579–586.

Comstock, G. W., and Partridge, K. B. [1972]. Church attendance and health. *Journal of Chronic Diseases*, **25**: 665–672. Used with permission of Pergamon Press, Inc.

Conover, W. J. [1974]. Some reasons for not using the Yates continuity correction on 2×2 contingency tables (with discussion). *Journal of the American Statistical Association*, **69**: 374–382.

Edwards, A. W. F., and Fraccaro, M. [1960]. Distribution and sequences of sex in a selected sample of Swedish families. *Annals of Human Genetics, London*, **24**: 245–252.

Feigl, P. [1978]. A graphical aid for determining sample size when comparing two independent proportions. *Biometrics*, **34**: 111–122.

Fisher, L. D., and Patil, K. [1974]. Matching and unrelatedness. *American Journal of Epidemiology*, **100**: 347–349.

Fisher, R. A. [1936]. Has Mendel's work been rediscovered? *Annals of Science*, **1**: 115–137.

Fisher, R. A. [1958]. *Statistical Methods for Research Workers*, 13th ed. Oliver & Boyd, London.

Fisher, R. A., Thornton, H. G., and MacKenzie, W. A. [1922]. The accuracy of the plating method of estimating the density of bacterial populations. *Annals of Applied Biology*, **9**: 325–359.

Fleiss, J. L., Levin, B., and Park, M. C. [2003]. *Statistical Methods for Rates and Proportions*, 3rd ed. Wiley, New York.

Geissler, A. [1889]. Beiträge zur Frage des Geschlechts Verhältnisses der Geborenen. *Zeitschrift des K. Sachsischen Statistischen Bureaus*.

Graunt, J. [1662]. *Natural and Political Observations Mentioned in a Following Index and Made Upon the Bills of Mortality*. Given in part in Newman, J. R. (ed.) [1956]. *The World of Mathematics*, Vol. 3. Simon & Schuster, New York.

Grizzle, J. E. [1967]. Continuity correction in the χ^2-test for 2×2 tables. *American Statistician*, **21**: 28–32.

Hanley, J. A., and Lippman-Hand, A. [1983]. If nothing goes wrong, is everything alright? *Journal of the American Medical Association*, **249**: 1743–1745.

Janerich, D. T., Piper, J. M., and Glebatis, D. M. [1980]. Oral contraceptives and birth defects. *American Journal of Epidemiology*, **112**: 73–79.

Karlowski, T. R., Chalmers, T. C., Frenkel, L. D., Zapikian, A. Z., Lewis, T. L., and Lynch, J. M. [1975]. Ascorbic acid for the common cold: a prophylactic and therapeutic trial. *Journal of the American Medical Association*, **231**: 1038–1042.

Kelsey, J. L., and Hardy, R. J. [1975]. Driving of motor vehicles as a risk factor for acute herniated lumbar intervertebral disc. *American Journal of Epidemiology*, **102**: 63–73.

Kendall, M. G., and Stuart, A. [1967]. *The Advanced Theory of Statistics*, Vol. 2, *Inference and Relationship*. Hafner, New York.

Kennedy, J. W., Kaiser, G. W., Fisher, L. D., Fritz, J. K., Myers, W., Mudd, J. G., and Ryan, T. J. [1981]. Clinical and angiographic predictors of operative mortality from the collaborative study in coronary artery surgery (CASS). *Circulation*, **63**: 793–802.

Lawson, D. H., and Jick, H. [1976]. Drug prescribing in hospitals: an international comparison. *American Journal of Public Health*, **66**: 644–648.

Little, R. J. A. [1989]. Testing the equality of two independent binomial proportions. *American Statistician*, **43**: 283–288.

Mantel, N., and Greenhouse, S. W. [1968]. What is the continuity correction? *American Statistician*, **22**: 27–30.

Mantel, N., and Haenszel, W. [1959]. Statistical aspects of the analysis of data from retrospective studies of disease. *Journal of the National Cancer Institute*, **22**: 719–748.

Mantel, N., Brown, C., and Byar, D. P. [1977]. Tests for homogeneity of effect in an epidemiologic investigation. *American Journal of Epidemiology*, **106**: 125–129.

Mendel, G. [1866]. Versuche über Pflanzenhybriden. *Verhandlungen Naturforschender Vereines in Brunn*, **10**: 1.

Meyer, M. B., Jonas, B. S., and Tonascia, J. A. [1976]. Perinatal events associated with maternal smoking during pregnancy. *American Journal of Epidemiology*, **103**: 464–476.

Miettinen, O. S. [1970]. Matching and design efficiency in retrospective studies. *American Journal of Epidemiology*, **91**: 111–118.

Odeh, R. E., Owen, D. B., Birnbaum, Z. W., and Fisher, L. D. [1977]. *Pocket Book of Statistical Tables*. Marcel Dekker, New York.

Ounsted, C. [1953]. The sex ratio in convulsive disorders with a note on single-sex sibships. *Journal of Neurology, Neurosurgery and Psychiatry*, **16**: 267–274.

Owen, D. B. [1962]. *Handbook of Statistical Tables*. Addison-Wesley, Reading, MA.

Peterson, D. R., van Belle, G., and Chinn, N. M. [1979]. Epidemiologic comparisons of the sudden infant death syndrome with other major components of infant mortality. *American Journal of Epidemiology*, **110**: 699–707.

Peterson, D. R., Chinn, N. M., and Fisher, L. D. [1980]. The sudden infant death syndrome: repetitions in families. *Journal of Pediatrics*, **97**: 265–267.

Pepe, M. S. [2003]. *The Statistical Evaluation of Medical Tests for Clarification and Prediction*. Oxford University Press, Oxford.

Remein, Q. R., and Wilkerson, H. L. C. [1961]. The efficiency of screening tests for diabetes. *Journal of Chronic Diseases*, **13**: 6–21. Used with permission of Pergamon Press, Inc.

Robinette, C. D., Silverman, C., and Jablon, S. [1980]. Effects upon health of occupational exposure to microwave radiation (radar). *American Journal of Epidemiology*, **112**: 39–53.

Rosenberg, L., Slone, D., Shapiro, S., Kaufman, D. W., Stolley, P. D., and Miettinen, O. S. [1980]. Coffee drinking and myocardial infarction in young women. *American Journal of Epidemiology*, **111**: 675–681.

Sartwell, P. E., Masi, A. T., Arthes, F. G., Greene, G. R., and Smith, H. E. [1969]. Thromboembolism and oral contraceptives: an epidemiologic case–control study. *American Journal of Epidemiology*, **90**: 365–380.

Schlesselman, J. J. [1982]. *Case–Control Studies: Design, Conduct, Analysis*. Monographs in Epidemiology and Biostatistics. Oxford University Press, New York.

Shapiro, S., Goldberg, J. D., and Hutchinson, G. B. [1974]. Lead time in breast cancer detection and implications for periodicity of screening. *American Journal of Epidemiology*, **100**: 357–366.

Smith, J. P., Delgado, G., and Rutledge, F. [1976]. Second-look operation in ovarian cancer. Cancer, **38**: 1438–1442. Used with permission from J. B. Lippincott Company.

Starmer, C. F., Grizzle, J. E., and Sen, P. K. [1974]. Comment. *Journal of the American Statistical Association*, **69**: 376–378.

U.S. Department of Health, Education, and Welfare [1964]. *Smoking and Health: Report of the Advisory Committee to the Surgeon General of the Public Health Service*. U.S. Government Printing Office, Washington, DC.

von Bortkiewicz, L. [1898]. *Das Gesetz der Kleinen Zahlen*. Teubner, Leipzig.

Weber, A., Jermini, C., and Grandjean, E. [1976]. Irritating effects on man of air pollution due to cigarette smoke. *American Journal of Public Health*, **66**: 672–676.

CHAPTER 7

Categorical Data: Contingency Tables

7.1 INTRODUCTION

In Chapter 6, *discrete variables* came up by counting the number of times that specific outcomes occurred. In looking at the presence or absence of a risk factor and a disease, *odds ratio* and *relative risk* were introduced. In doing this, we looked at the relationship between two discrete variables; each variable took on one of two possible states (i.e., risk factor present or absent and disease present or absent). In this chapter we show how to analyze more general discrete data. Two types of generality are presented.

The first generalization considers two jointly distributed discrete variables. Each variable may take on more than two possible values. Some examples of discrete variables with three or more possible values might be: smoking status (which might take on the values "never smoked," "former smoker," and "current smoker"); employment status (which could be coded as "full-time," "part-time," "unemployed," "unable to work due to medical reason," "retired," "quit," and "other"); and clinical judgment of improvement (classified into categories of "considerable improvement," "slight improvement," "no change," "slight worsening," "considerable worsening," and "death").

The second generalization allows us to consider three or more discrete variables (rather than just two) at the same time. For example, method of treatment, gender, and employment status may be analyzed jointly. With three or more variables to investigate, it becomes difficult to obtain a "feeling" for the interrelationships among the variables. If the data fit a relatively simple mathematical model, our understanding of the data may be greatly increased.

In this chapter, our first *multivariate statistical model* is encountered. The model is the *log-linear model* for multivariate discrete data. The remainder of the book depends on a variety of models for analyzing data; this chapter is an exciting, important, and challenging introduction to such models!

7.2 TWO-WAY CONTINGENCY TABLES

Let two or more discrete variables be measured on each unit in an experiment or observational study. In this chapter, methods of examining the relationship among the variables are studied. In most of the chapter we study the relationship of two discrete variables. In this case we count the number of occurrences of each pair of possibilities and enter them in a table. Such tables are called *contingency tables*. Example 7.1 presents two contingency tables.

Biostatistics: A Methodology for the Health Sciences, Second Edition, by Gerald van Belle, Lloyd D. Fisher, Patrick J. Heagerty, and Thomas S. Lumley
ISBN 0-471-03185-2

Example 7.1. In 1962, Wangensteen et al., published a paper in the *Journal of the American Medical Association* advocating gastric freezing. A balloon was lowered into a subject's stomach, and coolant at a temperature of −17 to −20°C was introduced through tubing connected to the balloon. Freezing was continued for approximately 1 hour. The rationale was that gastric digestion could be interrupted and it was thought that a duodenal ulcer might heal if treatment could be continued over a period of time. The authors advanced three reasons for the interruption of gastric digestion: (1) interruption of vagal secretory responses; (2) "rendering of the central mucosa nonresponsive to food ingestion . . . "; and (3) "impairing the capacity of the parietal cells to secrete acid and the chief cells to secrete pepsin." Table 7.1 was presented as evidence for the effectiveness of gastric freezing. It shows a decrease in acid secretion.

On the basis of this table and other data, the authors state: "These data provide convincing objective evidence of significant decreases in gastric secretory responses attending effective gastric freezing" and conclude: "When profound gastric hypothermia is employed with resultant freezing of the gastric mucosa, the method becomes a useful agent in the control of many of the manifestations of peptic ulcer diathesis. Symptomatic relief is the rule, followed quite regularly by x-ray evidence of healing of duodenal ulcer craters and evidence of effective depression of gastric secretory responses." *Time* [1962] reported that "all [the patients'] ulcers healed within two to six weeks."

However, careful studies attempting to confirm the foregoing conclusion failed. Two studies in particular failed to confirm the evidence, one by Hitchcock et al. [1966], the other by Ruffin et al. [1969]. The latter study used an elaborate sham procedure (control) to simulate gastric freezing, to the extent that the tube entering the patient's mouth was cooled to the same temperature as in the actual procedure, but the coolant entering the stomach was at room temperature, so that no freezing took place. The authors defined an endpoint to have occurred if one of the following criteria was met: "perforation; ulcer pain requiring hospitalization for relief; obstruction, partial or complete, two or more weeks after hyperthermia; hemorrhage, surgery for ulcer; repeat hypothermia; or x-ray therapy to the stomach."

Several institutions cooperated in the study, and to ensure objectivity and equal numbers, random allocations to treatment and sham were balanced within groups of eight. At the termination of the study, patients were classified as in Table 7.2. The authors conclude: "The results of

Table 7.1 Gastric Response of 10 Patients with Duodenal Ulcer Whose Stomachs Were Frozen at −17 to −20°C for 1 Hour

		Average Percent Decrease in HCl after Gastric Freezing		
Patients	Patients with Decrease in Free HCl	Overnight Secretion	Peptone Stimulation	Insulin
10	10[a]	87	51	71

Source: Data from Wangensteen et al. [1962].

[a] All patients, except one, had at least a 50% decrease in free HCl in overnight secretion.

Table 7.2 Causes of Endpoints

Group	Patients	With Hemorrhage	With Operation	With Hospitalization	Not Reaching Endpoint
F (freeze)	69	9	17	9	34
S (sham)	68	9	14	7	38

Source: Data from Ruffin et al. [1969].

Table 7.3 Contingency Table for Gastric Freezing Data

	j			
i	1	2	$\cdots$	c
1	n_{11}	n_{12}	$\cdots$	n_{1c}
2	n_{21}	n_{22}	$\cdots$	n_{2c}
$\vdots$	$\vdots$	$\vdots$	$\ddots$	$\vdots$
r	n_{r1}	n_{r2}	$\cdots$	n_{rc}

this study demonstrate conclusively that the 'freezing' procedure was not better than the sham in the treatment of duodenal ulcer, confirming the work of others. ... It is reasonable to assume that the relief of pain and subjective improvement reported by early investigators was probably due to the psychological effect of the procedure."

Contingency tables set up from two variables are called *two-way tables*. Let the variable corresponding to rows have r (for "row") possible outcomes, which we index by i ($i = 1, 2, \ldots, r$). Let the variables corresponding to the column headings have c (for "column") possible states indexed by j ($j = 1, 2, \ldots, c$). One speaks of an $r \times c$ *contingency table*. Let n_{ij} be the number of observations corresponding to the ith state of the row variable and the jth state of the column variable. In the example above, $n_{11} = 9, n_{12} = 17, n_{13} = 9, n_{14} = 34, n_{21} = 9, n_{22} = 14, n_{23} = 7$, and $n_{24} = 38$. In general, the data are presented as shown in Table 7.3. Such tables usually arise in one of two ways:

1. A sample of observations is taken. On each unit we observe the values of two traits. Let π_{ij} be the probability that the row variable takes on level i and the column variable takes on level j. Since one of the combinations must occur,

$$\sum_{i=1}^{r} \sum_{j=1}^{c} \pi_{ij} = 1 \tag{1}$$

2. Each row corresponds to a sample from a different population. In this case, let π_{ij} be the probability the column variable takes on state j when sampling from the ith population. Thus, for each i,

$$\sum_{j=1}^{c} \pi_{ij} = 1 \tag{2}$$

If the samples correspond to the column variable, the π_{ij} are the probabilities that the row variable takes on state i when sampling from population j. In this circumstance, for each j,

$$\sum_{i=1}^{r} \pi_{ij} = 1 \tag{3}$$

Table 7.2 comes from the second model since the treatment is assigned by the experimenter; it is not a trait of the experimental unit. Examples for the first model are given below.

The usual null hypothesis in a model 1 situation is that of independence of row and column variables. That is (assuming row variable $= i$ and column variable $= j$), $P[i \text{ and } j] = P[i]P[j]$,

$$H_0: \pi_{ij} = \pi_{i\cdot}\pi_{\cdot j}$$

In the model 2 situation, suppose that the row variable identifies the population. The usual null hypothesis is that all r populations have the same probabilities of taking on each value of the column variable. That is, for any two rows, denoted by i and i', say, and all j,

$$H_0: \pi_{ij} = \pi_{i'j}$$

If one of these hypotheses holds, we say that there is *no association*; otherwise, the table is said to have *association* between the categorical variables.

We will use the following notation for the sum over the elements of a row and/or column: $n_{i\cdot}$ is the sum of the elements of the ith row; $n_{\cdot j}$ is the sum of the elements of the jth column:

$$n_{i\cdot} = \sum_{j=1}^{c} n_{ij}, \qquad n_{\cdot j} = \sum_{i=1}^{r} n_{ij}, \qquad n_{\cdot\cdot} = \sum_{i=1}^{r}\sum_{j=1}^{c} n_{ij}$$

It is shown in Note 7.1 that under either model 1 or model 2, the null hypothesis is reasonably tested by comparing n_{ij} with

$$\frac{n_{i\cdot}n_{\cdot j}}{n_{\cdot\cdot}}$$

The latter is the value expected in the ijth cell given the observed marginal configuration and assuming either of the null hypotheses under model 1 or model 2. This is shown as

$n_{11} = 9$	$n_{12} = 17$	$n_{13} = 9$	$n_{14} = 34$	$n_{1\cdot} = 69$
$n_{21} = 9$	$n_{22} = 14$	$n_{23} = 7$	$n_{24} = 38$	$n_{2\cdot} = 68$
$n_{\cdot 1} = 18$	$n_{\cdot 2} = 31$	$n_{\cdot 3} = 16$	$n_{\cdot 4} = 72$	$n_{\cdot\cdot} = 137$

Under the null hypothesis, the table of expected values $n_{i\cdot}n_{\cdot j}/n_{\cdot\cdot}$ is

$69 \times 18/137$	$69 \times 31/137$	$69 \times 16/137$	$69 \times 72/137$
$68 \times 18/137$	$68 \times 31/137$	$68 \times 16/137$	$68 \times 72/137$

or

9.07	15.61	8.06	36.26
8.93	15.39	7.94	35.74

It is a remarkable fact that both null hypotheses above may be tested by the χ^2 statistic,

$$X^2 = \sum_{i=1}^{r}\sum_{j=1}^{c} \frac{(n_{ij} - n_{i\cdot}n_{\cdot j}/n_{\cdot\cdot})^2}{n_{i\cdot}n_{\cdot j}/n_{\cdot\cdot}}$$

Note that n_{ij} is the observed cell entry; $n_{i\cdot}n_{\cdot j}/n_{\cdot\cdot}$ is the expected cell entry, so this statistic may be remembered as

$$X^2 = \sum \frac{(\text{observed} - \text{expected})^2}{\text{expected}}$$

For example, the array above gives

$$X^2 = \frac{(9-9.07)^2}{9.07} + \frac{(17-15.61)^2}{15.61} + \frac{(9-8.06)^2}{8.06} + \frac{(34-36.26)^2}{36.26} + \frac{(9-8.93)^2}{8.93} + \frac{(14-15.39)^2}{15.39} + \frac{(7-7.94)^2}{7.94} + \frac{(38-35.76)^2}{35.76} = 0.752$$

Under the null hypothesis, the X^2 statistic has approximately a χ^2 distribution with $(r-1)(c-1)$ degrees of freedom. This approximation is for large samples and is appropriate when all of the *expected* values, $n_{i\cdot}n_{\cdot j}/n_{\cdot\cdot}$, are 5 or greater. There is some evidence to indicate that the approximation is valid if all the expected values, except possibly one, are 5 or greater.

For our example, the degrees of freedom for the example are $(2-1)(4-1) = 3$. The rejection region is for X^2 too large. The 0.05 critical value is 7.81. As $0.752 < 7.81$, we do *not* reject the null hypothesis at the 0.05 significance level.

Example 7.2. Robertson [1975] examined seat belt use in automobiles with starter interlock and buzzer/light systems. The use or nonuse of safety belts by drivers in their vehicles was observed at 138 sites in Baltimore, Maryland; Houston, Texas; Los Angeles, California; the New Jersey suburbs; New York City; Richmond, Virginia; and Washington, DC during late 1973 and early 1974. The sites were such that observers could see whether or not seat belts were being used. The sites were freeway entrances and exits, traffic-jam areas, and other points where vehicles usually slowed to less than 15 miles per hour. The observers dictated onto tape the gender, estimated age, and racial appearance of the driver of the approaching car; as the vehicles slowed alongside, the observer recorded whether or not the lap belt and/or shoulder belt was in use, not in use, or could not be seen. The license plate numbers were subsequently sent to the appropriate motor vehicle administration, where they were matched to records from which the manufacturer and year were determined. In the 1973 models, a buzzer/light system came on when the seat belt was not being used. The buzzer was activated for at least 1 minute when the driver's seat was occupied, the ignition switch was on, the transmission gear selector was in a forward position, and the driver's lap belt was not extended at least 4 inches from its normal resting position. Effective on August 15, 1973, a federal standard required that the automobile could be started only under certain conditions. In this case, when the driver was seated, the belts had to be extended more than 4 inches from their normally stored position and/or latched. Robertson states that as a result of the strong negative public reaction to the interlock system, federal law has banned the interlock system. Data on the buzzer/light-equipped models and interlock-equipped models are given in Table 7.4. As can be seen from the table, column percentages were presented to aid assimilation of the information in the table.

Table 7.4 Robertson [1975] Seat Belt Data

	1973 Models (Buzzer/Light)		1974 Models (Interlock)		
Belt Use	%	Number	%	Number	Total
Lap and shoulder	7	432	48	1007	1439
Lap only	21	1262	11	227	1489
None	72	4257	41	867	5124
Total	100	5951	100	2101	8052

Percentages in two-way contingency tables are useful in aiding visual comprehension of the contents. There are three types of percent tables:

1. *Column percent tables* give the percentages for each column (the columns add to 100%, except possibly for rounding errors). This is best for comparing the distributions of different columns.
2. *Row percent tables* give the percentages for each row (the rows add to 100%). This is best for comparing the distributions of different rows.
3. The *total percent table* gives percentages, so that all the entries in a table add to 100%. This aids investigation of the proportions in each combination.

The column percentages in Table 7.4 facilitate comparison of seat belt use in the 1973 buzzer/light models and the 1974 interlock models. They illustrate that there are strategies for getting around the interlock system, such as disabling it, connecting the seat belt and leaving it connected on the seat, as well as possible other strategies, so that even with an interlock system, not everyone uses it. The computed value of the chi-square statistic for this table is 1751.6 with two degrees of freedom. The p-value is effectively zero, as shown in Table A.3 in the Appendix.

Given that we have a statistically significant association, the next question that arises is: To what may we attribute this association? To determine why the association occurs, it is useful to have an idea of which entries in the table differ more than would be expected by chance from their value under the null hypothesis of no association. Under the null hypothesis, for each entry in the table, the following *adjusted residual value* is approximately distributed as a standard normal distribution. The term *residual* is used since it looks at the difference between the observed value and the value expected under the null hypothesis. This difference is then standardized by its standard error,

$$z_{ij} = \frac{n_{ij} - (n_{i\cdot} n_{\cdot j}/n_{\cdot\cdot})}{\sqrt{n_{i\cdot} n_{\cdot j}/n_{\cdot\cdot}\,(1 - n_{i\cdot}/n_{\cdot\cdot})\,(1 - n_{\cdot j}/n_{\cdot\cdot})}} \tag{4}$$

For example, for the (1, 1) entry in the table, a standardized residual, is given by

$$\frac{(432 - 1439 \times 5951/8052)}{\sqrt{\dfrac{1439(5951)}{8052}\left(1 - \dfrac{1439}{8052}\right)\left(1 - \dfrac{5951}{8052}\right)}} = 41.83$$

The matrix of the residual values observed with the corresponding normal probability p-values is given in Table 7.5. Note that the values add to zero for the residuals across each row. This occurs because there are only two columns. The adjusted residual values observed are so far from zero that the normal p-values are miniscule.

In general, there is a problem in looking at a contingency table with many cells. Because there are a large number of residual values in the table, it may be that one or more of them differs by chance from zero at the 5% significance level. Even *under the null hypothesis*, because of the many possibilities examined, *this would occur much more than 5% of the time*. One conservative way to deal with this problem is to multiply the p-values by the number of rows minus one and the number of columns minus one. If the corresponding p-value is less than 0.05, one can conclude that the entry is different from that expected by the null hypothesis at the 5% significance level *even after looking at all of the different entries*. (This problem of looking at many possibilities, called the *multiple comparison problem*, is dealt with in considerable detail in Chapter 12.) For this example, even after multiplying by the number of rows minus one and the number of columns minus one, all of the entries differ from those expected under the null hypothesis. Thus, one can conclude, using the sign of the residual to tell us whether the

Table 7.5 Adjusted Residual Values (Example 7.2)

i	j	Residual (Z_{ij})	p-value	p-value $\times (r-1) \times (c-1)$
1	1	−41.83	0+	0+
1	2	41.83	0+	0+
2	1	10.56	3×10^{-22}	6×10^{-22}
2	2	−10.56	3×10^{-22}	6×10^{-22}
3	1	24.79	9×10^{-53}	2×10^{-52}
3	2	−24.79	9×10^{-53}	2×10^{-52}

percentage is too high or too low, that in the 1973 models there is less lap and shoulder belt use than in the 1974 models. Further, if we look at the "none" category, there are fewer people without any belt use in the 1974 interlock models than in the 1973 buzzer/light-equipped models. One would conclude that the interlock system, although a system disliked by the public, was successful as a public health measure in increasing the amount of seat belt use.

Suppose that we decide there is an association in a contingency table. We can interpret the table by using residuals (as we have done above) to help to find out whether particular entries differ more than expected by chance. Another approach to interpretation is to characterize numerically the amount of association between the variables, or proportions in different groups, in the contingency table. To date, no single measure of the amount of association in contingency tables has gained widespread acceptance. There have been many proposals, all of which have some merit. Note 7.2 presents some measures of the amount of association.

7.3 CHI-SQUARE TEST FOR TREND IN 2 × k TABLES

There are a variety of techniques for improving the statistical power of χ^2 tests. Recall that power is a function of the alternative hypothesis. One weakness of the chi-square test is that it is an "omnibus" test; it tests for independence vs. dependence without specifying the nature of the latter. In some cases, a small subset of alternative hypotheses may be specified to increase the power of the chi-square test by defining a special test. One such situation occurs in $2 \times k$ tables when the alternative hypothesis is that there is an ordering in the variable producing the k categories. For example, exposure categories can be ordered, and the alternative hypothesis may be that the probability of disease *increases* with increasing exposure.

In this case the row variable takes on one of two states (say + or − for definiteness). For each state of the column variable ($j = 1, 2, \ldots, k$), let π_j be the conditional probability of a positive response. The test for trend is designed to have statistical power against the alternatives:

$$H_1 : \pi_1 \leq \pi_2 \leq \cdots \leq \pi_k, \qquad \text{with at least one strict inequality}$$

$$H_2 : \pi_1 \geq \pi_2 \geq \cdots \geq \pi_k, \qquad \text{with at least one strict inequality}$$

That is, the alternatives of interest are that the proportion of + responses increases or decreases with the column variable. For these alternatives to be of interest, the column variable will have a "natural" ordering. To compute the statistic, a score needs to be assigned to each state j of the column variable. The scores x_j are assigned so that they increase or decrease. Often, the x_j are consecutive integers. The data are laid out as shown in Table 7.6.

Table 7.6 Scores Assigned to State *j*

	j				
i	1	2	⋯	*k*	Total
1+	n_{11}	n_{12}	⋯	n_{1k}	$n_{1\cdot}$
2−	n_{21}	n_{22}	⋯	n_{2k}	$n_{2\cdot}$
Total	$n_{\cdot 1}$	$n_{\cdot 2}$	⋯	$n_{\cdot k}$	$n_{\cdot\cdot}$
Score	x_1	x_2	⋯	x_k	

Before stating the test, we define some notation. Let

$$[n_1 x] = \sum_{j=1}^{k} n_{1j} x_j - \frac{n_{1\cdot} \sum n_{\cdot j} x_j}{n_{\cdot\cdot}}$$

and

$$[x^2] = \sum_{j=1}^{k} n_{\cdot j} x_j^2 - \frac{(\sum n_{\cdot j} x_j)^2}{n_{\cdot\cdot}}$$

and

$$p = \frac{n_{1\cdot}}{n_{\cdot\cdot}}$$

Then the chi-square test for trend is defined to be

$$X^2_{\text{trend}} = \frac{[n_1 x]^2}{[x^2] p(1-p)}$$

and when there is no association, this quantity has approximately a chi-square distribution with one degree of freedom. [In the terminology of Chapter 9, this is a chi-square test for the slope of a weighted regression line with dependent variable $p_j = n_{1j}/n_{\cdot j}$, predictor variable x_j, and weights $n_{1j}/p(1-p)$, where $j = 1, 2, \ldots, k$.]

Example 7.3. For an example of this test, we use data of Maki et al. [1977], relating risk of catheter-related infection to the duration of catheterization. An infection was considered to be present if there were 15 or more colonies of microorganisms present in a culture associated with the withdrawn catheter. A part of the data dealing with the number of positive cultures as related to duration of catheterization is given in Table 7.7. A somewhat natural set of values of the scores x_i is the duration of catheterization in days. The designation ≥ 4 is, somewhat arbitrarily, scored 4.

Before carrying out the analysis, note that a graph of the proportion of positive cultures vs. duration such as in the one shown in Figure 7.1 clearly suggests a trend. The general chi-square test on the 2×4 table produces a value of $X^2 = 6.99$ with three degrees of freedom and a significance level of 0.072.

Table 7.7 Relations of Results of Semiquantitative Culture and Catheterization

	Duration of Catheterization (days)				
Culture	1	2	3	≥ 4	Total
Positive[a]	1[b]	5	5	14	25
Negative	46	64	39	76	225
Total	47	69	44	90	250

Source: Data from Maki et al. [1977].
[a]Culture is positive if 15 or more colonies on the primary plate.
[b]Numbers in the body of the table are the numbers of catheters.

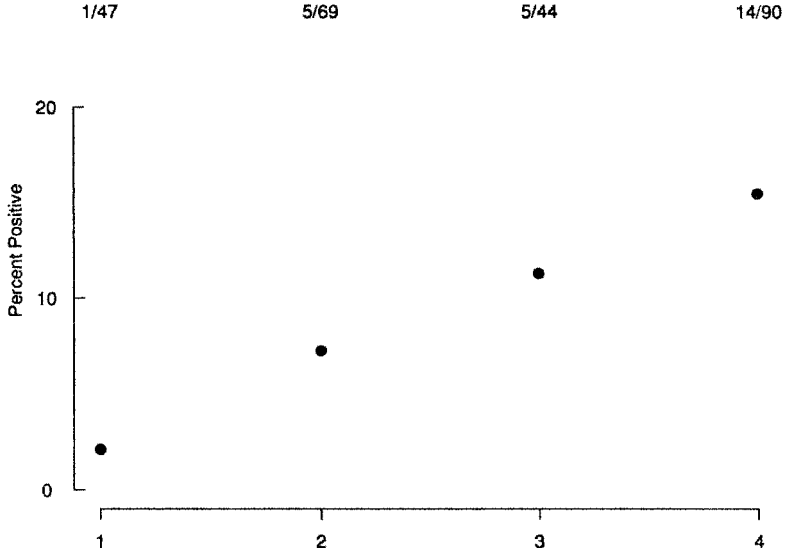


Figure 7.1 Graph of percentage of cultures positive vs. duration of catheterization. The fractions 1/47, etc., are the number of positive cultures to the total number of cultures for a particular day. (Data from Maki et al. [1977]; see Table 7.7.)

To calculate the chi-square test for trend, we calculate the quantities $[n_1x]$, $[x^2]$, and p as defined above.

$$[n_1x] = 82 - \frac{(25)(677)}{250} = 14.3$$

$$[x^2] = 2159 - \frac{677^2}{250} \doteq 325.6840$$

$$p = \frac{25}{250} = 0.1, \qquad (1 - p) = 0.9$$

$$X^2_{\text{trend}} = \frac{[n_1x]^2}{[x^2]p(1-p)} \doteq \frac{14.3^2}{325.6840(0.1)(0.9)} \doteq 6.98$$

This statistic has one degree of freedom associated with it, and from the chi-square Table A.3, it can be seen that $0.005 < p < 0.01$; hence there is a significant linear trend.

Note two things about the chi-square test for trend. First, the degrees of freedom are one, *regardless* of how large the value k. Second, the values of the scores chosen (x_j) are not too crucial, and evenly spaced scores will give more statistical power against a trend than will the usual χ^2 test. The example above indicates one type of contingency table in which ordering is clear: when the categories result from grouping a continuous variable.

7.4 KAPPA: MEASURING AGREEMENT

It often happens in measuring or categorizing objects that the variability of the measurement or categorization is investigated. For example, one might have two physicians independently judge a patient's status as "improved," "remained the same," or "worsened." A study of psychiatric patients might have two psychiatrists independently classifying patients into diagnostic categories. When we have two discrete classifications of the same object, we may put the entries into a two-way *square* ($r = c$) contingency table. The chi-square test of this chapter may then be used to test for association. Usually, when two measurements are taken of the same objects, there is not much trouble showing association; rather, the concern is to study the degree or amount of agreement in the association. This section deals with a statistic, *kappa* (κ), designed for such situations. We will see that the statistic has a nice interpretation; the value of the statistic can be taken as a measure of the degree of agreement. As we develop this statistic, we shall illustrate it with the following example.

Example 7.4. Fisher et al. [1982] studied the reproducibility of coronary arteriography. In the coronary artery surgery study (CASS), coronary arteriography is the key diagnostic procedure. In this procedure, a tube is inserted into the heart and fluid injected that is opaque to x-rays. By taking x-ray motion pictures, the coronary arteries may be examined for possible narrowing, or *stenosis*. The three major arterial systems of the heart were judged with respect to narrowing. Narrowing was significant if it was 70% or more of the diameter of the artery. Because the angiographic films are a key diagnostic tool and are important in the decision about the appropriateness of bypass surgery, the quality of the arteriography was monitored and the amount of agreement was ascertained.

Table 7.8 presents the results for randomly selected films with two readings. One reading was that of the patient's clinical site and was used for therapeutic decisions. The angiographic film was then sent to another clinical site designated as a quality control site. The quality control site read the films blindly, that is, without knowledge of the clinical site's reading. From these readings, the amount of disease was classified as "none" (entirely normal), "zero-vessel disease but some disease," and one-, two-, and three-vessel disease.

We wish to study the amount of agreement. One possible measure of this is the proportion of the pairs of readings that are the same. This quantity is estimated by adding up the numbers

Table 7.8 Agreement with Respect to Number of Diseased Vessels

Quality Control Site Reading	Clinical Site Reading					
	Normal	Some	One	Two	Three	Total
Normal	13	8	1	0	0	22
Some	6	43	19	4	5	77
One	1	9	155	54	24	243
Two	0	2	18	162	68	250
Three	0	0	11	27	240	278
Total	20	62	204	247	337	870

on the diagonal of the table; those are the numbers where both the clinical and quality control sites read the same quantity. In such a situation, the contingency table will be square. Let r be the number of categories (in the table of this example, $r = 5$). The proportion of cases with agreement is given by

$$P_A = \frac{n_{11} + n_{22} + \cdots + n_{rr}}{n_{..}} = \sum_{i=1}^{r} \frac{n_{ii}}{n_{..}}$$

For this table, the proportion with agreement is given by $P_A = (13+43+155+162+240)/870 = 613/870 \doteq 0.7046$.

The proportion of agreement is limited because it is determined heavily by the proportions of people in the various categories. Consider, for example, a situation where each of two judges places 90% of the measurements in one category and 10% in the second category, such as in the following array:

81	9	90
9	1	10
90	10	100

Here there is no association whatsoever between the two measurements. In fact, the chi-square value is precisely zero by design; there is no more agreement between the patients than that expected by chance. Nevertheless, because both judges have a large proportion of the cases in the first category, in 82% of the cases there is agreement; that is, $P_A = 0.82$. We have a paradox: On the one hand, the agreement seems good (there is an agreement 82% of the time); on the other hand, the agreement is no more than can be expected by chance. To have a more useful measure of the amount of agreement, the *kappa statistic* was developed to adjust for the amount of agreement that one expects purely by chance.

If one knows the totals of the different rows and columns, the proportion of observations expected to agree by chance is given by the following equation:

$$P_C = \frac{n_{1\cdot}n_{\cdot 1} + \cdots + n_{r\cdot}n_{\cdot r}}{n_{..}^2} = \sum_{i=1}^{r} \frac{n_{i\cdot}n_{\cdot i}}{n_{..}^2}$$

For the angiography example, the proportion of agreement expected by chance is given by

$$P_C = \frac{22 \times 20 + 77 \times 62 + 243 \times 204 + 250 \times 247 + 278 \times 337}{870^2} \doteq 0.2777$$

The kappa statistic uses the fact that the best possible agreement is 1 and that, by chance, one expects an agreement P_C. A reasonable measure of the amount of agreement is the proportion of difference between 1 and P_C that can be accounted for by actual observed agreement. That is, kappa is the ratio of the agreement actually observed minus the agreement expected by chance, divided by 1 (which corresponds to perfect agreement), minus the agreement expected by chance:

$$\kappa = \frac{P_A - P_C}{1 - P_C}$$

For our example, the computed value of kappa is

$$\kappa = \frac{0.7046 - 0.2777}{1 - 0.2777} \doteq 0.59$$

The kappa statistic runs from $-P_C/(1 - P_C)$ to 1. If the agreement is totally by chance, the expected value is zero. Kappa is equal to 1 if and only if there is complete agreement between the two categorizations [Cohen, 1968; Fleiss, 1981].

Since the kappa statistic is generally used where it is clear that there will be statistically significant agreement, the real issue is the amount of agreement. κ is a measure of the amount of agreement. In our example, one can state that 59% of the difference between perfect agreement and the agreement expected by chance is accounted for by the agreement between the clinical and quality control reading sites.

Now that we have a parameter to measure the amount of agreement, we need to consider the effect of the sample size. For small samples, the estimation of κ will be quite variable; for larger samples it should be quite good. For relatively large samples, when there is no association, the variance of the estimate is estimated as follows:

$$\text{var}_0(\kappa) = \frac{P_C + P_C^2 - \sum_{i=1}^{r}(n_{i\cdot}^2 n_{\cdot i} + n_{i\cdot} n_{\cdot i}^2)/n_{\cdot\cdot}^3}{n_{\cdot\cdot}(1 - P_C)^2}$$

The subscript on $\text{var}_0(\kappa)$ indicates that it is the variance under the null hypothesis. The standard error of the estimate is the square root of this quantity. κ divided by the standard error is approximately a standard normal variable when there is no association between the quantities. This may be used as a statistical test for association in lieu of the chi-square test [Fleiss et al., 1969].

A more useful function of the general standard error is construction of a confidence interval for the true κ. A $100(1-\alpha)\%$ confidence interval for the population value of κ for large samples is given by

$$(\kappa - z_{1-\alpha/2}\sqrt{\text{var}(\kappa)}, \kappa + z_{1-\alpha/2}\sqrt{\text{var}(\kappa)})$$

The estimated standard error, allowing for association, is the square root of

$$\text{var}(\kappa) = \frac{\sum_{i=1} \frac{n_{ii}}{n_{\cdot\cdot}} \left[1 - \left(\frac{n_{i\cdot} + n_{\cdot i}}{n_{\cdot\cdot}}\right)(1-\kappa)\right]^2 + \sum_{i \neq j}\sum \frac{n_{ij}}{n_{\cdot\cdot}} \left[\left(\frac{n_{\cdot i} + n_{j\cdot}}{n_{\cdot\cdot}}\right)(1-\kappa)\right]^2 - [\kappa - P_C(1-\kappa)]^2}{n_{\cdot\cdot}(1 - P_C)^2}$$

For our particular example, the estimated variance of κ is

$$\text{var}(\kappa) = 0.000449$$

The standard error of κ is approximately 0.0212. The 95% confidence interval is

$$(0.57 - 1.96 \times 0.0212, 0.57 + 1.96 \times 0.0212) \doteq (0.55, 0.63)$$

A very comprehensive discussion of the use of κ in medical research can be found in Kraemer et al. [2002], and a discussion in the context of other ways to measure agreement is given by Nelson and Pepe [2000].

The kappa statistic has drawbacks. First, as indicated, the small sample variance is quite complicated. Second, while the statistic is supposed to adjust for marginal agreement is does not really do so (see, e.g., Agresti [2002, p. 453]). Third, κ ignores the ordering of the categories (see Maclure and Willett [1987]). Finally, it is difficult to embed κ in a statistical model: as, for example, a function of the odds ratio or correlation coefficient. Be sure to consider alternatives to kappa when measuring agreement; for example, the odds ratio and logistic regression as in Chapter 6 or the log-linear models discussed in the next section.

*7.5 LOG-LINEAR MODELS

For the first time we will examine statistical methods that deal with more than two variables at one time. Such methods are important for the following reasons: In one dimension, we have been able to summarize data with the normal distribution and its two parameters, the mean and the variance, or equivalently, the mean and the standard deviation. Even when the data did not appear normally distributed, we could get a feeling for our data by histograms and other graphical methods in one dimension. When we observe two numbers at the same time, or are working with two-dimensional data, we can plot the points and examine the data visually. (This is discussed further in Chapter 9. Even in the case of two variables, we shall see that it is useful to have models summarizing the data.) When we move to three variables, however, it is much harder to get a "feeling" for the data. Possibly, in three dimensions, we could construct visual methods of examining the data, although this would be difficult. With more than three variables, such physical plots cannot be obtained; although mathematicians may think of space and time as being a four-dimensional space, we, living in a three-dimensional world, cannot readily grasp what the points mean. In this case it becomes very important to simplify our understanding of the data by fitting a model to the data. *If* the model fits, it may summarize the complex situation very succinctly. In addition, the model may point out relationships that may reasonably be understood in a simple way. The fitting of probability models or distributions to many variables at one time is an important topic.

The models are necessarily mathematically complex; thus, the reader needs discipline and perseverance to work through and understand the methods. It is a very worthwhile task. Such methods are especially useful in the analysis of observational biomedical data. We now proceed to our first model for multiple variables, the log-linear model.

Before beginning the details of the actual model, we define some terms that we will be using. The models we investigate are for *multivariate categorical data*. We already know the meaning of *categorical data*: values of a variable or variables that put subjects into one of a finite number of categories. The term *multivariate* comes from the prefix *multi-*, meaning "many," and *variate*, referring to variables; the term refers to multiple variables at one time.

Definition 7.1. *Multivariate data* are data for which each observation consists of values for more than one random variable on each experimental unit. *Multivariate statistical analysis* consists of data analysis of multivariate data.

The majority of data collected are, in fact, multivariate data. If one measures systolic and diastolic blood pressure on each subject, there are two variables—thus, multivariate data. If we administer a questionnaire on the specifics of brushing teeth, flossing, and so on, the response of a person to each question is a separate variable, and thus one has multivariate data. Strictly speaking, some of the two-way contingency table data we have looked at are multivariate data since they cross-classify by two variables. On the other hand, tables that arose from looking at one quantity in different subgroups are not multivariate when the group was not observed on experimental units picked from a population but was part of a data collection or experimental procedure.

Additional terminology is included in the term *log-linear models*. We already have an idea of the meaning of a model. Let us consider the two terms *log* and *linear*. The logarithm was discussed in connection with the likelihood ratio chi-square statistics. (In this section, and indeed throughout this book, the logarithm will be to the base e.) Recall, briefly some of the properties of the logarithm. Of most importance to us is that the log of the product of terms is the sum of the individual logs. For example, if we have three numbers, a, b, and c (all positive), then

$$\ln(abc) = \ln a + \ln b + \ln c$$

Here, "ln" represents the *natural logarithm*, the log to the base e. Recall that by the definition of natural log, if one exponentiates the logarithm—that is, takes the number e to the power

represented by the logarithm—one gets the original number back:

$$e^{\ln a} = a$$

Inexpensive hand calculators compute both the logarithm and the exponential of a number. If you are rusty with such manipulations, Problem 7.24 will give you practice in the use of logarithms and exponentials.

The second term we have used is the term *linear*. It is associated with a straight line or a linear relationship. For two variables x and y, y is a linear function of x if $y = a + bx$, where a and b are constants. For three variables, x, y, and z, z is a linear function of x and y if $z = a + bx + cy$, where a, b, and c are constant. In general, in a linear relationship, one *adds* a constant multiple for each of the variables involved. The linear models we use will look like the following: Let

$$g_{ij}^{IJ}$$

be the logarithm of the probability that an observation falls into the ijth cell in the two-dimensional contingency table. Let there be I rows and J columns. One possible model would be

$$g_{ij}^{IJ} = u + u_i^I + u_j^J$$

(For more detail on why the term *linear* is used for such models, see Note 7.4.)

We first consider the case of two-way tables. Suppose that we want to fit a model for independence. We know that independence in terms of the cell probabilities π_{ij} is equivalent to the following equation:

$$\pi_{ij} = \pi_{i\cdot}\pi_{\cdot j}$$

If we take logarithms of this equation and use the notation g_{ij} for the natural log of the cell probability, the following results:

$$g_{ij} = \ln \pi_{ij} = \ln \pi_{i\cdot} + \ln \pi_{\cdot j}$$

When we denote the natural logs of $\pi_{i\cdot}$ and $\pi_{\cdot j}$ by the quantities h_i^I and h_j^J, we have

$$g_{ij} = h_i^I + h_j^J$$

The quantities h_i^I and h_j^J are not all independent. They come from the marginal probabilities for the I row variables and the J column variables. For example, the h_i^I's satisfy the equation

$$e^{h_1^I} + e^{h_2^I} + \cdots + e^{h_I^I} = 1$$

This equation is rather awkward and unwieldy to work with; in particular, given $I - 1$ of the h_i's, determination of the other coefficient takes a bit of work. It is possible to choose a different normalization of the parameters if we add a constant. Rewrite the equation above as follows:

$$g_{ij} = \left(\sum_{i'=1}^{I} \frac{h_{i'}^I}{I}\right) + \left(\sum_{j'=1}^{J} \frac{h_{j'}^J}{J}\right) + \left(h_i^I - \sum_{i'=1}^{I} \frac{h_{i'}^I}{I}\right) + \left(h_j^J - \sum_{j'=1}^{J} \frac{h_{j'}^J}{J}\right)$$

The two quantities in parentheses farthest to the right both add to zero when we sum over the indices i and j, respectively. In fact, that is why those terms were added and subtracted. Thus, we can rewrite the equation for g_{ij} as follows:

$$g_{ij} = u + u_i^I + u_j^J, \qquad i = 1, \ldots, I, \quad j = 1, \ldots, J$$

where

$$\sum_{i=1}^{I} u_i^I = 0, \ \sum_{j=1}^{J} u_j^J = 0$$

It is easier to work with this normalization. Note that this is a linear model for the log of the cell probability π_{ij}; that is, this is a log-linear model.

Recall that estimates for the $\pi_{i\cdot}$ and $\pi_{\cdot j}$ were $n_{i\cdot}/n_{\cdot\cdot}$ and $n_{\cdot j}/n_{\cdot\cdot}$, respectively. If one follows through all of the mathematics involved, estimates for the parameters in the log-linear model result. At this point, we shall slightly abuse our notation by using the same notation for both the population parameter values and the estimated parameter values from the sample at hand. The estimates are

$$u = \frac{1}{I}\sum_{i=1}^{I} \ln \frac{n_{i\cdot}}{n_{\cdot\cdot}} + \frac{1}{J}\sum_{j=1}^{J} \ln \frac{n_{\cdot j}}{n_{\cdot\cdot}}$$

$$u_i^I = \ln \frac{n_{i\cdot}}{n_{\cdot\cdot}} - \frac{1}{I}\sum_{i'=1}^{I} \ln \frac{n_{i'\cdot}}{n_{\cdot\cdot}}$$

$$u_j^J = \ln \frac{n_{\cdot j}}{n_{\cdot\cdot}} - \frac{1}{J}\sum_{j'=1}^{I} \ln \frac{n_{\cdot j'}}{n_{\cdot\cdot}}$$

From these estimates we get fitted values for the number of observations in each cell. This is done as follows: By inserting the estimated parameters from the log-linear model and then taking the exponential, we have an estimate of the probability that an observation falls into the ijth cell. Multiplying this by $n_{\cdot\cdot}$, we have an estimate of the number of observations we should see in the cell if the model is correct. In this particular case, the fitted value for the ijth cell turns out to be the expected value from the chi-square test presented earlier in this chapter, that is, $n_{i\cdot}n_{\cdot j}/n_{\cdot\cdot}$.

Let us illustrate these complex formulas by finding the estimates for one of the examples above.

Example 7.1. (*continued*) We know that for the 2×4 table, we have the following values:

$$n_{\cdot 1} = 18, \quad n_{\cdot 2} = 31, \quad n_{\cdot 3} = 16, \quad n_{\cdot 4} = 72, \quad n_{1\cdot} = 69, \quad n_{2\cdot} = 68, \quad n_{\cdot\cdot} = 137$$

$$\ln(n_{1\cdot}/n_{\cdot\cdot}) \doteq -0.6859, \qquad \ln(n_{2\cdot}/n_{\cdot\cdot}) \doteq -0.7005$$

$$\ln(n_{\cdot 1}/n_{\cdot\cdot}) \doteq -2.0296, \qquad \ln(n_{\cdot 2}/n_{\cdot\cdot}) \doteq -1.4860$$

$$\ln(n_{\cdot 3}/n_{\cdot\cdot}) \doteq -2.1474, \qquad \ln(n_{\cdot 4}/n_{\cdot\cdot}) \doteq -0.6433$$

With these numbers, we may compute the parameters for the log-linear model. They are

$$u \doteq \frac{-0.6859 - 0.7005}{2} + \frac{-2.0296 - 1.4860 - 2.1474 - 0.6433}{4}$$
$$\doteq -0.6932 - 1.5766 = -2.2698$$

$$u_1^I \doteq -0.6859 - (-0.6932) \doteq 0.0073 \qquad u_1^J \doteq -2.0296 - (-1.5766) \doteq -0.4530$$
$$u_2^I \doteq -0.7004 - (-0.6932) \doteq -0.0073 \qquad u_2^J \doteq -1.4860 - (-1.5766) \doteq 0.0906$$
$$u_3^J \doteq -2.1474 - (-1.5766) \doteq -0.5708$$
$$u_4^J \doteq -0.6433 - (-1.5766) \doteq 0.9333$$

The larger the value of the coefficient, the larger will be the cell probability. For example, looking at the two values indexed by i, the second state having a minus sign will lead to a slightly smaller contribution to the cell probability than the term with the plus sign. (This is also clear from the marginal probabilities, which are 68/137 and 69/137.) The small magnitude of the term means that the difference between the two I state values has very little effect on the cell probability. We see that of all the contributions for the j variable values, $j = 4$ has the biggest effect, 1 and 3 have fairly large effects (tending to make the cell probability small), while 2 is intermediate.

The chi-square goodness of fit and the likelihood ratio chi-square statistics that may be applied to this setting are

$$X^2 = \sum \frac{(\text{observed} - \text{fitted})^2}{\text{fitted}}$$
$$\text{LRX}^2 = 2 \sum \left(\text{observed} \ln \frac{\text{observed}}{\text{fitted}} \right)$$

Finally, if the model for independence does not hold, we may add more parameters. We can find a log-linear model that will fit any possible pattern of cell probabilities. The equation for the log of the cell probabilities is given by the following:

$$g_{ij} = u + u_i^I + u_j^J + u_{ij}^{IJ}, \qquad i = 1, \ldots, I, \quad j = 1, \ldots, J$$

where

$$\sum_{i=1}^{I} u_i^I = 0, \qquad \sum_{j=1}^{J} u_j^J = 0, \qquad \sum_{i=1}^{I} u_{ij}^{IJ} = 0, \qquad \sum_{j=1}^{J} u_{ij}^{IJ} = 0$$

It seems rather paradoxical, or at least needlessly confusing, to take a value indexed by i and j and to set it equal to the sum of four values, including some indexed by i and j; the right-hand side is much more complex than the left-hand side. The reason for doing this is that, usually, the full (or saturated) model, which can give any possible pattern of cell probabilities, is not desirable. It is hoped during the modeling effort that the data will allow a simpler model, which would allow a simpler interpretation of the data. In the case at hand, we examine the possibility of the simpler interpretation that the two variables are independent. If they are not, the particular model is not too useful.

Note two properties of the fitted values. First, in order to fit the independence model, where each term depends on at most one factor or one variable, we only needed to know the marginal values of the frequencies, the $n_{i\cdot}$ and $n_{\cdot j}$. We did not need to know the complete distribution of the frequencies to find our fitted values. Second, when we had fit values to the frequency table, the fitted values summed to the marginal value used in the estimation; that is, if we sum across i or j, the sum of the expected values is equal to the sum actually observed.

At this point it seems that we have needlessly confused a relatively easy matter: the analysis of two-way contingency tables. If only two-way contingency tables were involved, this would be a telling criticism; however, the strength of log-linear models appears when we have more than two cross-classified categorical variables. We shall now discuss the situation for three cross-classified categorical variables. The analyses may be extended to any number of variables, but such extensions are not done in this book.

Suppose that the three variables are labeled X, Y, and Z, where the index i is used for the X variable, j for the Y variable, and k for the Z variable. (This is to say that X will take values $1, \ldots, I$, Y will take on $1, \ldots, J$, and so on.) The methods of this section are illustrated by the following example.

Example 7.5. The study of Weiner et al. [1979] is used in this example. The study involves exercise treadmill tests for men and women. Among men with chest pain thought probably to be angina, a three-way classification of the data is as follows: One variable looks at the resting electrocardiogram and tells whether or not certain parts of the electrocardiogram (the ST- and T-waves) are normal or abnormal. Thus, $J = 2$. A second variable considers whether or not the exercise test was positive or negative ($I = 2$). A positive exercise test shows evidence of an ischemic response (i.e., lack of appropriate oxygen to the heart muscles for the effort being exerted). A positive test is thought to be an indicator of coronary artery disease. The third variable was an evaluation of the coronary artery disease as determined by coronary arteriography. The disease is classified as normal or minimal disease, called zero-vessel disease, one-vessel disease, and multiple-vessel disease ($K = 3$). The data are presented in Table 7.9.

The most general log-linear model for the three factors is given by the following extension of the two-factor work:

$$g_{ijk} = u + u_i^I + u_j^J + u_k^K + u_{ij}^{IJ} + u_{ik}^{IK} + u_{jk}^{JK} + u_{ijk}^{IJK}$$

where

$$\sum_{i=1}^{I} u_i^I = \sum_{j=1}^{J} u_j^J = \sum_{k=1}^{K} u_k^K = 0$$

$$\sum_{i=1}^{I} u_{ij}^{IJ} = \sum_{j=1}^{J} u_{ij}^{IJ} = \sum_{i=1}^{I} u_{ik}^{IK} = \sum_{k=1}^{K} u_{ik}^{IK} = \sum_{j=1}^{J} u_{jk}^{JK} = \sum_{k=1}^{K} u_{jk}^{JK} = 0$$

$$\sum_{i=1}^{I} u_{ijk}^{IJK} = \sum_{j=1}^{J} u_{ijk}^{IJK} = \sum_{k=1}^{K} u_{ijk}^{IJK} = 0$$

Table 7.9 Exercise Test Data

		Number of Vessels Diseased (K)		
Exercise Test Response (I)	Resting Electrocardiogram ST- and T-Waves (J)	0 ($k = 1$)	1 ($k = 2$)	2 or 3 ($k = 3$)
+	Normal ($j = 1$)	30	64	147
($i = 1$)	Abnormal ($j = 2$)	17	22	80
−	Normal ($j = 1$)	118	46	38
($i = 2$)	Abnormal ($j = 2$)	14	7	11

Source: Weiner et al. [1979].

In other words, there is a u term for every possible combination of the variables, including no variables at all. For each term involving one or more variables, if we sum over any one variable, the sum is equal to zero. The term involving I, J, and K is called a *three-factor term*, or a *second-order interaction term*; in general, if a coefficient involves M variables, it is called an M*-factor term* or an $(M-1)$th*-order interaction term*.

With this notation we may now formulate a variety of simpler models for our three-way contingency table. For example, the model might be any one of the following simpler models:

$$H_1 : g_{ijk} = u + u_i^I + u_j^J + u_k^K$$
$$H_2 : g_{ijk} = u + u_i^I + u_j^J + u_k^K + u_{ij}^{IJ}$$
$$H_3 : g_{ijk} = u + u_i^I + u_j^J + u_k^K + u_{ij}^{IJ} + u_{ik}^{IK} + u_{jk}^{JK}$$

The notation has become so formidable that it is useful to introduce a shorthand notation for the hypotheses. One or more capitalized indices contained in brackets will indicate a hypothesis where the terms involving that particular set of indices as well as any terms involving subsets of the indices are to be included in the model. Any terms not specified in this form are assumed not to be in the model. For example,

$$[IJ] \longrightarrow u + u_i^I + u_j^J + u_{ij}^{IJ}$$
$$[K] \longrightarrow u + u_k^K$$
$$[IJK] \longrightarrow u + u_i^I + u_j^J + u_k^K + u_{ij}^{IJ} + u_{ik}^{IK} + u_{jk}^{JK} + u_{ijk}^{IJK}$$

The formulation of the three hypotheses given above in this notation would be simplified as follows:

$$H_1 : [I][J][K]$$
$$H_2 : [IJ][K]$$
$$H_3 : [IJ][IK][JK]$$

This notation describes a *hierarchical hypothesis*; that is, if we have two factor terms containing, say, variables I and J, we also have the one-factor terms for the same variables. The hypothesis would not be written $[IJ][I][J]$, for example, because the last two parts would be redundant, as already implied by the first. Using this bracket notation for the three-factor model, there are eight possible hypotheses of interest. All except the most complex one have a simple interpretation in terms of the probability relationships among the factors X, Y, and Z. This is given in Table 7.10.

Hypotheses 5, 6, and 7 are of particular interest. Take, for example, hypothesis 5. This hypothesis states that if you take into account the X variable, there is no association between Y and Z. In particular, if one only looks at the two-way table of Y and Z, an association may be seen, because in fact they are associated. However, if hypothesis 5 holds, one could then conclude that the association is due to interaction with the variable X and could be "explained away" by taking into account the values of X.

There is a relationship between hypotheses involving the bracket notation and the corresponding tables that one gets from the higher-dimensional contingency table. For example, consider the term $[IJ]$. This is related to the contingency table one gets by summing over K (i.e., over the Z variable). In general, a contingency table that results from summing over the cells for one or more variables in a higher-dimensional contingency table is called a *marginal table*. Very simple examples of marginal tables are the marginal total column and the marginal total row along the bottom of the two-way table.

Table 7.10 Three-Factor Hypotheses and their Interpretation

Hypothesis	Meaning in Words	Hypothesis Restated in Terms of the π_{ijk}'s
1. $[I][J][K]$	X, Y, and Z are independent	$\pi_{ijk} = \pi_{i\cdot\cdot}\pi_{\cdot j\cdot}\pi_{\cdot\cdot k}$
2. $[IJ][K]$	Z is independent of X and Y	$\pi_{ijk} = \pi_{ij\cdot}\pi_{\cdot\cdot k}$
3. $[IK][J]$	Y is independent of X and Z	$\pi_{ijk} = \pi_{i\cdot k}\pi_{\cdot j\cdot}$
4. $[I][JK]$	X is independent of Y and Z	$\pi_{ijk} = \pi_{i\cdot\cdot}\pi_{\cdot jk}$
5. $[IJ][IK]$	For X known, Y and Z are independent; that is, Y and Z are conditionally independent given X	$\pi_{ijk} = \pi_{ij\cdot}\pi_{i\cdot k}/\pi_{i\cdot\cdot}$
6. $[IJ][JK]$	X and Z are conditionally independent given Y	$\pi_{ijk} = \pi_{ij\cdot}\pi_{\cdot jk}/\pi_{\cdot j\cdot}$
7. $[IK][JK]$	X and Y are conditionally independent given Z	$\pi_{ijk} = \pi_{i\cdot k}\pi_{\cdot jk}/\pi_{\cdot\cdot k}$
8. $[IJ][IK][JK]$	No three-factor interaction	No simple form

Using the idea of marginal tables, we can discuss some properties of fits of the various hierarchical hypotheses for log-linear models. Three facts are important:

1. The fit is estimated using only the marginal tables associated with the bracket terms that state the hypothesis. For example, consider hypothesis 1, the independence of the X, Y, and Z variables. To compute the estimated fit, one only needs the one-dimensional frequency counts for the X, Y, and Z variables individually and does not need to know the joint relationship between them.
2. Suppose that one looks at the fitted estimates for the frequencies and sums the *fitted* values to give marginal tables. The marginal sum for the fit is equal to the marginal table for the actual data set when the marginal table is involved in the fitting.
3. The chi-square and likelihood ratio chi-square tests discussed above using the observed and fitted values still hold.

We consider fitting hypothesis 5 to the data of Example 7.5. The hypothesis stated that if one knows the response to the maximal treadmill test, the resting electrocardiogram ST- and T-wave abnormalities are independent of the number of vessels diseased. The observed frequencies and the fitted frequencies, as well as the values of the u-parameters for this model, are given in Table 7.11.

The relationship between the fitted parameter values and the expected, or fitted, number of observations in a cell is given by the following equations:

$$\widehat{\pi}_{ijk} = e^{u+u_i^I+u_j^J+u_k^K+u_{ij}^{IJ}+u_{ik}^{IK}}$$

The fitted value $= n_{\cdot\cdot\cdot}\widehat{\pi}_{ijk}$, where $n_{\cdot\cdot\cdot}$ is the total number of observations.
For these data, we compute the right-hand side of the first equation for the (1,1,1) cell. In this case,

$$\begin{aligned}\widehat{\pi}_{111} &= \exp(-2.885 + 0.321 + 0.637 - 0.046 - 0.284 - 0.680)\\ &= e^{-2.937} \doteq 0.053\end{aligned}$$

$$\text{fitted value} \doteq 594 \times 0.053 \doteq 31.48$$

Table 7.11 Fitted Model for the Hypothesis That the Resting Electrocardiogram ST- and T-Wave (Normal or Abnormal) Is Independent of the Number of Vessels Diseased (0, 1, and 2–3) Conditionally upon Knowing the Exercise Response (+ or −)

Cell (i, j, k)	Observed	Fitted	u-Parameters
(1,1,1)	30	31.46	$u = -2.885$
(1,1,2)	64	57.57	$u_1^I = -u_2^I = 0.321$
(1,1,3)	147	151.97	$u_1^J = -u_2^J = 0.637$
(1,2,1)	17	15.54	$u_1^K = -0.046, u_2^K = -0.200$
(1,2,2)	22	28.43	$u_3^K = 0.246$
(1,2,3)	80	75.04	$u_{1,1}^{IJ} = -0.284, u_{1,2}^{IJ} = 0.284$
(2,1,1)	118	113.95	$u_{2,1}^{IJ} = 0.284, u_{2,2}^{IJ} = -0.284$
(2,1,2)	46	45.75	$u_{1,1}^{IK} = -0.680, u_{1,2}^{IK} = 0.078$
(2,1,3)	38	42.30	$u_{1,3}^{IK} = 0.602$
(2,2,1)	14	18.05	$u_{2,1}^{IK} = 0.680, u_{2,2}^{IK} = -0.078$
(2,2,2)	7	7.25	$u_{2,3}^{IK} = -0.602$
(2,2,3)	11	6.70	

where exp(argument) is equal to the number e raised to a power equal to the argument. The computed value of 31.48 differs slightly from the tabulated value, because the tabulated value came from computer output that carried more accuracy than the accuracy used in this computation.

We may test whether the hypothesis is a reasonable fit by computing the chi-square value under this hypothesis. The likelihood ratio chi-square value is computed as follows:

$$\text{LRX}^2 = 2(30 \ln \frac{30}{31.46} + \cdots + 11 \ln \frac{11}{6.70}) \doteq 6.86$$

To assess the statistical significance we need the degrees of freedom to examine the chi-square value. For the log-linear model the degrees of freedom is given by the following rule:

Rule 1. The chi-square statistic for model fit of a log-linear model has degrees of freedom equal to the total number of cells in the table ($I \times J \times K$) minus the number of independent parameters fitted. By *independent parameters* we mean the following: The number of parameters fitted for the X variable is $I - 1$ since the u_i^I terms sum to zero. For each of the possible terms in the model, the number of independent parameters is given in Table 7.12.

For the particular model at hand, the number of independent parameters fitted is the sum of the last column in Table 7.13. There are 12 cells in the table, so that the number of degrees of freedom is $12 - 8$, or 4. The p-value for a chi-square of 6.86 for four degrees of freedom is 0.14, so that we cannot reject the hypothesis that this particular model fits the data.

We are now faced with a new consideration. Just because this model fits the data, there may be other models that fit the data as well, including some simpler model. In general, one would like as simple a model as possible (Occam's razor); however, models with more parameters generally give a better fit. In particular, a simpler model may have a p-value much closer to the significance level that one is using. For example, if one model has a p of 0.06 and is simple, and a slightly more complicated model has a p of 0.78, which is to be preferred? If the sample size is small, the p of 0.06 may correspond to estimated cell values that differ considerably from the actual values. For a very large sample, the fit may be excellent. There is no hard-and-fast rule in the trade-off between the simplicity of the model and the goodness of the fit. To understand the data, we are happy with the simple model that fits fairly well, although presumably, it is not precisely the probability model that would fit the entirety of the population values. Here we would hope for considerable scientific understanding from the simple model.

Table 7.12 Degrees of Freedom for Log-Linear Model Chi-Square

Term	Number of Parameters
u	1
u_i^I	$I-1$
u_j^J	$J-1$
u_k^K	$K-1$
u_{ij}^{IJ}	$(I-1)(J-1)$
u_{ik}^{IK}	$(I-1)(K-1)$
u_{jk}^{JK}	$(J-1)(K-1)$
u_{ijk}^{IJK}	$(I-1)(J-1)(K-1)$

Table 7.13 Parameters for Example 7.5

	Number of Parameters	
Model Terms	General	Example 7.5
u	1	1
u_i^I	$I-1$	1
u_j^J	$J-1$	1
u_k^K	$K-1$	2
u_{ij}^{IJ}	$(I-1)(J-1)$	1
u_{ik}^{IK}	$(I-1)(K-1)$	2

Table 7.14 Chi-Square Goodness-of-Fit Statistics for Example 7.5 Data

Model	d.f.	LRX^2	p-Value	X^2
$[I][J][K]$	7	184.21	< 0.0001	192.35
$[IJ][K]$	6	154.35	< 0.0001	149.08
$[IK][J]$	5	36.71	< 0.0001	34.09
$[I][JK]$	5	168.05	< 0.0001	160.35
$[IJ][IK]$	4	6.86	0.14	7.13
$[IJ][JK]$	4	138.19	< 0.0001	132.30
$[IK][JK]$	3	20.56	0.0001	21.84
$[IJ][IK][JK]$	2	2.96	0.23	3.03

For this example, Table 7.14 shows for each of the eight possible models the degrees of freedom (d.f.), the LRX^2 value (with its corresponding p-value for reference), and the "usual" goodness-of-fit chi-square value. We see that there are only two possible models if we are to simplify at all rather than using the entire data set as representative. They are the model fit above and the model that contains each of the three two-factor interactions. The model fit above is simpler, while the other model below has a larger p-value, possibly indicating a better fit. One way of approaching this is through what are called *nested hypotheses*.

Definition 7.2. One hypothesis is *nested* within another if it is the special case of the other hypothesis. That is, whenever the nested hypothesis holds it necessarily implies that the hypothesis it is nested in also holds.

If nested hypotheses are considered, one takes the difference between the likelihood ratio chi-square statistic for the more restrictive hypothesis, minus the likelihood ratio chi-square statistic for the more general hypothesis. This difference will itself be a chi-square statistic if the special case holds. The degrees of freedom of the difference is equal to the difference of freedom for the two hypotheses. In this case, the chi-square statistic for the difference is $6.86 - 2.96 = 3.90$. The degrees of freedom are $4 - 2 = 2$. This corresponds to a p-value of more than 0.10. At the 5% significance level, there is marginal evidence that the more general hypothesis does fit the data better than the restrictive hypothesis. In this case, however, because of the greater simplicity of the restrictive hypothesis, one might choose it to fit the data. Once again, there is no hard and fast answer to the payoff between fit of the data and simplicity of interpretation of a hypothesis.

This material is an introduction to log-linear models. There are many extensions, some of which are mentioned briefly in the Notes at the end of the chapter. An excellent introduction to log-linear models is given in Fienberg [1977]. Other elementary books on log-linear models are those by Everitt [1992] and Reynolds [1977]. A more advanced and thorough treatment is given by Haberman [1978, 1979]. A text touching on this subject and many others is Bishop et al. [1975].

NOTES

7.1 Testing Independence in Model 1 and Model 2 Tables

This note refers to Section 7.2.

1. *Model 1*. The usual null hypothesis is that the results are statistically independent. That is (assuming row variable $= i$ and column variable $= j$):

$$P[i \text{ and } j] = P[i]P[j]$$

The probability on the left-hand side of the equation is π_{ij}. From Section 7.2, the marginal probabilities are found to be

$$\pi_{i\cdot} = \sum_{j=1}^{c} \pi_{ij} \quad \text{and} \quad \pi_{\cdot j} = \sum_{i=1}^{r} \pi_{ij}$$

The null hypothesis of statistical independence of the variables is

$$H_0 : \pi_{ij} = \pi_{i\cdot}\pi_{\cdot j}$$

Consider how one might estimate these probabilities under two circumstances:

- **a.** Without assuming the variables are independent.
- **b.** Assuming the variables are independent.

In the first instance we are in a binomial situation. Let a success be the occurrence of the ijth pair. Let

$$n_{\cdot\cdot} = \sum_{i=1}^{r} \sum_{j=1}^{c} n_{ij}$$

The binomial estimate for π_{ij} is the number of successes divided by the number of trials:

$$p_{ij} = \frac{n_{ij}}{n_{..}}$$

If we assume independence, the natural approach is to estimate $\pi_{i\cdot}$ and $\pi_{\cdot j}$. But the occurrence of state i for the row variable is also a binomial event. The estimate of $\pi_{i\cdot}$ is the number of occurrences of state i for the row variable ($n_{i\cdot}$) divided by the sample size ($n_{..}$). Thus,

$$p_{i\cdot} = \frac{n_{i\cdot}}{n_{..}}$$

Similarly, $\pi_{\cdot j}$ is estimated by

$$p_{\cdot j} = \frac{n_{\cdot j}}{n_{..}}$$

Under the hypothesis of statistical independence, the estimate of $\pi_{i\cdot}\pi_{\cdot j} = \pi_{ij}$ is

$$\frac{n_{i\cdot}n_{\cdot j}}{n_{..}^2}$$

The chi-square test will involve comparing estimates of the expected number of observations with and without assuming independence. With independence, we expect to observe $n_{..}\pi_{ij}$ entries in the ijth cell. This is estimated by

$$n_{..}p_{i\cdot}p_{\cdot j} = \frac{n_{i\cdot}n_{\cdot j}}{n_{..}}$$

2. *Model 2*. Suppose that the row variable identifies the population. The null hypothesis is that all r populations have the same probabilities of taking on each value of the column variable. That is, for any two rows, denoted by i and i', say, and all j,

$$H_0 : \pi_{ij} = \pi_{i'j}$$

As in the first part above, we want to estimate these probabilities in two cases:

- **a.** Without assuming anything about the probabilities.
- **b.** Under H_0, that is, assuming that each population has the same distribution of the column variable.

Under (a), if no assumptions are made, π_{ij} is the probability of obtaining state j for the column variable in the $n_{i\cdot}$ trials from the ith population. Again the binomial estimate holds:

$$p_{ij} = \frac{n_{ij}}{n_{i\cdot}}$$

If the null hypothesis holds, we may "pool" all our $n_{..}$ trials to get a more accurate estimate of the probabilities. Then the proportion of times the column variable takes on state j is

$$p_j = \frac{n_{\cdot j}}{n_{...}}$$

As in the first part, let us calculate the numbers we expect in the cells under (a) and (b). If (a) holds, the expected number of successes in the $n_i.$ trials of the ith population is $n_i.\pi_{ij}$. We estimate this by

$$n_i.(\frac{n_{ij}}{n_i.}) = n_{ij}$$

Under the null hypothesis, the expected number $n_i.\pi_{ij}$ is estimated by

$$n_i.p_j = \frac{n_i.n._j}{n..}$$

In summary, under either model 1 or model 2, the null hypothesis is reasonably tested by comparing n_{ij} with $n_i.n._j/n...$

7.2 Measures of Association in Contingency Tables

Suppose that we reject the null hypothesis of no association between the row and column categories in a contingency table. It is useful then to have a measure of the degree of association. In a series of papers, Goodman and Kruskal [1979] argue that no single measure of association for contingency tables is best for all purposes. Measures must be chosen to help with the problem at hand. Among the measures they discuss are the following:

1. *Measure* λ_C. Call the row variable or row categorization R and the column variable or column categorization C. Suppose that we wish to use the value of R to predict the value of C. The measure λ_C is an estimate of the proportion of the errors made in classification if we do not know R that can be eliminated by knowing R before making a prediction. From the data, λ_C is given by

$$\lambda_C = \frac{\left(\sum_{i=1}^{r} \max_j n_{ij}\right) - \max_j n._j}{n.. - \max_j n._j}$$

λ_R is defined analogously.

2. *Symmetric measure* λ. λ_C does not treat the row and column classifications symmetrically. A symmetric measure may be found by assuming that the chances are 1/2 and 1/2 of needing to predict the row and column variables, respectively. The proportion of the errors in classification that may be reduced by knowing the other (row or column variable) when predicting is estimated by λ:

$$\lambda = \frac{\left(\sum_{i=1}^{r} \max_j n_{ij}\right) + \left(\sum_{j=1}^{c} \max_i n_{ij}\right) - \max_i n_i. - \max_j n._j}{2n.. - (\max_i n_i. + \max_j n._j)}$$

3. *Measure* γ *for ordered categories*. In many applications of contingency tables the categories have a natural order: for example, last grade in school, age categories, number of weeks hospitalized. Suppose that the orderings of the variables correspond to the indices i and j for the rows and columns. The γ measure is the difference in the proportion of the time that the two measures have the same ordering minus the proportion of the time that they have the opposite ordering, when there are no ties. Suppose that the indices for the two observations are i, j and i, j. The indices have the same ordering if

$$(1) i < i \text{ and } j < j \quad \text{or} \quad (2) i > i \text{ and } j > j$$

They have the opposite ordering if

$$(1)\ i < \boldsymbol{i} \text{ and } j > \boldsymbol{j} \quad \text{or} \quad (2)\ i > \boldsymbol{i} \text{ and } j < \boldsymbol{j}$$

There are ties if $i = \boldsymbol{i}$ and/or $j = \boldsymbol{j}$. The index is

$$\gamma = \frac{2S - 1 + T}{1 - T}$$

where

$$S = 2\sum_{i=1}^{r}\sum_{j=1}^{c} \frac{n_{ij}\sum_{\boldsymbol{i}>i}\sum_{\boldsymbol{j}>j} n_{\boldsymbol{ij}}}{n_{..}^2}$$

and

$$T = \frac{\sum_{i=1}^{r}\left(\sum_{j=1}^{c} n_{ij}\right)^2 + \sum_{j=1}^{c}\left(\sum_{i=1}^{r} n_{ij}\right)^2 - \sum_{i=1}^{r}\sum_{j=1}^{c} n_{ij}^2}{n_{..}^2}$$

4. *Karl Pearson's contingency coefficient*, C. Since the chi-square statistic (X^2) is based on the square of the difference between the values observed in the contingency table and the values estimated, if association does not hold, it is reasonable to base a measure of association on X^2. However, chi-square increases as the sample size increases. One would like a measure of association that estimated a property of the total population. For this reason, $X^2/n..$ is used in the next three measures. Karl Pearson proposed the measure C.

$$C = \sqrt{\frac{X^2/n..}{1 + X^2/n..}}$$

5. *Cramer's* V. Harold Cramer proposed a statistic with values between 0 and 1. The coefficient can actually attain both values.

$$V = \sqrt{\frac{X^2/n..}{\text{minimum}(r-1, c-1)}}$$

6. *Tshuprow's* T, *and the* Φ^2 *coefficient*. The two final coefficients based on X^2 are

$$T = \sqrt{\frac{X^2/n..}{\sqrt{(r-1)(c-1)}}} \quad \text{and} \quad \Phi = \sqrt{X^2/n..}$$

We compute these measures of association for two contingency tables. The first table comes from the Robertson [1975] seat belt paper discussed in the text. The data are taken for 1974 cars with the interlock system. They relate age to seat belt use. The data and the column percents are given in Table 7.15. Although the chi-square value is 14.06 with $p = 0.007$, we can see from the column percentages that the relationship is weak. The coefficients of association are

$$\begin{array}{llll} \lambda_C = 0, & \lambda = 0.003, & C = 0.08, & T = 0.04 \\ \lambda_R = 0.006, & \gamma = -0.03, & V = 0.06, & \Phi = 0.08 \end{array}$$

Table 7.15 Seat Belt Data by Age

	Age (Years)			Column Percents (Age)		
Belt Use	<30	30–49	≥ 50	< 30	30–49	≥ 50
Lap and shoulder	206	580	213	45	50	45
Lap only	36	125	65	8	11	14
None	213	459	192	47	39	41
				100	100	100

In general, all these coefficients lie between -1 or 0, and $+1$. They are zero if the variables are not associated at all. These values are small, indicating little association.

Consider the following data from Weiner et al. [1979], relating clinical diagnosis of chest pain to the results of angiographic examination of the coronary arteries:

	Frequency (Vessels Diseased)			**Row Percents (Vessels Diseased)**			
Chest Pain	**0**	**1**	**2 or 3**	**0**	**1**	**2 or 3**	**Total**
Definite angina	66	135	419	11	22	68	101
Probable angina	179	139	276	30	23	46	99
Nonischemic	197	39	15	78	16	6	100

The chi-square statistic is 418.48 with a p-value of effectively zero. Note that those with definite angina were very likely (89%) to have disease, and even the probability of having multivessel disease was 68%. Chest pain thought to be nonischemic was associated with "no disease" 78% of the time. Thus, there is a strong relationship. The measures of association are

$$\lambda_C = 0.24, \quad \lambda = \ \ 0.20, \quad C = 0.47, \quad T = 0.38$$
$$\lambda_R = 0.16, \quad \gamma = -0.64, \quad V = 0.38, \quad \Phi = 0.53$$

More information on these measures of association and other potentially useful measures is available in Reynolds [1977] and in Goodman and Kruskal [1979].

7.3 Testing for Symmetry in a Contingency Table

In a square table, one sometimes wants to test the table for symmetry. For example, when examining two alternative means of classification, one may be interested not only in the amount of agreement (κ), but also in seeing that the pattern of misclassification is the same. In this case, estimate the expected value in the ijth cell by $(n_{ij} + n_{ji})/2$. The usual chi-square value is appropriate with $r(r-1)/2$ degrees of freedom, where r is the number of rows (and columns). See van Belle and Cornell [1971].

7.4 Use of the Term Linear in Log-Linear Models

Linear equations are equations of the form $y = c + a_1X_1 + a_2X_2 + \cdots + a_nX_n$ for some variables $X_1, \ldots, X_n$ and constants c and $a_1, \ldots, a_n$. The log-linear model equations can be put into this form. For concreteness, consider the model $[IJ][K]$, where $i = 1, 2$, $j = 1, 2$, and $k = 1, 2$. Define new variables as follows:

$$X_1 = \begin{cases} 1 & \text{if } i = 1, \\ 0 & \text{if } i = 2; \end{cases} \qquad X_2 = \begin{cases} 1 & \text{if } i = 2, \\ 0 & \text{if } i = 1; \end{cases} \qquad X_3 = \begin{cases} 1 & \text{if } j = 1, \\ 0 & \text{if } j = 2; \end{cases}$$

$$X_4 = \begin{cases} 1 & \text{if } j = 2, \\ 0 & \text{if } j = 1 \end{cases} \qquad X_5 = \begin{cases} 1 & \text{if } k = 1, \\ 0 & \text{if } k = 2 \end{cases} \qquad X_6 = \begin{cases} 1 & \text{if } k = 2, \\ 0 & \text{if } k = 1, \end{cases}$$

$$X_7 = \begin{cases} 1 & \text{if } i = 1,\ j = 1, \\ 0 & \text{otherwise;} \end{cases} \qquad X_8 = \begin{cases} 1 & \text{if } i = 1,\ j = 2, \\ 0 & \text{otherwise;} \end{cases}$$

$$X_9 = \begin{cases} 1 & \text{if } i = 2,\ j = 1, \\ 0 & \text{otherwise} \end{cases} \qquad X_{10} = \begin{cases} 1 & \text{if } i = 2,\ j = 2, \\ 0 & \text{otherwise} \end{cases}$$

Then the model is

$$\log \pi_{ijk} = u + u_1^I X_1 + u_2^I X_2 + u_1^J X_3 + u_2^J X_4 + u_1^K X_5 + u_2^K X_6 + u_{1,1}^{IJ} X_7 + u_{1,2}^{IJ} X_8 + u_{2,1}^{IJ} X_9 + u_{2,2}^{IJ} X_{10}$$

Thus the log-linear model is a linear equation of the same form as $y = c + a_1 X_1 + a_2 X_2 + \cdots + a_n X_n$. We discuss such equations in Chapter 11. Variables created to pick out a certain state (e.g., $i = 2$) by taking the value 1 when the state occurs, and taking the value 0 otherwise, are called *indicator* or *dummy variables*.

7.5 Variables of Constant Probability in Log-Linear Models

Consider the three-factor X, Y, and Z log-linear model. Suppose that Z terms are entirely "omitted" from the model, for example, $[IJ]$ or

$$\log \pi_{ijk} = u + u_i^I + u_j^J + u_{ij}^{IJ}$$

The model then fits the situation where Z is uniform on its state; that is,

$$P[Z = k] = \frac{1}{k}, \qquad k = 1, \ldots, K$$

7.6 Log-Linear Models with Zero Cell Entries

Zero values in the contingency tables used for log-linear models are of two types. Some arise as *sampling zeros* (values could have been observed, but were not in the sample). In this case, if zeros occur in marginal tables used in the estimation:

- Only certain u-parameters may be estimated.
- The chi-square goodness-of-fit statistic has reduced degrees of freedom.

Some zeros are necessarily *fixed*; for example, some genetic combinations are fatal to offspring and will not be observed in a population. Log-linear models can be used in the analysis (see Bishop et al., [1975]; Haberman [1979]; Fienberg [1977]).

7.7 GSK Approach to Higher-Dimensional Contingency Tables

The second major method of analyzing multivariate contingency tables is due to Grizzle et al. [1969]. They present an analysis method closely related to multiple regression (Chapter 11). References in which this method are considered are Reynolds [1977] and Kleinbaum et al. [1988].

PROBLEMS

In Problems 7.1–7.9, perform the following tasks as well as any other work requested. Problems 7.1–7.5 are taken from the seat belt paper of Robertson [1975].

(a) If a table of expected values is given with one or more missing values, compute the missing values.

(b) If the chi-square value is not given, compute the value of the chi-square statistic.

(c) State the degrees of freedom.

(d) State whether the chi-square p-value is less than or greater than 0.01, 0.05, and 0.10 .

(e) When tables are given with missing values for the adjusted residual values, p-values and $(r-1)\times(c-1)\times p$-values, fill in the missing values.

(f) When percent tables are given with missing values, fill in the missing percentages for the row percent table, column percent table, and total percent table, as applicable.

(g) Using the 0.05 significance level, interpret the findings. (Exponential notation is used for some numbers, e.g., $34,000 = 3.4\times10^4 = 3.4\text{E}4$; $0.0021 = 2.1\times10^{-3} = 2.1\text{E}-3$.)

(h) Describe verbally what the row and column percents mean. That is, "of those with zero vessels diseased . . . ," and so on.

7.1 In 1974 vehicles, seat belt use was considered in association with the ownership of the vehicle. ("L/S" means "both lap and shoulder belt.")

	Ownership			
Belt Use	**Individuals**	**Rental**	**Lease**	**Other Corporate**
L/S	583	145	86	182
Lap Only	139	24	24	31
None	524	59	74	145

Expected				Adjusted Residuals			
615.6	112.6	90.9	176.9	−2.99	?	−0.76	0.60
134.7	24.7	19.9	38.7	0.63	−0.15	1.02	−1.44
495.7	90.7	?	?	2.65	−4.55	?	0.31

$p-$Values				$(r-1)\times(c-1)\times p-$ Values			
0.0028	5E − 6	0.4481	0.5497	0.017	3E − 5	1+	1+
0.5291	0.8821	?	?	1+	1+	1+	0.8869
0.0080	5.3E − 6	0.8992	0.7586	0.048	3E − 5	1+	1+

Column Percents			
47	?	47	51
11	11	13	9
42	?	?	41

$d.f. =?$
$X^2 = 26.72$

7.2 In 1974 cars, belt use and manufacturer were also examined. One hundred eighty-nine cars from "other" manufacturers are not entered into the table.

	Manufacturer					
Belt Use	**GM**	**Toyota**	**AMC**	**Chrysler**	**Ford**	**VW**
L/S	498	25	36	74	285	33
Lap only	102	5	12	29	43	11
None	334	18	30	67	259	51

Adjusted Residuals					
3.06	0.33	−0.65	−1.70	−0.69	−3.00
0.49	−0.03	?	2.89	−3.06	0.33
−3.43	−0.32	−0.23	−0.08	2.63	?

$p-$Values					
0.0022	0.7421	0.5180	0.0898	0.4898	0.0027
0.6208	0.9730	?	0.0039	0.0022	0.7415
0.0006	0.7527	?	0.9366	0.0085	0.0043

Column Percents					
53	52	46	44	49	?
11	10	15	17	7	?
36	38	38	39	?	?

d.f. =?
$X^2 = 34.30$

7.3 The relationship between belt use and racial appearance in the 1974 models is given here. Thirty-four cases whose racial appearance was "other" are excluded from this table.

	Racial Appearance	
Belt Use	**White**	**Black**
L/S	866	116
Lap only	206	20
None	757	102

Expected		Adjusted Residuals		$p-$Values	
868.9	113.1	−0.40	0.40	0.69	0.69
?	26.0	1.33	−1.33	?	?
?	98.9	?	?	0.67	0.67

d.f. =?
X^2 =?

7.4 The following data are given as the first example in Note 7.2. In the 1974 cars, belt use and age were cross-tabulated.

Expected			Adjusted Residuals		
217.59	556.64	?	?	2.06	−1.23
49.22	125.93	?	−2.26	−0.13	?
?	481.42	194.39	2.67	−2.00	−0.25

$p-$Values			$(r-1) \times (c-1) \times p-$Values		
0.219	?	0.217	0.88	0.16	0.87
0.024	0.895	0.017	?	?	?
0.007	?	0.799	0.03	0.18	1+

Column %s			Row %s			
45	?	45	?	?	?	d.f. =?
?	?	14	16	55	29	$X^2 = 14.06$
47	39	41	25	53	22	

7.5 In the 1974 cars, seat belt use and gender of the driver were related as follows:

	Gender	
Belt Use	**Female**	**Male**
L/S	267	739
Lap only	85	142
None	261	606

Expected		Adjusted Residuals		$p-$Values	
?	?	?	?	0.0104	0.0104
66.3	160.7	2.90	−2.90	0.0038	0.0038
253.1	613.9	0.77	−0.77	?	?

$(r-1) \times (c-1) \times p-$Values	
0.02	0.02
0.01	0.01
?	?

Column %s		Total %s		
44	50	13	35	d.f. =?
14	?	4	?	X^2 =?
43	?	?	?	

7.6 The data are given in the second example of Note 7.2. The association of chest pain classification and amount of coronary artery disease was examined.

Adjusted Residuals			$(r-1)\times(c-1)\times p$–Values		
−13.95	0.33	12.54	1.0E − 30	1+	4.3E − 27
?	1.57	−1.27	1+	0.47	0.82
18.32	−2.47	−14.80	1.4E − 40	0.05	8.8E − 33

Row %s			Column %s			
11	22	68	?	43	59	d.f. =?
30	23	46	?	44	39	$X^2 = 418.48$
?	?	?	?	12	2	

7.7 Peterson et al. [1979] studied the age at death of children who died from sudden infant death syndrome (SIDS). The deaths from a variety of causes, including SIDS, were cross-classified by the age at death, as in Table 7.16, taken from death records in King County, Washington, over the years 1969–1977.

Table 7.16 Death Data for Problem 7.7[a]

	Age at Death				
Cause	0 Days	1–6 Days	2–4 Weeks	5–26 Weeks	27–51 Weeks
Hyaline membrane disease	19	51	7	0	0
Respiratory distress syndrome	68	191	46	0	3
Asphyxia of the newborn	105	60	7	4	2
Immaturity	104	34	3	0	0
Birth injury	115	105	17	2	0
Congenital malformation	79	101	72	75	32
Infection	7	38	36	43	18
SIDS	0	0	24	274	24
All other	60	51	28	58	35

[a] d.f. =?; $X^2 = 1504.18$.

(a) The values of $(r-1)\times(c-1)\times p$-value for the adjusted residual are given here multiplied by −1 if the adjusted residual is negative and multiplied by +1 if the adjusted residual is positive.

−1+	1.4E − 9	−1+	−3.8E − 5	−0.89
−0.43	4.6E − 26	1+	−3.3E − 20	−3.2E − 3
3.0E − 18	1+	−0.02	−4.5E − 10	−0.18
2.3E − 26	−1+	−5.8E − 3	−1.2E − 9	−0.08
1.1E − 11	3.9E − 4	−0.42	−3.8E − 15	−1.6E − 3
−0.20	−1+	7.7E − 6	−1+	0.12
−1.1E − 8	−1+	1.3E − 5	0.90	6.5E − 3
−31.2E − 25	−3.4E − 28	−0.19	1.7E − 57	1+
−1+	−0.03	1+	1+	2.9E − 9

What is the distribution of SIDS cases under the null hypothesis that all causes have the same distribution?

(b) What percent display (row, column, or total) would best emphasize the difference?

7.8 Morehead [1975] studied the relationship between the retention of intrauterine devices (IUDs) and other factors. The study participants were from New Orleans, Louisiana. Tables relating retention to the subjects' age and to parity (the number of pregnancies) are studied in this problem (one patient had a missing age).

(a) Was age related to IUD retention?

Age	Continuers	Terminators
19–24	41	48
25–29	50	40
30+	63	27

Expected		Adjusted Residuals		$p-$Values	
50.95	?	−2.61	2.61	0.0091	0.0091
51.52	38.5	−0.40	0.40	?	?
51.52	38.5	?	?	0.0027	0.0027

Column %s		Row %s		
26.6	41.7	46.1	53.9	d.f. =?
?	34.8	?	?	X^2 =?
?	23.5	70.0	30.0	

(b) The relationship of parity and IUD retention gave these data:

Parity	Continuers	Terminators
1–2	59	53
3–4	39	34
5+	57	28

Adjusted Residuals		Total %s		
−1.32	1.32	?	19.6	d.f. =?
−0.81	0.81	14.4	?	$X^2 = 4.74$
?	?	21.1	?	

7.9 McKeown et al. [1952] investigate evidence that the environment is involved in infantile pyloric stenosis. The relationship between the age at onset of the symptoms in days, and the rank of the birth (first child, second child, etc.) was given as follows:

	Age at Onset of Symptoms (Days)						
Birth Rank	**0–6**	**7–13**	**14–20**	**21–27**	**28–34**	**35–41**	**≥ 42**
1	42	41	116	140	99	45	58
2	28	35	63	53	49	23	31
≥ 3	26	21	39	48	39	14	23

(a) Find the expected value (under independence) for cell ($i = 2, j = 3$). For this cell compute (observed - expected)^2/ expected.

(b) The chi-square statistic is 13.91. What are the degrees of freedom? What can you say about the p-value?

(c) In the paper, the authors present, the column percents, not the frequencies, as above. Fill in the missing values in both arrays below. The arrangement is the same as the first table.

44	42	53	58	53	55	52
29	36	29	?	26	28	28
?	?	18	20	21	17	21

The adjusted residual p-values are

0.076	0.036	0.780	0.042	0.863	0.636	0.041
0.667	0.041	0.551	0.035	0.710	0.874	0.734
0.084	0.734	?	0.856	0.843	0.445	0.954

What can you conclude?

(d) The authors note that the first two weeks appear to have different patterns. They also present the data as:

	Age at Onset (Days)	
Birth Rank	**0–13**	**≥ 14**
1	83	458
2	63	219
≥ 3	47	163

For this table, $X^2 = 8.35$. What are the degrees of freedom? What can you say about the p-value?

(e) Fill in the missing values in the adjusted residual table, p-value table, and column percent table. Interpret the data.

Adjusted Residuals		***p*−Values**		**Column %s**	
−2.89	2.89	0.0039	0.0039	43	55
?	?	0.065	0.065	33	?
1.54	−1.54	?	?	24	?

(f) Why is it crucial to know whether prior to seeing these data the investigators had hypothesized a difference in the parity distribution between the first two weeks and the remainder of the time period?

Problems 7.10–7.16 deal with the chi-square test for trend. The data are from a paper by Kennedy et al. [1981] relating operative mortality during coronary bypass operations

to various risk factors. For each of the tables, let the scores for the chi-square test for trend be consecutive integers. For each of the tables:

a. Compute the chi-square statistic for trend. Using Table A.3, give the strongest possible statement about the p-value.

b. Compute, where not given, the percentage of operative mortality, and plot the percentage for the different categories using equally spaced intervals.

c. The usual chi-square statistic (with $k - 1$ degrees of freedom) is given with its p-value. When possible, from Table A.3 or the chi-square values, tell which statistic is more highly significant (has the smallest p-value). Does your figure in (b) suggest why?

7.10 The amount of anginal (coronary artery disease) chest pain is categorized by the Canadian Heart Classification from mild (class I) to severe (class IV).

	Anginal Pain Classification			
Surgical Mortality	**I**	**II**	**III**	**IV**
Yes	6	19	47	59
No	242	1371	2494	1314
% surgical mortality	2.4	1.4	1.8	?

Usual
$X^2 = 31.19$
$p = 7.7\text{E} - 7$

7.11 Congestive heart failure occurs when the heart is not pumping sufficient blood. A heart damaged by a myocardial infarction, heart attack, can incur congestive heart failure. A score from 0 (good) to 4 (bad) for congestive heart failure is related to operative mortality.

	Congestive Heart Failure Score				
Operative Mortality	**0**	**1**	**2**	**3**	**4**
Yes	73	50	13	12	4
No	4480	1394	404	164	36
% operative mortality	1.6	3.4	?	6.8	10.0

Usual
$X^2 = 46.45$
$p = 1.8\text{E} - 9$

7.12 A measure of left ventricular performance, or the pumping action of the heart, is the *ejection fraction*, which is the percentage of the blood in the left ventricle that is pumped during the beat. A high number indicates a more efficient performance.

	Ejection Fraction (%)				
Operative Mortality	**< 19**	**20–29**	**30–39**	**40–49**	**≥ 50**
Yes	1	4	5	22	74
No	14	88	292	685	3839
% operative mortality	6.7	?	?	3.1	1.9

Usual
$X^2 = 8.34$
$p = 0.080$

7.13 A score was derived from looking at how the wall of the left ventricle moved while the heart was beating (details in CASS [1981]). A score of 5 was normal; the larger the score, the worse the motion of the left ventricular wall looked. The relationship to operative mortality is given here.

	Wall Motion Score					Usual
Operative Mortality	**5–7**	**8–11**	**12–15**	**16–19**	**≥ 20**	$X^2 = 28.32$
Yes	65	36	32	10	2	$p = 1.1\text{E} - 5$
No	3664	1605	746	185	20	
% operative mortality	1.7	2.2	?	5.1	9.1	

What do you conclude about the relationship? That is, if you were writing a paragraph to describe this finding in a medical journal, what would you say?

7.14 After the blood has been pumped from the heart, and the pressure is at its lowest point, a low blood pressure in the left ventricle is desirable. This left ventricular end diastolic pressure [LVEDP] is measured in millimeters of mercury (mmHg).

	LVEDP				Usual
Operative Mortality	**0–12**	**13–18**	**19–24**	**≥24**	$X^2 = 34.49$
Yes	56	43	22	26	$p = 1.6\text{E} - 7$
No	3452	1692	762	416	
% operative mortality	?	2.5	2.8	5.9	

7.15 The number of diseased vessels and operative mortality are given by:

	Diseased Vessels			Usual
Operative Mortality	**1**	**2**	**3**	$X^2 = 7.95$
Yes	17	43	91	$p = 0.019$
No	1196	2018	3199	
% operative mortality	1.4	2.1	?	

7.16 The left main coronary artery, if occluded (i.e., totally blocked), blocks two of the three major arterial vessels to the heart. Such an event almost always leads to death. Thus, people with much narrowing of the left main coronary artery usually receive surgical therapy. Is this narrowing also associated with higher surgical mortality?

	Percentage Narrowing				Usual
Operative Mortality	**0–49**	**50–74**	**75–89**	**≥ 90**	$X^2 = 37.75$
Yes	116	8	10	19	$p = 3.2\text{E} - 8$
No	5497	486	268	222	
% operative mortality	2.1	1.6	?	7.9	

7.17 In Robertson's [1975] seat belt study, the observers (unknown to them) were checked by sending cars through with a known seat belt status. The agreement numbers between the observers and the known status were:

	Belt Use in Vehicles Sent		
Belt Use Reported	**S/L**	**Lap Only**	**No Belt**
Shoulder and lap	28	2	0
Lap only	3	33	6
No belt	0	15	103

(a) Compute P_A, P_C, and κ.

(b) Construct a 95% confidence interval for κ.

(c) Find the two-sided p-value for testing $\kappa = 0$ (for the entire population) by using $Z = \kappa/\mathrm{SE}_0(\kappa)$.

7.18 The following table is from [Fisher et al., 1982]. The coronary artery tree has considerable biological variability. If the right coronary artery is normal-sized and supplies its usual share of blood to the heart, the circulation of blood is called *right dominant*. As the right coronary artery becomes less important, the blood supply is characterized as balanced and then *left dominant*. The data for the clinical site and quality control site joint readings of angiographic films are given here.

	Dominance (Clinical Site)		
Dominance (QC Site)	**Left**	**Balanced**	**Right**
Left	64	7	4
Balanced	4	35	32
Right	8	21	607

(a) Compute P_A, P_C, and κ (Section 7.4).

(b) Find var(κ) and construct a 90% confidence interval for the population value of κ.

7.19 Example 7.4 discusses the quality control data for the CASS arteriography (films of the arteries). A separate paper by Wexler et al. [1982] examines the study of the left ventricle. Problem 7.12 describes the ejection fraction. Clinical site and quality control site readings of ejection gave the following table:

	Ejection Fraction (QC Site)		
Ejection Fraction (Clinical Site)	**≥ 50%**	**30–49%**	**< 30%**
≥ 50%	302	27	5
30–49%	40	55	9
< 30%	1	9	18

(a) Compute P_A, P_C, and κ.

(b) Find SE(κ) and construct a 99% confidence interval for the population value of κ.

7.20 The value of κ depends on how we construct our categories. Suppose that in Example 7.4 we combine normal and other zero-vessel disease to create a zero-vessel disease category. Suppose also that we combine two- and three-vessel disease into a multivessel-disease category. Then the table becomes:

Vessels Diseased (QC Site)	Vessels Diseased (Clinical Site)		
	0	**1**	**Multi-**
0	70	20	9
1	10	155	78
Multi-	2	29	497

(a) Compute P_A, P_C, and κ.

(b) Is this kappa value greater than or less than the value in Example 7.4? Will this always occur? Why?

(c) Construct a 95% confidence interval for the population value of κ.

7.21 Zeiner-Henriksen [1972a] compared personal interview and postal inquiry methods of assessing infarction. His introduction follows:

> The questionnaire developed at the London School of Hygiene and Tropical Medicine and later recommended by the World Health Organization for use in field studies of cardiovascular disease has been extensively used in various populations. While originally developed for personal interviews, this questionnaire has also been employed for postal inquiries. The postal inquiry method is of course much cheaper than personal interviewing and is without interviewer error.
>
> A Finnish–Norwegian lung cancer study offered an opportunity to evaluate the repeatability at interview of the cardiac pain questionnaire, and to compare the interview symptom results with those of a similar postal inquiry. The last project, confined to a postal inquiry of the chest pain questions in a sub-sample of the 4092 men interviewed, was launched in April 1965, $2\frac{1}{2}$ to 3 years after the original interviews.
>
> The objective was to compare the postal inquiry method with the personal interview method as a means of assessing the prevalence of angina and possible infarction ....

The data are given in Table 7.17.

(a) Compute P_A, P_C, and κ.

(b) Construct a 90% confidence interval for the population value of κ ($\sqrt{\text{var}(\kappa)} = 0.0231$).

(c) Group the data in three categories by:

(**i**) combining PI + AP, PI only, and AP only; (**ii**) combining the two PI/AP negatives categories; (**iii**) leaving "incomplete" as a third category. Recompute P_A, P_C, and κ. (This new grouping has the categories "cardiovascular symptoms," "no symptoms," and "incomplete.")

Table 7.17 Interview Data for Problem 7.21

	Interview						
				PI/AP Negative			
Postal Inquiry	PI[a] + AP[a]	PI Only	AP Only	Nonspecific	Other	Incomplete	Total
PI + AP	23	15	9	6	—	1	54
PI only	14	18	14	24	8	—	78
AP only	3	5	20	12	17	3	60
PI/AP negative							
Nonspecific	2	8	8	54	24	5	101
Other	2	3	5	62	279	1	352
Incomplete	—	2	—	22	37	—	61
Total	44	51	56	180	365	10	706

[a]PI, possible infarction; AP, angina pectoris.

Table 7.18 Interview Results for Problem 7.22

	Interview					
				I− A−		
Postal Inquiry[a]	I+ A+	I+ A−	I− A+	Nonspecific	Other	Total
I+ A+	11	3	1	1	—	16
I+ A−	2	14	—	4	—	20
I− A+	5	2	7	1	1	16
I− A−						
Nonspecific	1	4	5	39	9	58
Other	1	8	6	40	72	127
Total	20	31	19	85	82	237

[a]I+, positive infarction; I−, negative infarction; A+ and A−, positive or negative indication of angina.

7.22 In a follow-up study, Zeiner-Henriksen [1972b] evaluated the reproducibility of their method using reinterviews. Table 7.18 shows the results.

(a) Compute P_A, P_C, and κ for these data.

(b) Construct a 95% confidence interval for the population value of kappa. $\text{SE}(\kappa) = 0.043$.

(c) What is the value of the Z-statistic for testing no association that is computed from kappa and its estimated standard error $\sqrt{\text{var}_0(\kappa)} = 0.037$?

7.23 Weiner et al. [1979] studied men and women with suspected coronary disease. They were studied by a maximal exercise treadmill test. A positive test ($\geq$ 1 mm of ST-wave depression on the exercise electrocardiogram) is thought to be indicative of coronary artery disease. Disease was classified into zero-, one- (or single-), and multivessel disease. Among people with chest pain thought probably anginal (i.e., due to coronary artery disease), the following data are found.

	Vessels Diseased		
Category	**0**	**1**	**Multi-**
Males, + test	47	86	227
Males, − test	132	53	49
Females, + test	62	28	44
Females, − test	83	14	9

The disease prevalence is expected to be significantly different in men and women. We want to see whether the exercise test is related to disease separately for men and women.

(a) For males, the relationship of + or − test and disease give the data below. Fill in the missing values, interpret these data, and answer the questions.

	Vessels Diseased		
Exercise Test	**0**	**1**	**Multi-**
+	47	86	?
−	132	?	49

Expected			Adjusted Residuals		
108.5	84.2	167.3	0+	0.73	0+
70.5	54.8	?	0+	0.73	0+

Row Percents			Column Percents		
?	?	63.1	26.3	61.9	?
56.4	22.6	20.9	73.7	38.1	?

Formulate a question for which the row percents would be a good method of presenting the data. Formulate a question where the column percents would be more appropriate.

***7.24** **(a)** Find the natural logarithms, ln x, of the following x: 1.24, 0.63, 0.78, 2.41, 2.7182818, 1.00, 0.10. For what values do you think ln x is positive? For what values do you think ln x is negative? (A plot of the values may help.)

(b) Find the exponential, e^x, of the following x: −2.73, 5.62, 0.00, −0.11, 17.3, 2.45. When is e^x less than 1? When is e^x greater than 1?

(c) $\ln(a \times b) = \ln a + \ln b$. Verify this for the following pairs of a and b:

a:	2.00	0.36	0.11	0.62
b:	0.50	1.42	0.89	0.77

(d) $e^{a+b} = e^a \cdot e^b$. Verify this for the following pairs of numbers:

a:	−2.11	0.36	0.88	−1.31
b:	2.11	1.59	−2.67	−0.45

Table 7.19 Angina Data for Problem 7.25

Model[a]	d.f.	LRX^2	$p-$Value
$[I\ ][J][K]$	7	114.41	0+
$[I\ ][K]$	6	103.17	0+
$[IK\ ][J]$	5	26.32	0+
$[I\ ][JK]$	5	94.89	0+
$[IJ\ ][IK]$	4	15.08	0.0045
$[IJ\ ][JK]$	4	83.65	0+
$[IK\ ][JK]$	3	6.80	0.079
$[IJ\ ][IK]\ [JK]$	2	2.50	0.286

[a] I, J, and K refer to variables as in Example 7.5.

Table 7.20 Hypothesis Data for Problem 7.25

Cell (i, j, k)	Observed	r Fitted	u-Parameters
(1,1,1)	17	18.74	$u = -3.37$
(1,1,2)	86	85.01	$u_1^I = -u_2^I = 0.503$
(1,1,3)	244	243.25	$u_1^J = -u_2^J = 0.886$
(1,2,1)	5	3.26	$u_1^K = -0.775, u_2^K = -0.128, u_3^K = 0.903$
(1,2,2)	14	14.99	$u_{1,1}^{IJ} = -u_{1,2}^{IJ} = -u_{2,1}^{IJ} = u_{2,2}^{IJ} = -0.157$
(1,2,3)	99	99.75	$u_{1,1}^{IK} = -u_{2,1}^{IK} = -0.728$
(2,1,1)	42	40.26	$u_{1,2}^{IK} = -u_{2,2}^{IK} = 0.143$
(2,1,2)	31	31.99	$u_{1,3}^{IK} = -u_{2,3}^{IK} = 0.586$
(2,1,3)	37	37.75	$u_{1,1}^{JK} = -u_{2,1}^{JK} = 0.145$
(2,2,1)	2	3.74	$u_{1,2}^{JK} = -u_{2,2}^{JK} = 0.138$
(2,2,2)	4	3.01	$u_{1,3}^{JK} = -u_{2,3}^{JK} = -0.283$
(2,2,3)	9	8.25	

***7.25** Example 7.5 uses Weiner et al. [1979] data for cases with probable angina. The results for the cases with definite angina are given in Table 7.19.

(a) Which models are at all plausible?

(b) The data for the fit of the $[IJ][IK][JK]$ hypothesis are given in Table 7.20. Using the u-parameters, compute the fitted value for the (1,2,3) cell, showing that it is (approximately) equal to 99.75 as given.

(c) Using the fact that hypothesis 7 is nested within hypothesis 8, compute the chi-square statistic for the additional gain in fit between the models. What is the p-value (as best as you can tell from the tables)?

***7.26** As in Problem 7.25, the cases of Example 7.5, but with chest pain thought not to be due to heart disease (nonischemic), gave the goodness-of-fit likelihood ratio chi-square statistics shown in Table 7.21.

(a) Which model would you prefer? Why?

(b) For model $[IJ]\ [IK]$, the information on the fit is given in Table 7.22. Using the u-parameter values, verify the fitted value for the (2,1,1) cell.

(c) Interpret the probabilistic meaning of the model in words for the variables of this problem.

Table 7.21 Goodness-of-Fit Data for Problem 7.23

Model	d.f.	LRX^2	$p-$Value
$[I][J][K]$	7	35.26	0+
$[IJ][K]$	6	28.45	0+
$[IK][J]$	5	11.68	0.039
$[I][JK]$	5	32.46	0+
$[IJ][IK]$	4	4.87	0.30
$[IJ][JK]$	4	25.65	0+
$[IK][JK]$	3	8.89	0.031
$[IJ][IK][JK]$	2	2.47	0.29

Table 7.22 Fit Data for Problem 7.23

Cell (i, j, k)	Observed	r Fitted	u-Parameters
(1,1,1)	33	32.51	$u = -3.378$
(1,1,2)	13	12.01	$u_1^I = -u_2^I = 0.115$
(1,1,3)	7	8.48	$u_1^J = -u_2^J = 0.658$
(1,2,1)	13	13.49	$u_1^K = 1.364, u_2^K = -0.097, u_3^K = -1.267$
(1,2,2)	4	4.99	$u_{1,1}^{IJ} = -u_{1,2}^{IJ} = -u_{2,1}^{IJ} = u_{2,2}^{IJ} = -0.218$
(1,2,3)	5	3.52	$u_{1,1}^{IK} = -u_{2,1}^{IK} = -0.584$
(2,1,1)	126	128.69	$u_{1,2}^{IK} = -u_{2,2}^{IK} = -0.119$
(2,1,2)	21	18.75	$u_{1,3}^{IK} = -u_{2,3}^{IK} = 0.703$
(2,1,3)	3	2.56	
(2,2,1)	25	22.31	
(2,2,2)	1	3.25	
(2,2,3)	0	0.44	

***7.27** Willkens et al. [1981] study possible diagnostic criteria for Reiter's syndrome. This rheumatic disease was considered in the context of other rheumatic diseases. Eighty-three Reiter's syndrome cases were compared with 136 cases with one of the following four diagnoses: ankylosing spondylitis, seronegative definite rheumatoid arthritis, psoriatic arthritis, and gonococcal arthritis. A large number of potential diagnostic criteria were considered. Here we consider two factors: the presence or absence of urethritis and/or cervicitis (for females); and the duration of the initial attack evaluated as greater than or equal to one month or less than one month. The data are given in Table 7.23, and the goodness-of-fit statistics are given in Table 7.24.

(a) Fill in the question marks in Table 7.24.

(b) Which model(s) seem plausible (at the 0.05 significance level)?

(c) Since we are looking for criteria to differentiate between Reiter's syndrome and the other diseases, one strategy that makes sense is to assume independence of the disease category ($[K]$) and then look for the largest departures from the observed and fitted cells. The model we want is then $[IJ][K]$. The fit is given in Table 7.25.

Which cell of Reiter's syndrome cases has the largest excess of observed minus fitted?

(d) If you use the cell found in part (c) as your criteria for Reiter's syndrome, what are the specificity and sensitivity of this diagnostic criteria for these cases?

Table 7.23 Reiter's Syndrome Data for Problem 7.27

Urethritis and/or Cervicitis [I]	Disease [K]	Initial Attack [J] <1 Month	Initial Attack [J] ≥1 Month
Yes	Reiter's	2	70
	Other	11	3
No	Reiter's	1	10
	Other	20	132

Table 7.24 Goodness-of-Fit Data for Problem 7.27

Model	d.f.	LRX^2	$p-$Value
$[I\ ][J][\ K]$	?	200.65	?
$[IJ\ ][\ K]$	?	200.41	?
$[IK\ ]][J]$	?	40.63	?
$[I\ ][\ JK]$	?	187.78	?
$[IJ\ ][\ IK]$	?	40.39	?
$[IJ\ ][\ JK]$	?	187.55	?
$[IK\ ][\ JK]$	?	27.76	?
$[IJ\ ][\ IK][\ JK]$	?	5.94	?

Table 7.25 Goodness-of-Fit Data for Problem 7.27

Cell (i, j, k)	Observed	Fitted
(1,1,1)	70	24.33
(1,1,2)	3	48.67
(1,2,1)	2	4.33
(1,2,2)	11	8.67
(2,1,1)	10	47.33
(2,1,2)	132	94.67
(2,2,1)	1	7.00
(2,2,2)	20	14.00

***7.28** We claim in the text that the three-factor log-linear model $[IJ][\ IK]$ means that the J and K variables are independent conditionally upon the I variable. Prove this by showing the following steps:

(a) By definition, Y and Z are independent conditionally upon X if

$$P[Y = j \text{ and } Z = k|X = i] = P[Y = j|X = i]P[Z = k|X = i]$$

Using the probabilities π_{ijk}, show that this is equivalent to

$$\frac{\pi_{ijk}}{\pi_{i\cdot\cdot}} = \left(\frac{\pi_{ij\cdot}}{\pi_{i\cdot\cdot}}\right)\left(\frac{\pi_{i\cdot k}}{\pi_{i\cdot\cdot}}\right)$$

(b) If the equation above holds true, show that

$$\ln \pi_{ijk} = u + u_i^I + u_j^J + u_k^K + u_{ij}^{IJ} + u_{ik}^{IK}$$

where

$$u_{ij}^{IJ} = \ln(\pi_{ij\cdot}) - \frac{1}{I}\sum_{\boldsymbol{i}=1}^{I} \ln(\pi_{\boldsymbol{i}j\cdot}) - \frac{1}{J}\sum_{\boldsymbol{j}=1}^{J} \ln(\pi_{i\boldsymbol{j}\cdot}) + \frac{1}{IJ}\sum_{\boldsymbol{i}=1}^{I}\sum_{\boldsymbol{j}=1}^{J} \ln(\pi_{\boldsymbol{ij}\cdot})$$

$$u_{ik}^{IK} = \ln(\pi_{i\cdot k}) - \frac{1}{I}\sum_{\boldsymbol{i}=1}^{I} \ln(\pi_{\boldsymbol{i}\cdot k}) - \frac{1}{K}\sum_{k=\boldsymbol{1}}^{K} \ln(\pi_{i\cdot\boldsymbol{k}}) + \frac{1}{IK}\sum_{\boldsymbol{i}=1}^{I}\sum_{k=\boldsymbol{1}}^{K} \ln(\pi_{\boldsymbol{i}\cdot\boldsymbol{k}})$$

$$u_i^I = \frac{1}{J}\sum_{\boldsymbol{j}=1}^{J} \ln(\pi_{i\boldsymbol{j}\cdot}) + \frac{1}{K}\sum_{\boldsymbol{k}=1}^{K} \ln(\pi_{i\cdot\boldsymbol{k}}) - \ln(\pi_{i\cdot\cdot}) + \frac{1}{IJ}\sum_{\boldsymbol{i}=1}^{I}\sum_{\boldsymbol{j}=1}^{J} \ln(\pi_{\boldsymbol{ij}\cdot})$$
$$+\frac{1}{IK}\sum_{\boldsymbol{i}=1}^{I}\sum_{\boldsymbol{k}=1}^{K} \ln(\pi_{\boldsymbol{i}\cdot\boldsymbol{k}}) - \frac{1}{I}\sum_{\boldsymbol{i}=1}^{I} \ln(\pi_{\boldsymbol{i}\cdot\cdot})$$

$$u_j^J = \frac{1}{I}\sum_{\boldsymbol{i}=1}^{I} \ln(\pi_{\boldsymbol{i}j\cdot}) - \frac{1}{IJ}\sum_{\boldsymbol{j}=1}^{J}\sum_{\boldsymbol{i}=1}^{I} \ln(\pi_{\boldsymbol{ij}\cdot})$$

$$u_k^J = \frac{1}{I}\sum_{\boldsymbol{i}=1}^{I} \ln(\pi_{\boldsymbol{i}\cdot k}) - \frac{1}{IK}\sum_{\boldsymbol{k}=1}^{K}\sum_{\boldsymbol{i}=1}^{I} \ln(\pi_{\boldsymbol{i}\cdot\boldsymbol{k}})$$

$$u = -\frac{1}{IJ}\sum_{\boldsymbol{i}=1}^{I}\sum_{\boldsymbol{j}=1}^{J} \ln(\pi_{\boldsymbol{ij}\cdot}) - \frac{1}{IK}\sum_{\boldsymbol{i}=1}^{I}\sum_{\boldsymbol{k}=1}^{K} \ln(\pi_{\boldsymbol{i}\cdot\boldsymbol{k}}) - \frac{1}{I}\sum_{\boldsymbol{i}=1}^{I} \ln(\pi_{\boldsymbol{i}\cdot\cdot})$$

(c) If the equation above holds, use $\pi_{ijk} = e^{\ln \pi_{ijk}}$ to show that the first equation then holds.

***7.29** The notation and models for the three-factor log-linear model extend to larger numbers of factors. For example, for variables W, X, Y, and Z (denoted by the indices i, j, k, and l, respectively), the following notation and model correspond:

$$[IJK][L] = u + u_i^I + u_j^J + u_k^K + u_l^L + u_{ij}^{IJ} + u_{ik}^{IK} + u_{jk}^{JK} + u_{ijk}^{IJK}$$

(a) For the four-factor model, write the log-linear u-terms corresponding to the following model notations: **(i)** $[IJ][KL]$; **(ii)** $[IJK][IJL][JKL]$; **(iii)** $[IJ][IK][JK][L]$.

(b) Give the bracket notation for the models corresponding to the u-parameters: **(i)** $u + u_i^I + u_j^J + u_k^K + u_l^L$; **(ii)** $u + u_i^I + u_j^J + u_k^K + u_l^L + u_{ij}^{IJ} + u_{kl}^{KL}$; **(iii)** $u + u_i^I + u_j^J + u_k^K + u_l^L + u_{ij}^{IJ} + u_{ik}^{IK} + u_{il}^{IL} + u_{jk}^{JK} + u_{ijk}^{IJK}$.

***7.30** Verify the values of the contingency coefficients, or measures of association, given in the first example of Note 7.2.

***7.31** Verify the values of the measures of association given in the second example of Note 7.2.

***7.32** Prove the following properties of some of the measures of association, or contingency coefficients, presented in Note 7.2.

(a) $0 \leq \lambda_C \leq 1$. Show by example that 0 and 1 are possible values.

(b) $0 \leq \lambda \leq 1$. Show by example that 0 and 1 are possible values. What happens if the two traits are independent in the sample $n_{ij} = n_{i\cdot} n_{\cdot j}/n_{\cdot\cdot}$?

(c) $-1 \leq \gamma \leq 1$. Can γ be -1 or $+1$? If the traits are independent in the sample, show that $\gamma = 0$. Can $\gamma = 0$ otherwise? If yes, give an example.

(d) $0 < C < 1$.

(e) $0 \leq V \leq 1$.

(f) $0 \leq T \leq 1$ [use part (e) to show this].

(g) Show by example that ϕ^2 can be larger than 1.

***7.33** Compute the contingency coefficients of Note 7.2, omitting γ, for the data of:

(a) Problem 7.1.

(b) Problem 7.5.

REFERENCES

Agresti, A. [2002]. *Categorical Data Analysis*, 2nd ed. Wiley, New York.

Bishop, Y. M. M., Fienberg, S. E., and Holland, P. W. [1975]. *Discrete Multivariate Analysis: Theory and Practice*. MIT Press, Cambridge, MA.

CASS [1981]. (Principal investigators of CASS and their associates); Killip, T. (ed.); Fisher, L., and Mock, M. (assoc. eds.) National Heart, Lung and Blood Institute Coronary Artery Surgery Study. *Circulation*, **63**: part II, I-1 to I-81.

Cohen, J. [1968]. Weighted kappa: nominal scale agreement with provision for scaled disagreement or partial credit. *Psychological Bulletin*, **70**: 213–220.

Everitt, B. S. [1992]. *The Analysis of Contingency Tables*, 2nd ed. Halstead Press, New York.

Fienberg, S. E. [1977]. *The Analysis of Cross-Classified Categorical Data*. MIT Press, Cambridge, MA.

Fisher, L. D., Judkins, M. P., Lesperance, J., Cameron, A., Swaye, P., Ryan, T. J., Maynard, C., Bourassa, M., Kennedy, J. W., Gosselin, A., Kemp, H., Faxon, D., Wexler, L., and Davis, K. [1982]. Reproducibility of coronary arteriographic reading in the Coronary Artery Surgery Study (CASS). *Catheterization and Cardiovascular Diagnosis*, **8**: 565–575. Copyright © 1982 by Wiley-Liss.

Fleiss, J. L., Levin, B., and Park, M. C. [2003]. *Statistical Methods for Rates and Proportions*, 3rd ed. Wiley, New York.

Fleiss, J. L., Cohen, J., and Everitt, B. S. [1969]. Large sample standard errors of kappa and weighted kappa. *Psychological Bulletin*, **72**: 323–327.

Goodman, L. A., and Kruskal, W. H. [1979]. *Measures of Association for Cross-Classifications*. Springer-Verlag, New York.

Grizzle, J. E., Starmer, C. F., and Koch, G. G. [1969]. Analysis of categorical data by linear models. *Biometrics*, **25**: 489–504.

Haberman, S. J. [1978]. *Analysis of Qualitative Data, Vol. 1, Introductory Topics*. Elsevier, New York.

Haberman, S. J. [1979]. *Analysis of Qualitative Data, Vol. 2, New Developments*. Elsevier, New York.

Hitchcock, C. R., Ruiz, E., Sutherland, D., and Bitter, J. E. [1966]. Eighteen-month follow-up of gastric freezing in 173 patients with duodenal ulcer. *Journal of the American Medical Association*, **195**: 115–119.

Kennedy, J. W., Kaiser, G. C., Fisher, L. D., Fritz, J. K., Myers, W., Mudd, J. G., and Ryan, T. J. [1981]. Clinical and angiographic predictors of operative mortality from the collaborative study in coronary artery surgery (CASS). *Circulation*, **63**: 793–802.

Kleinbaum, D. G., Kupper, L. L., Muller, K. E., and Nizam, A. [1997]. *Applied Regression Analysis and Multivariable Methods*, 3rd ed. Brooks/Cole, Pacific Grove, California.

Kraemer, H. C., Periyakoil, V. S., and Noda, A. [2002]. Tutorial in biostatistics: kappa coefficient in medical research. *Statistics in Medicine*, **21**: 2109–2119.

Maclure, M., and Willett, W. C. [1987]. Misinterpretation and misuses of the kappa statistic. *American Journal of Epidemiology*, **126**: 161–169.

Maki, D. G., Weise, C. E., and Sarafin, H. W. [1977]. A semi-quantitative culture method for identifying intravenous-catheter-related infection. *New England Journal of Medicine*, **296**: 1305–1309.

McKeown, T., MacMahon, B., and Record, R. G. [1952]. Evidence of post-natal environmental influence in the aetiology of infantile pyloric stenosis. *Archives of Diseases in Children*, **58**: 386–390.

Morehead, J. E. [1975]. Intrauterine device retention: a study of selected social-psychological aspects. *American Journal of Public Health*, **65**: 720–730.

Nelson, J. C., and Pepe, M. S. [2000]. Statistical description of interrater reliability in ordinal ratings. *Statistical Methods in Medical Research*, **9**: 475–496.

Peterson, D. R., van Belle, G., and Chinn, N. M. [1979]. Epidemiologic comparisons of the sudden infant death syndrome with other major components of infant mortality. *American Journal of Epidemiology*, **110**: 699–707.

Reynolds, H. T. [1977]. *The Analysis of Cross-Classifications*. Free Press, New York.

Robertson, L. S. [1975]. Safety belt use in automobiles with starter-interlock and buzzer-light reminder systems. *American Journal of Public Health*, **65**: 1319–1325. Copyright © 1975 by the American Health Association.

Ruffin, J. M., Grizzle, J. E., Hightower, N. C., McHarcy, G., Shull, H., and Kirsner, J. B. [1969]. A cooperative double-blind evaluation of gastric "freezing" in the treatment of duodenal ulcer. *New England Journal of Medicine*, **281**: 16–19.

Time [1962]. Frozen ulcers. *Time*, May 18, pp. 45–47.

van Belle, G., and Cornell, R. G. [1971]. Strengthening tests of symmetry in contingency tables. *Biometrics*, **27**: 1074–1078.

Wangensteen, C. H., Peter, E. T., Nicoloff, M., Walder, A. I., Sosin, H., and Bernstein, E. F. [1962]. Achieving "physiologic gastrectomy" by gastric freezing. *Journal of the American Medical Association*, **180**: 439–444. Copyright © 1962 by the American Medical Association.

Weiner, D. A., Ryan, T. J., McCabe, C. H., Kennedy, J. W., Schloss, M., Tristani, F., Chaitman, B. R., and Fisher, L. D. [1979]. Correlations among history of angina, ST-segment response and prevalence of coronary-artery disease in the Coronary Artery Surgery Study (CASS). *New England Journal of Medicine*, **301**: 230–235.

Wexler, L., Lesperance, J., Ryan, T. J., Bourassa, M. G., Fisher, L. D., Maynard, C., Kemp, H. G., Cameron, A., Gosselin, A. J., and Judkins, M. P. [1982]. Interobserver variability in interpreting contrast left ventriculograms (CASS). *Catheterization and Cardiovascular Diagnosis*, **8**: 341–355.

Willkens, R. F., Arnett, F. C., Bitter, T., Calin, A., Fisher, L., Ford, D. K., Good, A. E., and Masi, A. T. [1981]. Reiter's syndrome: evaluation of preliminary criteria. *Arthritis and Rheumatism*, **24**: 844–849. Used with permission from J. B. Lippincott Company.

Zeiner-Henriksen, T. [1972a]. Comparison of personal interview and inquiry methods for assessing prevalences of angina and possible infarction. *Journal of Chronic Diseases*, **25**: 433–440. Used with permission of Pergamon Press, Inc.

Zeiner-Henriksen, T. [1972b]. The repeatability at interview of symptoms of angina and possible infarction. *Journal of Chronic Diseases*, **25**: 407–414. Used with permission of Pergamon Press, Inc.

CHAPTER 8

Nonparametric, Distribution-Free, and Permutation Models: Robust Procedures

8.1 INTRODUCTION

In Chapter 4 we worked with the normal distribution, noting the fact that many populations have distributions that are approximately normal. In Chapter 5 we presented elegant one- and two-sample methods for estimating the mean of a normal distribution, or the difference of the means, and constructing confidence intervals. We also examined the corresponding tests about the mean(s) from normally distributed populations. The techniques that we learned are very useful. Suppose, however, that the population under consideration is not normal. What should we do? If the population is not normal, is it appropriate to use the same t-statistic that applies when the sample comes from a normally distributed population? If not, is there some other approach that can be used to analyze such data?

In this chapter we consider such questions. In Section 8.2 we introduce terminology associated with statistical procedures needing few assumptions and in Section 8.3 we note that some of the statistical methods that we have already looked at require very few assumptions.

The majority of this chapter is devoted to specific statistical methods that require weaker assumptions than that of normality. Statistical methods are presented that apply to a wide range of situations. Methods of constructing statistical tests for specific situations, including computer simulation, are also discussed. We conclude with

1. An indication of newer research in the topics of this chapter
2. Suggestions for additional reading if you wish to learn more about the subject matter

8.2 ROBUSTNESS: NONPARAMETRIC AND DISTRIBUTION-FREE PROCEDURES

In this section we present terminology associated with statistical procedures that require few assumptions for their validity.

The first idea we consider is *robustness*:

Definition 8.1. A statistical procedure is *robust* if it performs well when the needed assumptions are not violated "too badly" or if the procedure performs well for a large family of probability distributions.

Biostatistics: A Methodology for the Health Sciences, Second Edition, by Gerald van Belle, Lloyd D. Fisher, Patrick J. Heagerty, and Thomas S. Lumley
ISBN 0-471-03185-2

By a *procedure* we mean an estimate, a statistical test, or a method of constructing a confidence interval. We elaborate on this definition to give the reader a better idea of the meaning of the term. The first thing to note is that the definition is *not* a mathematical definition. We have talked about a procedure performing "well" but have not given a precise mathematical definition of what "well" means. The term *robust* is analogous to beauty: Things may be considered more or less beautiful. Depending on the specific criteria for beauty, there may be greater or lesser agreement about the beauty of an object. Similarly, different statisticians may disagree about the robustness of a particular statistical procedure depending on the probability distributions of concern and use of the procedure. Nevertheless, as the concept of beauty is useful, the concept of robustness also proves to be useful conceptually and in discussing the range of applicability of statistical procedures.

We discuss some of the ways that a statistical test may be robust. Suppose that we have a test statistic whose distribution is derived for some family of distributions (e.g., normal distributions). Suppose also that the test is to be applied at a particular significance level, which we designate the *nominal* significance level. When other distributions are considered, the *actual* probability of rejecting the null hypothesis when it holds may differ from the *nominal* significance level if the distribution is not one of those used to derive the statistical test. For example, in testing for a specific value of the mean with a normally distributed sample, the t-test may be used. Suppose, however, that the distribution considered is not normal. Then, if testing at the 5% significance level, the actual significance level (the true probability of rejecting under the *null* hypothesis that the population mean has the hypothesized value) may not be 5%; it may vary. A statistical test would be robust over a larger family of distributions if the true significance level and nominal significance level were close to each other. Also, a statistical test is robust if under specific alternatives, the probability of rejecting the null hypothesis tends to be large even when the alternatives are in a more extensive family of probability distributions.

A statistical test may be robust in a particular way for large samples, but not for small samples. For example, for most distributions, if one uses the t-test for the mean when the sample size becomes quite large, the central limit theory shows that the nominal significance level is approximately the same as the true significance level when the null hypothesis holds. On the other hand, if the samples come from a skewed distribution and the sample size is small, the t-test can perform quite badly. Lumley et al., [2002] reviewed this issue and reported that in most cases the t-test performs acceptably even with 30 or so observations, and even in a very extreme example the performance was excellent with 250 observations.

A technique of constructing confidence intervals is robust to the extent that the nominal confidence level is maintained over a larger family of distributions. For example, return to the t-test. If we construct 95% confidence intervals for the mean, the method is robust to the extent that samples from a nonnormal distribution straddle the mean about 95% of the time. Alternatively, a method of constructing confidence intervals is nonrobust if the confidence with which the parameters are in the interval differs greatly from the nominal confidence level. An estimate of a parameter is robust to the extent that the estimate is close to the true parameter value over a large class of probability distributions.

Turning to a new topic, the normal distribution model is useful for summarizing data, because two parameters (in this case, the mean and variance, or equivalently, the mean and the standard deviation) describe the entire distribution. Such a set or family of distribution functions with each member described (or indexed) by a few parameters is called a *parametric family*. The distributions used for test statistics are also parametric families. For example, the t-distribution, the F-distribution, and the χ^2-distribution depend on one or two integer parameters: the degrees of freedom. Other examples of parametric families are the binomial distribution, with its two parameters n and π, and the Poisson distribution, with its parameter λ.

By contrast, *semiparametric families* and *nonparametric families* of distributions are families that cannot be conveniently characterized, or indexed, by a few parameters. For example, if one looked at all possible continuous distributions, it is not possible to find a few parameters that characterize all these distributions.

Definition 8.2. A family of probability distributions that can be characterized by a few parameters is a *parametric family*. A family is *nonparametric* if it can closely approximate any arbitrary probability distribution. A family of probability distributions that is neither parametric nor nonparametric is *semiparametric*.

In small samples the t-test holds for the family of normal distributions, that is, for a parametric family. It would be nice to have a test statistic whose distribution was valid for a larger family of distributions. In large samples the t-test qualifies, but in small samples it does not.

Definition 8.3. Statistical procedures that hold, or are valid for a nonparametric family of distributions, are called *nonparametric statistical procedures*.

The definition of nonparametric here can be made precise in a number of nonequivalent ways, and no single definition is in universal use. See also Note 8.1. The usefulness of the t-distribution in small samples results from the fact that samples from a normal distribution give the same t-distribution for all normal distributions under the null hypothesis. More generally, it is very useful to construct a test statistic whose distribution is the same for all members of some family of distributions. That is, assuming that the sample comes from some member of the family, and the null hypothesis holds, the statistic has a known distribution; in other words, the distribution does not depend upon, or is *free* of, which member of the underlying family of distributions is sampled. This leads to our next definition.

Definition 8.4. A statistical procedure is *distribution-free* over a specified family of distributions if the statistical properties of the procedure do not depend on (or are free of) the underlying distribution being sampled.

A test statistic is distribution-free if under the null hypothesis, it has the same distribution for all members of the family. A method of constructing confidence intervals is distribution-free if the nominal confidence level holds for all members of the underlying family of distributions.

The usefulness of the (unequal variances) t-test in large samples results from the fact that samples from any distribution give the same large-sample normal distribution under the null hypothesis that the means are equal. That is, the t-statistic becomes free of any information about the shape of the distribution as the sample size increases. This leads to a definition:

Definition 8.5. A statistical procedure is *asymptotically distribution-free* over a specified family of distributions if the statistical properties of the procedure do not depend on (or are free of) the underlying distribution being sampled for sufficiently large sample sizes.

In practice, one selects statistical procedures that hold over a wide class of distributions. Often, the wide class of distributions is nonparametric, and the resulting statistical procedure is distribution-free for the family. The procedure would then be both nonparametric and distribution-free. The terms *nonparametric* and *distribution-free* are used somewhat loosely and are often considered interchangeable. The term *nonparametric* is used much more often than the term *distribution-free*.

One would expect that a nonparametric procedure would not have as much statistical power as a parametric procedure *if* the sample observed comes from the parametric family. This is frequently, but not necessarily, true. One method of comparing procedures is to look at their relative efficiency. *Relative efficiency* is a complex term when defined precisely (see Note 8.2), but the essence is contained in the following definition:

Definition 8.6. The *relative efficiency* of statistical procedure A to statistical procedure B is the ratio of the sample size needed for B to the sample size needed for A in order that both procedures have the same statistical power.

For example, if the relative efficiency of A to B is 1.5, then B needs 50% more observations than A to get the same amount of statistical power.

8.3 SIGN TEST

Suppose that we are testing a drug to reduce blood pressure using a crossover design with a placebo. We might analyze the data by taking the blood pressure while not on the drug and subtracting it from the blood pressure while on the drug. These differences resulting from the matched or paired data will have an expected mean of zero if the drug under consideration had no more effect than the placebo effect. If we want to assume normality, a one-sample t-test with a hypothesized mean of zero is appropriate. Suppose, however, that we knew from past experience that there were occasional large fluctuations in blood pressure due to biological variability. If the sample size were small enough that only one or two such fluctuations were expected, we would be hesitant to use the t-test because of the known fact that one or two large observations, or outliers, destroyed the probability distribution of the test (see Problem 8.20). What should we do?

An alternative nonparametric way of analyzing the data is the following. Suppose that there is no treatment effect. All of the difference between the blood pressures measured on-drug and on-placebo will be due to biological variability. Thus, the difference between the two measurements will be due to symmetric random variability; the number is equally likely to be positive or negative. The *sign test* is appropriate for the null hypothesis that observed values have the same probability of being positive or negative: If we look at the number of positive numbers among the differences (and exclude values equal to zero), under the null hypothesis of no drug effect, this number has a binomial distribution, with $\pi = \frac{1}{2}$. *A test of the null hypothesis could be a test of the binomial parameter* $\pi = \frac{1}{2}$. This was discussed in Chapter 6 when we considered McNemar's test. Such tests are called *sign tests*, since we are looking at the sign of the difference.

Definition 8.7. Tests based on the sign of an observation (i.e., plus or minus), and which test the hypothesis that the observation is equally likely to be a plus or minus, are called *sign test procedures*.

Note that it is possible to use a sign test in situations where numbers are not observed, but there is only a rating. For example, one could have a blinded evaluation of patients as worse on-drug than on-placebo, the same on-drug as on-placebo, and better on-drug than on-placebo. By considering only those who were better or worse on the drug, the null hypothesis of no effect is equivalent to testing that each outcome is equally likely; that is, the binomial probability is $1/2$, the sign test may be used. Ratings of this type are useful in evaluating drugs when numerical quantification is not available. As tests of $\pi = \frac{1}{2}$ for binomial random variables were discussed in Chapter 6, we will not elaborate here. Problems 8.1 to 8.3 use the sign test.

Suppose that the distribution of blood pressures *did* follow a normal distribution: How much would be lost in the way of efficiency by using the sign test? We can answer this question mathematically in large sample sizes. The relative efficiency of the sign test with respect to the t-test when the normal assumptions are satisfied is 0.64; that is, compared to analyzing data using the t-test, 36% of the samples are effectively thrown away. Alternatively, one needs 1/0.64, or 1.56 times as many observations for the sign test as one would need using the t-test to have the same statistical power in a normal distribution. On the other hand, if the data came from a different mathematical distribution, the Laplace or double exponential distribution, the sign test would be more efficient than the t-test.

In some cases a more serious price paid by switching to the sign test is that a different scientific question is being answered. With the t-test we are asking whether the average blood pressure is lower on drug than on placebo; with the sign test we are asking whether the majority of patients have lower blood pressure on drug than on placebo. The answers may be different and it is important to consider which is the more important question.

The sign test is useful in many situations. It is a "quick-and-dirty" test that one may compute mentally without the use of computational equipment; provided that statistical tables are available, you can get a quick estimate of the statistical significance of an appropriate null hypothesis.

8.4 RANKS

Many of the nonparametric, distribution-free tests are based on one simple and brilliant idea. The approach is motivated by an example.

Example 8.1. The following data are for people who are exercised on a treadmill to their maximum capacity. There were five people in a group that underwent heavy distance-running training and five control subjects who were sedentary and not trained. The maximum oxygen intake rate adjusted for body weight is measured in mL/kg per minute. The quantity is called VO_{2MAX}. The values for the untrained subjects were 45, 38, 48, 49, and 51. The values for the trained subjects were 63, 55, 59, 65, and 77. Because of the larger spread among the trained subjects, especially one extremely large VO_{2MAX} (as can be seen from Figure 8.1), the values do not look like they are normally distributed. On the other hand, it certainly appears that the training has some benefits, since the five trained persons all exceed the treadmill times of the five sedentary persons. Although we do not want to assume that the values are normally distributed, we should somehow use the fact that the larger observations come from one group and the smaller observations come from the other group. We desire a statistical test whose distribution can be tabulated under the null hypothesis that the probability distributions are the same in the two groups.

The crucial idea is the rank of the observation, which is the position of the observation among the other observations when they are arranged in order.

Definition 8.8. The *rank* of an observation, among a set of observations, is its position when the observations are arranged from smallest to largest. The smallest observation has rank 1, the next smallest has rank 2, and so on. If observations are tied, the rank assigned is the average of the ranks appropriate to the equal numbers.

For example, the ranks of the 10 observations given above would be found as follows: first, order the observations from the smallest to largest; then number them from left to right, beginning at 1.

Observation	38	45	48	49	51	55	59	63	65	77
Rank	1	2	3	4	5	6	7	8	9	10

We now consider several of the benefits of using ranks. In the example above, suppose there was no difference in the $VO_{2\ MAX}$ value between the two populations. Then we have 10 independent samples (five from each population). Since there would be nothing to distinguish between observations, the five observations from the set of people who experienced training would be equally likely to be any five of the given observations. That is, if we consider the

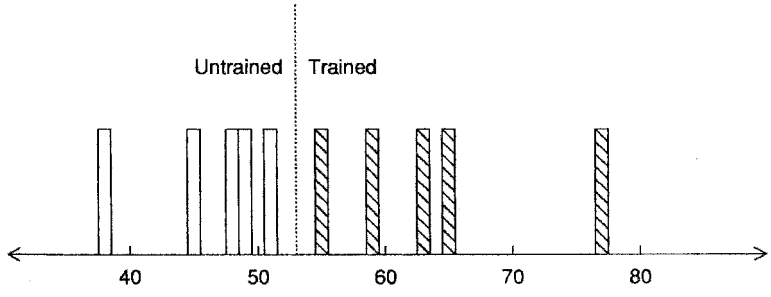


Figure 8.1 $VO_{2\ MAX}$ in trained and untrained persons.

ranks from 1 to 10, all subsets of size 5 would be equally likely to represent the ranks of the five trained subjects. This is true regardless of the underlying distribution of the 10 observations.

We repeat for emphasis: *If we consider continuous probability distributions (so that there are no ties) under the null hypothesis that two groups of observations come from the same distribution, the ranks have the same distribution*! Thus, tests based on the ranks will be nonparametric tests over the family of continuous probability distributions. Another way of making the same point: Any test that results from using the ranks will be distribution-free, because the distribution of the ranks does not depend on the underlying probability distribution under the null hypothesis.

There is a price to be paid in using rank tests. If we have a small number of observations, say two in each group, even if the two observations in one group are larger than both observations in the other group, a rank test will not allow rejection of the null hypothesis that the distributions are the same. On the other hand, if one knows that the data are approximately normally distributed if the two large observations are considerably larger than the smaller observations, the t-test would allow one to reject the null hypothesis that the distributions are the same. However, this increased statistical power in tiny samples *critically* depends on the normality assumptions. With small sample sizes, one cannot check the adequacy of the assumptions. One may reject the null hypothesis incorrectly (when, in fact, the two distributions are the same) because a large outlying value is observed. This price is specific to small samples: In large samples a particular rank-based test may be more or less powerful than the t-test. Note 8.6 describes another disadvantage of rank tests.

Many nonparametric statistical tests can be devised using the simple idea of ranks. In the next three sections of this chapter we present specific rank tests of certain hypotheses.

8.5 WILCOXON SIGNED RANK TEST

In this section we consider our first rank test. The test is an alternative to the one-sample t-test. Whenever the one-sample t-test of Chapter 5 is appropriate, this test may also be used, as its assumptions will be satisfied. However, since the test is a nonparametric test, its assumptions will be satisfied much more generally than under the assumptions needed for the one-sample t-test. In this section we first discuss the needed assumptions and null hypothesis for this test. The test itself is then presented and illustrated by an example. For large sample sizes, the value of the test statistic may be approximated by a standard normal distribution; the appropriate procedure for this is also presented.

8.5.1 Assumptions and Null Hypotheses

The signed rank test is appropriate for statistically independent observations. The null hypothesis to be tested is that each observation comes from a distribution that is symmetric with a mean of zero. That is, for any particular observation, the value is equally likely to be positive or negative.

For the one-sample t-test, we have independent observations from a normal distribution; suppose that the null hypothesis to be tested has a mean of zero. When the mean is zero, the distribution is symmetric about zero, and positive or negative values are equally likely. Thus, the signed rank test may be used wherever the one-sample t-test of mean zero is appropriate. For large sample sizes, the signed rank test has an efficiency of 0.955 relative to the t-test; the price paid for using this nonparametric test is equivalent to losing only 4.5% of the observations. In addition, when the normal assumptions for the t-test hold and the mean is not zero, the signed rank test has equivalent statistical power.

An example where the signed rank test is appropriate is a crossover experiment with a drug and a placebo. Suppose that subjects have the sequence "placebo, then drug" or "drug, then placebo," each assigned at random, with a probability of 0.5. The null hypothesis of interest is that the drug has the same effect as the placebo. If one takes the difference between measurements

taken on the drug and on the placebo, and if the treatment has no effect, the distribution of the difference will not depend on whether the drug was given first or second. The probability is one-half that the placebo was given first and that the observation being looked at is the second observation minus the first observation. The probability is also 1/2 that the observation being examined came from a person who took the drug first. In this case, the observation being used in the signed rank test would be the first observation minus the second observation. Since under the null hypothesis, these two differences have the same distribution except for a minus sign, the distribution of observations under the null hypothesis of "no treatment effect" is symmetric about zero.

8.5.2 Alternative Hypotheses Tested with Power

To use the test, we need to know what type of alternative hypotheses may be detected with some statistical power. For example, suppose that one is measuring blood pressure, and the drug supposedly lowers the blood pressure compared to a placebo. The difference between the measurements on the drug and the blood pressure will tend to be negative. If we look at the observations, two things will occur. First, there will tend to be more observations that have a negative value (i.e., a minus sign) than expected by chance. Second, if we look at the values of the data, the largest absolute values will tend to be negative values. The differences that are positive will usually have smaller absolute values. The signed rank test is designed to use both sorts of information. The signed rank statistic is designed to have power where the alternatives of interest correspond roughly to a shift of the distribution (e.g., the median, rather than being zero, is positive or negative).

8.5.3 Computation of the Test Statistic

We compute the signed rank statistic as follows:

1. Rank the absolute values of the observations from smallest to largest. Note that we do *not* rank the observations themselves, but rather, the absolute values; that is, we ignore minus signs. Drop observations equal to zero.
2. Add up the values of the ranks assigned to the positive observations. Do the same to the negative observations. The smaller of the two values is the value of the Wilcoxon signed rank statistic used in Table A.9 in the Appendix.

The procedure is illustrated in the following example.

Example 8.2. Brown and Hurlock [1975] investigated three methods of preparing the breasts for breastfeeding. The methods were:

1. Toughening the skin of the nipple by nipple friction or rolling
2. Creams to soften and lubricate the nipple
3. Prenatal expression of the first milk secreted before or after birth (colostrum)

Each subject had one randomly chosen treated breast and one untreated breast. Nineteen different subjects were randomized to each of three treatment groups; that is, each subject received the three treatments in random order. The purpose of the study was to evaluate methods of preventing postnatal nipple pain and trauma. The effects were evaluated by the mothers filling out a subjective questionnaire rating nipple sensitivity from "comfortable" (1) to "painful" (2) after each feeding. The data are presented in Table 8.1.

We use the signed rank test to examine the statistical significance of the nipple-rolling data. The first step is to rank the absolute values of the observations, omitting zero values. The observations ranked by absolute value and their ranks are given in Table 8.2.

Note the tied absolute values corresponding to ranks 4 and 5. The average rank 4.5 is used for both observations. Also note that two zero observations were dropped.

Table 8.1 Mean Subjective Difference between Treated and Untreated Breasts

Nipple Rolling	Masse Cream	Expression of Colostrum
−0.525	0.026	−0.006
0.172	0.739	0.000
−0.577	−0.095	−0.257
0.200	−0.040	−0.070
0.040	0.006	0.107
−0.143	−0.600	0.362
0.043	0.007	−0.263
0.010	0.008	0.010
0.000	0.000	−0.080
−0.522	−0.100	−0.010
0.007	0.000	0.048
−0.122	0.000	0.300
−0.040	0.060	0.182
0.000	−0.180	−0.378
−0.100	0.000	−0.075
0.050	0.040	−0.040
−0.575	0.080	−0.080
0.031	−0.450	−0.100
−0.060	0.000	−0.020

Source: Data from Brown and Hurlock [1975].

Table 8.2 Ranked Observation Data

Observation	Rank	Observation	Rank
0.007	1	−0.122	10
0.010	2	−0.143	11
0.031	3	0.172	12
0.040	4.5	0.200	13
−0.040	4.5	−0.522	14
0.043	6	−0.525	15
0.050	7	−0.575	16
−0.060	8	−0.577	17
−0.100	9		

The sum of the ranks of the positive numbers is $S = 1+2+3+4.5+6+7+12+13 = 48.5$. This is less than the sum of the negative ranks. For a sample size of 17, Table A.9 shows that the two-sided p-value is ≥ 0.10. If there are no ties, Owen [1962] shows that $P[S \geq 48.5] = 0.1$ and the two-sided p-value is 0.2. No treatment effect has been shown.

8.5.4 Large Samples

When the number of observations is moderate to large, we may compute a statistic that has approximately a standard normal distribution under the null hypothesis. We do this by subtracting the mean under the null hypothesis from the observed signed rank statistic, and dividing by the standard deviation under the null hypothesis. Here we do not take the minimum of the sums of positive and negative ranks; the usual one- and two-sided normal procedures can be used. The

mean and variance under the null hypothesis are given in the following two equations:

$$E(S) = \frac{n(n+1)}{4} \tag{1}$$

$$\text{var}(S) = \frac{n(n+1)(2n+1)}{24} \tag{2}$$

From this, one gets the following statistic, which is approximately normally distributed for large sample sizes:

$$Z = \frac{S - E(S)}{\sqrt{\text{var}(S)}} \tag{3}$$

Sometimes, data are recorded on such a scale that ties can occur for the absolute values. In this case, tables for the signed rank test are conservative; that is, the probability of rejecting the null hypothesis when it is true is *less* than the nominal significance level. The asymptotic statistic may be adjusted for the presence of ties. The effect of ties is to reduce the variance in the statistic. The rank of a term involved in a tie is replaced by the average of the ranks of those tied observations. Consider, for example, the following data:

$$6, -6, -2, 0, 1, 2, 5, 6, 6, -3, -3, -2, 0$$

Note that there are not only some ties, but zeros. In the case of zeros, the zero observations are omitted from the computation as noted before. These data, ranked by absolute value, with average ranks replacing the given rank when the absolute values are tied, are shown below. The first row (A) represents the data ranked by absolute value, omitting zero values; the second row (B) gives the ranks; and the third row (C) gives the ranks, with ties averaged (in this row, ranks of positive numbers are shown in bold type):

A	1	−2	2	−2	−3	−3	5	6	−6	6	6
B	1	2	3	4	5	6	**7**	8	9	10	11
C	**1**	3	**3**	3	5.5	5.5	**7**	**9.5**	9.5	**9.5**	**9.5**

Note that the ties are with respect to the absolute value (without regard to sign). Thus the three ranks corresponding to observations of −2 and +2 are 2, 3, and 4, the average of which is 3. The S-statistic is computed by adding the ranks for the positive values. In this case,

$$S = 1 + 3 + 7 + 9.5 + 9.5 + 9.5 = 39.5$$

Before computing the asymptotic statistic, the variance of S must be adjusted because of the ties. To make this adjustment, we need to know the number of groups that have ties and the number of ties in each group. In looking at the data above, we see that there are three sets of ties, corresponding to absolute values 2, 3, and 6. The number of ties corresponding to observations of absolute value 2 (the "2 group") is 3; the number of ties in the "3 group" is 2; and the number of ties in the "6 group" is 4. In general, let q be the number of groups of ties, and let t_i, where i goes from 1 to q, be the number of observations involved in the particular group. In this case,

$$t_1 = 3, \qquad t_2 = 2, \qquad t_3 = 4, \qquad q = 3$$

In general, the variance of S is reduced according to the equation:

$$\text{var}(S) = \frac{n(n+1)(2n+1) - \frac{1}{2}\sum_{i=1}^{q} t_i(t_i-1)(t_i+1)}{24} \tag{4}$$

For the data that we are working with, we started with 13 observations, but the n used for the test statistic is 11, since two zeros were eliminated. In this case, the expected mean and variance are

$$E(S) = 11 \times \frac{12}{4} = 33$$

$$\text{var}(S) = \frac{11 \times 12 \times 23 - \frac{1}{2}(3 \times 2 \times 4 + 2 \times 1 \times 3 + 4 \times 3 \times 5)}{24} \doteq 135.6$$

Using test statistic S gives

$$Z = \frac{S - E(S)}{\sqrt{\text{var}(S)}} = \frac{39.5 - 33}{\sqrt{135.6}} \doteq 0.56$$

With a Z-value of only 0.56, one would not reject the null hypothesis for commonly used values of the significance level. For testing at a 0.05 significance level, if n is 15 or larger with few ties, the normal approximation may reasonably be used. Note 8.4 and Problem 8.22 have more information about the distribution of the signed-rank test.

Example 8.2. (*continued*) We compute the asymptotic Z-statistic for the signed rank test using the data given. In this case, $n = 17$ after eliminating zero values. We have one set of two tied values, so that $q = 1$ and $t_1 = 2$. The null hypothesis mean is $17 \times 18/4 = 76.5$. This variance is $[17 \times 18 \times 35 - (1/2) \times 2 \times 1 \times 3]/24 = 446.125$. Therefore, $Z = (48.5 - 76.5)/21.12 \doteq -1.326$. Table A.9 shows that a two-sided p is about 0.186. This agrees with $p = 0.2$ as given above from tables for the distribution of S.

8.6 WILCOXON (MANN–WHITNEY) TWO-SAMPLE TEST

Our second example of a rank test is designed for use in the two-sample problem. Given samples from two different populations, the statistic tests the hypothesis that the distributions of the two populations are the same. The test may be used whenever the two-sample t-test is appropriate. Since the test given depends upon the ranks, it is nonparametric and may be used more generally. In this section, we discuss the null hypothesis to be tested, and the efficiency of the test relative to the two-sample t-test. The test statistic is presented and illustrated by two examples. The large-sample approximation to the statistic is given. Finally, the relationship between two equivalent statistics, the Wilcoxon statistic and the Mann–Whitney statistic, is discussed.

8.6.1 Null Hypothesis, Alternatives, and Power

The null hypothesis tested is that each of two independent samples has the same probability distribution. Table A.10 for the Mann–Whitney two-sample statistic assumes that there are no ties. Whenever the two-sample t-test may be used, the *Wilcoxon statistic* may also be used. The statistic is designed to have statistical power in situations where the alternative of interest has one population with generally larger values than the other. This occurs, for example, when the two distributions are normally distributed, but the means differ. For normal distributions with a shift in the mean, the efficiency of the Wilcoxon test relative to the two-sample t-test is 0.955.

For other distributions with a shift in the mean, the Wilcoxon test will have relative efficiency near 1 if the distribution is *light-tailed* and greater than 1 if the distribution is *heavy-tailed*.

However, as the Wilcoxon test is designed to be less sensitive to extreme values, it will have less power against an alternative that adds a few extreme values to the data. For example, a pollutant that generally had a normally distributed concentration might have occasional very high values, indicating an illegal release by a factory. The Wilcoxon test would be a poor choice if this were the alternative hypothesis. Johnson et al. [1987] shows that a *quantile test* (see Note 8.5) is more powerful than the Wilcoxon test against the alternative of a shift in the extreme values, and the U.S. EPA [1994] has recommended using this test. In large samples a t-test might also be more powerful than the Wilcoxon test for this alternative.

8.6.2 Test Statistic

The test statistic itself is easy to compute. The combined sample of observations from both populations are ordered from the smallest observation to the largest. The sum of the ranks of the population with the smaller sample size (or in the case of equal sample sizes, an arbitrarily designated first population) gives the value of the Wilcoxon statistic.

To evaluate the statistic, we use some notation. Let m be the number of observations for the smaller sample, and n the number of observations in the larger sample. The Wilcoxon statistic W is the sum of the ranks of the m observations when both sets of observations are ranked together.

The computation is illustrated in the following example:

Example 8.3. This example deals with a small subset of data from the Coronary Artery Surgery Study [CASS, 1981]. Patients were studied for suspected or proven coronary artery disease. The disease was diagnosed by coronary angiography. In coronary angiography, a tube is placed into the aorta (where the blood leaves the heart) and a dye is injected into the arteries of the heart, allowing x-ray motion pictures (angiograms) of the arteries. If an artery is narrowed by 70% or more, the artery is considered significantly diseased. The heart has three major arterial systems, so the disease (or lack thereof) is classified as zero-, one-, two-, or three-vessel disease (abbreviated 0VD, 1VD, 2VD, and 3VD). Narrowed vessels do not allow as much blood to give oxygen and nutrients to the heart. This leads to chest pain (angina) and total blockage of arteries, killing a portion of the heart (called a *heart attack* or *myocardial infarction*). For those reasons, one does not expect people with disease to be able to exercise vigorously. Some subjects in CASS were evaluated by running on a treadmill to their maximal exercise performance. The treadmill increases in speed and slope according to a set schedule. The total time on the treadmill is a measure of exercise capacity. The data that follow present treadmill time in seconds for men with normal arteries (but suspected coronary artery disease) and men with three-vessel disease are as follows:

Normal	1014	684	810	990	840	978	1002	1111		
3VD	864	636	638	708	786	600	1320	750	594	750

Note that $m = 8$ (normal arteries) and $n = 10$ (three-vessel disease). The first step is to rank the combined sample and assign ranks, as in Table 8.3. The sum of the ranks of the smaller normal group is 101. Table A.10, for the closely related Mann–Whitney statistic of Section 8.6.4, shows that we reject the null hypothesis of equal population distributions at a 5% significance level.

Under the null hypothesis, the expected value of the Wilcoxon statistic is

$$E(W) = \frac{m(m+n+1)}{2} \tag{5}$$

Table 8.3 Ranking Data for Example 8.3

Value	Rank	Group	Value	Rank	Group	Value	Rank	Group
594	1	3VD	750	7.5	3VD	978	13	Normal
600	2	3VD	750	7.5	3VD	990	14	Normal
636	3	3VD	786	9	3VD	1002	15	Normal
638	4	3VD	810	10	Normal	1014	16	Normal
684	5	Normal	840	11	Normal	1111	17	Normal
708	6	3VD	864	12	3VD	1320	18	3VD

In this case, the expected value is 76. As we conjectured (*before* seeing the data) that the normal persons would exercise longer (i.e., W would be large), a one-sided test that rejects the null hypothesis if W is too large might have been used. Table A.10 shows that at the 5% significance level, we would have rejected the null hypothesis using the one-sided test. (This is also clear, since the more-stringent two-sided test rejected the null hypothesis.)

8.6.3 Large-Sample Approximation

There is a large-sample approximation to the Wilcoxon statistic (W) under the null hypothesis that the two samples come from the same distribution. The approximation may fail to hold if the distributions are different, even if neither has systematically larger or smaller values. The mean and variance of W, with or without ties, is given by equations (5) through (7). In these equations, m is the size of the smaller group (the number of ranks being added to give W), n the number of observations in the larger group, q the number of groups of tied observations (as discussed in Section 8.6.2), and t_i the number of ranks that are tied in the ith set of ties. First, without ties,

$$\text{var}(W) = \frac{mn(m+n+1)}{12} \tag{6}$$

and with ties,

$$\text{var}(W) = \frac{mn(m+n+1)}{12} - \left[\sum_{i=1}^{q} t_i(t_i-1)(t_i+1)\right] \frac{mn}{12(m+n)(m+n-1)} \tag{7}$$

Using these values, an asymptotic statistic with an approximately standard normal distribution is

$$Z = \frac{W - E(W)}{\sqrt{\text{var}(W)}} \tag{8}$$

Example 8.3. (*continued*) The normal approximation is best used when $n \geq 15$ and $m \geq 15$. Here, however, we compute the asymptotic statistic for the data of Example 8.3.

$$E(W) = \frac{8(10+8+1)}{2} = 76$$

$$\text{var}(W) = \frac{8 \cdot 10(8+10+1)}{12} - 2(2-1)(2+1)\left[\frac{8 \cdot 10}{12(8+10)(8+10+1)}\right]$$

$$= 126.67 - 0.12 = 126.55$$

$$Z = \frac{101 - 76}{\sqrt{126.55}} \doteq 2.22$$

The one-sided p-value is 0.013, and the two-sided p-value is $2(0.013) = 0.026$. In fact, the exact one-sided p-value is 0.013. Note that the correction for ties leaves the variance virtually unchanged.

Example 8.4. The Wilcoxon test may be used for data that are ordered and ordinal. Consider the angiographic findings from the CASS [1981] study for men and women in Table 8.4. Let us test whether the distribution of disease is the same in the men and women studied in the CASS registry.

You probably recognize that this is a contingency table, and the χ^2-test may be applied. If we want to examine the possibility of a trend in the proportions, the χ^2-test for trend could be used. That test assumes that the proportion of females changes in a linear fashion between categories. Another approach is to use the Wilcoxon test as described here.

The observations may be ranked by the six categories (none, mild, moderate, 1VD, 2VD, and 3VD). There are many ties: 4517 ties for the lowest rank, 1396 ties for the next rank, and so on. We need to compute the average rank for each of the six categories. If J observations have come before a category with K tied observations, the average rank for the k tied observations is

$$\text{average rank} = \frac{2J + K + 1}{2} \tag{9}$$

For these data, the average ranks are computed as follows:

K	J	Average	K	J	Average
4,517	0	2,259	4,907	6,860	9,314
1,396	4,517	5,215.5	5,339	11,767	14,437
947	5,913	6,387	6,997	17,106	20,605

Now our smaller sample of females has 2360 observations with rank 2259, 572 observations with rank 5215.5, and so on. Thus, the sum of the ranks is

$$\begin{aligned} W &= 2360(2259) + 572(5215.5) + 291(6387) + 1020(9314) + 835(14{,}437) + 882(20{,}605) \\ &= 49{,}901{,}908 \end{aligned}$$

The expected value from equation (5) is

$$E(W) = \frac{5960(5960 + 18{,}143 + 1)}{2} = 71{,}829{,}920$$

Table 8.4 Extent of Coronary Artery Disease by Gender

Extent of Disease	Male	Female	Total
None	2,157	2,360	4,517
Mild	824	572	1,396
Moderate	656	291	947
Significant			
1VD	3,887	1,020	4,907
2VD	4,504	835	5,339
3VD	6,115	882	6,997
Total	18,143	5,960	24,103

Source: Data from CASS [1981].

From equation (7), the variance, taking into account ties, is

$$\begin{aligned}\text{var}(W) &= 5960 \times 18{,}143 \times \frac{5960 + 18{,}143 + 1}{12} \\ &\quad -(4517 \times 4516 \times 4518 + \cdots + 6997 \times 6996 \times 6998)\frac{5960 \times 18{,}143}{12 \times 20{,}103 \times 20{,}102} \\ &= 2.06 \times 10^{11}\end{aligned}$$

From this,

$$z = \frac{W - E(W)}{\sqrt{\text{var}(W)}} \doteq -48.29$$

The p-value is extremely small and the population distributions clearly differ.

8.6.4 Mann–Whitney Statistic

Mann and Whitney developed a test statistic that is equivalent to the Wilcoxon test statistic. To obtain the value for the Mann–Whitney test, which we denote by U, one arranges the observations from the smallest to the largest. The statistic U is obtained by counting the number of times an observation from the group with the smallest number of observations precedes an observation from the second group. With no ties, the statistics U and W are related by the following equation:

$$U + W = \frac{m(m + 2n + 1)}{2} \tag{10}$$

Since the two statistics add to a constant, using one of them is equivalent to using the other. We have used the Wilcoxon statistic because it is easier to compute by hand. The values of the two statistics are so closely related that books of statistical tables contain tables for only one of the two statistics, since the transformation from one to the other is almost immediate. Table A.10 is for the Mann–Whitney statistic.

To use the table for Example 8.3, the Mann–Whitney statistic would be

$$U = \frac{8[8 + 2(10) + 1]}{2} - 101 = 116 - 101 = 15$$

From Table A.10, the two-sided 5% significance levels are given by the tabulated values and mn minus the tabulated value. The tabulated two-sided value is 63, and $8 \times 10 - 63 = 17$. We do reject for a two-sided 5% test. For a one-sided test, the upper critical value is 60; we want the lower critical value of $8 \times 10 - 60 = 20$. Clearly, again we reject at the 5% significance level.

8.7 KOLMOGOROV–SMIRNOV TWO-SAMPLE TEST

Definition 3.9 showed one method of describing the distributions of values from a population: the *empirical cumulative distribution*. For each value on the real line, the empirical cumulative distribution gives the proportion of observations less than or equal to that value. One visual way of comparing two population samples would be a graph of the two empirical cumulative distributions. If the two empirical cumulative distributions differ greatly, one would suspect that

the populations being sampled were not the same. If the two curves were quite close, it would be reasonable to assume that the underlying population distributions were essentially the same.

The *Kolmogorov–Smirnov statistic* is based on this observation. The value of the statistic is the maximum absolute difference between the two empirical cumulative distribution functions. Note 8.7 discusses the fact that the Kolmogorov–Smirnov statistic is a rank test. Consequently, the test is a nonparametric test of the null hypothesis that the two distributions are the same. When the two distributions have the same shape but different locations, the Kolmogorov–Smirnov statistic is far less powerful than the Wilcoxon rank-sum test (or the t-test if it applies), but the Kolmogorov–Smirnov test can pick up any differences between distributions, whatever their form.

The procedure is illustrated in the following example:

Example 8.4. (*continued*) The data of Example 8.3 are used to illustrate the statistic. Using the method of Chapter 3, Figure 8.2 was constructed with both distribution functions.

From Figure 8.2 we see that the maximum difference is 0.675 between 786 and 810. Tables of the statistic are usually tabulated not in terms of the maximum absolute difference D, but in terms of $(mn/d)D$ or mnD, where m and n are the two sample sizes and d is the lowest common denominator of m and n. The benefit of this is that $(mn/d)D$ or mnD is always an integer. In this case, $m = 8$, $n = 10$, and $d = 2$. Thus, $(mn/d)D = (8)(10/2)(0.675) = 27$ and $mnD = 54$. Table 44 of Odeh et al. [1977] gives the 0.05 critical value for mnD as 48. Since $54 > 48$, we reject the null hypothesis at the 5% significance level. Tables of critical values are not given in this book but are available in standard tables (e.g., Odeh et al. [1977]; Owen [1962]; Beyer [1990]) and most statistics packages. The tables are designed for the case with no ties. If there are ties, the test is conservative; that is, the probability of rejecting the null hypothesis when it is true is even less than the nominal significance level.

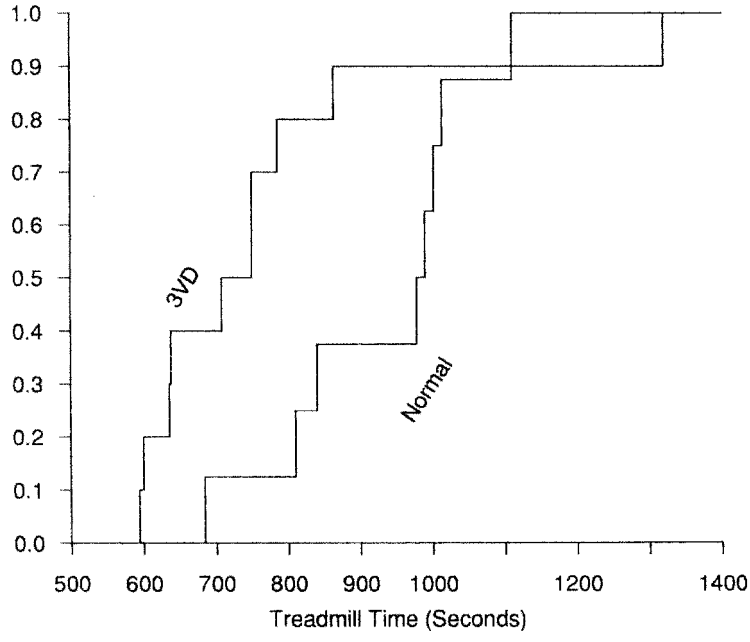


Figure 8.2 Empirical cumulative distributions for the data of Example 8.3.

The large-sample distribution of D is known. Let n and m both be large, say, both 40 or more. The large-sample test rejects the null hypothesis according to the following table:

Significance Level	Reject the Null Hypothesis if:
0.001	KS $\geq$ 1.95
0.01	KS $\geq$ 1.63
0.05	KS $\geq$ 1.36
0.10	KS $\geq$ 1.22

KS is defined as

$$\text{KS} = \max_x \sqrt{\frac{nm}{n+m}} |F_n(x) - G_m(x)| = \sqrt{\frac{nm}{n+m}} D \tag{11}$$

where F_n and G_m are the two empirical cumulative distributions.

8.8 NONPARAMETRIC ESTIMATION AND CONFIDENCE INTERVALS

Many nonparametric tests have associated estimates of parameters. Confidence intervals for these estimates are also often available. In this section we present two estimates associated with the Wilcoxon (or Mann–Whitney) two-sample test statistic. We also show how to construct a confidence interval for the median of a distribution.

In considering the Mann–Whitney test statistic described in Section 8.6, let us suppose that the sample from the first population was denoted by X's, and the sample from the second population by Y's. Suppose that we observe mX's and nY's. The Mann–Whitney test statistic U is the number of times an X was less than a Y among the nmX and Y pairs. As shown in equation (12), the Mann–Whitney test statistic U, when divided by mn, gives an unbiased estimate of the probability that X is less than Y.

$$E\left(\frac{U}{mn}\right) = P[X < Y] \tag{12}$$

Further, an approximate $100(1-\alpha)\%$ confidence interval for the probability that X is less than Y may be constructed using the asymptotic normality of the Mann–Whitney test statistic. The confidence interval is given by the following equation:

$$\frac{U}{mn} \pm Z_{1-\alpha/2} \sqrt{\frac{1}{\min(m,n)} \frac{U}{mn} \left(1 - \frac{U}{mn}\right)} \tag{13}$$

In large samples this interval tends to be too long, but in small samples it can be too short if U/mn is close to 0 or 1 [Church and Harris, 1970]. In Section 8.10.2 we show another way to estimate a confidence interval.

Example 8.5. This example illustrates use of the Mann–Whitney test statistic to estimate the probability that X is less than Y and to find a 95% confidence interval for $P[X < Y]$.

Examine the normal/3VD data in Example 8.3. We shall estimate the probability that the treadmill time of a randomly chosen person with normal arteries is less than that of a three-vessel disease patient.

Note that 1014 is less than one three-vessel treadmill time; 684 is less than 6 of the three-vessel treadmill times, and so on. Thus,

$$U = 1 + 6 + 2 + 1 + 2 + 1 + 1 + 1 = 15$$

We also could have found U by using equation (9) and $W = 101$ from Example 8.3. Our estimate of $P[X < Y]$ is $15/(8 \times 10) = 0.1875$. The confidence interval is

$$0.1875 \pm (1.96)\sqrt{\frac{1}{8}(0.1875)(1 - 0.1875)} = 0.1875 \pm 0.2704$$

We see that the lower limit of the confidence interval is below zero. As zero is the minimum possible value for $P[X < Y]$, the confidence interval could be rounded off to $[0, 0.458]$.

If it is known that the underlying population distributions of X and Y are the same shape and differ only by a shift in means, it is possible to use the Wilcoxon test (or any other rank test) to construct a confidence interval. This is an example of a *semiparametric* procedure: it does not require the underlying distributions to be known up to a few parameters, but it does impose strong assumptions on them and so is not *nonparametric*. The procedure is to perform Wilcoxon tests of $X + \delta$ vs. Y to find values of δ at which the p-value is exactly 0.05. These values of δ give a 95% confidence interval for the difference in locations.

Many statistical packages will compute this confidence interval and may not warn the user about the assumption that the distributions have the same shape but a different location. In the data from Example 8.5, the assumption does not look plausible: The treadmill times for patients with three-vessel disease are generally lower but with one outlier that is higher than the times for all the normal subjects.

In Chapter 3 we saw how to estimate the median of a distribution. We now show how to construct a confidence interval for the median that will hold for any distribution. To do this, we use *order statistics*.

Definition 8.9. Suppose that one observes a sample. Arrange the sample from the smallest to the largest number. The smallest number is the *first-order statistic*, the second smallest is the *second-order statistic*, and so on; in general, the ith-*order statistic* is the ith number in line.

The notation used for an order statistic is to put the subscript corresponding to the particular order statistic in parentheses. That is,

$$X_{(1)} \leq X_{(2)} \leq \cdots \leq X_{(n)}$$

To find a $100(1 - \alpha)\%$ confidence interval for the median, we first find from tables of the binomial distribution with $\pi = 0.5$, the largest value of k such that the probability of k or fewer successes is less than or equal to $\alpha/2$. That is, we choose k to be the largest value of k such that

$$P[\text{number of heads in } n \text{ flips of a fair coin} = 0 \text{ or } 1 \text{ or} \ldots \text{or } k] \leq \frac{\alpha}{2}$$

Given the value of k, the confidence interval for the median is the interval between the $(k + 1)$- and $(n - k)$-order statistics. That is, the interval is

$$(X_{(k+1)}, X_{(n-k)})$$

Example 8.6. The treadmill times of 20 females with normal or minimal coronary artery disease in the CASS study are

570, 618, 30, 780, 630, 738, 900, 750, 750, 540, 660,

780, 720, 750, 936, 900, 762, 840, 816, 690

We estimate the median time and construct a 90% confidence interval for the median of this population distribution. The order statistics (ordered observations) from 1 to 20 are

30, 540, 570, 618, 630, 660, 690, 720, 738, 750, 750,

750, 762, 780, 780, 816, 840, 900, 900, 936

Since we have an odd number of observations,

$$\text{median} = \frac{X_{(10)} + X_{(11)}}{2} = \frac{750 + 750}{2} = 750$$

If X is binomial, $n = 20$ and $\pi = 0.5$, $P[X \leq 5] = 0.0207$ and $P[X \leq 6] = 0.0577$. Thus, $k = 5$. Now, $X_{(6)} = 690$ and $X_{(15)} = 780$. Hence, the confidence interval is (690, 780). The actual confidence is $100(1 - 2 \times 0.0207)\% \doteq 95.9\%$. Because of the discrete nature of the data, the nominal 90% confidence interval is also a 95.9% confidence interval.

*8.9 PERMUTATION AND RANDOMIZATION TESTS

In this section we present a method that may be used to generate a wide variety of statistical procedures. The arguments involved are subtle; you need to pay careful attention to understand the logic. We illustrate the idea by working from an example.

Suppose that one had two samples, one of size n and one of size m. Consider the null hypothesis that the distributions of the two populations are the same. Let us suppose that, in fact, this null hypothesis is true; the combined $n + m$ observations are independent and sampled from the same population. Suppose now that you are told that one of the $n + m$ observations is equal to 10. Which of the $n + m$ observations is most likely to have taken the value 10? There is really nothing to distinguish the observations, since they are all taken from the same distribution or population. Thus, any of the $n + m$ observations is equally likely to be the one that was equal to 10. More generally, suppose that our samples are taken in a known order; for example, the first n observations come from the first population and the next m from the second. Let us suppose that the null hypothesis still holds. Suppose that you are now given the observed values in the sample, all $n + m$ of them, but not told which value was obtained from which ordered observation. Which arrangement is most likely? Since all the observations come from the same distribution, and the observations are independent, there is nothing that would tend to associate any one sequence or arrangement of the numbers with a higher probability than any other sequence. In other words, every assignment of the observed numbers to the $n + m$ observations is equally likely. This is the idea underlying a class of tests called *permutation tests*. To understand why they are called this, we need the definition of a permutation:

Definition 8.10. Given a set of $(n + m)$ objects arranged or numbered in a sequence, a *permutation* of the objects is a rearrangement of the objects into the same or a different order. The number of permutations is $(n + m)!$.

What we said above is that if the null hypothesis holds in the two-sample problem, all permutations of the numbers observed are equally likely. Let us illustrate this with a small example. Suppose that we have two observations from the first group and two observations from the second group. Suppose that we know that the four observations take on the values 3,

Table 8.5 Permutations of Four Observations

x		y		$\overline{x}-\overline{y}$	x		y		$\overline{x}-\overline{y}$
3	7	8	10		7	8	3	10	
3	7	10	8	-4	7	8	10	3	
7	3	8	10		8	7	3	10	1
7	3	10	8		8	7	10	3	
3	8	7	10		7	10	3	8	
3	8	10	7		7	10	8	3	
8	3	7	10	-3	10	7	3	8	3
8	3	10	7		10	7	8	3	
3	10	7	8		8	10	3	7	
3	10	8	7		8	10	7	3	
10	3	7	8	-1	10	8	3	7	4
10	3	8	7		10	8	7	3	

7, 8, and 10. Listed in Table 8.5 are the possible permutations where the first two observations would be considered to come from the first group and the second two from the second group. (Note that x represents the first group and y represents the second.)

If we only know the four values 3, 7, 8, and 10 but do not know in which order they came, any of the 24 possible arrangements listed above are equally likely. If we wanted to perform a two-sample test, we could generate a statistic and calculate its value for each of the 24 arrangements. We could then order the values of the statistic according to some alternative hypothesis so that the more extreme values were more likely under the alternative hypothesis. By looking at what sequence *actually occurred*, we can get a p-value for this set of data. The p-value is determined by the position of the statistic among the possible values. The p-value is the number of possibilities as extreme or more extreme than that observed divided by the number of possibilities.

Suppose, for example, that with the data above, we decided to use the difference in means between the two groups, $\overline{x}-\overline{y}$, as our test statistic. Suppose also that our alternative hypothesis is that group 1 has a larger mean than group 2. Then, if any of the last four rows of Table had occurred, the one-sided p-value would be 4/24, or 1/6. Note that this would be the most extreme finding possible. On the other hand, if the data had been 8, 7, 3, and 10, with an $\overline{x}-\overline{y}=1$, the p-value would be 12/24, or 1/2.

The tests we have been discussing are called *permutation tests*. They are possible when a permutation of all or some subset of the data is considered equally likely under the null hypothesis; the test is based on this fact. These tests are sometimes also called *conditional tests*, because the test takes some portion of the data as fixed or known. In the case above, we assume that we know the actual observed values, although we do not know in which order they occurred. We have seen an example of a conditional test before: Fisher's exact test in Chapter 6 treated the row and column totals as known; conditionally, upon that information, the test considered what happened to the entries in the table. The permutation test can be used to calculate appropriate p-values for tests such as the t-test when, in fact, normal assumptions do not hold. To do this, proceed as in the next example.

Example 8.7. Given two samples, a sample of size n of X observations and a sample of size m of Y observations, it can be shown (Problem 8.24) that the two-sample t-test is a monotone function of $\overline{x}-\overline{y}$; that is, as $\overline{x}-\overline{y}$ increases, t also increases. Thus, if we perform a permutation test on $\overline{x}-\overline{y}$, we are in fact basing our test on extreme values of the t-statistic. The illustration above is equivalent to a t-test on the four values given. Consider now the data

$$x_1=1.3, \qquad x_2=2.3, \qquad x_3=1.9, \qquad y_1=2.8, \qquad y_2=3.9$$

The 120 permutations $(3+2)!$ fall into 10 groups of 12 permutations with the same value of $\overline{x}-\overline{y}$ (a complete table is included in the Web appendix). The observed value of $\overline{x}-\overline{y}$ is -1.52, the lowest possible value. A one-sided test of $E(Y) < E(X)$ would have $p = 0.1 = 12/120$. The two-sided p-value is 0.2.

The Wilcoxon test may be considered a permutation test, where the values used are the ranks and not the observed values. For the Wilcoxon test we know what the values of the ranks will be; thus, one set of statistical tables may be generated that may be used for the entire sample. For the general permutation test, since the computation depends on the numbers actually observed, it cannot be calculated until we have the sample in hand. Further, the computations for large sample sizes are very time consuming. If n is equal to 20, there are over 2×10^{18} possible permutations. Thus, the computational work for permutation tests becomes large rapidly. This would appear to limit their use, but as we discuss in the next section, it is possible to sample permutations rather than evaluating every one.

We now turn to *randomization tests*. Randomization tests proceed in a similar manner to permutation tests. In general, one assumes that some aspects of the data are known. If certain aspects of the data are known (e.g., we might know the numbers that were observed, but not which group they are in), one can calculate a number of equally likely outcomes for the complete data. For example, in the permutation test, if we know the actual values, all possible permutations of the values are equally likely under the null hypothesis. In other words, it is as if a permutation were to be selected at random; the permutation tests are examples of randomization tests.

Here we consider another example. This idea is the same as that used in the signed rank test. Suppose that under the null hypothesis, the numbers observed are independent and symmetric about zero. Suppose also that we are given the absolute values of the numbers observed but not whether they are positive or negative. Take a particular number a. Is it more likely to be positive or negative? Because the distribution is symmetric about zero, it is not more likely to be either one. It is equally likely to be $+a$ or $-a$. Extending this to all the observations, every pattern of assigning pluses or minuses to our absolute values is equally likely to occur under the null hypothesis that all observations are symmetric about zero. We can then calculate the value of a test statistic for all the different patterns for pluses and minuses. A test basing the p-value on these values would be called a *randomization test*.

Example 8.8. One can perform a randomization one-sample t-test, taking advantage of the absolute values observed rather than introducing the ranks. For example, consider the first four paired observations of Example 8.2. The values are -0.0525, 0.172, 0.577, and 0.200. Assign all 16 patterns of pluses and minuses to the four absolute values (0.0525, 0.172, 0.577, and 0.200) and calculate the values of the paired or one-sample t-test. The 16 computed values, in increasing order, are -3.47, -1.63, -1.49, $\mathbf{-0.86}$, -0.46, -0.34, -0.08, -0.02, 0.02, 0.08, 0.34, 0.46, 0.86, 1.48, 1.63, and 3.47. The observed t-value (in bold type) is -0.86. It is the fourth of 16 values. The two-sided p-value is $2(4/16) = 0.5$.

*8.10 MONTE CARLO OR SIMULATION TECHNIQUES

*8.10.1 Evaluation of Statistical Significance

To compute statistical significance, we need to compare the observed values with something else. In the case of symmetry about the origin, we have seen it is possible to compare the observed value to the distribution where the plus and minus signs are independent with probability 1/2. In cases where we do not know a prior appropriate comparison distribution, as in a drug trial, the distribution without the drug is found by either using the same subjects in a crossover trial or forming a control group by a separate sample of people who are not treated with the drug. There are cases where one can conceptually write down the probability structure that would generate

the distribution under the null hypothesis, but in practice could not calculate the distribution. One example of this would be the permutation test. As we mentioned previously, if there are 20 different values in the sample, there are more than 2×10^{18} different permutations. To generate them all would not be feasible, even with modern electronic computers. However, one could evaluate the particular value of the test statistic by generating a second sample from the null distribution with all permutations being equally likely. If there were some way to generate permutations randomly and compute the value of the statistic, one could take the observed statistic (thinking of this as a sample of size 1) and compare it to the randomly generated value under the null hypothesis, the second sample. One would then order the observed and generated values of the statistic and decide which values are more extreme; this would lead to a rejection region for the null hypothesis. From this, a p-value could be computed. These abstract ideas are illustrated by the following examples.

Example 8.9. As mentioned above, for fixed observed values, the two-sample t-test is a monotone function of the value of $\overline{x}-\overline{y}$, the difference in the means of the two samples. Suppose that we have the $\overline{x}-\overline{y}$ observed. One might then generate random permutations and compute the values of $\overline{x}-\overline{y}$. Suppose that we generate n such values. For a two-sided test, let us order the *absolute* values of the statistic, including both our random sample under the null hypothesis and the actual observation, giving us $n+1$ values. Suppose that the actual observed value of the statistic from the data is the kth-order statistic, where we have ordered the absolute values from smallest to largest. Larger values tend to give more evidence against the null hypothesis of equal means. Suppose that we would reject for all observations as large as the kth-order statistic or larger. This corresponds to a p-value of $(n+2-k)/(n+1)$.

One problem that we have not discussed yet is the method for generating the random permutation and $\overline{x}-\overline{y}$ values. This is usually done by computer. The computer generates random permutations by using what are called *random number generators* (see Note 8.10). A study using the generation of random quantities by computer is called a *Monte Carlo study*, for the gambling establishment at Monte Carlo with its random gambling devices and games. Note that by using Monte Carlo permutations, we can avoid the need to generate all possible permutations! This makes permutation tests feasible for large numbers of observations.

Another type of example comes about when one does not know how to compute the distribution theoretically under the null hypothesis.

Example 8.10. This example will not give all the data but will describe how a Monte Carlo test was used. In the Coronary Artery Surgery Study (CASS [1981], Alderman et al. [1982]), a study was made of the reasons people that were treated by coronary bypass surgery or medical therapy. Among 15 different institutions, it was found that many characteristics affected the assignments of patients to surgical therapy. A multivariate statistical analysis of a type described later in this book (linear discriminant analysis) was used to identify factors related to choice of therapy and to estimate the probability that someone would have surgery. It was clear that the sites differed in the percentage of people assigned to surgery, but it was also clear that the clinical sites had patient populations with different characteristics. Thus, one could not immediately conclude that the clinics had different philosophies of assignment to therapy merely by running a χ^2 test. Conceivably, the differences between clinics could be accounted for by the different characteristics of the patient populations. Using the estimated probability that each patient would or would not have surgery, the total number of surgical cases was distributed among the clinics using a Monte Carlo technique. The corresponding χ^2 test for the observed and expected values was computed for each of these randomly generated assignments under the null hypothesis of no clinical difference. This was done 1000 times. The actual observed value for the statistic turned out to be larger than any of the 1000 simulations. Thus, the estimated p-value for the significance of the conjecture that the clinics had different methods of assigning

people to therapy was less than 1/1001. It was thus concluded that the clinics had different philosophies by which they assigned people to medical or surgical therapy.

We now turn to other possible uses of the Monte Carlo technique.

8.10.2 The Bootstrap

The motivation for distribution-free statistical procedures is that we need to know the distribution of a statistic when the frequency distribution F of the data is not known a priori. A very ingenious way around this problem is given by the *bootstrap*, a procedure due in its full maturity to Efron [1979], although special cases and related ideas had been around for many years.

The idea behind the bootstrap is that although we do not know F, we have a good estimate of it in the empirical frequency distribution F_n. If we can estimate the distribution of our statistic when data are sampled from F_n, we should have a good approximation to the distribution of the statistic when data are sampled from the true, unknown F. We can create data sets sampled from F_n simply by resampling the observed data: We take a sample of size n from our data set of size n (replacing the sampled observation each time). Some observations appear once, others twice, others not at all.

The bootstrap appears to be too good to be true (the name emphasizes this, coming from the concept of "lifting yourself by your bootstraps"), but both empirical and theoretical analysis confirm that it works in a fairly wide range of cases. The two main limitations are that it works only for independent observations and that it fails for certain extremely nonrobust statistics (the only simple examples being the maximum and minimum). In both cases there are more sophisticated variants of the bootstrap that relax these conditions.

Because it relies on approximating F by F_n the bootstrap is a large-sample method that is only asymptotically distribution-free, although it is successful in smaller samples than, for example, the t-test for nonnormal data. Efron and Tibshirani [1986, 1993] are excellent references; much of the latter is accessible to the nonstatistician. Davison and Hinckley [1997] is a more advanced book covering many variants on the idea of resampling. The Web appendix to this chapter links to more demonstrations and examples of the bootstrap.

Example 8.11. We illustrate the bootstrap by reexamining the confidence interval for $P[X < Y]$ generated in Example 8.5. Recall that we were comparing treadmill times for normal subjects and those with three-vessel disease. The observed $P[X < Y]$ was $15/80 = 0.1875$. In constructing a bootstrap sample we sample 8 observations from the normal and 10 from the three-vessel disease data and compute U/mn for the sample. Repeating this 1000 times gives an estimate of the distribution of $P[X < Y]$. Taking the upper and lower $\alpha/2$ percentage points of the distribution gives an approximate 95% confidence interval. In this case the confidence interval is $[0, 0.41]$. Figure 8.3 shows a histogram of the bootstrap distribution with the normal approximation from Example 8.5 overlaid on it.

Comparing this to the interval generated from the normal approximation, we see that both endpoints of the bootstrap interval are slightly higher, and the bootstrap interval is not quite symmetric about the observed value, but the two intervals are otherwise very similar. The bootstrap technique requires more computer power but is more widely applicable: It is less conservative in large samples and may be less liberal in small samples.

Related resampling ideas appear elsewhere in the book. The idea of splitting a sample to estimate the effect of a model in an unbiased manner is discussed in Chapters 11 and 13 and elsewhere. Systematically omitting part of a sample, estimating values, and testing on the omitted part is used; if one does this, say for all subsets of a certain size, a *jackknife* procedure is being used (see Efron [1982]; Efron and Tibshirani [1993]).

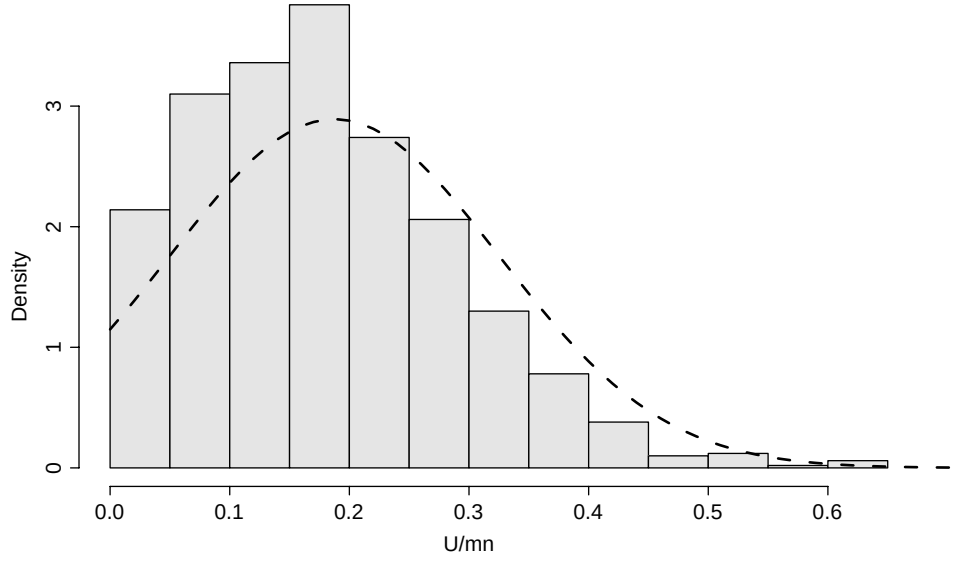


Figure 8.3 Histogram of bootstrap distribution of U/mn and positive part of normal approximation (dashed line). (Data from CASS [1981]; see Example 8.5.)

8.10.3 Empirical Evaluation of the Behavior of Statistics: Modeling and Evaluation

Monte Carlo generation on a computer is also useful for studying the behavior of statistics. For example, we know that the χ^2-statistic for contingency tables, as discussed in Chapter 7, has approximately a χ^2-distribution for large samples. But is the distribution approximately χ^2 for smaller samples? In other words, is the statistic fairly robust with respect to sample size? What happens when there are small numbers of observations in the cells? One way to evaluate small-sample behavior is a Monte Carlo study (also called a *simulation study*). One can generate multinomial samples with the two traits independent, compute the χ^2-statistic, and observe, for example, how often one would reject at the 5% significance level. The Monte Carlo simulation would allow evaluation of how large the sample needs to be for the asymptotic χ^2 critical value to be useful.

Monte Carlo simulation also provides a general method for estimating power and sample size. When designing a study one usually wishes to calculate the probability of obtaining statistically significant results under the proposed alternative hypothesis. This can be done by simulating data from the alternative hypothesis distribution and performing the planned test. Repeating this many times allows the power to be estimated. For example, if 910 of 1000 simulations give a statistically significant result, the power is estimated to be 91%. In addition to being useful when no simple formula exists for the power, the simulation approach is helpful in concentrating the mind on the important design factors. Having to simulate the possible results of a study makes it very clear what assumptions go into the power calculation.

Another use of the Monte Carlo method is to model very complex situations. For example, you might need to design a hospital communications network with many independent inputs. If you knew roughly the distribution of calls from the possible inputs, you could simulate by Monte Carlo techniques the activity of a proposed network if it were built. In this manner, you could see whether or not the network was often overloaded. As another example, you could model the hospital system of an area under the assumption of new hospitals being added and various assumptions about the case load. You could also model what might happen in catastrophic circumstances (*provided* that realistic assumptions could be made). In general, the modeling and simulation approach gives one method of evaluating how changes in an environment might

affect other factors without going through the expensive and potentially catastrophic exercise of actually building whatever is to be simulated. Of course, such modeling depends *heavily* on the skill of the people constructing the model, the realism of the assumptions they make, and whether or not the probabilistic assumptions used correspond approximately to the real-life situation.

A starting reference for learning about Monte Carlo ideas is a small booklet by Hoffman [1979]. More theoretical texts are Edgington [1987] and Ripley [1987] .

*8.11 ROBUST TECHNIQUES

Robust techniques cover more than the field of nonparametric and distribution-free statistics. In general, distribution-free statistics give robust techniques, but it is possible to make more classical methods robust against certain violations of assumptions.

We illustrate with three approaches to making the sample mean robust. Another approach discussed earlier, which we shall not discuss again here, is to use the sample median as a measure of location. The three approaches are modifications of the traditional mean statistic $\overline{x}$. Of concern in computing the sample mean is the effect that an outlier will have. An observation far away from the main data set can have an enormous effect on the sample mean. One would like to eliminate or lessen the effect of such outlying and possibly spurious observations.

An approach that has been suggested is the α-trimmed mean. With the α-trimmed mean, we take some of the largest and smallest observations and drop them from each end. We then compute the usual sample mean on the data remaining.

Definition 8.11. The *α-trimmed mean* of n observations is computed as follows: Let k be the smallest integer greater than or equal to αn. Let $X_{(i)}$ be the order statistics of the sample. The α-trimmed mean drops approximately a proportion α of the observations from both ends of the distribution. That is,

$$\alpha\text{-trimmed mean} = \frac{1}{n-2k}\sum_{i=k+1}^{n-k} X_{(i)}$$

We move on to the two other ways of modifying the mean, and then illustrate all three with a data set. The second method of modifying the mean is called *Winsorization*. The α-trimmed mean drops the largest and smallest observations from the samples. In the Winsorized mean, such observations are included, but the large effect is reduced. The approach is to shrink the smallest and largest observations to the next remaining observations, and count them as if they had those values. This will become clearer with the example below.

Definition 8.12. The *α-Winsorized mean* is computed as follows. Let k be the smallest integer greater than or equal to αn. The α-Winsorized mean is

$$\alpha\text{-Winsorized mean} = \frac{1}{n}\left[(k+1)(X_{(k+1)} + X_{(n-k)}) + \sum_{i=k+2}^{n-k-1} X_{(i)}\right]$$

The third method is to weight observations differentially. In general, we would want to weight the observations at the ends or tails less and those in the middle more. Thus, we will base the weights on the order statistics where the weights for the first few order statistics and

the last few order statistics are typically small. In particular, we define the weighted mean to be

$$\text{weighted mean} = \frac{\sum_{i=1}^{n} W_i X_{(i)}}{\sum_{i=1}^{n} W_i}, \qquad \text{where } W_i \geq 0$$

Problem 8.26 shows that the α-trimmed mean and the α-Winsorized mean are examples of weighted means with appropriately chosen weights.

Example 8.12. We compute the mean, median, 0.1-trimmed mean, and 0.1-Winsorized mean for the female treadmill data of Example 8.6.

$$\text{mean} = \overline{x} = \frac{30 + \cdots + 936}{20} = 708$$

$$\text{median} = \frac{X_{(10)} + X_{(11)}}{2} = 750$$

Now $0.1 \times 20 = 2$, so $k = 2$.

$$\alpha\text{-trimmed mean} = \frac{570 + \cdots + 900}{16} = 734.6$$

$$\alpha\text{-Winsorized mean} = \frac{1}{20}(3(579 + 900) + 618 + \cdots + 840) = 734.7$$

Note that the median and both robust mean estimates are considerably higher than the sample mean $\overline{x}$. This is because of the small outlier of 30.

The Winsorized mean was intended to give outlying observations the same influence on the estimate as the most extreme of the interior estimates. In fact, the trimmed mean does this and the Winsorized mean gives outlying observations rather more influence. This, combined with the simplicity of the trimmed mean, makes it more attractive.

Robust techniques apply in a much more general context than shown here, and indeed are more useful in other situations. In particular, for regression and multiple regression (subjects of subsequent chapters in this book), a large amount of statistical theory has been developed for making the procedures more robust [Huber, 1981].

*8.12 FURTHER READING AND DIRECTIONS

There are several books dealing with nonparametric statistics. Among these are Lehmann and D'Abrera [1998] and Kraft and van Eeden [1968]. Other books deal exclusively with nonparametric statistical techniques. Three that are accessible on a mathematical level suitable for readers of this book are Marascuilo and McSweeney [1977], Bradley [1968], and Siegel and Castellan [1990].

A book that gives more of a feeling for the mathematics involved at a level above this text but which does not require calculus is Hajek [1969]. Another very comprehensive text that outlines much of the theory of statistical tests but is on a somewhat more advanced mathematical level, is Hollander and Wolfe [1999]. Finally, a comprehensive text on robust methods, written at a very advanced mathematical level, is Huber [2003].

In other sections of this book we give nonparametric and robust techniques in more general settings. They may be identified by one of the words *nonparametric, distribution-free*, or *robust* in the title of the section.

NOTES

8.1 Definitions of Nonparametric and Distribution-Free

The definitions given in this chapter are close to those of Huber [2003]. Bradley [1968] states that "roughly speaking, a nonparametric test is a test which makes no hypothesis about the value of a parameter in a statistical density function, whereas a distribution-free test is one which makes no assumptions about the precise form of the sampled population."

8.2 Relative Efficiency

The statements about relative efficiency in this chapter refer to asymptotic relative efficiency [Bradley, 1968; Hollander and Wolfe, 1999; Marascuilo and McSweeney, 1977]. For two possible *estimates*, the asymptotic relative efficiency of A to B is the limit of the ratio of the variance of B to the variance of A as the sample size increases. For two possible *tests*, first select a sequence of alternatives such that as n becomes large, the power (probability of rejecting the null hypothesis) for test A converges to a fixed number greater than zero and less than 1. Let this number be C. For each member of the sequence, find sample sizes n_A and n_B such that both tests have (almost) power C. The limit of the ratio n_B to n_A is the asymptotic relative efficiency. Since the definition is for large sample sizes (asymptotic), for smaller sample sizes the efficiency may be more or less than the figures we have given. Both Bradley [1968] and Hollander and Wolfe [1999] have considerable information on the topic.

8.3 Crossover Designs for Drugs

These are subject to a variety of subtle differences. There may be carryover effects from the drugs. Changes over time—for example, extreme weather changes—may make the second part of the crossover design different than the first. Some drugs may permanently change the subjects in some way. Peterson and Fisher [1980] give many references germane to randomized clinical trials.

8.4 Signed Rank Test

The values of the ranks are known; for n observations, they are the integers $1 - n$. The only question is the sign of the observation associated with each rank. Under the null hypothesis, the sign is equally likely to be plus or minus. Further, knowing the rank of an observation based on the absolute values does not predict the sign, which is still equally likely to be plus or minus independently of the other observations. Thus, all 2^n patterns of plus and minus signs are equally likely. For $n = 2$, the four patterns are:

Ranks	1	2	1	2	1	2	1	2
Signs	−	−	+	−	−	+	+	+
S	0		1		2		3	

So $P[S \leq 0] = 1/4$, $P[S \leq 1] = 1/2$, $P[S \leq 2] = 3/4$, and $P[S \leq 3] = 1$.

8.5 Quantile Test

If the alternative hypothesis of interest is an increase in extreme values of the outcome variable, a more powerful rank test can be based on the number of values above a given threshold. That is, the outcome value X_i is recoded to 1 if it is above the threshold and 0 if it is below the threshold. This recoding reduces the data to a 2×2 table, and Fisher's exact test can be used to make the comparison (see Section 6.3). Rather than prespecifying a threshold, one could

specify that the threshold was to be, say, the 90th percentile of the combined sample. Again the data would be recoded to 1 for an observation in the top 10%, 0 for other observations, giving a 2×2 table. It is important that either a threshold or a percentile be specified in advance. Selecting the threshold that gives the largest difference in proportions gives a test related to the Kolmogorov–Smirnov test, and when proper control of the implicit multiple comparisons is made, this test is not particularly powerful.

8.6 Transitivity

One disadvantage of the rank tests is that they are not necessarily *transitive*. Suppose that we conclude from the Mann–Whitney test that group A has larger values than group B, and group B has larger values than group C. It would be natural to assume that group A has larger values than group C, but the Mann–Whitney test could conclude the reverse—that C was larger than A. This fact is important in the theory of elections, where different ways of running elections are generally equivalent to different rank tests. It implies that candidate A could beat B, B could beat C, and C could beat A in fair two-way runoff elections, a problem noted in the late eighteenth century by Condorcet. Many interesting issues related to nontransitivity were discussed in Martin Gardner's famous "Mathematical Games" column in *Scientific American* of December 1970, October 1974, and November 1997.

The practical importance of nontransitivity is unclear. It is rare in real data, so may largely be a philosophical issue. On the other hand, it does provide a reminder that the rank-based tests are not just a statistical garbage disposal that can be used for any data whose distribution is unattractive.

8.7 Kolmogorov–Smirnov Statistic Is a Rank Statistic

We illustrate one technique used to show that the Kolmogorov–Smirnov statistic is a rank test. Looking at Figure 8.2, we could slide both curves along the x-axis without changing the value of the maximum difference, D. Since the curves are horizontal, we can stretch them along the axis (as long as the order of the jumps does not change) and not change the value of D. Place the first jump at 1, the second at 2, and so on. We have placed the jumps then at the ranks! The height of the jumps depends on the sample size. Thus, we can compute D from the ranks (and knowing which group have the rank) and the sample sizes. Thus, D is nonparametric and distribution-free.

8.8 One-Sample Kolmogorov–Smirnov Tests and One-Sided Kolmogorov–Smirnov Tests

It is possible to compare one sample to a hypothesized distribution. Let F be the empirical cumulative distribution function of a sample. Let H be a hypothesized distribution function. The statistic

$$D = \max_x |F(x) - H(x)|$$

is the one-sample statistic. If H is continuous, critical values are tabulated for this nonparametric test in the tables already cited in this chapter. An approximation to the p-value for the one-sample Kolmogorov–Smirnov test is

$$P(D > d) \leq 2e^{-2d^2/n}$$

This is conservative regardless of sample size, the value of d, the presence or absence of ties, and the true underlying distribution F, and is increasingly accurate as the p-value decreases. This approximation has been known for a long time, but the fact that it is guaranteed to be conservative is a recent, very difficult mathematical result [Massart, 1990].

The Kolmogorov–Smirnov two-sample statistic was based on the largest difference between two empirical cumulative distribution functions; that is,

$$D = \max_x |F(x) - G(x)|$$

where F and G are the two empirical cumulative distribution functions. Since the absolute value is involved, we are not differentiating between F being larger and G being larger. If we had hypothesized as an alternative that the F population took on larger values in general, F would tend to be less than G, and we could use

$$D^+ = \max_x (G(x) - F(x))$$

Such one-sided Kolmogorov–Smirnov statistics are used and tabulated. They also are nonparametric rank tests for use with one-sided alternatives.

8.9 More General Rank Tests

The theory of tests based on ranks is well developed [Hajek, 1969; Hajek and Sidak, 1999; Huber, 2003]. Consider the two-sample problem with groups of size n and m, respectively. Let $R_i (i = 1, 2, \ldots, n)$ be the ranks of the first sample. Statistics of the following form, with a a function of R_i, have been studied extensively.

$$S = \frac{1}{n} \sum_{i=1}^{n} a(R_i)$$

The $a(R_i)$ may be chosen to be efficient in particular situations. For example, let $a(R_i)$ be such that a standard normal variable has probability $R_i/(n+m+1)$ of being less than or equal to this value. Then, when the usual two-sample t-test normal assumptions hold, the relative efficiency is 1. That is, this rank test is as efficient as the t-test for large samples. This test is called the *normal scores test* or *van der Waerden test*.

8.10 Monte Carlo Technique and Pseudorandom Number Generators

The term *Monte Carlo technique* was introduced by the mathematician Stanislaw Ulam [1976] while working on the Manhattan atomic bomb project.

Computers typically do not generate random numbers; rather, the numbers are generated in a sequence by a specific computer algorithm. Thus, the numbers are called *pseudorandom numbers*. Although not random, the sequence of numbers need to appear random. Thus, they are tested in part by statistical tests. For example, a program to generate random integers from zero to nine may have a sequence of generated integers tested by the χ^2 goodness-of-fit test to see that the "probability" of each outcome is 1/10. A generator of uniform numbers on the interval (0, 1) can have its empirical distribution compared to the uniform distribution by the one-sample Kolmogorov–Smirnov test (Note 8.8). The subject of pseudorandom number generators is very deep both philosophically and mathematically. See Chaitin [1975] and Dennett [1984, Chaps. 5 and 6] for discussions of some of the philosophical issues, the former from a mathematical viewpoint.

Computer and video games use pseudorandom number generation extensively, as do computer security systems. A number of computer security failures have resulted from poor-quality pseudorandom number generators being used in encryption algorithms. One can generally assume that the generators provided in statistical packages are adequate for statistical (not cryptographic) purposes, but it is still useful to repeat complex simulation experiments with a different generator if possible. A few computer systems now have "genuine" random number generators that collect and process randomness from sources such as keyboard and disk timings.

PROBLEMS

8.1 The following data deal with the treatment of essential hypertension (*essential* is a technical term meaning that the cause is unknown; a synonym is *idiopathic*) and is from a paper by Vlachakis and Mendlowitz [1976]. Seventeen patients received treatments C, A, and B, where C is the control period, A is propranolol + phenoxybenzamine, and B is propranolol + phenoxybenzamine + hydrochlorothiazide. Each patient received C first, then either A or B, and finally, B or A. The data in Table 8.6 consist of the systolic blood pressure in the recumbent position.

Table 8.6 Blood Pressure Data for Problem 8.1

Patient	C	A	B	Patient	C	A	B
1	185	148	132	10	180	132	136
2	160	128	120	11	176	140	135
3	190	144	118	12	200	165	144
4	192	158	115	13	188	140	115
5	218	152	148	14	200	140	126
6	200	135	134	15	178	135	140
7	210	150	128	16	180	130	130
8	225	165	140	17	150	122	132
9	190	155	138				

(a) Take the differences between the systolic blood pressures on treatments A and C. Use the sign test to test for a treatment A effect (two-sided test; give the p-value).

(b) Take the differences between treatments B and C. Use the sign test to test for a treatment B effect (one-sided test; give the p-value).

(c) Take the differences between treatments B and A. Test for a treatment difference using the sign test (two-sided test; give the p-value).

8.2 Several population studies have demonstrated an inverse correlation of sudden infant death syndrome (SIDS) rate with birthweight. The occurrence of SIDS in one of a pair of twins provides an opportunity to test the hypothesis that birthweight is a major determinant of SIDS. The set of data in Table 8.7 was collected by D. R. Peterson of the

Table 8.7 Birthweight Data for Problem 8.2

Dizygous Twins		Monozygous Twins		Dizygous Twins		Monozygous Twins	
SIDS	Non-SIDS	SIDS	Non-SIDS	SIDS	Non-SIDS	SIDS	Non-SIDS
1474	2098	1701	1956	2381	2608	1956	1588
3657	3119	2580	2438	2892	2693	2296	2183
3005	3515	2750	2807	2920	3232	3232	2778
2041	2126	1956	1843	3005	3005	1446	2268
2325	2211	1871	2041	2268	2325	1559	1304
2296	2750	2296	2183	3260	3686	2835	2892
3430	3402	2268	2495	3260	2778	2495	2353
3515	3232	2070	1673	2155	2552	1559	2466
1956	1701	1786	1843	2835	2693		
2098	2410	3175	3572	2466	1899		
3204	2892	2495	2778	3232	3714		

Department of Epidemiology, University of Washington, consists of the birthweights of each of 22 dizygous twins and each of 19 monozygous twins.

(a) For the dizygous twins test the alternative hypothesis that the SIDS child of each pair has the lower birthweight by taking differences and using the sign test. Find the one-sided p-value.

(b) As in part (a), but do the test for the monozygous twins.

(c) As in part (a), but do the test for the combined data set.

8.3 The following data are from Dobson et al. [1976]. Thirty-six patients with a confirmed diagnosis of phenylketonuria (PKU) were identified and placed on dietary therapy before reaching 121 days of age. The children were tested for IQ (Stanford–Binet test) between the ages of 4 and 6; subsequently, their normal siblings of closest age were also tested with the Stanford–Binet. The 15 pairs shown in Table 8.8 are the first 15 listed in the paper. The null hypothesis is that the PKU children, on average, have the same IQ as their siblings. Using the sign test, find the two-sided p-value for testing against the alternative hypothesis that the IQ levels differ.

Table 8.8 PKU/IQ Data for Problem 8.3

Pair	IQ of PKU Case	IQ of Sibling	Pair	IQ of PKU Case	IQ of Sibling
1	89	77	9	110	88
2	98	110	10	90	91
3	116	94	11	76	99
4	67	91	12	71	93
5	128	122	13	100	104
6	81	94	14	108	102
7	96	121	15	74	82
8	116	114			

8.4 Repeat Problem 8.1 using the signed rank test rather than the sign test. Test at the 0.05 significance level.

8.5 Repeat Problem 8.2, parts (a) and (b), using the signed rank test rather than the sign test. Test at the 0.05 significance level.

8.6 Repeat Problem 8.3 using the signed rank test rather than the sign test. Test at the 0.05 significance level.

8.7 Bednarek and Roloff [1976] deal with the treatment of apnea (a transient cessation of breathing) in premature infants using a drug called aminophylline. The variable of interest, "average number of apneic episodes per hour," was measured before and after treatment with the drug. An episode was defined as the absence of spontaneous breathing for more than 20 seconds, or less if associated with bradycardia or cyanosis. Table 8.9 details the response of 13 patients to aminophylline treatment at 16 hours compared with 24 hours before treatment (in apneic episodes per hour).

(a) Use the sign test to examine a treatment effect (give the two-sided p-value).

(b) Use the signed rank test to examine a treatment effect (two-sided test at the 0.05 significance level).

Table 8.9 Before/After Treatment Data for Problem 8.7

Patient	24 Hours Before	16 Hours After	Before–After (Difference)
1	1.71	0.13	1.58
2	1.25	0.88	0.37
3	2.13	1.38	0.75
4	1.29	0.13	1.16
5	1.58	0.25	1.33
6	4.00	2.63	1.37
7	1.42	1.38	0.04
8	1.08	0.50	0.58
9	1.83	1.25	0.58
10	0.67	0.75	−0.08
11	1.13	0.00	1.13
12	2.71	2.38	0.33
13	1.96	1.13	0.83

8.8 The following data from Schechter et al. [1973] deal with sodium chloride preference as related to hypertension. Two groups, 12 normal and 10 hypertensive subjects, were isolated for a week and compared with respect to Na^+ intake. The average daily Na^+ intakes are listed in Table 8.10. Compare the average daily Na^+ intake of the hypertensive subjects with that of the normal volunteers by means of the Wilcoxon two-sample test at the 5% significance level.

Table 8.10 Sodium Data for Problem 8.8

Normal	Hypertensive	Normal	Hypertensive
10.2	92.8	45.8	34.7
2.2	54.8	63.6	62.2
0.0	51.6	1.8	11.0
2.6	61.7	0.0	39.1
0.0	250.8	3.7	
43.1	84.5	0.0	

8.9 During July and August 1976, a large number of Legionnaires attending a convention died of a mysterious and unknown cause. Epidemiologists have talked of "an outbreak of Legionnaires' disease." Chen et al. [1977] examined the hypothesis of nickel contamination as a toxin. They examined the nickel levels in the lungs of nine cases and nine controls. The authors point out that contamination at autopsy is a possibility. The data are as follows (μg per 100 g dry weight):

Legionnaire Cases	65	24	52	86	120	82	399	87	139
Control Cases	12	10	31	6	5	5	29	9	12

Note that there was no attempt to match cases and controls. Use the Wilcoxon test at the one-sided 5% level to test the null hypothesis that the numbers are samples from similar populations.

Table 8.11 Plasma iPGE Data for Problem 8.10

Patient Number	Mean Plasma iPGE (pg/mL)	Mean Serum Calcium (ml/dL)
	Patients with Hypercalcemia	
1	500	13.3
2	500	11.2
3	301	13.4
4	272	11.5
5	226	11.4
6	183	11.6
7	183	11.7
8	177	12.1
9	136	12.5
10	118	12.2
11	60	18.0
	Patients without Hypercalcemia	
12	254	10.1
13	172	9.4
14	168	9.3
15	150	8.6
16	148	10.5
17	144	10.3
18	130	10.5
19	121	10.2
20	100	9.7
21	88	9.2

8.10 Robertson et al. [1976] discuss the level of plasma prostaglandin E (iPGE in pg/mL) in patients with cancer with and without hypercalcemia. The data are given in Table 8.11. Note that the variables are "mean plasma iPGE" and "mean serum Ca" levels; presumably more than one assay was carried out for each patient's level. The number of such tests for each patient is not indicated, nor is the criterion for the number. Using the Wilcoxon two-sample test, test for differences between the two groups in:

(a) Mean plasma iPGE.

(b) Mean serum Ca.

8.11 Sherwin and Layfield [1976] present data about protein leakage in the lungs of male mice exposed to 0.5 part per million of nitrogen dioxide (NO_2). Serum fluorescence data were obtained by sacrificing animals at various intervals. Use the two-sided Wilcoxon test, 0.05 significance level, to look for differences between controls and exposed mice.

(a) At 10 days:

Controls	143	169	95	111	132	150	141
Exposed	152	83	91	86	150	108	78

(b) At 14 days:

Controls	76	40	119	72	163	78
Exposed	119	104	125	147	200	173

8.12 Using the data of Problem 8.8:

(a) Find the value of the Kolmogorov–Smirnov statistic.

(b) Plot the two empirical distribution functions.

(c) Do the curves differ at the 5% significance level? For sample sizes 10 and 12, the 10%, 5%, and 1% critical values for *mnD* are 60, 66, and 80, respectively.

8.13 Using the data of Problem 8.9:

(a) Find the value of the Kolmogorov–Smirnov statistic.

(b) Do you reject the null hypothesis at the 5% level? For $m = 9$ and $n = 9$, the 10%, 5%, and 1% critical values of *mnD* are 54, 54, and 63, respectively.

8.14 Using the data of Problem 8.10:

(a) Find the value of the Kolmogorov–Smirnov statistic for both variables.

(b) What can you say about the p-value? For $m = 10$ and $n = 11$, the 10%, 5%, and 1% critical values of *mnD* are 57, 60, and 77, respectively.

8.15 Using the data of Problem 8.11:

(a) Find the value of the Kolmogorov–Smirnov statistic.

(b) Do you reject at 10%, 5%, and 1%, respectively? Do this for parts (a) and (b) of Problem 8.11. For $m = 7$ and $n = 7$, the 10%, 5%, and 1% critical values of *mnD* are 35, 42, and 42, respectively. The corresponding critical values for $m = 6$ and $n = 6$ are 30, 30, and 36.

8.16 Test at the 0.05 significance level for a significant improvement with the cream treatment of Example 8.2.

(a) Use the sign test.

(b) Use the signed rank test.

(c) Use the t-test.

8.17 Use the expression of colostrum data of Example 8.2, and test at the 0.10 significance level the null hypothesis of no treatment effect.

(a) Use the sign test.

(b) Use the signed rank test.

(c) Use the usual t-test.

8.18 Test the null hypothesis of no treatment difference from Example 8.2 using each of the tests in parts (a), (b), and (c).

(a) The Wilcoxon two-sample test.

(b) The Kolmogorov–Smirnov two-sample test. For $m = n = 19$, the 20%, 10%, 5%, 1%, and 0.1% critical values for *mnD* are 133, 152, 171, 190, and 228, respectively.

(c) The two-sample t-test.

Compare the two-sided p-values to the extent possible. Using the data of Example 8.2, examine each treatment.

(d) Nipple-rolling vs. masse cream.

(e) Nipple-rolling vs. expression of colostrum.

(f) Masse cream vs. expression of colostrum.

8.19 As discussed in Chapter 3, Winkelstein et al. [1975] studied systolic blood pressures of three groups of Japanese men: native Japanese, first-generation immigrants to the United States (Issei), and second-generation Japanese in the United States (Nisei). The data are listed in Table 8.12. Use the asymptotic Wilcoxon two-sample statistic to test:

(a) Native Japanese vs. California Issei.

(b) Native Japanese vs. California Nisei.

(c) California Issei vs. California Nisei.

Table 8.12 Blood Pressure Data for Problem 8.19

Blood Pressure (mmHg)	Native Japanese	Issei	Nisei
<106	218	4	23
106–114	272	23	132
116–124	337	49	290
126–134	362	33	347
136–144	302	41	346
146–154	261	38	202
156–164	166	23	109
>166	314	52	112

***8.20** Rascati et al. [2001] report a study of medical costs for children with asthma in which children prescribed steroids had a higher mean cost than other children, but lower costs according to a Wilcoxon rank-sum test. How can this happen, and what conclusions should be drawn?

***8.21** An outlier is an observation far from the rest of the data. This may represent valid data or a mistake in experimentation, data collection, or data entry. At any rate, a few outlying observations may have an extremely large effect. Consider a one-sample t-test of mean zero based on 10 observations with

$$\overline{x} = 10 \quad \text{and} \quad s^2 = 1$$

Suppose now that one observation of value x is added to the sample.

(a) Show that the value of the new sample mean, variance, and t-statistic are

$$\overline{x} = \frac{100 + x}{11}$$

$$s^2 = \frac{10x^2 - 200x + 1099}{11 \times 10}$$

$$t = \frac{100 + x}{\sqrt{x^2 - 20x + 109.9}}$$

***(b)** Graph t as a function of x.

(c) For which values of x would one reject the null hypothesis of mean zero? What does the effect of an outlier (large absolute value) do in this case?

(d) Would you reject the null hypothesis without the outlier?

(e) What would the graph look like for the Wilcoxon signed rank test? For the sign test?

***8.22** Using the ideas of Note 8.4 about the signed rank test, verify the values shown in Table 8.13 when $n = 4$.

Table 8.13 Signed-Rank Test Data for Problem 8.23

s	$P[S \le s]$	s	$P[S \le s]$
0	0.062	6	0.688
1	0.125	7	0.812
2	0.188	8	0.875
3	0.312	9	0.938
4	0.438	10	1.000
5	0.562		

Source: Owen [1962]; by permission of Addison-Wesley Publishing Company.

***8.23** The Wilcoxon two-sample test depends on the fact that under the null hypothesis, if two samples are drawn without ties, all $\binom{n+m}{n}$ arrangements of the n ranks from the first sample, and the m ranks from the second sample, are equally likely. That is, if $n = 1$ and $m = 2$, the three arrangements

$$\begin{array}{llll} \mathbf{1} & 2 & 3; & W = 1 \\ 1 & \mathbf{2} & 3; & W = 2 \\ 1 & 2 & \mathbf{3}; & W = 3 \end{array}$$

are equally likely. Here, the rank from population 1 appears in bold type.

(a) If $n = 2$ and $m = 4$, graph the distribution function of the Wilcoxon two-sample statistic when the null hypothesis holds.

(b) Find $E(W)$. Does it agree with equation (5)?

(c) Find $\text{var}(W)$. Does it agree with equation (6)?

***8.24** (Permutation Two-Sample t-Test) To use the permutation two-sample t-test, the text (in Section *8.9) used the fact that for $n + m$ fixed values, the t-test was a monotone function of $\overline{x} - \overline{y}$. To show this, prove the following equality:

$$t = \frac{1}{\sqrt{\dfrac{(n+m)\left(\sum_i x_i^2 + \sum_i y_i^2\right) - \left(\sum_i x_i + \sum_i y_i\right)^2 - nm(\overline{x} - \overline{y})^2}{nm(n+m-2)(\overline{x} - \overline{y})^2}}}$$

Note that the first two terms in the numerator of the square root are constant for all permutations, so t is a function of $\overline{x} - \overline{y}$.

***8.25** (One-Sample Randomization t-Test) For the randomization one-sample t-test, the paired x_i and y_i values give $\overline{x}-\overline{y}$ values. Assume that the $|x_i - y_i|$ are known but the signs are random, independently $+$ or $-$ with probability 1/2. The $2^n (i = 1, 2, \ldots, n)$ patterns of pluses and minuses are equally likely.

(a) Show that the one-sample t-statistic is a monotone function of $\overline{x - y}$ when the $|x_i - y_i|$ are known. Do this by showing that

$$t = \frac{\overline{x - y}}{\sqrt{\left[-n(\overline{x - y})^2 + \sum_i (x_i - y_i)^2\right] / n(n-1)}}$$

(b) For the data

i	X_i	Y_i
1	1	2
2	3	1
3	1	5

compute the eight possible randomization values of t. What is the two-sided randomization p-value for the t observed?

***8.26** (Robust Estimation of the Mean) Show that the α-trimmed mean and the α-Winsorized mean are weighted means by explicitly showing the weights W_i that are given the two means.

***8.27** (Robust Estimation of the Mean)

(a) For the combined data for SIDS in Problem 8.2, compute (**i**) the 0.05 trimmed mean; (**ii**) the 0.05 Winsorized mean; (**iii**) the weighted mean with weights $W_i = i(n + 1 - i)$, where n is the number of observations.

(b) The same as in Problem 8.27(a), but do this for the non-SIDS twins.

REFERENCES

Alderman, E., Fisher, L. D., Maynard, C., Mock, M. B., Ringqvist, I., Bourassa, M. G., Kaiser, G. C., and Gillespie, M. J. [1982]. Determinants of coronary surgery in a consecutive patient series from geographically dispersed medical centers: the Coronary Artery Surgery Study. *Circulation*, **66**: 562–568.

Bednarek, E., and Roloff, D. W. [1976]. Treatment of apnea of prematurity with aminophylline. *Pediatrics*, **58**: 335–339.

Beyer, W. H. (ed.) [1990]. *CRC Handbook of Tables for Probability and Statistics*. 2nd ed. CRC Press, Boca Raton, FL.

Bradley, J. V. [1968]. *Distribution-Free Statistical Tests*. Prentice Hall, Englewood Cliffs, NJ.

Brown, M. S., and Hurlock, J. T. [1975]. Preparation of the breast for breast-feeding. *Nursing Research*, **24**: 448–451.

CASS [1981]. (Principal investigators of CASS and their associates; Killip, T. (ed.); Fisher, L. D., and Mock, M. (assoc. eds.) National Heart, Lung and Blood Institute Coronary Artery Surgery Study. *Circulation*, **63**: part II, I–1 to I–81. Used with permission from the American Heart Association.

Chaitin, G. J. [1975]. Randomness and mathematical proof, *Scientific American*, **232**(5): 47–52.

Chen, J. R., Francisco, R. B., and Miller, T. E. [1977]. Legionnaires' disease: nickel levels. *Science*, **196**: 906–908.

Church, J. D., and Harris, B. [1970]. The estimation of reliability from stress–strength relationships. *Technometrics*, **12**: 49–54.

Davison, A. C., and Hinckley, D. V. [1997]. *Bootstrap Methods and Their Application*. Cambridge University Press, New York.

Dennett, D. C. [1984]. *Elbow Room: The Varieties of Free Will Worth Wanting*. MIT Press, Cambridge, MA.

Dobson, J. C., Kushida, E., Williamson, M., and Friedman, E. [1976]. Intellectual performance of 36 phenylketonuria patients and their nonaffected siblings. *Pediatrics*, **58**: 53–58.

Edgington, E. S. [1995]. *Randomization Tests*, 3rd ed. Marcel Dekker, New York.

Efron, B. [1979]. Bootstrap methods: another look at the jackknife. *Annals of Statistics*, **7**: 1–26.

Efron, B. [1982]. *The Jackknife, Bootstrap and Other Resampling Plans*. Society for Industrial and Applied Mathematics, Philadelphia.

Efron, B., and Tibshirani, R. [1986]. The bootstrap (with discussion). *Statistical Science*, **1**: 54–77.

Efron, B., and Tibshirani, R. [1993]. *An Introduction to the Bootstrap*. Chapman & Hall, London.

Hajek, J. [1969]. *A Course in Nonparametric Statistics*. Holden-Day, San Francisco.

Hajek, J., and Sidak, Z. [1999]. *Theory of Rank Tests*. 2nd ed. Academic Press, New York.

Hoffman, D. T. [1979]. *Monte Carlo: The Use of Random Digits to Simulate Experiments*. Models and monographs in undergraduate mathematics and its Applications, Unit 269, EDC/UMAP, Newton, MA.

Hollander, M., and Wolfe, D. A. [1999]. *Nonparametric Statistical Methods*, 2nd ed. Wiley, New York.

Huber, P. J. [2003]. *Robust Statistics*. Wiley, New York.

Johnson, R. A., Verill, S., and Moore D. H. [1987]. Two-sample rank tests for detecting changes that occur in a small proportion of the treated population. *Biometrics*, **43**: 641–655

Kraft, C. H., and van Eeden, C. [1968]. *A Nonparametric Introduction to Statistics*. Macmillan, New York.

Lehmann, E. L., and D'Abrera, H. J. M. [1998]. *Nonparametrics: Statistical Methods Based on Ranks*. Holden-Day, San Francisco.

Lumley, T., Diehr, P., Emerson, S., and Chen, L. [2002]. The importance of the normality assumption in large public health data sets. *Annual Review of Public Health*, **23**: 151–169.

Marascuilo, L. A., and McSweeney, M. [1977]. *Nonparametric and Distribution-Free Methods for the Social Sciences*. Brooks/Cole, Scituate, MA.

Massart, P. [1990]. The tight constant in the Dvoretsky-Kiefer-Wolfowitz inequality. *Annals of Probability*, **18**: 897–919.

Odeh, R. E., Owen, D. B., Birnbaum, Z. W., and Fisher, L. D. [1977]. *Pocket Book of Statistical Tables*. Marcel Dekker, New York.

Owen, D. B. [1962]. *Handbook of Statistical Tables*. Addison-Wesley, Reading, MA.

Peterson, A. P., and Fisher, L. D. [1980]. Teaching the principles of clinical trials design. *Biometrics*, **36**: 687–697.

Rascati, K. L., Smith, M. J., and Neilands, T. [2001]. Dealing with skewed data: an example using asthma-related costs of Medicaid clients. *Clinical Therapeutics*, **23**: 481–498.

Ripley B. D. [1987]. *Stochastic Simulation*. Wiley, New York.

Robertson, R. P., Baylink, D. J., Metz, S. A., and Cummings, K. B. [1976]. Plasma prostaglandin in patients with cancer with and without hypercalcemia. *Journal of Clinical Endocrinology and Metabolism*, **43**: 1330–1335.

Schechter, P. J., Horwitz, D., and Henkin, R. I. [1973]. Sodium chloride preference in essential hypertension. *Journal of the American Medical Association*, **225**: 1311–1315.

Sherwin, R. P., and Layfield, L. J. [1976]. Protein leakage in the lungs of mice exposed to 0.5 ppm nitrogen dioxide: a fluorescence assay for protein. *Archives of Environmental Health*, **31**: 116–118.

Siegel, S., and Castellan, N. J., Jr. [1990]. *Nonparametric Statistics for the Behavioral Sciences*, 2nd ed. McGraw-Hill, New York.

Ulam, S. M. [1976]. *Adventures of a Mathematician*. Charles Scribner's Sons, New York.

U.S. EPA [1994]. *Statistical Methods for Evaluating the Attainment of Cleanup Standards*, Vol. 3, *Reference-Based Standards for Soils and Solid Media*. EPA/600/R-96/005. Office of Research and Development, U.S. EPA, Washington, DC.

Vlachakis, N. D., and Mendlowitz, M. [1976]. Alpha- and beta-adrenergic receptor blocking agents combined with a diuretic in the treatment of essential hypertension. *Journal of Clinical Pharmacology*, **16**: 352–360.

Winkelstein, W., Jr., Kazan, A., Kato, H., and Sachs, S. T. [1975]. Epidemiologic studies of coronary heart disease and stroke in Japanese men living in Japan, Hawaii, and California: blood pressure distributions. *American Journal of Epidemiology*, **102**: 502–513.

CHAPTER 9

Association and Prediction: Linear Models with One Predictor Variable

9.1 INTRODUCTION

Motivation for the methods of this chapter is aided by the use of examples. For this reason, we first consider three data sets. These data are used to motivate the methods to follow. The data are also used to illustrate the methods used in Chapter 11. After the three examples are presented, we return to this introduction.

Example 9.1. Table 9.1 and Figure 9.1 contain data on mortality due to malignant melanoma of the skin of white males during the period 1950–1969 for each state in the United States as well as the District of Columbia. No mortality data are available for Alaska and Hawaii for this period. It is well known that the incidence of melanoma can be related to the amount of sunshine and, somewhat equivalently, the latitude of the area. The table contains the latitude as well as the longitude for each state. These numbers were obtained simply by estimating the center of the state and reading off the latitude as given in a standard atlas. Finally, the 1965 population and contiguity to an ocean are noted, where "1" indicates contiguity: the state borders one of the oceans.

In the next section we shall be particularly interested in the relationship between the melanoma mortality and the latitude of the states. These data are presented in Figure 9.1.

Definition 9.1. When two variables are collected for each data point, a plot is very useful. Such plots of the two values for each of the data points are called *scatter diagrams* or *scattergrams*.

Note several things about the scattergram of malignant melanoma rates vs. latitude. There appears to be a rough relationship. As the latitude increases, the melanoma rate decreases. Nevertheless, there is no one-to-one relationship between the values. There is considerable scatter in the picture. One problem is to decide whether or not the scatter could be due to chance or whether there is some relationship. It might be of interest to estimate the melanoma rate for various latitudes. In this case, how would we estimate the relationship? To convey the relationship to others, it would also be useful to have some simple way of summarizing the relationship. There are two aspects of the relationship that might be summarized. One is how the melanoma rate changes with latitude; it would also be useful to summarize the variability of the scattergram.

Biostatistics: A Methodology for the Health Sciences, Second Edition, by Gerald van Belle, Lloyd D. Fisher, Patrick J. Heagerty, and Thomas S. Lumley
ISBN 0-471-03185-2

Table 9.1 Mortality Rate [per 10 Million (10^7)] of White Males Due to Malignant Melanoma of the Skin for the Period 1950–1959 by State and Some Related Variables

State	Mortality per 10,000,000	Latitude (deg)	Longitude (deg)	Population (millions, 1965)	Ocean State[a]
Alabama	219	33.0	87.0	3.46	1
Arizona	160	34.5	112.0	1.61	0
Arkansas	170	35.0	92.5	1.96	0
California	182	37.5	119.5	18.60	1
Colorado	149	39.0	105.5	1.97	0
Connecticut	159	41.8	72.8	2.83	1
Delaware	200	39.0	75.5	0.50	1
Washington, DC	177	39.0	77.0	0.76	0
Florida	197	28.0	82.0	5.80	1
Georgia	214	33.0	83.5	4.36	1
Idaho	116	44.5	114.0	0.69	0
Illinois	124	40.0	89.5	10.64	0
Indiana	128	40.2	86.2	4.88	0
Iowa	128	42.2	93.8	2.76	0
Kansas	166	38.5	98.5	2.23	0
Kentucky	147	37.8	85.0	3.18	0
Louisiana	190	31.2	91.8	3.53	1
Maine	117	45.2	69.0	0.99	1
Maryland	162	39.0	76.5	3.52	1
Massachusetts	143	42.2	71.8	5.35	1
Michigan	117	43.5	84.5	8.22	0
Minnesota	116	46.0	94.5	3.55	0
Mississippi	207	32.8	90.0	2.32	1
Missouri	131	38.5	92.0	4.50	0
Montana	109	47.0	110.5	0.71	0
Nebraska	122	41.5	99.5	1.48	0
Nevada	191	39.0	117.0	0.44	0
New Hampshire	129	43.8	71.5	0.67	1
New Jersey	159	40.2	74.5	6.77	1
New Mexico	141	35.0	106.0	1.03	0
New York	152	43.0	75.5	18.07	1
North Carolina	199	35.5	79.5	4.91	1
North Dakota	115	47.5	100.5	0.65	0
Ohio	131	40.2	82.8	10.24	0
Oklahoma	182	35.5	97.2	2.48	0
Oregon	136	44.0	120.5	1.90	1
Pennsylvania	132	40.8	77.8	11.52	0
Rhode Island	137	41.8	71.5	0.92	1
South Carolina	178	33.8	81.0	2.54	1
South Dakota	86	44.8	100.0	0.70	0
Tennessee	186	36.0	86.2	3.84	0
Texas	229	31.5	98.0	10.55	1
Utah	142	39.5	111.5	0.99	0
Vermont	153	44.0	72.5	0.40	1
Virginia	166	37.5	78.5	4.46	1
Washington	117	47.5	121.0	2.99	1
West Virginia	136	38.8	80.8	1.81	0
Wisconsin	110	44.5	90.2	4.14	0
Wyoming	134	43.0	107.5	0.34	0

Source: U.S. Department of Health, Education, and Welfare [1974].

[a] 1 = state borders on ocean.

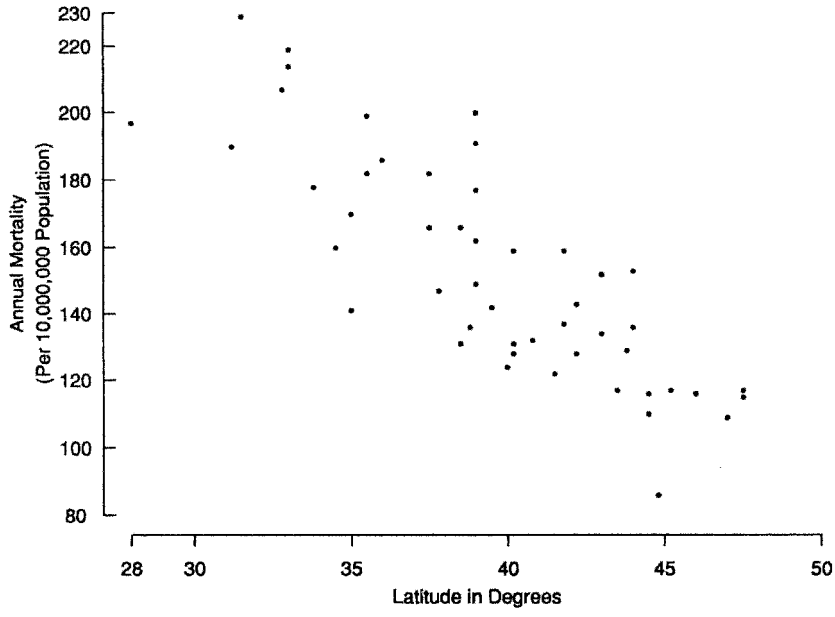


Figure 9.1 Annual mortality (per 10,000,000 population) due to malignant melanoma of the skin for white males by state and latitude of the center of the state for the period 1950–1959.

Example 9.2. To assess physical conditioning in normal subjects, it is useful to know how much energy they are capable of expending. Since the process of expending energy requires oxygen, one way to evaluate this is to look at the rate at which they use oxygen at peak physical activity. To examine the peak physical activity, tests have been designed where a person runs on a treadmill. At specified time intervals, the speed at which the treadmill moves and the grade of the treadmill both increase. The person is then run systematically to maximum physical capacity. The maximum capacity is determined by the person, who stops when unable to go further. Data from Bruce et al. [1973] are discussed.

The oxygen consumption was measured in the following way. The patient's nose was blocked off by a clip. Expired air was collected from a silicone rubber mouthpiece fitted with a very low resistance valve. The valve was connected by plastic tubes into a series of evacuated neoprene balloons. The inlet valve for each balloon was opened for 60 seconds to sample the expired air. Measurements were made of the volumes of expired air, and the oxygen content was obtained using a paramagnetic analyzer capable of measuring the oxygen. From this, the rate at which oxygen was used in mm/min was calculated. Physical conditioning, however, is relative to the size of the person involved. Smaller people need less oxygen to perform at the same speed. On the other hand, smaller people have smaller hearts, so relatively, the same level of effort may be exerted. For this reason, the maximum oxygen content is normalized by body weight; a quantity, $VO_{2\ MAX}$, is computed by looking at the volume of oxygen used per minute per kilogram of body weight. Of course, the effort expended to go further on the treadmill increases with the duration of time on the treadmill, so there should be some relationship between $VO_{2\ MAX}$ and duration on the treadmill. This relationship is presented below.

Other pertinent variables that are used in the problems and in additional chapters are recorded in Table 9.2, including the maximum heart rate during exercise, the subject's age, height, and weight. The 44 subjects listed in Table 9.2 were all healthy. They were classified as active if they usually participated at least three times per week in activities vigorous enough to raise a sweat.

Table 9.2 Exercise Data for Healthy Active Males

Case	Duration (s)	$VO_{2\ MAX}$	Heart Rate (beats/min)	Age	Height (cm)	Weight (kg)
1	706	41.5	192	46	165	57
2	732	45.9	190	25	193	95
3	930	54.5	190	25	187	82
4	900	60.3	174	31	191	84
5	903	60.5	194	30	171	67
6	976	64.6	168	36	177	78
7	819	47.4	185	29	174	70
8	922	57.0	200	27	185	76
9	600	40.2	164	56	180	78
10	540	35.2	175	47	180	80
11	560	33.8	175	46	180	81
12	637	38.8	162	55	180	79
13	593	38.9	190	50	161	66
14	719	49.5	175	52	174	76
15	615	37.1	164	46	173	84
16	589	32.2	156	60	169	69
17	478	31.3	174	49	178	78
18	620	33.8	166	54	181	101
19	710	43.7	184	57	179	74
20	600	41.7	160	50	170	66
21	660	41.0	186	41	175	75
22	644	45.9	175	58	173	79
23	582	35.8	175	55	160	79
24	503	29.1	175	46	164	65
25	747	47.2	174	47	180	81
26	600	30.0	174	56	183	100
27	491	34.1	168	82	183	82
28	694	38.1	164	48	181	77
29	586	28.7	146	68	166	65
30	612	37.1	156	54	177	80
31	610	34.5	180	56	179	82
32	539	34.4	164	50	182	87
33	559	35.1	166	48	174	72
34	653	40.9	184	56	176	75
35	733	45.4	186	45	179	75
36	596	36.9	174	45	179	79
37	580	41.6	188	43	179	73
38	550	22.7	180	54	180	75
39	497	31.9	168	55	172	71
40	605	42.5	174	41	187	84
41	552	37.4	166	44	185	81
42	640	48.2	174	41	186	83
43	500	33.6	180	50	175	78
44	603	45.0	182	42	176	85

Source: Data from Bruce et al. [1973].

The duration of the treadmill exercise and $VO_{2\ MAX}$ data are presented in Figure 9.2. In this scattergram, we see that as the treadmill time increases, by and large, the $VO_{2\ MAX}$ increases. There is, however, some variability. The increase is not an infallible rule. There are subjects who run longer but have less oxygen consumption than someone else who has exercised for a shorter time period. Because of the expense and difficulty in collecting the expired air volumes,

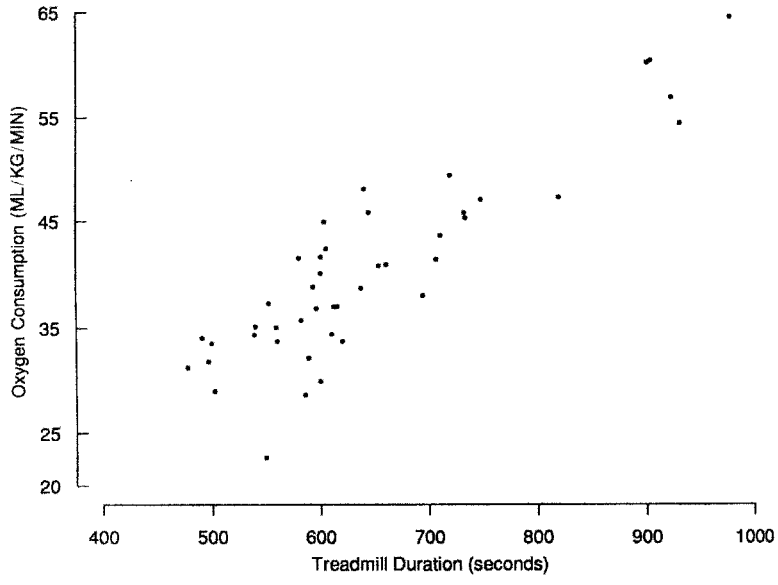


Figure 9.2 Oxygen consumption vs. treadmill duration.

it is useful to evaluate oxygen consumption and conditioning by having the subjects run on the treadmill and recording the duration. As we can see from Figure 9.2, this would not be a perfect solution to the problem. Duration would not totally determine the $VO_{2\ MAX}$ level. Nevertheless, it would give us considerable information. When we do this, how should we predict what the $VO_{2\ MAX}$ level would be from the duration? Clearly, such a predictive equation should be developed from the data at hand. When we do this, we want to characterize the accuracy of such predictions and succinctly summarize the relationship between the two variables.

Example 9.3. Dern and Wiorkowski [1969] collected data dealing with the erythrocyte adenosine triphosphate (ATP) levels in youngest and older sons in 17 families. The purpose of the study was to determine the effect of storage of the red blood cells on the ATP level. The level is important because it determines the ability of the blood to carry energy to the cells of the body. The study found considerable variation in the ATP levels, even before storage. Some of the variation could be explained on the basis of variation by family (genetic variation). The data for the oldest and youngest sons are extracted from the more complete data set in the paper. Table 9.3 presents the data for 17 pairs of brothers along with the ages of the brothers.

Figure 9.3 is a scattergram of the values in Table 9.3. Again, there appears to be some relationship between the two values, with both brothers tending to have high or low values at the same time. Again, we would like to consider whether or not such variability might occur by chance. If chance is not the explanation, how could we summarize the pattern of variation for the pairs of numbers?

The three scattergrams have certain features in common:

1. Each scattergram refers to a situation where two quantities are associated with each experimental unit. In the first example, the melanoma rate for the state and the latitude of the state are plotted. The state is the individual unit. In the second example, for each person studied on the treadmill, $VO_{2\ MAX}$ vs. the treadmill time in seconds was plotted. In the third example, the experimental unit was the family, and the ATP values of the youngest and oldest sons were plotted.

Table 9.3 Erythrocyte Adenosine Triphosphate (ATP) Levels[a] in Youngest and Oldest Sons in 17 Families Together with Age (Before Storage)

	Youngest		Oldest	
Family	Age	ATP Level	Age	ATP Level
1	24	4.18	41	4.81
2	25	5.16	26	4.98
3	19	4.85	27	4.48
4	28	3.43	32	4.19
5	22	4.53	25	4.27
6	7	5.13	23	4.87
7	21	4.10	24	4.74
8	17	4.77	25	4.53
9	25	4.12	26	3.72
10	24	4.65	25	4.62
11	12	6.03	25	5.83
12	16	5.94	24	4.40
13	9	5.99	22	4.87
14	18	5.43	24	5.44
15	14	5.00	26	4.70
16	24	4.82	26	4.14
17	20	5.25	24	5.30

Source: Data from Dern and Wiorkowski [1969].

[a] ATP levels expressed as micromoles per gram of hemoglobin.

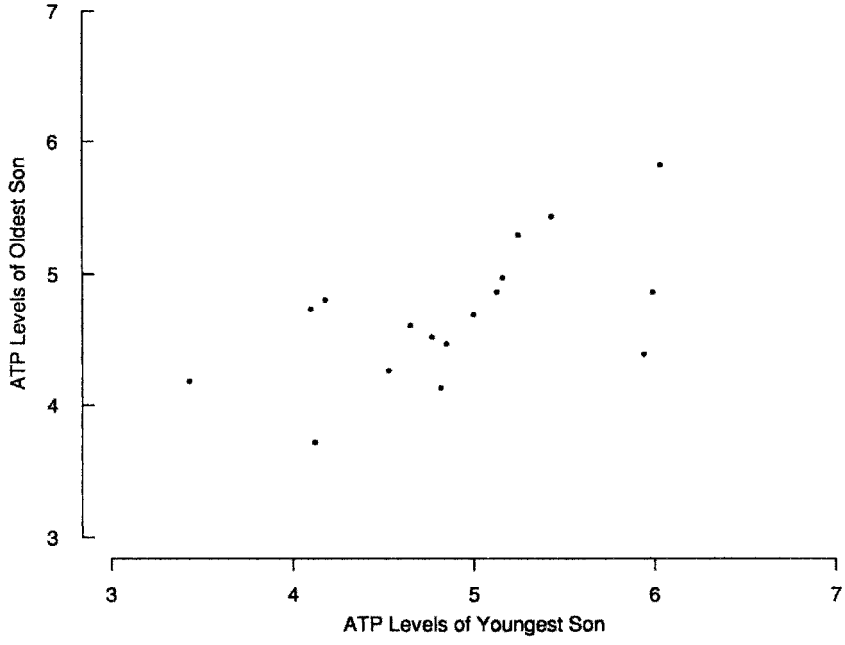


Figure 9.3 ATP levels (μmol/g of hemoglobin) of youngest and oldest sons in 17 families. (Data from Dern and Wiorkowski [1969].)

2. In each of the three diagrams, there appears to be a rough trend or association between the variables. In the melanoma rate date, as the latitude increases, the melanoma rate tends to decrease. In the treadmill data, as the duration on the treadmill increased, the $VO_{2\ MAX}$ also increased. In the ATP data, both brothers tended to have either a high or a low value for ATP.
3. Although increasing and decreasing trends were evident, there was not a one-to-one relationship between the two quantities. It was not true that every state with a higher latitude had a lower melanoma rate in comparison with a state at a lower latitude. It was not true that in each case when individual A ran on the treadmill a longer time than individual B that individual A had a higher $VO_{2\ MAX}$ value. There were some pairs of brothers for which one pair did not have the two highest values when compared to the other pair. This is in contrast to certain physical relationships. For example, if one plotted the volume of a cube as a function of the length of a side, there is the one-to-one relationship: the volume increases as the length of the side increases. In the data we are considering, there is a rough relationship, but there is still considerable variability or scatter.
4. To effectively use and summarize such scattergrams, there is a need for a method to quantitate how much of a change the trends represent. For example, if we consider two states where one has a latitude 5° south of the other, how much difference is expected in the melanoma rates? Suppose that we train a person to increase the duration of treadmill exercise by 70 seconds; how much of a change in $VO_{2\ MAX}$ capacity is likely to occur?
5. Suppose that we have some method of quantitating the overall relationship between the two variables in the scattergram. Since the relationship is not precisely one to one, there is a need to summarize how much of the variability the relationship explains. Another way of putting this is that we need a summary quantity which tells us how closely the two variables are related in the scattergram.
6. If we have methods of quantifying these things, we need to know whether or not any estimated relationships might occur by chance. If not, we still want to be able to quantify the uncertainty in our estimated relationships.

The remainder of this chapter deals with the issues we have just raised. In the next section we use a linear equation (a straight line) to summarize the relationship between two variables in a scattergram.

9.2 SIMPLE LINEAR REGRESSION MODEL

9.2.1 Summarizing the Data by a Linear Relationship

The three scattergrams above have a feature in common: the overall relationship is roughly linear; that is, a straight line that characterizes the relationships between the two variables could be placed through the data. In this and subsequent chapters, we look at linear relationships. A linear relationship is one expressed by a linear equation. For variables $U, V, W, \ldots$, and constants $a, b, c, \ldots$, a linear equation for Y is given by

$$Y = a + bU + cV + dW + \cdots$$

In the scattergrams for the melanoma data and the exercise data, let X denote the variable on the horizontal axis (*abscissa*) and Y be the notation for the variable on the vertical axis (*ordinate*). Let us summarize the data by fitting the straight-line equation $Y = a + bX$ to the data. In each case, let us think of the X variable as predicting a value for Y. In the first two

examples, that would mean that given the latitude of the state, we would predict a value for the melanoma rate; given the duration of the exercise test, we would predict the $VO_{2\ MAX}$ value for each subject.

There is terminology associated with this procedure. The variable being predicted is called the *dependent variable* or *response variable*; the variable we are using to predict is called the *independent variable*, the *predictor variable*, or the *covariate*. For a particular value, say, X_i of the predictor variable, our value predicted for Y is given by

$$\widehat{Y}_i = a + bX_i \tag{1}$$

The fit of the values predicted to the values observed (X_i, Y_i) may be summarized by the difference between the value Y_i observed and the value $\widehat{Y}_i$ predicted. This difference is called a *residual value*:

$$\text{residual value} = y_i - \widehat{y}_i = \text{value observed} - \text{value predicted} \tag{2}$$

It is reasonable to fit the line by trying to make the residual values as small as possible. The *principle of least squares* chooses a and b to minimize the sum of squares of the residual values. This is given in the following definition:

Definition 9.2. Given data $(x_i, y_i), i = 1, 2, \ldots, n$, the *least squares fit* to the data chooses a and b to minimize

$$\sum_{i=1}^{n} (y_i - \widehat{y}_i)^2$$

where $\widehat{y}_i = a + bx_i$.

The values a and b that minimize the sum of squares are described below. At this point, we introduce some notation similar to that of Section 7.3:

$$[y^2] = \sum_i (y_i - \overline{y})^2$$

$$[x^2] = \sum_i (x_i - \overline{x})^2$$

$$[xy] = \sum_i (x_i - \overline{x})(y_i - \overline{y})$$

We decided to choose values a and b so that the quantity

$$\sum_i (y_i - \widehat{y}_i)^2 = \sum_i (y_i - a - bx_i)^2$$

is minimized. It can be shown that the values for a and b that minimize the quantity are given by

$$b = \frac{\sum (x_i - \overline{x})(y_i - \overline{y})}{\sum (x_i - \overline{x})^2} = \frac{[xy]}{[x^2]}$$

and

$$a = \overline{y} - b\overline{x}$$

Note 9.4 gives another equivalent formula for b that emphasizes its role as a summary statistic of the slope of the X–Y relationship.

Table 9.4 Predicted Mortality Rates by Latitude for the Data of Table 9.1[a]

Latitude (x)	Predicted Mortality (y)	s_1	s_2	s_3
30	209.9	19.12	6.32	20.13
35	180.0	19.12	3.85	19.50
39.5 (mean)	152.9 (mean)	19.12	2.73	19.31
40	150.1	19.12	2.74	19.31
45	120.2	19.12	4.26	19.58
50	90.3	19.12	6.83	20.30

[a]For the quantities s_2 and s_3, see Section 9.2.3.

For the melanoma data, we have the following quantities:

$$\overline{x} = 39.533, \qquad \overline{y} = 152.878$$

$$\sum_i (x_i - \overline{x})(y_i - \overline{y}) = [xy] = -6100.171$$

$$\sum_i (x_i - \overline{x})^2 = [x^2] = 1020.499$$

$$\sum_i (y_i - \overline{y})^2 = [y^2] = 53,637.265$$

The least squares slope b is

$$b = \frac{-6100.171}{1020.499} = -5.9776$$

and the least squares intercept a is

$$a = 152.878 - (-5.9776 \times 39.533) = 389.190$$

Figure 9.4 presents the melanoma data with the line of least squares fit drawn in. Because of the method of selecting the line, the line goes through the data, of course. The least squares line always has the property that it goes through the point in the scattergram corresponding to the sample mean of the two variables. The sample means of the variables are located by the intersection of dotted lines. Further, the point for Tennessee is detailed in the box in the lower left-hand corner. The value predicted from the equation was 174, whereas the actual melanoma rate for this state was 186. Thus, the residual value is the difference, 12. We see that the value predicted, 174, is closer to the value observed than to the overall Y mean, which is 152.9.

For the melanoma data, the line of least squares fit is $Y = 389.19 - 5.9776X$. For each state's observed mortality rate, there is then a predicted mortality rate based on knowledge of the latitude. Some predicted values are listed in Table 9.4. The farther north the state, the lower the mortality due to malignant melanoma; but now we have quantified the change.

Note that the predicted mortality at the mean latitude (39.5°) is exactly the mean value of the mortalities *observed*; as noted above, the regression line goes through the point $(\overline{x}, \overline{y})$.

9.2.2 Linear Regression Models

With the line of least squares fit, we shall associate a mathematical model. This *linear regression model* takes the predictor or covariate observation as being fixed. Even if it is sampled at random,

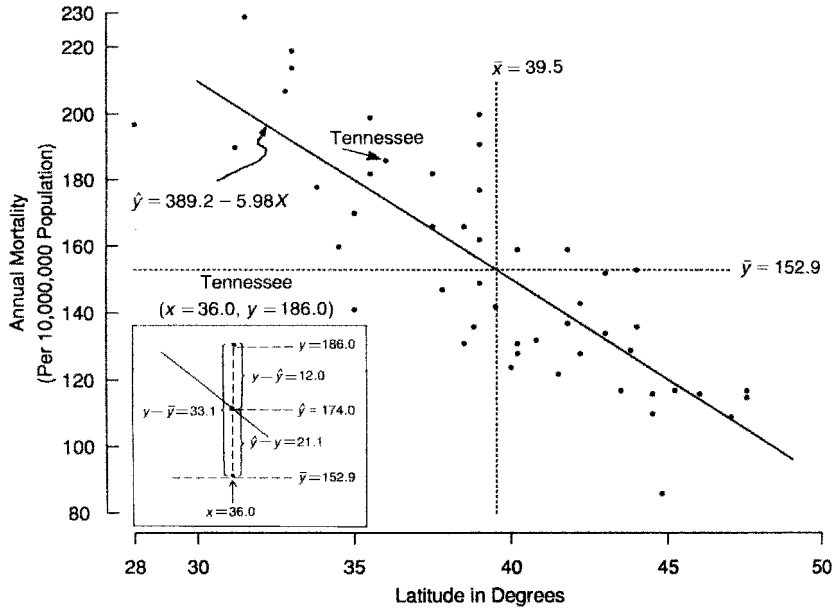


Figure 9.4 Annual mortality (per 10,000,000 population) due to malignant melanoma of the skin for white males by state and latitude of the center of the state for the period 1950–1959 (least squares regression line is given).

the analysis is conditional upon knowing the value of X. In the first example above, the latitude of each state is fixed. In the second example, the healthy people may be considered to be a representative—although not random—sample of a larger population; in this case, the duration may be considered a random quantity. In the linear regression analysis of this chapter, we know X and are interested in predicting the value of Y. The regression model assumes that for a fixed value of X, the expected value of Y is some function. In addition to this expected value, a random error term is added. It is assumed that the error has a mean value of zero. We shall restrict ourselves to situations where the expected value of Y for known X is a linear function. Thus, our linear regression model is the following:

$$\text{expected value of } Y \text{ knowing } X = E(Y|X) = \alpha + \beta X$$

$$Y = \alpha + \beta X + e, \qquad \text{where } e \text{ (error) has } E(e) = 0$$

The parameters α and β are population parameters. Given a sample of observations, the estimates a and b that we found above are estimates of the population parameters. In the mortality rates of the states, the random variability arises both because of the randomness of the rates in a given year and random factors associated with the state, other than latitude. These factors make the observations during a particular time period reasonably modeled as a random quantity. For the exercise test data, we may consider the normal subjects tested as a random sample from a population of active normal males who might have been tested.

Definition 9.3. The line $E(Y|X) = \alpha + \beta X$ is called the *population regression line*. Here, $E(Y|X)$ is the expected value of Y at X (assumed known). The coefficients α and β are called *population regression coefficients*. The line $Y = a + bX$ is called the *estimated regression line*,

and a and b are called *estimated regression coefficients*. The term *estimated* is often dropped, and *regression line* and *regression coefficients* are used for these estimated quantities.

For each X, $E(Y|X)$ is the mean of a population of observations. On the left of Figure is shown a linear regression situation; on the right, the regression $E(Y|X)$ is not linear.

To simplify statistical inference, another assumption is often added: that the error term is normally distributed with mean zero and variance σ_1^2. As we saw with the t-test, the assumption of normality is important for testing and confidence interval estimation only in fairly small samples. In larger samples the central limit theorem replaces the need for distributional assumptions. Note that the variance of the error term is *not* the variance of the Y variable. It is the variance of the Y variable *when* the value of the X variable is known.

Given data, the variance σ_1^2 is estimated by the quantity $s_{y\cdot x}^2$, where this quantity is defined as

$$s_{y\cdot x}^2 = \sum \frac{(Y_i - \widehat{Y}_i)^2}{n-2}$$

Recall that the usual sample variance was divided by $n-1$. The $n-2$ occurs because two parameters, α and β, are estimated in fitting the data rather than one parameter, the sample mean, that was estimated before.

9.2.3 Inference

We have the model

$$Y = \alpha + \beta X + e, \qquad \text{where } e \sim N(0, \sigma_1^2)$$

On the basis of n pairs of observations we presented estimates a and b of α and β, respectively. To test hypotheses regarding α and β, we need to assume the normality of the term e.

The left panel of Figure 9.5 shows a situation where these assumptions are satisfied. Note that:

1. $E(Y|X)$ is linear.
2. For each X, the normal Y-distribution has the same variance.
3. For each X, the Y-distribution is normal (less important as the sample size is large).

The right panel of Figure 9.5 shows a situation where all these assumptions don't hold.

1. $E(Y|X)$ is not a straight line; it curves.
2. The variance of Y increases as X increases.
3. The distribution becomes more highly skewed as X increases.

It can be shown, under the correct normal model or in large samples, that

$$b \sim N\left(\beta, \frac{\sigma_1^2}{[x^2]}\right) \quad \text{and} \quad a \sim N\left(\alpha, \sigma_1^2\left[\frac{1}{n} + \frac{\overline{x}^2}{[x^2]}\right]\right)$$

Recall that σ_1^2 is estimated by $s_{y.x}^2 = \sum(Y_i - \widehat{Y}_i)^2/(n-2)$. Note that the divisor is $n-2$: the number of degrees of freedom. The reason, as just mentioned, is that now *two* parameters are estimated: α and β. Given these facts, we can now either construct confidence intervals or tests of hypotheses after constructing appropriate pivotal variables:

$$\frac{b-\beta}{\sigma_1/\sqrt{[x^2]}} \sim N(0,1), \qquad \frac{b-\beta}{s_{y.x}/\sqrt{[x^2]}} \sim t_{n-2}$$

and similar terms involving the intercept a are discussed below.

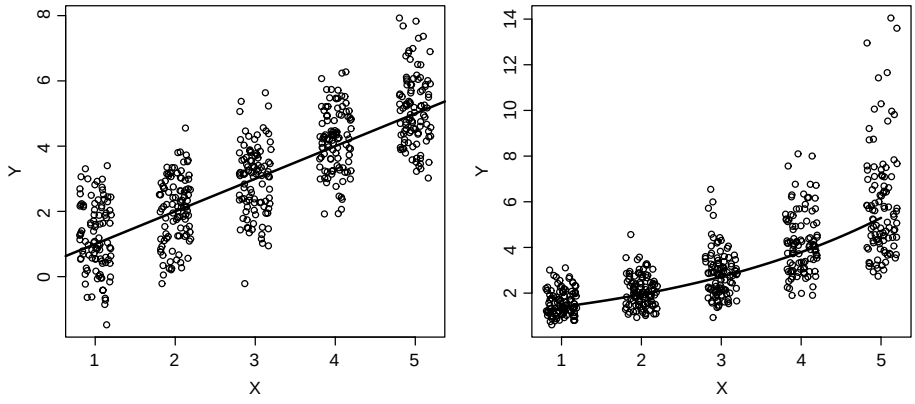


Figure 9.5 Linear regression assumptions and violations. On the left, the expected values of Y for given X values fall on a straight line. The variation about the line has the same variance at each X. On the right, the expected values fall on a curve, not a straight line. The distribution of Y is different for different X values, with variance and skewness increasing with X.

Returning to Example 9.1, the melanoma data by state, the following quantities are known or can be calculated:

$$a = 389.190, \qquad s^2_{y\cdot x} = \sum_i \frac{(Y_i - \widehat{Y}_i)^2}{n-2} = \frac{17{,}173.1}{47} = 365.3844$$

$$b = -5.9776, \qquad [x^2] = 1020.499, \qquad s_{y.x} = 19.1150$$

On the assumption that there is no relationship between latitude and mortality, that is, $\beta = 0$, the variable b has mean zero. A t-test yields

$$t_{47} \doteq \frac{-5.9776}{19.1150/\sqrt{1020.499}} \doteq \frac{-5.9776}{0.59837} \doteq -9.99$$

From Table A.4, the critical value for a t-variable with 47 degrees of freedom, at the 0.0001 level (two-tailed) is approximately 4.25; hence, the hypothesis is rejected and we conclude that there is a relationship between latitude and mortality; the mortality increases about 6.0 persons per 10,000,000 for every degree farther south. This, of course, comes from the value of $b = -5.9776 \doteq -6.0$. Similarly, a 95% confidence interval for β can be constructed using the t-value of 2.01, and the standard error of the slope, $0.59837 = s_{y.x}/\sqrt{[x^2]}$.

A 95% confidence interval is $-5.9776 \pm (2.01 \times 0.59837)$, producing lower and upper limits of -7.18 and -4.77, respectively. Again, the confidence interval does not include zero, and the same conclusion is reached as in the case of the hypothesis test.

The inference has been concerned with the slope β and intercept α up to now. We now want to consider two additional situations:

1. Inference about population means, $\alpha + \beta X$, for a fixed value of X
2. Inference about a future observation at a fixed value of X

To distinguish between the two cases, let $\widehat{\mu}_x$ and $\widehat{y}_x$ be the predicted mean and a new random single observation at the point x, respectively. It is important to note that for inference about a future observation the normality assumption is critical even in large samples. This is in contrast to inference about the predicted mean or about a and b, where normal distributions are required only in small samples and the central limit theorem substitutes in large samples.

First, then, inference about the population mean at a fixed X value: It is natural to estimate $\alpha + \beta X$ by $a + bx$; the predicted value of Y at the value of $X = x$. Rewrite this quantity as

$$\widehat{\mu}_x = \overline{y} + b(x - \overline{x})$$

It can be shown that $\overline{y}$ and b are statistically independent so that the variance of the quantity is

$$\begin{aligned} \text{var}[\overline{y} + b(x - \overline{x})] &= \text{var}(\overline{y}) + (x - \overline{x})^2 \text{ var}(b) \\ &= \frac{\sigma_1^2}{n} + (x - \overline{x})^2 \frac{\sigma_1^2}{[x^2]} \\ &= \sigma_1^2 \left[\frac{1}{n} + \frac{(x - \overline{x})^2}{[x^2]} \right] = \sigma_2^2, \qquad \text{say} \end{aligned}$$

Tests and confidence intervals for $E(Y|X)$ at a fixed value of x may be based on the t-distribution.

The quantity σ_2^2 reduces to the variance for the intercept, a, at $X = 0$. It is useful to study this quantity carefully; there are important implications for design (see Note 9.3). The variance, σ_2^2, is not constant but depends on the value of x. The more x differs from $\overline{x}$, the greater the contribution of $(x - \overline{x})^2/[x^2]$ to the variance of $a + bx$. The contribution is zero at $x = \overline{x}$. At $x = \overline{x}$, $y = \overline{y}$ the slope is not used. Regardless of the slope the line goes through mean point $(\overline{X}, \overline{Y})$. Consider Example 9.1 again. We need the following information:

$$\begin{aligned} s_{y \cdot x} &= 19.1150 \\ n &= 49 \\ \overline{x} &= 39.533 \\ [x^2] &= 1020.499 \end{aligned}$$

Let

$$s_2^2 = s_{y \cdot x}^2 \left[\frac{1}{n} + \frac{(x - \overline{x})^2}{[x^2]} \right]$$

That is, s_2^2 estimates σ_2^2. Values of s_2 as related to latitude are given in Table 9.4. Confidence interval bands for the mean, $\alpha + \beta X$ (at the 95% level), are given in Figure 9.6 by the narrower bands. The curvature is slight due to the large value of $[x^2]$ and the relatively narrow range of prediction.

We now turn to the second problem: predicting a future observation on the basis of the observed data. The variance is given by

$$s_3^2 = s_{y \cdot x}^2 \left[1 + \frac{1}{n} + \frac{(x - \overline{x})^2}{[x^2]} \right]$$

This is reasonable in view of the following argument: At the point $\alpha + \beta X$ an observation has variance σ_2^2 (estimated by $s_{y \cdot x}^2$). In addition, there is uncertainty in the true value $\alpha + \beta X$. This adds variability to the estimate. A future observation is assumed to be independent of past observations. Hence the variance can be added and the quantity s_3^2 results when σ_1^2 is estimated by $s_{y \cdot x}^2$. Confidence interval bands for future observations (95% level) are represented by outer lines in Figure 9.6. This band means that we are 95% certain that the next observation at the fixed point x will be within the given bands. Note that the curvature is not nearly as marked.

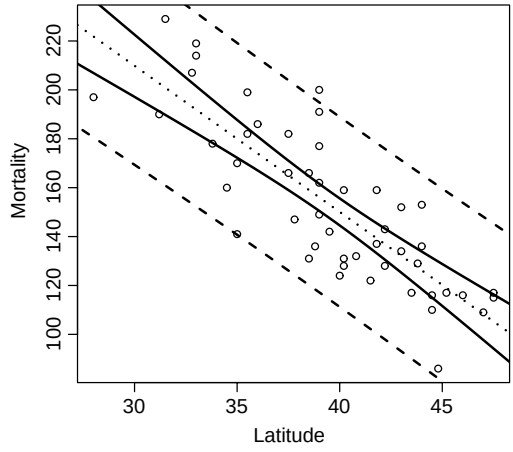


Figure 9.6 Data of Figure 9.1: 95% confidence bands for population means (solid) and 95% confidence bands for a future observation (dashed).

9.2.4 Analysis of Variance

Consider Example 9.1 and the data for Tennessee, as graphed in Figure 9.4. The basic data for this state are (omitting subscripts)

$$y = 186.0 = \text{observed mortality}$$
$$x = 36.0 = \text{latitude of center of state}$$
$$\widehat{y} = 174.0 = \text{predicted mortality using latitude of 36.0}$$
$$\overline{y} = 152.9 = \text{average mortality for United States}$$

Partition the data as follows:

$$(y - \overline{y}) = (\widehat{y} - \overline{y}) + (y - \widehat{y})$$
$$\text{total variation} = \text{attributable to regression} + \text{residual from regression}$$
$$186.0 - 152.9 = (174.0 - 152.9) + (186.0 - 174.0)$$
$$33.1 = 21.1 + 12.0$$

Note that the quantity

$$\begin{aligned}\widehat{y} - \overline{y} &= a + bx - \overline{y} \\ &= \overline{y} - b\overline{x} + bx - \overline{y} \\ &= b(x - \overline{x})\end{aligned}$$

The quantity is zero if $b = 0$, that is, if there is no regression relationship between Y and X. In addition, it is zero if prediction is made at the point $x = \overline{x}$.

These quantities can be calculated for each state, as indicated in abbreviated form in Table 9.5. The sums of squares of these quantities are given at the bottom of the table. The remarkable fact is that

$$\sum (y_i - \overline{y})^2 = \sum (\widehat{y}_i - \overline{y})^2 + \sum (y_i - \widehat{y}_i)^2$$
$$53{,}637.3 = 36{,}464.2 + 17{,}173.1$$

Table 9.5 Deviations from Mean and Regression Based on Data of Table 9.1

Case	State	Observed Mortality (y)	Latitude (x)	Predicted Mortality[a]	Variation: Total $y-\overline{y}$	=	Regression $\widehat{y}-\overline{y}$	+	Residual $y-\widehat{y}$
1	Alabama	219.0	33.0	191.9	66.1	=	39.0	+	27.1
2	Arizona	160.0	34.5	183.0	7.1	=	30.1	+	−23.0
⋮	⋮		⋮				⋮		
41	Tennessee	186.0	36.0	174.0	33.1	=	21.1	+	12.0
⋮	⋮		⋮				⋮		
48	Wisconsin	110.0	44.5	123.2	−42.9	=	−29.7	+	−13.2
49	Wyoming	134.0	43.0	132.2	−18.9	=	−20.7	+	1.8
Total					0	=	0	+	0
Mean		152.9	39.5	152.9	0	=	0	+	0
Sum of squares					53,637.3	=	36,464.2	+	17,173.1

[a]Predicted mortality based on regression line $y = 389.19 - 5.9776x$, where x is the latitude at the center of the state.

that is, the total variation as measured by $\sum(y_i - \overline{y})^2$ has been partitioned additively into a part attributable to regression and the residual from regression. The quantity $\sum(\widehat{y}_i - \overline{y})^2 = \sum b^2(x_i - \overline{x})^2 = b^2[x^2]$. (But since $b = [xy]/[x^2]$, this becomes $\sum(\widehat{y}_i - \overline{y})^2 = [xy]^2/[x^2]$.) Associated with each sum of squares is a degree of freedom (d.f.) which can also be partitioned as follows:

$$\text{total variation} = \text{attributable to regression} + \text{residual variation}$$

$$\text{d.f.} = n - 1 = 1 + n - 2$$

$$49 = 1 + 48$$

The total variation has $n-1$ d.f., not n, since we adjusted Y about the mean $\overline{Y}$. These quantities are commonly entered into an analysis of variance table as follows:

Source of Variation	d.f.	SS	MS	F-Ratio
Regression	1	36,464.2	36,464.2	99.80
Residual	47	17,173.1	365.384	
Total	48	53,637.3		

The quantity 365.384 is precisely $s^2_{y\cdot x}$. The F-ratio is discussed below. The mean square is the sum of squares divided by the degrees of freedom. The analysis of variance table of any set of n pairs of observations (x_i, y_i), $i = 1, \ldots, n$, is

Source of Variation	d.f.	SS	MS	F-Ratio
Regression	1	$[xy]^2/[x^2]$	$[xy]^2/[x^2]$	$\dfrac{[xy]^2/[x^2]}{s^2_{y\cdot x}}$
Residual	n - 2	By subtraction	$s^2_{y\cdot x}$	
Total	n - 1	$[y^2]$		

Several points should be noted about this table and the regression procedure:

1. Only five quantities need to be calculated from the raw data to completely determine the regression line and sums of squares: $\sum x_i, \sum y_i, \sum x_i^2, \sum y_i^2$, and $\sum x_i y_i$. From these quantities one can calculate

$$[x^2] = \sum (x_i - \overline{x})^2 = \sum x_i^2 - \frac{\left(\sum x_i\right)^2}{n}$$

$$[y^2] = \sum (y_i - \overline{y})^2 = \sum y_i^2 - \frac{\left(\sum y_i\right)^2}{n}$$

$$[xy] = \sum (x_i - \overline{x})(y_i - \overline{y}) = \sum x_i y_i - \frac{\sum y_i \sum x_i}{n}.$$

2. The greater the slope, the greater the SS due to regression. That is,

$$\text{SS(regression)} = b^2 \sum (x_i - \overline{x})^2 = \frac{[xy]^2}{[x^2]}$$

If the slope is "negligible," SS(regression) will tend to be "small."

3. The proportion of the total variation attributable to regression is usually denoted by r^2; that is,

$$r^2 = \frac{\text{variation attributable to regression}}{\text{total variation}}$$

$$= \frac{[xy]^2/[x^2]}{[y^2]}$$

$$= \frac{[xy]^2}{[x^2][y^2]}$$

It is clear that $0 \leq r^2 \leq 1$ (why?). If $b = 0$, then $[xy]^2/[x^2] = 0$ and the variation attributable to regression is zero. If $[xy]^2/[x^2]$ is equal to $[y^2]$, all of the variation can be attributed to regression; to be more precise, to *linear* regression; that is, all the observations fall on the line $a + bx$. Thus, r^2 measures the degree of *linear* relationship between X and Y. The *correlation coefficient*, r, is studied in Section 9.3. For the data in Table 9.4,

$$r^2 = \frac{36{,}464.2}{53{,}637.3} = 0.67983$$

That is, approximately 68% of the variation in mortality can be attributed to variation in latitude. Equivalently, the variation in mortality can be reduced 68% knowing the latitude.

4. Now consider the ratio

$$F = \frac{[xy]^2/[x^2]}{s^2_{y \cdot x}}$$

Under the assumption of the model [i.e., $y \sim N(\alpha + \beta X, \sigma_1^2)$], the ratio F tends to be near 1 if $\beta = 0$ and tends to be larger than 1 if $\beta \neq 0$ (either positively or negatively). F has the F-distribution, as introduced in Chapter 5. In the example $F_{1,47} = 99.80$, the critical value at the 0.05 level is $F_{1,47} = 4.03$ (by interpolation). The critical value at the 0.001 level is $F_{1,47} = 12.4$ (by interpolation). Hence, we reject the hypotheses that $\beta = 0$. We tested the significance of the slope using a t-test given the value

$$t_{47} = -9.9898$$

The F-value we obtained was

$$F_{1,47} = 99.80$$

In fact,

$$(-9.9898)^2 = 99.80$$

That is,

$$t_{47}^2 = F_{1,47}$$

Recall that

$$t_v^2 = F_{1,v}$$

Thus, the t-test and the F-test for the significance of the slope are equivalent.

9.2.5 Appropriateness of the Model

In Chapter 5 we considered the appropriateness of the model $y \sim N(\mu, \sigma^2)$ for a set of data and discussed briefly some ways of verifying the appropriateness of this model. In this section we have the model

$$y \sim N(\alpha + \beta X, \sigma_1^2)$$

and want to consider its validity. At least three questions can be asked:

1. Is the relationship between Y and X linear?
2. The variance σ_1^2 is assumed to be constant for all values of X (homogeneity of variable). Is this so?
3. Does the normal model hold?

Two very simple graphical procedures, both utilizing the residuals from regression $y_i - \widehat{y}_i$, can be used to verify the assumptions above. Also, one computation on the residuals is useful. The two graphical procedures are considered first.

To Check for:	Graphical Procedure
1. Linearity of regression and homogeneity of variance	Plot $(y_i - \widehat{y}_i)$ against $\widehat{y}_i$, $i = 1, \ldots, n$
2. Normality	Normal probability plot of $y_i - \widehat{y}_i, i = 1, \ldots, n$

We illustrate these with data created by Anscombe [1973]. As we noted above, just five summaries of the data specify everything about the linear regression model. Anscombe created four data sets in which these five summaries, and thus the fitted model, were identical, but where the data were very different. Only one of these sets of data is appropriate for linear regression.

Linearity of Regression and Homogeneity of Variance

Given only one predictor variable, X, the graph of Y vs. X will suggest nonlinearity or heterogeneity of variance, see the top row of regression patterns in Figure 9.7. But if there is more than one predictor variable, as in Chapter 11, the simple two-dimensional graph is not possible. But there is a way of detecting such patterns by considering residual plots $y - \widehat{y}$ against a variety of variables. A common practice is to plot $y - \widehat{y}$ against $\widehat{y}$; this graph is usually referred to as a *residual plot*. The advantage is, of course, that no matter how many predictor variables are used,

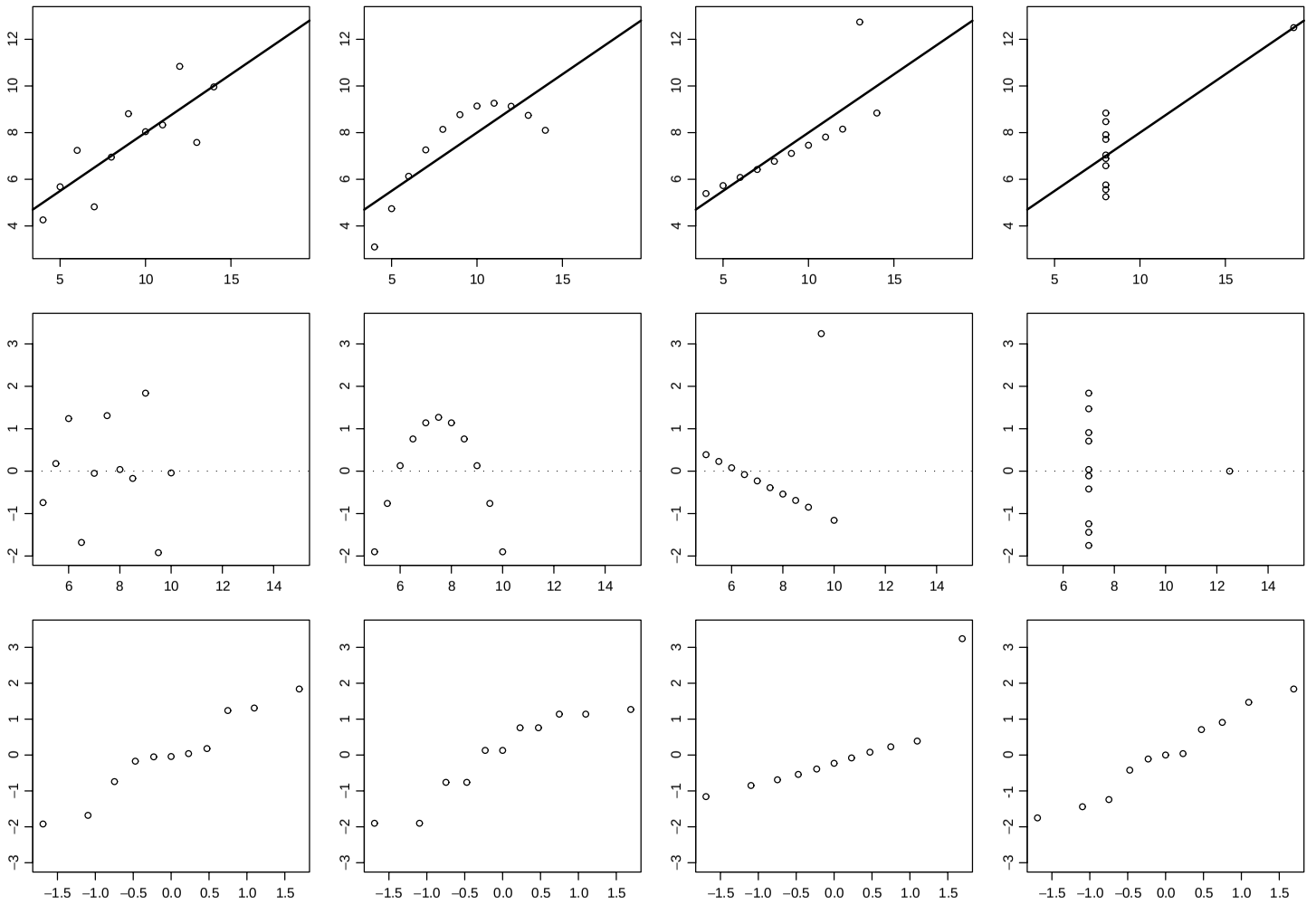


Figure 9.7 Regression patterns (Y vs. X), residuals patterns ($y - \widehat{y}$ vs. $\widehat{y}$) and normal probability plot of residuals ($y - \widehat{y}$).

it is always possible to plot $y - \widehat{y}$. The second row of graphs in Figure 9.7 indicate the residual patterns associated with the regression patterns of the top row. Pattern 1 indicates a reasonable linear trend, pattern 2 shows a very strong pattern in the residuals. Pattern 3 has a single very large residual, and in pattern 4 it is the distribution of X rather than Y that is suspicious.

Before turning to the questions of normality of the data, consider the same kind of analysis carried out on the melanoma data. The residuals are plotted in the left panel of Figure 9.8. There is no evidence that there is nonlinearity or heterogeneity of variance.

Normality

One way of detecting gross deviations from normality is to graph the residuals from regression against the expected quantiles of a normal distribution as introduced in Chapter 4. The last row of patterns in Figure 9.6 are the normal probability plots of the deviations from linear regression. The last row in Figure 9.6 indicates that a normal probability plot indicates outliers clearly but is not useful in detecting heterogeneity of variance or curvilinearity.

Of particular concern are points not fit closely by the data. The upper right and lower left points often tail in toward the center in least squares plot. Points on the top far to the right and on the bottom far to the left (as in pattern 2) are of particular concern.

The normal probability plot associated with the residuals of the melanoma are plotted in the right panel of Figure 9.8. There is no evidence against the normality assumption.

9.2.6 Two-Sample t-Test as a Regression Problem

In this section we show the usefulness of the linear model approach by illustrating how the two sample t-test can be considered a special kind of linear model. For an example, we again return to the data on mortality rates due to melanoma contained in Table 9.1. This time we consider the rates in relationship to contiguity to an ocean; there are two groups of states: those that border on an ocean and those that do not. The question is whether the average mortality rate for the first group differs from that of the second group. The t-test and analysis are contained in Table 9.6.

The mean difference, $\overline{y}_1 - \overline{y}_2 = 31.486$, has a standard error of 8.5468 so that the calculated t-value is $t = 3.684$ with 47 degrees of freedom, which exceeds the largest value in the t-table at 40 or 60 degrees of freedom and consequently, $p < 0.001$. The conclusion then is that the mortality rate due to malignant melanoma is appreciably higher in states contiguous to an ocean as compared to "inland" states, the difference being approximately 31 deaths per 10^7 population per year.

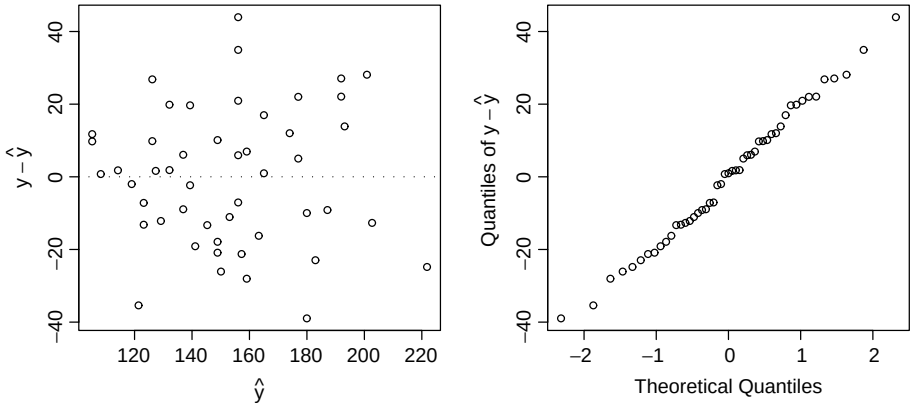


Figure 9.8 Melanoma data (left) residuals ($y - \widehat{y}$) from regression lines $Y = 389.19 - 589.8X$ plotted against $\widehat{y}$ and (right) normal quantile plot of residuals, $y - \widehat{y}$.

Table 9.6 Comparison by Two-Sample t-Test of Mortality Rates Due to Melanoma (Y) by Contiguity to Ocean

Contiguity to ocean	No = 0	Yes = 1
Number of states	$n_1 = 27$	$n_2 = 22$
Mean mortality	$\overline{y}_1 = 138.741$	$\overline{y}_2 = 170.227$
Variance[a]	$s_1^2 = 697.97$	$s_2^2 = 1117.70$
Pooled variance	$s_p^2 = 885.51$	
Standard error of difference	$s_p\sqrt{\frac{1}{n_1}+\frac{1}{n_2}} = 8.5468$	
Mean difference	$\overline{y}_2 - \overline{y}_1 = 31.487$	
t-Value	$t = 3.684$	
Degrees of freedom	d.f. = 47	
p-Value	$p < 0.001$	

[a] Subscripts on variances denote group membership in this table.

Now consider the following (equivalent) regression problem. Let Y be the mortality rate and X the predictor variable; "X = contiguity to ocean" and X takes on only two values, 0, 1. (For simplicity, we again label all the variables and parameters, Y, X, α, β, and σ_1^2, but except for Y, they obviously are different from the way they were defined in earlier sections.) The model is

$$Y \sim N(\alpha + \beta X, \sigma_1^2)$$

The data are graphed in Figure 9.9. The calculations for the regression line are as follows:

$$n = 49, \qquad b = \frac{[xy]}{[x^2]} = 31.487$$

$$[y^2] = 53637.265, \qquad a = 138.741$$

$$[xy] = 381.6939, \qquad \text{Regression line}$$

$$[x^2] = 12.12245, \qquad Y = 138.741 + 31.487\text{X}$$

$$\overline{y} = 152.8776, \qquad (n-2)s_{y\cdot x}^2 = [y^2] - \frac{[xy]^2}{[x^2]}$$

$$\overline{x} = 0.44898, \qquad = 41{,}619.0488$$

$$s_{y\cdot x}^2 = 885.51$$

The similarity to the t-test becomes obvious, the intercept $a = 138.741$ is precisely the mean mortality for the "inland" states. The "slope," $b = 31.487$, is the mean difference between the two groups of states, and $s_{y\cdot x}^2$, the residual variance, is the pooled variance. The t-test for the slope is equivalent to the t-test for the difference in the two means.

$$\text{variance of slope} = s_b^2 = \frac{s_{y\cdot x}^2}{[x^2]}$$

$$= \frac{885.51}{12.12245}$$

$$= 73.0471$$

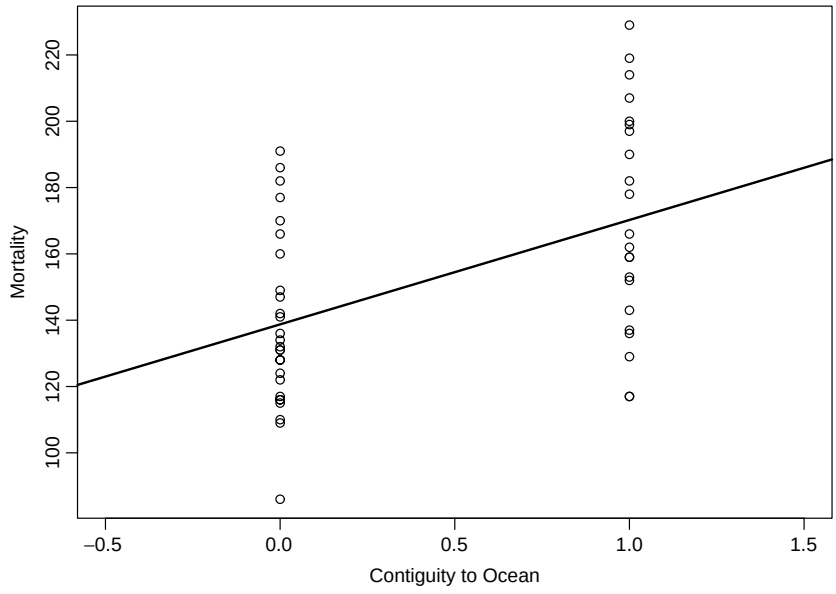


Figure 9.9 Melanoma data: regression of mortality rate on contiguity to ocean, coded 0 if not contiguous to ocean, 1 if contiguous to ocean.

$$
\begin{aligned}
s_b &= 8.5468 \\
t &= \frac{31.487}{8.5468} \\
&= 3.684
\end{aligned}
$$

The t-test for the slope has 47 degrees of freedom, as does the two-sample t-test. Note also that s_b is the standard error of the differences in the two-sample t-test.

Finally, the regression analysis can be put into analysis of variance form as displayed in Table 9.7:

$$
\begin{aligned}
\text{SS(regression)} &= \frac{[xy]^2}{[x^2]} \\
&= \frac{(381.6939)^2}{12.12245} \\
&= 12{,}018.22 \\
\text{SS(residual)} &= [y^2] - \frac{[xy]^2}{[x^2]} \\
&= 53{,}637.26 - 12{,}018.22 \\
&= 41{,}619.04
\end{aligned}
$$

We note that the proportion of variation in mortality rates attributable to "contiguity to ocean" is

$$
\begin{aligned}
r^2 &= \frac{[xy]^2/[x^2]}{[y^2]} \\
&= \frac{12{,}018.22}{53{,}637.06} \\
&= 0.2241
\end{aligned}
$$

Table 9.7 Regression Analysis of Mortality and Contiguity to Ocean

Source of Variation	d.f.	SS	MS	F-Ratio
Regression	1	12,018.22	12,018.22	13.57[a]
Residual	47	41,619.04	885.51	
Total	48	53,637.26		

[a] Significant at the 0.001 level.

Approximately 22% of the variation in mortality can be attributed to the predictor variable: "contiguity to ocean."

In Chapter 11 we deal with the relationships among the three variables: mortality, latitude, and contiguity to an ocean. The predictor variable "contiguity to ocean," which takes on only two values, 0 and 1 in this case, is called a *dummy variable* or *indicator variable*. In Chapter 11 more use is made of such variables.

9.3 CORRELATION AND COVARIANCE

In Section 9.2 the method of least squares was used to find a line for predicting one variable from the other. The response variable Y, or dependent variable Y, was random for given X. Even if X and Y were jointly distributed so that X was a random variable, the model only had assumptions about the distribution of Y given the value of X. There are cases, however, where both variables vary jointly, and there is a considerable amount of symmetry. In particular, there does not seem to be a reason to predict one variable from the other. Example 9.3 is of that type. As another example, we may want to characterize the length and weight relationship of newborn infants. The basic sampling unit is an infant, and two measurements are made, both of which vary. There is a certain symmetry in this situation: There is no "causal direction"—length does not cause weight, or vice versa. Both variables vary together in some way and are probably related to each other through several other underlying variables which determine (cause) length and weight. In this section we provide a quantitative measure of the strength of the relationship between the two variables and discuss some of the properties of this measure. The measure (the correlation coefficient) is a measure of the strength of the linear relationship between two variables.

9.3.1 Correlation and Covariance

We would like to develop a measure (preferable one number) that summarizes the strength of any linear relationship between two variables X and Y. Consider Example 9.2, the exercise test data. The X variable is measured in seconds and the Y variable is measured in milliliters per minute per kilogram. When totally different units are used on the two axes, one can change the units for one of the variables, and the picture seems to change. For example, if we went from seconds to minutes where 1 minute was graphed over the interval of 1 second in Figure 9.2, the data of Figure 9.2 would go almost straight up in the air. Whatever measure we use should not depend on the choice of units for the two variables. We already have one technique of adjusting for or removing the units involved: to standardize the variables. We have done this for the t-test, and we often had to do it for the construction of test statistics in earlier chapters. Further, since we are just concerned with how closely the family of points is related, if we shift our picture (i.e., change the means of the X and Y variables), the strength of the relationship between the two variables should not change. For that reason, we subtract the mean of each variable, so that the pictures will be centered about zero. In order that we have a solution that does not depend

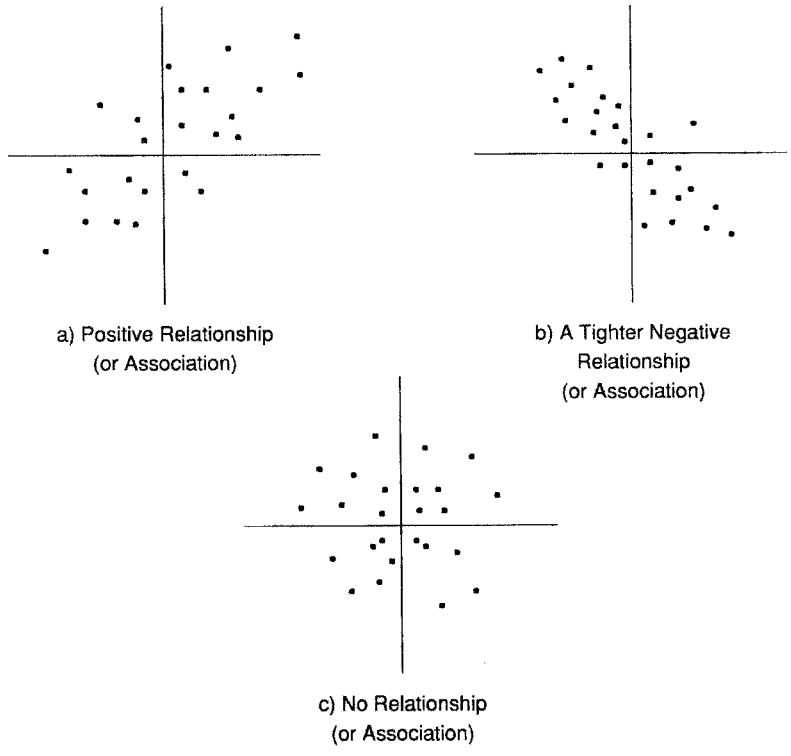


Figure 9.10 Scatter diagrams for the standardized variables.

on units, we standardize each variable by dividing by the standard deviation. Thus, we are now working with two new variables, say U and V, which are related to X and Y as follows:

$$U_i = \frac{X_i - \overline{X}}{s_x}, \qquad V_i = \frac{Y_i - \overline{Y}}{s_y}$$

where

$$s_x^2 = \sum \frac{(X_i - \overline{X})^2}{n-1} \quad \text{and} \quad s_y^2 = \sum \frac{(Y_i - \overline{Y})^2}{n-1}$$

Let us consider how the variables U_i and V_i vary together. In Figure 9.10 we see three possible types of association. Part (*a*) presents a positive relationship, or association between, the variables. As one increases, the other tends to increase. Part (*b*) represents a tighter, negative relationship. As one decreases, the other tends to increase, and vice versa. By the word *tighter*, we mean that the variability about a fitted regression line would not be as large. Part (*c*) represents little or no association, with a somewhat circular distribution of points.

One mathematical function that would capture these aspects of the data results from multiplying U_i and V_i. If the variables tend to be positive or negative together, the product will always be positive. If we add up those multiples, we would get a positive number. On the other hand, if one variable tends to be negative when the other is positive, and vice versa, when we multiply the U_i and V_i together, the product will be negative; when we add them, we will get a negative number of substantial absolute value.

On the other hand, if there is no relationship between U and V, when we multiply them, half the time the product will be positive and half the time the product will be negative; if we

sum them, the positive and negative terms will tend to cancel out and we will get something close to zero. Thus, adding the products of the standardized variables seems to be a reasonable method of characterizing the association between the variables. This gives us our definition of the correlation coefficient.

Definition 9.4. The *sample Pearson product moment correlation coefficient*, denoted by r, or r_{XY}, is defined to be

$$r = \frac{[xy]}{\sqrt{[x^2][y^2]}} = \frac{\sum(x_i - \overline{x})(y_i - \overline{y})}{\sqrt{\sum(x_i - \overline{x})^2 \sum(y_i - \overline{y})^2}} = \frac{1}{n-1} \sum u_i v_i$$

This quantity is usually called the *correlation coefficient*.

Note that the denominator looks like the product of the sample standard deviations of X and Y except for a factor of $n - 1$. If we define the sample covariance by the following equation, we could define the correlation coefficient according to the second alternative definition.

Definition 9.5. The *sample covariance*, s_{xy}, is defined by

$$s_{xy} = \sum_i \frac{(x_i - \overline{x})(y_i - \overline{y})}{n-1}$$

Alternative Definition 9.4. The *sample Pearson product moment correlation coefficient* is defined by

$$r = \frac{[xy]}{\sqrt{[x^2][y^2]}} = \frac{s_{xy}}{s_x s_y}$$

The prefix co- is a prefix meaning "with," "together," and "in association," occurring in words derived from Latin: thus, the co-talks about the two variables varying together or in association. The term *covariance* has the same meaning as the variance of one variable: how spread out or variable things are. It is hard to interpret the value of the covariance alone because it is composed of two parts; the variability of the individual variables and their linear association. A small covariance can occur because X and/or Y has small variability. It can also occur because the two variables are not associated. Thus, in interpreting the covariance, one usually needs to have some idea of the variability in both variables. A large covariance, however, does imply that at least one of the two variables has a large variance.

The correlation coefficient is a rescaling of the covariance by the standard deviations of X and Y. The motivation for the construction of the covariance and correlation coefficient is the following: s_{xy} is the average of the product of the deviations about the means of X and Y. If X tends to be large when Y is large, both deviations will be positive and the product will be positive. Similarly, if X is small when Y is small, both deviations will be negative but their products will still be positive. Hence, the average of the products for all the cases will tend to be positive. If there is no relationship between X and Y, a positive deviation in X may be paired with a positive or negative deviation in Y and the product will either be positive or negative, and on the average will tend to center around zero. In the first case X and Y are said to be positively correlated, in the second case there is no correlation between X and Y. A third case results when large values of X tend to be associated with small values of Y, and vice versa. In this situation, the product of deviations will tend to be negative and the variables are said to be negatively correlated. The statistic r rescales the average of the product of the deviations about the means by the standard deviations of X and Y.

The statistic r has the following properties:

1. r has value between -1 and 1.
2. $r = 1$ if and only if all the observations are on a straight line with positive slope.
3. $r = -1$ if and only if all observations are on a straight line with negative slope.
4. r takes on the same value if X, or Y, changes units or has a constant added or subtracted.
5. r measures the extent of *linear* association between two variables.
6. r tends to be close to zero if there is no linear association between X and Y.

Some typical scattergrams and associated values of r are given in Figure 9.11. Figure 9.11(a) and (b) indicate perfect linear relationships between two variables. Figure 9.11(c) indicates no correlation. Figure 9.11(d) and (e) indicate typical patterns representing less than perfect correlation. Figure 9.11(f) to (j) portray various pathological situations. Figure 9.11(f) indicates that although there is an explicit relationship between X and Y, the linear relationship is zero; thus $r = 0$ does not imply that there is no relationship between X and Y. In statistical terminology, $r = 0$ does not imply that the variables are statistically independent. There is one important exception to this statement that is discussed in Section 9.3.3. Figure 9.11(g) indicates that except for the one extreme point there is no correlation. The coefficient of correlation is very sensitive to such outliers, and in Section 9.3.7 we discuss correlations that are not as sensitive, that is, more robust. Figure 9.11(h) indicates that an explicit relationship between X and Y is not identified by the correlation coefficient if the relationship is not linear. Finally, Figure 9.11(j)

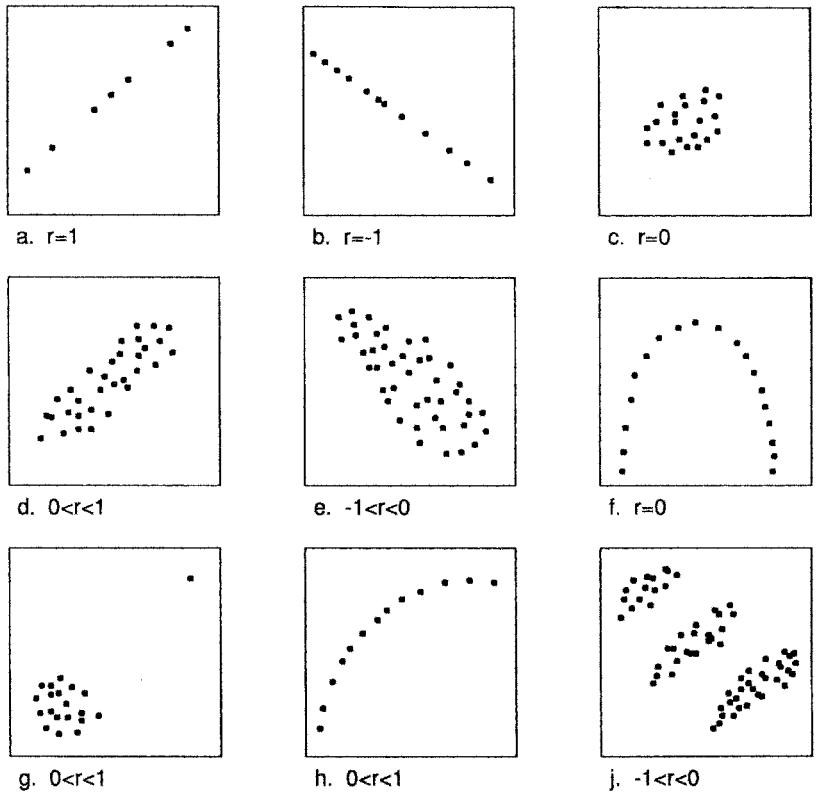


Figure 9.11 Some patterns of association.

suggests that there are three subgroups of cases; within each subgroup there is a positive correlation, but the correlation is negative when the subgroups are combined. The reason is that the subgroups have different means and care must be taken when combining data. For example, natural subgroups defined by gender or race may differ in their means in a direction opposite to the correlation within each subgroup.

Now consider Example 9.3. The scattergram in Figure 9.3 suggests a positive association between the ATP level of the youngest son (X) and that of the oldest son (Y). The data for this example produce the following summary statistics (the subscripts on the values of X and Y have been suppressed: for example, $\sum x_i = \sum x$).

$$
\begin{aligned}
&\mathrm{n} = 17, \\
&\sum x = 83.38, && \overline{x} = 4.90, \\
&\sum y = 79.89, && \overline{y} = 4.70, \\
&\sum x^2 = 417.1874, && \sum (x - \overline{x})^2 = 8.233024, && s_x = 0.717331 \\
&\sum y^2 = 379.6631, && \sum (y - \overline{y})^2 = 4.227094, && s_y = 0.513997 \\
&\sum xy = 395.3612, && \sum (x - \overline{x})(y - \overline{y}) = 3.524247, && s_{xy} = 0.220265
\end{aligned}
$$

$$
r = \frac{0.220265}{(0.717331)(0.513997)} = 0.597
$$

In practice, r will simply be calculated from the equivalent formula

$$
r = \frac{[xy]}{\sqrt{[x^2][y^2]}} = \frac{3.524247}{\sqrt{(8.233024)(4.227094)}} = \frac{3.524247}{5.899302} = 0.597
$$

The sample correlation coefficient and covariance estimate the population parameters. The expected value of the covariance is

$$
\begin{aligned}
E(S_{xy}) &= E((X - \mu_x)(Y - \mu_y)) \\
&= \sigma_{xy}
\end{aligned}
$$

where

$$
\mu_x = E(X) \quad \text{and} \quad \mu_y = E(Y)
$$

The population covariance is the average of the product of X about its mean times Y about its mean.

The sample correlation coefficient estimates the population correlation coefficient ρ, defined as follows:

Definition 9.6. Let (X, Y) be two jointly distributed random variables. The (*population*) *correlation coefficient* is

$$
\rho = \frac{\sigma_{xy}}{\sigma_x \sigma_y} = \frac{E((X - \mu_x)(Y - \mu_y))}{\sqrt{\mathrm{var}(X)\mathrm{var}(Y)}}
$$

where σ_{xy} is the covariance of X and Y, σ_x the standard deviation of X, and σ_y the standard deviation of Y. ρ is zero if X and Y are statistically independent variables.

There is now a question about the statistical "significance" of a value r. In practical terms, suppose that we have sampled 17 families and calculated the correlation coefficient in ATP

levels between the youngest son and the oldest son. How much variation could we have expected relative to the value observed for this set? Could the population correlation coefficient $\rho = 0$? In the next two sections we deal with this question.

9.3.2 Relationship between Correlation and Regression

In Section 9.2.4, r^2 was presented, indicating a close connection between correlation and regression. In this section, the connection will be made explicit in several ways. Formally, one of the variables X, Y could be considered the dependent variable and the other the predictor variable and the techniques of Section 9.2 applied. It is easy to see that in most cases the slope of the regression of Y on X will not be the same as that of X on Y. To keep the distinction clear, the following notation will be used:

b_{yx} = slope of the regression of the "dependent" variable Y on the "predictor" variable X

a_y = intercept of the regression of Y on X

Similarly,

b_{xy} = slope of the regression of the "dependent" variable X on the "predictor" variable Y

a_x = intercept of the regression of X on Y

These quantities are calculated as follows:

	Regress Y on X	**Regress X on Y**
Slope	$b_{yx} = \dfrac{[xy]}{[x^2]}$	$b_{xy} = \dfrac{[xy]}{[y^2]}$
Intercept	$a_y = \overline{y} - b_{yx}\overline{x}$	$a_x = \overline{x} - b_{xy}\overline{y}$
Residual variance	$S^2_{y\cdot x} = \dfrac{[y^2] - [xy]^2/[x^2]}{n-2}$	$S^2_{x\cdot y} = \dfrac{[x^2] - [xy]^2/[y^2]}{n-2}$

From these quantities, the following relationships can be derived:

1. Consider the product

$$b_{yx}b_{xy} = \frac{[xy]^2}{[x^2][y^2]} = r^2$$

Hence

$$r = \pm\sqrt{b_{yx}b_{xy}}$$

In words, r is the geometric mean of the slope of the regression of Y on X and the slope of the regression of X on Y.

2.

$$b_{yx} = r\frac{S_y}{S_x}, \qquad b_{xy} = r\frac{S_x}{S_y}$$

where S_x and S_y are the sample standard deviations of X and Y, respectively.

3. Using the relationships in (2), the regression line of Y on X,

$$\widehat{Y} = a_y + b_{yx}X$$

can be transformed to

$$\begin{aligned}\widehat{Y} &= a_y + \frac{rS_y}{S_x}X \\ &= \overline{y} + \frac{rS_y}{S_x}(X - \overline{x})\end{aligned}$$

4. Finally, the t-test for the slope, in the regression of Y on X,

$$\begin{aligned}t_{n-2} &= \frac{b_{yx}}{S_{b_{yx}}} \\ &= \frac{b_{yx}}{S_{y\cdot x}/\sqrt{[x^2]}}\end{aligned}$$

is algebraically equivalent to

$$r \Big/ \sqrt{\frac{1-r^2}{n-2}}$$

Hence, testing the significance of the slope is equivalent to testing the significance of the correlation.

Consider Example 9.3 again. The data are summarized in Table 9.8. This table indicates that the two regression lines are not the same but that the t-tests for testing the significance of the slopes produce the same observed value, and this value is identical to the test of significance of the correlation coefficient. If the corresponding analyses of variance are carried out, it will be found that the F-ratio in the two analyses are identical and give an equivalent statistical test.

9.3.3 Bivariate Normal Distribution

The statement that a random variable Y has a normal distribution with mean μ and variance σ^2 is a statement about the distribution of the values of Y and is written in a shorthand way as

$$Y \sim N(\mu, \sigma^2)$$

Such a distribution is called a *univariate distribution*.

Definition 9.7. A specification of the distribution of two (or more) variables is called a *bivariate* (or *multivariate*) *distribution*.

The definition of such a distribution will require the specification of the numerical characteristics of each of the variables separately as well as the relationships among the variables. The most common bivariate distribution is the normal distribution. The equation for the density of this distribution as well as additional properties are given in Note 9.6.

We write that (X, Y) have a bivariate normal distribution as

$$(X, Y) \sim N(\mu_x, \mu_y, \sigma_x^2, \sigma_y^2, \rho)$$

Table 9.8 Regression Analyses of ATP Levels of Oldest and Youngest Sons

Dependent variable	Y^a		X^a
Predictor variable	X^b		Y^b
Slope	$b_{yx} = 0.42806$		$b_{xy} = 0.83373$
Intercept	$a_y = 2.59989$		$a_x = 0.98668$
Regression line	$\widehat{Y} = 2.600 + 0.428X$		$\widehat{X} = 0.987 + 0.834Y$
Variance about mean	$s_y^2 = 0.26419$		$s_x^2 = 0.51456$
Residual variance	$s_{y\cdot x}^2 = 0.18123$		$s_{x\cdot y}^2 = 0.35298$
Standard error of slope	$s_{b_{y\cdot x}} = 0.14837$		$s_{b_{x\cdot y}} = 0.28897$
Test of significance	$t_{15} = \dfrac{0.42806}{0.14837} = 2.885$		$t_{15} = \dfrac{0.83373}{0.28897} = 2.885$
Correlation		$r_{xy} = r_{yx} = r = 0.597401$	
Test of significance		$t_{15} = \dfrac{0.597401}{\sqrt{\dfrac{1-(0.597401)^2}{17-2}}} = \dfrac{0.597401}{0.20706} = 2.885$	

Source: Data from Dern and Wiorkowski [1969].
[a] ATP level of oldest son.
[b] ATP level of youngest son.

Here μ_x, μ_y, σ_x^2, and σ_y^2 are the means and variances of X and Y, respectively. The quantity ρ is the (population) correlation coefficient. If we assume this model, it is this quantity, ρ, that is estimated by the sample correlation, r.

The following considerations may help to give you some feeling for the bivariate normal distribution. A continuous distribution of two variables, X and Y, may be modeled as follows. Pour 1 pound of sand on a floor (the X–Y plane). The probability that a pair (X, Y) falls into an area, say A, on the floor is the weight of the sand on the area A. For a bivariate normal distribution, the sand forms one mountain, or pile, sloping down from its peak at (μ_x, μ_y), the mean of (X, Y). Cross sections of the sand at constant heights are all ellipses. Figure 9.12 shows a bivariate normal distribution. On the left is shown a view of the sand pile; on the right, a topographical map of the terrain.

The bivariate normal distribution has the property that at every fixed value of X (or Y) the variable Y (or X) has a univariate normal distribution. In particular, write

$$Y_x = \text{random variable } Y \text{ at a fixed value of } X = x$$

It can be shown that at this fixed value of $X = x$,

$$Y_x \sim N\left(\alpha_y + \frac{\sigma_y}{\sigma_x}\rho x, \quad \sigma_y^2(1-\rho^2)\right)$$

This is the regression model discussed previously:

$$Y_x \sim N(\alpha + \beta x, \sigma_1^2)$$

where

$$\alpha = \mu_y - \beta\mu_x, \qquad \beta = \frac{\sigma_y}{\sigma_x}\rho, \qquad \sigma_1^2 = \sigma_y^2(1-\rho^2)$$

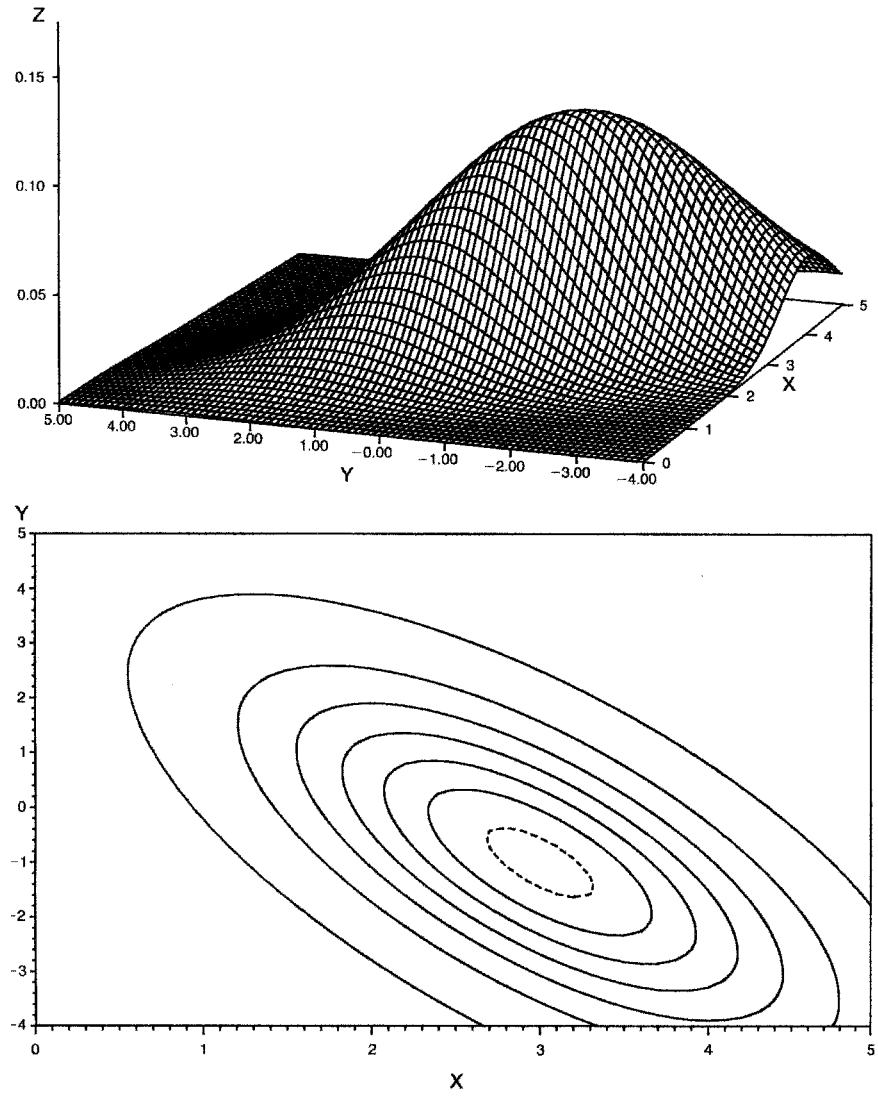


Figure 9.12 Bivariate normal distribution.

Similarly, for

$$X_y = \text{random variable } X \text{ at a fixed value of } Y = y$$

it can be shown that

$$X_y \sim N\left(\alpha_x + \frac{\sigma_x}{\sigma_y}\rho y, \sigma_x^2(1-\rho^2)\right)$$

The null hypothesis $\beta_{yx} = 0$ (or, $\beta_{xy} = 0$) is equivalent then to the hypothesis $\rho = 0$, and the t-test for $\beta = 0$ can be applied.

Suppose now that the null hypothesis is

$$\rho = \rho_0$$

where ρ_0 is an arbitrary but specified value. The sample correlation coefficient r does not have a normal distribution and the usual normal theory cannot be applied. However, R. A. Fisher showed that the quantity

$$Z_r = \frac{1}{2}\log_e \frac{1+r}{1-r}$$

has the following approximate normal distribution:

$$Z_r \sim N\left(\frac{1}{2}\log_e \frac{1+\rho}{1-\rho}, \frac{1}{n-3}\right)$$

where n is the number of pairs of values of X and Y from which r is computed. Not only does Z_r have approximately a normal distribution, but the variance of this normal distribution does not depend on the true value ρ; that is, $Z_r - Z_\rho$ is a pivotal quantity (5.2). This is illustrated graphically in Figure 9.13, which shows the distribution of 1000 simulated values of r and Z_r from distributions with $\rho = 0$ and $\rho = 1/\sqrt{2} \approx 0.71$. The distribution of r has a different variance and different shape for the two values of ρ, but the distribution of Z_r has the same shape and same variance, differing only in location.

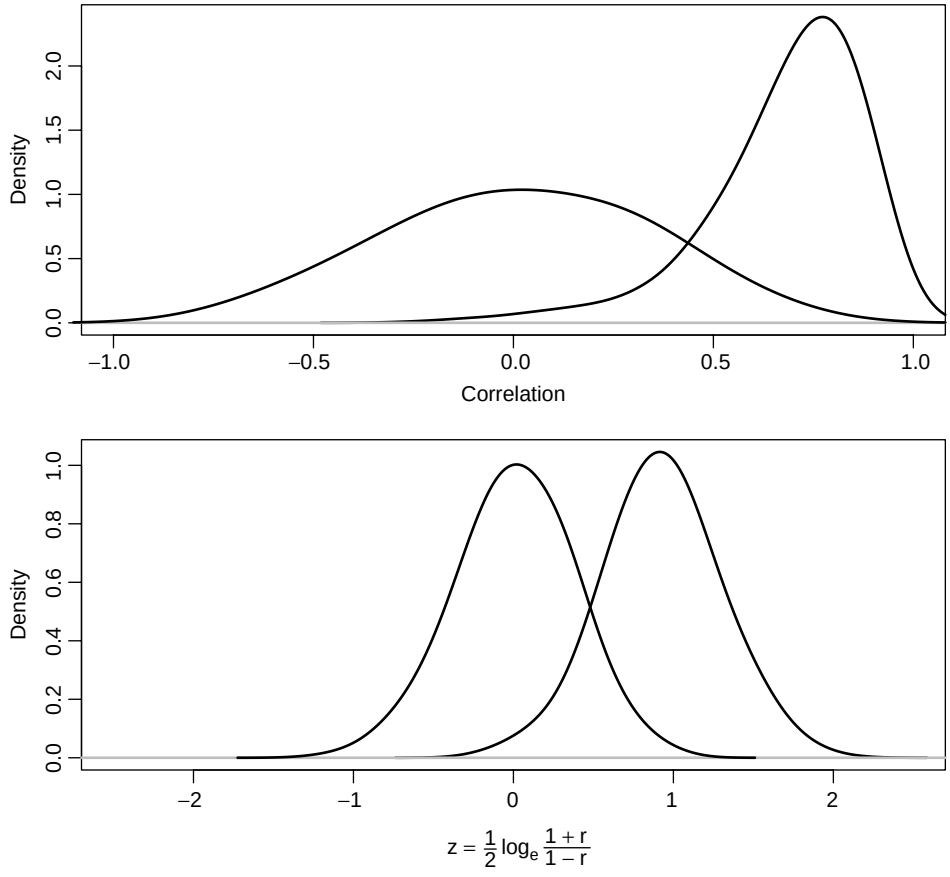


Figure 9.13 Sampling distribution of correlation coefficient, r, before and after transformation, for $\rho = 0, 1/\sqrt{2}$. Estimated from 1000 samples of size 10.

Although the approximate distribution of Z_r was derived under the assumption of a bivariate normal distribution for X and Y, it is not very sensitive to this assumption and is useful quite broadly. Z_r may be used to test hypotheses about ρ and to construct a confidence interval for ρ. This is illustrated below. The inverse, or reverse, function to r is $(e^{2Z} - 1)/(e^{2Z} + 1)$. Z_r is also the inverse of the hyperbolic tangent, tanh. To "undo" the operation, tanh is used.

Consider again Example 9.3 involving the ATP levels of youngest and oldest sons in the 17 families. The correlation coefficient was calculated to be

$$r = 0.5974$$

This value was significantly different from zero; that is, the null hypothesis $\rho = 0$ was rejected. However, the authors show in the paper that genetic theory predicts the correlation to be $\rho = 0.5$. Does the observed value differ significantly from this value? To test this hypothesis we use the Fisher Z_r transformation. Under the genetic theory, the null hypothesis stated in terms of Z_r is

$$\begin{aligned} Z_r &\sim N\left(\frac{1}{2}\log_e\left(\frac{1+0.5}{1-0.5}\right), \frac{1}{17-3}\right) \\ &\sim N(0.5493, 0.07143) \end{aligned}$$

The value observed is

$$Z_r = \frac{1}{2}\log_e\left(\frac{1+0.5974}{1-0.5974}\right) = 0.6891$$

The corresponding standard normal deviate is

$$z = \frac{0.6891 - 0.5493}{\sqrt{0.07143}} = \frac{0.1398}{0.2673} = 0.5231$$

This value does not exceed the critical values at, say, the 0.05 level, and there is no evidence to reject this null hypothesis.

Confidence intervals for ρ may be formed by first using Z_r to find a confidence interval for $1/2\log_e[(1+\rho)/(1-\rho)]$. We then transform back to find the confidence interval for ρ. To illustrate: a $100(1-\alpha)\%$ confidence interval for $1/2\log_e[(1+\rho)/(1-\rho)]$ is given by

$$Z_r \pm z_{1-\alpha/2}\sqrt{\frac{1}{n-3}}$$

For a 90% confidence interval with these data, the interval is $(0 : 6891 - 1.645\sqrt{1/14}, 0.6891 + 1.645\sqrt{1/14}) = (0.249, 1.13)$. When $Z_r = 0.249$, $r = 0.244$, and when $Z_r = 0.811$. Thus the 90% confidence interval for ρ is (0.244, 0.811). This value straddles 0.5.

9.3.4 Critical Values and Sample Size

We discussed the t-test for testing the hypothesis $\rho = 0$. The formula was

$$t_{n-2} = \frac{r}{\sqrt{(1-r^2)/(n-2)}}$$

This formula is very simple and can be used for finding critical values and for sample size calculations: Given that the number of observation pairs is specified, the critical value for t with

$n-2$ degrees of freedom is determined, and hence the r critical value can be calculated. For simplicity, write $t_{n-1} = t$; solving the equation above for r^2 yields

$$r^2 = \frac{t^2}{t^2 + n - 2}$$

For example, suppose that $n = 20$, the corresponding t-value with 18 degrees of freedom at the 0.05 level is $t_{18} = 2.101$. Hence,

$$r^2 = \frac{(2.101)^2}{(2.101)^2 + 18} = 0.1969$$

and the corresponding value for r is $r \pm 0.444$; that is, with 20 observations the value of r must exceed 0.444 or be less than -0.444 to be significant at the 0.05 level. Table A.11 lists critical values for r, as a function of sample size.

Another approach is to determine the sample size needed to "make" an observed value of r significant. Algebraic manipulation of the formula gives

$$n = \frac{t^2}{r^2} - t^2 + 2$$

A useful approximation can be derived if it is assumed that we are interested in reasonably small values of r, say $r < 0.5$; in this case, $t \doteq 2$ at the 0.05 level and the formula becomes

$$n = \left(\frac{2}{r}\right)^2 - 2$$

For example, suppose that $r = 0.3$; the sample size needed to make this value significant is

$$n = \left(\frac{2}{0.3}\right)^2 - 2 = 44 - 2 = 42$$

A somewhat more refined calculation yields $n = 43$, so the approximation works reasonably well.

9.3.5 Using the Correlation Coefficient as a Measure of Agreement for Two Methods of Measuring the Same Quantity

We have seen that for X and Y jointly distributed random variables, the correlation coefficient ρ is a population parameter value: ρ is a measure of how closely X and Y have a linear association, ρ^2 is the proportion of the Y variance that can be explained by linear prediction from X, and vice versa.

Suppose that the regression holds and we may choose X. Figure 9.14 shows data from a regression model with three different patterns of X variables chosen. The same errors were added in each figure. The X values were spread out over larger and larger intervals. Since the spread *about* the regression line remains the same and the range of Y increases as the X range increases, the proportion of Y variability explained by X increases: 0.50 to 0.68 to 0.79. For the same random errors and population regression line, r can be anywhere between 0 and 1, depending on which X values are used! In this case the correlation coefficient depends not only on the model, but also on experimental design, where the X's are taken. For this reason some authors say that the r should never be used unless one has a *bi*variate sample: Otherwise, we do not know what r means; another experimenter with the same regression model could choose different X values and obtain a radically different result.

We discuss these ideas in the context of the exercise data of Example 9.2. Suppose that we were strong supporters of maximal treadmill stress testing and wanted to show how closely treadmill duration and $VO_{2\ MAX}$ are related. Our strategy for obtaining a large correlation coefficient will be to obtain a large spread of X values, duration. We may know that some of the largest duration and $VO_{2\ MAX}$ values were obtained by world-class cross-country skiers; so we would recruit some. For low values we might search for elderly overweight and deconditioned persons. Taking a combined group of these two types of subjects should result in a large value of r. If the same experiment is run using only very old, very overweight, and very deconditioned subjects, the small range will produce a small, statistically insignificant r value.

Since the same treadmill test procedure is associated with large and small r values, what does r mean? A preferable summary indicator is the estimate, $s_{y \cdot x}$ of the residual standard deviation σ_1. If the linear regression model holds, this would be estimated to be the same in each case.

Is it wrong to calculate or present r when a bivariate sample is not obtained? Our answer is a qualified no; that is, it is all right to present r in regression situations provided that:

1. The limitations are kept in mind and discussed. Possible comments on the situation for other sorts of X values might be appropriate.
2. The standard deviation of the residuals should be estimated and presented.

In Chapter 7, the kappa statistic was presented. This was a measure of the amount of agreement when two categorical measurements of the same objects were available. If the two measurements were continuous, the correlation coefficient r is often used as a measure of the agreement of the two techniques. Such use of r is subject to the comments above.

9.3.6 Errors in Both Variables

An assumption in the linear regression model has been that the predictor variable could be measured without error and that the variation in the dependent variable was of one kind only

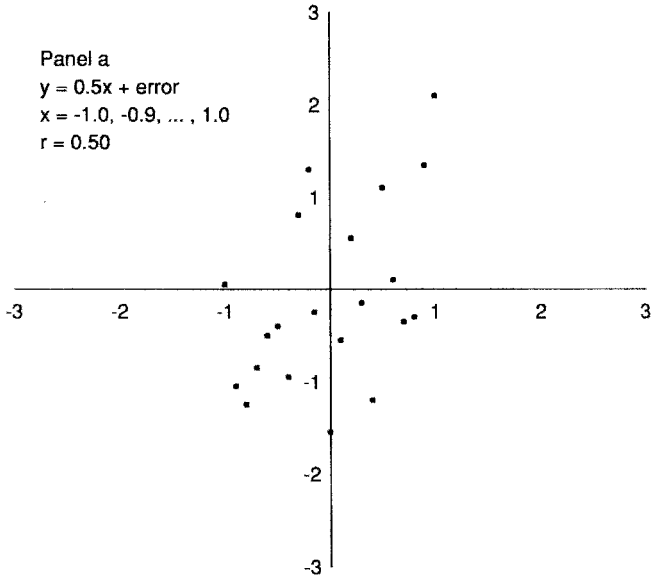


Figure 9.14 The regression model $Y = 0.5X + e$ was used. Twenty-one random $N(0, 1)$ errors were generated by computer. The same errors were used in each panel.

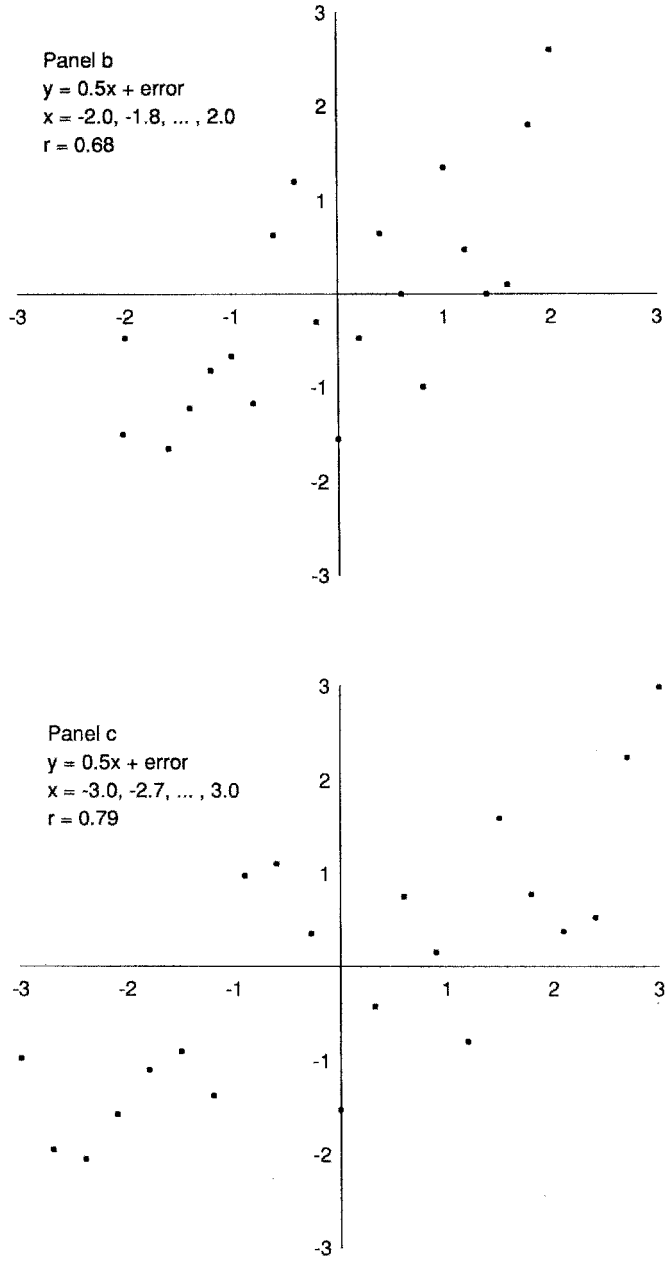


Figure 9.14 (*continued*)

and could be modeled completely if the value of the predictor variable was fixed. In almost all cases, these assumptions do not hold. For example, in measuring psychological characteristics of individuals, there is (1) variation in the characteristics from person to person; and (2) error in the measurement of these psychological characteristics. It is almost certainly true that this problem is present in all scientific work. However, it may be that the measurement error is "small" relative to the variation of the individuals, and hence the former can be neglected.

Another context where the error is unimportant is where the scientific interest is in the variable as measured, not some underlying quantity. For example, in examining how well blood pressure predicts stroke, we are interested in practical prediction, not in what might hypothetically be possible with perfect measurements.

The problem is difficult and we will not discuss it beyond the effect of errors on the correlation coefficient. For a more complete treatment, consult Acton [1984] or Kendall and Stuart [1967, Vol. 2], and for a discussion of measurement error in more complex models, see Carrol et al. [1995].

Suppose that we are interested in the correlation between two random variables X and Y which are measured with errors so that instead of X and Y, we observe that

$$W = X + d, \qquad V = Y + e$$

where d and e are errors. The sampling we have in mind is the following: a "case" is selected at random from the population of interest. The characteristics X and Y are measured but with random independent errors d and e. It is assumed that these errors have mean zero and variances σ_1^2 and σ_2^2, respectively. Another "case" is then selected and the measurement process is repeated with error. Of interest is the correlation ρ_{XY} between X and Y, but the correlation ρ_{VW} is estimated. What is the relationship between these two correlations? The correlation ρ_{XY} can be written

$$\rho_{XY} = \frac{\sigma_{XY}}{\sqrt{\sigma_X^2 \sigma_Y^2}}$$

The reason for writing the correlation this way can be understood when the correlation between V and W is considered:

$$\begin{aligned}
\rho_{VW} &= \frac{\sigma_{XY}}{\sqrt{(\sigma_X^2 + \sigma_1^2)(\sigma_Y^2 + \sigma_2^2)}} \\
&= \frac{\sigma_{XY}}{\sigma_X \sigma_Y \sqrt{\left(1 + \sigma_1^2/\sigma_X^2\right)\left(1 + \sigma_2^2/\sigma_Y^2\right)}} \\
&= \frac{\rho_{XY}}{\sqrt{\left(1 + \sigma_1^2/\sigma_X^2\right)\left(1 + \sigma_2^2/\sigma_Y^2\right)}}
\end{aligned}$$

The last two formulas indicate that the correlation between V and W is smaller in absolute value than the correlation between X and Y by an amount determined by the ratio of the measurement errors to the variance in the population. Table 9.9 gives the effect on ρ_{XY} as related to the ratios of σ_1^2/σ_X^2 and σ_2^2/σ_Y^2.

A 10% error of measurement in the variables X and Y produces a 9% reduction in the correlation coefficient. The conclusion is that errors of measurement reduce the correlation between two variables; this phenomenon is called *attenuation*.

Table 9.9 Effect of Errors of Measurement on the Correlation between Two Random Variables

$\frac{\sigma_1^2}{\sigma_X^2}$	$\frac{\sigma_2^2}{\sigma_Y^2}$	ρ_{VW}	$\frac{\sigma_1^2}{\sigma_X^2}$	$\frac{\sigma_2^2}{\sigma_Y^2}$	ρ_{VW}
0	0	1 ρ_{XY}	0.20	0.10	$0.87\rho_{XY}$
0.05	0.05	$0.95\rho_{XY}$	0.20	0.20	$0.83\rho_{XY}$
0.10	0.10	$0.91\rho_{XY}$	0.30	0.30	$0.77\rho_{XY}$

Table 9.10 Schema for Spearman Rank Correlation

Case	X	Rank(X)	Y	Rank(Y)	$d = \text{Rank}(X) - \text{Rank}(Y)$
1	x_1	R_{x_1}	y_1	R_{y_1}	$d_1 = R_{x_1} - R_{y_1}$
2	x_2	R_{x_2}	y_2	R_{y_2}	$d_2 = R_{x_2} - R_{y_2}$
3	x_3	R_{x_3}	y_3	R_{y_3}	$d_3 = R_{x_3} - R_{y_3}$
⋮	⋮	⋮	⋮	⋮	⋮
n	x_n	R_{x_n}	y_n	R_{y_n}	$d_n = R_{x_n} - R_{y_n}$

9.3.7 Nonparametric Estimates of Correlation

As indicated earlier, the correlation coefficient is quite sensitive to outliers. There are many ways of getting estimates of correlation that are more robust; the paper by Devlin et al. [1975] contains a description of some of these methods. In this section we want to discuss two methods of testing correlations derived from the ranks of observations.

The procedure leading to the Spearman rank correlation is as follows: Given a set of n observations on the variables X, Y, the values for X are replaced by their ranks, and similarly, the values for Y. Ties are simply assigned the average of the ranks associated with the tied observations. The scheme shown in Table 9.10 illustrates the procedure.

The correlation is then calculated between R_x and R_y. In practice, the *Spearman rank correlation formula* is used:

$$r_s = r_{R_x R_y} = 1 - \frac{6 \sum d_i^2}{n^3 - n}$$

It can be shown that the usual Pearson product-moment correlation formula reduces to this formula when the calculations are made on the ranks, if there are no ties. *Note:* For one or two ties, the results are virtually the same. It is possible to correct the Spearman formula for ties, but a simpler procedure is to calculate r_s by application of the usual product-moment formula to the ranks. Table A.12 gives percentile points for testing the hypothesis that X and Y are independent.

Example 9.4. Consider again the data in Table 9.3 dealing with the ATP levels of the oldest and youngest sons. These data are reproduced in Table 9.11 together with the ranks, the ATP levels being ranked from lowest to highest.

Note that the oldest sons in families 6 and 13 had the same ATP levels; they would have been assigned ranks 12 and 13 if the values had been recorded more accurately; consequently, they are both assigned a rank of 12.5. For this example,

$$n = 17$$
$$\sum d_i^2 = 298.5$$
$$r_s = 1 - \frac{(6)(298.5)}{17^3 - 17} = 1 - 0.3658 = 0.6342$$

This value compares reasonably well with the value $r_{xy} = 0.597$ calculated on the actual data. If the usual Pearson product-moment formula is applied to the ranks, the value $r_s = 0.6340$ is obtained. The reader may verify that this is the case. The reason for the slight difference is due to the tie in values for two of the oldest sons. Table A.12 shows the statistical significance at the two-sided 0.05 level since $r_s = 0.6342 > 0.490$.

The second nonparametric correlation coefficient is the *Kendall rank correlation coefficient*. Recall our motivation for the correlation coefficient r. If there is positive association, increase in

Table 9.11 Rank Correlation Analysis of ATP Levels in Youngest and Oldest Sons in 17 Families

	Youngest		Oldest		
Family	ATP Level	Rank (X)	ATP Level	Rank (Y)	d^a
1	4.18	4	4.81	11	−7
2	5.16	12	4.98	14	−2
3	4.85	9	4.48	6	3
4	3.43	1	4.19	3	−2
5	4.53	5	4.27	4	1
6	5.13	11	4.87	12.5	−1.51
7	4.10	2	4.74	10	−8
8	4.77	7	4.53	7	0
9	4.12	3	3.72	1	2
10	4.65	6	4.62	8	−2
11	6.03	17	5.83	17	0
12	5.94	15	4.40	5	10
13	5.99	16	4.87	12.5	3.5
14	5.43	14	5.44	16	−2
15	5.00	10	4.70	9	1
16	4.82	8	4.14	2	6
17	5.25	13	5.30	15	−2
					$\sum d = 0$
					$\sum d^2 = 298.5$

[a] Rank(X) − rank(Y).

X will tend to correspond to increase in Y. That is, given two data points (X_1, Y_1) and (X_2, Y_2), if $X_1 - X_2$ is positive, $Y_1 - Y_2$ is positive. In this case, $(X_1 - X_2)(Y_1 - Y_2)$ is usually positive. If there is negative association, $(X_1 - X_2)(Y_1 - Y_2)$ will usually be negative. If X and Y are independent, the expected value is zero. Kendall's rank correlation coefficient is based on this observation.

Definition 9.8. Consider a bivariate sample of size n, $(X_1, Y_1), \ldots, (X_n, Y_n)$. For each pair, count 1 if $(X_i - X_j)(Y_i - Y_j) > 0$. Count -1 if $(X_i - X_j)(Y_i - Y_j) < 0$. Count zero if $(X_i - X_j)(Y_i - Y_j) = 0$. Let κ be the sum of these $n(n-1)/2$ counts. (Note that this κ is not related to the kappa of Chapter 7.) Kendall's τ is

$$\tau = \frac{\kappa}{n(n-1)/2}$$

1. The value of τ is between -1 and 1. Under the null hypothesis of independence, τ is symmetric about zero.
2. Note that $(R_{X_i} - R_{X_j})(R_{Y_i} - R_{Y_j})$ has the same sign as $(X_i - X_j)(Y_i - Y_j)$. That is, both are positive or both are negative or both are zero. If we calculated τ from the ranks of the (X_i, Y_i), we get the same number. Thus, τ is a nonparametric quantity based on ranks; it does not depend on the distributions of X and Y.
3. The expected value of τ is

$$P[(X_i - X_j)(Y_i - Y_j) > 0] - P[(X_i - X_j)(Y_i - Y_j) < 0]$$

Table 9.12 Data for Example 9.4[a]

	j															
i	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
2	1															
3	−1	1														
4	1	1	1													
5	−1	1	1	1												
6	1	1	1	1	1											
7	1	1	−1	1	−1	1										
8	−1	1	−1	1	1	1	−1									
9	1	1	1	−1	1	1	−1	1								
10	−1	1	−1	1	1	1	−1	−1	1							
11	1	1	1	1	1	1	1	1	1	1						
12	−1	−1	−1	1	1	−1	−1	−1	1	−1	1					
13	1	−1	1	1	1	0	1	1	1	1	1	1				
14	1	1	1	1	1	1	1	1	1	1	1	−1	−1			
15	−1	1	1	1	1	1	−1	1	1	1	1	−1	1	1		
16	−1	1	1	−1	−1	1	−1	−1	1	−1	1	1	1	1	1	
17	1	1	1	1	1	1	1	1	1	1	1	−1	−1	1	1	1

[a]Consider $(X_i - X_j)(Y_i - Y_j)$: the entries are 1 if this is positive, 0 if this equals 0, and −1 if this is negative.

4. For moderate to large n and no or few ties, an approximate standard normal test statistic is

$$Z = \frac{\kappa}{\sqrt{n(n-1)(2n+5)/18}}$$

More information where there are ties is given in Note 9.7.

5. If $(X_i - X_j)(Y_i - Y_j) > 0$, the pairs are said to be concordant. If $(X_i - X_j)(Y_i - Y_j) < 0$, the pairs are discordant.

Return to the ATP data of Table 9.11. $(X_1 - X_2)(Y_1 - Y_2) = (4.18 - 5.16)(4.81 - 4.98) > 0$, so we count +1. Comparing each of the $17 \times 16/2 = 136$ pairs gives the +1's, 0's and −1's in Table 9.12. Adding these numbers, $\kappa = 67$, and $\tau = 67/(17 \times 16/2) = 0.493$. The asymptotic Z-value is

$$Z = \frac{67}{\sqrt{17 \times 16 \times 39/18}} = 2.67$$

with $p = 0.0076$ (two-sided).

9.3.8 Change and Association

Consider two continuous measurements of the same quantity on the same subjects at different times or under different circumstances. The two times might be before and after some treatment. They might be for a person taking a drug and not taking a drug. If we want to see if there is a difference in the means at the two times or under the two circumstances, we have several statistical tests: the paired t-test, the signed rank test, and the sign test. Note that we have observed pairs of numbers on each subject.

We now have new methods when pairs of numbers are observed: linear regression and correlation. Which technique should be used in a given circumstance? The first set of techniques looks for *changes between the two measurements*. The second set of techniques look for association and sometimes *the ability to predict*. The two concepts are different ideas:

1. Consider two independent length measurements from the same x-rays of a sample of patients. Presumably there is a "true" length. The measurements should fluctuate about the true length. Since the true length will fluctuate from patient to patient, the two readings should be associated, hopefully highly correlated. Since both measurements are of the same quantity, there should be little or no change. This would be a case where one expects association, but no change.
2. Consider cardiac measurements on patients before and after a heart transplant. The initial measurements refer to a failing heart. After heart transplant the measurements refer to the donor heart. There will be little or no association because the measurements of output, and so on, refer to different (somewhat randomly paired) hearts.

There are situations where both change and prediction or association are relevant. After observing a change, one might like to investigate how the new changed values relate to the original values.

9.4 COMMON MISAPPLICATION OF REGRESSION AND CORRELATION METHODS

In this section we discuss some of the pitfalls of regression and correlation methods.

9.4.1 Regression to the Mean

Consider Figure 9.15, which has data points with approximately zero correlation or association, considered as measurements before and after some intervention. On the left we see that the before and after measurements have no association. The solid line indicates before = 0, and the dashed line indicates before = after. On the right we plot the change against the value before intervention. Again, the two lines are before = 0 and before = after (i.e., change = 0), and we can see how selecting based on the value of the measurement before intervention distorts the average change.

Cases with low initial values (circles on the graph) tend to have positive changes; those with high initial values (triangles) have negative changes. If we admitted to our study only the subjects with low values, it would appear that the intervention led to an increase. In fact, the change would be due to random variability and the case selection. This phenomenon is called *regression to the mean*.

As another example, consider subjects in a quantitative measurement of the amount of rash due to an allergy. Persons will have considerable variability due to biology and environment. Over time, in a random fashion, perhaps related to the season, the severity of rash will ebb and flow. Such people will naturally tend to seek medical help when things are in a particularly bad state. Following the soliciting of help, biological variability will give improvement with or without treatment. Thus, if the treatment is evaluated (using before and after values), there would be a natural drop in the amount of rash simply because medical help was solicited during particularly bad times. This phenomenon again is *regression to the mean*. The phenomenon of regression to the mean is one reason that control groups are used in clinical studies. Some approaches to addressing it are given by Yanez et al. [1998].

9.4.2 Spurious Correlation

Consider a series of population units, for example, states. Suppose that we wish to relate the occurrence of death from two distinct causes, for example, cancer at two different sites on the body. If we take all the states and plot a scatter diagram of the number of deaths from the two causes, there will be a relationship simply because states with many more people, such as

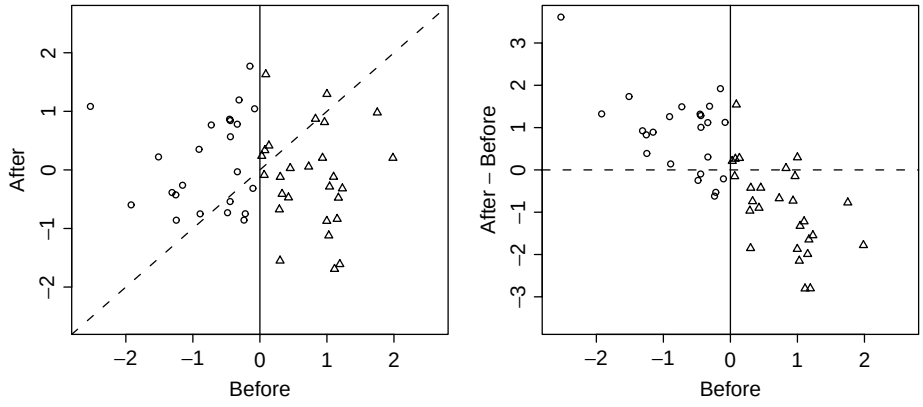


Figure 9.15 Regression to the mean in variables with no association: Before vs. after and before vs. change.

California or New York, will have a large number of deaths, compared to a smaller state such as Wyoming or New Hampshire.

It is necessary to somehow adjust for or take the population into account. The most natural thing to do is to take the death rate from certain causes, that is, to divide the number of deaths by the population of the state. This would appear to be a good solution to the problem. This introduces another problem, however. If we have two variables, X and Y, which are *not related* and we divide them by a third variable, Z, which is random, the two ratios X/Z and Y/Z *will be related*. Suppose that Z is the true denominator measured with error. The reason for the relationship is that when Z is on the low side, since we are dividing by Z, we will increase both numbers at the same time; when Z is larger than it should be and we divide X and Y by Z, we decrease both numbers. The introduction of correlation due to computing rates using the same denominator is called *spurious correlation*. For further discussion on this, see Neyman [1952] and Kronmal [1993], who gives a superb, readable review. A preferable way to adjust for population size is to use the techniques of multiple regression, which is discussed in Chapter 11.

9.4.3 Extrapolation beyond the Range of the Data

For many data sets, including the three of this chapter, the linear relationship does a reasonable job of summarizing the association between two variables. In other situations, the relationship may be reasonably well modeled as linear over a part of the range of X but not over the entire range of X. Suppose, however, that data had been collected on only a small range of X. Then a linear model might fit the accumulated data quite well. If one takes the regression line and uses it as an indication of what would happen for data values *outside the range covered by the actual data*, trouble can result. To have confidence in such extrapolation, one needs to know that indeed the linear relationship holds over a broader range than the range associated with the actual data. Sometimes this assumption is valid, but often, it is quite wrong. There is no way of knowing in general to what extent extrapolation beyond the data gives problems. Some of the possibilities are indicated graphically in Figure 9.16. Note that virtually any of these patterns of curves, when data are observed over a short range, can reasonably be approximated by a linear function. Over a wider range, a linear approximation is not adequate. But if one does not have data over the wide range, this cannot be seen.

Sometimes it is necessary to extrapolate beyond the range of the data. For example, there is substantial concern in Britain over the scale of transmission of "mad cow disease" to humans, causing variant Creutzfeld–Jakob disease (vCJD). Forecasting the number of future cases is

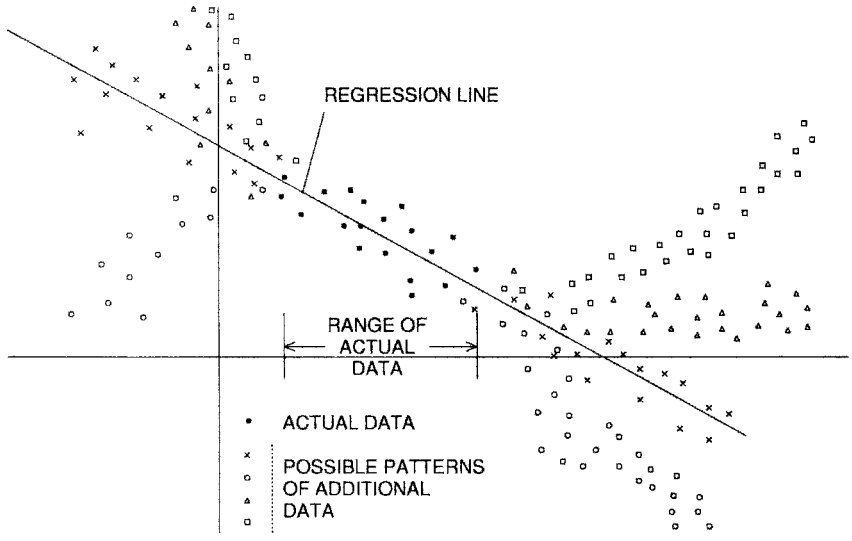


Figure 9.16 Danger of extrapolating beyond observed data.

important for public health, and intrinsically, requires extrapolation. A responsible approach to this type of problem is to consider carefully what models (linear or otherwise) are consistent with the data available and more important, with other existing knowledge. The result is a range of predictions that acknowledge both the statistical uncertainty within each model and the (often much greater) uncertainty about which model to use.

9.4.4 Inferring Causality from Correlation

Because two variables are associated does not necessarily mean that there is any causal connection between them. For example, if one recorded two numbers for each year—the numbers of hospital beds and the total attendance at major league baseball games—there would be a positive association because both of these variables have increased as the population increased. The direct connection is undoubtedly slight at best. Thus, regression and correlation approaches show observed relationships, which may or may not represent a causal relationship. In general, the strongest inference for causality comes from experimental data; in this case, factors are changed by the experimenter to observe change in a response. Regression and correlation from observational data may be very suggestive but do not definitively establish causal relationships.

9.4.5 Interpretation of the Slope of the Regression Line

During the discussion, we have noted that the regression equation implies that if the predictor or independent variable X is higher by an amount ΔX, then on the average, Y is higher by an amount $\Delta Y = b\,\Delta X$. This is sometimes interpreted to mean that if we can modify a situation such that the X variable is changed by ΔX, the Y variable will change correspondingly; this may or may not be the case. For example, if we look at a scatter diagram of adults' height and weight, it does not follow if we induce a change in a person's weight, either by dieting or by excess calories that the person's height will change correspondingly. Nevertheless, there is an association between height and weight. Thus, the particular inference depends on the science involved. Earlier in this chapter, it was noted that from the relation between $VO_{2\ MAX}$ and the duration of the exercise test that if a person is trained to have an increased duration, the $VO_{2\ MAX}$ will also increase. This particular inference is correct and has been documented by

serial studies recording both variables. It follows from other data and scientific understanding. It is *not* a logical consequence of the observed association.

9.4.6 Outlying Observations

As noted above, outlying observations can have a large effect on the actual regression line (see Figure 9.7, for example). If one examines these scattergrams or residual plots, the problem should be recognized. In many situations, however, people look at large numbers of correlations and do not have the time, the wherewithal, or possibly the knowledge to examine all of the necessary visual presentations. In such a case, an outlier can be missed and data may be interpreted inappropriately.

9.4.7 Robust Regression Models

The least squares regression coefficients result from minimizing

$$\sum_{i=1}^{n} g(Y_i - a - bX_i)$$

where the function $g(z) = z^2$. For large z (large residuals) this term is very large. In the second column of figures in Figure 9.7 we saw that one outlying value could heavily modify an otherwise nice fit.

One way to give less importance to large residuals is to choose the function g to put less weight on outlying values. Many robust regression techniques take this approach. We can choose g so that for most z, $g(z) = z^2$, as in the least squares estimates, but for very large $|z|$, $g(z)$ is less than z^2, even zero for extreme z! See Draper and Smith [1998, Chap. 25] and Huber [2003, Chap. 7]. These *resistant M–estimators* protect against outlying Y but not against outlying X, for which even more complex estimators are needed. It is also important to note that protection against outliers is not always desirable. Consider the situation of a managed care organization trying to determine if exercise reduces medical costs. A resistant regression estimator would effectively ignore information on occasional very expensive subjects, who may be precisely the most important in managing costs. See Chapter 8 and Lumley et al. [2002] for more discussion of these issues.

NOTES

9.1 Origin of the Term Regression

Sir Francis Galton first used the term in 1885. He studied the heights of parents and offspring. He found (on the average) that children of tall parents were closer to the average height (were shorter); children of short parents were taller and closer to the average height. The children's height *regressed* to the average.

9.2 Maximum Likelihood Estimation of Regression and Correlation Parameters

For a data set from a continuous probability density, the probability of observing the data is proportional to the probability density function. It makes sense to *estimate the parameters by choosing parameters to make the probability of the observed data as large as possible*. Such estimates are called *maximum likelihood estimates* (MLEs). Knowing $X_1, \ldots, X_n$ in the regression

problem, the likelihood function for the observed $Y_1, \ldots, Y_n$ is (assuming normality)

$$\prod_{i=1}^{n} \frac{1}{\sqrt{2\pi}\sigma} \exp\left\{-\frac{1}{2\sigma^2}[Y_i - (\alpha + \beta X_i)]^2\right\}$$

The maximum likelihood estimates of α and β are the least squares estimates a and b. For the bivariate normal distribution, the MLE of ρ is r.

9.3 Notes on the Variance of a, Variance of a + bx, and Choice of x for Small Variance (Experimental Design)

1. The variance of a in the regression equation $y = a + bx$ can be derived as follows: $a = \overline{y} + b\overline{x}$; it is true that $\overline{y}$ and b are statistically independent; hence,

$$\begin{aligned}
\text{var}(a) &= \text{var}(\overline{y} + b\overline{x}) \\
&= \text{var}(\overline{y}) + \overline{x}^2\text{var}(b) \\
&= \frac{\sigma_1^2}{n} + \overline{x}^2\frac{\sigma_1^2}{[x^2]} \\
&= \sigma_1^2\left(\frac{1}{n} + \frac{\overline{x}^2}{[x^2]}\right)
\end{aligned}$$

2. Consider the variance of the estimate of the mean of y at some arbitrary fixed point X:

$$\sigma_1^2\left(\frac{1}{n} + \frac{(x - \overline{x})^2}{[x^2]}\right)$$

- **a.** Given a choice of x, the quantity is minimized at $x = \overline{x}$.
- **b.** For values of x close to $\overline{x}$ the contribution to the variance is minimal.
- **c.** The contribution increase as the *square* of the distance the predictor variable x is from $\overline{x}$.
- **d.** If there was a choice in the selection of the predictor variables, the quantity $[x^2] = \sum(x_i - \overline{x})^2$ is maximized if the predictor variables are spaced as far apart as possible. If X can have a range of values, say, $X_{\min}$ to $X_{\max}$, the quantity $[x^2]$ is maximized if half the observations are placed at $X_{\min}$ and the other half at $X_{\max}$. The quantity $(x - \overline{x})^2/[x^2]$ will then be as small as possible. Of course, a price is paid for this design: it is not possible to check the linearity of the relationship between Y and X.

9.4 Average-Slope Formula for b

An alternative formula for the slope estimate b emphasizes the interpretation as an average difference in Y for each unit difference in X. Suppose that we had just two points (X_1, Y_1) and (X_2, Y_2). The obvious estimate of the slope comes from simply joining the points with a line:

$$b_{21} = \frac{Y_2 - Y_1}{X_2 - X_1}$$

With more than two points we could calculate all the pairwise slope estimates

$$b_{ij} = \frac{Y_i - Y_j}{X_i - X_j}$$

and then take some summary of these as the overall slope. More weight should be give to estimates b_{ij} where $X_i - X_j$ is larger, as the expected difference in Y, $\beta(X_i - X_j)$ is larger relative to the residual error in Y_i and Y_j. If we assign weights $w_{ij} = (X_i - X_j)^2$, a little algebra shows that an alternative formula for the least squares estimate b is

$$b = \frac{\sum_{i,j} w_{ij} b_{ij}}{\sum_{i,j} w_{ij}}$$

a weighted average of the pairwise slopes.

This formulation makes it clear that b estimates the average slope of Y with respect to X under essentially no assumptions. Of course, if the relationship is not at least roughly linear, the average slope may be of little practical interest, and in any case some further assumptions are needed for statistical inference.

9.5 Regression Lines through the Origin

Suppose that we want to fit the model $Y \sim N(\beta X, \sigma^2)$, that is, the line goes through the origin. In many situations this is an appropriate model (e.g., in relating body weight to height, it is reasonable to assume that the regression line must go through the origin). However, the regression relationship may not be linear over the entire range, and often, the interval of interest is quite far removed from the origin.

Given n pairs of observation (x_i, y_i), $i = 1, \ldots, n$, and a regression line through the origin is desired, it can be shown that the least squares estimate, b, of β is

$$b = \frac{\sum x_i y_i}{\sum x_i^2}$$

The residual sum of squares is based on the quantity

$$\sum (y_i - \widehat{y}_i)^2 = \sum (y_i - b x_i)^2$$

and has associated with it, $n - 1$ degrees of freedom, since only one parameter, β, is estimated.

9.6 Bivariate Normal Density Function

The formula for the density of the bivariate normal distribution is

$$f_{X,Y}(x, y) = \frac{1}{2\pi\sigma_X\sigma_Y\sqrt{1 - p^2}} \exp\left[-\frac{1}{2(1-\rho^2)}(Z_X^2 - 2\rho Z_X Z_Y + Z_Y^2)\right]$$

where

$$Z_X = \frac{x - \mu_X}{\sigma_X} \quad \text{and} \quad Z_Y = \frac{y - \mu_Y}{\sigma_Y}$$

The quantities μ_X, μ_Y, σ_X, and σ_Y are, as usual, the means and standard deviations of X and Y, respectively. Several characteristics of this distribution can be deduced from this formula:

1. If $\rho = 0$, the equation becomes

$$f_{X,Y}(x, y) = \frac{1}{2\pi\sigma_X\sigma_Y} \exp\left[-\frac{1}{2}(Z_X^2 + Z_Y^2)\right]$$

and can be written as

$$= \frac{1}{\sqrt{2\pi}\sigma_X} \exp\left(-\frac{1}{2}Z_X^2\right) \frac{1}{\sqrt{2\pi}\sigma_Y} \exp\left(-\frac{1}{2}Z_Y^2\right)$$
$$= f_X(x) f_Y(y)$$

Thus in the case of the bivariate normal distribution, $\rho = 0$ (i.e., the correlation is zero), implies that the random variables X and Y are statistically independent.

2. Suppose that $f_{X,Y}(x, y)$ is fixed at some specified value; this implies that the expression in the exponent of the density $f_{X,Y}(x, y)$ has a fixed value, say, K:

$$K = \frac{-1}{2(1-\rho^2)} \left[\left(\frac{x-\mu_X}{\sigma_X}\right)^2 - 2\rho \frac{x-\mu_X}{\sigma_X} \frac{y-\mu_Y}{\sigma_Y} + \left(\frac{y-\mu_Y}{\sigma_Y}\right)^2 \right]$$

This is the equation of an ellipse centered at (μ_X, μ_Y).

9.7 Ties in Kendall's Tau

When there are ties in the X_i and/or Y_i values for Kendall's tau, the variability is reduced. The asymptotic formula needs to be adjusted accordingly [Hollander and Wolfe, 1999]. Let the X_i values have g distinct values with ties with t_j tied observations at the jth tied value. Let the Y_i values have h distinct tied values with u_k tied observations at the kth tied value. Under the null hypothesis of independence between the X and Y values, the variance of K is

$$\begin{aligned}
\text{var}(K) = {} & \frac{n(n-1)(2n+5)}{18} \\
& - \sum_{j=1}^{g} \frac{t_j(t_j-1)(2t_j+5)}{18} \\
& - \sum_{j=1}^{h} \frac{u_k(u_k-1)(2u_k+5)}{18} \\
& + \frac{\left[\sum_{j=1}^{g} t_j(t_j-1)(t_j-2)\right]\left[\sum_{k=1}^{h} u_k(u_k-1)(u_k-2)\right]}{9n(n-1)(n-2)} \\
& + \frac{\left[\sum_{j=1}^{g} t_j(t_j-1)\right]\left[\sum_{k=1}^{h} u_k(u_k-1)\right]}{2n(n-1)}
\end{aligned}$$

The asymptotic normal Z value is

$$Z = \frac{K}{\sqrt{\text{var}(K)}}$$

Note that the null hypothesis is independence, not $\tau = 0$. If the data are not independent but nevertheless have $\tau = 0$ (e.g., a U-shaped relationship), the test will be incorrect.

9.8 Weighted Regression Analysis

In certain cases the assumption of homogeneity of variance of the dependent variable, Y, at all levels of X is not tenable. Suppose that the precision of value $Y = y$ is proportional to a value

W, the weight. Usually, the precision is the reciprocal of the variance at X_i. The data can then be modeled as follows:

Case	X	Y	W
1	x_1	y_1	w_1
2	x_2	y_2	w_2
⋮	⋮	⋮	⋮
i	x_i	y_i	w_i
⋮	⋮	⋮	⋮
n	x_n	y_n	w_n

Define $\sum w_i(x_i - \overline{x}_i)^2 = [wx^2]$, $\sum w(x_i - \overline{x})(y_i - \overline{y}) = [wxy]$. It can be shown that the *weighted* least squares line has slope and intercept,

$$b = \frac{[wxy]}{[wx^2]} \quad \text{and} \quad a = \overline{y} - b\overline{x}$$

where

$$\overline{y} = \frac{\sum w_i y_i}{\sum w_i} \quad \text{and} \quad \overline{x} = \frac{\sum w_i x_i}{\sum w_i}$$

It is a weighted least squares solution in that the quantity $\sum w_i(y_i - \widehat{y}_i)^2$ is minimized. If all the weights are the same, say equal to 1, the ordinary least squares solutions are obtained.

9.9 Model-Robust Standard Error Estimates

We showed that Student's t-test can be formulated as a regression problem. This raises the question of whether we can also find a regression formulation of the Z-test or the unequal-variance approximate t-test of Note 5.2. The answer is in the affirmative. Standard error estimates are available that remove subsidiary assumptions such as equality of variance for a wide range of statistical estimators. These model-robust or "sandwich" standard errors were discovered independently in different fields of statistics and are typically attributed to Huber in biostatistics and to White in econometrics. The Huber–White standard error estimates are available for linear models in SAS and for nearly all regression models in State. In the case of linear regression with a binary X variable, they are equivalent to the unequal-variance t-test except that there is not complete agreement on whether n or $n - 1$ should be used as a denominator in computing variances. See Huber [2003] for further discussion.

PROBLEMS

In most of the problems below, you are asked to perform some subset of the following tasks:

(a) Plot the scatter diagram for the data.
(b) Compute for $\overline{X}, \overline{Y}, [x^2], [y^2]$, and $[xy]$ those quantities not given.

(c) Find the regression coefficients a and b.

(d) Place the regression line on the scatter diagram.

(e) Give $s^2_{y \cdot x}$ and $s_{y \cdot x}$.

(f) Compute the missing predicted values, residuals, and normal deviates for the given portion of the table.

(g) Plot the residual plot.

(h) Interpret the residual plot.

(i) Plot the residual normal probability plot.

(j) Interpret the residual normal probability plot.

(k) **i.** Construct the 90% confidence interval for β.

ii. Construct the 95% confidence interval for β.

iii. Construct the 99% confidence interval for β.

iv. Compute the t-statistic for testing $\beta = 0$. What can you say about its p-value?

(l) **i.** Construct the 90% confidence interval for α.

ii. Construct the 95% confidence interval for α.

iii. Construct the 99% confidence interval for α.

(m) Construct the ANOVA table and use Table A.7 to give information about the p-value.

(n) Construct the 95% confidence interval for $\alpha + \beta X$ at the X value(s) specified.

(o) Construct the interval such that one is 95% certain that a new observation at the specified X value(s) will fall into the interval.

(p) Compute the correlation coefficient r.

(q) **i.** Construct the 90% confidence interval for ρ.

ii. Construct the 95% confidence interval for ρ.

iii. Construct the 99% confidence interval for ρ.

(r) Test the independence of X and Y using Spearman's rank correlation coefficient. Compute the coefficient.

(s) Test the independence of X and Y using Kendall's rank correlation coefficient. Compute the value of the coefficient.

(t) Compute Student's paired t-test for the data, if not given; in any case, interpret.

(u) Compute the signed rank statistic, if not given; in any case, interpret.

The first set of problems, 9.1 to 9.4, come from the exercise data in Example 9.2.

9.1 Suppose that we use duration, X, to predict $VO_{2\ MAX}$, Y. The scatter diagram is shown in Figure 9.2. $\overline{X} = 647.4$, $\overline{Y} = 40.57$, $[x^2] = 673{,}496.4$, $[y^2] = 3506.2$, and $[xy] = 43{,}352.5$. Do tasks (c), (e), (f), (h), (k-ii), (k-iv), (l-ii), (m), (n) at $x = 650$, (p), and (q-ii) (the residual plot is Figure 9.17). All the data are listed in Table 9.13. What proportion of the Y variance is explained by X? (In practice, duration is used as a reasonable approximation to $VO_{2\ MAX}$.)

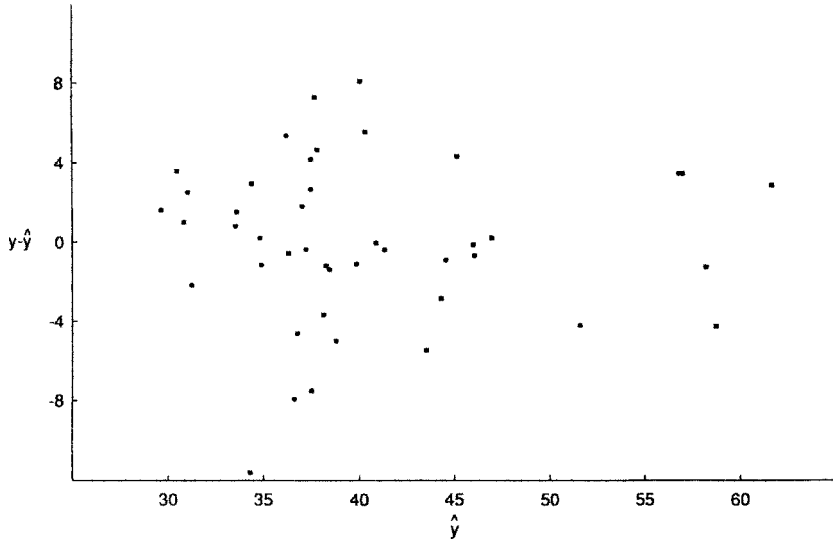


Figure 9.17 Residual plot for the data of Example 9.2; $VO_{2\ MAX}$ predicted from duration.

Table 9.13 Oxygen Data for Problem 9.1

X	Y	$\widehat{Y}$	$Y - \widehat{Y}$	Normal Deviate
706	41.5	44.5	−3.0	−0.80
732	45.9	46.13	−0.23	−0.06
930	54.5	?	?	?
900	60.3	?	3.59	0.96
903	60.5	56.90	3.60	0.97
976	64.6	61.50	3.10	0.83
819	47.4	?	−4.21	−1.13
922	57.0	58.10	−1.10	−0.29
600	40.2	37.82	?	0.64
540	35.2	?	1.16	0.31
560	33.8	35.30	−1.50	?
637	38.8	40.15	−1.35	−0.36
593	38.9	?	1.52	0.41
719	49.5	45.31	?	1.23
615	37.1	38.77	−1.67	−0.45
589	32.2	37.13	?	−1.32
478	31.3	30.14	1.16	0.31
620	33.8	39.08	−5.28	?
710	43.7	44.75	−1.05	−0.28
600	41.7	37.82	3.88	1.04
660	41.0	41.60	−0.60	−0.16

9.2 One expects exercise performance to reduce with age. In this problem, X = age and Y = duration. $\overline{X} = 47.2, \overline{Y} = 647.4, [x^2] = 4303.2, [y^2] = 673,496.4$, and $[xy] = -36,538.5$. Do tasks (c), (e), (k-i), (l-i), (p), and (q-i).

9.3 To see if maximum heart rate changes with age, the following numbers are found where X = age and Y = maximum heart rate. $\overline{X} = 47.2, \overline{Y} = 174.8, [x^2] = 4303.2, [y^2] = 5608.5$, and $[xy] = -2915.4$. Do tasks (c), (e), (k-iii), (k-iv), (m), (p), and (p-iii).

9.4 The relationship between height and weight was examined in these active healthy males. X = height, Y = weight, $\overline{X} = 177.7, \overline{Y} = 77.8, [x^2] = 1985.2, [y^2] = 3154.5$, and $[xy] = 1845.6$. Do tasks (c), (e), (m), (p), and (q-i). How do the p-values for the F-test [in part (m)] and for the transformed Z for r compare? There were two normal deviates of values 3.44 and 2.95. If these two people were removed from the calculation, $\overline{X} = 177.5, \overline{Y} = 76.7, [x^2] = 1944.5, [y^2] = 2076.12$, and $[xy] = 1642.5$. How much do the regression coefficients a and b, and correlation coefficient r, change?

Problems 9.5 to 9.8 also refer to the Bruce et al. [1973] paper, as did Example 9.2 and Problems 9.1 to 9.4. The data for 43 active females are given in Table 9.14.

9.5 The duration and $VO_{2\ MAX}$ relationship for the active females is studied in this problem. $\overline{X} = 514.9, \overline{Y} = 29.1, [x^2] = 251,260.4, [y^2] = 1028.7$, and $[xy] = 12,636.5$. Do tasks (c), (e), (f), (g), (h), (i), (j), (k-iv), (m), (p), and (q-ii). Table 9.15 contains the residuals. If the data are rerun with the sixth case omitted, the values of $\overline{X}, \overline{Y}, [x^2], [y^2]$, and $[xy]$ are changed to 512.9, 29.2, 243,843.1, 1001.5, and 13,085.6, respectively. Find the new estimates a, b, and r. By what percent are they changed?

9.6 With X = age and Y = duration, $\overline{X} = 45.1, \overline{Y} = 514.9, [x^2] = 4399.2, [y^2] = 251,260.4$, and $[xy] = -22,911.3$. For each 10-year increase in age, how much does duration tend to change? What proportion of the variability in $VO_{2\ MAX}$ is accounted for by age? Do tasks (m) and (q-ii).

9.7 With X = age and Y = maximum heart rate, $\overline{X} = 45.1, \overline{Y} = 180.6, [x^2] = 4399.2, [y^2] = 5474.6$, and $[xy] = -2017.3$. Do tasks (c), (e), (k-i), (k-iv), (l-i), (m), (n) at $X = 30$ and $X = 50$, (o) at $X = 45$, (p), and (q-ii).

9.8 X = height and Y = weight, $\overline{X} = 164.7, \overline{Y} = 61.3, [x^2] = 1667.1, [y^2] = 2607.4$, and $[xy] = 1006.2$. Do tasks (c), (e), (h), (k-iv), (m), and (p). Check that $t^2 = F$. The residual plot is shown in Figure 9.18.

For Problems 9.9 to 9.12, additional Bruce et al. [1973] data are used. Table 9.16 presents the data for 94 sedentary males.

9.9 The duration, X, and $VO_{2\ MAX}$, Y, give $\overline{X} = 577.1, \overline{Y} = 35.6, [x^2] = 1,425,990.9, [y^2] = 5245.3$, and $[xy] = 78,280.1$. Do tasks (c), (e), (j), (k-i), (k-iv), (l-i), (m), and (p). The normal probability plot is shown in Figure 9.19.

9.10 X = age is related to Y = duration. $\overline{X} = 49.8, \overline{Y} = 577.1, [x^2] = 11,395.7, [y^2] = 1,425,990.9$, and $[xy] = -87,611.9$. Do tasks (c), (e), (m), (p), and (q-ii).

9.11 The prediction of age by maximal heart rate for sedentary males is considered here. $\overline{X} = 49.8, \overline{Y} = 18.6, [x^2] = 11,395.7, [y^2] = 32,146.4$, and $[xy] = -12,064.1$. Do tasks (c), (m), and (p). Verify (to accuracy given) that $(\overline{X}, \overline{Y})$ lies on the regression line.

9.12 The height and weight data give $\overline{X} = 177.3, \overline{Y} = 79.0, [x^2] = 4030.1, [y^2] = 7060.0$, and $[xy] = 2857.0$. Do tasks (c), (e), (k-iv), (n) at $X = 160$, 170, and 180, and (p).

Table 9.14 Exercise Data for Healthy Active Females

Duration	$VO_{2\ MAX}$	Heart Rate	Age	Height	Weight
660	38.1	184	23	177	83
628	38.4	183	21	163	52
637	41.7	200	21	174	61
575	33.5	170	42	160	50
590	28.6	188	34	170	68
600	23.9	190	43	171	68
562	29.6	190	30	172	63
495	27.3	180	49	157	53
540	33.2	184	30	178	63
470	26.6	162	57	161	63
408	23.6	188	58	159	54
387	23.1	170	51	162	55
564	36.6	184	32	165	57
603	35.8	175	42	170	53
420	28.0	180	51	158	47
573	33.8	200	46	161	60
602	33.6	190	37	173	56
430	21.0	170	50	161	62
508	31.2	158	65	165	58
565	31.2	186	40	154	69
464	23.7	166	52	166	67
495	24.5	170	40	160	58
461	30.5	188	52	162	64
540	25.9	190	47	161	72
588	32.7	194	43	164	56
498	26.9	190	48	176	82
483	24.6	190	43	165	61
554	28.8	188	45	166	62
521	25.9	184	52	167	62
436	24.4	170	52	168	62
398	26.3	168	56	162	66
366	23.2	175	56	159	56
439	24.6	156	51	161	61
549	28.8	184	44	154	56
360	19.6	180	56	167	79
566	31.4	184	40	165	56
407	26.6	156	53	157	52
602	30.6	194	52	161	65
488	27.5	190	40	178	64
526	30.9	188	55	162	61
524	33.9	164	39	166	59
562	32.3	185	57	168	68
496	26.9	178	46	156	53

Source: Data from Bruce et al. [1973].

Mehta et al. [1981] studied the effect of the drug dipyridamole on blood platelet function in eight patients with at least 50% narrowing of one or more coronary arteries. Active platelets are sequestered in the coronary arteries, giving reduced platelet function in the coronary venous blood, that is, in blood leaving the heart muscle after delivering oxygen and nutrients. More active platelets in the coronary arteries can lead to thrombosis, blood clots, and a heart attack. Drugs lessening the chance of thrombosis may be useful in treatment.

Table 9.15 Data for Problem 9.5

X	Y	$\widehat{Y}$	Residual	Normal Deviate
660	38.1	36.35	1.75	0.56
628	38.4	34.74	3.66	1.18
637	41.7	35.19	6.51	2.10
575	33.5	32.08	1.42	0.46
590	28.6	32.83	−4.23	−1.37
600	23.9	?	?	?
562	29.6	31.42	−1.82	−0.59
495	27.3	28.05	−0.75	−0.24
540	33.2	?	2.88	0.93
470	26.6	26.80	−0.20	−0.06
408	23.6	23.68	−0.07	−0.02
387	23.1	22.62	0.48	0.15
564	36.6	31.52	5.08	1.64
603	35.8	33.49	2.21	0.75
420	28.0	24.28	3.72	1.20
573	33.8	?	?	0.59
602	33.6	33.43	0.17	0.05
430	21.0	24.78	−3.78	?
508	31.2	28.71	2.49	?
565	31.2	31.57	−0.37	−0.12
464	23.7	26.49	−2.79	−0.90
495	24.5	28.05	−3.55	−1.10
461	30.5	26.34	4.16	1.34
540	25.9	30.32	−4.42	−1.43
588	32.7	?	−0.03	−0.00
498	26.9	?	−1.30	−0.42
483	24.6	27.45	−2.85	−0.92
554	28.8	31.02	−2.22	−0.72
521	25.9	29.36	−3.46	−1.12
436	24.4	25.09	−0.69	−0.22
398	26.3	23.18	3.12	1.01
366	23.2	21.57	1.63	0.53
439	24.6	25.24	−0.64	−0.21
549	28.8	30.77	−1.97	−0.64
360	19.6	21.26	−1.66	−0.54
566	31.4	31.62	−0.22	−0.07
407	26.6	23.63	2.97	0.96
602	30.6	33.43	−2.83	−0.92
488	27.5	27.70	−0.20	−0.06
526	30.9	29.61	1.29	0.42
524	33.9	29.51	4.39	1.42
562	32.3	31.42	0.88	0.28
496	26.9	28.10	−1.20	−0.39

Platelet aggregation measures the extent to which platelets aggregate or cluster together in the presence of a chemical that stimulates clustering or aggregation. The measure used was the percent increase in light transmission after an aggregating agent was added to plasma. (The clustering of the cells make more "holes" in the plasma to let light through.) Two aggregating agents, adenosine diphosphate (ADP) and epinephrine (EPI), were used in this experiment. A second measure taken from the blood count was the count of platelets.

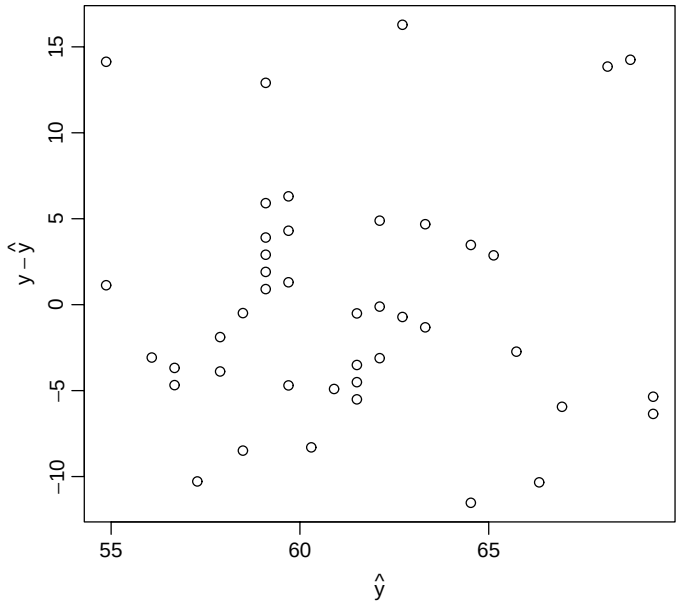


Figure 9.18 Residual plot for Problem 9.8.

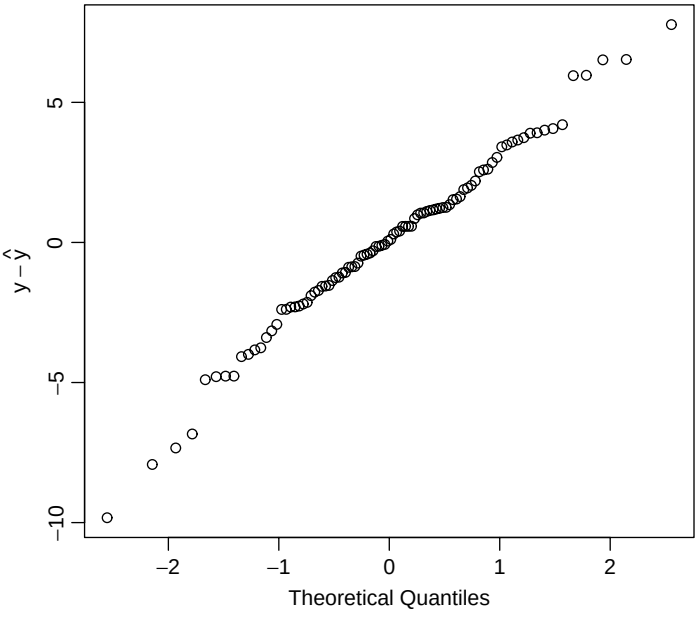


Figure 9.19 Normal probability plot for Problem 9.9.

Blood was sampled from two sites, the aorta (blood being pumped from the heart) and the coronary sinus (blood returning from nourishing the heart muscle). Control samples as well as samples after intravenous infusion of 100 mg of dipyridamole were taken. The data are given in Table 9.17 and 9.18. Problems 9.13 to 9.22 refer to these data.

Table 9.16 Exercise Data for Sedentary Males

Duration	$VO_{2\ MAX}$	Heart Rate	Age	Height	Weight
360	24.7	168	40	175	96
770	46.8	190	25	168	68
663	41.2	175	41	187	82
679	31.4	190	37	176	82
780	45.7	200	26	179	73
727	47.6	210	28	185	84
647	38.6	208	26	177	77
675	43.2	200	42	162	72
735	48.2	196	30	188	85
827	50.9	184	21	178	69
760	47.2	184	33	182	87
814	41.8	208	31	182	82
778	42.9	184	29	174	73
590	35.1	174	42	188	93
567	37.6	176	40	184	86
648	47.3	200	40	168	80
730	44.4	204	44	183	78
660	46.7	190	44	176	81
663	41.6	184	40	174	78
589	40.2	200	43	193	92
600	35.8	190	41	176	68
480	30.2	174	44	172	84
630	38.4	164	39	181	72
646	41.3	190	39	187	90
630	31.2	190	42	173	69
630	42.6	190	53	181	53
624	39.4	172	57	172	57
572	35.4	164	58	181	58
622	35.9	190	61	168	61
209	16.0	104	74	171	74
536	29.3	175	57	181	57
602	36.7	175	49	175	49
727	43.0	168	53	172	53
260	15.3	112	75	170	75
622	42.3	175	47	185	47
705	43.7	174	51	169	51
669	40.3	174	65	170	65
425	28.5	170	56	167	56
645	38.0	175	50	177	50
576	30.8	184	48	188	48
605	40.2	156	46	187	46
458	29.5	148	61	185	61
551	32.3	188	49	182	49
607	35.5	179	53	179	53
599	35.3	166	55	182	55
453	32.3	160	69	182	69
337	23.8	204	68	176	68
663	41.4	182	47	171	47
603	39.0	180	48	180	48
610	38.6	190	55	180	55
472	31.5	175	53	192	85

Table 9.16 (*continued*)

Duration	$VO_{2\ MAX}$	Heart Rate	Age	Height	Weight
458	25.7	166	58	178	81
446	24.6	160	50	178	77
532	30.0	160	51	175	82
656	42.0	186	52	176	73
583	34.4	175	52	172	77
595	34.9	180	48	179	78
552	35.5	156	45	167	89
675	38.7	162	58	183	85
622	38.4	186	45	175	76
591	32.4	170	62	175	79
582	33.6	156	63	171	69
518	30.0	166	57	174	75
444	28.9	170	48	180	105
473	29.5	175	52	177	77
490	30.4	168	59	173	74
596	34.4	192	46	190	92
529	37.0	175	54	168	82
652	43.4	156	54	180	85
714	46.0	175	46	174	77
646	43.0	184	45	178	80
551	29.3	160	54	172	86
601	36.8	184	48	169	82
579	35.0	170	54	180	80
325	21.9	140	61	175	76
392	25.4	168	60	180	89
659	40.7	178	45	181	81
631	33.8	184	48	173	74
405	28.8	170	63	168	79
560	35.8	180	60	181	82
615	40.3	190	47	178	78
580	33.4	180	66	173	68
530	39.0	174	47	169	64
495	23.2	145	69	171	84
330	20.5	138	60	185	87
600	36.4	200	50	182	81
443	23.5	166	50	175	84
508	29.7	188	61	188	80
596	43.2	168	57	174	66
461	30.4	170	47	171	65
583	34.7	164	46	187	83
620	37.1	174	61	165	71
620	41.4	190	45	171	79
180	19.8	125	71	185	80

Source: Data from Bruce et al. [1973]

9.13 Relate the control platelet counts in the aorta, X, and coronary sinus, Y. Do tasks (a), (b), (c), (d), (e), compute the (X, Y, $\widehat{Y}$, residual, normal deviate) table, (g), (h), (i), (j), (k-i), (k-iv), (l), (m), (p), (r), and (s).

9.14 Look at the association between the platelet counts in the aorta, X, and coronary sinus, Y, when being treated with dipyridamole. Do tasks (a), (b), (c), (d), (m), (r), and (s).

Table 9.17 Platelet Aggregation Data for Problem 9.12

	Platelet Aggregation (%)							
	Control				Dipyridamole			
	Aorta		Coronary Sinus		Aorta		Coronary Sinus	
Case	EPI	ADP	EPI	ADP	EPI	ADP	EPI	ADP
1	87	75	89	23	89	75	89	35
2	70	23	42	14	45	16	47	18
3	96	75	96	31	96	83	96	84
4	65	51	70	33	70	55	70	57
5	85	16	79	4	69	13	53	22
6	98	83	98	80	83	70	94	88
7	77	14	97	13	84	35	73	67
8	98	50	99	40	85	50	91	48
Mean	85	48	84	30	78	50	77	52
±SEM	5	10	7	8	6	9	7	9

Source: Data from Mehta et al. [1981].

9.15 Examine the control platelet aggregation percent for EPI, X, and ADP, Y, in the aorta. Do tasks (a), (b), (c), (d), (e), and (m).

9.16 Examine the association between the EPI, X, and ADP, Y, in the control situation at the coronary sinus. Do tasks (a), (b), (c), (d), (e), (m), (p), (r), and (s).

9.17 Interpret at the 5% significance level. Look at the platelet aggregation % for epinephrine in the aorta and coronary sinus under the control data. Do tasks (m), (p) and (t), (u). Explain in words how there can be association but no (statistical) difference between the values at the two locations.

9.18 Under dipyridamole treatment, study the platelet aggregation percent for EPI in the aorta, X, and coronary sinus, Y. Do tasks (a), (b), (c), (d), (e), (g), (h), (m), (p), (r), (s), (t), and (u).

9.19 The control aggregation percent for ADP is compared in the aorta, X, and coronary sinus, Y, in this problem. Do tasks (a), (b), (c), (d), (e), (f), (g), (h), (i), (j), (m), (p), and (q-ii).

9.20 Under dipyridamole, the aggregation percent for ADP in the aorta, X, and coronary sinus, Y, is studied here. Do tasks (b), (c), (e), (k-ii), (k-iv), (l-ii), (m), (p), (q-ii), (r), and (s).

9.21 The aortic platelet counts under the control, X, and dipyridamole, Y, are compared in this problem. Do tasks (b), (c), (e), (m), (p), (q-ii), (t), and (u). Do the platelet counts differ under the two treatments? (Use $\alpha = 0.05$.) Are the platelet counts associated under the two treatments? ($\alpha = 0.05$.)

9.22 The coronary sinus ADP aggregation percent was studied during the control period, the X variable, and on dipyridamole, the Y variable. Do tasks (b), (c), (d), (e), (m), and (t). At the 5% significance level, is there a change between the treatment and control periods? Can you show association between the two values? How do you reconcile these findings?

Table 9.18 Platelet Count Data for Problem 9.12

	Platelet Counts ($\times 1000/mm^3$)[a]			
	Control		Dipyridamole	
Case	Aorta	Coronary Sinus	Aorta	Coronary Sinus
1	390	355	455	445
2	240	190	248	205
3	135	125	150	145
4	305	268	285	290
5	255	195	230	220
6	283	307	291	312
7	435	350	457	374
8	290	250	301	284
Mean	292	255	302	284
±SEM	32	29	38	34

Source: Data from Mehta et al. [1981].

Problems 9.23 to 9.29 deal with the data in Tables 9.19 and 9.20. Jensen et al. [1980] studied 19 patients with coronary artery disease. Thirteen had a prior myocardial infarction (heart attack); three had coronary bypass surgery. The patients were evaluated before and after three months or more on a structured supervised training program.

The cardiac performance was evaluated using radionuclide studies while the patients were at rest and also exercising with bicycle pedals (while lying supine). Variables measured included (1) ejection fraction (EF), the fraction of the blood in the left ventricle ejected during a heart beat, (2) heart rate (HR) at maximum exercise in beats per minute, (3) systolic blood pressure (SBP) in millimeters of mercury, (4) the rate pressure product (RPP) maximum heart rate times the maximum systolic blood pressure divided by 100, and (5) the estimated maximum oxygen consumption in cubic centimeters of oxygen per kilogram of body weight per minute.

9.23 The resting ejection fraction is measured before, X, and after, Y, training. $\overline{X} = 0.574$, $\overline{Y} = 0.553$, $[x^2] = 0.29886$, $[y^2] = 0.32541$, $[xy] = 0.23385$, and paired $t = -0.984$. Do tasks (c), (e), (k-iv), (m), and (p). Is there a change in resting ejection fraction demonstrated with six months of exercise training? Are the two ejection fractions associated?

9.24 The ejection fraction at maximal exercise was measured before, X, and after, Y, training. $\overline{X} = 0.556$, $\overline{Y} = 0.564$, $[x^2] = 0.30284$, $[y^2] = 0.46706$, and $[xy] = 0.2809$. Is there association ($\alpha = 0.05$) between the two ejection fractions? If yes, do tasks (c), (k-iii), (l-iii), (p), and (q-ii). Is there a change ($\alpha = 0.05$) between the two ejection fractions? If yes, find a 95% confidence interval for the average difference.

9.25 The maximum systolic blood pressure was measured before, X, and after, Y, training. $\overline{X} = 173.8$, $\overline{Y} = 184.2$, $[x^2] = 11,488.5$, $[y^2] = 10,458.5$, $[xy] = 7419.5$, and paired $t = 2.263$. Do tasks (a), (b), (c), (d), (e), (m), (p), and (t). Does the exercise training produce a change? How much? Can we predict individually the maximum SBP after training from that before? How much of the variability in maximum SBP after exercise is accounted for by knowing the value before exercise?

9.26 The before, X, and after, Y, rate pressure product give $\overline{X} = 223.0$, $\overline{Y} = 245.7$, $[x^2] = 58,476$, $[y^2] = 85,038$, $[xy] = 54,465$, and paired $t = 2.256$ (Table 9.21). Do tasks (c), (e), (f), (g), (h), and (m). Find the large-sample p-value for Kendall's tau for association.

Table 9.19 Resting and Maximal Ejection Fraction Measured by Radionuclide Ventriculography, and Maximal Heart Rate

	Resting EF		Maximal EF		Maximal HR	
Case	Pre	Post	Pre	Post	Pre	Post
1	0.39	0.48	0.46	0.48	110	119
2	0.57	0.49	0.51	0.57	120	125
3	0.77	0.63	0.70	0.82	108	105
4	0.48	0.50	0.51	0.51	85	88
5	0.55	0.46	0.45	0.55	107	103
6	0.60	0.50	0.52	0.54	125	115
7	0.63	0.61	0.75	0.68	170	166
8	0.73	0.61	0.53	0.71	160	142
9	0.70	0.68	0.80	0.79	125	114
10	0.66	0.68	0.54	0.43	131	150
11	0.40	0.31	0.42	0.30	135	174
12	0.48	0.46	0.48	0.30	97	94
13	0.63	0.78	0.60	0.75	135	132
14	0.41	0.37	0.41	0.44	127	162
15	0.75	0.54	0.76	0.57	126	148
16	0.58	0.64	0.62	0.72	102	112
17	0.50	0.58	0.54	0.65	145	140
18	0.71	0.81	0.65	0.60	152	145
19	0.37	0.38	0.32	0.31	155	170
Mean	0.57	0.55	0.56	0.56	127	132
±SD	0.13	0.13	0.13	0.16	23	26

Table 9.20 Systolic Blood Pressure, Rate Pressure Product and Estimate $VO_{2\ MAX}$ before (Pre) and after (Post) Training

	Maximal SBP		Maximal RPP		Est. $VO_{2\ MAX}$ ($cm^3/kg \cdot min$)	
Case	Pre	Post	Pre	Post	Pre	Post
1	148	156	163	186	24	30
2	180	196	216	245	28	44
3	185	200	200	210	28	28
4	150	148	128	130	34	38
5	150	156	161	161	20	28
6	164	172	205	198	30	36
7	180	210	306	349	64	54
8	182	176	291	250	44	40
9	186	170	233	194	30	28
10	220	230	288	345	30	30
11	188	205	254	357	28	44
12	120	165	116	155	22	20
13	175	160	236	211	20	36
14	190	180	241	292	36	38
15	140	170	176	252	36	44
16	200	230	204	258	28	36
17	215	185	312	259	44	44
18	165	190	251	276	28	34
19	165	200	256	340	44	52
Mean	174	184	223	246	31	37
±SD	25	24	57	69	8	9

Table 9.21 Blood Pressure Data for Problem 9.26

Maximal SBP				
Pre	Post			
X	Y	$\widehat{Y}$	$Y - \widehat{Y}$	Normal Deviate
163	186	189.90	−3.80	−0.08
216	245	239.16	?	?
200	210	224.26	−14.26	−0.32
128	130	157.20	−27.20	−0.61
161	161	?	−26.94	?
205	198	228.92	−30.92	−0.69
306	349	322.99	26.01	?
291	250	309.02	−59.02	−1.31
233	194	255.00	−61.00	−1.36
288	345	306.22	38.77	0.86
254	357	?	?	?
116	155	146.02	8.98	0.20
236	211	257.79	−46.79	−1.04
241	292	262.45	29.55	0.66
176	252	201.91	50.09	1.12
204	258	227.99	30.01	0.67
312	259	328.58	−69.58	−1.55
251	276	271.76	4.24	0.09
256	340	276.42	63.58	1.42

9.27 The maximum oxygen consumption, $VO_{2\ MAX}$, is measured before, X, and after, Y. Here $\overline{X} = 32.53, \overline{Y} = 37.05, [x^2] = 2030.7, [y^2] = 1362.9, [xy] = 54465$, and paired $t = 2.811$. Do tasks (c), (k-ii), (m), (n), at $x = 30$, 35, and 40, (p), (q-ii), and (t).

9.28 The ejection fractions at rest, X, and at maximum exercise, Y, before training is used in this problem. $\overline{X} = 0.574, \overline{Y} = 0.556, [x^2] = 0.29886, [y^2] = 0.30284, [xy] = 0.24379$, and paired $t = -0.980$. Analyze these data, including a scatter diagram, and write a short paragraph describing the change and/or association seen.

9.29 The ejection fractions at rest, X, and after exercises, Y, for the subjects after training: (1) are associated, (2) do not change on the average, (3) explain about 52% of the variability in each other. Justify statements (1)–(3). $\overline{X} = 0.553, \overline{Y} = 0.564, [x^2] = 0.32541, [y^2] = 0.4671, [xy] = 0.28014$, and paired $t = 0.424$.

Problems 9.30 to 9.33 refer to the following study. Boucher et al. [1981] studied patients before and after surgery for isolated aortic regurgitation and isolated mitral regurgitation. The aortic valve is in the heart valve between the left ventricle, where blood is pumped from the heart, and the aorta, the large artery beginning the arterial system. When the valve is not functioning and closing properly, some of the blood pumped from the heart returns (or regurgitates) as the heart relaxes before its next pumping action. To compensate for this, the heart volume increases to pump more blood out (since some of it returns). To correct for this, open heart surgery is performed and an artificial valve is sewn into the heart. Data on 20 patients with aortic regurgitation and corrective surgery are given in Tables 9.22 and 9.23.

"NYHA Class" measures the amount of impairment in daily activities that the patient suffers: I is least impairment, II is mild impairment, III is moderate impairment, and IV is severe impairment; HR, heart rate; SBP, the systolic (pumping or maximum) blood pressure; EF, the ejection fraction, the fraction of blood in the left ventricle pumped out during a beat; EDVI,

Table 9.22 Preoperative Data for 20 Patients with Aortic Regurgitation

Case	Age (yr) and Gender	NYHA Class	HR (beats/min)	SBP (mmHG)	EF	EDVI (mL/m^2)	SVI (mL/m^2)	ESVI (mL/m^2)
1	33M	I	75	150	0.54	225	121	104
2	36M	I	110	150	0.64	82	52	30
3	37M	I	75	140	0.50	267	134	134
4	38M	I	70	150	0.41	225	92	133
5	38M	I	68	215	0.53	186	99	87
6	54M	I	76	160	0.56	116	65	51
7	56F	I	60	140	0.81	79	64	15
8	70M	I	70	160	0.67	85	37	28
9	22M	II	68	140	0.57	132	95	57
10	28F	II	75	180	0.58	141	82	59
11	40M	II	65	110	0.62	190	118	72
12	48F	II	70	120	0.36	232	84	148
13	42F	III	70	120	0.64	142	91	51
14	57M	III	85	150	0.60	179	107	30
15	61M	III	66	140	0.56	214	120	94
16	64M	III	54	150	0.60	145	87	58
17	61M	IV	110	126	0.55	83	46	37
18	62M	IV	75	132	0.56	119	67	52
19	64M	IV	80	120	0.39	226	88	138
20	65M	IV	80	110	0.29	195	57	138
Mean	49		75	143	0.55	162	85	77
±SD	14		14	25	0.12	60	26	43

Table 9.23 Postoperative Data for 20 Patients with Aortic Regurgitation

Case	Age (yr) and Gender	NYHA Class	HR (beats/min)	SBP (mmHG)	EF	EDVI (mL/m^2)	SVI (mL/m^2)	ESVI (mL/m^2)
1	33M	I	80	115	0.38	113	43	43
2	36M	I	100	125	0.58	56	32	24
3	37M	I	100	130	0.27	93	25	68
4	38M	I	85	110	0.17	160	27	133
5	38M	I	94	130	0.47	111	52	59
6	54M	I	74	110	0.50	83	42	42
7	56F	I	85	120	0.56	59	33	26
8	70M	I	85	130	0.59	68	40	28
9	22M	II	120	136	0.33	119	39	80
10	28F	II	92	160	0.32	71	23	48
11	40M	II	85	110	0.47	70	33	37
12	48F	II	84	120	0.24	149	36	113
13	42F	III	84	100	0.63	55	35	20
14	57M	III	86	135	0.33	91	72	61
15	61M	III	100	138	0.34	92	31	61
16	64M	III	60	130	0.30	118	35	83
17	61M	IV	88	130	0.62	63	39	24
18	62M	IV	75	126	0.29	100	29	71
19	64M	IV	78	110	0.26	198	52	147
20	65M	IV	75	90	0.26	176	46	130
Mean	49		87	123	0.40	102	38	65
±SD	14		13	15	0.14	41	11	39

Table 9.24 Preoperative Data for 20 Patients with Mitral Regurgitation

Case	Age (yr) and Gender	NYHA Class	HR (beats/min)	SBP (mmHG)	EF	EDVI (mL/m^2)	SVI (mL/m^2)	ESVI (mL/m^2)
1	23M	II	75	95	0.69	71	49	22
2	31M	II	70	150	0.77	184	142	42
3	40F	II	86	90	0.68	84	57	30
4	47M	II	120	150	0.51	135	67	66
5	54F	II	85	120	0.73	127	93	34
6	57M	II	80	130	0.74	149	110	39
7	61M	II	55	120	0.67	196	131	65
8	37M	III	72	120	0.70	214	150	64
9	52M	III	108	105	0.66	126	83	43
10	52F	III	80	115	0.52	167	70	97
11	52M	III	80	105	0.76	130	99	31
12	56M	III	80	115	0.60	136	82	54
13	58F	III	65	110	0.62	146	91	56
14	59M	III	102	90	0.63	82	52	30
15	66M	III	60	100	0.62	76	47	29
16	67F	III	75	140	0.71	94	67	27
17	71F	III	88	140	0.65	111	72	39
18	55M	IV	80	125	0.66	136	90	46
19	59F	IV	115	130	0.72	96	69	27
20	60M	IV	64	140	0.60	161	97	64
Mean	53		81	121	0.66	131	86	45
±SD	12		17	17	0.09	40	30	19

Table 9.25 Postoperative Data for 20 Patients with Mitral Regurgitation

Case	Age (yr) and Gender	NYHA Class	HR (beats/min)	SBP (mmHG)	EF	EDVI (mL/m^2)	SVI (mL/m^2)	ESVI (mL/m^2)
1	23M	II	90	100	0.60	67	40	27
2	31M	II	95	110	0.64	64	41	23
3	40F	II	80	110	0.77	59	45	14
4	47M	II	90	120	0.36	96	35	61
5	54F	II	100	110	0.41	59	24	35
6	57M	II	75	115	0.54	71	38	33
7	61M	II	140	120	0.41	165	68	97
8	37M	III	95	120	0.25	84	21	63
9	52M	III	100	125	0.43	67	29	38
10	52F	III	90	90	0.44	124	55	69
11	52M	III	98	116	0.55	68	37	31
12	56M	III	61	108	0.56	112	63	49
13	58F	III	88	120	0.50	76	38	38
14	59M	III	100	100	0.48	40	19	21
15	66M	III	85	124	0.51	31	16	15
16	67F	III	84	120	0.39	81	32	49
17	71F	III	100	100	0.44	76	33	43
18	55M	IV	108	124	0.43	63	27	36
19	59F	IV	100	110	0.49	62	30	32
20	60M	IV	90	110	0.36	93	34	60
Mean	53		93	113	0.48	78	36	42
±SD	12		15	9	0.11	30	14	21

the volume of the left ventricle after the heart relaxes (adjusted for physical size, to divide by an estimate of the patient's body surface area (BSA); SVI, the volume of the left ventricle after the blood is pumped out, adjusted for BSA; ESVI, the volume of the left ventricle pumped out during one cycle, adjusted for BSA; ESVI = EDVI − SVI. These values were measured before and after valve replacement surgery. The patients in this study were selected to have left ventricular volume overload; that is, expanded EDVI.

Another group of 20 patients with mitral valve disease and left ventricular volume overload were studied. The mitral valve is the valve allowing oxygenated blood from the lungs into the left ventricle for pumping to the body. Mitral regurgitation allows blood to be pumped "backward" and to be mixed with "new" blood coming from the lungs. The data for these patients are given in Tables 9.24 and 9.25.

9.30 **(a)** The preoperative, X, and postoperative, Y, ejection fraction in the patients with aortic valve replacement gave $\overline{X} = 0.549, \overline{Y} = 0.396, [x^2] = 0.26158, [y^2] = 0.39170, [xy] = 0.21981$, and paired $t = -6.474$. Do tasks (a), (c), (d), (e), (m), (p), and (t). Is there a change? Are ejection fractions before and after surgery related?

(b) The mitral valve cases had $\overline{X} = 0.662, \overline{Y} = 0.478, [x^2] = 0.09592, [y^2] = 0.24812, [xy] = 0.04458$, and paired $t = -7.105$. Perform the same tasks as in part (a).

(c) When the emphasis is on the change, rather than possible association and predictive value, a figure like Figure 9.20 may be preferred to a scatter diagram. Plot the scatter diagram for the aortic regurgitation data and comment on the relative merits of the two graphics.

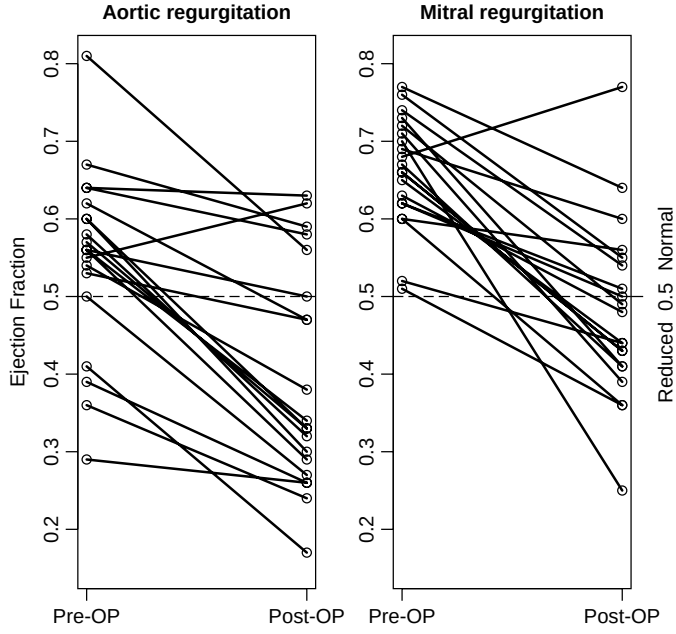


Figure 9.20 Figure for Problem 9.30(c). Individual values for ejection fraction before (pre-OP) and early after (post-OP) surgery are plotted; preoperatively, only four patients with aortic regurgitation had an ejection fraction below normal. After operation, 13 patients with aortic regurgitation and 9 with mitral regurgitation had an ejection fraction below normal. The lower limit of normal (0.50) is represented by a dashed line. (From Boucher et al. [1981].).

Table 9.26 Data for Problem 9.31

X	Y	$\widehat{Y}$	Residuals	Normal Deviate
22	67	51.26	15.74	0.75
42	64	74.18	−10.18	−0.48
30	59	60.42	−1.42	−0.06
66	96	101.68	−5.68	−0.27
34	59	65.01	−6.01	−0.28
39	71	70.74	0.26	0.01
65	165	?	?	?
64	84	99.39	15.29	−0.73
43	67	75.32	?	−0.39
97	124	137.20	−13.20	?
31	68	61.57	?	?
54	112	87.93	24.07	1.14
56	76	?	?	−0.67
30	40	?	−20.42	−0.97
29	31	?	?	?
27	81	56.99	24.01	1.14
39	76	70.74	5.26	0.25
46	63	78.76	−15.76	−0.75
27	62	56.99	5.01	0.24
64	93	99.39	−6.39	−0.30

9.31 **(a)** For the mitral valve cases, we use the end systolic volume index (ESVI) before surgery to try to predict the end diastolic volume index (EDVI) after surgery. $\overline{X} = 45.25, \overline{Y} = 77.9, [x^2] = 6753.8, [y^2] = 16,885.5$, and $[xy] = 7739.5$. Do tasks (c), (d), (e), (f), (h), (j), (k-iv), (m), and (p). Data are given in Table 9.26. The residual plot and normal probability plot are given in Figures 9.21 and 9.22.

(b) If subject 7 is omitted, $\overline{X} = 44.2, \overline{Y} = 73.3, [x^2] = 6343.2, [y^2] = 8900.1$, and $[xy] = 5928.7$. Do tasks (c), (m), and (p). What are the changes in tasks (a), (b), and (r) from part (a)?

(c) For the aortic cases; $\overline{X} = 75.8$, $\overline{Y} = 102.3$, $[x^2] = 35{,}307.2$, $[y^2] = 32{,}513.8$, $[xy] = 27,076$. Do tasks (c), (k-iv), (p), and (q-ii).

9.32 We want to investigate the predictive value of the preoperative ESVI to predict the postoperative ejection fraction, EF. For each part, do tasks (a), (c), (d), (k-i), (k-iv), (m), and (p).

(a) The aortic cases have $\overline{X} = 75.8, \overline{Y} = 0.396, [x^2] = 35307.2, [y^2] = 0.39170$, and $[xy] = 84.338$.

(b) The mitral cases have $\overline{X} = 45.3, \overline{Y} = 0.478, [x^2] = 6753.8, [y^2] = 0.24812$, and $[xy] = -18.610$.

9.33 Investigate the relationship between the preoperative heart rate and the postoperative heart rate. If there are outliers, eliminate (their) effect. Specifically address these questions: (1) Is there an overall change from preop to postop HR? (2) Are the preop and postop HRs associated? If there is an association, summarize it (Tables 9.27 and 9.28).

(a) For the aortic cases, $\sum X = 1502, \sum Y = 17.30, \sum X^2 = 116,446, \sum Y^2 = 152,662$, and $\sum XY = 130,556$. Data are given in Table 9.27.

(b) For the mitral cases: $\sum X = 1640, \sum Y = 1869, \sum X^2 = 140,338, \sum Y^2 = 179,089$, and $\sum XY = 152,860$. Data are given in Table 9.28.

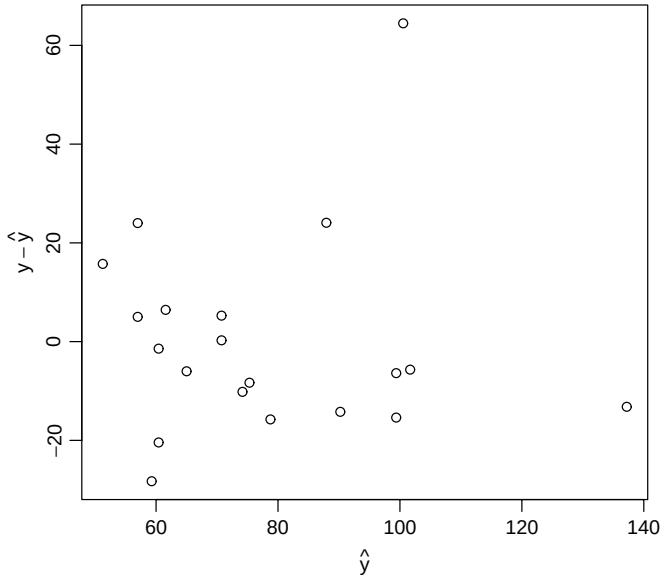


Figure 9.21 Residual plot for Problem 9.31(a).

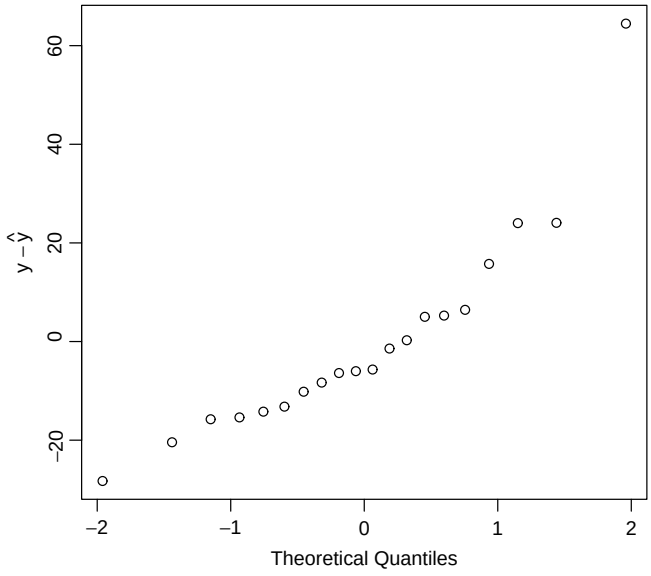


Figure 9.22 Normal probability plot for Problem 9.31(a).

9.34 The Web appendix to this chapter contains county-by-county electoral data for the state of Florida for the 2000 elections for president and for governor of Florida. The major Democratic and Republican parties each had a candidate for both positions, and there were two minor party candidates for president and one for governor. In Palm Beach County a poorly designed ballot was used, and it was suggested that this led to some voters who intended to vote for Gore in fact voting for Buchanan.

Table 9.27 Data for Problem 9.33(a)

X	Y	$\widehat{Y}$	Residuals	Normal Deviate
75	80	86.48	−6.48	−0.51
110	100	92.56	7.44	0.59
75	100	86.48	13.52	1.06
70	85	85.61	0.61	−0.04
68	94	85.27	8.73	0.69
76	74	86.66	−12.66	−1.00
60	85	83.88	1.12	0.08
70	85	85.61	0.61	−0.04
68	120	85.27	34.73	2.73
75	92	86.48	5.52	0.43
65	85	84.75	0.25	0.02
70	84	85.61	−1.61	−0.13
70	84	85.61	−1.61	−0.13
85	86	88.22	−2.22	−0.17
66	100	84.92	15.08	1.19
54	60	82.84	−22.84	−1.80
110	88	92.56	−4.56	0.36
75	75	86.48	−11.48	−0.90
80	78	87.35	−9.35	−0.74
80	75	87.35	−12.35	−0.97

Table 9.28 Data for Problem 9.33(b)

X	Y	$\widehat{Y}$	Residuals	Normal Deviate
75	90	93.93	−3.93	−0.25
70	95	94.27	0.73	0.04
86	80	93.18	−13.18	−0.84
120	90	90.87	−0.87	−0.05
85	100	93.25	6.75	0.43
80	75	93.59	−18.59	−1.19
55	140	95.28	44.72	2.86
72	95	94.13	0.87	0.05
108	100	91.68	8.32	0.53
80	90	93.59	−3.59	−0.23
80	98	93.59	4.41	0.28
80	61	93.95	−32.59	−2.08
65	88	94.61	−6.61	0.42
102	100	92.09	7.91	0.51
60	85	94.94	−9.94	−0.64
75	84	93.93	−9.93	−0.63
88	100	93.04	6.96	0.44
80	108	93.59	14.41	0.92
115	100	91.21	8.79	0.56
64	90	94.67	−4.67	−0.30

(a) Using simple linear regression and graphs, examine whether the data support this claim.

(b) Read the analyses linked from the Web appendix and critically evaluate their claims.

REFERENCES

Acton, F. S. [1984]. *Analysis of Straight-Line Data*. Dover Publications, New York.

Anscombe, F. J. [1973]. Graphs in statistical analysis. *American Statistician*, **27**: 17–21.

Boucher, C. A., Bingham, J. B., Osbakken, M. D., Okada, R. D., Strauss, H. W., Block, P. C., Levine, F. H., Phillips, H. R., and Phost, G. M. [1981]. Early changes in left ventricular volume overload. *American Journal of Cardiology*, **47**: 991–1004.

Bruce, R. A., Kusumi, F., and Hosmer, D. [1973]. Maximal oxygen intake and nomographic assessment of functional aerobic impairment in cardiovascular disease. *American Heart Journal*, **65**: 546–562.

Carroll, R. J., Ruppert, D., and Stefanski, L. A. [1995]. *Measurement Error in Nonlinear Models*. Chapman & Hall, London.

Dern, R. J., and Wiorkowski, J. J. [1969]. Studies on the preservation of human blood: IV. The hereditary component of pre- and post storage erythrocyte adenosine triphosphate levels. *Journal of Laboratory and Clinical Medicine*, **73**: 1019–1029.

Devlin, S. J., Gnanadesikan, R., and Kettenring, J. R. [1975]. Robust estimation and outlier detection with correlation coefficients. *Biometrika*, **62**: 531–545.

Draper, N. R., and Smith, H. [1998]. *Applied Regression Analysis*, 3rd ed. Wiley, New York.

Hollander, M., and Wolfe, D. A. [1999]. *Nonparametric Statistical Methods*. 2nd ed. Wiley, New York.

Huber, P. J. [2003]. *Robust Statistics*. Wiley, New York.

Jensen, D., Atwood, J. E., Frolicher, V., McKirnan, M. D., Battler, A., Ashburn, W., and Ross, J., Jr., [1980]. Improvement in ventricular function during exercise studied with radionuclide ventriculography after cardiac rehabilitation. *American Journal of Cardiology*, **46**: 770–777.

Kendall, M. G., and Stuart, A. [1967]. *The Advanced Theory of Statistics*, Vol. 2, *Inference and Relationships*, 2nd ed. Hafner, New York.

Kronmal, R. A. [1993]. Spurious correlation and the fallacy of the ratio standard revisited. *Journal of the Royal Statistical Society, Series A*, **60**: 489–498.

Lumley, T., Diehr, P., Emerson, S., and Chen, L. [2002]. The importance of the normality assumption in large public health data sets. *Annual Review of Public Health*, **23**: 151–169.

Mehta, J., Mehta, P., Pepine, C. J., and Conti, C. R. [1981]. Platelet function studies in coronary artery disease: X. Effects of dipyridamole. *American Journal of Cardiology*, **47**: 1111–1114.

Neyman, J. [1952]. On a most powerful method of discovering statistical regularities. *Lectures and Conferences on Mathematical Statistics and Probability*. U.S. Department of Agriculture, Washington, DC, pp. 143–154.

U.S. Department of Health, Education, and Welfare [1974].

U.S. Cancer Mortality by County: 1950–59. DHEW Publication (NIH) 74–615. U.S. Government Printing Office, Washington, DC.

Yanez, N. D., Kronmal, R. A., and Shemanski, L. R. [1998]. The effects of measurement error in response variables and test of association of explanatory variables in change models. *Statistics in Medicine* **17**(22): 2597–2606.

CHAPTER 10

Analysis of Variance

10.1 INTRODUCTION

The phrase *analysis of variance* was coined by Fisher [1950], who defined it as "the separation of variance ascribable to one group of causes from the variance ascribable to other groups." Another way of stating this is to consider it as a partitioning of total variance into component parts. One illustration of this procedure is contained in Chapter 9, where the total variability of the dependent variable was partitioned into two components: one associated with regression and the other associated with (residual) variation about the regression line. Analysis of variance models are a special class of linear models.

Definition 10.1. An *analysis of variance model* is a linear regression model in which the predictor variables are classification variables. The categories of a variable are called the *levels* of the variable.

The meaning of this definition will become clearer as you read this chapter.

The topics of analysis of variance and design of experiments are closely related, which has been evident in earlier chapters. For example, use of a paired t-test implies that the data are paired and thus may indicate a certain type of experiment. Similarly, a partitioning of total variation in a regression situation implies that two variables measured are linearly related. A general principle is involved: The analysis of a set of data should be appropriate for the design. We indicate the close relationship between design and analysis throughout this chapter.

The chapter begins with the one-way analysis of variance. Total variability is partitioned into a variance between groups and a variance within groups. The groups could consist of different treatments or different classifications. In Section 10.2 we develop the construction of an analysis of variance from group means and standard deviations, and consider the analysis of variance using ranks. In Section 10.3 we discuss the two-way analysis of variance: A special two-way analysis involving randomized blocks and the corresponding rank analysis are discussed, and then two kinds of classification variables (random and fixed) are covered. Special but common designs are presented in Sections 10.4 and 10.5. Finally, in Section 10.6 we discuss the testing of the assumptions of the analysis of variance, including ways of transforming the data to make the assumptions valid. Notes and specialized topics conclude our discussion.

Biostatistics: A Methodology for the Health Sciences, Second Edition, by Gerald van Belle, Lloyd D. Fisher, Patrick J. Heagerty, and Thomas S. Lumley
ISBN 0-471-03185-2

A few comments about notation and computations: The formulas for the analysis of variance look formidable but follow a logical pattern. The following rules are followed or held (we remind you on occasion):

1. Indices for groups follow a mnemonic pattern. For example, the subscript i runs from $1, \ldots, I$; the subscript j from $1, \ldots, J$; k from $1, \ldots, K$, and so on.

2. Sums of values of the random variables are indicated by replacing the subscript by a dot. For example,

$$Y_{i\cdot} = \sum_{j=1}^{J} Y_{ij}, \qquad Y_{\cdot jk} = \sum_{i=1}^{I} Y_{ijk}, \qquad Y_{\cdot j\cdot} = \sum_{i=1}^{I}\sum_{k=1}^{K} Y_{ijk}$$

3. It is expensive to print subscripts and superscripts on $\sum$ signs. A very simple rule is that summations are always over the given subscripts. For example,

$$\sum Y_i = \sum_{i=1}^{I} Y_i, \qquad \sum Y_{ijk} = \sum_{i=1}^{I}\sum_{j=1}^{J}\sum_{k=1}^{K} Y_{ijk}$$

We may write expressions initially with the subscripts and superscripts, but after the patterns have been established, we omit them. See Table 10.6 for an example.

4. The symbol n_{ij} denotes the number of Y_{ijk} observations, and so on. The total sample size is denoted by n rather than $n_{\cdots}$; it will be obvious from the context that the total sample size is meant.

5. The means are indicated by $\overline{Y}_{ij\cdot}$, $\overline{Y}_{\cdot j\cdot}$, and so on. The number of observations associated with a mean is always n with the same subscript (e.g., $\overline{Y}_{ij\cdot} = Y_{ij\cdot}/n_{ij}$ or $\overline{Y}_{\cdot j\cdot} = Y_{\cdot j\cdot}/n_{\cdot j}$).

6. The analysis of variance is an analysis of variability associated with a single observation. This implies that sums of squares of subtotals or totals must always be divided by the number of observations making up the total; for example, $\sum Y_{i\cdot}^2/n_i$ if $Y_{i\cdot}$ is the sum of n_i observations. The rule is then that the divisor is always the number of observations represented by the dotted subscripts. Another example: $Y_{\cdot\cdot}^2/n_{\cdot\cdot}$, since $Y_{\cdot\cdot}$ is the sum of $n_{\cdot\cdot}$ observations.

7. Similar to rules 5 and 6, a sum of squares involving means always have as weighting factor the number of observations on which the mean is based. For example,

$$\sum_{i=1}^{I} n_i(\overline{Y}_{i\cdot} - \overline{Y}_{\cdot\cdot})^2$$

because the mean $\overline{Y}_{i\cdot}$ is based on n_i observations.

8. The ANOVA models are best expressed in terms of means and deviations from means. The computations are best carried out in terms of totals to avoid unnecessary calculations and prevent rounding error. (This is similar to the definition and calculation of the sample standard deviation.) For example,

$$\sum n_i(\overline{Y}_{i\cdot} - \overline{Y}_{\cdot\cdot})^2 = \sum \frac{Y_{i\cdot}^2}{n_i} - \frac{Y_{\cdot\cdot}^2}{n_{\cdot\cdot}}$$

See Problem 10.25.

10.2 ONE-WAY ANALYSIS OF VARIANCE

10.2.1 Motivating Example

Example 10.1. To motivate the one-way analysis of variance, we return to the data of Zelazo et al. [1972], which deal with the age at which children first walked (see Chapter 5). The experiment involved reinforcement of the walking and placing reflexes in newborns. The walking and placing reflexes disappear by about 8 weeks of age. In this experiment, newborn children were randomly assigned to one of four treatment groups: active exercise; passive exercise; no exercise; or an 8-week control group. Infants in the active-exercise group received walking and placing stimulation four times a day for eight weeks, infants in the passive-exercise group received an equal amount of gross motor stimulation, infants in the no-exercise group were tested along with the first two groups at weekly intervals, and the eight-week control group consisted of infants observed only at 8 weeks of age to control for possible effects of repeated examination. The response variable was age (in months) at which the infant first walked. The data are presented in Table 10.1. For purposes of this example we have added the mean of the fourth group to that group to make the sample sizes equal; this will not change the mean of the fourth group. Equal sample sizes are not required for the one-way analysis of variance.

Assume that the age at which an infant first walks alone is normally distributed with variance σ^2. For the four treatment groups, let the means be $\mu_1, \mu_2, \mu_3,$ and μ_4. Since σ^2 is unknown, we could calculate the sample variance for each of the four groups and come up with a pooled estimate, s_p^2, of σ^2. For this example, since the sample sizes per group are assumed to be equal, this is

$$s_p^2 = \frac{1}{4}(2.0938 + 3.5938 + 2.3104 + 0.7400) = 2.1845$$

But we have one more estimate of σ^2. If the four treatments do not differ ($H_0 : \mu_1 = \mu_2 = \mu_3 = \mu_4 = \mu$), the sample means are normally distributed with variance $\sigma^2/6$. The quantity $\sigma^2/6$ can be estimated by $s_{\bar{Y}}^2$, the variance of the sample means. For this example it is

$$s_{\bar{Y}}^2 = 0.87439$$

Table 10.1 Distribution of Ages (in Months) at which Infants First Walked Alone

	Active Group	Passive Group	No-Exercise Group	Eight-Week Control Group
	9.00	11.00	11.50	13.25
	9.50	10.00	12.00	11.50
	9.75	10.00	9.00	12.00
	10.00	11.75	11.50	13.50
	13.00	10.50	13.25	11.50
	9.50	15.00	13.00	12.35[a]
Mean	10.125	11.375	11.708	12.350
Variance	2.0938	3.5938	2.3104	0.7400
$Y_i.$	60.75	68.25	70.25	74.10

Source: Data from Zelazo et al. [1972].

[a] This observation is missing from the original data set. For purposes of this illustration, it is estimated by the sample mean. See the text for further discussion.

Hence, $6s^2_{\bar{Y}} = 5.2463$ is also an estimate of σ^2. Under the null hypothesis, $6s^2_{\bar{Y}}/s^2_p$ will follow an F-distribution. How many degrees of freedom are involved? The quantity $s^2_{\bar{Y}}$ has three degrees of freedom associated with it (since it is a variance based on four observations). The quantity s^2_p has 20 degrees of freedom (since each of its four component variances has five degrees of freedom). So the quantity $6s^2_{\bar{Y}}/s^2_p$ under the null hypothesis has an F-distribution with 3 and 20 degrees of freedom. What if the null hypothesis is not true (i.e., the $\mu_1, \mu_2, \mu_3,$ and μ_4 are not all equal)? It can be shown that $6s^2_{\bar{Y}}$ then estimates $\sigma^2 +$ *positive constant*, so that the ratio $6s^2_{\bar{Y}}/s^2_p$ tends to be larger than 1. The usual hypothesis-testing approach is to reject the null hypothesis if the ratio is "too large," with the critical value selected from an F-table. The analysis is summarized in an *analysis of variance table* (ANOVA), as in Table 10.2.

The variances $6s^2_{\bar{Y}}/s^2_p$ and s^2_p are called *mean squares* for reasons to be explained later. It is clear that the first variance measures the variability between groups, and the second measures the variability within groups. The F-ratio of 2.40 is referred to an F-table. The critical value at the 0.05 level is $F_{3,20,0.95} = 3.10$, the observed value 2.40 is smaller, and we do not reject the null hypothesis at the 0.05 level. The data are displayed in Figure 10.1. From the graph it can be seen that the active group had the lowest mean value. The nonsignificance of the F-test suggests that the active group mean is not significantly lower than that of the other three groups.

Table 10.2 Simplified ANOVA Table of Data of Table 10.1

Source of Variation	d.f.	MS	F-Ratio
Between groups	3	$6s^2_{\bar{Y}} = 5.2463$	$\dfrac{6s^2_{\bar{Y}}}{s^2_p} = \dfrac{5.2463}{2.1845} = 2.40$
Within groups	20	$s^2_p = 2.1845$	

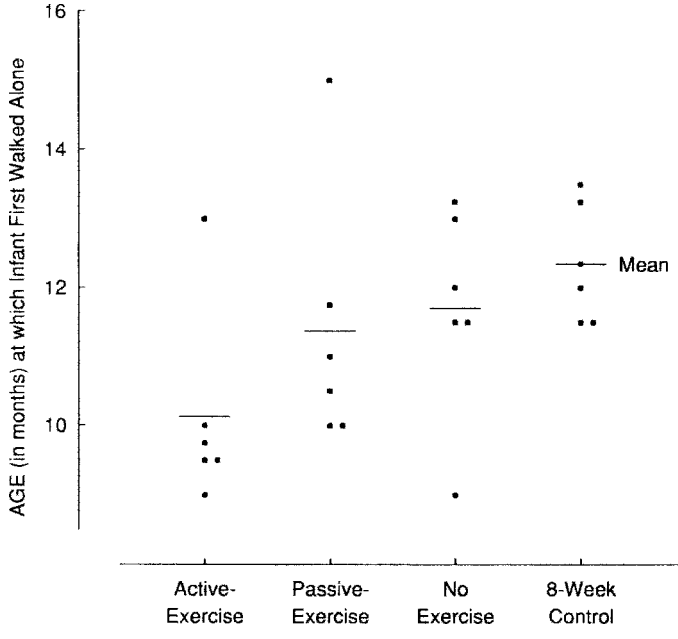


Figure 10.1 Distribution of ages at which infants first walked alone. (Data from Zelazo et al. [1972]; see Table 10.1.)

10.2.2 Using the Normal Distribution Model

Basic Approach

The one-way analysis of variance is a generalization of the t-test. As in the motivating example above, it can be used to examine the age at which groups of infants first walk alone, each group receiving a different treatment; or we may compare patient costs (in dollars per day) in a sample of hospitals from a metropolitan area. (There is a subtle distinction between the two examples; see Section 10.3.4 for a further discussion.)

Definition 10.2. An analysis of variance of observations, each of which belongs to one of I disjoint groups, is a *one-way analysis of variance of I groups*.

Suppose that samples are taken from I normal populations that differ at most in their means; the observations can be modeled by

$$Y_{ij} = \mu_i + \epsilon_{ij}, \qquad i = 1, \ldots, I, \quad j = 1, \ldots, n_i \tag{1}$$

The mean for normal population i is μ_i; we assume that there are n_i observations from this population. Also, by assumption, the ϵ_{ij} are independent $N(0, \sigma^2)$ variables. In words: Y_{ij} denotes the jth sample from a population with mean μ_i and variance σ^2. If $I = 2$, you can see that this is precisely the model for the two-sample t-test.

The only difference between the situation now and that of Section 10.2.1 is that we allow the number of observations to vary from group to group. The within-group estimate of the variance σ^2 now becomes a weighted sum of sample variances. Let s_i^2 be the sample variance from group i, where $i = 1, \ldots, I$. The within-group estimate σ^2 is

$$\frac{\sum(n_i - 1)s_i^2}{\sum(n_i - 1)} = \frac{\sum(n_i - 1)s_i^2}{n - I}$$

where $n = n_1 + n_2 + \cdots + n_I$ is the total number of observations.

Under the null hypothesis $H_0 : \mu_1 = \mu_2 = \cdots = \mu_I = \mu$, the variability among the group of sample means also estimates σ^2. We will show below that the proper expression is

$$\frac{\sum n_i(\overline{Y}_{i\cdot} - \overline{Y}_{\cdot\cdot})^2}{I - 1}$$

where

$$\overline{Y}_{i\cdot} = \sum_{j=1}^{n_i} \frac{Y_{ij}}{n_i}$$

is the sample mean for group i, and

$$\overline{Y}_{\cdot\cdot} = \sum_{i=1}^{I} \sum_{j=1}^{n_i} \frac{Y_{ij}}{n} = \sum \frac{n_i \overline{Y}_{i\cdot}}{n}$$

is the grand mean. These quantities can again be arranged in an ANOVA table, as displayed in Table 10.3. Under the null hypothesis, $H_0 : \mu_1 = \mu_2 = \cdots = \mu_I = \mu$, the quantity A/B in Table 10.3 follows an F-distribution with $(I - 1)$ and $(n - I)$ degrees of freedom.

We now reanalyze our first example in Section 10.2.1, deleting the sixth observation, 12.35, in the eight-week control group. The means and variances for the four groups are now:

Table 10.3 One-Way ANOVA Table for I Groups and n_i Observations per Group ($i = 1, \ldots, I$)

Source of Variation	d.f.	MS	F-Ratio
Between groups	$I-1$	$A = \dfrac{\sum n_i(\overline{Y}_{i\cdot} - \overline{Y}_{\cdot\cdot})^2}{I-1}$	A/B
Within groups	$n-I$	$B = \sum \dfrac{(n_i-1)s_i^2}{n-I}$	

Table 10.4 ANOVA of Data from Example 10.1, Omitting the Last Observation

Source of Variation	d.f.	MS	F-Ratio
Between groups	3	4.9253	2.14
Within groups	19	2.2994	

	Active	**Passive**	**No Exercise**	**Control**	**Overall**
Mean ($\overline{Y}_{i\cdot}$)	10.125	11.375	11.708	12.350	11.348
Variance (s_i^2)	2.0938	3.5938	2.3104	0.925	—
n_i	6	6	6	5	23

Therefore,

$$\begin{aligned}\sum n_i(\overline{Y}_{i\cdot} - \overline{Y}_{\cdot\cdot})^2 &= 6(10.125 - 11.348)^2 + 6(11.375 - 11.348)^2 \\ &\quad + 6(11.708 - 11.348)^2 + 5(12.350 - 11.348)^2 \\ &= 14.776\end{aligned}$$

The between-group mean square is $14.776/(4-1) = 4.9253$. The within-group mean square is

$$\frac{1}{23-4}[5(2.0938) + 5(3.5938) + 5(2.3104) + 4(0.925)] = 2.2994$$

The ANOVA table is displayed in Table 10.4.

The critical value $F_{3,19,0.95} = 3.13$, so again, the four groups do not differ significantly.

Linear Model Approach

In this section we approach the analysis of variance using linear models. The model $Y_{ij} = \mu_i + \epsilon_{ij}$ is usually written as

$$Y_{ij} = \mu + \alpha_i + \epsilon_{ij}, \qquad i = 1, \ldots, I, \quad j = 1, \ldots, n_i \tag{2}$$

The quantity μ is defined as

$$\mu = \sum_{i=1}^{I} \sum_{j=1}^{n_i} \frac{\mu_i}{n}$$

where $n = \sum n_i$ (the total number of observations). The quantity α_i is defined as $\alpha_i = \mu - \mu_i$. This implies that

$$\sum_{i=1}^{I} \sum_{j=1}^{n_i} \alpha_i = \sum n_i \alpha_i = 0 \tag{3}$$

Definition 10.3. The quantity $\alpha_i = \mu - \mu_i$ is the *main effect* of the ith population.

Comments:

1. The symbol α with a subscript will denote an element of the analysis of variance model, not the type I error. The context will make it clear which meaning is intended.
2. The equation $\sum n_i \alpha_i = 0$ is a constraint. It implies that fixing any $(I - 1)$ of the main effects determines the remaining value.

If we hypothesize that the I populations have the same means,

$$H_0 : \mu_1 = \mu_2 = \cdots = \mu_I = \mu$$

then an equivalent statement is

$$H_0 : \alpha_1 = \alpha_2 = \cdots = \alpha_I = 0 \quad \text{or} \quad H_0 : \alpha_i = 0, \qquad i = 1, \ldots, I$$

How are the quantities $\mu_i, i = 1, \ldots, I$ and σ^2 to be estimated from the data? (Or, equivalently, $\mu, \alpha_i, i = 1, \ldots, I$ and σ^2.) Basically, we follow the same strategy as in Section 10.2.1. The variances within the I groups are pooled to provide an estimate of σ^2, and the variability between groups provides a second estimate under the null hypothesis. The data can be displayed as shown in Table 10.5. For this set of data, a partitioning can be set up that mimics the model defined by equation (2):

$$\left.\begin{array}{ll} \text{Model :} & Y_{ij} = \mu + \alpha_i + \epsilon_{ij} \\ \text{Data :} & Y_{ij} = \overline{Y}.. + a_i + e_{ij} \end{array}\right\} i = 1, \ldots, I, \quad j = 1, \ldots, n_i \tag{4}$$

where $a_i = \overline{Y}_i. - \overline{Y}..$ and $e_{ij} = Y_{ij} - \overline{Y}_i.$ for $i = 1, \ldots, I$ and $j = 1, \ldots, n_i$. It is easy to verify that the condition $\sum n_i \alpha_i = 0$ is mimicked by $\sum n_i a_i = 0$. Each data point is partitioned into three component estimates:

$$Y_{ij} = \overline{Y}.. + (\overline{Y}_i - \overline{Y}..) + (Y_{ij} - \overline{Y}_i.) = \text{mean} + i\text{th main effect} + \text{error}$$

Table 10.5 Pooled Variances of I Groups

	Sample				
	1	2	3	$\cdots$	I
	Y_{11}	Y_{21}	Y_{31}	$\cdots$	Y_{I1}
	Y_{12}	Y_{22}	Y_{32}	$\cdots$	Y_{I2}
	$\vdots$	$\vdots$	$\vdots$	$\vdots$	$\vdots$
	Y_{1n_1}	Y_{2n_2}	Y_{3n_3}	$\cdots$	Y_{In_I}
Observations	n_1	n_2	n_3	$\cdots$	n_I
Means	$\overline{Y}_1.$	$\overline{Y}_2.$	$\overline{Y}_3.$	$\cdots$	$\overline{Y}_I.$
Totals	$Y_1.$	$Y_2.$	$Y_3.$	$\cdots$	$Y_I.$

The expression on the right side of Y_{ij} is an algebraic identity. It is a remarkable property of this partitioning that the sum of squares of the Y_{ij} is equal to the sum of the three sums of squares of the elements on the right side:

$$\sum_{i=1}^{I}\sum_{j=1}^{n_i} Y_{ij}^2 = \sum_{i=1}^{I}\sum_{j=1}^{n_i} \overline{Y}_{..}^2 + \sum_{i=1}^{I}\sum_{j=1}^{n_i} (\overline{Y}_{i.} - \overline{Y}_{..})^2 + \sum_{i=1}^{I}\sum_{j=1}^{n_i} (Y_{ij} - \overline{Y}_{i.})^2$$

$$= n\overline{Y}_{..}^2 + \sum_{i=1}^{I} n_i (\overline{Y}_{i.} - \overline{Y}_{..})^2 + \sum_{i=1}^{I}\sum_{j=1}^{n_i} (Y_{ij} - \overline{Y}_{i.})^2 \tag{5}$$

and the degrees of freedom can also be partitioned: $n = 1 + (I-1) + (n-I)$. You will recognize the terms on the right side as the ingredients needed for setting up the analysis of variance table as discussed in the preceding section. It should also be noted that the quantities on the right side are random variables (since they are based on statistics). It can be shown that their expected values are

$$E\left(\sum n_i (\overline{Y}_{i.} - \overline{Y}_{..})^2\right) = \sum n_i \alpha_i^2 + (I-1)\sigma^2 \tag{6}$$

and

$$E\left(\sum_{i=1}^{I}\sum_{j=1}^{n_i} (Y_{ij} - \overline{Y}_{i.})^2\right) = (n-I)\sigma^2 \tag{7}$$

If the null hypothesis $H_0 : \alpha_1 = \alpha_2 = \cdots = \alpha_I = 0$ is true (i.e., $\mu_1 = \mu_2 = \cdots = \mu_I = \mu$), then $\sum n_i \alpha_i^2 = 0$, and both of the terms above provide an estimate of σ^2 [after division by $(I-1)$ and $(n-I)$, respectively]. This layout and analysis is summarized in Table 10.6.

The quantities making up the component parts of equation (5) are called *sums of squares* (SS). "Grand mean" is usually omitted; it is used to test the null hypothesis that $\mu = 0$. This is rarely of very much interest, particularly if the null hypothesis $H_0 : \mu_1 = \mu_2 = \cdots = \mu_I$ is rejected (but see Example 10.7). "Between groups" is used to test the latter null hypothesis, or the equivalent hypothesis, $H_0 : \alpha_1 = \alpha_2 = \cdots = \alpha_I = 0$.

Before returning to Example 10.1, we give a few computational notes.

Computational Notes

As in the case of calculating standard deviations, the computations usually are not based on the means but rather, on the group totals. Only three quantities have to be calculated for the one-way ANOVA. Let

$$Y_{i.} = \sum_{j=1}^{n_i} Y_{ij} = \text{total in the } i\text{th treatment group} \tag{8}$$

and

$$Y_{..} = \sum Y_{i.} = \text{grand total} \tag{9}$$

The three quantities that have to be calculated are

$$\sum_{i=1}^{I}\sum_{j=1}^{n_i} Y_{ij}^2 = \sum\sum Y_{ij}^2, \qquad \sum_{i=1}^{I} \frac{Y_{i.}^2}{n_i} = \sum \frac{Y_{i.}^2}{n_i}, \quad \frac{Y_{..}^2}{n}$$

Table 10.6 Layout for the One-Way ANOVA

Source of Variation	d.f.	SS[a]	MS	F-Ratio	d.f. of F-Ratio	E(MS)	Hypothesis Tested
Grand mean	1	$\mathrm{SS}_\mu = n\overline{Y}_{\cdot\cdot}^2$	$\mathrm{MS}_\mu = \mathrm{SS}_\mu$	$\dfrac{\mathrm{MS}_\mu}{\mathrm{MS}_\epsilon}$	$(1, n-1)$	$n\mu^2 + \sigma^2$	$\mu = 0$
Between groups (main effects)	$I-1$	$\mathrm{SS}_\alpha = \sum n_i(\overline{Y}_{i\cdot} - \overline{Y}_{\cdot\cdot})^2$	$\mathrm{MS}_\alpha = \dfrac{\mathrm{SS}_\alpha}{I-1}$	$\dfrac{\mathrm{MS}_\alpha}{\mathrm{MS}_\epsilon}$	$(I-1, n-I)$	$\dfrac{\sum n_i\alpha_i^2}{I-1} + \sigma^2$	$\alpha_1 = \cdots = \alpha_I$ or $\mu_1 = \cdots = \mu_I$
Within groups (residuals)	$n-I$	$\mathrm{SS}_\epsilon = \sum\sum(\overline{Y}_{ij} - \overline{Y}_{i\cdot})^2$	$\mathrm{MS}_\epsilon = \dfrac{\mathrm{SS}_\epsilon}{n-I}$	—	—	σ^2	σ^2
Total	n	$\sum\sum Y_{ij}^2$					

[a] Summation is over all displayed subscripts.

$$\begin{aligned} \text{Model}: \quad Y_{ij} &= \mu_i + \epsilon_{ij}, \qquad \epsilon_{ij} \sim \text{iid } N(0, \sigma^2) \\ &= \mu + \alpha_i + \epsilon_{ij}, \qquad i = 1, \ldots, I, \quad j = 1, \ldots, n_i \\ \text{Data}: \quad Y_{ij} &= \overline{Y}_{\cdot\cdot} + (\overline{Y}_{i\cdot} - \overline{Y}_{\cdot\cdot}) + (Y_{ij} - Y_{i\cdot}) \end{aligned}$$

(iid = independent and identically distributed). An equivalent model is

$$Y_{ij} \sim N(\mu_i, \sigma^2), \qquad \text{where } Y_{ij}\text{'s are independent}$$

where $n = \sum n_i =$ total observations. It is easy to establish the following relationships:

$$\mathrm{SS}_\mu = \frac{Y_{\cdot\cdot}^2}{n} \tag{10}$$

$$\mathrm{SS}_\alpha = \sum \frac{Y_{i\cdot}^2}{n_i} - \frac{Y_{\cdot\cdot}^2}{n} \tag{11}$$

$$\mathrm{SS}_\epsilon = \sum\sum Y_{ij}^2 - \sum \frac{Y_{i\cdot}^2}{n_i} \tag{12}$$

The subscripts are omitted.

We have an algebraic identity in $\sum\sum Y_{ij}^2 = \mathrm{SS}_\mu + \mathrm{SS}_\alpha + \mathrm{SS}_\epsilon$. Defining $\mathrm{SS}_{\mathrm{TOTAL}}$ as $\mathrm{SS}_{\mathrm{TOTAL}} = \sum\sum Y_{ij}^2 - \mathrm{SS}_\mu$, we get $\mathrm{SS}_{\mathrm{TOTAL}} = \mathrm{SS}_\alpha + \mathrm{SS}_\epsilon$ and degrees of freedom $(n-1) = (i-1)+(n-I)$.

This formulation is a simplified version of equation (5). Note that the original data are needed only for $\sum\sum Y_{ij}^2$; all other sums of squares can be calculated from group or overall totals.

Continuing Example 10.1, omitting again the last observation (12.35):

$$\sum\sum Y_{ij}^2 = 9.00^2 + 9.50^2 + \cdots + 11.50^2 = 3020.2500$$

$$\sum \frac{Y_{i\cdot}^2}{n_i} = \frac{60.75^2}{6} + \frac{68.25^2}{6} + \frac{70.25^2}{6} + \frac{61.75^2}{5} = 2976.5604$$

$$\frac{Y_{\cdot\cdot}^2}{n} = \frac{261.00^2}{23} = 2961.7826$$

The ANOVA table omitting rows for SS_μ and $\mathrm{SS}_{\mathrm{TOTAL}}$ becomes

Source of Variation	d.f.	SS	MS	F-Ratio
Between groups	3	14.7778	4.9259	2.14
Within groups	19	43.6896	2.2995	

The numbers in this table are not subject to rounding error and differ slightly from those in Table 10.4.

Estimates of the components of the expected mean squares of Table 10.6 can now be obtained. The estimate of σ^2 is $\widehat{\sigma}^2 = 2.2995$, and the estimate of $\sum n_i \alpha_i^2/(I-1)$ is

$$\frac{\sum n_i \widehat{\alpha}_i^2}{I-1} = 4.9259 - 2.2995 = 2.6264$$

How is this quantity to be interpreted in view of the nonrejection of the null hypothesis? Theoretically, the quantity can never be less than zero (all the terms are positive). The best interpretation looks back to MS_α, which is a random variable which (under the null hypothesis) estimates σ^2. Under the null hypothesis, MS_α and MS_ϵ both estimate σ^2, and $\sum n_i \alpha_i^2/(I-1)$ is zero.

10.2.3 One-Way ANOVA from Group Means and Standard Deviation

In many research papers, the raw data are not presented but rather, the means and standard deviations (or variances) for each of the, say, I treatment groups under consideration. It is instructive to construct an analysis of variance from these data and see how the assumption

of the equality of the population variances for each of the groups enters in. Advantages of constructing the ANOVA table are:

1. Pooling the sample standard deviations (variances) of the groups produces a more precise estimate of the population standard deviation. This becomes very important if the sample sizes are small.
2. A simultaneous comparison of all group means can be made by means of the F-test rather than by a series of two-sample t-tests. The analysis can be modeled on the layout in Table 10.3.

Suppose that for each of I groups the following quantities are available:

Group	Sample Size	Sample Mean	Sample Variance
i	n_i	$\overline{Y}_{i\cdot}$	s_i^2

The quantities $n = \sum n_i$, $Y_{i\cdot} = n_i \overline{Y}_{i\cdot}$, and $Y_{\cdot\cdot} = \sum Y_{i\cdot}$ can be calculated. The "within groups" SS is the quantity B in Table 10.3 times $n - I$, and the "between groups" SS can be calculated as

$$\mathrm{SS}_\alpha = \sum \frac{Y_{i\cdot}^2}{n_i} - \frac{Y_{\cdot\cdot}^2}{n}$$

Example 10.2. Barboriak et al. [1972] studied risk factors in patients undergoing coronary bypass surgery for coronary artery disease. The authors looked for an association between cholesterol level (a putative risk factor) and the number of diseased blood vessels. The data are:

Diseased Vessels (i)	Sample Size (n_i)	Mean Cholesterol Level ($\overline{Y}_{i\cdot}$)	Standard Deviation (s_i)
1	29	260	56.0
2	49	289	87.5
3	76	295	72.4

Using equations (8)–(12), we get $n = 29 + 49 + 76 = 154$,

$$Y_{1\cdot} = n_1 \overline{Y}_{1\cdot} = 29(260) = 7540, \qquad Y_{3\cdot} = n_3 \overline{Y}_{3\cdot} = 76(295) = 22{,}420$$

$$Y_{2\cdot} = n_2 \overline{Y}_{2\cdot} = 49(289) = 14{,}161, \qquad Y_{\cdot\cdot} = \sum n_i \overline{Y}_{i\cdot} = \sum Y_{i\cdot} = 44{,}121$$

$$\mathrm{SS}_\alpha = \frac{7540^2}{29} + \frac{14{,}161^2}{49} + \frac{22{,}420^2}{76} - \frac{44{,}121^2}{154}$$

$$= 12{,}666{,}829.0 - 12{,}640{,}666.5 = 26{,}162.5$$

$$\mathrm{SS}_\epsilon = \sum (n_i - 1) s_i^2 = 28 \times 56.0^2 + 48 \times 87.5^2 + 75 \times 72.4^2 = 848{,}440$$

The ANOVA table (Table 10.7) can now be constructed. (There is no need to calculate the total SS.)

The critical value for F at the 0.05 level with 2 and 120 degrees of freedom is 3.07; the observed F-value does not exceed this critical value, and the conclusion is that the average cholesterol levels do not differ significantly.

Table 10.7 ANOVA of Data of Example 10.2

Source	d.f.	SS	MS	F-Ratio
Main effects (disease status)	2	26,162.50	13,081.2	2.33
Residual (error)	151	848,440.0	5,618.5	—

10.2.4 One-Way ANOVA Using Ranks

In this section the rank procedures discussed in Chapter 8 are extended to the one-way analysis of variance. For three or more groups, Kruskal and Wallis [1952] have given a one-way ANOVA based on ranks. The model is

$$Y_{ij} = \mu_i + \epsilon_{ij}, \qquad i = 1, \ldots, I, \quad j = 1, \ldots, n_i$$

The only assumption about the ϵ_{ij} is that they are independently and identically distributed, not necessarily normal. It is assumed that there are no ties among the observations. For a small number of ties in the data, the average of the ranks for the tied observations is usually assigned (see Note 10.1). The test procedure will be conservative in the presence of ties (i.e., the p-value will be smaller when adjustment for ties is made).

The null hypothesis of interest is

$$H_0 : \mu_1 = \mu_2 = \cdots = \mu_I = \mu$$

The procedure for obtaining the ranks is similar to that for the two-sample Wilcoxon rank-sum procedure: The $n_1 + n_2 + \cdots + n_I = n$ observations are ranked without regard to which group they belong. Let $R_{ij} =$ rank of observation j in group i.

$$T_{\mathrm{KW}} = \frac{12 \sum n_i (\overline{R}_{i\cdot} - \overline{R}_{\cdot\cdot})^2}{n(n+1)} \tag{13}$$

where $\overline{R}_{i\cdot}$ is the average of the ranks of the observations in group i:

$$\overline{R}_{i\cdot} = \sum_{j=1}^{n_i} \frac{R_{ij}}{n_i}$$

and $\overline{R}_{\cdot\cdot}$ is the grand mean of the ranks. The value of the mean ($\overline{R}_{\cdot\cdot}$) must be $(n+1)/2$ (why?) and this provides a partial check on the arithmetic. Large values of T_{KW} imply that the average ranks for the group differ, so that the null hypothesis is rejected for large values of this statistic. If the null hypothesis is true and all the n_i become large, the distribution of the statistic T_{KW} approaches a χ^2-distribution with $I-1$ degrees of freedom. Thus, for large sample sizes, critical values for T_{KW} can be read from a χ^2-table. For small values of n_i, say, in the range 2 to 5, exact critical values have been tabulated (see, e.g., CRC Table X.9 [Beyer, 1968]). Such tables are available for three or four groups.

An equivalent formula for T_{KW} as defined by equation (13) is

$$T_{\mathrm{KW}} = \frac{12 \sum R_{i\cdot}^2 / n_i}{n(n+1)} - 3(n+1) \tag{14}$$

where $R_{i\cdot}$ is the total of the ranks for the ith group.

Example 10.3. Chikos et al. [1977] studied errors in the reading of chest x-rays. The opinion of 10 radiologists about the status of the left ventricle of the heart ("normal" vs. "abnormal") was compared to data obtained by ventriculography (which consists of the insertion of a catheter into the left ventricle, injection of a radiopague fluid, and the taking of a series of x-rays). The ventriculography data were used to classify a subject's left ventricle as "normal" or "abnormal." Using this gold standard, the percentage of errors for each radiologist was computed. The authors were interested in the effect of experience, and for this purpose the radiologists were classified into one of three groups: senior staff, junior staff, and residents. The data for these three groups are shown in Table 10.8.

To compute the Kruskal–Wallis statistic T_{KW}, the data are ranked disregarding groups:

Observation	7.3	7.4	10.6	13.3	14.7	15.0	20.7	22.7	23.0	26.6
Rank	1	2	3	4	5	6	7	8	9	10
Group	1	1	2	2	3	2	2	3	3	3

The sums and means of the ranks for each group are calculated to be

$$R_1. = 1 + 2 = 3, \qquad \overline{R}_1. = 1.5$$
$$R_2. = 3 + 4 + 6 + 7 = 20, \qquad \overline{R}_2. = 5.0$$
$$R_3. = 5 + 8 + 9 + 10 = 32, \qquad \overline{R}_3. = 8.0$$

[The sum of the ranks is $R_1 + R_2 + R_3 = 55 = (10 \times 11)/2$, providing a partial check of the ranking procedure.]

Using equation (14), the T_{KW} statistic has a value of

$$T_{\mathrm{KW}} = \frac{12(3^2/2 + 20^2/4 + 32^2/4)}{10(10+1)} - 3(10+1) = 6.33$$

This value can be referred to as a χ^2-table with two degrees of freedom. The p-value is $0.025 < p < 0.05$. The exact p-value can be obtained from, for example, Table X.9 of the CRC tables [Beyer, 1968]. (This table does not list the critical values of T_{KW} for $n_1 = 2$, $n_2 = 4$, $n_3 = 4$; however, the order in which the groups are labeled does not matter, so that the values $n_1 = 4, n_2 = 4$, and $n_3 = 2$ may be used.) From this table it is seen that $0.011 < p < 0.046$, indicating that the chi-square approximation is satisfactory even for these small sample sizes. The conclusion from both analyses is that among staff levels there are significant differences in the accuracy of reading left ventricular abnormality from a chest x-ray.

Table 10.8 Data for Three Radiologist Groups

	Senior Staff	Junior Staff	Residents
i	1	2	3
n_i	2	4	4
Y_{ij}	7.3	13.3	14.7
	7.4	10.6	23.0
(Percent error)		15.0	22.7
		20.7	26.6

10.3 TWO-WAY ANALYSIS OF VARIANCE

10.3.1 Using the Normal Distribution Model

In this section we consider data that arise when a response variable can be classified in two ways. For example, the response variable may be blood pressure and the classification variables type of drug treatment and gender of the subject. Another example arises from classifying people by type of health insurance and race; the response variable could be number of physician contacts per year.

Definition 10.4. An analysis of variance of observations, each of which can be classified in two ways is called a *two-way analysis of variance*.

The data are usually displayed in "cells," with the row categories the values of one classification variable and the columns representing values of the second classification variable.

A completely general two-way ANOVA model with each cell mean any value could be

$$Y_{ijk} = \mu_{ij} + \epsilon_{ijk} \tag{15}$$

where $i = 1, \ldots, I$, $j = 1, \ldots, J$, and $k = 1, \ldots, n_{ij}$. By assumption, the ϵ_{ijk} are iid $N(0, \sigma^2)$: independently and identically distributed $N(0, \sigma^2)$. This model could be treated as a one-way ANOVA with IJ groups with a test of the hypothesis that all μ_{ij} are the same, implying that the classification variables are not related to the response variable. However, if there is a significant difference among the IJ group means, we want to know whether these differences can be attributed to:

1. One of the classification variables,
2. Both of the classification variables acting separately (no interaction), or
3. Both of the classification variables acting separately and jointly (interaction).

In many situations involving classification variables, the mean μ_{ij} may be modeled as the sum of two terms, an effect of variable 1 plus an effect of variable 2:

$$\mu_{ij} = u_i + v_j, \qquad i = 1, \ldots, I, \quad j = 1, \ldots, J \tag{16}$$

Here μ_{ij} depends, in an additive fashion, on the ith level of the first variable and the jth level of the second variable. One problem is that u_i and v_j are not defined uniquely; for any constant C, if $\mu_i^* = u_i + C$ and $v_j^* = v_j - C$, then $\mu_{ij} = u_i^* + v_j^*$. Thus, the values of u_i and v_j can be pinned down to within a constant. The constant is specified by convention and is associated with the experimental setup. Suppose that there are n_{ij} observations at the ith level of variable 1 and the jth level of variable 2. The frequencies of observations can be laid out in a contingency table as shown in Table 10.9.

The experiment has a total of $n..$ observations. The notation is identical to that used in a two-way contingency table layout. (A major difference is that all the frequencies are usually chosen by the experimenter; we shall return to this point when talking about a balanced ANOVA design.) Using the model of equation (16), the value of μ_{ij} is defined as

$$\mu_{ij} = \mu + \alpha_i + \beta_j \tag{17}$$

where $\mu = \sum\sum n_{ij}\mu_{ij}/n..$, $\sum n_{i\cdot}\alpha_i = 0$, and $\sum n_{\cdot j}\beta_j = 0$. This is similar to the constraints put on the one-way ANOVA model; see equations (2) and (10.3), and Problem 10.25(d).

Example 10.4. An experimental setup involves two explanatory variables, each at three levels. There are 24 observations distributed as shown in Table 10.10. The effects of the first

Table 10.9 Contingency Table for Variables

Levels of Variable 1	Levels of Variable 2						
	1	2	$\cdots$	j	$\cdots$	J	Total
1	n_{11}	n_{12}	$\cdots$	n_{1j}	$\cdots$	n_{1j}	$n_{1\cdot}$
2	n_{21}	n_{22}	$\cdots$	n_{2j}	$\cdots$	n_{2J}	$n_{2\cdot}$
$\vdots$	$\vdots$	$\vdots$	$\ddots$	$\vdots$	$\ddots$	$\vdots$	$\vdots$
i	n_{i1}	n_{i2}	$\cdots$	n_{ij}	$\cdots$	n_{iJ}	$n_{i\cdot}$
$\vdots$	$\vdots$	$\vdots$	$\ddots$	$\vdots$	$\ddots$	$\vdots$	$\vdots$
I	n_{I1}	n_{I2}	$\cdots$	n_{Ij}	$\cdots$	n_{IJ}	$n_{I\cdot}$
Total	$n_{\cdot 1}$	$n_{\cdot 2}$	$\cdots$	$n_{\cdot j}$	$\cdots$	$n_{\cdot J}$	$n_{\cdot\cdot}$

Table 10.10 Observation Data

Levels of Variable 1	Levels of Variable 2			
	1	2	3	Total
1	2	2	2	6
2	3	3	3	9
3	3	3	3	9
Total	8	8	8	24

Table 10.11 Data for Variable Effects

Effects of the First Variable	Effects of the Second Variable			
	$\beta_1 = 1$	$\beta_2 = -3$	$\beta_3 = 2$	Total
$\alpha_1 = 3$	$\mu_{11} = 24$	$\mu_{12} = 20$	$\mu_{13} = 25$	$\mu_{1\cdot} = 23$
$\alpha_2 = 6$	$\mu_{21} = 27$	$\mu_{22} = 23$	$\mu_{23} = 28$	$\mu_{2\cdot} = 26$
$\alpha_3 = -8$	$\mu_{31} = 13$	$\mu_{32} = 9$	$\mu_{33} = 14$	$\mu_{3\cdot} = 12$
Total	$\mu_{\cdot 1} = 21$	$\mu_{\cdot 2} = 17$	$\mu_{\cdot 3} = 22$	$\mu = 20$

variable are assumed to be $\alpha_1 = 3, \alpha_2 = 6,$ and $\alpha_3 = -8$; the effects of the second variable are $\beta_1 = 1, \beta_2 = -3,$ and $\beta_3 = 2$. The overall level is $\mu = 20$. If the model defined by equation (17) holds, the cell means μ_{ij} are specified completely as shown in Table 10.11.

For example, $\mu_{11} = 20 + 3 + 1 = 24$ and $\mu_{33} = 20 - 8 + 2 = 14$. Note that $\sum n_{i\cdot}\alpha_i = 6.3 + 9.6 + 9(-8) = 0$ and, similarly, $\sum n_{\cdot j}\beta_j = 0$. Note also that $\mu_{1\cdot} = \sum n_{1j}\mu_{1j} / \sum n_{ij} = \mu + \alpha_1 = 20 + 3 = 23$; that is, a marginal mean is just the overall mean plus the effect of the variable associated with that margin. The means are graphed in Figure 10.2. The points have been joined by dashed lines to make the pattern clear; there need not be any continuity between the levels. A similar graph could be made with the level of the second variable plotted on the abscissa and the lines indexed by the levels of the first variable.

Definition 10.5. A two-way ANOVA model satisfying equation (17) is called an *additive model*.

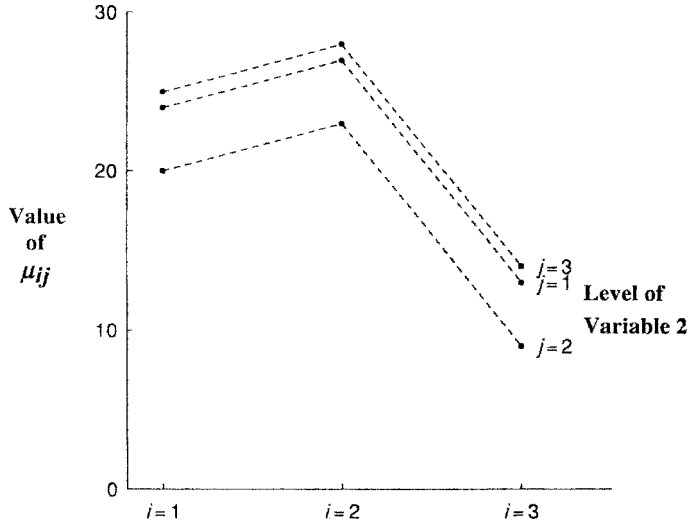


Figure 10.2 Graph of additive ANOVA model (see Example 10.4).

Some implications of this model are discussed. You will find it helpful to refer to Example 10.4 and Figure 10.2 in understanding the following:

1. The statement of equation (17) is equivalent to saying that "changing the level of variable 1 while the level of the second variable remains fixed changes the value of the mean by the same amount regardless of the (fixed) level of the second variable."
2. Statement 1 holds with variables 1 and 2 interchanged.
3. If the values of $\mu_{ij} (i = 1, \ldots, I)$ are plotted for the various levels of the second variable, the curves are parallel (see Figure 10.2).
4. Statement 3 holds with the roles of variables 1 and 2 interchanged.
5. The model defined by equation (17) imposes $1 + (I - 1) + (J - 1)$ constraints on the IJ means μ_{ij}, leaving $(I - 1)(J - 1)$ degrees of freedom.

We now want to define a nonadditive model, but before doing so, we must introduce one other concept.

Definition 10.6. A two-way ANOVA has a *balanced (orthogonal) design* if for every i and j,

$$n_{ij} = \frac{n_{i\cdot} n_{\cdot j}}{n_{\cdot\cdot}}$$

That is, the cell frequencies are functions of the product of the marginal totals. The reason this characteristic is needed is that only for balanced designs can the total variability be partitioned in an additive fashion. In Section 10.5 we introduce a discussion of unbalanced or nonorthogonal designs; the topic is treated in terms of multiple regression models in Chapter 11.

Definition 10.7. A *balanced two-way* ANOVA *model with interaction* (a nonadditive model) is defined by

$$Y_{ijk} = \mu + \alpha_i + \beta_j + \gamma_{ij} + \epsilon_{ijk}, \qquad \begin{matrix} i = 1, \ldots, I \\ j = 1, \ldots, J \\ k = 1, \ldots, n_{ij} \end{matrix} \tag{18}$$

subject to the following conditions:

1. $n_{ij} = n_{i\cdot}n_{\cdot j}/n_{\cdot\cdot}$ for every i and j.
2. $\sum n_{i\cdot}\alpha_i = \sum n_{\cdot j}\beta_j = 0$.
3. $\sum n_{i\cdot}\gamma_{ij} = 0$ for all $j = 1, \ldots, J$, $\sum n_{\cdot j}\gamma_{ij} = 0$ for all $i = 1, \ldots, I$.
4. The ϵ_{ijk} are iid $N(0, \sigma^2)$. This assumption implies homogeneity of variances among the IJ cells.

If the γ_{ij} are zero, the model is equivalent to the one defined by equation (17), there is no interaction, and the model is additive.

As in Section 10.2, equations (4) and (5), a set of data as defined at the beginning of this section can be partitioned into parts, each of which estimates the component part of the model:

$$Y_{ijk} = \overline{Y}\ldots + a_i + b_j + g_{ij} + e_{ijk} \tag{19}$$

where

$$\begin{aligned}
\overline{Y}\ldots &= \text{grand mean}\\
a_i = \overline{Y}_{i\cdot\cdot} - \overline{Y}\ldots &= \text{main effect of } i\text{th level of variable 1}\\
b_j = \overline{Y}_{\cdot j\cdot} - \overline{Y}\ldots &= \text{main effect of } j\text{th level of variable 2}\\
g_{ij} = \overline{Y}_{ij\cdot} - \overline{Y}_{i\cdot\cdot} - \overline{Y}_{\cdot j\cdot} + \overline{Y}\ldots &= \text{interaction of } i\text{th and } j\text{th levels of variables 1 and 2}\\
e_{ijk} = \overline{Y}_{ijk} - \overline{Y}_{ij\cdot} &= \text{residual effect (error)}
\end{aligned}$$

The quantities $\overline{Y}_{i\cdot\cdot}$ and $\overline{Y}_{\cdot j\cdot}$ are the means of the ith level of variable 1 and the jth level of variable 2. In symbols,

$$\overline{Y}_{i\cdot\cdot} = \sum_{j=1}^{J}\sum_{k=1}^{n_{ij}}\frac{Y_{ijk}}{n_{i\cdot}} \quad \text{and} \quad \overline{Y}_{\cdot j\cdot} = \sum_{i=1}^{I}\sum_{k=1}^{n_{ij}}\frac{Y_{ijk}}{n_{\cdot j}}$$

The interaction term, g_{ij}, can be rewritten as

$$g_{ij} = (\overline{Y}_{ij\cdot} - \overline{Y}\ldots) - (\overline{Y}_{i\cdot\cdot} - \overline{Y}\ldots) - (\overline{Y}_{\cdot j\cdot} - \overline{Y}\ldots)$$

which is the overall deviation of the mean of the ijth cell from the grand mean minus the main effects of variables 1 and 2. If the data can be fully explained by main effects, the term g_{ij} will be zero. Hence, g_{ij} measures the extent to which the data deviate from an additive model.

For a balanced design the total sum of squares, $\text{SS}_{\text{TOTAL}} = \sum\sum\sum(Y_{ijk} - \overline{Y}\ldots)^2$ and degrees of freedom can be partitioned additively into four parts:

$$\begin{aligned}
\text{SS}_{\text{TOTAL}} &= \text{SS}_\alpha + \text{SS}_\beta + \text{SS}_\gamma + \text{SS}_\epsilon\\
n_{\cdot\cdot} - 1 &= (I-1) + (J-1) + (I-1)(J-1) + (n_{\cdot\cdot} - IJ)
\end{aligned} \tag{20}$$

Let

$$Y_{ij\cdot} = \sum_{k=1}^{n_{ij}} Y_{ijk} = \text{total for cell } ij$$

$$Y_{i\cdot\cdot} = \sum_{j=1}^{J} Y_{ij\cdot} = \text{total for row } i$$

$$Y_{\cdot j\cdot} = \sum_{i=1}^{I} Y_{ij\cdot} = \text{total for column } j$$

Then the equations for the sums of squares together with computationally simpler formulas are

$$\begin{aligned}
\mathrm{SS}_\alpha &= \sum n_{i\cdot}(\overline{Y}_{i\cdot\cdot} - \overline{Y}_{\cdots})^2 = \sum \frac{Y_{i\cdot\cdot}^2}{n_{i\cdot}} - \frac{Y_{\cdots}^2}{n_{\cdot\cdot}} \\
\mathrm{SS}_\beta &= \sum n_{\cdot j}(\overline{Y}_{\cdot j\cdot} - \overline{Y}_{\cdots})^2 = \sum \frac{Y_{\cdot j\cdot}^2}{n_{\cdot j}} - \frac{Y_{\cdots}^2}{n_{\cdot\cdot}} \qquad (21) \\
\mathrm{SS}_\gamma &= \sum\sum n_{ij}(\overline{Y}_{ij\cdot} - \overline{Y}_{i\cdot\cdot} - \overline{Y}_{\cdot j\cdot} + \overline{Y}_{\cdots})^2 = \sum\sum \frac{Y_{ij\cdot}^2}{n_{ij}} - \frac{Y_{\cdots}^2}{n} - \mathrm{SS}_\alpha - \mathrm{SS}_\beta \\
\mathrm{SS}_\epsilon &= \sum\sum\sum (Y_{ijk} - \overline{Y}_{ij\cdot})^2 = \sum\sum\sum Y_{ijk}^2 - \sum\sum \frac{Y_{ij\cdot}^2}{n_{ij}}
\end{aligned}$$

The partition of the sum of squares, the mean squares, and the expected mean squares are given in Table 10.12.

A series of F-tests can be carried out to test the significance of the components of the model specified by equation (18). The first test carried out is usually the test for interaction: $\mathrm{MS}_\gamma/\mathrm{MS}_\epsilon$. Under the null hypothesis $H_0 : \gamma_{ij} = 0$ for all i and j, this ratio has an F-distribution with $(I-1)(J-1)$ and $n - IJ$ degrees of freedom. The null hypothesis is rejected for large values of this ratio. Interaction is indicated by nonparallelism of the treatment effects. In Figure 10.3, some possible patterns are indicated. The expected results of F-tests are given at the top of each graph. For example, pattern 1 shows NO–YES–NO, implying that the test for the main effect of variable 1 was not significant, the test for main effect of variable 2 was significant, and the test for interaction was not significant. It now becomes clear that if interaction is present, main effects are going to be difficult to interpret. For example, pattern 4 in Figure 10.3 indicates significant interaction but no significant main effects. But the significant interaction implies that at level 1 of variable 1 there is a significant difference in the main effect of variable 2. What is happening is that the effect of variable 2 is in the opposite direction at the second level of variable 1. This pattern is extreme. A more common pattern is that of pattern 6. How is this pattern to be interpreted? First, there is interaction; second, above the interaction there are significant main effects.

There are substantial practical problems associated with significant interaction patterns. For example, suppose that the two variables represent two drugs for pain relief administered simultaneously to a patient. With pattern 2, the inference would be that the two drugs together are more effective than either one acting singly. In pattern 4 (and pattern 3), the drugs are said to act *antagonistically*. In pattern 6, the drugs are said to act *synergistically*; the effect of both drugs combined is greater than the sum of each acting alone. (For some subtle problems associated with these patterns, see the discussion of transformations in Section 10.6.)

If interaction is not present, the main effects can be tested by means of the F-tests $\mathrm{MS}_\alpha/\mathrm{MS}_\epsilon$ and $\mathrm{MS}_\beta/\mathrm{MS}_\epsilon$ with $(I-1, n-IJ)$ and $(J-1, n-IJ)$ degrees of freedom, respectively. If a main effect is significant, the question arises: Which levels of the main effect differ significantly? At this point, a visual inspection of the levels may be sufficient to establish the pattern; in Chapter 12 we establish a more formal approach.

As usual, the test $\mathrm{MS}_\mu/\mathrm{MS}_\epsilon$ is of little interest, and this line is frequently omitted in an analysis of variance table.

Table 10.12 Layout for the Two-Way ANOVA[a]

Source of Variation	d.f.	SS[b]	MS	F-Ratio	d.f. of F-Ratio	E(MS)	Hypothesis Being Tested
Grand mean	1	$\mathrm{SS}_\mu = n\overline{Y}_{\cdots}^2$	$\mathrm{MS}_\mu = \mathrm{SS}_\mu$	$\frac{\mathrm{MS}_\mu}{\mathrm{MS}_\epsilon}$	$(1, n-IJ)$	$\sigma^2 + n\mu^2$	$\mu = 0$
Row main effects	$I-1$	$\mathrm{SS}_\alpha = \sum n_{i\cdot}(\overline{Y}_{i\cdot\cdot} - \overline{Y}_{\cdots})^2$	$\mathrm{MS}_\alpha = \frac{\mathrm{SS}_\alpha}{I-1}$	$\frac{\mathrm{MS}_\alpha}{\mathrm{MS}_\epsilon}$	$(I-1, n-IJ)$	$\sigma^2 + \frac{\sum n_{i\cdot}\alpha_i^2}{I-1}$	$\alpha_i = 0$ for all i
Column main effects	$J-1$	$\mathrm{SS}_\beta = \sum n_{\cdot j}(\overline{Y}_{\cdot j\cdot} - \overline{Y}_{\cdots})^2$	$\mathrm{MS}_\beta = \frac{\mathrm{SS}_\beta}{J-1}$	$\frac{\mathrm{MS}_\beta}{\mathrm{MS}_\epsilon}$	$(J-1, n-IJ)$	$\sigma^2 + \frac{\sum n_{\cdot j}\beta_j^2}{J-1}$	$\beta_j = 0$ for all j
Row × column interaction	$(I-1)(J-1)$	$\mathrm{SS}_\gamma = \sum n_{ij}(\overline{Y}_{ij\cdot} - \overline{Y}_{i\cdot\cdot} - \overline{Y}_{\cdot j\cdot} - \overline{Y}_{\cdots})^2$	$\mathrm{MS}_\gamma = \frac{\mathrm{SS}_\gamma}{(I-1)(J-1)}$	$\frac{\mathrm{MS}_\gamma}{\mathrm{MS}_\epsilon}$	$((I-1)(J-1), n-IJ)$	$\sigma^2 + \frac{\sum n_{ij}\gamma_{ij}^2}{(I-1)(J-1)}$	$\gamma_{ij} = 0$ for all i and j, or $\mu_{ij} = u_i + v_j$
Residual	$n-IJ$	$\mathrm{SS}_\epsilon = \sum(Y_{ijk} - \overline{Y}_{ij\cdot})^2$	$\mathrm{MS}_\epsilon = \frac{\mathrm{SS}_\epsilon}{n-IJ}$	—	—	σ^2	
Total	n	$\sum Y_{ijk}^2$	—				

[a] Model: $Y_{ijk} = \mu_{ij} + \epsilon_{ijk} = \mu + \alpha_i + \beta_j + \gamma_{ij} + \epsilon_{ijk}$ [where $\epsilon_{ijk} \sim$ iid $N(0, \sigma^2)$].
Data : $Y_{ijk} = \overline{Y}_{\cdots} + (\overline{Y}_{i\cdot\cdot} - \overline{Y}_{\cdots}) + (\overline{Y}_{\cdot j\cdot} - \overline{Y}_{\cdots}) + (\overline{Y}_{ij\cdot} - \overline{Y}_{i\cdot\cdot} - \overline{Y}_{\cdot j\cdot} - \overline{Y}_{\cdots}) + (Y_{ijk} - \overline{Y}_{ij\cdot})$.
Equivalent model : $Y_{ijk} \sim N(\mu_{ij}, \sigma^2)$, where the Y_{ijk}'s are independent.
[b] Summation is over all subscripts displayed.

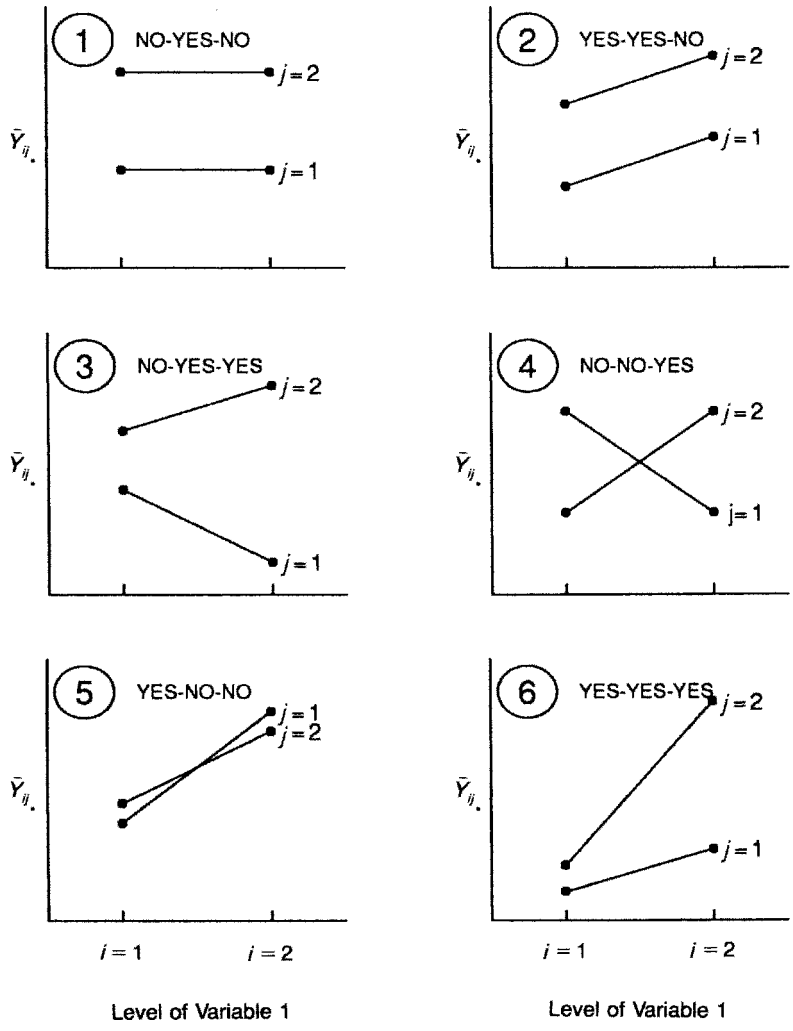


Figure 10.3 Some possible patterns for observed cell means in two-way ANOVA with two levels for each variable. Results of F-tests for main effects variable 1, variable 2, and interaction are indicated by YES or NO. See the text for a discussion.

Example 10.5. Nitrogen dioxide (NO_2) is an automobile emission pollutant, but less is known about its effects than those of other pollutants, such as particulate matter. Several animal models have been studied to gain an understanding of the effects of NO_2. Sherwin and Layfield [1976] studied protein leakage in the lungs of mice exposed to 0.5 part per million (ppm) NO_2 for 10, 12, and 14 days. Half of a total group of 44 animals was exposed to the NO_2; the other half served as controls. Control and experimental animals were matched on the basis of weight, but this aspect will be ignored in the analysis since the matching did not appear to influence the results. Thirty-eight animals were available for analysis; the raw data and some basic statistics are listed in Table 10.13.

The response is the percent of serum fluorescence. High serum fluorescence values indicate a greater protein leakage and some kind of insult to the lung tissue. The authors carried out t-tests and state that with regard to serum fluorescence, "no significant differences" were found.

Table 10.13 Serum Fluorescence Readings of Mice Exposed to Nitrogen Dioxide (NO_2) for 10, 12, and 14 Days Compared with Control Animals

	Serum Fluorescence		
	10 Days ($j = 1$)	12 Days ($j = 2$)	14 Days ($j = 3$)
Control ($i = 1$)	143	179	76
	169	160	40
	95	87	119
	111	115	72
	132	171	163
	150	146	78
	141	—	—
Exposed ($i = 2$)	152	141	119
	83	132	104
	91	201	125
	86	242	147
	150	209	200
	108	114	178
	75	—	—

n_{ij}

	j		
i	1	2	3
1	7	6	6
2	7	6	6

$Y_{ij\cdot}$

	j		
i	1	2	3
1	941	858	548
2	745	1039	873

$\overline{Y}_{ij\cdot}$

	j		
i	1	2	3
1	134.4	143.0	91.3
2	106.4	173.2	145.5

s_{ij}

	j		
i	1	2	3
1	24.7	35.5	43.2
2	32.1	51.0	37.1

The standard deviations are very similar, suggesting that the homogeneity of variance assumption is probably valid. It is a good idea again to graph the results to get some "feel" for the data, and this is done in Figure 10.4. We can see from this figure that there are no outlying observations that would invalidate the normality assumption of the two-way ANOVA model.

To obtain the entries for the two-way ANOVA table, we basically need six quantities:

$$n,\ Y\ldots,\quad \sum Y_{ijk}^2,\quad \sum \frac{Y_{i\cdot\cdot}^2}{n_{i\cdot}},\quad \sum \frac{Y_{\cdot j\cdot}^2}{n_{\cdot j}},\quad \sum \frac{Y_{ij\cdot}^2}{n_{ij}}$$

With these quantities, and using equations (20) and (21), the entire table can be computed. The values are as follows:

$$n = 38, \qquad Y\ldots = 5004, \qquad \sum Y_{ijk}^2 = 730{,}828$$

$$\sum \frac{Y_{i\cdot\cdot}^2}{n_{i\cdot}} = 661{,}476.74, \qquad \sum \frac{Y_{\cdot j\cdot}^2}{n_{\cdot j}} = 671{,}196.74, \qquad \sum \frac{Y_{ij\cdot}^2}{n_{ij}} = 685{,}472.90$$

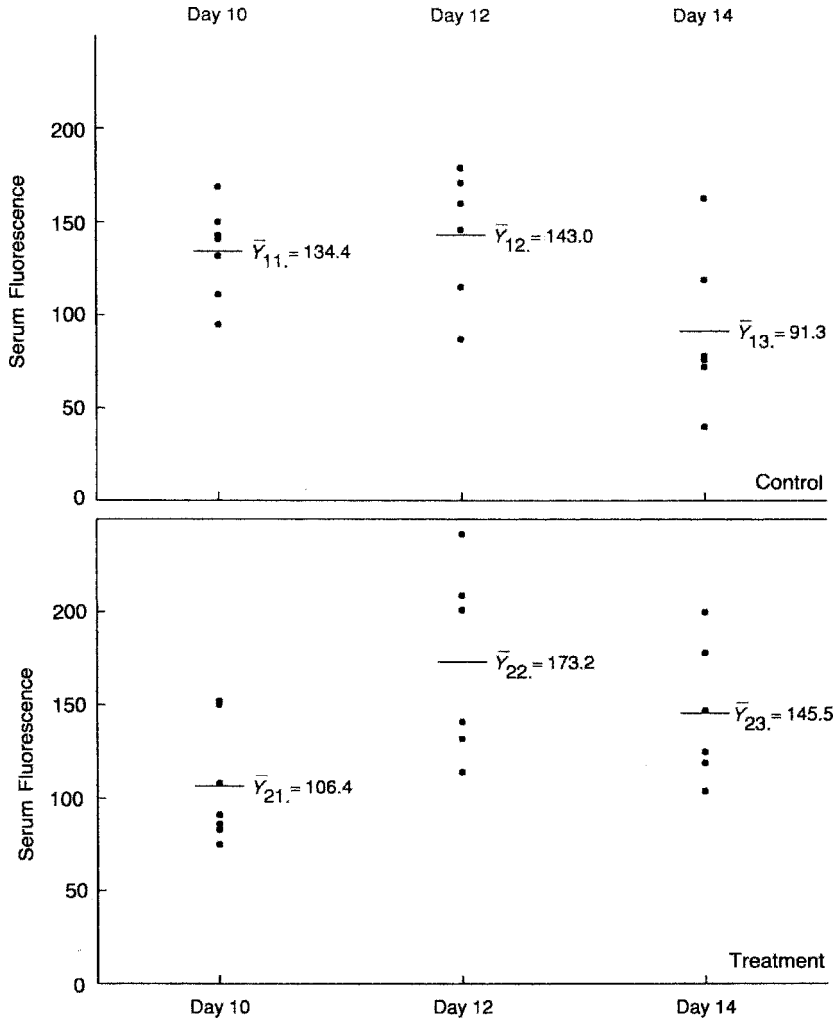


Figure 10.4 Serum fluorescence of mice exposed to nitrogen dioxide. (Data from Sherwin and Layfield [1976]; see Example 10.5.)

Sums of squares can now be calculated:

$$SS_\alpha = SS_{TREATMENT} = 661{,}476.74 - \frac{5004^2}{38} = 2528.95$$

$$SS_\beta = SS_{DAYS} = 671196.74 - \frac{5004^2}{38} = 12{,}248.95$$

$$SS_\gamma = SS_{TREATMENT \times DAYS} = 685{,}472.90 - \frac{5004^2}{38} - 2528.95 - 12{,}248.95 = 11{,}747.21$$

$$SS_\epsilon = SS_{RESIDUAL} = 730{,}828 - 685{,}472.90 = 45{,}355.10$$

(It can be shown that $SS_\epsilon = \sum(n_{ij} - 1)s_{ij}^2$. You can verify this for these data.) The ANOVA table is presented in Table 10.14.

Table 10.14 ANOVA of Serum Fluorescence Levels of Mice Exposed to Nitrogen Dioxide (NO_2)

Source of Variation	d.f.	SS	MS	F-Ratio	p-Value
Treatment	1	2,528.95	2528.95	1.78	> 0.10
Days	2	12,248.95	6124.48	4.32	< 0.05
Treatment × days	2	11,747.21	5873.60	4.14	< 0.05
Residual	32	45,355.10	1417.35	—	—
Total	37	71,880.21	—	—	—

Source: Data from Sherwin and Layfield [1976].

The MS for interaction is significant at the 0.05 level ($F_{2,32} = 4.14,\ p < 0.05$). How is this to be interpreted? The means $\overline{Y}_{ij\cdot}$ are graphed in Figure 10.5. There clearly is nonparallelism, and the model is not an additive one. But more should be said in order to interpret the results, particularly regarding the role of the control animals. Clearly, control animals were used to provide a measurement of background variation. The differences in mean fluorescence levels among the control animals indicate that the baseline response level changed from day 10 to day 14. If we consider the response of the animals exposed to nitrogen dioxide standardized by the control level, a different picture emerges. In Figure 10.5, the differences in means between exposed and unexposed animals is plotted as a dashed line with scale on the right-hand side of the graph. This line indicates that there is an increasing effect of exposure with time. The interpretation of the significant interaction effect then is, possibly, that exposure did induce increased protein leakage, with greater leakage attributable to longer exposure. This contradicts the authors' analysis of the data using t-tests. If the matching by weight was retained, it would

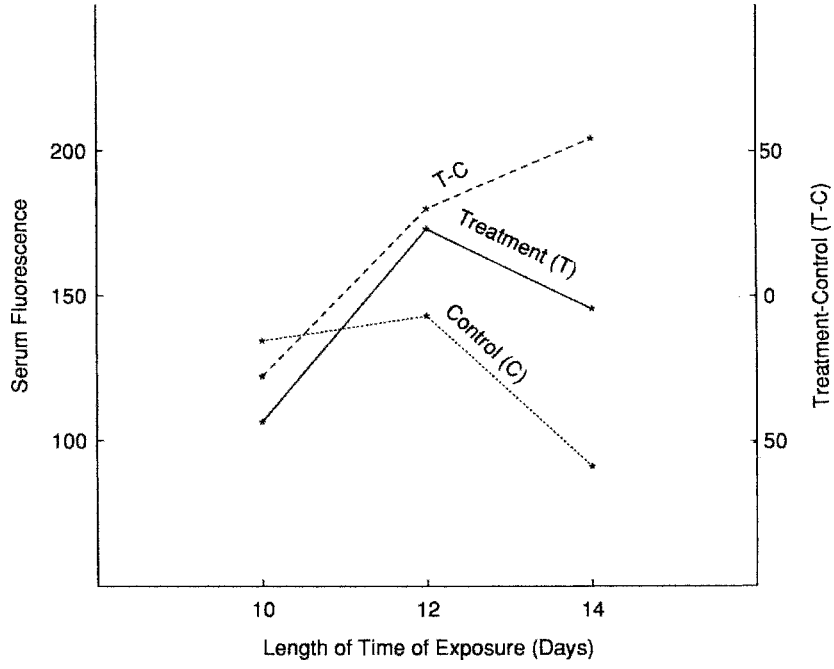


Figure 10.5 Mean serum fluorescence level of mice exposed to nitrogen dioxide, treatment vs. control. The difference (treatment − control) is given by the dashed line. (Data from Sherwin and Layfield [1976]; see Example 10.5.)

have been possible to consider the differences between exposed and control animals and carry out a one-way ANOVA on the differences. See Problem 10.5.

Two-Way ANOVA from Means and Standard Deviations

As in the one-way ANOVA, a two-way ANOVA can be reconstructed from means and standard deviations. Let $\overline{Y}_{ij\cdot}$ be the mean, s_{ij} the standard deviation, and n_{ij} the sample size associated with cell $ij (i = 1, \ldots, I, j = 1, \ldots, J)$, assuming a balanced design. Then

$$Y_{\cdots} = \sum_{i=1}^{I} \sum_{j=1}^{J} n_{ij} \overline{Y}_{ij\cdot}, \qquad Y_{i\cdot\cdot} = \sum_{j=1}^{J} n_{ij} \overline{Y}_{ij\cdot}, \qquad Y_{\cdot j\cdot} = \sum_{i=1}^{I} n_{ij} \overline{Y}_{ij\cdot}$$

Using equation (21), SS_α and SS_β can now be calculated. The term $\sum Y_{ij\cdot}^2/n_{ij}$ in SS_γ is equivalent to

$$\sum \frac{Y_{ij\cdot}^2}{n_{ij}} = \sum n_{ij} \overline{Y}_{ij\cdot}^2$$

Finally, SS_ϵ can be calculated from

$$\mathrm{SS}_\epsilon = \sum (n_{ij} - 1) s_{ij}^2 \tag{22}$$

Problems 10.22 and 10.23 deal with data presented in terms of means and standard deviations. There will be some round-off error in the two-way analysis constructed in this way, but it will not affect the conclusion.

It is easy to write a computer subroutine that produces such a table upon input of means, standard deviations, and sample sizes.

10.3.2 Randomized Block Design

In Chapter 2 we discussed the statistical concept of blocking. A block consists of a subset of homogeneous experimental units. The background variability among blocks is usually much greater than within blocks, and the experimental strategy is to assign all treatments randomly to the units of a block. A simple example of blocking is illustrated by the paired t-test. Suppose that two antiepileptic agents are to be compared. One possible (valid) design is to assign randomly half of a group of patients to one agent and half to the other. By this randomization procedure, the variability among patients is "turned" into error. Appropriate analyses are the two-sample t-test, the one-way analysis of variance, or a two-sample nonparametric test. However, if possible, a better design would be to test both drugs on the same patient; this would eliminate patient-to-patient variability, and comparisons are made within patients. The patients in this case act as *blocks*. A paired t-test or analogous nonparametric test is now appropriate. For this design to work, we would want to assign the drugs randomly within a patient. This would eliminate a possible additive sequence effect; hence, the term *randomized block design*. In addition, we would want to have a reasonably large time interval between drugs to eliminate possible carryover effects; that is, we cannot permit a treatment $\times$ period interaction. Other examples of naturally occurring blocks are animal litters, families, and classrooms. Constructed blocks could be made up of sets of subjects matched on age, race, and gender.

Blocking is done for two purposes:

1. To obtain smaller residual variability
2. To examine treatments under a wide range of conditions

A basic design principle is to partition a population of study units in such a way that background variability between blocks is maximized, and consequently, background variability within blocks is minimized.

Definition 10.8. In a *randomized block design*, each treatment is given once and only once in each block. Within a block, the treatments are assigned randomly to the experimental units.

Note that a randomized block design, by definition, is a balanced design: This is somewhat restrictive. For example, in animal experiments it would require litters to be of the same size.

The statistical model associated with the randomized block design is

$$Y_{ij} = \mu + \beta_i + \tau_j + \epsilon_{ij}, \qquad i = 1, \ldots, I, \quad j = 1, \ldots, J \tag{23}$$

and (**1**) $\sum \beta_i = \sum \tau_j = 0$ and (**2**) ϵ are iid $N(0, \sigma^2)$. In this model, β_i is the effect of block i and τ_j the effect of treatment j. In this model, as indicated, we assume no interaction between blocks and treatments (i.e., if there is a difference between treatments, the magnitude of this effect does not vary from block to block except for random variation). In Section 10.6 we discuss a partial check on the validity of the assumption of no interaction.

The analysis of variance table for this design is a simplified version of Table 10.12: The number of observations is the same in each block and for each treatment. In addition, there is no SS for interaction; another way of looking at this is that the SS for interaction is the error SS. The calculations are laid out in Table 10.15.

Tests of significance proceed in the usual way. The expected mean squares can be derived from Table 10.12, making use of the simpler design.

The computations for the randomized block design are very simple. You can verify that

$$\mathrm{SS}_\mu = \frac{Y_{\cdot\cdot}^2}{n}, \qquad \mathrm{SS}_\beta = \frac{\sum Y_{i\cdot}^2}{J} - \frac{Y_{\cdot\cdot}^2}{n}, \qquad \mathrm{SS}_\tau = \frac{\sum Y_{\cdot j}^2}{I} - \frac{Y_{\cdot\cdot}^2}{n} \tag{24}$$

$$\mathrm{SS}_\epsilon = \sum Y_{ij}^2 - \frac{Y_{\cdot\cdot}^2}{n} - \mathrm{SS}_\beta - \mathrm{SS}_\tau$$

Example 10.6. The pancreas, a large gland, secretes digestive enzymes into the intestine. Lack of this fluid results in bowel absorption problems (steatorrhea); this can be diagnosed by excess fat in feces. Commercial pancreatic enzyme supplements are available in three forms: capsule, tablets, and enteric-coated tablets. The enteric-coated tablets have a protective shell to prevent gastrointestinal reaction. Graham [1977] investigated the effectiveness of these three formulations in six patients with steatorrhea; the three randomly assigned treatments were preceded by a control period. For purposes of this example, we will consider the control period as a treatment, even though it was not randomized. The data are displayed in Table 10.16.

To use equation 4, we will need the quantities

$$Y_{\cdot\cdot} = 618.6, \qquad \frac{\sum Y_{i\cdot}^2}{4} = 21{,}532.80, \qquad \frac{\sum Y_{\cdot j}^2}{6} = 17{,}953.02, \qquad \sum Y_{ij}^2 = 25{,}146.8$$

The analysis of variance table, omitting SS_μ, is displayed in Table 10.17.

The treatment effects are highly significant. A visual inspection of Table 10.16 suggests that capsules and tablets are the most effective, enteric-coated tablets less effective. The author points out that the "normal" amount of fecal fat is less than 6 g per day, suggesting that, at best, the treatments are palliative. The F-test for patients is also highly significant, indicating that the levels among patients varied considerably: Patient 4 had the lowest average level at 6.1 g in 24 hours; patient 5 had the highest level, with 47.1 g in 24 hours.

Table 10.15 Layout for the Randomized Block Design[a]

Source of Variation	d.f.	SS[b]	MS	F-Ratio	d.f. of F-Ratio	E(MS)	Hypothesis Being Tested
Grand mean	1	$\mathrm{SS}_\mu = n\overline{Y}_{\cdot\cdot}^2$	$\mathrm{MS}_\mu = \mathrm{SS}_\mu$	$\frac{\mathrm{MS}_\mu}{\mathrm{MS}_\epsilon}$	$(1, (I-1)(J-1))$	$\sigma^2 + ij\mu^2$	$\mu = 0$
Blocks	$I-1$	$\mathrm{SS}_\beta = J\sum(\overline{Y}_{i\cdot} - \overline{Y}_{\cdot\cdot})^2$	$\mathrm{MS}_\beta = \frac{\mathrm{SS}_\beta}{I-1}$	$\frac{\mathrm{MS}_\beta}{\mathrm{MS}_\epsilon}$	$(I-1, (I-1)(J-1))$	$\sigma^2 + \frac{J\sum\beta_i^2}{I-1}$	$\beta_i = 0$ for all i
Treatments	$J-1$	$\mathrm{SS}_\tau = I\sum(\overline{Y}_{\cdot j} - \overline{Y}_{\cdot\cdot})^2$	$\mathrm{MS}_\tau = \frac{\mathrm{SS}_\tau}{J-1}$	$\frac{\mathrm{MS}_\tau}{\mathrm{MS}_\epsilon}$	$(J-1, (I-1)(J-1))$	$\sigma^2 + \frac{I\sum\tau_j^2}{J-1}$	$\tau_j = 0$ for all j
Residual	$(I-1)(J-1)$	$\mathrm{SS}_\epsilon = \sum(Y_{ij} - \overline{Y}_{i\cdot} - \overline{Y}_{\cdot j} + \overline{Y}_{\cdot\cdot})^2$	$\mathrm{MS}_\epsilon = \frac{\mathrm{SS}_\epsilon}{(I-1)(J-1)}$	—	—	σ^2	
Total	IJ	$\sum Y_{ij}^2$	—				

[a]Model: $Y_{ij} = \mu + \beta_i + \tau_j + \epsilon_{ij}$ [where $\epsilon_{ij} \sim$ iid $N(0, \sigma^2)$].
Data : $Y_{ij} = \overline{Y}_{\cdot\cdot} + (\overline{Y}_{i\cdot} - \overline{Y}_{\cdot\cdot}) + (\overline{Y}_{\cdot j} - \overline{Y}_{\cdot\cdot}) + (\overline{Y}_{ij} - Y_{i\cdot} - \overline{Y}_{\cdot j} + \overline{Y}_{\cdot\cdot})$.
Equivalent model : $Y_{ij} \sim N(\mu_{ij}, \sigma^2)$, where the Y_{ij}'s are independent.
[b]Summation is over all displayed subscripts.

Table 10.16 Effectiveness of Pancreatic Supplements on Fat Absorption in Patients with Steatorrhea (Grams/Day)

Case	None (Control)	Tablet	Capsule	Enteric-Coated Tablet	$Y_{i\cdot}$	$\overline{Y}_{i\cdot}$
1	44.5	7.3	3.4	12.4	67.6	16.9
2	33.0	21.0	23.1	25.4	102.5	25.6
3	19.1	5.0	11.8	22.0	57.9	14.5
4	9.4	4.6	4.6	5.8	24.4	6.1
5	71.3	23.3	25.6	68.2	188.4	47.1
6	51.2	38.0	36.0	52.6	177.8	44.4
$Y_{\cdot j}$	228.5	99.2	104.5	186.4	618.6	—
$\overline{Y}_{\cdot j}$	38.1	16.5	17.4	31.1	$\overline{Y}_{\cdot\cdot} = 25.8$	

Source: Data from Graham [1977].

Table 10.17 Randomized Block Analysis of Fecal Fat Excretion of Patients with Steatorrhea

Source of Variation	d.f.	SS	MS	F-Ratio	p-Value
Patients (blocks)	5	5588.38	1117.68	10.44	<0.001
Treatments	3	2008.60	669.53	6.26	<0.01
Residual	15	1605.40	107.03	—	—
Total	23	9202.38	—	—	—

Source: Data from Graham [1977].

10.3.3 Analyses of Randomized Block Designs Using Ranks

A nonparametric analysis of randomized block data using only the ranks was developed by Friedman [1937]. The model is that of equation (23), but the ϵ_{ij} are no longer required to be normally distributed. We assume that there are no ties in the data; for a small number of ties the average ranks may be used. The idea of the test is simple: If there are no treatment effects ($\tau_j = 0$ for all j), the ranks of the observations within a block are randomly distributed. For block i, let

$$R_{ij} = \text{rank of } Y_{ij} \text{ among } Y_{i1}, Y_{i2}, \ldots, Y_{iJ}$$

The Friedman statistic for testing the null hypothesis $H_0 : \tau_j = 0$ (where $j = 1, \ldots, J$) is

$$T_{\text{FR}} = 12I \sum_{j=1}^{J} \frac{(\overline{R}_{\cdot j} - \overline{R}_{\cdot\cdot})^2}{J(J+1)} \tag{25}$$

Computationally, the following formula is easier:

$$T_{\text{FR}} = \frac{12}{IJ(J+1)} \sum_{j=1}^{J} R_{\cdot j}^2 - 3(I)(J+1) \tag{26}$$

The null hypothesis is rejected for large values of T_{FR}. For small randomized block designs, the critical values of T_{FR} are tabulated; see, for example, Table 39 in Odeh et al. [1977], which goes up to $I = J = 6$. As the number of blocks becomes very large, the distribution of T_{FR}

approaches that of a χ^2-distribution with $(J-1)$ degrees of freedom. See also Notes 10.1 and 10.2.

Example 10.6. (*continued*) Replacing the observations for each *individual* by their ranks produces Table 10.18. For individual 4, the two tied observations are replaced by the average of the two ranks. [As a check, the total $R..$ of ranks must be $R.. = IJ(J+1)/2$. (Why?) For this example $I = 6$, $J = 4$, $IJ(J+1)/2 = (6 \cdot 4 \cdot 5)/2 = 60$, and $R.. = 22 + 8.5 + 9.5 + 20 = 60$.] The Friedman statistic, using equation (26), has the value

$$T_{\text{FR}} = \frac{12}{6 \times 4 \times 5}(22^2 + 8.5^2 + 9.5^2 + 20^2) - (3 \times 6 \times 5)$$
$$= 104.65 - 90 = 14.65$$

This quantity is compared to a χ^2 distribution with 3 d.f. $(14.65/3 = 4.88)$; the p-value is $p = 0.0021$. From exact tables such as Odeh et al. [1977], the exact p-value is $p < 0.001$. The conclusion is the same as that of the analysis of variance in Section 10.3.2. Note also that the ranking of treatments in terms of the total ranks is the same as in Table 10.11. For an alternative rank analysis of these data, see Problem 10.20.

10.3.4 Types of ANOVA Models

In Section 10.2.2, two examples were mentioned of one-way analyses of variance. The first dealt with the age at which children begin to walk as a function of various training procedures; the second example dealt with patient hospitalization costs, based on an examination of some hospitals (treatments) selected randomly from all the hospitals in a large metropolitan area (from each hospital selected, a specified number of patient records are selected for cost analysis). The experimental design associated with the first example differs from the second: In a repetition of the first study, the same set of treatments could be used; in the second study, a new set of hospitals could presumably be selected; that is, the "treatment levels" are randomly selected from a larger set of treatment levels.

Definition 10.9. If the levels of a classification variable in an ANOVA situation are selected at random from a population, the variable is said to be a *random factor* or *random effect*. Factors with the levels fixed by those conducting the study or which are fixed classifications (e.g., gender) are called *fixed factors* or *fixed effects*.

Table 10.18 Rank Values for Supplement Use

	Treatment			
Case	Control	Tablet	Capsule	Enteric-Coated Tablet
1	4	2	1	3
2	4	1	2	3
3	3	1	2	4
4	4	1.5	1.5	3
5	4	1	2	3
6	3	2	1	4
$R._j$	22	8.5	9.5	20

Definition 10.10. ANOVA situations with all classification variables fixed are called *fixed effects models* (model I). If all the classification variables are random effects, the design is a *random effects model* (model II). If both random and fixed effects are present, the design is a *mixed effects model*.

Historically, no distinction was made between model I and II designs, in part due to identical analyses in simple situations and similar analyses in more complicated situations. Eisenhart [1947] was the first to describe systematically the differences between the two models. Some other examples of random effects models are:

1. A manufacturer of spectrophotometers randomly selects five instruments from its production line and obtains a series of replicated readings on each machine.
2. To estimate the maximal exercise performance in a healthy adult population, 20 subjects are selected randomly and 10 independent estimates of maximal exercise performance for each person are obtained.
3. To determine knowledge about the effect of drugs among sixth graders, a researcher randomly selects five sixth-grade classes from among the 100 sixth-grade classes in a large school district. Each child selected fills out a questionnaire.

How can we determine whether a design is model I or model II? The basic criterion deals with the population to which inferences are to be made. Another way of looking at this is to consider the number of times randomness is introduced (ideally). In Example 10.2 there are two sources of randomness: subjects and observations within subjects. If more than one "layer of randomness" has to be passed through in order to reach the population of interest, we have a random effects model.

An example of a mixed model is example 2 above with a further partitioning of subjects into male and female. The factor, gender, is fixed.

Sometimes a set of data can be modeled by either a fixed or random effects model. Consider example 1 again. Suppose that a cancer research center has bought the five instruments and is now running standardization experiments. For the purpose of the research center, the effects of machines are fixed effects.

To distinguish a random effects model from a fixed effects model, the components of the model are written as random variables. The two-way random effects ANOVA model with interaction is written as

$$Y_{ijk} = \mu + A_i + B_j + G_{ij} + e_{ijk}, \qquad i = 1, \ldots, I, \quad j = 1, \ldots, J, \quad k = 1, \ldots, n_{ij} \quad (27)$$

The assumptions are:

1. e_{ijk} are iid $N(0, \sigma^2)$, as before.
2. A_i are iid $N(0, \sigma_\alpha^2)$.
3. B_j are iid $N(0, \sigma_\beta^2)$.
4. G_{ij} are iid $N(0, \sigma_\gamma^2)$.

The total variance can now be partitioned into several components (hence another term for these models: *components of variance models*). Assume that the experiment is balanced with $n_{ij} = m$ for all i and j. The difference between the fixed effect and random effect model is in the expected mean squares. Table 10.19 compares the EMS for both models, taking the EMS for the fixed effect model from Table 10.12.

The test for interaction is the same in both models. However, if interaction is present, to be valid the test for main effects in the random effects model must use MS_γ in the denominator rather than MS_ϵ.

Table 10.19 Comparison of Expected Mean Squares in the Two-Way ANOVA, Fixed Effect vs. Random Effect Models[a]

Source of Variation	d.f.	EMS	
		Fixed Effect	Random Effect
Row main effects	$I-1$	$\sigma^2+\dfrac{Jm\sum\alpha_i^2}{I-1}$	$\sigma^2+m\sigma_\gamma^2+mJ\sigma_\alpha^2$
Column main effects	$J-1$	$\sigma^2+\dfrac{Im\sum\beta_j^2}{J-1}$	$\sigma+m\sigma_\gamma^2+mI\sigma_\beta^2$
Row × column interaction	$(I-1)(J-1)$	$\sigma^2+\dfrac{IJm\sum\gamma_{ij}^2}{(I-1)(J-1)}$	$\sigma^2+m\sigma_\gamma^2$
Residual	$n..-IJ$	σ^2	σ^2

[a] There are m observations in each cell.

The null hypothesis

$$H_0:\gamma_{ij}=0 \qquad \text{all } i \text{ and } j$$

in the fixed effect model has as its counterpart,

$$H_0:\sigma_\gamma^2=0$$

in the random effect model. In both cases the test is carried out using the ratio $\mathrm{MS}_\gamma/\mathrm{MS}_\epsilon$ with $(I-1)(J-1)$ and $n-IJ$ degrees of freedom. If interaction is not present, the tests for main effects are the same in both models. However, if H_0 is not rejected, the tests for main effects are different in the two models. In the random effects model the expected mean square for main effects now contains a term involving σ_γ^2. Hence the appropriate F-test involves MS_γ in the denominator rather than MS_ϵ; the degrees of freedom are changed accordingly.

Several comments can be made:

1. Frequently, the degrees of freedom associated with MS_γ are fewer than those of MS_ϵ, so that there is a loss of precision if MS_γ has to be used to test main effects.

2. From a design point of view, if m, I, and J can be chosen, it may pay to choose m small and I, J relatively large if a random effects model is appropriate. A minimum of two replicates per treatment combination is needed to obtain an estimate of σ^2. If possible, the rest of the observations should be allocated to the levels of the variables. This may not always be possible, due to costs or other considerations. If the total cost of the experiment is fixed, an algorithm can be developed for choosing the values of m, I, and J.

3. The difference between the fixed and random effects models for the two-way ANOVA designs is not as crucial as it seems. We have indicated caution in proceeding to the tests of main effects if interaction is present in the fixed model (see Figure 10.3 and associated discussion). In the random effects model, the same precaution holds. It is perhaps too strong to say that main effects should not be tested when interaction is present, but you should certainly be able to explain what information you hope to obtain from such tests after a full interpretation of the (significant) interaction.

4. Expected mean squares for an unbalanced random effects model are not derivable or are very complicated. A more useful approach is that of multiple regression, discussed in Chapter 11. See also Section 10.5.

5. For the randomized block design the MS_ϵ can be considered the mean square for interaction. Hence, in this case the F-tests are appropriate for both models. (Does this contradict the

statement made in comment 3?) Note also that there is little interest in the test of block effects, except as a verification that the blocking was effective.

Good discussions about inference in the case of random effects models can be found in Snedecor and Cochran [1988] and Winer [1991].

10.4 REPEATED MEASURES DESIGNS AND OTHER DESIGNS

10.4.1 Repeated Measures Designs

Consider a situation in which blood pressures of two populations are to be compared. One person is selected at random from each population. The blood pressure of each of the two subjects is measured 100 times. How would you react to data analysis that used the two-sample t-test with two samples of size 100 and showed that the blood pressures differed in the two populations? The idea is ridiculous, but in one form or another appears frequently in the research literature. Where does the fallacy lie? There are two sources of variability: within individuals and among individuals. The variability within individuals is assumed incorrectly to represent the variability among individuals. Another way of saying this is that the 100 readings are not independent samples from the population of interest. They are repeated measurements on the same experimental unit. The repeated measures may be useful in this context in pinning down more accurately the blood pressure of the two people, but they do not make up for the small sample size. Another feature we want to consider is that the sequence of observations within the person cannot be randomized, for example, a sequence of measurements of growth. Thus, typically, we do not have a randomized block design.

Definition 10.11. In a *repeated measures design*, multiple (two or more) measurements are made sequentially on the same observational unit.

A repeated measures design usually is an example of a mixed model with the observational unit a random effect (e.g., persons or animals, and the treatments on the observational units fixed effects). Frequently, data from repeated measure designs are somewhat unbalanced and this makes the analysis more difficult. One approach is to summarize the repeated measures in some meaningful way by single measures and then analyze the single measures in the usual way. This is the way many computer programs analyze such data. We motivate this approach by an example. See Chapter 18 for further discussion.

Example 10.7. Hillel and Patten [1990] were interested in the effect of accessory nerve injury as result of neck surgery in cancer. The surgery frequently decreases the strength of the arm on the affected side. To assess the potential recovery, the unaffected arm was to be used as a control. But there is a question of the comparability of arms due to dominance, age, gender, and other factors. To assess this effect, 33 normal volunteers were examined by several measurements. The one discussed here is that of torque, or the ability to abduct (move or pull) the shoulder using a standard machine built for that purpose. The subjects were tested under three consecutive conditions (in order of increasing strenuousness): 90°, 60°, and 30° per second. The data presented in Table 10.20 are the best of three trials under each condition. For completeness, the age and height of each of the subjects are also presented. The researchers wanted answers to at least five questions, all dealing with differences between dominant and nondominant sides:

1. Is there a difference between the dominant and nondominant arms?
2. Does the difference vary between men and women?

Table 10.20 Peak Torque for 33 Subjects by Gender, Dominant Arm, and Age Group under Three Conditions

					90°		60°		30°	
Subject		Age	Height (in.)	Weight (lb)	DM[a]	ND[a]	DM	ND	DM	ND
Female	1	20	64	107	17	13	20	17	23	22
	2	23	68	140	25	25	28	29	31	31
	3	23	67	135	27	28	30	31	32	33
	4	23	67	155	23	28	27	29	27	32
	5	25	65	115	15	11	15	13	17	17
	6	26	68	147	27	17	25	21	32	27
	7	31	62	147	25	17	25	21	29	24
	8	31	66	137	19	15	17	17	21	19
	9	33	66	160	28	26	31	27	31	31
	10	36	66	118	23	23	26	27	27	25
	11	56	67	210	23	31	37	44	49	53
	12	59	67	130	15	17	17	19	20	20
	13	60	63	132	17	15	19	21	24	28
	14	60	64	180	15	15	17	19	19	21
	15	67	62	135	13	5	15	8	15	14
	16	73	62	124	11	9	13	13	19	17
Male	1	26	69	140	43	43	44	43	49	41
	2	28	71	175	45	43	48	45	53	52
	3	28	70	125	25	29	29	37	39	41
	4	28	70	175	39	41	49	47	55	44
	5	29	72	150	38	33	40	33	44	37
	6	30	68	145	53	41	51	40	59	44
	7	31	74	240	60	49	71	54	68	53
	8	32	67	168	32	31	37	31	39	30
	9	40	69	174	47	37	43	47	49	53
	10	41	72	190	33	25	29	25	39	27
	11	41	68	184	39	24	43	25	39	33
	12	56	70	200	21	11	23	12	33	24
	13	58	72	168	41	35	45	37	49	39
	14	59	73	170	31	32	31	31	35	38
	15	60	73	225	39	41	47	45	55	49
	16	68	67	140	31	23	33	27	37	33
	17	72	69	125	13	17	17	19	17	25

Source: Data from Hillel and Patten [1990].

[a]DM, dominant arm; ND, nondominant arm.

3. Does the difference depend on age, height, or weight?

4. Does the difference depend on treatment condition?

5. Is there interaction between any of the factors or variables mentioned in questions 1 to 4?

For purposes of this example, we only address questions 1, 2, 4, and 5, leaving question 3 for the discussion of analysis of covariance in Chapter 11.

The second to fourth columns in Table 10.21 contain the differences between the dominant and nondominant arms; the fifth to seventh columns are reexpressions of the three differences as follows. Let d90, d60, and d30 be the differences between the dominant and nondominant

Table 10.21 Differences in Torque under Three Conditions and Associated Orthogonal Contrasts[a]

		DM–ND			Orthogonal Contrasts		
		90°	60°	30°	Constant	Linear	Quadratic
Female	1	4	3	1	4.6	2.1	−0.4
	2	0	−1	0	−0.6	0.0	0.8
	3	−1	−1	−1	−1.7	0.0	0.0
	4	−5	−2	−5	−6.9	0.0	−2.4
	5	4	2	0	3.5	2.8	0.0
	6	10	4	5	11.0	3.5	2.9
	7	8	4	5	9.8	2.1	2.0
	8	4	0	2	3.5	1.4	2.4
	9	2	4	0	3.5	1.4	−2.4
	10	0	−1	2	0.6	−1.4	1.6
	11	−8	−7	−4	−11.0	−2.8	0.8
	12	−2	−2	0	−2.3	−1.4	0.8
	13	2	−2	−4	−2.3	4.2	0.8
	14	0	−2	−2	−2.3	1.4	0.8
	15	8	7	1	9.2	4.9	−2.0
	16	2	0	2	2.3	0.0	1.6
Male	1	0	1	8	5.2	−5.7	2.4
	2	2	3	1	3.5	0.7	−1.2
	3	−4	−8	−2	−8.1	−1.4	4.1
	4	−2	2	11	6.4	−9.2	2.0
	5	5	7	7	11.0	−1.4	−0.8
	6	12	11	15	21.9	−2.1	2.0
	7	11	17	15	24.8	−2.8	−3.3
	8	1	6	9	9.2	−5.7	−0.8
	9	10	−4	−4	1.2	9.9	5.7
	10	8	4	12	13.9	−2.8	4.9
	11	15	18	6	22.5	6.4	−6.1
	12	10	11	9	17.3	0.7	−1.2
	13	6	8	10	13.9	−2.8	0.0
	14	−1	0	−3	−2.3	1.4	−1.6
	15	−2	2	6	3.5	−5.7	0.0
	16	8	6	4	10.4	2.8	0.0
	17	−4	−2	−8	−8.1	2.8	−3.3

Source: Data from Hillel and Patten [1990].

[a] See Table 10.20 for notation.

arms under each of the three conditions. Then we define

$$\text{constant} = \frac{\text{d90} + \text{d60} + \text{d30}}{\sqrt{3}}$$

$$\text{linear} = \frac{\text{d90} - \text{d30}}{\sqrt{2}}$$

$$\text{quadratic} = \frac{\text{d90} - 2 \cdot \text{d60} + \text{d30}}{\sqrt{6}}$$

For example, for the first female subject, rounding off to one decimal place yields

$$\frac{4 + 3 + 1}{\sqrt{3}} = 4.6$$

$$\frac{4-1}{\sqrt{2}} = 9.9$$

$$\frac{4-2\times(3)+1}{\sqrt{6}} = -0.4$$

The first component clearly represents an average difference of dominance over the three conditions. The divisor is chosen to make the variance of this term equal to the variance of a single difference. The second term represents a slope within an individual. If the three conditions were considered as values of a predictor variable with values -1 (for 30°), 0 (for 60°), and 1 (for 90°), the slope would be expressed as in the second, or linear, term. The linear term assesses a possible trend in the differences over the three conditions within an individual. The last term, the quadratic term, fits a quadratic curve through the data assessing possible curvature or nonlinearity within an individual. This partitioning of the observations within an individual has the property that sums of squares are maintained. For example, for the first female subject,

$$4^2 + 3^2 + 1^2 = 26 = (4.6)^2 + (2.1)^2 + (-0.4)^2$$

except for rounding. (If you were to calculate these terms to more decimal places, you would find that the right side is identical to the left side.) In words, the variability in response within an individual has been partitioned into a constant component, a linear component, and a quadratic component. The questions posed can now be answered unambiguously since the three components have been constructed to be *orthogonal*, or uncorrelated. An analysis of variance is carried out on the three terms; unlike the usual analysis of variance, a term for the mean is included; results are summarized in Table 10.22. We start by discussing the analysis of the quadratic component. The analysis indicates that there are no significant differences between males and females in terms of the quadratic or nonlinear component. Nor is there an overall effect. Next, conclusions are similar for the linear effect. We conclude that there is no linear trend for abductions at 90°, 60°, and 30°. This leaves the constant term, which indicates (1)

Table 10.22 ANOVA and Means of the Data in Table 10.21

Source of Variation		d.f.	SS	MS	F-Ratio
		Analysis of Variance			
Constant	Mean	1	900.7	900.7	13.3
	Gender	1	438.5	438.5	6.48
	Error 1	31	2099.2	67.72	
Linear	Mean	1	0.33	0.33	0.02
	Gender	1	33.43	33.43	2.43
	Error 2	31	426.0	13.74	
Quadratic	Mean	1	3.09	3.09	0.50
	Gender	1	0.70	0.70	0.11
	Error 3	31	191.2	6.17	

Means

		Constant	Linear	Quadratic
Female ($n = 16$)	Mean	1.306	1.138	0.456
	Standard deviation	5.920	2.121	1.609
Male ($n = 17$)	Mean	8.600	−0.876	0.165
	Standard deviation	9.917	4.734	3.085

that there is a significant gender effect of dominance ($F_{1,31} = 6.48$, $p < 0.05$) and an overall dominance effect. The average of the constant term for females is 1.31, for males is 8.6. One question that can be raised is whether the difference between female and male is a true gender difference or can be attributed to differences is size. An analysis of covariance can answer this question (see Problem 11.38).

Data from a repeated measures design often look like those of a randomized block design. The major difference is the way the data are generated. In the randomized block, the treatments are allocated randomly to a block. In the repeated measures design, this is not the case; not being possible, as in the case of observations over time, or because of experimental constraints, as in the example above. If the data are analyzed as a randomized block, care must be taken that the assumptions of the randomized block design are satisfied. The key assumption is that of *compound symmetry*: The sample correlations among treatments over subjects must all estimate the same population correlation. The randomization ensures this in the randomized block design. For example, for the data in Table 10.16, the correlations are as follows:

	Control	**Tablet**	**Capsule**
Tablet	0.658		
Capsule	0.599	0.960	
Coated tablet	0.852	0.784	0.833

These correlations are reasonably comparable. If the correlations are not assumed equal, a conservative F-test can be carried out by referring the observed value of F for treatments to an F-table with 1 and $(I - 1)$ [rather than $(J - 1)$ and $(I - 1)(J - 1)$] degrees of freedom). Alternatives to the foregoing two approaches include multivariate analyses. There is a huge literature on repeated measures analysis. The psychometric literature contains many papers on this topic. To explore this area, consult recent issues of journals such as *American Statistician*. One example is a paper by Looney and Stanley [1989]. See also Chapter 18.

10.4.2 Factorial Designs

An experimental layout that is very common in agricultural and nutritional studies is the balanced factorial design. It is less common in medical research, due to the ever-present risk of missing observations and ethical constraints.

Definition 10.12. In a *factorial design* each level of a factor occurs with every level of every other factor. Experimental units are assigned randomly to treatment combinations.

Suppose that there are three factors with levels $I = 3$, $J = 2$, and $K = 4$. Then there are $3 \times 2 \times 4 = 24$ treatment combinations. If there are three observations per combination, 72 experimental units are needed. Factorial designs, if feasible, are very economical and permit assessment of joint effects of treatments that are not possible with experiments dealing with one treatment at a time. The two-way analysis of variance can be thought of as dealing with a two-factor experiment. The generalization to three or more factors does not require new concepts or strategies, just increased computational complexity.

10.4.3 Hierarchical or Nested Designs

A hierarchical or nested design is illustrated by the following example. As part of a program to standardize measurement of the blood level of phenytoin, an antiepileptic drug, samples with known amounts of active ingredients are sent to four commercial laboratories for analysis. Each

laboratory employs a number of technicians who make one or more determinations of the blood level. A possible layout is the following:

Laboratory	1	2	3	4
Technician	1 2	3 4 5	6 7	8 9
Assay	⋀⋀	⋀⋀⋀	⋀⋀	⋀⋀

In this example, laboratory 2 employs three technicians who routinely do this assay; all other laboratories use two technicians. In laboratory 3, each technician runs three assays; in the other laboratories each technician runs two assays. There are three factors: laboratories, technicians, and assays; the arrangement is *not* factorial: there is no reason to match technician 1 with any technician from another laboratory.

Definition 10.13. In a *hierarchical or nested design* levels of one or more factors are subsampled within one or more other factors. In other words, the levels of one or more factors are not crossed with one or more other factors.

In the example above, the factors, "technicians" and "assay," are not "crossed" with the first factor but rather nested within that factor. For the factor "technician" to be "crossed," its levels would have to repeat within each level of "laboratory." That is why we deliberately labeled the levels of "technician" consecutively and introduced some imbalance. Determining whether a design is factorial or hierarchical is not always easy. If the first of the two technicians within a laboratory was the senior technician and the second (or second and third) a junior technician, then "technician" could perhaps be thought of as having two levels, "senior" and "junior," which could then be crossed with "laboratory." A second reason is that designs are sometimes mixed, having both factorial and hierarchical components. In the example above, if "technician" occurred at two levels, "technician" and "laboratory" could be crossed or factorial, but "assay" would continue to be nested within "technician."

10.4.4 Split-Plot Designs

A related experimental design is the split-plot design. We illustrate it with an example. We want to test the effect of physiotherapy in conjunction with drug therapy on the mobility of patients with arthritis. Patients are randomly assigned to physiotherapy, and each patient is given a standard drug and a placebo in random order. The experimental layout is as follows:

		Physiotherapy			
		$i = 1$ **(Yes)**		$i = 2$ **(No)**	
k	**Patient**	**1**	**2 ⋯ J**	**1**	**2 ⋯ J**
1	Drug	Y_{111}	— ⋯ —	Y_{211}	— ⋯ —
2	Placebo	Y_{112}	— ⋯ —	Y_{212}	— ⋯ —

The patients form the "whole plots" and the drug administration, the "split plot." These designs are characterized by almost separate analyses of specified effects. To illustrate in this example, let

$$D_{ij} = Y_{ij1} - Y_{ij2} \quad \text{and} \quad T_{ij} = Y_{ij1} + Y_{ij2}, \qquad i = 1, 2, \quad j = 1, \ldots, J$$

In words, D_{ij} is the difference between drug and placebo for patient j receiving physiotherapy level i; T_{ij} is the sum of readings for drug and placebo. Now carry out an analysis of variance (or two-sample t-test) on each of these variables; see Table 10.23.

Table 10.23 ANOVA Table for Split-Plot Design

		Interpretation of Split-Plot Analyses	
One-Way ANOVA	d.f.	Differences	Sums
Mean	1	Mean differences	Mean sums
Between groups	1	Differences × physiotherapy	Sums × physiotherapy
Within groups	$2(J-1)$	Differences within physiotherapy	Sums within physiotherapy
Total	$2J$	"Total"	"Total"

An analysis of variance of the sums is, in effect, an assessment of physiotherapy (averaged or summed over drug and placebo), that is, a comparison of $\overline{T}_{1\cdot}$ and $\overline{T}_{2\cdot}$.

The analysis of differences is very interesting. The assessment of the significance of "between groups" is a comparison of the average differences between drug and placebo with physiotherapy and without physiotherapy; that is, $\overline{D}_{1\cdot} - \overline{D}_{2\cdot}$ is a test for interaction. Additionally, the "mean differences" term can be used to test the hypothesis that $\overline{D}_{\cdot\cdot}$ comes from a population with mean zero, that is, it is a comparison of drug and placebo. This test makes sense only if the null hypothesis of no interaction is not rejected.

These remarks are intended to give you an appreciation for these designs. For more details, consult a text on design of experiments, such as Winer [1971].

10.5 UNBALANCED OR NONORTHOGONAL DESIGNS

In previous sections we have discussed balanced designs. The balanced design is necessary to obtain an additive partition of the sum of squares. If the design is not balanced, there are basically three strategies available; the first is to try to restore balance. If only one or two observations are "missing," this is a possible strategy, but if more than two or three are missing, a second or third alternative will have to be used. The second alternative is to use an unweighted means analysis. The third strategy is to use a multiple regression approach; this is discussed in detail in Section 11.10.

10.5.1 Causes of Imbalance

Perhaps the most important thing you can do in the case of unbalanced data is to reflect on the reason(s) for the imbalance. If the imbalance is due to some random mechanism unrelated to the factors under study, the procedures discussed below are appropriate. If the imbalance is due to a specific reason, perhaps related to the treatment, it will be profitable to think very carefully about the implications. Usually, such imbalance suggests a bias in the treatment effects. For example, if a drug has major side effects which cause patients to drop out of a study, the effect of the drug may be estimated inappropriately if only the remaining patients are used in the analysis; if one does the analysis only on patients for whom "all data are available," biased estimates may result.

10.5.2 Restoring Balance

Missing Data in the Randomized Block Design

Suppose that the ijth observation is missing in a randomized block design consisting of I blocks and J treatments. The usual procedure is to:

1. Estimate the missing data point by least squares using the formula

$$\widehat{Y}_{ij} = \frac{IY_{i\cdot} + JY_{\cdot j} - Y_{\cdot\cdot}}{(I-1)(J-1)} \tag{28}$$

where the row, column, and grand totals are those for the values present.

2. Carry out the usual analysis of variance on this augmented data set.

3. Reduce the degrees of freedom for MS_ϵ by 1.

If more than one observation is missing, say two or three, values are guessed for all but one, the latter is estimated by equation (28), a second missing value is deleted, and the process is repeated until convergence. The degrees of freedom for MS_ϵ are now reduced by the number of observations that are missing.

Example 10.6. (*continued*) We return to Table 10.11. Suppose that observation $Y_{31} = 19.1$ is missing and we want to estimate it. For this example, $I = 6$, $J = 4$, $Y_{3\cdot} = 38.8$, $Y_{\cdot 1} = 209.4$, and $Y_{\cdot\cdot} = 599.5$. We estimate Y_{31} by

$$\widehat{Y}_{31} = \frac{6(38.8) + 4(209.4) - 599.5}{(6-1)(4-1)} = 31.4$$

This value appears to be drastically different from 19.1; it is. It also indicates that there is no substitute for real data. The analysis of variance is not altered a great deal (see Table 10.24).

The F-ratios have not changed much from those in Table 10.12. So in this case, the conclusions are unchanged. Note that the degrees of freedom for residual are reduced by 1. This means that the critical values of the F-statistics are increased slightly. Therefore, this experiment has less power than the one without missing data.

Missing Data in Two-Way and Factorial Designs

If a cell in a two-way design has a missing observation, it is possible to replace the missing point by the mean for that cell, carry out the analysis as before, and subtract one degree of freedom for MS_ϵ. A second approach is to carry out an unweighted means analysis. We illustrate both procedures by means of an example.

Example 10.8. These data are part of data used in Wallace et al. [1977]. The observations are from a patient with prostatic carcinoma. The question of interest is whether the immune system of such a patient differs from that of noncarcinoma subjects. One way of assessing this is to stimulate in vitro the patient's lymphocytes with phytohemagglutinin (PHA). This causes blastic transformation. Of interest is the amount of blastogenic generation as measured by DNA incorporation of a radioactive compound. The data observed are the mean radioactive counts per minute both when stimulated with PHA and when not stimulated by PHA. As a control, the amount of PHA stimulation in a pooled sera of normal blood donors was used. To examine the response of a subject's lymphocytes, the quantity

$$\frac{\dfrac{\text{subject's mean count/minute stimulated with PHA}}{\text{subject's mean count/minute without PHA}}}{\dfrac{\text{normal sera mean count/minute stimulated with PHA}}{\text{normal sera mean count/minute without PHA}}} = \frac{X_{11}/X_{12}}{X_{21}/X_{22}} \tag{29}$$

Table 10.24 ANOVA for Example 10.6

Source of Variable	d.f.	SS	MS	F-Ratio
Patients (blocks)	5	5341.93	1068.39	9.90
Treatments	3	2330.30	776.77	7.20
Residual	14	1510.94	107.92	—
Total	22	9183.17	—	—

Table 10.25 DNA Incorporation of Sera of Patient with Prostatic Carcinoma Compared to Sera from Normal Blood Donors[a]

	Radioactivity (counts/min)	
Subject	With PHA	Without PHA
Patient sera	129,594 (11.772)	301 (5.707)
	143,687 (11.875)	333 (5.808)
	115,953 (11.661)	295 (5.687)
	103,098 (11.543)	285 (5.652)
	98,125 (11.494)	
Blood donor sera	43,125 (10.672)	247 (5.509)
	46,324 (10.743)	298 (5.697)
	42,117 (10.648)	387 (5.958)
	45,482 (10.725)	
	31,192 (10.348)	

[a] $\log_e$ of counts in parentheses.

was used. If the lymphocytes responded in the same way to the subject's sera and the pooled sera, the ratio should be approximately equal to 1. The data are displayed in Table 10.25.

There is a great deal of variability in the counts/minute values as related to level. In Section 10.6.3 we suggest that logarithms are appropriate for stabilization of the variability. There is a bonus involved in this case. Under the null hypothesis of no difference in patient and blood donor sera, the ratio in equation (28) is 1; that is,

$$H_0 : \frac{E(X_{11})/E(X_{12})}{E(X_{21})/E(X_{22})} = 1$$

This is equivalent to

$$H_0 : \log_e \frac{E(X_{11})/E(X_{12})}{E(X_{21})/E(X_{22})} = \log_e 1 = 0$$

or

$$\log_e E(X_{11}) - \log_e E(X_{12}) - \log_e E(X_{21}) + \log_e E(X_{22}) = 0 \tag{30}$$

Now define

$$Y_{ijk} = \log_e X_{ijk}, \qquad i = 1, 2, \quad j = 1, 2, \quad k = 1, \ldots, n_{ij}$$

It can be shown that equation (30) is zero only if the true interaction term is zero. Thus, the hypothesis that the patient's immune system does not differ from that of noncarcinoma subjects is translated into a null hypothesis about interaction involving the logarithms of the radioactive counts.

We finally get to the "missing data" problem. The data are not balanced: $n_{ij} \neq n_{i\cdot} n_{\cdot j}/n_{\cdot\cdot}$ [we could delete one observation from the (1,2) cell, but considering the small numbers, we want to retain as much information as possible]. One strategy is to add an observation to cell (2,2) equal to the mean for that cell and adjust the degrees of freedom for interaction. The mean $\overline{Y}_{22\cdot}$ is 5.721. The analysis of variance becomes as shown in Table 10.26.

Note that the MS for error has 13 degrees of freedom, not 14. The MS for error will be the correct estimate using this procedure, but the MS for interaction (and main effects) will not be the same as the one obtained by techniques of Chapter 11. However, it should be close.

Table 10.26 ANOVA for the Missing Data Problem

Source	d.f.	SS	MS	F-Ratio	p-Value
Subject	1	1.4893	1.4893	—	—
PHA	1	131.0722	131.0722	—	—
PHA × subject	1	1.2247	1.2247	50.0	<0.001
Error	13	0.3184	0.02449	—	—
Total	16	—	—	—	—

10.5.3 Unweighted Means Analysis

The second approach is that of unweighted mean analysis. Again, assuming that the unequal cell frequencies are not due to treatment effects, the cell means are used and an average sample size calculated for each cell. The appropriate average sample size is given by the harmonic mean. In the context of our example, the harmonic mean is defined to be

$$\widetilde{n} = \frac{IJ}{1/n_{11} + 1/n_{12} + 1/n_{21} + 1/n_{22}}$$

where n_{ij} is the number of observations in cell (i, j). The harmonic mean is used because the standard error of the mean of cell (i, j) is proportional to $1/n_{ij}$. All calculations for row and column effects are now based on cell means and the harmonic mean of the cell sample sizes. Write the cell means and marginal means as follows:

$$\begin{array}{cc|c} \overline{Y}_{11\cdot} & \overline{Y}_{12\cdot} & \widehat{M}_{1\cdot} \\ \overline{Y}_{21\cdot} & \overline{Y}_{22\cdot} & \widehat{M}_{2\cdot} \\ \hline \widehat{M}_{\cdot 1} & \widehat{M}_{\cdot 2} & \widehat{M}_{\cdot\cdot} \end{array}$$

The marginal and overall means are just the arithmetic average of the cell means, that is, the unweighted average (hence the name *unweighted mean analysis*). The row and column sums of squares are calculated as follows:

$$\mathrm{SS}_\alpha = \widetilde{n} J \sum (\overline{M}_{i\cdot} - \overline{M}_{\cdot\cdot})^2$$

$$\mathrm{SS}_\beta = \widetilde{n} I \sum (\overline{M}_{\cdot j} - \overline{M}_{\cdot\cdot})^2$$

$$\mathrm{SS}_\gamma = \widetilde{n} \sum (\overline{Y}_{ij\cdot} - \overline{M}_{i\cdot} - \overline{M}_{\cdot j} + \overline{M}_{\cdot\cdot})^2$$

SS_ϵ is calculated in the usual way: $\mathrm{SS}_\epsilon = \sum (Y_{ijk} - \overline{Y}_{ij\cdot})^2$. For the example, the calculations are

Means

11.669000	5.713500	8.691250
10.627200	5.721333	8.174266
11.148100	5.717416	8.432758

The harmonic mean $\widetilde{n}$ is

$$\widetilde{n} = \frac{(2)(2)}{1/5 + 1/4 + 1/5 + 1/3} = 4.067797$$

$$\mathrm{SS}_\mu = (4.067797)(2)\left[(8.691250 - 8.432758)^2 + (8.174266 - 8.432758)^2\right] = 1.0872$$

Table 10.27 ANOVA Table for Unweighted Means

Source	d.f.	SS	MS	F-Ratio	p-Value
Subject	1	1.0872	1.0872		
PHA	1	119.688	119.6888	1	
PHA × subject	1	1.1204	1.1204	45.7	<0.001
Error	13	0.3184	0.02449		
Total	16				

$$SS_\beta = (4.067797)(2)\left[(11.148100 - 8.432758)^2 + (5.717416 - 8.432758)^2\right] = 119.6888$$

$$SS_\gamma = (4.067797)\left[(4)(0.262408)^2\right] = 1.1204$$

making use of the fact that all the interaction deviations are equal in absolute value:

$$\overline{Y}_{11\cdot} - \overline{M}_{1\cdot} - \overline{M}_{\cdot 1} + \overline{M}_{\cdot\cdot} = 0.262408$$
$$\overline{Y}_{12\cdot} - \overline{M}_{1\cdot} - \overline{M}_{\cdot 2} + \overline{M}_{\cdot\cdot} = -0.262408, \ldots$$

The ANOVA table based on the unweighted means is shown in Table 10.27.

The conclusion remains unchanged. It turns out in this case that the test for interaction is identical to the multiple regression procedure of Chapter 11.

10.6 VALIDITY OF ANOVA MODELS

10.6.1 Assumptions in ANOVA Models

All the models considered in this chapter have assumed at least the following:

1. Homogeneity of variance
2. Normality of the residual error
3. Statistical independence of the residual errors
4. Linearity of the model

For example, consider again the model associated with the one-way analysis of variance (omitting the subscripts):

$$Y = \mu + \alpha + \epsilon$$

We assumed that (1) the error term ϵ had constant variance for all values of μ and α, and was normally distributed; (2) values of ϵ were randomly (independently) selected; and (3) the response Y was related linearly to μ, α, and ϵ.

In addition, the random effects and repeated measures models made assumptions about the covariances of the random factors and the residual error; other models assumed zero interaction (additivity).

If one or more of the assumptions does not hold, one of the following approaches is frequently used:

1. The data are analyzed by a method that makes fewer assumptions: for example, nonparametric analysis.

2. Part of the data is eliminated or not used, for example, extreme values (i.e., outliers) are deleted or replaced by less extreme values. Deletion usually induces bias.

3. The measurement variables are replaced by categorical variables and some kind of analysis of frequencies is carried out; for example, "age at first pregnancy" is replaced by "teenage mother: yes–no," and the number of observations in various categories is now the outcome variable.

4. A weighted analysis is done; for example, if the variance is not constant at all levels of response, the responses are weighted by the inverse of the variances. The log-linear models of Chapter 7 are an example of a weighting procedure.

5. The data are "transformed" to make the assumptions valid. Typical transformations are: logarithmic, square root, reciprocal, and arcsin $\sqrt{\ }$. These transformations are nonlinear. Linear transformations do not alter the analysis of variance tests.

6. Finally, appeal is made to the "robustness" of the ANOVA and the analysis is carried out anyway. This is a little bit like riding a bicycle without holding onto the handle bars; it takes experience and courage. If you arrive safely, everyone is impressed, if not, they told you so.

The most common approach is to transform the data. There are advantages and disadvantages to transformations. A brief discussion is presented in the next section. In the other sections we present specific tests of the assumptions of the ANOVA model.

10.6.2 Transformations

Some statisticians recommend routine transformations of data before any analysis is carried out. We recommend the contrary approach; do not carry out transformations unless necessary, and then be very careful, particularly in estimation. We discuss this more fully below, but first we present some common transformations. Table 10.28 lists seven of the most commonly used transformations and one somewhat more specialized one. Each row in the table lists some of the characteristics of the transformation and its uses. A large number of these transformations are variance stabilizing. For example, if the variance of Y is $\lambda^2\mu_Y$, where λ is a constant and μ_Y is the expected value of Y, then $\sqrt{Y}$ tends to have a variance that is constant and equal to $\lambda^2/4$. Hence, this transformation is frequently associated with a Poisson random variable: in this case $\lambda = 1$, so that $\sqrt{Y}$ tends to have a variance of 1/4 regardless of the value of μ_Y. This result is approximate in that it holds for large values of μ_Y. However, the transformation works remarkably well even for small μ_Y, say, equal to 10. Freeman and Tukey [1950] have proposed a modification of the square root transformation which stabilizes the variance for even smaller values of μ_Y. Variance stabilizing transformations tend to be normalizing as well and can be derived explicitly as a function of the variance of the original variable.

The logarithmic transformation is used to stabilize the variance and/or change a multiplicative model into an linear model. When the standard deviation of Y is proportional to μ_Y the logarithmic transformation tends to stabilize the variance. The reciprocal transformation (one per observation) is used when the variance is proportional to μ_Y^4. These first three transformations deal with a progression in the dependence of the variance of Y on μ_Y: from μ_Y to μ_Y^4. The transformations consist of raising Y to an exponent from $Y^{1/2}$ to Y^{-1}. If we define the limit of Y^b to be $\log_e Y$ as b approaches 0, these transformations represent a gradation in exponents. A further logical step is to let the data determine the value of b. This transformation, Y^b, is an example of a power transformation. (*Power* here does not imply "powerful" but simply that Y is raised to the bth power.) See Note 10.4 for additional comments.

The next two transformations are used with proportions or rates. The first one of these is the ubiquitous logistic transformation, which is not variance stabilizing but does frequently induce linearity (cf. Section 7.5). The angle transformation is variance stabilizing but has a finite range; it is not used much anymore because computational power is now available to use the more complex but richer logistic transformation.

Table 10.28 Characteristics of Some Common Transformations of a Random Variable Y

$W = g(Y)$	Range of Y	Variance[a] Y	Variance[a] W	Normalizing	Stabilizing	Linearity	Comments	Uses
$\sqrt{Y}$	$0 \le Y \le \infty$	$\lambda^2\mu_Y$	$\lambda^2/4$	U	Y	—	for $\mu_Y < 10$ use : $W = 1/2(\sqrt{Y} + \sqrt{Y+1})$ (Freeman Tukey transformation)	Poisson
$\log_e Y$	$0 \le Y \le \infty$	$\lambda^2\mu_Y^2$	λ^2	U	Y	C	Use $\log_e(Y+1)$ if zeroes occur	Wide range of Y, e.g., 1–1000
$\frac{1}{Y}$	$0 \le Y \le \infty$	$\lambda^2\mu_Y^4$	λ^2	U	Y	C	Use $1/(Y+1)$ if zeroes occur	Survival time, response time
Y^b	$0 \le Y \le \infty$	—	1	Y	Y	C	Box–Cox transformation, Power transformation	Generalized transformation
$\log_e \frac{Y}{1-Y}$	$0 < Y < 1$	$\lambda^2\mu_Y(1-\mu_Y)$	$\frac{\lambda^2}{\mu_Y(1-\mu_Y)}$	U	N	C	Logit transformation	Logistic regression, binomial
$\arcsin\sqrt{Y}$	$0 \le Y \le 1$	$\lambda^2\mu_Y(1-\mu_Y)$	$\lambda^2/4$	U	Y	C	"Angle" transformation	Binomial
$1/2\log_e \frac{1+Y}{1-Y}$	$-1 \le Y \le 1$	$\lambda^2(1-\mu_Y^2)^2$	λ^2	Y	Y	C	R. A. Fisher's Z-transformation	Normalize correlation coefficient
$\Phi^{-1}\left(\frac{\text{rank } Y}{n}\right)$	$-\infty \le Y \le \infty$	—	1	Y	Y	—	Normal scores transformation $(\text{Rank}(Y) - 1/2)/n$ is sometimes used	Nonparametric analysis

[a] C, could; N, no; U, usually; Y, yes.

The Fisher Z-transformation is used to transform responses whose range is between -1 and $+1$. It was developed specifically for the Pearson product-moment correlation coefficient and discussed in Chapter 9. Finally, we mention one transformation via ranks, the normal scores transformation. This transformation is used extensively in nonparametric analyses and discussed in Chapter 8.

There are benefits to the use of transformations. It is well to state them explicitly since we also have some critical comments. The benefits include the following:

1. Methods using the normal distribution can be used.
2. Tables, procedures, and computer programs are available.
3. A transformation derived for one purpose tends to achieve some other purposes as well—but not always.
4. Inferences (especially relating to hypothesis testing) can be made more easily.
5. Confidence intervals in the transformed scale can be "transformed back" (but estimates of standard errors cannot).

Transformations are more useful for testing purposes than for estimation. The following drawbacks of transformations should be kept in mind:

1. The order of statistics may not be preserved. Consider the following two sets of data: sample 1 : 1, 10; sample 2 : 5, 5. The arithmetic means are 5.5 and 5.0, respectively. The geometric means (i.e., the antilogarithms of the arithmetic mean of the logarithms of the observations) are 3.2 and 5.0, respectively. Hence, the ordering of the *means* is not preserved by the transformation (the ordering of the *raw* data is preserved).
2. Contrary to some, we think that there may be a "natural scale" of measurement. Some examples of variables with a natural scale of measurement are "life expectancy" measured in years, days, or months; cost of medical care in dollars; number of accidents attributable to alcoholism. Administrators or legislators may not be impressed with, or willing to think about, the cost of medical care in terms of "square root of millions of dollars expended."
3. Closely related is the problem of bias. An obvious approach to the criticism in our discussion of drawback 2 is to do the analysis in the transformed units and then transform back to the original scale. Unfortunately, this introduces bias as mentioned in our discussion of drawback 1. Formally, if Y is the variable of interest and $W = g(Y)$ its transform, then it is usually the case that

$$E(W) \neq g(E(Y))$$

   There are ways of assessing this bias and eliminating it but such methods are cumbersome and require an additional layer of computations, something the transformation was often designed to reduce!
4. Finally, many of the virtues of transformations are asymptotic virtues; they are approached as the sample size becomes very large. This should be kept in mind when analyzing relatively small data sets.

10.6.3 Testing of Homogeneity of Variance

It is often the case that the variance or standard deviation is proportional to the mean level of response. There are two common situations where this occurs. First, where the range of response varies over two or more orders of magnitude; second, in situations where the range of response is bounded, on the left, the right or both. Examples of the former are Poisson random variables; examples of the latter, responses such as proportions, rates, or random variables that cannot be negative.

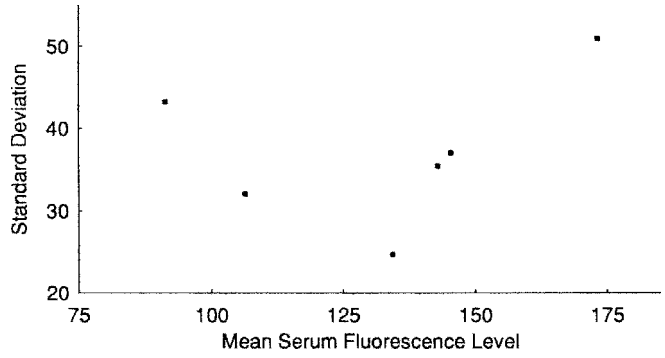


Figure 10.6 Mean serum fluorescence level and standard deviation. (Data from Sherwin and Layfield [1976]; see Example 10.5.)

The simplest verification of homogeneity of variance is provided by a graph, plotting the variance or standard deviation vs. the level of response.

Example 10.5. (*continued*) In Table 10.8, the means and standard deviations of serum fluorescence readings of mice exposed to nitrogen dioxide are given. In Figure 10.6 the standard deviations are plotted against the means of the various treatment combinations. This example does not demonstrate any pattern between the standard deviation and the cell means. It would not be expected because the range of the cell means is fairly small.

Example 10.9. A more interesting example is the data of Quesenberry et al. [1976] discussed in Problem 3.14. Samples of peanut kernels were analyzed for aflatoxin levels. Each sample was divided into 15 or 16 subsamples. There was considerable variability in mean levels and corresponding standard deviations.

A plot of means vs. standard deviations displays an increasing pattern, suggesting a logarithmic transformation to stabilize the variance. This transformation as well as two other transformations ($\sqrt{Y}$, $Y^{1/4}$) are summarized in Table 10.29. Means vs. standard deviations are

Table 10.29 Aflatoxin Levels in Peanut Kernels: Means and Standard Deviations for 11 Samples Using Transformations

		Mean and Standard Deviation of Aflatoxin Level							
		Y		$W = Y^{1/4}$		$W = \sqrt{Y}$		$W = \log Y$	
Sample	n	Mean	SD	Mean	SD	Mean	SD	Mean	SD
1	16	110	25.6	3.2	0.192	10.4	1.24	4.7	0.240
2	16	79	20.6	3.0	0.204	8.8	1.19	4.3	0.281
3	16	21	3.9	2.1	0.109	4.5	0.45	3.0	0.213
4	16	33	12.2	2.4	0.192	5.7	0.96	3.4	0.311
5	15	32	10.6	2.4	0.194	5.6	0.92	3.4	0.328
6	16	15	2.7	2.0	0.089	3.8	0.35	2.7	0.183
7	15	33	6.2	2.4	0.111	5.8	0.54	3.5	0.183
8	16	31	2.8	2.4	0.054	5.6	0.26	3.4	0.092
9	16	17	4.2	2.0	0.129	4.1	0.51	2.8	0.261
10	16	8	3.1	1.7	0.143	2.9	0.49	2.1	0.339
11	15	84	17.7	3.0	0.164	9.1	0.98	4.4	0.221

Source: Data from Quesenberry et al. [1976].

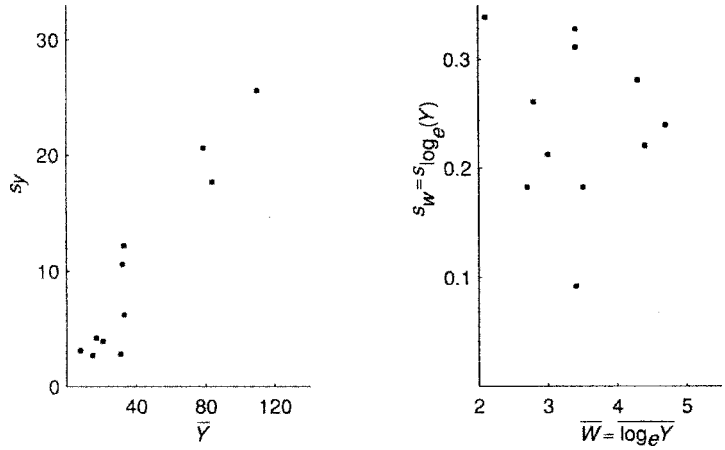


Figure 10.7 Means vs. standard deviation, arithmetic and logarithmic scales. (Data from Wallace et al. [1977]; see Example 10.8.)

plotted in Figure 10.7. The first pattern clearly indicates a linear trend; the plot for the data expressed as logarithms suggests very little pattern. This does not prove that the lognormal model is appropriate. Quesenberry et al. [1976], in fact, considered two classes of models: the 11 samples are from normal distributions with means and variances $\mu_i, \sigma_i^2, i = 1, \ldots, 11$; the second class of models assumes that the logarithms of the aflatoxin levels for the 11 samples come from normal distributions with means and variances $\gamma_i, \theta^2, i = 1, \ldots, 11$.

On the basis of their analysis, they conclude that the normal models are more appropriate. The cost is, of course, that 10 more parameters have to be estimated. Graphs of means vs. standard deviation for the $\sqrt{Y}$ and $Y^{1/4}$ scale still suggest a relationship.

The tests of homogeneity of variance developed here are graphical. There are more formal tests. All of the tests assume normality and are sensitive to departure from normality. In view of the robustness of the analysis of variance to heterogeneity of variance, Box [1953] remarked that "... to make the preliminary tests on variances is rather like putting to sea in a rowing boat to find out whether conditions are sufficiently calm for an ocean liner to leave port." There are four common tests of homogeneity of variance, associated with the names of Hartley, Cochran, Bartlett, and Scheffé. Only the first two are described here, they will be adequate for most purposes. For a description of the other tests see, for example, Winer [1971]. Suppose that there are k samples with sample size n_i and sample variance $s_i^2, i = 1, \ldots, k$. For the moment, assume that all n_i are equal to n. Hartley's test calculates

$$F_{\text{MAX}} = \frac{s^2_{\text{maximum}}}{s^2_{\text{minimum}}}$$

Cochran's test calculates

$$C = \frac{s^2_{\text{maximum}}}{\sum S_i^2}$$

In the absence of software for computing critical values, both statistics can be referred to appropriate tables in the Web appendix. If the sample sizes are not equal, the tables can be entered with the minimum sample size to give a conservative test and with the maximum

Table 10.30 Calculations for Example 10.9

Scale	$F_{\max}$	C
Y	$\left(\frac{25.6}{2.7}\right)^2 = 89.9$	$\frac{(25.7)^2}{1758.1} = 0.38$
$\sqrt{Y}$	$\left(\frac{1.24}{0.26}\right)^2 = 22.7$	$\frac{(1.24)^2}{9.787} = 0.16$
$Y^{1/4}$	$\left(\frac{0.204}{0.054}\right)^2 = 14.1$	$\frac{(0.204)^2}{0.252} = 0.16$
$\log_e Y$	$\left(\frac{0.339}{0.092}\right)^2 = 13.6$	$\frac{(0.339)^2}{0.694} = 0.17$
Critical value at 0.05 level	5.8	0.15

sample size to give a "liberal" test (i.e., the null hypothesis is rejected more frequently than the nominal significance level).

Example 10.9. (*continued*) For the transformations considered, the F_{MAX} test and C test statistics are as shown in Table 10.30.

The critical values have been obtained by interpolation. The F_{MAX} test indicates that none of the transformations achieve satisfactory homogeneity of variance, validating one of Quesenberry et al.'s conclusions. The Cochran test suggests that there is little to choose between the three transformations.

A question remains: How valid is the analysis of variance under heterogeneity of variance? Box [1953] indicates that for three treatments a ratio of 3 in the maximum-to-minimum *population* variance does not alter the significance level of the test appreciably (one-way ANOVA model with $n_i. = 5, I = 3$). The analysis of variance is therefore reasonably robust with respect to deviation from homogeneity of variance.

10.6.4 Testing of Normality in ANOVA

Tests of normality are not as common or well developed as tests of homogeneity of variance. There are at least two reasons: first, they are not as crucial because even if the underlying distribution of the data is not normal, appeal can be made to the central limit theorem. Second, it turns out that fairly large sample sizes are needed (say, $n > 50$) to discriminate between distributions. Again, most tests are graphical.

Consider for simplicity the one-way analysis of variance model

$$Y_{ij} = \mu + \alpha_i + \epsilon_{ij}, \qquad i = 1, \ldots, I, \quad j = 1, \ldots, n_i$$

By assumption the ϵ_{ij} are iid $N(0, \sigma^2)$. The ϵ_{ij} are estimated by

$$\epsilon_{ij} = Y_{ij} - \overline{Y}_i.$$

The e_{ij} are normally distributed with population mean zero; $\sum e_{ij}^2/(n - I)$ is an unbiased estimate of σ^2 but the e_{ij} are not statistically independent. They can be made statistically independent, but it is not worthwhile for testing the normality. Some kind of normal probability plot is usually made and a decision made based on a visual inspection. Frequently, such a plot is used to identify outliers. Before giving an example, we give a simple procedure which is based on the use of order statistics.

Definition 10.14. Given a sample of n observations, $Y_1, Y_2, \ldots, Y_n$, the *order statistics* $Y_{(1)}, Y_{(2)}, \ldots, Y_{(n)}$ are the values ranked from lowest to highest.

Now suppose that we generate samples of size n from an $N(0, 1)$ distribution and average the values of the order statistics.

Definition 10.15. *Rankits* are the expected values of the order statistics of a sample of size n from an $N(0, 1)$ distribution. That is, let $Z_{(1)}, \ldots, Z_{(n)}$ be the order statistics from an $N(0, 1)$ population; then the rankits are $E(Z_{(1)}), E(Z_{(2)}), \ldots, E(Z_{(n)})$.

Rankits have been tabulated in Table A.13. A plot of the order statistics of the residuals against the rankits is equivalent to a normal probability plot. A reasonable approximation for the ith rankit is given by the formula

$$E(Z_{(i)}) \doteq 4.91[p^{0.14} - (1 - p)^{0.14}] \tag{31}$$

where

$$p = \frac{i - 3/8}{n + 1/4}$$

For a discussion, see Joiner and Rosenblatt [1971]. To illustrate its use we return to Example 10.1. A one-way analysis of variance was constructed for these data and we now want to test the normality assumption.

Example 10.1. (*continued*) The distribution of ages at which infants first walked [discussed in Section 10.2.1 (see Table 10.1)] is now analyzed for normality. The residuals $Y_{ij} - \overline{Y}_{i\cdot}$ for the 23 observations are:

−1.125	−0.375	−0.208	0.900
−0.625	−1.375	0.292	−0.850
−0.375	−1.375	−2.708	−0.350
−0.125	0.375	−0.208	1.150
2.875	−0.875	1.542	−0.850
−0.625	3.625	1.292	

Note that the last observation has been omitted again so that we are working with the 23 observations given in the paper. These observations are now ranked from smallest to largest to be plotted on probability paper. To illustrate the use of rankits, we will calculate the expected values of the 23 normal (0,1) order statistics using equation (31). The 23 order statistics for e_{ij}, $e_{(ij)}$, and the corresponding rankits are presented in Table 10.31.

For example, the largest deviation is −2.708; the expected value of $Z_{(1)}$ associated with this deviation is calculated as follows:

$$p = \frac{1 - 3/8}{23 + 1/4} = 0.02688$$

$$E(Z_{(1)}) = 4.91[(0.02688)^{0.14} - (1 - 0.02688)^{0.14}]$$

$$= -1.93$$

The rankits and the ordered residuals are plotted in Figure 10.8. What do we do with this graph? Is there evidence of nonnormality?

Table 10.31 Order Statistics for Example 10.1

$e_{(ij)}$	$E(Z_{(ij)})$	$e_{(ij)}$	$E(Z_{(ij)})$	$e_{(ij)}$	$E(Z_{(ij)})$
−2.708	−1.93	−0.625	−0.33	0.375	0.57
−1.375	−1.48	−0.375	−0.22	0.900	0.70
−1.375	−1.21	−0.375	−0.11	1.150	0.84
−1.125	−1.01	−0.350	0.0	1.292	1.01
−0.875	−0.84	−0.208	0.11	1.542	1.21
−0.850	−0.70	−0.208	0.22	2.875	1.48
−0.850	−0.57	−0.125	0.33	3.625	1.93
−0.625	−0.44	−0.292	0.44		

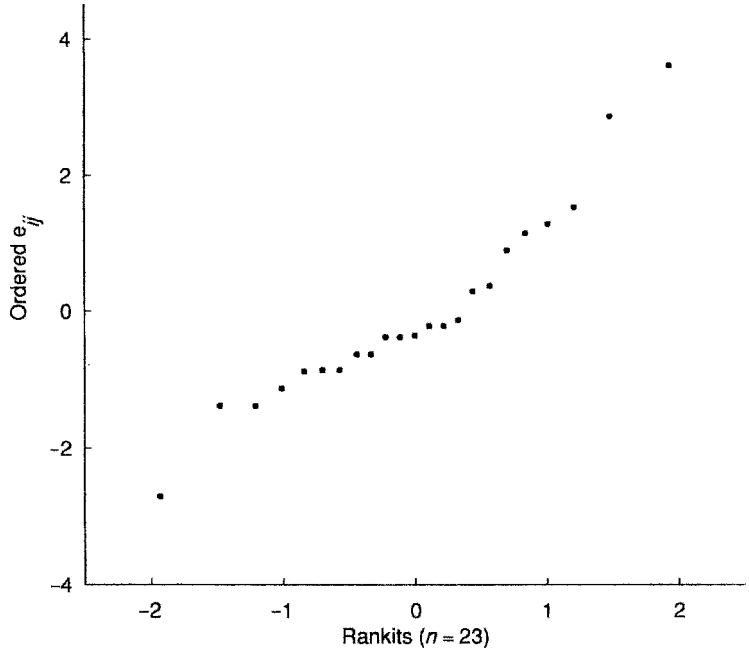


Figure 10.8 Normal probability plot of residuals from linear model. (Data from Zelazo et al. [1972]; see Example 10.1.)

There does seem to be some excessive deviation in the tails. The question is: How important is it? One way to judge this would be to generate many plots for normal and nonnormal data and compare the plots to develop a visual "feel" for the data. This has been done by Daniel and Wood [1999] and Daniel [1976]. Comparison of this plot with the plots in Daniel and Wood suggests that these data deviate moderately from normality. For a further discussion, see Section 11.8.1.

More formal tests of normality can be carried out using the Kolmogorov–Smirnov test of Chapter 8. A good test is based on the Pearson product-moment correlation of the order statistics and corresponding rankits. If the residuals are normally distributed, there should be a very high correlation between the order statistics and the rankits. The (null) hypothesis of normality is rejected when the correlation is *not large enough*. Weisberg and Bingham [1975] show that this is a very effective procedure. The critical values for the correlation have been tabulated; see, for example, Ryan et al. [1980]. For $n \geq 15$, the critical value is on the order of 0.95 or more. This

is a simple number to remember. For Example 10.1, the correlation between the order statistics of the residuals, $e_{(ij)}$ and the rankits $E(Z_{(ij)})$ is $r = 0.9128$ for $n = 23$. This is somewhat lower than the critical value of 0.95 again, suggesting that the residuals are "not quite" normally distributed.

10.6.5 Independence

One of the most difficult assumptions to verify is that of statistical independence of the residuals. There are two problems. First, tests of independence for continuous variables are difficult to implement. Frequently, such tests are, in fact, tests of no correlation among the residuals, so that if the errors are normally distributed and uncorrelated, they are independent. Second, the observed residuals in the analysis of variance have a built-in dependence due to the constraints on the linear model. For example, in the one-way analysis of variance with I treatments and, say, $n_{i\cdot} = m$ observations per treatment, there are mI residuals but only $(m-1)I$ degrees of freedom; this induces some correlation among the residuals. This is not an important dependence and can be taken care of.

Tests for dependence usually are tests for serial correlation (i.e., correlation among adjacent values). This assumes that the observations can be ordered in space or time. The most common test statistic for serial correlation is the Durbin–Watson statistic. See, for example, Draper and Smith [1998]. Computer packages frequently will print this statistic assuming that the observations are entered in the same sequence in which they were obtained. This, of course, is rarely the case and the statistic and its value should not be used. Such "free information" is sometimes hard to ignore; the motto for computer output is *caveat lector* (let the reader beware).

10.6.6 Linearity in ANOVA

Like independence, linearity is difficult to verify. In Example 10.7 we illustrated a multiplicative model. The model was transformed to a linear (nonadditive) model by considering the logarithm of the original observations. Other types of nonlinear models are discussed in Chapters 11 to 15. Evidence for a nonlinear model may consist of heterogeneity of variance or interaction. However, this need not always be the case. Scheffé [1959] gives the following example. Suppose that there are $I + J + 1$ independent Poisson variables defined as follows: $U_1, U_2, \ldots, U_I$ have means $\alpha_1, \alpha_2, \ldots, \alpha_I$; $V_1, V_2, \ldots, V_J$ have means $\beta_1, \beta_2, \ldots, \beta_J$; and W has mean γ. Let $Y_{ij} = W + U_i + V_j$; then $E(Y_{ij}) = \gamma + \alpha_i + \beta_j$; that is, we have an additive, linear model. But $\text{var}(Y_{ij}) = \gamma + \alpha_i + \beta_j$, so that there is heterogeneity of variance (unless all the α_i are equal and all the β_j are equal). The square root transformation destroys the linearity and the additivity. Scheffé [1959] states: "It is not obvious whether Y or $\sqrt{Y}$ is more nearly normal ... but in the present context it hardly matters." A linear model is frequently assumed to be appropriate for a set of data without any theoretical basis. It may be a reasonable first-order approximation to the "state of nature" but should be recognized as such.

Sometimes a nonlinear model can be derived from theoretical principles. The form of the model may then suggest a transformation to linearity. But as the example above illustrates, the transformation need not induce other required properties of ANOVA models, or may even destroy them.

Another strategy for testing linearity is to add some nonlinear terms to the model and then test their significance. In Sections 11.7 and 11.8 we elaborate on this strategy.

10.6.7 Additivity

The term *additivity* is used somewhat ambiguously in the statistical literature. It is sometimes used to describe the transformation of a multiplicative model to a linear model. The effects of the treatment variables become "additive" rather than multiplicative. We have called such a transformation a *linearizing transformation*. It is not always possible to find such a transformation

(see Section 11.10.5). We have reserved the term *additivity* for the additive model illustrated by the two-way analysis of variance model (see Definition 10.4). A test for additivity then becomes a test for "no interaction." Scheffé [1959] proves that transformations to additivity exists for a very broad class of models.

The problem is that the existence of interaction may be of key concern. Consider Example 10.8. The existence of interaction in this example is taken as evidence that the immune system of a patient with prostatic carcinoma differed from that of normal blood donors. This finding has important implications for a theory of carcinogenesis. These data are an example of the importance of expressing observations in an appropriate scale. Of course, what evidence is there that the logarithms of the radioactive count is the appropriate scale? There is some arbitrariness, but the original model was stated in terms of percentage changes, and this implies constant changes on a logarithmic scale.

So the problem has been pushed back one step: Why state the original problem in terms of percentage changes? The answer must be found in the experimental situation and the nature of the data. Ultimately, the researcher will have to provide justification for the initial model used.

This discussion has been rather philosophical. One other situation will be considered: the randomized block design. There is no test for interaction because there is only one observation per cell. Tukey [1949] suggested a procedure that is an example of a general class of procedures. The validity of a model is evaluated by considering an enlarged model and testing the significance of the terms in the enlarged model. To be specific, consider the randomized block design model of equation (23):

$$Y_{ij} = \mu + \beta_i + \tau_j + \varepsilon_{ij}, \qquad i = 1, \ldots, I, \quad j = 1, \ldots, J$$

Tukey [1949] embedded this model in the "richer" model

$$Y_{ij} = \mu + \beta_i + \tau_j + \lambda\beta_i\tau_j + \varepsilon_{ij}, \qquad i = 1, \ldots, I, \quad j = 1, \ldots, J \tag{32}$$

He then proposed to test the null hypothesis,

$$H_0 : \lambda = 0$$

as a test for nonadditivity. Why this form? It is the simplest nonlinear effect involving both blocks and treatments. The term λ is estimated and tested as follows. Let the model without interaction be estimated by

$$Y_{ij} = \overline{Y}.. + b_i + t_j + e_{ij}$$

where

$$b_i = \overline{Y}_i. - \overline{Y}.., \; t_j = \overline{Y}._j - \overline{Y}.. \quad \text{and} \quad e_{ij} = Y_{ij} - \overline{Y}.. - b_i - t_j$$

We have the usual constraints,

$$\sum b_i = \sum t_j = 0$$

and

$$\sum_i e_{ij} = \sum_j e_{ij} = 0 \qquad \text{for all } i \text{ and } j$$

Now define

$$X_{ij} = b_i t_j, \qquad i = 1, \ldots, I, \quad j = 1, \ldots, J \tag{33}$$

It can be shown that the least squares estimate, $\widehat{\lambda}$, of λ is

$$\widehat{\lambda} = \frac{\sum X_{ij} Y_{ij}}{\sum X_{ij}^2} \tag{34}$$

Since $\overline{X} = 0$ (why?), the quantity $\widehat{\lambda}$ is precisely the regression of Y_{ij} on X_{ij}. The sum of squares for regression is the sum of squares for nonadditivity in the ANOVA table:

$$SS_\lambda = SS_{\text{nonadditivity}} = \frac{\left(\sum X_{ij} Y_{ij}\right)^2}{\sum X_{ij}^2} \tag{35}$$

The ANOVA table for the randomized block design including the test for nonadditivity is displayed in Table 10.32. As expected, the SS_λ has one degree of freedom since we are estimating a slope. But who "pays" for the one degree of freedom? A little reflection indicates that it must come out of the error term; the number of constraints on the block and treatment effects remain the same. A graph of Y_{ij} vs. X_{ij} (or equivalently, e_{ij} vs. X_{ij}) will indicate whether there is any pattern.

The idea of testing models within larger models as a way of testing the validity of the model is discussed further in Section 11.8.2.

Example 10.6. (*continued*) We now apply the Tukey test for additivity to the experiment assessing the effect of pancreatic supplements on fat absorption in patients with steatorrhea, discussed in Section 10.3.2. We need to calculate SS_λ from equation (35) and this involves the regression of Y_{ij} on X_{ij}, where X_{ij} is defined by equation (33). To save space we calculate only a few of the X_{ij}. For example,

$$\begin{aligned} X_{11} &= \left(\overline{Y}_{1\cdot} - \overline{Y}_{\cdot\cdot}\right)\left(\overline{Y}_{\cdot 1} - \overline{Y}_{\cdot\cdot}\right) \\ &= (16.9 - 25.775)(38.083 - 25.775) \\ &= -109.2 \end{aligned}$$

and

$$\begin{aligned} X_{23} &= \left(\overline{Y}_{2\cdot} - \overline{Y}_{\cdot\cdot}\right)\left(\overline{Y}_{\cdot 3} - \overline{Y}_{\cdot\cdot}\right) \\ &= (25.625 - 25.775)(17.417 - 25.775) \\ &= 1.3 \end{aligned}$$

(Note that a few more decimal places for the means are used here as compared to Table 10.15.) A graph of Y_{ij} vs. X_{ij} is presented in Figure 10.9. The estimate of the slope is

$$\begin{aligned} \widehat{\lambda} &= \frac{\sum X_{ij} Y_{ij}}{\sum X_{ij}^2} \\ &= \frac{(-109.2)(44.5) + (82.0)(7.3) + \cdots + (98.8)(52.6)}{(-109.2)^2 + (82.0)^2 + \cdots + (98.8)^2} \\ &= \frac{13{,}807}{467{,}702} \\ &= 0.029521 \end{aligned}$$

SS_λ is

$$SS_\lambda = \frac{(13{,}807)^2}{467{,}702} = 407.60$$

The analysis of variance is tabulated in Table 10.33.

Table 10.32 ANOVA of Randomized Block Design Incorporating Tukey Test for Additivity[a]

Source of Variation	d.f.	SS[b]	MS	F-Ratio	d.f.	E(MS)	Hypothesis Tested
Grand mean	1	$\mathrm{SS}_\mu = n\overline{Y}_{..}^2$	$\mathrm{MS}_\mu = \mathrm{SS}_\mu$	$\dfrac{\mathrm{MS}_\mu}{\mathrm{MS}_\epsilon}$	$(1, IJ - I - J)$	$n\mu^2 + \sigma^2$	$\mu = 0$
Blocks	$I - 1$	$\mathrm{SS}_\beta = J\sum(\overline{Y}_{i.} - \overline{Y}_{..})^2$	$\mathrm{MS}_\beta = \dfrac{\mathrm{SS}_\beta}{I-1}$	$\dfrac{\mathrm{MS}_\beta}{\mathrm{MS}_\epsilon}$	$(I-1, IJ - I - J)$	$\dfrac{J\sum\beta_i^2}{I-1} + \sigma^2$	$\beta_i = 0$ all i
Treatments	$J - 1$	$\mathrm{SS}_\tau = I\sum(\overline{Y}_{\cdot j} - \overline{Y}_{..})^2$	$\mathrm{MS}_\tau = \dfrac{\mathrm{SS}_\tau}{J-1}$	$\dfrac{\mathrm{MS}_\tau}{\mathrm{MS}_\epsilon}$	$(J-1, IJ - I - J)$	$\dfrac{I\sum\tau_j^2}{J-1} + \sigma^2$	$\tau_i = 0$ all j
Nonadditivity	1	$\mathrm{SS}_\lambda^c = \dfrac{\left(\sum X_{ij}Y_{ij}\right)^2}{\sum X_{ij}^2}$	$\mathrm{MS}_\lambda = \mathrm{SS}_\lambda$	$\dfrac{\mathrm{MS}_\lambda}{\mathrm{MS}_\epsilon}$	$(1, IJ - I - J)$	$\lambda^2 C^d + \sigma^2$	$\lambda = 0$
Residual	$IJ - I - J$	SS_ϵ = by subtraction	$\mathrm{MS}_\epsilon = \dfrac{\mathrm{SS}_\epsilon}{IJ - I - J}$				
Total	IJ	$\sum Y_{ij}^2$					

[a] Model: $Y_{ij} = \mu + \beta_i + \tau_j + \lambda\beta_i\tau_j + \epsilon_{ij}$ [$\epsilon_{ij} \sim$ iid $N(0, \sigma^2)$]. Data: $Y_{ij} = \overline{Y}_{..} + (\overline{Y}_{i.} - \overline{Y}_{..}) + (Y_{.j} - Y_{..}) + \widehat{\lambda}X_{ij} + \widetilde{e}_{ij}$ (residual obtained by subtraction).

[b] Summation is over all subscripts displayed.

[c] $X_{ij} = (\overline{Y}_{i.} - \overline{Y}_{..})(\overline{Y}_{.j} - \overline{Y}_{..})$.

[d] C is a constant that depends on the cell means; it is zero if the additive model holds.

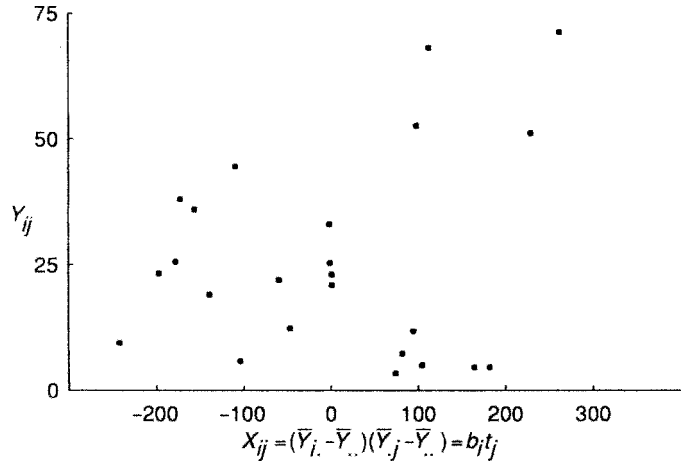


Figure 10.9 Plot of the Tukey test for additivity. See the text for an explanation.

Table 10.33 Randomized Block Analysis with Tukey Test for Additivity of Fecal Fat Excretion of Patients with Steatorrhea

Source of Variation	d.f.	SS	MS	F-Ratio	p-Value
Patients	5	5588.38	1117.68	13.1	<0.001
Treatments	3	2008.60	669.53	7.83	<0.01
Additivity	1	407.60	407.60	4.76	$0.025 < p < 0.05$
Residual	14	1197.80	85.557		
Total	23	9202.38			

Source: Data from Graham [1977].

The test for additivity indicates significance at the 0.05 level ($p = 0.047$); thus there is some evidence that the data cannot be represented by an additive model. Tukey [1949] related the constant a in Y^a (power transformation) to the degree of nonadditivity by the following formula:

$$\widehat{a} = 1 - \widehat{\lambda}\overline{Y}...$$

The quantity $\widehat{a}$ is a statistic and hence a random variable. For a particular set of data, the confidence interval on $\widehat{a}$ will tend to be fairly wide; hence, a "nice" value of "a" is usually chosen. For the example, $\widehat{a} = 1 - (0.029521)(25.775) = 0.239$. A "nice" value for "$a$" is thus 0.25, or even 0.20.

10.6.8 Strategy for Analysis of Variance

It is useful to have a checklist in carrying out an ANOVA. Not every item on the list needs to be considered, nor necessarily in the order given, but you will find it useful to be reminded of these items:

1. Describe how the data were generated: from what population? To what population will inferences be made? State explicitly at what steps in the data generation randomness entered.

2. Specify the ANOVA null hypotheses, alternative hypotheses; whether the model is fixed, random, or mixed.
3. Graph the data to get some idea of treatment effects, variability, and possible outliers.
4. If necessary, test the homogeneity of variance and the normality.
5. If ANOVA is inappropriate on the data as currently expressed, consider alternatives. If transformations are used, repeat steps 2 and 4.
6. Carry out the ANOVA. Calculate F-ratios. Watch out for F-ratios much less than 1; they usually indicate an inappropriate model.
7. State conclusions and limitations.
8. If null hypotheses are not rejected, consider the power of the study and of the analysis.
9. For more detailed analyses and estimation procedures, see Chapter 12.

NOTES

10.1 Ties in Nonparametric Analysis of Variance (One-Way and Randomized Block)

As indicated, both the Kruskal–Wallis and the Friedman tests are conservative in the presence of ties. The adjustment procedure is similar to those used in Chapter 8, equation (4). For the Kruskal–Wallis situation, let

$$C_{\mathrm{KW}} = \frac{\sum_{l=1}^{L} \left(t_l^3 - t_l\right)}{n^3 - n}$$

where L is the number of groups of tied ranks and t_l is the number of ties in group l, $l = 1, \ldots, L$. Then the statistic T_{KW} [equation (13)] is adjusted to $T_{\mathrm{ADJ}} = T_{\mathrm{KW}}/(1 - C_{\mathrm{KW}})$. Since $0 \le C_{\mathrm{KW}} \le 1$, $T_{\mathrm{ADJ}} \ge T_{\mathrm{KW}}$. Hence, if the null hypothesis is rejected with T_{KW}, it will certainly be rejected with T_{ADJ} since the degrees of freedom remain unchanged. Usually, C_{KW} will be fairly small: Suppose that there are 10 tied observations in an ANOVA of 20 observations; in this case $C_{\mathrm{KW}}(10^3 - 10)/(20^3 - 20) = 0.1241$, so that $T_{\mathrm{ADJ}} = T_{\mathrm{KW}}/(1 - 0.1241) = 1.14T_{\mathrm{KW}}$. The adjusted value is only 14% larger than the value of T_{KW} even in this extreme situation. (If the 10 ties are made up of five groups of two ties each, the adjustment is less than 0.5%).

A similar adjustment is made for the Friedman statistic, given by equations (25) and (26). In this case,

$$C_{\mathrm{FR}} = \frac{\sum_{i=1}^{I} \sum_{l=1}^{L_i} \left(t_{il}^3 - t_{il}\right)}{I(J^3 - J)}$$

where t_{il} is the number of ties in group l within block i and untied values within a block are counted as a group of size 1. (Hence $\sum_{l=1}^{L_i} t_{il} = J$ for every i.) The adjusted Friedman statistic, T_{ADJ}, is $T_{\mathrm{ADJ}} = T_{\mathrm{FR}}/(1 - C_{\mathrm{FR}})$. Again, unless there are very many ties, the adjustment factor, C_{FR} will be relatively small.

10.2 Nonparametric Analyses with Ordered Alternatives

All the tests considered in this chapter have been "omnibus tests"; that is, the alternative hypotheses have been general. In the one-way ANOVA, the null hypothesis is $H_0 : \mu_1 = \mu_2 = \cdots = \mu_I = \mu$, the alternative hypothesis $H_1 : \mu_i \ne \mu_i'$ for at least one i and i'. Since the power of a test is determined by the alternative hypothesis, we should be able to "do better" using more specific alternative hypotheses. One such hypothesis involves ordered alternatives. For the one-way ANOVA (see Section 10.2), let $H_1 : \mu_1 \le \mu_2 \le \cdots \le \mu_I$ with at least one strict

inequality. A regression-type parametric analysis could be carried out by coding the categories $X = 1$, $X = 2, \ldots, X = I$.

A nonparametric test of H_0 against an ordered alternative H_1 was developed by Terpstra and Jonckheere (see, e.g., Hollander and Wolfe [1999]). The test is based on the Mann–Whitney statistic (see Section 8.6). The Terpstra–Jonckheere statistic is

$$T_{\mathrm{TJ}} = \sum_{i=1}^{I-1} \sum_{k=i+1}^{I} M_{ik} = \sum_{i<k} M_{ik}$$

where M_{ik} is the number of pairs with the observation in group i less than that of group $k (i < k)$ among the $n_i n_k$ pairs.

Under the null hypothesis $H_0 : \mu_1 = \mu_2 = \cdots = \mu_I = \mu$, the statistic T_{TJ} has a distribution that approaches a normal distribution as n becomes large, with mean and variance given by

$$E\,[T_{\mathrm{TJ}}] = \frac{n^2 - \sum n_i^2}{4}$$

and

$$\mathrm{var}[T_{\mathrm{TJ}}] = \frac{[n^2(2n+3) - \sum n_i^2(2n_i+3)]}{72}$$

where $n = n_1 + n_2 + \cdots + n_I$. See Problems 10.3 and 10.11 for an application.

In Section 10.3.3, a nonparametric analysis of randomized block design was presented to test the null hypothesis $H_0 : \tau_1 = \tau_2 = \cdots = \tau_J = 0$. Again, we consider an ordered alternative, $H_1 : \tau_1 \le \tau_2 \le \cdots \le \tau_J$ with at least one strict inequality. Using the notation of Section 10.3.3, let $R_{\cdot j}$ = sum of ranks for treatment j. Page [1963] developed a nonparametric test of H_0 against H_1. The statistic $T_{\mathrm{PAGE}} = \sum_{j=1}^{J} j R_{\cdot j}$ under the null hypothesis approaches a normal distribution (as I become large) with mean and variance

$$E\,[T_{\mathrm{PAGE}}] = \frac{I J^2 (J+1)}{4}$$

and

$$\mathrm{var}\,[T_{\mathrm{PAGE}}] = \frac{I(J^3 - J)^2}{144(J-1)}$$

10.3 Alternative Rank Analyses

Conover and Iman [1981] in a series of papers have advocated a very simple rank analysis: Replace observations by their ranks and then carry out the usual parametric analysis. These procedures must be viewed with caution when models are nonadditive [Akritas, 1990] and discussion in Chapter 8. Hettmansperger and McKean [1978] provide an illustration of another class of rank-based analytical procedures that can be developed. There are three steps in this type of approach:

1. Define a robust or nonparametric estimate of dispersion.
2. State an appropriate statistical model for the data.
3. Given a set of data, estimate the values of the parameters of the model to minimize the robust estimate of dispersion.

A drawback of such procedures is that estimates cannot be written explicitly, and more important, the estimation procedure is nonlinear, requiring a computer to carry it out. However, with the increasing availability of microcomputers, it will only be a matter of time until software will be developed, making such procedures widely accessible.

It is possible to run a parametric analysis of the raw data routinely and compare it with some alternative rank analysis. If the two analyses do not agree, the data should be examined more carefully to determine the cause of the discrepant results; usually, it will be due to the *nonnormality* of the data. The researcher then has two choices: if the nonnormality is thought to be a characteristic of the biological system from which the data came, the rank analysis would be preferred. On the other hand, if the nonnormality is due to outliers (see Chapter 8), there are other options available, all the way from redoing the experiment (more carefully this time), to removing the outliers, to sticking with the analysis of the ranks. Clearly, there are financial, ethical, and professional costs and risks. What should *not* be done in the case of disagreement is to pick the analysis that conforms, in some sense, to the researcher's preconceptions or desires.

10.4 Power Transformation

Let Y^δ be a transformation of Y. The assumption is that Y^δ is normally distributed with mean μ (which will depend on the experimental model) and variance σ^2. The SS_ε will now be a function of δ. It can be shown that the appropriate quantity to be minimized is

$$L(\delta) = \frac{n}{2}SS_\varepsilon - \sum \ln(\delta y^\delta)$$

and defined to be

$$= \frac{n}{2}SS_\epsilon - \sum \ln y$$

for $\delta = 0$ (corresponding to the logarithmic transformation). Typically, this equation is solved by trial and error. With a computer this can be done quickly. Usually, there will be a range of values of δ over which the values of $L(\delta)$ will be close to the minimum; it is customary then to pick a value of δ that is simple. For example, if the minimum of $L(\delta)$ occurs at $\delta = 0.49$, the value chosen will be $\delta = 0.50$ to correspond to the square root transformation. For an example, see Weisberg [1985]. Empirical evidence suggests that the value of δ derived from the data is frequently close to some "natural" rescaling of the data. (This may just be a case of perfect 20/20 hindsight.)

PROBLEMS

For Problems 10.1 to 10.23, carry out one or more of the following tasks. Additional tasks are indicated at each problem.

- **(a)** State an appropriate ANOVA model, null hypotheses, and alternative hypotheses. State whether the model is fixed, random, or mixed. Define the population to which inferences are to be made.
- **(b)** Test the assumption of homogeneity of variance.
- **(c)** Test the assumption of normality using a probability plot.
- **(d)** Test the assumption of normality correlating residuals and rankits.
- **(e)** Graph the data. Locate the cell means on the graph.
- **(f)** Transform the data. Give a rationale for transformation.

(g) Carry out the analysis of variance. State conclusions and reservations. Compare with the conclusions of the author(s) of the paper. If possible, estimate the power if the results are not significant.

(h) Carry out a nonparametric analysis of variance. Compare with conclusions of parametric analysis.

(i) Partition each observation into its component parts [see, e.g., equations (4) and (19)] and verify that the sum of squares of each component is equal to one of the sums of squares in the ANOVA table.

(j) Construct the ANOVA table from means and standard deviations (or standard errors). Do relevant parts of (g).

10.1 Olsen et al. [1975] studied "morphine and phenytoin binding to plasma proteins in renal and hepatic failure." Twenty-eight subjects with uremia were classified into four groups. The percentage of morphine that was bound is the endpoint.

Chronic ($n_1 = 18$): 31.5, 35.1, 32.1, 34.2, 26.7, 31.9, 30.8,
27.3, 27.3, 29.0, 30.0, 36.4, 39.8, 32.0, 35.9, 29.9, 32.2, 31.8

Acute ($n_2 = 2$): 31.6, 28.5

Dialysis ($n_3 = 3$): 29.3, 32.1, 26.9

Anephric ($n_4 = 5$): 26.5, 22.7, 27.5, 24.9, 23.4

(a) Do tasks (a) to (e) and (g) to (i).

(b) In view of the nature of the response variable (percent of morphine bound), explain why, strictly speaking, the assumption of homogeneity of variance cannot hold.

10.2 Graham [1977] assayed 16 commercially available pancreatic extracts for six types of enzyme activity. See also Example 10.6. Data for one of these enzymes, proteolytic activity, are presented here. The 16 products were classified by packaging form: capsule, tablet, and enteric-coated tablets. The following data were obtained:

	Proteolytic Activity (U/unit)						
Tablet ($n = 5$)	6640	4440	240	990	410		
Capsule ($n = 4$)	6090	5840	110	195			
Coated tablet ($n = 7$)	1800	1420	980	1088	2200	870	690

(a) Do tasks (a) to (e) and (g) to (i).

(b) Is there a transformation that would make the variance more homogeneous? Why is this unlikely to be the case? What is peculiar about the values for the coated tablets?

10.3 The following data from Rifkind et al. [1976] consist of antipyrine clearance of males suffering from β-thalassemia, a chronic type of anemia. In this disease, abnormally thin red blood cells are produced. The treatment of the disease has undesirable side effects, including liver damage. Antipyrine is a drug used to assess liver function with a high clearance rate, indicating satisfactory liver function. These data deal with the antipyrine clearance rate of 10 male subjects classified according to pubertal stage.

The question is whether there is any significant difference in clearance rate among the pubertal stages (I = infant; V = adult).

Pubertal Stage	Clearance Rate (Half-Life in Hours)				
I	7.4	5.6	3.7	6.6	6.0
IV	10.9	12.2			
V	11.3	10.0	13.3		

(a) Do tasks (a) to (e) and (g) to (i).

***(b)** Assuming that the antipyrine clearance rate increases with age, carry out a nonparametric test for trend (see Note 10.2). What is the alternative hypothesis in this case?

10.4 It is known that organisms react to stress. A more recent discovery is that the immune system's response is altered as a function of stress. In a paper by Keller et al. [1981], the immune response of rats as measured by the number of circulating lymphocytes (cells per milliliter $\times 10^{-6}$) was related to the level of stress. The following data are taken from this paper:

Group	Number of Rats	Mean Number of Lymphocytes	SE
Home-cage control	12	6.64	0.80
Apparatus control	12	4.84	0.70
Low shock	12	3.98	1.13
High shock	12	2.92	0.42

(a) Do tasks (a), (b), (e), and (j).

(b) The authors state: "a significant lymphocytopenia [$F(3, 44) = 3.86$, $p < 0.02$] was induced by the stressful conditions." Does your F-ratio agree with theirs?

(c) Sharpen the analysis by considering a trend in the response levels as a function of increasing stress level.

10.5 This problem deals with the data in Table 10.8. The authors of the paper state that the animals were matched on the basis of weight but that there was no correlation with weight. Assume that the data are presented in the order in which the animals were matched, that is, $Y_{111} = 143$ is matched with $Y_{211} = 152$; in general, Y_{1jk} is matched with Y_{2jk}.

(a) Construct a table of differences $D_{jk} = Y_{2jk} - Y_{1jk}$.

(b) Carry out a one-way ANOVA on the differences; include SS_μ in your table.

(c) Interpret SS_μ for these data.

(d) State your conclusions and compare them with the conclusions of Example 10.5.

(e) Relate the MS(between groups) in the one-way ANOVA to one of the MS terms in Table 10.14. Can you identify the connection and the reason for it?

***(f)** We want to correlate the Y_{1jk} observations with the Y_{2jk} observations, but the problem is that the response level changes from day to day, which would induce a correlation. So we will use the following "trick." Calculate $Y^*_{ijk} = Y_{ijk} - \overline{Y}_{ij\cdot}$;

and correlate Y^*_{1jk} with Y^*_{2jk}. Test this correlation using a t-test with $16-1=15$ degrees of freedom. Why $16-1$? There are $7-1=6$ independent pairs for day 10, 5 each for day 12, and day 14, for a total of 16. Since the observations sum to zero already, we subtract one more degree of freedom for estimating the correlation. If matching was not effective, this correlation should be zero.

10.6 Ross and Bras [1975] investigated the relationship between diet and length of life in 121 randomly bred rats. After 21 days of age, each rat was given a choice of several diets *ad libitum* for the rest of its life. The daily food intake (g/day) was categorized into one of six intervals, so that an equal number of rats (except for the last interval) appeared in each interval. The response variable was life span in days. The following data were obtained:

Mean food intake (g/day)	18.3	19.8	20.7	21.6	22.4	24.1
Food intake category	1	2	3	4	5	6
Number of rats	20	20	20	20	20	21
Mean life span (days)	733	653	630	612	600	556
Standard error	117	126	111	115	113	106

(a) Carry out tasks (a), (b), (e), and (j).

(b) Can this be thought of as a regression problem? How would the residual MS from regression be related to the MS error of the analysis of variance?

***(c)** Can you relate in detail the ANOVA procedure and the regression analysis; particularly an assessment of a nonlinear trend?

10.7 The following data from Florey et al. [1977] are the fasting serum insulin levels for adult Jamaican females after an overnight fast:

	Fasting Serum Insulin Level (μU/mL)			
Age	25–34	35–44	45–54	55–64
Number	73	97	74	53
Mean	22.9	26.2	22.0	23.8
SD	10.3	13.0	7.4	10.0

(a) Do tasks (a), (b), (e), and (j).

(b) Why did the authors partition the ages of the subjects into intervals? Are there other ways of summarizing and analyzing the data? What advantages or disadvantages are there to your alternatives?

10.8 The assay of insulin was one of the earliest topics in bioassay. A variety of methods have been developed over the years. In the mid-1960s an assay was developed based on the fact that insulin stimulates glycogen synthesis in mouse diaphragm tissue, in vitro. A paper by Wardlaw and van Belle [1964] describes the statistical aspects of this assay. The data in this problem deal with a qualitative test for insulin activity. A pool of 36 hemidiaphragms was collected for each day's work and the tissues incubated in tubes containing medium with or without insulin. Each tube contained three randomly selected diaphragms. For parts of this problem we ignore tube effects and assume that each treatment was based on six hemidiaphragms. Four unknown samples were

Table 10.34 Glycogen Content Data

Medium Only		Standard Insulin (0.5 mU/mL)		Test Preparation							
				A		B		C		D	
280	290	460	465	470	480	430	300	510	505	310	290
240	275	400	460	440	390	385	505	610	570	350	330
225	350	470	470	425	445	380	485	520	570	250	300

Source: Data adapted from Wardlaw and van Belle [1964].

assayed. Since the diaphragms synthesize glycogen in medium, a control preparation of medium only was added as well as a standard insulin preparation. The glycogen content (optical density in anthrone TEST $\times$ 1000) data are given in Table 10.34.

(a) Carry out tasks (a) to (e) and (g) to (i). (To simplify the arithmetic if you are using a calculator, divide the observations by 100.)

(b) Each column in the data layout represents one tube in which the three hemidiaphragms were incubated so that the design of the experiment is actually hierarchical. To assess the effect of tubes, we partition the SS_ε (with 30 d.f.) into two parts: SS(between tubes within preparations) = $SS_{BT(WP)}$ with six degrees of freedom (why?) and SS(within tubes) = SS_{WT} with 24 degrees of freedom (why?). The latter SS can be calculated by considering each tube as a treatment. The former can then be calculated as $SS_{BT(WP)} = SS_\varepsilon - SS_{WT}$. Carry out this analysis and test the null hypothesis that the variability between tubes within preparations is the same as the within-tube variability.

10.9 Schizophrenia is one of the psychiatric illnesses that is thought to have a definite physiological basis. Lake et al. [1980] assayed the concentration of norepinephrine in the cerebrospinal fluid of patients (NE in CSF) with one of three types of schizophrenia and controls. They reported the following means and *standard errors*:

NE in CSF (pg/mL)	Control Group	Schizophrenic Group		
		Paranoid	Undifferentiated	Schizoaffective
N	29	14	10	11
Mean	91	144	101	122
Standard error	6	20	11	21

Carry out tasks (a), (b), (e), and (j).

10.10 Corvilain et al. [1971] studied the role of the kidney in the catabolism (conversion) of insulin by comparing the metabolic clearance rate in seven control subjects, eight patients with chronic renal failure, and seven anephric (without kidneys) patients. The data for this problem consist of the plasma insulin concentrations (ng/mL) at 45 and 90 min after the start of continuous infusion of labeled insulin. A low plasma concentration is associated with a high metabolic clearance rate, as shown in Table 10.35.

(a) Consider the plasma insulin concentration at 45 minutes. Carry out tasks (a) to (e) and (g) to (i).

Table 10.35 Plasma Concentration Data (ng/mL)

Control			Renal Failure			Anephric		
Patient	45	90	Patient	45	90	Patient	45	90
1	3.7	3.8	1	3.0	4.2	1	6.7	9.6
2	3.4	4.2	2	3.1	3.9	2	2.6	3.4
3	2.4	3.1	3	4.4	6.1	3	3.4	—[a]
4	3.3	4.4	4	5.1	7.0	4	4.0	5.1
5	2.4	2.9	5	1.9	3.5	5	3.1	4.2
6	4.8	5.4	6	3.4	5.7	6	2.7	3.8
7	3.2	4.1	7	2.9	4.3	7	5.3	6.6
			8	3.8	4.8			

[a] Missing observation.

(b) Consider the plasma insulin concentration at 90 minutes. Carry out tasks (a) to (e) and (g) to (i).

(c) Calculate the difference in concentrations between 90 and 45 minutes for each patient. Carry out tasks (a) to (e) and (g) to (i). Omit Patient 3 in the anephric group.

(d) Graph the means for the three groups at 45 and 90 minutes on the same graph. What is the overall conclusion that you draw from the three analyses? Were all three analyses necessary? Would two of three have sufficed? Why or why not?

10.11 We return to the data of Zelazo et al. [1972] one more time. Carry out the Terpstra–Jonckheere test for ordered alternatives as discussed in Note 10.2. Justify the use of an ordered alternative hypothesis. Discuss in terms of power the reason that this analysis does indicate a treatment effect, in contrast to previous analyses.

10.12 One of the problems in the study of SIDS is the lack of a good animal model. Baak and Huber [1974] studied the guinea pig as a possible model observing the effect of lethal histamine shock on the guinea pig thymus. The purpose was to determine if changes in the thymus of the guinea pig correspond to pathological changes observed in SIDS victims. In the experiment 40 animals (20 male, 20 female) were randomly assigned either to "control" or "histamine shock." On the basis of a Wilcoxon two-sample test—which ignored possible gender differences—the authors concluded that the variable medullary blood vessel surface (mm^2/mm^3) did not differ significantly between "control" and "histamine shock." The data below have been arranged to keep track of gender differences.

	Control					**Histamine Shock**				
Female	6.4	6.2	6.9	6.9	5.4	8.4	10.2	6.2	5.4	5.5
	7.5	6.1	7.3	5.9	6.8	7.3	5.2	5.1	5.7	9.8
Male	4.3	7.5	5.2	4.9	5.7	7.5	6.7	5.7	4.9	6.8
	4.3	6.4	6.2	5.0	5.0	6.6	6.9	11.8	6.7	9.0

(a) Do tasks (a) to (e), (g), and (i).

(b) Replace the observations by their ranks and repeat the analysis of variance. Compare your conclusions with those of part (a).

10.13 In tumor metastasis, tumor cells spread from the original site to other organs. Usually, a particular tumor will spread preferentially to specific organs. There are two possibilities as to how this may occur: The tumor cells gradually adapt to the organ to which they have spread, or tumor cells that grow well at this organ are selected preferentially. Nicolson and Custead [1982] studied this problem by comparing the metastatic potential of melanoma tumor cells mechanically lodged in the lungs of mice or injected intravenously and allowed to metastasize to the lung. Each of these cell lines was then harvested and injected subcutaneously. The numbers of pulmonary tumor colonies were recorded for each of three treatments: original line (control), mechanical placement (adaptation), and selection. The data in Table 10.36 were obtained in three experiments involving 84 mice.

Table 10.36 Experimental Data for Three Treatments

	Number of Pulmonary Tumor Colonies										
Experiment	Control				Adaption				Selection		
1	0	4	20	32	0	3	20	7	92	141	
		0	9	22		0	6	24	64	96	149
		1	11	31		2	14	29	79	100	151
2	0	8	31	41	0	10	13	0	101	132	
		3	8	32		0	11	14	52	109	136
		6	22	39		5	12	14	89	110	140
3	0	4	36	49	0	11	21	30	79	111	
		0	18	39		0	13	27	46	89	114
		2	29	42		3	13	28	51	100	114

(a) Carry out tasks (a) to (g). You may want to try several transformations: for example, $\sqrt{\ }$, $Y^{1/4}$. An appropriate transformation is logarithmic. To avoid problems with zero values, use $\log(Y + 1)$.

(b) How would you interpret a significant "experiment × treatment" interaction?

10.14 A paper by Gruber [1976] evaluated interactions between two analgesic agents: fenoprofen and propoxyphene. The design of the study was factorial with respect to drug combinations. Propoxyphene (P) was administered in doses of 0, 5, 100, and 150 mg.; fenoprofen (F) in doses of 0, 200, 400, and 600 mg. Each combination of the two factors was studied. In addition, postepisiotomy postpartum patients were categorized into one of four pain classes: "little," "some," "lot," and "terrible" pain; for each of the 16 medication combinations, 8, 10, 10, and 2 patients in the four pain classes were used. The layout of the number of patients could be constructed as shown in Table 10.37.

(a) One response variable was "analgesic score" for a medication combination. Table 10.38 is a partial ANOVA table for this variable. Fill in the lines in the table, completing the table.

(b) The total analgesic score for the 16 sets of 30 patients classified by the two drug levels is given in Table 10.39. Carry out a "randomized block analysis" on these total scores dividing the sums of squares by 30 to return the analysis to a single reading status. Link this analysis with the table in part (a). You have, in effect, partitioned the SS for medications in that table into three parts. Test the significance of the *three* mean squares.

(c) Graph the mean analgesia score (per patient) by plotting the dose on the x-axis for fenoprofen, indicating the levels of the propoxyphene dose in the graph. State your conclusions.

Table 10.37 Design of Medication Combinations

	Medication Combination						
Pain Level	$(0P, 0F)$	$(0P, 200F)$	$\cdots$	$(0P, 600F)$	$(50P, 0F)$	$\cdots$	$(150P, 600F)$
"Little"	8	8	$\cdots$	8	8	$\cdots$	8
"Some"	10	10	$\cdots$	10	10	$\cdots$	10
"Lot"	10	10	$\cdots$	10	10	$\cdots$	10
"Terrible"	2	2	$\cdots$	2	2	$\cdots$	2

Table 10.38 ANOVA Table for Analgesic Score

Source	d.f.	SS	MS	F-Ratio	P-Value
Pain class	—	3,704	—	—	—
Medications	—	9,076	—	—	—
Interaction	—	3,408	—	—	—
Residual	—	—	—		
Total	479	41,910			

Table 10.39 Total Analgesia Score

	Fenoprofen Calcium Dose (mg)			
Propoxyphene Dose (mg)	0	200	400	600
0	409	673	634	756
50	383	605	654	785
100	496	773	760	755
150	496	723	773	755

10.15 Although the prescription, "Take two aspirins, drink lots of fluids, and go to bed," is usually good advice, it is known that aspirin induces "microbleeding" in the gastrointestinal system, as evidenced by minute amounts of blood in the stool. Hence, there is constant research to develop other anti-inflammatory and antipyretic (fever-combating) agents. Arsenault et al. [1976] reported on a new agent, R-803, studying its effect in a Latin square design, comparing it to placebo and aspirin (900 mg, q.i.d). For purposes of this exercise the data are extracted in the form of a randomized block design. Each subject received each of three treatments for a week. We will assume that the order was random. The variable measured is the amount of blood lost in mL/day as measured over a week.

	Mean Blood Loss (ml/day)								
Subject	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**
Placebo	0.45	0.54	0.69	0.53	3.03	0.78	0.14	0.82	0.96
R-803	0.82	0.39	0.67	1.19	1.18	1.07	0.49	0.14	0.80
Aspirin	18.00	6.46	6.19	6.52	7.18	9.39	6.93	1.57	4.03

(a) Do tasks (a) to (e) and (g) to (i).

(b) Carry out the Tukey test for additivity. What are your conclusions?

Table 10.40 COHb Data for Problem 10.16

	No. Hours Since Beginning of Exposure				
Subject	0	2	4	6	8
1	4.4	4.9	5.2	5.7	5.7
2	3.3	5.3	6.9	7.0	8.8
3	5.0	6.4	7.2	7.7	9.3
4	5.3	5.3	7.4	7.0	8.3
5	4.1	6.8	9.6	11.5	12.0
6	5.0	6.0	6.8	8.3	8.1
7	4.6	5.2	6.6	7.4	7.1

10.16 Occupational exposures to toxic substances are being investigated more and more carefully. Ratney et al. [1974] studied the effect of daily exposure of 180 to 200 ppm of methylene chloride on carboxyhemoglobin (COHb) measured during the workday. The COHb data (% COHb) for seven subjects measured five times during the day is given in Table 10.40.

(a) Carry out tasks (a), (c) to (e), and (g) to (i).

(b) Suppose that the observation for subject 3 at time 6 ($Y_{34} = 7.7$) is missing. Estimate its value and redo the ANOVA.

(c) Carry out the Tukey test for additivity.

(d) Carry out the Page test for trend (see Note 10.2).

(e) Why do the data not form a randomized block design?

(f) Could this problem be treated by regression methods, where X = hours since exposure and Y = % COHb? Why or why not?

(g) Calculate all 10 pairwise correlations between the treatment combinations. Do they look "reasonably close"?

10.17 Wang et al. [1976] studied the effects on sleep of four hypnotic agents and a placebo. The preparations were: lorazepam 2 and 4 mg, and flurazepam 15 and 30 mg. Each of 15 subjects received all five treatments in a random order in five-night units. The analysis of variance of length of sleep is presented here.

Source	d.f.	SS	MS	F-Ratio	p-Value
Treatments	—	—	12.0	—	—
Patients	—	—	14.8	—	—
Residual	—	—	2.2		
Total	74	—			

(a) Do task (a).

(b) Fill in the missing values in the ANOVA table.

(c) State your conclusions.

(d) The article does not present any raw data or means. How satisfactory is this in terms of clinical significance?

10.18 High blood pressure is a known risk factor for cardiovascular disease, and many drugs are now on the market that provide symptomatic as well as therapeutic relief. One of

Table 10.41 Blood Pressure Data (mmHg) for Problem 10.18

	Recumbent		Upright	
Patient	Placebo	Propranolol	Placebo	Propranolol
N.F.	96	71	73	87
A.C.	96	85	104	76
P.D.	92	89	83	90
J.L.	97	110	101	85
G.P.	104	85	112	94
A.H.	100	73	101	93
C.L.	93	81	88	85

these drugs is propranolol. Hamet et al. [1973] investigated the effect of propranolol in labile hypertension. Among the variables studied was mean blood pressure measured in mmHg (diastolic + 1/3 pulse pressure). A placebo treatment was included in a double-blind fashion. The blood pressure was measured in the recumbent and upright positions. The blood pressure data is given in Table 10.41.

(a) Assuming that the treatments are just four treatments, carry out tasks (a) to (e) and (g) to (i) (i.e., assume a randomized block design).

(b) The sum of squares for treatments (3 d.f.) can be additively partitioned into three parts: SS_{DRUG}, $SS_{POSITION}$, and $SS_{DRUG\times POSITION}$, each with one degree of freedom. To do this, construct an "interaction table" of treatment totals.

$$SS_{DRUGS} = \frac{1340^2}{14} + \frac{1204^2}{14} - \frac{2544^2}{28} = 660.57$$

$$SS_{POSITION} = \frac{1272^2}{14} + \frac{1272^2}{14} - \frac{2544^2}{28} = 0[sic]$$

$$SS_{DRUGS\times POSITION} = \frac{678^2}{7} + \frac{594^2}{4} + \frac{662^2}{7} + \frac{610^2}{7} - \frac{2544^2}{28} - SS_{DRUGS} - SS_{POSITION} = 36.57$$

Expand the ANOVA table to include these terms. (The $SS_{POSITION} = 0$ is most unusual; the raw data are as reported in the table.)

(c) This analysis could have been carried out as a series of three paired t-tests as follows: for each subject, calculate the following three quantities "$++--$," "$+-+-$," and "$+--+$." For example, for subject N.F. "$++--$" = $96 + 71 - 73 - 87 = 7$, "$+-+-$" = $96 - 71 + 73 - 87 = 11$, and "$+--+$" = $96 - 71 - 73 + 87 = 39$. These quantities represent effects of position, drug treatment, and interaction, respectively, and are called *contrasts* (see Chapter 12 for more details). Each contrast can be tested against zero by means of a one-sample t-test. Carry out these t-tests. Compare the variances for each contrast; one assumption in the analysis of variance is that these contrast variances all estimate the same variance. How is the sum of the contrast variances related to the SS_ε in the ANOVA?

(d) Let d_1 be the sum of the observations associated with the pattern $++--$, d_2 the sum of the observations associated with the pattern $+-+-$, and d_3 the sum

of the observations associated with the pattern $+--+$. How is $(d_1^2 + d_2^2 + d_3^2)$ related to $SS_{TREATMENT}$?

10.19 Consider the data in Example 10.5. Rank all 38 observations from lowest to highest and carry out the usual analysis of variance on these ranks. Compare your p-values with the p-values of Table 10.14. In view of Note 10.3, does this analysis give you some concern?

10.20 Consider the data of Table 10.16 dealing with the effectiveness of pancreatic supplements on fat absorption. Rank all of the observations from 1 to 24 (i.e., ignoring both treatment and block categories).

(a) Carry out an analysis of variance on the ranks obtained above.

(b) Compare your analysis with the analysis using the Friedman statistic. What is a potential drawback in the analysis of part (a)?

(c) Return to the Friedman ranks in Section 10.3.3 and carry out an analysis of variance on them. How is the Friedman statistic related to SS_τ of the ANOVA of the Friedman ranks?

10.21 These data are from the same source as those in Problem 10.3. We add data for females to generate the two-way layout shown in Table 10.42.

Table 10.42 Two-Way Layout for Problem 10.21

	Antipyrine Clearance (Half-Life in Hours)					
	Stage I		Stage IV		Stage V	
Males	7.4	5.6	3.7	10.9	11.3	13.3
	6.6	6.0		12.2	10.0	
Females	9.1	6.3	7.1	11.0	8.3	
	11.3	9.4	7.9		4.3	

(a) Do tasks (a) to (d).

(b) Graph the data. Is there any suggestion of interaction? Of main effects?

(c) Carry out a weighted means analysis.

(d) Partition each observation into its component parts and verify that the sums of squares are *not* additive.

10.22 Fuertes-de la Haba et al. [1976] measured intelligence in offspring of oral and nonoral contraceptive users in Puerto Rico. In the early 1960s, subjects were randomly assigned to oral conceptive use or other methods of birth control. Subsequently, mothers with voluntary pregnancies were identified and offspring between ages 5 and 7 were administered a Spanish–Puerto Rican version of the Wechsler Intelligence Scale for Children (WISC). Table 10.43 lists the data for boys only, taken from the article.

(a) Carry out tasks (a), (b), and (e).

(b) Do an unweighted means analysis. Interpret your findings.

(c) The age categories have obviously been "collapsed." What effect could such a collapsing have on the analysis? (Why introduce age as a variable since IQ is standardized for age?)

(d) Suppose that we carried out a contingency table analysis on the cell frequencies. What could such an analysis show?

Table 10.43 Data for Problem 10.22

	Age Groups (Years)		
	5	6	7–8
Oral contraceptive WISC score			
n	9	18	14
Mean	81.44	88.50	76.00
SD	9.42	11.63	9.29
Other birth control WISC score			
n	11	28	21
Mean	82.91	87.75	83.24
SD	10.11	10.85	9.60

Table 10.44 Data for Problem 10.23

	Gender	
	Boys	Girls
Oral contraceptive WISC score		
n	41	55
Mean	82.68	86.87
SD	11.78	14.66
Other birth control WISC score		
n	60	54
Mean	85.28	85.83
SD	10.55	12.22

10.23 The data in Table 10.44 are also from the article by Fuertes-de la Haba [1976] but have been "collapsed over age" and are presented by treatment (type of contraceptive) by gender. The response variable is, again, Wechsler IQ score.

(a) Carry out tasks (a), (b), and (e).

(b) Do an unweighted means analysis.

(c) Compare your conclusions with those of Problem 10.22.

10.24 This problem considers some implications of the additive model for the two-way ANOVA as defined by equation (18) and illustrated in Example 10.4.

(a) Graph the means of Example 10.4 by using the level of the second variable for the abscissa. Interpret the difference in the patterns.

(b) How many degrees of freedom are left for the means assuming that the model defined by equation (18) holds?

(c) We now want to define a nonadditive model retaining the values of the α's, β's, and μ, equivalently, retaining the same marginal and overall means. You are free to vary any of the cell means subject to the constraints above. Verify that you can manipulate only four cell means. After changing the cell means, calculate for each cell ij the quantity $Y_{ij} = \mu - \alpha_i - \beta_j$. What are some characteristics of these quantities?

(d) Graph the means derived in part (c) and compare the pattern obtained with that of Figure 10.2.

***10.25** This problem is designed to give you some experience with algebraic manipulation. It is not designed to teach you algebra but to provide additional insight into the mathematical structure of analysis of variance models. You will want to take this medicine in small doses.

(a) Show that equation (5) follows from the model defined by equation (4).

(b) Prove equations (6) and (7).

(c) Prove equations (10) to (12) starting with the components of equation (5).

(d) Consider equation (17). Let $\mu_i = \sum n_{ij}\mu_{ij}/n_{i\cdot}$, and so on. Relate α_i and β_j to $\mu_{i\cdot}$ and $\mu_{\cdot j}$.

(e) For the two-way ANOVA model as defined by equation (21), show that $\text{SS}_\varepsilon = \text{SS}_{\text{ERROR}} = \sum(n_{ij} - 1)s_{ij}^2$, where s_{ij}^2 is the variance of the observations in cell (i, j).

(f) Derive the expected mean squares for MS_α and MS_γ in the fixed and random effects models, as given in Table 10.19.

REFERENCES

Akritas, M. G. [1990]. The rank transform in some two-factor designs. *Journal of the American Statistical Association*, **85**: 73–78.

Arsenault, A., Le Bel, E., and Lussier, E. [1976]. Gastrointestinal microbleeding in normal subjects receiving acetylsalicylic acid, placebo and R-803, a new antiinflammatory agent, in a design balanced for residual effects. *Journal of Clinical Pharmacology*, **16**: 473–480. Used with permission from J.B. Lippincott Company.

Baak, J. P. A., and Huber, J. [1974]. Effects of lethal histamine shock in the guinea pig thymus. In *SIDS 1974, Proceedings of the Francis E. Camps International Symposium of Sudden and Unexpected Deaths in Infancy*, R. R. Robertson (ed.). Canadian Foundation for the Study of Infant Death, Toronto, Ontario, Canada.

Barboriak, J. J., Rimm, A., Tristani, F. E., Walker, J. R., and Lepley, D., Jr. [1972]. Risk factors in patients undergoing aorta-coronary bypass surgery. *Journal of Thoracic and Cardiovascular Surgery*, **64**: 92–97.

Beyer, W. H. (ed.) [1968]. *CRC Handbook of Tables for Probability and Statistics*. CRC Press, Cleveland, OH.

Box, G. E. P. [1953]. Non-normality and tests on variances. *Biometrika*, **40**: 318–335. Used with permission of the Biometrika Trustees.

Chikos, P. M., Figley, M. M., and Fisher, L. D. [1977]. Visual assessment of total heart volume and chamber size from standard chest radiographs. *American Journal of Roentgenology*, **128**: 375–380. Copyright © 1977 by the American Roentgenology Society.

Conover, W. J., and Iman, R. L. [1981]. Rank transformations as a bridge between parametric and nonparametric statistics. *American Statistician*, **35**: 124–133.

Corvilain, J., Brauman, H., Delcroix, C., Toussaint, C., Vereerstraeten, P., and Franckson, J. R. M. [1971]. Labeled insulin catabolism in chronic renal failure and the anephric state. *Diabetes*, **20**: 467–475.

Daniel, C. [1976]. *Applications of Statistics to Industrial Experiments*. Wiley, New York.

Daniel, C., and Wood, F. [1999]. *Fitting Equations to Data*, 2nd ed. Wiley, New York.

Draper, N. R., and Smith, H. [1998]. *Applied Regression Analysis*, 3rd ed. Wiley, New York.

Eisenhart, C. [1947]. The assumptions underlying the analysis of variance. *Biometrics*, **3**: 1–21.

Fisher, R. A. [1950]. *Statistical Methods for Research Workers*, 11th ed. Oliver & Boyd, London.

Florey, C. du V., Milner, R. D. G., and Miall, W. I. [1977]. Serum insulin and blood sugar levels in a rural population of Jamaican adults. *Journal of Chronic Diseases*, **30**: 49–60. Used with permission of Pergamon Press, Inc.

Freeman, M. F., and Tukey, J. W. [1950]. Transformations related to the angular and the square root. *Annals of Mathematical Statistics*, **21**: 607–611.

Friedman, M. [1937]. The use of ranks to avoid the assumption of normality implicit in the analysis of variance. *Journal of the American Statistical Association*, **32**: 675–701.

Fuertes-de la Haba, A., Santiago, G., and Bangdiwala, I. S. [1976]. Measured intelligence in offspring of oral and non-oral contraceptive users. *American Journal of Obstetrics and Gynecology*, **7**: 980–982.

Graham, D. Y. [1977]. Enzyme replacement therapy of exocrine pancreatic insufficiency in man. *New England Journal of Medicine*, **296**: 1314–1317.

Gruber, C. M., Jr. [1976]. Evaluating interactions between fenoprofen and propoxyphene: analgesic and adverse reports by postepisiotomy patients. *Journal of Clinical Pharmacology*, **16**: 407–417. Used with permission from J.B. Lippincott Company.

Hamet, P., Kuchel, O., Cuche, J. L., Boucher, R., and Genest, J. [1973]. Effect of propranolol on cyclic AMP excretion and plasma renin activity in labile essential hypertension. *Canadian Medical Association Journal*, **1**: 1099–1103.

Hettmansperger, T. P., and McKean, J. W. [1978]. Statistical inference based on ranks. *Psychometrika*, **43**: 69–79.

Hillel, A., and Patten, C. [1990]. Effects of age and gender on dominance for lateral abduction of the shoulder. Unpublished data; used by permission.

Hollander, M., and Wolfe, D. A. [1999]. *Nonparametrical Statistical Methods*, 2nd ed. Wiley, New York.

Joiner, B. L., and Rosenblatt, J. R. [1971]. Some properties of the range in samples from Tukey's symmetric lambda distributions. *Journal of the American Statistical Association*, **66**: 394–399.

Keller, S. E., Weiss, J. W., Schleifer, S. J., Miller, N. E., and Stein, M. [1981]. Suppression of immunity by stress. *Science*, **213**: 1397–1400. Copyright © 1981 by the AAAS.

Kruskal, W. H., and Wallis, W. A. [1952]. Use of ranks in one-criterion variance analysis. *Journal of the American Statistical Association*, **47**: 583–621.

Lake, C. R., Sternberg, D. E., van Kammen, D. P., Ballenger, J. C., Ziegler, M. G., Post, R. M., Kopin, I. J., and Bunney, W. E. [1980]. Schizophrenia: elevated cerebrospinal fluid norepinephrine. *Science*, **207**: 331–333. Copyright © 1980 by the AAAS.

Looney, S. W., and Stanley, W. B. [1989]. Exploratory repeated measures analysis for two or more groups. *American Statistician*, **43**: 220–225.

Nicolson, G. L., and Custead, S. E. [1982]. Tumor metastasis is not due to adaptation of cells to a new organ environment. *Science*, **215**: 176–178. Copyright © 1982 by the AAAS.

Odeh, R. E., Owen, D. B., Birnbaum, Z. W., and Fisher, L. D. [1977]. *Pocket Book of Statistical Tables*. Marcel Dekker, New York.

Olsen, G. D., Bennett, W. M., and Porter, G. A. [1975]. Morphine and phenytoin binding to plasma proteins in renal and hepatic failure. *Clinical Pharmaceuticals and Therapeutics*, **17**: 677–681.

Page, E. B. [1963]. Ordered hypotheses for multiple treatments: a significance test for linear ranks. *Journal of the American Statistical Association*, **58**: 216–230.

Quesenberry, P. D., Whitaker, T. B., and Dickens, J. W. [1976]. On testing normality using several samples: an analysis of peanut aflatoxin data. *Biometrics*, **32**: 753–759.

Ratney, R. S., Wegman, D. H., and Elkins, H. B. [1974]. In vivo conversion of methylene chloride to carbon monoxide. *Archives of Environmental Health*, **28**: 223–226. Reprinted with permission of the Helen Dwight Reid Educational Foundation. Published by Heldref Publications, 4000 Albemarle Street, N.W., Washington DC 20016. Copyright © 1974.

Rifkind, A. B., Canale, V., and New, M. I. [1976]. Antipyrine clearance in homozygous beta-thalassemia. *Clinical Pharmaceuticals and Therapeutics*, **20**: 476–483.

Ross, M. H., and Bras, G. [1975]. Food preference and length of life. *Science*, **190**: 165–167. Copyright © 1975 by the AAAS.

Ryan, T. A., Jr., Joiner, B. L., and Ryan, B. F. [1980]. *Minitab Reference Manual*, Release 1/10/80. Statistics Department, Pennsylvania State University, University Park, PA.

Scheffé, H. [1959]. *The Analysis of Variance*. Wiley, New York.

Sherwin, R. P., and Layfield, L. J. [1976]. Protein leakage in lungs of mice exposed to 0.5 ppm nitrogen dioxide: a fluorescence assay for protein. *Archives of Environmental Health*, **31**: 116–118.

Snedecor, G. W., and Cochran, W. G. [1988]. *Statistical Methods*, 8th ed. Iowa State University Press, Ames, IA.

Tukey, J. W. [1949]. One degree of freedom for additivity. *Biometrics*, **5**: 232–242.

Wallace S. S, Fisher, L. D., and Tremann, J. A. [1977]. Unpublished manuscript.

Wang, R. I. H., Stockdale, S. L., and Hieb, E. [1976]. Hypnotic efficacy of lorazepam and flurazepam. *Clinical Pharmaceuticals and Therapeutics*, **19**: 191–195.

Wardlaw, A. C., and van Belle, G. [1964]. Statistical aspects of the mouse diaphragm test for insulin. *Diabetes*, **13**: 622–634.

Weisberg, S. [1985]. *Applied Linear Regression*, 2nd ed. Wiley, New York.

Weisberg, S., and Bingham, C. [1975]. Approximate analysis of variance test for non-normality suitable for machine calculation. *Technometrics*, **17**: 133–134.

Winer, B. J. [1991]. *Statistical Principles in Experimental Design*, 3rd ed. McGraw-Hill, New York.

Zelazo, P. R., Zelazo, N. A., and Kalb, S. [1972]. "Walking" in the newborn. *Science*, **176**: 314–315.

CHAPTER 11

Association and Prediction: Multiple Regression Analysis and Linear Models with Multiple Predictor Variables

11.1 INTRODUCTION

We looked at the linear relationship between two variables, say X and Y, in Chapter 9. We learned to estimate the regression line of Y on X and to test the significance of the relationship. Summarized by the correlation coefficient, the square of the correlation coefficient is the percent of the variability explained.

Often, we want to predict or explain the behavior of one variable in terms of more than one variable, say k variables $X_1, \ldots, X_k$. In this chapter we look at situations where Y may be explained by a linear relationship with the explanatory or predictor variables $X_1, \ldots, X_k$. This chapter is a generalization of Chapter 9, where only one explanatory variable was considered. Some additional considerations will arise. With more than one potential predictor variable, it will often be desirable to find a simple model that explains the relationship. Thus we consider how to select a subset of predictor variables from a large number of potential predictor variables to find a reasonable predictive equation. Multiple regression analyses, as the methods of this chapter are called, are one of the most widely used tools in statistics. If the appropriate limitations are kept in mind, they can be useful in understanding complex relationships. Because of the difficulty of calculating the estimates involved, most computations of multiple regression analyses are performed by computer. For this reason, this chapter includes examples of output from multiple regression computer runs.

11.2 MULTIPLE REGRESSION MODEL

In this section we present the multiple regression mathematical model. We discuss the methods of estimation and the assumptions that are needed for statistical inference. The procedures are illustrated with two examples.

11.2.1 Linear Model

Definition 11.1. A *linear equation* for the variable Y in terms of $X_1, \ldots, X_k$, is an equation of the form

$$Y = a + b_1 X_1 + \cdots + b_k X_k \tag{1}$$

The values of a, $b_1, \ldots, b_k$, are fixed constant values. These values are called *coefficients*.

Biostatistics: A Methodology for the Health Sciences, Second Edition, by Gerald van Belle, Lloyd D. Fisher, Patrick J. Heagerty, and Thomas S. Lumley
ISBN 0-471-03185-2

Suppose that we observe Y and want to model its behavior in terms of independent, predictor, explanatory, or covariate variables, $X_1, \ldots, X_k$. For a particular set of values of the covariates, the Y value will not be known with certainty. As before, we model the expected value of Y for given or known values of the X_j. Throughout this chapter, we consider the behavior of Y for fixed, known, or observed values for the X_j. We have a multiple linear regression model if the expected value of Y for the known $X_1, \ldots, X_k$ is linear. Stated more precisely:

Definition 11.2. Y has a linear regression on $X_1, \ldots, X_k$ if the expected value of Y for the known X_j values is linear in the X_j values. That is,

$$E(Y|X_1, \ldots, X_k) = \alpha + \beta_1 X_1 + \cdots + \beta_k X_k \tag{2}$$

Another way of stating this is the following. Y is equal to a linear function of the X_j, plus an error term whose expectation is zero:

$$Y = \alpha + \beta_1 X_1 + \cdots + \beta_k X_k + \varepsilon \tag{3}$$

where

$$E(\varepsilon) = 0$$

We use the Greek letters α and β_j for the population parameter values and Latin letters a and b_j for the estimates to be described below. Analogous to definitions in Chapter 9, the number α is called the *intercept* of the equation and is equal to the expected value of Y when all the X_j values are zero. The β_j coefficients are the regression coefficients.

11.2.2 Least Squares Fit

In Chapter 9 we fitted the regression line by choosing the estimates a and b to minimize the sum of squares of the differences between the Y values observed and those predicted or modeled. These differences were called *residuals*; another way of explaining the estimates is to say that the coefficients were chosen to minimize the sum of squares of the residual values. We use this same approach, for the same reasons, to estimate the regression coefficients in the multiple regression problem. Because we have more than one predictor or covariate variable and multiple observations, the notation becomes slightly more complex. Suppose that there are n observations; we denote the observed values of Y for the ith observation by Y_i and the observed value of the jth variable X_j by X_{ij}. For example, for two predictor variables we can lay out the data in the array shown in Table 11.1.

Table 11.1 Data Layout for Two Predictor Variables

Case	Y	X_1	X_2
1	Y_1	X_{11}	X_{12}
2	Y_2	X_{21}	X_{22}
⋮	⋮	⋮	⋮
i	Y_i	X_{i1}	X_{i2}
⋮	⋮	⋮	⋮
n	Y_n	X_{n1}	X_{n2}

The following definition extends the definition of least squares estimation to the multiple regression situation.

Definition 11.3. Given data $(Y_i, X_{i1}, \ldots, X_{ik})$, $i = 1, \ldots, n$, the *least squares fit* of the regression equation chooses $a, b_1, \ldots, b_k$ to minimize

$$\sum_{i=1}^{n} (Y_i - \widehat{Y}_i)^2$$

where $\widehat{Y}_i = a + b_1 X_{i1} + \cdots + b_k X_{ik}$. The b_j are the *(sample) regression coefficients*, a is the *sample intercept*. The difference $Y_i - \widehat{Y}_i$ is the ith *residual*.

The actual fitting is usually done by computer, since the solution by hand can be quite tedious. Some details of the solution are presented in Note 11.1.

Example 11.1. We consider a paper by Cullen and van Belle [1975] dealing with the effect of the amount of anesthetic agent administered during an operation. The work also examines the degree of trauma on the immune system, as measured by the decreasing ability of lymphocytes to transform in the presence of mitogen (a substance that enhances cell division). The variables measured (among others) were X_1, the duration of anesthesia (in hours); X_2, the trauma factor (see Table 11.2 for classification); and Y, the percentage depression of lymphocyte transformation following anesthesia. It is assumed that the amount of anesthetic agent administered is directly proportional to the duration of anesthesia. The question of the influence of each of the two predictor variables is the crucial one, which will not be answered in this section. Here we consider the combined effect. The set of 35 patients considered for this example consisted of those receiving general anesthesia. The basic data are reproduced in Table 11.3. The predicted values and deviations are calculated from the least squares regression equation, which was $Y = -2.55 + 1.10X_1 + 10.38X_2$.

11.2.3 Assumptions for Statistical Inference

Recall that in the simple linear regression models of Chapter 9, we needed assumptions about the distribution of the error terms before we proceeded to statistical inference, that is, before we tested hypotheses about the regression coefficient using the F-test from the analysis of variance table. More specifically, we assumed:

Simple Linear Regression Model Observe (X_i, Y_i), $i = 1, \ldots, n$. The model is

$$Y_i = \alpha + \beta X_i + \varepsilon_i \tag{4}$$

Table 11.2 Classification of Surgical Trauma

0	Diagnostic or therapeutic regional anesthesia; examination under general anesthesia
1	Joint manipulation; minor orthopedic procedures; cystoscopy; dilatation and curettage
2	Extremity, genitourinary, rectal, and eye procedures; hernia repair; laparoscopy
3	Laparotomy; craniotomy; laminectomy; peripheral vascular surgery
4	Pelvic extenteration; jejunal interposition; total cystectomy

Table 11.3 Effect of Duration of Anesthesia (X_1) and Degree of Trauma (X_2) on Percentage Depression of Lymphocyte Transformation following Anesthesia (Y)

Patient	X_1: Duration	X_2: Trauma	Y: Percent Depression	Predicted Value of Y	$Y - \widehat{Y}$ Residual
1	4.0	3	36.7	33.0	3.7
2	6.0	3	51.3	35.2	16.1
3	1.5	2	40.8	19.9	20.9
4	4.0	2	58.3	22.6	35.7
5	2.5	2	42.2	21.0	21.2
6	3.0	2	34.6	21.5	13.1
7	3.0	2	77.8	21.5	56.3
8	2.5	2	17.2	21.0	−3.8
9	3.0	3	−38.4	31.9	−70.3
10	3.0	3	1.0	31.9	−30.9
11	2.0	3	53.7	20.8	22.9
12	8.0	3	14.3	37.4	−23.1
13	5.0	4	65.0	44.5	20.5
14	2.0	2	5.6	20.4	−14.8
15	2.5	2	4.4	21.0	−16.6
16	2.0	2	1.6	20.4	−18.8
17	1.5	2	6.2	19.9	−13.7
18	1.0	1	12.2	8.9	3.3
19	3.0	3	29.9	31.9	−2.0
20	4.0	3	76.1	33.0	43.1
21	3.0	3	11.5	32.0	−20.5
22	3.0	3	19.8	31.9	−12.1
23	7.0	4	64.9	46.7	18.2
24	6.0	4	47.8	45.6	2.2
25	2.0	2	35.0	20.4	14.6
26	4.0	2	1.7	22.6	−20.9
27	2.0	2	51.5	20.4	31.1
28	1.0	1	20.2	8.9	11.3
29	1.0	1	−9.3	8.9	−18.2
30	2.0	1	13.9	10.0	3.9
31	1.0	1	−19.0	8.9	−27.9
32	3.0	1	−2.3	11.1	−13.4
33	4.0	3	41.6	33.0	8.6
34	8.0	4	18.4	47.8	−29.4
35	2.0	2	9.9	20.4	−10.5
Total	112.5	83	896.1	896.3	−0.2[a]
Mean	3.21	2.37	25.60	25.60	−0.006

[a]Zero except for round-off error.

or

$$Y_i = E(Y_i|X_i) + \varepsilon_i$$

where the "error" terms ε_i are statistically independent of each other and all have the same normal distribution with mean zero and variance σ^2; that is, $\varepsilon_i \sim N(0, \sigma^2)$.

Using this model, it is possible to set up the analysis of variance table associated with the regression line. The ANOVA table has the following form:

Source of Variation	Degrees of Freedom (df)	Sum of Squares (SS)	Mean Square (MS)	F-Ratio
Regression	1	$SS_{REG} = \sum_i (\widehat{Y}_i - \overline{Y})^2$	$MS_{REG} = SS_{REG}$	$\frac{MS_{REG}}{MS_{RESID}}$
Residual	$n-2$	$SS_{RESID} = \sum_i (Y_i - \widehat{Y}_i)^2$	$MS_{RESID} = \frac{SS_{RESID}}{n-2}$	
Total	$n-1$	$\sum_i (Y_i - \overline{Y}_i)^2$		

The mean square for residual is an estimate of the variance σ^2 about the regression line. (In this chapter we change notation slightly from that used in Chapter 9. The quantity σ^2 used here is the variance about the regression line. This was σ_1^2 in Chapter 9.)

The F-ratio is an F-statistic having numerator and denominator degrees of freedom of 1 and $n-2$, respectively. We may test the hypothesis that the variable X has linear predictive power for Y, that is, $\beta \neq 0$, by using tables of critical values for the F-statistic with 1 and $n-2$ degrees of freedom. Further, using the estimate of the variance about the regression line MS_{RESID}, it was possible to set up confidence intervals for the regression coefficient β.

For multiple regression equations of the current chapter, the same assumptions needed in the simple linear regression analyses carry over in a very direct fashion. More specifically, our assumptions for the multiple regression model are the following.

Multiple Regression Model Observe $(Y_i, X_{i1}, \ldots, X_{ik})$, $i = 1, 2, \ldots, n$ (n observations). The distribution of Y_i for fixed or known values of $X_{i1}, \ldots, X_{ik}$ is

$$Y_i = E(Y_i | X_{i1}, \ldots, X_{ik}) + \varepsilon_i \tag{5}$$

where $E(Y_i | X_{i1}, \ldots, X_{ik}) = \alpha + \beta_1 X_{i1} + \cdots + \beta_k X_{ik}$ or $Y_i = \alpha + \beta_1 X_{i1} + \cdots + \beta_k X_{ik} + \varepsilon_i$. The ε_i are statistically independent and all have the same normal distribution with mean zero and variance σ^2; that is, $\varepsilon_i \sim N(0, \sigma^2)$.

With these assumptions, we use a computer program to find the least squares estimate of the regression coefficients. From these estimates we have the predicted value for Y_i given the values of $X_{i1}, \ldots, X_{ik}$. That is,

$$\widehat{Y}_i = a + b_1 X_{i1} + \cdots + b_k X_{ik} \tag{6}$$

Using these values, the ANOVA table for the one-dimensional case generalizes. The ANOVA table in the multidimensional case is now the following:

Source of Variation	Degrees of Freedom (df)	Sum of Squares (SS)	Mean Square (MS)	F-Ratio
Regression	k	$SS_{REG} = \sum_i (\widehat{Y}_i - \overline{Y})^2$	$MS_{REG} = \frac{SS_{REG}}{k}$	$\frac{MS_{REG}}{MS_{RESID}}$
Residual	$n-k-1$	$SS_{RESID} = \sum_i (Y_i - \widehat{Y}_i)^2$	$MS_{RESID} = \frac{SS_{RESID}}{n-k-1}$	
Total	$n-1$	$\sum_i (Y_i - \overline{Y}_i)^2$		

For the ANOVA table and multiple regression model, note the following:

1. If $k = 1$, there is one X variable; the equations and ANOVA table reduce to that of the simple linear regression case.

2. The F-statistic tests the hypothesis that the regression line has no predictive power. That is, it tests the hypothesis

$$H_0{:}\beta_1 = \beta_2 = \cdots = \beta_k = 0 \tag{7}$$

This hypothesis says that all of the beta coefficients are zero; that is, the X variables do not help to predict Y. The alternative hypothesis is that one or more of the regression coefficients $\beta_1, \ldots, \beta_k$ are nonzero. Under the null hypothesis, H_0, the F-statistic, has an F-distribution with k and $n-k-1$ degrees of freedom. Under the alternative hypotheses that one or more of the β_j are nonzero, the F-statistic tends to be too large. Thus the hypothesis that the regression line has predictive power is tested by using tables of the F-distribution and rejection when F is too large.

3. The residual sum of squares is an estimate of the variability about the regression line; that is, it is an estimate of σ^2. Introducing notation similar to that of Chapter 9, we write

$$\hat{\sigma}^2 = S^2_{Y \cdot X_1, \ldots, X_k} = \text{MS}_{\text{RESID}} = \frac{\sum_i (Y_i - \widehat{Y}_i)^2}{n-k-1} \tag{8}$$

4. Using the estimated value of σ^2, it is possible to find estimated standard errors for the b_j, the estimates of the regression coefficients β_j. The estimated standard error is associated with the t distribution with $n-k-1$ degrees of freedom. The test of $\beta_j = 0$ and an appropriate $100(1-\alpha)\%$ confidence interval are given by the following equations. To test H_j: $\beta_j = 0$ at significance level α, use two-sided critical values for the t-distribution with $n-k-1$ degrees of freedom and the test statistic

$$t = \frac{b_j}{\text{SE}(b_j)} \tag{9}$$

where b_j and $\text{SE}(b_j)$ are taken from computer output. Reject H_j if

$$|t| \geq t_{n-k-1, 1-\alpha/2}$$

A $100(1-\alpha)\%$ confidence interval for β_j is given by

$$b_j \pm \text{SE}(b_j) t_{n-k-1, 1-\alpha/2} \tag{10}$$

These two facts follow from the pivotal variable

$$t = \frac{b_j - \beta_j}{\text{SE}(b_j)}$$

which has a t-distribution with $n-k-1$ degrees of freedom.

5. Interpretations of the estimated coefficients in a multiple regression equation must be done cautiously. Recall (from the simple linear regression chapter) that we used the example of height and weight; we noted that if we managed to get the subjects to eat and/or diet to change their weight, this would not have any substantial effect on a person's height despite a relationship between height and weight in the population. Similarly, when we look at the estimated multiple regression equation, we can say that for the observed X values, the regression coefficients β_j have the following interpretation. If all of the X variables except for one, say X_j, are kept fixed, and if X_j changes by one unit, the expected value of Y changes by β_j. Let us consider this statement again for emphasis. *If all the X variables except for one X variable, X_j, are held constant, and the observation has X_j changed by an amount 1, the expected value of Y_i changes by the amount β_j.* This is seen by looking at the difference in the expected values:

$$\alpha + \beta_1 X_1 + \cdots + \beta_j (X_j + 1) + \cdots + \beta_k X_k - (\alpha + \cdots + \beta_j X_j + \cdots + \beta_k X_k) = \beta_j$$

This does not mean that when the regression equation is estimated, by changing X by a certain amount we can therefore change the expected value of Y. Consider a medical example where X_j might be systolic blood pressure and other X variables are other measures of physiological performance. Any maneuvers taken to change X_j might also result in changing some or all of the other X's in the population. The change in Y of β_j holds for the distribution of X's in the population sampled. By changing the values of X_j we might change the overall relationship between the Y_i's and the X_j's, so that the estimated regression equation no longer holds. (Recall again the height and weight example for simple linear regression.) For these reasons, interpretations of multiple regression equations must be made tentatively, especially when the data result from observational studies rather than controlled experiments.

6. If two variables, say X_1 and X_2, are closely related, it is difficult to estimate their regression coefficients because they tend to get confused. Take the extreme case where the variables X_1 and X_2 are actually the same value. Then if we look at $\beta_1 X_1 + \beta_2 X_2$ we can factor out the X_1 variable that is equal to X_2. That is, if $X_1 = X_2$, then $\beta_1 X_1 + \beta_2 X_2 = (\beta_1 + \beta_2) X_1$. We see that β_1 and β_2 are not determined uniquely in this case, but any values for β_1 and β_2 whose sum is the same will give the "same" regression equation. More generally, if X_1 and X_2 are very closely associated in a linear fashion (i.e., if their correlation is large), it is very difficult to estimate the betas. This difficulty is referred to as *collinearity*. We return to this fact in more depth below.

7. In Chapter 9 we saw that the assumptions of the simple linear regression model held if the two variables X and Y have a bivariate normal distribution. This fact may be extended to the considerations of this chapter. If the variables $Y, X_1, \ldots, X_k$ have a multivariate normal distribution, then conditionally upon knowing the values of $X_1, \ldots, X_k$, the assumptions of the multiple regression model hold. Note 11.2 has more detail on the multivariate normal distribution. We shall not go into this in detail but merely mention that if the variables have a multivariate normal distribution, any one of the variables has a normal distribution, any two of the variables have a bivariate normal distribution, and any linear combination of the variables also has a normal distribution.

These generalizations of the findings for simple linear regression are illustrated in the next section, which presents several examples of multiple regression.

11.2.4 Examples of Multiple Regression

Example 11.1. (*continued*) We modeled the percent depression of lymphocyte transformation following anesthesia by using the duration of the anesthesia in hours and trauma factor. The least squares estimates of the regression coefficients, the estimated standard errors and the ANOVA table are given below.

Constant or Variable j	b_j	SE(b_j)
Duration of anesthesia	1.105	3.620
Trauma factor	10.376	7.460
Constant	−2.555	12.395

Source	d.f.	SS	MS	F-Ratio
Regression	2	4,192.94	2,096.47	3.18
Residual	32	21,070.09	658.44	
Total	34	25,263.03		

From tables of the F-distribution, we see that at the 5% significance level the critical value for 2 and 30 degrees of freedom is 3.32, while for 2 and 40 degrees of freedom it is 3.23. Thus,

$F_{2,32,0.95}$ is between 3.23 and 3.32. Since the observed F-ratio is 3.18, which is smaller at the 5% significance level, we would not reject a null hypothesis that the regression equation has no contribution to the prediction. (Why is the double negative appropriate here?) This being the case, it would not pay to proceed further to examine the significance of the individual regression coefficients. (You will note that a standard error for the constant term in the regression is also given. This is also a feature of the computer output for most multiple regression packages.)

Example 11.2. This is a continuation of Example 9.1 regarding malignant melanoma of the skin in white males. We saw that mortality was related to latitude by a simple linear regression equation and also to contiguity to an ocean. We now consider the modeling of the mortality result using a multiple regression equation with both the "latitude" variable and the "contiguity to an ocean" variable. When this is done, the following estimates result:

Constant or Variable	b_j	SE(b_j)
Latitude in degrees	−5.449	0.551
Contiguity to ocean (1 = contiguous to ocean, 0 = does not border ocean)	18.681	5.079
Constant	360.28	22.572

Source	d.f.	SS	MS	F-Ratio
Regression	2	40,366.82	20,183.41	69.96
Residual	46	13,270.45	288.49	
Total	48	53,637.27		

The F critical values at the 0.05 level with 2 and 40 and 2 and 60 degrees of freedom are 3.23 and 3.15, respectively. Thus the F-statistic for the regression is very highly statistically significant. This being the case, we might then wonder whether or not the significance came from one variable or whether both of the variables contributed to the statistical significance. We first test the significance of the latitude variable at the 5% significance level and also construct a 95% confidence interval. $t = -5.449/0.551 = -9.89$, $|t| > t_{48,0.975} \doteq 2.01$; reject $\beta_1 = 0$ at the 5% significance level. The 95% confidence interval is given by $-5.449 \pm 2.01 \times 0.551$ or $(-6.56, -4.34)$.

Consider a test of the significance of β_2 at the 1% significance level and a 99% confidence interval for β_2. $t = 18.681/5.079 = 3.68$, $|t| > t_{48,0.995} \doteq 2.68$; reject $\beta_2 = 0$ at the 1% significance level. The 99% confidence interval is given by $18.681 \pm 2.68 \times 5.079$ or (5.07, 32.29).

In this example, from the t statistic we conclude that both latitude in degrees and contiguity to the ocean contribute to the statistically significant relationship between the melanoma of the skin mortality rates and the multiple regression equation.

Example 11.3. The data for this problem come from Problems 9.5 to 9.8. These data consider maximal exercise treadmill tests for 43 active women. We consider two possible multiple regression equations from these data. Suppose that we want to predict or explain the variability in $VO_{2\ MAX}$ by using three variables: X_1, the duration of the treadmill test; X_2, the maximum heart rate attained during the test; and X_3, the height of the subject in centimeters. Data resulting from the least squares fit are:

Covariate or Constant	b_j	SE(b_j)	t ($t_{39,0.975} \doteq 2.02$)
Duration (seconds)	0.0534	0.00762	7.01
Maximum heart rate (beats/min)	−0.0482	0.05046	−0.95
Height (cm)	0.0199	0.08359	0.24
Constant	6.954	13.810	

Source	d.f.	SS	MS	F-Ratio ($F_{3,39,0.95} \doteq 2.85$)
Regression	3	644.61	214.87	21.82
Residual	39	384.06	9.85	
Total	42	1028.67		

Note that the overall F-test is highly significant, 21.82, compared to a 5% critical value for the F-distribution with 3 and 39 degrees of freedom of approximately 2.85. When we look at the t statistic for the three individual terms, we see that the t value for duration, 7.01, is much larger than the corresponding 0.05 critical value of 2.02. The other two variables have values for the t statistic with absolute value much less than 2.02. This raises the possibility that duration is the only variable of the three that contributes to the predictive equation. Perhaps we should consider a model where we predict the maximum oxygen consumption in terms of duration rather than using all three variables. In sections to follow, we consider the question of selecting a "best" predictive equation using a subset of a given set of potential explanatory or predictor variables.

Example 11.3. (*continued*) We use the same data but consider the dependent variable to be age. We shall try to model this from three explanatory, or independent, or predictor variables. Let X_1 be the duration of the treadmill test in seconds; let X_2 be $VO_{2\ MAX}$, the maximal oxygen consumption; and let X_3 be the maximum heart rate during the treadmill test. Analysis of these data lead to the following:

Covariate or Constant	b_j	SE(b_j)	t-Statistic ($t_{39,0.975} \doteq 2.02$)
Duration	−0.0524	0.0268	−1.96
$VO_{2\ MAX}$	−0.633	0.378	−1.67
Maximum heart rate	−0.0884	0.119	−0.74
Constant	106.51	18.63	

Source	d.f.	SS	MS	F-Ratio ($F_{3,39,0.95} \doteq 2.85$)
Regression	3	2256.97	752.32	13.70
Residual	39	2142.19	54.93	
Total	42	4399.16		

The overall F value of 13.7 is very highly statistically significant, indicating that if one has the results of the treadmill test, including duration, $VO_{2\ MAX}$, and maximum heart rate, one can gain a considerable amount of knowledge about the subject's age. Note, however, that when we look at the p-values for the individual variables, not one of them is statistically significant!

How can it be that the overall regression equation is very highly statistically significant but none of the variables individually can be shown to have contributed at the 5% significance level? This paradox results because the predictive variables are highly correlated among themselves; they are *collinear*, as mentioned above. For example, we already know from Chapter 9 that the duration and $VO_{2\ MAX}$ are highly correlated variables; there is much overlap in their predictive information. We have trouble showing that the prediction comes from one or the other of the two variables.

11.3 LINEAR ASSOCIATION: MULTIPLE AND PARTIAL CORRELATION

The simple linear regression equation was very closely associated with the correlation coefficient between the two variables; the square of the correlation coefficient was the proportion of the variability in one variable that could be explained by the other variable using a linear predictive equation. In this section we consider a generalization of the correlation coefficient.

11.3.1 Multiple Correlation Coefficient

In considering simple linear regression, we saw that r^2 was the proportion of the variability of the Y_i about the mean that could be explained from the regression equation. We generalize this to the case of multiple regression.

Definition 11.4. The *squared multiple correlation coefficient*, denoted by R^2, is the proportion of the variability in the dependent variable Y that may be accounted for by the multiple regression equation. Algebraically,

$$R^2 = \frac{\text{regression sum of squares}}{\text{total sum of squares}}$$

Since

$$\sum_i (Y_i - \overline{Y})^2 = \sum_i (Y_i - \widehat{Y}_i)^2 + \sum_i (\widehat{Y}_i - \overline{Y}_i)^2$$

$$R^2 = \frac{\text{SS}_{\text{REG}}}{\text{SS}_{\text{TOTAL}}} = \frac{\sum_i (\widehat{Y}_i - \overline{Y})^2}{\sum_i (Y_i - \overline{Y})^2} \tag{11}$$

Definition 11.5. The positive square root of R^2 is denoted by R, the *multiple correlation coefficient*.

The multiple correlation coefficient may also be computed as the correlation between the Y_i and the estimated best linear predictor, $\widehat{Y}_i$. If the data come from a multivariate sample rather than having the X's fixed by experimental design, the quantity R is an estimate of the correlation between Y and the best linear predictor for Y in terms of $X_1, \ldots, X_k$, that is, the correlation between Y and $\mathrm{a} + \mathrm{b}_1 X_1 + \cdots + \mathrm{b}_k X_k$. The population correlation will be zero if and only if all the regression coefficients $\beta_1, \ldots, \beta_k$ are equal to zero. Again, the value of R^2 is an estimate (for a multivariate sample) of the square of the correlation between Y and the best linear predictor for Y in the overall population. Since the population value for R^2 will be zero if and only if the multiple regression coefficients are equal to zero, a test of the statistical significance of R^2 is the F-test for the regression equation. R^2 and F are related (as given by the definition of R^2 and the F test in the analysis of variance table). It is easy to show that

$$R^2 = \frac{kF}{kF + n - k - 1}, \qquad F = \frac{(n - k - 1)R^2}{k(1 - R^2)} \tag{12}$$

The multiple correlation coefficient thus has associated with it the same degrees of freedom as the F distribution: k and $n - k - 1$. Statistical significance testing for R^2 is based on the statistical significance test of the F-statistic of regression.

At significance level α, reject the null hypothesis of the no linear association between Y and $X_1, \ldots, X_k$ if

$$R^2 \geq \frac{kF_{k,n-k-1,1-\alpha}}{kF_{k,n-k-1,1-\alpha} + n - k - 1}$$

where $F_{k,n-k-1,1-\alpha}$ is the $1 - \alpha$ percentile for the F-distribution with k and $n - k - 1$ degrees of freedom.

For any of the examples considered above, it is easy to compute R^2. Consider the last part of Example 11.3, the active female exercise test data, where duration, $VO_{2\ MAX}$, and the maximal heart rate were used to "explain" the subject's age. The value for R^2 is given by $2256.97/4399.16 = 0.51$; that is, 51% of the variability in Y (age) is explained by the three explanatory or predictor variables. The multiple regression coefficient, or positive square root, is 0.72.

The multiple regression coefficient has the same limitations as the simple correlation coefficient. In particular, if the explanatory variables take values picked by an experimenter and the variability about the regression line is constant, the value of R^2 may be increased by taking a large spread among the explanatory variables $X_1, \ldots, X_k$. The value for R^2, or R, may be presented when the data do *not* come from a multivariate sample; in this case it is an indicator of the amount of the variability in the dependent variable explained by the covariates. *It is then necessary to remember that the values do not reflect something inherent in the relationship between the dependent and independent variables, but rather, reflect a quantity that is subject to change according to the value selection for the independent or explanatory variables.*

Example 11.4. Gardner [1973] considered using environmental factors to explain and predict mortality. He studied the relationship between a number of socioenvironmental factors and mortality in county boroughs of England and Wales. Rates for all sizable causes of death in the age bracket 45 to 74 were considered separately. Four social and environmental factors were used as independent variables in a multiple regression analysis of each death rate. The variables included social factor score, "domestic" air pollution, latitude, and the level of water calcium. He then examined the residuals from this regression model and considered relating the residual variability to other environmental factors. The only factors showing sizable and consistent correlation were the long-period average rainfall and latitude, with rainfall being the more significant variable for all causes of death. When rainfall was included as a fifth regressor variable, no new factors were seen to be important. Tables 11.4 and 11.5 give the regression coefficients, not for the raw variables but for standardized variables.

These data were developed for 61 English county boroughs and then used to predict the values for 12 other boroughs. In addition to taking the square of the multiple correlation coefficient for the data used for the prediction, the correlation between observed and predicted values for *the other 12 boroughs* were calculated. Table 11.5 gives the results of these data.

This example has several striking features. Note that Gardner tried to fit a variety of models. This is often done in multiple regression analysis, and we discuss it in more detail in Section 11.8. Also note the dramatic drop (!) in the amount of variability in the death rate that can be explained between the data used to fit the model and the data used to predict values for other boroughs. This may be due to several sources. First, the value of R^2 is always nonnegative and can only be zero if variability in Y can be perfectly predicted. In general, R^2 tends to be too large. There is a value called *adjusted* R^2, which we denote by R_a^2, which takes this effect into account.

Table 11.4 Multiple Regression[a] of Local Death Rates on Five Socioenvironmental Indices in the County Boroughs[b]

Gender/Age Group	Period	Social Factor Score	"Domestic" Air Pollution	Latitude	Water Calcium	Long Period Average Rainfall
Males/45–64	1948–1954	0.16	0.48***	0.10	−0.23	0.27***
	1958–1964	0.19*	0.36***	0.21**	−0.24**	0.30***
Males/65–74	1950–1954	0.24*	0.28*	0.02	−0.43***	0.17
	1958–1964	0.39**	0.17	0.13	−0.30**	0.21
Females/45–64	1948–1954	0.16	0.20	0.32**	−0.15	0.40***
	1958–1964	0.29*	0.12	0.19	−0.22*	0.39***
Females/65–74	1950–1954	0.39***	0.02	0.36***	−0.12	0.40***
	1958–1964	0.40***	−0.05	0.29***	−0.27**	0.29**

[a] A standardized partial regression coefficients given; that is, the variables are reduced to the same mean (0) and variance (1) to allow values for the five socioenvironmental indices in each cause of death to be compared. The higher of two coefficients is not necessarily the more significant statistically.
[b] $^{*}p < 0.05$; $^{**}p < 0.01$; $^{***}p < 0.001$.

Table 11.5 Results of Using Estimated Multiple Regression Equations from 61 County Boroughs to Predict Death Rates in 12 Other County Boroughs

Gender/Age Group	Period	$\widehat{R}^2$	r_2^a
Males/45–64	1948–1954	0.80	0.12
	1958–1964	0.84	0.26
Males/65–74	1950–1954	0.73	0.09
	1958–1964	0.76	0.25
Females/45–64	1948–1954	0.73	0.46
	1958–1964	0.72	0.48
Females/65–74	1950–1954	0.80	0.53
	1958–1964	0.73	0.41

[a] r is the correlation coefficient in the second sample between the value predicted for the dependent variable and its observed value.

This estimate of the population, R^2, is given by

$$R_a^2 = 1 - (1 - R^2)\frac{n-1}{n-k} \tag{13}$$

For the Gardner data on males from 45 to 64 during the time period 1948–1954, the adjusted R^2 value is given by

$$R_a^2 = 1 - (1 - 0.80)\left(\frac{61-1}{61-5}\right) = 0.786$$

We see that this does not account for much of the drop. Another possible effect may be related to the fact that Gardner tried a variety of models; in considering multiple models, one may get a very good fit just by chance because of the many possibilities tried. The most likely explanation, however, is that a model fitted in one environment and then used in another setting may lose much

predictive power because *variables important to one setting may not be as important in another setting*. As another possibility, there could be an important variable that is not even known by the person analyzing the data. If this variable varies between the original data set and the new data set, where one desires to predict, extreme drops in predictive power may occur. As a general rule of thumb, *the more complex the model, the less transportable the model is in time and/or space*. This example illustrates that whenever possible, when fitting a multivariate model including multiple linear regression models, if the model is to be used for prediction it is useful to try the model on an independent sample. Great degradation in predictive power is not an unusual occurrence.

In one example above, we had the peculiar situation that the relationship between the dependent variable age and the independent variables duration, $VO_{2\ MAX}$, and maximal heart rate was such that there was a very highly statistically significant relationship between the regression equation and the dependent variable, but at the 5% significance level we were not able to demonstrate the statistical significance of the regression coefficients of any of the three independent variables. That is, we could not demonstrate that any of the three predictor variables actually added statistically significant information to the prediction. We mentioned that this may occur because of high correlations between variables. This implies that they contain much of the same predictive information. In this case, estimation of their individual contribution is very difficult. This idea may be expressed quantitatively by examining the variance of the estimate for a regression coefficient, say β_j. This variance can be shown to be

$$\text{var}(b_j) = \frac{\sigma^2}{[x_j^2](1 - R_j^2)} \tag{14}$$

In this formula σ^2 is the variance about the regression line and $[x_j^2]$ is the sum of the squares of the difference between the values observed for the jth predictor variable and its mean (this bracket notation was used in Chapter 9). R_j^2 is the square of the multiple correlation coefficient between X_j as dependent variable and the other predictor variables as independent variables. Note that if there is only one predictor, R_j^2 is zero; in this case the formula reduces to the formula of Chapter 9 for simple linear regression. On the other hand, if X_j is very highly correlated with other predictor variables, we see that the variance of the estimate of b_j increases dramatically. This again illustrates the phenomenon of *collinearity*. A good discussion of the problem may be found in Mason [1975] as well as in Hocking [1976].

In certain circumstances, more than one multiple regression coefficient may be considered at one time. It is then necessary to have notation that explicitly gives the variables used.

Definition 11.6. The multiple correlation coefficient of Y with the set of variables $X_1, \ldots, X_k$ is denoted by

$$R_{Y(X_1,\ldots,X_k)}$$

when it is necessary to explicitly show the variables used in the computation of the multiple correlation coefficient.

11.3.2 Partial Correlation Coefficient

When two variables are related linearly, we have used the correlation coefficient as a measure of the amount of association between the two variables. However, we might suspect that a relationship between two variables occurred because they are both related to another variable. For example, there may be a positive correlation between the density of hospital beds in a geographical area and an index of air pollution. We probably would not conjecture that the number of hospital beds increased the air pollution, although the opposite could conceivably be true. More likely, both are more immediately related to population density in the area; thus we might like to examine the relationship between the density of hospital beds and air pollution

after controlling or adjusting for the population density. We have previously seen examples where we controlled or adjusted for a variable. As one example this was done in the combining of 2×2 tables, using the various strata as an adjustment. A partial correlation coefficient is designed to measure the amount of linear relationship between two variables after adjusting for or controlling for the effect of some set of variables. The method is appropriate when there are linear relationships between the variables and certain model assumptions such as normality hold.

Definition 11.7. The *partial correlation coefficient* of X and Y adjusting for the variables $X_1, \ldots, X_k$ is denoted by $\rho_{X,Y.X_1,\ldots,X_k}$. The sample partial correlation coefficient of X and Y adjusting for $X_1, \ldots, X_k$ is denoted by $r_{X,Y.X_1,\ldots,X_k}$. The partial correlation coefficient is the correlation of Y minus its best linear predictor in terms of the X_j variables with X minus its best linear predictor in terms of the X_j variables. That is, letting $\widehat{Y}$ be a predicted value of Y from multiple linear regression of Y on $X_1, \ldots, X_k$ and letting $\widehat{X}$ be the predicted value of X from the multiple linear regression of X on $X_1, \ldots, X_k$, the partial correlation coefficient is the correlation of $X - \widehat{X}$ and $Y - \widehat{Y}$.

If all of the variables concerned have a multivariate normal distribution, the partial correlation coefficient of X and Y adjusting for $X_1, \ldots, X_k$ is the correlation of X and Y conditionally upon knowing the values of $X_1, \ldots, X_k$. The conditional correlation of X and Y in this multivariate normal case is the same for each fixed set of the values for $X_1, \ldots, X_k$ and is equal to the partial correlation coefficient.

The statistical significance of the partial correlation coefficient is equivalent to testing the statistical significance of the regression coefficient for X if a multiple regression is performed with Y as a dependent variable with $X, X_1, \ldots, X_k$ as the independent or explanatory variables. In the next section on nested hypotheses, we consider such significance testing in more detail.

Partial regression coefficients are usually estimated by computer, but there is a simple formula for the case of three variables. Let us consider the partial correlation coefficient of X and Y adjusting for a variable Z. In terms of the correlation coefficients for the pairs of variables, the partial correlation coefficient in the population and its estimate from the sample are given by

$$\rho_{X,Y\cdot Z} = \frac{\rho_{X,Y} - \rho_{X,Z}\rho_{Y,Z}}{\sqrt{(1-\rho_{X,Z}^2)(1-\rho_{Y,Z}^2)}}$$

$$r_{X,Y.Z} = \frac{r_{X,Y} - r_{X,Z}r_{Y,Z}}{\sqrt{(1-r_{X,Z}^2)(1-r_{Y,Z}^2)}} \tag{15}$$

We illustrate the effect of the partial correlation coefficient by the exercise data for active females discussed above. We know that age and duration are correlated. For the data above, the correlation coefficient is -0.68913. Let us consider how much of the linear relationship between age and duration is left if we adjust out the effect of the oxygen consumption, $\mathrm{VO_2\ MAX}$, for the same data set. The correlation coefficients for the sample are as follows:

$$r_{\text{AGE, DURATION}} = -0.68913$$

$$r_{\text{AGE, VO}_2\text{ MAX}} = -0.65099$$

$$r_{\text{DURATION, VO}_2\text{ MAX}} = 0.78601$$

The partial correlation coefficient of age and duration adjusting $\mathrm{VO_2\ MAX}$ using the equation above is estimated by

$$r_{\text{AGE,DURATION}\cdot\text{VO}_2\text{ MAX}} = \frac{-0.68913 - [(-0.65099)(-0.78601)]}{\sqrt{[1-(-0.65099)^2][1-(0.78601)^2]}} = -0.37812$$

If we consider the corresponding multiple regression problem with a dependent variable of age and independent variables duration and $VO_{2\ MAX}$, the t-statistic for duration is -2.58. The two-sided 0.05 critical value is 2.02, while the critical value at significance level 0.01 is 2.70. Thus, we see that the p-value for statistical significance of this partial correlation coefficient is between 0.05 and 0.01.

11.3.3 Partial Multiple Correlation Coefficient

Occasionally, one wants to examine the linear relationship, that is, the correlation between one variable, say Y, and a second group of variables, say $X_1, \ldots, X_k$, while adjusting or controlling for a third set of variables, $Z_1, \ldots, Z_p$. If it were not for the Z_j variables, we would simply use the multiple correlation coefficient to summarize the relationship between Y and the X variables. The approach taken is the same as for the partial correlation coefficient. First subtract out for each variable its best linear predictor in terms of the Z_j's. From the remaining residual values compute the multiple correlation between the Y residuals and the X residuals. More formally, we have the following definition.

Definition 11.8. For each variable let $\widehat{Y}$ or $\widehat{X}_j$ denote the least squares linear predictor for the variable in terms of the quantities $Z_1, \ldots, Z_p$. The best linear predictor for a sample results from the multiple regression of the variable on the independent variables $Z_1, \ldots, Z_p$. The *partial multiple correlation coefficient* between the variable Y and the variables $X_1, \ldots, X_k$ adjusting for $Z_1, \ldots, Z_p$ is the multiple correlation between the variable $Y - \widehat{Y}$ and the variables $X_1 - \widehat{X}_1, \ldots, X_k - \widehat{X}_k$. The partial multiple correlation coefficient of Y and $X_1, \ldots, X_k$ adjusting for $Z_1, \ldots, Z_p$ is denoted by

$$R_{Y(X_1,\ldots,X_k).Z_1,\ldots,Z_p}$$

A significance test for the partial multiple correlation coefficient is discussed in Section 11.4. The coefficient is also called the *multiple partial correlation coefficient*.

11.4 NESTED HYPOTHESES

In the second part of Example 11.3, we saw a multiple regression equation where we could not show the statistical significance of individual regression coefficients. This raised the possibility of reducing the complexity of the regression equation by eliminating one or more variables from the predictive equation. When we consider such possibilities, we are considering what is called a *nested hypothesis*. In this section we discuss nested hypotheses in the multiple regression setting. First we define nested hypotheses; we then introduce notation for nested hypotheses in multiple regression. In addition to notation for the hypotheses, we need notation for the various sums of squares involved. This leads to appropriate F-statistics for testing nested hypotheses. After we understand nested hypotheses, we shall see how to construct F-tests for the partial correlation coefficient and the partial multiple correlation coefficient. Furthermore, the ideas of nested hypotheses are used below in stepwise regression.

Definition 11.9. One hypothesis, say hypothesis H_1, is *nested* within a second hypothesis, say hypothesis H_2, if whenever hypothesis H_1 is true, hypothesis H_2 is also true. That is to say, hypothesis H_1 is a special case of hypothesis H_2.

In our multiple regression situation most nested hypotheses will consist of specifying that some subset of the regression coefficients β_j have the value zero. For example, the larger first

hypothesis might be H_2, as follows:

$$H_2\colon Y = \alpha + \beta_1 X_1 + \cdots + \beta_k X_k + \epsilon$$
$$\epsilon \sim N(0, \sigma^2)$$

The smaller (nested) hypothesis H_1 might specify that some subset of the β's, for example, the last $k - j$ betas corresponding to variables $X_{j+1}, \ldots, X_k$, are all zero. We denote this hypothesis by H_1.

$$H_1\colon Y = \alpha + \beta_1 X_1 + \cdots + \beta_j X_j + \epsilon$$
$$\epsilon \sim N(0, \sigma^2)$$

In other words, H_2 holds *and*

$$\beta_{j+1} = \beta_{j+2} = \cdots = \beta_k = 0$$

A more abbreviated method of stating the hypothesis is the following:

$$H_1\colon \beta_{j+1} = \beta_{j+2} = \cdots = \beta_k = 0 | \beta_1, \ldots, \beta_j$$

To test such nested hypotheses, it will be useful to have a notation for the regression sum of squares for any subset of independent variables in the regression equation. If variables $X_1, \ldots, X_j$ are used as explanatory or independent variables in a multiple regression equation for Y, we denote the regression sum of squares by

$$\mathrm{SS}_{\mathrm{REG}}(X_1, \ldots, X_j)$$

We denote the residual sum of squares (i.e., the total sum of squares of the dependent variable Y about its mean minus the regression sum of squares) by

$$\mathrm{SS}_{\mathrm{RESID}}(X_1, \ldots, X_j)$$

If we use more variables in a multiple regression equation, the sum of squares explained by the regression can only increase, since one potential predictive equation would set all the regression coefficients for the new variables equal to zero. This will almost never occur in practice if for no other reason than the random variability of the error term allows the fitting of extra regression coefficients to explain a little more of the variability. The increase in the regression sum of squares, however, may be due to chance. The F-test used to test nested hypotheses looks at the increase in the regression sum of squares and examines whether it is plausible that the increase could occur by chance. Thus we need a notation for the increase in the regression sum of squares. This notation follows:

$$\mathrm{SS}_{\mathrm{REG}}(X_{j+1}, \ldots, X_k | X_1, \ldots, X_j) = \mathrm{SS}_{\mathrm{REG}}(X_1, \ldots, X_k) - \mathrm{SS}_{\mathrm{REG}}(X_1, \ldots, X_j)$$

This is the sum of squares attributable to $X_{j+1}, \ldots, X_k$ after fitting the variables $X_1, \ldots, X_j$. With this notation we may proceed to the F-test of the hypothesis that adding the last $k - j$ variables does not increase the sum of squares a statistically significant amount beyond the regression sum of squares attributable to $X_1, \ldots, X_k$.

Assume a regression model with k predictor variables, $X_1, \ldots, X_k$. The F-statistic for testing the hypothesis

$$H_1\colon \beta_{j+1} = \cdots = \beta_k = 0 | \beta_1, \ldots, \beta_j$$

is

$$F = \frac{\text{SS}_{\text{REG}}(X_{j+1}, \ldots, X_k | X_1, \ldots, X_j)/(k-j)}{\text{SS}_{\text{RESID}}(X_1, \ldots, X_k)/(n-k-1)}$$

Under H_1, F has an F-distribution with $k-j$ and $n-k-1$ degrees of freedom. Reject H_1 if $F > F_{k-j,n-k-1,1-\alpha}$, the $1-\alpha$ percentile of the F-distribution.

The partial correlation coefficient is related to the sums of squares as follows. Let X be a predictor variable in addition to $X_1, \ldots, X_k$.

$$r^2_{X,Y \cdot X_1,\ldots,X_k} = \frac{\text{SS}_{\text{REG}}(X | X_1, \ldots, X_k)}{\text{SS}_{\text{RESID}}(X_1, \ldots, X_k)} \tag{16}$$

The sign of $r_{X,Y \cdot X_1,\ldots,X_k}$ is the same as the sign of the X regression coefficient when Y is regressed on $X, Y \cdot X_1, \ldots, X_k$. The F-test for statistical significance of $r_{X,Y \cdot X_1,\ldots,X_k}$ uses

$$F = \frac{\text{SS}_{\text{REG}}(X | X_1, \ldots, X_k)}{\text{SS}_{\text{RESID}}(X, X_1, \ldots, X_k)/(n-k-2)} \tag{17}$$

Under the null hypothesis that the partial correlation is zero (or equivalently, that $\beta_X = 0 | \beta_1, \ldots, \beta_k$), F has an F-distribution with 1 and $n-k-2$ degrees of freedom. F is sometimes called the *partial F-statistic*. The t-statistic for the statistical significance of β_X is related to F by

$$t^2 = \frac{\beta_X^2}{\text{SE}(\beta_X)^2} = F$$

Similar results hold for the partial multiple correlation coefficient. The correlation is always positive and its square is related to the sums of squares by

$$R^2_{Y(X_1,\ldots,X_k) \cdot Z_1,\ldots,Z_p} = \frac{\text{SS}_{\text{REG}}(X_1, \ldots, X_k | Z_1, \ldots, Z_p)}{\text{SS}_{\text{RESID}}(Z_1, \ldots, Z_p)} \tag{18}$$

The F-test for statistical significance uses the test statistic

$$F = \frac{\text{SS}_{\text{REG}}(X_1, \ldots, X_k | Z_1, \ldots, Z_p)/k}{\text{SS}_{\text{RESID}}(X_1, \ldots, X_k, Z_1, \ldots, Z_p)/(n-k-p-1)} \tag{19}$$

Under the null hypothesis that the population partial multiple correlation coefficient is zero, F has an F-distribution with k and $n-k-p-1$ degrees of freedom. This test is equivalent to testing the nested multiple regression hypothesis:

$$H\colon \beta_{X_1} = \cdots = \beta_{X_k} = 0 | \beta_{Z_1}, \ldots, \beta_{Z_p}$$

Note that in each case above, the contribution to R^2 after adjusting for additional variables is the increase in the regression sum of squares divided by the residual sum of squares after taking the regression on the adjusting variables. The corresponding F-statistic has a numerator degrees of freedom equal to the number of predictive variables added, or equivalently, the number of additional parameters being estimated. The denominator degrees of freedom are equal to the number of observations minus the total number of parameters estimated. The reason for the -1 in the denominator degrees of freedom in equation (19) is the estimate of the constant in the regression equation.

Example 11.3. (*continued*) We illustrate some of these ideas by returning to the 43 active females who were exercise-tested. Let us compute the following quantities:

$$r_{\mathrm{VO_2\ MAX,DURATION}\,\cdot\,\mathrm{AGE}}$$

$$R^2_{\mathrm{AGE(VO_2\ MAX,\ HEART\ RATE)}\,\cdot\,\mathrm{DURATION}}$$

To examine the relationship between $\mathrm{VO_2\ MAX}$ and duration adjusting for age, let duration be the dependent or response variable. Suppose that we then run two multiple regressions: one predicting duration using only age as the predictive variable and a second regression using both age and $\mathrm{VO_2\ MAX}$ as the predictive variable. These runs give the following data: for $Y =$ duration and $X_1 =$ age:

Covariate or Constant	b_j	$\mathrm{SE}(b_j)$	t-statistic ($t_{41,0.975} \doteq 2.02$)
Age	−5.208	0.855	−6.09
Constant	749.975	39.564	

Source	d.f.	SS	MS	F-Ratio ($F_{1,41,0.95} \doteq 4.08$)
Regression of duration on age	1	119,324.47	119,324.47	37.08
Residual	41	131,935.95	3,217.95	
Total	42	251,260.42		

and for $Y =$ duration, $X_1 =$ age, and $X_2 = \mathrm{VO_2\ MAX}$:

Covariate or Constant	b_j	$\mathrm{SE}(b_j)$	t-statistic ($t_{40,0.975} \doteq 2.09$)
Age	−2.327	0.901	−2.583
$\mathrm{VO_2\ MAX}$	9.151	1.863	4.912
Constant	354.072	86.589	

Source	d.f.	SS	MS	F-Ratio ($F_{2,40,0.95} \doteq 3.23$)
Regression of duration on age and $\mathrm{VO_2\ MAX}$	2	168,961.48	84,480.74	41.06
Residual	40	82,298.94	2,057.47	
Total	42	251,260.42		

Using equation (16), we find the square of the partial correlation coefficient:

$$\begin{aligned} r^2_{\mathrm{VO_2\ MAX,\ DURATION\cdot AGE}} &= \frac{168{,}961.48 - 119{,}324.47}{131{,}935.95} \\ &= \frac{49{,}637.01}{131{,}935.95} \\ &= 0.376 \end{aligned}$$

Since the regression coefficient for $VO_{2\ MAX}$ is positive (when regressed with age) having a value of 9.151, the positive square root gives r:

$$r_{VO_2\ MAX,\ DURATION\ \cdot\ AGE} = +\sqrt{0.376} = 0.613$$

To test the statistical significance of the partial correlation coefficient, equation (17) gives

$$F = \frac{168{,}961.48 - 119{,}324.467}{82{,}298.94/(43 - 1 - 1 - 1)} = 24.125$$

Note that $t^2_{VO_2MAX} = 24.127 = F$ within round-off error. As $F_{1,40,0.999} = 12.61$, this is highly significant ($p < 0.001$). In other words, the duration of the treadmill test and the maximum oxygen consumption are significantly related even after adjustment for the subject's age.

Now we turn to the computation and testing of the partial multiple correlation coefficient. To use equations (18) and (19), we need to regress age on duration, and also regress age on duration, $VO_{2\ MAX}$, and the maximum heart rate. The ANOVA tables follow. For age regressed upon duration:

Source	d.f.	SS	MS	F-Ratio ($F_{1,41,0.95} \doteq 4.08$)
Regression	1	2089.18	2089.18	37.08
Residual	41	2309.98	56.34	
Total	42	4399.16		

and for age regressed upon duration, $VO_{2\ MAX}$, and maximum heart rate:

Source	d.f.	SS	MS	F-Ratio ($F_{3,39,0.95} \doteq 2.85$)
Regression	3	2256.97	752.32	13.70
Residual	39	2142.19	54.93	
Total	42	4399.16		

From equation (18),

$$R^2_{AGE(VO_2\ MAX,\ HEART\ RATE)\ \cdot\ DURATION} = \frac{2256.97 - 2089.18}{2309.98} = 0.0726$$

and $R = \sqrt{R^2} = 0.270$.

The F-test, by equation (19), is

$$F = \frac{(2256.97 - 2089.18)/2}{2142.19/(43 - 2 - 1 - 1)} = 1.53$$

As $F_{2,39,0.90} \doteq 2.44$, we have not shown statistical significance even at the 10% significance level. In words: $VO_{2\ MAX}$ and maximum heart rate have no more additional linear relationship with age, after controlling for the duration, than would be expected by chance variability.

11.5 REGRESSION ADJUSTMENT

A common use of regression is to make inference regarding a specific predictor of inference from observational data. The primary explanatory variable can be a treatment, an environmental exposure, or any other type of measured covariate. In this section we focus on the common biomedical situation where the predictor of interest is a treatment or exposure, but the ideas naturally generalize to any other type of explanatory factor.

In observational studies there can be many uncontrolled and unmeasured factors that are associated with seeking or receiving treatment. A naive analysis that compares the mean response among treated individuals to the mean response among nontreated subjects may be distorted by an unequal distribution of additional key variables across the groups being compared. For example, subjects that are treated surgically may have poorer function or worse pain prior to their being identified as candidates for surgery. To evaluate the long-term effectiveness of surgery, each patient's functional disability one year after treatment can be measured. Simply comparing the mean function among surgical patients to the mean function among patients treated nonsurgically does not account for the fact that the surgical patients probably started at a more severe level of disability than the nonsurgical subjects. When important characteristics systematically differ between treated and untreated groups, crude comparisons tend to distort the isolated effect of treatment. For example, the average functional disability may be higher among surgically treated subjects compared to nonsurgically treated subjects, even though surgery has a beneficial effect for each person treated since only the most severe cases may be selected for surgery. Therefore, without adjusting for important predictors of the outcome that are also associated with being given the treatment, unfair or invalid treatment comparisons may result.

11.5.1 Causal Inference Concepts

Regression models are often used to obtain comparisons that "adjust" for the effects of other variables. In some cases the adjustment variables are used purely to improve the precision of estimates. This is the case when the adjustment covariates are not associated with the exposure of interest but are good predictors of the outcome. Perhaps more commonly, regression adjustment is used to alleviate bias due to confounding. In this section we review causal inference concepts that allow characterization of a well-defined estimate of treatment effect, and then discuss how regression can provide an adjusted estimate that more closely approximates the desired causal effect.

To discuss causal inference concepts, many authors have used the *potential outcomes framework* [Neyman, 1923; Rubin, 1974; Robins, 1986]. With any medical decision we can imagine the outcome that would result if each possible future path were taken. However, in any single study we can observe only one realization of an outcome per person at any given time. That is, we can only measure a person's response to a single observed and chosen history of treatments and exposures. We can still envision the hypothetical, or "potential" outcome that would have been observed had a different set of conditions occurred. An outcome that we believe could have happened but was not actually observed is called a *counterfactual outcome*. For simplicity we assume two possible exposure or treatment conditions. We define the *potential outcomes* as:

$Y_i(0)$: reponse for subject i at a specific measurement time after treatment $X = 0$ is experienced

$Y_i(1)$: reponse for subject i at a specific measurement time after treatment $X = 1$ is experienced

Given these potential outcomes, we can define the *causal effect* for subject i as

$$\text{causal effect for subject } i : \Delta_i = Y_i(1) - Y_i(0)$$

The causal effect Δ_i measures the difference in the outcome for subject i if they were given treatment $X = 1$ vs. the outcome if they were given treatment $X = 0$. For a given population of N subjects, we can define the *average causal effect* as

$$\overline{\Delta} = \frac{1}{N}\sum_{i=1}^{N}\Delta_i$$

The average causal effect is a useful overall summary of the treatment under study. Individual causal effects would be useful for selecting the best intervention for a given person. In general, we can only reliably estimate average causal effects for specific populations of subjects. Using covariates, we may try to narrow the population such that it closely approximates the particular persons identified for possible treatment.

There are a number of important implications associated with the potential outcomes framework:

1. In any given study we can only observe either $Y_i(0)$ or $Y_i(1)$ and not both. We are assuming that $Y_i(0)$ and $Y_i(1)$ represent outcomes under different treatment schemes, and in nature we can only realize one treatment and one subsequent outcome per subject.
2. Each subject is assumed to have an individual causal effect of treatment, Δ_i. Thus, there is no assumption of a single effect of treatment that is shared for all subjects.
3. Since we cannot observe $Y_i(0)$ and $Y_i(1)$, we cannot measure the individual treatment effect Δ_i.

Example 11.4. Table 11.6 gives a hypothetical example of potential outcomes. This example is constructed to approximate the evaluation of surgical and nonsurgical interventions for treatment of a herniated lumbar disk (see Keller et al. [1996] for an example). The outcome represents a measure of functional disability on a scale of 1 to 10, where the intervention has a beneficial effect by reducing functional disability. Here $Y_i(0)$ represents the postintervention outcome if subject i is given a conservative nonsurgical treatment and $Y_i(1)$ represents the postintervention outcome if subject i is treated surgically. Since only one course of treatment

Table 11.6 Hypothetical Example of Potential Outcomes and Individual Causal Effects

Subject i	Potential Outcome $Y_i(0)$	Potential Outcome $Y_i(1)$	Causal Effect Δ_i	Subject i	Potential Outcome $Y_i(0)$	Potential Outcome $Y_i(1)$	Causal Effect Δ_i
1	4.5	2.7	−1.8	11	7.5	5.1	−2.3
2	3.1	1.0	−2.1	12	6.7	5.2	−1.5
3	3.9	2.0	−1.9	13	6.0	4.4	−1.6
4	4.3	2.2	−2.1	14	5.6	3.2	−2.4
5	3.3	1.5	−1.9	15	6.5	4.0	−2.4
6	3.3	0.8	−2.5	16	7.7	6.0	−1.8
7	4.0	1.5	−2.5	17	7.1	5.1	−2.1
8	4.9	3.2	−1.7	18	8.3	6.0	−2.3
9	3.8	2.0	−1.9	19	7.0	4.6	−2.4
10	3.6	2.0	−1.6	20	6.9	5.3	−1.5
				Mean	5.40	3.39	−2.01

is actually administered, these outcomes are conceptual and only one can actually be measured. The data are constructed such that the effect of surgical treatment is a reduction in the outcome. For example, the individual causal effects range from a -1.5- to a -2.5-point difference between the outcome if treated and the outcome if untreated. The average causal effect for this group is -2.01. To be interpreted properly, the population over which we are averaging needs to be detailed. For example, if these subjects represent veterans over 50 years of age, then -2.01 represents the average causal effect for this specific subpopulation. The value -2.01 may not generalize to represent the average causal effect for other populations (i.e., nonveterans, younger subjects).

Although we cannot measure individual causal effects, we can estimate average causal effects if the mechanism that assigns treatment status is essentially an unbiased random mechanism. For example, if $P[X_i = 1 \mid Y_i(0), Y_i(1)] = P(X_i = 1)$, the mean of a subset of observations, $Y_i(1)$, observed for those subjects with $X_i = 1$ will be an unbiased estimate of the mean for the entire population if all subjects are treated. Formally, the means observed for the treatment, $X = 1$, and control, $X = 0$, groups can be written as

$$\overline{Y}_1 = \frac{1}{n_1} \sum_{j=1}^{N} Y_j(1) \cdot 1(X_j = 1)$$

$$\overline{Y}_0 = \frac{1}{n_0} \sum_{j=1}^{N} Y_j(0) \cdot 1(X_j = 0)$$

where $n_1 = \sum_j 1(X_j = 1)$, $n_0 = \sum_j 1(X_j = 0)$, and $1(X_j = 0)$, $1(X_j = 1)$ are indicator functions denoting assignment to control and treatment, respectively. For example, if we assume that $P(X_i = 1) = 1/2$ and that $n_1 = n_0 = N/2$, then with random allocation to treatment,

$$\begin{aligned} E(\overline{Y}_1) &= \frac{1}{N/2} \sum_{j=1}^{N} Y_j(1) \cdot E[1(X_j = 1)] \\ &= \frac{1}{N/2} \sum_{j=1}^{N} Y_j(1) \cdot 1/2 \\ &= \frac{1}{N} \sum_{j} Y_j(1) \\ &= \mu_1 \end{aligned}$$

where we define μ_1 as the mean for the population if all subjects receive treatment. A similar argument shows that $E(\overline{Y}_0) = \mu_0$, the mean for the population if all subjects were not treated. Essentially, we are assuming the existence of parallel and identical populations, one of which is treated and one of which is untreated, and sample means from each population under simple random sampling are obtained.

Under random allocation of treatment and control status, the observed means $\overline{Y}_1$ and $\overline{Y}_0$ are unbiased estimates of population means. This implies that the sample means can be used to estimate the average causal effect of treatment:

$$\begin{aligned} E(\overline{Y}_1 - \overline{Y}_0) &= E(\overline{Y}_1) - E(\overline{Y}_1) \\ &= \mu_1 - \mu_0 \end{aligned}$$

$$= \frac{1}{N}\sum_i Y_i(1) - \frac{1}{N}\sum_i Y_i(0)$$

$$= \frac{1}{N}\sum_i [Y_i(1) - Y_i(0)]$$

$$= \frac{1}{N}\sum_i \Delta_i$$

$$= \overline{\Delta}$$

Example 11.5. An example of the data observed from a hypothetical randomized study that compares surgical ($X = 1$) to nonsurgical ($X = 0$) interventions is presented in Table 11.7. Notice that for each subject, only one of $Y_i(0)$ or $Y_i(1)$ is observed, and therefore a treatment vs. control comparison can only be calculated using the group averages rather than using individual potential outcomes. Since the study was randomized, the difference in the averages observed is a valid (unbiased) estimate of the average causal effect of surgery. The mean difference observed in this experimental realization is -1.94, which approximates the unobservable target value of $\overline{\Delta} = -2.01$ shown in Table 11.6. In this example the key random variable is the treatment assignment, and because the study was randomized, the distribution for the treatment assignment indicator, $X_i = 0/1$, is completely known and independent of the potential outcomes.

Often, inference regarding the benefit of treatment is based on observational data where the assignment to $X = 0$ or $X = 1$ is not controlled by the investigator. Consequently, the factors

Table 11.7 Example of Data that would Be Observed in a Randomized Treatment Trial

Subject		Outcome Observed		
i	Assignment	$Y_i(0)$	$Y_i(1)$	Difference
1	0	4.5		
2	1		1.0	
3	1		2.0	
4	1		2.2	
5	0	3.3		
6	1		0.8	
7	1		1.5	
8	0	4.9		
9	0	3.8		
10	0	3.6		
11	1		5.1	
12	0	6.7		
13	0	6.0		
14	0	5.6		
15	0	6.5		
16	1		6.0	
17	1		5.1	
18	0	8.3		
19	1		4.6	
20	1		5.3	
Mean		5.48	3.42	−1.94

that drive treatment assignment need to be considered if causal inference is to be attempted. If sufficient covariate information is collected, regression methods can be used to control for confounding.

Definition 11.10. *Confounding* refers to the presence of an additional factor, Z, which when not accounted for leads to an association between treatment, X, and outcome, Y, that does not reflect a causal effect. Confounding is ultimately a "confusion" of the effects of X and Z. For a variable Z to be a confounder, it must be associated with X in the population, be a predictor of Y in the control ($X = 0$) group, and not be a consequence of either X or Y.

This definition indicates that confounding is a form of selection bias leading to biased estimates of the effect of treatment or exposure (see Rothman and Greenland [1998, Chap. 8] for a thorough discussion of confounding and for specific criteria for the identification of a confounding factor). Using the potential outcomes framework allows identification of the research goal: estimating the average causal effect, $\overline{\Delta}$. When confounding is present, the expected difference between $\overline{Y}_1$ and $\overline{Y}_0$ is no longer equal to the desired average causal effect, and additional analytical approaches are required to obtain approximate causal effects.

Example 11.6. Table 11.8 gives an example of observational data where subjects in stratum 2 are more likely to be treated surgically than subjects in stratum 1. The strata represent a baseline assessment of the severity of functional disability. In many settings those subjects with more severe disease or symptoms are treated with more aggressive interventions, such as surgery. Notice that both potential outcomes, $Y_i(0)$ and $Y_i(1)$, tend to be lower for subjects in stratum 1 than for subjects in stratum 2. Despite the fact that subjects in stratum 1 are much less likely to actually receive surgical intervention, treatment with surgery remains a beneficial intervention for both strata 1 and 2 subjects. The benefit of treatment for all subjects is apparent in the negative individual causal effects shown in Table 11.6. The imbalanced allocation of more severe cases to surgical treatment leads to crude summaries of $\overline{Y}_1 = 4.46$ and $\overline{Y}_0 = 4.32$. Thus the subjects who receive surgery have a slightly higher posttreatment mean functional score than those subjects who do not receive surgery. Does this comparison indicate the absence of a causal effect of surgery? The overall comparison is based on a treated group that has 80% of subjects drawn from stratum 2, the more severe group, while the control group has only 20% of subjects from stratum 2. The crude comparison of $\overline{Y}_1$ to $\overline{Y}_0$ is roughly a comparison of the posttreatment functional scores among severe subjects (80% of the $X = 1$ group) to the posttreatment functional scores among less severe subjects (80% of the $X = 0$ group). It is "unfair" to attribute the crude difference between treatment groups solely to the effect of surgery since the groups are clearly not comparable. A mixing of the effect of surgery with the effect of baseline severity is an illustration of bias due to confounding. The observed difference $\overline{Y}_1 - \overline{Y}_0 = 0.14$ is a distorted estimate of the average causal effect, $\overline{\Delta} = -2.01$.

11.5.2 Adjustment for Measured Confounders

There are several statistical methods that can be used to adjust for measured confounders. The goal of adjustment is to obtain an estimate of the treatment effect that more closely approximates the average causal effect. Commonly used methods include:

1. *Stratified methods*. In stratified methods the sample is broken into *strata*, $k = 1, 2, \ldots, K$, based on the value of a covariate, Z. Within each stratum, k, a treatment comparison can be calculated. Let $\delta^{(k)} = \overline{Y}_1^{(k)} - \overline{Y}_0^{(k)}$, where $\overline{Y}_1^{(k)}$ is the mean among treated subjects in strata k, and $\overline{Y}_0^{(k)}$ is the mean among control subjects in strata k. An overall summary of the stratum-specific treatment contrasts can be computed using a simple or weighted average of the stratum-specific comparisons, $\overline{\delta} = \sum_{k=1}^{K} w_k \cdot \delta^{(w_k)}$, where w_k is a weight. In the example presented in Table 11.8

Table 11.8 Example of an Observational Study Where Factors That Are Associated with the Potential Outcomes Are Predictive of the Treatment Assignment

Subject i	Assignment	Outcome Observed $Y_i(0)$	Outcome Observed $Y_i(1)$	Stratum	Difference
1	1		2.7	1	
2	0	3.1		1	
3	0	3.9		1	
4	1		2.2	1	
5	0	3.3		1	
6	0	3.3		1	
7	0	4.0		1	
8	0	4.9		1	
9	0	3.8		1	
10	0	3.6		1	
Mean		3.74	2.45		−1.29
11	1		5.1	2	
12	1		5.2	2	
13	1		4.4	2	
14	0	5.6		2	
15	1		4.0	2	
16	0	7.7		2	
17	1		5.1	2	
18	1		6.0	2	
19	1		4.6	2	
20	1		5.3	2	
Mean		6.65	4.96		−1.69
Overall mean		4.32	4.46		0.14

the subjects are separated into two strata, and mean differences of $\delta^{(1)} = -1.29$ and $\delta^{(2)} = -1.69$ are obtained comparing treatment and controls within strata 1 and strata 2, respectively. These estimates are much closer to the true average causal effect of $\overline{\Delta} = -2.01$ in Table 11.6 than the comparison of crude means, $\overline{Y}_1 - \overline{Y}_0 = 0.14$.

2. *Regression analysis*. Regression methods extend the concept of stratification to allow use with continuously measured adjustment variables and with multiple predictor variables. A regression model

$$E(Y \mid X, Z) = \alpha + \beta_1 X + \beta_2 Z$$

can be used to obtain an estimate of treatment, X, that adjusts for the covariate Z. Using the regression model, we have

$$\beta_1 = E(Y \mid X = 1, Z = z) - E(Y \mid X = 0, Z = z)$$

indicating that the parameter β_1 represents the average or common treatment comparison formed within groups determined by the value of the covariate, $Z = z$.

3. *Propensity score methods*. Propensity score methods are discussed by Rosenbaum and Rubin [1983]. In this approach the *propensity score*, $P(X = 1 \mid Z)$, is estimated using logistic regression or discriminant analysis, and then used either as a stratifying factor, a covariate in

regression, or a matching factor (see Little and Rubin [2000] and the references therein for further detail on use of the propensity score for adjustment).

The key assumption that is required for causal inference is the "no unmeasured confounding" assumption. This states that for fixed values of a covariate, Z_i (this may be multiple covariates), the assignment to treatment, $X_i = 1$, or control, $X_i = 0$, is unrelated to the potential outcomes. This assumption can be stated as

$$P[X_i = 1 \mid Y_i(0), Y_i(1), Z_i] = P[X_i = 1 \mid Z_i]$$

One difficult aspect of this concept is the fact that we view potential outcomes as being measured after the treatment is given, so how can the potential outcomes predict treatment assignment? An association can be induced by another variable, such as Z_i. For example, in the surgical example presented in Table 11.8, an association between potential outcomes and treatment assignment is induced by the baseline severity. The probability that a subject is assigned $X_i = 1$ is predicted by baseline disease severity, and the potential outcomes are associated with the baseline status. Thus, if we ignore baseline severity, treatment assignment X_i is associated with both $Y_i(0)$ and $Y_i(1)$. The goal of collecting covariates Z_i is to measure sufficient predictors of treatment such that within the strata defined by Z_i, the treatment assignment is approximately randomized. A causal interpretation for effects formed using observational data requires the assumption that there is no unmeasured confounding within any strata. This assumption cannot be verified empirically.

Example 11.1. (*continued*) We return to the data from Cullen and van Belle [1975]. We use the response variable DMPA, the disintegrations per minute of lymphocytes measured after surgery. We focus on the effect of anesthesia used for the surgery: $X = 0$ for general anesthesia and $X = 1$ for local anesthesia. The following crude analysis uses a regression of DMPA on anesthesia (X), which is equivalent to the two-sample t-test:

	Coefficient	**SE**	t	p**-Value**
Intercept	109.03	11.44	9.53	<0.001
Anesthesia	38.00	15.48	2.45	0.016

The analysis suggests that local anesthesia leads to a mean DMPA that is 38.00 units greater than the mean DMPA when general anesthesia is used. This difference is statistically significant with p-value 0.016.

Recall that these data are comprised of patients undergoing a variety of surgical procedures that are broadly classified using the variable TRAUMA, whose values 0 to 4 were introduced in Table 11.2. The type of anesthesia that is used varies by procedure type and therefore TRAUMA, as shown in Table 11.9. From this table we see that use of local anesthesia occurs more frequently for TRAUMA 0, 1, or 2, and that general anesthesia is used more frequently for TRAUMA 3 or 4. In addition, in earlier analyses we have found TRAUMA to be associated with the outcome. Thus, the crude analysis of anesthesia that estimates a 38.00 unit (S.E. = 15.48) effect of local anesthesia is confounded by TRAUMA and does not reflect an average causal effect. To adjust for TRAUMA, we use regression with the indicator variables, TRAUMA(j) = 1 if TRAUMA = j and 0 otherwise, for $j = 1, 2, 3, 4$. We use a model that includes an intercept and therefore do not also include an indicator for TRAUMA 0. The regression results are shown in Table 11.10.

After controlling for TRAUMA, the estimated comparison of local to general anesthesia within TRAUMA groups is 23.47 (S.E. = 18.24), and this difference is no longer statistically significant. This example shows that for causal analysis of observational data, any factors that are associated with treatment and associated with the outcome need to be considered in the analysis. In order to use 23.47 as the average causal effect of anesthesia, we would need to justify the required

Table 11.9 Anesthesia Use by Type of TRAUMA

	Anesthesia		
TRAUMA	0 = General	1 = Local	Total
0	0	11	11
1	6	12	18
2	14	16	30
3	11	3	14
4	4	0	4
Total	35	42	77

Table 11.10 Regression Results with Anesthesia and Trauma Predictors

	Coefficient	SE	t	p-Value
Intercept	129.53	27.40	4.73	<0.001
Anesthesia	23.47	18.24	1.29	0.202
TRAUMA 1	3.66	26.66	0.14	0.891
TRAUMA 2	−13.68	25.38	−0.54	0.592
TRAUMA 3	−25.34	30.86	−0.82	0.414
TRAUMA 4	−67.28	43.60	−1.54	0.127

assumption of no additional measured or unmeasured confounding factors. The assumption of no unmeasured confounding can only be supported by substantive considerations specific to the study design and the scientific process under investigation. Finally, since there are no empirical contrasts comparing local to general anesthesia within the TRAUMA 0 and TRAUMA 4 strata, we would need to either consider the average causal effect as only pertaining to the TRAUMA 1, 2, and 3 groups, or be willing to extrapolate to the TRAUMA 0 and 4 groups.

11.5.3 Model Selection Issues

One of the most difficult and controversial issues regarding the use of regression models is the procedure for specifying which variables are to be used to control for confounding. The epidemiological and biostatistical literature has introduced and evaluated several schemes for choosing adjustment variables. In the next section we discuss methods that can be used to identify a parsimonious explanatory or predictive model. However, the motivation for selecting covariates to control for confounding is different from the goal of identifying a good predictive model. To control for confounding, we identify adjustment variables in order to remove bias in the regression estimate for a predictor of primary interest, typically a treatment or exposure variable.

Pocock et al. [2002] discuss covariate choice issues in the analysis of data from clinical trials. The authors note that post hoc choice of covariates may not be done objectively and thus leads to estimates that reflect the investigators bias (e.g., choose to control for a variable if it makes the effect estimate larger!). In addition, simulation studies have shown that popular automatic variable-selection schemes can lead to biased estimates and distorted significance levels [Mickey and Greenland, 1989; Maldonado and Greenland, 1993; Sun et al., 1996; Hurvich and Tsai, 1990].

Kleinbaum [1994] discusses the a priori specification of the covariates to be used for regression analysis. The main message is that substantive considerations should drive the specification of the regression model when confirmatory estimation and inference are desired. This position is also supported by Raab et al. [2000].

11.5.4 Further Reading

Little and Rubin [2000] provide a comprehensive review of causal inference concepts. These authors also discuss the importance of the *stable unit treatment assumption* that is required for causal inference.

An overview of causal inference and discussion of the use of graphs for representing causal relationships are given in the text by Pearl [2000].

11.6 SELECTING A "BEST" SUBSET OF EXPLANATORY VARIABLES

11.6.1 The Problem

Given a large number of potential explanatory variables, one can sometimes select a smaller subset that explains the variability in the dependent variable. We have seen examples above where it appears that one or more of the variables in a multiple regression do not contribute, beyond an amount consistent with chance, to the explanation of the variability in the dependent variable. Thus, consider a response variable Y with a large number of potential predictor variables X_j. How should we choose a "best" subset of variables to explain the Y variability? This topic is addressed in this section. If we knew the number of predictor variables we wanted, we could use some criterion for the best subset. One natural criterion from the concepts already presented would be to choose the subset that gives the largest value for R^2. Even then, selection of the subset can be a formidable task. For example, suppose that there are 30 predictor variables and a subset of 10 variables is wanted; there are

$$\binom{30}{10} = 30{,}045{,}015$$

possible regression equations that have 10 predictor variables. This is not a routinely manageable number even with modern high-speed computers. Furthermore, in many instances we will not know how many possible variables we should place into our prediction equation. If we consider all possible subsets of 30 variables, there are over 1 billion possible combinations for the prediction. Thus once again, one cannot examine all subsets. There has been much theoretical work on selecting the best subset according to some criteria; the algorithms allow one to find the best subset without looking explicitly at all of the possible subsets. Still, for large numbers of variables, we need another procedure to select the predictive subset.

A further complication arises when we have a very large number of observations; then we may be able to show statistically that all of the potential predictor variables contribute additional information to explain the variability in the dependent variable Y. However, the large majority of the predictor variables may add so little to the explanation that we would prefer a much smaller subset that explains almost as much of the variability and gives a much simpler model. In general, simple models are desirable because they may be used more readily, and often when applied in a different setting, turn out to be more accurate than a model with a large number of variables.

In summary, the task before us in this section is to consider a means of choosing a subset of predictor variables from a pool of potential predictor variables.

11.6.2 Approaches to the Problem That Consider All Possible Subsets of Explanatory Variables

We discuss two approaches and then apply both approaches to an example. The first approach is based on the following idea: If we have the appropriate predictive variables in a multiple regression equation, plus possibly some other variables that have no predictive power, then the residual mean square for the model will estimate σ^2 the variability about the true regression line.

On the other hand, if we do not contain enough predictive variables, the residual mean square will contain additional variability due to the poor multiple regression fit and will tend to be too large. We want to use this fact to allow us to get some idea of the number of variables needed in the model. We do this in the following way. Suppose that we consider all possible predictions for some fixed number, say p, of the total possible number of predictor variables. Suppose that the correct predictive equation has a much smaller number of variables than p. Then when we look at all of the different subsets of p predictor variables, most of them will contain the *correct* variables for the predictive equation plus other variables that are not needed. In this case, the mean square residual will be an estimate of σ^2. If we average all of the mean square residuals for the equations with p variables, since most of them will contain the correct predictive variables, we should get an estimate fairly close to σ^2. We examine the mean square residuals by plotting the average mean square residuals for all the regression equations using p variables vs. p. As p becomes large, this average value should tend to level off at the true residual variability. By drawing a horizontal line at approximately the value where things average out, we can get some idea of the residual variability. We would then search for a simple model that has approximately this asymptotic estimate of σ^2. That is, we expect a picture such as Figure 11.1.

The second approach, due to C. L. Mallows, is called *Mallow's C_p statistic*. In this case, let p equal the number of predictive variables in the model, *plus one*. This is a change from the preceding paragraph, where p was the number of predictive variables. The switch to this notation is made because in the literature for Mallow's C_p, this is the value used. The statistic is as follows:

$$C_p(\text{model with } p-1 \text{ explanatory variables}) = \frac{\text{SS}_{\text{RESID}}(\text{model})}{\text{MS}_{\text{RESID}}(\text{using all possible predictors})} - (N - 2p)$$

where MS_{RESID} (using all possible predictors) is the residual mean square when the dependent variable Y is regressed on all possible independent predictors; SS_{RESID} (model) is the residual sum of squares for the possible model being considered (this model uses $p - 1$ explanatory variables), N is the total number of observations, and p is the number of explanatory variables in the model plus one.

To use Mallow's C_p, we compute the value of C_p for each possible subset of explanatory variables. The points (C_p, p) are then plotted for each possible model. The following facts about the C_p statistics are true:

1. If the model fits, the expected value for each C_p is approximately p.
2. If C_p is larger than p, the difference, $C_p - p$, gives approximately the amount of bias in the sum of squares involved in the estimation. The bias occurs because the estimating

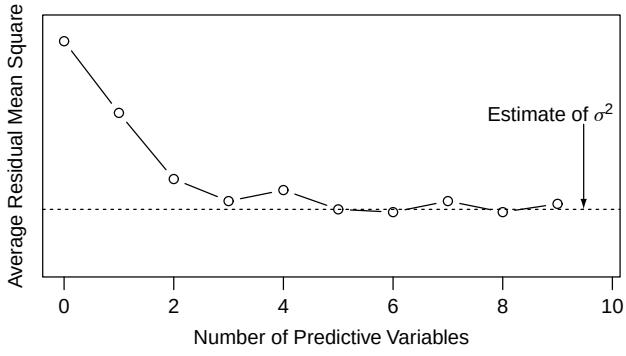


Figure 11.1 Average residual mean square as a function of the number of predictive variables.

predictive equation is not the true equation and thus estimates something other than the correct Y value.

3. The value of C_p itself gives an overall estimate of the sum of the squares of the average difference between correct Y values and the Y values predicted from the model. This difference is composed of two parts, one part due to bias because the estimating equation is not correct (and cannot be correct if the wrong variables are included), and a second part because of variability in the estimate. If the expected value of Y may be modeled by a few variables, there is a cost to adding more variables to the estimation procedure. In this case, statistical noise enters into the estimation of the additional variables, so that by using the more complex estimated predictive equation, future predictions would be off by more.
4. Thus what we would like to look for in our plot is a value C_p that is close to the 45° line, $C_p = p$. Such a value would have a low bias. Further, we would like the value of C_p itself to be small, so that the total error sum of squares is not large. The nicest possible case occurs when we can more or less satisfy both demands at the same time.
5. If we have to choose between a C_p value, which is close to p, or one that is smaller but above p, we are choosing between an equation that has a small bias (when $C_p = p$) but in further prediction is likely to have a larger predictive error, and a second equation (the smaller value for C_p) which in the future prediction is more likely to be close to the true value but where we think that the estimated predictive equation is probably biased. Depending on the use of the model, the trade-off between these two ills may or may not be clearcut.

Example 11.1. (*continued*) In this example we return to the data of Cullen and van Belle [1975]. We shall consider the response variable, DPMA, which is the disintegrations per minute of lymphocytes after the surgery. The viability of the lymphocytes was measured in terms of the uptake of nutrients that were labeled radioactively. A large number of disintegrations per minute suggests a high cell division rate, and thus active lymphocytes. The potential predictive variables for explaining the variability in DPMA are trauma factor (as discussed previously), duration (as discussed previously), the disintegrations per minute before the surgery, labeled DPMB, and the lymphocyte count in thousands per cubic millimeter before the surgery, LYMPHB, as well as the lymphocyte count in thousands per cubic millimeter after the surgery, LYMPHA. Let these variables have the following labels: Y = DPMA; X_1 = DURATION; X_2 = TRAUMA; X_3 = DPMB; X_4 = LYMPHB; X_5 = LYMPHA.

Table 11.11 presents the results for the 32 possible regression runs using subsets of the five predictor variables. For each run the value of p, C_p, the residual mean square, the average residual mean square for runs with the same number of variables, the multiple R^2, and the adjusted R^2, R_a^2, are presented. For a given number of variables, the entries are ordered in terms of increasing values of C_p. Note several things in Table 11.11. For a fixed number, $p - 1$, of predictor variables, if we look at the values for C_p, the residual mean square, R^2, and R_a^2, we see that as C_p increases, the residual mean square increases while R^2 and R_a^2 decrease. This relationship is a mathematical fact. Thus, if we know how many predictor variables, p, we want in our equation, any of the following six criteria for the best subset of predictor variables are equivalent:

1. Pick the predictive equation with a minimum value of C_p.
2. Pick the predictive equation with the minimum value of the residual mean square.
3. Pick the predictive equation with the maximum value of the multiple correlation coefficient, R^2.
4. Pick the predictive equation with the maximum value of the adjusted multiple correlation coefficient, R_a^2.
5. Pick the predictive equation with a maximum sum of squares due to regression.
6. Pick the predictive equation with the minimum sum of squares for the residual variability.

Table 11.11 Results from the 32 Regression Runs on the Anesthesia Data of Cullen and van Belle [1975]

Numbers of Explanatory Variables in Predictive Equation	p	C_p	Residual Mean Square	Residual Average Mean Square	R^2	R_a^2
None	1	60.75	4047	4047	0	0
3	2	5.98	1645		0.606	0.594
1		49.45	3578		0.142	0.116
2		57.12	3919	3476	0.060	0.032
4		60.48	4069		0.024	−0.005
5		62.70	4168		0.000+	−0.030
2,3	3	2.48	1444		0.664	0.643
1,3		2.82	1459		0.661	0.639
3,5		6.26	1617		0.624	0.600
3,4		6.91	1647		0.617	0.593
1,4		48.37	3549	2922	0.175	0.123
1,2		51.06	3672		0.146	0.093
1,5		51.43	3689		0.142	0.088
2,4		56.32	3914		0.090	0.033
2,5		59.10	4041		0.060	0.001
4,5		62.39	4192		0.024	−0.036
2,3,4	4	3.03	1422		0.680	0.648
1,3,4		3.32	1435		0.677	0.645
1,3,5		3.36	1438		0.676	0.645
2,3,5		3.52	1445		0.674	0.643
1,2,3		3.96	1466	2396	0.670	0.639
3,4,5		7.88	1651		0.628	0.592
1,2,4		50.03	3647		0.178	0.099
1,4,5		50.15	3653		0.177	0.097
1,2,5		52.98	3787		0.146	0.064
2,4,5		57.75	4013		0.096	0.008
1,2,3,4	5	4.44	1440		0.686	0.644
1,3,4,5		4.64	1450		0.684	0.642
2,3,4,5		4.69	1453	1913	0.683	0.641
1,2,3,5		4.83	1460		0.682	0.640
1,2,4,5		51.91	3763		0.180	0.070
1,2,3,4,5	6	6	1468	1468	0.691	0.637

The C_p data are more easily assimilated if we plot them. Figure 11.2 is a C_p plot for these data. The line $C_p = p$ is drawn for reference. Recall that points near this line have little bias in terms of the fit of the model; for points above this line we have biased estimates of the regression equation. We see that there are a number of models that have little bias. All things being equal, we prefer as small a C_p value as possible, since this is an estimate of the amount of variability between the true values and predicted values, which takes into account two components, the bias in the estimate of the regression line as well as the residual variability due to estimation. For this plot we are in the fortunate position of the lowest C_p value showing no bias. In addition, a minimal number of variables are involved. This point is circled, and going back to Table 11.11, corresponds to a model with $p = 3$, that is, two predictor variables. They are variables 2 and 3, the TRAUMA variable, and DPMB, the lymphocyte count in thousands per cubic millimeters before the surgery. This is the model we would select using Mallow's C_p approach.

We now turn to the average residual mean square plot to see if that would help us to decide how many variables to use. Figure 11.3 gives this plot. We can see that this plot does not level

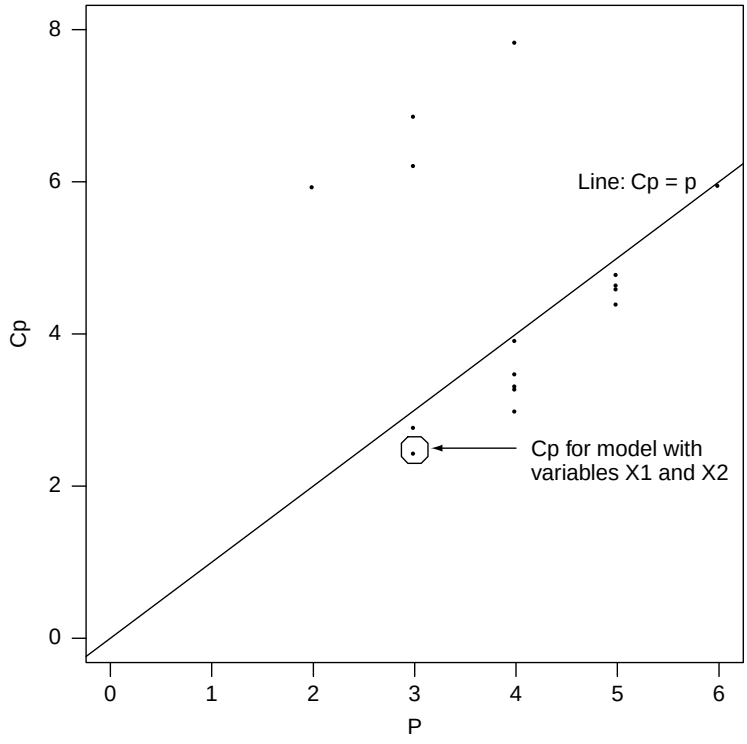


Figure 11.2 Mallow's C_p plot for the data of Cullen and van Belle [1975]. Only points with $C_p < 8$ are plotted.

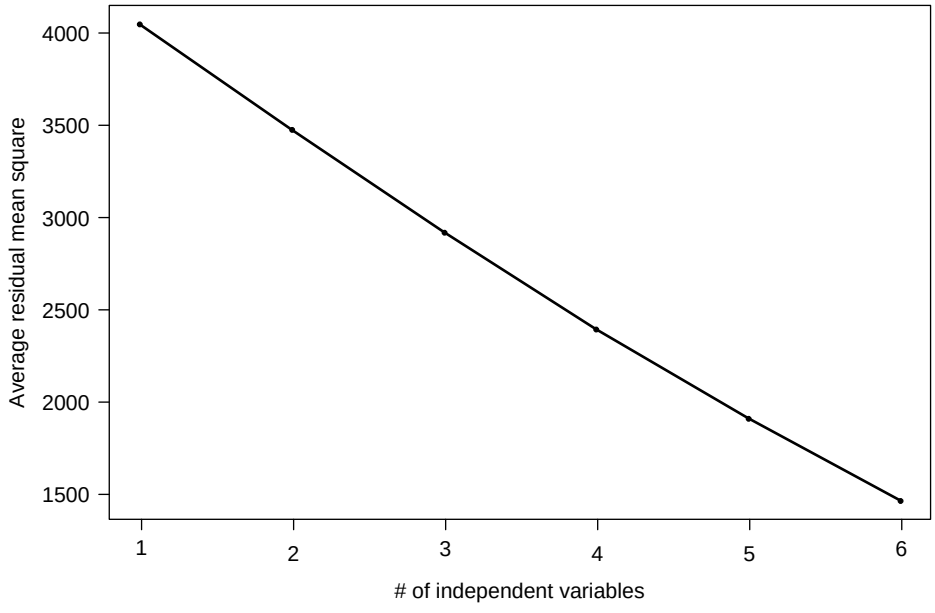


Figure 11.3 Average mean square plot for the Cullen and van Belle data [1975].

out but decreases until we have five variables. Thus this plot does not help us to decide on the number of variables we might consider in the final equation. If we look at Table 11.11, we can see why this happens. Since the final model has two predictive variables, even with three variables, many of the subsets, namely four, do not include the most predictive variable, variable 3, and thus have very large mean squares. We have not considered enough variables in the model above and beyond the final model for the curve to level out. With a relatively small number of potential predictor variables, five in this model, the average residual mean square plot is usually not useful.

Suppose that we have too many predictor variables to consider all combinations; or suppose that we are worried about the problem of looking at the huge number of possible combinations because we feel that the multiple comparisons may allow random variability to have too much effect. In this case, how might we proceed? In the next section we discuss one approach to this problem.

11.6.3 Stepwise Procedures

In this section we consider building a multiple regression model variable by variable.

Step 1

Suppose that we have a dependent variable Y and a set of potential predictor variables, X_i, and that we try to explain the variability in Y by choosing only one of the predictor variables. Which would we want? It is natural to choose the variable that has the largest squared correlation with the dependent variable Y. Because of the relationships among the sums of squares, this is equivalent to the following step.

Step 2

1. Choose i to maximize r^2_{Y,X_i}.
2. Choose i to maximize $\mathrm{SS}_{\mathrm{REG}}(X_i)$.
3. Choose i to minimize $\mathrm{SS}_{\mathrm{RESID}}(X_i)$.

By renumbering our variables if necessary, we can assume that the variable we picked was X_1. Now suppose that we want to add one more variable, say X_i, to X_1, to give us as much predictive power as possible. Which variable shall we add? Again we would like to maximize the correlation between Y and the predicted value of Y, $\widehat{Y}$; equivalently, we would like to maximize the multiple correlation coefficient squared. Because of the relationships among the sums of squares, this is equivalent to any of the following at this next step.

Step 3

X_1 is in the model; we now find $X_i (i \neq 1)$.

1. Choose i to maximize $R^2_{Y(X_1,X_i)}$.
2. Choose i to maximize $r^2_{Y,X_i \cdot X_1}$.
3. Choose i to maximize $\mathrm{SS}_{\mathrm{REG}}(X_1, X_i)$.
4. Choose i to maximize $\mathrm{SS}_{\mathrm{REG}}(X_i | X_1)$.
5. Choose i to minimize $\mathrm{SS}_{\mathrm{RESID}}(X_1, X_i)$.

Our stepwise regression proceeds in this manner. Suppose that j variables have entered. By renumbering our variables if necessary, we can assume without loss of generality that the variables that have entered the predictive equation are $X_1, \ldots, X_j$. If we are to add one more

variable to the predictive equation, which variable might we add? As before, we would like to add the variable that makes the correlation between Y and the predictor variables as large as possible. Again, because of the relationships between the sums of squares, this is equivalent to any of the following:

Step $j+1$

$X_1, \ldots, X_j$ are in the model; we want $X_i (i \neq 1, \ldots, j)$.

1. Choose i to maximize $R^2_{Y(X_1,\ldots,X_j,X_i)}$.
2. Choose i to maximize $r^2_{Y,X_i \cdot X_1,\ldots,X_j}$.
3. Choose i to maximize $\mathrm{SS}_{\mathrm{REG}}(X_1, \ldots, X_j, X_i)$.
4. Choose i to maximize $\mathrm{SS}_{\mathrm{REG}}(X_i | X_1, \ldots, X_j)$.
5. Choose i to minimize $\mathrm{SS}_{\mathrm{RESID}}(X_1, \ldots, X_j, X_i)$.

If we continue in this manner, eventually we will use all of the potential predictor variables. Recall that our motivation was to select a simple model. Thus we would like a small model; this means that we would like to stop at some step before we have included all of our potential predictor variables. How long shall we go on including predictor variables in this model? There are several mechanisms for stopping. We present the most widely used stopping rule. We would not like to add a new variable if we cannot show statistically that it adds to the predictive power. That is, if in the presence of the other variables already in the model, there is no statistically significant relationship between the response variable and the next variable to be added, we will stop adding new predictor variables. Thus, the most common method of stopping is to test the significance of the partial correlation of the next variable and the response variable Y after adjusting for the variables entered previously. We use the partial F-test as discussed above. Commonly, the procedure is stopped when the p-value for the F level is greater than some fixed level; often, the fixed level is taken to be 0.05. This is equivalent to testing the statistical significance of the partial correlation coefficient. The partial F-statistic in the context of regression analysis is also often called the *F to enter*, since the value of F, or equivalently its p-value, is used as a criteria for entering the equation.

Since the F-statistic always has numerator degrees of freedom 1 and denominator degrees of freedom $n - j - 2$, and n is usually much larger than j, the appropriate critical value is effectively the F critical value with 1 and ∞ degrees of freedom. For this reason, rather than using a p-value, often the entry criterion is to enter variables as long as the F-statistic itself is greater than some fixed amount.

Summarizing, we stop when:

1. The p-value for $r^2_{Y,X_i \cdot X_1,\ldots,X_j}$ is greater than a fixed level.
2. The partial F-statistic

$$\frac{\mathrm{SS}_{\mathrm{REG}}(X_i | X_1, \ldots, X_j)}{\mathrm{SS}_{\mathrm{RESID}}(X_1, \ldots, X_j, X_i)/(n - j - 2)}$$

is less than some specified value, or its p-value is greater than some fixed level.

All of this is summarized in Table 11.12; we illustrate by an example.

Example 11.3. (*continued*) Consider the active female exercise data used above. We shall perform a stepwise regression with VO_2 MAX as the dependent variable and DURATION, MAXIMUM HEART RATE, AGE, HEIGHT, and WEIGHT as potential independent variables. Table 11.13 contains a portion of the BMDP computer output for this run.

Table 11.12 Stepwise Regression Procedure (Forward) Selection for p Variable Case

Step	Variable Entered[a]	Intercept and Slopes Calculated[b]	Total SS Attributable to Regression	Contribution of Entered Variable to Regression	F-Ratio to Test Significance of Entered Variable
1	X_1	$a^{(1)}, b_1^{(1)}$	$\mathrm{SS}_{\mathrm{REG}}(X_1)$	$\mathrm{SS}_{\mathrm{REG}}(X_1)$	$\dfrac{\mathrm{SS}(X_1)(n-2)}{\mathrm{SS}_{\mathrm{RESID}}(X_1)} = F_{1,n-2}$
2	X_2	$a^{(2)}, b_1^{(2)}, b_2^{(2)}$	$\mathrm{SS}_{\mathrm{REG}}(X_1, X_2)$	$\mathrm{SS}_{\mathrm{REG}}(X_2 \mid X_1)$	$\dfrac{\mathrm{SS}(X_2 \mid X_1)(n-3)}{\mathrm{SS}_{\mathrm{RESID}}(X_1, X_2)} = F_{1,n-3}$
3	X_3	$a^{(3)}, b_1^{(3)}, b_2^{(3)}, b_3^{(3)}$	$\mathrm{SS}_{\mathrm{REG}}(X_1, X_2, X_3)$	$\mathrm{SS}_{\mathrm{REG}}(X_3 \mid X_1, X_2)$	$\dfrac{\mathrm{SS}(X_3 \mid X_1, X_2)(n-4)}{\mathrm{SS}_{\mathrm{RESID}}(X_1, X_2, X_3)} = F_{1,n-4}$
⋮	⋮	⋮	⋮	⋮	⋮
j	X_j	$a^{(j)}, b_1^{(j)}, b_2^{(j)}, \ldots, b_j^{(j)}$	$\mathrm{SS}_{\mathrm{REG}}(X_1, X_2, \ldots, X_j)$	$\mathrm{SS}_{\mathrm{REG}}(X_j \mid X_1, \ldots, X_{j-1})$	$\dfrac{\mathrm{SS}(X_j \mid X_1, \ldots, X_{j-1})(n-j-1)}{\mathrm{SS}_{\mathrm{RESID}}(X_1, \ldots, X_j)} = F_{1,n-j-1}$
⋮	⋮	⋮	⋮	⋮	⋮
p	X_p	$a^{(p)}, b_1^{(p)}, b_2^{(p)}, \ldots, b_p^{(p)}$	$\mathrm{SS}_{\mathrm{REG}}(X_1, X_2, \ldots, X_p)$	$\mathrm{SS}_{\mathrm{REG}}(X_p \mid X_1, \ldots, X_{p-1})$	$\dfrac{\mathrm{SS}(X_p \mid X_1, \ldots, X_p)(n-p-1)}{\mathrm{SS}_{\mathrm{RESID}}(X_1, \ldots, X_p)} = F_{1,n-p-1}$

[a] To simplify notation, variables are labeled by the step at which they entered the equation.
[b] The superscript notation indicates that the estimate of α changes from step to step, as well as the estimates of $\beta_1, \beta_2, \ldots, \beta_{p-1}$.

Table 11.13 Stepwise Multiple Linear Regression for the Data of Example 11.3

STEP NO. 0

STD. ERROR OF EST. 4.9489

ANALYSIS OF VARIANCE

	SUM OF SQUARES	DF	MEAN SQUARE
RESIDUAL	1028.6670	42	24.49208

VARIABLES IN EQUATION FOR VO2MAX

VARIABLE	COEFFICIENT	STD. ERROR OF COEFF	STD REG COEFF	TOLERANCE	F TO REMOVE	LEVEL
(Y-INTERCEPT	29.05349)					

VARIABLES NOT IN EQUATION

	VARIABLE	PARTIAL CORR.	TOLERANCE	F TO ENTER	LEVEL
DUR	1	0.78601	1.00000	66.28	1
HR	3	0.33729	1.00000	5.26	1
AGE	4	−0.65099	1.00000	30.15	1
HT	5	−0.29942	1.00000	4.04	1
WT	6	−0.12618	1.00000	0.66	1

STEP NO. 1

VARIABLE ENTERED 1 DUR

MULTIPLE R 0.7860

MULTIPLE R-SQUARE 0.6178

ADJUSTED R-SQUARE 0.6085

STD. ERROR OF EST. 3.0966

ANALYSIS OF VARIANCE

	SUM OF SQUARES	DF	MEAN SQUARE	F RATIO
REGRESSION	635.51730	1	635.5173	66.28
RESIDUAL	393.15010	41	9.589027	

VARIABLES IN EQUATION FOR VO2MAX

VARIABLE	COEFFICIENT	STD. ERROR OF COEFF	STD REG COEFF	TOLERANCE	F TO REMOVE	LEVEL
(Y-INTERCEPT	3.15880)					
DUR 1	0.05029	0.0062	0.786	1.00000	66.28	1

VARIABLES NOT IN EQUATION

VARIABLE		PARTIAL CORR.	TOLERANCE	F TO ENTER	LEVEL
HR	3	−0.14731	0.72170	0.89	1
AGE	4	−0.24403	0.52510	2.53	1
HT	5	0.01597	0.86364	0.01	1
WT	6	−0.32457	0.99123	4.71	1

(*continued overleaf*)

Table 11.13 (*continued*)

STEP NO. 2

VARIABLE ENTERED	6 WT
MULTIPLE R	0.8112
MULTIPLE R-SQUARE	0.6581
ADJUSTED R-SQUARE	0.6410
STD. ERROR OF EST.	2.9654

ANALYSIS OF VARIANCE

	SUM OF SQUARES	DF	MEAN SQUARE	F RATIO
REGRESSION	676.93490	2	338.4675	38.49
RESIDUAL	351.73250	40	8.793311	

VARIABLES IN EQUATION FOR VO2MAX

VARIABLE	COEFFICIENT	STD. ERROR OF COEFF	STD REG COEFF	TOLERANCE	F TO REMOVE	LEVEL
(Y-INTERCEPT	10.30026)					
DUR 1	0.05150	0.0059	0.805	0.99123	75.12	1
WT 6	−0.12659	0.0583	−0.202	0.99123	4.71	1

VARIABLES NOT IN EQUATION

VARIABLE	CORR.	PARTIAL TOLERANCE	TO ENTER	F LEVEL	
HR	3	−0.08377	0.68819	0.28	1
AGE	4	−0.24750	0.52459	2.54	1
HT	5	0.20922	0.66111	1.79	1

The 0.05 F critical value with degrees of freedom 1 and 42 is approximately 4.07. Thus at step 0, duration, maximum heart rate, and age are all statistically significantly related to the dependent variable $VO_{2\ MAX}$.

We see this by examining the F-to-enter column in the output from step 0. This is the F-statistic for the square of the correlation between the individual variable and the dependent variable. In step 0 up on the left, we see the analysis of variance table with only the constant coefficient. Under partial correlation we have the correlation between each variable and the dependent variable. At the first step, the computer program scans the possible predictor variables to see which has the highest absolute value of the correlation with the dependent variable. This is equivalent to choosing the largest F-to-enter. We see that this variable is DURATION. In step 1, DURATION has entered the predictive equation. Up on the left, we see the multiple R, which in this case is simply the correlation between the $VO_{2\ MAX}$ and DURATION variables, the value for R^2, and the standard error of the estimate; this is the estimated standard deviation about the regression line. This value squared is the mean square for the residual, or the estimate for σ^2 if this is the correct model. Below this is the analysis of variance table, and below this, the value of the regression coefficient, 0.050, for the DURATION variable. The standard error of the regression coefficient is then given. The standardized regression coefficient is the value of the regression coefficient if we had replaced DURATION by its standardized value. The value F-to-remove in a stepwise regression is the statistical significance of the partial correlation between the variable in the model and the dependent variable when adjusting for other variables in the model. The left-hand side lists the variables not already in the equation. Again

we have the partial correlations between the potential predictor variables and the dependent variable after adjusting for the variables in the model, in this case one variable, DURATION. Let us focus on the variable AGE at step 0 and at step 1. In step 0 there was a very highly statistically significant relationship between $VO_{2\ MAX}$ and AGE, the F-value being 30.15. After DURATION enters the predictive equation, in step 1 we see that the statistical significance has disappeared, with the F-to-enter decreasing to 2.53. This occurs because AGE is very closely related to DURATION and is also highly related to $VO_{2\ MAX}$. The explanatory power of AGE may, equivalently, be explained by the explanatory power of DURATION. We see that *when a variable does not enter a predictive model, this does not mean that the variable is not related to the dependent variable but possibly that other variables in the model can account for its predictive power*. An equivalent way of viewing this is that the partial correlation has dropped from -0.65 to -0.24. There is another column labeled "tolerance". The tolerance is 1 minus the square of the multiple correlation between the particular variable being considered and all of the variables already in the stepwise equation. Recall that if this correlation is large, it is very difficult to estimate the regression coefficient [see equation (14)]. The tolerance is the term $(1 - R_j^2)$ in equation (14). If the tolerance becomes too small, the numerical accuracy of the model is in doubt.

In step 1, scanning the F-to-enter column, we see the variable WEIGHT, which is statistically significantly related to $VO_{2\ MAX}$ at the 5% level. This variable enters at step 2. After this variable has entered, there are no statistically significant relationships left between the variables not in the equation and the dependent variable after adjusting for the variables in the model. The stepwise regression would stop at this point unless directed to do otherwise.

It is possible to modify the stepwise procedure so that rather than starting with 0 variables and building up, we start with all potential predictive variables in the equation and work down. In this case, at the first step we discard from the model the variable whose regression coefficient has the largest p-value, or equivalently, the variable whose correlation with the dependent variable after adjusting for the other variables in the model is as small as possible. At each step, this process continues removing a variable as long as there are variables to remove from the model that are not statistically significantly related to the response variable at some particular level. The procedure of adding in variables that we have discussed in this chapter is called a *step-up stepwise procedure*, while the opposite procedure of removing variables is called a *step-down stepwise procedure*. Further, as the model keeps building, it may be that a variable entered earlier in the stepwise procedure no longer is statistically significantly related to the dependent variable in the presence of the other variables. For this reason, when performing a step-up regression, most regression programs have the ability at each step to remove variables that are no longer statistically significant. All of this aims at a simple model (in terms of the number of variables) which explains as much of the variability as possible. The step-up and step-down procedures do not look at as many alternatives as the C_p plot procedure, and thus may not be as prone to overfitting the data because of the many models considered. If we perform a step-up or step-down fit for the anesthesia data discussed above, the resulting model is the same as the model picked by the C_p plot.

11.7 POLYNOMIAL REGRESSION

We motivate this section by an example. Consider the data of Bruce et al. [1973] for 44 active males with a maximal exercise treadmill test. The oxygen consumption $VO_{2\ MAX}$ was regressed on, or explained by, the age of the participants. Figure 11.4 shows the residual plot.

Examination of the residual plot shows that the majority of the points on the left are positive with a downward trend. The points on the right have generally higher values with an upward trend. This suggests that possibly the simple linear regression model does not fit the data well.

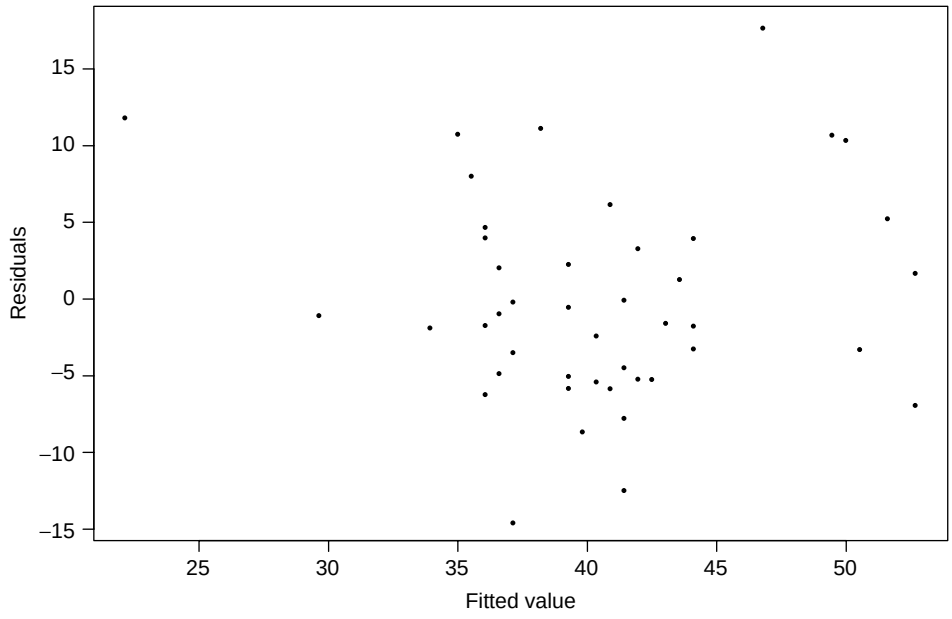


Figure 11.4 Residual plot of the regression of $VO_{2\ MAX}$ on age, active males.

The fact that the residuals come down and then go up suggests that possibly rather than being linear, the regression curve should be a second-order curve, such as

$$Y = a + b_1 X + b_2 X^2 + e$$

Note that this equation looks like a multiple linear regression equation. We could write this equation as a multiple regression equation,

$$Y = a + b_1 X_1 + b_2 X_2 + e$$

with $X_1 = X$ and $X_2 = X^2$. This simple observation allows us to fit polynomial equations to data by using multiple linear regression techniques. Observe what we are doing with multiple linear regression: The equation must be linear in the unknown parameters, but we may insert *known* functions of an explanatory variable. If we create the new variables $X_1 = X$ and $X_2 = X^2$ and run a multiple regression program, we find the following results:

Variable or Constant	b_j	$SE(b_j)$	t-statistic ($t_{41,0.975} \doteq 2.02$)
Age	−1.573	0.452	−3.484
Age^2	0.011	0.005	2.344
Constant	89.797	11.023	

We note that both terms age and age^2 are statistically significant. Recall that the t-test for the age^2 term is equivalent to the partial correlation of the age squared, with $VO_{2\ MAX}$ adjusting for the effect of age. This is equivalent to considering the hypothesis of linear regression *nested* within the hypothesis of quadratic regression. Thus, we reject the hypothesis of linear regression

and could use this quadratic regression formula. A plot of the residuals using the quadratic regression shows no particular trend and is not presented here. One might wonder, now that we have a second-order term, whether perhaps a third-order term might help the situation. If we run a multiple regression with three variables ($X_3 = X^3$), the following results obtain:

Variable or Constant	b_j	SE(b_j)	t-statistic ($t_{40,0.975} \doteq 2.02$)
Age	−0.0629	2.3971	−0.0264
Age^2	−0.0203	0.0486	−0.4175
Age^3	0.0002	0.0003	0.6417
Constant	1384.49	783.15	

Since the age^3 term, which tests the nested hypothesis of the quadratic equation within the cubic equation, is nonsignificant, we may accept the quadratic equation as appropriate.

Figure 11.5 is a scatter diagram of the data as well as the linear and quadratic curves. Note that the quadratic curve is higher at the younger ages and levels off more around 50 to 60. Within the high range of the data, the quadratic or second-order curve increases. This may be an artifact of the curve fitting because all physiological knowledge tells us that the capacity for conditioning does not increase with age, although some subjects may improve their exercise performance with extra training. Thus, the second-order curve would seem to indicate that in a population of healthy active males, the decrease in $VO_{2\ MAX}$ consumption is not as rapid at the higher ages as at the lower ages. This is contrary to the impression that one would get from a linear fit. One would not, however, want to use the quadratic curve to extrapolate beyond or even to the far end of the data in this particular example.

We see that the real restrictions of multiple regression is not that the equation be linear in the variables observed, but rather that it be linear in the unknown coefficients. The coefficients

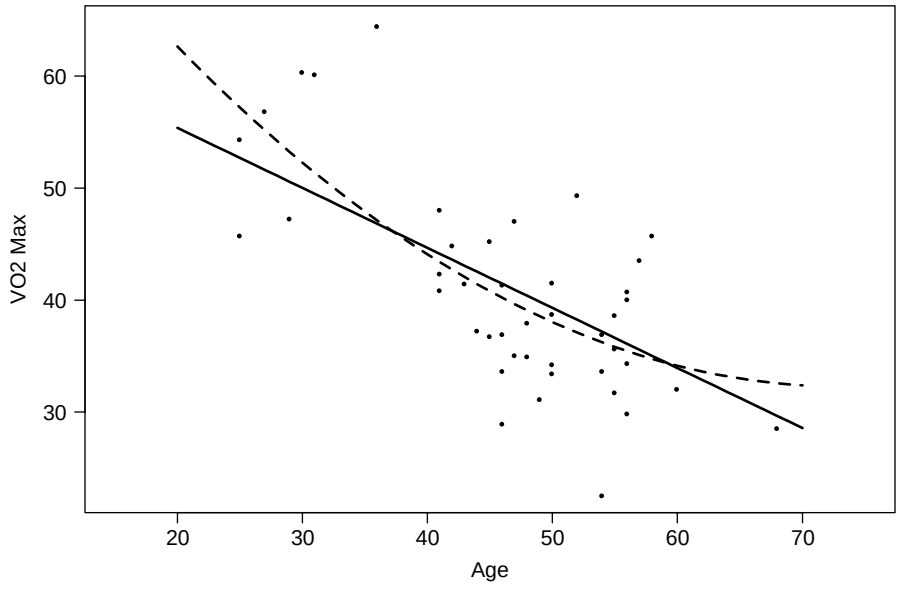


Figure 11.5 Active males with treadmill test: linear (solid line) and quadratic (dashed line) fits. (From Bruce et al. [1973].)

may be multiplied by known functions of the observed variables; this makes a variety of models possible. For example, with *two variables* we could also consider as an alternative to a linear fit (as given below) a second-order equation or polynomial in two variables:

$$Y = a + b_1 X_1 + b_2 X_2 + e$$

(linear in X_1 and X_2), and

$$Y = a + b_1 X_1 + b_2 X_2 + b_3 X_1^2 + b_4 X_1 X_2 + b_5 X_2^2 + e$$

(a second-order polynomial in X_1 and X_2).

Other functions of variables may be used. For example, if we observe a response that we believe is a periodic function of the variable X with a period of length L, we might try an equation of the form

$$Y = a + b_1 \sin \frac{\pi X}{L} + b_2 \cos \frac{\pi X}{L} + b_3 \sin \frac{2\pi X}{L} + b_4 \cos \frac{2\pi X}{L} + e$$

The important point to remember is that not only can polynomials in variables be fit, but any model may be fit where the response is a linear function of known functions of the variables involved.

11.8 GOODNESS-OF-FIT CONSIDERATIONS

As in the one-dimensional case, we need to check the fit of the regression model. We need to see that the form of the model roughly fits the data observed; if we are engaged in statistical inference, we need to see that the error distribution looks approximately normal. As in simple linear regression, one or two outliers can greatly skew the results; also, an inappropriate functional form can give misleading conclusions. In doing multiple regression it is harder than in simple linear regression to check the assumptions because there are more variables involved. We do not have nice two-dimensional plots that display our data completely. In this section we discuss some of the ways in which multiple regression models may be examined.

11.8.1 Residual Plots and Normal Probability Plots

In the multiple regression situation, a variety of plots may be useful. We discussed in Chapter 9 the residual plots of the predicted value for Y vs. the residual. Also useful is a normal probability plot of the residuals. This is useful for detecting outliers and for examining the normality assumption. Plots of the residual as a function of the independent or explanatory variables may point out a need for quadratic terms or for some other functional form. It is useful to have such plots even for potential predictor variables not entered into the predictive equation; they might be omitted because they are related to the response variable in a nonlinear fashion. This might be revealed by such residual plots.

Example 11.3. (*continued*) We return to the healthy normal active females. Recall that the $VO_{2\ MAX}$ in a stepwise regression was predicted by DURATION and WEIGHT. Other variables considered were MAXIMUM HEART RATE, AGE, and HEIGHT. We now examine some of the residual plots as well as normal probability plots. The left panel of Figure 11.6 is a plot of residuals vs. fitted values. The residuals look fairly good except for the point circled on the right-hand margin, which lies farther from the value of zero than the rest of the points. The right-hand panel gives the square of the residuals. These values will have approximately a chi-square distribution with

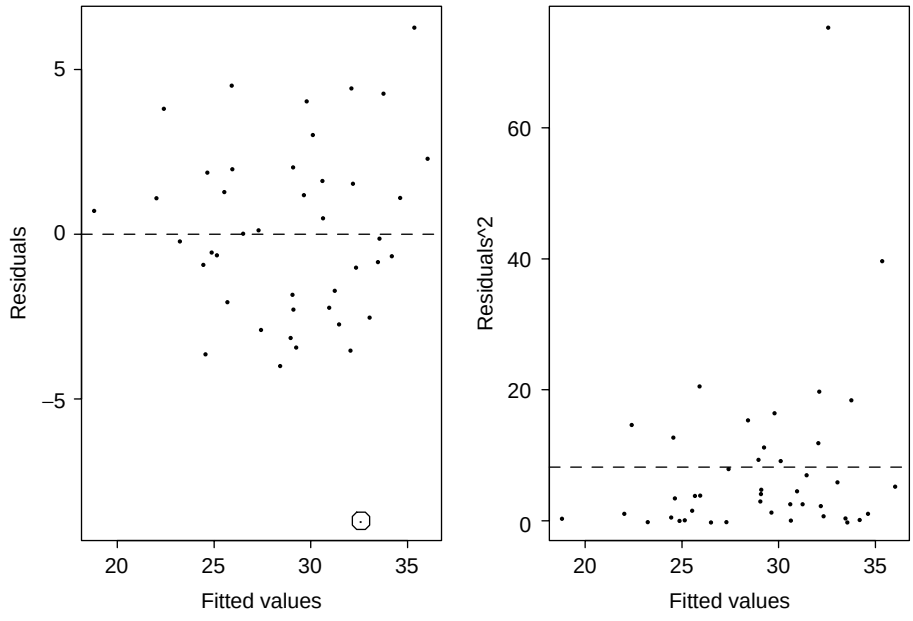


Figure 11.6 Residual plots.

one degree of freedom if normality holds. If the model is correct, there will not be a change in the variance with increasing predicted values. There is no systematic change here. However, once again the one value has a large deviation.

Figure 11.7 gives the normal probability plot for the residuals. In this output, the values predicted are on the horizontal axis rather than on the vertical axis, as plotted previously. Again, the residuals look quite nice except for the point on the far left; this point corresponds to the circled value in Figure 11.6. This raises the possibility of rerunning the analysis omitting the one outlier to see what effect it had on the analysis. We discuss this below after reviewing more graphical data.

Figures 11.8 to 11.12 deal with the residual values as a function of the five potential predictor variables. In each figure the left-hand panel presents the observed and predicted values for the data points and the right-hand panel for the observed values of those data present the residual values. In Figure 11.7, for DURATION, note that the values predicted are almost linear. This is because most of the predictive power comes from the DURATION variable, so that the value predicted is not far removed from a linear function of DURATION. The residual plot looks nice, with the possible exception of the outlier. In Figure 11.8, with respect to WEIGHT, we have the same sort of behavior as we do in the last three figures for AGE, MAXIMAL HEART RATE, and HEIGHT. In no case does there appear to be systematic unexplained variability than might be explained by adding a quadratic term or other terms to the equation.

If we rerun these data removing the potential outlier, the results change as given below.

	All Data		**Removing the Outlier Point**	
Variable or Constant	b_j	t	b_j	t
DURATION	0.0515	8.67	0.0544	10.17
WEIGHT	−0.127	−2.17	−0.105	−2.02
Constant	10.300		7.704	

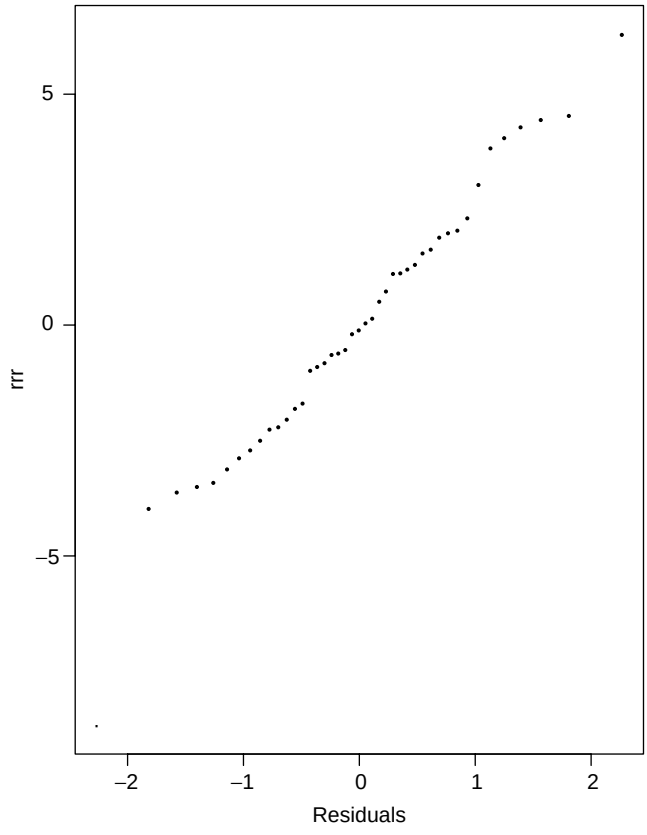


Figure 11.7 Normal residual plot.

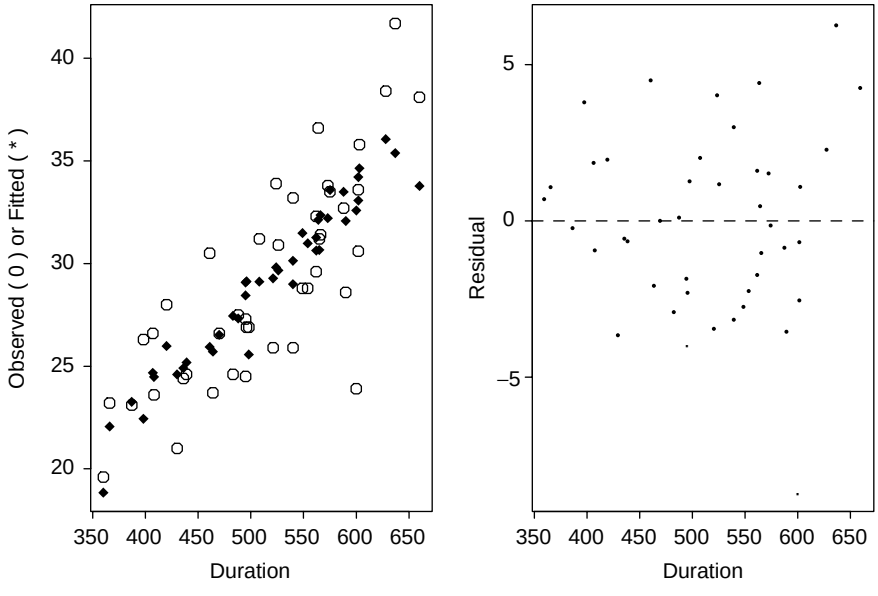


Figure 11.8 Duration vs. residual plots.

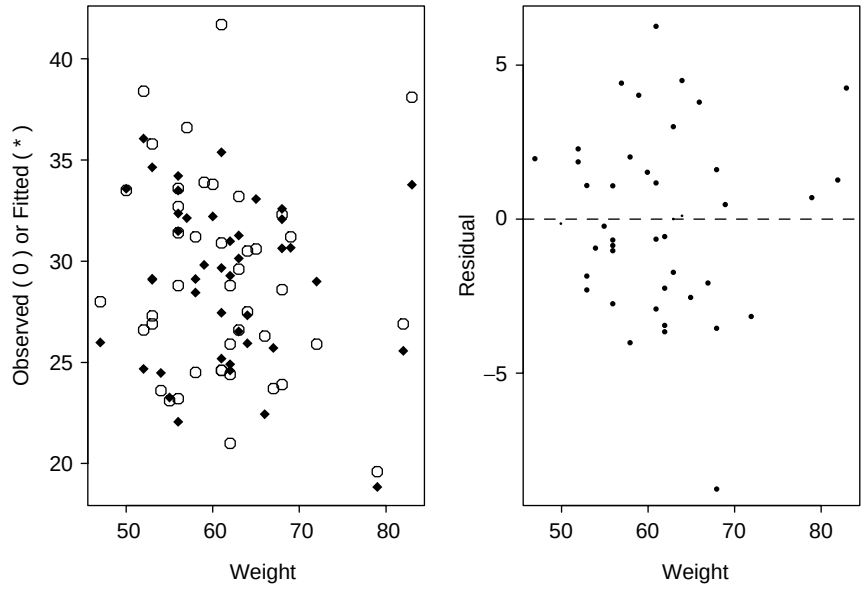


Figure 11.9 Weight vs. residual plots.

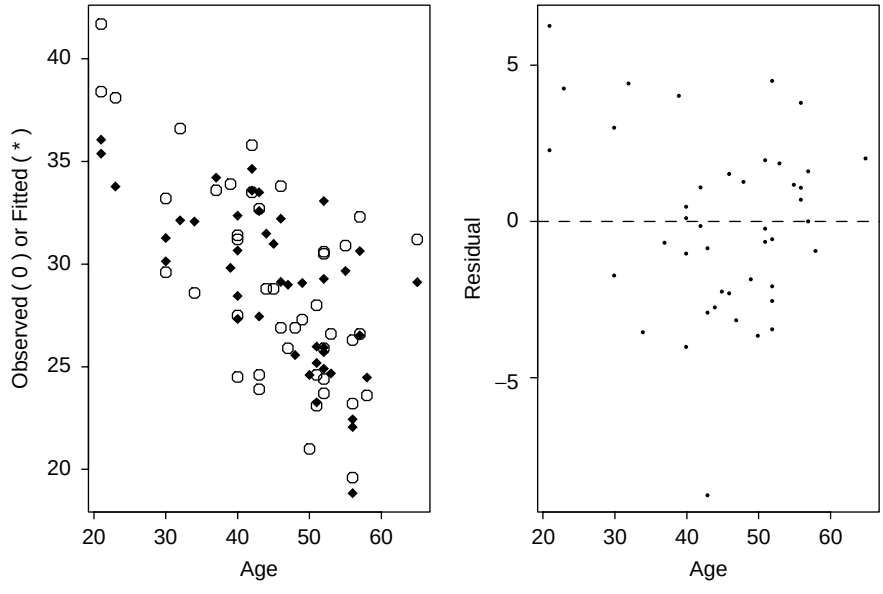


Figure 11.10 Age vs. residual plots.

We see a moderate change in the coefficient for WEIGHT; the change increases the importance of DURATION. The t statistic for WEIGHT is now right on the precise edge of statistical significance of the 0.05 level. Thus, although the original model did not mislead us, part of the contribution from WEIGHT came from the data point that was removed. This brings up the issue of how such data might be presented in a scientific paper or talk. One possibility would be to present both results and discuss the issue. The removal of outlying values may allow one to get a

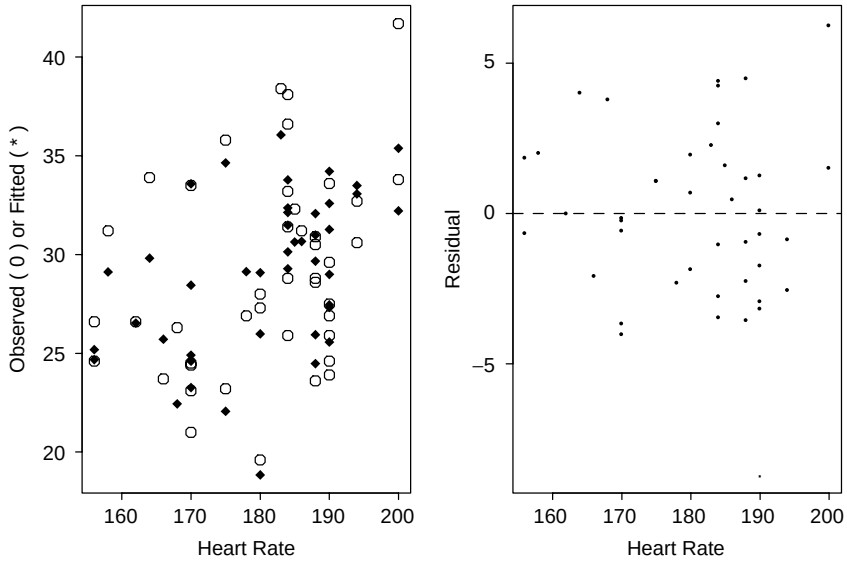


Figure 11.11 Maximum heart rate vs. residual plots.

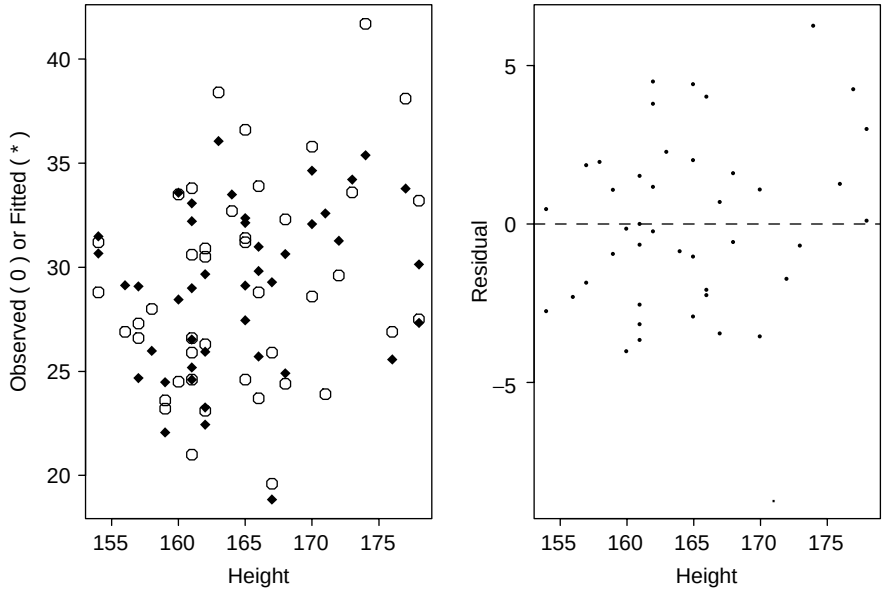


Figure 11.12 Height vs. residual plots.

closer fit to the data, and in this case the residual variability decreased from an estimated σ^2 of 2.97 to 2.64. Still, if the outlier is not considered to be due to bad data, but rather is due to an exceptional individual, in applying such relationships, other exceptional individuals may be expected to appear. In such cases, interpretation necessarily becomes complex. This shows, again, that although there is a nice precision to significance levels, in practice, interpretation of the statistical analysis is an art as well as a science.

11.8.2 Nesting in More Global Hypothesis

Since it is difficult to inspect multidimensional data visually, one possibility for testing the model fit is to embed the model in a more global hypothesis; that is, nest the model used within a more general model. One example of this would be adding quadratic terms and cross-product terms as discussed in Section 11.7. The number of such possible terms goes up greatly as the number of variables increases; this luxury is available only when there is a considerable amount of data.

11.8.3 Splitting the Samples; Jackknife Procedures

An estimated equation will fit data better than the true population equation because the estimate is designed to fit the data at hand. One way to get an estimate of the precision in a multiple regression model is to split the sample size into halves at random. One can estimate the parameters from one-half of the data and then predict the values for the remaining unused half of the data. The evaluation of the fit can be performed using the other half of the data. This gives an unbiased estimate of the appropriateness of the fit and the precision. There is, however, the problem that one-half of the data is "wasted" by not being used for the estimation of the parameters. This may be overcome by estimating the precision in this split-sampling manner but then presenting final estimates based on the entire data set.

Another approach, which allows more precision in the estimate, is to delete subsets of the data and to estimate the model on the remaining data; one then tests the fit on the smaller subsets removed. If this is done systematically, for example by removing one data point at a time, estimating the model using the remaining data and then examining the fit to the data point omitted, the procedure is called a *jackknife procedure* (see Efron [1982]). Resampling from the observed data, the *bootstrap* method may also be used [Efron and Tibshirani, 1986]. We will not go further into such issues here.

11.9 ANALYSIS OF COVARIANCE

11.9.1 Need for the Analysis of Covariance

In Chapter 10 we considered the analysis of variance. Associated with categorical classification variables, we had a continuous response. Let us consider the simplest case, where we have a one-way analysis of variance consisting of two groups. Suppose that there is a continuous variable X in the background: a covariate. For example, the distribution of the variable X may differ between the groups, or the response may be very closely related to the value for the variable X. Suppose further that the variable X may be considered a more fundamental cause of the response pattern than the grouping variable. We illustrate some of the potential complications by two figures.

On the left-hand side of Figure 11.13, suppose that we have data as shown. The solid circles show the response values for group 1 and the crosses the response values for group 2. There is clearly a difference in response between the two groups. Suppose that we think that it is not the grouping variable that is responsible but the covariate X. On the right-hand side we see a possible pattern that could lead to the response pattern given. In this case we see that the observations from both groups 1 and 2 have the same response pattern *when the value of X is taken into account*; that is, they both fall around one fixed regression line. In this case, the difference observed between the groups may alternatively be explained because they differ in the covariate value X. Thus in certain situations, in the analysis of variance one would like to adjust for potential differing values of a covariate. Another way of stating the same thing is: *In certain analysis of variance situations there is a need to remove potential bias, due to the fact that categories differ in their values of a covariate X*. (See also Section 11.5.)

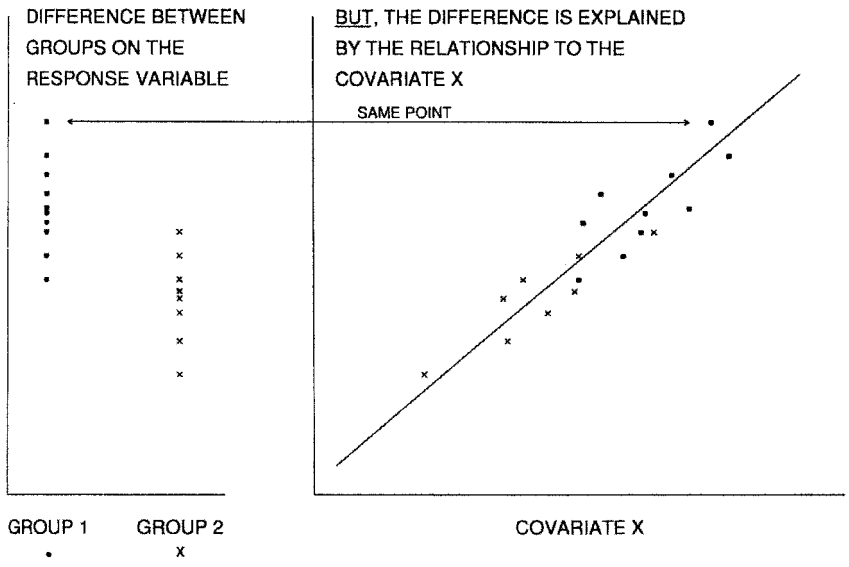


Figure 11.13 One-way analysis of variance with two categories: group difference because of bias due to different distribution on the covariate X.

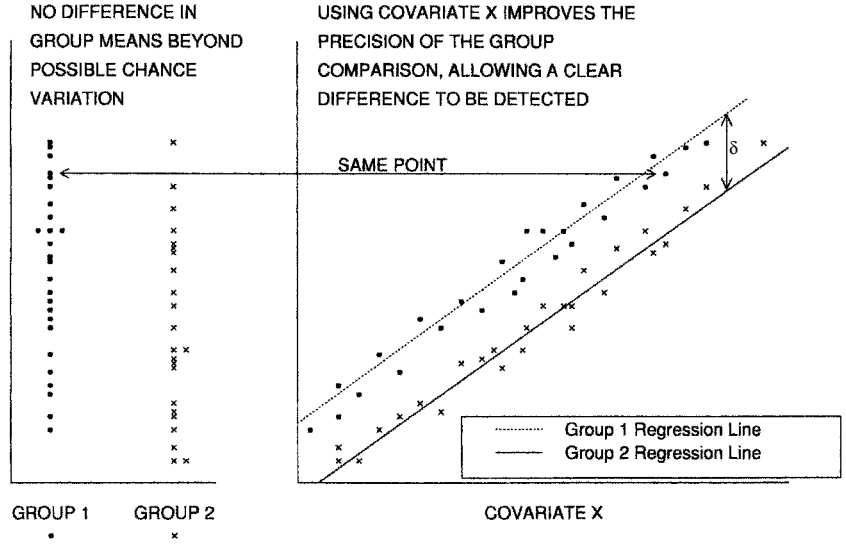


Figure 11.14 Two groups with close distribution on the covariate X. By using the relationship of the response to X separately in each group, a group difference obscured by the variation in X is revealed.

Figure 11.14 shows a pattern of observations on the left for groups 1 and 2. There is no difference between the response in the groups given the variability of the observations. Consider the same points, however, where we consider the relationship to a covariate X as plotted on the right. The right-hand figure shows that the two groups have parallel regression lines that differ by an amount delta. Thus for a fixed value of the covariate X, on the average, the observations from the two groups differ. In this plot, there is clearly a statistically significant difference between

the two groups because their regression lines will clearly have different intercepts. Although the two groups have approximately the same distribution of the covariate values, if we consider the covariate we are able to improve the precision of the comparison between the two groups. On the left, most of the variability is not due to intrinsic variability within the groups, but rather is due to the variability in the covariate X. On the right, when the covariate X is taken into account, we can see that there is a difference. Thus a second reason for considering covariates in the analysis of variance is: *Consideration of a covariate may improve the precision of the comparison of the categories in the analysis of variance.*

In this section we consider methods that allow one or more covariates to be taken into account when performing an analysis of variance. Because we take into account those variables that vary with the variables of interest, the models and the technique are called the *analysis of covariance*.

11.9.2 Analysis of Covariance Model

In this section we consider the one-way analysis of covariance. This is a sufficient introduction to the subject so that more general analysis of variance models with covariates can then be approached.

In the one-way analysis of covariance, we observe a continuous response for each of a fixed number of categories. Suppose that the analysis of variance model is

$$Y_{ij} = \mu + \alpha_i + \varepsilon_{ij}$$

where $i = 1, \ldots, I$ indexes the I categories; α_i, the category effect, satisfies $\sum_i \alpha_i = 0$; and $j = 1, \ldots, n_i$ indexes the observations in the ith category. The ε_{ij} are independent $N(0, \sigma^2)$ random variables.

Suppose now that we wish to take into account the effect of the continuous covariate X. As in Figures 11.13 and 11.14, we suppose that the response is linearly related to X, where the slope of the regression line, γ, is the same for each of the categories (see Figure 11.15). That is, our analysis of covariance model is

$$Y_{ij} = \mu + \alpha_i + \gamma X_{ij} + \varepsilon_{ij} \tag{20}$$

with the assumptions as before.

Although we do not pursue the matter, the analogous analysis of covariance model for the two-way analysis of variance without interaction may be given by

$$Y_{ijk} = \mu + \alpha_i + \beta_j + \gamma X_{ijk} + \varepsilon_{ijk}$$

Analysis of covariance models easily generalize to include more than one covariate. For example, if there are p covariates to adjust for, the appropriate equation is

$$Y_{ij} = \mu + \alpha_i + \gamma_1 X_{ij}(1) + \gamma_2 X_{ij}(2) + \cdots + \gamma_p X_{ij}(p) + \varepsilon_{ij}$$

where $X_{ij}(k)$ is the value for the kth covariate when the observation comes from the ith category and the jth observation in that category. Further, if the response is not linear, one may model a different form of the response. For example, the following equation models a quadratic response to the covariate X_{ij}:

$$Y_{ij} = \mu + \alpha_i + \gamma_1 X_{ij} + \gamma_2 X_{ij}^2 + \epsilon_{ij}$$

In each case in the analysis of covariance, *the assumption is that the response to the covariates is the same within each of the strata or cells for the analysis of covariance.*

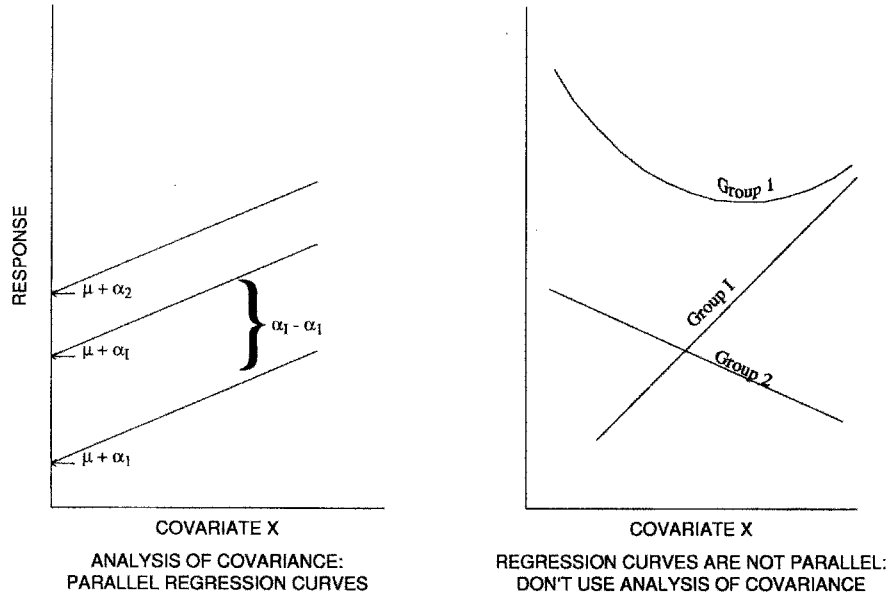


Figure 11.15 Parallel regression curves are assumed in the analysis of covariance.

It is possible to perform both the analysis of variance and the analysis of covariance by using the methods of multiple linear regression analysis, as given earlier in this chapter. The trick to thinking of an analysis of variance problem as a multiple regression problem is to use *dummy* or *indicator variables*, which allow us to consider the unknown parameters in the analysis of variance to be parameters in a multiple regression model.

Definition 11.11. A *dummy*, or *indicator variable* for a category or condition is a variable taking the value 1 if the observation comes from the category or satisfies the condition; otherwise, taking the value zero.

We illustrate this definition with two examples. A dummy variable for the male gender is

$$X = \begin{cases} 1, & \text{if the subject is male} \\ 0, & \text{otherwise} \end{cases}$$

A series of dummy variables for blood types (A, B, AB, O) are

$$X_1 = \begin{cases} 1, & \text{if the blood type is A} \\ 0, & \text{otherwise} \end{cases}$$

$$X_2 = \begin{cases} 1, & \text{if the blood type is B} \\ 0, & \text{otherwise} \end{cases}$$

$$X_3 = \begin{cases} 1, & \text{if the blood type is AB} \\ 0, & \text{otherwise} \end{cases}$$

$$X_4 = \begin{cases} 1, & \text{if the blood type is O} \\ 0, & \text{otherwise} \end{cases}$$

By using dummy variables, analysis of variance models may be turned into multiple regression models. We illustrate this by an example.

Consider a one-way analysis of variance with three groups. Suppose that we have two observations in each of the first two groups and three observations in the third group. Our model is

$$Y_{ij} = \mu + \alpha_i + \varepsilon_{ij} \tag{21}$$

where i denotes the group and j the observation within the group. Our data are Y_{11}, Y_{12}, Y_{21}, Y_{22}, Y_{31}, Y_{32}, and Y_{33}. Let X_1, X_2, and X_3 be indicator variables for the three categories.

$$X_1 = \begin{cases} 1, & \text{if the observation is in group 1} \\ 0, & \text{otherwise} \end{cases}$$

$$X_2 = \begin{cases} 1, & \text{if the observation is in group 2} \\ 0, & \text{otherwise} \end{cases}$$

$$X_3 = \begin{cases} 1, & \text{if the observation is in group 3} \\ 0, & \text{otherwise} \end{cases}$$

Then equation (21) becomes (omitting subscript on Y and e)

$$Y = \mu + \alpha_1 X_1 + \alpha_2 X_2 + \alpha_3 X_3 + \varepsilon \tag{22}$$

Note that X_1, X_2, and X_3 are related. If $X_1 = 0$ and $X_2 = 0$, then X_3 must be 1. Hence there are only two independent dummy variables. In general, for k groups there are $k-1$ independent dummy variables. This is another illustration of the fact that the k treatment effects in the one-way analysis of variance have $k-1$ degrees of freedom. Our data, renumbering the Y_{ij} to be Y_k, $k = 1, \ldots, 7$, are given in Table 11.14. For technical reasons, we do not estimate equation (22). Since

$$\sum_i X_i = 1, \qquad R^2_{X_1(X_2,X_3)} = 1$$

Recall that we cannot estimate regression coefficients well if the multiple correlation is near 1. Instead, an equivalent model

$$Y = \delta + \gamma_1 X_1 + \gamma_2 X_2 + \epsilon$$

is used. Here $\delta = \mu + \alpha_3$, $\gamma_1 = \alpha_1 - \alpha_3$, and $\gamma_2 = \alpha_2 - \alpha_3$. That is, all effects are compared relative to group 3. We may now use a multiple regression program to perform the one-way analysis of variance.

To move to an analysis of covariance, we use $Y = \delta + \gamma_1 X_1 + \gamma_2 X_2 + \beta X + \epsilon$, where X is the covariate. If there is no group effect, we have the same expected value (for fixed X) regardless of the group; that is, $\gamma_1 = \gamma_2 = 0$.

Table 11.14 Data Using Dummy Variables

Y_k	Y_{ij}	X_1	X_2	X_3
Y_1	Y_{11}	1	0	0
Y_2	Y_{12}	1	0	0
Y_3	Y_{21}	0	1	0
Y_4	Y_{22}	0	1	0
Y_5	Y_{31}	0	0	1
Y_6	Y_{32}	0	0	1
Y_7	Y_{33}	0	0	1

More generally, for I groups the model is

$$Y = \delta + \gamma_1 X_1 + \cdots + \gamma_{I-1} X_{I-1} + \beta X + \epsilon$$

The null hypothesis is H_0:$\gamma_1 = \gamma_2 = \cdots = \gamma_{I-1} = 0$. This is tested using nested hypotheses. Let $\mathrm{SS}_{\mathrm{REG}}(X)$ be the regression sum of squares for the model $Y = \delta + \beta X + e$. Let

$$\mathrm{SS}_{\mathrm{REG}}(\gamma|X) = \mathrm{SS}_{\mathrm{REG}}(X_1, \ldots, X_{I-1}, X) - \mathrm{SS}_{\mathrm{REG}}(X)$$

and

$$\mathrm{SS}_{\mathrm{RESID}}(\gamma, X) = \mathrm{SS}_{\mathrm{TOTAL}} - \mathrm{SS}_{\mathrm{REG}}(X_1, \ldots, X_{I-1}, X)$$

The analysis of covariance table is:

Source	d.f.	SS	MS	F-Ratio
Regression on X	1	$\mathrm{SS}_{\mathrm{REG}}(X)$	$\mathrm{MS}_{\mathrm{REG}}(X)$	$\dfrac{\mathrm{MS}_{\mathrm{REG}}(X)}{\mathrm{MS}_{\mathrm{RESID}}}$
Groups adjusted for X	$I-1$	$\mathrm{SS}_{\mathrm{REG}}(\gamma\|X)$	$\mathrm{MS}_{\mathrm{REG}}(\gamma\|X)$	$\dfrac{\mathrm{MS}_{\mathrm{REG}}(\gamma\|X)}{\mathrm{MS}_{\mathrm{RESID}}}$
Residual	$n-I-1$	$\mathrm{SS}_{\mathrm{RESID}}(\gamma\|X)$	$\mathrm{MS}_{\mathrm{RESID}}$	
Total	$n-1$	$\mathrm{SS}_{\mathrm{TOTAL}}$		

The F-test for the equality of group means has $I-1$ and $n-I-1$ degrees of freedom. If there is a statistically significant group effect, there is an interest in the separation of the parallel regression lines. The regression lines are:

Group	Line
1	$\widehat{\delta} + \widehat{\gamma}_1 + \widehat{\beta} X$
2	$\widehat{\delta} + \widehat{\gamma}_2 + \widehat{\beta} X$
$\vdots$	$\vdots$
$I-1$	$\widehat{\delta} + \widehat{\gamma}_{I-1} + \widehat{\beta} X$
I	$\widehat{\delta} + \widehat{\beta} X$

where the "hat" denotes the usual least squares multiple regression estimate. Customarily, these values are calculated for X equal to the average X value over all the observations. These values are called *adjusted means* for the group. This is in contrast to the mean observed for the observations in each group. Note again that group I is the reference group. It may sometimes be useful to rearrange the groups to have a specific group be the reference group. For example, suppose that there are three treatment groups and one reference group. Then the effects γ_1, γ_2, and γ_3 are, naturally, the treatment effects relative to the reference group.

We illustrate these ideas with two examples. In each example there are two groups ($I = 2$) and one covariate for adjustment.

Example 11.1. (*continued*) The data of Cullen and van Belle [1975] are considered again. In this case a larger set of data is used. One group received general anesthesia ($n_1 = 35$) and another group regional anesthesia ($n_2 = 42$). The dependent variable, Y, is the percent

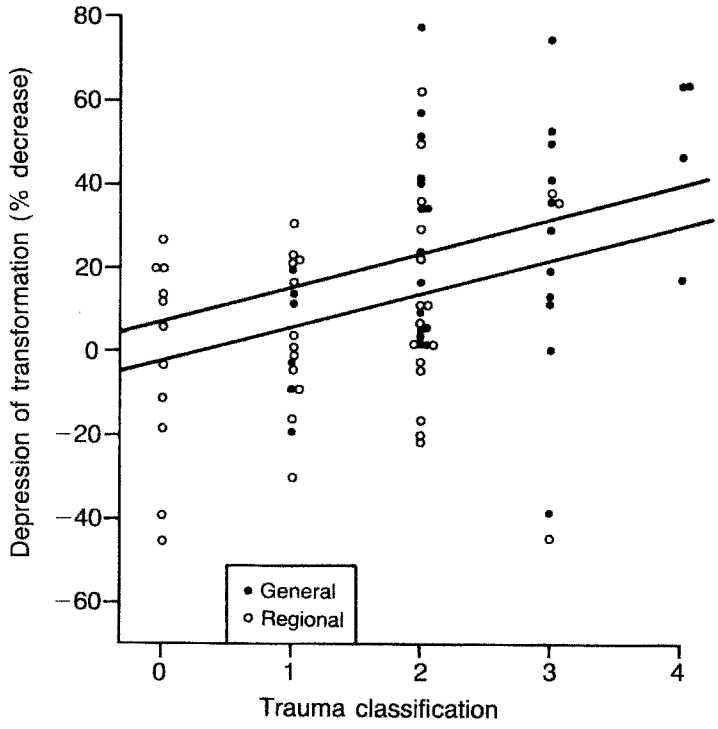


Figure 11.16 Relationship of postoperative depression of lymphocyte transformation to the level of trauma. Each point represents the response of one patient.

depression of lymphocyte transformation following surgery. The covariate, X, is the degree of trauma of the surgical procedure.

Figure 11.16 shows the data with the estimated analysis of covariance regression lines. The top line is the regression line for the general anesthesia group (which had a higher average trauma, 2.4 vs. 1.4). The analysis of covariance table is:

Source	d.f.	SS	MS	F-Ratio
Regression on trauma	1	4,621.52	4,621.52	7.65
General vs. regional anesthesia adjusted for trauma	1	1,249.78	1,249.78	2.06
Residual	74	44,788.09	605.24	
Total	76	56,201.52		

Note that trauma is significantly related to the percent depression of lymphocyte transformation, $F = 7.65 > F_{1,74,0.95}$. In testing the adjusted group difference,

$$F = 2.06 < 3.97 = F_{1,74,0.95}$$

so there is not a statistically significant difference between regional and general anesthesia after adjusting for trauma.

The two regression lines are

$$Y_1 = 25.6000 + 8.4784(X - 2.3714)$$
$$Y_2 = 6.7381 + 8.4784(X - 1.2619)$$

At the average value of $\overline{X} = 1.7552$, the predicted or adjusted means are

$$\widehat{Y}_1 = 25.6000 + (-5.1311) = 20.47$$
$$\widehat{Y}_2 = 6.7381 + (4.2757) = 11.01$$

The original difference is $\overline{Y}_1. - \overline{Y}_2. = 25.6000 - 6.7381 = 18.86$. The adjusted (nonsignificant) difference is $\widehat{Y}_1 - \widehat{Y}_2 = 20.47 - 11.01 = 9.46$, a considerable drop. In fact the unadjusted one-way analysis of variance, or equivalently unpaired t-test, is significant: $p < 0.01$. The observed difference may be due to bias in the differing amount of surgical trauma in the two groups.

Example 11.8. Do men and women use the same level of oxygen when their maximal exercise limit is the same? The Bruce et al. [1973] maximal exercise data are used. The limit of exercise is expressed by the duration on the treadmill. Thus we wish to know if there is a $VO_{2\ MAX}$ difference between genders when adjusting for the duration of exercise. The analysis of covariance table is:

Source	d.f.	SS	MS	F-Ratio
Duration	1	6049.51	6049.51	504.97
Gender, adjusting for duration	1	229.83	229.83	19.18
Residual	84	1006.05	11.98	
Total	86	7285.39		

The gender difference is highly statistically significant after adjusting for the treadmill duration. The estimated regression lines are:

$$\text{Females:} \quad VO_{2\ MAX} = -1.59 + 0.0595 \times \text{duration}$$
$$\text{Males:} \quad VO_{2\ XMAX} = 2.27 + 0.0595 \times \text{duration}$$

The overall duration mean is 581.89. The means are:

	$VO_{2\ MAX}$ Means	
	Observed	Adjusted
Female	29.05	33.03
Male	40.80	36.89

The fact that at maximum exercise normal males use more oxygen per unit of body weight is not accounted for entirely by their average longer duration on the treadmill (647 s vs. 515 s). Even when adjusting for duration, more oxygen per kilogram per minute is used.

Model assumptions may be tested by residual plots and normal probability plots as above. One assumption was that the regression lines were parallel. This may be tested by using the model (in the one-way ANOVA)

$$Y = \delta + \gamma_1 X_1 + \cdots + \gamma_{I-1} X_{I-1} + \beta X + \beta_1 X \cdot X_1 + \cdots + \beta_I X \cdot X_I + \epsilon$$

If an observation is in group $i (i = 1, \ldots, I-1)$, this reduces to

$$Y = \delta + \gamma_i + \beta_i X + \epsilon$$

Nested within this model is the special case $\beta_1 = \beta_2 = \cdots = \beta_I$.

Source	d.f.	SS	MS	F-Ratio
Model with $\gamma_1, \ldots, \gamma_{I-1}, \beta$	I	$SS_{REG}(\gamma_1, \ldots, \gamma_{I-1})$	$MS_{REG}(\gamma's)$	
Model with $\gamma_1, \ldots, \gamma_{I-1}, \beta, \beta_1, \ldots, \beta_I$; extra ss	$I-1$	$SS_{REG}(\beta_1, \ldots, \beta_I \mid \gamma_1, \ldots, \gamma_{I-1}, \beta)$	$MS_{REG}(\beta_i's \mid \gamma_i's, \beta)$	$\dfrac{MS_{REG}(\beta_i's \mid \gamma_i's, \beta)}{MS_{RESID}(\gamma_i's, \beta_i's)}$
Residual	$n-2I$	$SS_{RESID}(\gamma_1, \ldots, \gamma_{I-1}, \beta_1, \ldots, \beta_I)$	$MS_{RESID}(\gamma_i's, \beta_i's)$	
Total	$n-1$	SS_{TOTAL}		

For the exercise test example, we have:

Source	d.f.	SS	MS	F-Ratio
Model with group, equal slopes, and duration	2	6279.34	3139.67	
Model with unequal slopes (minus SS for nested equal-slope model)	1	29.40	29.40	2.50
Residual	83	976.65	11.77	
Total	86	7285.39		

As $F = 2.50 < F_{1,83,0.95}$, the hypothesis of equal slopes (parallelism) is reasonable and the analysis of covariance was appropriate. This use of a nested hypothesis is an example of the method of Section 11.8.2 for testing the goodness of fit of a model.

11.10 ADDITIONAL REFERENCES AND DIRECTIONS FOR FURTHER STUDY

11.10.1 There Are Now Many References on Multiple Regression Methods

Draper and Smith [1981] present extensive coverage of the topics of this chapter, plus much more material and a large number of examples with solutions. The text is on a more advanced mathematical level, making use of matrix algebra. Kleinbaum and Kupper [1998] present material on a level close to that of this chapter; taking more pages for the topics of this chapter, they have a more leisurely presentation. The text is an excellent supplementary reference to the material of this chapter. Another useful text is Daniel and Wood [1999].

11.10.2 Time-Series Data

It would appear that the multiple regression methods of this chapter would apply when one of the explanatory variables is time. This may be true in certain limited cases, but it is not usually true. Analyzing data with time as an independent variable is called *time-series analysis*. Often, in time, the errors are dependent at different time points. Box, Jenkins, and Reinsel [1994] are one source for time-series methods.

11.10.3 Causal Models: Structural Models and Path Analysis

In many studies, especially observational studies of human populations, one might conjecture that certain variables contribute in a causal fashion to the value of another variable. For example, age and gender might be hypothesized to contribute to hospital bed use, but not vice versa. In a statistical analysis, bed use would be modeled as a linear function of age and gender plus other unexplained variability. If only these three variables were considered, we would have a multiple regression situation. Bed use with other variables might be considered an explanatory variable for number of nursing days used. *Structural models* consist of a series of multiple regression equations; the equations are selected to model conjectured causal pathways. The models do not prove causality but can examine whether the data are consistent with certain causal pathways.

Three books addressing structural models (from most elementary to more complex) are Li [1975], Kaplan [2000], and Goldberger and Duncan [1973]. Issues of causality are addressed in Blalock [1985], Cook et al. [2001], and Pearl [2000].

11.10.4 Multivariate Multiple Regression Models

In this chapter we have analyzed the response of one dependent variable as explained by a linear relationship with multiple independent or predictor variables. In many circumstances there are multiple (more than one) dependent variables whose behavior we want to explain in terms of the independent variables. When the models are linear, the topic is called *multivariate multiple regression*. The mathematical complexity increases, but in essence each dependent variable is modeled by a separate linear equation. Morrison [1976] and Timm [1975] present such models.

11.10.5 Nonlinear Regression Models

In certain fields it is not possible to express the response of the dependent variable as a linear function of the independent variables. For example, in pharmacokinetics and compartmental analysis, equations such as

$$Y = \beta_1 e^{\beta_2 x} + \beta_3 e^{\beta_4 x} + e$$

and

$$Y = \frac{\beta_1}{x - \beta_2} + e$$

may arise where the β_i's are unknown coefficients and the e is an error (unexplained variability) term. See van Belle et al. [1989] for an example of the latter equation. Further examples of *nonlinear* regression equations are given in Chapters 13 and 16.

There are computer programs for estimating the unknown parameters.

1. The estimation proceeds by trying to get better and better approximations to the "best" (maximum likelihood) estimates. Sometimes the programs do not come up with an estimate; that is, they do not converge.
2. Estimation is much more expensive (in computer time) than it is in the linear models program.
3. The interpretation of the models may be more difficult.
4. It is more difficult to check the fit of many of the models visually.

NOTES

11.1 Least Squares Fit of the Multiple Regression Model

We use the sum of squares notation of Chapter 9. The regression coefficients b_j are solutions to the k equations

$$[x_1^2]b_1 + [x_1x_2]b_2 + \cdots + [x_1x_k]b_k = [x_1y]$$
$$[x_1x_2]b_1 + [x_2^2]b_2 + \cdots + [x_2x_k]b_k = [x_2y]$$
$$\vdots$$
$$[x_1x_k]b_1 + [x_2x_k]b_2 + \cdots + [x_k^2]b_k = [x_ky]$$

For readers familiar with matrix notation, we give a Y vector and covariate matrix.

$$\mathbf{Y} = \begin{pmatrix} Y_1 \\ \vdots \\ Y_n \end{pmatrix}, \qquad \mathbf{X} = \begin{pmatrix} X_{11} & \cdots & X_{1k} \\ X_{21} & \cdots & X_{2k} \\ \vdots & \ddots & \vdots \\ X_{n1} & \cdots & X_{nk} \end{pmatrix}$$

The b_j are given by

$$\begin{pmatrix} b_1 \\ \vdots \\ b_k \end{pmatrix} = (\mathbf{X}'\mathbf{X})^{-1}\mathbf{X}'\mathbf{Y}$$

where the prime denotes the matrix transpose and -1 denotes the matrix inverse. Once the b_j's are known, a is given by

$$a = \overline{Y} - (b_1\overline{X}_1 + \cdots + b_k\overline{X}_k)$$

11.2 Multivariate Normal Distribution

The density function for *multivariate normal distribution* is given for those who know matrix algebra. Consider jointly distributed variables

$$\mathbf{Z} = \begin{pmatrix} Z_1 \\ \vdots \\ Z_p \end{pmatrix}$$

written as a vector. Let the *mean vector* and *covariance matrix* be given by

$$\mu = \begin{pmatrix} E(Z_1) \\ \vdots \\ E(Z_p) \end{pmatrix}, \qquad \Sigma = \begin{pmatrix} \operatorname{var}(Z_1) & \operatorname{cov}(Z_1, Z_2) & \cdots & \operatorname{cov}(Z_1, Z_p) \\ \vdots & & & \vdots \\ \operatorname{cov}(Z_p, Z_1) & \cdots & \cdots & \operatorname{var}(Z_p) \end{pmatrix}$$

The density is

$$f(z_1, \ldots, z_p) = (2\pi)^{-p/2}|\Sigma|^{-1/2}\exp[-(Z-\mu)'\sum^{-1}(Z-\mu)/2]$$

where $|\Sigma|$ is the determinant of Σ and -1 denotes the matrix inverse. See Graybill [2000] for much more information about the multivariate normal distribution.

Table 11.15 ANOVA Table Incorporating Pure Error

Source	d.f.	SS	MS	F-Ratio
Regression	p	SS_{REG}	MS_{REG}	$\frac{MS_{REG}}{MS_{RESID}}$
Residual	$n-p-1$	SS_{RESID}	MS_{RESID}	
*Model	*$d.f._{MODEL}$	SS_{MODEL}	MS_{MODEL}	$\frac{MS_{MODEL}}{MS_{PURE\ ERROR}}$
*Pure error	*$d.f._{PURE\ ERROR}$	$SS_{PURE\ ERROR}$	$MS_{PURE\ ERROR}$	
Total	$n-1$	SS_{TOTAL}		

11.3 Pure Error

We have seen that it is difficult to test goodness of fit without knowing at least one large model that fits the data. This allows estimation of the residual variability. There is a situation where one can get an accurate estimate of the residual variability without any knowledge of an appropriate model. Suppose that for some fixed value of the X_i's, there are *repeated* measurements of Y. These Y variables will be multiple independent observations with the same mean and variance. By subtracting the sample mean for the point in question, we can estimate the variance. More generally, if more than one X_i combination has multiple observations, we can pool the sum of squares (as in one-way ANOVA) to estimate the residual variability.

We now show how to partition the sum of squares. Suppose that there are K combinations of the covariates X_i for which we observe two or more Y values. Let Y_{ik} denote the ith observation ($i = 1, 2, \ldots, n_k$) at the kth covariate values. Let $\overline{Y}_k$ be the mean of the Y_{ik}:

$$\overline{Y}_k = \sum_{i=1}^{n_k} \frac{Y_{ik}}{n_k}$$

We define the pure error sum of squares and model of squares as follows:

$$SS_{PURE\ ERROR} = \sum_{k=1}^{K} \sum_{i=1}^{n_k} (Y_{ik} - \overline{Y}_k)^2$$

$$SS_{MODEL\ FIT} = SS_{RESID} - SS_{PURE\ ERROR}$$

Also,

$$MS_{PURE\ ERROR} = \frac{SS_{PURE\ ERROR}}{d.f._{PURE\ ERROR}}$$

$$MS_{MODEL\ FIT} = \frac{SS_{MODEL}}{d.f._{MODEL}}$$

where

$$d.f._{PURE\ ERROR} = \sum_{k=1}^{K} n_k - K$$

$$d.f._{MODEL} = n + K - \sum_{k=1}^{K} n_k - p - 1$$

n is the total number of observations, and p is the number of covariates in the multiple regression model. The analysis of variance table becomes that shown in Table 11.15. The terms with an

asterisk further partition the residual sum of squares. The F-statistic $MS_{MODEL}/MS_{PURE\ ERROR}$ with $d.f._{MODEL}$ and $d.f._{PURE\ ERROR}$ degrees of freedom tests the model fit. If the model is not rejected as unsuitable, the usual F-statistic tests whether or not the model has predictive power (i.e., whether all the $\beta_i = 0$).

PROBLEMS

Problems 11.1 to 11.7 deal with the fitting of one multiple regression equation. Perform each of the following tasks as indicated. Note that various parts are from different sections of the chapter. For example, tasks (e) and (f) are discussed in Section 11.8.

- **(a)** Find the t-value for testing the statistical significance of each of the regression coefficients. Do we reject $\beta_j = 0$ at the 5% significance level? At the 1% significance level?
- **(b)** **i.** Construct a 95% confidence interval for each β_j.
  ii. Construct a 99% confidence interval for each β_j.
- **(c)** Fill in the missing values in the analysis of variance table. Is the regression significant at the 5% significance level? At the 1% significance level?
- **(d)** Fill in the missing values in the partial table of observed, predicted, and residual values.
- **(e)** Plot the residual plot of Y vs. $Y - \widehat{Y}$. Interpret your plot.
- **(f)** Plot the normal probability plot of the residual values. Do the residuals seem reasonably normal?

11.1 The 94 sedentary males with treadmill tests of Problems 9.9 to 9.12 are considered here. The dependent and independent variables were $Y = VO_{2\ MAX}$, $X_1 =$ duration, $X_2 =$ maximum heart rate, $X_3 =$ height, $X_4 =$ weight.

Constant or Covariate	b_j	SE(b_j)
X_1	0.0510	0.00416
X_2	0.0191	0.0258
X_3	−0.0320	0.0444
X_4	0.0089	0.0520
Constant	2.89	11.17

Source	d.f.	SS	MS	F-Ratio
Regression	?	4314.69	?	?
Residual	?	?	?	
Total	?	5245.31		

Do tasks (a), (b-i), and (c). What is R^2?

11.2 The data of Mehta et al. [1981] used in Problems 9.13 to 9.22 are used here. The aorta platelet aggregation percent under dipyridamole, using epinephrine, was regressed on the control values in the aorta and coronary sinus. The results were:

Constant or Covariate	b_j	SE(b_j)
Aorta control	−0.0306	0.301
Coronary sinus control	0.768	0.195
Constant	15.90	

Source	d.f.	SS	MS	F-Ratio
Regression	?	?	?	?
Residual	?	231.21	?	
Total	?	1787.88		

Y	$\hat{Y}$	Residual	Y	$\hat{Y}$	Residual
89	81.58	7.42	69	?	?
45	?	?	83	88.15	−5.15
96	86.68	?	84	88.03	−4.03
70	?	2.34	85	88.92	−3.92

Do tasks (a), (b-ii), (c), (d), (e), and (f) [with small numbers of points, the interpretation in (e) and (f) is problematic].

11.3 This problem uses the 20 aortic valve surgery cases of Chapter 9; see the introduction to Problems 9.30 to 9.33. The response variable is the end diastolic volume adjusted for body size, EDVI. The two predictive variables are the EDVI before surgery and the systolic volume index, SVI, before surgery; Y = EDVI postoperatively, X_1 = EDVI preoperatively, and X_2 = SVI preoperatively. See the following tables and Table 11.16. Do tasks (a), (b-i), (c), (d), (f). Find R^2.

Constant or Covariate	b_j	SE(b_j)
X_1	0.889	0.155
X_2	−1.266	0.337
Constant	65.087	

Source	d.f.	SS	MS	F-Ratio
Regression	?	21,631.66	?	?
Residual	?	?	?	
Total	?	32,513.75		

Problems 11.4 to 11.7 refer to data of Hossack et al. [1980, 1981]. Ten normal men and 11 normal women were studied during a maximal exercise treadmill test. While being exercised they had a catheter (tube) inserted into the pulmonary (lung) artery and a short tube into the left radial or brachial artery. This allowed sampling and observation of

Table 11.16 Data for Problem 11.3

Y	$\widehat{Y}$	Residual	Y	$\widehat{Y}$	Residual
111	112.8	0.92	70	84.75	−14.75
56	?	?	149	165.13	−16.13
93	?	−39.99	55	?	?
160	148.78	11.22	91	88.89	2.11
111	?	5.76	118	103.56	−11.56
83	86.00	?	63	?	?
59	?	4.64	100	86.14	13.86
68	93.87	?	198	154.74	43.26
119	62.27	56.73	176	166.39	9.61
71	86.72	?			

arterial pressures and the oxygen content of the blood. From this, several parameters as described below were measured or calculated. The data for the 11 women are given in Table 11.17; the data for the 10 normal men are displayed in Table 11.18. Descriptions of the variables follow.

- *Activity:* a subject who routinely exercises three or more times per week until perspiring was active (Act); otherwise, the subject was sedentary (Sed).
- *Wt*: weight in kilograms.
- *Ht*: height in centimeters.
- VO_{2MAX}: oxygen (in millimeters per kilogram of body weight) used in 1 min at maximum exercise.
- *FAI*: functional aerobic impairment. For a patient's age and activity level (active or sedentary) the expected treadmill duration (ED) is estimated from a regression equation. The excess of observed duration (OD) to expected duration (ED) as a percentage of ED is the FAI. FAI $= 100 \times (\text{OD} - \text{ED})/\text{ED}$.
- $\dot{Q}_{MAX}$: output of the heart in liters of blood per minute at maximum.
- HR_{MAX}: heart rate in beats per minute at maximum exercise.
- SV_{MAX}: volume of blood pumped out of the heart in milliliters during each stroke (at maximum cardial output).
- CaO_2: oxygen content of the arterial system in milliliters of oxygen per liter of blood.
- $C\bar{v}O_2$: oxygen content of the venous (vein) system in milliliters of oxygen per liter of blood.
- $a\bar{v}O_2 D_{MAX}$: difference in the oxygen content (in milliliters of oxygen per liter of blood) between the arterial system and the venous system (at maximum exercise); thus, $a\bar{v}O_2D_{MAX} = CaO_2 - C\bar{v}O_2$.
- $\overline{P}_{SA,\ MAX}$: average pressure in the arterial system at the end of exercise in milliliters of mercury (mmHg).
- $\overline{P}_{PA,\ MAX}$: average pressure in the pulmonary artery at the end of exercise in mmHg.

Table 11.17 Physical and Hemodynamic Variables in 11 Normal Women

Case	Activity	Age (yr)	Wt	Ht	$VO_{2\ MAX}$	FAI	Q_{MAX}	HR_{MAX}	SV_{MAX}	CaO_2	$C\bar{v}O_2$	$a\bar{v}O_2D_{MAX}$	$\overline{P}_{SA,MAX}$	$\overline{P}_{PA,MAX}$
1	Sed	45	63.2	163	28.81	−12	12.43	194	64	193	46	147	109	27
2	Sed	52	56.6	166	24.04	−3	12.19	158	87	181	73	108	137	16
3	Sed	43	65.0	155	26.66	−1	11.52	194	59	212	61	151	?	30
4	Sed	51	58.2	161	24.34	−3	10.78	188	63	173	41	132	154	15
5	Sed	61	74.1	167	21.42	−6	11.71	178	66	198	62	136	140	29
6	Sed	52	69.0	161	26.72	−15	12.89	188	72	193	50	143	125	30
7	Sed	60	50.9	166	23.74	−15	10.94	164	68	160	42	118	95	26
8	Sed	56	66.0	158	28.72	−31	13.93	184	81	168	52	136	148	21
9	Sed	56	66.0	165	20.77	6	10.25	166	62	171	53	118	102	27
10	Sed	51	64.3	168	24.77	−4	11.98	176	68	187	54	133	152	38
11	Act	28	55.5	160	47.72	−37	14.36	200	76	202	31	171	132	25
Mean		50.5	62.6	163	27.07	−11	12.09	181	70	187	51	136	129	26
SD		9.3	6.7	4.1	7.34	13	1.27	14	9	15	10	18	21	7

Table 11.18 Physical and Hemodynamic Variables in 10 Normal Men

Case	Age (yr)	Wt	Ht	$VO_{2\ MAX}$	FAI	$\dot{Q}_{MAX}$	HR_{MAX}	SV_{MAX}	$\overline{P}_{SA,MAX}$	$\overline{P}_{PA,MAX}$
1	64	73.6	170	30.3	−4	13.4	156	85	114	24
2	61	90.9	191	27.1	12	17.8	156	115	104	30
3	38	76.8	180	44.4	5	19.4	190	102	100	24
4	62	92.7	185	24.6	18	15.8	173	91	78	33
5	59	92.0	183	41.2	−18	21.1	167	127	133	36
6	47	83.2	185	48.9	−20	22.4	173	132	160	22
7	24	69.8	178	62.1	−2	24.9	188	133	127	25
8	26	78.6	191	50.9	5	20.1	169	119	115	15
9	54	95.9	183	33.2	9	19.2	154	125	108	31
10	20	83.0	176	32.5	34	15.0	196	77	120	18
Mean	46	83.7	182	39.2	4	18.9	169	114	117	26
SD	17	8.9	7	12.0	16	3.5	21	25	22	7

11.4 For the 10 men, let $Y = VO_{2\ MAX}$, $X_1 =$ weight, $X_2 = HR_{MAX}$, and $X_3 = SV_{MAX}$. (In practice, one would not use three regression variables with only 10 data points. This is done here so that the small data set may be presented in its entirety.)

Constant or Covariate	b_j	SE(b_j)
Weight	−0.699	0.128
HR_{MAX}	0.289	0.078
SV_{MAX}	0.448	0.0511
Constant	−1.454	

Source	d.f.	SS	MS	F-Ratio
Regression	?	?	?	?
Residual	?	55.97	?	
Total	?	1305.08		

Y	$\hat{Y}$	Residual	Y	$\hat{Y}$	Residual
30.3	30.38	−0.08	48.9	?	−0.75
27.1	?	−4.64	62.1	63.80	−1.70
44.4	45.60	−1.20	50.9	45.88	?
24.6	24.65	?	33.2	32.15	1.05
41.2	39.53	1.67	32.5	?	?

Do tasks (a), (c), (d), (e), and (f).

11.5 After examining the normal probability plot of residuals, the regression of Problem 11.4 was rerun omitting cases 2 and 8. In this case we find:

Constant or Covariate	b_j	SE(b_j)
Weight	−0.615	0.039
HR_{MAX}	0.274	0.024
SV_{MAX}	0.436	0.015
Constant	−4.486	

Source	d.f.	SS	MS	F-Ratio
Regression	?	1017.98	?	?
Residual	?	?	?	
Total	?	1021.18		

Y	$\widehat{Y}$	Residual	Y	$\widehat{Y}$	Residual
30.3	?	?	48.9	49.35	?
44.4	?	−0.45	62.1	?	?
24.6	25.62	?	33.2	33.28	−0.08
41.2	?	1.09	32.5	31.77	0.73

Do tasks (a), (b-i), (c), (d), and (f). *Comment*: The very small residual (high R^2) indicates that the data are very likely highly "over fit." Compute R^2.

11.6 Selection of the regression variables of Problems 11.4 and 11.5 was based on Mallow's C_p plot. With so few cases, the multiple comparison problem looms large. As an independent verification, we try the result on the data of the 11 normal women. We find:

Constant or Covariate	b_j	SE(b_j)
Weight	−0.417	0.201
HR_{MAX}	0.441	0.098
SV_{MAX}	0.363	0.160
Constant	−51.96	

Source	d.f.	SS	MS	F-Ratio
Regression	?	419.96	?	?
Residual	?	117.13	?	
Total	?	?		

Y	$\widehat{Y}$	Residual	Y	$\widehat{Y}$	Residual
28.81	?	−1.75	23.72	23.89	−0.15
24.04	?	−1.72	28.72	31.14	−2.42
26.66	27.99	?	20.77	16.30	4.46
24.34	29.63	?	24.77	23.60	1.17
21.42	?	?	47.72	40.77	6.95
26.72	?	?			

Do tasks (a), (b-i), (c), (d), (e), and (f). Do (e) or (f) look suspicious? Why?

11.7 Do another run with the data of Problem 11.6 omitting the last point.

Constant or Covariate	b_j	SE(b_j)
Weight	−0.149	0.074
HR_{MAX}	0.233	0.042
SV_{MAX}	0.193	0.056
Constant	−20.52	

Source	d.f.	SS	MS	F-Ratio
Regression	?	?	?	?
Residual	?	?	?	
Total	?	?		

Note the large change in the b_j's when omitting the outlier.

Y	$\hat{Y}$	Residual	Y	$\hat{Y}$	Residual
28.81	27.54	1.27	26.72	?	−0.11
24.04	24.59	−0.55	23.72	?	0.57
26.66	?	?	28.72	28.08	?
24.34	26.70	−2.36	20.77	20.23	?
21.42	?	?	24.77	23.96	0.81

Do tasks (a), (c), and (d). Find R^2. Do you think the female findings roughly support the results for the males?

11.8 Consider the regression of Y on $X_1, X_2, \ldots, X_6$. Which of the following five hypotheses are *nested* within other hypotheses?

$$H_1\colon \beta_1 = \beta_2 = \beta_3 = \beta_4 = \beta_5 = \beta_6 = 0$$

$$H_2\colon \beta_1 = \beta_5 = 0$$

$$H_3\colon \beta_1 = \beta_5$$

$$H_4\colon \beta_2 = \beta_5 = \beta_6 = 0$$

$$H_5\colon \beta_5 = 0$$

11.9 Consider a hypothesis H_1 nested within H_2. Let R_1^2 be the multiple correlation coefficient for H_1 and R_2^2 the multiple correlation coefficient for H_2. Suppose that there are n observations and H_2 regresses on Y and $X_1, \ldots, X_k$, while H_1 regresses Y only on the first j X_i's ($j < k$). Show that the F statistic for testing $\beta_{j+1} = \cdots = \beta_k = 0$ may be written as

$$F = \frac{(R_2^2 - R_1^2)/(k - j)}{(1 - R_2^2)/(n - k - 1)}$$

Table 11.19 Simple Correlation Coefficients between Nine Variables for Black Men, United States, 1960–1962[a]

Variable	1	2	3	4	5	6	7	8	9
1. Height	—								
2. Weight	0.34	—							
3. Right triceps skinfold	−0.04	0.61	—						
4. Infrascapular skinfold	−0.05	0.72	0.72	—					
5. Arm girth	0.10	0.89	0.60	0.70	—				
6. Glucose	−0.20	−0.05	0.09	0.10	−0.03	—			
7. Cholesterol	−0.08	0.15	0.17	0.20	0.17	0.12	—		
8. Age	−0.23	−0.09	−0.05	0.02	−0.10	0.37	0.34	—	
9. Systolic blood pressure	−0.18	0.11	0.07	0.12	0.12	0.29	0.20	0.47	—
10. Diastolic blood pressure	−0.09	0.17	0.08	0.16	0.18	0.20	0.17	0.33	0.79

[a]Number of observations for samples: $N = 358$ and $\underline{N = 349}$. Figures underlined were derived from persons in the sample for whom glucose and cholesterol measurements were available.

Florey and Acheson [1969] studied blood pressure as it relates to physique, blood glucose, and serum cholesterol separately for males and females, blacks and whites. Table 11.19 presents sample correlation coefficients for black males on the following variables:

- *Height:* in inches
- *Weight:* in pounds
- *Right triceps skinfold:* in thickness in centimeters of skin folds on the back of the right arm, measured with standard calipers
- *Infrascapular skinfold:* skinfold thickness on the back below the tip of the right scapula
- *Arm girth:* circumference of the loose biceps
- *Glucose:* taken 1 hour after a challenge of 50 g of glucose in 250 cm^3 of water
- *Total serum cholesterol concentration*
- *Age:* in years
- *Systolic blood pressure* (mmHg)
- *Diastolic blood pressure* (mmHg)

An additional variable considered was the *ponderal index*, defined to be the height divided by the cube root of the weight. Note that the samples sizes varied because of a few uncollected blood specimens. For Problem 11.10, use $N = 349$.

11.10 Using the Florey and Acheson [1969] data above, the correlation squared of systolic blood pressure, variable 9, with the age and physical variables (variables 1, 2, 3, 4, 5, and 8) is 0.266. If we add variables 6 and 7, the blood glucose and cholesterol variables, R^2 increases to 0.281. Using the result of Problem 11.9, is this a statistically significant difference?

11.11 Suppose that the following description of a series of multiple regression runs was presented. Find any incorrect or inconsistent statements (if they occur). Forty-five people

were given a battery of psychological tests. The dependent variable of self-image was analyzed by multiple regression analysis with five predictor variables: 1, tension index; 2, perception of success in life; 3, IQ; 4, aggression index; and 5, a hypochondriacal index. The multiple correlation with variables 1, 4, and 5 was -0.329, $p < 0.001$. When variables 2 and 3 were added to the predictive equation, $R^2 = 0.18$, $p > 0.05$. The relationship of self-image to the variables was complex; the correlation with variables 2 and 3 was low (0.03 and -0.09, respectively), but the multiple correlation of self-image with variables 2 and 3 was higher than expected, $R^2 = 0.22$, $p < 0.01$.

11.12 Using the definition of R^2 (Definition 11.4) and the multiple regression F test in Section 11.2.3, show that

$$R^2 = \frac{kF}{kF + n - k - 1}$$

and

$$F = \frac{(n - k - 1)R^2}{k(1 - R^2)}$$

Haynes et al. [1978] consider the relationship of psychological factors and coronary heart disease. As part of a long ongoing study of coronary heart disease, the Framingham study, from 1965 to 1967, questionnaires were given to 1822 individuals. Of particular interest was type A behavior. Roughly speaking, type A individuals feel considerable time pressure, are very driving and aggressive, and feel a need for perfection. Such behavior has been linked with coronary artery disease. The questions used in this study follow. The scales (indicated by the superscript numbers) are explained following the questions.

Psychosocial Scale and Items Used in the Framingham Study

Note: The superscript numbers in this list refer to the response sets that follow item 17.

1. Framingham type A behavior pattern:
Traits and qualities which describe you:[1]

Being hard-driving and competitive
Usually pressed for time
Being bossy and dominating
Having a strong need to excel in most things
Eating too quickly

Feeling at the end of an average day of work:

Often felt very pressed for time
Work stayed with you so you were thinking about it after hours
Work often stretched you to the very limits of your energy and capacity
Often felt uncertain, uncomfortable, or dissatisfied with how you were doing

Do you get upset when you have to wait for anything?

2. Emotional lability:
Traits and qualities which describe you:[1]

Having feelings easily hurt
Getting angry very easily

Getting easily excited
Getting easily sad or depressed
Worrying about things more than necessary

Do you cry easily?
Are you easily embarrassed?
Are your feeling easily hurt?
Are you generally a high-strung person?
Are you usually self-conscious?
Are you easily upset?
Do you feel sometimes that you are about to go to pieces?
Are you generally calm and not easily upset?

3. Ambitiousness:
Traits and qualities which describe you:[1]

Being very socially ambitious
Being financially ambitious
Having a strong need to excel in most things

4. Noneasygoing:
Traits and qualities which describe you:[1]

Having a sense of humor
Being easygoing
Having ability to enjoy life

5. Nonsupport from boss:
Boss (the person directly above you):[2]

Is a person you can trust completely
Is cooperative
Is a person you can rely upon to carry his or her load
Is a person who appreciates you
Is a person who interferes with you or makes it difficult for you to get your work done
Is a person who generally lets you know how you stand
Is a person who takes a personal interest in you

6. Marital dissatisfaction:

Everything considered, how happy would you say that your marriage has been?[3]
Everything considered, how happy would you say that your spouse has found your marriage to be?[3]
About marriage, are you more satisfied, as satisfied, or less satisfied than most of your close friends are with their marriages?[4]

7. Marital disagreement:
How often do you and your spouse disagree about:[5]

Handling family finances or money matters
How to spend leisure time
Religious matters
Amount of time that should be spent together

Gambling
Sexual relations
Dealings with in-laws
On bringing up children
Where to live
Way of making a living
Household chores
Drinking

8. Work overload:
Regular line of work fairly often involves:[2]

Working overtime
Meeting deadlines or rigid time schedules

9. Aging worries:
Worry about:[6]

Growing old
Retirement
Sickness
Death
Loneliness

10. Personal worries:
Worry about:[6]

Sexual problems
Change of life
Money matters
Family problems
Not being a success

11. Tensions:
Often troubled by feelings of tenseness, tightness, restlessness, or inability to relax?[5]

Often bothered by nervousness or shaking?
Often have trouble sleeping or falling asleep?
Feel under a great deal of tension?
Have trouble relaxing?
Often have periods of restlessness so that you cannot sit for long?
Often felt difficulties were piling up too much for you to handle?

12. Reader's daily stress:
At the end of the day I am completely exhausted mentally and physically[1]

There is a great amount of nervous strain connected with my daily activities
My daily activities are extremely trying and stressful
In general I am usually tense and nervous

13. Anxiety symptoms:
Often become tired easily or feel continuously fatigued?[2]

Often have giddiness or dizziness or a feeling of unsteadiness?

Often have palpitations, or a pounding or racing heart?
Often bothered by breathlessness, sighing respiration or difficulty in getting a deep breath?
Often have poor concentration or vagueness in thinking?

14. Anger symptoms:
When really angry or annoyed:[7]

Get tense or worried
Get a headache
Feel weak
Feel depressed
Get nervous or shaky

15. Anger-in:
When really angry or annoyed:[7]

Try to act as though nothing much happened
Keep it to yourself
Apologize even though you are right

16. Anger-out:
When really angry or annoyed:[7]

Take it out on others
Blame someone else

17. Anger-discuss:
When really angry or annoyed:[7]

Get it off your chest
Talk to a friend or relative

Response Sets

1. Very well, fairly well, somewhat, not at all
2. Yes, no
3. Very happy, happy, average, unhappy, very unhappy
4. More satisfied, as satisfied, less satisfied
5. Often, once in a while, never
6. A great deal, somewhat, a little, not at all
7. Very likely, somewhat likely, not too likely

The correlations between the indices are reported in Table 11.20.

11.13 We use the Haynes et al. [1978] data of Table 11.20. The multiple correlation squared of the Framingham type A variable with all 16 of the other variables is 0.424. Note the high correlations for variables 2, 3, 14, 15, and 17.

$$R^2_{1(2,3,14,15,17)} = 0.352$$

Table 11.20 Correlations among 17 Framingham Psychosocial Scales with Continuous Distributions

Psychosocial Scales	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
1. Framingham type A		0.43	0.31	0.09	0.12	0.23	0.29	0.06	0.27	0.32	−0.04	0.19	0.11	0.47	0.42	0.24	0.34
2. Emotional lability			0.12	0.26	0.08	0.05	0.21	0.12	0.37	0.31	0.10	0.23	0.11	0.43	0.61	0.42	0.60
3. Ambitiousness				−0.23	0.01	0.01	−0.05	−0.04	0.04	0.06	0.08	0.03	0.09	0.12	0.06	−0.01	0.07
4. Noneasygoing					0.05	0.03	0.15	0.22	0.18	0.17	−0.12	0.16	0.00	0.19	0.22	0.17	0.18
5. Nonsupport from boss						0.11	0.11	−0.01	0.09	0.10	−0.06	−0.01	−0.02	0.12	0.10	0.06	0.06
6. Work overload							0.11	−0.07	0.04	0.06	−0.03	−0.07	0.04	0.15	0.11	0.02	0.06
7. Marital disagreement								0.44	0.33	0.47	−0.08	0.15	−0.01	0.21	0.22	0.18	0.19
8. Marital dissatisfaction									0.12	0.25	0.00	0.02	−0.02	0.11	0.12	0.13	0.13
9. Aging worries										0.53	0.01	0.16	0.04	0.27	0.33	0.29	0.31
10. Personal worries											−0.05	0.19	0.03	0.31	0.33	0.21	0.31
11. Anger-in												−0.18	−0.07	0.06	0.11	0.12	0.18
12. Anger-out													0.11	0.11	0.13	0.09	0.19
13. Anger-discuss														0.08	0.10	0.06	0.12
14. Daily stress															0.51	0.34	0.41
15. Tension																0.49	0.61
16. Anxiety symptoms																	0.45
17. Anger symptoms																	

Source: Data from Haynes et al. [1978].

(a) Is there a statistically significant ($p < 0.05$) gain in R^2 by adding the remainder of the variables?

(b) Find the partial correlation of variables 1 and 2 after adjusting for variable 15. That is, what is the correlation of the Framingham type A index and emotional lability if adjustment is made for the amount of tension?

Stoudt et al. [1970] report on the relationship between certain body size measurements and anthropometric indices. As one would expect, there is considerable correlation among such measurements. The details of the measurements are reported in the reference above. The correlation for women are given in Table 11.21.

11.14 This problem deals with partial correlations.

(a) For the Stoudt et al. [1970] data, the multiple correlation of seat breadth with height and weight is 0.64826. Find

$$r_{\text{seat breadth, height.weight}} \quad \text{and} \quad r_{\text{seat breadth, weight.height}}$$

(b) The Florey and Acheson [1969] data show that the partial multiple correlation between systolic blood pressure and the two predictor variables glucose and cholesterol adjusting for the weight and measurement variables is

$$R^2_{9(6,7).1,2,3,4,5,8} = 0.207, \qquad R = 0.144$$

What are the numerator and denominator degrees of freedom for testing statistical significance? What is (approximately) the 0.05 (0.01) critical value? Find F in terms of R^2. Do we reject the null hypothesis of no correlation at the 5% (1%) level?

11.15 Suppose that you want to regress Y on $X_1, X_2, \ldots, X_8$. There are 73 observations. Suppose that you are given the following sums of squares:

$$\text{SS}_{\text{TOTAL}}, \quad \text{SS}_{\text{REG}}(X_1), \quad \text{SS}_{\text{REG}}(X_4), \quad \text{SS}_{\text{REG}}(X_1, X_5),$$
$$\text{SS}_{\text{REG}}(X_3, X_6), \quad \text{SS}_{\text{REG}}(X_7, X_8), \quad \text{SS}_{\text{REG}}(X_1, X_5, X_6),$$
$$\text{SS}_{\text{REG}}(X_1, X_3, X_6), \quad \text{SS}_{\text{REG}}(X_4, X_7, X_8), \quad \text{SS}_{\text{REG}}(X_3, X_5, X_6, X_8),$$
$$\text{SS}_{\text{REG}}(X_3, X_4, X_7, X_8), \quad \text{SS}_{\text{REG}}(X_3, X_5, X_6, X_7, X_8)$$

For each of the following: (1) state that the quantity cannot be estimated, or (2) show (a) how to compute the quantity in terms of the sums of squares, and (b) give the F-statistic in terms of the sums of squares, and give the degrees of freedom.

(a) r^2_{Y,X_3}

(b) $R^2_{Y(X_1,X_5,X_6)}$

(c) $R^2_{Y(X_1,X_5,X_6).X_3}$

(d) $R^2_{Y(X_3,X_4,X_7,X_8)}$

(e) $r^2_{Y,X_6.X_1,X_5}$

(f) $R^2_{Y(X_5,X_6).X_3,X_4}$

(g) $R^2_{Y(X_3,X_4).X_7,X_8}$

(h) $R^2_{Y(X_3,X_5,X_6).X_7,X_8}$

Table 11.21 Correlations for Women Regarding Body Size

Body Measurement	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19
1. Sitting height, erect	0.907	0.440	0.364	0.585	0.209	0.347	0.231	−0.032	0.204	0.350	0.059	−0.076	0.052	0.057	−0.063	0.772	0.197	−0.339
2. Sitting height, normal		0.420	0.352	0.533	0.199	0.327	0.230	−0.029	0.197	0.317	0.045	−0.091	0.034	0.064	−0.063	0.729	0.165	−0.300
3. Knee height			0.747	0.023	0.196	0.689	0.585	0.106	0.254	0.406	0.180	−0.121	0.128	0.100	0.041	0.782	0.322	−0.128
4. Popliteal height				−0.095	−0.141	0.429	0.387	−0.200	−0.101	0.255	−0.126	0.166	−0.219	−0.193	−0.248	0.723	−0.035	−0.196
5. Elbow rest height					0.293	0.051	−0.045	0.143	0.275	0.094	0.179	0.111	0.222	0.191	0.150	0.258	0.253	−0.177
6. Thigh clearance height						0.465	0.352	0.597	0.609	0.370	0.594	0.523	0.641	0.539	0.541	0.137	0.693	−0.026
7. Buttock–knee length							0.786	0.413	0.552	0.426	0.441	0.410	0.450	0.343	0.296	0.609	0.620	−0.036
8. Buttock–popliteal length								0.326	0.390	0.341	0.371	0.333	0.355	0.269	0.243	0.514	0.490	−0.005
9. Elbow to elbow breadth									0.696	0.331	0.878	0.870	0.835	0.619	0.751	−0.070	0.844	0.393
10. Seat breadth										0.327	0.680	0.666	0.746	0.614	0.596	0.137	0.805	0.187
11. Biacromial diameter											0.433	0.301	0.331	0.209	0.243	0.407	0.443	−0.116
12. Chest girth												0.862	0.843	0.615	0.762	0.016	0.882	0.317
13. Waist girth													0.803	0.589	0.747	−0.090	0.844	0.432
14. Right arm girth														0.740	0.774	−0.026	0.888	0.272
15. Right arm skinfold															0.755	−0.022	−0.641	0.203
16. Infrascapular skinfold																−0.136	0.729	0.278
17. Height																	0.189	−0.289
18. Weight																		0.204
19. Age																		

Source: Data from Stoudt et al. [1970].

11.16 Suppose that in the Framingham study [Haynes et al., 1978] we want to examine the relationship between type A behavior and anger (as given by the four anger variables). We would like to be sure that the relationship does not occur because of joint relationships with the other variables; that is, we want to adjust for all the variables other than type A (variable 1) and the anger variables 11, 12, 13, and 17.

(a) What quantity would you use to look at this?

(b) If the value (squared) is 0.019, what is the value of the F-statistic to test for significance? The degrees of freedom?

11.17 Suppose that using the Framingham data, we decide to examine emotional lability. We want to see how it is related to four areas characterized by variables as follows:

Work :	variables 5 and 6
Worry and anxiety :	variables 9, 10, and 16
Anger :	variables 11, 12, 13, and 17
Stress and tension :	variables 14 and 15

(a) To get a rough idea of how much relationship one might expect, we calculate

$$R^2_{2(5,6,9,10,16,11,12,13,17,14,15)} = 0.49$$

(b) To see which group or groups of variables may be contributing the most to this relationship, we find

$$\begin{aligned} R^2_{2(5,6)} &= 0.01 \quad \text{work} \\ R^2_{2(9,10,16)} &= 0.26 \quad \text{worry/anxiety} \\ R^2_{2(11,12,13,17)} &= 0.38 \quad \text{anger} \\ R^2_{2(14,15)} &= 0.39 \quad \text{stress/tension} \end{aligned}$$

(c) As the two most promising set of variables were the anger and the stress/tension, we compute

$$R^2_{2(11,12,13,14,15,17)} = 0.48$$

(i) Might we find a better relationship (larger R^2) by working with indices such as the average score on variables 11, 12, 13, and 17 for the anger index? Why or why not?

(ii) After using the anger and stress/tension variables, is there statistical significance left in the relationship of lability and work and work/anxiety? What quantity would estimate this relationship? (In Chapter 14 we show some other ways to analyze these data.)

11.18 The Jensen et al. [1980] data of 19 subjects were used in Problems 9.23 to 9.29. Here we consider the data before training. The exercise $VO_{2,\ MAX}$ is to be regressed upon three variables.

$$Y = VO_{2,\ MAX}$$

$$X_1 = \text{maximal ejection fraction}$$

$$X_2 = \text{maximal heart rate}$$

$$X_3 = \text{maximal systolic blood pressure}$$

The residual mean square with all three variables in the model is 73.40. The residual sums of squares are:

$$SS_{RESID}(X_1, X_2) = 1101.58$$
$$SS_{RESID}(X_1, X_3) = 1839.80$$
$$SS_{RESID}(X_2, X_3) = 1124.78$$
$$SS_{RESID}(X_1) = 1966.32$$
$$SS_{RESID}(X_2) = 1125.98$$
$$SS_{RESID}(X_3) = 1885.98$$

(a) For each model, compute C_p.

(b) Plot C_p vs. p and select the best model.

(c) Compute and plot the average mean square residual vs. p.

11.19 The 20 aortic valve cases of Problem 11.3 give the data about the values of C_p and the residual mean square as shown in Table 11.22.

Table 11.22 Mallow's C_p for Subset of Data from Example 11.3

Numbers of the Explanatory Variables	p	C_p	Residual Mean Square	Numbers of the Explanatory Variables	p	C_p	Residual Mean Square
None	1	14.28	886.99	2,4,5	4	2.29	468.36
				1,4,5		2.41	472.20
4	2	3.87	578.92	3,4,5		2.69	481.50
5		11.60	804.16	1,3,4		6.91	619.81
3		13.63	863.16	1,2,4		6.91	619.90
2		14.14	877.97	2,3,4		7.80	648.81
1		16.00	932.21	2,3,5		14.14	856.68
				1,3,5		14.40	866.45
4,5	3	0.72	454.10	1,2,5		14.45	866.75
1,4		4.94	584.23	1,2,3		15.21	891.72
2,4		5.82	611.35				
3,4		5.87	612.75	1,2,4,5	5	4.05	491.14
1,5		12.76	825.45	2,3,4,5		4.16	494.92
3,5		12.96	831.53	1,3,4,5		4.41	503.66
2,5		13.17	838.17	1,2,3,4		8.90	660.65
2,3		13.23	839.87	1,2,3,5		15.83	903.14
1,3		15.60	912.88				
1,2		15.96	924.03	1,2,3,4,5	6	6	524.37

(a) Plot Mallow's C_p plot and select the "best" model.

(b) Plot the average residual mean square vs. p. Is it useful in this context? Why or why not?

11.20 The blood pressure, physique, glucose, and serum cholesterol work of Florey and Acheson [1969] was mentioned above. The authors first tried using a variety of regression analyses. It was known that the relationship between age and blood pressure is often curvilinear, so an age^2 term was used as a potential predictor variable. After exploratory

analyses, stepwise regression of blood pressure (systolic or diastolic) upon five variables (age, age^2, ponderal index, glucose, and cholesterol) was run. The four regressions (black and white, female and male) for systolic blood pressure are given in Tables 11.23 to 11.26. The "standard error of the estimate" is the estimate of σ^2 at each stage.

(a) For the black men, give the values of the partial F-statistics and the degrees of freedom as each variable entered the equation.

(b) Are the F values in part (a) significant at the 5% significance level?

(c) For a fixed ponderal index of 32 and a glucose level of 125 mg%, plot the regression curve for systolic blood pressure for white women aged 20 to 70.

(d) Can you determine the partial correlation of systolic blood pressure and glucose adjusting for age in black women from these data? If so, give the value.

***(e)** Consider all the multiple regression R^2 values of systolic blood pressure with subsets of the five variables used. For white males and these data, give all possible

Table 11.23 Selected Regression Statistics for Systolic Blood Pressure and Selected Independent Variables of White Men, United States, 1960–1962[a]

Step	Variables Entered	Multiple R	Multiple R^2	Increase in R^2	Regression Coefficient	Standard Error of Estimate
1	Age squared	0.439	0.193	0.193	0.0104	17.9551
2	Ponderal index	0.488	0.238	0.045	−6.1775	17.4471
3	Glucose	0.499	0.249	0.011	0.0500	17.3221
4	Cholesterol	0.503	0.253	0.004	0.0351	17.2859
5	Age	0.507	0.257	0.004	−0.5136	17.2386

[a]Dependent variable, systolic blood pressure. Constant term = 194.997; $N = 2599$.

Table 11.24 Selected Regression Statistics for Systolic Blood Pressure and Selected Independent Variables of Black Men, United States, 1960–1962[a]

Step	Variables Entered	Multiple R	Multiple R^2	Increase in R^2	Regression Coefficient	Standard Error of Estimate
1	Age squared	0.474	0.225	0.225	0.6685	21.9399
2	Ponderal index	0.509	0.259	0.034	−6.4515	21.4769
3	Glucose	0.523	0.273	0.014	0.0734	21.3048

[a]Dependent variable = systolic blood pressure. Constant term = 180.252; $N = 349$.

Table 11.25 Selected Regression Statistics for Systolic Blood Pressure and Selected Independent Variables of White Women, United States, 1960–1962[a]

Step	Variables Entered	Multiple R	Multiple R^2	Increase in R^2	Regression Coefficient	Standard Error of Estimate
1	Age squared	0.623	0.388	0.388	0.00821	18.9317
2	Ponderal index	0.667	0.445	0.057	−7.3925	18.0352
3	Glucose	0.676	0.457	0.012	0.0650	17.8445

[a]Dependent variable = systolic blood pressure. Constant term = 193.260; $N = 2931$.

Table 11.26 Selected Regression Statistics for Systolic Blood Pressure and Selected Independent Variables of Black Women, United States, 1960–1962[a]

Step	Variables Entered	Multiple R	Multiple R^2	Increase in R^2	Regression Coefficient	Standard Error of Estimate
1	Age squared	0.590	0.348	0.348	0.9318	24.9930
2	Ponderal index	0.634	0.401	0.053	0.1388	23.9851
3	Glucose	0.656	0.430	0.029	−6.0723	23.4223

[a]Dependent variable = systolic blood pressure. Constant term = 153.149; $N = 443$.

inequalities that are *not* of the obvious form

$$R^2_{Y(X_{i_1},\ldots,X_{i_m})} \leq R^2_{Y(X_{j_1},\ldots,X_{j_n})}$$

where $X_{i_1}, \ldots, X_{i_m}$ is a subset of $X_{j_1}, \ldots, X_{j_n}$.

11.21 From a correlation matrix it is possible to compute the order in which variables enter a stepwise multiple regression. The partial correlations, F statistics, and regression coefficients for the standardized variables (except for the constant) may be computed. The first 18 women's body dimension variables (as given in Stoudt et al. [1970] and mentioned above) were used. The dependent variable was weight, which we are trying to predict in terms of the 17 measured dimension variables. Because of the large sample size, it is "easy" to find statistical significance. In such cases the procedure is sometimes terminated while statistically significant predictor variables remain. In this case, the addition of predictor variables was stopped when R^2 would increase by less than 0.01 for the next variable. The variable numbers, the partial correlation with the dependent variable (conditioning upon variables in the predictive equation) for the variables not in the model, and the corresponding F-value for step 0 are given in Table 11.27, those for step 1 in Table 11.28, those for step 5 in Table 11.29, and those for the final step in Table 11.30.

(a) Fill in the question marks in Tables 11.27 and 11.28.

(b) Fill in the question marks in Table 11.29.

(c) Fill in the question marks in Table 11.30.

(d) Which variables entered the predictive equation?

***(e)** What can you say about the proportion of the variability in weight explained by the measurements?

Table 11.27 Values for Step 0[a]

var	PCORR	F-Ratio[a]	var	PCORR	F-Ratio[a]
1	0.1970	144.506	10	0.8050	6589.336
2	?	100.165	11	0.4430	873.872
3	0.3230	?	12	0.8820	12537.104
4	−0.0350	4.390	13	0.8440	8862.599
5	0.2530	244.755	14	0.8880	13346.507
6	0.6930	3306.990	15	0.6410	2496.173
7	0.6200	?	16	0.7290	4059.312
8	0.4900	1130.830	17	0.1890	132.581
9	?	8862.599			

[a]The F-statistics have 1 and 3579 d.f.

Table 11.28 Values for Step 1[a]

var	PCORR	F-Ratio[a]	var	PCORR	F-Ratio[a]
1	0.3284	432.622	9	0.4052	?
2	0.2933	?	10	0.4655	989.824
3	0.4568	943.565	11	0.3435	478.797
4	0.3554	517.351	12	0.5394	1467.962
5	0.1246	56.419	13	0.4778	1058.297
6	?	501.893	15	−0.0521	9.746
7	0.5367	1447.655	16	?	74.882
8	0.4065	708.359	17	0.4614	967.603

[a]The F-statistics have 1 and 3578 d.f.

Table 11.29 Values for Step 5[a]

var	PCORR	F-Ratio[a]	var	PCORR	F-Ratio[a]
1	?	323.056	8	0.0051	0.093
2	0.2285	196.834	9	0.0083	0.252
3	0.1623	96.676	11	0.1253	?
4	0.1157	48.503	15	−0.1298	61.260
5	?	183.520	16	−0.0149	?
6	0.2382	214.989	17	0.3131	388.536

[a]The F-statistics have 1 and ? d.f.

Table 11.30 Values for the Final Step[a]

var	PCORR	F-Ratio[a]	var	PCORR	F-Ratio[a]
1	?	5.600	8	−0.0178	1.143
2	−0.0289	2.994	9	0.0217	1.685
3	−0.0085	0.263	11	0.0043	0.067
4	−0.0172	1.062	15	−0.1607	94.635
5	0.0559	?	16	−0.0034	0.042

[a]The F-statistics have 1 and 3572 d.f.

(f) What can you say about the p-value of the next variable that would have entered the stepwise equation? (Note that this small p has less than 0.01 gain in R^2 if entered into the predictive equation.)

11.22 Data from Hossack et al. [1980, 1981] for men and women (Problems 11.4 to 11.7) were combined. The maximal cardiac output, Q_{DOT}, was regressed on the maximal oxygen uptake, $\mathrm{VO}_{2\ \mathrm{MAX}}$. From other work, the possibility of a curvilinear relationship was entertained. Polynomials of the zeroth, first, second, and third degree (or highest power of X) were considered. Portions of the BMDP output are presented below, with appropriate questions (see Figures 11.17 to 11.19).

(a) *Goodness-of-fit test*: For the polynomial of each degree, a test is made for additional information in the orthogonal polynomials of higher degree, with data as shown in Table 11.31. The numerator sum of squares for each of these tests is the sum of squares attributed to all orthogonal polynomials of higher degree,

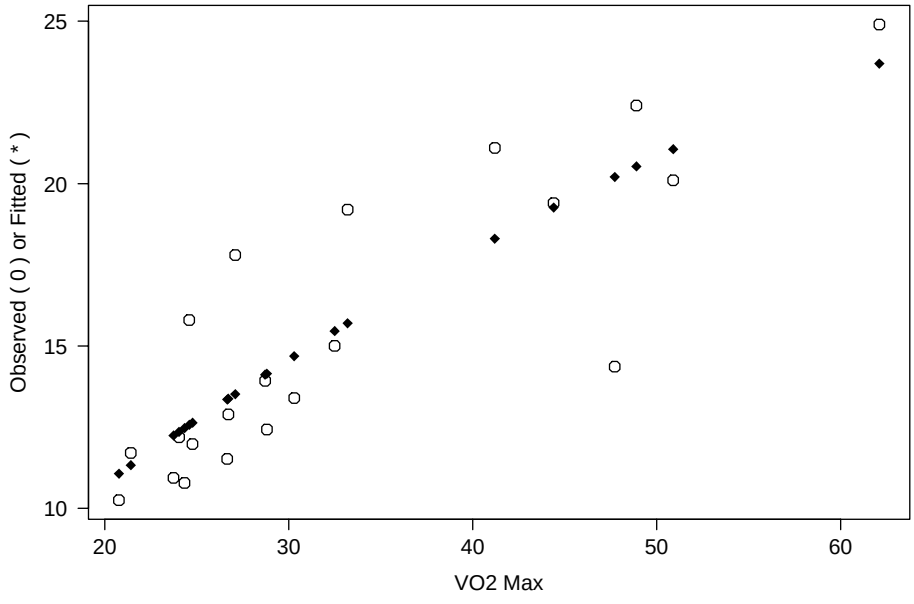


Figure 11.17 Polynomial regression of QDOT on $VO_{2\ MAX}$. Figure for Problem 11.22.

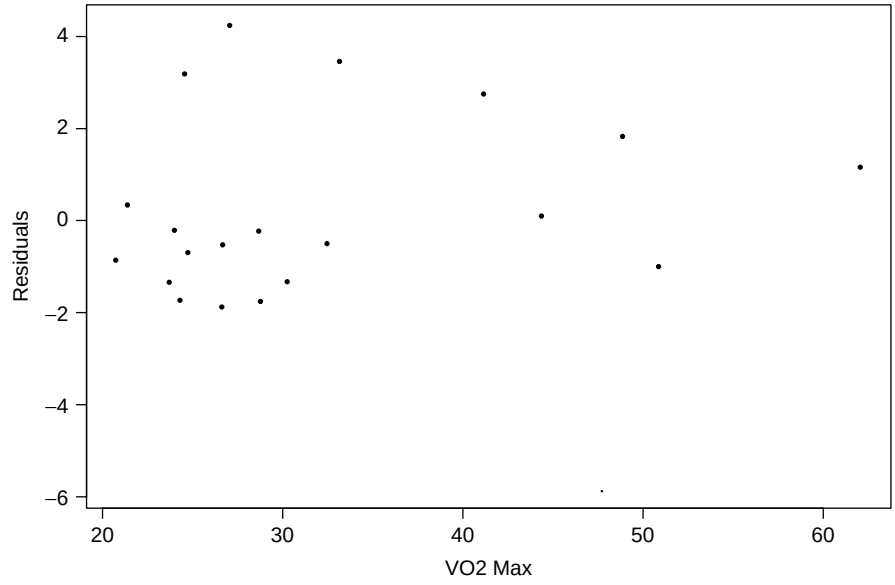


Figure 11.18 Figure for Problem 11.22.

and the denominator sum of squares is the residual sum of squares from the fit to the highest-degree polynomial (fit to all orthogonal polynomials). A significant F-statistic thus indicates that a higher-degree polynomial should be considered. What degree polynomial appears most appropriate? Why do the degrees of freedom in Table 11.31 add up to more than the total number of observations (21)?

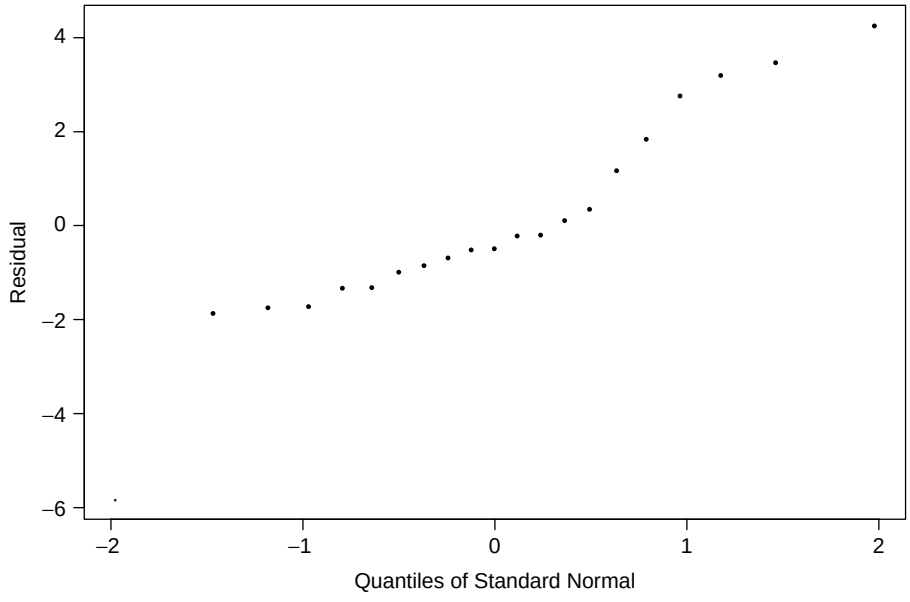


Figure 11.19 Figure for Problem 11.22.

Table 11.31 Goodness of Fit for Figure 11.22

Degree	SS	d.f.	MS	F-Ratio	Tail Probability
0	278.50622	4	69.62656	12.04	0.00
1	12.23208	3	4.07736	0.70	0.56
2	10.58430	2	5.29215	0.91	0.42
3	5.22112	1	5.22112	0.90	0.36
Residual	92.55383	16	5.78461		

(b) For a linear equation, the coefficients, observed and predicted values, residual plot, and normal residual are:

Degree	**Regression Coefficient**	**Standard Error**	***t*-Value**
0	4.88737	1.58881	3.08
1	0.31670	0.04558	6.95

What would you conclude from the normal probability plot? Is the most outlying point a male or female? Which subject number in its table?

(c) For those with access to a polynomial regression program: Rerun the problem, removing the outlying point.

11.23 As in Problem 11.22, this problem deals with a potential polynomial regression equation. Weight and height were collected from a sample of the U.S. population in surveys done in

Table 11.32 Weight by Height Distribution for Men 25–34 Years of Age, Health Examination Survey, 1960–1962[a]

Height (in.)	Number of Examinees at Weight (lb)										
	Total	Under 130	130–139	140–149	150–159	160–169	170–179	180–189	190–199	200–209	210+
Total	675	39	50	78	93	92	87	74	56	48	58
<63	11	3	2	2	4	—	—	—	—	—	—
63	11	2	2	1	4	1	1	—	—	—	—
64	34	10	4	5	5	4	3	1	—	1	1
65	28	6	3	—	7	2	6	1	—	2	1
66	67	6	7	8	11	14	9	2	5	2	3
67	70	4	6	17	9	11	5	5	5	5	3
68	120	5	14	18	25	11	13	13	12	5	4
69	80	1	5	9	10	11	14	11	8	8	3
70	103	2	4	9	9	17	16	14	9	8	15
71	48	—	1	5	4	7	7	7	4	5	8
72	57	—	2	2	4	8	8	8	9	5	11
≥73	46	—	—	2	1	6	5	12	4	7	9

[a]Height without shoes; weight partially clothed; clothing weight estimated as averaging 2 (lb).

Table 11.33 Number of Men Aged 25–34 Years by Weight for Height; United States, 1971–1974[a]

	Number of Examinees at Weight (lb)										
Height (in.)	Total	Under 130	130–139	140–149	150–159	160–169	170–179	180–189	190–199	200–209	210+
Total	804	33	54	86	129	102	103	84	72	42	99
<63	6	1	3	1	—	—	1	—	—	—	—
63	17	4	3	5	3	—	—	—	1	—	1
64	23	3	5	8	2	1	1	1	1	1	—
65	41	5	6	7	11	3	3	1	2	2	1
66	70	5	10	11	11	10	9	5	6	2	1
67	86	3	10	6	19	15	11	9	5	4	4
68	92	5	4	15	12	15	14	13	7	2	5
69	120	3	5	10	26	17	22	8	10	4	15
70	112	2	5	12	15	14	11	18	13	10	12
71	73	2	1	8	14	10	8	7	13	1	9
72	69	—	2	1	10	9	8	9	5	6	19
≥73	95	—	—	2	2	8	15	13	9	10	32

[a]Height without shoes; weight partially clothed; clothing weight estimated as averaging 2 (lb).

Table 11.34 Coefficients and t-values for Problem 11.23

Degree	Regression Coefficient	Standard Error	t-Value
0	61.04225	0.60868	100.29
1	0.04408	0.00355	12.40
0	50.89825	3.85106	13.22
1	0.16548	0.04565	3.62
2	−0.00036	0.00013	−2.67
0	34.30283	25.84667	1.33
1	0.46766	0.46760	1.00
2	−0.00216	0.00278	−0.78
3	0.00000	0.00001	0.65

1960–1962 [Roberts, 1966] and in 1971–1974 [Abraham et al., 1979]. The data for males 25 to 34 years of age are given in Tables 11.32 and 11.33. In this problem we use only the 1960–1962 data. Both data sets are used in Problem 11.36. The weight categories were coded as values 124.5, 134.5, . . . , 204.5, 214.5 and the height categories as 62, 63, . . . , 72, 73. The contingency table was replaced by 675 "observations." As before, we present some of the results from a BMDP computer output. The height was regressed upon weight.

(a) *Goodness-of-Fit Test:* For the polynomial of each degree, a test is made for additional information in the orthogonal polynomials of higher degree. The numerator sum of squares attributed to all orthogonal polynomials of higher degree and the denominator sum of squares is the residual sum of squares from the fit to the highest-degree polynomial (fit to all polynomials). A significant F-statistic thus indicates that a higher-degree polynomial should be considered.

Degree	SS	d.f.	MS	F-Ratio	Tail Probability
0	900.86747	3	300.28916	54.23	0.00
1	41.69944	2	20.84972	3.77	0.02
2	2.33486	1	2.33486	0.42	0.52
Residual	3715.83771	671	5.53776		

Which degree polynomial appears most satisfactory?

(b) Coefficients with corresponding t-statistics are given in Table 11.34 for the first-, second-, and third-degree polynomials. Does this confirm the results of part (a)? How can the second-order term be significant for the second-degree polynomial, but neither the second or third power has a statistically significant coefficient when a third-order polynomial is used?

(c) The normal probability plot of residuals for the second-degree polynomials is shown in Figure 11.20. What does the tail behavior indicate (as compared to normal tails)? Think about how we obtained those data and how they were generated. Can you explain this phenomenon? This may account for the findings. The original data would be needed to evaluate the extent of this problem.

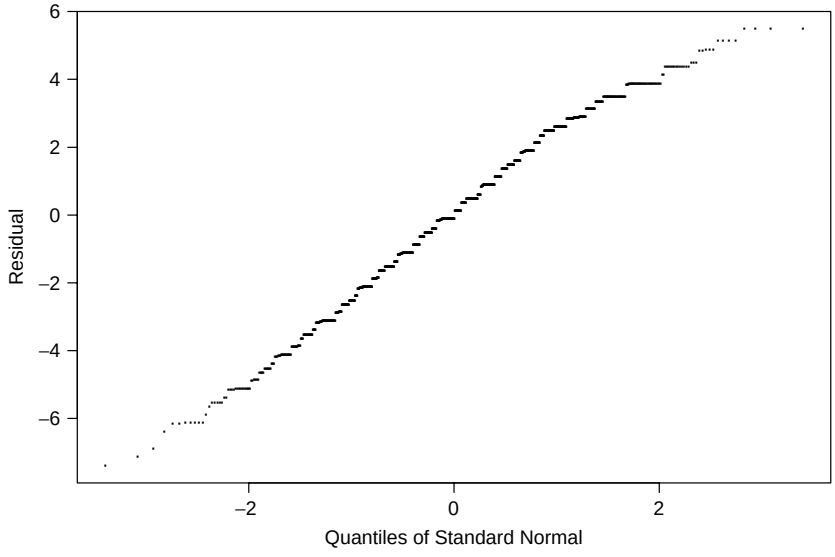


Figure 11.20 Normal probability plot of residuals of degree 2. Figure for Problem 11.23.

Table 11.35 Data for Problems 11.24 to 11.29

Indices of Variables in the Multiple Regression Equation (SS_{TOTAL})	Regression Sum of Squares SS_{REG} ($SS_{TOTAL} = 32513.75$)	Indices of Variables in the Multiple Regression Equation (SS_{TOTAL})	Regression Sum of Squares SS_{REG} ($SS_{TOTAL} = 32513.75$)
1	671.04	1,5	2,397.10
2	926.11	2,3	2,547.67
3	1,366.28	2,4	12,619.61
4	12,619.27	2,5	1,145.53
5	658.21	3,4	13,090.47
1,2	1,607.06	3,5	2,066.16
1,3	1,620.17	4,5	21,631.66
1,4	14,973.55		

Most multiple regression analyses (other than examining fit and model assumptions) use sums of squares rather than the original data. Problems 11.24 to 11.29 illustrate this point. The problems and the data in Table 11.35 are based on the 20 aortic valve surgery cases of Chapter 9 (see the introduction to Problems 9.30 to 9.33); Problem 11.3 uses these data. We consider the regression sums of squares for all possible subsets of five predictor variables. Here Y = EDVI postoperative, X_1 = age in years, X_2 = heart rate, X_3 = systolic blood pressure, X_4 = EDVI preoperative, X_5 = SVI preoperative.

11.24 From the regression sums of squares, compute and plot C_p-values for the smallest C_p-value for each p (i.e., for the largest SS_{REG}). Plot these values. Which model appears best?

11.25 From the regression sums of squares, perform a step-up stepwise regression. Use the 0.05 significance level to stop adding variables. Which variables are in the final model?

***11.26** From the regression sums of squares, perform a *stepdown* stepwise regression. Use the 0.10 significance level to stop removing variables. What is your final model?

11.27 Compute the following multiple correlation coefficients:

$$R_{Y(X_4,X_5)}, \qquad R_{Y(X_1,X_2,X_3,X_4,X_5)}, \qquad R_{Y(X_1,X_2,X_3)}$$

Which are statistically significant at the 0.05 significance level?

11.28 Compute the following squared partial correlation coefficients and test their statistical significance at the 1% level.

$$r^2_{Y,X_4 \cdot X_1,X_2,X_3,X_5}, \qquad r^2_{Y,X_5 \cdot X_1,X_2,X_3,X_4}$$

11.29 Compute the following partial multiple correlation coefficients and test their statistical significance at the 5% significance level.

$$R_{Y(X_4,X_5) \cdot X_1,X_2,X_3}, \qquad R_{Y(X_1,X_2,X_3,X_4) \cdot X_5}$$

Data on the 94 sedentary males of Problems 9.9 to 9.12 are used here. The dependent variable was age. The idea is to find an equation that predicted age; this equation might give an approximation to an "exercise age." Subjects might be encouraged, or convinced, to exercise if they heard a statement such as "Mr. Jones, although you are 28, your exercise performance is that of a 43-year-old sedentary man." The potential predictor variables with the regression sum of squares is given below for all combinations.

Y = age in years, X_1 = duration in seconds

$X_2 = \mathrm{VO}_{2\ \mathrm{MAX}}$, X_3 = heart rate in beats/minute

X_4 = height in centimeters, X_5 = weight in kilograms

$\mathrm{SS}_{\mathrm{TOTAL}} = 11,395.74$

Problems 11.30 to 11.35 are based on the data listed in Table 11.36.

11.30 Compute and plot for each p, the smallest C_p-value. Which predictive model would you choose?

11.31 At the 10% significance level, perform stepwise regression (do not compute the regression coefficients) selecting variables. Which variables are in the final model? How does this compare to the answer to Problem 11.30?

***11.32** At the 0.01 significance level, select variables using a *step-down* regression equation (no coefficients computed).

11.33 What are the values of the following correlation and multiple coefficients? Are they significantly nonzero at the 5% significance level?

$$R_{Y(X_1,X_2)}, \qquad R_{Y(X_3,X_4,X_5)},$$

$$R_{YX_1}, \qquad R_{YX_2}, \qquad R_{Y(X_4,X_5)}$$

Table 11.36 Data for Problems 11.30 to 11.35

Indexes of Variables in Multiple Regression Equation	Regression Sum of Squares SS_{REG}	Indexes of Variables in Multiple Regression Equation	Regression Sum of Squares SS_{REG}
1	5382.81	1,2,4	5658.66
2	4900.82	1,2,5	5777.12
3	4527.51	1,3,4	6097.58
4	295.26	1,3,5	6151.91
5	54.80	1,4,5	5723.50
1,2	5454.48	2,3,4	5851.44
1,3	5953.18	2,3,5	5923.41
1,4	5597.08	2,4,5	5243.27
1,5	5685.88	3,4,5	4630.28
2,3	5731.40	1,2,3,4	6128.27
2,4	5089.15	1,2,3,5	6201.39
2,5	5221.73	1,2,4,5	5805.06
3,4	4628.83	1,3,4,5	6179.52
3,5	4568.73	2,3,4,5	5940.03
4,5	299.81	1,2,3,4,5	6223.12
1,2,3	5988.09		

11.34 Compute the following squares of partial correlation coefficients. Are they statistically significant at the 0.10 level?

$$r^2_{Y,X_1\cdot X_2}, \qquad r^2_{Y,X_2\cdot X_1}, \qquad r^2_{Y,X_3X_1\cdot X_2}$$

Describe these quantities in words.

11.35 Compute the following partial multiple correlation coefficients. Are they significant at the 5% level?

$$R_{Y(X_1,X_2,X_3)X_4\cdot X_5}, \qquad R_{Y(X_1,X_3)\cdot X_2},$$
$$R_{Y(X_2,X_3)\cdot X_1}, \qquad R_{Y(X_1,X_2)\cdot X_3}$$

Problems 11.36 and 11.38 are analysis of covariance problems. They use BMDP computer output, which is addressed in more detail in the first problem. This problem should be done before Problem 11.38.

11.36 This problem uses the height and weight data of 25 to 34-year-old men as measured in 1960–1962 and 1971–1974 samples of the U.S. populations. These data are described and presented in Problem 11.23.

(a) The groups are defined by a year variable taking on the value 1 for the 1960 survey and the value 2 for the 1971 survey. Means for the data are:

		Estimates of Means		
		1960	**1971**	**Total**
Height	1	68.5081	68.9353	68.7403
Weight	2	169.3890	171.4030	170.4838

Which survey had the heaviest men? The tallest men? There are at least two possible explanations for weight gain: (1) the weight is increasing due to more overweight and/or building of body muscle; (2) the taller population naturally weighs more.

(b) To distinguish between two hypotheses, an analysis of covariance adjusting for height is performed. The analysis produced the following output, where the dependent variable is weight.

Covariate	Regression Coefficient	Standard Error	*t*-Value
Height	4.22646	0.22742	18.58450

Group	*N*	Group Mean	Adjusted Group Mean	Standard Error
1960	675	169.38904	170.37045	0.89258
1971	804	171.40295	170.57901	0.91761

The ANOVA table is as follows:

Source	d.f.	SS	MS	*F*-Ratio	Tail Area Probability
Equality of adjusted cell means	1	15.7500	15.7500	0.0294	0.8639
Zero slope	1	185,086.0000	185,086.0000	345.3833	0.0000
Error	1475	790,967.3750	535.8857		
Equality of slopes	1	0.1250	0.1250	0.0002	0.9878
Error	1475	790,967.2500	536.2490		

Data for the slope within each group:

		1960	1971
Height	1	4.2223	4.2298

The *t*-test matrix for adjusted group means on 1476 degrees of freedom looks as follows:

		1960	1971
1960	1	0.0000	
1971	2	0.1720	0.0000

The probabilities for the *t*-values above are:

	1960_1	1971_2
1960_1	1.0000	
1971_2	0.8634	1.0000

(i) Note the "equality of slopes" line of output. This gives the *F*-test for the equality of the slopes with the corresponding *p*-value. Is the hypothesis of the equality of the slopes feasible? If estimated separately, what are the two slopes?

(ii) The test for equal (rather than just parallel) regression lines in the groups corresponds to the line labeled "equality of adjusted cell means." Is there a statistically significant difference between the groups? What are the adjusted cell means? By how many pounds do the adjusted cell means differ? Does hypothesis (1) or (2) seem more plausible with these data?

(iii) A t-test for comparing each pair of groups is presented. The p-value 0.8643 is the same (to round off) as the F-statistic. This occurs because only two groups are compared.

11.37 The cases of Bruce et al. [1973] are used. We are interested in comparing $VO_{2,MAX}$, after adjusting for duration and age, in three groups: active males, sedentary males, and active females. The analysis gives the following results:

Number of Cases per Group	
ACTMALE	44
SEDMALE	94
ACTFEM	43
Total	181

The estimates of means is as follows:

		ACTMALE	SEDMALE	ACTFEM	Total
$VO_{2,\ MAX}$	1	40.8046	35.6330	29.0535	35.3271
Duration	2	647.3864	577.1067	514.8837	579.4091
Age	3	47.2046	49.7872	45.1395	48.0553

Data are as follows when the dependent variable is $VO_{2,\ MAX}$:

Covariate	Regression Coefficient	Standard Error	t-Value
Duration	0.05242	0.00292	17.94199
Age	−0.06872	0.03160	−2.17507

Group	N	Group Mean	Adjusted Group Mean	Standard Error
ACTMALE	44	40.80456	37.18298	0.52933
SEDMALE	94	35.63297	35.87268	0.34391
ACTFEM	43	29.05349	32.23531	0.56614

The ANOVA table is:

Source	DF	SS	MS	F-Ratio	Tail Area Probability
Equality of adjusted cell means	2	422.8359	211.4180	19.4336	0.0000
Zero slope	2	7612.9980	3806.4990	349.6947	0.0000
Error	176	1914.7012	10.8790		
Equality of slopes	4	72.7058	18.1765	1.6973	0.1528
Error	172	1841.9954	10.7093		

Values of the slopes within each group are:

		ACTMALE	SEDMALE	ACTFEM
Duration	2	0.0552	0.0522	0.0411
Age	3	−0.1439	−0.0434	−0.1007

The t-test matrix for adjusted group means on 176 degrees of freedom looks as follows:

		ACTMALE	SEDMALE	ACTFEM
ACTMALE	1	0.0000		
SEDMALE	2	−2.1005	0.0000	
ACTFEM	3	−5.9627	−5.3662	0.0000

The probabilities for the t-values above are:

		ACTMALE	SEDMALE	ACTFEM
ACTMALE	1	1.0000		
SEDMALE	2	0.0371	1.0000	
ACTFEM	3	0.0000	0.0000	1.0000

(a) Are the slopes of the adjusting variables (covariates) statistically significant?

(b) Is the hypothesis of parallel regression equations (equal β's in the groups) tenable?

(c) Does the adjustment bring the group means closer together?

(d) After adjustment, is there a statistically significant difference between the groups?

(e) If the answer to part (d) is yes, which groups differ at the 10%, 5%, and 1% significance level?

11.38 This problem deals with the data of Example 10.7 presented in Tables 10.20, 10.21, and 10.22.

(a) Using the quadratic term of Table 10.21 correlate this term with height, weight, and age for the group of females and for the group of males. Are the correlations comparable?

(b) Do part (a) by setting up an appropriate regression analysis with dummy variables.

(c) Test whether gender makes a significant contribution to the regression model of part (b).

(d) Repeat the analyses for the linear and constant terms of Table 10.21.

(e) Do your conclusions differ from those of Example 10.7?

11.39 This problem examines the heart rate response in normal males and females as reported in Hossack et al. [1980, 1981]. As heart rate is related to age and the males were older, this was used as an adjustment covariate. The data are:

Number of Cases per Group	
Male	11
Female	10
Total	21

The estimates of means are:

		Male	Female	Total
Heart rate	1	180.9091	172.2000	176.7619
Age	2	50.4546	45.5000	48.0952

The dependent variable is heart rate:

Covariate	Regression Coefficient	Standard Error	*t*-Value
Age	−0.75515	0.17335	−4.35610

Group	*N*	Group Mean	Adjusted Group Mean	Standard Error
Male	11	180.90909	182.69070	3.12758
Female	10	172.19998	170.24017	3.28303

The ANOVA table:

Source	d.f.	SS	MS	*F*-Ratio	Tail Area Probability
Equality of adjusted cell means	1	783.3650	783.3650	7.4071	0.0140
Zero slope	1	2006.8464	2006.8464	18.9756	0.0004
Error	18	1903.6638	105.7591		
Equality of slopes	1	81.5415	81.5415	0.7608	0.3952
Error	17	1822.1223	107.1837		

The slopes within each group are:

Age	Male	Female
2	−1.0231	−0.6687

(a) Is it reasonable to assume equal age response in the two groups?

(b) Are the adjusted cell means closer or farther apart than the unadjusted cell means? Why?

(c) After adjustment what is the p-value for a difference between the two groups? Do men or women have a higher heart rate on maximal exercise (after age adjustment) in these data?

REFERENCES

Abraham, S., Johnson, C. L., and Najjar, M. F. [1979]. *Weight by Height and Age for Adults 18–74 Years: United States, 1971–1974*. Data from the National Health Survey, Series 11, No. 208. DHEW Publication (PHS) 79-1656. U.S. Government Printing Office, Washington, DC.

Blalock, H. M., Jr. (ed.) [1985]. *Causal Inferences in Nonexperimental Research*. de Gruyter, Aldine, Inc.

Boucher, C. A., Bingham, J. B., Osbakken, M. D., Okada, R. D., Strauss, H. W., Block, P. C., Levine, R. B., Phillips, H. R., and Pohost, G. B. [1981]. Early changes in left ventricular size and function after correction of left ventricular volume overload. *American Journal of Cardiology*, **47**: 991–1004.

Box, G. E. P., Jenkins, G. M., and Reinsel, G. C. [1994]. *Time Series Analysis, Forecasting and Control*. Holden-Day, San Francisco, CA.

Bruce, R. A., Kusumi, F., and Hosmer, D. [1973]. Maximal oxygen intake and nomographic assessment of functional aerobic impairment in cardiovascular disease. *American Heart Journal*, **85**: 546–562.

Cook, T. D., Campbell, D. T., Stanley, J. C., and Shadish, W. [2001]. *Experimental and Quasi-experimental Designs for Generalized Causal Inference*. Houghton Miflin, New York.

Cullen, B. F., and van Belle, G. [1975]. Lymphocyte transformation and changes in leukocyte count: effects of anesthesia and operation. *Anesthesiology*, **43**: 577–583. Used with permission of J. B. Lippincott Company.

Daniel, C., and Wood, F. S. [1999]. *Fitting Equations to Data*, 2nd ed. Wiley, New York.

Dixon, W. J. (chief ed.) [1988]. *BMDP-81 Statistical Software Manual*, BMDP 1988, Vols. 1 and 2. University of California Press, Berkeley, CA.

Draper, N. R., and Smith, H. [1998]. *Applied Regression Analysis*, 3rd ed. Wiley, New York.

Efron, B., and Tibshirani, R. [1986]. The bootstrap (with discussion), *Statistical Science*, **1**: 54–77.

Efron, B., and Tibshirani, R. [1994]. An Introduction to the Bootstrap. CRC Press, Boca Raton, FL.

Florey, C. du V., and Acheson, R. M. [1969]. Blood pressure as it relates to physique, blood glucose and cholesterol. Vital and Health Statistics. Data from the National Health Survey. Public Health Service Publication 1000, Ser. 11, No. 34. Washington, DC.

Gardner, M. J. [1973]. Using the environment to explain and predict mortality. *Journal of the Royal Statistical Society, Series A*, **136**: 421–440.

Goldberger, A. S., and Duncan, O. D. [1973]. *Structural Equation Models in the Social Sciences*. Elsevier, New York.

Graybill, F. A. [2000]. *Theory and Application of the Linear Model*. Brooks/Cole, Pacific Grove, CA.

Haynes, S. G., Levine, S., Scotch, N., Feinleib, M., and Kannel, W. B. [1978]. The relationship of psychosocial factors to coronary heart disease in the Framingham study. *American Journal of Epidemiology*, **107**: 362–283.

Hocking, R. R. [1976]. The analysis and selection of variables in linear regression. *Biometrics*, **32**: 1–50.

Hossack, K. F., Bruce, R. A., Green, B., Kusumi, F., DeRouen, T. A., and Trimble, S. [1980]. Maximal cardiac output during upright exercise: approximate normal standards and variations with coronary heart disease. *American Journal of Cardiology*, **46**: 204–212.

Hossack, K. F., Kusumi, F., and Bruce, R. A. [1981]. Approximate normal standards of maximal cardiac output during upright exercise in women. *American Journal of Cardiology*, **47**: 1080–1086.

Hurvich, C. M., and Tsai, C.-L. [1990]. The impact of model selection on inference in linear regression. *American Statistician*, **44**: 214–217.

Jensen, D., Atwood, J. E., Frolicher, V., McKirnan, M. D., Battler, A., Ashburn, W., and Ross, J., Jr. [1980]. Improvement in ventricular function during exercise studied with radionuclide ventriculography after cardiac rehabilitation. *American Journal of Cardiology*, **46**: 770–777.

Kaplan, D. [2000]. *Structural Equations Modeling*. Sage Publications.

Keller, R. B., Atlas, S. J., Singer, D. E., Chapin, A. M., Mooney, N. A., Patrick, D. L., and Deyo, R. A. [1996]. The Maine lumbar spine study: I. Background and concepts. *Spine*, **21**: 1769–1776.

Kleinbaum, D. G. [1994]. *Logistic Regression: A Self-Learning Text*. Springer-Verlag, New York.

Kleinbaum, D. G., Kupper, L. L., Muller, K. E., and Nizam A. [1998]. *Applied Regression Analysis and Other Multivariate Methods*, 3rd ed. Duxbury Press, North Scituate, MA.

Li, C. C. [1975]. *Path Analysis: A Primer*. Boxwood Press, Pacific Grove, CA.

Little, R. J., and Rubin, D. B. [2000]. Causal effects in clinical and epidemiologic studies via potential outcomes: concepts and analytical approaches. *Annual Review of Public Health*, **21**: 121–145.

Maldonado, G., and Greenland, S. [1993]. Simulation study of confounder-selection strategies. *American Journal of Epidemiology*, **138**: 923–936.

Mason, R. L. [1975]. Regression analysis and problems of multicollinearity. *Communications in Statistics*, **4**: 277–292.

Mehta, J., Mehta, P., Pepine, C. J., and Conti, C. R. [1981]. Platelet function studies in coronary artery disease: X. Effects of dipyridamole. *American Journal of Cardiology*, **47**: 1111–1114.

Mickey, R. M., and Greenland, S. [1989]. The impact of confounder selection criteria on effect estimation. *American Journal of Epidemiology*, **129**: 125–137.

Morrison, D. F. [1990]. *Multivariate Statistical Methods*, 3rd ed. McGraw-Hill, New York.

Neyman, J. [1923]. On the application of probability theory to agricultural experiments: essay on principles, section 9. Translated in *Statistical Science*, 1990, **5**: 65–80.

Pearl, J. [2000]. *Causality: Models, Reasoning, and Inference*. Cambridge University Press, Cambridge.

Pocock, S. J., Assmann, S. E., Enos, L. E., and Kasten, L. E. [2002]. Subgroup analysis, covariate adjustment and baseline comparisons in clinical trial reporting: current practice and problems. *Statistics in Medicine*, **21**: 2917–2930.

Raab, G. M., Day, S., and Sales, J. [2000]. How to select covariates to include in the analysis of a clinical trial. *Controlled Clinical Trials*, **21**: 330–342.

Roberts, J. [1966]. *Weight by Height and Age of Adults: United States, 1960–1962*. Vital and Health Statistics. Data from the National Health Survey. Public Health Service Publication 1000, Series 11, No. 14. U.S. Government Printing Office, Washington, DC.

Robins, J. M. [1986]. A new approach to causal inference in mortality studies with sustained exposure periods: application to the control of the healthy worker survivor effect. *Mathematical Modelling*, **7**: 1393–1512.

Rosenbaum, P. R., and Rubin, D. R. [1983]. The central role of the propensity score in observational studies for causal effects. *Biometrika*, **70**: 41–55.

Rothman, K. J., and Greenland, S. [1998]. *Modern Epidemiology*. Lippincott-Raven, Philadelphia.

Rubin, D. B. [1974]. Estimating causal effects of treatments in randomized and non-randomized studies. *Journal of Education Psychology*, **66**: 688–701.

Stoudt, H. W., Damon, A., and McFarland, R. A. [1970]. *Skinfolds, Body Girths, Biacromial Diameter, and Selected Anthropometric Indices of Adults: United States, 1960–62*. Vital and Health Statistics. Data from the National Health Survey. Public Health Service Publication 1000, Series 11, No. 35. U.S. Government Printing Office, Washington, DC.

Sun, G.-W., Shook, T. L., and Kay, G. L. [1996]. Inappropriate use of bivariable analysis to screen risk factors for use in multivariable analysis. *Journal of Clinical Epidemiology*, **8**: 907–916.

Timm, N. H. [2001]. *Applied Multivariate Analysis*. Springer-Verlag, New York.

van Belle, G., Leurgans, S., Friel, P., Guo, S., and Yerby, M. [1989]. Determination of enzyme binding constants using generalized linear models, with particular reference to Michaelis–Menten models. *Journal of Pharmaceutical Science*, **78**: 413–416.

CHAPTER 12

Multiple Comparisons

12.1 INTRODUCTION

Most of us are aware of the large number of coincidences that appear in our lives. "Imagine meeting you here!" "The ticket number is the same as our street address." One explanation of such phenomena is statistical. There are so many different things going on in our lives that a few events of small probability (the coincidences) are likely to happen at the same time. See Diaconis and Mosteller [1989] for methods for studying coincidences.

In a more formal setting, the same phenomenon can occur. If many tests or comparisons are carried out at the 0.05 significance level (with the null hypothesis holding in all cases), the probability of deciding that the null hypothesis may be rejected in one or more of the tests is considerably larger. If *many* 95% confidence intervals are set up, there is not 95% confidence that *all* parameters are "in" their confidence intervals. If many treatments are compared, each comparison at a given significance level, the overall probability of a mistake is much larger. If significance tests are done continually while data accumulate, stopping when statistical significance is reached, the significance level is much larger than the nominal "fixed sample size" significance level. The category of problems being discussed is called the *multiple comparison* problem: Many (or multiple) statistical procedures are being applied to the same data. We note that one of the most important practical cases of multiple comparisons, the interim monitoring of randomized trials, is discussed in Chapter 19.

This chapter provides a quantitative feeling for the problem. Statistical methods to handle the situation are also described. We first describe the multiple testing or multiple comparison problem in Section 12.2. In Section 12.3 we present three very common methods for obtaining simultaneous confidence intervals for the regression coefficients of a linear model. In Section 12.4 we discuss how to choose between them. The chapter concludes with notes and problems.

12.2 MULTIPLE COMPARISON PROBLEM

Suppose that n statistically independent tests are being considered in an experiment. Each test is evaluated at significance level α. Suppose that the null hypothesis holds in each case. What is the probability, α^*, of incorrectly rejecting the null hypothesis in one or more of the tests? For $n = 1$, the probability is α, by definition. Table 12.1 gives the probabilities for several values of α and n. Note that if each test is carried out at a 0.05 level, then for 20 tests, the probability is 0.64 of incorrectly rejecting at least one of the null hypotheses.

Biostatistics: A Methodology for the Health Sciences, Second Edition, by Gerald van Belle, Lloyd D. Fisher, Patrick J. Heagerty, and Thomas S. Lumley
ISBN 0-471-03185-2

Table 12.1 Probability, α^*, of Rejecting One or More Null Hypotheses When n independent Tests Are Carried Out at Significance Level α and Each Null Hypothesis Is True

Number of Tests, n	α		
	0.01	0.05	0.10
1	0.01	0.05	0.10
2	0.02	0.10	0.19
3	0.03	0.14	0.27
4	0.04	0.19	0.34
5	0.05	0.23	0.41
6	0.06	0.26	0.47
7	0.07	0.30	0.52
8	0.08	0.34	0.57
9	0.09	0.37	0.61
10	0.10	0.40	0.65
20	0.18	0.64	0.88
50	0.39	0.92	0.99
100	0.63	0.99	1.00
1000	1.00	1.00	1.00

The table may also be related to confidence intervals. Suppose that each of $n100(1-\alpha)\%$ confidence intervals comes from an independent data set. The table gives the probability that one or more of the estimated parameters is not straddled by its confidence interval. For example, among five 90% confidence intervals, the probability is 0.41 that at least one of the confidence intervals does not straddle the parameter being estimated.

Now that we see the magnitude of the problem, what shall we do about it? One solution is to use a smaller α level for each test or confidence interval so that the probability of one or more mistakes over all n tests is the desired (nominal) significance level. Table 12.2 shows the α level needed for each test in order that the combined significance level, α^*, be as given at the column heading.

The values of α and α^* are related to each other by the equation

$$\alpha^* = 1 - (1-\alpha)^n \quad \text{or} \quad \alpha = 1 - (1-\alpha^*)^{1/n} \tag{1}$$

where $(1-\alpha)^{1/n}$ is the nth root of $1-\alpha$.

If p-values are being used without a formal significance level, the p-value from an individual test is adjusted by the opposite of equation (1). That is, p^*, the overall p-value, taking into account the fact that there are n tests, is given by

$$p^* = 1 - (1-p)^n \tag{2}$$

For example, if there are two tests and the p-value of each test is 0.05, the overall p-value is $p^* = 1 - (1-0.05)^2 = 0.0975$. For small values of α (or p) and n by the binominal expansion $\alpha^* = 1/n\alpha$ (and $p^* = np$), a relationship that will also be derived in the context of the Bonferroni inequality.

Before giving an example, we introduce some terminology and make a few comments. We consider an "experiment" in which n tests or comparisons are made.

Definition 12.1. The significance level at which each test or comparison is carried out in an experiment is called the *per comparison* error rate.

Table 12.2 Significance Level, α, Needed for Each Test or Confidence Interval So That the Overall Significance Level (Probability of One or More Mistakes) Is α^* When Each Null Hypothesis Is True

Number of Tests, n	α^*		
	0.01	0.05	0.10
1	0.010	0.05	0.10
2	0.005	0.0253	0.0513
3	0.00334	0.0170	0.0345
4	0.00251	0.0127	0.0260
5	0.00201	0.0102	0.0209
6	0.00167	0.00851	0.0174
7	0.00143	0.00730	0.0150
8	0.00126	0.00639	0.0131
9	0.00112	0.00568	0.0116
10	0.00100	0.00512	0.0105
20	0.00050	0.00256	0.00525
50	0.00020	0.00103	0.00210
100	0.00010	0.00051	0.00105
1000	0.00001	0.00005	0.00011

Definition 12.2. The probability of incorrectly rejecting at least one of the true null hypotheses in an experiment involving one or more tests or comparisons is called the *per experiment error rate*.

The terminology is less transparent than it seems. In particular, what defines an "experiment"? You could think of your life as an experiment involving many comparisons. If you wanted to restrict your "per experiment" error level to, say, $\alpha^* = 0.05$, you would need to carry out each of the comparisons at ridiculously low values of α. This has led some to question the entire idea of multiple comparison adjustment [Rothman, 1990; O'Brien, 1983; Proschan and Follman, 1995]. Frequently, groups of tests or comparisons form a natural unit and a suitable adjustment can be made. In some cases it is reasonable to control the total error rate only over tests that in some sense ask the same question.

Example 12.1. The liver carries out many complex biochemical tasks in the body. In particular, it modifies substances in the blood to make them easier to excrete. Because of this, it is very susceptible to damage by foreign substances that become more toxic as they are metabolized. As liver damage often causes no noticeable symptoms until far too late, biochemical tests for liver damage are very important in investigating new drugs or monitoring patients with liver disease. These include measuring substances produced by the healthy liver (e.g., albumin), substances removed by the healthy liver (e.g., bilirubin), and substances that are confined inside liver cells and so not found in the blood when the liver is healthy (e.g., transaminases).

It is easy to end up with half a dozen or more indicators of liver function, creating a multiple comparison problem if they are to be tested. Appropriate solutions to the problem vary with the intentions of the analyst. They might include:

1. *Controlling the Type I error rate*. If a deterioration in any of the indicators leads to the same qualitative conclusion — liver damage — they form a single hypothesis that deserves a single α.

2. *Controlling the Type II error rate*. When a new drug is first being tested, it is important not to miss even fairly rare liver damage. The safety monitoring program must have a low Type II error rate.
3. *Controlling Type I error over smaller groups*. Different indicators are sensitive to various types of liver damage. For a researcher interested in the mechanism of the toxicity, separating the indicators into these groups would be more appropriate.
4. *Combining the indicators*. In some cases the multiple comparison problem can be avoided by creating a composite outcome such as some sort of weighted sum of the indicators. This will typically increase power for alternatives where more than one indicator is expected to be affected.

The fact that different strategies are appropriate for different people suggests that it is useful to report p-values and confidence intervals without adjustment, perhaps in addition to adjusted versions.

Two of the key assumptions in the derivation of equations (1) and (2) are (1) statistical independence and (2) the null hypothesis being true for each comparison. In the next two sections we discuss their relevance and ways of dealing with these assumptions when controlling Type I error rates.

Example 12.2. To illustrate the methods, consider responses to maximal exercise testing within eight groups by Bruce et al. [1974]. The subjects were all males. An indication of exercise performance is functional aerobic impairment (FAI). This index is age- and gender-adjusted to compare the duration of the maximal treadmill test to that expected for a healthy person of the subject's age and gender. A larger score indicates more exercise impairment. Working at a 5% significance level, it is desired to compare the average levels in the eight groups. The data are shown in Table 12.3.

Because it was expected that the healthy group would have a smaller variance, a one-way ANOVA was not performed (in the next section you will see how to handle such problems). Instead, we construct eight *simultaneous* 95% confidence intervals. Hence, $\alpha = 1 - (1 - 0.05)^{1/8} \doteq 0.0064$ is to be the α-level for each interval. The intervals are given by

$$\overline{Y} \pm \frac{\text{SD}}{\sqrt{n}} t_{n-1,1-(0.0064/2)}$$

The t-values are estimated by interpolation from the table of t-critical values and the normal table ($n > 120$). The eight confidence intervals work out to be as shown in Table 12.4. Displaying these intervals graphically and indicating which group each interval belongs to gives Figure 12.1.

Table 12.3 Functional Aerobic Impairment Data for Example 12.2

	Group	N	Mean	Standard Deviation
1	Healthy individuals	1275	0.6	11
2	Hypertensive subjects (HT)	193	8.5	19
3	Postmyocardial infarction (PMI)	97	24.5	21
4	Angina pectoris, chest pain (AP)	306	30.3	24
5	PMI + AP	228	36.9	26
6	HT + AP	138	36.6	23
7	HT + PMI	20	27.6	18
8	PMI + AP + HT	75	44.9	22

Table 12.4 FAI Confidence Intervals by Group for Example 12.2

		Limits	
Group	Critical t-Value	Lower	Upper
1	2.73	−0.2	1.4
2	2.73	4.8	12.2
3	2.79	18.5	30.5
4	2.73	26.6	34.0
5	2.73	32.2	41.6
6	2.77	31.2	42.0
7	3.06	15.3	39.9
8	2.81	37.7	52.1

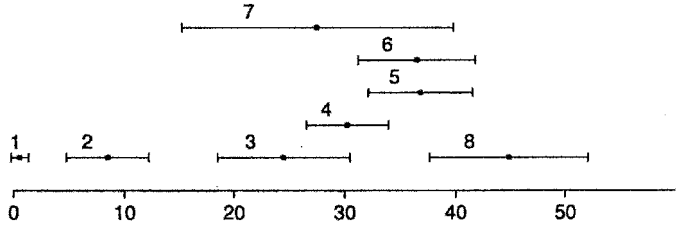


Figure 12.1 Functional aerobic impairment level.

Since all eight groups have a simultaneous 95% confidence interval, it is sufficient (but not necessary) to decide that any two means whose confidence intervals do not overlap are significantly different. Let $\mu_1, \mu_2, \ldots, \mu_8$, be the population means associated with groups $1, 2, \ldots, 8$, respectively. The following conclusions are in order:

1. μ_1 has the smallest mean ($\mu_1 < \mu_i, i = 2, \ldots, 8$).
2. μ_2 is the second smallest mean ($\mu_1 < \mu_2 < \mu_i, i = 3, \ldots, 8$).
3. $\mu_3 < \mu_5$, $\mu_3 < \mu_6$, $\mu_3 < \mu_8$.
4. $\mu_4 < \mu_8$.

There are seeming paradoxes. We know that $\mu_3 < \mu_5$, but we cannot decide whether μ_7 is larger or smaller than those two means.

Restating the conclusions in words: The healthy group had the best exercise performance, followed by the hypertensive subjects, who were better than the rest. The postmyocardial infarction group performed better than the PMI + AP, PMI + AP + HT, and HT + AR groups. The angina pectoris group had better performance than angina pectoris plus an MI and hypertension. The other orderings were not clear from this data set.

12.3 SIMULTANEOUS CONFIDENCE INTERVALS AND TESTS FOR LINEAR MODELS

12.3.1 Linear Combinations and Contrasts

In the linear models, the estimates of the parameters are usually not independent. Even when the estimates of the parameters are independent, the same error mean square, MS_e, is used for each

test or confidence interval. Thus, the method of Section 12.2 does not apply. In this section, several techniques dealing with the linear model are considered.

Before introducing the Scheffé method, we need additional concepts of linear combinations and contrasts.

Definition 12.3. A *linear combination of the parameters* $\beta_1, \beta_2, \ldots, \beta_p$ is a sum $\theta = c_1\beta_1 + c_2\beta_2 + \cdots + c_p\beta_p$, where $c_1, c_2, \ldots, c_p$ are known constants.

Associated with any parameter set $\beta_1, \beta_2, \ldots, \beta_p$ is a number that is equal to the number of linearly estimated independent parameters. In ANOVA tables, this is the number of degrees of freedom associated with a particular sum of squares.

A linear combination is a parameter. An estimate of such a parameter is a statistic, a random variable. Let $b_1, b_2, \ldots, b_p$ be unbiased estimates of $\beta_1, \beta_2, \ldots, \beta_p$; then $\widehat{\theta} = c_1b_1 + c_2b_2 + \cdots + c_pb_p$ is an unbiased estimate of θ. If $b_1, b_2, \ldots, b_p$ are jointly normally distributed, $\widehat{\theta}$ will be normally distributed with mean θ and variance $\sigma_{\widehat{\theta}^2}$. The standard error of $\widehat{\theta}$ is usually quite complex and depends on possible relationships among the β's as well as correlations among the estimates of the β's. It will be of the form

$$\text{constant}\sqrt{\text{MS}_e}$$

where MS_e is the residual mean square from either the regression analysis or the analysis of variance. A simple set of linear combinations can be obtained by having only one of the c_i take on the value 1 and all others the value 0.

A particular class of linear combinations that will be very useful is given by:

Definition 12.4. A linear combination $\theta = c_1\beta_1 + c_2\beta_2 + \cdots + c_p\beta_p$ is a *contrast* if $c_1 + c_2 + \cdots + c_p = 0$. The contrast is *simple* if exactly two constants are nonzero and equal to 1 and -1.

The following are examples of linear combinations that are contrasts: $\beta_1 - \beta_2$ (a simple contrast); $\beta_1 - \frac{1}{2}(\beta_2 + \beta_3) = \beta_1 - \frac{1}{2}\beta_2 - \frac{1}{2}\beta_3$, and $(\beta_1 + \beta_8) - (\beta_2 + \beta_4) = \beta_1 + \beta_8 - \beta_2 - \beta_4$. The following are linear combinations that are not contrasts: β_1, $\beta_1 + \beta_6$, and $\beta_1 + \frac{1}{2}\beta_2 + \frac{1}{2}\beta_3$. The linear combinations and contrasts have been defined and illustrated using regression notation. They are also applicable to analysis of variance models (which are special regression models), so that the examples can be rewritten as $\mu_1 - \mu_2$, $\mu_1 - \frac{1}{2}(\mu_2 + \mu_3)$, and so on. The interpretation is now a bit more transparent: $\mu_1 - \mu_2$ is a comparison of treatment 1 and treatment 2; $\mu_1 - \frac{1}{2}(\mu_2 + \mu_3)$ is a comparison of treatment 1 with the average of treatment 2 and treatment 3.

Since hypothesis testing and estimation are equivalent, we state most results in terms of simultaneous confidence intervals.

12.3.2 Scheffé Method (S-Method)

A very general method for protecting against a large per experiment error rate is provided by the Scheffé method. It allows unlimited "fishing," at a price.

Result 12.1. Given a set of parameters $\beta_1, \beta_2, \ldots, \beta_p$, the probability is $1 - \alpha$ that simultaneously *all* linear combinations of $\beta_1, \beta_2, \ldots, \beta_p$, say, $\theta = c_1\beta_1 + c_2\beta_2 + \cdots + c_p\beta_p$, are in the confidence intervals

$$\widehat{\theta} \pm \sqrt{d\,F_{d,m,1-\alpha}}\,\widehat{\sigma}_{\widehat{\theta}}$$

where the estimate of θ is $\widehat{\theta} = c_1 b_1 + c_2 b_2 + \cdots + c_p b_p$ with estimated standard error $\widehat{\sigma}_{\widehat{\theta}}$, F is the usual F-statistic with (d, m) degrees of freedom, d is the number of linearly independent parameters, and m is the number of degrees of freedom associated with MS_e.

Note that these confidence intervals are of the usual form, "statistic $\pm$ constant $\times$ standard error of statistic," the only difference being the constant, which now depends on the number of parameters involved as well as the degrees of freedom for the error sum of squares. When $d = 1$, for any α,

$$\sqrt{dF_{d,m,1-\alpha}} = \sqrt{F_{1,m,1-\alpha}} = t_{m,1-\alpha}$$

That is, the constant reduces to the usual t-statistic with m degrees of freedom. After discussing some examples, we assess the price paid for the unlimited number of comparisons that can be made.

The easiest way to understand the S-method is to work through some examples.

Example 12.3. In Table 12.5 we present part of the computer output from Cullen and van Belle [1975] discussed in Chapters 9 and 11. We construct simultaneous 95% confidence intervals for the slopes β_i. In this case, the first linear combination is

$$\theta_1 = 1 \times \beta_1 + 0 \times \beta_2 + 0 \times \beta_3 + 0 \times \beta_4 + 0 \times \beta_5$$

the second linear combination is

$$\theta_2 = 0 \times \beta_1 + 1 \times \beta_2 + 0 \times \beta_3 + 0 \times \beta_4 + 0 \times \beta_5$$

and so on.

The standard errors of these linear combinations are simply the standard errors of the slopes. There are five slopes $\beta_1, \beta_2, \ldots, \beta_5$, which are linearly independent, but their estimates $b_1, b_2, \ldots, b_5$ are correlated. The MS_e upon which the standard errors of the slopes are based has 29 degrees of freedom. The F-statistic has value $F_{5,29,0.95} = 2.55$.

The 95% *simultaneous* confidence intervals will be of the form

$$b_i \pm \sqrt{(5)(2.55)} s_{b_i}$$

Table 12.5 Analysis of Variance, Regression Coefficients, and Confidence Intervals

	Analysis of Variance				
Source	d.f.	SS	MS	F-Ratio	Significance
Regression	5.0	95,827	18,965	12.9	0.000
Residual	29.0	42,772	1,474		
				95% Limits	
Variable	b	Standard-Error b	t	Lower	Upper
DPMB	0.575	0.0834	6.89	0.404	0.746
Trauma	−9.21	11.6	−0.792	−33.0	14.6
Lymph B	−8.56	10.2	−0.843	−29.3	12.2
Time	−4.66	5.68	−0.821	−16.3	6.96
Lymph A	−4.55	6.72	−0.677	−18.3	9.19
Constant	−96.3	36.4	2.65	22.0	171

or

$$b_i \pm 3.57 s_{b_i}, \qquad i = 1, 2, \ldots, 5$$

For the regression coefficient of DPMB the interval is

$$0.575 \pm (3.57)(0.0834)$$

resulting in 95% confidence limits of (0.277, 0.873).

Computing these values, the confidence intervals are as follows:

	Limits			Limits	
Variable	**Lower**	**Upper**	**Variable**	**Lower**	**Upper**
DPMB	0.277	0.873	Time	−24.9	15.6
Trauma	−50.8	32.3	Lymph A	−28.5	19.4
Lymph B	−44.8	27.7			

These limits are much wider than those based on a per comparison t-statistic. This is due solely to the replacement of $t_{29,0.975} = 2.05$ by $\sqrt{5F_{5,29,0.95}} = 3.57$. Hence, the confidence interval width is increased by a factor of $3.57/2.05 = 1.74$ or 74%.

Example 12.4. In a one-way ANOVA situation, using the notation of Section 10.2.2, if we wish simultaneous confidence intervals for all I means, then $d = I$, $m = n_\cdot - I$, and the standard error of the estimate of μ_i is

$$\sqrt{\frac{\text{MS}_e}{n_i}}, \qquad i = 1, \ldots, I$$

Thus, the confidence intervals are of the form

$$\overline{Y}_{i\cdot} \pm \sqrt{I F_{I,n_\cdot - I,1-\alpha}} \sqrt{\frac{\text{MS}_e}{n_i}}, \qquad i = 1, \ldots, I$$

Suppose that we want simultaneous 99% confidence intervals for the morphine binding data of Problem 10.1. The confidence interval for the chronic group is

$$31.9 \pm \sqrt{(4)\underbrace{(4.22)}_{F_{4,24,0.99}}} \sqrt{\frac{9.825}{18}} = 31.9 \pm 3.0$$

or

$$31.9 \pm 3.0$$

The four simultaneous 99% confidence intervals are:

	Limits			Limits	
Group	**Lower**	**Upper**	**Group**	**Lower**	**Upper**
μ_1 = Chronic	28.9	34.9	μ_3 = Dialysis	22.0	36.8
μ_2 = Acute	21.0	39.2	μ_4 = Anephric	19.2	30.8

As all four intervals overlap, we cannot conclude immediately from this approach that the means differ (at the 0.01 level). To compare two means we can also consider confidence intervals for $\mu_i - \mu_i'$. As the Scheffé method allows us to look at all linear combinations, we may also consider the confidence interval for $\mu_i - \mu_i'$.

The formula for the simultaneous confidence intervals is

$$\overline{Y}_{i\cdot} - \overline{Y}_{i'\cdot} \pm \sqrt{I F_{I,n.-I,1-\alpha}} \sqrt{\text{MS}_e \left(\frac{1}{n_i} + \frac{1}{n_{i'}} \right)}, \qquad i, i' = 1, \ldots, I, i \neq i'$$

In this case, the confidence intervals are:

	Limits			Limits	
Contrast	**Lower**	**Upper**	**Contrast**	**Lower**	**Upper**
$\mu_1 - \mu_2$	−7.8	11.4	$\mu_2 - \mu_3$	−11.1	12.5
$\mu_1 - \mu_3$	−5.5	10.5	$\mu_2 - \mu_4$	−5.7	15.9
$\mu_1 - \mu_4$	0.4	13.4	$\mu_3 - \mu_4$	−5.0	13.8

As the interval for $\mu_1 - \mu_4$ does not contain zero, we conclude that $\mu_1 - \mu_4 > 0$ or $\mu_1 > \mu_4$. This example is typical in that comparison of the linear combination of interest is best done through a confidence interval for that combination.

The comparisons are in the form of contrasts but were not considered so explicitly. Suppose that we restrict ourselves to contrasts. This is equivalent to deciding which mean values differ, so that we are no longer considering confidence intervals for a particular mean. This approach gives smaller confidence intervals.

Contrast comparisons among the means μ_i, $i = 1, \ldots, I$ are equivalent to comparisons of α_i, $i = 1, \ldots, I$ in the one-way ANOVA model $Y_{ij} = \mu + \alpha_i + \epsilon_{ij}$, $i = 1, \ldots, I$, $j = 1, \ldots, n_i$; for example, $\mu_1 - \mu_2 = \alpha_1 - \alpha_2$. There are only $(I - 1)$ linearly independent values of α_i since we have the constraint $\sum_i \alpha_i = 0$. This is, therefore, the first example in which the parameters are not linearly independent. (In fact, the main effects are contrasts.) Here, we set up confidence intervals for the simple contrasts $\mu_i - \mu_i'$. Here $d = 3$ and the simultaneous confidence intervals are given by

$$\overline{Y}_{i\cdot} - \overline{Y}_{i'\cdot} \pm \sqrt{(I-1) F_{I-1,n.-I,1-\alpha}} \sqrt{\text{MS}_e \left(\frac{1}{n_i} + \frac{1}{n_{i'}} \right)}, \qquad i, i' = 1, \ldots, I, i \neq i'$$

In the case at hand, the intervals are:

	Limits			Limits	
Contrast	**Lower**	**Upper**	**Contrast**	**Lower**	**Upper**
$\mu_1 - \mu_2$	−7.0	10.6	$\mu_2 - \mu_3$	−10.1	11.5
$\mu_1 - \mu_3$	−4.9	9.9	$\mu_2 - \mu_4$	−4.8	15.0
$\mu_1 - \mu_4$	0.9	12.9	$\mu_3 - \mu_4$	−1.9	10.7

As the $\mu_1 - \mu_4$ interval does not contain zero, we conclude that $\mu_1 > \mu_4$. Note that these intervals are shorter then in the first illustration. If you are interested in comparing each pair of means, this method will occasionally detect differences not found if we require confidence intervals for the mean as well.

Example 12.5.

1. *Main effects*. In two-way ANOVA situations there are many possible sets or linear combinations that may be studied; here we consider a few. To study all cell means, consider the IJ cells to be part of a one-way ANOVA and use the approach of Example 12.2 or 12.4.

Now consider Example 10.5 in Section 10.3.1. Suppose that we want to compare the differences between the means for the different days at a 10% significance level. In this case we are working with the β_j main effects. The intervals for $\overline{\mu}_{\cdot j} - \overline{\mu}_{\cdot j'} = \beta_j - \beta_{j'}$ are given by

$$\overline{Y}_{\cdot j\cdot} - \overline{Y}_{\cdot j'\cdot} \pm \sqrt{(J-1)F_{J-1,n_{\cdot\cdot}-IJ,1-\alpha}}\sqrt{\mathrm{MS}_e\left(\frac{1}{n_{\cdot j}} + \frac{1}{n_{\cdot j'}}\right)}$$

The means are 120.4, 158.1, and 118.4, respectively. The following contrasts are of interest:

		90% Limits	
Contrast	**Estimate**	**Lower**	**Upper**
$\beta_1 - \beta_2$	−37.7	−70.7	−4.7
$\beta_2 - \beta_3$	39.7	5.5	73.9
$\beta_1 - \beta_3$	2.0	−31.0	35.0

At the 10% significance level, we conclude that $\mu_{\cdot 1} - \mu_{\cdot 2} < 0$ or $\mu_{\cdot 1} < \mu_{\cdot 2}$, and that $\mu_{\cdot 3} < \mu_{\cdot 2}$. Thus, the means (combining cases and controls) of days 10 and 14 are less than the means of day 12.

2. *Main effects assuming no interaction*. We illustrate the procedure using Problem 10.12 as an example. This example discussed the effect of histamine shock on the medullary blood vessel surface of the guinea pig thymus.

The sex of the animal was used as a covariate. The ANOVA table is shown in Table 12.6. There is little evidence of interaction. Suppose that we want to fit the model

$$Y_{ijk} = \mu + \alpha_i + \beta_j + \epsilon_{ijk}, \qquad \begin{array}{l} i = 1, \ldots, I \\ j = 1, \ldots, J \\ k = 1, \ldots, n_{ij} \end{array}$$

That is, we ignore the interaction term. It can be shown that the appropriate estimates in the balanced model for the cell means $\mu + \alpha_i + \beta_j$ are

$$\overline{Y}_{\cdots} + a_i + b_j, \qquad \begin{array}{l} i = 1, \ldots, I \\ j = 1, \ldots, J \end{array}$$

Table 12.6 ANOVA Table for Control vs. Histamine Shock

Source	d.f.	Mean Square	F-Ratio	p-Value
Treatment	1	11.56	5.20	<0.05
Sex	1	1.26	0.57	>0.05
Treatment by sex	1	5.40	2.43	>0.05
Error	36	2.225		
Total	39			

or

$$\overline{Y}... + (\overline{Y}_{i\cdot\cdot} - \overline{Y}...) + (\overline{Y}_{\cdot j\cdot} - \overline{Y}...) = \overline{Y}_{i\cdot\cdot} + \overline{Y}_{\cdot j\cdot} - \overline{Y}...$$

The estimates are $\overline{Y}... = 6.53$, $\overline{Y}_{1\cdot\cdot} = 6.71$, $\overline{Y}_{2\cdot\cdot} = 6.35$, $\overline{Y}_{\cdot 1\cdot} = 5.99$, $\overline{Y}_{\cdot 2\cdot} = 7.07$. The estimated cell means fitted to the model $E(Y_{ijk}) = \mu + \alpha_i + \beta_j$ by $\overline{Y}... + a_i + b_j$ are:

	Treatment	
Sex	**Control**	**Shock**
Male	6.17	7.25
Female	5.81	6.89

For multiple comparisons the appropriate formula for simultaneous confidence intervals for each cell mean assuming that the interaction term is zero is given by the formula

$$\overline{Y}_{i\cdot\cdot} + \overline{Y}_{\cdot j\cdot} - \overline{Y}... \pm \sqrt{(I+J-1)F_{I+J-1,n..-IJ+1,1-\alpha}}\sqrt{\text{MS}_e\left(\frac{1}{n_{i\cdot}} + \frac{1}{n_{\cdot j}} - \frac{1}{n_{\cdot\cdot}}\right)}$$

The degrees of freedom for the F-statistic are $(I+J-1)$ and $(n..-IJ+1)$ because there are $I+J-1$ linearly independent cell means and the residual MS_e has $(n..-IJ+1)$ degrees of freedom. This MS_e can be obtained by pooling the $\text{SS}_{\text{INTERACTION}}$ and $\text{SS}_{\text{RESIDUAL}}$ in the ANOVA table. For our example,

$$\text{MS}_e = \frac{1 \times 5.40 + 36 \times 2.225}{37} = 2.311$$

We will construct the 95% confidence intervals for the four cell means. The confidence interval for the first cell is given by

$$6.17 \pm \sqrt{(2+2-1)\underbrace{F_{3,37,0.95}}_{2.86}}\sqrt{2.311\left(\frac{1}{20} + \frac{1}{20} - \frac{1}{40}\right)}$$

yielding 6.17 ± 1.22 for limits (4.95, 7.39). The four simultaneous 95% confidence limits are:

	Treatment	
Sex	**Control**	**Shock**
Male	(4.95, 7.39)	(6.03, 8.47)
Female	(4.59, 7.03)	(5.67, 8.11)

Requiring this degree of confidence gives intervals that overlap. However, using the Scheffé method, all linear combinations can be examined. With the same 95% confidence, let us examine the sex and treatment differences. The intervals for sex are defined by

$$\overline{Y}_{1\cdot\cdot} - \overline{Y}_{2\cdot\cdot} \pm \sqrt{3F_{3,37,0.95}}\sqrt{\text{MS}_e\left(\frac{1}{n_{1\cdot}} + \frac{1}{n_{2\cdot}}\right)}$$

or 0.36 ± 1.41 for limits $(-1.05, 1.77)$. Thus, in these data there is no reason to reject the null hypothesis of no difference in sex. The simultaneous 95% confidence interval for treatment is -1.08 ± 1.41 or $(-2.49, 0.33)$. This confidence interval also straddles zero, and at the 95% simultaneous confidence level we conclude that there is no difference in the treatment. This result nicely illustrates a dilemma. The two-way analysis of variance did indicate a significant treatment effect. Is this a contradiction? Not really, we are "protecting" ourselves against an increased Type I error. Since the results are "borderline" even with the analysis of variance, it may be best to conclude that the results are suggestive but not clearly significant. A more substantial point may be made by asking why we should test the effect of sex anyway? It is merely a covariate or blocking factor. This argument raises the question of the appropriate set of comparisons. What do you think?

3. *Randomized block designs*. Usually, we are interested in the treatment means only and not the block means. The confidence interval for the contrast $\tau_j - \tau_j'$ has the form

$$\overline{Y}_{\cdot j} - \overline{Y}_{\cdot j'} \pm \sqrt{(J-1)F_{J-1,IJ-I-J+1,1-\alpha}}\sqrt{\mathrm{MS}_e \frac{2}{I}}$$

The treatment effect τ_j has confidence interval

$$\overline{Y}_{\cdot j} - \overline{Y}_{\cdot\cdot} \pm \sqrt{(J-1)F_{J-1,IJ-I-J+1,1-\alpha}}\sqrt{\mathrm{MS}_e \left(1 - \frac{1}{J}\right)\frac{1}{I}}$$

Problem 12.16 uses these formulas in a randomized block analysis.

12.3.3 Tukey Method (T-Method)

Another method that holds in nicely balanced ANOVA situations is the Tukey method, which is based on an extension of the Student t-test. Recall that in the two-sample t-test, we use

$$t = \sqrt{\frac{n_1 n_2}{n_1 + n_2}}\frac{\overline{Y}_{1\cdot} - \overline{Y}_{2\cdot}}{s}$$

where $\overline{Y}_{1\cdot}$ is the mean of the first sample, $\overline{Y}_{2\cdot}$ is the mean of the second sample, and $s = \sqrt{\mathrm{MS}_e}$ is the pooled standard deviation. The process of dividing by s is called *studentizing* the range.

For more than two means, we are interested in the sampling distribution of the (largest–smallest) mean.

Definition 12.5. Let $Y_1, Y_2, \ldots, Y_k$ be independent and identically distributed (iid) $N(\mu, \sigma^2)$. Let s^2 be an estimate of σ^2 with m degrees of freedom, which is independent of the Y_i's. Then the quantity

$$Q_{k,m} = \frac{\mathrm{MAX}(Y_1, Y_2, \ldots, Y_k) - \mathrm{MIN}(Y_1, Y_2, \ldots, Y_k)}{s}$$

is called the *studentized range*.

Tukey derived the distribution of $Q_{k,m}$ and showed that it does not depend on μ or σ; a description is given in Miller [1981]. The distribution of the studentized range is given by some

statistical packages and is tabulated in the Web appendix. Let $q_{k,m,1-\alpha}$ denote the upper critical value; that is,

$$P[Q_{k,m} \geq q_{k,m,1-\alpha}] = 1 - \alpha$$

You can verify from the table that for $k = 2$, two groups,

$$q_{2,m,1-\alpha} = \sqrt{2} t_{2,m,1-\alpha/2}$$

We now state the main result for using the T-method of multiple comparisons, which will then be specialized and illustrated with some examples.

The result is stated in the analysis of variance context since it is the most common application.

Result 12.2. Given a set of p population means $\mu_1, \mu_2, \ldots, \mu_p$ estimated by p independent sample means $\overline{Y}_1, \overline{Y}_2, \ldots, \overline{Y}_p$ each based on n observations and residual error s^2 based on m degrees of freedom, the probability is $1 - \alpha$ that simultaneously all *contrasts* of $\mu_1, \mu_2, \ldots, \mu_p$, say, $\theta = c_1\mu_1 + c_2\mu_2 + \cdots + c_p\mu_p$, are in the confidence intervals

$$\widehat{\theta} \pm q_{p,m,1-\alpha}\widehat{\sigma_{\theta}}$$

where

$$\widehat{\theta} = c_1\overline{Y}_1 + c_2\overline{Y}_2 + \cdots + c_p\overline{Y}_p \quad \text{and} \quad \widehat{\sigma_{\theta}} = \frac{s}{\sqrt{n}} \sum_{i=1}^{p} \frac{|c_i|}{2}$$

The Tukey method is used primarily with pairwise comparisons. In this case, $\widehat{\sigma_{\theta}}$ reduces to $s/\sqrt{n}$, the standard error of a mean. A requirement is that there be equal numbers of observations in each mean; this implies a balanced design. However, reasonably good approximations can be obtained for some unbalanced situations, as illustrated next.

One-Way Analysis of Variance

Suppose that there are I groups with n observations per group and means $\mu_1, \mu_2, \ldots, \mu_I$. We are interested in all pairwise comparisons of these means. The estimate of $\mu_i - \mu_i'$ is $\overline{Y}_{i\cdot} - \overline{Y}_{i'\cdot}$, the variance of each sample mean estimated by $\text{MS}_e(1/n)$ with $m = I(n-1)$ degrees of freedom. The $100(1-\alpha)\%$ simultaneous confidence intervals are given by

$$\overline{Y}_{i\cdot} - \overline{Y}_{i'\cdot} \pm q_{I,I(n-1),1-\alpha} \frac{1}{\sqrt{n}} \sqrt{\text{MS}_e}, \qquad i, i' = 1, \ldots, I, i \neq i'$$

This result cannot be applied to the example of Section 12.3.2 since the sample sizes are not equal. However, Dunnett [1980] has shown that the $100(1-\alpha)\%$ simultaneous confidence intervals can be reasonably approximated by replacing

$$\sqrt{\frac{\text{MS}_e}{n}} \quad \text{by} \quad \sqrt{\text{MS}_e \left(\frac{1}{2}\right)\left(\frac{1}{n_i} + \frac{1}{n_{i'}}\right)}$$

where n_i and $n_{i'}$ are the sample sizes in groups i and i', respectively, and the degrees of freedom associated with MS_e are the usual ones from the analysis of variance.

We now apply this approximation to the morphine binding data in Section 12.3.2. For this example, $1 - \alpha = 0.99$, $I = 4$, and the $\text{MS}_e = 9.825$ has 24 d.f., resulting in $q_{4,24,0.99} = 4.907$. Simultaneous 99% confidence intervals are listed in Table 12.7.

Table 12.7 Morphine Binding Data

Contrast	n_i	n_i'	$\overline{Y}_{i\cdot} - \overline{Y}_{i'\cdot}$	Estimated Standard Error	99% Limits	
					Lower	Upper
$\mu_1 - \mu_2$	18	2	1.7833	1.6520	−6.32	9.98
$\mu_1 - \mu_3$	18	3	2.4500	1.3822	−4.33	9.23
$\mu_1 - \mu_4$	18	5	6.8833	1.1205	1.39	12.4
$\mu_2 - \mu_3$	2	3	0.6167	2.0233	−9.31	10.5
$\mu_2 - \mu_4$	2	5	5.0500	1.8544	−4.05	14.1
$\mu_3 - \mu_4$	3	5	4.4333	1.6186	−3.51	12.4

We conclude, at a somewhat stringent 99% confidence level, that simultaneously, only one of the pairwise contrasts is significantly different: group 1 (normal) differing significantly from group 4 (anephric).

Two-Way ANOVA *with Equal Numbers of Observations per Cell*

Suppose that in the two-way ANOVA of Section 10.3.1, there are n observations for each cell. The T-method may then be used to find intervals for either set of main effects (but not both simultaneously). For example, to find intervals for the α_i's, the intervals are:

Contrast	Interval
α_i	$\overline{Y}_{i\cdot\cdot} - \overline{Y}_{\cdot\cdot\cdot} \pm \frac{1}{\sqrt{Jn}} q_{I,IJ(n-1),1-\alpha} \sqrt{\mathrm{MS}_e \left(1 - \frac{1}{I}\right)}$
$\alpha_i - \alpha_{i'}$	$\overline{Y}_{i\cdot\cdot} - \overline{Y}_{i'\cdot\cdot} \pm \frac{1}{\sqrt{Jn}} q_{I,IJ(n-1),1-\alpha} \sqrt{\mathrm{MS}_e}$

We again consider the last example of Section 12.3.2 and want to set up 95% confidence intervals for α_1, α_2, and $\alpha_1 - \alpha_2$. In this example $I = 2$, $J = 2$, and $n = 10$. Using $q_{2,36,0.95} = 2.87$ (by interpolation), the intervals are:

Contrast	Estimate	Standard Error	95% Limits	
			Lower	Upper
α_1	−0.54	0.2358	−1.22	0.68
α_2	0.54	0.2358	−0.68	1.22
$\alpha_1 - \alpha_2$	−1.08	0.3335	−2.04	−0.12

We have used the MS_e with 36 degrees of freedom; that is, we have fitted a model with interaction. The interpretation of the results is that treatment effects do differ significantly at the 0.05 level; even though there is not enough evidence to reject the null hypothesis that the treatment effects differ from zero.

Randomized Block Designs

Using the notation of Section 12.3.2, suppose that we want to compare contrasts among the treatment means (the $\mu + \tau_j$). The τ_j themselves are contrasts among the means. In this case, $m = (I - 1)(J - 1)$. The intervals are:

Table 12.8 Confidence Intervals for the Six Comparisons

		95% Limits	
Contrast	Estimate	Upper	Lower
$\mu_1 - \mu_2$	21.6	4.4	38.8
$\mu_1 - \mu_3$	20.7	3.5	37.9
$\mu_1 - \mu_4$	7.0	−10.2	24.2
$\mu_2 - \mu_3$	−0.9	−18.1	16.3
$\mu_2 - \mu_4$	−14.6	−31.8	2.6
$\mu_3 - \mu_4$	−13.7	−30.9	3.5

Contrast	**Interval**
τ_j	$\overline{Y}_{\cdot j} - \overline{Y}_{\cdot\cdot} \pm \frac{1}{\sqrt{I}} q_{J,(I-1)(J-1),1-\alpha} \sqrt{\text{MS}_e \left(1 - \frac{1}{J}\right)}$
$\tau_j - \tau_{j'}$	$\overline{Y}_{\cdot j} - \overline{Y}_{\cdot j'} \pm \frac{1}{\sqrt{2I}} q_{J,(I-1)(J-1),1-\alpha} \sqrt{\text{MS}_e}$

Consider Example 10.6. We want to compare the effectiveness of pancreatic supplements on fat absorption. The treatment means are

$$\overline{Y}_{\cdot 1} = 38.1, \qquad \overline{Y}_{\cdot 2} = 16.5, \qquad \overline{Y}_{\cdot 3} = 17.4, \qquad \overline{Y}_{\cdot 4} = 31.1$$

The estimate of σ^2 is $\text{MS}_e = 107.03$ with 15 degrees of freedom. To construct simultaneous 95% T-confidence intervals, we need $q_{4,15,0.95} = 4.076$. The simultaneous 95% confidence interval for $\tau_1 - \tau_2$ is

$$(38.1 - 16.5) \pm \frac{1}{\sqrt{6}}(4.076)\sqrt{107.03}$$

or

$$21.6 \pm 17.2$$

yielding (4.4, 38.8).

Proceeding similarly, we obtain simultaneous 95% confidence intervals for the six pairwise comparisons (Table 12.8). From this analysis we conclude that treatment 1 differs from treatments 2 and 3 but has not been shown to differ from treatment 4. All other contrasts are not significant.

12.3.4 Bonferroni Method (B-Method)

In this section a method is presented that may be used in all situations. The method is conservative and is based on Bonferroni's inequality. Called the Bonferroni method, it states that the probability of occurrence of one or more of a set of events occurring is less that or equal to the sum of the probabilities. That is, the Bonferroni inequality states that

$$P(A_1 U \cdots U A_n) \leq \sum_{i=1}^{n} P(A_i)$$

We know that for disjoint events, the probability of one or more of $A_1, \ldots, A_n$ is equal to the sum of probabilities. If the events are not disjoint, part of the probability is counted twice or more and there is strict inequality.

Suppose now that n simultaneous tests are to be performed. It is desired to have an overall significance level α. That is, if the null hypothesis is true in all n situations, the probability of incorrectly rejecting one or more of the null hypothesis is less than or equal to α. *Perform each test at significance level α/n; then the overall significance level is less that or equal to α.* Let A_i be the event of incorrectly rejecting in the ith test. Bonferroni's inequality shows that the probability of rejecting one or more of the null hypotheses is less than or equal to $(\alpha/n + \cdots + \alpha/n)$ (n terms), which is equal to α.

We now state a result that makes use of this inequality:

Result 12.3. Given a set of parameters $\beta_1, \beta_2, \ldots, \beta_p$ and N linear combinations of these parameters, the probability is greater than or equal to $1 - \alpha$ that simultaneously these linear combinations are in the intervals

$$\widehat{\theta} \pm t_{m,1-\alpha/2N}\widehat{\sigma}_{\widehat{\theta}}$$

The quantity $\widehat{\theta}$ is $c_1b_1 + c_2b_2 + \cdots + c_pb_p$, $t_{m,1-\alpha/2N}$ is the $100(1 - \alpha/2N)$th percentile of a t-statistic with m degrees of freedom, and $\widehat{\sigma}_{\widehat{\theta}}$ is the estimated standard error of the estimate of the linear combination based on m degrees of freedom.

The value of N will vary with the application. In the one-way ANOVA with all the pairwise comparisons among the I treatment means $N = \begin{pmatrix} I \\ 2 \end{pmatrix}$. Simultaneous confidence intervals, in this case, are of the form

$$\overline{Y}_{i\cdot} - \overline{Y}_{i'\cdot} \pm t_{m,1-\alpha/2\begin{pmatrix} I \\ 2 \end{pmatrix}} \sqrt{\mathrm{MS}_e\left(\frac{1}{n_i} + \frac{1}{n_i'}\right)}, \qquad i, i' = 1, \ldots, I, i \neq i'$$

The value of α need not be partitioned into equal multiples. The simplest is $\alpha = \alpha/N + \alpha/N + \cdots + \alpha/N$, but any partitions of $\alpha = \alpha_1 + \alpha_2 + \cdots + \alpha_N$ is permissible, yielding a per experiment error rate of at most α. However, any such decision must be made a priori—obviously, one cannot decide after seeing one p-value of 0.04 and 14 larger ones to allow all the Type I error to the 0.04 and declare it significant. Partly for this reason, unequal allocation is very unusual outside group sequential clinical trials (where it is routine but does not use the Bonferroni inequality).

When presenting p-values, when N simultaneous tests are being done, multiplication of the p-value for each test by N gives p-values allowing simultaneous consideration of all N tests.

An example of the use of Bonferroni's inequality is given in a paper by Gey et al. [1974]. This paper considers heartbeats that have an irregular rhythm (or arrythmia). The study examined the administration of the drug procainamide and evaluated variables associated with the maximal exercise test with and without the drug. Fifteen variables were examined using paired t-tests. All the tests came from data on the *same* 23 patients, so the test statistics were not independent. To correct for the multiple comparison values, the p-values were multiplied by 15. Table 12.9 presents 14 of the 15 comparisons. The table shows that even taking the multiple comparisons into account, many of the variables differed when the subject was on the procainamide medication. In particular, the frequency of arrythmic beats was decreased by administration of the drug.

Improved Bonferroni Methods

The Bonferroni adjustment is often regarded as too drastic, causing too great a loss of power. In fact, the adjustment is fairly close to optimal in any situation where only one of the null hypotheses is false. When many of the null hypotheses are false, however, there are better corrections. A number of these are described by Wright [1992]; we discuss two here.

Table 12.9 Variables at Rest and Exercise before and after Oral Procainamide[a]

		Rest						Exercise							
	Procainamide Plasma Level, 1 h	HR		SP		DP		HR Maximum		SP Maximum		DP Maximum		Arrhythmia Frequency	
		Control	1 h	Control	1 h	Control	Hr	Control	1 h	Control	1 h	Control	1 h	Control	1 h
Number of patients	23	23		23		23		23		23		23		23	
Mean	5.99	73	87	129	118	81	81	171	170	187	168	85	76	105	38
±SD	±1.33	±11	±13	±17	±11.8	±11	±9.2	±13.5	±14	±20.6	±20	±12	±10	±108	±69
t		5.053		4.183		0.3796		0.9599		5.225		5.005		3.422	
P^b		<0.0015		<0.0060		NS		NS		<0.0015		<0.015		<0.0360	

	Severity Index		$VO_{2\ MAX}$		Computer ST_B									
					FAI(%)		Rest		Maximum		Slope		Zero Recovery	
	Control	1 h	Control	1 h	Control	1 h	Control	1 h	Control	1 h	Control	1 h	Control	1 h
Number of patients	23		22		23		22		22		22		23	
Mean	12.9	4.9	33.2	33.0	12.9	13.5	0.036	0.044	−0.190	−0.122	−2.31	−2.05	−0.065	−0.0302
±SD	±3.0	±4.67	±5.8	±6.0	±12.5	±11.5	±0.044	±0.051	±0.126	±0.095	±1.401	±1.29	±0.0003	±0.077
t	5.870		0.3852		0.5253		0.8861		3.915		1.132		4.320	
P^b	<0.0015		NS		NS		NS		<0.0120		NS		<0.0045	

[a] Dose, 15 mg per kilogram body weight; HR, heart rate; SP, systolic pressure (mmHg); DP, diastolic pressure (mmHg); VO_{2MAX}, maximal oxygen consumption (mL/min); FAI, functional aerobic impairment; ST_B, 100-beat averaged S-T depression, from monitored CB, lead, taken 50 to 69 ms after nadir of S-wave; slope, $\delta HR/\delta ST_B$; *t*, paired *t*-test; NS, not significant; h, hour.

[b] Probability multiplied by 15 to correct for multiple comparisons (Bonferroni's inequality correction).

Table 12.10 Application of the Three Methods

Original p	$\times$	$=$	Hochberg	Holm	Bonferroni
0.001	6	0.006	0.006	0.006	0.006
0.01	5	0.05	0.04	0.05	0.06
0.02	4	0.08	0.04	0.08	0.12
0.025	3	0.075	0.04	0.08	0.15
0.03	2	0.06	0.04	0.08	0.18
0.04	1	0.04	0.04	0.08	0.24

Consider a situation where you perform six tests and obtain p-values of 0.001, 0.01, 0.02, 0.025, 0.03, and 0.04, and you wish to use $\alpha = 0.05$. All the p-values are below 0.05, something that is very unlikely to occur by chance, but the Bonferroni adjustment declares only one of them significant.

Given n p-values, the Bonferroni adjustment multiplies each by n. The Hochberg and Holm adjustments multiply the smallest by n, the next smallest by $n - 1$, and so on (Table 12.10).

This may change the relative ordering of p-values, so they are then restored to the original order. For the Hochberg method this is done by decreasing them where necessary; for the Holm method it is done by increasing them. The Holm adjustment guarantees control of Type I error; the Hochberg adjustment controls Type I error in most but not all circumstances.

Although there is little reason other than tradition to prefer the Bonferroni adjustment over the Holm adjustment, there is often not much difference.

12.4 COMPARISON OF THE THREE PROCEDURES

Of the three methods presented, which should be used? In many situations there is not sufficient balance in the data (e.g., equal numbers in each group in a one-way analysis of variance) to use the T-method; the Scheffé method procedure or the Bonferroni inequality should be used. For paired comparisons, the T-method is preferable. For more complex contrasts, the S-method is preferable. A comparison between the B-method and the S-method is more complicated, depending heavily on the type of application. The Bonferroni method is easier to carry out, and in many situations the critical value will be less than that for the Scheffé method.

In Table 12.11 we compare the critical values for the three methods for the case of one-way ANOVA with k treatments and 20 degrees of freedom for error MS. With two treatments ($k = 2$ and therefore $\nu = 1$) the three methods give identical multipliers (the q statistic has to be divided by $\sqrt{2}$ to have the same scale as the other two statistics).

Table 12.11 Comparison of the Critical Values for One-Way ANOVA with k Treatments[a]

Number of Treatments, k	Degrees of Freedom, $\nu = k - 1$	$\sqrt{\nu F_{\nu,20,0.95}}$	$\frac{1}{\sqrt{2}} q_{\nu,20,0.95}$	$t_{20,1-\alpha/2\binom{k}{2}}$
2	1	2.09	2.09	2.09
3	2	2.64	2.53	2.61
4	3	3.05	2.80	2.93
5	4	3.39	2.99	3.15
11	10	4.85	3.61	3.89
21	20	6.52	4.07	4.46

[a] Assume $\binom{k}{2}$ comparisons for the Tukey and Bonferroni procedures. Based on 20 degrees of freedom for error mean square.

Hence, if pairwise comparisons are carried out, the Tukey procedure will produce the shortest simultaneous confidence intervals. For the type of situation illustrated in the table, the B-method is always preferable to the S-method. It assumes, of course, that the total, N, of comparisons to be made is known. If this is not the case, as in "fishing expeditions," the Scheffé method provides more adequate protection.

For an informative discussion of the issues in multiple comparisons, see comments by O'Brien [1983] in *Biometrics*.

12.5 FALSE DISCOVERY RATE

With the rise of high-throughput genomics in recent years there has been renewed concern about the problem of very large numbers of multiple comparisons. An RNA expression array (gene chip) can measure the activity of several thousand genes simultaneously, and scientists often want to ask which genes differ in their expression between two samples. In such a situation it may be infeasible, but also unnecessary, to design a procedure that prevents a single Type I error out of thousands of comparisons. If we reject a few hundred null hypotheses, we might still be content if a dozen of them were actually Type I errors. This motivates a definition:

Definition 12.6. The *positive false discovery rate* (pFDR) is the expected proportion of rejected hypotheses that are actually true given that at least some null hypotheses are rejected. The *false discovery rate* (FDR) is the positive false discovery rate times the probability that no null hypotheses are rejected.

Example 12.6. Consider an experiment comparing the expression levels of 12,625 RNA sequences on an Affymetrix HG-u95A chip, to see which genes had different expression in benign and malignant colon polyps. Controlling the Type I error rate at 5% means that if we declare 100 sequences to be significantly different, we are not prepared to take more than a 5% chance of even 1 of these 100 being a false positive.

Controlling the positive false discovery rate at 5% means that if we declare 100 sequences to be significantly different, we are not prepared to have, on average, more than 5 of these 100 being false positives.

The pFDR and FDR apparently require knowledge of which hypotheses are true, but we will see that, in fact, it is possible to control the pFDR and FDR without this knowledge and that such control is more effective when we are testing a very large number of hypotheses.

Although like many others, we discuss the FDR and pFDR under the general heading of multiple comparisons, they are very different quantities from the Type I error rates in the rest of this chapter. The Type I error rate is the probability of making a certain decision (rejecting the null hypothesis) conditional on the state of nature (the null hypothesis is actually true). The simplest interpretation of the pFDR is the probability of a state of nature (the null hypothesis is true) given a decision (we reject it). This should cause some concern, as we have not said what we might mean by the probability that a hypothesis is true.

Although it is possible to define probabilities for states of nature, leading to the interesting and productive field of Bayesian statistics, this is not necessary in understanding the false discovery rates. Given a large number N of tests, we know that in the worst case, when all the null hypotheses are true, there will be approximately αN hypotheses (falsely) rejected. In general, fewer that N of the null hypotheses will be true, and there will be fewer than N false discoveries. If we reject R of the null hypotheses and $R > \alpha N$, we would conclude that at least roughly $R - \alpha N$ of the discoveries were correct, and so would estimate the positive false

discovery rate as

$$\text{pFDR} \approx \frac{R - \alpha N}{R}$$

This is similar to a graphical diagnostic proposed by Schweder and Spjøtvoll [1982], which involves plotting R/N against the p-value, with a line showing the expected relationship. As it stands, this estimator is not a very good one. The argument can be improved to produce fairly simple estimators of FDR and pFDR that are only slightly conservative [Storey, 002].

As the FDR and pFDR are primarily useful when N is very large (at least hundreds of tests), hand computation is not feasible. We defer the computational details to the Web appendix of this chapter, where the reader will find links to programs for computing the FDR and pFDR.

12.6 POST HOC ANALYSIS

12.6.1 The Setting

A particular form of the multiple comparison problem is post hoc *analysis*. Such an analysis is not explicitly planned at the start of the study but suggested by the data. Other terms associated with such analyses are *data driven* and *subgroup analysis*. Aside from the assignment of appropriate p-values, there is the more important question of the scientific status of such an analysis. Is the study to be considered exploratory, confirmatory, or both? That is, can the post hoc analysis only suggest possible connections and associations that have to be confirmed in future studies, or can it be considered as confirming them as well? Unfortunately, no rigid lines can be drawn here. Every experimenter does, and should do, post hoc analyses to ensure that all aspects of the observations are utilized. There is no room for rigid adherence to artificial schema of hypothesis which are laid out row upon boring row. But what is the status of these analyses? Cox [1977] remarks:

> Some philosophies of science distinguish between exploratory experiments and confirmatory experiments and regard an effect as well established only when it has been demonstrated in a confirmatory experiment. There are undoubtedly good reasons, not specifically concerned with statistical technique, for proceeding this way; but there are many fields of study, especially outside the physical sciences, where mounting confirmatory investigations may take a long time and therefore where it is desirable to aim at drawing reasonably firm conclusions from the same data as used in exploratory analysis.

What statistical approaches and principles can be used? In the following discussion we follow closely suggestions of Cox and Snell [1981] and Pocock [1982, 1984].

12.6.2 Statistical Approaches and Principles

Analyses Must Be Planned

At the start of the study, specific analyses must be planned and agreed to. These may be broadly outlined but must be detailed enough to, at least theoretically, answer the questions being asked. Every practicing statistician has met the researcher who has a filing cabinet full of crucial data "just waiting to be analyzed" (by the statistician, who may also feel free to suggest appropriate questions that can be answered by the data).

Planned Analyses Must Be Carried Out and Reported

This appears obvious but is not always followed. At worst it becomes a question of scientific integrity and honesty. At best it is potentially misleading to omit reporting such analyses. If

the planned analysis is amplified by other analyses which begin to take on more importance, a justification must be provided, together with suggested adjustments to the significance level of the tests. The researcher may be compared to the novelist whose minor character develops a life of his own as the novel is written. The development must be rational and believable.

Adjustment for Selection

A post hoc analysis is part of a multiple-comparison procedure, and appropriate adjustments can be made if the family of comparisons is known. Use of the Bonferroni adjustment or other methods can have a dramatic effect. It may be sufficient, and is clearly necessary, to report analyses in enough detail that readers know how much testing was done.

Split-Sample Approach

In the split-sample approach, the data are randomly divided into two parts. The first part is used to generate the exploratory analyses, which are then "confirmed" by the second part. Cox [1977] says that there are "strong objections on general grounds to procedures where different people analyzing the same data by the same method get different answers." An additional aspect of such analyses is that it does not provide a solution to the problem of subgroup analysis.

Interaction Analysis

The number of comparisons is frequently not defined, and most of the foregoing approaches will not work very well. Interaction analysis of subgroups provides valid protection in such post hoc analyses. Suppose that a treatment effect has been shown for a particular subgroup. To assess the validity of this effect, analyze all subgroups jointly and test for an interaction of subgroup and treatment. This procedure embeds the subgroup in a meaningful larger family. If the global test for interaction is significant, it is warranted to focus on the subgroup suggested by the data. Pocock [1984] illustrates this approach with data from the Multiple Risks Factor Intervention Trial Research Group [1982] "MR. FIT". This randomized trial of "12,866 men at high risk of coronary heart disease compared to special intervention (SI) aimed at affecting major risk factors (e.g., hypertension, smoking, diet) and usual care (UC). The overall rates of coronary mortality after an average seven year follow-up (1.79% on SI and 1.93% on UC) are not significantly different." The paper presented four subgroups. The extreme right-hand column in Table 12.12 lists the odds ratio comparing mortality in the special intervention and usual care groups. The first three subgroups appear homogeneous, suggesting a beneficial effect of special intervention. The fourth subgroup (with hypertension and ECG abnormality) appears different. The average odds ratio for the first three subgroups differs significantly from the odds ratio for the fourth group ($p < 0.05$). However, this is a post hoc analysis, and a test for the homogeneity of the odds ratios over all four subgroups shows no significant differences, and furthermore, the average of the odds ratio does not differ significantly from 1. Thus, on the basis of the global interaction test there are no significant differences in mortality among the eight groups. (A chi-square analysis of the 2×8 contingency table formed by the two treatment groups and the eight subgroups shows a value of $\chi^2 = 8.65$ with 7 d.f.) Pocock concludes: "Taking into account the fact that this was not the only subgroup analysis performed, one should feel confident that there are inadequate grounds for supposing that the special intervention did harm to those with hypertension and ECG abnormalities."

If the overall test of interaction had been significant, or if the comparison had been suggested before the study was started, the "significant" p-value would have had clinical implications.

12.6.3 Simultaneous Tests in Contingency Tables

In $r \times c$ contingency tables, there is frequently interest in comparing subsets of the tables. Goodman [1964a,b] derived the large sample form for $100(1 - \alpha)\%$ simultaneous contrasts for

Table 12.12 Interaction Analysis: Data for Four MR. FIT Subgroups

		No. of Coronary Death/No. of Men				
Hypertension	ECG Abnormality	Special Intervention (%)		Usual Care (%)		Odds Ratio
No	No	24/1817	(1.3)	30/1882	(1.6)	0.83
No	Yes	11/592	(1.9)	15/583	(2.6)	0.72
Yes	No	44/2785	(1.6)	58/2808	(2.1)	0.76
Yes	Yes	36/1233	(2.9)	21/1185	(1.8)	1.67

all 2×2 comparisons. This is equivalent to examining all $\binom{r}{2}\binom{c}{2}$ possible odds ratios. The intervals are constructed in terms of the logarithms of the ratio. Let

$$\widehat{\omega} = \log n_{ij} + \log n_{i'j'} - \log n_{i'j} - \log n_{ij}$$

be the log odds associated with the frequencies indicated. In Chapter 7 we showed that the approximate variance of this statistic is

$$\widehat{\sigma}^2_{\widehat{\omega}} \doteq \frac{1}{n_{ij}} + \frac{1}{n_{i'j'}} + \frac{1}{n_{i'j}} + \frac{1}{n_{ij'}}$$

Simultaneous $100(1-\alpha)\%$ confidence intervals are of the form

$$\widehat{\omega} \pm \sqrt{\chi^2_{(r-1)(c-1),(1-\alpha)}}\,\widehat{\sigma}_{\widehat{\omega}}$$

This again is of the same form as the Scheffé approach, but now based on the chi-square distribution rather that the F-distribution. The price, again, is fairly steep. At the 0.05 level and a 6×6 contingency table, the critical value of the chi-square statistic is

$$\sqrt{\chi^2_{25,0.95}} = \sqrt{37.65} = 6.14$$

Of course, there are $\binom{6}{2}\binom{6}{2} = 225$ such tables. It may be more efficient to use the Bonferroni inequality. In the example above, the corresponding Z-value using the Bonferroni inequality is

$$Z_{1-0.025/225} = Z_{0.999889} \doteq 3.69$$

So if only 2×2 tables are to be examined, the Bonferroni approach will be more economical.

However, the Goodman approach works and is valid for *all* linear contrasts. See Goodman [1964a,b] for additional details.

12.6.4 Regulatory Statistics and Game Theory

In reviewing newly developed pharmaceuticals, the Food and Drug Administration, takes a very strong view on multiple comparisons and on control of Type I error, much stronger than we have taken in this chapter. Regulatory decision making, however, is a special case because it is in part adversarial. Statistical decision theory deals with decision making under uncertainty and is appropriate for scientific research, but is insufficient as a basis for regulation.

The study of decision making when dealing with multiple rational actors who do not have identical interests is called game theory. Unfortunately, it is much more complex than statistical decision theory. It is clear that FDA policies affect the supply of new treatments not only through

their approval of specific products but also through the resulting economic incentives for various sorts of research and development, but it is not clear how to go from this to an assessment of the appropriate p-values.

12.6.5 Summary

Post hoc comparisons should usually be considered exploratory rather than confirmatory, but this rule should not be followed slavishly. It is clear that some adjustment to the significance level must be made to maintain the validity of the statistical procedure. In each instance the p-value will be adjusted upward. The question is whether this should be done by a formal adjustment, and if so, what groups of hypotheses should the fixed Type I error be divided over. One important difficulty in specifying how to divide up the Type I error is that different readers may group hypotheses differently. It is also important to remember that controlling the total Type I error unavoidably increases the Type II error. If your conclusions are that an exposure makes no difference, these conclusions are weakened, rather than strengthened, by controlling Type I error.

When reading research reports that include post hoc analyses, it is prudent to keep in mind that in all likelihood, many such analyses were tried by the authors but not reported. Thus, scientific caution must be the rule. To be confirmatory, results from such analyses must not only make excellent biological sense but must also satisfy the principle of Occam's razor. That is, there must not be a simpler explanation that is also consistent with the data.

NOTES

12.1 Orthogonal Contrasts

Orthogonal contrasts form a special group of contrasts. Consider two contrasts:

$$\theta_1 = c_{11}\beta_1 + \cdots + c_{1p}\beta_p$$

and

$$\theta_2 = c_{21}\beta_1 + \cdots + c_{2p}\beta_p$$

The two contrasts are said to be *orthogonal* if

$$\sum_{j=1}^{p} c_{1j}c_{2j} = 0$$

Clearly, if θ_1, θ_2 are orthogonal, then $\widehat{\theta}_1$, $\widehat{\theta}_2$ will be orthogonal since orthogonality is a property of the coefficients. Two orthogonal contrasts are *orthonormal* if, in addition,

$$\sum c_{1j}^2 = \sum c_{2j}^2 = 1$$

The advantage to considering orthogonal (and orthonormal) contrasts is that they are uncorrelated, and hence, if the observations are normally distributed, the contrasts are statistically independent. Hence, the Bonferroni inequality becomes an equality. But there are other advantages. To see those we extend the orthogonality to more than two contrasts. A set of contrasts is orthogonal (orthonormal) if all pairs of contrasts are orthogonal (orthonormal).

Now consider the one-way analysis of variance with I treatments. There are $I - 1$ degrees of freedom associated with the treatment effect. It can be shown that there are precisely $I - 1$ orthogonal contrasts to compare the treatment means. The set is not unique; let $\theta_1, \theta_2, \ldots, \theta_{I-1}$

form a set of such contrasts. Assume that they are orthonormal, and let $\widehat{\theta}_1, \widehat{\theta}_2, \ldots, \widehat{\theta}_{I-1}$ be the estimate of the orthonormal contrasts. Then it can be shown that

$$\text{SS}_{\text{TREATMENTS}} = \widehat{\theta}_1^2 + \widehat{\theta}_2^2 + \cdots + \widehat{\theta}_{I-1}^2$$

We have thus partitioned the $\text{SS}_{\text{TREATMENTS}}$ into $I - 1$ components (each with one degree of freedom, it turns out) and uncorrelated as well. This is a very nice summary of the data. To illustrate this approach, assume an experiment with four treatments. Let the means be μ_1, μ_2, μ_3, μ_4. A possible set of contrasts is given by the following pattern:

Contrast	μ_1	μ_2	μ_3	μ_4
θ_1	$1/\sqrt{2}$	$-1/\sqrt{2}$	0	0
θ_2	$1/\sqrt{6}$	$1/\sqrt{6}$	$-2/\sqrt{6}$	0
θ_3	$1/\sqrt{12}$	$1/\sqrt{12}$	$1/\sqrt{12}$	$-3/\sqrt{12}$

You can verify that:

- These contrasts are orthonormal.
- There are no additional *orthogonal contrasts*.
- $\theta_1^2 + \theta_2^2 + \theta_3^2 = \sum(\mu_i - \mu)^2$.

The pattern can clearly be extended to any number of means (it is known as the *Gram-Schmidt orthogonalization process*).

The nonuniqueness of this decomposition becomes obvious from starting the first contrast, say, with

$$\theta_1^* = \frac{1}{\sqrt{2}}\mu_1 - \frac{1}{\sqrt{2}}\mu_4$$

Sometimes a meaningful set of orthogonal contrasts can be used to summarize an experiment. This approach, using the statistical independence to determine the significance level, will minimize the cost of multiple testing. Of course, if these contrasts were carefully specified beforehand, you might argue that each one should be tested at level α!

12.2 Tukey Test

The assumptions underlying the Tukey test include that the variances of the means are equal; this translates into equal sample sizes in the analysis of variance situation. Although the procedure is commonly associated with pairwise comparisons among independent means, it can be applied to arbitrary linear combinations and even allows for a common correlation among the means. For further discussion, see Miller [1981, pp. 37–48]. There are extensions of the Tukey test similar in principle to the Holm extension of the Bonferroni adjustment. These are built on the idea of sequential testing. Suppose that we have tested the most extreme pair of means and rejected the hypothesis that they are the same. There are two possibilities:

1. The null hypothesis is actually false, in which case we have not used any Type I error.
2. The null hypothesis is actually true, which happens with probability less than α.

In either case, if we now perform the next-most extreme test we can ignore the fact that we have already done one test without affecting the per experiment Type I error. The resulting procedure is called the *Newman–Keuls* or *Student–Newman–Keuls test* and is available in many statistical packages.

12.3 Likelihood Principle

The likelihood principle is a philosophical principle in statistics which says that all the evidence for or against a hypothesis is contained in the likelihood ratio. It can be derived in various ways from intuitively plausible assumptions. The likelihood principle implies that the evidence about one hypothesis does not depend on what other hypotheses were investigated. One view of this is that it shows that multiple comparison adjustment is undesirable; another is that it shows the that likelihood principle is undesirable. A fairly balanced discussion of these issues can be found in Stuart et al. [1999].

There is no entirely satisfactory resolution to this conflict, which is closely related to the question of what counts as an experiment for the per experiment error rate. One possible resolution is to conclude that the main danger in the multiple comparison problem comes from incomplete publication. That is, the danger is more that other people will be misled than that you yourself will be misled (see also Problem 12.13). In this case the argument from the likelihood principle does not hold in any simple form. The relevant likelihood would now be the likelihood of seeing the results given the selective reporting process as well as the randomness in the data, and this likelihood does depend on what one does with multiple comparisons. This intermediate position suggests that multiple comparison adjustments are critical primarily when only selected results of an exploratory analysis are reported.

PROBLEMS

For the problems in this chapter, the following tasks are defined. Additional tasks are indicated in each problem. Unless otherwise indicated, assume that $\alpha^* = 0.05$.

- **(a)** Calculate simultaneous confidence intervals as discussed in Section 12.2. Graph the intervals and state your conclusions.
- **(b)** Apply the Scheffé method. State your conclusions.
- **(c)** Apply the Tukey method. State your conclusions.
- **(d)** Apply the Bonferroni method. State your conclusions.
- **(e)** Compare the methods indicated. Which result is the most reasonable?

12.1 This problem deals with Problem 10.1. Use a 99% confidence level.

- **(a)** Carry out task (a).
- **(b)** Compare your results with those obtained in Section 12.3.2.
- **(c)** A more powerful test can be obtained by considering the groups to be ranked in order of increasingly severe disorder. A test for trend can be carried out by coding the groups 1, 2, 3, and 4 and regressing the percentage morphine bound on the regressor variable and testing for significance of the slope. Carry out this test and describe its pros and cons.
- **(d)** Carry out task (c) using the approximation recommended in Section 12.3.3.
- **(e)** Carry out task (e).

12.2 This problem deals with Problem 10.2.

- **(a)** Do tasks (a) through (e) for pairwise comparisons of all treatment effects.

12.3 This problem deals with Problem 10.3.

- **(a)** Do tasks (a) through (d) for all pairwise comparisons.
- **(b)** Do task (c) defined in Problem 12.1.
- **(c)** Do task (e).

12.4 This problem deals with Problem 10.4.

(a) Do tasks (a) through (e) setting up simultaneous confidence intervals on both main effects and all pairwise comparisons.

(b) A further comparison of interest is control vs. shock. Using the Scheffé approach, test this effect.

(c) Summarize the results from this experiment in a short paragraph.

12.5 Sometimes we are interested in comparing several treatments against a standard treatment. Dunnett [1954] has considered this problem. If there are I groups, and group 1 is the standard group, $I - 1$ comparisons can be made at level $1 - \alpha/2(I - 1)$ to maintain a per experiment error rate of α. Apply this approach to the data of Bruce et al. [1974] in Section 12.2 by comparing groups $2, \ldots, 8$ with group 1, the healthy individuals. How do your conclusions compare with those of Section 12.2?

12.6 This problem deals with Problem 10.6.

(a) Carry out tasks (a) through (e).

(b) Suppose that we treat these data as a regression problem (as suggested in Chapter 10). Does it still make sense to test the significance of the difference of adjacent means? Why or why not? What if the trend was nonlinear?

12.7 This problem deals with Problem 10.7.

(a) Carry out tasks (a) through (e).

12.8 This problem deals with Problem 10.8.

(a) Carry out tasks (b), (c), and (d).

(b) Of particular interest are the comparisons of each of the test preparations A through D with the standard insulin. The "medium" treatment is not relevant for this analysis. How does this alter task (d)?

(c) Why would it not be very wise to ignore the "medium" treatment totally? What aspect of the data for this treatment can be usefully incorporated into the analysis in part (b)?

12.9 This problem deals with Problem 10.9.

(a) Compare each of the means of the schizophrenic group with the control group using S, T, and B methods.

(b) Which method is preferred?

12.10 This problem deals with Problem 10.10.

(a) Carry out tasks (b) through (e) on the plasma concentration of 45 minutes, comparing the two treatments with controls.

(b) Carry out tasks (b) through (d) on the difference in the plasma concentration at 90 minutes and 45 minutes (subtract the 45-minute reading from the 90-minute reading). Again, compare the two treatments with controls.

(c) Synthesize the conclusions of parts (a) and (b).

(d) Can you think of a "nice" graphical way of presenting part (c)?

(e) Consider parts (a) and (b) combined. From a multiple-comparison point of view, what criticism could you level at this combination? How would you resolve it?

12.11 Data for this problem are from a paper by Winick et al. [1975]. The paper examines the development of adopted Korean children differing greatly in early nutritional status. The study was a retrospective study of children admitted to the Holt Adoption Service and ultimately placed in homes in the United States. The children were divided into three groups on the basis of how their height, at the time of admission to Holt, related to a reference standard of normal Korean children of the same age:

- *Group 1*. designated "malnourished"—below the third percentile for both height and weight.
- *Group 2*. "moderately nourished"—from the third to the twenty-fourth percentile for both height and weight.
- *Group 3*."well-nourished or control"—at or above the twenty-fifth percentile for both height and weight.

Table 12.13 has data from this paper.

Table 12.13 Current Height (Percentiles, Korean Reference Standard) Comparison of Three Nutrition Groups[a]

Group	N	Mean Percentile	SD	F Probability	Contrast Group	t-Test t	P
1	41	71.32	24.98	0.068	1 vs. 2	−1.25	0.264
2	50	76.86	21.25		1 vs. 3	−2.22	0.029[b]
3	47	82.81	23.26		2 vs. 3	−1.31	0.194
Total	138	77.24	23.41				

[a] F probability is the probability that the F calculated from the one-way ANOVA ratio would occur by chance
[b] Statistically significant.

(a) Carry out tasks (a) through (e) for all pairwise comparisons and state your conclusions.

(b) Read the paper, then compare your results with that of the authors.

(c) A philosophical point may be raised about the procedure of the paper. Since the overall F-test is not significant at the 0.05 level (see Table 12.13), it would seem inappropriate to "fish" further into the data. Discuss the pros and cons of this argument.

(d) Can you suggest alternative, more powerful analyses? (What is meant by "more powerful"?)

12.12 Derive equation (1). Indicate clearly how the independence assumption and the null hypotheses are crucial to this result.

12.13 A somewhat amusing—but also serious—example of the multiple comparison problem is the following. Suppose that a journal tends to accept only papers that show "significant" results. Now imagine multiple groups of independent researchers (say, 20 universities in the United States and Canada) all working on roughly the same topic

and hence testing the same null hypothesis. If the null hypothesis is true, we would expect only one of the researchers to come up with a "significant" result. Knowing the editorial policy of the journal, the 19 researchers with nonsignificant results do not bother to write up their research, but the remaining researcher does. The paper is well written, challenging, and provocative. The editor accepts the paper and it is published.

(a) What is the per experiment error rate? Assume 20 independent researchers.

(b) Define an appropriate editorial policy in view of an unknown number of comparisons.

12.14 This problem deals with the data of Problem 10.13. The primary interest in these data involves comparisons of three treatments; that is, the experiments represent blocks. Carry out tasks (a) through (e) focusing on comparison of the means for tasks (b) through (d).

12.15 This problem deals with the data of Problem 10.14.

(a) Carry out the Tukey test for pairwise comparisons on the total analgesia score presented in part (b) of that question. Translate your answers to obtain confidence intervals applicable to single readings.

***(b)** The sum of squares for analgesia can be partitioned into three orthogonal contrasts as follows:

	μ_1	μ_2	μ_3	μ_4	Divisor
θ_1	-1	-1	-1	3	$\sqrt{12}$
θ_2	1	-1	-1	1	$\sqrt{4}$
θ_3	-1	3	-3	1	$\sqrt{20}$

(c) Verify that these contrasts are orthogonal. If the coefficients are divided by the divisors at the right, verify that the contrasts are orthonormal.

***(d)** Interpret the contrasts θ_1, θ_2, θ_3 defined in part (b).

***(e)** Let $\widehat{\theta}_1$, $\widehat{\theta}_2$, $\widehat{\theta}_3$ be the estimates of the orthonormal contrasts. Verify that

$$\mathrm{SS}_{\mathrm{TREATMENTS}} = \widehat{\theta}_1^2 + \widehat{\theta}_2^2 + \widehat{\theta}_3^2$$

Test the significance of each of these contrasts and state your conclusion.

12.16 This problem deals with Problem 10.15.

(a) Carry out tasks (b) through (e) on all pairwise comparisons of treatment means.

***(b)** How would the results in part (a) be altered if the Tukey test for additivity is used? Is it worth reanalyzing the data?

12.17 This problem deals with Problem 10.16.

(a) Carry out tasks (b) through (e) on the treatment effects and on all pairwise comparisons of treatment means.

***(b)** Partition the sums of squares of treatments into two pieces, a part attributable to linear regression and the remainder. Test the significance of the regression, adjusting for the multiple comparison problem.

***12.18** This problem deals with the data of Problem 10.18.

(a) We are going to "mold" these data into a regression problem as follows; define six dummy variables I_1 to I_6.

$$I_i = \begin{cases} 1, & \text{data from subject } i,\ i = 1, \ldots, 6 \\ 0, & \text{otherwise} \end{cases}$$

In addition, define three further dummy variables:

$$I_7 = \begin{cases} 1, & \text{recumbent position} \\ 0, & \text{otherwise} \end{cases}$$

$$I_8 = \begin{cases} 1, & \text{placebo} \\ 0, & \text{otherwise} \end{cases}$$

$$I_9 = I_7 \times I_8$$

(b) Carry out the regression analyses of part (a) forcing in the dummy variables I_1 to I_6 first. Group those into one SS with six degrees of freedom. Test the significance of the regression coefficients of I_7, I_8, I_9 using the Scheffé procedure.

(c) Compare the results of part (c) of Problem 10.18 with the analysis of part (b). How can the two analyses be reconciled?

12.19 This problem deals with the data of Example 10.5 and Problem 10.19.

(a) Carry out tasks (c) and (d) on pairwise comparisons.

(b) In the context of the Friedman test, suggest a multiple-comparison approach.

12.20 This problem deals with Problem 10.4.

(a) Set up simultaneous 95% confidence intervals on the three regression coefficients using the Scheffé method.

(b) Use the Bonferroni method to construct comparable 95% confidence intervals.

(c) Which method is preferred?

(d) In regression models, the usual tests involve null hypotheses of the form H_0: $\beta_i = 0$, $i = 1, \ldots, p$. In general, how do you expect the Scheffé method to behave as compared with the Bonferroni method?

(e) Suppose that we have another kind of null hypothesis, for example, H_0: $\beta_1 = \beta_2 = \beta_3 = 0$. Does this create a multiple-comparison problem? How would you test this null hypothesis?

(f) Suppose that we wanted to test, simultaneously, two null hypotheses, H_0: $\beta_1 = \beta_2 = 0$ and H_0: $\beta_3 = 0$. Carry out this test using the Scheffé procedure. State your conclusion. Also use nested hypotheses; how do the two tests compare?

***12.21** **(a)** Verify that the contrasts defined in Problem 10.18, parts (c), (d), and (e) are orthogonal.

(b) Define another set of orthogonal contrasts that is also meaningful. Verify that $SS_{TREATMENTS}$ can be partitioned into three sums of squares associated with this set. How do you interpret these contrasts?

REFERENCES

Bruce, R. A., Gey, G. O., Jr., Fisher, L. D., and Peterson, D. R. [1974]. Seattle heart watch: initial clinical, circulatory and electrocardiographic responses to maximal exercise. *American Journal of Cardiology*, **33**: 459–469.

Cox, D. R. [1977]. The role of significance tests. *Scandinavian Journal of Statistics*, **4**: 49–62.

Cox, D. R., and Snell, E. J. [1981]. *Applied Statistics*. Chapman & Hall, London.

Cullen, B. F., and van Belle, G. [1975]. Lymphocyte transformation and changes in leukocyte count: effects of anesthesia and operation. *Anesthesiology*, **43**: 577–583.

Diaconis, P., and Mosteller, F. [1989]. Methods for studying coincidences. *Journal of the American Statistical Association*, **84**: 853–861.

Dunnett, C. W. [1954]. A multiple comparison procedure for comparing several treatments with a control. *Journal of the American Statistical Association*, **50**: 1096–1121.

Dunnett, C. W. [1980]. Pairwise multiple comparison in the homogeneous variance, unequal sample size case. *Journal of the American Statistical Association*, **75**: 789–795.

Gey, G. D., Levy, R. H., Fisher, L. D., Pettet, G., and Bruce, R. A. [1974]. Plasma concentration of procainamide and prevalence of exertional arrythmias. *Annals of Internal Medicine*, **80**: 718–722.

Goodman, L. A. [1964a]. Simultaneous confidence intervals for contrasts among multinomial populations. *Annals of Mathematical Statistics*, **35**: 716–725.

Goodman, L. A. [1964b]. Simultaneous confidence limits for cross-product ratios in contingency tables. *Journal of the Royal Statistical Society, Series B*, **26**: 86–102.

Miller, R. G. [1981]. *Simultaneous Statistical Inference*, 2nd ed. Springer-Verlag, New York.

Multiple Risks Factor Intervention Trial Research Group [1982]. Multiple risk factor intervention trial: risk factor changes and mortality results. *Journal of the American Medical Association*, **248**: 1465–1477.

O'Brien, P. C. [1983]. The appropriateness of analysis of variance and multiple comparison procedures. *Biometrics*, **39**: 787–794.

Pocock, S. J. [1982]. Interim analyses for randomized clinical trials: the group sequential approach. *Biometrics*, **36**: 153–162.

Pocock, S. J. [1984]. Current issues in design and interpretation of clinical trials. *Proceedings of the 12th International Biometric Conference*, Tokyo, pp. 31–39.

Proschan, M., and Follman, D. [1995]. Multiple comparisons with control in a single experiment versus separate experiments: Why do we feel differently? *American Statistician*, **49**:144–149.

Rothman, K. [1990]. No adjustments are needed for multiple comparisons. *Epidemiology*, **1**: 43–46

Schweder, T., and Spjøtvoll, E. [1982]. Plots of P-values to evaluate many tests simultaneously. *Biometrika*, **69**: 493–502.

Storey, J. D. [2002]. A direct approach to false discovery rates. *Journal of the Royal Statistical Society, Series B*, **64**: 479-498.

Stuart, A., Ord, K., and Arnold, S. [1999]. *Kendall's Advanced Theory of Statistics*, Vol. 2A, *Classical Inference and the Linear Model*. Edward Arnold, London.

Winick, M., Meyer, K. K., and Harris, R. C. [1975]. Malnutrition and environmental enrichment by early adoption. *Science*, **190**: 1173–1175.

Wright, S. P. [1992] Adjusted p-values for simultaneous inference. *Biometrics*, **48**: 1005–1013.

CHAPTER 13

Discrimination and Classification

13.1 INTRODUCTION

Discrimination or classification methods attempt to use measured characteristics to divide people or objects into prespecified groups. As in regression modeling for prediction in Chapter 11, the criteria for assessing classification models are accuracy of prediction and possibly cost of measuring the relevant characteristics. There need not be any relationship between the model and the actual causal processes involved. The computer science literature refers to classification as *supervised learning*, as distinguished from *cluster analysis* or *unsupervised learning*, in which groups are not prespecified and must be discovered as part of the analysis. We discuss cluster analysis briefly in Note 13.5.

In this chapter we discuss the general problem of classification. We present two simple techniques, logistic and linear discrimination, and discuss how to choose and evaluate classification models. Finally, we describe briefly a number of more modern classification methods and give references for further study.

13.2 CLASSIFICATION PROBLEM

In the classification problem we have a group variable Y for each individual, taking values $1, 2, \ldots, K$, called *classes*, and a set of characteristics $X_1, X_2, \ldots, X_p$. Both X and Y are observed for a *training set* of data, and the goal is to create a rule to predict Y from X for new observations and to estimate the accuracy of these predictions.

The most common examples of classification problems in biostatistics have just two classes: with and without a given disease. In screening and diagnostic testing, the classes are based on whether the disease is currently present; in prognostic models, the classes are those who will and will not develop the disease over some time frame.

For example, the Framingham risk score [Wilson et al., 1998] is used widely to determine the probability of having a heart attack over the next 10 years based on blood pressure, age, gender, cholesterol levels, and smoking. It is a prognostic model used in screening for heart disease risk, to help choose interventions and motivate patients. Various diagnostic classification rules also exist for coronary heart disease. A person presenting at a hospital with chest pain may be having a heart attack, in which case prompt treatment is needed, or may have muscle strain or indigestion-related pain, in which case the clot-dissolving treatments used for heart attacks would be unnecessary and dangerous. The decision can be based on characteristics of the pain,

Biostatistics: A Methodology for the Health Sciences, Second Edition, by Gerald van Belle, Lloyd D. Fisher, Patrick J. Heagerty, and Thomas S. Lumley
ISBN 0-471-03185-2

blood enzyme levels, and electrocardiogram abnormalities. Finally, for research purposes it is often necessary to find cases of heart attack from medical records. This retrospective diagnosis can use the same information as the initial diagnosis and later follow-up information, including the doctors' conclusions at the time of discharge from a hospital.

It is useful to separate the classification problem into two steps:

1. Estimate the probability p_k that $Y = k$.
2. Choose a predicted class based on these probabilities.

It might appear that the second step is simply a matter of choosing the most probable class, but this need not be the case when the consequences of making incorrect decisions depend on the decision. For example, in cancer screening a *false positive*, calling for more investigation of what turns out not to be cancer, is less serious than a *false negative*, missing a real case of cancer. About 10% of women are recalled for further testing after a mammogram [Health Canada, 2001], but the great majority of these are false positives and only 6 to 7% of these women are diagnosed with cancer.

The consequences of misclassification can be summarized by a *loss function* $L(j, k)$, which gives the relative seriousness of choosing class j when in fact class k is the correct one. The loss function is defined to be zero for a correct decision and positive for incorrect decisions. If $L(j, k)$ has the same value for all incorrect decisions, the correct strategy is to choose the most likely class. In some cases these losses might be actual monetary costs; in others the losses might be probabilities of dying as a result of the decision, or something less concrete. What the theory requires is that a loss of 2 is twice as bad as a loss of 1. In Note 13.3 we discuss some of the practical and philosophical issues involved in assigning loss functions.

Finally, the expected proportion in each class may not be the same in actual use as in training data. This imbalance may be deliberate: If some classes are very rare, it will be more efficient if they are overrepresented in the training data. The imbalance may also be due to a variation in frequency of classes between different times or places; for example, the relative frequency of common cold and influenza will depend on the season. We will write π_k for the expected proportion in class k if it is specified separately from the training data. These are called *prior probabilities*.

Given a large enough training set, the classification problem is straightforward (assume initially that we do not have separately specified proportions π_k). For any new observations with characteristics $x_1, \ldots, x_p$, we find all the observations in the training set that have exactly the same characteristics and estimate p_k, the probability of being in class k, as the proportion of these observations that are in class k.

Now that we have probabilities for each class k, we can compute the expected loss for each possible decision. Suppose that there are two classes and we decide on class 1. The probability that we are correct is p_1, in which case there is no loss. The probability that we are incorrect is p_2, in which case the loss is $L(1, 2)$. So the expected loss is $0 \times p_1 + L(1, 2) \times p_2$. Conversely, if we decide on class 2, the expected loss is $L(2, 1) \times p_1 + 0 \times p_2$. We should choose whichever class has the lower expected loss. Even though we are assuming unlimited amounts of training data, the expected loss will typically not be zero. Problems where the loss can be reduced to zero are called *noiseless*. Medical prediction problems are typically very noisy.

Bayes' theorem, discussed in Chapter 6, now tells us how to incorporate separately specified expected proportions (*prior probabilities*) into this calculation: We simply multiply p_1 by π_1, p_2 by π_2, and so on. The expected loss from choosing class 1 is $0 \times p_1 \times \pi_1 + L(1, 2) \times p_2 \times \pi_2$.

Classification is more difficult when we do not have enough training data to use this simple approach to estimation, or when it is not feasible to keep the entire training set available for making predictions. Unfortunately, at least one of these limitations is almost always present. In this chapter we consider only the first problem, the most important in biostatistical applications. It is addressed by building regression models to estimate the probabilities p_k and then following the same strategy as if p_k were known. The accuracy of prediction, and thus the actual average

loss, will be greater than in our ideal setting. The error rates in the ideal setting give a lower bound on the error rates attainable by any model; if these are low, improving a model may have a large payoff; if they are high, no model can predict well and improvements in the model may provide little benefit in error rates.

13.3 SIMPLE CLASSIFICATION MODELS

Linear and logistic models for classification have a long history and often perform reasonably well in clinical and epidemiologic classification problems. We describe them for the case of two classes, although versions for more than two classes are available. Linear and logistic discrimination have one important restriction in common: They separate the classes using a linear combination of the characteristics.

13.3.1 Logistic Regression

Example 13.1. Pine et al. [1983] followed patients with intraabdominal sepsis (blood poisoning) severe enough to warrant surgery to determine the incidence of organ failure or death (from sepsis). Those outcomes were correlated with age and preexisting conditions such as alcoholism and malnutrition. Table 13.1 lists the patients with the values of the associated variables. There are 21 deaths in the set of 106 patients. Survival status is indicated by the variable Y. Five potential predictor variables: shock, malnutrition, alcoholism, age, and bowel infarction were labeled X_1, X_2, X_3, X_4, and X_5, respectively. The four variables X_1, X_2, X_3, and X_5 were binary variables, coded 1 if the symptom was present and 0 if absent. The variable $X_4 =$ age in years, was retained as a continuous variable. Consider for now just variables Y and X_1; a 2×2 table could be formed as shown in Table 13.2.

With this single variable we can use the simple approach of matching new observations exactly to the training set. For a patient with shock, we would estimate a probability of death of $7/10 = 0.70$; for a patient without shock, we would estimate a probability of $14/96 = 0.15$.

Once we start to incorporate the other variables, this simple approach will break down. Using all four binary variables would lead to a table with 2^5 cells, and each cell would have too few observations for reliable estimates. The problem would be enormously worse when age is added to the model—there might be no patient in our training set who was an exact match on age.

We clearly need a way to simplify the model. One approach is to assume that to a reasonable approximation, the effect of one variable does not depend on the values of other variables, leading to a linear regression model:

$$P(\text{death}) = \pi = \alpha + \beta_1 X_1 + \beta_2 X_2 + \cdots + \beta_5 X_5$$

This model is unlikely to be ideal: If having shock increases the risk of death by 0.55, and the probability can be no larger than 1, the effects of other variables are severely limited. For this reason it is usual to transform the probability to a scale that is not limited by 0 and 1.

The most common reexpression of π leads to the logistic model

$$\log_e \frac{\pi}{1-\pi} = \alpha + \beta_1 X_1 + \beta_2 X_2 + \cdots + \beta_5 X_5 \tag{1}$$

commonly written as

$$\text{logit}(\pi) = \alpha + \beta_1 X_1 + \beta_2 X_2 + \cdots + \beta_5 X_5 \tag{2}$$

Table 13.1 Survival Status of 106 Patients Following Surgery and Associated Preoperative Variables[a]

ID	Y	X_1	X_2	X_3	X_4	X_5	ID	Y	X_1	X_2	X_3	X_4	X_5
1	0	0	0	0	56	0	301	1	0	1	0	50	1
2	0	0	0	0	80	0	302	0	0	0	0	20	0
3	0	0	0	0	61	0	303	0	0	0	0	74	1
4	0	0	0	0	26	0	304	0	0	0	0	54	0
5	0	0	0	0	53	0	305	1	0	1	0	68	0
6	1	0	1	0	87	0	306	0	0	0	0	25	0
7	0	0	0	0	21	0	307	0	0	0	0	27	0
8	1	0	0	1	69	0	308	0	0	0	0	77	0
9	0	0	0	0	57	0	309	0	0	1	0	54	0
10	0	0	1	0	76	0	401	0	0	0	0	43	0
11	1	0	0	1	66	1	402	0	0	1	0	27	0
12	0	0	0	0	48	0	501	1	0	1	1	66	1
13	0	0	0	0	18	0	502	0	0	1	1	47	0
14	0	0	0	0	46	0	503	0	0	0	1	37	0
15	0	0	1	0	22	0	504	0	0	1	0	36	1
16	0	0	1	0	33	0	505	1	1	1	0	76	0
17	0	0	0	0	38	0	506	0	0	0	0	33	0
19	0	0	0	0	27	0	507	0	0	0	0	40	0
20	1	1	1	0	60	1	508	0	0	1	0	90	0
22	0	0	0	0	31	0	510	0	0	0	1	45	0
102	0	0	0	0	59	1	511	0	0	0	0	75	0
103	0	0	0	0	29	0	512	1	0	0	1	70	1
104	0	1	0	0	60	0	513	0	0	0	0	36	0
105	1	1	0	0	63	1	514	0	0	0	1	57	0
106	0	0	0	0	80	0	515	0	0	1	0	22	0
107	0	0	0	0	23	0	516	0	0	0	0	33	0
108	0	0	0	0	71	0	518	0	0	1	0	75	0
110	0	0	0	0	87	0	519	0	0	0	0	22	0
111	1	1	1	0	70	0	520	0	0	1	0	80	0
112	0	0	0	0	22	0	521	1	0	1	0	85	0
113	0	0	0	0	17	0	523	0	0	1	0	90	0
114	1	0	0	1	49	0	524	1	0	0	1	71	0
115	0	1	0	0	50	0	525	0	0	0	1	51	0
116	0	0	0	0	51	0	526	1	0	1	1	67	0
117	0	0	1	1	37	0	527	0	0	1	0	77	0
118	0	0	0	0	76	0	529	0	0	0	0	20	0
119	0	0	0	1	60	0	531	0	0	0	0	52	1
120	1	1	0	0	78	1	532	1	1	0	1	60	0
122	0	0	1	1	60	0	534	0	0	0	0	29	0
123	1	1	1	0	57	0	535	0	0	0	0	30	1
202	0	0	0	0	28	1	536	0	0	0	0	20	0
203	0	0	0	0	94	0	537	0	0	0	0	36	0
204	0	0	0	0	43	0	538	0	0	1	1	54	0
205	0	0	0	0	70	0	539	0	0	0	0	65	0
206	0	0	0	0	70	0	540	1	0	0	0	47	0
207	0	0	0	0	26	0	541	0	0	0	0	22	0
208	0	0	0	0	19	0	542	1	0	0	1	69	0
209	0	0	0	0	80	0	543	1	0	1	1	68	0
210	0	0	1	0	66	0	544	0	0	1	1	49	0
211	0	0	1	0	55	0	545	0	0	0	0	25	0
214	0	0	0	0	36	0	546	0	1	1	0	44	0
215	0	0	0	0	28	0	549	0	0	0	1	56	0
217	0	0	0	0	59	1	550	0	0	1	1	42	0

Source: Data from Pine et al. [1983].
[a]See the text for labels.

Table 13.2 2 × 2 Table for Survival by Shock Status

		Y		
		Death	Survive	
X_1		1	0	
Shock	1	7	3	10
No Shock	0	14	82	96
		21	85	106

Four comments are in order:

1. The logit of p has range $(-\infty, \infty)$. The following values can easily be calculated:

$$\text{logit}(1) = +\infty$$
$$\text{logit}(0) = -\infty$$
$$\text{logit}(0.5) = 0$$

2. If we solve for π, the expression that results is

$$\pi = \frac{e^{\alpha+\beta_1 X_1+\cdots+\beta_5 X_5}}{1 + e^{\alpha+\beta_1 X_1+\cdots+\beta_5 X_5}} = \frac{1}{1 + e^{-(\alpha+\beta_1 X_1+\cdots+\beta_5 X_5)}} \tag{3}$$

3. We will write a for the estimate of α, b_1 for the estimate of β_1, and so on. Our estimated probability of death is obtained by inserting these values into equation (3) to get

$$\widehat{P}(\text{death}) = a + b_1 X_1 + b_2 X_2 + \cdots + b_5 X_5$$

4. The estimates are obtained by *maximum likelihood*. That is, we choose the values of a, b_1, b_2, ..., b_5 that maximize the probability of getting the death and survival values that we observed. In the simple situation where we can estimate a probability for each possible combination of characteristics, maximum likelihood gives the same answer as our rule of using the observed proportions. Note 13.1 gives the mathematical details. Any general-purpose statistical program will perform logistic regression.

We can check that with a single variable, logistic regression gives the same results as our previous analysis. In the previous analysis we used only the variable X_1, the presence of shock. If we fit this model to the data, we get

$$\text{logit}(\widehat{\pi}) = -1.768 + 2.615 X_1$$

If $X_1 = 0$ (i.e., there is no shock),

$$\text{logit}(\widehat{\pi}) = -1.768$$

or

$$\widehat{\pi} = \frac{1}{1 + e^{-(-1.768)}} = 0.146$$

If $X_1 = 1$ (i.e., there is shock),

$$\text{logit}(\widehat{\pi}) = -1.768 + 2.615 = 0.847$$

$$\widehat{\pi} = \frac{1}{1 + e^{-0.847}} = 0.700$$

This is precisely the probability of death given no preoperative shock. The coefficient of X_1, 2.615, also has a special interpretation: It is the logarithm of the odds ratio and the quantity $e^{b_1} = e^{2.615} = 13.7$ is the odds ratio associated with shock (as compared to no shock). This can be shown algebraically to be the case (see Problem 13.1).

Example 13.1. (*continued*) We now continue the analysis of the data of Pine et al. listed in Table 13.1. The output and calculations shown in Table 13.3 can be generated for all the variables. We would interpret these results as showing that in the presence of the remaining variables, malnutrition, is not an important predictor of survival status. All the other variables are significant predictors of survival status. All but variable X_4 are discrete binary variables. If malnutrition is dropped from the analysis, the estimates and standard errors are as given in Table 13.4.

If $\widehat{\pi}$ is the predicted probability of death, the equation is

$$\text{logit}(\widehat{\pi}) = -8.895 + 3.701X_1 + 3.186X_3 + 0.08983X_4 + 2.386X_5$$

For each of the values of X_1, X_3, X_5 (a total of eight possible combinations), a regression curve can be drawn for logit($\widehat{\pi}$) vs. age. In Figure 13.1 the lines are drawn for each of the eight combinations. For example, corresponding to $X_1 = 1$ (shock present), $X_3 = 0$ (no alcoholism), and $X_5 = 0$ (no infarction), the line

Table 13.3 Logistic Regression for Example 13.1

Variable	Regression Coefficient	Standard Error	Z-Value	p-Value
Intercept	−9.754	2.534	—	—
X_1 (shock)	3.674	1.162	3.16	0.0016
X_2 (malnutrition)	1.217	0.7274	1.67	0.095
X_3 (alcoholism)	3.355	0.9797	3.43	0.0006
X_4 (age)	0.09215	0.03025	3.04	0.0023
X_5 (infarction)	2.798	1.161	2.41	0.016

Table 13.4 Estimates and Standard Errors for Example 13.1

Variable	Regression Coefficient	Standard Error
Intercept	−8.895	2.314
X_1 (shock)	3.701	1.103
X_3 (alcoholism)	3.186	0.9163
X_4 (age)	0.08983	0.02918
X_5 (infarction)	2.386	1.071

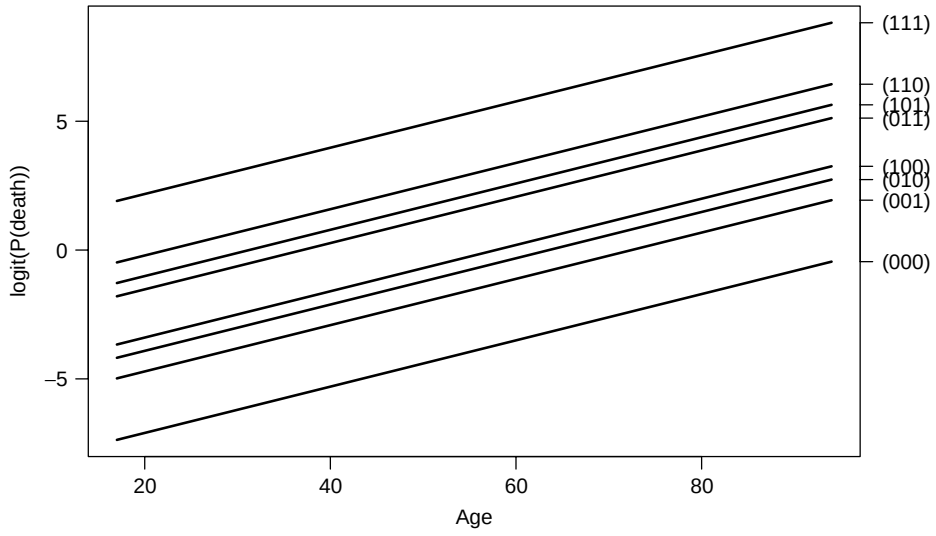


Figure 13.1 Logit of estimated probability of death as a function of age in years and category of status of (X_1, X_3, X_5). (Data from Pine et al. [1983].)

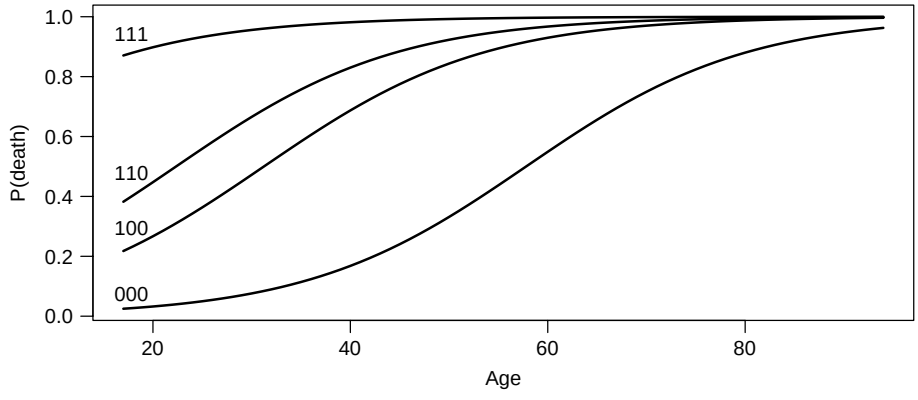


Figure 13.2 Estimated probability of death as a function of age in years and selected values of (X_1, X_3, X_5). (Data from Pine et al. [1983].)

$$\begin{aligned}\text{logit}(\widehat{\pi}) &= -8.895 + 3.701 + 0.08983X_4 \\ &= -5.194 + 0.08983X_4\end{aligned}$$

is drawn.

This line is indicated by "(100)" as a shorthand way of writing $(X_1 = 1, X_3 = 0, X_5 = 0)$. The eight lines seem to group themselves into four groups: the top line representing all three symptoms present; the next three lines, groups with two symptoms present; the next three lines, groups with one symptom present; and finally, the group at lowest risk with no symptoms present. In Figure 13.2 the probability of death is plotted on the original probability scale; only four of the eight groups have been graphed. The group at highest risk is the one with all three binary risk factors present. One of the advantages of the model is that we can draw a curve for

the situation with all three risk factors present even though there are no patients in that category; but the estimate depends on the model. The curve is drawn on the assumption that the risks are additive in the logistic scale (that is what we *mean* by a linear model). This assumption can be partially tested by including interaction terms involving these three covariates in the model and testing their significance. When this was done, none of the interaction terms were significant, suggesting that the additive model is a reasonable one. Of course, as there are no patients with all three risk factors present, there is no way to perform a complete test of the model.

13.3.2 Linear Discrimination

The first statistical approach to classification, as with so many other problems, was invented by R. A. Fisher. Fisher's linear discriminant analysis is designed for continuous characteristics that have a normal distribution (in fact, a multivariate normal distribution; any sums or differences of multiples of the variables should be normally distributed).

Definition 13.1. A set of random variables $X_1, \ldots, X_k$ is *multivariate normal* if every linear combination of $X_1, \ldots, X_k$ has a normal distribution.

In addition, we assume that the variances and covariances of the characteristics are the same in the two groups. Under these assumptions, Fisher's method finds a combination of variables (a *discriminant function*) for distinguishing the classes:

$$\Delta = \alpha + \beta_1 X_1 + \beta_2 X_2 + \cdots + \beta_p X_p$$

Assuming equal losses for different errors, an observation is assigned to class 1 if $\Delta > 0$ and class 2 if $\Delta < 0$. Estimation of the parameters β again uses maximum likelihood. It is also possible to compute probabilities p_k for membership of each class using the normal cumulative distribution function: $p_1 = \Phi(\Delta)$, $p_2 = 1 - \Phi(\Delta)$, where Φ is the symbol for the cumulative normal distribution.

Because linear discrimination makes more assumptions about the structure of the X's than logistic regression does, it gives more precise estimates of its parameters and more precise predictions [Efron, 1975]. However, in most medical examples the uncertainty in the parameters is a relatively small component of the overall prediction error, compared to model uncertainty and to the inherent unpredictability of human disease. In addition to requiring extra assumptions to hold, linear discrimination is likely to give substantial improvements only when the characteristics determine the classes very accurately so that the main limitation is the accuracy of statistical estimation of the parameters (i.e., a nearly "noiseless" problem).

The robustness can be explained by considering another equivalent way to define Δ. Let D_1 and D_2 be the mean of Δ in groups 1 and 2, respectively, and V be the variance of Δ within each group (assumed to be the same). Δ is the linear combination that maximizes

$$\frac{(D_1 - D_2)^2}{V}$$

the ratio of the between-group and within-group variances.

Truett et al. [1967] applied discriminant analysis to the data of the Framingham study. This was a longitudinal study of the incidence of coronary heart disease in Framingham, Massachusetts. In their prediction model the authors used continuous variables such as age (years) and serum cholesterol (mg/100 mL) as well as discrete or categorical variables such as cigarettes per day (0 = never smoked, 1 = less than one pack a day, 2 = one pack a day, 3 = more than a pack a day) and ECG (0 = normal, 1 = certain kinds of abnormality). It was found that the linear discriminant model gave reasonable predictions. Halperin [1971] came to five

conclusions, which have stood the test of time. If the logistic model holds but the normality assumptions for the predictor variables are violated, they concluded that:

1. β_i that are zero will tend to be estimated as zero for large samples by the method of maximum likelihood but not necessarily by the discrimination function method.
2. If any β_i are nonzero, they will tend to be estimated as nonzero by either method, but the discriminant function approach will give asymptotically biased estimates for those β_i and for α.
3. Empirically, the assessment of significance for a variable, as measured by the ratio of the estimated coefficient to its estimated standard error, is apt to be about the same whichever method is used.
4. Empirically, the maximum likelihood method usually gives slightly better fits to the model as evaluated from observed and expected numbers of cases per decile of risk.
5. There is a theoretical basis for the possibility that the discriminant function will give a very poor fit even if the logistic model holds.

Some of these empirical conclusions are supported theoretically by Li and Duan [1989] and Hall and Li [1993], who considered situations similar to this one, where a linear combination

$$\Delta = \beta_1 X_1 + \beta_2 X_2 + \cdots + \beta_p X_p$$

is to be estimated under either of two models. They showed that under some assumptions about the distribution of variables X, using the wrong model would typically lead to estimating

$$\Delta = c\beta_1 X_1 + c\beta_2 X_2 + \cdots + c\beta_p X_p$$

for some constant c. When these conditions apply, using linear discrimination would tend to lead to a similar discriminant function Δ but to poor estimation of the actual class probabilities. See also Knoke [1982]. Problems 13.4, 13.6, and 13.7 address some of these issues.

In the absence of software specifically designed for this method, linear discrimination can be performed with software for linear regression. The details, which are of largely historical interest, are given in Note 13.4.

13.4 ESTIMATING AND SUMMARIZING ACCURACY

When choosing between classification models or describing the performance of a model, it is necessary to have some convenient summaries of the error rates. It is usually important to distinguish between different kinds of errors, although occasionally a simple estimate of the expected loss will suffice.

Statistical methodology is most developed for the case of two classes. In biostatistics, these are typically presence and absence of disease.

13.4.1 Sensitivity and Specificity

In assigning people to two classes (disease and no disease) we can make two different types of error:

1. Detecting disease when none is present
2. Missing disease when it is there

As in Chapter 6, we define the *sensitivity* as the probability of detecting disease given that disease is present (avoiding an error of the first kind) and *specificity* as the probability of not detecting disease given that no disease is present (avoiding an error of the second kind).

The sensitivity and specificity are useful because they can be estimated from separate samples of persons with and without disease, and because they often generalize well between populations. However, in actual use of a classification rule, we care about the probability that a person has disease given that disease was detected (the *positive predictive value*) and the probability that a person is free of disease given that no disease was detected (the *negative predictive value*).

It is a common and serious error to confuse the sensitivity and the positive predictive value. In fact, for a reasonably good test and a rare disease, the positive predictive value depends almost entirely on the disease prevalence and on the specificity. Consider the mammography example mentioned in Section 13.2. Of 1000 women who have a mammogram, about 100 will be recalled for further testing and 7 of those will have cancer. The positive predictive value is 7%, which is quite low, not because the sensitivity of the mammogram is poor but because 93 of those 1000 women are falsely testing positive. Because breast cancer is rare, false positives greatly outnumber true positives, regardless of how sensitive the test is.

When a single binary characteristic is all that is available, the sensitivity and specificity describe the properties of the classification rule completely. When classification is based on a summary criterion such as the linear discriminant function, it is useful to consider the sensitivity and specificity based on a range of possible thresholds.

Example 13.2. Tuberculosis testing is important in attempts to control the disease, which can be quite contagious but in most countries is still readily treatable with a long course of antibiotics. Tests for tuberculosis involve injecting a small amount of antigen under the skin and looking for an inflamed red area that appears a few days later, representing an active T-cell response to the antigen. The size of this indurated area varies from person to person both because of variations in disease severity and because of other individual factors. Some people with HIV infection have no reaction even with active tuberculosis (a state called *anergy*). At the other extreme, migrants from countries where the BCG vaccine is used will have a large response irrespective of their actual disease status (and since the vaccine is incompletely effective, they may or may not have disease).

The diameter of the indurated area is used to classify people as disease-free or possibly infected. It is important to detect most cases of TB (high sensitivity) without too many false positives being subjected to further investigation and unnecessary treatment (high positive predictive value). The diameter used to make the classification varies depending on characteristics of the patient. A 5-mm induration is regarded as positive for close contacts of people with active TB infection or those with chest x-rays suggestive of infection because the prior probability of risk is high. A 5-mm induration is also regarded as positive for people with compromised immune systems due to HIV infection or organ transplant, partly because they are likely to have weaker T-cell responses (so a lower threshold is needed to maintain sensitivity) and partly because TB is much more serious in these people (so the loss for a false negative is higher).

For people at moderately high risk because they are occupationally at higher risk or because they come from countries where TB is common, a 10-mm induration is regarded as positive (their prior probability is moderately elevated). The 10-mm rule is also used for people with poor access to health care or those with diseases that make TB more likely to become active (again, the loss for a false negative is higher in these groups).

Finally, for everyone else, a 15-mm threshold is used. In fact, the recommendation is that they typically not even be screened, implicitly classifying everyone as negative.

Given a continuous variable predicting disease (whether an observed characteristic or a summary produced by logistic or linear discrimination), we would like to display the sensitivity and specificity not just for one threshold but for all possible thresholds. The *receiver operating characteristic* (ROC) *curve* is such a display. It is a graph with "sensitivity" on the y-axis and "1 − specificity" on the x-axis, evaluated for each possible threshold.

If the variable is completely independent of disease, the probability of detecting disease will be the same for people with and without disease, so "sensitivity" and "1 − specificity"

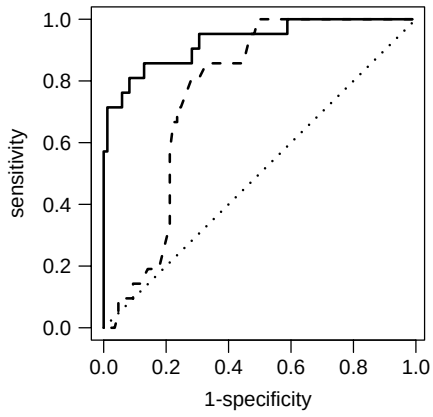


Figure 13.3 Receiver operating characteristic curve for data of Pine et al. [1983]. The solid line is the prediction from all five variables; the dashed line is the prediction from age alone.

will be the same. This is indicated by a diagonal line in Figure 13.3. If higher values of the variable are associated with higher risks of disease, the curve will lie above the diagonal line. By convention, if lower values of the variable are associated with higher risks of disease, the variable is transformed to reverse this, so ROC curves should always lie above the diagonal line.

The area under the ROC curve is a measure of how well the variable discriminates a disease state: If you are given one randomly chosen person with disease and one randomly chosen person without disease, the area under the ROC curve is the probability that the person with disease has the higher value of the variable. The area under the ROC curve is a good analog for binary data of the r^2 value for linear models.

Drawing the ROC curve for two classification rules allows you to compare their accuracy at a range of different thresholds. It might be, for example, that two rules have very different sensitivity when their specificity is low but very similar sensitivity when their specificity is high. In that case, the rules would be equivalently useful in screening low-risk populations, where specificity must be high, but might be very different in clinical diagnostic use.

13.4.2 Internal and External Error Rates

The *internal* or *apparent* or *training* or *in-sample error rates* are those obtained on the same data as those used to fit the model. These always underestimate the true error rate, sometimes very severely. The underestimation becomes more severe when many characteristics are available for modeling, when the model is very flexible in form, and when the data are relatively sparse.

An extreme case is given by a result from computer science called the *perceptron capacity bound* [Cover, 1965]. Suppose that there are d continuous characteristics and n observations from two classes in the training set, and suppose that the characteristics are purely random, having no real association whatsoever with the classes. The probability of obtaining an in-sample error rate of zero for some classification rule based on a single linear combination of characteristics is then approximately

$$1 - \Phi\left(\frac{n - 2d}{\sqrt{n}}\right)$$

If d is large and $n/d < 2$, this probability will be close to 1. Even without considering nonlinear models and interactions between characteristics, it is quite possible to obtain an apparent error rate of zero for a model containing no information whatsoever. Note that $n/d > 2$ does not guarantee a good in-sample estimate of the error rate; it merely rules out this worst possible case.

Estimates of error rates are needed for model selection and in guiding the use of classification models, so this is a serious problem. The only completely reliable solution is to compute the error rate on a completely new sample of data, which is often not feasible.

When no separate set of data will be available, there are two options:

1. Use only part of the data for building the model, saving out some data for testing.
2. Use all the data for model building and attempt to estimate the true error rate statistically.

Experts differ on which of these is the best strategy, although the majority probably leans toward the second strategy. The first strategy has the merit of simplicity and requires less programming expertise. We discuss one way to estimate the true error rate, cross-validation, and one way to choose between models without a direct error estimate, the Akaike information criterion.

13.4.3 Cross-Validation

Statistical methods to estimate true error rate are generally based on the idea of refitting a model to part of the data and using the refitted model to estimate the error rate on the rest of the data. Refitting the model is critical so that the data left out are genuinely independent of the model fit. It is important to note that refitting ideally means redoing the entire model selection process, although this is feasible only when the process was automated in some way.

In *10-fold cross-validation*, the most commonly used variant, the data are randomly divided into 10 equal pieces. The model is then refitted 10 times, each time with one of the 10 pieces left out and the other nine used to fit the model. The classification errors (either the expected loss or the false positive and false negative rates) are estimated for the left-out data from the refitted model. The result is an estimate of the true error rate, since each observation has been classified using a model fitted to data not including that observation. Clearly, 10-fold cross-validation takes 10 times as much computer time as a single model selection, but with modern computers this is usually negligible. Cross-validation gives an approximately unbiased estimate of the true error rate, but a relatively noisy one.

13.4.4 Akaike's Information Criterion

Akaike's information criterion (AIC) [Akaike, 1973] is an asymptotic estimate of expected loss for a particular loss function, one that is proportional to the logarithm of the likelihood. It is extremely simple to compute but can only be used for models fitted by maximum likelihood and requires great caution when used to compare models fitted by different modeling techniques. In the case of linear regression, model selection with AIC is equivalent to model selection with Mallow's C_p, discussed in Chapter 11, so it can be seen as a generalization of Mallow's C_p to nonlinear models.

The primary difficulty in model selection is that increasing the number of variables always decreases the apparent error rate even if the variables contain no useful information. The AIC is based on the observation that for one particular loss function, the log likelihood, the decrease depends only on the number of variables added to the model. If a variable is uninformative, it will on average increase the log likelihood by 1 unit. When comparing model A to model B, we can compute

$$\log(\text{likelihood of A}) - \log(\text{likelihood of B})$$
$$-(\text{no. parameters in A} - \text{no. parameters in B}) \tag{4}$$

If this is positive, we choose model A, if it is negative we choose model B. The AIC is most often defined as

$$\text{AIC} = -2\log(\text{likelihood of model}) + 2(\text{no. parameters in model}) \tag{5}$$

so that choosing the model with the lower AIC is equivalent to our strategy based on equation (4). Sometimes the AIC is defined without the factor of −2, in which case the largest value indicates the best model: It is important to check which definition is being used.

Akaike showed that given two fixed models and increasing amounts of data, this criterion would eventually pick the best model. When the number of candidate models is very large, like the 2^p models in logistic regression with p characteristics, AIC still tends to overfit to some extent. That is, the model chosen by the AIC tends to have more variables than the best model.

In principle, the AIC can be used to compare models fitted by different techniques, but caution is needed. The log likelihood is only defined up to adding or subtracting an arbitrary constant, and different programs or different procedures within the same program may use different constants for computational convenience. When comparing models fitted by the same procedure, the choice of constant is unimportant, as it cancels out of the comparison. When comparing models fitted by different procedures, the constant does matter, and it may be difficult to find out what constant has been used.

13.4.5 Automated Stepwise Model Selection

Automated stepwise model selection has a deservedly poor reputation when the purpose of a model is causal inference, as model choice should then be based on a consideration of the probable cause-and-effect relationships between variables. When modeling for prediction, however, this is unimportant: We do not need to know *why* a variable is predictive to know that it *is* predictive.

Most statistical packages provide tools that will automatically consider a set of variables and attempt to find the model that gives the best prediction. Some of these use AIC, but more commonly they use significance testing of predictors. Stepwise model selection based on AIC can be approximated by significance-testing selection using a critical p-value of 0.15.

Example 13.3. We return to the data of Pine et al. [1983] and fit a logistic model by stepwise search, optimizing the AIC. We begin with a model using none of the characteristics and giving the same classification for everyone. Each of the five characteristics is considered for adding to the model, and the one optimizing the AIC is chosen. At subsequent steps, every variable is considered either for adding to the model or for removal from the model. The procedure stops when no change improves the AIC.

This procedure is not guaranteed to find the best possible model but can be carried out much more quickly than an exhaustive search of all possible models. It is at least as good as, and often better than, forward or backward stepwise procedures that only add or only remove variables.

Starting with an empty model the possible changes were as follows:

	d.f.	Deviance	AIC		d.f.	Deviance	AIC
+ X4	1	90.341	94.341	+ X5	1	97.877	101.877
+ X1	1	91.977	95.977	+ X2	1	99.796	103.796
+ X3	1	95.533	99.533	<none>		105.528	107.528

The d.f. column counts the number of degrees of freedom for each variable (in this case, one for each variable, but more than one if a variable had multiple categories). The deviance is −2 log likelihood. The best (lowest AIC) choice was to add X4 (age). In the second step, X1 (shock) was added, and then X3 (alcoholism). The possible changes in the fourth step were:

	d.f.	Deviance	AIC		d.f.	Deviance	AIC
+ X5	1	56.073	66.073	− X4	1	76.970	82.970
<none>		61.907	69.907	− X3	1	79.088	85.088
+ X2	1	60.304	70.304	− X1	1	79.925	85.925

Table 13.5 Step 1 Using Linear Discrimination

	d.f.	SS	RSS	AIC
+ X1	1	2.781	14.058	−210.144
+ X4	1	2.244	14.596	−206.165
+ X3	1	1.826	15.014	−203.172
+ X5	1	1.470	15.370	−200.691
+ X2	1	0.972	15.867	−197.312
<none>			16.840	−193.009

Table 13.6 Subsequent Steps Using Linear Discrimination

	d.f.	SS	RSS	AIC
<none>			10.031	−239.922
+ X2	1	0.164	9.867	−239.673
− X5	1	0.733	10.764	−234.447
− X4	1	0.919	10.950	−232.627
− X3	1	1.733	11.764	−225.029
− X1	1	2.063	12.094	−222.095

and the lowest AIC came with adding X5 (infarction) to the model. Finally, adding X2 also reduced the AIC, and no improvement could be obtained by deleting a variable, so the procedure terminated. The model minimizing AIC uses all five characteristics.

We can perform the same classification using linear discrimination. The characteristics clearly do not have a multivariate normal distribution, but it will be interesting to see how well the robustness of the methods stands up in this example.

At the first step we have the data shown in Table 13.5.

For this linear model the residual sum of squares and the change in residual sum of squares are given and used to compute the AIC. The first variable added is X1. In subsequent steps X3, X4, and X5 are added, and then we have the data shown in Table 13.6.

The procedure ends with a model using the four variables X1, X3, X4, and X5. The fifth variable (malnutrition) is not used. We can now compare the fitted values from the two models shown in Figure 13.4. It is clear that both discriminant functions separate the surviving and dying patients very well and that the two functions classify primarily the same people as being at high risk. Looking at the ROC curves suggests that the logistic discriminant function is very slightly better, but this conclusion could not be made reliably without independent data.

13.5 MODERN CLASSIFICATION TECHNIQUES

Most modern classification techniques are similar in spirit to automated stepwise logistic regression. A computer search is made through a very large number of possible models for p_k, and a criterion similar to AIC or an error estimate similar to cross-validation is used to choose a model. All these techniques are capable of approximating any relationship between p_k and X arbitrarily well, and as a consequence will give very good prediction if n is large enough in relation to p.

Modern classification techniques often produce "black-box" classifiers whose internal structure can be difficult to understand. This need not be a drawback: As the models are designed for prediction rather than inference about associations, the opaqueness of the model reduces the

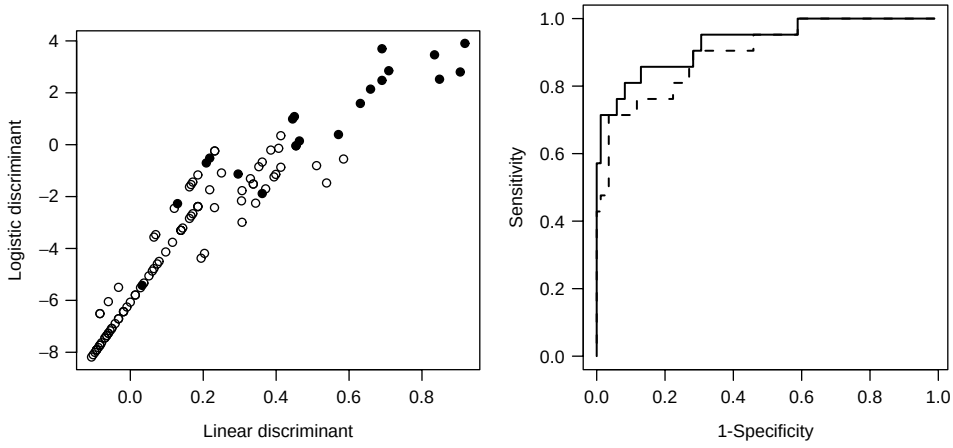


Figure 13.4 Comparison of discriminant functions and ROC curves from logistic and linear models for data of Pine et al. [1983]. Solid circles are deaths; open circles are survival. The solid line is the logistic model; the dashed line is the linear model.

temptation to leap to unjustified causal conclusions. On the other hand, it can be difficult to decide which variables are important in the classification and how strongly the predictions have been affected by outliers. There is some current statistical research into ways of opening up the black box, and techniques may become available over the next few years.

At the time of writing, general-purpose statistical packages often have little classification functionality beyond logistic and linear discrimination. It is still useful for the nonspecialist to understand the concepts behind some of these techniques; we describe two samples.

13.5.1 Recursive Partitioning

Recursive partitioning is based on the idea of classifying by making repeated binary decisions. A *classification tree* such as the left side of Figure 13.5 is constructed step by step:

1. Search every value c of every variable X for the best possible prediction by $X > c$ vs. $X \leq c$.
2. For each of the two resulting subsets of the data, repeat step 1.

In the tree displayed, each split is represented by a logical expression, with cases where the expression is true going left and others going right, so in the first split in Figure 13.5 the cases with white blood cell counts below 391.5 mL^{-1} go to the left.

An exhaustive search procedure such as this is sure to lead to overfitting, so the tree is then *pruned* by snipping off branches. The pruning is done to minimize a criterion similar to AIC:

$$\text{loss} + \text{CP} \times \text{number of splits}$$

The value of CP, called the *cost-complexity penalty*, is most often chosen by 10-fold cross-validation (Section 13.4.3). Leaving out 10% of the data, a tree is grown and pruned with many different values of CP. For each tree pruned, the error rate is computed on the 10% of data left out. This is repeated for each of the ten 10% subsets of the data. The result is a cross-validation estimate of the loss (error rate) for each value of CP, as in the right-hand side of Figure 13.5.

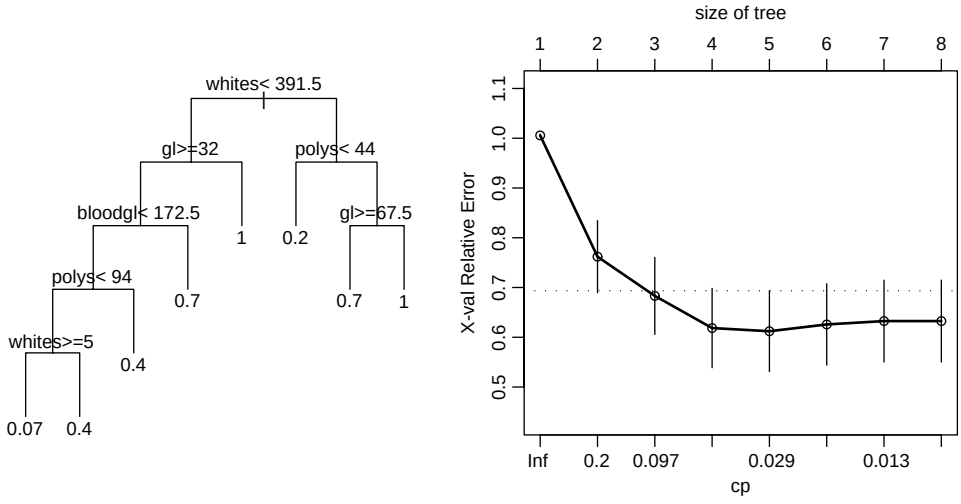


Figure 13.5 Classification tree and cross-validated error rates for differential diagnosis of acute meningitis.

Because cross-validation is relatively noisy (see the standard error bars on the graph), we choose the largest CP (smallest tree) that gives an error estimate within one standard error of the minimum, represented by the horizontal dotted line on the graph.

Example 13.4. In examining these methods we use data from Spanos et al. [1989], made available by Frank Harrell at a site linked from the Web appendix to the chapter. The classification problem is to distinguish viral from bacterial meningitis, based on a series of 581 patients treated at Duke University Medical Center. As immediate antibiotic treatment for acute bacterial meningitis is often life-saving, it is important to have a rapid and accurate initial classification. The definitive classification based on culturing bacteria from cerebrospinal fluid samples will take a few days to arrive. In some cases bacteria can be seen in the cerebrospinal fluid, providing an easy decision in favor of bacterial meningitis with good specificity but inadequate sensitivity.

The initial analysis used logistic regression together with transformations of the variables, but we will explore other possibilities. We will use the following variables:

- *AGE*: in years
- *SEX*
- *BLOODGL*: glucose concentration in blood
- *GL*: glucose concentration in cerebrospinal fluid
- *PR*: protein concentration in cerebrospinal fluid
- *WHITES*: white blood cells per milliliter of cerebrospinal fluid
- *POLYS*: % of white blood cells that are polymorphonuclear leukocytes
- *GRAM*: result of Gram smear (bacteria seen under microscope): 0 negative, > 0 positive
- *ABM*: 1 for bacterial, 0 for viral meningitis

The original analysis left GRAM out of the model and used it only to override the predicted classification if GRAM > 0. This is helpful because the variable is missing in many cases, and because the decision to take a Gram smear appears to be related to suspicion of bacterial meningitis.

In the resulting tree, each *leaf* is labeled with the probability of bacterial meningitis for cases ending up in that leaf. Note that they range from 1 down to 0.07, so that in some cases bacterial meningitis is almost certain, but it is harder to be certain of viral meningitis.

It is interesting to note what happens when Gram smear status is added to the variable list for growing a tree. It is by far the most important variable, and prediction error is distinctly reduced. On the other hand, bacterial meningitis is predicted not only in those whose Gram smear is positive, but also in those whose Gram smear is negative. Viral meningitis is predicted only in a subset of those whose Gram smear is missing. If the goal of the model were to classify the cases retrospectively from hospital records, this would not be a problem. However, the original goal was to construct a diagnostic tool, where it is undesirable to have the prediction strongly dependent on another physician choice. Presumably, the Gram smear was being ordered based on other information available to the physician but not to the investigators.

Classification trees are particularly useful where there are strong interactions between characteristics. Completely different variables can be used to split each subset of the data. In our example tree, blood glucose is used only for those with high white cell counts and high glucose in the cerebrospinal fluid. This ability is particularly useful when there are missing data.

On the other hand, classification trees do not perform particularly well when there are smooth gradients in risk with a few characteristics. For example, the prediction of acute bacterial meningitis can be improved by adding a new variable with the ratio of blood glucose to cerebrospinal fluid glucose.

The best known version of recursive partitioning, and arguably the first to handle overfitting carefully, is the CART algorithm of Breiman et al. [1984]. Our analysis used the free "rpart" package [Therneau, 2002], which automates both fitting and the cross-validation analysis. It follows the prescriptions of Breiman et al. [1984] quite closely.

A relatively nontechnical overview of recursive partitioning in biostatistics is given by Zhang and Singer [1999]. More recently, techniques using multiple classification trees (*bagging*, *boosting*, and *random forests*) have become popular and appear to work better with very large numbers of characteristics than do other methods.

13.5.2 Neural Networks

The terminology *neural network* and the original motivation were based on a model for the behavior of biological neurons in the brain. It is now clear that real neurons are much more complicated, and that the fitting algorithms for neural networks bear no detailed relationship to anything happening in the brain. Neural networks are still very useful black-box classification tools, although they lack the miraculous powers sometimes attributed to them.

A computational neuron in a neural net is very similar to a logistic discrimination function. It takes a list of inputs $Z_1, Z_2, \ldots, Z_m$ and computes an output that is a function of a weighted combination of the inputs, such as

$$\text{logit}(\alpha + \beta_1 Z_1 + \cdots + \beta_m Z_m) \tag{6}$$

There are many variations on the exact form of the output function, but this is one widely used variation. It is clear from equation (6) that even a single neuron can reproduce any classification from logistic regression.

The real power of neural network models comes from connecting multiple neurons together in at least two layers, as shown in Figure 13.6. In the first layer the inputs are the characteristics $X_1, \ldots, X_p$. The outputs of these neurons form a "hidden layer" and are used as inputs to the second layer, which actually produces the classification probability p_k.

Example 13.5. A neural net fitted to the acute meningitis data has problems because of missing observations. Some form of imputation or variable selection would be necessary for a

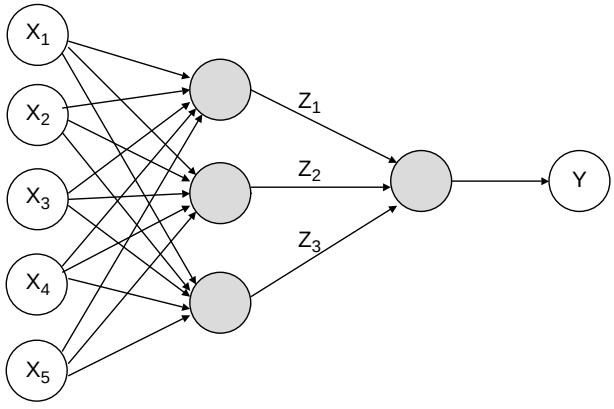


Figure 13.6 Simple neural network with three hidden nodes.

serious analysis of these data. We used the neural network package that accompanies Venables and Ripley [2002], choosing a logistic output function and two hidden nodes (Z_1 and Z_2). That is, the model was

$$\begin{aligned}
\text{logit}(p) &= -0.52 + 2.46Z_1 - 2.31Z_2 \\
\text{logit}(Z_1) &= 0.35 + 0.11\text{POLYS} + 0.58\text{WHITES} - 0.31\text{SEX} + 0.39\text{AGE} \\
&\quad - 0.47\text{GL} - 2.02\text{BLOODGL} - 2.31\text{PR} \\
\text{logit}(Z_2) &= 0.22 + 0.66\text{POLYS} + 0.25\text{WHITES} - 0.06\text{SEX} + 0.31\text{AGE} \\
&\quad + 0.03\text{GL} + 0.33\text{BLOODGL} - 0.02\text{PR}
\end{aligned}$$

The sensitivity of the classification was approximately 50% and the specificity nearly 90%.

Two hidden nodes is the minimum interesting number (one hidden node just provides a transformation of a logistic regression model), and we did not want to use more than this because of the relatively small size of the data set.

NOTES

13.1 Maximum Likelihood for Logistic Regression

The regression coefficients in the logistic regression model are estimated using the maximum likelihood criterion. A full discussion of this topic is beyond the scope of this book, but in this note we outline the procedure for the situation involving one covariate. Suppose first that we have a Bernoulli random variable, Y, with probability function

$$\begin{aligned}
P[Y = 1] &= p \\
P[Y = 0] &= 1 - p
\end{aligned}$$

A mathematical trick allows us to combine these into one expression:

$$P[Y = y] = p^y(1 - p)^{(1-y)}$$

using the fact that any number to the zero power is 1. We observe n values of Y, $y_1, y_2, \ldots, y_n$ (a sequence of zeros and ones). The probability of observing this sequence is proportional to

$$\prod_{j=1}^{n} p^{y_j}(1-p)^{1-y_j} = p^{\Sigma y_j}(1-p)^{n-\Sigma y_j} \tag{7}$$

This quantity is now considered as a function of p and defined to be the likelihood. To emphasize the dependence on p, we write

$$L\left(p|\sum y_j, n\right) = p^{\Sigma y_j}(1-p)^{n-\Sigma y_j} \tag{8}$$

Given the value of $\sum y_j$, what is the "best" choice for a value for p? The maximum likelihood principle states that the value of p that maximizes $L(p|\sum y_j, n)$ should be chosen. It can be shown by elementary calculus that the value of p that maximizes $L(p|\sum y_j, n)$ is equal to $\sum y_j/n$. You will recognize this as the proportion of the n values of Y that have the value 1. This can also be shown graphically; Figure 13.7 is a graph of $L(p|\sum y_j, n)$ as a function of p for the situation $\sum y = 6$ and $n = 10$. Note that the graph has one maximum and that it is not quite symmetrical.

In the logistic regression model the probability p is assumed to be a function of an underlying covariate, X; that is, we model

$$\text{logit}(p) = \alpha + \beta X$$

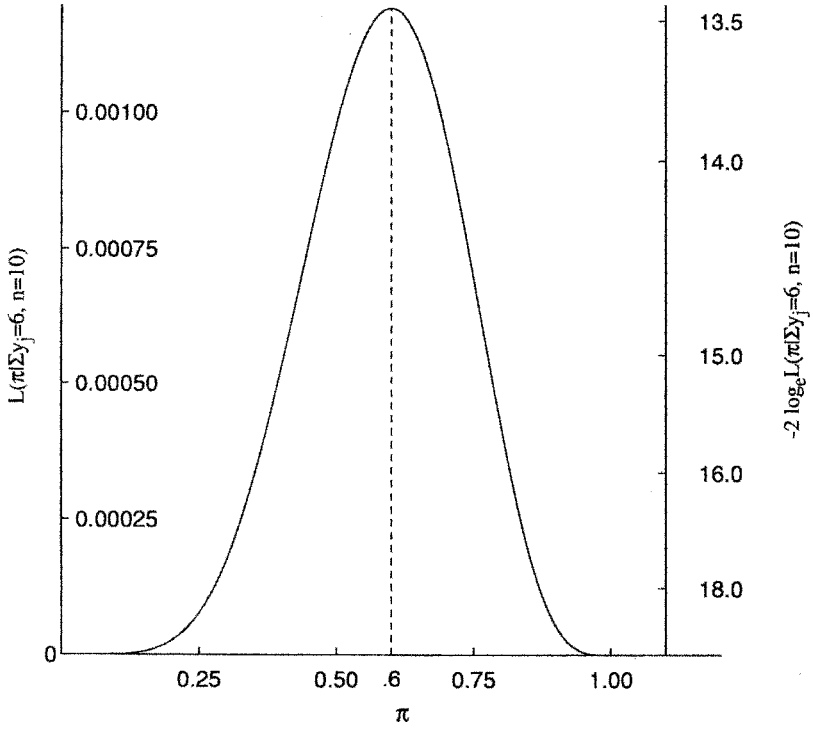


Figure 13.7 Likelihood function, $L(\pi|6, 10)$.

where α and β are constants. Conversely,

$$p = \frac{e^{\alpha+\beta X}}{1+e^{\alpha+\beta X}} = \frac{1}{1+e^{-(\alpha+\beta X)}} \tag{9}$$

For fixed values of X the probability p is determined (since α and β are parameters to be estimated from the data). A set of data now consists of *pairs* of observations: (y_j, x_j), $j = 1, \ldots, n$, where y_j is again a zero–one variable and x_j is an observed value of X for set j. For each outcome, indexed by set j, there is now a probability $p(j)$ determined by the value of x_j. The likelihood function is written

$$L(p(1), \ldots, p(n)|y_1, \ldots, y_n, x_1, \ldots, x_n, n) = \prod_{j=1}^{n} p(j)^{y_j}[1-p(j)]^{1-y_j} \tag{10}$$

but $p(j)$ can be expressed as

$$p(j) = \frac{e^{\alpha+\beta X_j}}{1+e^{\alpha+\beta X_j}} \tag{11}$$

where x_j is the value of the covariate for subject j. The likelihood function can then be written and expressed as a function of α and β as follows:

$$\begin{aligned} L(\alpha, \beta|y_1, \ldots, y_n; x_1, \ldots, x_n; n) &= \prod_{j=1}^{n} \left(\frac{e^{\alpha+\beta x_j}}{1+e^{\alpha+\beta x_j}}\right)^{y_j} \left(\frac{1}{1+e^{\alpha+\beta x_j}}\right)^{1-y_j} \\ &= \prod_{j=1}^{n} \frac{(e^{\alpha+\beta x_j})^{y_j}}{1+e^{\alpha+\beta x_j}} \\ &= \frac{e^{\sum_{j=1}^{n} y_j(\alpha+\beta x_j)}}{\prod_{j=1}^{n}(1+e^{\alpha+\beta x_j})} \end{aligned} \tag{12}$$

The maximum likelihood criterion then requires values for α and β to be chosen so that the likelihood function above is maximized. For more than one covariate, the likelihood function can be deduced similarly.

13.2 Logistic Discrimination with More Than Two Groups

Anderson [1972] and Jones [1975], among others, have considered the case of logistic discrimination with more than two groups. Following Anderson [1972], let for two groups

$$P(G_1|X) = \frac{\exp(\alpha_0 + \alpha_1 X_1 + \cdots + \alpha_p X_p)}{1+\exp(\alpha_0 + \alpha_1 X_1 + \cdots + \alpha_p X_p)}$$

Then

$$P(G_2|X) = \frac{1}{1+\exp(\alpha_0 + \alpha_1 X_1 + \cdots + \alpha_p X_p)}$$

This must be so because $P(G_1|X) + P(G_2|X) = 1$; that is, the observation X belongs to either the G_1 or G_2. For k groups, define

$$P(G_s|X) = \frac{\exp(\alpha_{s0} + \alpha_{s1} X_1 + \cdots + \alpha_{sp} X_p)}{1+\sum_{j=1}^{k-1} \exp(\alpha_{j0} + \alpha_{j1} X_1 + \cdots + \alpha_{jp} X_p)}$$

for groups $s = 1, \ldots, k-1$, and for group G_k, let

$$P(G_k|X) = \frac{1}{1 + \sum_{j=1}^{k-1} \exp(\alpha_{j0} + \alpha_{j1}X_1 + \cdots + \alpha_{jp}X_p)} \tag{13}$$

Most statistical packages provide this analysis, which is often called *polytomous logistic regression* (or occasionally and incorrectly, "polychotomous" logistic regression).

13.3 Defining Losses

In order to say that one prediction is better than another, we need some way to compare the relative importance of false positive and false negative errors. Even looking at total error rate implicitly assigns a relative importance. When the main adverse or beneficial effects are directly comparable, this is straightforward. We can compare the monetary costs of false negatives and false positives, or the probability of death caused by a false positive or false negative. In most cases, however, there will not be direct comparability. When evaluating a cancer screening program, the cost of false negatives is an increase in the risk of death, due to untreated cancer. The cost of a false positive includes the emotional effects and health risks of further testing needed to rule out disease. Even without weighing monetary costs against health costs we can see that it is not clear how many false negatives are worth one false positive. The problem is much more controversial, although perhaps no more difficult when monetary costs are important, as they usually are.

It can be shown [Savage, 1954] that the ability to make consistent choices between courses of action whose outcome is uncertain implies the ability to rate all the possible outcomes on the same scale, so this problem cannot be avoided. Perhaps the most important general guidance we can give is that it is important to recognize that different people will assign different losses and so prefer different classification rules.

13.4 Linear Discrimination Using Linear Regression Software

Given two groups of size n_1 and n_2, it has been shown by Fisher [1936] that the discriminant analysis is equivalent to a multiple regression on the dummy variable Y defined as follows:

$$\begin{aligned} Y &= \frac{n_2}{n_1 + n_2} \text{members of group 1} \\ &= \frac{-n_1}{n_1 + n_2} \text{members of group 2} \end{aligned} \tag{14}$$

We can now treat this as a regression analysis problem. The multiple regression equation obtained will define the regions in the sample space identical to these defined by the discriminant analysis model.

13.5 Cluster Analysis

Cluster analysis is a set of techniques for dividing observations into classes based on a set of characteristics, without the classes being specified in advance. Cluster analysis may be carried out in an attempt to discover classes that are hypothesized to exist but whose structure is unknown, but may also be used simply to create relatively homogeneous subsets of the data.

One application of cluster analysis to clinical epidemiology is in refining the definition of a new syndrome. The controversial *Gulf War syndrome* has been analyzed this way by various authors. Everitt et al. [2002] found five clusters: one *healthy* cluster and four with different distributions of symptoms. On the other hand, Hallman et al. [2003] found only two clusters: healthy and not. Cherry et al. [2001] found six clusters, three of which were relatively healthy

and three representing distinct clusters of symptoms. This lack of agreement suggests that there is little evidence for genuine, strongly differentiated clusters.

Cluster analysis has become more visible in biostatistics in recent years with the rise of genomic data. A popular analysis for RNA expression data is to cluster genes based on their patterns of expression across tissue samples or experimental conditions, following Eisen et al. [1998]. The goal of these analyses is intermediate: The clusters are definitely not biologically meaningful in themselves, but are likely to contain higher concentrations of related genes, thus providing a useful starting point for further searches.

Another very visible example of cluster analysis is given by the Google News service (*http://news.google.com*). Google News extracts news stories from a very large number of traditional newspapers and other sources on the Web and finds clusters that indicate popular topics. The most prominent clusters are then displayed on the Web page.

Cluster analysis has a number of similarities to both factor analysis and principal components analysis, discussed in Chapter 14.

13.6 Predicting Categories of a Continuous Variable

In some cases the categorical outcome being predicted is defined in terms of a continuous variable. For example, low birthweight is defined as birthweight below 2500 g, diabetes may be diagnosed by a fasting blood glucose concentration over 140 mg/dL on two separate occasions, hypertension is defined as blood pressure greater than 140/90 mmHg. An obvious question is whether it is better to predict the categorical variable directly or to predict the continuous variable and then divide into categories.

In contrast to the question of whether a predictor should be dichotomized, to which we can give a clear "no!," categorizing an outcome variable may be helpful or harmful. Using the continuous variable has the advantage of making more information available, but the disadvantage of requiring the model to fit well over the entire range of the response. For example, when fitting a model to (continuous) birthweight, the parameter values are chosen by giving equal weight to a 100-g error at a weight of 4000 g as at 2450 g. When fitting a model to (binary) low birthweight, more weight is placed on errors near 2500 g, where they are more important. See also Problem 13.5.

13.7 Further Reading

Harrell [2001] discusses regression modeling for prediction, including binary outcomes, in a medical context. This is a good reference for semiautomatic modeling that uses the available features of statistical software and incorporates background knowledge about the scientific problem. Lachenbruch [1977] covers discriminant analysis, and Hosmer and Lemeshow [2000] discuss logistic regression for prediction (as well as for inference). Excellent but very technical summaries of modern classification methods are given by Ripley [1996] and Hastie et al. [2001]. Venables and Ripley [2002] describe how to use many of these methods in widely available software. As already mentioned, Zhang and Singer [1999] describe recursive partitioning and its use in health sciences. Two excellent texts on screening are Pepe [2003] and Zhou et al. [2002].

PROBLEMS

13.1 For the logistic regression model $\text{logit}(\pi) = \alpha + \beta X$, where X is a dichotomous 0–1 variable, show that e^{β} is the odds ratio associated with the exposure to X.

13.2 For the data of Table 13.7, the logistic regression model using only the variable X_1, malnutrition, is

$$\text{logit}(\widehat{\pi}) = -0.646 + 1.210X_1$$

Table 13.7 Comparison of Logistic Regression and Linear Regression (One Predictor Variable)

	Logistic Regression	Normal Regression
Dependent variable	Y discrete (binary)	Y continuous
Covariates	X categorical or continuous	X categorical or continuous
Distribution of Y (given X)	Binomial($n\pi$)	Normal(μ, σ^2)
Model	$E(Y) = \pi$	$E(Y) = \mu$
Link to X	$\text{logit}(\pi_j) = \alpha + \beta X_j$	$\mu_j = \alpha + \beta X_j$
Data	$y_1, y_2, \ldots, y_n; x_1, x_2, \ldots, x_n$	$y_1, y_2, \ldots, y_n; x_1, x_2, \ldots, x_n$
Likelihood function (LF)	$\prod_{j=1}^{n} \pi_j^{y_j}(1-\pi_j)^{1-y_j}$ $= \prod_{j=1}^{n} \left(\frac{e^{\alpha+\beta x_j}}{1+e^{\alpha+\beta x_j}}\right)^{y_j} \left(\frac{1}{1+e^{\alpha+\beta x_j}}\right)^{1-y_j}$	$\prod_{j=1}^{n} \left(\frac{1}{\sqrt{2\sigma\pi}}\right)^{n} \exp\left(-1/2 \sum \left(\frac{y_j-\mu_j}{\sigma}\right)\right)$ $= \prod_{j=1}^{n} \left(\frac{1}{\sqrt{2\sigma\pi}}\right)^{n} \exp\left(-1/2 \sum \left(\frac{y_j-\alpha-\beta x_j}{\sigma}\right)^2\right)$
Fitting criterion (for choosing estimates of α, β)	Maximize LF	Maximize LF
-2 log LF (is proportional to)	$-2\sum y_j(\alpha+\beta X_j) + 2\sum \ln(1+e^{\alpha+\beta X_j})$	$\frac{1}{\sigma^2}\sum (y_j-\alpha-\beta X_j)^2$
Equivalent fitting criterion	Minimize -2 log LF (*not* least squares)	Minimize -2 log LF (least squares)
Notation	$D(X) = \underset{\text{over } \alpha,\beta}{\text{minimum}} (-2 \log LF) = \text{deviance}$	$D(X) = \underset{\text{over } \alpha,\beta}{\text{minimum}} (-2 \log LF) = \text{deviance}$
Testing: $H_0 : \beta = 0$ in model	$D - D(X)$ is approximately chi-square	$D - D(X)$ is chi-square
Alternative test $H_0 : \beta = 0$ in model	$\frac{D-D(X)}{D(X)/(n-2)}$ is approximately $F_{1,n-2}$	$\frac{D-D(X)}{D(X)/(n-2)} = F_{1,n-2}$

Table 13.8 2 × 2 Table for Vital Status vs. Nutritional Status

		Y		
		Death	Survive	
X_1		1	0	
Malnutrition	1	11	21	32
No malnutrition	0	10	64	74
		21	85	106

The 2 × 2 table associated with these data is shown in Table 13.8.

(a) Verify that the coefficient of X_1 is equal to the logarithm of the odds ratio for malnutrition.

(b) Calculate the probability of death given malnutrition using the model above and compare it with the probability observed.

(c) The standard error of the regression coefficient is 0.5035; test the significance of the observed value, 1.210. Set up 95% confidence limits on the population value and translate these limits into limits for the population odds ratio.

(d) Calculate the standard error of the logarithm of the odds ratio from the 2 × 2 table and compare it with the value in part (c).

13.3 The full model for the data of Table 13.2 is given in Section 13.2.

(a) Calculate the logit line for $X_2 = 0$, $X_3 = 1$, and $X_5 = 1$. Plot logit($\widehat{\pi}$) vs. age in years.

(b) Plot $\widehat{\pi}$ vs. age in years for part (a).

(c) What is the probability of death for a 60-year-old patient with no evidence of shock, but with symptoms of alcoholism and prior bowel infarction?

13.4 One of the problems in the treatment of acute appendicitis is that perforation of the appendix cannot be predicted accurately. Since the consequences of perforation are serious, surgeons tend to be conservative by removing the appendix. Koepsell et al. [1981] attempted to relate the occurrence (or absence) of perforation to a variety of risk factors to enable better assessment of the risk of perforation. A consecutive series of 281 surgery patients was selected initially; of these, 192 were appropriate for analysis, 41 of whom had demonstrable perforated appendices according to the pathology report. The data are listed in Table 13.9. Of the 12 covariates studied, six are listed here, with the group indicator Y.

Y = perforation status (1 = yes; 0 = no)

X_1 = gender (1 = male; 0 = female)

X_2 = age (in years)

X_3 = duration of symptoms in hours prior to physician contact

X_4 = time from physician contact to operation (in hours)

X_5 = white blood count (in thousands)

X_6 = gangrene (1 = yes; 0 = no)

Table 13.9 Data for Problem 13.4

	Y	X_1	X_2	X_3	X_4	X_5	X_6		Y	X_1	X_2	X_3	X_4	X_5	X_6
1	0	0	41	19	1	16	0	49	0	1	15	6	6	19	0
2	1	1	42	48	0	24	1	50	0	0	17	10	4	9	0
3	0	0	11	24	5	14	0	51	0	0	10	72	6	17	0
4	0	1	17	12	2	9	0	52	0	1	9	8	999	15	0
5	1	1	45	36	3	99	1	53	1	1	3	4	2	18	1
6	0	0	15	24	5	14	0	54	0	0	7	16	1	24	0
7	0	1	17	11	24	8	0	55	0	1	60	14	2	11	0
8	0	1	52	30	1	13	0	56	0	1	11	48	3	8	0
9	0	1	15	26	6	13	0	57	0	1	8	48	24	14	0
10	1	1	18	48	2	20	1	58	0	1	9	12	1	12	0
11	0	0	23	48	5	14	0	59	0	1	19	36	1	99	0
12	1	1	9	336	11	13	1	60	1	0	44	24	1	11	1
13	0	0	18	24	3	13	0	61	0	0	46	9	4	12	0
14	0	0	30	8	15	11	0	62	0	1	11	36	2	13	0
15	0	0	16	19	9	10	0	63	0	1	18	8	2	19	0
16	0	1	9	8	2	15	0	64	0	0	21	24	5	12	0
17	0	1	15	48	4	12	0	65	0	0	31	24	8	16	0
18	1	1	25	120	4	8	1	66	0	0	14	7	4	12	0
19	0	0	17	7	17	14	0	67	0	1	17	6	6	19	0
20	0	1	17	12	2	14	0	68	0	0	15	24	1	9	0
21	1	0	63	72	7	11	1	69	0	0	18	24	4	9	0
22	0	0	19	8	1	15	0	70	0	0	38	48	2	99	0
23	0	1	9	48	24	9	0	71	0	1	13	18	4	18	0
24	1	0	9	48	12	14	1	72	1	0	23	168	4	18	0
25	0	0	17	5	1	14	0	73	0	0	15	3	2	14	0
26	0	0	12	48	3	15	0	74	1	0	34	48	3	16	1
27	0	1	6	48	1	26	0	75	0	1	21	24	47	8	1
28	0	0	8	48	3	99	0	76	0	1	50	8	4	12	0
29	1	1	17	30	6	12	1	77	0	0	10	23	6	16	1
30	0	0	11	8	7	15	0	78	0	0	14	48	12	15	0
31	0	1	16	48	2	11	0	79	0	1	26	48	12	13	0
32	0	1	15	10	12	12	0	80	1	0	16	22	1	14	1
33	0	1	13	24	11	15	1	81	1	0	9	24	12	16	1
34	1	1	26	48	4	11	1	82	0	1	26	5	1	16	0
35	0	1	14	7	4	16	0	83	0	1	29	24	1	30	0
36	0	0	44	20	2	13	0	84	0	1	35	408	72	6	0
37	1	1	13	168	999	10	1	85	0	0	18	168	16	12	0
38	0	0	13	14	22	13	0	86	0	1	12	18	4	12	0
39	0	1	24	10	2	19	0	87	0	1	14	7	3	21	0
40	1	0	12	72	2	16	1	88	1	1	45	24	3	18	1
41	0	1	18	15	1	16	0	89	0	1	16	5	21	12	0
42	0	0	19	15	0	9	0	90	0	0	19	240	163	6	0
43	0	0	11	336	20	8	0	91	1	1	9	48	7	23	1
44	0	1	13	14	1	99	0	92	1	1	50	30	5	15	1
45	0	1	25	10	10	11	0	93	0	0	18	2	10	15	0
46	0	1	16	72	5	7	0	94	0	0	27	2	24	17	1
47	0	1	25	72	45	7	0	95	0	1	48	27	5	16	0
48	0	1	42	12	33	19	1	96	0	1	7	18	5	14	0
97	0	1	16	13	1	11	0	145	0	1	41	24	4	14	0
98	0	1	29	5	24	19	1	146	0	0	28	6	1	15	0
99	0	1	18	48	3	11	0	147	1	0	13	48	9	15	1

Table 13.9 (*continued*)

	Y	X_1	X_2	X_3	X_4	X_5	X_6		Y	X_1	X_2	X_3	X_4	X_5	X_6
100	0	1	18	9	2	14	0	148	0	1	10	15	1	99	0
101	1	1	14	14	1	15	1	149	0	1	16	18	4	14	0
102	0	1	32	240	24	7	0	150	0	1	17	18	10	17	0
103	0	1	23	18	2	17	1	151	0	1	38	9	7	11	0
104	0	1	26	16	2	13	0	152	0	1	12	18	2	13	0
105	0	0	30	24	4	20	0	153	0	0	12	72	3	15	0
106	0	1	44	39	15	11	0	154	0	0	27	16	0	14	1
107	1	1	17	24	4	16	1	155	0	1	31	7	8	14	0
108	0	1	30	36	3	15	1	156	0	0	45	20	4	27	0
109	0	1	18	24	2	11	1	157	1	1	52	48	3	15	1
110	0	1	34	96	1	10	0	158	1	1	26	48	13	16	1
111	0	1	15	12	2	10	0	159	0	0	38	15	1	16	0
112	0	1	10	24	4	99	0	160	0	0	19	24	5	99	0
113	0	1	12	14	13	5	0	161	0	1	14	20	2	15	0
114	0	1	10	12	17	17	0	162	0	0	27	22	8	18	0
115	0	1	28	24	2	15	0	163	0	1	20	21	1	99	0
116	0	1	10	96	8	8	0	164	1	1	11	24	8	10	1
117	0	0	22	12	2	12	0	165	0	1	17	72	20	10	0
118	0	0	30	15	5	12	0	166	0	0	27	24	3	9	0
119	0	1	16	36	3	12	0	167	1	0	52	16	4	13	1
120	0	0	16	30	4	15	0	168	1	1	38	48	2	13	1
121	0	1	9	12	12	15	0	169	0	1	16	19	3	12	0
122	1	1	16	144	4	15	1	170	0	1	19	9	4	17	0
123	0	1	17	36	13	6	0	171	0	0	24	24	2	11	0
124	1	1	12	120	2	11	1	172	0	1	12	17	20	6	1
125	0	1	28	17	26	10	0	173	1	1	51	72	2	16	1
126	1	0	13	48	3	21	1	174	1	1	50	72	6	11	1
127	0	0	23	72	3	13	0	175	0	0	28	12	3	13	0
128	1	0	62	72	2	12	1	176	0	0	19	48	8	14	1
129	0	1	17	24	4	14	0	177	0	1	9	24	999	99	0
130	0	0	12	24	12	15	0	178	0	0	40	48	7	14	0
131	0	1	10	12	10	11	0	179	0	0	17	504	7	99	0
132	0	1	47	48	8	9	0	180	0	1	51	24	1	9	1
133	0	1	43	11	8	13	0	181	0	1	31	24	2	10	0
134	1	1	18	36	2	15	1	182	0	0	25	8	9	8	0
135	0	0	6	24	1	9	0	183	0	0	14	24	8	10	0
136	0	0	24	2	22	10	0	184	0	1	7	24	4	15	0
137	0	0	22	11	24	7	0	185	0	1	27	7	2	14	0
138	1	1	39	36	3	15	1	186	0	1	35	72	3	19	1
139	1	1	43	48	2	11	1	187	0	0	11	12	9	11	0
140	0	1	12	7	1	14	0	188	0	1	20	8	6	12	0
141	0	1	14	48	6	16	0	189	0	1	50	48	27	19	0
142	0	1	21	24	1	17	0	190	0	1	16	6	7	7	0
143	1	1	34	48	12	9	1	191	0	1	45	24	4	20	0
144	1	0	60	24	3	14	1	192	1	1	47	336	4	9	1

For X_4 the code 999 is for unknown; for X_5 the code 99 is an unknown code.

(a) Compare the means of the continuous variables (X_2, X_3, X_4, X_5) in the two outcome groups ($Y = 0, 1$) by some appropriate test. Make an appropriate comparison of the association of X_5 and Y. State your conclusion at this point.

(b) Carry out a stepwise discriminant analysis. Which variables are useful predictors? How much improvement in prediction is there in using the discriminant procedure? How appropriate is the procedure?

(c) Carry out a stepwise logistic regression and compare your results with those of part (b).

(d) The authors introduced two additional variables in their analysis: $X_7 = \log(X_2)$ and $X_8 = \log(X_3)$. Test whether these variables improve the prediction scheme. Interpret your findings.

(e) Plot the probability of perforation as a function of the duration of symptoms; using the logistic model, generate a separate curve for subjects aged 10, 20, 30, 40, and 50 years. Interpret your findings.

13.5 The Web appendix to this chapter has a data set with daily concentrations of particulate air pollution in Seattle, Washington. The air quality index for fine particulate pollution below 2.5 μm in diameter (PM2.5) will be "unhealthy for sensitive groups" at 40 $\mu g/m^3$ and "moderate" at 20 $\mu g/m^3$. The Puget Sound Clean Air Agency is interested in predicting high air pollution days so that it can issue burn bans to reduce fireplace use. Using information on weather and pollution from previous days and the time of year, build logistic models to predict when PM2.5 will exceed 20 or 40 $\mu g/m^3$. Also build a linear regression model for predicting PM2.5 or log(PM2.5). Summarize the predictive accuracy of these models. Do you get more accurate prediction using the logistic model or categorizing the prediction from the linear model? Does the answer depend on what losses you assign to false positive and false negative predictions?

13.6 A classic in the use of discriminant analysis is the paper by Truett et al. [1967], in which the authors attempted to predict the risk of coronary heart disease using data from the Framingham study, a longitudinal study of the incidence of coronary heart disease in Framingham, Massachusetts. The two groups under consideration were those who did and did not develop coronary heart disease (CHD) in a 12-year follow-up period. There were 2669 women and 2187 men, aged 30 to 62, involved in the study and free from CHD at their first examination. The variables considered were:

- Age (years)
- Serum cholesterol (mg/100 mL)
- Systolic blood pressure (mmHg)
- Relative weight (100 × actual weight ÷ median for sex–height group)
- Hemoglobin (g/100 mL)
- Cigarettes per day, coded as 0 = never smoked, 1 = less than a pack a day, 2 = one pack a day, and 3 = more than a pack a day
- ECG, coded as 0 = for normal, and 1 = for definite or possible left ventricular hypertrophy, definite nonspecific abnormality, and intraventricular block

Note that the variables "cigarettes" and "ECG" cannot be distributed normally, as they are discrete variables. Nevertheless, the linear discriminant function model was tried. It was found that the predictions (in terms of the risk or estimated probability of being in the coronary heart disease groups) fitted the data well. The coefficients of the linear discriminant functions for men and women, including the standard errors, are shown in Table 13.10.

Table 13.10 Coefficients and Standard Errors for Predicting Coronary Heart Disease.

Risk Factors	Women	Men	Standard Errors of Estimated Coefficients	
Constant ($\widehat{\alpha}$)	−12.5933	−10.8986		
Age (years)	0.0765	0.0708	0.0133	0.0083
Cholesterol (mg %)	0.0061	0.0105	0.0021	0.0016
Systolic blood pressure (mmHg)	0.0221	0.0166	0.0043	0.0036
Relative weight	0.0053	0.0138	0.0054	0.0051
Hemoglobin (g %)	0.0355	−0.0837	0.0844	0.0542
Cigarettes smoked (*see code*)	0.0766	0.3610	0.1158	0.0587
ECG abnormality (*see code*)	1.4338	1.0459	0.4342	0.2706

(a) Determine for both women and men in terms of the p-value the most significant risk factor for CHD in terms of the p-value.

(b) Calculate the probability of CHD for a male with the following characteristics: age = 35 years; cholesterol = 220 mg %; systolic blood pressure = 110 mmHg; relative weight = 110; hemoglobin = 130 g%; cigarette code = 3; and ECG code = 0.

(c) Calculate the probability of CHD for a female with the foregoing characteristics.

(d) How much is the probability in part (b) changed for a male with all the characteristics above except that he does not smoke (i.e., cigarette code = 0)?

(e) Calculate and plot the probability of CHD for the woman in part (c) as a function of age.

13.7 In a paper that appeared four years later, Halperin et al. [1971] reexamined the Framingham data analysis (see Problem 13.6) by Truett et al. [1967] using a logistic model. Halperin et al. analyzed several subsets of the data; for this problem we abstract the data for men aged 29 to 39 years, and three variables: cholesterol, systolic blood pressure, and cigarette smoking (0 = never smoked; 1 = smoker); cholesterol and systolic blood pressure are measured as in Problem 13.6. The following coefficients for the logistic and discriminant models (with standard errors in parentheses) were obtained:

	Intercept	**Cholesterol (mg/100 mL)**	**Systolic Blood Pressure**	**Cigarettes**
Logistic	−11.6246	0.0179(0.0036)	0.0277(0.0085)	1.7346(0.6236)
Discriminant	−13.5300	0.0236(0.0039)	0.0302(0.0100)	1.1191(0.3549)

(a) Calculate the probability of CHD for a male with relevant characteristics defined in Problem 13.6, part (b), for both the logistic and discriminant models.

(b) Interpret the regression coefficients of the logistic model.

(c) In comparing the two methods, the authors state: "Empirically, the assessment of significance of a variable, as measured by the ratio of the estimated coefficient to its estimated standard error, is apt to be about the same whichever method is used." Verify that this is so for this problem. (However, see also the discussion in Section 13.3.2.)

13.8 In a paper in *American Statistician*, Hauck [1983] derived confidence bands for the logistic response curve. He illustrated the method with data from the Ontario Exercise Heart Collaborative Study. The logistic model dealt with the risk of myocardial infarction (MI) during a study period of four years. A logistic model based on the two most important variables, smoking (X_1) and serum triglyceride level (X_2), was calculated to be

$$\text{logit}(P) = -2.2791 + 0.7682X_1 + 0.001952(X_2 - 100)$$

where P is the probability of an MI during the four-year observation period. The variable X_1 had values $X_1 = 0$ (nonsmoker) and $X_1 = 1$ (smoker). As in ordinary regression, the confidence band for the entire line is narrowest at the means of X_1 and $(X_2 - 100)$ and spreads out the farther you go from the means. (See the paper for more details.)

(a) The range of values of triglyceride levels is assumed to be from 0 to 550. Graph the probability of MI for smokers and nonsmokers separately.

(b) The standard errors of regression coefficients for smoking and serum triglyceride are 0.3137 and 0.001608, respectively. Test their significance.

13.9 One of the earliest applications of the logistic model to medical screening by Anderson et al. [1972] involved the diagnosis of keratoconjunctivitis sicca (KCS), also known as "dry eyes." It is known that rheumatoid arthritic patients are at greater risk, but the definitive diagnosis requires an ophthalmologist; hence it would be advantageous to be able to predict the presence of KCS on the basis of symptoms such as a burning sensation in the eye. In this study, 40 rheumatoid patients with KCS and 37 patients without KCS were assessed with respect to the presence (scored as 1) or absence (scored as 0) of each of the following symptoms: (1) foreign body sensation; (2) burning; (3) tiredness; (4) dry feeling; (5) redness; (6) difficulty in seeing; (7) itchiness; (8) aches; (9) soreness or pain; and (10) photosensitivity and excess of secretion. The data are reproduced in Table 13.11.

(a) Fit a stepwise logistic model to the data. Test the significance of the coefficients.

(b) On the basis of the proportions of positive symptoms displayed at the bottom of the table, select that variable that should enter the regression model first.

(c) Estimate the probability of misclassification.

(d) It is known that approximately 12% of patients suffering from rheumatoid arthritis have KCS. On the basis of this information, calculate the appropriate logistic scoring function.

(e) Define X = number of symptoms reported (out of 10). Do a logistic regression using this variable. Test the significance of the regression coefficient. Now do a t-test on the X variable comparing the two groups. Discuss and compare your results.

13.10 This problem deals with the data of Pine et al. [1983]. Calculate the posterior probabilities of survival for a patient in the fourth decade arriving at the hospital in shock and history of myocardial infarction and without other risk factors:

(a) Using the logistic model.

(b) Using the discriminant model.

Table 13.11 Data for Problem 13.8

	KCS Patients											Patients Without KCS									
Patient	1	2	3	4	5	6	7	8	9	10	Patient	1	2	3	4	5	6	7	8	9	10
1	1	1	1		1		1			1	1	1						1			
2	1	1	1	1	1			1			2										
3	1	1		1	1	1			1		3		1	1				1			
4	1	1		1	1			1	1		4										
5	1	1	1	1			1			1	5								1		
6	1	1			1					1	6										
7	1	1	1			1		1			7			1				1			
8	1	1		1		1			1		8										
9	1	1	1	1	1		1	1			9										
10	1										10									1	
11	1	1	1	1		1		1			11		1					1			
12	1	1					1	1	1		12										
13	1	1	1	1	1	1	1			1	13							1			
14	1	1	1	1	1		1	1		1	14										
15			1	1			1	1			15							1			
16	1	1		1					1		16										
17		1	1			1		1		1	17							1			
18	1		1	1	1			1			18										
19	1		1	1	1		1				19					1					
20	1	1	1	1			1			1	20										
21					1						21										
22	1	1	1	1	1	1	1				22						1				

continued overleaf

Table 13.11 (*continued*)

	KCS Patients											Patients Without KCS									
Patient	1	2	3	4	5	6	7	8	9	10	Patient	1	2	3	4	5	6	7	8	9	10
23	1	1	1		1					1	23										
24	1	1		1			1	1	1		24					1					
25	1	1	1	1				1			25	1								1	
26				1			1				26										
27	1	1		1	1			1	1	1	27										
28	1	1	1	1						1	28										
29	1		1		1				1		29							1			
30	1	1		1		1				1	30										
31		1	1	1						1	31				1						
32	1	1	1	1	1	1	1			1	32										
33			1	1	1		1		1		33							1			
34	1	1	1	1		1	1			1	34										
35	1		1		1			1			35										1
36	1	1	1	1				1			36										
37	1	1	1	1	1						37							1			1
38	1	1																			
39																					
40		1	1	1			1			1											
Proportion position	$\frac{32}{40}$	$\frac{30}{40}$	$\frac{26}{40}$	$\frac{28}{40}$	$\frac{19}{40}$	$\frac{10}{40}$	$\frac{16}{40}$	$\frac{15}{40}$	$\frac{9}{40}$	$\frac{15}{40}$	Proportion position	$\frac{2}{37}$	$\frac{2}{37}$	$\frac{2}{37}$	$\frac{1}{37}$	$\frac{2}{37}$	$\frac{1}{37}$	$\frac{10}{37}$	$\frac{1}{37}$	$\frac{2}{37}$	$\frac{2}{37}$

(c) Graph the two survival curves as a function of age. Use the values 5, 15, 25, ... for the ages in the discriminant model.

(d) Assume that the prior probabilities are $\pi_1 = P[\text{survival}] = 0.60$ and $\pi_2 = 1 - 0.60 = 0.40$. Recalculate the probabilities in parts (a) and (b).

(e) Define a new variable for the data of Table 13.2 as follows: $X_6 = X_1 + X_2 + X_3 + X_5$. Interpret this variable.

(f) Do a logistic regression and discriminant analysis using variables X_4 and X_6 (defined above). Interpret your results.

(g) Is any information "lost" using the approach of parts (e) and (f)? If so, what is lost? When is this likely to be important?

13.11 This problem requires some programming. Create 100 observations of 20 independent random characteristics (e.g., from a uniform distribution) and one random 0–1 variable. Fit a logistic discrimination model using 1, 2, 5, 10, 15, or 20 of your characteristics, and 20, 40, 60, 80, and 100 of the observations. Compute the in-sample error rate and compare it to the true error rate (1/2).

13.12 This problem deals with the data of Problem 5.14, comparing the effect of the drug nifedipine on vasospasm attacks in patients suffering from Raynaud's phenomenon. We want to make a multivariate comparison of the seven patients with a history of digital ulcers ("yes" in column 4) with the eight patients without a history of digital ulcers ("no" in column 4). Variables to be used are age, gender, duration of phenomenon, total number of attacks on placebo, and total number of attacks on nifedipine.

(a) Carry out a stepwise logistic regression on these data.

(b) Which variable entered first?

(c) State your conclusion.

(d) Make a scatter plot of the logistic scores and indicate the dividing point.

***13.13** This problem deals with the data of Problem 10.10, comparing metabolic clearance rates in three groups of subjects.

(a) Use a discriminant analysis on the *three* groups.

(b) Interpret your results.

(c) Graph the data using different symbols to denote the three groups.

(d) Suppose you "create" a third variable: concentration at 90 minutes minus concentration at 45 minutes. Will this improve the discrimination? Why or why not?

***13.14** Consider two groups, G_1 and G_2 (e.g., "death," "survive"; "disease," "no disease"), and a binary covariate, X, with values 0 or 1 (e.g., "don't smoke," "smoke"; "symptom absent," "symptom present"). The data can be arranged in a 2×2 table:

	Group	
X	G_1	G_2
1		
0		
	π_1	π_2

Here π_1 is the prior probability of group G_1 membership; $P(X = i|G_1)$ the likelihood of $X = i$ given G_1 membership, $i = 0, 1$; and $P(G_1|X = i)$ the posterior probability of G_1 membership given that $X = i, i = 0, 1$.

(a) Show that

$$\frac{P(G_1|X = i)}{P(G_2|X = i)} = \frac{\pi_1}{\pi_2}\frac{P(X = i|G_1)}{P(X = i|G_2)}$$

Hint: Use Bayes' theorem.

(b) The expression in part (a) can be written as

$$\frac{P(G_1|X = i)}{1 - P(G_1|X = i)} = \frac{\pi_1}{1 - \pi_1}\frac{P(X = i|G_1)}{P(X = i|G_2)}$$

In words:

posterior odds of group 1 membership = prior odds of group 1 membership × ratio of likelihoods of observed values of X.

Relate the ratio of likelihoods to the sensitivity and specificity of the procedure.

(c) Take logarithms of both sides of the equation in part (b). Relate your result to Note 6.7.

(d) The result in part (b) can be shown to hold for X continuous or multivariate. What are the assumptions [go back to the simple set-up of part (a)].

REFERENCES

Akaike, H. [1973]. Information theory and an extension of the maximum likelihood principle. *Proceedings of the 2nd International Symposium on Information Theory.*

Anderson, J. A. [1972]. Separate sample logistic regression. *Biometrika*, **59**: 19–35.

Anderson, J. A., Whaley, K., Williamson, J., and Buchanan, W. W. [1972]. A statistical aid to the diagnosis of keratoconjunctivitis sicca. *Quarterly Journal of Medicine, New Series*, **41**: 175–189. Used with permission from Oxford University Press.

Breiman, L., Friedman, J. H., Olshen, R. A., and Stone, C. J. [1984]. *Classification and Regression Trees.* Wadsworth Press, Belmont, CA.

Cherry, N., Creed, F., Silman, A., Dunn, G., Baxter, D., Smedley, J., Taylor, S., and Macfarlane, G. J. [2001]. Health and exposure of United Kingdom Gulf War veterans: I. The pattern and extent of ill health. *Occupational and Environmental Medicine*, **58**: 291–298.

Cover, T. M. [1965]. Geometrical and statistical properties of linear inequalities with applications in pattern recognition. *IEEE Transactions on Electronic Computing*, **14**: 326–334.

Efron, B. [1975]. The efficiency of logistic regression compared to normal discriminant analysis. *Journal of the American Statistical Association*, **70**: 892–898.

Eisen, M. B., Spellman, P. T., Brown, P. O., and Botstein, D. [1998]. Cluster analysis and display of genome-wise expression patterns. *Proceedings of the National Academy of Sciences*, **95**(25): 14863–14868.

Everitt, B., Ismail, K., David, A. S., and Wessely, S. [2002]. Searching for a Gulf War syndrome using cluster analysis. *Psychological Medicine*, **32**(8): 1335–1337.

Fisher, R. A. [1936]. The use of multiple measurements in taxonomic problems. *Annals of Eugenics*. **7**: 179–188.

Hall, P. and Li, K-C. [1993]. On almost linearity of low dimensional projections from high dimensional data. *The Annals of Statistics*, **21**: 867–889.

Hallman, W. K., Kipen, H. M., Diefenbach, M., Boyd, K., Kang, H., Leventhal, H., and Wartenberg, D. [2003]. Symptom patterns among Gulf War registry veterans. *American Journal of Public Health*, **93**(4): 624–630.

Halperin, M. and Gurian, J. [1971]. A note on estimation in straight line regression when both variables are subject to error. *Journal of the American Statistical Association*, **66**: 587–589.

Halperin, M., Blockwelder, W. C., and Verter, J. I. [1971]. *Estimation* of the multivariate logistic risk function: a comparison of the discriminant function and maximum likelihood approaches. *Journal of Chronic Diseases*, **24**: 125–158.

Harrell, F. E. [2001]. *Regression Modeling Strategies*. SpringerVerlag, New York.

Hastie, T., Tibshirani, R., and Friedman, J. H. [2001]. *The Elements of Statistical Learning*. SpringerVerlag, New York.

Hauck, W. W. [1983]. A note on confidence bands for the logistic response curve. *American Statistician*, **37**: 158–160.

Health Canada [2001]. *Organized Breast Cancer Screening Programs in Canada: 1997 and 1998 report*. Downloaded from *http://www.hc-sc.gc.ca/pphb-dgspsp/publications_e.html*.

Hosmer, D. W., and Lemeshow, S. [2000]. *Applied Logistic Regression*, 2nd ed. Wiley, New York.

Jones, R. H. [1975]. Probability estimation using a multinomial logistic function. *Journal of Statistical Computation and Simulation*, **3**: 315–329.

Knoke, J. D. [1982]. Discriminant analysis with discrete and continuous variables. *Biometrics*, **38**: 191–200. See also correction in *Biometrics*, **38**: 1143.

Koepsell, T. D., Inui, T. S., and Farewell, V. T. [1981]. Factors affecting perforation in acute appendicitis. *Surgery, Gynecology and Obstetrics*, **153**: 508–510. Used with permission.

Lachenbruch, P. A. [1977]. *Discriminant Analysis*. Hafner Press, New York.

Li, K-C. and Duan, N. [1989]. Regression analysis under link violation, *The Annals of Statistics*, **17**: 1009–1052.

Pepe, M. S. [2003]. *The Statistical Evaluation of Medical Tests for Classification and Prediction*. Oxford University Press, Oxford.

Pine, R. W. Wertz, M. J., Lennard, E. S., Dellinger, E. P., Carrico, C. J., and Minshew, H. [1983]. Determinants of organ malfunction or death in patients with intra-abdominal sepsis. *Archives of Surgery*, **118**: 242–249. Copyright © 1983 by the American Medical Association.

Ripley, B. D. [1996]. *Pattern Recognition and Neural Networks*. Cambridge University Press, Cambridge.

Savage, L. J. [1954]. *The Foundations of Statistics*. Wiley, New York.

Spanos, A., Harrell, F. E. and Durack, F. T. [1989]. Differential diagnosis of acute meningitis. An analysis of the predictive value of initial observations. *Journal of the American Medical Association*, **262**(19): 2700–2707.

Therneau, T. M. [2002]. *Rpart Software*. Mayo Foundation for Medical Research, Rochester, MN.

Truett, J., Cornfield, J., and Kannel, W. [1967]. A multivariate analysis of the risk of coronary heart disease in Framingham. *Journal of Chronic Diseases*, **20**: 511–524.

Venables, W. N., and Ripley, B. D. [2002]. *Modern Applied Statistics with S*, 4th ed. SpringerVerlag, New York.

Wilson P. W. F., D'Agostino, R. B., Levy, D., Belanger, A. M., Silbershatz, H., and Kannel, W. B. [1998]. Prediction of coronary heart disease using risk factor categories. *Circulation*, **97**: 1837–1847.

Zhang, H., and Singer, B. [1999]. *Recursive Partitioning in the Health Sciences*. SpringerVerlag, New York.

Zhou, X.-H., McClish, D. K., and Obuchowski, A. [2002]. *Statistical Methods in Diagnostic Medicine*. Wiley, New York.

CHAPTER 14

Principal Component Analysis and Factor Analysis

14.1 INTRODUCTION

In Chapters 10 and 11 we considered the dependence of a specified response variable on other variables. The response variable identified played a special role among the variables being considered. This is appropriate in many situations because of the scientific question and/or experimental design. What do you do, however, if you have a variety of variables and desire to examine the relationships between them without identifying a specific response variable?

In this chapter we present two methods of examining the relationships among a set of variables without identifying a specific response variable. For these methods, no single variable has a more distinguished role or importance than any other variable. The first technique we examine, principal component analysis, explains as much variability as possible in terms of a few linear combinations of the variables. The second technique, factor analysis, explains the relationships between variables by a few unobserved factors. Both methods depend on the covariances, or correlations, between variables.

14.2 VARIABILITY IN A GIVEN DIRECTION

Consider the 20 observations on two variables X and Y listed in Table 14.1. These data are such that the original observations had their means subtracted, so that the means of the points are zero. Figure 14.1 plots these points, that is, plots the data points about their common mean.

Rather than thinking of the data points as X and Y values, think of the data points as a point in a plane. Consider Figure 14.2(a); when an origin is identified, each point in the plane is identified with a pair of numbers x and y. The x value is found by dropping a line perpendicular to the horizontal axis; the y value is found by dropping a line perpendicular to the vertical axis. These axes are shown in Figure 14.2(b). It is not necessary, however, to use the horizontal and vertical directions to locate our points, although this is traditional. Lines at any angle θ from the horizontal and vertical, as shown in Figure 14.2(c), might be used. In terms of these two lines, the data point has values found by dropping perpendicular lines to these two directions; Figure 14.2(d) shows the two values. We will call the new values x' and y' and the old values x and y. It can be shown that x' and y' are linear combinations of x and y. This idea of lines in different directions with perpendiculars to describe the position of points is used in principal component analysis.

Biostatistics: A Methodology for the Health Sciences, Second Edition, by Gerald van Belle, Lloyd D. Fisher, Patrick J. Heagerty, and Thomas S. Lumley
ISBN 0-471-03185-2

Table 14.1 Twenty Biometric Observations

Observation	X	Y	Observation	X	Y
1	−0.52	0.60	11	0.08	0.23
2	0.04	−0.51	12	−0.06	−0.59
3	1.29	−1.19	13	1.25	−1.25
4	−1.12	1.90	14	0.53	−0.45
5	−1.02	0.31	15	0.14	0.47
6	0.10	−1.15	16	0.48	−0.11
7	−0.32	−0.13	17	−0.61	1.04
8	0.08	−0.17	18	−0.47	0.34
9	0.49	0.18	19	0.41	0.29
10	−0.54	0.20	20	−0.22	0.00

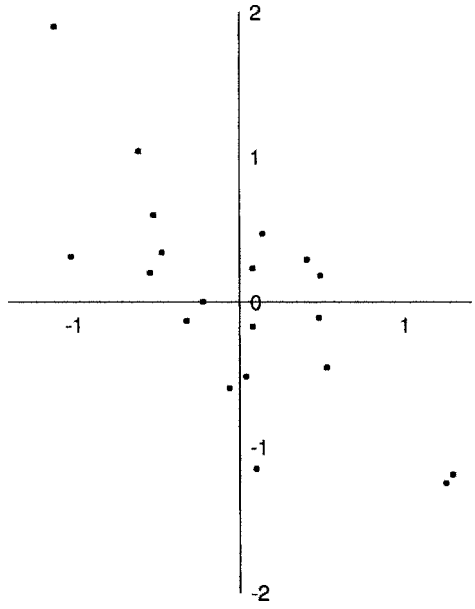


Figure 14.1 Plot of the 20 data points of Table 14.1.

For our data set, the variability in x and y may be summarized by the standard deviation of the x and y values, respectively, as well as the covariance, or equivalently, the correlation between them. Consider now the data of Figure 14.1 and Table 14.1. Suppose that we draw a line in a direction of 30° to the horizontal. The 20 observations give 20 x' values in the X' direction when the perpendicular lines are dropped. Figure 14.3 shows the values in the x' direction. Consider now the points along the line in the x' direction corresponding to the feet of the perpendicular lines. We may summarize the variability among these points by our usual measure of variability, the standard deviation. This would be computed in our usual manner from the 20 values x'. The variability of the data may be summarized by plotting the standard deviation, say $s(\theta)$, in each direction θ at a distance s from the origin. When we look at the standard deviation in all directions, this results in an egg-shaped curve with dents in the side; or a symmetric curve in the shape of a violin or cello body. For the data at hand, this curve is shown in Figure 14.4; the curve is identified as the standard deviation curve. Note that the standard deviation is not the same in all directions. For our data set, the data are spread out more

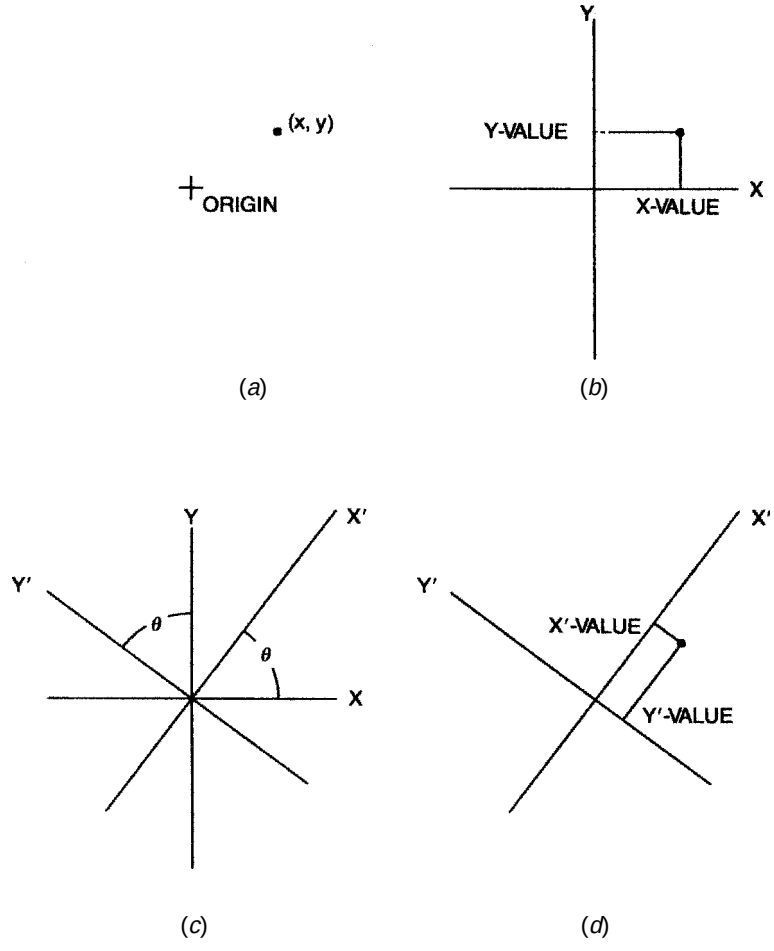


Figure 14.2 Points in the plane, coordinates, and rotation of axes.

along a northwest–southeast direction than in the southwest–northeast direction. The standard deviation curve has a minimum distance at about 38°. The standard deviation increases steadily to a maximum; the maximum is positioned along the line in Figure 14.4, running from the upper left to the lower right. These two directions are labeled directions 1 and 2. If we want to pick one direction that contains as much variability as possible, we would choose direction 1, because the standard deviation is largest in that direction. If all the data points lie on a line, the variability will be a maximum in the direction of the line that contains all the data.

There is some terminology used in finding the value of a data point in a particular direction. The process of dropping a line perpendicular to a direction is called *projecting* the point onto the direction. The value in the particular direction [x' in Figure 14.2(d) or Figure 14.3] is called the *projection of the point*. If we know the values x and y, or if we know the values x' and y', we know where the point is in the plane. Two such variables x and y, or equivalently, x' and y', which allow us to find the values of the data, are called a *basis for the variables*.

These concepts may be generalized when there are more than two variables. If we observe three variables x, y, and z, the points may be thought of as points in three dimensions. Suppose that we subtract the means from all the data so that the data are centered about the origin of a three-dimensional plot. As you sit reading this material, picture the points suspended about the

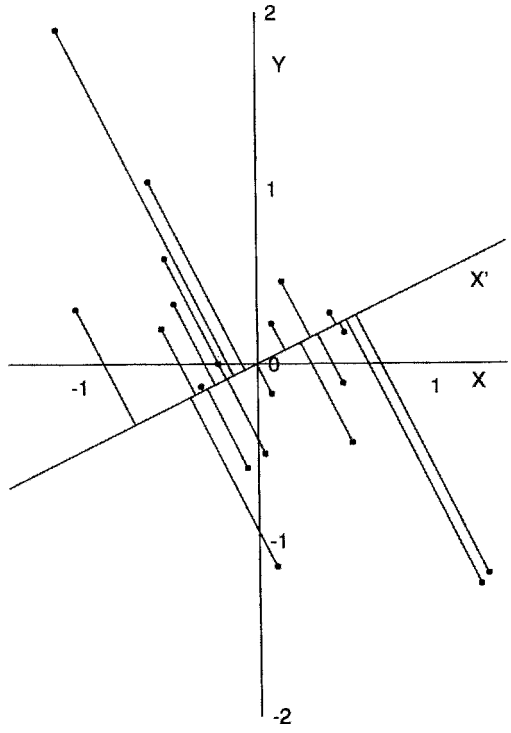


Figure 14.3 Values in the X-direction. X' axis at 30° to the x-axis.

room. Pick an origin. You may draw a line through the origin in any direction. For any point that you have picked in the room, you may drop a perpendicular to the line. Given a line, the point on the line where the perpendicular meets the line is the projection of the point onto the line. We may then calculate the standard deviation for this direction. If the standard deviations are plotted in all directions, a dented egg-shaped surface results. There will be one direction with the greatest variability. When more than three variables are observed, although we cannot picture the situation mentally, mathematically the ideas may be extended; the concept of a direction may be extended in a natural manner. In fact, mathematical statistics is one part of mathematics that heavily uses the geometry of n-dimensional space when there are n variables observed. Fortunately, to understand the statistical methods, we do not need to understand the mathematics!

Let us turn our attention again to Figure 14.4. Rather than plotting the standard deviation curve, it is traditional to summarize the variability in the data by an ellipse. The two perpendicular axes of the ellipse lie along the directions of the greatest variability and the least variability. The ellipse, called the *ellipsoid of concentration*, meets the standard deviation curve along its axes at the points of greatest and least variation. In other directions the standard deviation curve will be larger, that is, farther removed from the origin. In three dimensions, rather than plotting an ellipse we plot an egg-shaped surface, the ellipsoid. (One reason the ellipsoid is used: If you have a bivariate normal distribution in the plane, take a very large sample, divide the plane up into small squares as on graph paper, and place columns whose height is proportional to the number of points; the columns of constant height would lie on an ellipsoid.)

Out of the technical discussion above, we want to remember the following ideas:

1. If we observe a set of variables, we may think of each data point as a point in a space. In this space, when the points are centered about their mean, there is variability in each direction.

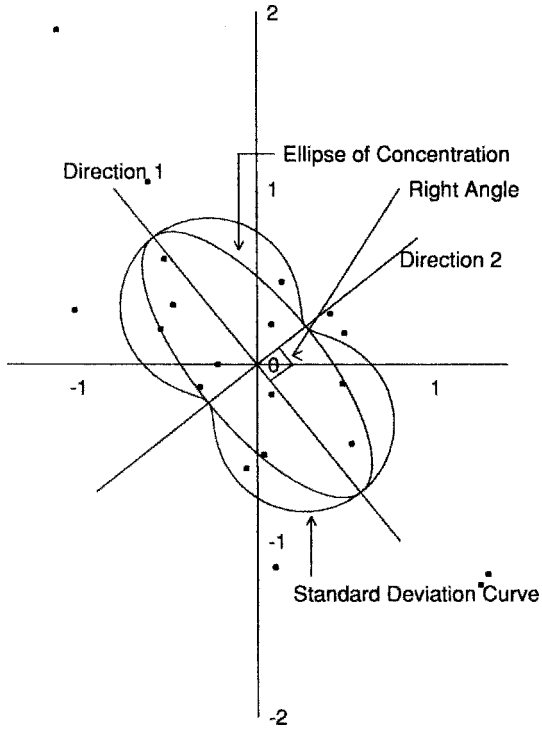


Figure 14.4 Standard deviation in each direction and the ellipse of concentration.

2. The variability is a maximum in one direction. In two dimensions (or more) the minimum lies in a perpendicular direction.
3. The variability is symmetric about each of the particular directions identified.

It is possible to identify the various directions with linear combinations of the variables or coordinates. Each direction for $X_1, \ldots, X_p$ is associated with a sum

$$Y = a_1X_1 + a_2X_2 + \cdots + a_pX_p \tag{1}$$

where

$$a_1^2 + a_2^2 + \cdots + a_p^2 = 1$$

The constants $a_1, a_2, \ldots, a_p$ are uniquely associated with the direction, except that we may multiply each a by -1. The sum that is given in equation (1) is the value of the projection of the points x_1 to x_p corresponding to the given direction.

14.3 PRINCIPAL COMPONENTS

The motivation behind principal component analysis is to find a direction, or a few directions, that explain as much of the variability as possible. Since each direction is associated with a linear sum of the variables, we may say that we want to find a few new variables, which are

linear sums of the old variables, which explain as much of the variability as possible. Thus, the first principal component is the linear sum corresponding to the direction of greatest variability:

Definition 14.1. The *first principal component* is the sum

$$Y = a_1X_1 + \cdots + a_pX_p, \qquad a_1^2 + \cdots + a_p^2 = 1 \tag{2}$$

corresponding to the direction of greatest variability when variables $X_1, \ldots, X_p$ are under consideration.

Usually, the first principal component will leave much of the variability unexplained. (In the next section, we discuss a method of quantifying the amount of variability explained.) For this reason we wish to search for a second principal component that explains much of the remaining variability. You might think we would take the next linear combination of variables that explains as much of the variability as possible. But when you examine Figure 14.4, you see that the closer the direction gets to the first principal component (which would be direction 1 in Figure 14.4), the more variability one would have. Thus, essentially, we would be driven to the same variable. Therefore, the search for the second principal component is restricted to variables that are uncorrelated with the first principal component. Geometrically, it can be shown that this is equivalent to considering directions that are perpendicular to the direction of the first principal component. In two dimensions such as Figure 14.4, direction 2 would be the direction of the second principal component. However, in three dimensions, when we have the line corresponding to the direction of the first principal component, the set of all directions perpendicular to it correspond to a plane, and there are a variety of possible directions in which to search for the second principal component. This leads to the following definition:

Definition 14.2. Suppose that we have the first $k-1$ principal components for variables $X_1, \ldots, X_p$. The kth *principal component* corresponds to the variable or direction that is uncorrelated with the first $k-1$ principal components and has the largest possible variance.

As a summary of these difficult ideas, you should remember the following:

1. Each principal component is chosen to explain as much of the remaining variability as possible after the preceding principal components have been chosen.
2. Each principal component is uncorrelated to the other principal components. In the case of a multivariate normal distribution, the principal components are statistically independent.
3. Although it is not clear from the above, the following is true: For each k, the first k principal components explain as much of the variability in a sample as may be explained by any k directions, or equivalently, k variables.

14.4 AMOUNT OF VARIABILITY EXPLAINED BY THE PRINCIPAL COMPONENTS

Suppose that we want to perform a principal component analysis upon variables $X_1, \ldots, X_p$. If we were dealing with only one variable, say variable X_j, we summarize its variability by the variance. Suppose that there are a total of n observations, so that for each of the p variables, we have n values. Let X_{ij} be the ith observation on the jth variable. Let $\overline{X}_j$ be the mean of the n observations on the jth variable. Then we estimate the variability, that is, the variance, of

the variable X_j by

$$\widehat{\text{var}}(X_j) = \sum_{i=1}^{n} \frac{(X_{ij} - \overline{X}_j)^2}{n-1} \tag{3}$$

A reasonable summary of the variability in the p variables is the sum of the individual variances. This leads us to the next definition.

Definition 14.3. The *total variance, denoted by V*, for variables $X_1, \ldots, X_p$ is the sum of the individual variances. That is,

$$\text{total variance} = V = \sum_{j=1}^{p} \text{var}(X_j) \tag{4}$$

The sample total variance, which we will also denote by V since that is the only type of total variance used in this section, is

$$\text{sample total variance} = V = \sum_{j=1}^{p} \sum_{i=1}^{n} \frac{(X_{ij} - \overline{X}_j)^2}{n-1}$$

We now characterize the amount of variability explained by the principal components. Recall that the principal components are themselves variables; they are linear combinations of the X_j variables. Each principal component has a variance itself. It is natural, therefore, to compare the variance of the principal components with the variance of the X_j's. This leads us to the following definitions.

Definition 14.4. Let $Y_1, Y_2, \ldots$ be the first, second, and subsequent principal components for the variables $X_1, \ldots, X_p$. In a sample the variance of each Y_k is estimated by

$$\text{var}(Y_k) = \sum_{i=1}^{n} \frac{(Y_{ik} - \overline{Y}_k)^2}{n-1} = V_k \tag{5}$$

where Y_{ik} is the value of the kth principal component for the ith observation. That is, we first estimate the coefficients for the kth principal component. The value for the ith observation uses those coefficients and the observed values of the X_j's to compute the value of Y_{ik}. The variance for the kth principal component in the sample is then given by the sample variance for Y_{ik}, $i = 1, 2, \ldots, n$. We denote this variance as seen above by V_k. Using this notation, we have the following two definitions:

1. *The percent of variability explained by the k*th *principal component is*

$$\frac{100 V_k}{V}$$

2. *The percent of the variability explained by the first m principal components is*

$$100 \sum_{k=1}^{m} \frac{V_k}{V} \tag{6}$$

The following facts about the principal components can be stated:

1. There are exactly p principal components, where p is the number of X variables considered. This is because with p uncorrelated variables, there is a one-to-one correspondence between the values of the principal components and the values of the original data; that is, we can go back and forth so that all of the variability is accounted for; the percent of variability explained by the p principal components is 100%.
2. Because we chose the principal components successively to explain more and more of the variance, we have

$$V_1 \geq V_2 \geq \cdots \geq V_p \geq 0$$

3. The first m principal components explain as much of the total variability as it is possible to explain by m linear functions of the X_j variables.

We now proceed to a geometric interpretation of the principal components. Consider the case where $p = 2$. That is, we observe two variables X_1 and X_2. Plot, as previously in this chapter, the ith data point in the coordinate system that is centered about the means for the X_1 and X_2 variables. Draw a line in the direction of the first principal component and project the data point onto the line. This is done in Figure 14.5.

The square of the distance of the data point from the new origin, which is the sample mean, is given by the following equation, using the Pythagorean theorem:

$$d_i^2 = (X_{i1} - \overline{X}_1)^2 + (X_{i2} - \overline{X}_2)^2 = \sum_{j=1}^{2} (X_{ij} - \overline{X}_j)^2$$

The square of the distance f_i of the projection turns out to be the difference between the value of the first principal component for the ith observation and the mean of the first principal component squared. That is,

$$f_i^2 = (Y_{i1} - \overline{Y}_1)^2$$

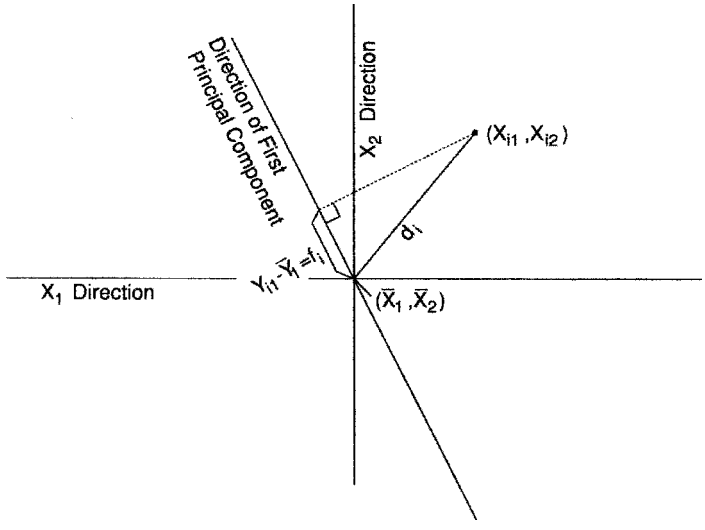


Figure 14.5 Projection of a data point onto the first principal component direction.

It is geometrically clear that the distance d_i is larger than f_i. The ith data point will be better represented by its position along the line if it lies closer to the line, that is, if f_i is close to d_i. One way we might judge the adequacy of the variability explained by the first principal component would be to take the ratio of the sum of the lengths of the f_i's squared to the sum of the lengths of the d_i's squared. If we do this, we have

$$\frac{\sum_{i=1}^{n} f_i^2}{\sum_{i=1}^{n} d_i^2} = \frac{\sum_{i=1}^{n} (Y_{i1} - \overline{Y}_1)^2}{\sum_{i=1}^{n} \sum_{j=1}^{2} (X_{ij} - \overline{X}_j)^2} = \frac{V_1}{V} \tag{7}$$

That is, we have the proportion of the variability explained. If we multiplied the equation throughout by 100, we would have the percent of the variability explained by the first principal component. This gives us an alternative way of characterizing the first principal component. The direction of the first principal component is the line for which the following holds: When the data are projected onto this line, the sum of the squares of the projections is as large as possible; equivalently, the sum of squares is as close as possible to the sum of squares of the lengths of the lines to the original data points from the origin (which is also the mean). From this we see that the percent of variability explained by the first principal component will be 100 if and only if the lengths d_i and f_i are all the same; that is, the first principal component will explain all the variability if and only if all of the data points lie on a single line. The closer all the data points come to lie on a single line, the larger the percent of variability explained by the first principal component.

We now proceed to examine the geometric interpretation in three dimensions. In this case we consider a data point plotted not in terms of the original axes X_1, X_2, and X_3 but rather, in terms of the coordinate system given by the principal components Y_1, Y_2, and Y_3. Figure 14.6 presents such a plot for a particular data point. The figure is a two-dimensional representation of a three-dimensional situation; two of the axes are vertical and horizontal on the paper. The third axis recedes into the plane formed by the page in this book. Consider the ith data point,

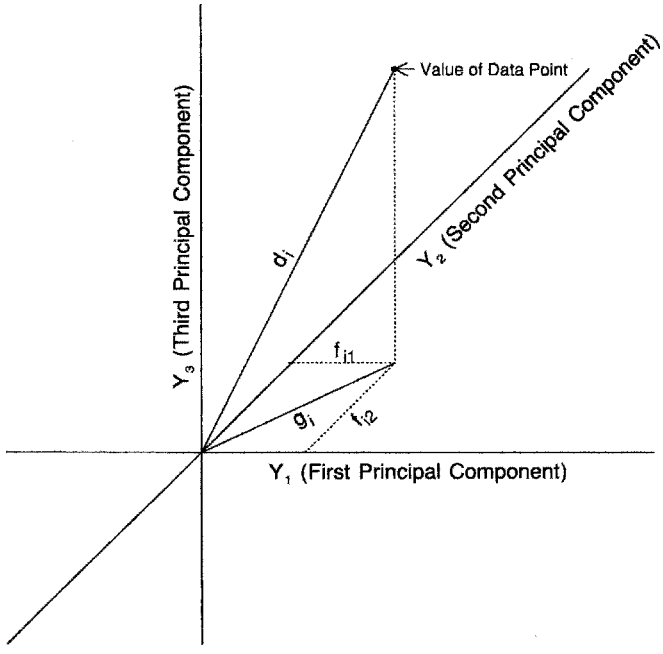


Figure 14.6 Geometric interpretation of principal components for three variables.

which lies at a distance d_i from the origin that is at the mean of the data points. This point also turns out to be the mean of the principal component values. Suppose, now, that we drop a line down into the plane that contains the axes corresponding to the first two principal components. This is indicated by the vertical dotted line in the figure. This point in the plane we could now project onto the value for the first and second principal components. These values, with lengths f_{i1} and f_{i2}, are the same as we would get by dropping perpendiculars directly from the point to those two axes. Again, we might assess the adequacy of the characterization of the data point by the first two principal components by comparing the length of its projection in the plane, g_i, with the length of the line from the origin to the original data point, d_i. If we compare the squares of these two lengths, each summed over all of the data points, and use the Pythagorean theorem again, the following results hold:

$$\begin{aligned}\frac{\sum_{i=1}^n g_i^2}{\sum_{i=1}^n d_i^2} &= \frac{\sum_{i=1}^n f_{i1}^2 + \sum_{i=1}^n f_{i2}^2}{\sum_{i=1}^n d_i^2} \\ &= \frac{\sum_{i=1}^n [(Y_{i1} - \overline{Y}_1)^2/(n-1)] + \sum_{i=1}^n [(Y_{i1} - \overline{Y}_2)^2/(n-1)]}{\sum_{i=1}^n d_i^2/(n-1)} \\ &= \frac{V_1 + V_2}{V}\end{aligned}$$

Using this equation, we see that the percent of the variability explained by the first two principal components is the ratio of the squared lengths of the projections onto the plane of the first two principal components divided by the squared lengths of the original data points about their mean. This also gives us a geometric interpretation of the total variance. It is the sum for all the data points of the squares of the distance between the point corresponding to the mean of the sample and the original data points. In other words, the first two principal components may be characterized as giving a plane for which the projected points onto the plane contain as high a proportion as possible of the squared lengths associated with the original data points. From this we see that the percent of variability explained by the first two principal components will be 100 if and only if all of the data points lie in some plane through the origin, which is the mean of the data.

The coefficients associated with the principal components are usually calculated by computer; in general, there is no easy formula to obtain them. Thus, the examples in this chapter will begin with the coefficients for the principal components and their variance. (There is an explicit solution when there are only two variables, and this is given in Problem 14.9.)

Example 14.1. We turn to the data of Table 14.1. Equations for the principal components are

$$\begin{aligned}Y_1 &= -0.6245X + 0.7809Y \\ Y_2 &= 0.7809X + 0.6245Y\end{aligned}$$

For the first data point, $(X, Y) = (-0.52, 0.60)$, the values are

$$\begin{aligned}Y_1 &= -0.6245 \times (-0.52) + 0.7809 \times 0.60 = 0.79 \\ Y_2 &= 0.7809 \times (-0.52) + 0.6245 \times 0.60 = -0.03\end{aligned}$$

If we compute all of the numbers, we find that the values for each of the 20 data points on the principal components are as given in Table 14.2.

Table 14.2 Data Point Values

Data		Principal Component Values		Data		Principal Component Values	
X	Y	Y_1	Y_2	X	Y	Y_1	Y_2
−0.52	0.60	0.79	−0.03	0.08	0.23	0.13	0.21
0.04	−0.51	−0.42	−0.28	−0.06	−0.59	−0.42	−0.42
1.29	−1.19	−1.74	0.26	1.25	−1.25	−1.76	0.19
−1.12	1.90	2.19	0.31	0.53	−0.45	−0.68	0.13
−1.02	0.31	0.88	−0.60	0.14	0.47	0.28	0.40
0.10	−1.15	−0.96	−0.64	0.48	−0.11	−0.39	0.31
−0.32	−0.13	0.10	−0.33	−0.61	1.04	1.20	0.17
0.08	−0.17	−0.18	−0.04	−0.47	0.34	0.56	−0.16
0.49	0.18	−0.16	0.50	0.41	0.29	−0.02	0.50
0.54	0.20	0.49	−0.29	−0.22	−0.00	0.13	−0.18

From these data we may compute the sample variance of Y_1 and Y_2 as well as the variance of X and Y. We find the following values:

$$V_1 = 0.861, \qquad V_2 = 0.123, \qquad \text{var}(X) = 0.411, \qquad \text{var}(Y) = 0.573$$

From these data we may compute the percent of variability explained by the two principal components, individually and together.

1. Percent of variability explained by the first principal component $= 100 \times 0.861/(0.411 + 0.573) = 87.5\%$.
2. Percent of variability explained by the second principal component $= 100 \times 0.123/(0.411 + 0.573) = 12.5\%$.
3. Percent of variability explained by the first two principal components $= 100 \times (0.861 + 0.123)/(0.411 + 0.573) = 100\%$.

We see that the first principal component of the data in Figure 14.4 contains a high proportion of the variability. This may also be seen visually by examining the plot while orienting your eyes so that the horizontal line is the direction of the first principal component. Certainly, there is much more variability in that direction than in direction 2, the direction of the second principal component.

14.5 USE OF THE COVARIANCE, OR CORRELATION, VALUES AND PRINCIPAL COMPONENT ANALYSIS

The coefficients of the principal components and their variances can be computed by knowing the covariances between the X_j's. One might think that as a general search for relationships among X_j's, the principal component will be appropriate as an exploratory tool. Sometimes, this is true. However, consider what happens when we have different scales of measurement. Suppose, for example, that among our units, one unit is height in inches and another is systolic blood pressure in mmHg. In principal component analysis we are adding the variability in the two variables. Suppose now that we change our measurement of height from inches to feet. Then the standard deviation of the height variable will be divided by 12 and the variance will be divided by 144. In the total variance the contribution of height will have dropped greatly.

Equivalently, the blood pressure contribution (and any other variables) will become much more important. Recomputing the principal components will produce a different answer. In other words, the measurement units are important in finding the principal component because the variance of any individual variable is compared directly to the variance of another variable without regard to whether or not the units are appropriate for the comparison. We reiterate: *The importance of a variable in principal component analysis changes with a change of scale of one or more of the variables*. For this reason, principal component analysis is most appropriate and probably has its best applications when all the variables are measured in the same units; for example, the X_j variables may be measurements of length in inches, with the variables being measurements of different parts of the body, and the covariances between variables such as arm length, leg length, and body length.

In some situations with differing units, one still wants to try principal component analyses. In this case, standardized variables are often used; that is, we divide each variable by its standard deviation. Each rescaled variable then has a variance of 1 and the covariance matrix of the new standardized variables is the correlation matrix of the original variables. The interpretation of the principal components is now less clear. If many of the variables are highly correlated, the first principal component will tend to pick up this fact; for example, with two variables, a high correlation means the variables lie along a line. The ellipse of concentration has one axis along the line; that direction gives us the direction of the first principal component. When standardized variables are used, since each variable has a variance of 1, the sum of the variances is p. In looking at the percent of variability explained, there is no need to compute the total variance separately; it is p, the number of variables. We emphasize that when the correlations are used, there should be some reason for doing this beside the fact that the variables do not have measurements in comparable units.

14.6 STATISTICAL RESULTS FOR PRINCIPAL COMPONENT ANALYSIS

Suppose that we have a sample of size n from a multivariate normal distribution with unknown covariances. Let $V_i(\text{pop})$ be the true (unknown) population value for the variance of the ith principal component when computed from the (unknown) true variances; let V_i be the variance of the principal components computed from the sample covariances. Then the following are true:

1.

$$\frac{V_i - V_i(\text{pop})}{V_i(\text{pop})\sqrt{2/(n-1)}}, \qquad i = 1, \ldots, p \tag{8}$$

for large n is approximately a standard normal, $N(0, 1)$, random variable. These variables are approximately statistically independent.

2. $100(1-\alpha)\%$ confidence intervals for $V_i(\text{pop})$ for large n are given by

$$\left(\frac{V_i}{1 + z_{1-\alpha/2}\sqrt{2/(n-1)}}, \frac{V_i}{1 - z_{1-\alpha/2}\sqrt{2/(n-1)}} \right) \tag{9}$$

where $z_{1-\alpha/2}$ is the $1-\alpha/2$ percentile value of the $N(0, 1)$ distribution.

Further statistical results on principal component analysis are given in Morrison [1976] and Timm [1975].

Principal component analysis is a least squares technique, as were analysis of variance and multiple linear regression. Outliers in the data can have a large effect on the results (as in other cases where least squares techniques are used).

14.7 PRESENTING THE RESULTS OF A PRINCIPAL COMPONENT ANALYSIS

We have seen that principal component analysis is designed to explain the variability in data. Thus, any presentation should include:

1. The variance of the principal components
2. The percent of the total variance explained by each individual principal component
3. The percent of the total variance explained cumulatively by the first m terms (for each m)

It is also useful to know how closely each variable X_j is related to the values of the principal components Y_i; this is usually done by presenting the correlations between each variable and each of the principal components. Let

$$Y_i = a_{i1}X_1 + \cdots + a_{ip}X_p$$

The correlation between one of the original variables X_j and the kth principal component Y_i is given by

$$r_{jk} = \text{correlation of } X_j \text{ and } Y_k = \frac{a_{kj}\sqrt{V_k}}{s_j} \tag{10}$$

In this equation, V_i is the variance of the ith principal component, while s_j is the standard deviation of X_j. These results are summarized in Table 14.3.

By examining the variables that are highly correlated with a principal component, we can see which variables contribute most to the principal component. Alternatively, glancing across the rows for each variable X_j we may see which principal component has the highest correlation with the variable. An X_i that has the highest correlations with the first few principal components is contributing more to the overall variability than variables with small correlations with the first few principal components. In Section 14.9, several examples of principal component analysis are given, including an example of the use of such a summary table (Table 14.4).

Table 14.3 Summary of a Principal Component Analysis Using Covariances

	Correlation of the Principal Components and the X_j's				Standard
Variables	1	2	$\cdots$	p	Deviations of the X_j
X_1	$\frac{a_{11}\sqrt{V_1}}{s_1}$	$\cdots$	$\cdots$	$\frac{a_{p1}\sqrt{V_p}}{s_1}$	s_1
$\vdots$	$\vdots$	$\vdots$	$\vdots$	$\vdots$	$\vdots$
X_p	$\frac{a_{1p}\sqrt{V_1}}{s_p}$	$\cdots$	$\cdots$	$\frac{a_{pp}\sqrt{V_p}}{s_p}$	s_p
Variance of principal component	V_1	V_2	$\cdots$	V_p	
% of total variance	$\frac{100V_1}{V}$	$\cdots$	$\cdots$	$\frac{100V_p}{V}$	
Cumulative % of total variance	$\frac{100V_1}{V}$	$\frac{100(V_1+V_2)}{V}$	$\cdots$	1	

Table 14.4 Data for Example 14.2

Principal Component	Variance Explained	Percent of Total Variance	Cumulative Percent of Total Variance
1	7.82	41.1	41.1
2	4.46	23.5	64.6
3	1.91	10.1	74.7
4	0.88	4.6	79.4
5	0.76	4.0	83.3
6	0.56	2.9	86.3
7	0.45	2.4	88.6
8	0.38	2.0	90.7
9	0.35	1.9	92.5
10	0.31	1.6	94.1
11	0.19	1.0	95.1
12	0.18	0.9	96.1
13	0.16	0.8	96.9
14	0.14	0.7	97.7
15	0.13	0.7	98.3
16	0.10	0.5	98.9
17	0.10	0.5	99.4
18	0.06	0.3	99.7
19	0.05	0.3	100.0

14.8 USES AND INTERPRETATION OF PRINCIPAL COMPONENT ANALYSIS

Principal component analysis is a technique for explaining variability. Following are some of the uses of principal components:

1. Principal component analysis is a search for linear relationships for explaining variability in a multivariate sample. The first few principal components are important because they may summarize a large proportion of the variability. However, the understanding of which variables contribute to the variability is important only if most of the variance comes about because of important relationships among the variables. After all, we can increase the variance of a variable, say X_1, by increasing the error of measurement. If we have a phenomenally large error of measurement, the variance of X_1 will be much larger than the variances of the rest of the variables. In this case, the first principal component will be approximately equal to X_1, and the amount of variability explained will be close to 1. However, such knowledge is not particularly useful, since the variability in X_1 does not make X_1 the most important variable, but in this case, reflects a very poorly measured quantity. Thus, to decide that the first few principal components are important summary variables, you must feel that the relationships among them come from linear relationships which may shed some light on the data being studied.

2. In some cases the first principal component is relatively uninteresting, with more informative relationships being found in the next few components. One simple case comes from analyzing physical measurements of plants or animals to display species differences: the first principal component may simply reflect differences in size, and the next few components give the more interesting differences in shape.

3. We may take the first two principal components and plot the values for the first two principal components of the data points. We know that among all possible plots in only two dimensions, this one gives the best fit in one precise mathematical sense. However, it should be noted that other techniques of multivariate analysis give two-dimensional plots that are the best fit or most interesting in other precise mathematical senses (see Note 14.1).

4. In some situations we have many measurements of somewhat related variables. For example, we might have a large number of size measurements on different portions of the human body. It may be that we want to perform a statistical inference, but the large number of variables for the relatively small number of cases involved makes such statistical analysis inappropriate. We may summarize the data by using the values on the first few principal components. *If the variability is important* (!), we have then reduced the number of variables without getting involved in multiple comparison problems. We may proceed to statistical analysis. For example, suppose that we are trying to perform a discriminant analysis and want to use size as one of the discriminating variables. However, for each of a relatively small number of cases we may have many anthropometric measurements. We might take the first principal component as a variable to summarize all the size relationships. One of the examples of principal component analysis below gives a principal component analysis of physical size data.

14.9 PRINCIPAL COMPONENT ANALYSIS EXAMPLES

Example 14.2. Stoudt et al. [1970] consider measurements taken on a sample of adult females from the United States. The correlations among these measurements (as well as weight and age) are given in Table 11.21. The variance explained for each principal component is presented in Table 14.4.

These data are very highly structured. Only three (of 19) principal components explain over 70% of the variance. Table 14.5 summarizes the first three principal components. The

Table 14.5 Example 14.2: First Three Principal Components

	Correlation of the Principal Components and the Variables		
Variables	1	2	3
SITHTER	0.252	0.772	0.485
SITHTNORM	0.235	0.748	0.470
KNEEHT	0.385	0.722	−0.392
POPHT	0.005	0.759	−0.444
ELBOWHT	0.276	0.243	0.783
THIGHHT	0.737	−0.007	0.204
BUTTKN	0.677	0.476	−0.348
BUTTPOP	0.559	0.411	−0.444
ELBOWBR	0.864	−0.325	−0.033
SEATBR	0.832	−0.050	0.096
BIACROM	0.504	0.350	−0.053
CHEST	0.890	−0.228	−0.018
WAIST	0.839	−0.343	−0.106
ARMGTH	0.893	−0.267	0.068
ARMSKIN	0.733	−0.231	0.124
INFRASCA	0.778	−0.371	0.056
HT	0.251	0.923	−0.051
WT	0.957	−0.057	0.001
AGE	0.222	−0.488	−0.289
Variance of principal components	7.82	4.46	1.91
Percent of total variance	41.1	23.5	10.1
Cumulative percent of total variance	41.1	64.6	74.7

first component, in the direction of greatest variation, is associated heavily with the weight variables. The highest correlation is with weight, 0.957. Other variables associated with size—such as chest and waist measurements, arm girth, and skinfolds—also are highly correlated with the first principal component. The second component is most closely associated with physical length measurements. Height is the most highly correlated variable. Other variables with correlations above 0.7 are the sitting heights (normal and erect), knee height, and popliteal height.

Since we are working with a correlation matrix, the total variance is 19, the number of variables. The average variance, in fact the exact variance, per variable is 1. Only these first three principal components have variance greater than 1. The other 16 directions correspond to a variance of less than 1.

Example 14.3. Reeck and Fisher [1973] performed a statistical analysis of the amino acid composition of protein. The mole percent of the 18 amino acids in a sample of 207 proteins was examined. The covariances and correlations are given in Table 14.6. The diagonal entries and numbers above them give the variances and covariances; the lower numbers are the correlations. The mnemonics are:

Asp	Aspartic acid	Met	Methionine
Thr	Threonine	Ile	Isoleucine
Ser	Serine	Leu	Leucine
Glu	Glutamic acid	Tyr	Tyrosine
Pro	Proline	Phe	Phenylalanine
Gly	Glycine	Trp	Tryptophan
Ala	Alanine	Lys	Lysine
Cys/2	Half-cystine	His	Histidine
Val	Valine	Arg	Arginine

The principal component analysis applied to the data produced Table 14.7, where k is the dimension of the subspace used to represent the data and C is the proportion of the total variance accounted for in the best k-dimensional representation.

In contrast to Example 14.2, eight principal components are needed to account for 70% of the variance. In this example there are no simple linear relationships (or directions) that account for most of the variability. In this case the principal component correlations are not presented, as the results are not very useful.

14.10 FACTOR ANALYSIS

As in principal component analysis, factor analysis looks at the relationships among variables as expressed by their correlations or covariances. While principal component analysis is designed to model and explain as much of the variability as possible, factor analysis seeks to explain the relationships among the variables. The assumption of the model is that the relationships may be explained by a few unobserved variables, which will be called *factors*. It is hoped that fewer factors than the original number of variables will be needed to explain the relationships among the variables. Thus, conceptually, one may simplify the understanding of the correlations between the variables.

It is difficult to present the technique without having the model and many of the related issues discussed first. However, it is also difficult to understand the related issues without examples. Thus, it is suggested that you read through the material about the mathematical model, go through the examples, and then with this understanding, reread the material about the mathematical model.

Table 14.6 Example 14.3: Reeck and Fisher [1973] Covariance/Correlation Matrix[a]

	Asp	Thr	Ser	Glu	Pro	Gly	Ala	Cys/2	Val	Met	Ile	Leu	Tyr	Phe	Trp	Lys	His	Arg
Asp	6.5649	0.2449	0.7879	−1.5329	−1.9141	−1.8328	−1.7003	−0.4974	−0.1374	0.0810	0.6332	−1.0855	0.6413	0.1879	0.3873	0.7336	0.0041	−1.5633
Thr	0.0517	3.4209	1.3998	−1.3341	−0.3531	−0.7752	−0.6428	0.4468	0.3603	−0.3502	0.1620	−1.2836	0.1804	−0.0978	0.1114	−0.3348	−0.2594	−0.8938
Ser	0.1219	0.2999	6.3687	−1.6465	0.1876	−0.8922	−1.3593	−0.3123	0.6659	−0.6488	−0.3738	−1.1125	0.4403	0.0432	0.2552	−1.6972	−0.3025	−1.4289
Glu	−0.1789	−0.2157	−0.1951	11.1880	−0.5866	−2.1665	−0.7732	−0.1443	−1.5346	0.0002	−0.3804	1.6210	−1.1824	−0.6684	−0.6778	0.0192	−0.3154	0.1169
Pro	−0.3566	−0.0911	−0.0355	−0.0837	4.3891	1.4958	−0.4259	1.0159	−0.7017	−0.4171	−0.8453	−0.9980	−0.0868	−0.1187	0.1163	−0.7021	−0.1612	0.4801
Gly	−0.2324	−0.1362	−0.1149	−0.2105	0.2320	9.4723	1.2857	0.1737	−0.3883	−0.4226	−0.2812	−2.3936	−0.8971	−0.7784	−0.2637	−1.0861	−0.2526	−0.0037
Ala	−0.2417	−0.1266	−0.1962	−0.0842	−0.0741	0.1522	7.5371	−2.1250	0.8498	0.1810	−0.4183	1.2480	−1.3374	−0.4320	−0.5219	−1.1641	−0.2730	0.0701
Cys/2	−0.0717	0.0892	−0.0457	−0.0159	0.1790	0.0208	−0.2857	7.3393	−1.3667	−0.4788	−1.3959	−2.3443	0.5408	−0.6282	0.1136	0.2727	−0.7482	0.1447
Val	−0.0275	0.1001	0.1356	−0.2357	−0.1721	−0.0648	0.1590	−0.2592	3.7885	−0.0632	0.5700	0.2767	−0.1348	−0.2303	−0.2792	−0.7921	−0.0632	−0.8223
Met	0.0294	−0.1759	−0.2388	0.0001	−0.1849	−0.1275	0.0612	−0.1642	−0.0302	1.1589	0.2493	0.2438	−0.1397	0.2060	−0.0159	0.1715	0.1457	0.0945
Ile	0.1426	0.0505	−0.0855	−0.0656	−0.2328	−0.0527	−0.0879	−0.2974	0.1690	0.1337	3.0023	−0.1857	−0.2785	−0.0870	−0.1296	0.2361	−0.0829	−0.3956
Leu	−0.1701	−0.2786	−0.1770	0.1946	−0.1912	−0.3122	0.1825	−0.3474	0.0571	0.0928	−0.0430	6.2047	−1.0362	0.2515	−0.2332	−0.6337	0.3951	1.0593
Tyr	0.1605	0.0625	0.1119	−0.2267	−0.0266	−0.1869	−0.3123	0.1280	−0.0444	−0.0832	−0.1031	−0.2667	0.1823	0.1659	0.9201	−0.5061	0.0855	0.1436
Phe	0.0525	−0.0379	0.0123	−0.1431	−0.0406	−0.1811	−0.1126	−0.1660	−0.0847	0.1370	−0.0360	0.0723	0.2262	1.9512	0.2223	−0.8382	0.3434	0.1796
Trp	0.1576	0.0628	0.1054	−0.2113	0.0579	−0.0893	−0.1982	0.0437	−0.1495	−0.0154	−0.0780	−0.0976	0.1823	0.1659	0.9201	−0.5061	0.0855	0.1436
Lys	0.1061	−0.0670	−0.2491	0.0021	−0.1241	−0.1307	−0.1571	0.0373	−0.1507	0.0590	0.0505	−0.0942	0.0733	−0.2223	−0.1954	7.2884	−0.1830	−1.0898
His	0.0014	−0.1194	−0.1020	−0.0803	−0.0655	−0.0699	−0.0847	−0.2351	−0.0276	0.1152	−0.0408	0.1350	0.0314	0.2093	0.0759	0.0577	1.3795	0.2280
Arg	−0.3068	−0.2430	−0.2847	0.0176	0.1152	−0.0006	0.0128	0.0269	−0.2124	0.0441	−0.1148	0.2138	−0.0882	0.0646	0.0753	−0.2030	0.0976	3.9550

[a]Diagonal and upper entries are variances and covariances. Below the diagonal are the correlations.

Table 14.7 Principal Component Analysis Data

k	C	k	C	k	C
1	0.13	7	0.66	13	0.90
2	0.26	8	0.70	14	0.93
3	0.37	9	0.75	15	0.95
4	0.46	10	0.79	16	0.98
5	0.55	11	0.83	17	1.00
6	0.61	12	0.86	18	1.00

We now turn to the model. We observe jointly distributed random variable $X_1, \ldots, X_p$. The assumption is that each X is a linear sum of the factors plus some remaining residual variability. That is, the model is the following:

$$\begin{array}{ccccccccccccc} X_1 & = & E(X_1) & + & \lambda_{11}F_1 & + & \lambda_{12}F_2 & + & \cdots & + & \lambda_{1k}F_k & + & e_1 \\ \vdots & & \vdots & & \vdots & & \vdots & & & & \vdots & & \vdots \\ X_p & = & E(X_p) & + & \lambda_{p1}F_1 & + & \lambda_{p2}F_2 & + & \cdots & + & \lambda_{pk}F_k & + & e_p \end{array} \tag{11}$$

In this model, each X_i is equal to its expected value, plus a linear sum of k factors and a term for residual variability. This looks like a series of multiple regression equations; each of the variables X_i is regressed on the variables $F_1, \ldots, F_k$. There are, however, major differences between this model and the multiple regression model of Chapter 11. Observations and assumptions about this model are the following:

1. The factors F_j are *not* observed; only the $X_1, \ldots, X_p$ are observed, although the X_i variables are expressed in terms of these smaller number of factors F_j.
2. The e_i (which are also unobserved) represent variability in the X_i not explained by the factors. We do *not* assume that these residual variability terms have the same distribution.
3. Usually, the number of factors k is unknown and must be determined from the data. We shall first consider the model and the analysis where the number of factors is known; later, we consider how one might search for the appropriate number of factors.

Assumptions made in the model, in addition to the linear equations given above, are the following:

1. The factors F_j are standardized; that is, they have mean zero and variance 1.
2. The factors F_j are uncorrelated with each other, and they are uncorrelated with the e_i terms. See Section 14.12 for a relaxation of this requirement.
3. The e_i's have mean zero and are uncorrelated with each other as well as with the F_j's. They may have different variances.

It is a fact that if p factors F are allowed, there is no need for the residual variability terms e_i. One can reproduce any pattern of covariances or correlations using p factors when p variables X_i are observed. This, however, is not very useful because we have summarized the p variables which were observed with p unknown variables. Thus, in general, we will be interested in k factors, where k is less than p.

Let ψ_i be the variance of e_i. With the assumptions of the model above, the variance of each X_i can be expressed in terms of the coefficients λ_{ij} of the factors and the residual variance ψ_i.

The equation giving the relationship for k factors is

$$\text{var}(X_i) = \lambda_{i1}^2 + \cdots + \lambda_{ik}^2 + \psi_i \tag{12}$$

In words, the variance of each X_i is the sum of the squares of the coefficients of the factors, plus the variance of e_i. The variance of X_i has two parts. The sum of the coefficients λ_{ij} squared depends on the factors; the factors contribute in common to all of the X_i's. The e_i's correlate only with their own variable X_i and not with other variables in the model. In particular, they are uncorrelated with all of the X_i's except for the one corresponding to their index. Thus, we have broken down the variance into a part related to the factors that each variable has in common, and the unique part related to the residual variability term. This leads to the following definition.

Definition 14.5. $c_i = \sum_{j=1}^{k} \lambda_{ij}^2$ is called the *common part of the variance* of X_i, c_i is also called the *communality* of X_i, ψ_i is called the *unique* or *specific part of the variance* of X_i, and ψ_i is also called the *uniqueness* or *specificity*.

Although factor analysis is designed to explain the relationships between the variables and not the variance of the individual variables, if the communalities are large compared to the specificities of the variables, the model has also succeeded in explaining not only the relationships among the variables but the variability in terms of the common factors.

Not only may the variance be expressed in terms of the coefficients of the factors, but the covariance between any two variables may also be expressed by

$$\text{cov}(X_i, X_j) = \lambda_{i1}\lambda_{j1} + \cdots + \lambda_{ik}\lambda_{jk} \qquad \text{for } i \neq j \tag{13}$$

These equations explain the relationships among the variables. If both X_i and X_j have variances equal to 1, this expression gives the correlation between the two variables. There is a standard name for the coefficients of the common factors.

Definition 14.6. The coefficients λ_{ij} are called the *factor loadings* or *loadings*. λ_{ij} represents the loading of variable X_i and factor F_j.

In general, $\text{cov}(X_i, F_j) = \lambda_{ij}$. That is, λ_{ij} is the covariance between X_i and F_j. If X_i has variance 1, for example if it is standardized, then since F_j has variance 1, the factor loading is the correlation coefficient between the variable and the factor.

We illustrate the method by two examples.

Example 14.4. We continue with the measurement data of U.S. females of Example 14.2. A factor analysis with three underlying factors was performed on these data. Since we are trying to explain the correlations between the variables, it is useful to examine the fit of the model by comparing the observed and modeled correlations. We do this by examining the residual correlation.

Definition 14.7. The *residual correlation* is the observed correlation minus the fitted correlation from the factor analysis model.

Table 14.8 gives the residual correlations below the diagonal; on the diagonal are the estimated uniquenesses, the part of the (standardized) variance not explained by the three factors.

A rule of thumb is that the correlation has been explained reasonably when the residual is less than 0.1 in absolute value. This is convenient because it is easy to scan the residual matrix for a zero after a decimal point. Of course, depending on the purpose, more stringent requirements may be considered.

Table 14.8 Residual Correlations: Example 14.4

		STHTER 1	STHTNORM 2	KNEEHT 3	POPHT 4	ELBOWHT 5
STHTER	1	0.034				
STHTNORM	2	0.002	0.151			
KNEEHT	3	−0.001	0.001	0.191		
POPHT	4	0.001	0.002	0.048	0.276	
ELBOWHT	5	−0.001	−0.011	0.011	−0.004	0.474
THIGHHT	6	−0.009	0.004	0.003	−0.076	0.035
BUTTKN	7	−0.002	0.000	−0.016	−0.056	−0.021
BUTTPOP	8	−0.002	0.011	−0.042	−0.064	−0.035
ELBOWBR	9	0.000	0.013	−0.004	0.014	−0.010
SEATBR	10	−0.002	0.013	0.016	−0.041	0.020
BIACROM	11	0.004	−0.005	−0.000	0.014	−0.089
CHEST	12	0.003	0.004	0.003	0.030	−0.015
WAIST	13	0.005	−0.004	0.002	0.032	0.006
ARMGTH	14	−0.001	−0.004	0.004	−0.009	0.003
ARMSKIN	15	−0.005	0.016	0.025	−0.012	−0.004
INFRASCA	16	−0.002	0.006	0.020	0.016	0.004
HT	17	0.000	−0.001	−0.000	0.003	0.008
WT	18	−0.000	−0.009	−0.004	−0.005	0.008
AGE	19	0.002	0.024	0.003	0.024	−0.042

		THIGHHT 6	BUTTKN 7	BUTTPOP 8	ELBOWBR 9	SEATBR 10
THIGHHT	6	0.499				
BUTTKN	7	0.062	0.251			
BUTTPOP	8	0.040	**0.136**	0.425		
ELBOWBR	9	−0.012	−0.017	−0.016	0.158	
SEATBR	10	0.035	0.070	0.010	−0.016	0.338
BIACROM	11	0.049	−0.035	−0.039	0.012	−0.042
CHEST	12	−0.038	−0.044	−0.017	0.036	−0.056
WAIST	13	−0.067	−0.023	−0.021	0.037	−0.029
ARMGTH	14	0.005	0.005	0.007	−0.014	0.008
ARMSKIN	15	0.048	0.019	0.021	−0.030	0.047
INFRASCA	16	0.004	−0.025	−0.007	−0.003	−0.030
HT	17	−0.003	−0.001	0.001	0.004	−0.014
WT	18	0.017	0.009	−0.004	−0.011	0.019
AGE	19	**−0.172**	−0.056	−0.034	0.078	0.002

		BIACROM 11	CHESTGRH 12	WSTGRTH 13	RTARMGRH 14	RTARMSKN 15
BIACROM	11	0.679				
CHEST	12	0.072	0.148			
WAIST	13	−0.008	0.032	0.172		
ARMGTH	14	−0.014	−0.014	−0.031	0.134	
ARMSKIN	15	−0.053	−0.041	−0.046	0.075	0.487
INFRASCA	16	−0.010	0.013	0.003	0.013	**0.171**
HT	17	0.002	−0.000	−0.002	−0.001	0.003
WT	18	−0.003	0.000	0.004	0.009	−0.030
AGE	19	**−0.106**	0.033	0.105	−0.017	−0.012

		INFRASCA 16	HT 17	WT 18	AGE 19
INFRASCA	16	0.317			
HT	17	0.002	0.056		
WT	18	−0.018	0.001	0.057	
AGE	19	−0.017	0.016	−0.034	0.770

Table 14.9 Factor Loadings for a Three-Factor Model: Example 14.4

		Factor Loadings (Pattern)[a]		
Variable	Number	Factor 1	Factor 2	Factor 3
SITHTER	1		0.346	0.920
SITHTNORM	2		0.332	0.859
KNEEHT	3		0.884	0.146
POPHT	4	−0.271	0.801	
ELBOWHT	5	0.222	−0.120	0.680
THIGHHT	6	0.672	0.125	0.181
BUTTKN	7	0.436	0.741	
BUTTPOP	8	0.339	0.679	
ELBOWBR	9	0.914		
SEATBR	10	0.781	0.171	0.150
BIACROM	11	0.344	0.390	0.225
CHEST	12	0.916	0.114	
WAIST	13	0.898		−0.126
ARMGTH	14	0.929		
ARMSKIN	15	0.714		
INFRASCA	16	0.823		
HT	17		0.804	0.538
WT	18	0.929	0.265	0.103
AGE	19	0.328	−0.124	−0.328
VP		7.123	3.632	2.628
Proportion var.		0.375	0.191	0.138
Cumulative var.		0.375	0.566	0.704

[a]Loadings less than 0.1 have been omitted.

In this example there are four large absolute values of residuals (−0.172, 0.171, 0.136, and −0.106). This suggests that more factors are needed. (In Problem 14.10 we consider analysis of these data with more factors.) The factor loadings are presented in Table 14.9. Loadings below 0.1 in absolute value are omitted, making it easier to see which variables are related to which factors. In this example the first factor has high loadings on weight and bulk measurements (variables 14, 18, 12, 9, 13, 16, 10, 15, and 6) and might be called a *weight* factor. The second factor has high loadings on length or height measurements (variables 3, 17, 4, 7, and 8) and might be considered a *height* factor. The third factor seems to be a *sitting height* factor.

The variables have been reordered so that variables loading on the same factor appear together. When this is done, clusters of correlated variables often appear, which may be appreciated visually by replacing correlations by symbols or colors. Figure 14.7 is a graph of the correlation data from Table 11.21 using circles whose radius is proportional to the correlation, shaded light gray for positive correlations and dark gray for negative correlations.

The sum of the squares of loadings for a factor (VP) is the portion of the sum of the X_i variances (the total variance) that is explained by the factor. The table also gives this as a proportion of the total and as a cumulative proportion of the total. In all, these factors explain 70% of the variability in the measurements.

Example 14.5. As a second example, consider coronary artery disease patients with left main coronary artery disease. This patient group was discussed in Chaitman et al. [1981]. In this factor analysis, 12 variables were considered and four factors were used with 357 cases. The factor analysis was based on the correlation matrix. The variables and their mnemonics (names) are:

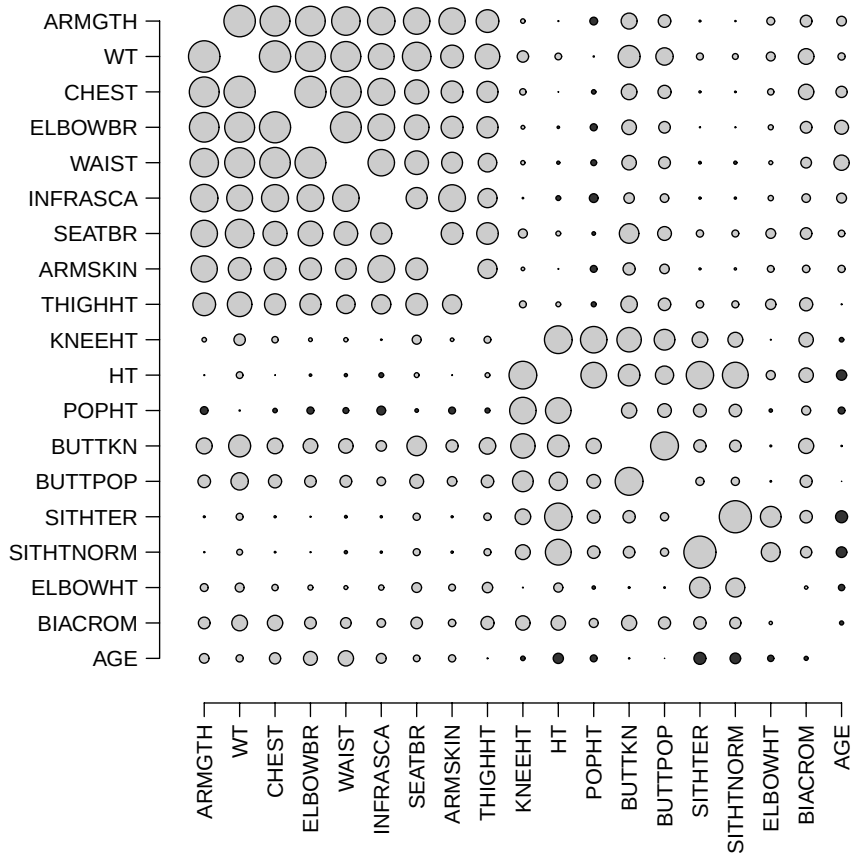


Figure 14.7 Correlations for Example 14.4. The radius of the circle is proportional to the absolute value of the correlation. Light gray circles indicate positive correlations; dark gray circles, negative. (Data from Stoudt et al. [1970].)

- *SEX*: 0 = male, 1 = female.
- *PREVMI*: 0 = history of prior myocardial infarction, 1 = no such history.
- *FEPCHEP*: time in weeks since the first episode of anginal chest pain; this analysis was restricted to patients with anginal chest pain.
- *CHCLASS*: severity of impairment due to angina (chest pain); ranging from I (mildly impaired) to IV (any activity is limited; almost totally bedridden).
- *LMCA*: the percent diameter narrowing of the left main coronary artery; this analysis was restricted to 50% or more narrowing.
- *AGE*: in years.
- *SCORE*: the amount of impairment of the pumping chamber (left ventricle) of the heart; score ranges from 5 (normal) to 30 (not attained).
- *PS70*: the number of proximal (near the beginning of the blood supply) segments of the coronary arteries with 70% or more diameter narrowing.
- *LEFT*: this variable (and RIGHT) tells if the right artery of the heart carries as much blood as normal. LEFT (dominant) implies that the right coronary artery carries little blood; 8.8% of these cases fell into this category. Code: LEFT = 1 (left dominant); LEFT = 0 otherwise.

Table 14.10 Correlations (as the Bottom Entry in Each Cell) and the Residual Correlations (as the Top Entry) in Each Cell[a]

	SEX	PREMI	FEPCHEP	CHCLASS	LMCA	AGE
SEX	0.933					
	1.000					
PREVMI	0.053	0.802				
	0.040	1.000				
FEPCHEP	−0.013	−0.043	0.714			
	−0.002	−0.161	1.000			
CHCLASS	0.056	−0.000	−0.001	0.796		
	0.073	−0.117	0.217	1.000		
LMCA	0.010	0.049	0.005	−0.037	0.989	
	0.012	0.036	0.041	0.004	1.000	
AGE	−0.026	0.019	0.012	−0.001	0.024	0.727
	−0.013	−0.107	0.286	0.227	0.065	1.000
SCORE	0.000	−0.001	−0.000	0.000	0.000	0.000
	0.030	−0.427	0.143	0.185	0.019	0.175
PS70	−0.028	−0.057	−0.027	0.062	−0.016	0.013
	−0.054	−0.188	0.129	0.087	−0.034	0.044
LEFT	0.015	−0.011	−0.015	0.025	0.011	−0.005
	−0.027	−0.022	0.014	0.099	0.063	0.064
RIGHT	0.009	−0.007	−0.009	0.015	0.006	−0.003
	0.054	0.017	−0.033	−0.062	−0.049	−0.077
NOVESLS	0.000	0.000	0.000	−0.000	0.000	0.000
	−0.033	−0.183	0.206	0.014	−0.034	0.130
LVEDP	0.014	0.023	0.001	0.024	0.019	−0.015
	0.020	−0.072	0.119	0.135	0.041	0.109

	SCORE	PS70	LEFT	RIGHT	NOVESLS	LVEDP
SCORE	0.021					
	1.000					
PS70	0.001	0.514				
	0.198	1.000				
LEFT	−0.000	−0.004	0.281			
	0.007	0.004	1.000			
RIGHT	−0.000	−0.004	0.002	0.175		
	−0.041	−0.013	−0.767	1.000		
NOVESLS	0.000	0.000	0.000	0.000	0.000	
	0.284	0.693	−0.071	0.073	1.000	
LVEDP	0.000	−0.025	−0.007	−0.004	0.000	0.930
	0.175	0.029	0.068	−0.086	0.063	1.000

[a]The diagonal entry on top is the estimated uniqueness for each variable. Four factors were used.

- *RIGHT*: there are three types of dominance of the coronary arteries: LEFT above, unbalanced (implicitly coded when LEFT = 0 and RIGHT = 0), and RIGHT. Right dominance is the usual case and occurs when the right coronary artery carries a usual amount of blood. 85.8% of these cases are right dominant: RIGHT = 1; otherwise, RIGHT = 0.
- *NOVESLS*: the number of diseased vessels with $\geq$ 70% stenosis or narrowing of the three major arterial branches above and beyond the left main disease.
- *LVEDP*: the left ventricular end diastolic pressure. This is the pressure in the heart when it is relaxed between beats. A damaged or failing heart has a higher pressure.

Table 14.11 Factor Loadings: Example 14.5

	Factor[a]			
	1	2	3	4
SEX				
PREVMI	−0.103	−0.396	−0.174	
FEPCHEP	0.152		0.535	
CHCLASS			0.125	0.428
LMCA				
AGE				0.502
SCORE		0.108	0.981	0.158
PS70		0.683	0.117	
LEFT	−0.818			0.124
RIGHT	0.917			−0.121
NOVESLS		0.980	0.166	
LVEDP			0.143	0.215
VP[b]	1.525	1.487	1.210	0.872
Proportion var.	0.127	0.124	0.101	0.073
Cumulative var.	0.127	0.251	0.352	0.425

[a] Loadings below 0.100 are omitted.
[b] VP is the portion of sum of squares explained by the factor.

Factor analysis is designed primarily for continuous variables. In this example we have many discrete variables, and even dummy or indicator variables. The analysis is considered more descriptive or explanatory in this case.

Examining the residual values in Table 14.10, we see a fairly satisfactory fit; the maximum absolute value of a residual is 0.062, but most are much smaller. Examination of the uniqueness diagonal column on top shows that the number of vessels diseased, NOVESLS, and SCORE are explained essentially by the factors (uniqueness = 0.000). Some other variables retain almost all of their variability: SEX (uniqueness = 0.993) and LMCA (uniqueness = 0.989). Since we have explained most of the relationships among the variables without using the variability of these factors, SEX and LMCA must be weakly related to the other factors. This is readily verified by looking at the correlation matrix; the maximum absolute correlation involving either of the variables is $r = 0.073$, $r^2 = 0.005$. They explain $\frac{1}{2}$ of 1% or less of the variability in the other variables.

Let us now look at the factor loading (or correlation) values in Table 14.11. The first factor has heavy loadings on the two *dominance* variables. This factor could be labeled a dominance factor. The second factor looks like a *coronary artery disease* (CAD) *factor*. The third is a heart attack, a *ventricular function* factor. The fourth might be labeled a *history* variable.

The first factor exists largely by definition; if LEFT = 1, then RIGHT = 0, and vice versa. The second factor is also expected; if proximal segments are diseased, the arteries are diseased. The third factor makes biological sense. A damaged ventricle often occurs because of a heart attack. The factor with moderate loadings on AGE, FEPCHEP, and CHCLASS is not as clear.

14.11 ESTIMATION

Many methods have been suggested for estimation of the factor loadings and the specificities, that is, the coefficients λ_{ij} and the variance of the residual term e_i. Consider equation (11) and suppose that we change the scale of X_i. Effectively, this is the same as looking at a new variable cX_i; the new value is the old value multiplied by a constant. Multiplying through the equations of equation (11) by the constant, and remembering that we have restricted the factors

to have variance 1, we see that factor loading should be multiplied by the same factor as X_i. Only one method of estimation has this property, which also implies that we can use either the covariance matrix or correlation matrix as input to the estimation. This method is the maximum likelihood method; it is our method of choice. The method seems to give the best fit, where fit is examined as described below. There are drawbacks to the method. There can be multiple possible solutions, and software may not converge to the best solution, particularly if the best solution involves a communality of 1.00 for some variable (the "Heywood case"). The examples in this chapter are fairly well behaved, and essentially the same solution was obtained with the programs BMDP and R. For a review of other methods, we recommend the book by Gorsuch [1983]. This book, which is cited extensively below, contains a nice review of many of the issues of factor analysis. Two shorter volumes are those of Kim and Mueller [1983, 1999].

14.12 INDETERMINACY OF THE FACTOR SPACE

There appears to be something magical about factor analysis; we are estimating coefficients of variables that are not even observed. It is difficult to imagine that one can estimate this at all. In point of fact, it is not possible to estimate the F_i uniquely, but one can estimate the F_i up to a certain indeterminacy. It is necessary to describe this indeterminacy in mathematical terms.

Mathematically, the factors are unique except for possible linear combinations. Geometrically, suppose that we think of the factors (e.g., a model with $k = 2$) as corresponding to values in a plane. Let this plane exist in three-dimensional space. For example, the subspace corresponding to the two factors (i.e., the plane) might be the plane of the paper of this book. Within this three-dimensional space, factor analysis would determine which plane contains the two factors. However, any two perpendicular directions in the factor plane would correspond to factors that equally well fit the data in terms of explaining the covariances or correlations between the variables. Thus, we have the factors identified up to a certain extent, but we are allowed to rotate them within a subspace.

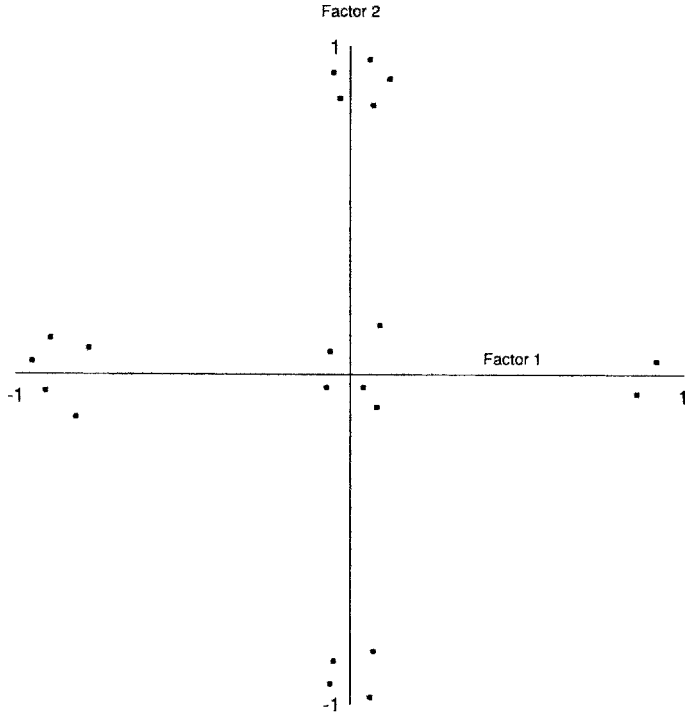
This indeterminacy allows one to "fiddle" with different combinations of factors (i.e., rotations) so that the factors are considered "easy to interpret." As discussed at some length below, one of the strengths and weaknesses of factor analysis is the possibility of finding factors that represent some abstract concept. This task is easiest when the factors are associated with some subset of the variables. That is, one would like factors that have high loadings (in terms of absolute value) on some subset of variables and very low (near zero in absolute value) loadings on the rest of the variables. In this case, the factor is closely associated with the subset of the variables that have large absolute loadings. If these variables have something in common conceptually (e.g., they are all measures of blood pressure) or in a psychological study they all seem to be related to aggressive behavior, one might then identify the specific factor as a blood pressure factor or an aggression factor.

Another complication in the literature of factor analysis is related to the choice of a specific basis in the factor subspace. Suppose for the moment that we are dealing with the correlations among the X_i's. In this case, as we saw before, the loadings on the factors are correlations of the factor with the variable. Thus each loading will be in absolute value less than or equal to 1. It will be easy to interpret our factors if the absolute value is near zero or near 1. Consider Figure 14.8(a) and (b), plots of the loadings on factors 1 and 2, with a separate point for each of the variables X_i. In Figure 14.8(a) there is a very nice pattern. The variables corresponding to points on the factor 1 axis of ± 1 or on the factor 2 axis of ± 1 are variables associated with each of the factors. The variables plotted near zero on both factors have little relationship to the two factors; in particular, factor 1 would be associated with the variables having points near ± 1 along its axis, including variables 1 and 10 as labeled. This would be considered a very nice loading pattern, and easy to interpret, having the simple structure as described above. In Figure 14.8(b) we see that if we look at the original factors 1 and 2, it is difficult to interpret

the data points, but should we rotate by θ as indicated in the figure, we would have factors easy to interpretation (i.e., each factor associated with a subset of the X_i variables). By looking at such plots and then drawing lines and deciding on the angle θ visually, we have what is called *visual rotation*. When the factor subspace contains a variety of factors (i.e., $k > 2$), the situation is not as simple. If we rotate factors 1 and 2 to find a simple interpretation, we will have altered the relationship between factors 1 and 2 and the other factors, and thus, in improving the relationship between 1 and 2 to have a simple form, we may weaken the relationship between 1 and 5, for example. Visual rotation of factors is an art that can take days or even weeks. The advantage of such rotation is that the mind can weigh the different trade-offs. One drawback of visual rotation is that it may be rotated to give factors that conform to some pet hypothesis. Again, the naming and interpretation of factors are discussed below. Thus, visual rotation can take an enormous amount of time and is subject to the biases of the data analyst (as well as to his or her creativity).

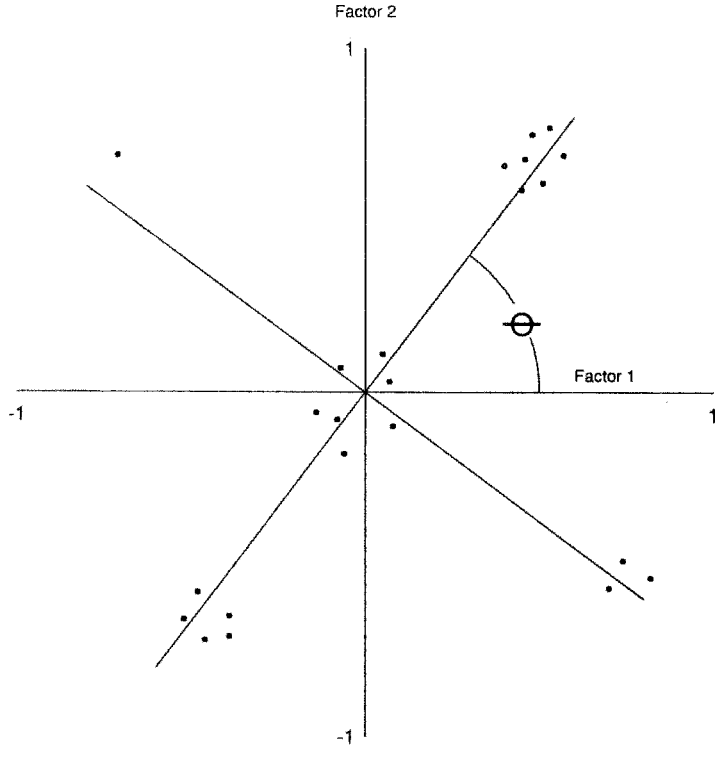
Because of the time constraints for analysis, the complexity of the rotation, and the potential biases, considerable effort has been devoted to developing analytic methods of rotating the factors to get the best rotation. By *analytic* we mean that there is an algorithm describing whether or not a particular rotation for all of the factors is desirable. The computer software, then, finds the best orientation.

Note 14.2 describes two popular criteria, the *varimax method* and the *quartimax method*. A factor analysis is said to have a *general factor* if there is a factor that is associated with all or almost all of the variables. The varimax method can be useful but does not allow general factors and should not be used when such factors may occur. Otherwise, it is considered one of the most



a. Very good loading pattern.
All loadings with absolute value near zero or one.

Figure 14.8 Two-factor loading patterns. (*Continued overleaf*)



b. This pattern suggests rotating
the factors by the angle $\ominus$ to have a simple structure.

Figure 14.8 *continued*

satisfactory methods. (In fact, factor analysis was developed in conjunction with the study of intelligence. In particular, one of the issues was: Does intelligence consist of one general factor or a variety of uncorrelated factors corresponding to different types of intelligence? Another alternative model for intelligence is a general factor plus other factors associated with some subset of measures of performance thought to be associated with intelligence.)

The second popular method is the quartimax method. This method, in contrast to the varimax method, tends to have one factor with large loadings on all the variables and not many large loadings among the rest of the factors. In the examples of this chapter we have used the varimax method. We do not have the space to get into all the issues involved in the selection of a rotation method.

Returning to visual rotation, suppose that we have the pattern shown in Figure 14.9. We see that there are no perpendicular axes for which the loadings are 1 or -1, but if we took two axes corresponding to the dashed lines, the interpretation might be simplified. Factors corresponding to the two dashed lines are no longer uncorrelated with each other, and one may wonder to what extent they are "separate" factors. Such factors are called *oblique factors,* the word *oblique* coming from the geometric picture and the fact that in geometry, oblique lines are lines that do not intersect at a right angle. There are a number of analytic methods for getting oblique rotations, with snappy names such as *oblimax*, *biquartimin*, *binormamin*, and *maxplane*. References to these may be found in Gorsuch [1983]. If oblique axes or bases are used, the formulas for the variance and covariances of the X_i's as given above no longer hold. Again, see Gorsuch for more in-depth consideration of such issues.

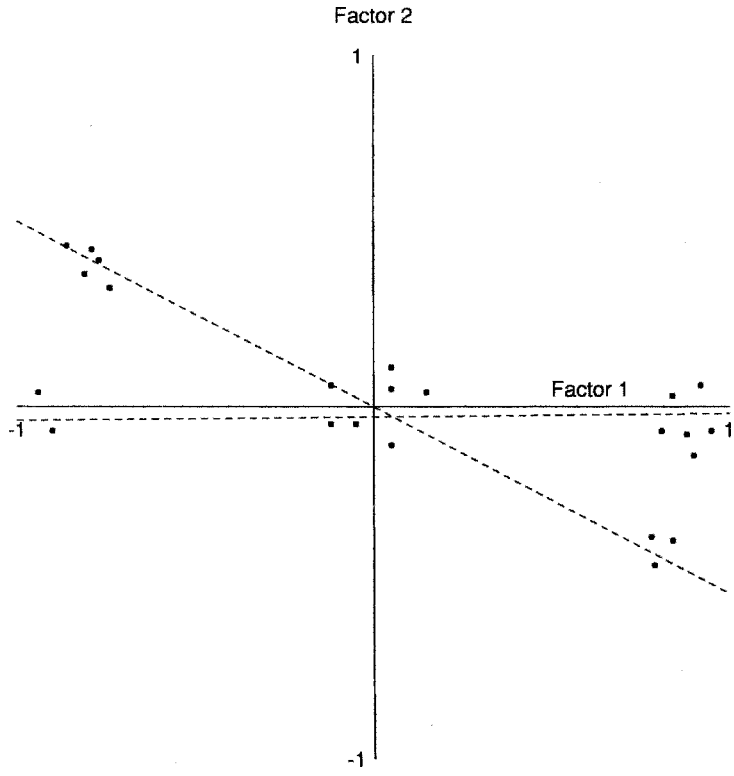


Figure 14.9 Orthogonal and oblique axes for factor loadings.

To try a factor analysis it is not necessary to be expert with every method of estimation and rotation. An exploratory data analysis may be performed to see the extent to which things simplify. We suggest the use of the maximum likelihood estimation method for estimating the coefficients λ_{ij}, where the rotation is performed using the varimax method unless one large general factor is suspected to occur.

Example 14.6. We return to Examples 14.4 and 14.5 and examine plots of the correlations of the variables with the factors. Figure 14.10 shows the plots for Example 14.4, where the numbers on the plot correspond to the variable numbers in Table 14.9.

The plot for factors 2 and 3 looks reasonable (absolute values near 0 or 1). The other two plots have in-between points making interpretation of the factors difficult. This, along with the large residuals mentioned above, suggests trying an analysis with a few more factors.

The plots for Example 14.5 are given in Figure 14.11. These plots suggest factors fairly easy of interpretation, with few, if any, points with moderate loadings on several factors. The interpretation of the factors, discussed in Example 14.5, was fairly straightforward.

14.13 CONSTRAINED FACTOR ANALYSIS

In some situations there are physical constraints on the factors that affect the fitting and interpretation of the factor analysis model. One important application of this sort is in the study of air pollution. Particulate air pollution consists of small particles of smoke, dust, or haze, typically 10 μm in size or smaller. These particles come from a relatively small number of sources, such

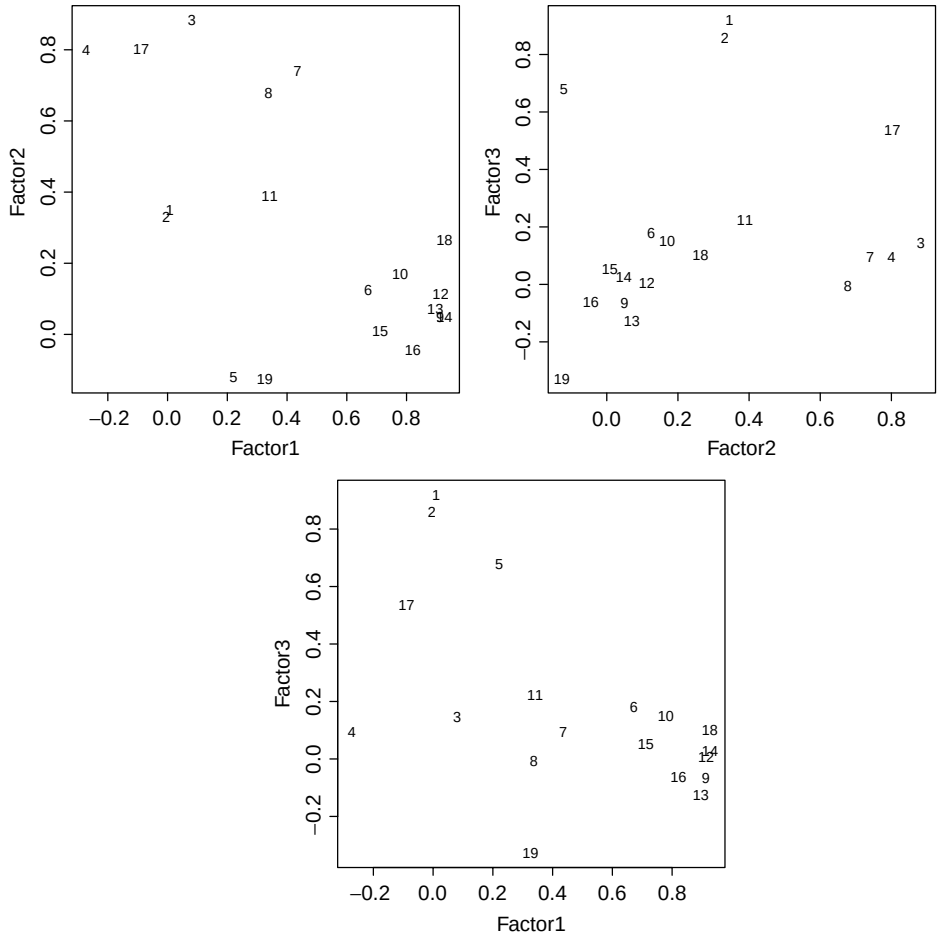


Figure 14.10 Factor loadings for Example 14.4.

as car and truck exhaust, smoke from fireplaces, road dust, and chemical reactions between gases in the air. Particles from different sources have differing distributions of chemical composition, so the chemical composition of particles in the air will be approximately an average of those for each source, weighted according to that source's contribution to overall pollution. That is, we have a factor analysis model in which the factor loadings λ represent the contribution of each source to overall particulate air pollution, the factors F characterize the chemical composition of each source, and the uniquenesses c_i are due largely to measurement error.

In this context the factor analysis model is modified slightly by removing the intercept in each of the regression models of equation (11). Rather than constraining each factor to have zero mean and unit variance, we constrain all the coefficients F and λ to be nonnegative. That is, a source cannot contain a negative amount of some chemical element and cannot contribute a negative concentration of particles. These physical constraints reduce the rotational indeterminacy of the model considerably. On the other hand, it is not reasonable to require that factors are orthogonal to each other, so that oblique rotations must be considered, restoring some of the indeterminacy.

The computation is even more difficult than for ordinary factor analysis, and specialized software is needed [Paatero, 1997, 1999; Henry, 1997]. The full data are needed rather than just a correlation or covariance matrix.

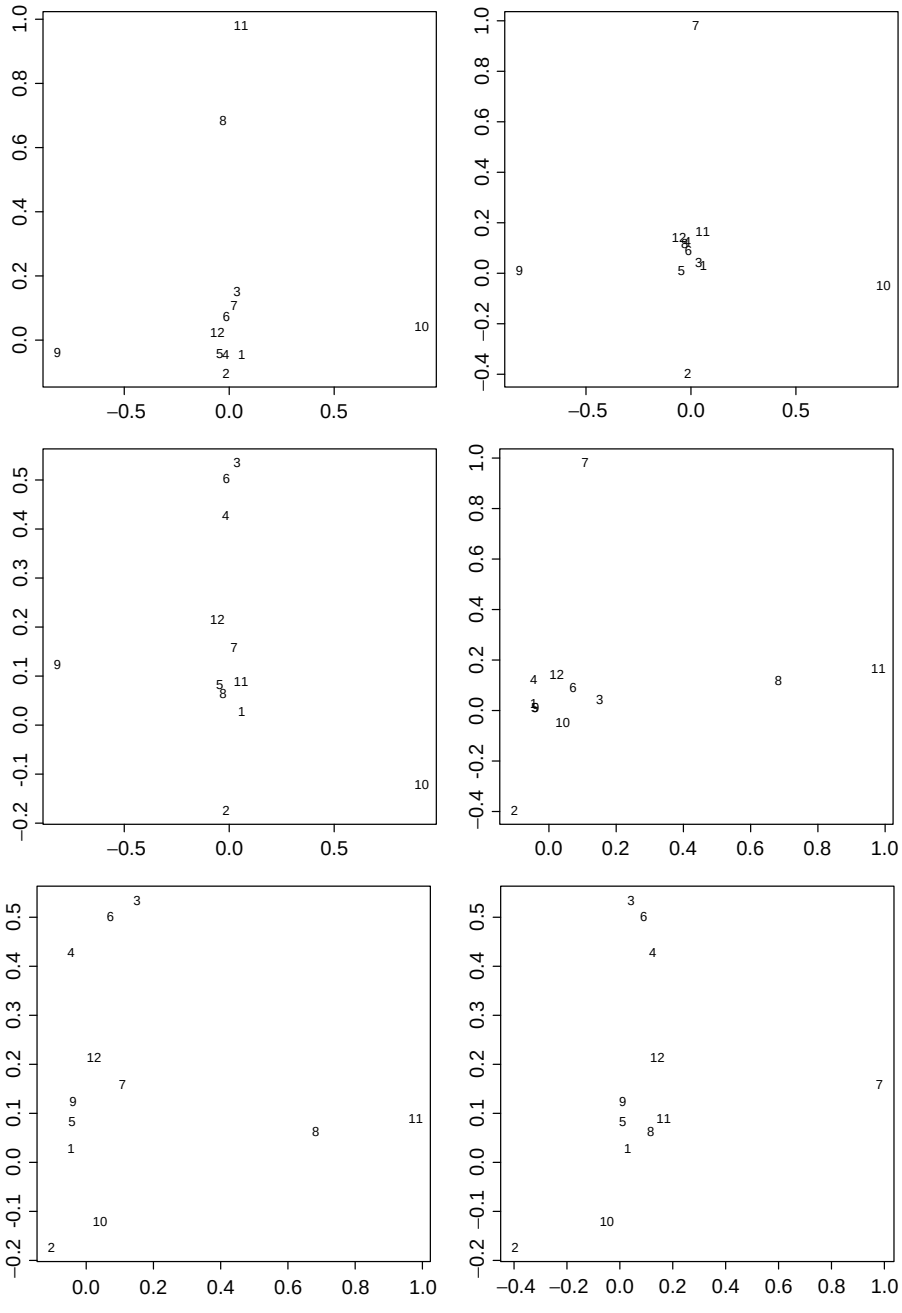


Figure 14.11 Factor loadings for Example 14.5.

Example 14.7. In February 2000, the U.S. Environmental Protection Agency held a workshop on source apportionment for particulate air pollution [U.S. EPA, 2000]. The main part of the workshop was a discussion of two constrained factor analysis methods which were used to investigate fine particulate air pollution from Phoenix, Arizona. Data were available for 981 days, from March 1995 through June 1998, on concentrations of 44 chemical elements and on carbon content, divided into organic carbon and elemental carbon.

The UNMIX method [Henry, 1997] gave a five-factor model:

Source	Concentration ($\mu g/m^3$)
Vehicles	4.7
Secondary aerosol	2.6
Soil	1.8
Diesel	1.2
Vegetative burning	0.7
Unidentified	1.6

and the PMF method [Paatero, 1997] gave a six-factor model:

Source	Concentration ($\mu g/m^3$)
Motor vehicles	3.5
Coal-fired power	2.1
Soil	1.9
Smelter	0.5
Biomass burning	4.4
Sea salt	0.1

Some of these factors were expected and their likely composition known a priori, such as vehicle exhaust with large amounts of both organic and elemental carbon, and soil with aluminium and silicon. Others were found and interpreted as a result of the analysis; the diesel source had both the elemental carbon characteristic of diesel exhaust and the maganese attributed to fuel additives. The secondary aerosol source in the UNMIX results probably corresponds to the coal-fired power source of PMF and perhaps some of the other burning; it would consist of sulfate and nitrate particles formed by chemical reactions in the atmosphere.

The attributions of fine particles to combustion, soil, and chemical reactions in the atmosphere were reasonably consistent between these methods, but separating different types of combustion proved much more difficult. This is probably a typical case and illustrates that the indeterminacy in the basic factor analysis model can partly, but not entirely, be overcome by substantive knowledge.

14.14 DETERMINING THE NUMBER OF FACTORS

In this section we consider what to do when the number of factors is unknown. Estimation methods of factor analysis begin with knowledge of k, the number of factors. But this number is usually not known or hypothesized. There is no universal agreement on how to select k; below we examine a number of ways of doing this. The first step is always carried out.

1. Examine the values of the residual correlations. In this section we suppose that we are trying to model the correlations between variables rather than their covariances. Recall that with maximum likelihood estimation, fitting one is the same as fitting the other. In looking at the residual correlations, as done in Examples 14.4 and 14.5, we may feel that we have done a good job if all of the correlations have been fit to within a specified difference. If the residual correlations reveal large discrepancies, the model does not fit.

2. There are statistical tests *if* we can assume that multivariate normality holds and we use the maximum likelihood estimation method. In this case, there is an asymptotic chi-square test for any hypothesized fixed number of factors. Computation of the test statistic is complex

and given in Note 14.3. However, it is available in many statistical computer programs. One approach is to look at successively more factors until the statistic is not statistically significant; that is, there are enough factors so that one would not reject at a fixed significance level the hypothesis that the number of factors is as given. This is analogous to a stepwise regression procedure. If we do this, we are performing a stepwise procedure, and the true and nominal significance levels differ (as usual in a stepwise analysis).

3. Looking at the roots of the correlation matrix:

a. If the correlations are arranged in a square pattern or matrix, as usually done, this pattern is called a *correlation matrix*. Suppose that we perform a principal component analysis and examine the variances of the principal components $V_1 \geq V_2 \geq \cdots \geq V_p$. These values are called the *eigenvalues* or *roots* of the correlation matrix. If we have the correlation matrix for the entire population, Guttman [1954] showed that the number of factors, k, must be greater than or equal to the number of roots greater than or equal to 1. That is, the number of factors in the factor analytic model must be greater than or equal to the number of principal components whose variance is greater than or equal to 1. Of course, in practice we do not have the population correlation matrix but an estimate. The number of such roots greater than or equal to 1 in a sample may turn out to be smaller or larger. However, because of Guttman's result, a reasonable starting value for k is the number of roots greater than or equal to 1 for the sample correlation matrix. For a thorough factor analysis, values of k above and below this number should be tried and the residual patterns observed. The number of factors in Examples 14.4 and 14.5 was chosen by this method.

b. *Scree* is the name for the rubble at the bottom of a cliff. The scree test plots the variances of the principal components. If the plot looks somewhat like Figure 14.12, one looks to separate the climb of the cliff from the scree at the bottom of the cliff. We are directed to pick the cliff, components 1, 2, 3, and possibly 4, rather than the rubble. A clear plastic ruler is laid across the bottom points, and the number of values above the line is the number of important factors. This advice is reasonable when a sharp demarcation can be seen, but often the pattern has no clear breakpoint.

c. Since we are interested in the correlation structure, we might plot as a function of k (the number of factors) the maximum absolute value of all the residuals of the estimated

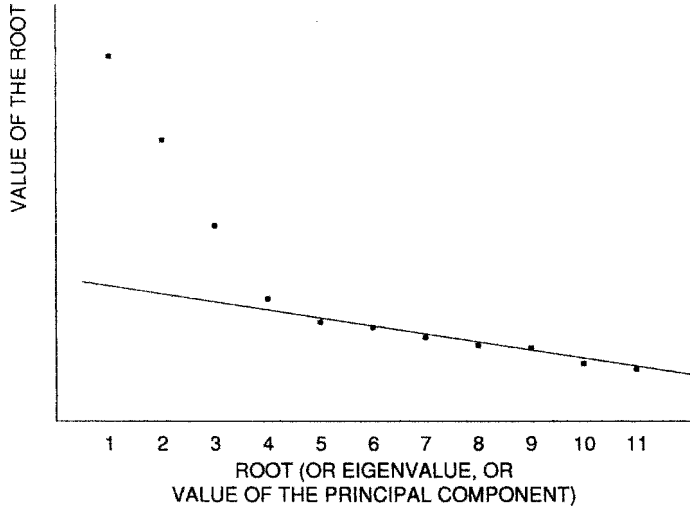


Figure 14.12 Plot for the scree test.

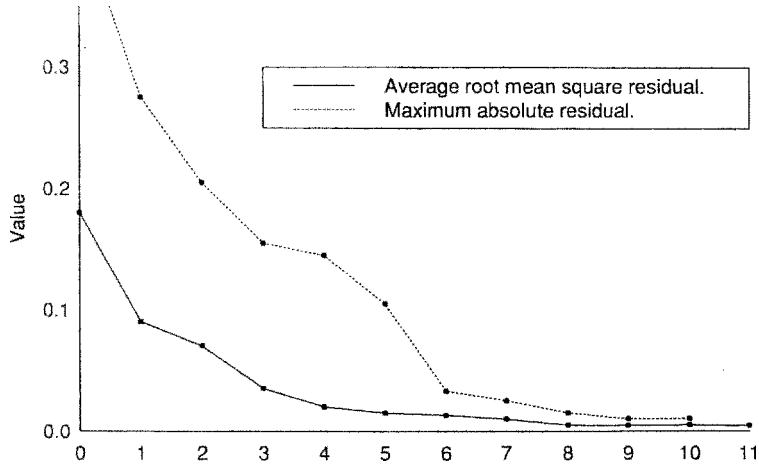


Figure 14.13 Plot of the maximum absolute residual and the average root mean square residual.

correlations. Another useful plot is the square root of the sum of the squares of all of the residual correlations divided by the number of such residual correlations, which is $p(p-1)/2$. If there is a break in the plots of the curves, we would then pick k so that the maximum and average squared residual correlations are small. For example, in Figure 14.13 we might choose three or four factors. Gorsuch suggests: "In the final report, interpretation could be limited to those factors which are well stabilized over the range which the number of factors may reasonably take."

14.15 INTERPRETATION OF FACTORS

Much of the debate about factor analysis stems from the naming and interpretation of factors. Often, after a factor analysis is performed, the factors are identified with concepts or objects. *Is a factor an underlying concept or merely a convenient way of summarizing interrelationships among variables*? A useful word in this context is *reify*, meaning to convert into or to regard something as a concrete thing. Should factors be reified?

As Gorsuch states: "A prime use of factor analysis has been in the development of both the theoretical constructs for an area and the operational representatives for the theoretical constructs." In other words, a prime use of factor analysis requires reifying the factors. Also, "The first task of any research program is to establish empirical referents for the abstract concepts embodied in a particular theory."

In psychology, how would one deal with an abstract concept such as aggression? On a questionnaire a variety of possible "aggression" questions might be used. If most or all of them have high loadings on the same factor, and other questions thought to be unrelated to aggression had low loadings, one might identify that factor with aggression. Further, the highest loadings might identify operationally the questions to be used to examine this abstract concept.

Since our knowledge is of the original observations, without a unique set of variables loading a factor, interpretation is difficult. Note well, however, that there is no law saying that one must interpret and name any or all factors.

Gorsuch makes the following points:

1. "The factor can only be interpreted by an individual with extensive background in the substantive area."

2. "The summary of the interpretation is presented as the factor's name. The name may be only descriptive or it may suggest a causal explanation for the occurrence of the factor. Since the name of the factor is all most readers of the research report will remember, it should be carefully chosen." *Perhaps it should not be chosen at all in many cases.*
3. "The widely followed practice of regarding interpretation of a factor as confirmed solely because the post-hoc analysis 'makes sense' is to be deplored. Factor interpretations can only be considered hypotheses for another study."

Interpretation of factors may be strengthened by using cases from other populations. Also, collecting other variables thought to be associated with the factor and including them in the analysis is useful. They should load on the same factor. Taking "marker" variables from other studies is useful in seeing whether an abstract concept has been embodied in more or less the same way in two different analyses.

For a perceptive and easy-to-understand discussion of factor analysis, see Chapter 6 in Gould [1996], which deals with scientific racism. Gould discusses the reification of intelligence in the Intelligence Quotient (IQ) through the use of factor analysis. Gould traces the history of factor analysis starting with the work of Spearman. Gould's book is a cautionary tale about scientific presuppositions, predilections, and perceptions affecting the interpretation of statistical results (it is not necessary to agree with all his conclusions to benefit from his explanations). A recent book by McDonald [1999] has a more technical discussion of reification and factor analysis. For a semihumorous discussion of reification, see Armstrong [1967].

NOTES

14.1 Graphing Two-Dimensional Projections

As noted in Section 14.8, the first two principal components can be used as plot axes to give a two-dimensional representation of higher-dimensional data. This plot will be best in the sense that it shows the maximum possible variability. Other multivariate graphical techniques give plots that are "the best" in other senses.

Multidimensional scaling gives a two-dimensional plot that reproduces the distances between points as accurately as possible. This view will be similar to the first two principal components when the data form a football (ellipsoid) shape, but may be very different when the data have a more complicated structure. Other *projection pursuit techniques* specifically search for views of the data that reveal holes, clusters, lines, and other departures from an ellipsoidal shape. A relatively nontechnical review of this concept is given by Jones and Sibson [1987].

Rather than relying on a single two-dimensional projection, it is also possible to display animated sequences of projections on a computer screen. The projections can be generated by random rotations of the data or by projection pursuit methods that attempt to show "interesting" projections. The free computer program GGobi (*http://www.ggobi.org*) implements many of these techniques.

Of course, more sophisticated searches performed by computer mean that more caution in interpretation is needed from the analyst. Substantial experience with these techniques is needed to develop a feeling for which graphs indicate real structure as opposed to overinterpreted noise.

14.2 Varimax and Quartimax Methods of Choosing Factors in a Factor Analysis

Many analytic methods of choosing factors have been developed so that the loading matrix is easy to interpret, that is, has a simple structure. These many different methods make the factor analysis literature very complex. We mention two of the methods.

1. *Varimax method.* The varimax method uses the idea of maximizing the sum of the variances of the squares of loadings of the factors. Note that the variances are high when the λ_{ij}^2 are near 1 and 0, some of each in each column. In order that variables with large communalities are not overly emphasized, weighted values are used. Suppose that we have the loadings λ_{ij} for one selection of factors. Let θ_{ij} be the loadings for a different set of factors (the linear combinations of the old factors). Define the weighted quantities

$$\gamma_{ij} = \theta_{ij} \Big/ \sqrt{\sum_{j=1}^{m} \lambda_{ij}^2}$$

The method chooses the θ_{ij} to maximize the following:

$$\sum_{j=1}^{k} \left[\frac{1}{p} \sum_{i=1}^{p} \gamma_{ij}^4 - \frac{1}{p^2} \left(\sum_{i=1}^{p} \gamma_{ij}^2 \right)^2 \right]$$

Some problems have a factor where all variables load high (e.g., general IQ). Varimax should not be used if a general factor may occur, as the low variance discourages general factors. Otherwise, it is one of the most satisfactory methods.

2. *Quartimax method.* The quartimax method works with the variance of the square of all p_k loadings. We maximize over all possible loadings θ_{ij}:

$$\max_{\theta_{ij}} \left[\sum_{i=1}^{p} \sum_{j=1}^{k} \theta_{ij}^4 - \frac{1}{pm} \left(\sum_{i=1}^{p} \sum_{j=1}^{k} \theta_{ij}^2 \right) \right]$$

Quartimax is used less often, since it tends to include one factor with all major loadings and no other major loadings in the rest of the matrix.

14.3 Statistical Test for the Number of Factors in a Factor Analysis When $X_1, \ldots, X_p$ Are Multivariate Normal and Maximum Likelihood Estimation Is Used

This note presupposes familiarity with matrix algebra. Let A be a matrix and A' denote the transpose of A; if A is square, let $|A|$ be the determinant of A and $\mathrm{Tr}(A)$ be the trace of A. Consider a factor analysis with k factors and estimated *loading matrix*

$$\Lambda = \begin{pmatrix} \lambda_{11} & \cdots & \lambda_{1k} \\ \vdots & \ddots & \vdots \\ \lambda_{n1} & \cdots & \lambda_{nk} \end{pmatrix}$$

The test statistic is

$$X^2 = \left(n - 1 - \frac{2p+5}{6} - \frac{2k}{3} \right) \log_e \left(\frac{|\Lambda\Lambda' + \psi|}{|S|} \right) \mathrm{Tr}(S(\Lambda\Lambda' + \psi)^{-1})p$$

where S is the sample covariance matrix, ψ a diagonal matrix where $\psi_{ii} = s_i - (\Lambda\Lambda')_{ii}$, and s_i the sample variance of X_i. If the true number of factors is less than or equal to k, X^2 has a chi-square distribution with $[(p-k)^2 - (p+k)]/2$ degrees of freedom. The null hypothesis of only k factors is rejected if X^2 is too large.

One could try successively more factors until this is not significant. The true and nominal significance levels differ as usual in a stepwise procedure. (For the test to be appropriate, the degrees of freedom must be > 0.)

PROBLEMS

The first four problems present principal component analyses using correlation matrices. Portions of computer output (BMDP program 4M) are given. The coefficients for principal components that have a variance of 1 or more are presented. Because of the connection of principal component analysis and factor analysis mentioned in the text (when the correlations are used), the principal components are also called *factors* in the output. With a correlation matrix the coefficient values presented are for the standardized variables. You are asked to perform a subset of the following tasks.

- **(a)** Fill in the missing values in the "variance explained" and "cumulative proportion of total variance" table.
- **(b)** For the principal component(s) specified, give the percent of the total variance accounted for by the principal component(s).
- **(c)** How many principal components are needed to explain 70% of the total variance? 90%? Would a plot with two axes contain most (say, $\geq$ 70%) of the variability in the data?
- **(d)** For the case(s) with the value(s) as given, compute the case(s) values on the first two principal components.

14.1 This problem uses the psychosocial Framingham data in Table 11.20. The mnemonics go in the same order as the correlations presented. The results are presented in Tables 14.12 and 14.19. Perform tasks (a) and (b) for principal components 2 and 4, and task (c).

14.2 Measurement data on U.S. females by Stoudt et al. [1970] were discussed in this chapter. The same correlation data for adult males were also given (Table 14.14). The principal

Table 14.12 Problem 14.1: Variance Explained by Principal Components[a]

Factor	Variance Explained	Cumulative Proportion of Total Variance
1	4.279180	0.251716
2	1.633777	0.347821
3	1.360951	?
4	1.227657	0.500092
5	1.166469	0.568708
6	?	0.625013
7	0.877450	0.676627
8	0.869622	0.727782
9	0.724192	0.770381
10	0.700926	0.811612
11	0.608359	?
12	0.568691	0.880850
13	0.490974	0.909731
14	?	0.935451
15	0.386540	0.958189
16	0.363578	0.979576
17	?	?

[a]The variance explained by each factor is the eigenvalue for that factor. Total variance is defined as the sum of the diagonal elements of the correlation (covariance) matrix.

Table 14.13 Problem 14.1: Principal Components

		Unrotated Factor Loadings (Pattern) for Principal Components				
		Factor 1	Factor 2	Factor 3	Factor 4	Factor 5
TYPEA	1	0.633	−0.203	0.436	−0.049	0.003
EMOTLBLE	2	0.758	−0.198	−0.146	0.153	−0.005
AMBITIOS	3	0.132	−0.469	0.468	−0.155	−0.460
NONEASY	4	0.353	0.407	−0.268	0.308	0.342
NOBOSSPT	5	0.173	0.047	0.260	−0.206	0.471
WKOVRLD	6	0.162	−0.111	0.385	−0.246	0.575
MTDISSAG	7	0.499	0.542	0.174	−0.305	−0.133
MGDISSAT	8	0.297	0.534	−0.172	−0.276	−0.265
AGEWORRY	9	0.596	0.202	0.060	−0.085	−0.145
PERSONWY	10	0.618	0.346	0.192	−0.174	−0.206
ANGERIN	11	0.061	−0.430	−0.470	−0.443	−0.186
ANGEROUT	12	0.306	0.178	0.199	0.607	−0.215
ANGRDISC	13	0.147	−0.181	0.231	0.443	−0.108
STRESS	14	0.665	−0.189	0.062	−0.053	0.149
TENSION	15	0.771	−0.226	−0.186	0.039	0.118
ANXSYMPT	16	0.594	−0.141	−0.352	0.022	0.067
ANGSYMPT	17	0.723	−0.242	−0.256	0.086	−0.015
	VP[a]	4.279	1.634	1.361	1.228	1.166

[a]The VP for each factor is the sum of the squares of the elements of the column of the factor loading matrix corresponding to that factor. The VP is the variance explained by the factor.

component analysis gave the results of Table 14.15. Perform tasks (a) and (b) for principal components 2, 3, and 4, and task (c).

14.3 The Bruce et al. [1973] exercise data for 94 sedentary males are used in this problem (see Table 9.16). These data were used in Problems 9.9 to 9.12. The exercise variables used are DURAT (duration of the exercise test in seconds), $VO_{2\ MAX}$ [the maximum oxygen consumption (normalized for body weight)], HR [maximum heart rate (beats/min)], AGE (in years), HT (height in centimeters), and WT (weight in kilograms). The correlation values are given in Table 14.17. The principal component analysis is given in Table 14.18. Perform tasks (a) and (b) for principal components 4, 5, and 6, and task (c) (Table 14.19). Perform task (d) for a case with DURAT $= 600$, $VO_{2\ MAX} = 38$, HR $= 185$, AGE $= 29$, HT $= 165$, and WT $= 71$. (*N.B.*: Find the value of the *standardized* variables.)

14.4 The variables are the same as in Problem 14.3. In this analysis 43 active females (whose individual data are given in Table 9.14) are studied. The correlations are given in Table 14.21. the principal component analysis in Tables 14.22 and 14.23. Perform tasks (a) and (b) for principal components 1 and 2, and task (c). Do task (d) for the two cases in Table 14.24 (use standard variables). See Table 14.21.

Problems 14.5, 14.7, 14.8, 14.10, 14.11, and 14.12 consider maximum likelihood factor analysis with varimax rotation (from computer program BMDP4M). Except for Problem 14.10, the number of factors is selected by Guttman's root criterion (the number of eigenvalues greater than 1). Perform the following tasks as requested.

Table 14.14 Problem 14.2: Correlations

		STHTER 1	STHTHL 2	KNEEHT 3	POPHT 4	ELBWHT 5
STHTER	1	1.000				
STHTHL	2	0.873	1.000			
KNEEHT	3	0.446	0.443	1.000		
POPHT	4	0.410	0.382	0.798	1.000	
ELBWHT	5	0.544	0.454	−0.029	−0.062	1.000
THIGHHT	6	0.238	0.284	0.228	−0.029	0.217
BUTTKNHT	7	0.418	0.429	0.743	0.619	0.005
BUTTPOP	8	0.227	0.274	0.626	0.524	−0.145
ELBWELBW	9	0.139	0.212	0.139	−0.114	0.231
SEATBRTH	10	0.365	0.422	0.311	0.050	0.286
BIACROM	11	0.365	0.335	0.352	0.275	0.127
CHESTGRH	12	0.238	0.298	0.229	0.000	0.258
WSTGRTH	13	0.106	0.184	0.138	−0.097	0.191
RTARMGRH	14	0.221	0.265	0.194	−0.059	0.269
RTARMSKN	15	0.133	0.191	0.081	−0.097	0.216
INFRASCP	16	0.096	0.152	0.038	−0.166	0.247
HT	17	0.770	0.717	0.802	0.767	0.212
WT	18	0.403	0.433	0.404	0.153	0.324
AGE	19	−0.272	−0.183	−0.215	−0.215	−0.192

		THIGH-HT 6	BUTT-KNHT 7	BUTT-POP 8	ELBW-ELBW 9	SEAT-BRTH 10
THIGHHT	6	1.000				
BUTTKNHT	7	0.348	1.000			
BUTTPOP	8	0.237	0.736	1.000		
ELBWELBW	9	0.603	0.299	0.193	1.000	
SEATBRTH	10	0.579	0.449	0.265	0.707	1.000
BIACROM	11	0.303	0.365	0.252	0.311	0.343
CHESTGRH	12	0.605	0.386	0.252	0.833	0.732
WSTGRTH	13	0.537	0.323	0.216	0.820	0.717
RTARMGRH	14	0.663	0.342	0.224	0.755	0.675
RTARMSKN	15	0.480	0.240	0.128	0.524	0.546
INFRASCP	16	0.503	0.212	0.106	0.674	0.610
HT	17	0.210	0.751	0.600	0.069	0.309
WT	18	0.684	0.551	0.379	0.804	0.813
AGE	19	−0.190	−0.151	−0.108	0.156	0.043

		BIACROM 11	CHESTGRH 12	WSTGRTH 13	RTARMGRH 14	RTARMSKN 15
BIACROM	11	1.000				
CHESTGRH	12	0.418	1.000			
WSTGRTH	13	0.249	0.837	1.000		
RTARMGRH	14	0.379	0.784	0.712	1.000	
RTARMSKN	15	0.183	0.558	0.552	0.570	1.000
INFRASCP	16	0.242	0.710	0.727	0.667	0.697
HT	17	0.381	0.189	0.054	0.139	0.060
WT	18	0.474	0.885	0.821	0.849	0.562
AGE	19	−0.261	0.062	0.299	−0.115	−0.039

		INFRASCP 16	HT 17	WT 18	AGE 19
INFRASCP	16	1.000			
HT	17	−0.003	1.000		
WT	18	0.709	0.394	1.000	
AGE	19	0.045	−0.270	−0.058	1.000

Table 14.15 Problem 14.2: Variance Explained by the Principal Components[a]

Factor	Variance Explained	Cumulative Proportion of Total Variance
1	7.839282	0.412594
2	4.020110	0.624179
3	1.820741	0.720007
4	1.115168	0.778700
5	0.764398	0.818932
6	?	0.850389
7	0.475083	?
8	0.424948	0.897759
9	0.336247	0.915456
10	?	0.931210
11	0.252205	0.944484
12	?	0.955404
13	0.202398	0.966057
14	0.169678	0.974987
15	0.140613	0.982388
16	0.119548	?
17	0.117741	0.994872
18	0.055062	0.997770
19	0.042365	1.000000

[a]The variance explained by each factor is the eigenvalue for that factor. Total variance is defined as the sum of the diagonal elements of the correlation (covariance) matrix.

Table 14.16 Exercise Data for Problem 14.3

		Univariate Summary Statistics	
	Variable	Mean	Standard Deviation
1	DURAT	577.10638	123.83744
2	$VO_{2\ MAX}$	35.63298	7.51007
3	HR	175.39362	18.59195
4	AGE	49.78723	11.06955
5	HT	177.39851	6.58285
6	WT	79.00000	8.71286

Table 14.17 Problem 14.3: Correlation Matrix

		DURAT	$VO_{2\ MAX}$	HR	AGE	HT	WT
DURAT	1	1.000					
$VO_{2\ MAX}$	2	0.905	1.000				
HR	3	0.678	0.647	1.000			
AGE	4	−0.687	−0.656	−0.630	1.000		
HT	5	0.035	0.050	0.107	−0.161	1.000	
WT	6	−0.134	−0.147	0.015	−0.069	0.536	1.000

Table 14.18 Problem 14.3: Variance Explained by the Principal Components[a]

Factor	Variance Explained	Cumulative Proportion of Total Variance
1	3.124946	0.520824
2	1.570654	?
3	0.483383	0.863164
4	?	0.926062
5	?	0.984563
6	0.092621	1.000000

[a]The variance explained by each factor is the eigenvalue for that factor. Total variance is defined as the sum of the diagonal elements of the correlation (covariance) matrix.

Table 14.19 Problem 14.3: Principal Components

		Unrotated Factor Loadings (Pattern) for Principal Components	
		Factor 1	Factor 2
DURAT	1	0.933	−0.117
$VO_{2\ MAX}$	2	0.917	−0.120
HR	3	0.832	0.057
AGE	4	−0.839	−0.134
HT	5	0.128	0.860
WT	6	−0.057	0.884
	VP[a]	3.125	1.571

[a]The VP for each factor is the sum of the squares of the elements of the column of the factor loading matrix corresponding to that factor. The VP is the variance explained by the factor.

Table 14.20 Exercise Data for Problem 14.4

		Univariate Summary Statistics	
	Variable	Mean	Standard Deviation
1	DURAT	514.88372	77.34592
2	$VO_{2\ MAX}$	29.05349	4.94895
3	HR	180.55814	11.41699
4	AGE	45.13953	10.23435
5	HT	164.69767	6.30017
6	WT	61.32558	7.87921

Table 14.21 Problem 14.4: Correlation Matrix

		DURAT	$VO_{2\ MAX}$	HR	AGE	HT	WT
DURAT	1	1.000					
$VO_{2\ MAX}$	2	0.786	1.000				
HR	3	0.528	0.337	1.000			
AGE	4	−0.689	−0.651	−0.411	1.000		
HT	5	0.369	0.299	0.310	−0.455	1.000	
WT	6	0.094	−0.126	0.232	−0.042	0.483	1.000

Table 14.22 Problem 14.4: Variance Explained by the Principal Components[a]

Factor	Variance Explained	Cumulative Proportion of Total Variance
1	3.027518	?
2	1.371342	0.733143
3	?	?
4	0.416878	0.918943
5	?	0.972750
6	?	1.000000

[a]The variance explained by each factor is the eigenvalue for that factor. Total variance is defined as the sum of the diagonal elements of the correlation (covariance) matrix.

Table 14.23 Problem 14.4: Principal Components

		Unrotated Factor Loadings (Pattern) for Principal Components	
		Factor 1	Factor 2
DURAT	1	0.893	−0.201
$VO_{2\ MAX}$	2	0.803	−0.425
HR	3	0.658	0.162
AGE	4	−0.840	0.164
HT	5	0.626	0.550
WT	6	0.233	0.891
	VP[a]	3.028	1.371

[a]The VP for each factor is the sum of the squares of the elements of the column of the factor loading matrix corresponding to that factor. The VP is the variance explained by the factor.

Table 14.24 Data for Two Cases, Problem 14.3

	Subject 1	Subject 2
DURAT	660	628
$VO_{2\ MAX}$	38.1	38.4
HR	184	183
AGE	23	21
HT	177	163
WT	83	52

a. Examine the residual correlation matrix. What is the maximum residual correlation? Is it < 0.1? < 0.5?

b. For the pair(s) of variables, with mnemonics given, find the fitted residual correlation.

c. Consider the plots of the rotated factors. Discuss the extent to which the interpretation will be simple.

d. Discuss the potential for naming and interpreting these factors. Would you be willing to name any? If so, what names?

e. Give the uniqueness and communality for the variables whose numbers are given.

f. Is there any reason that you would like to see an analysis with fewer or more factors? If so, why?

g. If you were willing to associate a factor with variables (or a variable), identify the variables on the shaded form of the correlations. Do the variables cluster (form a dark group), which has little correlation with the other variables?

14.5 A factor analysis is performed upon the Framingham data of Problem 14.1. The results are given in Tables 14.25 to 14.27 and Figures 14.14 and 14.15. Communalities were obtained from five factors after 17 iterations. The communality of a variable is its squared multiple correlation with the factors; they are given in Table 14.26. Perform tasks (a), (b)

Table 14.25 Problem 14.5: Residual Correlations

		TYPEA 1	EMOTLBLE 2	AMBITIOS 3	NONEASY 4	NOBOSSPT 5	WKOVRLD 6
TYPEA	1	0.219					
EMOTLBLE	2	0.001	0.410				
AMBITIOS	3	0.001	0.041	0.683			
NONEASY	4	0.003	0.028	−0.012	0.635		
NOBOSSPT	5	−0.010	−0.008	0.001	−0.013	0.964	
WKOVRLD	6	0.005	−0.041	−0.053	−0.008	0.064	0.917
MTDISSAG	7	0.007	−0.010	−0.062	−0.053	0.033	0.057
MGDISSAT	8	0.000	0.000	0.000	0.000	0.000	0.000
AGEWORRY	9	0.002	0.030	0.015	0.017	0.001	−0.017
PERSONWY	10	−0.002	−0.010	0.007	0.007	−0.007	−0.003
ANGERIN	11	0.007	−0.006	−0.028	0.005	−0.018	0.028
ANGEROUT	12	0.001	0.056	0.053	0.014	−0.070	−0.135
ANGRDISC	13	−0.011	0.008	0.044	−0.019	−0.039	0.006
STRESS	14	0.002	−0.032	−0.003	0.018	0.030	0.034
TENSION	15	−0.004	−0.006	−0.016	−0.017	0.013	0.024
ANXSYMPT	16	0.004	−0.026	−0.028	−0.019	0.009	−0.015
ANGSYMPT	17	−0.000	0.018	−0.008	−0.012	−0.006	0.009

		MTDISSAG 7	MTDISSAT 8	AGEWORRY 9	PERSONWY 10	ANGERIN 11	ANGEROUT 12
MTDISSAG	7	0.574					
MGDISSAT	8	0.000	0.000				
AGEWORRY	9	0.001	−0.000	0.572			
PERSONWY	10	−0.002	0.000	0.001	0.293		
ANGERIN	11	0.010	−0.000	0.015	−0.003	0.794	
ANGEROUT	12	0.006	−0.000	−0.006	−0.001	−0.113	0.891
ANGRDISC	13	−0.029	−0.000	0.000	0.001	−0.086	0.080
STRESS	14	−0.017	−0.000	−0.015	0.013	0.022	−0.050
TENSION	15	0.004	−0.000	−0.020	0.007	−0.014	−0.045
ANXSYMPT	16	0.026	−0.000	0.037	−0.019	0.011	−0.026
ANGSYMPT	17	0.004	−0.000	−0.023	0.006	0.012	0.049

		ANGRDISC 13	STRESS 14	TENSION 15	ANXSYMPT 16	ANGSYMPT 17
ANGRDISC	13	0.975				
STRESS	14	−0.011	0.599			
TENSION	15	−0.005	0.035	0.355		
ANXSYMPT	16	−0.007	0.015	0.020	0.645	
ANGSYMPT	17	0.027	−0.021	−0.004	−0.008	0.398

Table 14.26 Problem 14.5: Communalities

1	TYPEA	0.7811
2	EMOTLBLE	0.5896
3	AMBITIOS	0.3168
4	NONEASY	0.3654
5	NOBOSSPT	0.0358
6	WKOVRLD	0.0828
7	MTDISSAG	0.4263
8	MGDISSAT	1.0000
9	AGEWORRY	0.4277
10	PERSONWY	0.7072
11	ANGERIN	0.2063
12	ANGEROUT	0.1087
13	ANGRDISC	0.0254
14	STRESS	0.4010
15	TENSION	0.6445
16	ANXSYMPT	0.3555
17	ANGSYMPT	0.6019

Table 14.27 Problem 14.5: Factors (Loadings Smaller Than 0.1 Omitted)

		Factor 1	Factor 2	Factor 3	Factor 4	Factor 5
TYPEA	1	0.331	0.185	0.133	0.753	0.229
EMOTLBLE	2	0.707	0.194		0.215	
AMBITIOS	3				0.212	0.515
NONEASY	4	0.215	0.105	0.163	0.123	−0.516
NOBOSSPT	5		0.101		0.142	
WKOVRLD	6				0.281	
MTDISSAG	7		0.474	0.391	0.178	
MGDISSAT	8		0.146	0.971	−0.143	
AGEWORRY	9	0.288	0.576			
PERSONWY	10	0.184	0.799	0.138	0.127	
ANGERIN	11	0.263			−0.238	0.272
ANGEROUT	12	0.128	0.179		0.196	−0.148
ANGRDISC	13	0.117			0.102	
STRESS	14	0.493	0.189		0.337	
TENSION	15	0.753	0.193		0.190	
ANXSYMPT	16	0.571	0.138			
ANGSYMPT	17	0.748	0.191			
	VP[a]	2.594	1.477	1.181	1.112	0.712

[a]The VP for each factor is the sum of the squares of the elements of the column of the factor pattern matrix corresponding to that factor. When the rotation is orthogonal, the VP is the variance explained by the factor.

(TYPEA, EMOTLBLE) and (ANGEROUT, ANGERIN), (c), (d), and (e) for variables 1, 5, and 8, and tasks (f) and (g). In this study, the TYPEA variable was of special interest. Is it associated particularly with one of the factors?

14.6 This question requires you to do the fitting of the factor analysis model. Use the Florida voting data of Problem 9.34 available on the Web appendix to examine the structure of

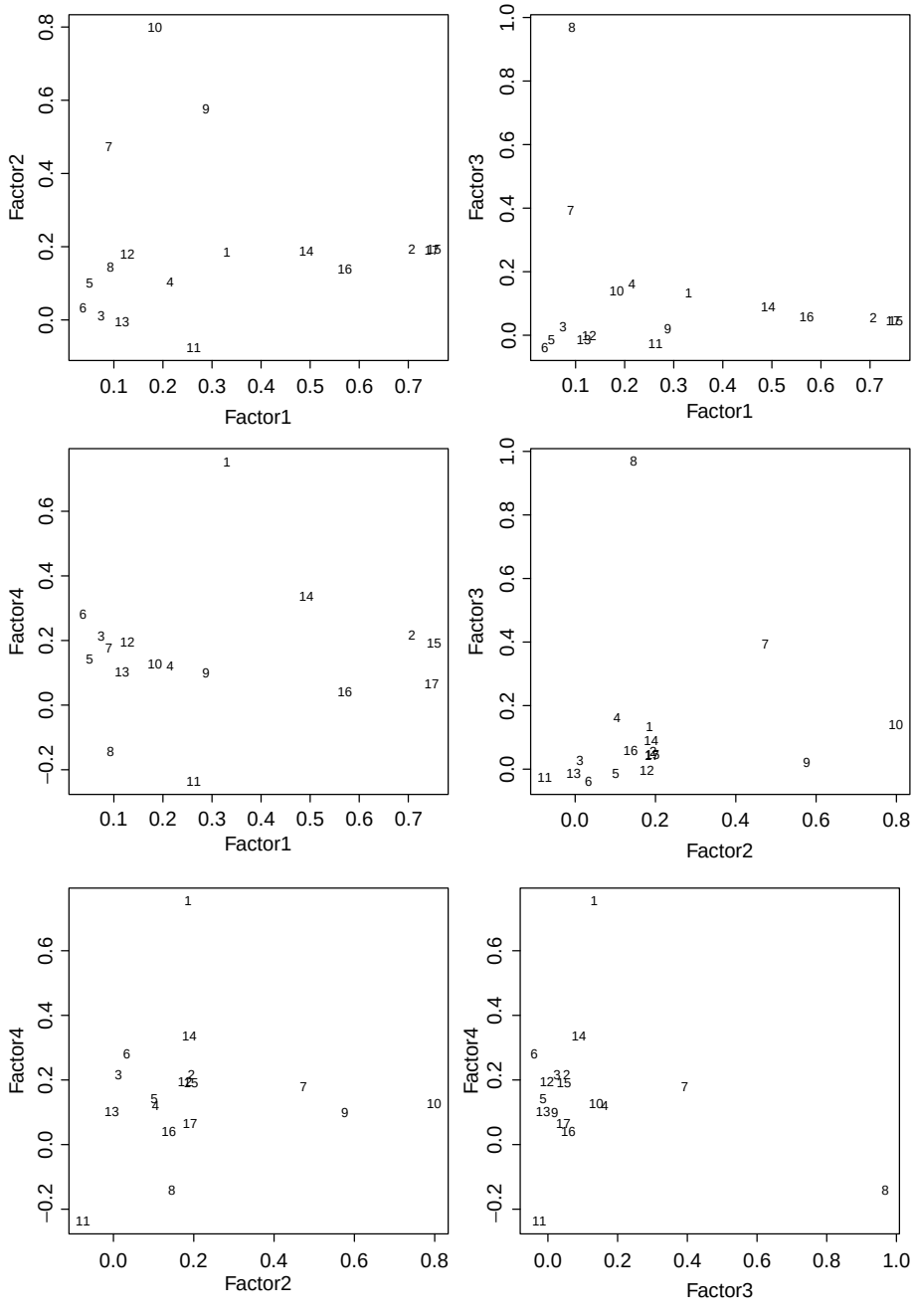


Figure 14.14 Problem 14.5, plots of factor loadings.

voting in the two Florida elections. As the counties are very different sizes, you will need to convert the counts to proportions voting for each candidate, and it may be useful to use the logarithm of this proportion. Fit models with one, two, or three factors and try to interpret them.

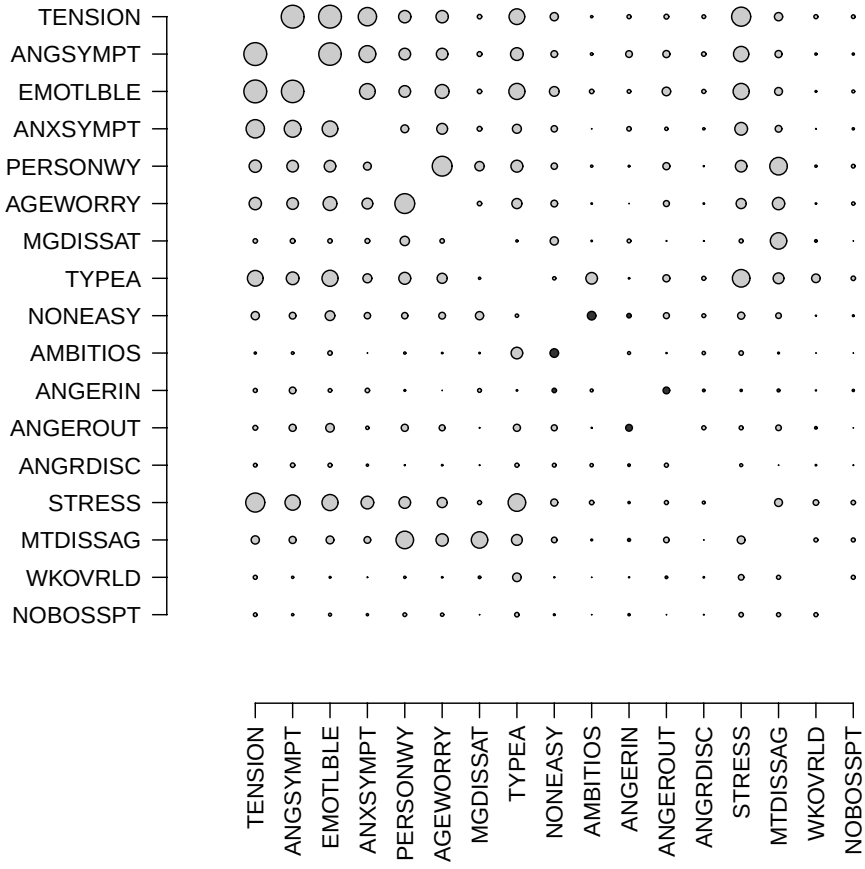


Figure 14.15 Shaded correlation matrix for Problem 14.5.

14.7 Starkweather [1970] performed a study entitled "Hospital Size, Complexity, and Formalization." He states: "Data on 704 United States short-term general hospitals are sorted into a set of dependent variables indicative of organizational formalism and a number of independent variables separately measuring hospital size (number of beds) and various types of complexity commonly associated with size." Here we used his data for a factor analysis of the following variables:

- *SIZE:* number of beds.
- *CONTROL:* a hospital was scored: 1 proprietary control; 2 nonprofit community control; 3 church operated; 4 public district hospital; 5 city or county control; 6 state control.
- *SCOPE* (of patient services): "A count was made of the number of services reported for each sample hospital. Services were weighted 1, 2, or 3 according to their relative impact on hospital operations, as measured by estimated proportion of total operating expenses."
- *TEACHVOL:* "The number of students in each of several types of hospital training programs was weighted and the products summed. The number of paramedical students

Table 14.28 Problem 14.7: Correlation Matrix

		SIZE 1	CONTROL 2	SCOPE 3	TEACHVOL 4	TECHTYPE 5	NONINPRG 6
SIZE	1	1.000					
CONTROL	2	−0.028	1.000				
SCOPE	3	0.743	−0.098	1.000			
TEACHVOL	4	0.717	−0.040	0.643	1.000		
TECHTYPE	5	0.784	−0.034	0.547	0.667	1.000	
NONINPRG	6	0.523	−0.051	0.495	0.580	0.440	1.000

Table 14.29 Problem 14.7: Communalities[a]

1	SIZE	0.8269
2	CONTROL	0.0055
3	SCOPE	0.7271
4	TEACHVOL	0.6443
5	TECHTYPE	1.0000
6	NONINPRG	0.3788

[a] Communalities obtained from two factors after eight iterations. The communality of a variable is its squared multiple correlation with the factors.

Table 14.30 Problem 14.7: Residual Correlations

		SIZE 1	CONTROL 2	SCOPE 3	TEACHVOL 4	TECHTYPE 5	NONINPRG 6
SIZE	1	0.173					
CONTROL	2	0.029	0.995				
SCOPE	3	0.013	−0.036	0.273			
TEACHVOL	4	−0.012	0.012	−0.014	0.356		
TECHTYPE	5	−0.000	0.000	−0.000	−0.000	0.000	
NONINPRG	6	−0.020	−0.008	−0.027	0.094	−0.000	0.621

was weighted by 1.5, the number of RN students by 3, and the number of interns and residents by 5.5. These weights represent the average number of years of training typically involved, which in turn constitute a rough measure of the relative impact of students on hospital operations."

- *TECHTYPE:* types of teaching programs. The following scores were summed: 1 for practical nurse training program; 2 for RN; 3 for medical students; 4 for interns; 5 for residents.
- *NONINPRG:* noninpatient programs. Sum the following scores: 1 for emergency service; 2 for outpatient care; 3 for home care.

The results are given in Tables 14.28 to 14.31, and Figures 14.16 and 14.17. The factor analytic results follow. Perform tasks (a), (c), (d), and (e) for 1, 2, 3, 4, 5, and 6, and tasks (f) and (g).

Table 14.31 Problem 14.7: Factors (Loadings 14.31 Smaller Than 0.1 Omitted)

		Factor 1	Factor 2
SIZE	1	0.636	0.650
CONTROL	2		
SCOPE	3	0.357	0.774
TEACHVOL	4	0.527	0.605
TECHTYPE	5	0.965	0.261
NONINPRG	6	0.312	0.530
	VP[a]	1.840	1.743

[a]The VP for each factor is the sum of the squares of the elements of the column of the factor pattern matrix corresponding to that factor. When the rotation is orthogonal, the VP is the variance explained by the factor.

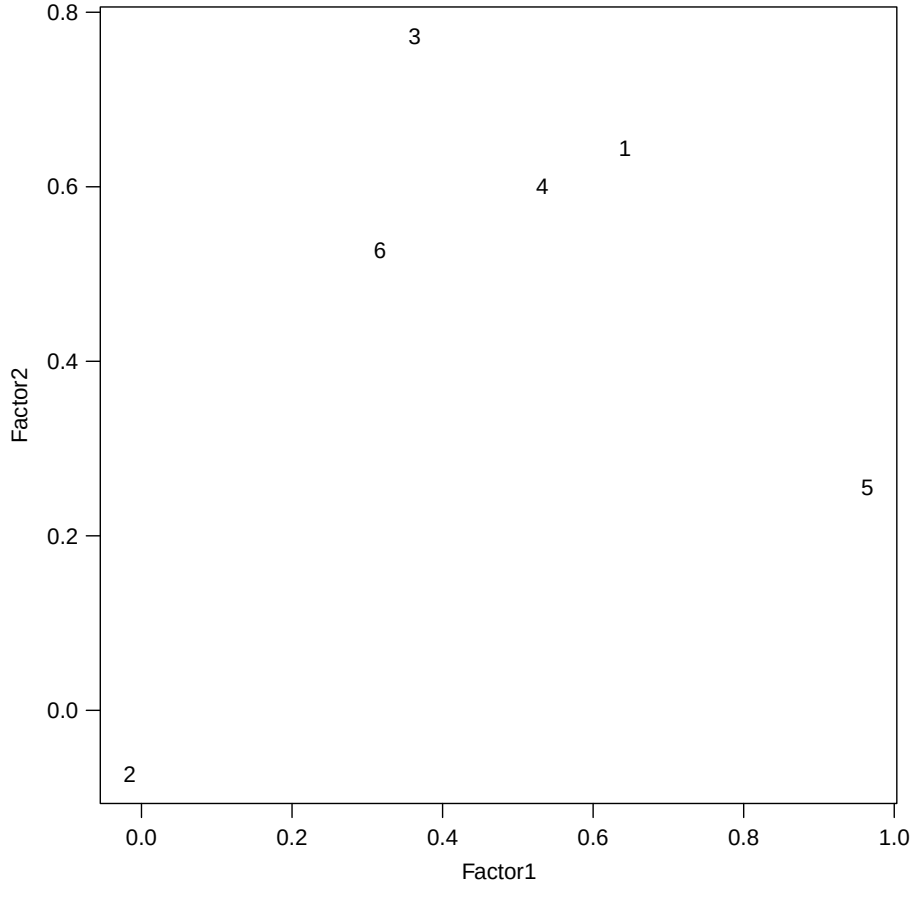


Figure 14.16 Problem 14.7, plot of factor loadings.

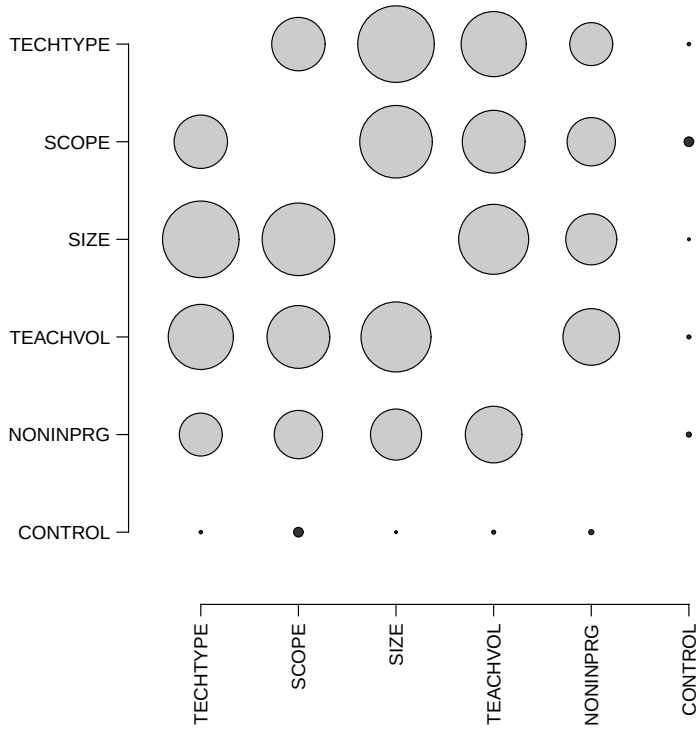


Figure 14.17 Shaded correlation matrix for Problem 14.7.

Table 14.32 Problem 14.8: Residual Correlations

		DURAT	$VO_{2\ MAX}$	HR	AGE	HT	WT
DURAT	1	0.067					
$VO_{2\ MAX}$	2	0.002	0.126				
HR	3	−0.005	−0.011	0.678			
AGE	4	0.004	0.011	−0.092	0.441	6	
HT	5	−0.006	0.018	−0.021	0.0106	0.574	
WT	6	0.004	−0.004	−0.008	0.007	0.605	0.301

14.8 This factor analysis examines the data used in Problem 14.3, the maximal exercise test data for sedentary males. The results are given in Tables 14.32 to 14.34 and Figures 14.18 and 14.19. Perform tasks (a), (b) (HR, AGE), (c), (d), and (e) for variables 1 and 5, and tasks (f) and (g).

14.9 Consider two variables, X and Y, with covariances (or correlations) given in the following notation. Prove parts (a) and (b) below.

	Variable	
Variable	**1**	**2**
X	*a*	*c*
Y	*c*	*b*

Table 14.33 Problem 14.8: Communalities[a]

1	DURAT	0.9331
2	$VO_{2\ MAX}$	0.8740
3	HR	0.5217
4	AGE	0.5591
5	HT	0.4264
6	WT	0.6990

[a]Communalities obtained from two factors after six iterations. The communality of a variable is its squared multiple correlation with the factors.

Table 14.34 Problem 14.8: Factors

		Factor 1	Factor 2
DURAT	1	0.962	0.646
$VO_{2\ MAX}$	2	0.930	−0.092
HR	3	0.717	
AGE	4	−0.732	−0.154
HT	5		0.833
WT	6		0.833
	VP[a]	2.856	1.158

[a]The VP for each factor is the sum of the squares of the elements of the column of the factor pattern matrix corresponding to that factor. When the rotation is orthogonal, the VP is the variance explained by the factor.

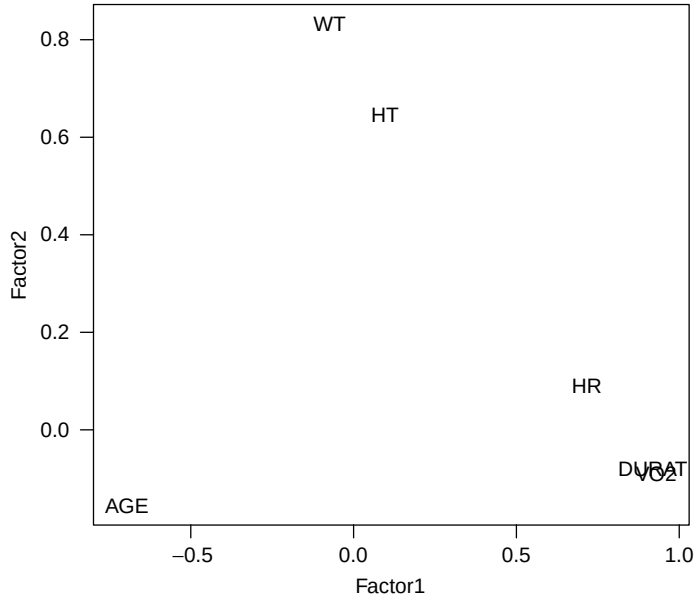


Figure 14.18 Problem 14.8, plot of factor loadings.

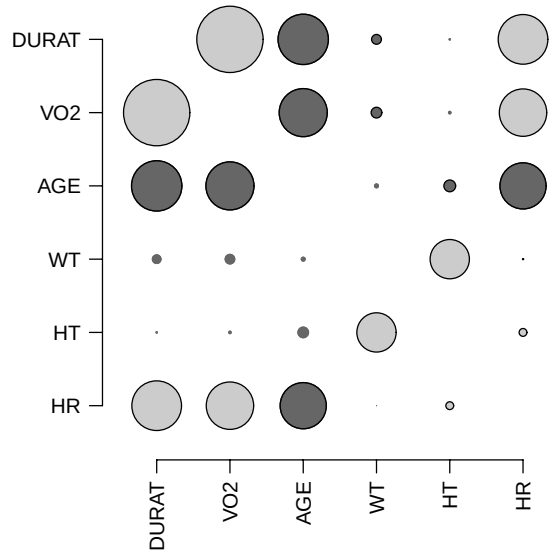


Figure 14.19 Shaded correlation matrix for Problem 14.8.

(a) We suppose that $c \neq 0$. The variance explained by the first principal component is

$$V_1 = \frac{(a+b) + \sqrt{(a-b)^2 + 4c^2}}{2}$$

The first principal component is

$$\sqrt{\frac{c^2}{c^2 + (V_1 - a)^2}} X + \frac{c}{|c|} \sqrt{\frac{(V_1 - a)^2}{c^2 + (V_1 - a)^2}} Y$$

(b) Suppose that $c = 0$. The first principal component is X if $a \geq b$, and is Y if $a < b$.

(c) The introduction to Problems 9.30–9.33 presented data on 20 patients who had their mitral valve replaced. The systolic blood pressure before and after surgery had the following variances and covariance:

	SBP	
	Before	**After**
Before	349.74	21.63
After	21.63	91.94

Find the variance explained by the first and second principal components.

14.10 The exercise data of the 43 active females of Problem 14.4 are used here. The findings are given in Tables 14.35 to 14.37 and Figures 14.20 and 14.21. Perform tasks (a), (c), (d), (f), and (g). Problem 14.8 examined similar exercise data for sedentary males.

Table 14.35 Problem 14.10: Residual Correlations

		DURAT	$VO_{2\ MAX}$	HR	AGE	HT	WT
DURAT	1	0.151					
$VO_{2\ MAX}$	2	0.008	0.241				
HR	3	0.039	−0.072	0.687			
AGE	4	0.015	0.001	−0.013	0.416		
HT	5	−0.045	0.013	−0.007	−0.127	0.605	
WT	6	0.000	0.000	0.000	−0.000	0.000	0.000

Table 14.36 Problem 14.10: Communalities[a]

1	DURAT	0.8492
2	$VO_{2\ MAX}$	0.7586
3	HR	0.3127
4	AGE	0.5844
5	HT	0.3952
6	WT	1.0000

[a]Communalities obtained from two factors after 10 iterations. The communality of a variable is its squared multiple correlation with the factors.

Table 14.37 Problem 14.10: Factors

		Factor 1	Factor 2
DURAT	1	0.907	0.165
$VO_{2\ MAX}$	2	0.869	
HR	3	0.489	0.271
AGE	4	−0.758	−0.102
HT	5	0.364	0.513
WT	6		0.997
	VP[a]	2.529	1.371

[a]The VP for each factor is the sum of the squares of the elements of the column of the factor pattern matrix corresponding to that factor. When the rotation is orthogonal, the VP is the variance explained by the factor.

Which factor analysis do you feel was more satisfactory in explaining the relationship among variables? Why? Which analysis had the more interpretable factors? Explain your reasoning.

14.11 The data on the correlation among male body measurements (of Problem 14.2) are factor analyzed here. The computer output gave the results given in Tables 14.38 to 14.40 and Figure 14.22. Perform tasks (a), (b) (POPHT, KNEEHT), (STHTER, BUTTKNHT), (RTARMSKN, INFRASCP), and (e) for variables 1 and 11, and tasks (f) and (g). Examine the diagonal of the residual values and the communalities. What values are on the diagonal of the residual correlations? (The diagonals are the 1–1, 2–2, 3–3, etc. entries.)

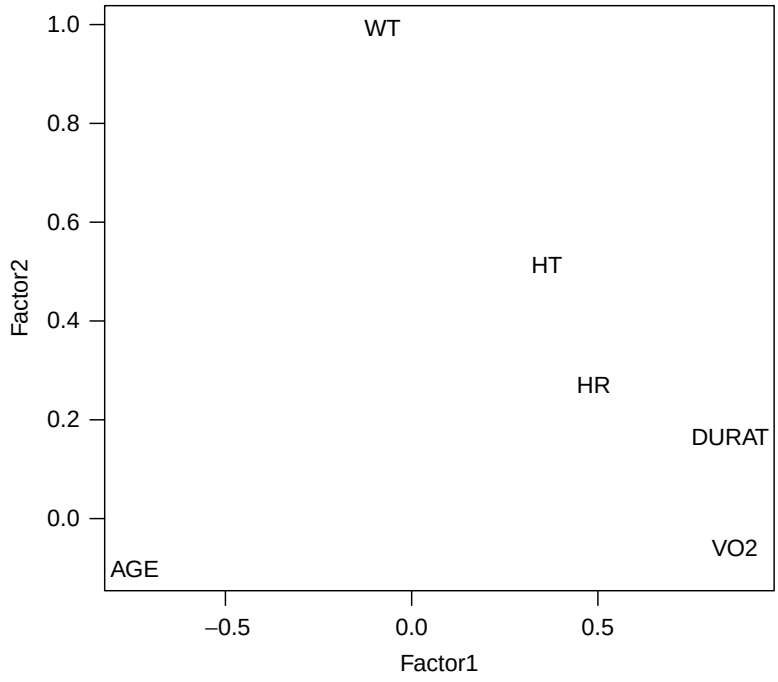


Figure 14.20 Problem 14.10, plot of factor loadings.

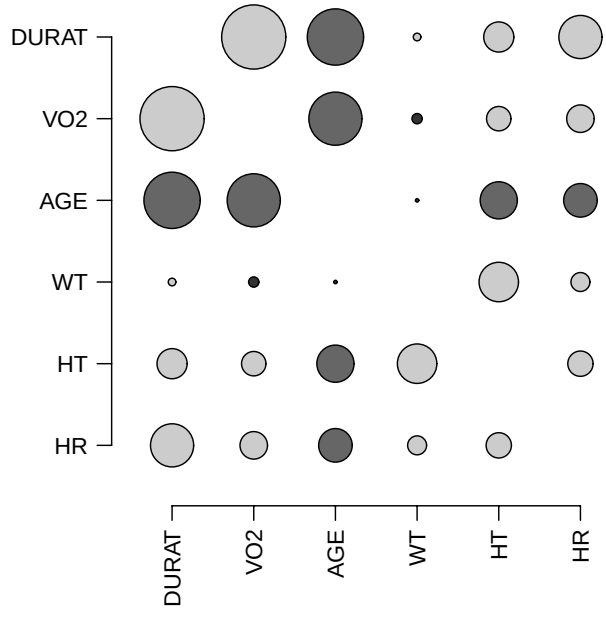


Figure 14.21 Shaded correlation matrix for Problem 14.10.

Table 14.38 Problem 14.11: Residual Correlations

		STHTER 1	STHTNORM 2	KNEEHT 3	POPHT 4	ELBWHT 5
STHTER	1	0.028				
STHTNORM	2	0.001	0.205			
KNEEHT	3	0.000	−0.001	0.201		
POPHT	4	0.000	−0.006	0.063	0.254	
ELBWHT	5	−0.001	−0.026	−0.012	0.011	0.519
THIGHHT	6	−0.003	0.026	0.009	−0.064	−0.029
BUTTKNHT	7	0.001	−0.004	−0.024	−0.034	−0.014
BUTTPOP	8	−0.001	0.019	−0.038	−0.060	−0.043
ELBWELBW	9	−0.001	0.008	0.007	−0.009	0.004
SEATBRTH	10	−0.002	0.023	0.015	−0.033	−0.013
BIACROM	11	0.006	−0.009	0.009	0.035	−0.077
CHESTGRH	12	−0.001	0.004	−0.004	0.015	−0.007
WSTGRTH	13	0.001	−0.004	−0.002	0.008	0.006
RTARMGRH	14	0.002	0.011	0.012	−0.006	−0.021
RTARMSKN	15	−0.002	0.025	−0.002	−0.012	0.009
INFRASCP	16	−0.002	0.003	−0.009	−0.002	0.020
HT	17	−0.000	0.001	−0.003	−0.003	0.007
WT	18	0.000	−0.007	0.001	0.004	0.007
AGE	19	−0.001	0.006	0.010	−0.014	−0.023

		THIGHHT 6	BUTTKNHT 7	BUTTPOP 8	ELBWELBW 9	SEATBRTH 10
THIGHHT	6	0.462				
BUTTKNHT	7	0.012	0.222			
BUTTPOP	8	0.016	0.076	0.409		
ELBWELBW	9	0.032	−0.002	0.006	0.215	
SEATBRTH	10	0.023	0.020	−0.017	0.007	0.305
BIACROM	11	−0.052	−0.019	−0.027	0.012	−0.023
CHESTGRH	12	−0.020	−0.013	−0.011	0.025	−0.020
WSTGRTH	13	−0.002	0.006	0.009	−0.006	−0.009
RTARMGRH	14	0.009	0.000	0.013	0.011	−0.017
RTARMSKN	15	0.038	0.039	0.015	−0.019	0.053
INFRASCP	16	−0.025	0.008	−0.000	−0.022	0.001
HT	17	0.005	0.005	0.005	0.000	−0.001
WT	18	−0.004	−0.005	−0.007	−0.006	0.004
AGE	19	−0.012	−0.010	−0.014	0.011	0.007

		BIACROM 11	CHESTGRH 12	WSTGRTH 13	RTARMGRH 14	RTARMSKN 15
BIACROM	11	0.684				
CHESTGRH	12	0.051	0.150			
WSTGRTH	13	−0.011	0.000	0.095		
RTARMGRH	14	−0.016	−0.011	−0.010	0.186	
RTARMSKN	15	−0.065	−0.011	0.009	0.007	0.601
INFRASCP	16	−0.024	−0.005	0.014	−0.022	0.199
HT	17	−0.008	0.000	−0.003	−0.005	0.004
WT	18	0.006	0.002	0.002	0.006	−0.023
AGE	19	−0.015	−0.006	−0.002	0.014	−0.024

		INFRASCP 16	HT 17	WT 18	AGE 19
INFRASCP	16	0.365			
HT	17	0.003	0.034		
WT	18	−0.003	0.001	0.033	
AGE	19	−0.022	0.002	0.002	0.311

Table 14.39 Problem 14.11: Communalities[a]

1	STHTER	0.9721
2	STHTNORM	0.7952
3	KNEEHT	0.7991
4	POPHT	0.7458
5	ELBWHT	0.4808
6	THIGHHT	0.5379
7	BUTTKNHT	0.7776
8	BUTTPOP	0.5907
9	ELBWELBW	0.7847
10	SEATBRTH	0.6949
11	BIACROM	0.3157
12	CHESTGRH	0.8498
13	WSTGRTH	0.9054
14	RTARMGRH	0.8144
15	RTARMSKN	0.3991
16	INFRASCP	0.6352
17	HT	0.9658
18	WT	0.9671
19	AGE	0.6891

[a]Communalities obtained from four factors after six iterations. The communality of a variable is its squared multiple correlation with the factors.

Table 14.40 Problem 14.11: Factors (Loadings Smaller Than 0.1 Omitted)

		Factor 1	Factor 2	Factor 3	Factor 4
		Unrotated[a]			
STHTER	1	0.100	0.356	0.908	−0.104
STHTNORM	2	0.168	0.367	0.795	
KNEEHT	3	0.113	0.875	0.128	
POPHT	4	−0.156	0.836	0.133	
ELBWHT	5	0.245	−0.151	0.617	−0.131
THIGHHT	6	0.675	0.131	0.114	−0.230
BUTTKNHT	7	0.308	0.819	0.100	
BUTTPOP	8	0.188	0.742		
ELBWELBW	9	0.873			0.131
SEATBRTH	10	0.765	0.209	0.247	
BIACROM	11	0.351	0.298	0.213	−0.242
CHESTGRH	12	0.902	0.137	0.118	
WSTGRTH	13	0.892			0.323
RTARMGRH	14	0.873			−0.198
RTARMSKN	15	0.625			
INFRASCP	16	0.794			
HT	17		0.836	0.507	−0.098
WT	18	0.907	0.308	0.218	−0.049
AGE	19		−0.135	−0.160	0.801
	VP[a]	6.409	3.964	2.370	0.978

[a]The VP for each factor is the sum of the squares of the elements of the column of the factor pattern matrix corresponding to that factor. When the rotation is orthogonal, the VP is the variance explained by the factor

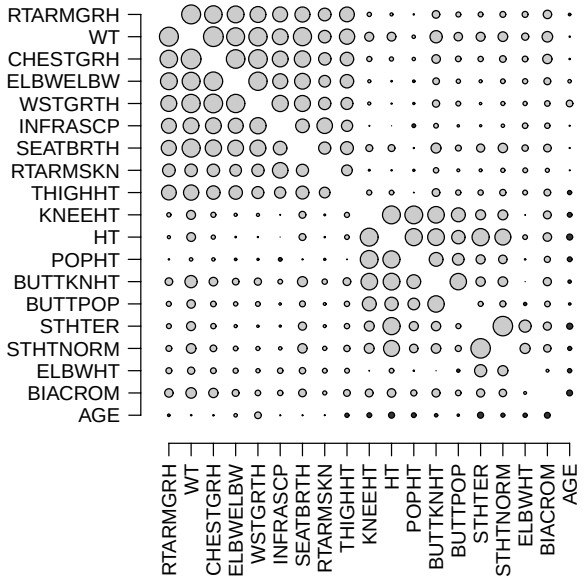


Figure 14.22 Shaded correlation matrix for Problem 14.11.

REFERENCES

Armstrong, J. S. [1967]. Derivation of theory by means of factor analysis, or, Tom Swift and his electric factor analysis machine. *American Statistician* **21**: 17–21.

Bruce, R. A., Kusumi, F., and Hosmer, D. [1973]. Maximal oxygen intake and nomographic assessment of functional aerobic impairment in cardiovascular disease. *American Heart Journal*, **85**: 546–562.

Chaitman, B. R., Fisher, L., Bourassa, M., Davis, K., Rogers, W., Maynard, C., Tyros, D., Berger, R., Judkins, M., Ringqvist, I., Mock, M. B., Killip, T., and participating CASS Medical Centers [1981]. Effects of coronary bypass surgery on survival in subsets of patients with left main coronary artery disease. Report of the Collaborative Study on Coronary Artery Surgery. *American Journal of Cardiology*, **48**: 765–777.

Gorsuch, R. L. [1983]. *Factor Analysis*. 2nd ed. Lawrence Erlbaum Associates, Mahwah, NJ.

Gould, S. J. [1996]. *The Mismeasure of Man*. Revised, Expanded Edition. W.W. Norton, New York.

Guttman, L. [1954]. Some necessary conditions for common factor analysis. *Psychometrika*, **19**(2): 149–161.

Henry, R. C. [1997]. History and fundamentals of multivariate air quality receptor models. *Chemometrics and Intelligent Laboratory Systems* **37**: 525–530.

Jones, M. C., and Sibson, R. [1987]. What is projection pursuit? *Journal of the Royal Statistical Society, Series A*, **150**: 1–36.

Kim, J.-O., and Mueller, C. W. [1999]. *Introduction to Factor Analysis: What It Is and How to Do It.* Sage University Paper 13. Sage Publications, Beverly Hills, CA.

Kim, J.-O., and Mueller, C. W. [1983]. *Factor Analysis: Statistical Methods and Practical Issues.* Sage University Paper 14. Sage Publications, Beverly Hills, CA.

McDonald, R. P. [1999]. *Test Theory: A Unified Treatment. Lawrence* Erlbaum Associates, Mahwah, NJ.

Morrison, D. R. [1990]. *Multivariate Statistical Methods*, 3rd ed. McGraw-Hill, New York.

Paatero, P. [1997]. Least squares formulation of robust, non-negative factor analysis. *Chemometrics and Intelligent Laboratory Systems*, **37**: 23–35.

Paatero, P. [1999]. The multilinear engine: a table-driven least squares program for solving multilinear problems, including *n*-way parallel factor analysis model. *Journal of Computational and Graphical Statistics*, **8**: 854–888.

Reeck, G. R., and Fisher, L. D. [1973]. A statistical analysis of the amino acid composition of proteins. *International Journal of Peptide Protein Research*, **5**: 109–117.

Starkweather, D. B. [1970]. Hospital size, complexity, and formalization. *Health Services Research*, Winter, 330–341. Used with permission from the Hospital and Educational Trust.

Stoudt, H. W., Damon, A., and McFarland, R. A. [1970]. *Skinfolds, Body Girths, Biacromial Diameter, and Selected Anthropometric Indices of Adults: United States, 1960–62*. Vital and Health Statistics. Data from the National Survey. Public Health Service Publication 1000, Series 11, No. 35. U.S. Government Printing Office, Washington, DC.

Timm, N. H. [2001]. *Applied Multivariate Analysis*. Springer-Verlag, New York.

U.S. EPA [2000]. *Workshop on UNMIX and PMF as Applied to* $PM_{2.5}$. National Exposure Research Laboratory, Research Triangle Park, NC. *http://www.epa.gov/ttn/amtic/unmixmtg.html*.

CHAPTER 15

Rates and Proportions

15.1 INTRODUCTION

In this chapter and the next we want to study in more detail some of the topics dealing with counting data introduced in Chapter 6. In this chapter we want to take an epidemiological approach, studying populations by means of describing incidence and prevalence of disease. In a sense this is where statistics began: with a numerical description of the characteristics of a state, frequently involving mortality, fecundity, and morbidity. We call the occurrence of one of those outcomes an *event*. In the next chapter we deal with more recent developments, which have focused on a more detailed modeling of survival (hence also death, morbidity, and fecundity) and dealt with such data obtained in experiments rather than observational studies. An implication of the latter point is that sample sizes have been much smaller than used traditionally in the epidemiological context. For example, the evaluation of the success of heart transplants has, by necessity, been based on a relatively small set of data.

We begin the chapter with definitions of incidence and prevalence rates and discuss some problems with these "crude" rates. Two methods of standardization, direct and indirect, are then discussed and compared. In Section 15.4, a third standardization procedure is presented to adjust for varying exposure times among individuals. In Section 15.5, a brief tie-in is made to the multiple logistic procedures of Chapter 13. We close the chapter with notes, problems, and references.

15.2 RATES, INCIDENCE, AND PREVALENCE

The term *rate* refers to the amount of change occurring in a quantity with respect to time. In practice, *rate* refers to the amount of change in a variable over a specified time interval divided by the length of the time interval.

The data used in this chapter to illustrate the concepts come from the Third National Cancer Survey [National Cancer Institute, 1975]. For this reason we discuss the concepts in terms of incidence rates. The *incidence* of a disease in a fixed time interval is the number of new cases diagnosed during the time interval. The *prevalence* of a disease is the number of people with the disease at a fixed time point. For a chronic disease, incidence and prevalence may present markedly different ideas of the importance of a disease.

Consider the Third National Cancer Survey [National Cancer Institute, 1975]. This survey examined the incidence of cancer (by site) in nine areas during the time period 1969–1971.

Biostatistics: A Methodology for the Health Sciences, Second Edition, by Gerald van Belle, Lloyd D. Fisher, Patrick J. Heagerty, and Thomas S. Lumley
ISBN 0-471-03185-2

The areas were the Detroit SMSA (Standard Metropolitan Statistical Area); Pittsburgh SMSA, Atlanta SMSA, Birmingham SMSA, Dallas–Fort Worth SMSA, state of Iowa, Minneapolis–St. Paul SMSA, state of Colorado, and the San Francisco–Oakland SMSA. The information used in this chapter refers to the combined data from the Atlanta SMSA and San Francisco–Oakland SMSA. The data are abstracted from tables in the survey. Suppose that we wanted the rate for all sites (of cancer) combined. The rate per year in the 1969–1971 time interval would be simply the number of cases divided by 3, as the data were collected over a three-year interval. The rates are as follows:

$$\text{Combined area :} \quad \frac{181{,}027}{3} = 60{,}342.3$$

$$\text{Atlanta :} \quad \frac{9{,}341}{3} = 3{,}113.7$$

$$\text{San Francisco–Oakland :} \quad \frac{30{,}931}{3} = 10{,}310.3$$

Can we conclude that cancer incidence is worse in the San Francisco–Oakland area than in the Atlanta area? The answer is "yes and no." Yes, in that there are more cases to take care of in the San Francisco–Oakland area. If we are concerned about the chance of a person getting cancer, the numbers would not be meaningful. As the San Francisco–Oakland area may have a larger population, the number of cases per number of the population might be less. To make comparisons taking the population size into account, we use

$$\text{incidence per time interval} = \frac{\text{number of new cases}}{\text{total population} \times \text{time interval}} \tag{1}$$

The result of equation (1) would be quite small, so that the number of cases per 100,000 population is used to give a more convenient number. The rate per 100,000 population per year is then

$$\text{incidence per 100,000 per time interval} = \frac{\text{number of new cases}}{\text{total population} \times \text{time interval}} \times 100{,}000$$

For these data sets, the values are:

$$\text{Combined area :} \quad \frac{181{,}027 \times 100{,}000}{21{,}003{,}451 \times 3} = 287.3 \text{ new cases per } 100{,}000 \text{ per year}$$

$$\text{Atlanta :} \quad \frac{9{,}341 \times 100{,}000}{1{,}390{,}164 \times 3} = 224.0 \text{ new cases per } 100{,}000 \text{ per year}$$

$$\text{San Francisco-Oakland :} \quad \frac{30{,}931 \times 100{,}000}{3{,}109{,}519 \times 3} = 331.6 \text{ new cases per } 100{,}000 \text{ per year}$$

Even after adjusting for population size, the San Francisco–Oakland area has a higher overall rate.

Note several facts about the estimated rates. The estimates are binomial proportions times a constant (here 100,000/3). Thus, the rate has a standard error easily estimated. Let N be the total population and n the number of new cases; the rate is $n/N \times C$ ($C = 100{,}000/3$ in this example) and the standard error is estimated by

$$\sqrt{C^2 \frac{1}{N} \frac{n}{N} \left(1 - \frac{n}{N}\right)}$$

or

$$\text{standard error of rate per time interval} = C\sqrt{\frac{1}{N} \frac{n}{N} \left(1 - \frac{n}{N}\right)}$$

For example, the combined area estimate has a standard error of

$$\frac{100{,}000}{3}\sqrt{\frac{1}{21{,}003{,}451}\frac{181{,}027}{21{,}003{,}451}\left(1-\frac{181{,}027}{21{,}003{,}451}\right)}=0.67$$

As the rates are assumed to be binomial proportions, the methods of Chapter 6 may be used to get adjusted estimates or standardized estimates of proportions.

Rates computed by the foregoing methods,

$$\frac{\text{number of new cases in the interval}}{\text{population size} \times \text{time interval}}$$

are called *crude* or *total rates*. This term is used in distinction to *standardized* or *adjusted rates*, as discussed below.

Similarly, a *prevalence rate* can be defined as

$$\text{prevalence} = \frac{\text{number of cases at a point in time}}{\text{population size}}$$

Sometimes a distinction is made between *point prevalence* and *prevalence* to facilitate discussion of chronic disease such as epilepsy and a disease of shorter duration, for example, a common cold or even accidents. It is debatable whether the word *prevalence* should be used for accidents or illnesses of short duration.

15.3 DIRECT AND INDIRECT STANDARDIZATION

15.3.1 Problems with the Use of Crude Rates

Crude rates are useful for certain purposes. For example, the crude rates indicate the load of new cases per capita in a given area of the country. Suppose that we wished to use the cancer rates as epidemiologic indicators. The inference would be that it was likely that environmental or genetic differences were responsible for a difference, if any. There may be simpler explanations, however. Breast cancer rates would probably differ in areas that had differing gender proportions. A retirement community with an older population will tend to have a higher rate. To make fair comparisons, we often want to adjust for the differences between populations in one or more factors (covariates). One approach is to find an index that is adjusted in some fashion. We discuss two methods of adjustment in the next two sections.

15.3.2 Direct Standardization

In direct standardization we are interested in adjusting by one or more variables that are divided (or naturally fall) into discrete categories. For example, in Table 15.1 we adjust for gender and for age divided into a total of 18 categories. The idea is to find an answer to the following question: Suppose that the distribution with regard to the adjusting factors was not as observed, but rather, had been the same as this other (reference) population; what would the rate have been? In other words, we apply the risks observed in our study population to a reference population.

In symbols, the adjusting variable is broken down into I cells. In each cell we know the number of events (the numerator) n_i and the total number of individuals (the denominator) N_i:

Level of adjusting factor, i:	1	2	$\cdots$	i	$\cdots$	I
Proportion observed in study population:	$\frac{n_1}{N_1}$	$\frac{n_2}{N_2}$	$\cdots$	$\frac{n_i}{N_i}$	$\cdots$	$\frac{n_1}{N_1}$

Table 15.1 Rate for Cancer of All Sites for Blacks in the San Francisco–Oakland SMSA and Reference Population

	Study Population n_i/N_i		Reference Population M_i	
Age	Females	Males	Females	Males
<5	8/16,046	6/16,493	872,451	908,739
5–9	6/18,852	7/19,265	1,012,554	1,053,350
10–14	6/19,034	3/19,070	1,061,579	1,098,507
15–19	7/16,507	6/16,506	971,894	964,845
20–24	16/15,885	9/14,015	919,434	796,774
25–29	27/12,886	19/12,091	755,140	731,598
30–34	28/10,705	18/10,445	620,499	603,548
35–39	46/9,580	25/8,764	595,108	570,117
40–44	83/9,862	47/8,858	650,232	618,891
45–49	109/10,341	108/9,297	661,500	623,879
50–54	125/8,691	131/8,052	595,876	558,124
55–59	120/6,850	189/6,428	520,069	481,137
60–64	102/5,017	158/4,690	442,191	391,746
65–69	119/3,806	159/3,345	367,046	292,621
70–74	75/2,264	154/1,847	300,747	216,929
75–79	44/1,403	72/931	224,513	149,867
80–84	28/765	51/471	139,552	84,360
>85	25/629	26/416	96,419	51,615
Subtotal	974/169,123	1,188/160,984	10,806,804	10,196,647
Total	2,162/330,107		21,003,451	

Source: National Cancer Institute [1975].

Both numerator and denominator are presented in the table. The crude rate is estimated by

$$C\frac{\sum_{i=1}^{I} n_i}{\sum_{i=1}^{I} N_i}$$

Consider now a *standard or reference population*, which instead of having N_i persons in the ith cell has M_i.

	Reference Population					
Level of adjusting factor	1	2	⋯	i	⋯	I
Number in reference population	M_1	M_2	⋯	M_i	⋯	M_I

The question now is: If the study population has M_i instead of N_i persons in the ith cell, what would the crude rate have been? We cannot determine what the crude rate was, but we can estimate what it might have been. In the ith cell the proportion of observed deaths was n_i/N_i. If the same proportion of deaths occurred with M_i persons, we would expect

$$n_i^* = \frac{n_i}{N_i} M_i \text{ deaths}$$

Thus, if the adjusting variables had been distributed with M_i persons in the ith cell, we estimate that the data would have been:

Level of adjusting factor:	1	2	$\cdots$	i	$\cdots$	I
Expected proportion of cases:	$\frac{n_1 M_1/N_1}{M_1}$	$\frac{n_2 M_2/N_2}{M_2}$	$\cdots$	$\frac{n_i^*}{M_i}$	$\cdots$	$\frac{n_I M_I/N_I}{M_I}$

The *adjusted rate*, r, is the crude rate for this estimated standard population:

$$r = \frac{C \sum_{i=1}^{I} n_i M_i/N_i}{\sum_{i=1}^{I} M_i} = \frac{C \sum_{i=1}^{I} n_i^*}{\sum_{i=1}^{I} M_i}$$

As an example, consider the rate for cancer for all sites for blacks in the San Francisco–Oakland SMSA, adjusted for gender and age to the total combined sample of the Third Cancer Survey, as given by the 1970 census. There are two gender categories and 18 age categories, for a total of 36 cells. The cells are laid out in two columns rather than in one row of 36 cells. The data are given in Table 15.1.

The crude rate for the San Francisco–Oakland black population is

$$\frac{100{,}000}{3} \frac{974 + 1188}{169{,}123 + 160{,}984} = 218.3$$

Table 15.2 gives the values of $n_i M_i/N_i$.

The gender- and age-adjusted rate is thus

$$\frac{100{,}000}{3} \frac{193{,}499.42}{21{,}003{,}451} = 307.09$$

Note the dramatic change in the estimated rate. This occurs because the San Francisco–Oakland SMSA black population differs in its age distribution from the overall sample.

The variance is estimated by considering the denominators in the cell as fixed and using the binomial variance of the n_i's. Since the cells constitute independent samples,

$$\begin{aligned} \operatorname{var}(r) &= \operatorname{var}\left(C \sum_{i=1}^{I} \frac{n_i M_i}{N_i} \Big/ \sum_{i=1}^{I} M_i \right) \\ &= \frac{C^2}{M_\cdot^2} \sum_{i=1}^{I} \left(\frac{M_i}{N_i} \right)^2 \operatorname{var}(n_i) \end{aligned}$$

Table 15.2 Estimated Number of Cases per Cell ($n_i M_i/N_i$) if the San Francisco–Oakland Area Had the Reference Population Age and Gender Distribution

Age	Females	Males	Age	Females	Males
<5	434.97	330.59	55–59	9,110.70	14,146.69
5–9	322.26	382.74	60–64	8,990.13	13,197.41
10–14	334.64	172.81	65–69	11,476.21	13,909.34
15–19	412.14	350.73	70–74	9,962.91	18,087.20
20–24	926.09	511.66	75–79	7,041.03	11,590.14
25–29	1,582.24	1,149.65	80–84	5,107.79	9,134.52
30–34	1,622.98	1,040.10	>85	3,832.23	3,225.94
35–39	2,857.51	1,629.30			
40–44	5,472.45	3,283.80	Subtotal	85,029.16	108,470.26
45–49	6,972.58	7,247.38	Total	193,499.42	
50–54	8,570.30	9,080.26			

$$= \frac{C^2}{M_\cdot^2} \sum_{i=1}^{I} \left(\frac{M_i}{N_i}\right)^2 N_i \frac{n_i}{N_i} \left(1 - \frac{n_i}{N_i}\right)$$

$$= \frac{C^2}{M_\cdot^2} \sum_{i=1}^{I} \frac{M_i}{N_i} \frac{n_i M_i}{N_i} \left(1 - \frac{n_i}{N_i}\right)$$

where $M_\cdot = \sum_{i=1}^{I} M_i$.

If n_i/N_i is small, then $1 - n_i/N_i \doteq 1$ and

$$\text{var}(r) \doteq \frac{C^2}{M_\cdot^2} \sum_{i=1}^{I} \frac{M_i}{N_i} \left(\frac{n_i M_i}{N_i}\right) \tag{2}$$

We use this to compute a 95% confidence interval for the adjusted rate computed above. Using equation (2), the standard error is

$$\text{SE}(r) = \frac{C}{M_\cdot} \sqrt{\sum_{i=1}^{I} \frac{M_i}{N_i} \left(\frac{n_i M_i}{N_i}\right)}$$

$$= \frac{100{,}000}{3} \frac{1}{21{,}003{,}451} \left(\frac{872{,}451}{16{,}046} 434.97 + \cdots\right)^{1/2}$$

$$= 7.02$$

The quantity r is approximately normally distributed, so that the interval is

$$307.09 \pm 1.96 \times 7.02 \quad \text{or} \quad (293.3, 320.8)$$

If adjusted rates are estimated for two different populations, say r_1 and r_2, with standard errors $\text{SE}(r_1)$ and $\text{SE}(r_2)$, respectively, equality of the adjusted rates may be tested by using

$$z = \frac{r_1 - r_2}{\sqrt{\text{SE}(r_1)^2 + \text{SE}(r_2)^2}}$$

The $N(0,1)$ critical values are used, as z is approximately $N(0,1)$ under the null hypothesis of equal rates.

15.3.3 Indirect Standardization

In indirect standardization, the procedure of direct standardization is used in the opposite direction. That is, we ask the question: What would the mortality rate have been for the study population if it had the same rates as the population reference? That is, we apply the observed risks in the reference population to the study population.

Let m_i be the number of deaths in the reference population in the ith cell. The data are:

Level of adjusting factor:	1	2	$\cdots$	i	$\cdots$	I
Observed proportion in reference population:	$\frac{m_1}{M_1}$	$\frac{m_2}{M_2}$	$\cdots$	$\frac{m_i}{M_i}$	$\cdots$	$\frac{m_I}{M_I}$

where both numerator and denominators are presented in the table. Also,

Level of adjusting factor:	1	2	$\cdots$	i	$\cdots$	I
Denominators in study population:	N_1	N_2	$\cdots$	N_i	$\cdots$	N_I

The estimate of the rate the study population would have experienced is (analogous to the argument in Section 15.3.2)

$$r_{\text{REF}} = \frac{C \sum_{i=1}^{I} N_i (m_i / M_i)}{\sum_{i=1}^{I} N_i}$$

The crude rate for the study population is

$$r_{\text{STUDY}} = \frac{C \sum_{i=1}^{I} n_i}{\sum_{i=1}^{I} N_i}$$

where n_i is the observed number of cases in the study population at level i. Usually, there is not much interest in comparing the values r_{REF} and r_{STUDY} as such, because the distribution of the study population with regard to the adjusting factors is not a distribution of much interest. For this reason, attention is usually focused on the *standardized mortality ratio* (SMR), when death rates are considered, or the *standardized incidence ratio* (SIR), defined to be

$$\text{standardized ratio} = s = \frac{r_{\text{STUDY}}}{r_{\text{REF}}} = \frac{\sum_{i=1}^{I} n_i}{\sum_{i=1}^{I} N_i m_i / M_i} \tag{3}$$

The main advantage of the indirect standardization is that the SMR involves only the total number of events, so you do not need to know in which cells the deaths occur for the study population. An alternative way of thinking of the SMR is that it is the observed number of deaths in the study population divided by the expected number if the cell-specific rates of the reference population held.

As an example, let us compute the SIR of cancer in black males in the Third Cancer Survey, using white males of the same study as the reference population and adjusting for age. The data are presented in Table 15.3. The standardized incidence ratio is

$$s = \frac{8793}{7474.16} = 1.17645 = 1.18$$

One reasonable question to ask is whether this ratio is significantly different from 1. An approximate variance can be derived as follows:

$$s = \frac{O}{E} \qquad \text{where} \quad O = \sum_{i=1}^{I} n_i = n. \quad \text{and} \quad E = \sum_{i=1}^{I} N_i \left(\frac{m_i}{M_i} \right)$$

The variance of s is estimated by

$$\text{var}(s) = \frac{\text{var}(O) + s^2 \text{ var}(E)}{E^2} \tag{4}$$

The basic "trick" is to (1) assume that the number of cases in a particular cell follows a Poisson distribution and (2) to note that the sum of independent Poisson random variables is Poisson. Using these two facts yields

$$\text{var}(O) \doteq \sum_{i=1}^{I} n_i = n \tag{5}$$

Table 15.3 Cancer of All Areas Combined, Number of Cases, Black and White Males by Age and Number Eligible by Age

Age	Black Males		White Males			
	n_1	N_1	m_1	M_1	$\frac{N_i m_i}{M_i}$	$\left(\frac{N_i}{M_i}\right)^2 m_i$
<5	45	120,122	450	773,459	69.89	10.85
5–9	34	130,379	329	907,543	47.26	6.79
10–14	39	134,313	300	949,669	42.43	6.00
15–19	45	112,969	434	837,614	58.53	7.89
20–24	49	86,689	657	694,670	81.99	10.23
25–29	63	71,348	688	647,304	75.83	8.36
30–34	84	57,844	724	533,856	78.45	8.50
35–39	129	54,752	1,097	505,434	118.83	12.87
40–44	318	57,070	2,027	552,780	209.27	21.61
45–49	582	56,153	3,947	559,241	396.31	39.79
50–54	818	48,753	6,040	503,163	585.23	56.71
55–59	1,170	42,580	8,711	432,982	856.65	84.24
60–64	1,291	33,892	10,966	352,315	1,054.91	101.48
65–69	1,367	27,239	11,913	261,067	1,242.97	129.69
70–74	1,266	17,891	11,735	196,291	1,069.59	97.49
75–79	788	9,827	10,546	138,532	748.10	53.07
80–84	461	4,995	6,643	78,044	425.17	27.21
>85	244	3,850	3,799	46,766	312.75	25.75
Total	8,793	1,070,700	81,006	8,970,730	7,474.16	708.53

and

$$\operatorname{var}(E) \doteq \operatorname{var}\left(\sum_{i=1}^{I} \frac{N_i}{M_i} m_i\right)$$

$$= \sum_{i=1}^{I} \left(\frac{N_i}{M_i}\right)^2 m_i \tag{6}$$

The variance of s is estimated by using equations (4), (5), and (6):

$$\operatorname{var}(s) = \frac{n_\cdot + s^2 \sum (N_i/M_i)^2 m_i}{E^2}$$

A test of the hypothesis that the population value of s is 1 is obtained from

$$z = \frac{s - 1}{\sqrt{\operatorname{var}(s)}}$$

and $N(0, 1)$ critical values.

For the example,

$$\sum_{i=1}^{I} n_i = n_\cdot = 8793$$

$$E = \sum_{i=1}^{I} \frac{N_i}{M_i} m_i = 7474.16$$

$$\text{var}(E) \doteq \sum_{i=1}^{I} \left(\frac{N_i}{M_i}\right)^2 m_i = 708.53$$

$$\text{var}(s) \doteq \frac{8793 + (1.17645)^2 \times 708.53}{(7474.16)^2} = 0.000174957$$

From this and a standard error of $s \doteq 0.013$, the ratio is significantly different from one using

$$z = \frac{s - 1}{\text{SE}(s)} = \frac{0.17645}{0.013227} = 13.2$$

and $N(0, 1)$ critical values.

If the reference population is much larger than the study population, $\text{var}(E)$ will be much less than $\text{var}(O)$ and you may approximate $\text{var}(s)$ by $\text{var}(O)/E^2$.

15.3.4 Drawbacks to Using Standardized Rates

Any time a complex situation is summarized in one or a few numbers, considerable information is lost. There is always a danger that the lost information is crucial for understanding the situation under study. For example, two populations may have almost the same standardized rates but may differ greatly within the different cells; one population has much larger values in one subset of the cells and the reverse situation in another subset of cells. Even when the standardized rates differ, it is not clear if the difference is somewhat uniform across cells or results mostly from one or a few cells with much larger differences.

The moral of the story is that whenever possible, the rates in the cells used in standardization should be examined individually in addition to working with the standardized rates.

15.4 HAZARD RATES: WHEN SUBJECTS DIFFER IN EXPOSURE TIME

In the rates computed above, each person was exposed (eligible for cancer incidence) over the same length of time (three years, 1969–1971). (This is not quite true, as there is some population mobility, births, and deaths. The assumption that each person was exposed for three years is valid to a high degree of approximation.) There are other circumstances where people are observed for varying lengths of time. This happens, for example, when patients are recruited sequentially as they appear at a medical care facility. One approach would be to restrict the analysis to those who had been observed for at least some fixed amount of time (e.g., for one year). If large numbers of persons are not observed, this approach is wasteful by throwing away valuable and needed information. This section presents an approach that allows the rates to use all the available information if certain assumptions are satisfied.

Suppose that we observe subjects over time and look for an event that occurs only once. For definiteness, we speak about observing people where the event is death. Assume that over the time interval observed, if a subject has survived to some time t_0, the probability of death in a short interval from t_0 to t_1 is almost $\lambda(t_1 - t_0)$. The quantity λ is called the *hazard rate, force of mortality*, or *instantaneous death rate*. The units of λ are deaths per time unit.

How would we estimate λ from data in a real-life situation? Suppose that we have n individuals and begin observing the ith person at time B_i. If the person dies, let the time of death be D_i. Let the time of last contact be C_i for those people who are still alive. Thus, the time we are observing each person at risk of death is

$$O_i = \begin{cases} C_i - B_i & \text{if the subject is alive} \\ D_i - B_i & \text{if the subject is dead} \end{cases}$$

An unbiased estimate of λ is

$$\text{estimated hazard rate} = \widehat{\lambda} = \frac{\text{number of observed deaths}}{\sum_{i=1}^{n} O_i} = \frac{L}{\sum_{i=1}^{n} O_i} \tag{7}$$

As in the earlier sections of this chapter, $\widehat{\lambda}$ is often normalized to have different units. For example, suppose that $\widehat{\lambda}$ is in deaths per day of observation. That is, suppose that O_i is measured in days. To convert to deaths per 100 observation years, we use

$$\widehat{\lambda} \times 365 \frac{\text{days}}{\text{year}} \times 100$$

As an example, consider the paper by Clark et al. [1971]. This paper discusses the prognosis of patients who have undergone cardiac (heart) transplantation. They present data on 20 transplanted patients. These data are presented in Table 15.4. To estimate the deaths per year of exposure, we have

$$\frac{12 \text{ deaths}}{3599 \text{ exposure days}} \frac{365 \text{ days}}{\text{year}} = 1.22 \frac{\text{deaths}}{\text{exposure year}}$$

To compute the variance and standard error of the observed hazard rate, we again assume that L in equation (7) has a Poisson distribution. So conditional on the total observation period, the variability of the estimated hazard rate is proportional to the variance of L, which is estimated by L itself. Let

$$\widehat{\lambda} = \frac{CL}{\sum_{i=1}^{n} O_i}$$

where C is a constant that standardizes the hazard rate appropriately.

Table 15.4 Stanford Heart Transplant Data

i	Date of Transplantation	Date of Death	Time at Risk in Days (*if alive)[a]
1	1/6/68	1/21/68	15
2	5/2/68	5/5/68	3
3	8/22/68	10/7/68	46
4	8/31/68	—	608*
5	9/9/68	1/14/68	127
6	10/5/68	12/5/68	61
7	10/26/68	—	552*
8	11/20/68	12/14/68	24
9	11/22/68	8/30/69	281
10	2/8/69	—	447*
11	2/15/69	2/25/69	10
12	3/29/69	5/7/69	39
13	4/13/69	—	383*
14	5/22/69	—	344*
15	7/16/69	11/29/69	136
16	8/16/69	8/17/69	1
17	9/3/69	—	240*
18	9/14/69	11/13/69	60
19	1/3/70	—	118*
20	1/16/70	—	104*

[a] Total exposure days = 3599, $L = 12$.

Then the standard error of $\widehat{\lambda}$, $\mathrm{SE}(\widehat{\lambda})$, is approximately

$$\mathrm{SE}(\widehat{\lambda}) \doteq \frac{C}{\sum_{i=1}^{n} O_i}\sqrt{L}$$

A confidence interval for λ can be constructed by using confidence limits (L_1, L_2) for $E(L)$ as described in Note 6.8:

$$\text{confidence interval for } \lambda = \left(\frac{CL_1}{\sum_{i=1}^{n} O_i}, \frac{CL_2}{\sum_{i=1}^{n} O_i}\right)$$

For the example, a 95% confidence interval for the number of deaths is (6.2–21.0). A 95% confidence interval for the hazard rate is then

$$\left(\frac{6.2}{3599} \times 365, \frac{21.0}{3599} \times 365\right) = (0.63, 2.13)$$

Note that this assumes a constant hazard rate from day of transplant; this assumption is suspect. In Chapter 16 some other approaches to analyzing such data are given.

As a second more complicated illustration, consider the work of Bruce et al. [1976]. This study analyzed the experience of the Cardiopulmonary Research Institute (CAPRI) in Seattle, Washington. The program provided medically supervised exercise programs for diseased subjects. Over 50% of the participants dropped out of the program. As the subjects who continued participation and those who dropped out had similar characteristics, it was decided to compare the mortality rates for men to see if the training prevented mortality. It was recognized that subjects might drop out because of factors relating to disease, and the inference would be weak in the event of an observed difference.

The interest of this example is in the appropriate method of calculating the rates. All subjects, *including the dropouts*, enter into the computation of the mortality for active participants! The reason for this is that had they died during training, they would have been counted as active participant deaths. Thus, training must be credited with the exposure time or observed time when the dropouts were in training. For those who did not die and dropped out, the date of last contact *as an active participant* was the date at which the subjects left the training program. (Topics related to this are dealt with in Chapter 16).

In summary, to compute the mortality rates for active participants, all subjects have an observation time. The times are:

1. O_i = (time of death − time of enrollment) for those who died as active participants
2. O_i = (time of last contact − time of enrollment) for those in the program at last contact
3. O_i = (time of dropping the program−time of enrollment) for those who dropped whether or not a subsequent death was observed

The rate $\widehat{\lambda}_A$ for active participants is then computed as

$$\widehat{\lambda}_A = \frac{\text{number of deaths observed during training}}{\sum_{\text{all individuals}} O_i} = \frac{L_A}{\sum O_i}$$

To estimate the rate for dropouts, only those who drop out have time at risk of dying as a dropout. For those who have died, the time observed is

$$O_i' = (\text{time of death} - \text{time the subject dropped out})$$

For those alive at the last contact,

$$O_i' = (\text{time of last contact} - \text{time the subject dropped out})$$

The hazard rate for the dropouts, $\widehat{\lambda}_D$, is

$$\widehat{\lambda}_D = \frac{\text{number of deaths observed during dropout period}}{\sum_{\text{dropouts}} O_i'} = \frac{L_D}{\sum O_i'}$$

The paper reports rates of 2.7 deaths per 100 person-years for the active participants based on 16 deaths. The mortality rate for dropouts was 4.7 based on 34 deaths.

Are the rates statistically different at a 5% significance level? For a Poisson variable, L, the variance equals the expected number of observations and is thus estimated by the value of the variable itself. The rates $\widehat{\lambda}$ are of the form

$$\widehat{\lambda} = CL \qquad (L \text{ the number of events})$$

Thus, $\text{var}(\widehat{\lambda}) = C^2 \text{ var}(L) \doteq C^2 L = \widehat{\lambda}^2/L$.

To compare the two rates,

$$\text{var}(\widehat{\lambda}_A - \widehat{\lambda}_D) = \text{var}(\widehat{\lambda}_A) + \text{var}(\widehat{\lambda}_D) = \frac{\widehat{\lambda}_A^2}{L_A} + \frac{\widehat{\lambda}_D^2}{L_D}$$

The approximation is good for large L.

An approximate normal test for the equality of the rates is

$$z = \frac{\widehat{\lambda}_A - \widehat{\lambda}_D}{\sqrt{\widehat{\lambda}_A^2/L_A + \widehat{\lambda}_D^2/L_D}}$$

For the example, $L_A = 16, \widehat{\lambda}_A = 2.7$, and $L_D = 34, \widehat{\lambda}_D = 4.7$, so that

$$\begin{aligned} z &= \frac{2.7 - 4.7}{\sqrt{(2.7)^2/16 + (4.7)^2/34}} \\ &= -1.90 \end{aligned}$$

Thus, the difference between the two groups was not statistically significant at the 5% level.

15.5 MULTIPLE LOGISTIC MODEL FOR ESTIMATED RISK AND ADJUSTED RATES

In Chapter 13 the linear discriminant model or multiple logistic model was used to estimate the probability of an event as a function of covariates, $X_1, \ldots, X_n$. Suppose that we want a direct adjusted rate, where $X_1(i), \ldots, X_n(i)$ was the covariate value at the midpoints of the ith cell. For the study population, let p_i be the adjusted probability of an event at $X_1(i), \ldots, X_n(i)$. An adjusted estimate of the probability of an event is

$$\widehat{p} = \frac{\sum_{i=1}^{I} M_i p_i}{\sum_{i=1}^{I} M_i}$$

where M_i is the number of reference population subjects in the ith cell. This equation can be written as

$$\widehat{p} = \sum_{i=1}^{I} \left(\frac{M_i}{M.} p_i \right)$$

where $M. = \sum_{i=1}^{I} M_i$.

If the study population is small, it is better to estimate the p_i using the approach of Chapter 13 rather than the direct standardization approach of Section 15.3. This will usually be the case when there are several covariates with many possible values.

NOTES

15.1 More Than One Event per Subject

In some studies, each person may experience more than one event: for example, seizures in epileptic patients. In this case, each person could contribute more than once to the numerator in the calculation of a rate. In addition, exposure time or observed time would continue beyond an event, as the person is still at risk for another event. You need to check in this case that there are not people with "too many" events; that is, events "cluster" in a small subset of the population. A preliminary test for clustering may then be called for. This is a complicated topic. See Kalbfleisch and Prentice [2002] for references. One possible way of circumventing the problem is to record the time to the second or kth event. This builds a certain robustness into the data, but of course, makes it not possible to investigate the clustering, which may be of primary interest.

15.2 Standardization with Varying Observation Time

It is possible to compute standardized rates when the study population has the rate in each cell determined by the method of Section 15.4; that is, people are observed for varying lengths of time. In this note we discuss only the method for direct standardization.

Suppose that in each of the i cells, the rates in the study population is computed as CL_i/O_i, where C is a constant, L_i the number of events, and O_i the sum of the times observed for subjects in that cell. The adjusted rate is

$$\frac{\sum_{i=1}^{I} (M_i/L_i)\, O_i}{\sum_{i=1}^{I} M_i} = \frac{C \sum_{i=1}^{I} M_i \widehat{\lambda}_i}{M.} \qquad \text{where} \quad \widehat{\lambda}_i = \frac{L_i}{O_i}$$

The standard error is estimated to be

$$\frac{C}{M.} \sqrt{\sum_{i=1}^{I} \left(\frac{M_i}{O_i} \right) L_i}$$

15.3 Incidence, Prevalence, and Time

The *incidence* of a disease is the rate at which new cases appear; the *prevalence* is the proportion of the population that has the disease. When a disease is in a steady state, these are related via the average duration of disease:

$$\text{prevalence} = \text{incidence} \times \text{duration}$$

That is, if you catch a cold twice per year and each cold lasts a week, you will spend two weeks per year with a cold, so $2/52$ of the population should have a cold at any given time.

This equation breaks down if the disease lasts for all or most of your life and does not describe transient epidemics.

15.4 Sources of Demographic and Natural Data

There are many government sources of data in all of the Western countries. Governments of European countries, Canada, and the United States regularly publish vital statistics data as well as results of population surveys such as the Third National Cancer Survey [National Cancer Institute, 1975]. In the United States, the National Center for Health Statistics (*http://www.cdc.gov/nhcs*) publishes more than 20 series of monographs dealing with a variety of topics. For example, Series 20 provides natural data on mortality; Series 21, on natality, marriage, and divorce. These reports are obtainable from the U.S. government.

15.5 Binomial Assumptions

There is some question whether the binomial assumptions (see Chapter 6) always hold. There may be "extrabinomial" variation. In this case, standard errors will tend to be underestimated and sample size estimates will be too low, particularly in the case of dependent Bernoulli trials. Such data are not easy to analyze; sometimes a logarithmic transformation is used to stabilize the variance.

PROBLEMS

15.1 This problem will give practice by asking you to carry out analyses similar to the ones in each of the sections. The numbers from the National Cancer Institute [1975] for lung cancer cases for white males in the Pittsburgh and Detroit SMSAs are given in Table 15.5.

Table 15.5 Lung Cancer Cases by Age for White Males in the Detroit and Pittsburgh SMSAs

	Detroit		Pittsburgh	
Age	Cases	Population Size	Cases	Population Size
<5	0	149,814	0	82,242
5–9	0	175,924	0	99,975
10–14	2	189,589	1	113,146
15–19	0	156,910	0	100,139
20–24	5	113,003	0	68,062
25–29	1	113,919	0	61,254
30–34	10	92,212	7	53,289
35–39	24	90,395	21	55,604
40–44	101	108,709	56	70,832
45–49	198	110,436	148	74,781
50–54	343	98,756	249	72,247
55–59	461	82,758	368	64,114
60–64	532	63,642	470	50,592
65–69	572	47,713	414	36,087
70–74	473	35,248	330	26,840
75–79	365	25,094	259	19,492
80–84	133	12,577	105	10,987
>85	51	6,425	52	6,353
Total	3271	1,673,124	2480	1,066,036

(a) Carry out the analyses of Section 15.2 for these SMSAs.

(b) Calculate the direct and indirect standardized rates for lung cancer for white males adjusted for age. Let the Detroit SMSA be the study population and the Pittsburgh SMSA be the reference population.

(c) Compare the rates obtained in part (b) with those obtained in part (a).

15.2 **(a)** Calculate crude rates and standardized cancer rates for the white males of Table 15.5 using black males of Table 15.3 as the reference population.

(b) Calculate the standard error of the indirect standardized mortality rate and test whether it is different from 1.

(c) Compare the standardized mortality rates for blacks and whites.

15.3 The data in Table 15.6 represent the mortality experience for farmers in England and Wales 1949–1953 as compared with national mortality statistics.

Table 15.6 Mortality Experience Data for Problem 15.3

Age	National Mortality (1949–1953) Rate per 100,000/Year	Population of Farmers (1951 Census)	Deaths in 1949–1953
20–24	129.8	8,481	87
25–34	152.5	39,729	289
35–44	280.4	65,700	733
45–54	816.2	73,376	1,998
55–64	2,312.4	58,226	4,571

(a) Calculate the crude mortality rates.

(b) Calculate the standardized mortality rates.

(c) Test the significance of the standardized mortality rates.

(d) Construct a 95% confidence interval for the standardized mortality rates.

(e) What are the units for the ratios calculated in parts (a) and (b)?

15.4 Problems for discussion and thought:

(a) Direct and indirect standardization permit comparison of rates in two populations. Describe in what way this can also be accomplished by multiway contingency tables.

(b) For calculating standard errors of rates, we assumed that events were binomially (or Poisson) distributed. State the assumption of the binomial distribution in terms of, say, the event "death from cancer" for a specified population. Which of the assumptions is likely to be valid? Which is not likely to be invalid?

(c) Continuing from part (b), we calculate standard errors of rates that are population based; hence the rates are not samples. Why calculate standard errors anyway, and do significance testing?

15.5 This problem deals with a study reported in Bunker et al. [1969]. Halothane, an anesthetic agent, was introduced in 1956. Its early safety record was good, but reports of massive hepatic damage and death began to appear. In 1963, a Subcommittee on the National Halothane Study was appointed. Two prominent statisticians, Frederick Mosteller and Lincoln Moses, were members of the committee. The committee designed a large cooperative retrospective study, ultimately involving 34 institutions

Table 15.7 Mortality Data for Problem 15.5

	Number of Operations			Number of Deaths		
Physical Status	Total	Halothane	Cyclopropane	Total	Halothane	Cyclopropane
Unknown	69,239	23,684	10,147	1,378	419	297
1	185,919	65,936	27,444	445	125	91
2	104,286	36,842	14,097	1,856	560	361
3	29,491	8,918	3,814	2,135	617	403
4	3,419	1,170	681	590	182	127
5	21,797	6,579	7,423	314	74	101
6	11,112	2,632	3,814	1,392	287	476
7	2,137	439	749	673	111	253
Total	427,400	146,200	68,169	8,783	2,375	2,109

that completed the study. "The primary objective of the study was to compare halothane with other general anesthetics as to incidence of fatal massive hepatic necrosis within six weeks of anesthesia." A four-year period, 1959–1962, was chosen for the study. One categorization of the patients was by physical status at the time of the operation. Physical status varies from good (category 1) to moribund (category 7). Another categorization was by mortality level of the surgical procedure, having values of low, middle, high. The data in Table 15.7 deal with middle-level mortality surgery and two of the five anesthetic agents studied, the total number of administrations, and the number of patients dying within six weeks of the operation.

(a) Calculate the crude death rates per 100,000 per year for total, halothane, and cyclopropane. Are the crude rates for halothane and cyclopropane significantly different?

(b) By direct standardization (relative to the total), calculate standardized death rates for halothane and cyclopropane. Are the standardized rates significantly different?

(c) Calculate the standardized mortality rates for halothane and cyclopropane and test the significance of the difference.

(d) The calculations of the standard errors of the standardized rates depend on certain assumptions. Which assumptions are likely not to be valid in this example?

15.6 In 1980, 45 SIDS (sudden infant death syndrome) deaths were observed in King County. There were 15,000 births.

(a) Calculate the SIDS rate per 100,000 births.

(b) Construct a 95% confidence interval on the SIDS rate per 100,000 using the Poisson approximation to the binomial.

(c) Using the normal approximation to the Poisson, set up the 95% limits.

(d) Use the square root transformation for a Poisson random variable to generate a third set of 95% confidence intervals. Are the intervals comparable?

(e) The SIDS rate in 1970 in King County is stated to be 250 per 100,000. Someone wants to compare this 1970 rate with the 1980 rate and carries out a test of two proportions, $p_1 = 300$ per 100,000 and $p_2 = 250$ per 100,000, using the binomial distributions with $N_1 = N_2 = 100{,}000$. The large-sample normal approximation is used. What part of the Z-statistic: $(p_1 - p_2)$/standard error$(p_1 - p_2)$ will be right? What part will be wrong? Why?

Table 15.8 Heart Disease Data for Problem 15.7

Gender	Age	Epileptics: Person-Years at Risk	New and Nonfatal IHD Cases	Incidence in General Population per 100,000/year
Male	30–39	354	2	76
	40–49	303	2	430
	50–59	209	3	1291
	60–69	143	4	2166
	70+	136	4	1857
Female	30–39	534	0	9
	40–49	363	1	77
	50–59	218	3	319
	60–69	192	4	930
	70+	210	2	1087

15.7 Annegers et al. [1976] investigated ischemic heart disease (IHD) in patients with epilepsy. The hypothesis of interest was whether patients with epilepsy, particularly those on long-term anticonvulsant medication, were at less than expected risk of ischemic heart disease. The study dealt with 516 cases of epilepsy; exposure time was measured from time of diagnosis of epilepsy to time of death or time last seen alive.

(a) For males aged 60 to 69, the number of years at risk was 161 person-years. In this time interval, four IHD deaths were observed. Calculate the hazard rate for this age group in units of 100,000 persons/year.

(b) Construct a 95% confidence interval.

(c) The expected hazard rate in the general population is 1464 per 100,000 persons/year. How many deaths would you have expected in the age group 60 to 69 on the basis of the 161 person-years experience?

(d) Do the number of observed and expected deaths differ significantly?

(e) The raw data for the incidence of ischemic heart disease are given in Table 15.8. Calculate the expected number of deaths for males and the expected number of deaths for females by summing the expected numbers in the age categories (for each gender separately). Treat the total observed as a Poisson random variable and set up 95% confidence intervals. Do these include the expected number of deaths? State your conclusion.

(f) Derive a formula for an indirect standardization of these data (see Note 15.2) and apply it to these data.

15.8 A random sample of 100 subjects from a population is divided into two age groups, and for each age group the number of cases of a certain disease is determined. A reference population of 2000 persons has the following age distribution:

	Sample		Reference Population
Age	Total Number	Number of Cases	Total Number
1	80	8	1000
2	20	8	1000

(a) What is the crude case rate per 1000 population for the sample?

(b) What is the standard error of the crude case rate?

(c) What is the age-adjusted case rate per 1000 population using direct standardization and the reference population above?

(d) How would you test the hypothesis that the case rate at age 1 is not significantly different from the case rate at age 2?

15.9 The data in Table 15.9 come from a paper by Friis et al. [1981]. The mortality among male Hispanics and non-Hispanics was as shown.

Table 15.9 Mortality Data for Problem 15.9

	Hispanic Males		Non-Hispanic Males	
Age	Number	Number of Deaths	Number	Number of Deaths
0–4	11,089	0	51,250	0
5–14	18,634	0	120,301	0
15–24	10,409	0	144,363	2
25–34	16,269	2	136,808	9
35–44	11,050	0	106,492	46
45–54	6,368	7	91,513	214
55–64	3,228	8	70,950	357
65–74	1,302	12	34,834	478
75+	1,104	27	16,223	814
Total	79,453	56	772,734	1,920

(a) Calculate the crude death rate among Hispanic males.

(b) Calculate the crude death rate among non-Hispanic males.

(c) Compare parts (a) and (b) using an appropriate test.

(d) Calculate the SMR using non-Hispanic males as the reference population.

(e) Test the significance of the SMR as compared with a ratio of 1. Interpret your results.

15.10 The data in Table 15.10, abstracted from National Center for Health Statistics [1976], deal with the mortality experience in poverty and nonpoverty areas of New York and Seattle.

(a) Using New York City as the "standard population," calculate the standardized mortality rates for Seattle taking into account race and poverty area.

(b) Estimate the variance of this quantity and calculate 99% confidence limits.

(c) Calculate the standardized death rate per 100,000 population.

Table 15.10 Mortality Data for Problem 15.10

		New York City		Seattle	
Area	Race	Population	Death Rate per 1000	Population	Death Rate per 1000
Poverty	White	974,462	9.9	29,016	22.9
	All others	1,057,125	8.5	14,972	12.5
Nonpoverty	White	5,074,379	11.6	434,854	11.7
	All other	788,897	6.4	51,989	6.5

(d) Interpret your results.

(e) Why would you caution a reviewer of your analysis about the interpretation?

15.11 In a paper by Foy et al. [1983] the risk of getting *Mycoplasma* pneumonia in a two-year interval was determined on the basis of an extended survey of schoolchildren. Of interest was whether children previously exposed to *Mycoplasma pneumoniae* had a smaller risk of recurrence. In the five- to nine-year age group, the following data were obtained:

	Exposed Previously	**Not Exposed Previously**
Person-years at risk	680	134
Number with *Mycoplasma* pneumonia	7	8

(a) Calculate 95% confidence intervals for the infection rate per 100 person-years for each of the two groups.

(b) Test the significance of the difference between the infection rates.

***(c)** A statistician is asked to calculate the study size needed for a new prospective study between the two groups. He assumes that $\alpha = 0.05$, $\beta = 0.20$, and a two-tailed, two-sample test. He derives the formula

$$\lambda_2 = \sqrt{\lambda_1} - \frac{2.8}{\sqrt{n}}$$

where λ_i is the two-year infection rate for group i and n is the number of persons per group. He used the fact that the square root transformation of a Poisson random variable stabilizes the variance (see Section 10.6). Derive the formula and calculate the infection rate in group 2, λ_2 for $\lambda_1 = 10$ or 6, and sample sizes of 20, 40, 60, 80, and 100.

15.12 In a classic paper dealing with mortality among women first employed before 1930 in the U.S. radium dial–painting industry, Polednak et al. [1978] investigated 21 malignant neoplasms among a cohort of 634 women employed between 1915 and 1929. The five highest mortality rates (observed divided by expected deaths) are listed in Table 15.11.

(a) Test which ratios are significantly different from 1.

(b) Assuming that the causes of death were selected without a particular reason, adjust the observed p-values using an appropriate multiple-comparison procedure.

(c) The painters had contact with the radium through the licking of the radium-coated paintbrush to make a fine point with which to paint the dial. On the basis of this

Table 15.11 Mortality Data for Problem 15.12

Ranked Cause of Death	Observed Number	Expected Number	Ratio
Bone cancer	22	0.27	81.79
Larynx	1	0.09	11.13
Other sites	18	2.51	7.16
Brain and CNS	3	0.97	3.09
Buccal cavity, pharynx	1	0.47	2.15

information, would you have "preselected" certain malignant neoplasms? If so, how would you "adjust" the observed p-value?

15.13 Consider the data in Table 15.12 (from Janerich et al. [1974]) listing the frequency of infants with Simian creases by gender and maternal smoking status.

Table 15.12 Influence of Smoking on Development of Simian Creases

Gender of Infant	Maternal Smoking	Birthweight Interval (lb)			
		<6	6–6.99	7–7.99	≥8
Female	No	2/45	5/156	9/242	11/216
	Yes	4/48	8/107	6/110	3/44
Male	No	5/40	5/109	23/265	18/278
	Yes	10/55	6/84	10/106	6/74

(a) These data can be analyzed by the multidimensional contingency table approach of Chapter 7. However, we can also treat it as a problem in standardization. Describe how indirect standardization can be carried out using the total sample as the reference population, to compare "risk" of Simian creases in smokers and nonsmokers adjusted for birthweight and gender of the infants.

(b) Carry out the indirect standardization procedure and compare the standardized rates for smokers and nonsmokers. State your conclusions.

(c) Carry out the logistic model analysis of Chapter 7.

***15.14** Show that the variance of the standardized mortality ratio, equation (3), is approximately equal to equation (4).

REFERENCES

Annegers, J. F., Elveback, L. R., Labarthe, D. R., and Hauser, W. A. [1976]. Ischemic heart disease in patients with epilepsy. *Epilepsia*, **17**: 11–14.

Bruce, E., Frederick, R., Bruce, R., and Fisher, L. D. [1976]. Comparison of active participants and dropouts in CAPRI cardiopulmonary rehabilitation programs. *American Journal of Cardiology*, **37**: 53–60.

Bunker, J. P., Forest, W. H., Jr., Mosteller, F., and Vandam, L. D. [1969]. *The National Halothane Study: A Study of the Possible Association between Halothane Anesthesia and Postoperative Hepatic Necrosis*. National Institute of Health/National Institute of Several Medical Sciences, Bethesda, MD.

Clark, D. A., Stinson, E. B., Griepp, R. B., Schroeder, J. S., Shumway, N. E., and Harrison, D. C. [1971]. Cardiac transplantation: VI. Prognosis of patients selected for cardiac transplantation. *Annals of Internal Medicine*, **75**: 15–21. Used with permission.

Foy, H. M., Kenny, G. E., Cooney, M. K., Allan, I. D., and van Belle, G. [1983]. Naturally acquired immunity to mycoplasma pneumonia infections. *Journal of Infectious Diseases*, **147**: 967–973. Used with permission from University of Chicago Press.

Friis, R., Nanjundappa, G., Prendergast, J. J., Jr., and Welsh, M. [1981]. Coronary heart disease mortality and risk among hispanics and non-hispanics in Orange County, CA. *Public Health Reports*, **96**: 418–422.

Janerich, D. T., Skalko, R. G., and Porter, I. H. (eds.) [1974]. *Congenital Defects: New Directions in Research*. Academic Press, New York.

Kalbfleisch, J. D., and Prentice, R. L. [2002]. *The Statistical Analysis of Failure Time Data*, 2nd ed. Wiley, New York.

National Cancer Institute [1975]. *Third National Cancer Survey: Incidence Data*. Monograph 41. DHEW Publication (NIH) 75–787. U.S. Government Printing Office, Washington, DC.

National Center for Health Statistics [1976]. *Selected Vital and Health Statistics in Poverty and Non-poverty Areas of 19 Large Cities: United States, 1969–1971*. Series 21, No. 26. U.S. Government Printing Office, Washington, DC.

Polednak, A. P., Stehney, A. F., and Rowland, R. E. [1978]. Mortality among women first employed before 1930 in the U.S. radium dial-painting industry. *American Journal of Epidemiology*, **107**: 179–195.

CHAPTER 16

Analysis of the Time to an Event: Survival Analysis

16.1 INTRODUCTION

Many biomedical analyses study the time to an event. A cancer study of combination therapy using surgery, radiation, and chemotherapy may examine the time from the onset of therapy until death. A study of coronary artery bypass surgery may analyze the time from surgery until death. In each of these two cases, the event being used is death. Other events are also analyzed. In some cancer studies, the time from successful therapy (i.e., a patient goes into remission) until remission ends is studied. In cardiovascular studies, one may analyze the time to a heart attack or death, whichever event occurs first. A health services project may consider the time from enrollment in a health plan until the first use of the facilities. An analysis of children and their need for dental care may use the time from birth until the first cavity is filled. An assessment of an ointment for contact skin allergies may consider the time from treatment until the rash has cleared up.

In each of the foregoing situations, the data consisted of the time from a fixed or designated initial point until an event occurs. In this chapter we show how to analyze such *event data*. When the event of interest is death, the subject is called *survival analysis*. In medicine and public health this name is often used generically, even when the endpoint or event being studied is not death but something else. In industrial settings the study of the lifetime of a component (until failure) is called *reliability theory*, and social scientists use the term *event history analysis*. For concreteness, we often speak of the event as death and the time as survival time. However, it should always be kept in mind that there are other uses.

In this chapter we consider the presentation of time to event data, estimation of the time to an event, and its statistical variability. We also consider potential predictor or explanatory variables. A third topic is to compare the time to event in several different groups. For example, a study of two alternative modes of cancer therapy may examine which group has the best survival experience.

When the event is not death, there may be multiple occurrences for a given person or multiple types of event. It is usually possible to restrict the analysis to the first event as we did in the situations described above. This restriction trades a considerable gain statistical simplicity for an often modest loss in power. We discuss the analysis of multiple events only briefly.

16.2 SURVIVORSHIP FUNCTION OR SURVIVAL CURVE

In previous chapters we examined means of characterizing the distribution of a variable using, for example, the cumulative distribution function and histograms. One might take survival data

Biostatistics: A Methodology for the Health Sciences, Second Edition, by Gerald van Belle, Lloyd D. Fisher, Patrick J. Heagerty, and Thomas S. Lumley
ISBN 0-471-03185-2

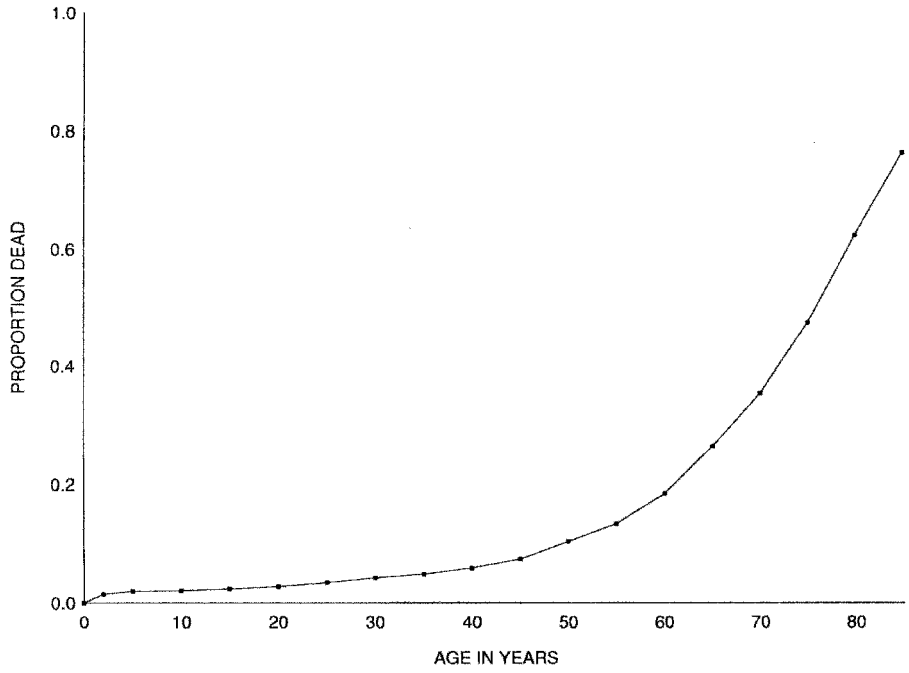


Figure 16.1 Cumulative probability of death, United States, 1974. (From U.S. Department of Health, Education, and Welfare [1976].)

and present the cumulative distribution function. Figure 16.1 shows an estimate for the U.S. population in 1974 of the probability of dying before a fixed age. This is an estimate of the cumulative distribution of survival in the United States in 1974. Note that there is an increase in deaths during the first year; after this the rate levels off but then climbs progressively in the later years. This cumulative probability of death is then an estimate of the probability that a person dies at or before the given time. That is,

$$F(t) = P[\text{person dies at a time} \leq t]$$

If we had observed the entire survival experience of the 1974 population, we would estimate this quantity as we estimated the cumulative distribution function previously. We would estimate it as

$$F(t) = \frac{\text{number of people who die at or before time } t}{\text{total number observed}} \tag{1}$$

Note, however, that we cannot estimate the survival experience of the 1974 population this way because we have not observed all of its members until death. This is a most fortunate circumstance since the population includes all of the authors of this book as well as many of its readers. In the next section, we discuss some methods of estimating survival when one does not observe the true survival of the entire population.

It is depressing to speak of death; it is more pleasant to speak of life. In analyzing survival data, the custom has grown not of using the cumulative probability of death but of using an equivalent function called the *survivorship function* or *survival curve*. This function is merely the percent of people who live to a fixed time or beyond.

Definition 16.1. The *survival curve*, or *survivorship function*, is the proportion or percent of people living to a fixed time t or beyond. The curve is then a function of t:

$$S(t) = \begin{cases} \text{percent of people surviving to time } t \text{ or beyond if} \\ \quad \text{expressed as a percent} \\ \text{proportion of people surviving to time } t \text{ or beyond} \\ \quad \text{if expressed as a proportion} \end{cases} \tag{2}$$

If we have a sample from a population, there is a distinction between the population survival curve and the sample or estimated population survival curve. In practice, there is no distinct notation unless it is necessary to emphasize the difference. The context will usually show which of the two is meant.

The cumulative distribution function of the survival and the survival curve are closely related. If the two curves are continuous, they are related by

$$S(t) = 100[1 - F(t)] \quad \text{or} \quad S(t) = 1 - F(t)$$

(When we look at the sample curves, the curves are equal at all points except for the points where the curves jump. At these points there is a slight technical problem because we have used $\leq$ in one instance and $\geq$ in the other instance. But for all practical purposes, the two curves are related by the equation above.)

Figure 16.2 shows the survival curve for the U.S. population as given in Figure 16.1. As you can see, the survival curve results by "flipping over" the cumulative probability of death and using percentages. As mentioned above, the estimate of the curve in Figure 16.2 is complicated by the fact that many people in the 1974 U.S. population are happily alive. Thus, their true

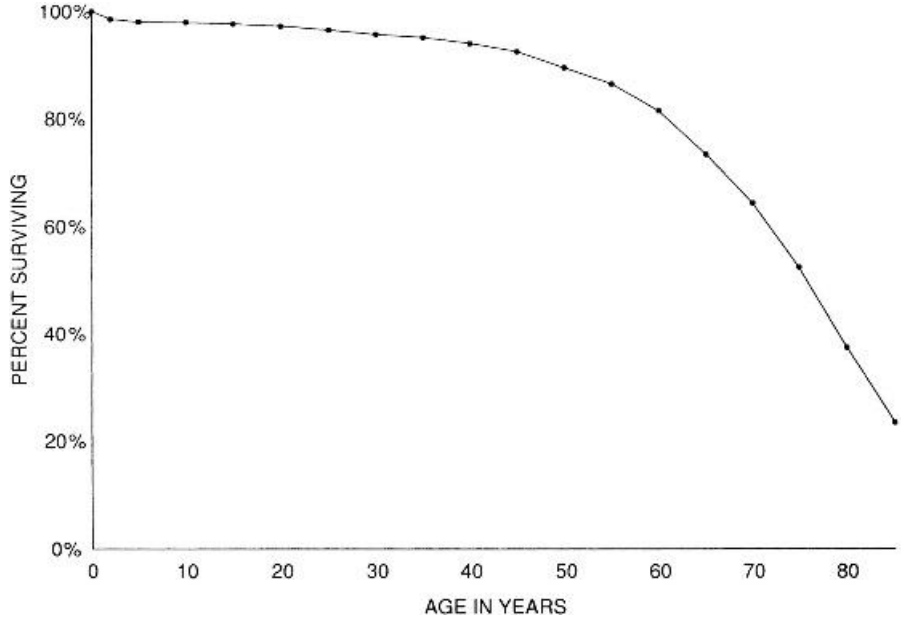


Figure 16.2 Survival curve of the U.S. population, 1974. Same data as used in Figure 16.1.

survival is not yet observed. The survival in the overall population is not yet observed. The survival in the overall population is estimated by the method discussed in the next section.

Sometimes the *proportion* surviving to time t or beyond is used. We will use them interchangeably. The two are simply related; to find the percent, merely multiply the proportion by 100.

If we observe the survival of all persons, it is easy to estimate the survival curve. In analogy with the estimate of the cumulative distribution function, the estimate of the survival curve at a fixed t is merely the percent of people whose survival was equal to the value t or greater. That is,

$$S(t) = 100\left(\frac{\text{number of people who survive to or beyond } t}{\text{total number observed}}\right) \tag{3}$$

In many instances, we are not able to observe everyone until they reach the event of interest. This makes the estimation problem more challenging. We discuss the estimates in the next section.

16.3 ESTIMATION OF THE SURVIVAL CURVE: ACTUARIAL OR LIFE TABLE METHOD

Consider a clinical study of a procedure with a high initial mortality rate: for example, very delicate high-risk surgery during its development period. Suppose that we design a study to follow a group of such people for two years. Because most of the mortality is expected during the first year, it is decided to concentrate the effort on the first year. Two thousand people are to be entered in the study; half of them will be followed for two years, while one-half will be followed only for the critical first year. The people are randomized into two groups, group 1 to be followed for one year and group 2 to be followed for both years. Suppose that the data are as follows:

	Group 1		Group 2	
Year	Number Observed	Number Who Died	Number Observed	Number Who Died
1	1000	240	1000	200
2	—	—	800	16

We wish to estimate one- and two-year survival. We consider three methods of estimation. The first two methods will not be appropriate but are used to motivate the correct life table method to follow.

One way of estimating survival might be to estimate separately the one- and two-year survival. Since it is wasteful to "throw away" data and the reason that 2000 people were observed for one year was because that year was considered crucial, it is natural to estimate the percent surviving for one year by the total population. This percentage is as follows:

$$\text{percent of one-year survival} = 100\left(\frac{2000 - 240 - 200}{2000}\right) = 78.0\%$$

To estimate two-year survival, we did not observe what happened to the subjects in group 1 during the second year. Thus, we might estimate the survival using only those in group 2. This

estimate is

$$\text{percent of two-year survival} = 100\left(\frac{1000-200-16}{1000}\right) = 78.4\%$$

There are two problems with this estimation method. The first is that we need to know the potential follow-up time (one year or two years) for everyone. In a clinical trial this is reasonable, but in a cohort study we may not know whether someone who in fact died after six months would have been followed up for one year or two years if he or she had not died. Nor is it reasonable that our estimate of the survival should depend on this unobservable potential follow-up.

More importantly, we have a problem in that the estimated percent surviving one year is less than the percent surviving two years! Clearly, as time increases, the percent surviving must decrease, but the sampling variability in the estimate has led to the second-year estimate being larger than the first-year estimate. Although this method is approximately unbiased and uses all the available data, it is not a desirable way to estimate our survival curve.

One way to get around this problem is to use only the subjects from group 2 who are observed for two years. Then we have a straightforward estimate of survival at each time period. The percent surviving one year or more is 80%, while the percent surviving two or more years is, as before, 78.4%. This gives a consistent pattern of survival but seems quite wasteful; we deliberately designed the study to allow us to observe more subjects in the first year, when the mortality was expected to be high. It does not seem appropriate to throw away the 1000 subjects who were only observed for one year. If we need to do this, we had an extremely poor experimental design.

The solution to our problem is to note that we can efficiently estimate the probability of one-year survival using both groups of people. Further, using the second group, we can estimate the probability of surviving the second year *conditionally upon having survived the first year*. The two estimates as percentages are

$$\text{percent of one-year survival} = 78.0\%$$

$$\text{percent surviving year 2} = 100\left(\frac{800-16}{800}\right) = 98.0\%$$

We can then combine these to get an estimate of the probability of surviving in the first year and the second year by using the concept of conditional probability. We see that the probability of two-year survival is the probability of one-year survival times the probability of two-year survival given one-year survival, and so cannot be larger than the probability of one-year survival. The probability of two-year survival is as follows:

$$P[A \text{ and } B] = P[A]P[B|A]$$

Let A be the survival of one year and B the survival of two years. Then

$$\begin{aligned} P[\text{one-year survival}] &= P[\text{one-year survival}] \\ &\quad \times P[\text{two-year survival}|\text{one-year survival}] \\ &= 0.78 \times 0.98 = 0.7644 \end{aligned}$$

For these probability calculations, note that it is more convenient to have probabilities than percents because the probabilities multiply. If we had percents, the formula would have an extra factor of 100. For this reason the calculations on the survival curves are usually done as probabilities and then switched to percentages for graphical presentation. We will adhere to this.

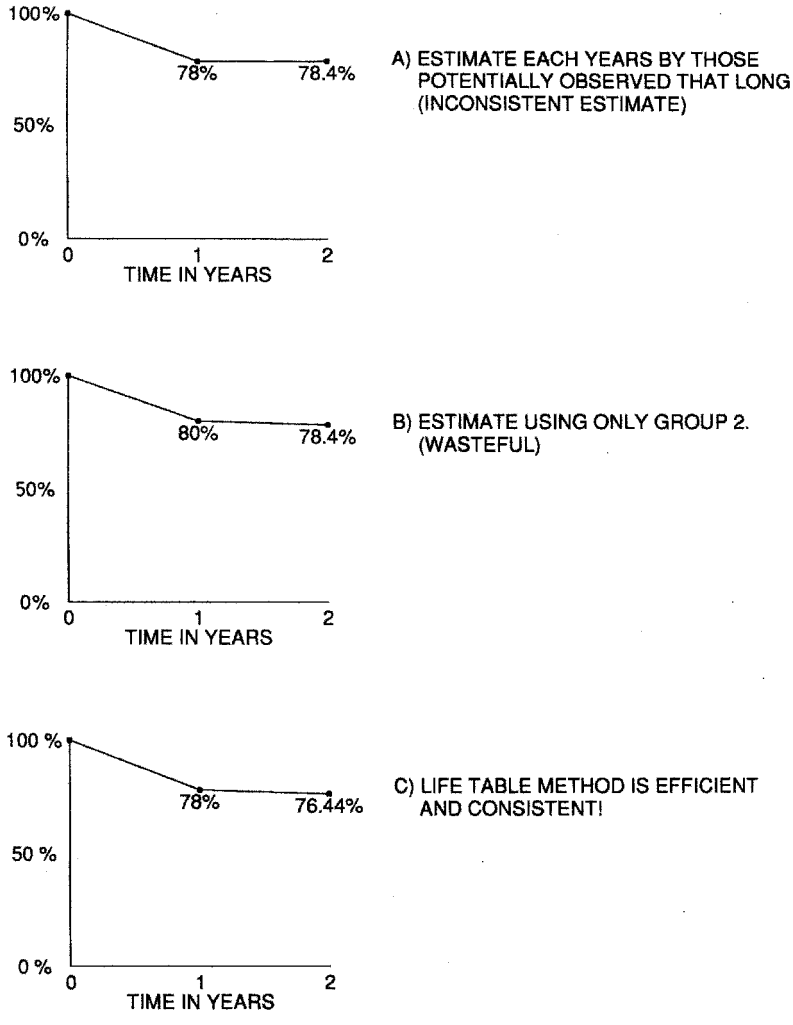


Figure 16.3 Three methods of estimating survival.

Figure 16.3 presents the three estimates; for these data they are all close. The third estimate gives a self-consistent estimate of the curve (i.e., the curve will never increase) and the estimate is efficient (because it uses all the data); it is the correct method for estimating survival. This idea can easily be generalized to more than two intervals.

When the data are grouped into time intervals, we can estimate the survival in each interval. Let x denote the lower endpoint of each interval. [x rather than t is used here to conform to standard notation in the actuarial field. When it is necessary to index the intervals, we will use $i(x)$ to denote the inverse relationship.] Let $\prod_i$ denote the probability of surviving to $x(i)$, where $x(i)$ is the lower endpoint of the ith interval; that is,

$$\prod_i = S(x(i))$$

where S is the survival curve (expressed here as the proportion surviving). Further, let π_i be the probability of living through the interval, with lower endpoint $x(i)$, conditionally upon the event

of being alive at the beginning of the interval. Using the definition of a conditional probability,

$$\pi_i = \frac{\prod_{i+1}}{\prod_i} = \frac{P[\text{survive to the end of the } i\text{th interval}]}{P[\text{survive to the end of the } (i-1)\text{st interval}]} \tag{4}$$

From this,

$$\prod_{i+1} = \pi_i \prod_i$$

and

$$\prod_{i+1} = \pi_1 \pi_2 \cdots \pi_i \qquad \text{where} \quad \prod_1 = 1 \tag{5}$$

In presenting group data graphically, one plots points corresponding to the time of the lower endpoint of the interval and the corresponding $\prod_i$ value. The plotted points are then joined by straight-line segments, as in Figure 16.4.

There is one further complication before we present the life table estimates. If we are following people periodically (e.g., every six months or every year), it will occasionally happen that people cannot be located. Such subjects are called *lost to follow-up* in the study. Further, subjects may be withdrawn from the study for a variety of reasons. In clinical studies in the United States, all subjects have the right to withdraw from participation at any time. Or we might be trying to examine a medical survival in patients who could potentially be treated with surgery. Some of them may subsequently receive surgery; we could withdraw such patients from the analysis at the time they received surgery. The rationale for this would be that after they received surgery, their survival experience is potentially altered. Whatever the reason for a person being lost to follow-up or withdrawn, this fact must be considered in the life table analysis.

To estimate the survival curve from data, the method is to estimate the π_i and $\prod_i$ by the product of the estimates of the π_i according to equation (5). The data are usually presented in the form of Table 16.1. How might one estimate the probability of dying in the interval whose

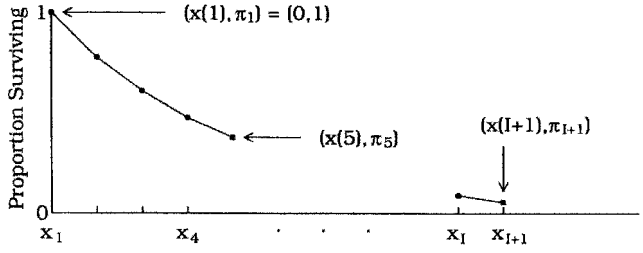


Figure 16.4 Form of the presentation of the survival curve for grouped survival data.

Table 16.1 Presentation of Life Table Data

Interval	Number of Subjects Observed Alive at Beginning of Interval	Died during Interval	Lost to Follow-up during Interval	Withdrawn Alive during Interval
x to $x + \Delta x$	l_x	d_x	u_x	w_x
$x(1) - x(2)$	$l_{x(1)}$	$d_{x(1)}$	$u_{x(1)}$	$w_{x(1)}$
$x(2) - x(3)$	$l_{x(2)}$	$d_{x(2)}$	$u_{x(2)}$	$w_{x(2)}$
$\vdots$	$\vdots$	$\vdots$	$\vdots$	$\vdots$
$x(I) - x(I+1)$	$l_{x(I)}$	$d_{x(I)}$	$u_{x(I)}$	$w_{x(I)}$

lower endpoint is x conditionally upon being alive at the beginning of the interval? At first glance one might reason that there were l_x subjects, of whom (a binomial) d_x died, so that the estimate should be d_x/l_x. The problem is that those who were lost to follow-up or withdrew during the interval might have died during the interval *after* withdrawing, and this would not be counted. If such persons were equally likely to withdraw at any time during the interval, on the average they would be observed only one-half of the time. Thus, they really represent only one-half a person at risk. Thus the effective number of persons at risk, l'_x, is

$$\begin{aligned} l'_x &= \underbrace{l_x - (u_x + w_x)}_{\substack{\text{number observed} \\ \text{over entire interval}}} + \underbrace{\tfrac{1}{2}(u_x + w_x)}_{\substack{\text{number observed} \\ \text{over } \frac{1}{2} \text{ interval}}} \\ &= l_x - \tfrac{1}{2}(u_x + w_x) \end{aligned} \tag{6}$$

where the u_x is the number lost to follow-up and w_x is the number withdrawing. The estimate of the proportion dying, q_x, is thus

$$q_x = \frac{d_x}{l'_x}$$

The estimate of π_i, the probability of surviving the interval $x(i)$ to $x(i+1)$, is

$$p_{x(i)} = 1 - q_{x(i)}$$

Finally, the estimate of $\prod_i = \pi_1 \pi_2 \cdots \pi_{i-1}$, $\prod_1 = 1$ is

$$P_{x(i)} = p_{x(1)} p_{x(2)} \cdots p_{x(i-1)}, \quad P_{x(0)} = 1 \tag{7}$$

Note that those who are lost to follow-up and those who are withdrawn alive are treated together; that is, in the estimates, only the sum of the two is used. In many presentations such people are lumped together as *withdrawn* or *censored*.

Before presenting the estimates, it is also clear that an estimate of the survival curve will be more useful if some idea of its variability is given.

An estimate of the standard error of the P_x is given by Greenwood's formula [Greenwood, 1926]:

$$\begin{aligned} \mathrm{SE}(P_{x(i)}) &= P_{x(i)} \sqrt{\sum_{j=1}^{i-1} \frac{q_{x(j)}}{l'_{x(j)} - d_{x(j)}}} \\ &= P_{x(i)} \sqrt{\sum_{j=1}^{i-1} \frac{q_{x(j)}}{l'_{x(j)} p_{x(j)}}} \end{aligned} \tag{8}$$

Confidence intervals constructed using ± 1.96 times this standard error are valid only in relatively large samples. For example, it is easy to see that these confidence intervals could extend outside the interval [0, 1], where the probability must lie. Better confidence intervals in small samples can be obtained by transforming $P(t)$; they are discussed in the Notes to this chapter.

Example 16.1. The method is illustrated by data of Parker et al. [1946], as discussed in Gehan [1969]. Those data are from 2418 males with a diagnosis of angina pectoris (chest pain thought to be of cardiac origin) at the Mayo Clinic between January 1, 1927 and December 31, 1936. The life table of survival time from diagnosis (in yearly intervals) is shown in Table 16.2.

Table 16.2 Life Table Analysis of 2418 Males with Angina Pectoris

x to $x + \Delta x$ (yr)	l_x	d_x	u_x	w_x	l'_x	q_x	p_x	P_x	SE(P_x)
0–1	2418	456	0	0	2418	0.1886	0.8114	1.0000	—
1–2	1962	226	39	0	1942.5	0.1163	0.8837	0.8114	0.0080
2–3	1697	152	22	0	1686.0	0.0902	0.9098	0.7170	0.0092
3–4	1523	171	23	0	1511.5	0.1131	0.8869	0.6524	0.0097
4–5	1329	135	24	0	1317.0	0.1025	0.8975	0.5786	0.0101
5–6	1170	125	107	0	1116.5	0.1120	0.8880	0.5139	0.0103
6–7	938	83	133	0	871.5	0.0952	0.9048	0.4611	0.0104
7–8	722	74	102	0	671.0	0.1103	0.8897	0.4172	0.0105
8–9	546	51	68	0	512.0	0.0996	0.9004	0.3712	0.0106
9–10	427	42	64	0	395.0	0.1063	0.8937	0.3342	0.0107
10–11	321	43	45	0	298.5	0.1441	0.8559	0.2987	0.0109
11–12	233	34	53	0	206.5	0.1646	0.8354	0.2557	0.0111
12–13	146	18	33	0	129.5	0.1390	0.8610	0.2136	0.0114
13–14	95	9	27	0	81.5	0.1104	0.8896	0.1839	0.0118
14–15	59	6	23	0	47.5	0.1263	0.8737	0.1636	0.0123

Source: Data from Gehan [1969].

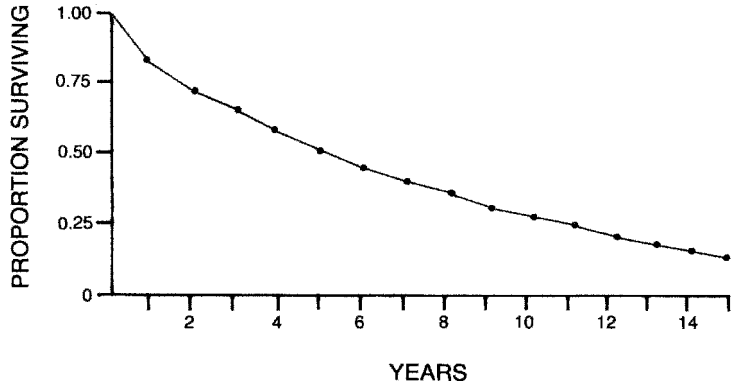


Figure 16.5 Survivorship function. (Data from Gehan [1969]; see Table 16.2.)

The survival data are given graphically in Figure 16.5. Note that in this case the proportion rather than the percent is presented.

As a second example, we consider patients with the same diagnosis, angina pectoris; these data are more recent.

Example 16.2. Passamani et al. [1982] studied patients with chest pain who were studied for possible coronary artery disease. Chest pain upon exertion is often associated with coronary artery disease. The chest pain was evaluated by a physician as definitely angina, probably angina, probably not angina, and definitely not angina. The definitions of these four classes were:

- *Definitely angina:* a substantial discomfort that is precipitated by exertion, relieved by rest and/or nitroglycerin in less than 10 minutes, and has a typical radiation to either shoulder, jaw, or the inner aspect of the arm. At times, definite angina may be isolated to the shoulder, jaw, arm, or upper abdomen.

- *Probably angina:* has most of the features of definite angina but may not be entirely typical in some aspects.
- *Probably not angina:* an atypical overall pattern of chest pain symptoms which does not fit the description of definite angina.
- *Definitely not angina:* a pattern of chest pain symptoms that are unrelated to activity, unrelieved by nitroglycerin and/or rest, and appear clearly noncardiac in origin.

The data are plotted in Figure 16.6. Note how much improved the survival of the angina patients (definite and probable) is compared with the Mayo data of Figure 16.5. Those data had a 52% five-year survival. These data have 91% and 85% five-year survival! This indicates the great difficulty of using historical control data. A statistic and p-value for testing differences among the four groups is discussed in Section 16.6.

Table 16.3 gives the calculation using 91-day intervals and four intervals to approximate a year for one of the four groups, the definite angina patients. As a sample calculation, consider the interval from 637 to 728 days. We see that

$$
\begin{aligned}
l_x &= 2704, \qquad u_x + d_x = 281 \\
l'_x &= 2704 - \frac{281}{2} = 2563.5 \\
q_x &= \frac{12}{2563.5} = 0.0047 \\
p_x &= 1 - 0.0047 = 0.9953 \\
P_x &= 0.9350 \times 0.9953 = 0.9306
\end{aligned}
$$

Note that the definite angina cases have the worst survival, followed by the probable angina cases (91%). The other two categories are almost indistinguishable.

As we have seen, in the life table method we have some data for which the event in question is not observed, often because at the time of the end of data collection and analysis, patients are still alive. One term used for such data is *censoring*, a term that brings to mind a powerful, possibly sinister figure throwing away data to mislead one in the data analysis. In this context

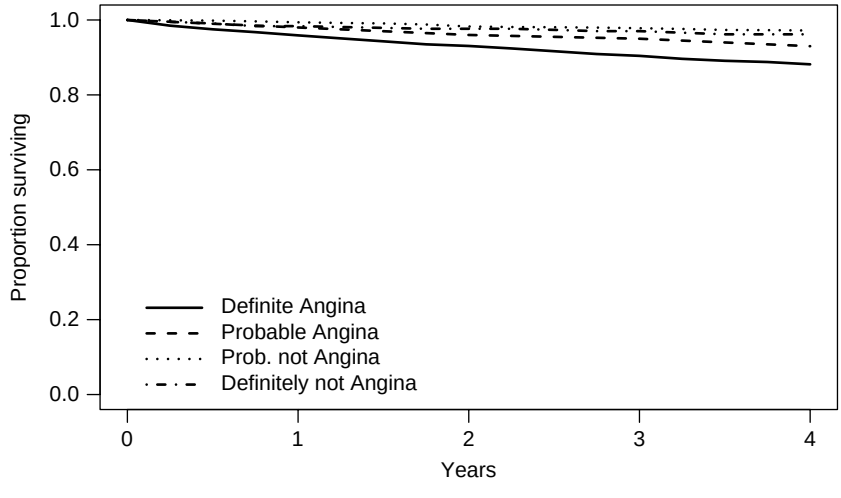


Figure 16.6 Survival by classification of chest pain. (Data from Passamani et al. [1982].)

Table 16.3 Life Table for Definite Angina Patients. Time in Days

$t(i)$	Enter	At Risk	Dead	Withdrawn Alive	Proportion Dead	Cumulative Survival of the End of Interval	SE	Effective Sample Size
0.0–90.9	2894	2894.0	44	0	0.0152	0.9848	0.002	2893.99
91.0–181.9	2850	2850.0	28	0	0.0098	0.9751	0.003	2893.99
182.0–272.9	2822	2822.0	22	0	0.0078	0.9675	0.003	2894.00
273.0–363.9	2800	2799.0	25	2	0.0089	0.9589	0.004	2893.77
364.0–454.9	2773	2773.0	23	0	0.0083	0.9509	0.004	2893.46
455.0–545.9	2750	2750.0	23	0	0.0084	0.9430	0.004	2893.23
546.0–636.9	2727	2727.0	23	0	0.0084	0.9350	0.005	2893.06
637.0–727.9	2704	2563.5	12	281	0.0047	0.9306	0.005	2882.32
728.0–818.9	2411	2394.0	17	34	0.0071	0.9240	0.005	2850.22
819.0–909.9	2360	2359.0	19	2	0.0081	0.9166	0.005	2818.52
910.0–1000.9	2339	2336.5	19	5	0.0081	0.9091	0.005	2792.12
1001.0–1091.9	2315	2035.5	11	559	0.0054	0.9042	0.006	2753.73
1092.0–1182.9	1745	1722.5	15	45	0.0087	0.8963	0.006	2654.36
1183.0–1273.9	1685	1685.0	19	0	0.0059	0.8910	0.006	2596.11
1274.0–1364.9	1675	1670.5	6	9	0.0036	0.8878	0.006	2564.52
1365.0–1455.9	1660	1274.5	9	771	0.0071	0.8816	0.007	2449.65

it refers to the fact that although one is interested in survival times, the actual survival times are not observed for all the subjects. We have seen several sources of censored data. Subjects may be alive at the time of analysis; (subjects) may be lost to follow-up; (subjects) may refuse to participate further in research; or (subjects) may undergo a different therapy which removes them from estimates of the survival in a particular therapeutic group.

The *life table* or *actuarial method* that we have used above has the strength of allowing censored data and also uses the data with maximum efficiency. There is an important underlying assumption if we are to get unbiased estimates of the survival in a population from which such subjects may be considered to come. *It is necessary that the withdrawal or censoring not be associated with the endpoint*. Obviously, if everyone is withdrawn because their situation deteriorates, one would expect a bias in the estimation of death. Let us emphasize this again. The life table estimate gives *biased* estimates if subjects who are censored at a given time have higher or lower chance of failure than those not censored at that time. The assumption we need is technically called *noninformative censoring*; the term *independent censoring* is also used.

We return later in the chapter to the related but distinct problem of competing causes of death, for example, examining the differences in death from cardiovascular causes in an elderly population where many people die of cancer or infectious disease during the study.

16.4 HAZARD FUNCTION OR FORCE OF MORTALITY

In the analysis of survival data, one is often interested in examining which periods have the highest or lowest risk of death. By risk of death, one has in mind the risk or probability among those alive at that time. For example, in very old age there is a high risk of dying each year *among* those reaching that age. The probability of any person dying, say, in the 100th year is small because so few people live to be 100 years old.

This concept is made rigorous by the idea of the hazard function or *hazard rate*. (A very precise definition of the hazard function requires ideas beyond the scope of this book and is discussed briefly in the Notes at the end of this chapter.) The hazard function is also called the *force of mortality*, *age-specific death rate, conditional failure rate*, and *instantaneous death rate*.

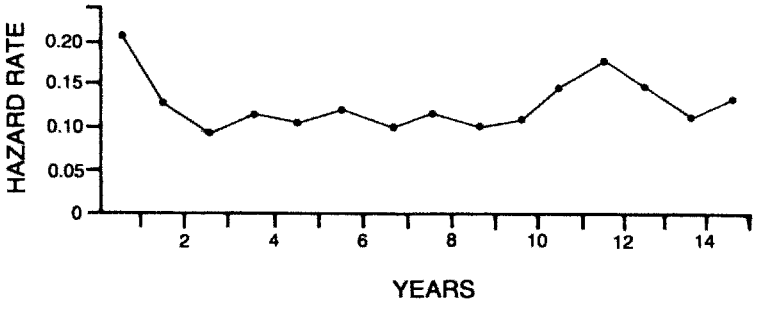


Figure 16.7 Hazard function for Example 16.1. (Data from Parker et al. [1946].)

Definition 16.2. In a life table situation, the (*interval or actuarial*) *hazard rate* is the expected number dying in the interval, divided by the product of the average number exposed in the interval and the interval width.

In other words, the hazard rate, λ, is the probability of dying per unit time given survival to the time point in question. The estimate h of the hazard function is given by

$$h_x = \frac{d_x}{l'_x - d_x/2} \frac{1}{\Delta x} \tag{9}$$

where $\Delta x(1) = x(i+1) - x(i)$, the interval width. This is an estimate of the form

$$\frac{\text{number dying}}{\text{total exposure time}}$$

l'_x is an estimate of the number at risk of death. Note that this estimate is analogous to the definition in Section 15.4. Those who die will on average have been exposed for approximately one-half of the time interval, so the number of intervals of observed time is approximately $(l'_x - d_x/2)\Delta x$. Thus, the hazard rate is a death rate; its units are proportion per unit time (e.g., percent per year). If the hazard rate has a constant value λ over time, the survival is exponential, that is, $S(t) = 100e^{-\lambda t}$, a point returned to later. The estimated hazard rate for Parker's data of Example 16.1 is given in Figure 16.7.

A large-sample approximation from Gehan [1969] for the SE of h is

$$\text{SE}(h_x) = \left\{ \frac{h_x^3}{l_x q_x} \left[1 - \left(\frac{h_x \Delta x}{2} \right)^2 \right] \right\}^{1/2} \tag{10}$$

For the data of Example 16.1, we compute the hazard function for the second interval. We find that

$$h_1 = \left(\frac{226}{1942.5 - 226/2} \right) \left(\frac{1}{1} \right) = 0.124$$

16.5 PRODUCT LIMIT OR KAPLAN–MEIER ESTIMATE OF THE SURVIVAL CURVE

If survival data are recorded in great detail, accuracy is preserved by placing the data into smaller rather than larger intervals. Obviously, if data are grouped, for example, into five-year

intervals while the time of death is recorded to the nearest day, considerable detail is lost. The *product limit* or *Kaplan–Meier estimate* is based on the idea of taking more and more intervals. In the limit, the intervals become arbitrarily small.

Suppose in the following that the time at which data are censored (lost to follow-up or withdrawn from the study) and the time of death (when observed) are measured to a high degree of accuracy. The product limit *or* Kaplan–Meier (see Kaplan and Meier [1958]) estimate (KM estimate) results from the actuarial or life table method of Section 16.4 as the number of intervals increases in such a way that the maximum interval width approaches zero. In this case it can be seen that the estimated survival curve is constant except for jumps at the observed times of death. The values of the survival probability before a time of death(s) is multiplied by the estimated probability of surviving past the time of death to find the new value of the survival curve.

To be more precise, suppose that n persons are observed. Further, suppose that the time of death is observed in l of the subjects at k distinct times $t_1 < t_2 < \cdots < t_k$. Let m_i be the number of deaths at time t_i. The other $n - l$ subjects are censored observations. If a censoring time and a death occur at the same time, it is assumed that the true time of death for the censored subject is greater than the censoring time observed. Let n_i be the number of subjects at risk of dying at time t_i. That is, $n_i = n$ minus the number of deaths prior to t_i and minus the number of subjects whose observations were censored prior to time t_i. The product limit estimate of the survival curve expressed as a proportion is

$$S(t) = \begin{cases} 1 & \text{for } t < t_1 \\ \prod_{j=1}^{i} \dfrac{n_i - m_i}{n_i}, & t_i \le t < t_{i+1} (i < k) \\ 0 & \text{for } t_k \le t \quad \text{if } m_k = n_k \text{ (i.e., no one survives past time } t_k) \\ \prod_{j=1}^{k} \dfrac{n_i - m_i}{n_i} & \text{for } t_k \le t \le \text{ largest observed censored observation} \end{cases} \tag{11}$$

If $m_k < n_k$, then $S(t)$ is undefined for $t >$ largest observed censored observation. Some software will report either $S(t) = 0$ or $S(t) = S(t_k)$ for times after the last censored observation, but this should not be encouraged.

We illustrate the method with an example.

Example 16.3. We again use the Stanford heart transplant data discussed in Section 15.4. Suppose that we wished to estimate the survival of these patients given medical treatment only. A complication is that when a donor heart becomes available, the patient has a heart transplant; we can no longer observe what the survival without a transplant would have been. One *incorrect* way to analyze such data would be the following. Since we are interested in medical survival, we should not worry about patients who have had surgery. We should go through the records and look at the survival curves only for patients who did not have surgery. Since by definition such people died awaiting the donor heart, their early survival experience would be quite poor.

At the time of the Stanford study, waiting lists were short and a donor heart was transplanted to the best-matching recipient on the waiting list [Crowley and Hu, 1977]. Thus, we may use surgery for heart transplantation as a source of censoring for medical survival: The availability of a heart should not be related to the severity of illness of the recipient. Current practice is quite different; more seriously ill patients are more likely to receive a transplant (*http://www.optn.org/*), so the censoring by surgery would be *informative* (biased) in a modern study.

Table 16.4 presents the medical survival data using surgery as the source of censoring for the Stanford heart transplant patients. The computations as described above are given. The product limit estimate of the correct survival curve is shown by solid lines in Figure 16.8. Lines with x's is the incorrect curve if one ignores the effect of surgery as censoring and totally eliminates

Table 16.4 Survival Data for Heart Transplant Patients

t (days)	Death (*)	n_i	$(n_i - m_i)/n_i$	$S(t),\ t_i \le t < t_{i+1}$
1	*	34	33/34	0.971
1		33		
2		32		
5	*	31	30/31	0.939
7	*	30	29/30	0.908
7		29		
11		28		
11		27		
12	*	26	25/26	0.873
15	*	25	24/25	0.838
15		24		
16		23		
17	*	22	21/22	0.800
17		21		
17		20		
19		19		
22		18		
24		17		
24		16		
26		15		
34	*	14	13/14	0.743
34		13		
35	*	12	11/12	0.681
36	*	11	10/11	0.619
36		10		
40	*	9	8/9	0.550
49	*	8	7/8	0.481
49		7		
50		6		
69		5		
81		4		
84	*	3	2/3	0.321
111	*	2	1/2	0.160
480		1		

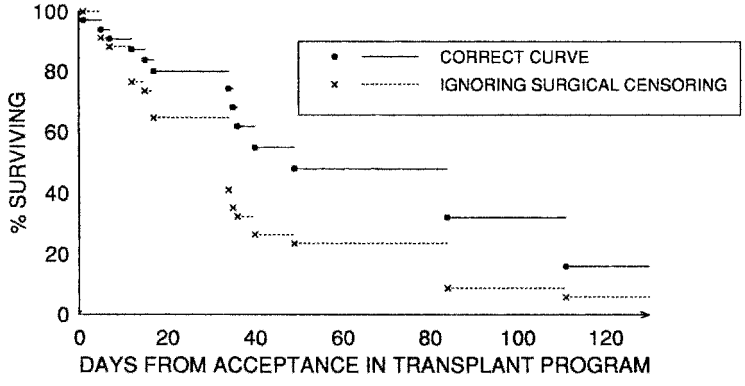


Figure 16.8 Days from acceptance in transplant program. Kaplan–Meier survival curve.

such subjects from the analysis. Finally, note that there was one patient who spontaneously improved under medical treatment and was reported alive at 16 months. The data of that subject are reported in the medical survival data as a 480-day survivor. As before, an asymptotic formula for the standard error of the estimate may be given. Greenwood's formula for the approximate standard error of the estimate also holds in this case. The form it takes is

$$\mathrm{SE}(S(t)) \doteq S(t)\sqrt{\sum_{j=1}^{i}\frac{m_j}{n_j(n_j-m_j)}} \qquad \text{for } t_i \le t < t_{i+1} \tag{12}$$

16.6 COMPARISON OF DIFFERENT SURVIVAL CURVES: LOG-RANK TEST

In this section we consider a test statistic for comparing two or more survival curves for different groups of subjects. This statistic is based on the following idea. Take a particular interval in which deaths occur, or in the case of the product limit curve, a time when one or more deaths occur. Suppose that the first group considered has one-third of the subjects being observed. How many deaths would we expect in the first group if, in fact, the survival experience is the same for all the groups? We expect the number of deaths to be proportional to the fraction of the people at risk of dying in the group. That is, for the first group the expected number of deaths would be the observed number of deaths at that time divided by 3. The log-rank test uses this simple fact. At each interval or time of death we take the observed number of deaths and calculate the expected number of deaths that would occur in each of the groups if all had the same risk of dying. For each group, the expected number of deaths is summed over all intervals and then compared to the observed number of deaths. Using this comparison, we get a statistic, the *log-rank statistic*, which has approximately a chi-square distribution with $k-1$ degrees of freedom when k groups are observed. We formalize this.

Suppose that one is interested in comparing the survival experience of k populations. Suppose that there are M different times at which deaths appear. For the life table method, this will usually be each interval. In the product limit approach, each death observed will be associated with a unique time. At the mth time, let d_{im} be the number of deaths observed in the ith population and l_{im} be the number at risk of dying. (For the life table approach with withdrawals, l_{ij} is the appropriate l'_x.) The data may be presented in M $2 \times k$ contingency tables with totals:

1	2	$\cdots$	k		
d_{1m}	d_{2m}	$\cdots$	d_{km}	D_m	dying
$l_{1m}-d_{1m}$	$l_{2m}-d_{2m}$	$\ldots$	$l_{km}-d_{km}$	A_m	alive
l_{1m}	l_{2m}	$\cdots$	l_{km}	T_m	total

$$m = 1, 2, \ldots, M$$

If all of the k populations are at equal risk of death, the probability of death will be the same in each population, and conditionally upon the row and column totals,

$$E(d_{im}) = \frac{l_{im}D_m}{T_m} \tag{13}$$

as in the chi-square test for contingency tables.

In the ith population, the total number of deaths observed is

$$O_i = \sum_{m=1}^{M} d_{im} \tag{14}$$

Examining all of the times of death, the expected number of deaths in the ith population is

$$E_i = \sum_{m=1}^{M} E(d_{im}) = \sum_{m=1}^{M} \frac{l_{im} D_m}{T_m} \tag{15}$$

The test statistic is then computed from the observed minus expected values. A simple approximate statistic suitable for hand calculation is

$$X^2 = \sum_{i=1}^{k} (O_i - E_i)^2 \Big/ E_i \tag{16}$$

The statistic is written in the familiar form of the chi-square test for comparing observed and expected values. [If any $E_i = 0$, define $(O_i - E_i)^2/E_i = 0$.] Under the null hypothesis of equal survival curves in the k groups this statistic will have approximately a chi-square distribution with $k-1$ degrees of freedom. The approximation is good when the subjects at risk are distributed over the k groups in roughly the same proportions at all times. The complete formulas for the log-rank test, which is implemented in most major statistics packages, are given in Note 16.3.

The log-rank test is illustrated by using the data of the Stanford transplant patients (Table 16.4) and comparing them with the data of Houston heart transplant patients, as reported in Messmer et al. [1969]. The time of survival for 15 Houston patients is read from Figure 16.9 and therefore has some inaccuracy.

Ordering both the Stanford and Houston transplant patients by their survival time after transplantation and status (dead or alive) gives Table 16.5. The dashes for the d_{im} values indicate where withdrawals occur, and those lines could have been omitted in the calculation. One stops when there are no future deaths at a time when members of both populations are present.

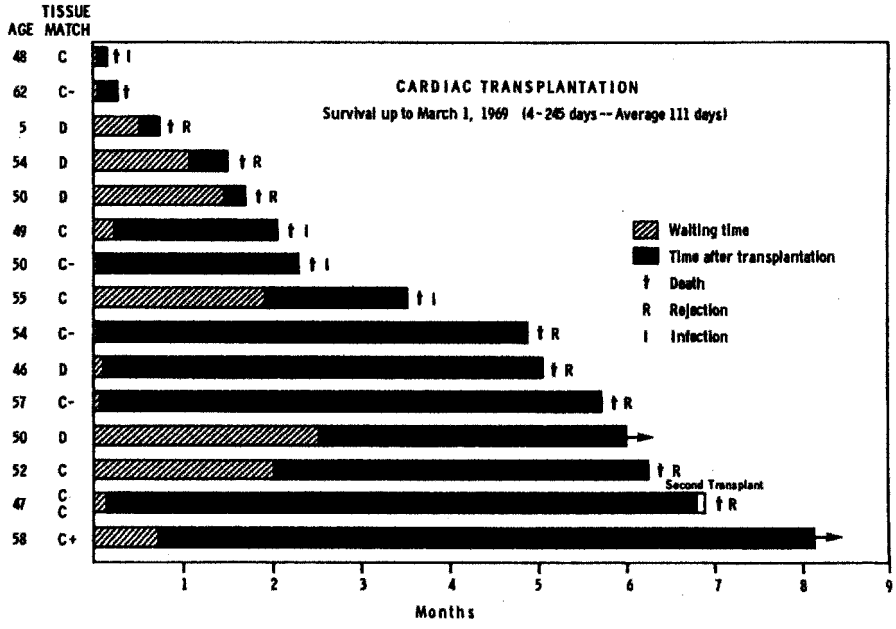


Figure 16.9 Survival of 15 patients given a cardiac allograft. Arrows indicate patients still alive on March 1, 1969. (Data from Messmer et al. [1969].)

Table 16.5 Stanford and Houston Survival Data

	Stanford		Houston			
Day	l_{1m}	d_{1m}	l_{2m}	d_{2m}	$E(d_{1m})$	$E(d_{2m})$
1	20	1	15	0	0.571	0.429
3	19	1	15	0	0.559	0.441
4	18	0	15	1	0.545	0.455
6	18	0	14	2	1.125	0.875
7	18	0	12	1	0.600	0.400
10	18	1	11	0	0.621	0.379
12	17	0	11	1	0.607	0.393
15	17	1	10	0	0.630	0.370
24	16	1	10	0	0.615	0.385
39	15	1	10	0	0.600	0.400
46	14	1	10	0	0.583	0.417
48	13	0	10	1	0.565	0.435
54	13	0	9	1	0.591	0.409
60	13	1	8	0	0.619	0.381
61	12	1	8	1	1.200	0.800
102	11	0	7	0	—	—
104	10	0	6	0	—	—
110	10	0	6	1	0.625	0.375
118	10	0	5	0	—	—
127	9	1	5	0	0.643	0.357
136	8	1	5	0	0.615	0.385
146	7	0	5	1	0.583	0.417
148	7	0	4	1	0.636	0.364
169	7	0	3	1	0.700	0.300
200	7	0	2	1	0.778	0.222

Summing the appropriate columns, one finds that

$$O_1 = \sum_m d_{1m} = 11$$

$$E_1 = \sum_m E(d_{1m}) = 14.611$$

$$O_2 = \sum_m d_{2m} = 13$$

$$E_2 = \sum_m E(d_{2m}) = 9.389$$

The log-rank statistic is 2.32. The simple, less powerful approximation is $X^2 = (11 - 14.611)^2/14.611 + (13 - 9.389)^2/9.389 = 2.28$. Looking at the critical values of the chi-square distribution with one degree of freedom, there is not a statistically significant difference in the survival experience of the two populations.

Another approach is to look at the difference between survival curves at a fixed time point. Using either the life table or Kaplan–Meier product limit estimate at a fixed time T_o, one can estimate the probability of survival to T_o, say, $S(T_o)$ and the standard error of $S(T_o)$, $\mathrm{SE}(S(T_o))$, as described in the sections above. Suppose that a subscript is used on S to denote estimates for different populations. To compare the survival experience of two populations with regard to

surviving to T_o, the following statistic is $N(0, 1)$, as the sample sizes become large [when the null hypothesis of $S_1(T_o) = S_2(T_o)$ is valid]:

$$Z = \frac{S_1(T_o) - S_2(T_o)}{\sqrt{\text{SE}(S_1(T_o))^2 + \text{SE}(S_2(T_o))^2}} \tag{17}$$

A one- or two-sided test may be performed, depending on the alternative hypothesis of interest. For k groups, to compare the probability of survival to time T_o, the estimated values may be compared by constructing multiple comparison confidence intervals.

16.7 ADJUSTMENT FOR CONFOUNDING FACTORS BY STRATIFICATION

In Example 16.2, in the Coronary Artery Surgery Study (Passamani et al., 1982), the degree of impairment due to chest pain pattern was related to survival. Patients with pain definitely not angina had a better survival pattern than patients with definite angina. The chest pain status is predictive of survival. These patients were studied by coronary angiography; the amount of disease in their coronary arteries as well as their left ventricular performance (the performance of the pumping part of the heart) were also evaluated. One might argue that the amount of disease is a more fundamental predictor than type of chest pain. If the pain results from coronary artery disease that affects the arteries and ventricle, the latter affects survival more fundamentally. We might ask the question: Is there additional prognostic information in the type of chest pain if one takes into account, or adjusts for, the angiographic findings?

We have used various methods of adjusting for variables. As discussed in Chapter 2, twin studies adjust for genetic variation by matching people with the same genetic pattern. Analogously, matched-pairs studies match people to be (effectively) twins in the pertinent variables; this adjusts for covariates. One step up from this is *stratified analysis*. In this case, the strata are to be quite homogeneous. People in the same strata are (to a good approximation) the same with respect to the variable or variables used to define the strata. One example of stratified analysis occurred with the Mantel–Haenszel procedure for summing 2×2 tables. The point of the stratification was to adjust for the variable or variables defining the strata. In this section we consider the same approach to the analysis of the life table or actuarial method of comparing survival curves from different groups.

16.7.1 Stratification of Life Table Analyses: Log-Rank Test

To extend the life table approach to stratification is straightforward. The first step is to perform the life table survival analysis *within each stratum*. If we do this for the four chest pain classes as discussed in Example 16.2 to adjust for angiographic data, we would use strata that depend on the angiographic findings. This is done below. Within each of the strata, we will be comparing persons with the same angiographic findings but different chest pain status. The log-rank statistic may be computed *separately* for each of the strata, giving us an observed and expected number of deaths for each group being studied. Somehow we want to combine the information across all the strata. This was done, for example, in the Mantel–Haenszel approach to 2×2 tables. We do this by summing the values for each group of the observed and expected numbers of deaths for the different strata. These observed and expected numbers are then combined into a final log-rank statistic. Note 16.3 gives the details of the computation of the statistic. Because it is based on many more subjects, the final statistic will be much more powerful then the log-rank statistic for any one stratum, *provided* that there is a consistent trend in the same direction within strata. We illustrate this by example.

Example 16.2. (*continued*) We continue with our study of chest pain groups. We would like to adjust for angiographic variables. A study of the angiographic variables showed that most of the prognostic information is contained within these variables:

1. The number of vessels diseased of the three major coronary vessels
2. The number of proximal vessels diseased (i.e., the number of diseased vessels where the disease is near the point where the blood pumps into the heart)
3. The left ventricular function, measured by a variable called LVSCORE

Various combinations of these three variables were used to define 30 different strata. Table 16.6 gives the values of the variables and the strata. Separate survival curves result in the differing strata. Figures 16.10 and 16.11 present the survival curves for two of the different strata used.

Note that the overall p-value is 0.69, a result that is not statistically significant. Thus although the survival patterns differ among chest pain categories, the differences may be explained by different amounts of underlying coronary artery disease. In other words, adjustment for the arteriographic and ventriculographic findings removed the group differences.

Note that of 30 strata, one p-value, that of stratum 25, is less than 0.05. Because of the multiple comparison problem, this is not a worry. Further, in this stratum, the definite angina cases have one observed and 0.03 expected deaths. As the log-rank statistic has an *asymptotic* chi-square distribution, the small expected number of deaths make the asymptotic distribution inappropriate in this stratum.

16.8 COX PROPORTIONAL HAZARD REGRESSION MODEL

In earlier work on the life table method, we observed various ways of dealing with factors that were related to survival. One method is to plot data for different groups, where the groups were defined by different values on the factor(s) being analyzed. When we wanted to adjust for covariates, we examined stratified life table analyses. These approaches are limited, however, by the numbers involved. If we want to divide the data into strata on 10 variables simultaneously, there will be so many strata that most strata will contain no one or at most one person. This makes comparisons impossible. One way of getting around the number problem is to have an appropriate mathematical model with covariates. In this section we consider the *Cox proportional hazards regression model*. This model is a mathematical model of survival that allows covariate values to be taken into account. Use of the model in survival analysis is quite similar to the multiple regression analysis of Chapter 11. We first turn to examination of the model itself.

16.8.1 Cox Proportional Hazard Model

Suppose that we want to examine the survival pattern of two people, one of whom initially is at higher risk than the other. A natural way to quantify the idea of risk is the hazard function discussed previously. We may think of the hazard function as the instantaneous probability of dying given that a person has survived to a particular time. The person with the higher risk will have a higher value for the hazard function than a person who has lower risk at the particular time. The Cox proportional hazard model works with covariates; the model expresses the hazard as a function of the covariate values. The major assumption of the model is that if the first person has a risk of death at the initial time point that is, say, twice as high as that of a second person, the risk of death at later times is also twice as large. We now express this mathematically.

Suppose that at the average value of all of our covariates in the population, the hazard at time t, is denoted by $h_0(t)$. Any other person whose values on the variables being considered are not equal to the mean values will have a hazard function proportional to $h_0(t)$. This proportionality constant varies from person to person depending on the values of the variables. We develop this

Table 16.6 Stratified Analysis of Survival by Chest Pain Classification

Stratification Variables				Deaths								
				Definite Angina		Probable Angina		Probably Not Angina		Definitely Not Angina		Log-Rank Statistic
Stratum Number	Number of Vessels	Number of Prox. Vessels	Left Ventricular Score	Obs.	Exp.	Obs.	Exp.	Obs.	Exp.	Obs.	Exp.	*p*-Value
1	0	0	5–11	9	10.07	42	38.33	39	43.35	9	7.25	0.74
2	0	0	12–16	0	0.79	2	1.25	1	0.87	0	0.09	0.73
3	0	0	17–30	0	0.00	0	0.00	0	0.00	0	0.00	1.00
4	1	0	5–11	19	18.88	26	23.84	5	6.71	0	0.56	0.85
5	1	0	12–16	3	3.46	5	3.25	0	1.06	0	0.23	0.52
6	1	0	17–30	1	0.31	0	0.62	0	0.08	—	—	0.43
7	1	1	5–11	14	13.36	13	13.19	2	2.00	0	0.45	0.96
8	1	1	12–16	1	2.53	3	2.05	0	0.27	1	0.15	0.15
9	1	1	17–30	4	3.49	2	2.22	0	0.30	—	—	0.93
10	2	0	5–11	17	18.54	16	14.62	2	2.29	1	0.55	0.93
11	2	0	12–16	7	6.81	2	3.90	3	1.11	0	0.18	0.20
12	2	0	17–30	5	3.49	3	3.99	1	0.98	0	0.53	0.72
13	2	1	5–11	18	15.50	10	14.91	1	1.07	2	0.24	0.11
14	2	1	12–16	9	9.06	6	4.99	0	0.80	0	0.14	0.77
15	2	1	17–30	3	3.40	3	2.38	0	0.22	—	—	0.93
16	2	2	5–11	18	17.36	13	13.56	1	0.92	0	0.16	0.99
17	2	2	12–16	19	6.70	4	5.98	0	0.32	—	—	0.59
18	2	2	17–30	3	4.67	4	2.33	—	—	—	—	0.62
19	3	0	5–11	11	11.75	9	7.44	0	0.72	0	0.10	0.76
20	3	0	12–16	8	7.49	7	6.69	—	—	0	0.83	0.83
21	3	0	17–30	4	4.31	1	0.69	—	—	—	—	0.98
22	3	1	5–11	28	23.67	15	17.78	0	1.54	—	—	0.37
23	3	1	12–16	17	16.66	6	6.34	—	—	—	—	1.00
24	3	1	17–30	9	7.32	5	6.15	0	0.53	—	—	0.72
25	3	2	5–11	36	32.08	11	17.55	2	0.34	1	0.03	0.01
26	3	2	12–16	20	16.48	6	8.45	0	1.07	—	—	0.42
27	3	2	17–30	8	9.34	7	5.17	—	—	0	0.49	0.72
28	3	3	5–11	17	22.42	19	14.36	1	0.22	—	—	0.11
29	3	3	12–16	16	14.62	6	8.24	1	0.14	—	—	0.09
30	3	3	17–30	11	12.93	4	2.07	—	—	—	—	0.56
Total				325	317.49	250	251.63	59	66.91	14	11.97	0.69[a]

[a] A dash indicates no individuals in the group in the given stratum. Obs., observed; Exp., expected; log-rank statistic = 1.47 with 3 degrees of freedom.

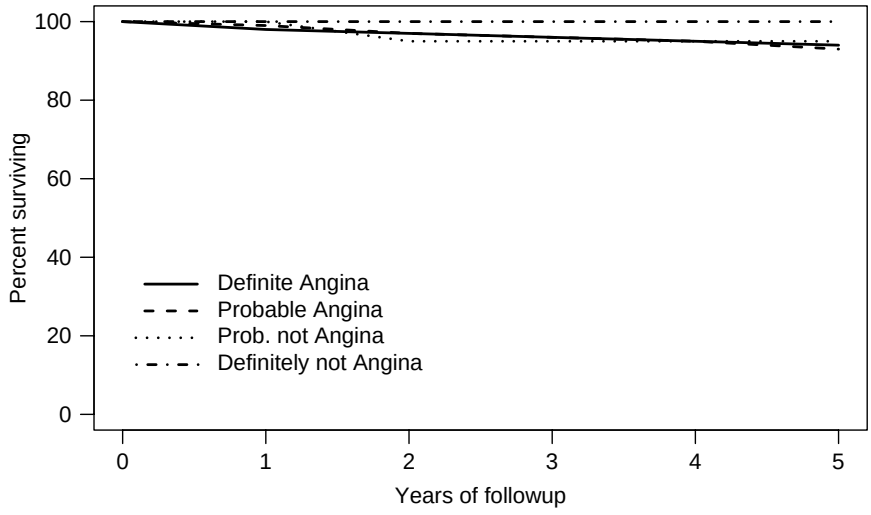


Figure 16.10 Example 16.4: survival curves for stratum 7. Cases have one proximal vessels diseased with good ventricular function (LVSCORE of 5–11).

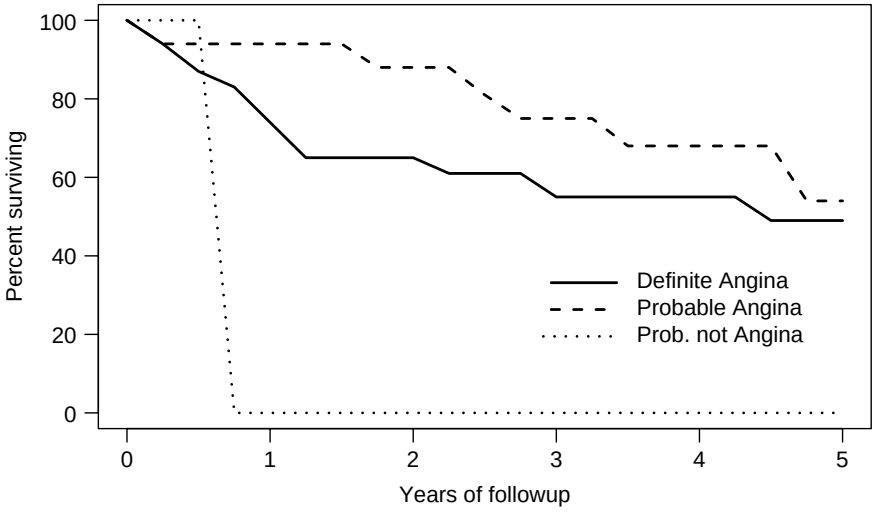


Figure 16.11 Example 16.4: survival curves for stratum 29. Cases have three proximal vessels diseased with impaired ventricular function (LVSCORE of 12–17).

algebraically. There are variables $X_1, \ldots, X_p$ to be considered. Let $\mathbf{X}$ denote the values of all the X_i, that is, $\mathbf{X} = (X_1, \ldots, X_p)$.

1. If a person has $\mathbf{X} = \overline{\mathbf{X}} = (\overline{X}_1, \ldots, \overline{X}_p)$, the hazard function is $h_0(t)$.
2. If a person has different values for $\mathbf{X}$, the hazard function is $h_0(t)C$, where C is a constant that depends on the values of $\mathbf{X}$. If we think of the hazard as depending on $\mathbf{X}$, as well as t, the hazard is

$$h_0(t)C(\mathbf{X})$$

3. For any two people with values of $\mathbf{X} = \mathbf{X}(1)$ and $\mathbf{X} = \mathbf{X}(2)$, respectively, the ratio of their two hazard functions is

$$\frac{h_0(t)C(\mathbf{X}(1))}{h_0(t)C(\mathbf{X}(2))} = \frac{C(\mathbf{X}(1))}{C(\mathbf{X}(2))} \tag{18}$$

The hazard functions are *proportional*; the ratio does not depend on t.

Let us reiterate this last point. Given two people, if one has one-half as much risk initially as a second person, then at all time points, risk is one-half that of the second person. Thus, the two hazard functions are proportional, and such models are called *proportional hazard models*.

Note that proportionality of the hazard function is an assumption that does not necessarily hold. For example, if two people were such that one is to be treated medically and the second surgically by open heart surgery, the person being treated surgically may be at higher risk initially because of the possibility of operative mortality; later, however, the risk may be the same or even less than that of the equivalent person being treated medically. In this case, if one of the covariate values indicates whether a person is treated medically or surgically, the proportional hazards model will not hold. In a given situation you need to examine the plausibility of the assumption. The model has been shown empirically to hold reasonably well for many populations over moderately long periods, say five to 10 years. Still, proportional hazards is an assumption.

As currently used, one particular parametric form has been chosen for the proportionality constant $C(\mathbf{X})$. Since it multiplies a hazard function, this constant must always be positive because the resulting hazard function is an instantaneous probability of an endpoint and consequently must be nonnegative. A convenient functional form that reasonably fits many data sets is

$$C(\mathbf{X}) = e^{\alpha+\beta_1 X_1+\cdots+\beta_p X_p}, \qquad \text{where} \quad \alpha = -\beta_1 \overline{X}_1 - \cdots - \beta_p \overline{X}_p \tag{19}$$

In this parameterization, the unknown population parameters β_i are to be estimated from a data set at hand.

With hazard $h_0(t)$, let $S_{0,\text{pop}}(t)$ be the corresponding survival curve. For a person with covariate values $\mathbf{X} = (X_1, \ldots, X_p)$, let the survival be $S(t|\mathbf{X})$. Using the previous equations, the survival curve is

$$S(t|\mathbf{X}) = (S_{0,\text{pop}}(t))^{\exp(\alpha+\beta_1 X_1+\cdots+\beta_p X_p)} \tag{20}$$

That is, the survival curve for any person is obtained by raising a standard survival curve $[S_{0,\text{pop}}(t)]$ to an appropriate power. To estimate this quantity, the following steps are performed:

1. Estimate $S_{0,\text{pop}}$ and $\alpha, \beta_1, \ldots, \beta_p$ by $S_0(t), a, b_1, \ldots, b_p$. This is done by a computer program. The estimation is too complex to do by hand.
2. Compute $Y = a + b_1 X_1 + \cdots + b_p X_p$ [where $\mathbf{X} = (X_1, \ldots, X_p)$].
3. Compute $k = e^Y$.
4. Finally, compute $S_0(t)^k$.

The estimated survival curve is the population curve (the curve for the mean covariate values) raised to a power. If the power k is equal to 1, corresponding to e^0, the underlying curve for S_0 results. If k is greater than 1, the curve lies below S_0, and if k is less than 1, the curve lies above S_0. This is presented graphically in Figure 16.12.

Note several factors about these curves:

1. The curves do not cross each other. This means that a procedure having a high initial mortality, such as a high dose of radiation in cancer therapy, but better long-term survival,

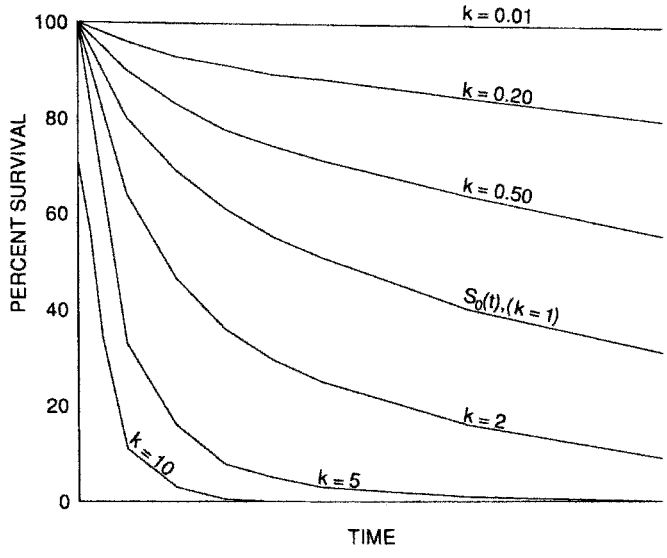


Figure 16.12 Proportional hazard survival curves as a function of $k = e^{a+b_1x_1+\cdots+b_px_p}$.

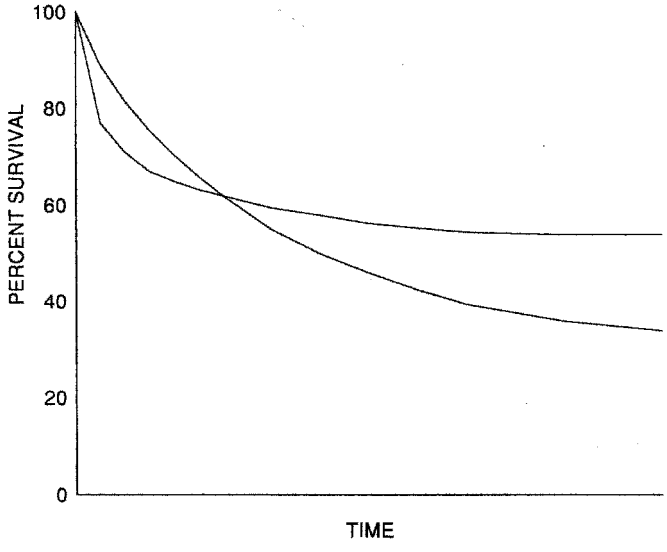


Figure 16.13 Two survival curves without proportional hazards.

as in Figure 16.13, could not be modeled by the proportional hazard model with one of the variables, say X_1, equal to 1 if the therapy were radiation and 0 if an alternative therapy were used.

2. The proportionality constant in the proportional hazard model,

$$e^{\alpha+\beta_1x_1+\cdots+\beta_px_p}$$

is parametric. We have not specified the form of the underlying survival S_0. This curve is not estimated by a parametric model but by other means.

3. Where there is a plateau in one curve, the other curve has a plateau at the same time points. The proportional hazards assumption implies that covariates do not affect the timing of plateaus or other distinctive features of the curves, only their height.

16.8.2 Example of the Cox Proportional Hazard Regression Model

The *Cox proportional hazard model* is also called the *Cox proportional regression model* or the *Cox regression model*. The reason for calling this model a regression model is that the dependent variable of interest, survival, is modeled upon or "regressed upon" the values of the covariates or independent variables. The analogies between multiple regression and the Cox regression are quite good, although there is not a one-to-one correspondence between the techniques. Computer software for Cox regression typically produces at least the quantities shown in Table 16.7.

The following example illustrates the use of the Cox proportional hazards model.

Example 16.4. The left main coronary artery is a short segment of the arteries delivering blood to the heart. Two of the three major arterial systems branch off the left main coronary artery. If this artery should close, death is almost certain. Two randomized clinical trials (Veterans' Administration Study Group, Takaro et al. [1976] and the European Coronary Surgery Study Group [1980]) reported superior survival in patients undergoing coronary artery bypass surgery. Chaitman et al. [1981] examined the observational data of the Coronary Artery Surgery Study (CASS), registry. Patients were analyzed as being in the medical group until censored at the time of surgery. They were then entered into the surgical survival experience at the day of surgery.

A Cox model using a therapy indicator variable was used to examine the effect of therapy. Eight variables were used in this model:

- *CHFSCR:* a score for congestive heart failure (CHF). The score ranged from 0 to 4; 0 indicated no CHF symptoms. A score of 4 was indicative of severe, treated CHF.
- *LMCA:* the percent of diameter narrowing of the left main coronary artery due to atherosclerotic heart disease. By selection, all cases had at least 50% narrowing of the left main coronary artery (LMCA).
- *LVSCR:* a measure of ventricular function, the pumping action of the heart. The score ranged from 5 (normal) to a potential maximum of 30 (not attained). The higher the score, the worse the ventricular function.
- *DOM:* the dominance of the heart shows whether the right coronary artery carries the usual amount of blood; there is great biological variability. Patients are classed as right or balanced dominance (DOM = 0). A left-dominant subject has a higher proportion of blood flow through the LMCA, making left main disease even more important (DOM = 1).
- *AGE:* the patient's age in years.
- *HYPTEN:* Is there a history of hypertension? HYPTEN = 1 for yes and HYPTEN = 0 for no.
- *THRPY:* This is 1 for medical therapy and 2 for surgical therapy.
- *RCA:* This variable is 1 if the right coronary artery has $\geq$ 70% stenosis and is zero otherwise.

The Cox model produces the results shown in Table 16.8. The chi-square value for CHFSCR is found by the square of β divided by the standard error. For example, $(0.2985/0.0667)^2 = 20.03$, which is the chi-square value to within the numerical accuracy. The underlying survival curve (at the mean covariate values) has probabilities 0.944 and 0.910 of one- and two-year survival, respectively. The first case in the file has values CHFSCR = 3, LMCA = 90, LVSCR = 18, DOM = 0, AGE = 49, HYPTEN = 1, THRPY = 1, and RCA = 1. What is the estimated

Table 16.7 Computer Output for Cox Regression

Output	Description	Use of Output
b_i	Estimate of the regression coefficient β_i	**1.** The b_i give an estimate of the increase in risk (the hazard function) for different values of $X_1, \ldots, X_p$. **2.** The regression coefficients allow estimation of $e^{\alpha+\beta_1 X_1+\cdots+\beta_p X_p}$ by $e^{a+b_1 x_1+\cdots+b_p x_p}$. By using this and the estimate of $S_0(t)$, we can estimate survival for any person in terms of the values of $X_1, \ldots, X_p$ for each time t.
$\mathrm{SE}(b_i)$	Estimated standard error of b_i	**1.** The distribution of b_i is approximately $N(\beta_i, \mathrm{SE}(b_i)^2)$ for large sample sizes. We can obtain $100(1-\alpha)\%$ confidence intervals for β_i as $(b_i - z_{1-\alpha/2}\mathrm{SE}(b_i), b_i + z_{1-\alpha/2}\mathrm{SE}(b_i))$. **2.** We test for statistical significance of β_i (in a model with the other X_j's) by rejecting $\beta_i = 0$ if $b_i^2/[\mathrm{SE}(b_i)]^2 \geq \chi^2_{1,1-\alpha}$. $\chi^2_{1,1-\alpha}$ is the $1-\alpha$ percentile of the χ^2 distribution with one degree of freedom. This χ^2 test or the equivalent z test is also given by most software.
Model chi-square	Chi-square value for the entire model with p degrees of freedom	**1.** For nested models the chi-square values may be subtracted (as are the degrees of freedom) to give a chi-square test. **2.** For a single model this chi-square statistic tests for *any* relationships among the $X_1, \ldots, X_p$ and the survival experience. The null hypothesis tested is $\beta_1 = \cdots = \beta_p = 0$, which is only occasionally an interesting null hypothesis. This is analogous to testing for zero multiple correlation between survival and $(X_1, \ldots, X_p)$ in a multiple regression setting.
$S_0(t)$ and α, or $S_0(t)^\alpha$	Estimate of the survival function for a person with covariate values equal to the mean of each variable, or for a person with zero values of the covariate	**1.** With $S_0(t)$ and a, or $S_0(t)^\alpha$ and the b_i, we may plot the estimated survival experience of the population for any fixed value of the covariates. **2.** For a fixed time, say t_0, by varying the values of the covariates $\mathbf{X}$, we may present the effect of combinations of the covariate values (see Example 16.5).

probability of one- and two-year survival for this person?

$$\begin{aligned} a + b_1 X_1 + \cdots + b_n X_n &= -2.8968 + (0.2985 \times 3) + (0.0178 \times 90) \\ &\quad + (0.1126 \times 18) + (1.2331 \times 0) + (0.0423 \times 49) \\ &\quad + (-0.5428 \times 1) + (-1.0777 \times 1) \\ &\quad + (0.5285 \times 1) \\ &= 2.6622 \end{aligned}$$

Table 16.8 Results of Cox Model Fitting

Variable	Beta	Standard Error	Chi-Square	Probability
CHFSCR	0.2985	0.0667	20.01	0.0000
LMCA	0.0178	0.0049	13.53	0.0002
LVSCR	0.1126	0.0182	38.41	0.0000
DOM	1.2331	0.3564	11.97	0.0006
AGE	0.0423	0.0098	18.75	0.0000
HYPTEN	−0.5428	0.1547	12.31	0.0005
THRPY	−1.0777	0.1668	41.77	0.0000
RCA	0.5285	0.2923	3.27	0.0706
Constant	−2.8968			

$$\begin{aligned}\text{estimated probability of one-year survival} &= 0.944^{e^{2.6622}}\\ &= 0.944^{14.328}\\ &= 0.438\\ \text{estimated probability of two-year survival} &= 0.910^{14.328}\\ &= 0.259\end{aligned}$$

The estimated probability of survival under medical therapy is 44% for one year and 26% for two years. This bad prognosis is due largely to heart failure (CHFSCR) and very poor ventricular function (LVSCR).

16.8.3 Interpretation of the Regression Coefficients β_i

In the multiple regression setting, the regression coefficients may be interpreted as the average difference in the response variables between cases where the predictor variable differs by one unit, with everything else the same. In this section we look at the interpretation of the β_i for the Cox proportional hazard model. Recall that the hazard function is proportional to the probability of failure in a short time interval. Suppose that we have two patients whose covariate values are the same on all the p regression variables for the Cox model with the exception of the ith variable. If we take the ratio of the hazard functions for the two people at some time t, we have the ratio of the probability of an event in a short interval after time t. The ratio of these two probabilities is the relative risk of an event during this time period. This is also called the *instantaneous relative risk*. For the Cox proportional hazards model, we find that

$$\begin{aligned}\text{instantaneous relative risk (RR)} &= \frac{h_0(t)e^{\alpha+\beta_1 X_1+\cdots+\beta_i X_i^{(1)}+\cdots+\beta_p X_p}}{h_0(t)e^{\alpha+\beta_1 X_1+\cdots+\beta_i X_i^{(2)}+\cdots+\beta_p X_p}}\\ &= e^{\beta_i(X_i^{(1)}-X_i^{(2)})}\end{aligned} \tag{21}$$

An equivalent formulation is to take the logarithm of the instantaneous relative risk (RR). The logarithm is given by

$$\ln(\text{RR}) = \beta_i(X_i^{(1)} - X_i^{(2)}) \tag{22}$$

In words, the regression coefficients β of the Cox proportional hazard model are equal to the logarithm of the relative risk if the variable X is increased by one unit.

16.8.4 Evaluating the Proportional Hazards Assumption

One graphical assessment of the proportional hazards assumption for binary (or categorical) variables plots the cumulative hazard in each group on a logarithmic scale. Under the proportional hazards assumption, the resulting curves should be parallel, that is, separated by a constant vertical difference (the reason is given in Section 16.8.3). Although popular, these *log-log plots* are not particularly useful. Judging whether two curves (as opposed to straight lines) are parallel is difficult, and the problem is compounded by the fact that the uncertainty in the estimated log hazard varies substantially along the curves.

An better approach to judging proportional hazards involves smoothed plots of the *scaled Schoenfeld residuals*, proposed by Therneau and Grambsch [2000]. These plots, available in Stata and S, estimate how a coefficient β_i varies over time. In addition to an easier visual interpretation, the Schoenfeld residual methods provide a formal test of the proportional hazards assumption and are valid for continuous as well as categorical variables.

The technical details of the Schoenfeld residual methods are complex, but there is a simple underlying heuristic. Suppose that the hazard ratio for, say, hypertension is greater than unity. Hypertensive persons will be overrepresented among the deaths in any given period. If, in addition, the hazard ratio increases with time, overrepresentation of hypertensives among the deaths will increase with time. By calculating the proportion of hypertensives among the deaths and the population at risk in each short interval of time, we should be able to detect the increasing hazard ratio.

If there is substantial nonproportionality of hazards, it may be desirable to stratify the model (see Section 16.10.2) on the variable in question, or to define a time-dependent variable as in Example 16.7 in Section 16.10.2.

Example 16.5. Primary biliary cirrhosis is a rare, autoimmune disease of the liver. Until the advent of liver transplantation, it was untreatable and eventually fatal. The Mayo Clinic performed a randomized trial of one proposed treatment, D–penicillamine, in 312 patients. The treatment was not effective, but the data from the trial have been used to develop a widely used prognostic model for survival of this disease. The data for this model have been made available on the Web by Terry Therneau of the Mayo Clinic and are linked in the Web appendix.

The Mayo model includes five covariates:

- *BILI:* logarithm of serum bilirubin concentration. Bilirubin is excreted in the bile and accumulates in liver disease.
- *PROTIME:* logarithm of the prothrombin time, a measure of blood clotting. Prothrombin time is increased when the liver fails to produce certain clotting factors.
- *ALBUMIN:* logarithm of serum albumin concentration. The liver produces albumin to prevent blood plasma from leaking out of capillaries.
- *EDTRT:* edema (fluid retention), coded as 0 for no edema, $\frac{1}{2}$ for untreated edema or edema resolved by treatment, 1 for edema present despite treatment.
- *AGE:* in tens of years. Age affects the risk for almost any cause of death.

Figure 16.14 shows scatter plots for two of these covariates against survival time. The censored observations are indicated by open triangles, the deaths by filled circles. There is clearly a relationship with both variables. It is also interesting to note that according to Fleming and Harrington [1991, Chap. 5], the outlying value of 18 for prothrombin time was a data-entry error; it should be 11.

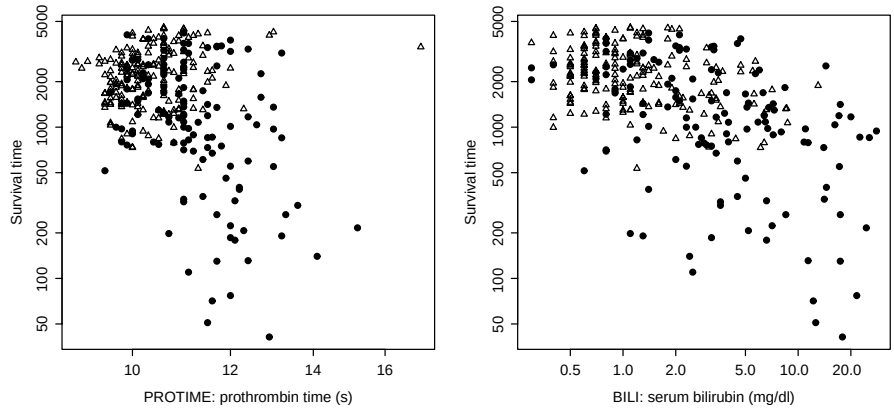


Figure 16.14 Scatter plots of survival time vs. PROTIME and BILI in the Mayo PBC data. Triangles indicate censored times.

The Mayo model has the following coefficients:

Variable	b	SE(b)
BILI	0.88	0.10
EDTRT	0.79	0.30
ALBUMIN	−3.06	0.72
PROTIME	3.01	1.02
AGE	0.33	0.08

The survival function for someone with no edema, albumin of 3.5 mg/dL, prothrombin time of 10 seconds, bilirubin of 1.75 mg/dL, and age 50 is:

t (yr)	$S(t)$ (%)	t (yr)	$S(t)$ (%)
1	98	6	80
2	97	7	74
3	92	8	68
4	88	9	61
5	84	10	51

Figure 16.15 shows a scaled Schoenfeld residual plot for PROTIME. The smooth curve that estimates $\beta(t)$ shows that the logarithm of the hazard ratio for elevated prothrombin time is very high initially and then decreases to near zero over the first three to four years. That is, a patient with high prothrombin time is at greatly increased risk of death, but a patient who had a high prothrombin time four years ago and is still alive is not at particularly high risk. The p-value for nonproportionality for PROTIME is 0.055, so there is moderately strong evidence that the pattern we see in Figure 16.15 is real.

16.8.5 Use of the Cox Model as a Method of Adjustment

In Section 16.7 we considered stratified life table analyses to adjust for confounding factors or covariates. The Cox model may be used for the same purpose. As in the multiple linear regression model, there are two ways in which we may adjust. One is to consider a variable whose effect we want to study in relationship to survival. Suppose that we want adjust for

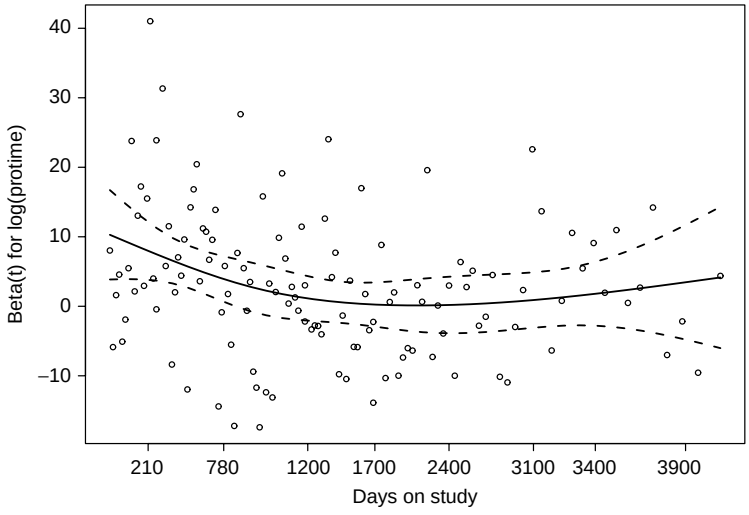


Figure 16.15 Assessing proportional hazards for PROTIME with scaled Schoenfeld residuals.

variables $X_1, \ldots, X_k$. We run the Cox proportional hazards regression model with the variable of interest and the adjustment covariates in the model. The statistical significance of the variable of interest may be tested by taking its estimated regression coefficient, dividing by its standard error and using a normal probability critical value. An equivalent approach, similar to nested hypotheses in the multiple linear regression model, is to run the Cox proportional hazards model with only the adjusting covariates. This will result in a chi-square statistic for the entire model. A second Cox proportional hazards model may be run with the variable of interest in the model in addition to the adjustment covariates. This will result in a second chi-square statistic for the model. The chi-square statistic for the second model minus the chi-square statistic for the first model will have approximately a chi-square distribution with one degree of freedom if the variable of interest has no effect on the survival after adjustment for the covariates $X_1, \ldots, X_p$.

Example 16.5. (*continued*) Of the 418 patients in the Mayo Clinic PBC data set, 312 agreed to participate in the randomized trial and 106 refused. As the data from the randomized trial were used to develop a predictive model for survival, it is important to know whether the randomized and nonrandomized patients differ in important ways.

A simple comparison of survival times in these two groups does not answer quite the right question. Suppose that patients agreeing to be randomized had longer survival times but also had lower levels of bilirubin that were sufficient to explain their improved survival. This discrepancy in survival times does not invalidate the model. Conversely, if the two groups had very similar survival times despite a difference in average bilirubin levels, this would be evidence against the model.

We can estimate the adjusted difference between the randomized and nonrandomized patients by fitting a Cox model that has the five Mayo model predictors and an additional variable indicating which group the patient is in. The estimated hazard ratio for nonrandomized patients is 0.97, with a 95% confidence interval from 0.66 to 1.41. We would not typically report coefficients and confidence intervals for the other adjusting covariates; their associations with survival are not of direct interest in this analysis.

There is no evidence of any difference in survival between randomized and nonrandomized patients in this study, but the confidence intervals are quite wide, so these differences have not been ruled out.

Other examples of estimating adjusted contrasts using the Cox model appear in Section 16.10.

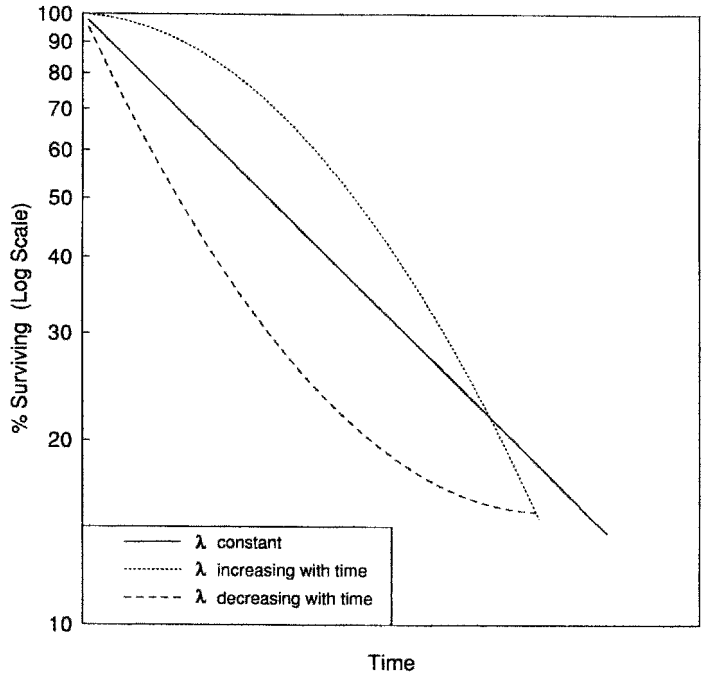


Figure 16.16 Log plot for exponential survival.

16.9 PARAMETRIC MODELS

16.9.1 Exponential Model; Rates

Suppose that at each instant of time, the instantaneous probability of death is the same. That is, suppose that the hazard rate or force of mortality is constant. Although in human populations this is not a useful assumption over a wide time interval, it may be a valid assumption over a five- or 10-year interval, say.

If the constant hazard rate is λ, the survival curve is $S(t) = e^{-\lambda t}$. From this expression the term *exponential survival* arises. The expected length of survival is $1/\lambda$. If the exponential situation holds, the parameter λ is estimated by the number of events divided by total exposure time. The methods and interpretation of rates are then appropriate. If $S(t)$ is exponential, $\log S(t) = -\lambda t$ is a straight line with slope $-\lambda$. Plotting an estimate of $S(t)$ on a logarithmic scale is one way of visually examining the appropriateness of assuming an exponential model. Figure 16.16 shows some of the patterns that one might observe.

To illustrate this we return to the Mayo primary biliary cirrhosis data set but now consider an analysis of time until loss to follow-up, that is, a survival analysis where the event is loss to follow-up. To avoid confusing patients lost to follow-up with those alive and under observation at the end of the study, we look at just the first eight years of the study. From the plot one sees that the data do *not* look exponential (Figure 16.17). Rather, it appears that the hazard of dropping out is initially very low and increases progressively.

16.9.2 Two Other Parametric Models for Survival Analysis

There are a variety of parametric models for survival distributions. In this section, two are mentioned. For details of the distributions and parameter estimates, the reader is referred to

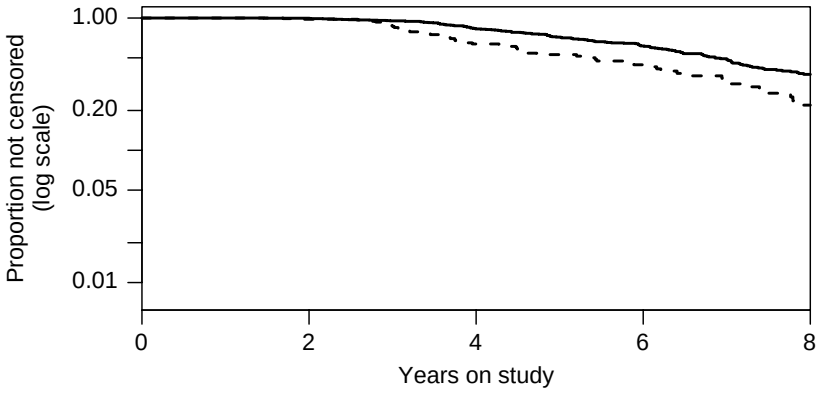


Figure 16.17 Loss to follow-up of 312 randomized and 106 nonrandomized patients with primary biliary cirrhosis.

texts by Mann et al. [1974] and Gross and Clark [1975]. These books also present a variety of models not touched on here.

The two-parameter *Weibull distribution* has a survival curve of the form

$$S(t) = e^{-\alpha t^{\beta}} \qquad \text{for } t > 0\,(\alpha > 0, \beta > 0) \tag{23}$$

If $\beta = 1$, the Weibull distribution is the exponential model with constant hazard rate. The hazard rate decreases with time if $\beta < 1$ and increases with time if $\beta > 1$. Often, if the time of survival is measured from diagnosis of a disease, a Weibull with $\beta > 1$ will reasonably model the situation. Estimates are made by computer.

Another distribution, the *lognormal distribution*, assumes that the logarithm of the survival time is normally distributed. If there is no censoring of data, one may work with the logarithm of the survival times and use methods appropriate for the normal distribution.

Regression versions of the exponential, lognormal, Weibull, and other parametric survival models are also available in many statistical packages. The exponential and Weibull models are special cases of the Cox proportional hazards model and have little advantage over the Cox model. The lognormal model is not related to the Cox model.

16.10 EXTENSIONS

16.10.1 Cox Model with Time-Dependent Covariates

If two groups are defined by some baseline measurement, such as smokers and nonsmokers, their hazard ratio would be expected to change over time simply because some of the smokers will stop smoking and lower their risk of death. For this reason it may be desirable to base the hazard ratio at time t on the most recent available values of covariates rather than on the values at the start of follow-up. The Cox model is then most naturally written in terms of the hazard rather than the survival:

$$\text{hazard at time } t = h_0(t) \exp\left[\alpha + \beta_1 X_1(t) + \beta_2 X_2(t) + \cdots + \beta_p X_p(t)\right]$$

and we write $X_1(t)$ for the value of X_1 at time t.

The hazard ratio between two subjects with covariates $\mathbf{X}^{(1)}$ and $\mathbf{X}^{(2)}$ is then

$$\begin{aligned}\frac{h(t;\mathbf{X}^{(1)})}{h(t;\mathbf{X}^{(2)})} &= \frac{h_0(t)\exp[\alpha+\beta_1 X_1(t)^{(1)}+\beta_2 X_2(t)^{(1)}+\cdots+\beta_p X_p(t)^{(1)}]}{h_0(t)\exp[\alpha+\beta_1 X_1(t)^{(2)}+\beta_2 X_2(t)^{(2)}+\cdots+\beta_p X_p(t)^{(2)}]} \\ &= \frac{\exp[\beta_1 X_1(t)^{(1)}+\beta_2 X_2(t)^{(1)}+\cdots+\beta_p X_p(t)^{(1)}]}{\exp[\beta_1 X_1(t)^{(1)}+\beta_2 X_2(t)^{(1)}+\cdots+\beta_p X_p(t)^{(1)}]} \\ &= \exp\left\{\beta_1\left[X_1(t)^{(1)}-(X_1(t)^{(2)}\right]+\beta_2\left[X_2(t)^{(1)}-(X_2(t)^{(2)}\right]\right. \\ &\quad \left.+\cdots+\beta_p\left[X_p(t)^{(1)}-(X_p(t)^{(2)}\right]\right\}\end{aligned}$$

In the constant-covariate situation, the proportional hazards assumption means that the hazard ratio does not change over time; in the time-dependent situation, it means that the hazard ratio changes only due to changes in the covariates over time.

Example 16.6. An example of time-dependent covariates comes from a study by Holt and colleagues [2002] that examined the effects of court protective orders on abuse of women by their domestic partners. In this study the time-dependent covariates were the presence (1) or absence (0) of temporary restraining orders and permanent restraining orders. At the start of the study, after the first police report of abuse, both variables would be zero. Most of the women in the study (2366) never obtained a protection order, so the variable remained at zero. Of those who obtained a two-week temporary order (325), about half (185) later obtained a permanent order. The time-dependent Cox model compares the risk of abuse in women who do and do not have each type of protective order *at the same time after their initial incident*. Cox models thus reduce the potential for confounding by time since the initial incident: Since permanent protective orders tend to happen later in time, when risks are already lower, they might appear protective even if they actually had no effect.

Temporary restraining orders were associated with an increase in the hazard of psychological abuse (hazard ratio 4.9, 95% confidence interval 2.6 to 8.6) and no change in the hazard of physical abuse (hazard ratio 1.6, 95% CI 0.6 to 4.4). Permanent restraining orders appeared to reduce physical abuse (hazard ratio 0.2, 95% CI 0.1 to 0.8) and have no effect on psychological abuse (hazard ratio 0.9, 95% CI 0.5 to 1.7).

In some settings it may be more appropriate to use values of covariates for some short or long period in the past rather than the instantaneously updated values. These time-dependent variables reflect the history of exposure rather than just the current status.

Example 16.7. Heckbert et al. [2001] studied how the risk of a recurrent heart attack changed over time in women who had already had one heart attack and were taking hormone replacement therapy (HRT). Estrogen, the active ingredient of HRT, is known to improve cholesterol levels but also to increase blood clotting, and so might have positive or negative effects on heart disease. A recent randomized trial, HERS [Hulley et al., 1998], suggested that the balance of risk and benefit might change over time.

The researchers hypothesized that having recently started hormone replacement therapy would increase the risk of heart attack, but that long-term therapy might not increase the risk. They defined three time-dependent exposure variables:

- *STARTING:* 1 for women taking HRT who started less than 60 days ago, 0 otherwise
- *RECENT:* 1 for women taking HRT who started between 60 and 365 days previously, 0 otherwise
- *LONGTERM:* 1 for women taking HRT who started more than a year ago, 0 otherwise

The hypothesis was that the coefficients for STARTING would be positive (increased risk), but that coefficients for RECENT and LONGTERM would be lower, and possibly negative. They found that the hazard ratio e^b for STARTING was 2.16, with a 95% confidence interval, 0.94 to 4.95, not quite excluding 1. The hazard ratio for LONGTERM was 0.76, a with 95% confidence interval 0.42 to 1.36.

Time-dependent covariates are not always appropriate. In particular, they do not result in useful predictive models: In order to estimate the chance of surviving for the next five years, it is necessary to have covariate values for the next five years to plug into the model.

Even when time-dependent models are appropriate, they involve significantly more complex computation, however, good facilities for time-dependent Cox models are now available in many major statistics packages. Computational details vary between packages, and between versions of the same package, but the basic approach is to break each person's data into many short time intervals on which their covariates are constant. These time intervals are treated as if they came from separate people, which is valid as long as each person can have only one event.

Time-dependent covariates are discussed in many of the recent textbooks on survival analysis, including Therneau and Grambsch [2000], Klein and Moeschberger [1997], and Kleinbaum [1996] and in older references such as Kalbfleisch and Prentice [1980] and Breslow and Day [1987].

16.10.2 Stratification in the Cox Model

The Cox model, which assumes that hazards are proportional over time, can be extended to a stratified model in which hazards need only be proportional within the same stratum and can differ arbitrarily between strata. Stratification can be useful when a small number of important variables do not satisfy the proportional hazards assumption. In addition to the usual difficulties that occur with stratifying on too many variables, the stratified model also suffers from the fact that it is not possible to test the effects of the stratifying variables.

For example, Lumley et al. [2002] constructed a predictive model for the risk of stroke in elderly people. The rates of stroke were not proportional between men and women, so a model stratified by gender was used. Instead of a single underlying survival curve $S_o(t)$, the model has curves $S_m(t)$ for men and $S_w(t)$ for women. The hazard ratio for other covariates, such as diabetes or smoking, is assumed to be constant over time within each stratum. The hazard ratio may be constrained to be the same for women and men or allowed to differ. As Table 16.9 shows, the stroke prediction model used a common hazard ratio for diabetes in men and women, but the hazard ratio for history of heart disease was allowed to differ between men and women. A Java applet showing this model is linked from the Web appendix.

Table 16.9 Stratified Cox Model for Risk of Stroke

	Mean		Coefficient	
	2495 Men	3393 Women	Men	Women
Left ventricular hypertrophy by ECG (%)	5.1	4.9	0.501	
Diabetes (%)	14.9	12.5	0.521	
Elevated fasting glucose (%)	19.0	14.4	0.347	
Creatinine >1.25 mg/dL (%)	39.6	8.1	0.141	
Time to walk 15 ft (s)	5.5	6.0	0.099	
Systolic blood pressure (mmHg)	143	144	172/10	
History of heart disease (%)	26.5	16.1	0.445	0.073
Atrial fibrillation by ECG (%)	3.5	2.1	0.4097	1.346
Age (yr)	73	73	0.382/10	0.613/10

16.10.3 Left Truncation

In the examples discussed so far, the survival time has been measured from the beginning of the study, so that all subjects are under observation from time 0 under they die or are censored. There are situations where this is not feasible. Consider a study of occupational exposure to a potential carcinogen, where workers at a factory are interviewed about their past exposure and other risk factors such as cancer, and then followed up.

It would be desirable to set time zero to be when each worker was first employed at the factory rather than the date when the study was performed. This would more accurately approximate the ideal study that recruited everyone as they entered employment and followed them for the rest of their lives. There is a serious complication, however. Workers who died before the study started will not be included, making the sample biased. This phenomenon is called *left truncation*. Truncation is not quite the same as censoring, although both involve incomplete information. With censoring, we have information on only part of a person's life. With truncation, we have no information on some people and complete information on others.

The solution to left truncation is similar to the solution to right censoring. If we break time up into short intervals, each person contributes information about the probability of surviving through an interval given that one is alive at the start of the interval. These probabilities can be multiplied to give an overall survival probability. Most statistical software will allow you to specify an *entry* time as well as a survival or censoring time, and will fit Cox regression models to data specified in this way.

In the occupational exposure example, consider a worker who started at the factory in 1955, who entered the study in 1985, and who died in 1995. We want to take time to be 0 in 1955, so the *entry* time is $1985 - 1955$, or 30 years, and the survival time is $1995 - 1955$, or 40 years. Another worker might have started at the factory in 1975, been recruited in 1985, and still be alive at the end of the study in 2000. This would give an *entry* time of $1985 - 1975$, or 10 years, and a censoring time of $2000 - 1975$, or 25 years.

Breslow and Day [1987] discuss an example of this sort in some detail, comparing the effects of placing time zero at different events in analyzing the cancer risks of workers at a nickel refinery.

16.10.4 Other References Dealing with Survival Analysis and Heart Transplant Data

The first heart transplant data has been used extensively as an illustration in the development of survival techniques. Further references are Mantel and Byar [1974], Turnbull et al. [1974], and Crowley and Hu [1977].

NOTES

16.1 Recurrent Events

Some events can occur more than once for the same person. Although it is usually possible to study just the time until the first event, it may be useful to incorporate subsequent events to increase the information available. The hazard formulation of survival analysis extends naturally to recurrent events. The hazard (now often called the *intensity*) is still defined in terms of the probability of having an event in a small interval of time, conditional on being alive and under observation. The difference is that now a person can still be alive and under observation after an event occurs. Although computation for recurrent event models is fairly straightforward, there are a number of important methodologic issues that need to be considered. In particular, there is no really satisfactory way to handle recurrent events and deaths in the same analysis. Volume 16, No. 18 of *Statistics in Medicine* (April 30, 1997) has a number of papers discussing these issues. The Web appendix to this chapter includes some examples of analyses of recurrent infections in children with chronic granulomatous disease, a genetic immune deficiency.

16.2 More on the Hazard Rate and Proportional Hazards

Many of the concepts presented in this chapter are analogs of continuous quantities that are best defined in terms of calculus. If the survival function is $S(t)$, its probability density function is

$$f(t) = -\frac{dS(t)}{dt}$$

The hazard rate is then

$$h(t) = \frac{f(t)}{S(t)}$$

From this it follows that the survival is found from the hazard rate by the equation

$$S(t) = e^{-\int_0^t h(x)\,dx}$$

The quantity

$$H(t) = \int_0^t h(x)\ dx = -\log S(t)$$

is called the *cumulative hazard*. Under the proportional hazards assumption, the cumulative hazards H_1 and H_2 for two groups of cases are related by

$$H_1(t) = \lambda \times H_2(t)$$

so

$$\log H_1(t) = \log \lambda + \log H_2(t)$$

16.3 Log-Rank Statistic and Log-Rank Statistic for Stratified Data

We present the statistic using some matrix ideas. The notation is that of Section 16.6 on the log-rank test. For the ith group at the mth time of a death (or deaths), there were d_{im} deaths and l_{im} persons at risk. Suppose that we have k groups and M times of death. For $i, j = 1, \ldots, k$, let

$$V_{ij} = \begin{cases} \sum_{m=1}^{M} \dfrac{l_{im}(T_m - l_{im})D_m(T_m - D_m)}{T_m^2(T_m - 1)}, & i = j \\ \sum_{m=1}^{M} \dfrac{-l_{im}l_{jm}D_m(T_m - D_m)}{T_m^2(T_m - 1)}, & i \neq j \end{cases}$$

Define the $(k-1) \times (k-1)$ matrix V by

$$V = \begin{pmatrix} V_{11} & V_{12} & \cdots & V_{1,k-1} \\ V_{21} & & & \vdots \\ \vdots & & & \vdots \\ V_{k-1,1} & \cdots & \cdots & V_{k-1,k-1} \end{pmatrix}$$

Define vectors of observed and expected number of deaths in groups $1, 2, \ldots, k-1$ by

$$\mathbf{O} = \begin{pmatrix} O_1 \\ \vdots \\ O_{k-1} \end{pmatrix}, \qquad \mathbf{E} = \begin{pmatrix} E_1 \\ \vdots \\ E_{k-1} \end{pmatrix}$$

The log-rank statistic is

$$(\mathbf{O} - \mathbf{E})' V^{-1} (\mathbf{O} - \mathbf{E})$$

where $'$ denotes a transpose and -1 a matrix inverse. If there are $s = 1, \ldots, S$ strata, for each stratum we have **O, E,** and V. Let these values be indexed by s to denote the strata. The log-rank statistic is

$$\left[\sum_{s=1}^{S} (\mathbf{O}_s - \mathbf{E}_s)\right]' \left(\sum_{s=1}^{S} V_s\right)^{-1} \left[\sum_{s=1}^{S} (\mathbf{O}_s - \mathbf{E}_s)\right]$$

16.4 Estimating the Probability Density Function in Life Table Methods

The density function in the interval from $x(i)$ to $x(i+1)$ for the life table is estimated by

$$f_i = \frac{P_i - P_{i+1}}{x(i+1) - x(i)}$$

The standard error of f_i is estimated by

$$\frac{p_i q_i}{\sqrt{x(i+1) - x(i)}} \left(\sum_{j=1}^{i-1} \frac{q_j}{l'_j p_j} + \frac{p_i}{l'_i q_i}\right)^{1/2}$$

16.5 Other Confidence Intervals for the Survival Function

Direct use of Greenwood's formula to construct confidence intervals in small samples can lead to confidence intervals that cross 0% or 100% survival. Even when this does not occur, the confidence intervals do not perform very well. Better confidence intervals are obtained by multiplying, rather than adding, the same quantity above and below the estimated survival function. That is, the confidence interval is given by

$$\left[\hat{S}(t) \times \exp\left(-z_{\alpha/2} \frac{\text{SE}(\hat{S}(t))}{\hat{S}(t)}\right), \hat{S}(t) \times \exp\left(z_{\alpha/2} \frac{\text{SE}(\hat{S}(t))}{\hat{S}(t)}\right)\right]$$

Bie et al. [1987] studied this interval and a more complicated one based on transforming $S(t)$ to $\arcsin\{\exp[-S(t)/2]\}$ and found that both performed well even with only 25 observations, half of which were censored.

16.6 Group Expected Survival

The baseline survival curve $S_0(t)$ estimates the survival probability at time t for a person whose covariates equal the average of the population. This is not the same as the survival curve expected for the population $S(t)$ as estimated by the Kaplan–Meier method. The population curve $S(t)$

decreases faster than $S_0(t)$ initially, as those with worse-than-average covariates die and then flattens out relative to $S_0(t)$, as the remaining sample has better-than-average covariates. The difference between $S(t)$ and $S_0(t)$ is more pronounced when covariate effects are strong and when there is little censoring.

The relationship between the curves is that the population curve is the average of all the predicted individual survival curves:

$$S(t) = \sum_i S_0(t)^{e^{\alpha+\beta_1 X_1+\beta_2 X_2+\cdots+\beta_p X_p}}$$

This relationship can be used to predict the population curve for a new population and compare it to the expected population, an extension of the direct standardization of rates in Chapter 15. For example, the predictions of a Cox model can be validated in a new population by dividing the new population into groups and comparing the expected $S(t)$ for each group with the observed survival curve calculated by the Kaplan–Meier method.

Example 16.5. (*continued*) Figure 16.18 compares the expected and observed survival rates for the 106 nonrandomized patients from the Mayo Clinic PBC data. These patients were divided into three equal groups based on the risk predicted by the Mayo model. The Kaplan–Meier survival curve and the group expected survival curve were calculated for each of the three groups. The relatively smooth lines are the expected survival; the stepped lines are the Kaplan–Meier estimates. There is no suggestion that the expected and observed curves differ importantly.

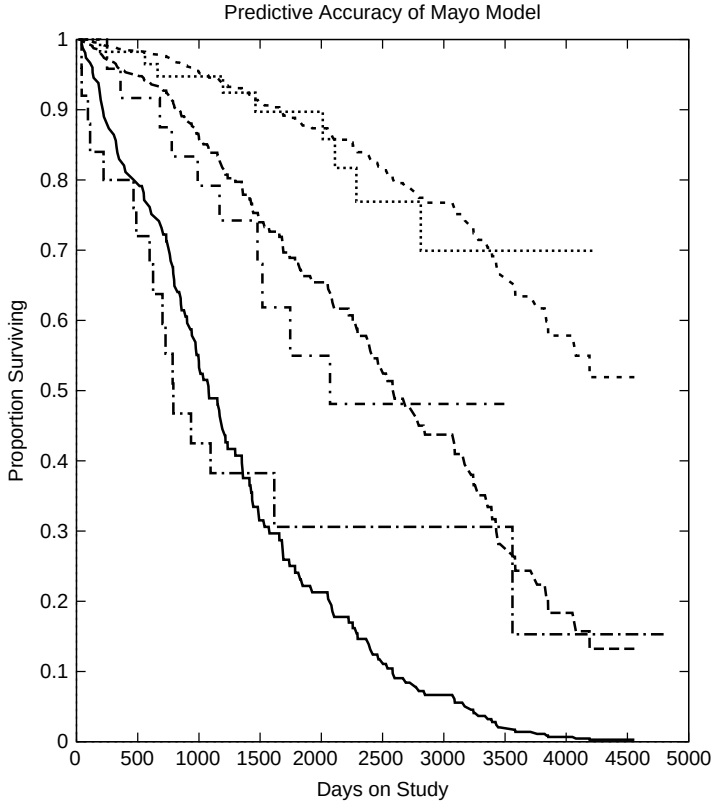


Figure 16.18 Expected and observed survival curves for three groups of nonrandomized patients.

For a stratified life table analysis, the same calculation of expected survival can be done more easily. In this context it is called the method of *direct adjustment*. Suppose that we want to compare survival in treatment groups $j = 1, 2$ and we have strata $i = 1, 2, \ldots, m$. We calculate the survival curve for each treatment group in each stratum $S_{ij}(t)$ and then add up over strata

$$S_j(t) = \sum_{i=1}^{m} S_{ij}(t) r_i$$

where r_i is the proportion of subjects in stratum i.

16.7 Competing Risks

In certain situations one is only interested in certain causes of death that may be linked to the disease in question. For example, in a study of heart disease a death in a plane crash might be considered an unreasonable endpoint to attribute to the disease. It is tempting to censor people who die of genuinely unrelated causes. This cannot be true *noninformative censoring*, as someone who dies in a plane crash certainly has a reduced (zero) risk of heart disease in the future. On the other hand, there seems to be no way that these deaths would bias the remaining sample. It turns out that conclusions from Cox regression in this case are basically valid but that estimated survival curves need to be rethought. Such endpoints are called *competing risks*.

In a more complicated version of the problem, there is often interest in the effects of a treatment on more than one type of event. Lowering blood pressure reduces the risk of death from stroke, heart attack, cardiac arrest, and congestive heart failure, but different drugs may affect these events differently. Inference for these *dependent* competing risks is much more difficult and is complicated further by the fact that it is theoretically impossible to determine whether competing risks are dependent or independent. When all the events are rare, as in primary prevention of cardiovascular disease, ignoring the competing-risks problem may be a satisfactory practical approach. With more common events, this is not possible.

In some cases it is appropriate to treat deaths from other causes as indicating indefinitely long "survival" for the cause of interest. For example, consider a study of time to stroke in elderly people (e.g., Section 16.10.2). If a subject dies from breast cancer at 3.5 years follow-up, her chance of ever having a stroke is known exactly: She never will. This can be represented by censoring her observation time not at the time of death but at a time after the end of the study. The resulting survival curve will estimate the proportion of people who have not had strokes, which will not decrease to zero as follow-up time increases. In other cases this approach is undesirable because decreases in stroke risk and increases in other risks have the same impact—in a clinical trial of stroke prevention one would not want to declare the treatment successful just because it made people die of other causes.

Kalbfleisch and Prentice [2003], Gross and Clark [1975], and Prentice et al. [1978] discuss such issues. Pepe and Mori [1993] discuss alternatives to estimating the cause-specific survival function. Misuse of the cause-specific survival function has been an important issue in radiation oncology and is discussed by Gelman et al. [1990]. The impossibility of testing for dependent competing risks was shown by Tsiatis [1978]. The proof is highly technical but the result should be intuitively plausible: No data are available after censoring, so there should be no way to tell if survival is the same as for noncensored people.

A related issue is multivariate failure time, where events of different types can be observed for the same person. These could be ordered events, such as cancer recurrence and death; multiple versions of the same event, such as time to vision impairment in left and right eyes; or separate events, such as time to marriage and time to having children. Therneau and Grambsch [2000] discuss multivariate failure times, as does Lin [1994]. Somewhat surprisingly, this is a more tractable problem than competing risks.

16.8 Counting Process Notation

Many modern books on survival analysis and most recent statistical papers on the subject use a different mathematical notation from ours, the *counting process notation*. We have described each person's data by a covariate vector $\mathbf{X}_i$, an observation time T_i, and a censoring indicator Δ_i. The counting process notation replaces the time and censoring indicator with two functions of time: $N_i(t)$, which counts the number of times the person has been observed to "die" by time t, and $Y_i(t)$, which is 1 when the person is under observation and 0 otherwise. The covariate vector is usually called $\mathbf{Z}_i(t)$ rather than $\mathbf{X}_i$.

For ordinary survival data this means $N_i(t) = 0$ and $Y_i(t) = 1$ for $t < T_i$, $N_i(t) = \Delta_i$ and $Y_i(t) = 1$ for $t = T_i$, and $N_i(t) = \Delta_i$ and $Y_i(t) = 0$ for $t > T_i$. The notation $dN_i(t)$ means the jump in N_i at time t. This is zero except at the time of a death, when it is 1.

As a final complication, integral notation is used to indicate sums over a time point. For example, the notation $\int Z_i(t)\, dNi(t)$ means the sum of $Z_i(t) \times dN_i(t)$ over all time points. As $dNi(t) = 0$ except at the time of death, this is 0 if the person is censored and is $Z_i(T_i)$ if the person dies at time T_i.

This apparently cumbersome notation was introduced initially for purely mathematical reasons. It becomes more obviously useful when handling recurrent events [when $N_i(t)$ counts the number of events that have occurred], or left-truncation, when $Y_i(t) = 0$ before entry into the study to indicate that a death at that time would not have been observed. Klein and Moeschberger [1997] provide a reasonably accessible treatment of survival analysis using counting process notation.

PROBLEMS

The first four problems deal with the life table or actuarial method of estimating the survival curve. In each case, fill in the question marks from the other numbers given in the table.

16.1 Example 16.2 deals with chest pain in groups in the Coronary Artery Surgery Study; all times are in days. The life table for the individuals with chest pain thought probably not to be angina is given in Table 16.10.

16.2 From Example 16.2 for patients with chest pain thought definitely to be angina the life table is as given in Table 16.11.

16.3 Patients from Example 16.4 on a beta-blocking drug are used here and those not on a beta-blocking drug in Problem 16.4. The life table for those using such drugs at enrollment is given in Table 16.12.

16.4 Those not using beta-blocking drugs have the survival experience shown in Table 16.13.

16.5 Take the Stanford heart transplant data of Example 16.3. Place the data in a life table analysis using 50-day intervals. Plot the data over the interval from zero to 300 days. (Do not compute the Greenwood standard errors.)

16.6 For Problem 16.1, compute the hazard function (in probability of dying/day) for intervals:

- **(a)** 546–637
- **(b)** 1092–1183
- **(c)** 1456–1547

16.7 For the data of Problem 16.2, compute the hazard rate for the patients:

- **(a)** 0–91
- **(b)** 91–182
- **(c)** 819–910

Table 16.10 Life Table for Patients with Chest Pain Probably Not Angina

$t(i)$	Enter	At Risk	Dead	Withdraw Alive	Proportion Dead	Cumulative Survival	SE
0.0–90.9	2404	2404.0	2	0	0.0008	0.9992	?
91.0–181.9	2402	?	2	0	0.0008	0.9983	?
182.0–272.9	2400	2400.0	?	0	0.0021	0.9963	0.001
273.0–363.9	2395	2395.0	6	0	?	0.9938	0.002
364.0–454.9	?	2388.0	4	2	0.0017	0.9921	0.002
455.0–545.9	2383	2383.0	3	0	0.0013	?	0.002
546.0–636.9	2380	2380.0	7	0	0.0029	0.9879	0.002
637.0–727.9	2373	?	12	300	?	?	0.003
728.0–818.9	2061	2051.5	?	19	0.0015	0.9812	0.003
819.0–909.9	?	2039.0	1	0	0.0005	0.9807	0.003
910.0–1000.9	2038	2037.0	2	?	0.0010	0.9797	0.003
1001.0–1091.9	2034	?	3	517	0.0017	0.9781	0.003
1092.0–1182.9	1514	1494.0	3	40	0.0020	0.9761	0.003
1183.0–1273.9	1471	1471.0	4	0	?	0.9734	0.004
1274.0–1364.9	1467	1466.5	1	1	0.0007	0.9728	0.004
1365.0–1455.9	?	1144.0	1	642	0.0009	0.9719	0.004
1456.0–1546.9	822	777.5	1	?	0.0013	0.9707	0.004
1547.0–1637.9	732	732.0	1	0	0.0014	?	0.004
1638.0–1728.9	731	730.0	2	2	0.0027	0.9667	0.004
1729.0–1819.9	727	449.0	1	?	0.0022	0.9645	0.005

Table 16.11 Life Table for Patients with Definite Angina

$t(i)$	Enter	At Risk	Dead	Withdraw Alive	Proportion Dead	Cumulative Survival	SE
0.0–90.9	426	426.0	2	?	0.0047	0.9953	0.003
91.0–181.9	?	424.0	2	0	0.0047	0.9906	?
182.0–272.9	422	?	3	0	?	?	0.006
273.0–363.9	419	419.0	0	0	0.0000	0.9836	0.006
364.0–454.9	419	419.0	1	0	0.0024	0.9812	0.007
455.0–545.9	418	417.5	?	1	0.0024	0.9789	0.007
546.0–636.9	416	416.0	1	0	0.0024	0.9765	0.007
637.0–727.9	415	382.0	0	?	0.0000	0.9765	0.007
728.0–818.9	349	343.0	0	11	0.0000	0.9765	0.007
819.0–909.9	338	338.0	1	0	0.0030	0.9736	0.008
910.0–1000.9	337	336.5	0	1	0.0000	0.9736	0.008
1001.0–1091.9	336	?	1	97	?	?	0.009
1092.0–1182.9	238	232.5	0	11	0.0000	0.9702	0.009
1183.0–1273.9	227	?	1	1	0.0044	0.9660	0.010
1274.0–1364.9	?	224.5	1	1	0.0045	0.9617	0.010
1365.0–1455.9	?	170.0	0	106	0.0000	0.9617	0.010
1456.0–1446.9	117	114.0	?	6	0.0000	0.9617	0.010
1547.0–1637.9	?	?	0	1	0.0000	0.9617	0.010
1638.0–1728.9	110	109.5	0	1	0.0000	0.9617	0.010
1729.0–1819.9	109	65.5	0	87	0.0000	0.9617	0.010

Table 16.12 Life Table for Patients Taking a β-Blocker

$t(i)$	Enter	At Risk	Dead	Withdraw Alive	Proportion Dead	Cumulative Survival	SE
0.0–90.9	4942	4942.0	?	0	0.0097	0.9903	0.001
91.0–181.9	4894	4894.0	33	0	0.0067	0.9836	0.002
182.0–272.9	4861	4861.0	?	?	0.0058	0.9779	?
273.0–363.9	4833	4832.5	28	1	0.0058	0.9723	0.002
364.0–454.9	4804	4804.0	17	0	0.0035	?	0.002
455.0–545.9	4787	4786.5	29	1	?	?	0.003
546.0–636.9	4757	4757.0	22	0	0.0046	0.9585	0.003
637.0–727.9	4735	4376.0	25	718	0.0057	0.9530	0.003
728.0–818.9	?	?	?	62	0.0043	0.9489	0.003
819.0–909.9	3913	3912.0	23	2	?	0.9434	0.003
910.0–1000.9	3888	3884.5	19	7	0.0049	0.9388	0.004
1001.0–1091.9	?	?	?	1191	0.0040	0.9350	0.004
1092.0–1182.9	2658	2624.5	14	67	0.0053	0.9300	0.004
1183.0–1273.9	2577	2576.5	11	1	0.0043	0.9261	0.004
1274.0–1364.9	2565	2561.0	15	8	?	0.9206	0.004
1365.0–1455.9	2542	1849.5	12	1385	0.0065	0.9147	0.005
1456.0–1446.9	1145	1075.0	5	?	0.0047	?	0.005
1547.0–1637.9	1000	999.0	4	2	0.0040	0.9068	0.005
1638.0–1728.9	994	989.0	4	10	0.0040	0.9031	0.006
1729.0–1819.9	980	580.0	5	800	0.0086	0.8953	0.006

Table 16.13 Life Table for Patients Not Taking a β-Blocker

$t(i)$	Enter	At Risk	Dead	Withdraw Alive	Proportion Dead	Cumulative Survival	SE
0.0–90.9	6453	?	45	0	?	?	?
91.0–181.9	6408	?	28	0	?	?	?
182.0–272.9	6380	?	42	0	?	?	?
273.0–363.9	6338	?	25	2	?	?	?
364.0–454.9	6311	6310.0	24	2	0.0038	0.9746	0.002
455.0–545.9	6285	6285.0	32	0	0.0051	0.9696	0.002
546.0–636.9	6253	6253.0	?	0	0.0048	0.9650	0.002
637.0–727.9	6223	5889.0	23	668	0.0039	0.9612	0.002
728.0–818.9	?	?	23	40	0.0042	0.9572	0.003
819.0–909.9	?	5467.0	17	4	?	0.9542	0.003
910.0–1000.9	5448	5444.5	23	7	0.0042	0.9502	0.003
1001.0–1091.9	5418	4787.4	25	1261	0.0052	0.9452	0.003
1092.0–1182.9	4132	4082.0	?	100	0.0054	0.9401	0.003
1183.0–1273.9	4010	4010.0	23	0	0.0057	0.9347	0.003
1274.0–1364.9	3987	3981.0	18	?	0.0020	0.9329	0.003
1365.0–1455.9	3967	3100.0	13	1734	0.0042	0.9289	0.003
1456.0–1446.9	2220	2104.0	13	?	0.0062	0.9232	0.004
1547.0–1637.9	1975	1974.0	?	2	0.0020	0.9213	0.004
1638.0–1728.9	1969	1961.5	11	15	0.0056	0.9162	0.004
1729.0–1819.9	1943	1212.0	17	7	0.0058	0.9109	0.005

16.8 Data used by Pike [1966] are quoted in Kalbfleisch and Prentice [2003]. Two groups of rats with different pretreatment regimes were exposed to the carcinogen DBMA. The time to mortality from vaginal cancer in the two groups was: (* indicates a censored observation):

- *Group 1:* 143, 164, 188, 188, 190, 192, 206, 209, 213, 216, 216*, 220, 227, 230, 234, 244*, 246, 265, 304
- *Group 2:* 142, 156, 163, 198, 204*, 205, 232, 232, 233, 233, 233, 233, 239, 240, 261, 280, 280, 296, 296, 323, 344*

(a) Compute and graph the two product limit curves of the groups.

(b) Compute the expected number of deaths in each group and the value of the approximation $[\sum(O - E)^2/E]$ to the log-rank test. Are the survival times different in the two groups at the 5% significance level?

(c) How close is the approximate log-rank statistic to the exact value reported by your favorite statistics software?

16.9 The data of Problems 16.3 and 16.4, where stratified into the 30 strata discussed in the text, give the results shown in Table 16.14.

(a) What are the observed and expected numbers in the two groups? (Why do you have to add only three columns?)

(b) Two strata (12 and 17) are significant with $p = 0.02$. If the true survival patterns (in the conceptual underlying populations) are the same, does this surprise you?

(c) What is $\sum(O-E)^2/E$? How does this compare to the more complicated log-rank statistic which can be shown to be 6.510?

16.10 The paper by Chaitman et al. [1981] studied patients with left main coronary artery disease, as discussed in Example 16.4. Separate Cox survival runs were performed for the medical and surgical groups. The data are presented in Table 16.15. The survival, at the mean covariate values, for one, two, and three years are given by $S_0(1)$, $S_0(2)$, and $S_0(3)$, respectively. The zero–one variables are 0 for no and 1 for yes. Consider five patients with the variable values given in Table 16.16.

(a) What is the estimate of the two-year medical survival for patients 1, 2, and 3?

(b) What is the estimate of the three-year surgical survival for patients 4 and 5?

(c) What are the estimated one-year medical and one-year surgical survival rates for patient 1? For patient 3?

(d) What is the logarithm of the instantaneous relative risk for two individuals treated medically who differ by 20 years, but otherwise have the same values for the variables? What is the instantaneous relative risk?

(e) What is the instantaneous relative risk due to diabetes (yes vs. no) for surgical cases?

***(f)** What is the standard error for the LV score coefficient for the surgical group? For the age coefficient for the medical group? Form an approximate 95% confidence interval for the age coefficient in the medical group.

16.11 Alderman et al. [1983] studied the medical and surgical survival of patients with poor left ventricular function; that is, they studied patients whose hearts pumped poorly. Their model (in one analysis) included the following variables:

Table 16.14 Drug Use Data for Problem 16.9

	Drug Use		No Drug Use		
Stratum	Obs.	Exp.	Obs.	Exp.	p-Value
1	45	43.30	71	72.70	0.74
2	2	2.23	4	3.77	0.84
3	0	0.20	1	0.80	0.54
4	27	28.54	37	35.46	0.69
5	6	4.84	5	6.16	0.48
6	2	0.76	1	2.24	0.08
7	20	16.87	20	23.13	0.31
8	4	5.25	10	8.75	0.49
9	3	3.17	5	4.83	0.90
10	18	16.55	21	22.45	0.63
11	5	6.68	9	7.32	0.35
12	8	4.58	1	4.42	0.02
13	21	16.04	13	17.96	0.08
14	6	8.95	16	13.05	0.19
15	2	2.63	5	4.37	0.61
16	16	16.82	20	19.81	0.78
17	5	9.86	15	10.14	0.02
18	4	4.40	5	4.60	0.78
19	7	11.48	16	11.52	0.06
20	10	8.98	8	9.02	0.62
21	4	2.89	2	3.11	0.34
22	21	19.67	24	25.33	0.68
23	13	14.59	20	18.41	0.56
24	5	6.86	11	9.14	0.32
25	35	29.64	21	26.36	0.14
26	18	14.82	13	16.18	0.24
27	7	8.89	8	6.11	0.29
28	22	17.08	18	22.92	0.10
29	11	11.24	15	14.76	0.92
30	8	9.11	8	6.89	0.52

- *Impairment:* impairment due to congestive heart failure (CHF); 0 = never had CHF; 1 = had CHF but have no impairment; 2 = mild CHF impairment; 3 = moderate CHF impairment; and 4 = severe CHF impairment
- *Age:* in years
- *LMCA:* percent of diameter narrowing of the left main coronary artery
- *EF:* ejection fraction, the percent of the blood in the pumping chamber (left ventricle) of the heart pumped out during heartbeat
- *Digitalis:* Does the patient use digitalis? 1 = yes, 2 = no
- *Therapy:* 1 = medical; 2 = surgical
- *Vessel:* number (0 to 3) of vessels diseased with 70% or more stenosis

The β values and their standard errors are given in Table 16.17.

(a) Fill in the chi-square value column where missing.

(b) For which variables is $p < 0.10$? 0.05? 0.01? 0.001?

Table 16.15 Significant Independent Predictors of Mortality in Patients with Greater Than 50% Stenosis of the Left Main Coronary Artery

	Medical Group		Surgical Group	
Variable	X^{2a}	β_i	X^{2a}	β_i
LV score (5–30)	19.12	0.1231	18.54	0.1176
CHF score (0–4)	9.39	0.2815	8.16	0.2964
Age	14.42	0.0526	6.98	0.0402
% LMCA stenosis (50–100)	19.81	0.0293	—	—
Hypertension (0–1)	9.41	0.7067	5.74	0.5455
Left dominance (0–1)	—	—	10.23	1.0101
Smoking (1 = never, 2 = ever, 3 = present)	7.26	0.4389	—	—
MI status (0 = none, 1 = single, 2 = multiple)	4.41	−0.2842	—	—
Diabetes (0–1)	—	—	4.67	0.5934
Total chi-square	90.97	—	67.11	—
Degrees of freedom	7	—	6	—
p	<0.0001	—	<0.0001	—
Constant c		−7.2956		−3.7807
Estimated survival				
$S_0(1)$		0.90		0.97
$S_0(2)$		0.83		0.95
$S_0(3)$		0.76		0.93

[a] Adjusted chi-square (X^2) statistics were computed with all variables considered together. Chi-square >6.63 corresponds to $p < 0.01$, and chi-square >10.83, to $p < 0.001$. β, beta coefficient; CHF, congestive heart failure; LMCA, left main coronary artery; LV, left ventricular; MI, myocardial infarction. Dashes indicate a variable not in the particular model.

Table 16.16 Variable Data for Problem 16.10

	Patient Number				
Variable	1	2	3	4	5
LV score	13	5	7	8	12
CHF score	2	0	1	0	3
Age	71	62	42	55	46
Percent LMCA stenosis	75	90	50	70	95
Hypertension	No	Yes	Yes	No	No
Left dominance	No	No	No	Yes	No
Smoking	Ever	Present	Ever	Ever	Present
MI status	Multiple	None	Single	None	Single
Diabetes	No	No	No	Yes	No

Table 16.17 Data for Problem 16.11

Variable	Beta	Standard Error	Chi-Square
Impairment	0.2677	0.0505	?
Age	0.0430	0.0084	26.02
LMCA	0.0090	0.0024	?
EF	−0.0362	0.0098	?
Digitalis	−0.3802	0.1625	?
Therapy	−0.3418	0.1458	5.49
Vessel	0.2081	0.1012	4.23
Constant	−1.2873		

Table 16.18 Variable Data for Problem 16.11

	Patient Number		
Variable	1	2	3
Impairment	Severe	Mild	Moderate
Age	64	51	59
LMCA	50%	0%	0%
EF	15	32	23
Digitalis	Yes	Yes	Yes
Therapy	Medical	Surgical	Medical
Vessel	3	2	3

(c) What is the instantaneous relative risk of 70% LMCA compared to 0% LMCA?

(d) Consider three patients with the covariate values given in Table 16.18.

At the mean values of the data, the one- and two-year survival were 88.0% and 80.16%, respectively. Find the probability of one- and two-year survival for these three patients.

(e) With this model: (**i**) Can surgery be better for one person and medical treatment for another? Why? What does this say about unthinking application of the model? (**ii**) Under surgical therapy, can the curve cross over the estimated medical survival for some patients? For heavy surgical mortality, would a proportional hazard model always seem appropriate?

16.12 The Clark et al. [1971] heart transplant data were collected as follows. People with failing hearts waited for a donor heart to become available; this usually occurred within 90 days. However, some patients died before a donor heart became available. Figure 16.19 plots the survival curves of (1) those not transplanted (indicated by circles) and (2) the transplant patients from time of surgery (indicated by the triangles).

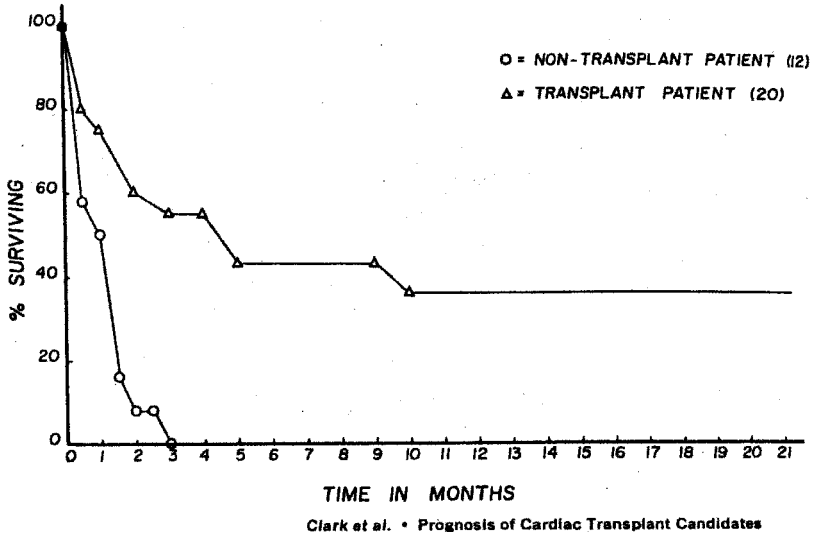


Figure 16.19 Survival calculated by the life table method. Survival for transplanted patients is calculated from the time of operation; survival of nontransplanted patients is calculated from the time of selection for transplantation.

(a) Is the survival of the nontransplanted patients a reasonable estimate of the nonoperative survival of candidates for heart transplant? Why or why not?

(b) Would you be willing to conclude from the figure (assuming a statistically significant result) that 1960s heart transplant surgery prolonged life? Why or why not?

(c) Consider a Cox model fitted with transplantation as a time-dependent covariate:

$$h_i(t) = h_0(t)e^{\exp(\alpha+\beta\times\text{TRANSPLANT}(t))}$$

The estimate of β is 0.13, with a 95% confidence interval $(-0.46, 0.72)$. (Verify this if you have access to suitable software.) What is the interpretation of this estimate? What would you conclude about whether 1960s-style heart transplant surgery prolongs life?

(d) A later, expanded version of the Stanford heart transplant data includes the age of the participant and the year of the transplant (from 1967 to 1973). Adding these variables gives the following coefficients:

Variable	β	SE(β)	p-value
Transplant	−0.030	0.318	0.92
Age	0.027	0.014	0.06
Year	−0.179	0.070	0.01

What would you conclude from these results, and why?

16.13 Simes et al. [2002] analyzed results from the LIPID trial that compared the cholesterol-lowering drug pravastatin to placebo in preventing coronary heart disease events. The outcome defined by the trial was time until fatal coronary heart disease or nonfatal myocardial infarction.

(a) The authors report that Cox model with one variable coded 1 for pravastatin and 0 for placebo gives a reduction in the risk of 24% (95% confidence interval, 15 to 32%). What is the hazard ratio? What is the coefficient for the treatment variable?

(b) A second model had three variables: treatment, HDL (good) cholesterol level after treatment, and total cholesterol level after treatment. The estimated risk reduction for the treatment variable in this model is 9% (95% confidence interval, −7 to 22%). What is the interpretation of the coefficient for treatment in this model?

16.14 In an elderly cohort, the death rate from heart disease was approximately constant at 2% per year, and from other causes was approximately constant at 3% per year.

(a) Suppose that a researcher computed a survival curve for time to heart disease death, treating deaths from other causes as censored. As described in Section 16.9.1, the survival function would be approximately $S(t) = e^{-0.02t}$. Compute this function at 1, 2, 3, . . . ,10 years.

(b) Another researcher computed a survival curve for time to non-heart-disease death, censoring deaths from heart disease. What would the survival function be? Compute it at 1, 2, 3, . . . ,10 years.

(c) What is the true survival function for deaths from all causes? Compare it to the two cause-specific functions and discuss why they appear inconsistent.

REFERENCES

Alderman, E. L., Fisher, L. D., Litwin, P., Kaiser, G. C., Myers, W. O., Maynard, C., Levine, F., and Schloss, M. [1983]. Results of coronary artery surgery in patients with poor left ventricular function (CASS). *Circulation*, **68**: 785–789. Used with permission from the American Heart Society.

Bie, O., Borgan, Ø., and Liestøl, K. [1987]. Confidence intervals and confidence bands for the cumulative hazard rate function and their small sample properties. *Scandinavian Journal of Statistics*, **14**: 221–223.

Breslow, N. E., and Day, N. E. [1987]. *Statistical Methods in Cancer Research*, Vol. II. International Agency for Research on Cancer, Lyon, France.

Chaitman, B. R., Fisher, L. D., Bourassa, M. G., Davis, K., Rogers, W. J., Maynard, C., Tyras, D. H., Berger, R. L., Judkins, M. P., Ringqvist, I., Mock, M. B., and Killip, T. [1981]. Effect of coronary bypass surgery on survival patterns in subsets of patients with left main coronary disease. *American Journal of Cardiology*, **48**: 765–777.

Clark, D. A., Stinson, E. B., Grieppe, R. B., Schroeder, J. S., Shumway, N. E., and Harrison, D. B. [1971]. Cardiac transplantation in man: VI. Prognosis of patients selected for cardiac transplantation. *Annals of Internal Medicine*, **75**: 15–21.

Crowley, J., and Hu, M. [1977]. Covariance analysis of heart transplant survival data. *Journal of the American Statistical Association*, **72**: 27–36.

European Coronary Surgery Study Group [1980]. Prospective randomized study of coronary artery bypass surgery in stable angina pectoris: second interim report. *Lancet*, Sept. 6, **2**: 491–495.

Fleming, T. R., and Harrington, D. [1991]. *Counting Processes and Survival Analysis.* Wiley, New York.

Gehan, E. A. [1969]. Estimating survival functions from the life table. *Journal of Chronic Diseases*, **21**: 629–644. Copyright © 1969 by Pergamon Press, Inc. Used with permission.

Gelman, R., Gelber, R., Henderson I. C., Coleman, C. N., and Harris, J. R. [1990]. Improved methodology for analyzing local and distant recurrence. *Journal of Clinical Oncology*, **8**(3): 548–555.

Greenwood, M. [1926]. *Reports on Public Health and Medical Subjects*, No. 33, App. I, The errors of sampling of the survivorship tables. H. M. Stationary Office, London.

Gross, A. J. and Clark, V. A. [1975]. *Survival Distributions: Reliability Applications in the Biomedical Sciences*. Wiley, New York.

Heckbert, S. R., Kaplan, R. C., Weiss, N. S., Psaty, B. M., Lin, D., Furberg, C. D., Starr, J. S., Anderson, G. D., and LaCroix, A. Z. [2001]. Risk of recurrent coronary events in relation to use and recent initiation of postmenopausal hormone therapy. *Archives of Internal Medicine*, **161**(14): 1709–1713.

Holt, V. L., Kernic, M. A., Lumley, T., Wolf, M. E., and Rivara, F. P. [2002]. Civil protection orders and risk of subsequent police-reported violence. *Journal of the American Medical Association*, **288**(5): 589–594

Hulley, S., Grady, D., Bush, T., Furberg, C., Herrington, D., Riggs, B., and Vittinghoff, E. [1998]. Randomized trial of estrogen plus progestin for secondary prevention of coronary heart disease in postmenopausal women. *Journal of the American Medical Association*, **280**(7): 605–613.

Kalbfleisch, J. D., and Prentice, R. L. [2003]. *The Statistical Analysis of Failure Time Data*. 2nd edition Wiley, New York.

Kaplan, E. L., and Meier, P. [1958]. Nonparametric estimation for incomplete observations. *Journal of the American Statistical Association*, **53**: 457–481.

Klein, J. P., and Moeschberger, M. L. [1997]. *Survival Analysis: Techniques for Censored and Truncated Data*. Springer-Verlag, New York.

Kleinbaum, D. G. [1996]. *Survival Analysis: A Self-Learning Text*. Springer-Verlag, New York.

Lin, D. Y. [1994]. Cox regression analysis of multivariate failure time data: the marginal approach. *Statistics in Medicine*, **13**: 2233–2247.

Lumley, T., Kronmal, D., Cushman, M., Monolio, T. A. and Goldstein, S. [2002]. Predicting stroke in the elderly: validation and web-based application. *Journal of Clinical Epidemiology*, **55**: 129–136.

Mann, N. R., Schafer, R. C. and Singpurwalla, N. D. [1974]. *Methods for Statistical Analysis of Reliability and Life Data*. Wiley, New York.

Mantel, N., and Byar, D. [1974]. Evaluation of response time 32 data involving transient states: an illustration using heart transplant data. *Journal of the American Statistical Association*, **69**: 81–86.

Messmer, B. J., Nora, J. J., Leachman, R. E., and Cooley, D. A. [1969]. Survival times after cardiac allographs. *Lancet*, May 10, **1**: 954–956.

Miller, R. G. [1981]. *Survival Analysis*. Wiley, New York.

Parker, R. L., Dry, T. J., Willius, F. A., and Gage, R. P. [1946]. Life expectancy in angina pectoris. *Journal of the American Medical Association*, **131**: 95–100.

Passamani, E. R., Fisher, L. D., Davis, K. B., Russel, R. O., Oberman, A., Rogers, W. J., Kennedy, J. W., Alderman, E., and Cohen, L. [1982]. The relationship of symptoms to severity, location and extent of coronary artery disease and mortality. Unpublished study.

Pepe, M. S., and Mori, M. [1993]. Kaplan–Meier, marginal, or conditional probability curves in summarizing competing risks failure time data. *Statistics in Medicine*, **12:** 737–751.

Pike, M. C. [1966]. A method of analysis of a certain class of experiments in carcinogenesis. *Biometrics*, **26**: 579–581.

Prentice, R. L., Kalbfleisch, J. D., Peterson, A. V., Flournoy, N., Farewell, V. T., and Breslow, N. L. [1978]. The analysis of failure times in the presence of competing risks. *Biometrics*, **34**: 541–554.

Simes, R. S., Masschner, I. C., Hunt, D., Colquhoun, D., Sullivan, D., Stewart, R. A. H., Hague, W., Kelch, A., Thompson, P., White, H., Shaw, V., and Torkin, A. [2002]. Relationship between lipid levels and clinical outcomes in the long-term intervention with Pravastatin in ischemic disease (LIPID) trial: to what extent is the reduction in coronary events with Pravastatin explained by on-study lipid levels? *Circulation*, **105**: 1162–1169.

Takaro, T., Hultgren, H. N., Lipton, M. J., Detre, K. M., and participants in the study group [1976]. The Veteran's Administration cooperative randomized study of surgery for coronary arterial occlusive disease: II. Subgroup with significant left main lesions. *Circulation Supplement 3*, **54**: III-107 to III-117.

Therneau, T. M., and Grambsch, P. [2000]. *Modelling Survival Data: Extending the Cox Model*. Springer-Verlag, New York.

Tsiatis, A. A. [1978]. An example of non-identifiability in competing risks. *Scandinavian Actuarial Journal*, 235–239.

Turnbull, B., Brown, B., and Hu, M. [1974]. Survivorship analysis of heart transplant data. *Journal of the American Statistical Association*, **69**: 74–80.

U.S. Department of Health, Education, and Welfare [1976]. *Vital Statistics of the United States, 1974*, Vol. II, Sec. 5, Life tables. U.S. Government Printing Office, Washington, DC.

CHAPTER 17

Sample Sizes for Observational Studies

17.1 INTRODUCTION

In this chapter we deal with the problem of calculating sample sizes in various observational settings. There is a very diverse literature on sample size calculations, dealing with many interesting areas. We can only give you a feeling for some approaches and some pointers for further study.

We start the chapter by considering the topic of screening in the context of adverse effects attributable to drug usage, trying to accommodate both the "rare disease" assumption and the multiple comparison problem. Section 17.3 discusses sample-size considerations when costs of observations are not equal, or the variability is unequal; some very simple but elegant relationships are derived. Section 17.4 considers sample size consideration in the context of discriminant analysis. Three questions are considered: (1) how to select variables to be used in discriminating between two populations in the face of multiple comparisons; (2) given that m variables have been selected, what sample size is needed to discriminate between two populations with satisfactory power; and (3) how large a sample size is needed to estimate the probability of correct classification with adequate precision and power. Notes, problems, and references complete the chapter.

17.2 SCREENING STUDIES

A screening study is a scientific fishing expedition: for example, attempting to relate exposure to one of several drugs to the presence or absence of one or more side effects (disease). In such screening studies the number of drug categories is usually very large—500 is not uncommon—and the number of diseases is very large—50 or more is not unusual. Thus, the number of combinations of disease and drug exposure can be very large—25,000 in the example above. In this section we want to consider the determination of sample size in screening studies in terms of the following considerations: many variables are tested and side effects are rare. A cohort of exposed and unexposed subjects is either followed or observed. We have looked at many diseases or exposures, want to "protect" ourselves against a large Type I error, and want to know how many observations are to be taken. We proceed in two steps: First, we derive the formula for the sample size without consideration of the multiple testing aspect, then we incorporate the multiple testing aspect. Let

$$X_1 = \text{number of occurrences of a disease of interest (per 100,000 person-years, say) in the unexposed population}$$

Biostatistics: A Methodology for the Health Sciences, Second Edition, by Gerald van Belle, Lloyd D. Fisher, Patrick J. Heagerty, and Thomas S. Lumley
ISBN 0-471-03185-2

X_2 = number of occurrences (per 100,000 person-years) in the exposed population

If X_1 and X_2 are rare events, $X_1 \sim \text{Poisson}(\theta_1)$ and $X_2 \sim \text{Poisson}(\theta_2)$. Let $\theta_2 = R\theta_1$; that is, the risk in the exposed population is R times that in the unexposed population ($0 < R < \infty$). We can approximate the distributions by using the variance stabilizing transformation (discussed in Chapter 10):

$$Y_1 = \sqrt{X_1} \sim N(\sqrt{\theta_1}, \sigma^2 = 0.25)$$
$$Y_2 = \sqrt{X_2} \sim N(\sqrt{\theta_2}, \sigma^2 = 0.25)$$

Assuming independence,

$$Y_2 - Y_1 \sim N\left(\sqrt{\theta_1}(\sqrt{R} - 1), \sigma^2 = 0.5\right) \tag{1}$$

For specified Type I and Type II errors α and β, the *number of events* n_1 and n_2 in the unexposed and exposed groups required to detect a relative risk of R with power $1 - \beta$ are given by the equation

$$n_1 = \frac{(Z_{1-\alpha/2} + Z_{1-\beta})^2}{2(\sqrt{R} - 1)^2}, \qquad n_2 = Rn_1 \tag{2}$$

Equation (2) assumes a two-sided, two-sample test with an equal number of subjects observed in each group. It is an approximation, based on the normality of the square root of a Poisson random variable. If the prevalence, π_1, in the unexposed population is known, the number of subjects per group, N, can be calculated by using the relationship

$$N\pi_1 = n_1 \quad \text{or} \quad N = n_1/\pi_1 \tag{3}$$

Example 17.1. In Section 15.4, mortality was compared in active participants in an exercise program and in dropouts. Among the active participants, there were 16 deaths in 593 person-years of active participation; in dropouts there were 34 deaths in 723 person-years. Using an α of 0.05, the results were not significantly different. The relative risk, R, for dropouts is estimated by

$$R = \frac{34/723}{16/593} = 1.74$$

Assuming equal exposure time in the active participants and dropouts, how large should the sample sizes n_1 and n_2 be to declare the relative risk, $R = 1.74$, significant at the 0.05 level with probability 0.95? In this case we use a two-tailed test and $Z_{1-\alpha/2} = 1.960$ and $Z_{1-\beta} = 1.645$, so that

$$n_1 = \frac{(1.960 + 1.645)^2}{2(\sqrt{1.74} - 1)^2} = 63.4 \doteq 64 \quad \text{and} \quad n_2 = (1.74)n_1 = 111$$

for a total number of observed events $= n_1 + n_1 = 64 + 111 = 175$ deaths. We would need approximately $(111/34) \times 723 = 2360$ person-years exposure in the dropouts and the same number of years of exposure among the controls. The exposure years in the observed data are not split equally between the two groups. We discuss this aspect further in Note 17.1.

If there is only one observational group, the group's experience perhaps being compared with that of a known population, the sample size required is $n_1/2$, again illustrating the fact that comparing two groups requires four times more exposure time than comparing one group with a known population.

Table 17.1 Relationship between Overall Significance Level α, Significance Level per Test, Number of Tests, and Associated Z-Values, Using the Bonferroni Inequality

Number of Tests (K)	Overall α Level	Required Level per Test (α)	Z-Values	
			One-Tailed	Two-Tailed
1	0.05	0.05	1.645	1.960
2	0.05	0.025	1.960	2.241
3	0.05	0.01667	2.128	2.394
4	0.05	0.0125	2.241	2.498
5	0.05	0.01	2.326	2.576
10	0.05	0.005	2.576	2.807
100	0.05	0.0005	3.291	3.481
1000	0.05	0.00005	3.891	4.056
10000	0.05	0.000005	4.417	4.565

We now turn to the second aspect of our question. Suppose that the comparison above is one of a multitude of comparisons? To maintain a per experiment significance level of α, we use the Bonferroni inequality to calculate the per comparison error rate. Table 17.1 relates the per comparison critical values to the number of tests performed and the per experiment error rate. It is remarkable that the critical values do not increase too rapidly with the number of tests.

Example 17.2. Suppose that the FDA is screening a large number of drugs, relating 10 kinds of congenital malformations to 100 drugs that could be taken during pregnancy. A particular drug and a particular malformation is now being examined. Equal numbers of exposed and unexposed women are to be selected and a relative risk of $R = 2$ is to be detected with power 0.80 and per experiment one-sided error rate of $\alpha = 0.05$. In this situation $\alpha^* = \alpha/1000$ and $Z_{1-\alpha^*} = Z_{1-\alpha/1000} = Z_{0.99995} = 3.891$. The required number of events in the unexposed group is

$$n_1 = \frac{(3.891 + 0.842)^2}{2(\sqrt{2} - 1)^2} = \frac{22.4013}{0.343146} = 65.3 \doteq 66$$

$$n_2 = 2n_1 = 132$$

In total, $66 + 132 = 198$ malformations must be observed. For a particular malformation, if the congenital malformation rate is on the order of 3/1000 live births, approximately 22,000 unexposed women and 22,000 women exposed to the drug must be examined. This large sample size is not only a result of the multiple testing but also the rarity of the disease. [The comparable number testing only once, $\alpha^* = \alpha = 0.05$, is $n_1 = \frac{1}{2}(1.645 + 0.842)^2/(\sqrt{2} - 1)^2 = 18$, or 3000 women per group.]

17.3 SAMPLE SIZE AS A FUNCTION OF COST AND AVAILABILITY

17.3.1 Equal-Variance Case

Consider the comparison of means from two independent groups with the same variance σ; the standard error of the difference is

$$\sigma\sqrt{\frac{1}{n_1} + \frac{1}{n_2}} \tag{4}$$

where n_1 and n_2 are the sample sizes in the two groups. As is well known, for fixed N the standard error of the difference is minimized (maximum precision) when

$$n_1 = n_2 = N$$

That is, the sample sizes are equal. Suppose now that there is a differential cost in obtaining the observations in the two groups; then it may pay to choose n_1 and n_2 unequal, subject to the constraint that the standard error of the difference remains the same. For example,

$$\frac{1}{10} + \frac{1}{10} = \frac{1}{6} + \frac{1}{30}$$

Two groups of equal sample size, $n_1 = n_2 = 10$, give the same precision as two groups with $n_1 = 6$ and $n_2 = 30$. Of course, the total number of observations N is larger, 20 vs. 36.

In many instances, sample size calculations are based on additional considerations, such as:

1. Relative cost of the observations in the two groups
2. Unequal hazard or potential hazard of treatment in the two groups
3. The limited number of observations available for one group

In the last category are case–control studies where the number of cases is limited. For example, in studying sudden infant death syndrome (SIDS) by means of a case–control study, the number of cases in a defined population is fairly well fixed, whereas an arbitrary number of (matching) controls can be obtained.

We now formalize the argument. Suppose that there are two groups, G_1 and G_2, with costs per observations c_1 and c_2, respectively. The total cost, C, of the experiment is

$$C = c_1 n_1 + c_2 n_2 \tag{5}$$

where n_1 and n_2 are the number of observations in G_1 and G_2, respectively. The values of n_1 and n_2 are to be chosen to minimize (maximum precision),

$$\frac{1}{n_1} + \frac{1}{n_2}$$

subject to the constraint that the total cost is to be C. It can be shown that under these conditions the required sample sizes are

$$n_1 = \frac{C}{c_1 + \sqrt{c_1 c_2}} \tag{6}$$

and

$$n_2 = \frac{C}{c_2 + \sqrt{c_1 c_2}} \tag{7}$$

The ratio of the two sample sizes is

$$\frac{n_2}{n_1} = \sqrt{\frac{c_1}{c_2}} = h, \qquad \text{say} \tag{8}$$

That is, if costs per observation in groups G_1 and G_2, are c_1 and c_2, respectively, then choose n_1 and n_2 on the basis of the ratio of the square root of the costs. This rule has been termed the *square root rule* by Gail et al. [1976]; the derivation can also be found in Nam [1973] and Cochran [1977].

If the costs are equal, $n_1 = n_2$, as before. Application of this rule can decrease the cost of an experiment, although it will increase the total number of observations. Note that the population means and standard deviation need not be known to determine the ratio of the sample sizes, only the costs. If the desired precision is specified—perhaps on the basis of sample size calculations assuming equal costs—the values of n_1 and n_2 can be determined. Compared with an experiment with equal sample sizes, the ratio ρ of the costs of the two experiments can be shown to be

$$\rho = \frac{1}{2} + \frac{h}{1+h^2} \tag{9}$$

If $h = 1$, then $\rho = 1$, as expected; if h is very close to zero or very large, $\rho = \frac{1}{2}$; thus, no matter what the relative costs of the observations, the savings can be no larger than 50%.

Example 17.3. (After Gail et al. [1976]) A new therapy, G_1, for hypertension is introduced and costs \$400 per subject. The standard therapy, G_2, costs \$16 per subject. On the basis of power calculations, the precision of the experiment is to be equivalent to an experiment using 22 subjects per treatment, so that

$$\frac{1}{22} + \frac{1}{22} = 0.09091$$

The square root rule specifies the ratio of the number of subjects in G_1 and G_2 by

$$\begin{aligned} n_2 &= \sqrt{\frac{400}{16}} n_1 \\ &= 5n_1 \end{aligned}$$

To obtain the same precision, we need to solve

$$\frac{1}{n_1} + \frac{1}{5n_1} = 0.09091$$

or

$$n_1 = 13.2 \quad \text{and} \quad n_2 = 66.0$$

(i.e., $1/13.2 + 1/66.0 = 0.09091$, the same precision). Rounding up, we require 14 observations in G_1 and 66 observations in G_2. The costs can also be compared as in Table 17.2.

A savings of \$3896 has been obtained, yet the precision is the same. The total number of observations is now 80, compared to 44 in the equal-sample-size experiment. The ratio of the savings is

$$\rho = \frac{6656}{9152} = 0.73$$

Table 17.2 Costs Comparisons for Example 17.3

	Equal Sample Size		Sample Size Determined by Cost	
	n	Cost	n	Cost
G_1	22	8800	14	5600
G_2	22	352	66	1056
Total	44	9152	80	6656

The value for ρ calculated from equation (9) is

$$\rho = \frac{1}{2} + \frac{5}{26} = 0.69$$

The reason for the discrepancy is the rounding of sample sizes to integers.

17.3.2 Unequal-Variance Case

Suppose that we want to compare the means from groups with unequal variance. Again, suppose that there are n_1 and n_2 observations in the two groups. Then the standard error of the difference between the two means is

$$\sqrt{\frac{\sigma_1^2}{n_1} + \frac{\sigma_2^2}{n_2}}$$

Let the ratio of the variances be $\eta^2 = \sigma_2^2/\sigma_1^2$. Gail et al. [1976] show that the sample size should now be allocated in the ratio

$$\frac{n_2}{n_1} = \sqrt{\frac{\sigma_2^2}{\sigma_1^2}\frac{c_1}{c_2}} = \eta h$$

The calculations can then be carried out as before. In this case, the cost relative to the experiment with equal sample size is

$$\rho^* = \frac{(h+\eta)^2}{(1+h^2)(1+\eta^2)} \tag{10}$$

These calculations also apply when the costs are equal but the variances unequal, as is the case in binomial sampling.

17.3.3 Rule of Diminishing Precision Gain

One of the reasons advanced at the beginning of Section 17.3 for distinguishing between the sample sizes of two groups is that a limited number of observations may be available for one group and a virtually unlimited number in the second group. Case–control studies were cited where the number of cases per population is relatively fixed. Analogous to Gail et al. [1976], we define a rule of diminishing precision gain. Suppose that there are n cases and that an unlimited number of controls are available. Assume that costs and variances are equal. The precision of the difference is then proportional to

$$\sigma\sqrt{\frac{1}{n} + \frac{1}{hn}}$$

where hn is the number of controls selected for the n cases.

We calculate the ratio P_h:

$$P_h = \frac{\sqrt{1/n + 1/hn}}{\sqrt{1/n + 1/n}}$$

$$= \sqrt{\frac{1}{2}\left(1 + \frac{1}{h}\right)}$$

This ratio P_h is a measure of the precision of a case–control study with n and hn cases and controls, respectively, relative to the precision of a study with an equal number, n, of cases and controls. Table 17.3 presents the values of P_h and $100(P_h - P_\infty)/P_\infty$ as a function of h.

Table 17.3 Comparison of Precision of Case Control Study with n and hn Cases and Controls, Respectively

h	P_h	$100[(P_h - P_\infty)/P_\infty]\%$
1	1.00	41
2	0.87	22
3	0.82	15
4	0.79	12
5	0.77	10
10	0.74	5
∞	0.71	0

This table indicates that in the context above, the gain in precision with, say, more than four controls per case is minimal. At $h = 4$, one obtains all but 12% of the precision associated with a study using an infinite number of controls. Hence, in the situation above, there is little merit in obtaining more than four or five times as many controls as cases. Lubin [1980] approaches this from the point of view of the logarithm of the odds ratio and comes to a similar conclusion.

17.4 SAMPLE-SIZE CALCULATIONS IN SELECTING CONTINUOUS VARIABLES TO DISCRIMINATE BETWEEN POPULATIONS

In certain situations, there is interest in examining a large number of continuous variables to explain the difference between two populations. For example, an investigator might be "fishing" for clues explaining the presence (one population) or absence (the other population) of a disease of unknown etiology. Or in a disease where a variety of factors are known to affect prognosis, the investigator may desire to find a good set of variables for predicting which subjects will survive for a fixed number of years. In this section, the determination of sample size for such studies is discussed.

There are a variety of approaches to the data analysis in this situation. With a large, say 50 or more, number of variables, we would hesitate to run stepwise discriminant analysis to select a few important variables, since (1) in typical data sets there are often many dependencies that make the method numerically unstable (i.e., the results coming forth from some computers cannot be relied on); (2) the more complex the mathematical model used, the less faith we have that it is useful in other situations (i.e., the more parameters that are used and estimated, the less confidence we can have that the result is transportable to another population in time or space; here we might be envisioning a discriminant function with a large number of variables); and (3) the multiple-comparison problems inherent in considering the large number of variables at each step in the stepwise procedure make the result of doubtful value.

One approach to the analysis is first to perform a *univariate screen*. This means that variables (used singly, that is, univariately) with the most power to discriminate between the two populations are selected. Second, use these univariate discriminating variables in the discriminant analysis. The sample-size calculations below are based on this method of analysis. There is some danger in this approach, as variables that univariately are not important in discrimination could be important when used in conjunction with other variables. In many practical situations, this is not usually the case. Before discussing the sample-size considerations, we will consider a second approach to the analysis of such data as envisioned here.

Often, the discriminating variables fall naturally in smaller subsets. For example, the subsets for patients may involve data from (1) the history, (2) a physical exam, and (3) some routine tests. In many situations the predictive information of the variables within each subset is roughly

the same. This being the case, a two-step method of selecting the predictive variables is to (1) use stepwise selection within subsets to select a few variables from each subset, and (2) combine the selected variables into a group to be used for another stepwise selection procedure to find the final subset of predictive variables.

After selecting a smaller subset of variables to use in the prediction process, one of two steps is usually taken. (1) The predictive equation is validated (tested) on a new sample to show that it has predictive power. That is, an F-test for the discriminant function is performed. Or, (2) a larger independent sample is used to provide an indication of the accuracy of the prediction. The second approach requires a larger sample size than merely establishing that there is some predictive ability, as in the first approach. In the next three sections we make this general discussion precise.

17.4.1 Univariate Screening of Continuous Variables

To obtain an approximate idea of the sample size needed to screen among k variables, the following is assumed: The variables are normally distributed with the same variance in each population and possibly different means. The power to classify into the two populations depends on δ, the number of standard deviations distance between the two populations means:

$$\delta = \frac{\mu_1 - \mu_2}{\sigma}$$

Some idea of the relationship of classificatory power to δ is given in Figure 17.1.

Suppose that we are going to screen k variables and want to be sure, with probability at least $1 - \alpha$, to include all variables with $\delta \geq D$. In this case we must be willing to accept some variables with values close to but less than D. Suppose that at the same time we want probability at least $1 - \alpha$ of not including any variables with $\delta \leq fD$, where $0 < f < 1$. One approach is to look at confidence intervals for the difference in the population means. If the absolute value of the difference is greater than $fD + (1 - f)D/2$, the variable is included. If the

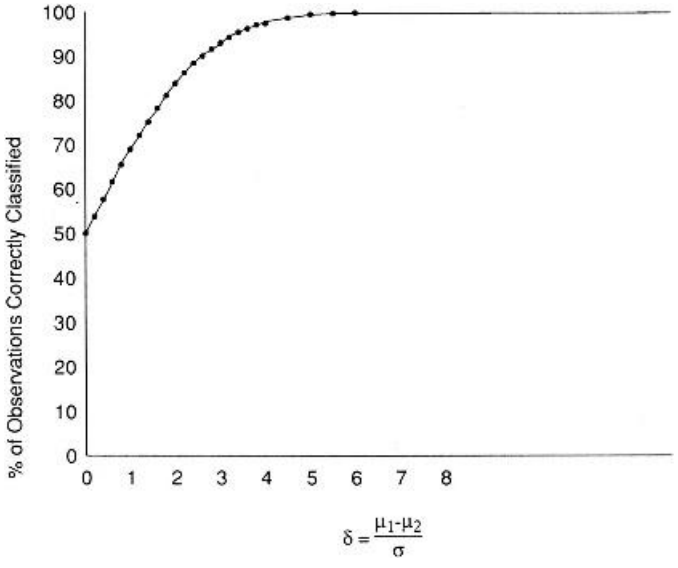


Figure 17.1 Probability of correct classification between $N(0, \sigma^2)$ and $N(\delta\sigma, \sigma^2)$ populations, assuming equal priors and $\delta\sigma/2$ as the cutoff values for classifying into the two populations.

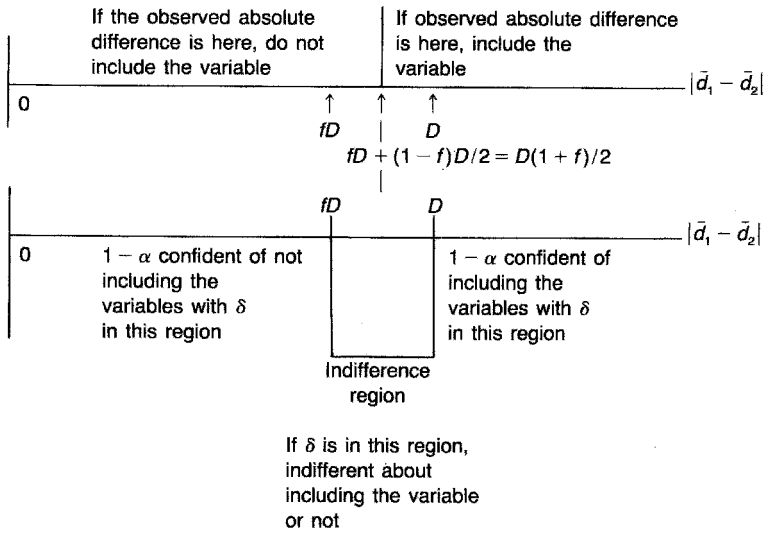


Figure 17.2 Inclusion and exclusion scheme for differences in sample means $|d_1 - d_2|$ from populations G_1 and G_2.

absolute value of the difference is less than this value, the variable is not included. Figure 17.2 presents the situation. To recap, with probability at least $1 - \alpha$, we include for use in prediction all variables with $\delta \geq D$ and do not include those with $\delta \leq fD$. In between, we are willing for either action to take place. The dividing line is placed in the middle.

Let us suppose that the number of observations, n, is large enough so that a normal approximation for confidence intervals will hold. Further, suppose that a fraction p of the data is from the first population and that $1 - p$ is from the second population. If we choose $1 - \alpha^*$ confidence intervals so that the probability is about $1 - \alpha$ that all intervals have half-width $\sigma(1 - f)D/2$, the result will hold.

If n is large, the pooled variance is approximately σ and the half-interval has width (in standard deviation units) of about

$$\sqrt{\frac{1}{Np} + \frac{1}{N(1-p)}} Z_{1-\alpha^*}$$

where $Z_{1-\alpha^*}$ is the $N(0, 1)$ critical value. To make this approximately $(1 - f)D/2$, we need

$$N = \frac{4z^2_{1-\alpha^*}}{p(1-p)D^2(1-f)^2} \tag{11}$$

In Chapter 12 it was shown that $\alpha^* = \alpha/2k$ was an appropriate choice by Bonferroni's inequality. In most practical situations, the observations tend to vary together, and the probability of all the confidence statements holding is greater than $1 - \alpha$. A slight compromise is to use $\alpha^* = [1 - (1 - \alpha)^{1/k}]/2$ as if the tests are independent. This α^* was used in computing Table 17.4.

From the table it is very clear that there is a large price to be paid if the smaller population is a very small fraction of the sample. There is often no way around this if the data need to be collected prospectively before subjects have the population membership determined (by having a heart attack or myocardial infarction, for example).

Table 17.4 Sample Sizes Needed for Univariate Screening When $f = \frac{2}{3}$[a]

	$p = 0.5$			$p = 0.6$			$p = 0.7$			$p = 0.8$			$p = 0.9$		
D	0.5	1	2	0.5	1	2	0.5	1	2	0.5	1	2	0.5	1	2
$k = 20$	2121	527	132	2210	553	136	2525	629	157	3315	829	204	5891	1471	366
	2478	616	153	2580	642	157	2950	735	183	3872	965	238	6881	1717	429
	3289	825	204	3434	859	213	3923	978	242	5151	1288	319	9159	2287	570
$k = 100$	2920	721	179	3043	761	187	3477	867	217	4565	1139	285	8118	2028	506
	3285	820	204	3421	854	213	3910	978	242	5134	1284	319	9129	2282	570
	4118	1029	255	4288	1071	268	4905	1224	306	6435	1607	400	11445	2860	714
$k = 300$	3477	867	217	3625	905	225	4140	1033	255	5436	1356	336	9665	2414	604
	3846	961	238	4008	999	247	4577	1143	285	6010	1500	374	10685	2669	667
	4684	1169	289	4879	1220	302	5576	1394	349	7323	1828	455	13018	3251	812

[a]For each entry the top, middle, and bottom numbers are for $\alpha = 0.10$, 0.05, and 0.01, respectively.

17.4.2 Sample Size to Determine That a Set of Variables Has Discriminating Power

In this section we find the answer to the following question. Assume that a discriminant analysis is being performed at significance level α with m variables. Assume that one population has a fraction p of the observations and that the other population has a fraction $1 - p$ of the observations. What sample size, n, is needed so that with probability $1 - \beta$, we reject the null hypothesis of no predictive power (i.e., Mahalanobis distance equal to zero) when in fact the Mahalanobis distance is $\Delta > 0$ (where Δ is fixed and known)? (See Chapter 13 for a definition of the Mahalanobis distance.)

The procedure is to use tables for the power functions of the analysis of variance tests as given in the CRC tables [Beyer, 1968 pp. 311–319]. To enter the charts, first find the chart for $v_1 = m$, the number of predictive variables.

The charts are for $\alpha = 0.05$ or 0.01. It is necessary to iterate to find the correct sample size n. The method is as follows:

1. Select an estimate of n.
2. Compute
$$\phi_n = \Delta\sqrt{\frac{p(1-p)}{m+1}} \times \sqrt{n} \tag{12}$$
This quantity indexes the power curves and is a measure of the difference between the two populations, adjusting for p and m.
3. Compute $v_2 = n - 2$.
4. On the horizontal axis, find ϕ and go vertically to the v_2 curve. Follow the intersection horizontally to find $1 - \widetilde{\beta}$.
5. **a.** If $1 - \widetilde{\beta}$ is greater than $1 - \beta$, decrease the estimate of n and go back to step 2.
   b. If $1 - \widetilde{\beta}$ is less than $1 - \beta$, increase the estimate of n and go back to step 2.
   c. If $1 - \widetilde{\beta}$ is approximately equal to $1 - \beta$, stop and use the given value of n as your estimate.

Example 17.4. Working at a significance level 0.05 with five predictive variables, find the total sample size needed to be 90% certain of establishing predictive power when $\cdot\Delta = 1$ and $p = 0.34$. Figure 17.3 is used in the calculation.

We use
$$\phi_n = 1 \times \sqrt{\frac{0.3 \times 0.7}{5+1}}\sqrt{n} = 0.187\sqrt{n}$$

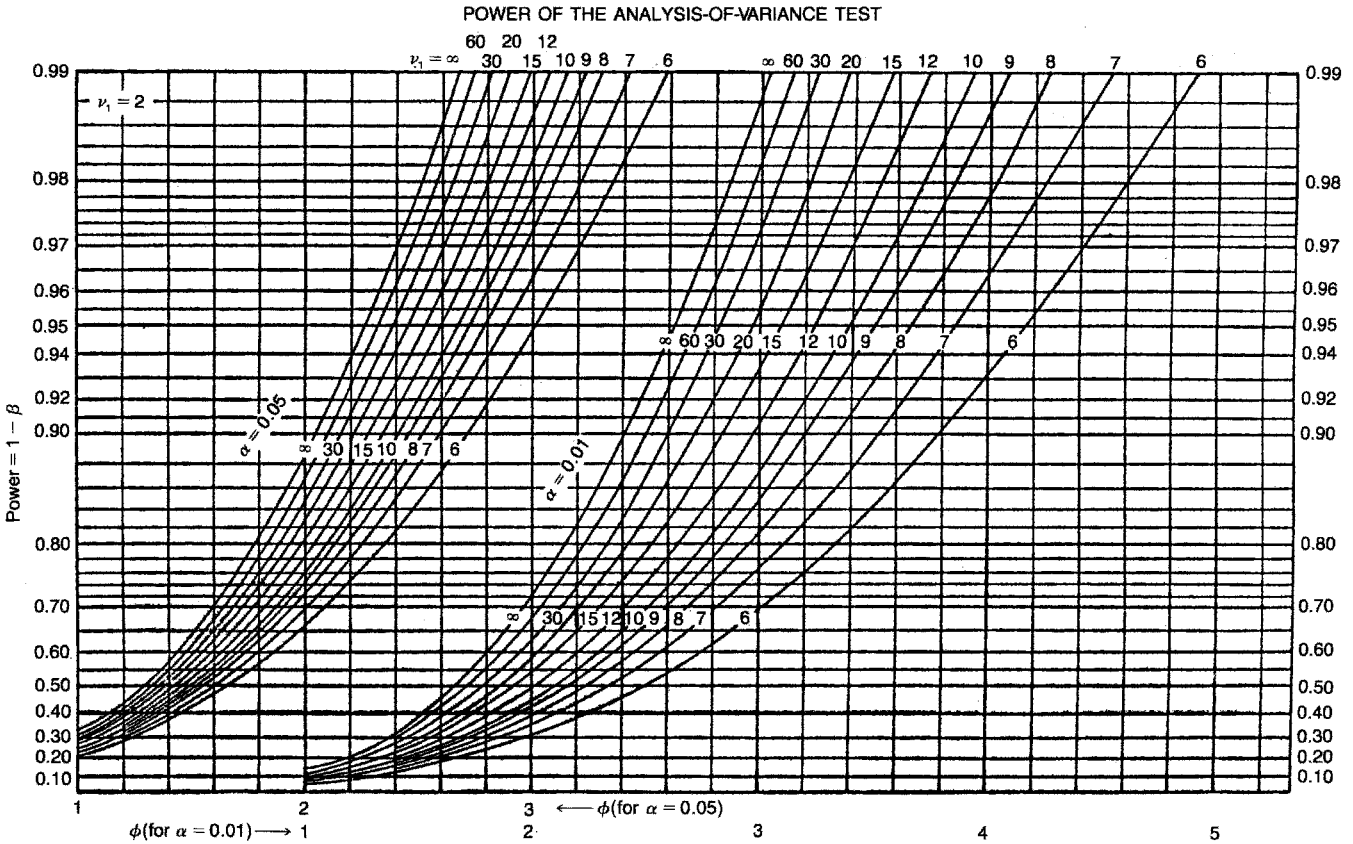


Figure 17.3 Power of the analysis of variance test. (From Beyer [1968].)

The method proceeds as follows:

1. Try $n = 30, \phi = 1.024, v_2 = 28, 1 - \beta \doteq 0.284$.
2. Try $n = 100, \phi = 1.870, v_2 = 98, 1 - \beta \doteq 0.958$.
3. Try $n = 80, \phi = 1.672, v_2 = 78, 1 - \beta \doteq 0.893$.
4. Try $n = 85, \phi = 1.724, v_2 = 83, 1 - \beta \doteq 0.92$.

Use $n = 83$. Note that the method is somewhat approximate, due to the amount of interpolation (rough visual interpretation) needed.

17.4.3 Quantifying the Precision of a Discrimination Method

After developing a method of classification, it is useful to validate the method on a new independent sample from the data used to find the classification algorithm. The approach of Section 17.4.2 is designed to show that there is some classification power. Of more interest is to be able to make a statement on the amount of correct and incorrect classification. Suppose that one is hoping to develop a classification method that classifies correctly $100\pi\%$ of the time.

To estimate with $100(1 - \alpha)\%$ confidence the correct classification percentage to within $100\varepsilon\%$, what number of additional observations are required? The confidence interval (we'll assume n large enough for the normal approximation) will be, letting c equal the number of n trials correctly classified,

$$\frac{c}{n} \pm \sqrt{\frac{1}{n}\frac{c}{n}\left(1 - \frac{c}{n}\right)} z_{1-\alpha/2}$$

where $z_{1-\alpha/2}$ is the $N(0, 1)$ critical value. We expect $c/n \doteq \pi$, so it is reasonable to choose n to satisfy $z_{1-\alpha/2} = \varepsilon\sqrt{\pi(1 - \pi)/n}$. This implies that

$$n = z^2_{1-\alpha/2}\pi(1 - \pi)/\varepsilon^2 \tag{13}$$

where $\varepsilon =$ (predicted - actual) probability of misclassification.

Example 17.5. If one plans for $\pi = 90\%$ correct classification and wishes to be 99% confident of estimating the correct classification to within 2%, how many new experimental units must be allowed? From Equation (13) and $z_{0.995} = 2.576$, the answer is

$$n = (2.576)^2 \times \frac{0.9(1 - 0.9)}{(0.02)^2} \doteq 1493$$

17.4.4 Total Sample Size for an Observational Study to Select Classification Variables

In planning an observational study to discriminate between two populations, if the predictive variables are few in number and known, the sample size will be selected in the manner of Section 17.4.2 or 17.4.3. The size depends on whether the desire is to show some predictive power or to have desired accuracy of estimation of the probability of correct classification. In addition, a different sample is needed to estimate the discriminant function. Usually, this is of approximately the same size.

If the predictive variables are to be culled from a large number of choices, an *additional* number of observations must be added for the selection of the predictive variables (e.g., in the manner of Section 17.4.1). Note that the method cannot be validated by application to the observations used to select the variables and to construct the discriminant function: This would lead to an exaggerated idea of the accuracy of the method. As the coefficients and variables were chosen specifically for these data, the method will work better (often considerably better) on these data than on an independent sample chosen as in Section 17.4.2 or 17.4.3.

NOTES

17.1 Sample Sizes for Cohort Studies

Five major journals are sources for papers dealing with sample sizes in cohort and case–control studies: *Statistics in Medicine*, *Biometrics, Controlled Clinical Trials, Journal of Clinical Epidemiology*, and the *American Journal of Epidemiology*. In addition, there are books by Fleiss [1981], Schlesselman [1982], and Schuster [1993].

A cohort study can be thought of as a cross-sectional study; there is no selection on case status or exposure status. The table generated is then the usual 2×2 table. Let the sample proportions be as follows:

	Exposure	No Exposure	
Case	p_{11}	p_{12}	$p_{1\cdot}$
Control	p_{21}	p_{22}	$p_{2\cdot}$
	$p_{\cdot 1}$	$p_{\cdot 2}$	1

If p_{11}, $p_{1\cdot}$, $p_{2\cdot}$, $p_{\cdot 1}$, and $p_{\cdot 2}$ estimate $\pi_{11}, \pi_{1\cdot}, \pi_{2\cdot}, \pi_{\cdot 1}$, and $\pi_{\cdot 2}$, respectively, then the required total sample size for significance level α, and power $1 - \beta$ is approximately

$$n = \frac{\left(Z_{1-\alpha/2} + Z_{1-\beta}\right)^2 \pi_{11}\pi_{1\cdot}\pi_{2\cdot}\pi_{\cdot 1}\pi_{\cdot 2}}{(\pi_{11} - \pi_{1\cdot}\pi_{\cdot 1})^2} \tag{14}$$

Given values of $\pi_{1\cdot}$, $\pi_{\cdot 1}$, and $R = (\pi_{11}/\pi_{\cdot 1})/(\pi_{12}/\pi_{\cdot 2}) =$ the relative risk, the value of π_{11} is determined by

$$\pi_{11} = \frac{R\pi_{\cdot 1}\pi_{1\cdot}}{R\pi_{\cdot 1} + \pi_{\cdot 2}} \tag{15}$$

The formula for the required sample size then becomes

$$n = \left(Z_{1-\alpha/2} + Z_{1-\beta}\right)^2 \frac{\pi_{\cdot 1}}{1 - \pi_{\cdot 1}} \frac{1 - \pi_{\cdot 1}}{\pi_{\cdot 1}} \left[1 + \frac{1}{\pi_{\cdot 1}(R - 1)}\right]^2 \tag{16}$$

If the events are rare, the Poisson approximation derived in the text can be used. For a discussion of sample sizes in $r \times c$ contingency tables, see Lachin [1977] and Cohen [1988].

17.2 Sample-Size Formulas for Case–Control Studies

There are a variety of sample-size formulas for case–control studies. Let the data be arranged in a table as follows:

	Exposed	Not Exposed	
Case	X_{11}	X_{12}	n
Control	X_{21}	X_{22}	n

and

$$P[\text{exposure}|\text{case}] = \pi_1, \qquad P[\text{exposure}|\text{control}] = \pi_2$$

estimated by $P_1 = X_{11}/n$ and $P_2 = X_{21}/n$ (we assume that $n_1 = n_2 = n$). For a two-sample, two-tailed test with

$$P[\text{Type I error}] = \alpha \quad \text{and} \quad P[\text{Type II error}] = \beta$$

the approximate sample size per group is

$$n = \frac{[Z_{1-\alpha/2}\sqrt{2\overline{\pi}(1-\overline{\pi})} + Z_{1-\beta}\sqrt{\pi_1(1-\pi_1)+\pi_2(1-\pi_2)}]^2}{(\pi_1-\pi_2)^2} \tag{17}$$

where $\overline{\pi} = \frac{1}{2}(\pi_1 + \pi_2)$. The total number of subjects is $2n$, of which n are cases and n are controls. Another formula is

$$n = \frac{[\pi_1(1-\pi) + \pi_2(1-\pi_2)](Z_{1-\alpha/2} + Z_{1-\beta})^2}{(\pi_1-\pi_2)^2} \tag{18}$$

All of these formulas tend to give the same answers, and underestimate the sample sizes required. The choice of formula is primarily a matter of aesthetics.

The formulas for sample sizes for case–control studies are approximations, and several corrections are available to get closer to the exact value. Exact values for equal sample sizes have been tabulated in Haseman [1978]. Adjustment for the approximate sample size have been presented by Casagrande et al. [1978], who give a slightly more complicated and accurate formulation. See also Lachin [1981, 2000] and Ury and Fleiss [1980].

Two other considerations will be mentioned. The first is unequal sample size. Particularly in case–control studies, it may be difficult to recruit more cases. Suppose that we can select n observations from the first population and rn from the second ($0 < r < \infty$). Following Schlesselman [1982], a very good approximation for the exact sample size for the number of cases is

$$n_1 = n\left(\frac{r+1}{2r}\right) \tag{19}$$

and for the number of controls

$$n_2 = n\left(\frac{r+1}{2}\right) \tag{20}$$

where n is determined by equation (17) or (18). The total sample size is then $n((r+1)^2/2r)$. Note that the number of cases can never be reduced to more than $n/2$ no matter what the number of controls. This is closely related to the discussion in Section 17.3. Following Fleiss et al. [1980], a slightly improved estimate can be obtained by using

$$n_1^* = n_1 + \frac{r+1}{r\Delta} = \text{number of cases}$$

and

$$n_2^* = rn_1^* = \text{number of controls}$$

A second consideration is cost. In Section 17.3 we considered sample sizes as a function of cost and related the sample sizes to precision. Now consider a slight reformulation of the problem in the case–control context. Suppose that enrollment of a case costs c_1 and enrollment of a control costs c_2. Pike and Casagrande [1979] show that a reasonable sample size approximation is

$$n_1 = n\left(1 + \sqrt{\frac{c_1}{c_0}}\right)$$

$$n_2 = n\left(1 + \sqrt{\frac{c_0}{c_1}}\right)$$

where n is defined by equations (17) or (18).

Finally, frequently case–control study questions are put in terms of odds ratios (or relative risks). Let the odds ratio be $R = \pi_1(1-\pi_2)/\pi_2(1-\pi_1)$, where π_1 and π_2 are as defined at the beginning of this section. If the control group has known exposure rate π_2, that is, $P[\text{exposure}|\text{control}] = \pi_2$, then

$$\pi_1 = \frac{R\pi_2}{1+\pi_2(R-1)}$$

To calculate sample sizes, use equation (17) for specified values of π_2 and R.

Mantel [1983] gives some clever suggestions for making binomial sample-size tables more useful by making use of the fact that sample size is "inversely proportional to the square of the difference being sought, everything else being more or less fixed."

Newman [2001] is a good reference for sample-size questions involving survival data.

17.3 Power as a Function of Sample Size

Frequently, the question is not "How big should my sample size be" but rather, "I have 60 observations available; what kind of power do I have to detect a specified difference, relative risk, or odds ratio?" The charts by Feigl illustrated in Chapter 6 provided one answer. Basically, the question involves inversion of formulas such as given by equations (17) and (18), solving them for $Z_{1-\beta}$, and calculating the associated area under the normal curve. Besides Feigl, several authors have studied this problem or variations of it. Walter [1977] derived formulas for the smallest and largest relative risk, R, that can be detected as a function of sample size, Type I and Type II errors. Brittain and Schlesselman [1982] present estimates of power as a function of possibly unequal sample size and cost.

17.4 Sample Size as a Function of Coefficient of Variation

Sometimes, sample-size questions are asked in the context of percent variability and percent changes in means. With an appropriate, natural interpretation, valid answers can be provided. Specifically, assume that by *percent variability* is meant the coefficient of variation, call it V, and that the second mean differs from the first mean by a factor f.

Let two normal populations have means μ_1 and μ_2 and standard deviations σ_1 and σ_2. The usual sample-size formula for two independent samples needed to detect a difference $\mu_1 - \mu_2$ in means with Type I error α and power $1-\beta$ is given by

$$n = \frac{(z_{1-\alpha/2} + z_{1-\beta})^2(\sigma_1^2 + \sigma_2^2)}{(\mu_1 - \mu_2)^2}$$

where $z_{1-\gamma}$ is the $100(1-\gamma)$th percentile of the standard normal distribution. This is the formula for a two-sided alternative; n is the number of observations per group. Now assume that $\mu_1 = f\mu_2$ and $\sigma_1/\mu_1 = \sigma_2/\mu_2 = V$. Then the formula transforms to

$$n = (z_{1-\alpha/2} + z_{1-\beta})^2 V^2 \left[1 + \frac{2f}{(f-1)^2}\right] \tag{21}$$

The quantity V is the usual coefficient of variation and f is the ratio of means. It does not matter whether the ratio of means is defined in terms of $1/f$ rather than f.

Sometimes the problem is formulated with the variability V as specified but a percentage change between means is given. If this is interpreted as the second mean, μ_2, being a percent change from the first mean, this percentage change is simply $100(f-1)\%$ and the formula again applies. However, sometimes, the relative status of the means cannot be specified, so an

interpretation of *percent change* is needed. If we know only that $\sigma_1 = V\mu_1$ and $\sigma_2 = V\mu_2$, the formula for sample size becomes

$$n = \frac{V^2(z_{1-\alpha/2} + z_{1-\beta})^2}{\left((\mu_1 - \mu_2)/\sqrt{\mu_1\mu_2}\right)^2}$$

The quantity $\left((\mu_1 - \mu_2)/\sqrt{\mu_1\mu_2}\right)$ is the proportional change from μ_1 to μ_2 as a function of their geometric mean. If the questioner, therefore, can only specify a percent change, this interpretation is quite reasonable. Solving equation (21) for $z_{1-\beta}$ allows us to calculate values for power curves:

$$z_{1-\beta} = -z_{1-\alpha/2} + \frac{\sqrt{n}|f-1|}{V\sqrt{f^2+1}} \tag{22}$$

A useful set of curves as a function of n and a common coefficient of variation $V = 1$ can be constructed by noting that for two coefficients of variation V_1 and V_2, the sample sizes $n(V_1)$ and $n(V_2)$, as functions of V_1 and V_2, are related by

$$\frac{n(V_1)}{n(V_2)} = \frac{\sigma_1^2}{\sigma_2^2}$$

for the same power and Type I error. See van Belle and Martin [1993] and van Belle [2001].

PROBLEMS

17.1 **(a)** Verify that the odds ratio and relative risk are virtually equivalent for

$$P[\text{exposure}] = 0.10, \qquad P[\text{disease}] = 0.01$$

in the following two situations:

$$\pi_{11} = P[\text{exposed and disease}] = 0.005$$

and $$\pi_{11} = 0.0025.$$

(b) Using equation (2), calculate the number of disease occurrences in the exposed and unexposed groups that would have to be observed to detect the relative risks calculated above with $\alpha = 0.05$ (one-tailed) and $\beta = 0.10$.

(c) How many exposed persons would have to be observed (and hence, unexposed persons as well)?

(d) Calculate the sample size needed if this test is one of K tests for $K = 10, 100,$ and 1000.

(e) In part (d), plot the logarithm of the sample size as a function of $\log K$. What kind of relationship is suggested? Can you state a general rule?

17.2 (After N. E. Breslow) Workers at all nuclear reactor facilities will be observed for a period of 10 years to determine whether they are at excess risk for leukemia. The rate in the general population is 7.5 cases per 100,000 person-years of observation. We want to be 80% sure that a doubled risk will be detected at the 0.05 level of significance.

(a) Calculate the number of leukemia cases that must be detected among the nuclear plant workers.

(b) How many workers must be observed? That is, assuming the null hypothesis holds, how many workers must be observed to accrue 9.1 leukemia cases?

(c) Consider this as a binomial sampling problem. Let $\pi_1 = 9.1/$answer in part (b), and let $\pi_2 = 2\pi_1$. Now use equation (17) to calculate $n/2$ as the required sample size. How close is your answer to part (b)?

17.3 (After N. E. Breslow) The rate of lung cancer for men of working age in a certain population is known to be on the order of 60 cases per 100,000 person-years of observation. A cohort study using equal numbers of exposed and unexposed persons is desired so that an increased risk of $R = 1.5$ can be detected with power $1 - \beta = 0.95$ and $\alpha = 0.01$.

(a) How many cases will have to be observed in the unexposed population? The exposed population?

(b) How many person-years of observation at the normal rates will be required for either of the two groups?

(c) How many workers will be needed assuming a 20-year follow-up?

17.4 (After N. E. Breslow) A case–control study is to be designed to detect an odds ratio of 3 for bladder cancer associated with a certain medication that is used by about one person out of 50 in the general population.

(a) For $\alpha = 0.05$, and $\beta = 0.05$, calculate the number of cases and number of controls needed to detect the increased odds ratio.

(b) Use the Poisson approximation procedure to calculate the sample sizes required.

(c) Four controls can be provided for each case. Use equations (19) and (20) to calculate the sample sizes. Compare this result with the total sample size in part (a).

17.5 The sudden infant death syndrome (SIDS) occurs at a rate of approximately three cases per 1000 live births. It is thought that smoking is a risk factor for SIDS, and a case–control study is initiated to check this assumption. Since the major effort was in the selection and recruitment of cases and controls, a questionnaire was developed that contained 99 additional questions.

(a) Calculate the sample size needed for a case–control study using $\alpha = 0.05$, in which we want to be 95% certain of picking up an increased relative risk of 2 associated with smoking. Assume that an equal number of cases and controls are selected.

(b) Considering smoking just one of the 100 risk factors considered, what sample sizes will be needed to maintain an $\alpha = 0.05$ per experiment error rate?

(c) Given the increased value of Z in part (b), suppose that the sample size is not changed. What is the effect on the power? What is the power now?

(d) Suppose in part (c) that the power also remains fixed at 0.95. What is the minimum relative risk that can be detected?

(e) Since smoking was the risk factor that precipitated the study, can an argument be made for not testing it at a reduced α level? Formulate your answer carefully.

***17.6** Derive the square root rule starting with equations (4) and (5).

***17.7** Derive formula (16) from equation (14).

17.8 It has been shown that coronary bypass surgery does not prolong life in selected patients with relatively mild angina (but may relieve the pain). A surgeon has invented a new

bypass procedure that, she claims, will prolong life substantially. A trial is planned with patients randomized to surgical treatment or standard medical therapy. Currently, the five-year survival probability of patients with relatively mild symptoms is 80%. The surgeon claims that the new technique will increase survival to 90%.

(a) Calculate the sample size needed to be 95% certain that this difference will be detected using an $\alpha = 0.05$ significance level.

(b) Suppose that the cost of a coronary bypass operation is approximately \$50,000; the cost of general medical care is about \$10,000. What is the most economical experiment under the conditions specified in part (a)? What are the total costs of the two studies?

(c) The picture is more complicated than described in part (b). Suppose that about 25% of the patients receiving the medical treatment will go on to have a coronary bypass operation in the next five years. Recalculate the sample sizes under the conditions specified in part (a).

***17.9** Derive the sample sizes in Table 17.4 for $D = 0.5$, $p = 0.8$, $\alpha = 0.5$, and $k = 20, 100, 300$.

***17.10** Consider the situation in Example 17.4.

(a) Calculate the sample size as a function of m, the number of variables, by considering $m = 10$ and $m = 20$.

(b) What is the relationship of sample size to variables?

17.11 Two groups of rats, one young and the other old, are to be compared with respect to levels of nerve growth factor (NGF) in the cerebrospinal fluid. It is estimated that the variability in NGF from animal to animal is on the order of 60%. We want to look at a twofold ratio in means between the two groups.

(a) Using the formula in Note 17.4, calculate the sample size per group using a two-sided alternative, $\alpha = 0.05$, and a power of 0.80.

(b) Suppose that the ratio of the means is really 1.6. What is the power of detecting this difference with the sample sizes calculated in part (a)?

REFERENCES

Beyer, W. H. (ed.) [1968]. *CRC Handbook of Tables for Probability and Statistics*, 2nd ed. CRC Press, Cleveland, OH.

Brittain, E., and Schlesselman, J. J. [1982]. Optimal allocation for the comparison of proportions. *Biometrics*, **38**: 1003–1009.

Casagrande, J. T., Pike, M. C., and Smith, P. C. [1978]. An improved approximate formula for calculating sample sizes for comparing two binomial distributions. *Biometrics*, **34**: 483–486.

Cochran, W. G. [1977]. *Sampling Techniques*, 3rd ed. Wiley, New York.

Cohen, J. [1988]. *Statistical Power Analysis for the Behavioral Sciences*, 2nd ed. Lawrence Erlbaum Associates, Hillsdale, NJ.

Fleiss, J. L., Levin, B., and Park, M. C. [2003]. *Statistical Methods for Rates and Proportions*, 3rd ed. Wiley, New York.

Fleiss, J. L., Tytun, A., and Ury, H. K. [1980]. A simple approximation for calculating sample sizes for comparing independent proportions. *Biometrics*, **36**: 343–346.

Gail, M., Williams, R., Byar, D. P., and Brown, C. [1976]. How many controls. *Journal of Chronic Diseases*, **29**: 723–731.

Haseman, J. K. [1978]. Exact sample sizes for the use with the Fisher–Irwin test for 2×2 tables. *Biometrics*, **34**: 106–109.

Lachin, J. M. [1977]. Sample size determinations for $r \times c$ comparative trials. *Biometrics*, **33**: 315–324.

Lachin, J. M. [1981]. Introduction to sample size determination and power analysis for clinical trials. *Controlled Clinical Trials*, **2**: 93–113.

Lachin, J. M. [2000]. *Biostatistical Methods*. Wiley, New York.

Lubin, J. H. [1980]. Some efficiency comments on group size in study design. *American Journal of Epidemiology*, **111**: 453–457.

Mantel, H. [1983]. Extended use of binomial sample-size tables. *Biometrics*, **39**: 777–779.

Nam, J. M. [1973]. Optimum sample sizes for the comparison of a control and treatment. *Biometrics*, **29**: 101–108.

Newman, S. C. [2001]. *Biostatistical Methods in Epidemiology*. Wiley, New York.

Pike, M. C., and Casagrande, J. T. [1979]. Cost considerations and sample size requirements in cohort and case-control studies. *American Journal of Epidemiology*, **110**: 100–102.

Schlesselman, J. J. [1982]. *Case–Control Studies: Design, Conduct, Analysis*. Oxford University Press, New York.

Schuster, J. J. [1993]. *Practical Handbook of Sample Size Guidelines for Clinical Trials*. CRC Press, Boca Raton, FL.

Ury, H. K., and Fleiss, J. R. [1980]. On approximate sample sizes for comparing two independent proportions with the use of Yates' correction. *Biometrics*, **36**: 347–351.

van Belle, G. [2001]. *Statistical Rules of Thumb*. Wiley, New York.

van Belle, G., and Martin, D. C. [1993]. Sample size as a function of coefficient of variation and ratio of means. *American Statistician*, **47**: 165–167.

Walter, S. D. [1977]. Determination of significant relative risks and optimal sampling procedures in prospective and retrospective comparative studies of various sizes. *American Journal of Epidemiology*, **105**: 387–397.

CHAPTER 18

Longitudinal Data Analysis

18.1 INTRODUCTION

One of the most common medical research designs is a "pre–post" study in which a single baseline health status measurement is obtained, an intervention is administered, and a single follow-up measurement is collected. In this experimental design, the *change* in the outcome measurement can be associated with the *change* in the exposure condition. For example, if some subjects are given placebo while others are given an active drug, the two groups can be compared to see if the change in the outcome is different for those subjects who are actively treated as compared to control subjects. This design can be viewed as the simplest form of a prospective longitudinal study.

Definition 18.1. A *longitudinal study* refers to an investigation where participant outcomes and possibly treatments or exposures are collected at multiple follow-up times.

A longitudinal study generally yields multiple or "repeated" measurements on each subject. For example, HIV patients may be followed over time and monthly measures such as CD4 counts or viral load are collected to characterize immune status and disease burden, respectively. Such repeated-measures data are correlated within subjects and thus require special statistical techniques for valid analysis and inference.

A second important outcome that is commonly measured in a longitudinal study is the time until a key clinical event such as disease recurrence or death. Analysis of event-time endpoints is the focus of *survival analysis*, which is covered in Chapter 16.

Longitudinal studies play a key role in epidemiology, clinical research, and therapeutic evaluation. Longitudinal studies are used to characterize normal growth and aging, to assess the effect of risk factors on human health, and to evaluate the effectiveness of treatments.

Longitudinal studies involve a great deal of effort but offer several benefits, which include:

1. *Incident events recorded.* A prospective longitudinal study measures the new occurrence of disease. The timing of disease onset can be correlated with recent changes in patient exposure and/or with chronic exposure.

2. *Prospective ascertainment of exposure*. In a prospective study, participants can have their exposure status recorded at multiple follow-up visits. This can alleviate recall bias where subjects who subsequently experience disease are more likely to recall their exposure (a form of measurement error). In addition, the temporal order of exposures and outcomes is observed.

Biostatistics: A Methodology for the Health Sciences, Second Edition, by Gerald van Belle, Lloyd D. Fisher, Patrick J. Heagerty, and Thomas S. Lumley
ISBN 0-471-03185-2

3. *Measurement of individual change in outcomes*. A key strength of a longitudinal study is the ability to measure change in outcomes and/or exposure at the individual level. Longitudinal studies provide the opportunity to observe individual patterns of change.

4. *Separation of time effects: cohort, period, age*. When studying change over time, there are many time scales to consider. The *cohort scale* is the time of birth, such as 1945 or 1963; *period* is the current time, such as 2003; and *age* is (period − cohort), for example, $58 = 2003 - 1945$, and $40 = 2003 - 1963$. A longitudinal study with measurements at times $t_1, t_2, \ldots, t_n$ can simultaneously characterize multiple time scales such as age and cohort effects using covariates derived from the calendar time of visit and the participant's birth year: the age of subject i at time t_j is $\text{age}_{ij} = t_j - \text{birth}_i$; and their cohort is simply $\text{cohort}_{ij} = \text{birth}_i$. Lebowitz [1996] discusses age, period, and cohort effects in the analysis of pulmonary function data.

5. *Control for cohort effects*. In a cross-sectional study the comparison of subgroups of different ages combines the effects of aging and the effects of different cohorts. That is, comparison of outcomes measured in 2003 among 58-year-old subjects and among 40-year-old subjects reflects both the fact that the groups differ by 18 years (aging) and the fact that the subjects were born in different eras. For example, the public health interventions, such as vaccinations available for a child under 10 years of age, may differ in 1945–1955 compared to the preventive interventions experienced in 1963–1973. In a longitudinal study, the cohort under study is fixed, and thus changes in time are not confounded by cohort differences.

An overview of longitudinal data analysis opportunities in respiratory epidemiology is presented in Weiss and Ware [1996].

The benefits of a longitudinal design are not without cost. There are several challenges posed:

1. *Participant follow-up*. There is the risk of bias due to incomplete follow-up, or dropout of study participants. If subjects who are followed to the planned end of a study differ from subjects who discontinue follow-up, a naive analysis may provide summaries that are not representative of the original target population.

2. *Analysis of correlated data*. Statistical analysis of longitudinal data requires methods that can properly account for the intrasubject correlation of response measurements. If such correlation is ignored, inferences such as statistical tests or confidence intervals can be grossly invalid.

3. *Time-varying covariates*. Although longitudinal designs offer the opportunity to associate changes in exposure with changes in the outcome of interest, the direction of causality can be complicated by "feedback" between the outcome and the exposure. For example, in an observational study of the effects of a drug on specific indicators of health, a patient's current health status may influence the drug exposure or dosage received in the future. Although scientific interest lies in the effect of medication on health, this example has reciprocal influence between exposure and outcome and poses analytical difficulty when trying to separate the effect of medication on health from the effect of health on drug exposure.

18.1.1 Example studies

In this section we give some examples of longitudinal studies and focus on the primary scientific motivation in addition to key outcome and covariate measurements.

Child Asthma Management Program

In the Child Asthma Management Program (CAMP) study, children are randomized to different asthma management regimes. CAMP is a multicenter clinical trial whose primary aim is evaluation of the long-term effects of daily inhaled anti-inflammatory medication use on asthma status and lung growth in children with mild to moderate asthma [The Childhood Asthma Management

Program Research group, 2000]. Outcomes include continuous measures of pulmonary function and categorical indicators of asthma symptoms. Secondary analyses have investigated the association between daily measures of ambient pollution and the prevalence of symptoms. Analysis of an environmental exposure requires specification of a lag between the day of exposure and the resulting effect. In the air pollution literature, short lags of 0 to 2 days are commonly used [Samet et al., 2000; Yu et al., 2000]. For both the evaluation of treatment and exposure to environmental pollution, the scientific questions focus on the association between an exposure (treatment, pollution) and health measures. The within-subject correlation of outcomes is of secondary interest, but must be acknowledged to obtain valid statistical inference.

Cystic Fibrosis Foundation Registry

The Cystic Fibrosis Foundation maintains a registry of longitudinal data for subjects with cystic fibrosis. Pulmonary function measures, such as the 1-second forced expiratory volume (FEV1), and patient health indicators, such as infection with *Pseudomonas aeruginosa*, have been recorded annually since 1966. One scientific objective is to characterize the natural course of the disease and to estimate the average rate of decline in pulmonary function. Risk factor analysis seeks to determine whether measured patient characteristics such as gender and genotype correlate with disease progression or with an increased rate of decline in FEV1. The registry data represent a typical observational design where the longitudinal nature of the data are important for determining individual patterns of change in health outcomes such as lung function.

Multicenter AIDS Cohort Study

The Multicenter AIDS Cohort Study (MACS) enrolled more than 3000 men who were at risk for acquisition of HIV1 [Kaslow et al., 1987]. This prospective cohort study observed $N = 479$ incident HIV1 infections and has been used to characterize the biological changes associated with disease onset. In particular, this study has demonstrated the effect of HIV1 infection on indicators of immunologic function such as CD4 cell counts. One scientific question is whether baseline characteristics such as viral load measured immediately after seroconversion are associated with a poor patient prognosis as indicated by a greater rate of decline in CD4 cell counts. We use these data to illustrate analysis approaches for continuous longitudinal response data.

HIVNET Informed Consent Substudy

Numerous reports suggest that the process of obtaining informed consent in order to participate in research studies is often inadequate. Therefore, for preventive HIV vaccine trials a prototype informed consent process was evaluated among $N = 4892$ subjects participating in the Vaccine Preparedness Study (VPS). Approximately 20% of subjects were selected at random and asked to participate in a mock informed consent process [Coletti et al., 2003]. Participant knowledge of key vaccine trial concepts was evaluated at baseline prior to the informed consent visit, which occurred during a special three-month follow-up visit for the intervention subjects. Vaccine trial knowledge was then assessed for all participants at the scheduled six-, 12-, and 18-month visits. This study design is a basic longitudinal extension of a pre–post design. The primary outcomes include individual knowledge items and a total score that calculates the number of correct responses minus the number of incorrect responses. We use data on a subset of men and women VPS participants. We focus on subjects who were considered at high risk of HIV acquisition, due to injection drug use.

18.1.2 Notation

In this chapter we use Y_{ij} to denote the outcome measured on subject i at time t_{ij}. The index $i = 1, 2, \ldots, N$ is for subject, and the index $j = 1, 2, \ldots, n$ is for observations within a subject. In a designed longitudinal study the measurement times will follow a protocol with

a common set of follow-up times, $t_{ij} = t_j$. For example, in the HIVNET Informed Consent Study, subjects were measured at baseline, $t_1 = 0$, at six months after enrollment, $t_2 =$ six months, and at 12 and 18 months, $t_3 = 12$ months, $t_4 = 18$ months. We let X_{ij} denote covariates associated with observation Y_{ij}. Common covariates in a longitudinal study include the time, t_{ij}, and person-level characteristics such as treatment assignment or demographic characteristics.

Although scientific interest often focuses on the mean response as a function of covariates such as treatment and time, proper statistical inference must account for the within-person correlation of observations. Define $\rho_{jk} = \text{corr}(Y_{ij}, Y_{ik})$, the within-subject correlation between observations at times t_j and t_k. In the following section we discuss methods for exploring the structure of within-subject correlation, and in Section 18.5 we discuss estimation methods that model correlation patterns.

18.2 EXPLORATORY DATA ANALYSIS

Exploratory analysis of longitudinal data seeks to discover patterns of systematic variation across groups of patients, as well as aspects of random variation that distinguish individual patients.

18.2.1 Group Means over Time

When scientific interest is in the average response over time, summary statistics such as means and standard deviations can reveal whether different groups are changing in a similar or different fashion.

Example 18.1. Figure 18.1 shows the mean knowledge score for the informed consent subgroups in the HIVNET Informed Consent Substudy. At baseline the intervention and control groups have very similar mean scores. This is expected since the group assignment is determined by randomization that occurs after enrollment. At an interim three-month visit the intervention subjects are given a mock informed consent for participation in a hypothetical phase III vaccine efficacy trial. The impact of the intervention can be seen by the mean scores at the six-month visit. In the control group the mean at six months is 1.49(SE = 0.11), up slightly from the baseline mean of 1.16(SE = 0.11). In contrast, the intervention group has a six-month mean score of 3.43(SE = 0.24), a large increase from the baseline mean of 1.09(SE = 0.24). The intervention and control groups are significantly different at six months based on a two-sample t-test. At later follow-up times, further change is observed. The control group has a mean that increases to 1.98 at the 12-month visit and to 2.47 at the 18-month visit. The intervention group fluctuates slightly with means of 3.25(SE = 0.27) at month 12 and 3.76(SE = 0.25) at 18 months. These summaries suggest that the intervention has a significant effect on knowledge, and that a small improvement is seen over time in the control group.

Example 18.2. In the MACS study we compare different groups of subjects formed on the basis of their initial viral load measurement. Low viral load is defined by a baseline value less than 15×10^3, medium as 15×10^3 to 46×10^3, and high viral load is classified for subjects with a baseline measurement greater than 46×10^3. Table 18.1 gives the average CD4 count for each year of follow-up. The mean CD4 declines over time for each of the viral load groups. The subjects with the lowest baseline viral load have a mean of 744.8 for the first year after seroconversion and then decline to a mean count of 604.8 during the fourth year. The $744.8 - 604.8 = 140.0$-unit reduction is smaller than the decline observed for the medium-viral-load group, $638.9 - 470.0 = 168.9$, and the high-viral-load group, $600.3 - 353.9 = 246.4$. Therefore, these summaries suggest that higher baseline viral-load measurements are associated with greater subsequent reduction in mean CD4 counts.

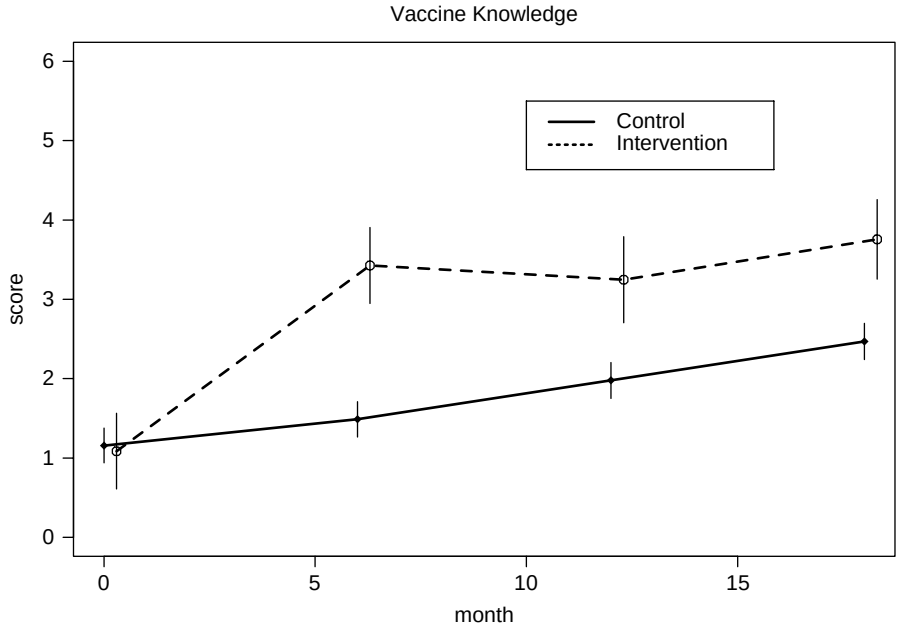


Figure 18.1 Mean knowledge scores over time by treatment group, HIVNET informed consent substudy.

Table 18.1 Mean CD4 Count and Standard Error over Time[a]

	Baseline Viral Load					
	Low		Medium		High	
Year	Mean	SE	Mean	SE	Mean	SE
0–1	744.8	35.8	638.9	27.3	600.3	30.4
1–2	721.2	36.4	588.1	25.7	511.8	22.5
2–3	645.5	37.7	512.8	28.5	474.6	34.2
3–4	604.8	46.8	470.0	28.7	353.9	28.1

[a]Separate summaries are given for groups defined by baseline viral load level.

Example 18.1. (*continued*) In the HIVNET informed consent substudy we saw a substantial improvement in the knowledge score. It is also relevant to consider key individual items that comprise the total score, such as the "safety item" or "nurse item." Regarding safety, participants were asked whether it was true or false that "Once a large-scale HIV vaccine study begins, we can be sure the vaccine is completely safe." Table 18.2 shows the number of responding subjects at each visit and the percent of subjects who correctly answered that the safety statement is false. These data show that the control and intervention groups have a comparable understanding of the safety item at baseline with 40.9% answering correctly among controls, and 39.2% answering correctly among the intervention subjects. A mock informed consent was administered at a three-month visit for the intervention subjects only. The impact of the intervention appears modest, with only 50.3% of intervention subjects correctly responding at six months. This represents a 10.9% increase in the proportion answering correctly, but a two-sample comparison of intervention and control proportions at six months (e.g., 50.3% vs. 42.7%) is not significant

Table 18.2 Number of Subjects and Percent Answering Correctly for the Safety Item from the HIVNET Informed Consent Substudy

	Control Group		Intervention Group	
Visit	*N*	% Correct	*N*	% Correct
Baseline	946	40.9	176	39.2
six-month	838	42.7	171	50.3
12-month	809	41.5	163	43.6
18-month	782	43.5	153	43.1

Table 18.3 Number of Subjects and Percent Answering Correctly for the Nurse Item from the HIVNET Informed Consent Substudy

	Control Group		Intervention Group	
Visit	*n*	% Correct	*n*	% Correct
Baseline	945	54.1	176	50.3
six-month	838	44.7	171	72.1
12-month	808	46.3	163	60.1
18-month	782	48.2	153	66.0

statistically. Finally, the modest intervention impact does not appear to be retained, as the fraction correctly answering this item declines to 43.6% at 12 months and 43.1% at 18 months. Therefore, these data suggest a small but fleeting improvement in participant understanding that a vaccine studied in a phase III trial cannot be guaranteed to be safe.

Other items show different longitudinal trends. Subjects were also asked whether it was true or false that "The study nurse will decide who gets the real vaccine and who gets the placebo." Table 18.3 shows that the groups are again comparable at baseline, but for the nurse item we see a large increase in the fraction answering correctly among intervention subjects at six months with 72.1% answering correctly that the statement is false. A cross-sectional analysis indicates a statistically significant difference in the proportion answering correctly at six months with a confidence interval for the difference in proportions of $(0.199, 0.349)$. Although the magnitude of the separation between groups decreases from 27.4% at six months to 17.8% at 18 months, the confidence interval for the difference in proportions at 18 months is $(0.096, 0.260)$ and excludes the null comparison, $p_1 - p_0 = 0$. Therefore, these data suggest that the intervention has a substantial and lasting impact on understanding that research nurses do not determine allocation to real vaccine or placebo.

18.2.2 Variation among Subjects

With independent observations we can summarize the uncertainty or variability in a response measurement using a single variance parameter. One interpretation of the variance is given as one-half the expected squared distance between any two randomly selected measurements, $\sigma^2 = \frac{1}{2}E[(Y_i - Y_j)^2]$. However, with longitudinal data the "distance" between measurements on different subjects is usually expected to be greater than the distance between repeated measurements taken on the same subject. Thus, although the total variance may be obtained with outcomes from subjects i and i' observed at time t_j, $\sigma^2 = \frac{1}{2}E[(Y_{ij} - Y_{i'j})^2]$ [assuming that $E(Y_{ij}) = E(Y_{i'j}) = \mu$], the expected variation for two measurements taken on the same person

(subject i) but at times t_j and t_k may not equal the total variation σ^2 since the measurements are correlated: $\sigma^2(1-\rho_{jk}) = \frac{1}{2}E[(Y_{ij}-Y_{ik})^2]$ [assuming that $E(Y_{ij}) = E(Y_{ik}) = \mu$]. When $\rho_{jk} > 0$, this shows that *between-subject variation* is greater than *within-subject variation*. In the extreme, $\rho_{jk} = 1$ and $Y_{ij} = Y_{ik}$, implying no variation for repeated observations taken on the same subject.

Graphical methods can be used to explore the magnitude of person-to-person variability in outcomes over time. One approach is to create a panel of individual line plots for each study participant. These plots can then be inspected for both the amount of variation from subject to subject in the overall "level" of the response and the magnitude of variation in the "trend" over time in the response. Such exploratory data analysis can be useful for determining the types of correlated data regression models that would be appropriate. In Section 18.5 we discuss random effects regression models for longitudinal data. In addition to plotting individual series, it is also useful to plot multiple series on a single plot, stratifying on the value of key covariates. Such a plot allows determination of whether the type and magnitude of intersubject variation appears to differ across the covariate subgroups.

Example 18.2. (*continued*) In Figure 18.2 we plot an array of individual series from the MACS data. In each panel the observed CD4 count for a single subject is plotted against the times that measurements were obtained. Such plots allow inspection of the individual response patterns and whether there is strong heterogeneity in the trajectories. Figure 18.2 shows that there can be large variation in the "level" of CD4 for subjects. Subject ID = 1120 in the upper right corner has CD4 counts greater than 1000 for all times, while ID = 1235 in the lower left corner has all measurements below 500. In addition, individuals plots can be evaluated for the change over time. Figure 18.2 indicates that most subjects are either relatively stable in their measurements over time, or tend to be decreasing.

In the common situation where we are interested in correlating the outcome to measured factors such as treatment group or exposure, it will also be useful to plot individual series stratified by covariate group. Figure 18.3 takes a sample of the MACS data and plots lines for each subject stratified by the level of baseline viral load. This figure suggests that the highest viral load group has the lowest mean CD4 count and suggests that variation among measurements may also be lower for the high baseline viral-load group compared to the medium- and low-viral-load groups. Figure 18.3 can also be used to identify those who exhibit time trends that differ markedly from the profiles of others. In the high-viral-load group there is a person who appears to improve dramatically over time, and there is a single unusual measurement where the CD4 count exceeds 2000. Plotting individual series is a useful exploratory prelude to more careful confirmatory statistical analysis.

18.2.3 Characterizing Correlation and Covariance

With correlated outcomes it is useful to understand the strength of correlation and the pattern of correlations across time. Characterizing correlation is useful for understanding components of variation and for identifying a variance or correlation model for regression methods such as mixed-effects models or *generalized estimating equations* (GEEs), discussed in Section 18.5.2. One summary that is used is an estimate of the *covariance matrix*, which is defined as

$$\begin{bmatrix} E[(Y_{i1}-\mu_{i1})^2] & E[(Y_{i1}-\mu_{i1})(Y_{i2}-\mu_{i2})] & \cdots & E[(Y_{i1}-\mu_{i1})(Y_{in}-\mu_{in})] \\ E[(Y_{i2}-\mu_{i2})(Y_{i1}-\mu_{i1})] & E[(Y_{i2}-\mu_{i2})^2] & \cdots & E[(Y_{i2}-\mu_{i2})(Y_{in}-\mu_{in})] \\ \vdots & & \ddots & \cdots \\ E[(Y_{in}-\mu_{in})(Y_{i1}-\mu_{i1})] & E[(Y_{in}-\mu_{in})(Y_{i2}-\mu_{i2})] & \cdots & E[(Y_{in}-\mu_{in})^2] \end{bmatrix}$$

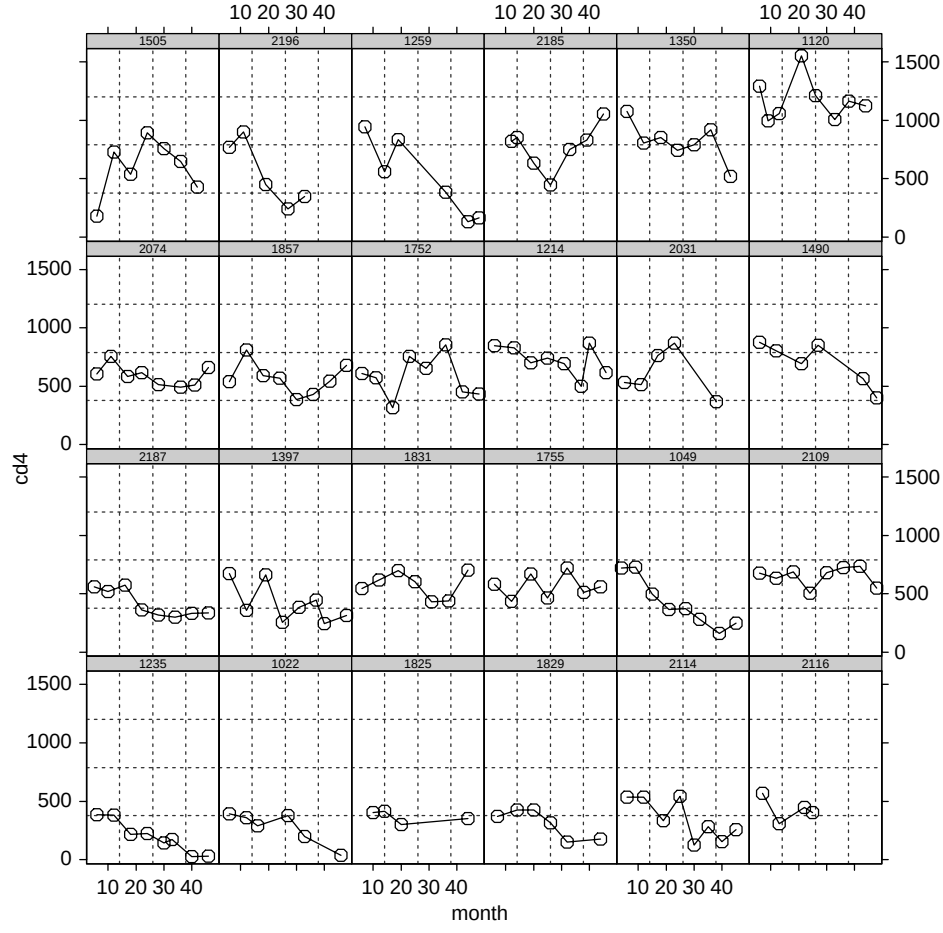


Figure 18.2 A sample of individual CD4 trajectories from the MACS data.

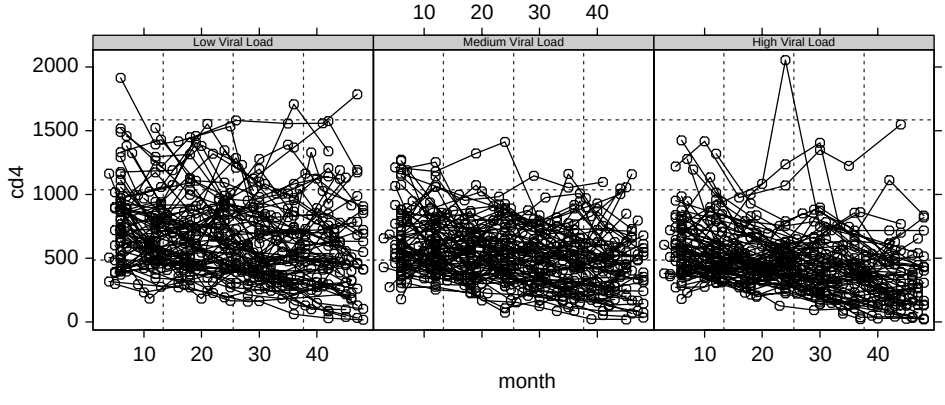


Figure 18.3 Individual CD4 trajectories from the MACS data by tertile of viral load.

The covariance can also be written in terms of the variances σ_j^2 and the correlations ρ_{jk}:

$$\text{cov}(Y_i) = \begin{bmatrix} \sigma_1^2 & \sigma_1\sigma_2\rho_{12} & \cdots & \sigma_1\sigma_n\rho_{1n} \\ \sigma_2\sigma_1\rho_{21} & \sigma_2^2 & \cdots & \sigma_2\sigma_n\rho_{2n} \\ \vdots & & \ddots & \vdots \\ \sigma_n\sigma_1\rho_{n1} & \sigma_n\sigma_2\rho_{n2} & \cdots & \sigma_n^2 \end{bmatrix}$$

Finally, the *correlation matrix* is given as

$$\text{corr}(Y_i) = \begin{bmatrix} 1 & \rho_{12} & \cdots & \rho_{1n} \\ \rho_{21} & 1 & \ldots & \rho_{2n} \\ \vdots & & \ddots & \vdots \\ \rho_{n1} & \rho_{2n} & \ldots & 1 \end{bmatrix}$$

which is useful for comparing the strength of association between pairs of outcomes, particularly when the variances σ_j^2 are not constant. Sample estimates of the correlations can be obtained using

$$\widehat{\rho}_{jk} = \frac{1}{N-1} \sum_i \frac{(Y_{ij} - \overline{Y}_{\cdot j})}{\widehat{\sigma}_j} \frac{(Y_{ik} - \overline{Y}_{\cdot k})}{\widehat{\sigma}_k}$$

where $\widehat{\sigma}_j^2$ and $\widehat{\sigma}_k^2$ are the sample variances of Y_{ij} and Y_{ik}, respectively (i.e., across subjects for times t_j and t_k).

Graphically, the correlation can be viewed using plots of Y_{ij} vs. Y_{ik} for all possible pairs of times t_j and t_k. These plots can be arranged in an array that corresponds to the covariance matrix and patterns of association across rows or columns can reveal changes in the correlation as a function of increasing time separation between measurements.

Example 18.1. (*continued*) For the HIVNET informed consent data, we focus on correlation analysis of outcomes from the control group. Parallel summaries would usefully characterize the similarity or difference in correlation structures for the control and intervention groups. The correlation matrix is estimated as follows:

	Month 0	**Month 6**	**Month 12**	**Month 18**
Month 0	1.00	0.471	0.394	0.313
Month 6	0.471	1.00	0.444	0.407
Month 12	0.394	0.444	1.00	0.508
Month 18	0.313	0.407	0.508	1.00

The matrix suggests that the correlation in outcomes from the same person is slightly decreasing as the time between the measurements increases. For example, the correlation between knowledge scores from baseline and month 6 is 0.471, while the correlation between baseline and month 12 decreases to 0.394, and decreases further to 0.313 for baseline and month 18. Correlation that decreases as a function of time separation is common among biomedical measurements and often reflects slowly varying underlying processes.

Example 18.2. (*continued*) For the MACS data the timing of measurement is only approximately regular. The following displays both the correlation matrix and the covariance matrix:

	Year 1	Year 2	Year 3	Year 4
Year 1	92,280.4	[0.734]	[0.585]	[0.574]
Year 2	63,589.4	81,370.0	[0.733]	[0.695]
Year 3	48,798.2	57,457.5	75,454.5	[0.806]
Year 4	55,501.2	63,149.9	70,510.1	101,418.2

The correlations are shown in brackets above. The variances are shown on a diagonal below the correlations. For example, the standard deviation among year 1 CD4 counts is $\sqrt{92{,}280.4} = 303.8$, while the standard deviations for years 2 through 4 are $\sqrt{81{,}370.0} = 285.3$, $\sqrt{75{,}454.5} = 274.7$, and $\sqrt{101{,}418.2} = 318.5$, respectively. Below the diagonal are the covariances, which together with the standard deviations determine the correlations. These data have a correlation for measurements that are one year apart of 0.734, 0.733, and 0.806. For measurements two years apart, the correlation decreases slightly to 0.585 and 0.695. Finally, measurements that are three years apart have a correlation of 0.574. Thus, the CD4 counts have a within-person correlation that is high for observations close together in time, but the correlation tends to decrease with increasing time separation between the measurement times.

An alternative method for exploring the correlation structure is through an array of scatter plots showing CD4 measured at year j versus CD4 measured at year k. Figure 18.4 displays these scatter plots. It appears that the correlation in the plot of year 1 vs. year 2 is stronger than for year 1 vs. year 3, or for year 1 vs. year 4. The sample correlations $\widehat{\rho}_{12} = 0.734$, $\widehat{\rho}_{13} = 0.585$, and $\widehat{\rho}_{14} = 0.574$ summarize the linear association presented in these plots.

18.3 DERIVED VARIABLE ANALYSIS

Formal statistical inference with longitudinal data requires either that a univariate summary be created for each subject or that methods for correlated data are used. In this section we review and critique common analytic approaches based on creation of summary measures.

A *derived variable analysis* is a method that takes a collection of measurements and collapses them into a single meaningful summary feature. In classical multivariate methods principal component analysis is one approach for creating a single major factor. With longitudinal data the most common summaries are the average response and the time slope. A second approach is a pre–post analysis which analyzes a single follow-up response in conjunction with a baseline measurement. In Section 18.3.1 we first review average or slope analyses, and then in Section 18.3.2 we discuss general approaches to pre–post analysis.

18.3.1 Average or Slope Analysis

In any longitudinal analysis the substantive aims determine which aspects of the response trajectory are most important. For some applications the repeated measures over time may be averaged, or if the timing of measurement is irregular, an area under the curve (AUC) summary can be the primary feature of interest. In these situations statistical analysis will focus on $\overline{Y}_i = 1/n \sum_{j=1}^{n} Y_{ij}$. A key motivation for computing an individual average and then focusing analysis on the derived averages is that standard methods can be used for inference such as a two-sample t-test. However, if there are any incomplete data, the advantage is lost since either subjects with partial data will need to be excluded, or alternative methods need to be invoked to handle the missingness. Attrition in longitudinal studies is unfortunately quite common, and thus derived variable methods are often more difficult to apply validly than they may first appear.

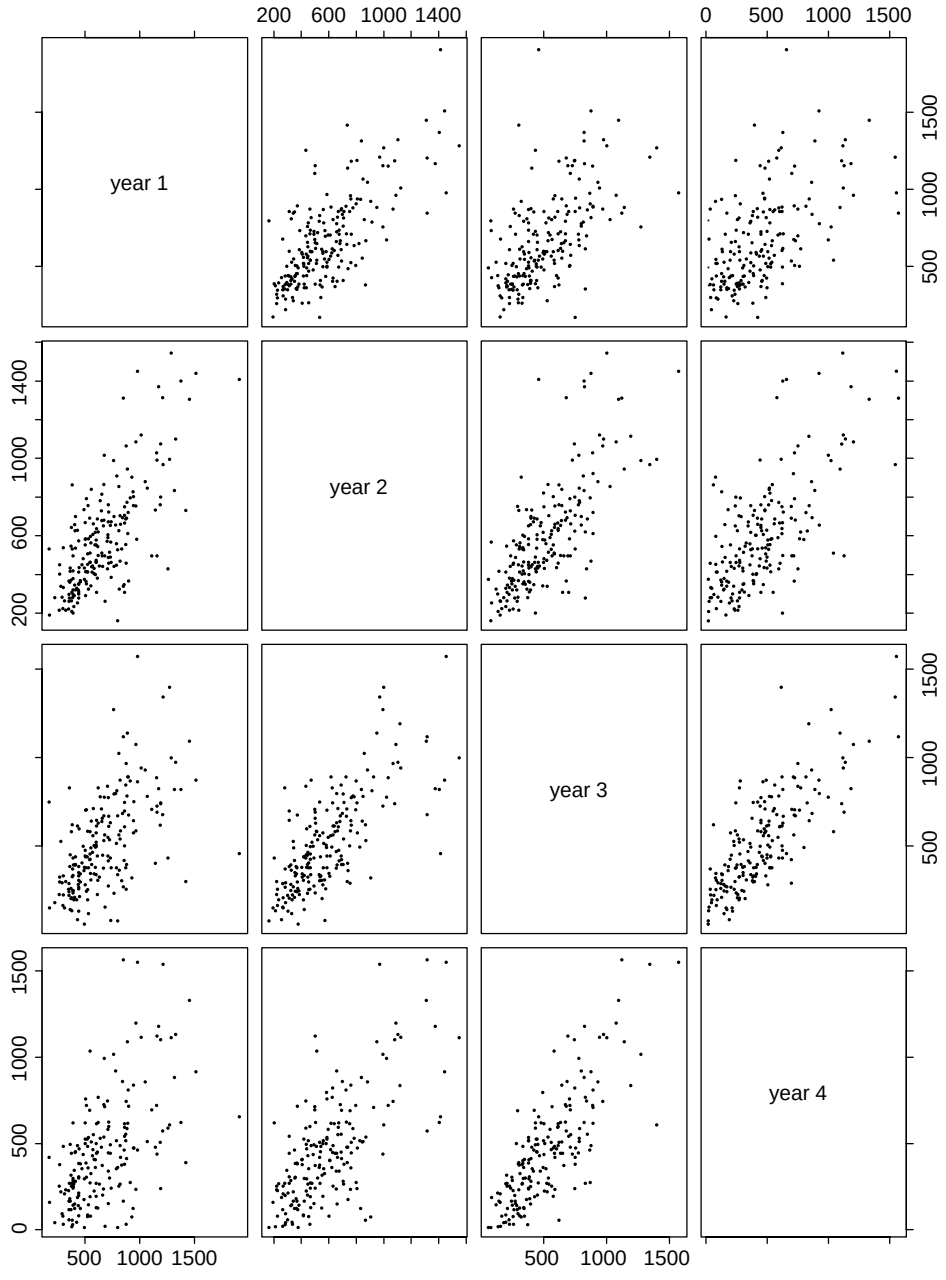


Figure 18.4 Scatter plots of CD4 measurements (counts/mL) taken at years 1 to 4 after seroconversion.

Example 18.1. (*continued*) In the HIVNET informed consent study, the goal is to improve participant knowledge. A derived variable analysis to evaluate evidence for an effect due to the mock informed consent process can be conducted using $\overline{Y}_i = (Y_{i1} + Y_{i2} + Y_{i3})/3$ for the post-baseline times $t_1 =$ six months, $t_2 = 12$ months, and $t_3 = 18$ months. The following table summarizes the data for subjects who have all three post-baseline measurements:

Group	Baseline *N*	Final *N*	Mean	SE	95% CI
Control	947	714	2.038	0.095	
Intervention	177	147	3.444	0.223	
Difference			1.406	0.243	[0.928, 1.885]

First, notice that only $714/947 = 75.4\%$ of control subjects, and $147/177 = 83.1\%$ of intervention subjects have complete data and are therefore included in the analysis. This highlights one major limitation to derived variable analysis: There may be selection bias due to exclusion of subjects with missing data. We discuss missing data issues in Section 18.6. Based on the data above, we would conclude that there is a statistically significant difference between the mean knowledge for the intervention and control groups with a two-sample t-test of $t = 5.796$, $p < 0.001$. Analysis of the single summary for each subject allows the repeated outcome variables to be analyzed using standard independent sample methods.

In other applications, scientific interest centers on the rate of change over time and therefore an individual's slope may be considered as the primary outcome. Typically, each subject in a longitudinal study has only a small number of outcomes collected at the discrete times specified in the protocol. For example, in the MACS data, each subject was to complete a study visit every 6 months and with complete data would have nine measurements between baseline and 48 months. If each subject has complete data, an individual summary statistic can be computed as the regression of outcomes Y_{ij} on times t_j: $Y_{ij} = \beta_{i,0} + \beta_{i,1} t_j + \epsilon_{ij}$; and $\widehat{\beta}_i$ is the ordinary least squares estimate based on data from subject i only. In the case where all subjects have the same collection of measurement times and have complete data, the variation in the estimated slope, $\widehat{\beta}_{i,1}$, will be equal across subjects provided that the variance of ϵ_{ij} is also constant across subjects. Therefore, if

1. The measurement times are common to all subjects: $t_1, t_2, \ldots, t_n$,
2. Each subject has a complete collection of measurements: $Y_{i1}, Y_{i2}, \ldots, Y_{in}$,
3. The within-subject variation $\sigma_i^2 = \text{var}(\epsilon_{ij})$ is constant across subjects: $\sigma_i^2 \equiv \sigma^2$,

then the summaries $\widehat{\beta}_{i,1}$ will have equal variances attributable to using simple linear regression to estimate individual slopes. If any of points 1 to 3 above do not hold, the variance of individual summaries may vary across subjects. This will be the case when each subject has a variable number of outcomes, due to missing data.

When points 1 to 3 are satisfied, simple inference on the derived outcomes $\widehat{\beta}_{i,1}$ can be performed using standard two-sample methods or regression methods. This allows inference regarding factors that are associated with the rate of change over time. If any of points 1 to 3 do not hold, mixed model regression methods (Section 18.5) may be preferable to simple derived variable methods. See Frison and Pocock [1992, 1997] for further discussion of derived variable methods.

Example 18.2. (*continued*) For the MACS data, we are interested in determining whether the rate of decline in CD4 is correlated with the baseline viral load measurement. In Section 18.2 we looked at descriptive statistics comparing the mean CD4 count over time for categories of viral load. We now explore the association between the rate of decline and baseline viral load by obtaining a summary statistic, using the individual time slope $\widehat{\beta}_i$ obtained from a regression of the CD4 count Y_{ij} on measurement time t_{ij}. Figure 18.5 shows a scatter plot of the individual slope estimates plotted against the log of baseline viral load. First notice that plotting symbols of different sizes are used to reflect the fact that the number of measurements per subject, n_i,

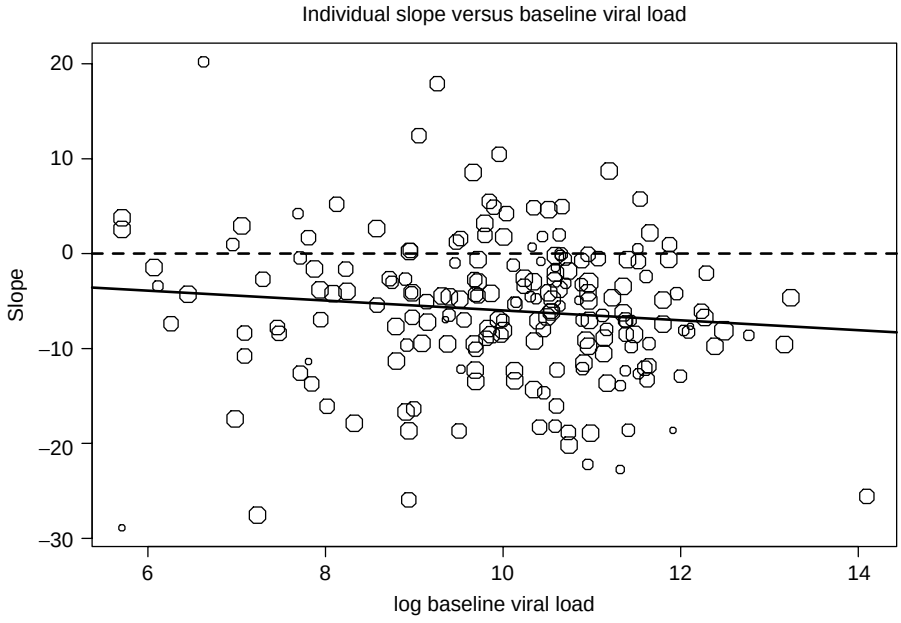


Figure 18.5 Individual CD4 slopes (count/month) vs. log of baseline viral load, MACS data.

is not constant. The plotting symbol size is proportional to n_i. For the MACS data we have the following distribution for the number of observations per subjects over the first four years:

	Number of Observations, n_i								
	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**
Number of subjects	5	13	8	10	25	44	82	117	3

For Figure 18.5 the $(5 + 13) = 18$ subjects with either one or two measurements were excluded as a summary slope is either unestimable ($n_i = 1$) or highly variable ($n_i = 2$). Figure 18.5 suggests that there is a pattern of decreasing slope with increasing log baseline viral load. However, there is also a great deal of subject-to-subject variation in the slopes, with some subjects having $\widehat{\beta}_{i,1} > 0$ count/month, indicating a stable or increasing trend, and some subjects having $\widehat{\beta}_{i,1} < 15$ count/month, suggesting a steep decline in their CD4. A linear regression using the individual slope as the response and log baseline viral load as the predictor yields a p-value of 0.124, implying a nonsignificant linear association between the summary statistic $\widehat{\beta}_{i,1}$ and log baseline viral load.

A categorical analysis using tertiles of baseline viral load parallels the descriptive statistics presented in Table 18.1. The average rate of decline in CD4 can be estimated as the mean of the individual slope estimates:

	***N* Subjects**	**Average Slope**	**SE**
Low viral load	66	−5.715	1.103
Medium viral load	69	−4.697	0.802
High viral load	65	−7.627	0.789

We find similar average rates of decline for the medium- and low-viral-load groups and find a greater rate of decline for the high-viral-load group. Using ANOVA, we obtain an F-statistic of 2.68 on 2 and 197 degrees of freedom, with a p-value of 0.071, indicating that we would not reject equality of average rates of decline using the nominal 5% significance level.

Note that neither simple linear regression nor ANOVA accounts for the fact that response variables $\widehat{\beta}_{i,1}$ may have unequal variance due to differing n_i. In addition, a small number of subjects were excluded from the analysis since a slope summary was unavailable. In Section 18.5 we discuss regression methods for correlated data that can efficiently use all of the available data to make inferences with longitudinal data.

18.3.2 Pre–Post Analysis

In this section we discuss analytic methods appropriate when a single baseline and a single follow-up measurement are available. We focus on the situation where interest is in the comparison of two groups: $X_i = 0$ denotes membership in a reference or control group; and $X_i = 1$ denotes membership in an exposure or intervention group. Assume for each subject i that we have a baseline measurement denoted as Y_{i0} and a follow-up measurement denoted as Y_{i1}. The following table summarizes three main analysis options using regression methods to characterize the two-group comparison:

Follow-up only:	$Y_{i1} = \beta_0 + \beta_1 X_i + \epsilon_i$
Change analysis:	$Y_{i1} - Y_{i0} = \beta_0^* + \beta_1^* X_i + \epsilon_i^*$
ANCOVA:	$Y_{i1} = \beta_0^{**} + \beta_1^{**} X_i + \beta_2^{**} Y_{i0} + \epsilon_i^{**}$

Since X_i is a binary response variable we can interpret the coefficients β_1, β_1^*, and β_1^{**} as differences in means comparing $X_i = 1$ to $X_i = 0$. Specifically, for the follow-up only analysis the coefficient β_1 represents the difference in the *mean response at follow-up* comparing $X_i = 1$ to $X_i = 0$. If the assignment to $X_i = 0/1$ was randomized, the simple follow-up comparison is a valid causal analysis of the effect of the treatment. For change analysis the coefficient β_1^* is interpreted as the difference between the *average change* for $X_i = 1$ as compared to the average change for $X_i = 0$. Finally, using ANCOVA estimates β_1^{**}, which represents the difference in the mean follow-up outcome comparing exposed ($X_i = 1$) to unexposed ($X_i = 0$) subjects who are *equal in their baseline response*. Equivalently, we interpret β_1^{**} as the comparison of treated versus control subjects after adjusting for baseline.

It is important to recognize that each of these regression models provides parameters with different interpretations. In situations where the selection of treatment or exposure is not randomized, the ANCOVA analysis can control for "confounding due to indication," or where the baseline value Y_{i0} is associated with a greater or lesser likelihood of receiving the treatment $X_i = 1$. When treatment is randomized, Frison and Pocock [1992] show that $\beta_1 = \beta_1^* = \beta_1^{**}$. This result implies that for a randomized exposure each approach can provide a valid estimate of the average causal effect of treatment. However, Frison and Pocock [1992] also show that the most *precise* estimate of β_1 is obtained using ANCOVA, and that final measurement analysis is more precise than the change analysis when the correlation between baseline and follow-up measurements is less than 0.50. This results from $\text{var}(Y_{i1} - Y_{i0}) = 2\sigma^2(1 - \rho)$, which is less than σ^2 only when $\rho > \frac{1}{2}$.

Example 18.1. (*continued*) To evaluate the effect of the HIVNET mock informed consent, we focus analysis on the baseline and six-month knowledge scores. The following tables give

inference for the follow-up, Y_{i1}:

Group	N	6-month Mean	SE	95% CI
Control	834	1.494	0.111	
Intervention	169	3.391	0.240	
Difference		1.900	0.264	[1.375, 2.418]

and for the change in knowledge score, $Y_{i1} - Y_{i0}$, for the 834/947 control subjects and 169/177 intervention subjects who have both baseline and six-month outcomes:

Group	N	Mean Change	SE	95% CI
Control	834	0.243	0.118	
Intervention	169	2.373	0.263	
Difference		2.130	0.288	[1.562, 2.697]

The correlation between baseline and month 6 knowledge score is 0.462 among controls and 0.411 among intervention subjects. Since $\rho < 0.5$, we expect an analysis of the change in knowledge score to lead to a larger standard error for the treatment effect than a simple cross-sectional analysis of scores at the six-month visit.

Alternatively, we can regress the follow-up on baseline and treatment:

Coefficients	Estimate	SE	Z-value
(Intercept)	0.946	0.105	9.05
Treatment	1.999	0.241	8.30
Baseline (Y_{i0})	0.438	0.027	16.10

In this analysis the estimate of the treatment effect is 1.999, with a standard error of 0.241. The estimate of β_1 is similar to that obtained from a cross-sectional analysis using six-month data only, and to the analysis of the change in knowledge score. However, as predicted, the standard error is smaller that the standard error for each alternative analysis approach. Finally, in Figure 18.6, the six-month knowledge score is plotted against the baseline knowledge score. Separate regression lines are fit and plotted for the intervention and control groups. We see that the fitted lines are nearly parallel, indicating that the ANCOVA assumption is satisfied for these data.

For discrete outcomes, different pre–post analysis options can be considered. For example, with a binary baseline, $Y_{i0} = 0/1$, and a binary follow-up, $Y_{i1} = 0/1$, the difference, $Y_{i1} - Y_{i0}$, takes the values $-1, 0, +1$. A value of -1 means that a subject has changed from $Y_{i0} = 1$ to $Y_{i1} = 0$, while $+1$ means that a subject has changed from $Y_{i0} = 0$ to $Y_{i1} = 1$. A difference of 0 means that a subject had the same response at baseline and follow-up and does not distinguish between $Y_{i0} = Y_{i1} = 0$ and $Y_{i0} = Y_{i1} = 1$. Rather than focus on the difference, it is useful to consider an analysis of change by subsetting on the baseline value. For example, in a comparative study we can subset on subjects with baseline value $Y_{i0} = 1$ and then assess the difference between intervention and control groups with respect to the percent that respond $Y_{i1} = 1$ at follow-up. This analysis allows inference regarding differential change from 0 to 1 comparing

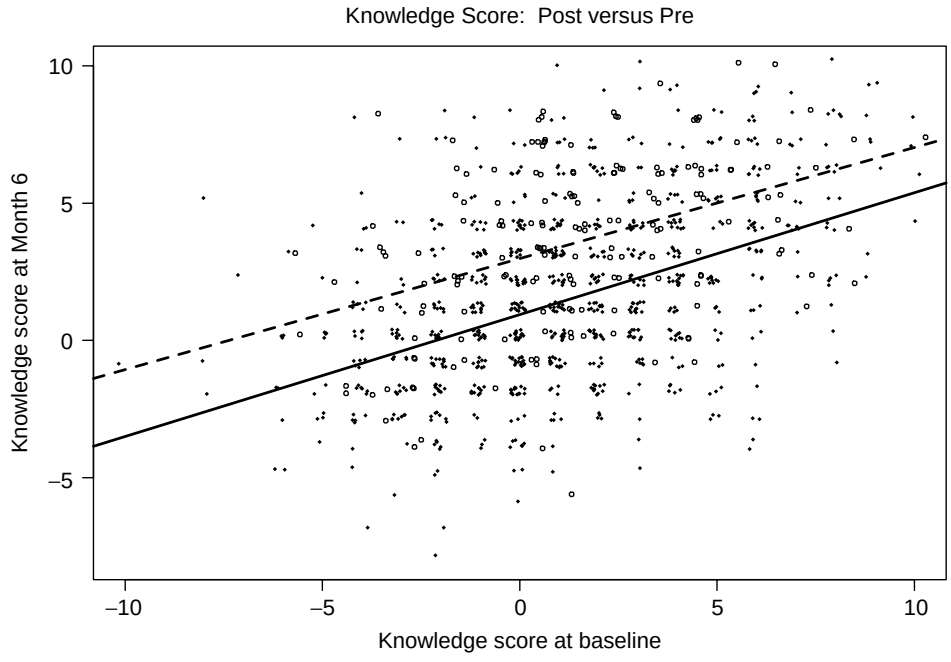


Figure 18.6 Month 6 knowledge score vs. baseline knowledge score (jittered), HIVNET informed consent substudy. Open points and dashed line represent intervention; solid points and line represent control.

the two groups. When a response value of 1 indicates a positive outcome, this analysis provides information about the "corrective" potential for intervention and control groups. An analysis that restricts to subjects with baseline $Y_{i0} = 1$ and then comparing treatment and control subjects at follow-up will focus on a second aspect of change. In this case we are summarizing the fraction of subjects that start with $Y_{i0} = 1$ and then remain with $Y_{i1} = 1$ and thus do not change their outcome but rather, maintain the outcome. When the outcome $Y_{ij} = 1$ indicates a favorable status, this analysis summarizes the relative ability of intervention and control groups to "maintain" the favorable status. Statistical inference can be based on standard two-sample methods for binary data (see Chapter 6). An analysis that summarizes current status at follow-up stratifying on the baseline, or previous outcome, is a special case of a transition model (see Diggle et al. [2002, Chap. 10]).

Example 18.1. (*continued*) The HIVNET informed consent substudy was designed to evaluate whether an informed consent procedure could correct misunderstanding regarding vaccine trial conduct and to reinforce understanding that may be tentative. In Section 18.2 we saw that for the safety item assessment at six months the intervention group had 50% of subjects answer correctly as compared to only 43% of control subjects. For the nurse item the fractions answering correctly at six months were 72% and 45% for intervention and control groups, respectively. By analyzing the six-month outcome separately for subjects that answered incorrectly at baseline, $Y_{i0} = 0$, and for subjects that answered correctly at baseline, $Y_{i0} = 1$, we can assess the mechanisms that lead to the group differences at six months: Does the intervention experience lead to greater rates of "correction" where answers go from $0 \rightarrow 1$ for baseline and six-month assessments; and does intervention appear to help "maintain" or reinforce correct knowledge by leading to increased rates of $1 \rightarrow 1$ for baseline and six-month responses?

The following table stratifies the month 6 safety knowledge item by the baseline response:

Safety Item

"Correction" : $Y_{i0} = 0$		Percent Correct	"Maintain" : $Y_{i0} = 1$		Percent Correct
	N	$Y_{i1} = 1$		N	$Y_{i1} = 1$
Control	488	160/488 = 33%	Control	349	198/349 = 57%
Intervention	105	43/105 = 41%	Intervention	65	42/65 = 65%

This table shows that of the 105 intervention subjects that answered the safety item at baseline incorrectly, a total of 43, or 41%, subsequently answered the item correctly at the 6-month follow-up visit. In the control group only 160/488 = 33% answered this item correctly at six months after they had answered incorrectly at baseline. A two-sample test of proportions yields a p-value of 0.118, indicating a nonsignificant difference between the intervention and control groups in their rates of correcting knowledge of this item. For subjects that answered this item correctly at baseline, 42/65 = 65% of intervention subjects and 198/349 = 57% of control subjects continued to respond correctly. A two-sample test of proportions yields a p-value of 0.230, indicating a nonsignificant difference between the intervention and control groups in their rates of maintaining correct knowledge of the safety item. Therefore, although the intervention group has slightly higher proportions of subjects that switch from incorrect to correct, and that stay correct, these differences are not statistically significant.

For the nurse item we saw that the informed consent led to a large fraction of subjects who answered the item correctly. At six months the intervention group had 72% of subjects answer correctly, while the control group had 45% answer correctly. Focusing on the mechanisms for this difference we find:

Nurse Item

"Correction" : $Y_{i0} = 0$		Percent Correct	"Maintain" : $Y_{i0} = 1$		Percent Correct
	N	$Y_{i1} = 1$		N	$Y_{i1} = 1$
Control	382	122/382 = 32%	Control	455	252/455 = 55%
Intervention	87	59/87 = 68%	Intervention	85	65/85 = 76%

Thus intervention led to a correction for 68% of subjects with an incorrect baseline response compared to 32% among controls. A two-sample test of proportions yields a p-value of <0.001, and a confidence interval for the difference in proportions of (0.250, 0.468). Therefore, the intervention has led to a significantly different rate of correction for the nurse item. Among subjects who correctly answered the nurse item at baseline, only 55% of control subjects answered correctly again at month 6, while 76% of intervention subjects maintained a correct answer at six months. Comparison of the proportion that maintain correct answers yields a p-value of <0.001 and a 95% confidence interval for the difference in probability of a repeat correct answer of (0.113, 0.339). Therefore, the informed consent intervention led to significantly different rates of both correction and maintenance for the safety item.

These categorical longitudinal data could also be considered as multiway contingency tables and analyzed by the methods discussed in Chapter 7.

18.4 IMPACT OF CORRELATION ON INFERENCE

For proper analysis of longitudinal data the within-subject correlation needs to be addressed. In Section 18.3.1 we discussed one method that avoids considering correlation among repeated measures by reducing the multiple measurements to a single summary statistic. In situations where there are variable numbers of observations per subject, alternative approaches are preferable. However, to analyze longitudinal outcomes, either a model for the correlation needs to be adopted or the standard error for statistical summaries needs to be adjusted. In this section we discuss some common correlation models and discuss the impact of the correlation on the standard errors and sample size.

18.4.1 Common Types of Within-Subject Correlation

The simplest correlation structure is the *exchangeable* or *compound symmetric* model, where

$$\text{corr}(Y_i) = \begin{bmatrix} 1 & \rho & \rho & \cdots & \rho \\ \rho & 1 & \rho & \cdots & \rho \\ \rho & \rho & 1 & \cdots & \rho \\ \vdots & & & \ddots & \vdots \\ \rho & \rho & \rho & \cdots & 1 \end{bmatrix}$$

In this case the correlation between any two measurements on a given subject is assumed to be equal, $\text{corr}(Y_{ij}, Y_{ik}) = \rho_{jk} \equiv \rho$. The longitudinal outcomes form a simple "cluster" of responses, and the time ordering is not considered when characterizing correlation.

In other models the measurement time or measurement order is used to model correlation. For example, a *banded* correlation is

$$\text{corr}(Y_i) = \begin{bmatrix} 1 & \rho_1 & \rho_2 & \rho_3 & \cdots & \rho_{n-1} \\ \rho_1 & 1 & \rho_1 & \rho_2 & \cdots & \rho_{n-2} \\ \rho_2 & \rho_1 & 1 & \rho_1 & \cdots & \rho_{n-3} \\ \rho_3 & \rho_2 & \rho_1 & 1 & \cdots & \rho_{n-4} \\ \vdots & & & \ddots & \vdots & \\ \rho_{n-1} & \rho_{n-2} & \rho_{n-3} & \rho_{n-4} & \cdots & 1 \end{bmatrix}$$

and an *autoregressive* structure is

$$\text{corr}(Y_i) = \begin{bmatrix} 1 & \rho^{|t_1-t_2|} & \rho^{|t_1-t_3|} & \cdots & \rho^{|t_1-t_n|} \\ \rho^{|t_2-t_1|} & 1 & \rho^{|t_2-t_3|} & \cdots & \rho^{|t_2-t_n|} \\ \rho^{|t_3-t_1|} & \rho^{|t_3-t_2|} & 1 & \cdots & \rho^{|t_3-t_n|} \\ \vdots & & & \ddots & \vdots \\ \rho^{|t_n-t_1|} & \rho^{|t_n-t_2|} & \rho^{|t_n-t_3|} & \cdots & 1 \end{bmatrix}$$

Each of these models is a special case of a serial correlation model where the distance between observations determines the correlation. In a banded model correlation between observations is determined by their order. All observations that are adjacent in time are assumed to have an equal correlation: $\text{corr}(Y_{i1}, Y_{i2}) = \text{corr}(Y_{i2}, Y_{i3}) = \cdots = \text{corr}(Y_{in-1}, Y_{in}) = \rho_1$. Similarly, all observations that are two visits apart have correlation ρ_2, and in general all pairs of observations that are k visits apart have correlation ρ_k. A banded correlation matrix will have a total of $n-1$ correlation parameters. The autoregressive correlation model uses a single correlation parameter and assumes that the time separation between measurements determines their correlation through the model

$\text{corr}(Y_{ij}, Y_{ik}) = \rho^{|t_j - t_k|}$. Thus, if $\rho = 0.8$ and observations are 1 unit apart in time, their correlation will be $0.8^1 = 0.8$, while if they are 2 units apart, their correlation will be $0.8^2 = 0.64$. In an autoregressive model the correlation will decay as the distance between observations increases.

There are a large number of correlation models beyond the simple exchangeable and serial models given above. See Verbeke and Molenberghs [2000] and Diggle et al. [2002] for further examples.

18.4.2 Variance Inflation Factor

The impact of correlated observations on summaries such as the mean of all observations taken over time and across all subjects will depend on the specific form of the within-subject correlation. For example,

$$\overline{Y} = \frac{1}{\sum_i n_i} \sum_{i=1}^{N} \sum_{j=1}^{n_i} Y_{ij}$$

$$\text{var}(\overline{Y}) = \frac{1}{(\sum_i n_i)^2} \sum_{i=1}^{N} \left[\sum_{j=1}^{n_i} \text{var}(Y_{ij}) \; + \; \sum_{j=1}^{n_i - 1} \sum_{k=(j+1)}^{n_i} 2 \times \text{cov}(Y_{ij}, Y_{ik}) \right]$$

If the variance is constant, $\text{var}(Y_{ij}) = \sigma^2$, we obtain

$$\text{var}(\overline{Y}) = \frac{\sigma^2}{(\sum_i n_i)^2} \sum_{i=1}^{N} \left[n_i \; + \; \sum_{j=1}^{n_i - 1} \sum_{k=(j+1)}^{n_i} 2 \times \text{corr}(Y_{ij}, Y_{ik}) \right]$$

Finally, if all subjects have the same number of observations, $n_i \equiv n$, and the correlation is exchangeable, $\rho_{jk} \equiv \rho$, the variance of the mean is

$$\text{var}(\overline{Y}) = \frac{\sigma^2}{Nn} [1 \; + \; (n-1)\rho]$$

The factor $[1 + (n-1) \cdot \rho]$ is referred to as the *variance inflation factor*, since this measures the increase (when $\rho > 0$) in the variance of the mean (calculated using $N \cdot n$ observations) that is due to the within-subject correlation of measurements.

To demonstrate the impact of correlation on the variance of the mean, we calculate the variance inflation factor, $1 + (n-1)\rho$, for various values of cluster size, n, and correlation, ρ, in Table 18.4. This shows that even very small within-cluster correlations can have an important impact on standard errors if clusters are large. For example, a variance inflation factor of 2.0 arises with ($\rho = 0.001, n = 1001$), ($\rho = 0.01, n = 101$), or ($\rho = 0.10, n = 11$). The variance

Table 18.4 Variance Inflation Factors

n Cluster Size	ρ				
	0.001	0.01	0.02	0.05	0.1
2	1.001	1.01	1.02	1.05	1.10
5	1.004	1.04	1.08	1.20	1.40
10	1.009	1.09	1.18	1.45	1.90
100	1.099	1.99	2.98	5.95	10.90
1000	1.999	10.99	20.98	50.95	100.90

inflation factor becomes important when planning a study. In particular, when treatment is given to groups of subjects (e.g., a cluster randomized study), the variance inflation factor needs to be estimated to power the study properly. See Koepsell et al. [1991] or Donner and Klar [1994, 1997] for a discussion of design and analysis issues in cluster randomized studies. For longitudinal data each subject is a "cluster," with individual measurements taken within each subject.

18.5 REGRESSION METHODS

Regression methods permit inference regarding the average response trajectory over time and how this evolution varies with patient characteristics such as treatment assignment or other demographic factors. However, standard regression methods assume that all observations are independent and if applied to longitudinal outcomes may produce invalid standard errors. There are two main approaches to obtaining valid inference: A complete model that includes specific assumptions regarding the correlation of observations within a subject can be adopted and used to estimate the standard error of regression parameter estimates; general regression methods can be used and the standard errors can be corrected to account for the correlated outcomes. In the following section we review a regression method for continuous outcomes that models longitudinal data by assuming random errors within a subject and random variation in the trajectory among subjects.

18.5.1 Mixed Models

Figure 18.7 presents hypothetical longitudinal data for two subjects. In the figure monthly observations are recorded for up to one year, but one person drops out prior to the eight-month visit, and thus the observations for months 8 through 12 are not recorded. Notice that each subject

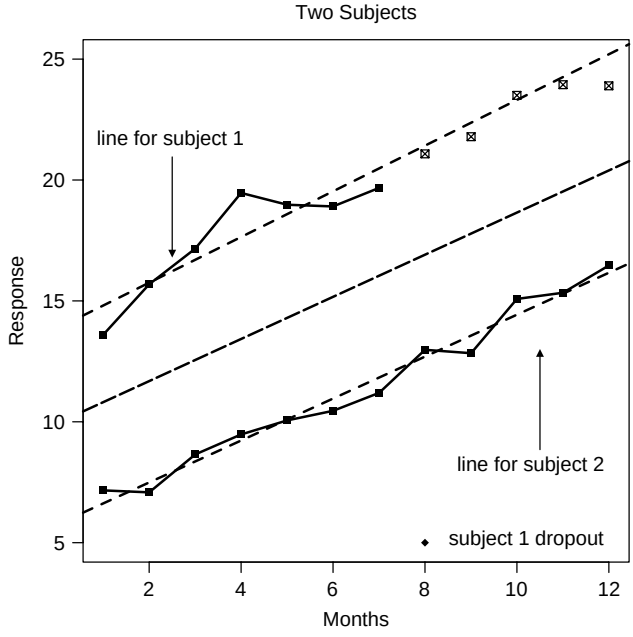


Figure 18.7 Hypothetical longitudinal data for two subjects. Each subject has an individual linear trajectory, and one subject has incomplete data due to dropout.

appears to be tracking his or her own linear trajectory but with small fluctuations about the line. The deviations from the individual observations to the individual's line are referred to as the within-subject variation in the outcomes. If we only had data for a single subject, these would be the typical error terms in a regression equation. In most situations the subjects in a study represent a random sample from a well-defined target population. In this case the specific individual line that a subject happens to follow is not of primary interest, but rather the *typical* linear trajectory and perhaps the magnitude of subject-to-subject variation in the longitudinal process. A dashed line in the center of Figure 18.7 shows the average of individual linear-time trajectories. This average curve characterizes the average for the population as a function of time. For example, the value of the dashed line at month 2 denotes the cross-sectional mean response if the two-month observation for all subjects was averaged. Similarly, the fitted value for the dashed line at 10 months represents the average in the population for the 10-month measurement. Therefore, the average line in Figure 18.7 represents both the typical trajectory and the population average as a function of time.

Linear mixed models make specific assumptions about the variation in observations attributable to variation within a subject and to variation among subjects. The within-subject variation is seen in Figure 18.7 as the deviation between individual observations, Y_{ij}, and the individual linear trajectory. Let $\beta_{i,0} + \beta_{i,1}X_{ij}$ denote the line that characterizes the observation path for subject i. In this example X_{ij} denotes the time of measurement j on subject i. Note that each subject has an individual-specific intercept and slope. Within-subject variation is seen in the magnitude of variation in the deviation between the observations and the individual trajectory, $Y_{ij} - (\beta_{i,0} + \beta_{i,1}X_{ij})$. The between-subject variation is represented by the variation among the intercepts, $\text{var}(\beta_{i,0})$, and the variation among subjects in the slopes, $\text{var}(\beta_{i,1})$.

If parametric assumptions are made regarding the within- and between-subject components of variation, maximum likelihood methods can be used to estimate the regression parameters which characterize the population average, and the variance components which characterize the magnitude of within- and between-subject heterogeneity. For continuous outcomes it is convenient to assume that within-subject errors are normally distributed and to assume that intercepts and slopes are normally distributed among subjects. Formally, these assumptions are written as:

$$\begin{aligned}
\text{within-subjects} \quad : \quad E(Y_{ij} \mid \beta_i) &= \beta_{i,0} + \beta_{i,1}X_{ij} \\
Y_{ij} &= \beta_{i,0} + \beta_{i,1}X_{ij} + \epsilon_{ij} \\
\epsilon_{ij} &\sim N(0, \sigma^2) \\
\text{between-subjects} \quad : \quad \begin{pmatrix} \beta_{i,0} \\ \beta_{i,1} \end{pmatrix} &\sim N\left[\begin{pmatrix} \beta_0 \\ \beta_1 \end{pmatrix}, \begin{pmatrix} D_{00} & D_{01} \\ D_{10} & D_{11} \end{pmatrix} \right]
\end{aligned}$$

The model can be rewritten using $b_{i,0} = (\beta_{i,0} - \beta_0)$ and $b_{i,1} = (\beta_{i,1} - \beta_1)$:

$$Y_{ij} = \underbrace{\beta_0 + \beta_1 X_{ij}}_{\text{systematic}} + \underbrace{b_{i,0} + b_{i,1}X_{ij} + \epsilon_{ij}}_{\text{random}} \tag{1}$$

In this representation the terms $b_{i,0}$ and $b_{i,1}$ represent deviations from the population average intercept and slope, respectively. These "random effects" now have mean 0 by definition, but their variance and covariance is still given by the elements of the matrix D. For example, $\text{var}(b_{i,0}) = D_{00}$ and $\text{var}(b_{i,0}) = D_{11}$. In equation (1) the "systematic" variation in outcomes is given by the regression parameters β_0 and β_1. These parameters determine how the average for subpopulations differs across distinct values of the covariates, X_{ij}.

In equation (1) the random components are partitioned into the observation-level and subject-level fluctuations:

$$Y_{ij} = \beta_0 + \beta_1 X_{ij} + \underbrace{b_{i,0} + b_{i,1} X_{ij}}_{\text{between-subject}} + \underbrace{\epsilon_{ij}}_{\text{within-subject}}$$

A more general form is

$$Y_{ij} = \underbrace{\beta_0 + \beta_1 X_{i1} + \cdots + \beta_p X_{ip}}_{\text{fixed effects}} + \underbrace{b_{i,0} + b_{i,1} X_{i1} + \cdots + b_{i,q} X_{iq}}_{\text{random effects}} + \epsilon_{ij}$$

$$Y_{ij} = X'_{ij}\beta + Z'_{ij} b_i + \epsilon_{ij}$$

where $X'_{ij} = [X_{ij,1}, X_{ij,2}, \ldots, X_{ij,p}]$ and $Z'_{ij} = [X_{ij,1}, X_{ij,2}, \ldots, X_{ij,q}]$. In general, we assume that the covariates in Z_{ij} are a subset of the variables in X_{ij} and thus $q < p$. In this model the coefficient of covariate k for subject i is given as $(\beta_k + b_{i,k})$ if $k \leq q$ and is simply β_k if $q < k \leq p$. Therefore, in a linear mixed model there may be some regression parameters that vary among subjects, while some regression parameters are common to all subjects. For example, in Figure 18.7 it is apparent that each subject has his or her own intercept, but the subjects may have a common slope. A *random intercept model* assumes parallel trajectories for any two subjects and is given as a special case of the general mixed model:

$$Y_{ij} = \beta_0 + \beta_1 X_{i1} + b_{i,0} + \epsilon_{ij}$$

In this model the intercept for subject i is given by $\beta_0 + b_{i,0}$, while the slope for subject i is simply β_1, since there is no additional random slope, $b_{i,1}$, in the random intercept model.

Laird and Ware [1982] discuss the linear mixed model and specific methods to obtain maximum likelihood estimates. Although linear mixed models can be computationally difficult to fit, modern software packages contain excellent numerical routines for estimating parameters and computing standard errors. For example, the SAS package contains the MIXED procedure and S-PLUS has the lme() function.

Example 18.2. (*continued*) In Section 18.3.1 we explored the change over time in CD4 counts for groups of subjects according to their baseline viral load value. Using linear mixed models we can estimate the average rate of decline for each baseline viral load category, and test for differences in the rate of decline.

To test for differences in the rate of decline, we use linear regression with

$$\begin{aligned} E(Y_{ij} \mid X_{ij}) = \beta_0 &+ \\ &\beta_1 \cdot \text{month} + \\ &\beta_2 \cdot I(\text{medium viral load}) + \\ &\beta_3 \cdot I(\text{high viral load}) + \\ &\beta_4 \cdot \text{month} \cdot I(\text{medium viral load}) + \\ &\beta_5 \cdot \text{month} \cdot I(\text{high viral load}) \quad . \end{aligned}$$

Here $X_{ij,3} = I(\text{medium viral load}) = 1$ if subject i has a medium value for baseline viral load and otherwise $= 0$, and $X_{ij,4} = I(\text{high viral load}) = 1$ if subject i has a high baseline viral load and otherwise $= 0$. Using this regression model, the average slope for the low baseline viral category is given by β_1, while the average slope for the other viral load categories are given by $(\beta_1 + \beta_4)$ and $(\beta_1 + \beta_5)$ for the medium- and high-viral-load categories, respectively. If the

estimate of β_4 is not significantly different from 0, we cannot reject equality of the average rates of decline for the low- and medium-viral-load subjects. Similarly, inference regarding β_5 determines whether there is evidence that the rate of decline for high-viral-load subjects is different than for low-viral-load subjects.

The linear mixed model is specified by the regression model for $E(Y_{ij} \mid X_{ij}) = \mu_{ij}$ and assumptions about random effects. We first assume random intercepts, $Y_{ij} = \mu_{ij} + b_{i,0} + \epsilon_{ij}$, and then allow random intercepts and slopes, $Y_{ij} = \mu_{ij} + b_{i,0} + b_{i,1} \cdot \text{month} + \epsilon_{ij}$. Maximum likelihood estimates are presented in Tables 18.5 and 18.6. In Table 18.5 the mixed model assumes that each subject has a random intercept, $b_{i,0}$, but assumes a common slope. In this model there are two estimated variance components: $162.5 = \widehat{\sigma} = \sqrt{\widehat{\text{var}}(\epsilon_{ij})}$ and $219.1 = \sqrt{\widehat{D_{00}}} = \sqrt{\widehat{\text{var}}(b_{i,0})}$. The total variation in CD4 is estimated as $162.5^2 + 219.1^2 = 272.8^2$, and the proportion of total variation that is attributed to within-person variability is $162.5^2/272.8^2 = 35\%$ with $219.1^2/272.8^2 = 65\%$ of total variation attributable to individual variation in their general level of CD4 (e.g., attributable to random intercepts).

Estimates from Table 18.5 are interpreted as follows:

- *(Intercept)* $\widehat{\beta}_0 = 803.4$. The intercept is an estimate of the mean CD4 count at seroconversion (i.e., month = 0) among the low-viral-load subjects.
- *month* $\widehat{\beta}_1 = -5.398$: Among subjects in the low-viral-load group, the mean CD4 declines -5.398 units per month.
- *I[Medium Viral Load]* $\widehat{\beta}_2 = -123.72$. At seroconversion the average CD4 among subjects with a medium value for baseline viral load is 123.72 units lower than the average CD4 among the low-viral-load subjects.
- *I[High Viral Load]* $\widehat{\beta}_3 = -146.40$. At seroconversion the average CD4 among subjects with a high value for baseline viral load is 146.40 units lower than the average CD4 among the low-viral-load subjects.
- *month * I[Medium Viral Load]* $\widehat{\beta}_4 = 0.169$. The rate of decline for subjects in the medium-viral-load category is estimated to be 0.169 count/month higher than the rate of decline among subjects with a low-baseline viral load. The rate of change in mean CD4 is estimated as $-5.398 + 0.169 = -5.229$ counts/month among subjects with medium-baseline viral load.

Table 18.5 Linear Mixed Model Results for the CD4 Data Assuming Random Intercepts[a]

Linear mixed-effects model fit by maximum likelihood

Data: MACS

AIC	BIC	logLik
19838.98	19881.38	−9911.491

Random effects:

Formula: ~ 1 | id

	(Intercept)	Residual
StdDev:	219.1106	162.5071

Fixed effects: cd4 ~ month * vcat

	Value	Std.Error	DF	t-value	p-value
(Intercept)	803.356	29.712	1250	27.04	<.0001
month	−5.398	0.578	1250	−9.34	<.0001
I[Medium Viral Load]	−123.724	42.169	223	−2.93	0.0037
I[High Viral Load]	−146.401	42.325	223	−3.46	0.0006
month * I[Medium Viral Load]	0.169	0.812	1250	0.21	0.8351
month * I[High Viral Load]	−1.968	0.817	1250	−2.41	0.0162

[a]Output from S-PLUS.

Table 18.6 Linear Mixed Model Results for the CD4 Data Assuming Random Intercepts and Slopes[a]

Linear mixed-effects model fit by maximum likelihood

Data: MACS

AIC	BIC	logLik
19719.85	19772.84	−9849.927

Random effects:

Formula: ~ 1 + month | id

Structure: General positive-definite

	StdDev	Corr
(Intercept)	244.05874	(Inter
month	5.68101	−0.441
Residual	142.22835	

Fixed effects: cd4 ~ month * vcat

	Value	Std.Error	DF	t-value	p-value
(Intercept)	803.509	31.373	1250	25.61	<.0001
month	−5.322	0.857	1250	−6.21	<.0001
I[Medium Viral Load]	−125.548	44.536	223	−2.82	0.0053
I[High Viral Load]	−142.177	44.714	223	−3.18	0.0017
month * I[Medium Viral Load]	0.159	1.205	1250	0.13	0.8954
month * I[High Viral Load]	−2.240	1.212	1250	−1.85	0.0648

[a]Output from S-PLUS.

- *month * I[High Viral Load]* $\widehat{\beta}_5 = -1.967$. The rate of decline for subjects in the high-viral-load category is estimated to be -1.967 counts/month lower than the rate of decline among subjects with a low-baseline viral load. The rate of change in mean CD4 is estimated as $-5.398 - 1.967 = -7.365$ counts/month among subjects with a high-baseline viral load.

Although the regression output also includes standard errors for each of the regression estimates, we defer making inference since a model with random intercepts and random slopes appears more appropriate and affects the resulting confidence intervals or tests for the regression estimates (see Table 18.6).

In Table 18.6 we present maximum likelihood estimates assuming random intercepts and random slopes. To assess whether the additional flexibility is warranted, we can evaluate the improvement in the fit to the data as measured by the maximized log likelihood. The maximized log likelihood for random intercepts is -9911.49 (see Table 18.5), while the maximized log likelihood is increased by 61.56 to -9849.93 when also allowing random intercepts. A formal likelihood ratio test is possible since the random intercepts and random intercepts plus slopes form nested models, but since the null hypothesis restriction involves $D_{11} = 0$, which is on the boundary of the allowable values for variance components (i.e., $D_{11} \geq 0$), the null reference distribution is of nonstandard form [Stram and Lee, 1994; Verbeke and Molenberghs, 2000]. However, the increase in maximized log likelihood of 61.56 is quite substantial and statistically significant with $p < 0.001$. Although the variance assumptions can be further relaxed to allow serial correlation in the measurement errors, ϵ_{ij}, the improvement in the maximized log likelihood is small and does not substantially affect the conclusions. We refer the reader to Diggle et al. [2002] and Verbeke and Molenberghs [2000] for further detail regarding linear mixed models that also include serial correlation in the errors.

Table 18.6 gives estimates of the variance components. For example, the standard deviation in intercepts is estimated as $\sqrt{\widehat{D}_{00}} = 244.1$ and the standard deviation of slopes is given

as $\sqrt{\widehat{D}_{11}} = 5.681$. Under the assumption of normally distributed random effects, these estimates imply that 95% of subjects with a low-baseline viral load would have a *mean* CD4 at seroconversion between $803.5 - 1.96 \times 244.1 = 325.1$ and $803.5 + 1.96 \times 244.1 = 1281.9$. We emphasize that this interval is for individual values of the mean CD4 at baseline rather than for individual measurements at baseline. The interval (325.1, 1281.9) does not include the measurement variation attributable to ϵ_{ij} so only describes the variation in the means, $\beta_0 + b_{i,0}$, and not the actual CD4 measurements, $Y_{ij} = \beta_0 + b_{i,0} + \epsilon_{ij}$. Similarly, 95% of low-viral-load subjects are expected to have a slope of $-5.322 \pm 1.96 \times 5.681 = (-16.456, 5.813)$ counts/month.

The estimated regression parameters can be used to make inference regarding the average rate of decline for each of the baseline viral load categories. For example, $\widehat{\beta}_4 = 0.159$ estimates the difference between the rate of decline among medium-viral-load subjects and low-viral-load subjects and is not significantly different from 0 using the standardized regression coefficient as test statistic: $0.159/1.205 = 0.13$ with $p = 0.8954$. Although the estimated rate of decline is lower for the high-viral-load group, $\widehat{\beta}_5 = -2.240$, this is also not significantly different from 0 with p-value 0.0648. It is important to point out that inference using linear mixed models can be quite sensitive to the specific random effects assumptions. If a random intercepts model were used, the comparison of high- versus low-viral-load group slopes over time becomes statistically significant, as seen in Table 18.5, where the p-value for testing $H_0 : \beta_5 = 0$ is $p = 0.0162$, which would naively lead to rejection of the null hypothesis. This inference is invalid, as it assumes that slopes do not vary among individuals, and the data clearly suggest between-subject variation in slopes.

Residual plots can be useful for checking the assumptions made by the linear mixed model. However, there are two types of residuals that can be used. First, the *population residuals* are defined as

$$\begin{aligned} R_{ij}^P &= Y_{ij} - (\widehat{\beta}_0 + \widehat{\beta}_1 X_{ij,1} + \cdots + \widehat{\beta}_p X_{ij,p}) \\ &= Y_{ij} - X_{ij}' \widehat{\beta} \end{aligned}$$

The population residuals measure the deviation from the individual measurement to the fitted population mean value. These residuals contain all components of variation, including between- and within-subject deviations since

$$Y_{ij} - X_{ij}' \beta = Z_{ij}' b_i + \epsilon_{ij}$$

The population residuals can be used to evaluate evidence for systematic departures from linear assumptions. Similar to standard multiple regression, plots of residuals versus predictors can be inspected for curvature.

Individual random effects b_i can also be estimated and used to form a second type of residual. Under the linear mixed model, these random effects are typically not estimated simply by using subject i data only to estimate b_i, but rather by using both the individual data $Y_{i1}, Y_{i2}, \ldots, Y_{i,n_i}$ and the assumption that random effects are realizations from a normal distribution among subjects. Empirical Bayes' estimates of b_i balance the assumption that b_i is intrinsic to generating the data Y_{ij} in addition to the assumption that the distribution of b_i is multivariate normal with mean 0. Thus, empirical Bayes' estimates are typically closer to 0 than estimates that would be obtained solely by using individual i data. See Carlin and Louis [1996] for more detail on empirical Bayes' estimation. Using the estimated random effects provides a second residual:

$$\begin{aligned} R_{ij}^W &= Y_{ij} - (\widehat{\beta}_0 + \widehat{\beta}_1 X_{ij,1} + \cdots + \widehat{\beta}_p X_{ij,p}) \\ &\quad - (\hat{b}_{i,0} + \hat{b}_{i,1} X_{ij,1} + \cdots + \hat{b}_{i,q} X_{ij,q}) \\ &= Y_{ij} - X_{ij}' \widehat{\beta} - Z_{ij}' \widehat{b}_i \end{aligned}$$

If the regression parameter β and the random effects b were known rather than estimated, the residual R_{ij}^W would equal the within-subject error ϵ_{ij}. The within-subject residuals R_{ij}^W can be used to assess the assumptions regarding the within-subject errors.

Example 18.2. (*continued*) We use the random intercepts and random slopes model for the CD4 data to illustrate residual analysis for linear mixed models. The population residuals are plotted in Figure 18.8, and the within-subject residuals are plotted in Figure 18.9. First, no violation of the linearity assumption for month is apparent in either of these plots. Second, the population residuals are weakly suggestive of an increasing variance over time. However, it is important to note that under the assumption of random intercepts and random slopes, the total variance, $\text{var}(b_{i,0} + b_{i,1} \cdot \text{month} + \epsilon_{ij})$, may be an increasing or decreasing function of time. The population residuals suggest right skewness in the cross-sectional distribution of CD4. Since the within-subject residuals do not appear skewed, the population residuals suggest that the random effects may not be normally distributed. Figure 18.10 presents histograms of the estimated intercepts and slopes obtained using ordinary linear regression for subject i data rather than the empirical Bayes estimates. The histograms for the individual intercepts appear to be right skewed, while the individual slopes appear symmetrically distributed. Therefore, residual analysis coupled with exploratory analysis of individual regression estimates suggests that linearity assumptions appear satisfied, but normality of random effects may be violated. The linear mixed model is known to be moderately robust to distributional assumptions, so large-sample inference regarding the average rate of decline for baseline viral load groups can be achieved.

Mixed models can be adopted for use with categorical and count response data. For example, random effects can be included in logistic regression models for binary outcomes and can be included in log-linear models for count data. Maximum likelihood estimation for these models requires specialized software. Extensions of mixed models to alternate regression contexts is discussed in Chapters 7 and 9 of Diggle et al. [2002].

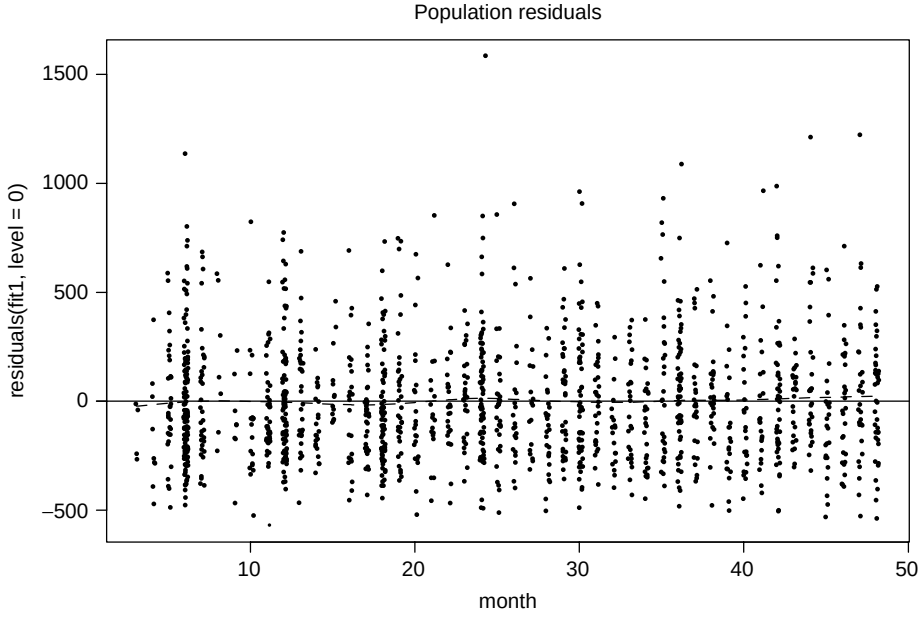


Figure 18.8 Population residuals, R_{ij}^P, vs. visit month for the MACS CD4 data. The dashed line is a smooth curve through the residuals.

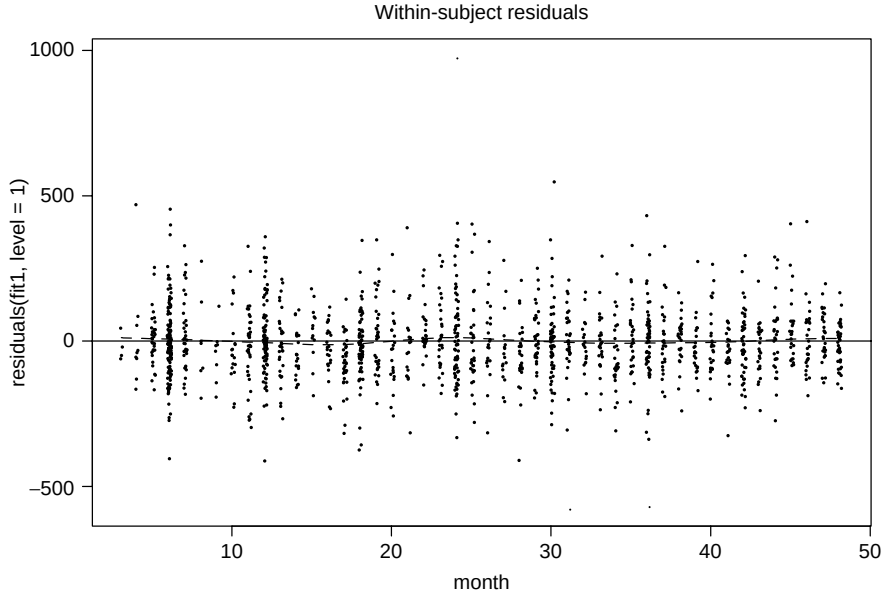


Figure 18.9 Within-subject residuals, R_{ij}^{W}, vs. visit month for the MACS CD4 data. The dashed line is a smooth curve through the residuals.

18.5.1.1 Summary

- Linear mixed models permit regression analysis with correlated data.
- Mixed models specify variance components that represent within-subject variance in outcomes and between-subject variation in trajectories.
- Linear mixed model parameters can be estimated using maximum likelihood.

18.5.2 Generalized Estimating Equations

A second regression approach for inference with longitudinal data is known as *generalized estimating equations* (GEE) [Liang and Zeger, 1986]. In this approach two models are specified. First, a regression model for the mean response is selected. The form of the regression model is completely flexible and can be a linear model, a logistic regression model, a log-linear model, or any generalized linear model [McCullagh and Nelder, 1989]. Second, a model for the within-subject correlation is specified. The correlation model serves two purposes: It is used to obtain weights (covariance inverse) that are applied to the vectors of observations from each subject to obtain regression coefficient estimates; and the correlation model is used to provide model-based standard errors for the estimated coefficients.

A regression model specifies a structure for the mean response, $\mu_{ij} = E(Y_{ij} \mid X_{ij})$, as a function of covariates. For longitudinal data the mean μ_{ij} has been called the *marginal mean* since it does not involve any additional variables, such as random effects, b_i, or past outcomes, Y_{ij-1}. Mixed models consider means conditional on random effects, and transition models include past outcomes as covariates. Adding additional variables leads to subtle changes in the interpretation of covariate coefficients, which becomes particularly important for nonlinear models such as logistic regression. See Diggle et al. [2002, Chaps. 7 and 11] for further discussion.

GEE has two important robustness properties. First, the estimated regression coefficients, $\widehat{\beta}$, obtained using GEE are broadly valid estimates that approach the correct value with increasing

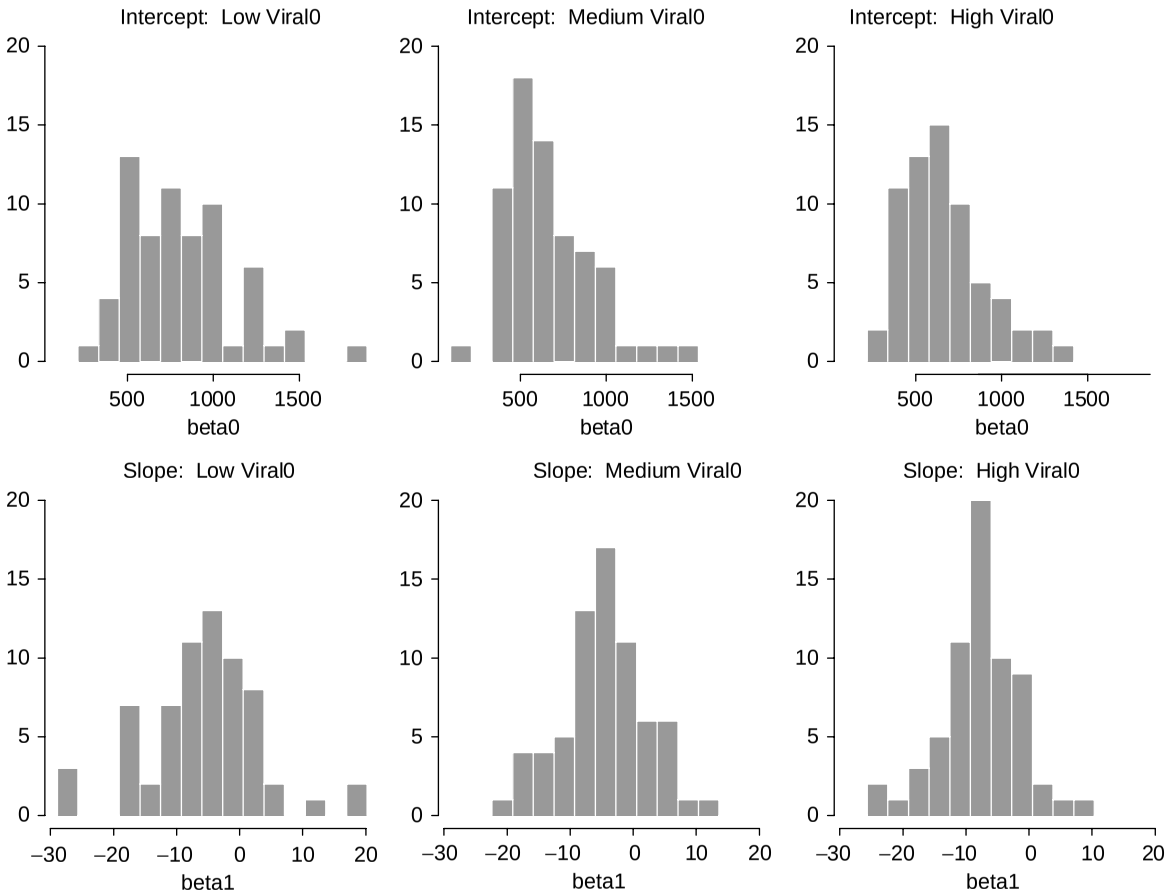


Figure 18.10 Estimates of individual intercepts and slopes by baseline viral load category for the MACS CD4 data.

sample size regardless of the choice of correlation model. In this respect the correlation model is used simply to weight observations, and a good correlation model choice can lead to more precise estimation of regression coefficients than can a poor choice. Based on optimal estimation theory (e.g., Gauss–Markov theory), the best correlation model choice for efficiency of estimation is the true correlation structure. Second, the correlation choice is used to obtain model-based standard errors, and these do require that the correlation model choice is correct in order to use the standard errors for inference. A standard feature of GEE is the additional reporting of *empirical standard errors*, which provide valid estimates of the uncertainty in $\widehat{\beta}$, even if the correlation model is not correct. Therefore, the correlation model can be any model, including one that assumes observations are independent, and proper large-sample standard errors obtained using the empirical estimator. Liang and Zeger [1993] provide an overview of regression methods for correlated data, and Hanley et al. [2003] give an introduction to GEE for an epidemiological audience.

Example 18.2. (*continued*) We return to the CD4 data and use GEE to investigate whether the rate of decline in CD4 over the first 48 months postseroconversion seems to depend on the baseline viral load category. Table 18.7 presents the estimates obtained using GEE and an independence correlation model. Standard errors using the independence correlation model are identical to those obtained from linear regression and are labeled as "model-based." In this application the key feature provided by GEE are the "empirical" standard errors, which are generally valid estimates of the uncertainty associated with the regression estimates. Notice that most of the empirical standard errors are larger than the naive model-based standard errors, which assume that the data are independent. However, corrected standard errors can be either larger or smaller than standard errors obtained under an independence assumption, and the nature of the covariate and the correlation structure interact to determine the proper standard error. It is an oversimplification to state that correction for correlation will lead to larger standard errors. Using GEE we obtain conclusions similar to that obtained using linear mixed models: The high-viral-load group has a steeper estimated rate of decline, but the difference between low and high groups is not statistically significant.

Example 18.1. (*continued*) GEE is particularly useful for binary data and count data. We now turn to analysis of the nurse item from the HIVNET informed consent study. We need to choose a regression model and a correlation model. For our first analysis we assume a common proportion answering correctly after randomization. For this analysis we create the covariate "post," which takes the value 1 if the visit occurs at month 6, 12, or 18, and takes the value 0 for the baseline visit. We use the variable "ICgroup" to denote the intervention and control group, where $\text{ICgroup}_{ij} = 1$ for all visits $j = 1, 2, 3, 4$ if the subject was randomized to the mock informed consent, and $\text{ICgroup}_{ij} = 0$ for all visits, $j = 1, 2, 3, 4$, if the subject was randomized to the control group. Since the response is binary, $Y_{ij} = 1$ if the item was correctly answered by subject i at visit j and 0 otherwise, we use logistic regression to characterize the

Table 18.7 GEE Estimates for the CD4 Data Using an Independence Working Correlation Model

		Standard Error		Z-statistic	
	Estimate	Model	Empirical	Model	Empirical
(Intercept)	792.897	26.847	36.651	29.534	21.633
Month	−4.753	0.950	1.101	−5.001	−4.318
I(Medium viral load)	−121.190	37.872	46.886	−3.200	−2.585
I(high viral load)	−150.705	37.996	45.389	−3.966	−3.320
Month · I(medium viral load)	−0.301	1.341	1.386	−0.224	−0.217
Month · I(high viral load)	−1.898	1.346	1.297	−1.410	−1.464

probability of a correct response as a function of time and treatment group:

$$\begin{aligned}\text{logit}P(Y_{ij} = 1 \mid X_i) = \beta_0 + \\ \beta_1 \cdot \text{post}_{ij} + \\ \beta_2 \cdot \text{ICgroup}_{ij} + \\ \beta_3 \cdot \text{ICgroup}_{ij} \cdot \text{post}_{ij}\end{aligned}$$

Since the visits are equally spaced and each subject is scheduled to have a total of four measurements, we choose to use an unstructured correlation matrix. This allows the correlations ρ_{jk} to be different for each pair of visit times (j, k).

In Table 18.8 we provide GEE estimates obtained using the SAS procedure GENMOD. The estimated working correlation is printed and indicates correlation that decreases as the time separation between visits increases. For example, the estimated correlation for Y_{i1} and Y_{i2} is $\widehat{\rho}_{12} = 0.204$, while for Y_{i1} and Y_{i3}, $\widehat{\rho}_{13} = 0.194$, and for Y_{i1} and Y_{i4}, $\widehat{\rho}_{14} = 0.163$. The correlation between sequential observations also appears to increase over time with $\widehat{\rho}_{23} = 0.302$ and $\rho_{34} = 0.351$.

Regression parameter estimates are reported along with the empirical standard error estimates. These parameters are interpreted as follows:

- *(Intercept)* $\widehat{\beta}_0 = 0.1676$. The intercept is an estimate of log odds of a correct response to the nurse item at baseline for the control group. This implies an estimate for the probability of

Table 18.8 GEE Analysis of the Nurse Item from the HIVNET Informed Consent Study[a]

GEE Model Information

Correlation Structure	Unstructured
Subject Effect	id (1123 levels)
Number of Clusters	1123
Correlation Matrix Dimension	4
Maximum Cluster Size	4
Minimum Cluster Size	1

Working Correlation Matrix

	Col1	Col2	Col3	Col4
Row1	1.0000	0.2044	0.1936	0.1625
Row2	0.2044	1.0000	0.3022	0.2755
Row3	0.1936	0.3022	1.0000	0.3511
Row4	0.1625	0.2755	0.3511	1.0000

Analysis Of GEE Parameter Estimates
Empirical Standard Error Estimates

Parameter	Estimate	Standard Error	95% Confidence Limits		Z	Pr > |Z|
Intercept	0.1676	0.0652	0.0398	0.2954	2.57	0.0102
Post	−0.3238	0.0704	−0.4618	−0.1857	−4.60	<.0001
ICgroup	−0.1599	0.1643	−0.4819	0.1622	−0.97	0.3306
ICgroup*Post	1.0073	0.2012	0.6128	1.4017	5.01	<.0001

[a]Output from SAS procedure GENMOD.

a correct response at baseline among controls of $\exp(0.1676)/[1+\exp(0.1676)] = 0.5418$, which agrees closely with the observed proportion presented in Table 18.3.

- *Post* $\widehat{\beta}_1 = -0.3238$. The coefficient of Post is an estimate of the log of the odds ratio comparing the odds of a correct response among control subjects after randomization (either month 6, 12, or 18) relative to the odds of a correct response among the control group at baseline. Since the odds ratio estimate is $\exp(-0.3238) = 0.7234 < 1$, the odds of a correct response is lower after baseline. A test for equality of odds comparing postbaseline to baseline yields a p-value $p < 0.001$.
- *ICgroup* $\widehat{\beta}_2 = -0.1599$. The coefficient of ICgroup is an estimate of the log of the odds ratio comparing the odds of a correct response among intervention subjects at baseline relative to the odds of a correct response among the control subjects at baseline. Since the assignment to treatment and control was based on randomization, we expect this odds ratio to be 1.0, and the log odds ratio estimate is not significantly different from 0.0.
- *ICgroup* * *Post* $\widehat{\beta}_3 = 1.0073$. This interaction coefficient measures the difference between the comparison of treatment and control after randomization and the comparison of treatment and control at baseline. Specifically, $(\beta_3+\beta_2)$ represents the log odds ratio comparing the odds of a correct response among intervention subjects postbaseline to the odds of a correct response among control subjects postbaseline. Since β_2 represents the group comparison at baseline, $\beta_3 = (\beta_3 + \beta_2) - \beta_2$, or β_3 measures the difference between the comparison after baseline and the group comparison at baseline. Therefore, the parameter β_3 becomes the primary parameter of interest in this study, as it assesses the change in the treatment/control comparison that is attributable to the intervention. A test of $\beta_3 = 0$ is statistically significant with $p < 0.001$.

GEE is a convenient analysis tool for the informed consent data, as it allows inference regarding the differences between treatment and control groups over time. A standard logistic regression model is adopted and valid standard errors are calculated that account for the within-subject correlation of outcomes.

In Table 18.8 we used a single time variable that was an indicator for the postbaseline visits at six, 12, and 18 months. However, inspection of crude proportions responding correctly suggest that the treatment/control comparison may be decreasing over time. For example, in Table 18.3 we see (treatment, control) proportions of (72.1%, 44.7%) at month 6, (60.1%, 46.3%) and (66.0%, 48.2%) at months 12 and 18. To assess whether the treatment effect appears to be decreasing over time, we fit a second logistic regression model that uses indicator variables for months 6, 12, and 18. Table 18.9 presents GEE estimates using an exchangeable working correlation model. In this model the coefficient of month6*ICgroup contrasts the treatment/control log odds ratio at the six-month visit and at baseline. Similar to our earlier analysis, this difference in time-specific log odds ratios is the primary treatment effect observed at six months. Similarly, the coefficients of month12*ICgroup and month18*ICgroup represent treatment effects at 12 and 18 months. Each of the estimated differences in log odds ratios are significant as indicated by the individual p-values in Table 18.9. In addition, we contrast the observed treatment effect at six months with the treatment effect observed at 12 and 18 months. The difference between the estimated coefficient of month6*ICgroup and month12*ICgroup assesses the change in the treatment effect and is estimated as $1.3232 - 0.7362 = -0.5871$. A test of this contrast yields a p-value of 0.0035, indicating a different treatment effect at 12 months as compared to the treatment effect at 6 months. A similar analysis for the 18-month effect as compared to 6 months is barely statistically significant with $p = 0.041$. Therefore, there is evidence that the effect of the intervention may be changing over time. Once again GEE provides a general tool for evaluating the evolution of mean outcomes over time for different subgroups of subjects.

There are a number of extensions of the GEE approach introduced by Liang and Zeger [1986]. More flexible and tailored dependence models have been proposed for binary data [Lipsitz et al.,

Table 18.9 GEE Analysis of the Nurse Item from the HIVNET Informed Consent Study[a]

Analysis Of GEE Parameter Estimates
Empirical Standard Error Estimates

Parameter	Estimate	Standard Error	95% Confidence Limits		Z	Pr > |Z|
Intercept	0.1644	0.0653	0.0364	0.2923	2.52	0.0118
month6	−0.3803	0.0839	−0.5448	−0.2158	−4.53	<.0001
month12	−0.3261	0.0854	−0.4934	−0.1587	−3.82	0.0001
month18	−0.2460	0.0886	−0.4197	−0.0723	−2.78	0.0055
ICgroup	−0.1536	0.1639	−0.4748	0.1676	−0.94	0.3487
month6*ICgroup	1.3232	0.2319	0.8687	1.7777	5.71	<.0001
month12*ICgroup	0.7362	0.2358	0.2739	1.1984	3.12	0.0018
month18*ICgroup	0.9101	0.2273	0.4647	1.3556	4.00	<.0001

Contrast Estimate Results

Label	Estimate	Standard Error	Alpha	Confidence Limits		Chi-Square
Effect at 12 versus 6	−0.5871	0.2014	0.05	−0.9817	−0.1924	8.50
Effect at 18 versus 6	−0.4131	0.2023	0.05	−0.8097	−0.0166	4.17

Contrast Estimate Results

Label	Pr > ChiSq
Effect at 12 versus 6	0.0035
Effect at 18 versus 6	0.0412

[a]Output from SAS procedure GENMOD.

1991; Carey et al., 1993], and extension for multiple survival times has been developed [Wei et al., 1989; Lee et al., 1992].

Summary

- GEE permits regression analysis with correlated continuous, binary, or count data.
- GEE requires specification of a regression model and a working correlation model.
- Two standard error estimates are provided with GEE: a model-based standard error that is valid if the correlation model is specified correctly; and empirical standard errors that are valid even if the correlation model is not correct provided that the data contain a large number of independent clusters.
- Estimation with GEE does not involve a likelihood function; rather, it is based on the solution to regression equations that use models only for the mean and covariance.

18.6 MISSING DATA

One of the major issues associated with the analysis of longitudinal data is missing data, or more specifically, *monotone missing data*, which arise when subjects drop out of the study. It is assumed that once a participant drops out, he or she provides no further outcome information. Missing data can lead to biased estimates of means and/or regression parameters when the probability of missingness is associated with outcomes. In this section we first review a standard taxonomy of missing data mechanisms and then briefly discuss methods that can be used to alleviate bias due to attrition. We also discuss some simple exploratory methods that can help determine whether subjects who complete the longitudinal study appear to differ from those who drop out.

18.6.1 Classification of Missing Data Mechanisms

To discuss factors that are associated with missing data, it is useful to adopt the notation $R_{ij} = 1$ if observation Y_{ij} is observed, and $R_{ij} = 0$ if Y_{ij} is missing. Let $R_i = (R_{i1}, R_{i2}, \ldots, R_{in})$. Monotone missing data imply that if $R_{ij} = 0$, then $R_{ij+k} = 0$ for all $k > 0$. Let Y_i^O denote the subset of the outcomes $Y_i = (Y_{i1}, Y_{i2}, \ldots, Y_{in})$ that are observed, and let Y_i^M denote the missing outcomes. For longitudinal data a missing data classification is based on whether observed or unobserved outcomes are predictive of missing data [Laird, 1988]:

$$\text{Missing completely at random (MCAR)}: \quad P(R_i \mid Y_i^O, Y_i^M, X_i) = P(R_i \mid X_i)$$

$$\text{Missing at random (MAR)}: \quad P(R_i \mid Y_i^O, Y_i^M, X_i) = P(R_i \mid Y_i^O, X_i)$$

$$\text{Nonignorable (NI)}: \quad P(R_i \mid Y_i^O, Y_i^M, X_i) \text{ depends on } Y_i^M$$

In Figure 18.7 an example of monotone missing data is presented. For subject 1, all observations after the 7-month visit are missing. If the reason that these observations are missing is purely unrelated to outcomes (observed or not), the missing data are called *MCAR*. However, if the observed data are predictive of missingness, the missing data are called *MAR*, and the mechanism introduces a form of selection bias. MAR data could occur if an attending physician decides to disenroll any participant who appears to be failing treatment, particularly when the decision is based on the value of past measurements or factors associated with the past outcomes, Y_{ij}. Finally, the unobserved outcomes may be associated with missingness if, for example, subjects who are the most ill refuse to travel to attend their scheduled study visit.

The missing data taxonomy translates directly into implications for potential selection bias. If data are MCAR, both the missing and the observed outcomes are representative of the source population. Therefore, when data are MCAR, standard statistical summaries based on the observed data remain valid. However, if data are MAR or NI, summaries based on the available cases may be biased. Returning to Figure 18.7, if the dropout for patient 1 is indicative of a general process by which those subjects who have a high response value do not return for study, the observed mean for the measured outcomes will not be representative of what would be observed had the entire population been followed. In this example, the mean among available subjects would underestimate the population mean for later months.

Formally, we write $E(Y_{ij} \mid X_i, R_{ij} = 1)$ to denote the expected response conditional on responding, and we write $E(Y_{ij} \mid X_i)$ for the target of inference. If the data are MCAR, then $E(Y_{ij} \mid X_i, R_{ij} = 1) = E(Y_{ij} \mid X_i)$. However, if data are either MAR or NI, then $E(Y_{ij} \mid X_i, R_{ij} = 1) \neq E(Y_{ij} \mid X_i)$, implying that the available data, $R_{ij} = 1$, may not provide valid estimates of population parameters.

In any given application, serious thought needs to be given to the types of processes that lead to missing data. External information can help determine whether missingness mechanisms may be classified as MCAR, MAR, or NI. Unfortunately, since NI missingness implies that unobserved data, Y_i^M, predicts dropout, we cannot empirically test whether data are NI vs. MAR or MCAR. Essentially, one would need the unobserved data to check to see if they are associated with missingness, but these data are missing! The observed data can be used to assess whether the missingness appears to be MAR or MCAR. First, the dropout time can be considered a discrete-time "survival" outcome, and methods introduced in Chapter 16 can be used to assess whether past outcomes $Y_{ij-1}, Y_{ij-2}, \ldots$ are predictive of dropout, $R_{ij} = 0$. Second, each subject will have a dropout time, or equivalently, a "last measurement" time, with those completing the study having the final assessment time as their time of last measurement. The longitudinal data can be stratified according to the dropout time. For example, the mean at baseline can be calculated separately for those subjects that dropout at the first visit, second visit, through those that complete the study. Similarly, the mean response at the first follow-up visit can be computed for all subjects who have data for that visit. Such analyses can be used to determine whether the outcomes for the dropout subjects appear to be different from those

of the "completers." Naturally, subjects who are lost can only be compared to others at the visit times prior to their dropout. These exploratory analyses are complementary: The first approach assesses whether outcomes predict dropout, and the second approach evaluates whether the dropout time predicts the outcomes. An example of such modeling can be found in Zhou and Castelluccio [2004].

18.6.2 Approaches to Analysis with Missing Data

There are several statistical approaches that attempt to alleviate bias due to missing data. General methods include:

1. *Data imputation*. See Little and Rubin [1987], Schafer [1997], or Koepsell and Weiss [2003] for more information on imputation methods. Imputation refers to "filling in" missing data. Proper methods of imputation use multiple imputation to account for uncertainty in the missing data. Imputation methods require that a model be adopted that links the missing data to the observed data.

2. *Data modeling*. In this method the missing data process and the longitudinal data are both modeled using maximum likelihood for estimation. Use of a linear mixed model estimated with maximum likelihood is one example of this approach. However, to correct validly for MAR missingness, the mean and the covariance must be specified correctly. See Verbeke and Molenberghs [2000] for more details.

3. *Data weighting*. Nonresponse methods with available data are used to weight the observed data to account for the missing data. Use of inverse probability weighting or nonresponse weighting can be applied to general statistical summaries and has been proposed to allow for use of GEE in MAR situations. See Robins et al. [1995] for the statistical theory and Preisser et al. [2002] for a simulation study of the performance of weighted GEE methods.

However, it is important to note that these methods are designed to address data that are assumed to be MAR rather than the more serious nonignorable (NI) missing data. Nonignorable missing data can lead to bias, which cannot be corrected simply through modeling and estimation of the dropout model and/or the response model since unidentifiable parameters that link the probability of missingness to the unobserved data are needed. Therefore, reliance on statistical methods to correct for bias due to attrition either requires an untestable assumption that the data are MAR or requires some form of sensitivity analysis to characterize plausible estimates based on various missingness assumptions. See Diggle et al. [2002, Chap. 13] for discussion and illustration.

Example 18.1. (*continued*) In the HIVNET Informed Consent Study, there was substantial missing data due to attrition. In Tables 18.2 and 18.3 we see a decreasing number of subjects over time. In the control group there are 946 subjects with baseline data and only 782 with 18-month data. Is the knowledge score for subjects who complete the study different from the score for those who dropout? Figure 18.11 shows the mean response over time stratified by dropout time. For example, among subjects that dropout at the 12-month visit, their mean knowledge score at baseline and 6 months is plotted. This plot suggests that subjects who complete only the baseline interview have a lower mean baseline knowledge score than that of all other subjects. In addition, for subjects who complete the study, the average knowledge score at six and 12 months appears greater than the mean knowledge score among subjects who do not complete the 18-month visit. Thus, Figure 18.11 suggests that the completers and the dropout subjects differ with respect to their knowledge scores. Any analysis that does not account for differential dropout is susceptible to selection bias.

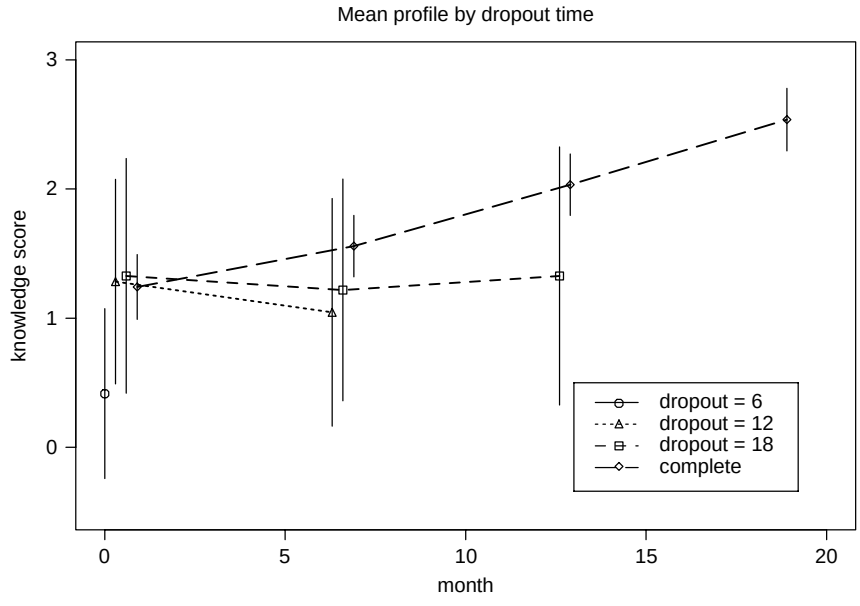


Figure 18.11 Patterns of mean knowledge score by dropout time for the control group. HIVNET informed consent substudy.

18.7 SUMMARY

Longitudinal data provide unique opportunities for inference regarding the effect of an intervention or an exposure. Changes in exposure conditions can be correlated with changes in outcome conditions. However, analysis of longitudinal data requires methods that account for the within-subject correlation of repeated measures. Texts by Diggle et al. [2002], Verbeke and Molenberghs [2000], Brown and Prescott [1999], and Crowder and Hand [1990] provide comprehensive discussions of statistical methods for the analysis of longitudinal data. There are a number of additional issues that warrant attention but are beyond the scope of this book.

NOTES

18.1 Nonlinear Mixed Models

We have introduced linear mixed models and GEE. However, mixed models have also been extended to logistic regression and other nonlinear model settings. See Diggle et al. [2002, Chap. 8 and 11] for illustrations.

18.2 Models for Survival and Repeated Measurements

In many longitudinal studies information on both repeated measurements and on ultimate time until death or key clinical endpoint is collected. Methods have been developed to analyze such data jointly. See Hogan and Laird [1997a, b] for an overview of approaches for the joint analysis of survival and repeated measures.

18.3 Models for Time-Dependent Covariates

In designed experiments the exposures X_{ij} may be controlled by the investigator. However, in many observational studies, exposures or treatments that are selected over time may be related to

past health outcomes. For example, subjects with low values of CD4 may be more likely to be exposed to a therapeutic agent. Analysis of such serial data to assess the effect of the intervention is complicated by the feedback between outcome and exposure. Robins [1986] and Robins et al. [1999] have identified proper causal targets of inference and methods for estimation in settings where time-varying covariates are both causes and effects. See Diggle et al. [2002, Chap. 12].

PROBLEMS

18.1 This exercise considers the interplay between the covariate distribution and the correlation. For each of the following scenarios, assume that there are a total of N pairs of observations, (Y_{i1}, Y_{i2}), with covariates (X_{i1}, X_{i2}). Assume that the covariate is binary: $X_{ij} = 0$ or $X_{ij} = 1$, denoting control and treatment exposures. Let $\overline{Y}_1$ denote the mean of all observations where $X_{ij} = 1$, and let $\overline{Y}_0$ denote the mean of all observations where $X_{ij} = 0$. Assume a constant variance $\sigma^2 = \text{var}(Y_{ij} \mid X_{ij})$ and a correlation $\rho = \text{corr}(Y_{i1}, Y_{i2})$.

- **(a)** Assume that half of the subjects are assigned to control for both visits, $(X_{i1}, X_{i2}) = (0, 0)$, and half of the subjects are assigned to intervention for both visits, $(X_{i1}, X_{i2}) = (1, 1)$. What is the variance of the estimated mean difference, $\widehat{\Delta} = (\overline{Y}_1 - \overline{Y}_0)$?
- **(b)** Assume that subjects change their treatment over time with half of the subjects are assigned to control and then treatment, $(X_{i1}, X_{i2}) = (0, 1)$, and half of the subjects assigned to treatment and then control, $(X_{i1}, X_{i2}) = (1, 0)$. This design is referred to as a *crossover study*. What is the variance of the estimated mean difference $\widehat{\Delta} = (\overline{Y}_1 - \overline{Y}_0)$?
- **(c)** Comment on the advantages and disadvantages of these two study designs.

18.2 Consider a study with a single prerandomization measurement, Y_{i0}, and a single postrandomization measurement, Y_{i1}. For any constant a we can define the average contrast, $\overline{D}(a) = \text{mean}[d_i(a)]$, where $d_i(a) = Y_{i1} - aY_{i0}$. Let $\overline{D}_0(a)$ denote the mean for the control group, and let $\overline{D}_1(a)$ denote the mean for the intervention group. Assume that $\sigma^2 = \text{var}(Y_{ij})$ for $j = 0, 1$, and let $\rho = \text{corr}(Y_{i0}, Y_{i1})$. We assume that the subjects are randomized to treatment and control after randomization at baseline. Therefore, the following table illustrates the mean response as a function of treatment and time:

	Control	**Intervention**
Baseline	μ_0	μ_0
Follow-up	μ_1	$\mu_1 + \Delta$

- **(a)** Show that the expected value of $\widehat{\Delta}(a) = \overline{D}_1(a) - \overline{D}_0(a)$ equals Δ for any choice of a.
- **(b)** When $a = 0$, we effectively do not use the baseline value, and $\widehat{\Delta}(0)$ is the difference of means at follow-up. What is the variance of $\widehat{\Delta}(0)$?
- **(c)** When $a = 1$, we effectively analyze the change in outcomes since $d_i(1) = Y_{i1} - Y_{i0}$. What is the variance of $\widehat{\Delta}(1)$?
- **(d)** What value of a leads to the smallest variance for $\widehat{\Delta}(a)$?

18.3 Use the data from the Web page to perform GEE analysis of the HIVNET Informed Consent Substudy "safety" item.

18.4 For the random intercepts and slopes model given in Table 18.6, the proportion of total variation that is attributable to within-subject variation is not constant over time. Compute estimates of the proportion of total variation at 0, 12, 24, and 36 months that is attributable to within-subject variation, ϵ_{ij}, as opposed to between subject variation, $b_{i,0} + b_{i,1} \cdot \text{month}$.

18.5 For the HIVNET Informed Consent Substudy data, create pairs of plots:

(a) Plot month 12 vs. month 6 knowledge score. Add a pair of lines that show the ordinary least squares estimate for the intervention and the control group.

(b) Plot month 18 vs. month 12 knowledge score. Add a pair of lines that shows the ordinary least squares estimate for the intervention and the control group.

(c) Do these plots suggest that there are additional differences between the intervention and control groups that is not captured by the difference that manifests at the six-month visit?

18.6 For the NURSE and SAFETY items from the HIVNET Informed Consent Substudy, evaluate the transition from incorrect to correct, and from correct to correct again, for the times (six-month $\rightarrow$ 12-month visit) and (12-month $\rightarrow$ 18-month visit). Is there evidence that the intervention and control groups differ in terms of the "correction" and "maintenance" of knowledge at the later times?

REFERENCES

Brown, H., and Prescott, R. [1999]. *Applied Mixed Models in Medicine*. Wiley, New York.

Carlin, B. P., and Louis, T. A. [1996]. *Bayes and Empirical Bayes Methods for Data Analysis*. Chapman & Hall, London.

Coletti, A. S., Heagerty, P. J., Sheon, A. R., Gross, M., Koblin, B. A., Metzger, D. S., and Seage G. R. [2003]. Randomized, controlled evaluation of a prototype informed consent process for HIV vaccine efficacy trials. *Journal of Acquired Immune Deficiency Syndrome*, **32**: 161–169.

Carey, V., Zeger, S. L., and Diggle, P. [1993]. Modelling multivariate binary date with alternating logistic regressions. *Biometrika*, **80**: 517–526.

Crowder, M. J., and Hand, D. J. [1990]. *Analysis of Repeated Measures*. Chapman & Hall, New York.

Diggle, P. J., Heagerty, P. J., Liang, K.-Y., and Zeger, S. L. [2002]. *Analysis of Longitudinal Data*. Oxford University Press, Oxford.

Donner, A., and Klar, N. [1994]. Cluster randomization trials in epidemiology: theory and application. *Journal of Statistical Planning and Inference*, **42**: 37–56.

Donner, A., and Klar, N. [1997]. Statistical considerations in the design and analysis of community intervention trials. *Journal of Clinical Epidemiology*, **49**: 435–439.

Frison, L. J., and Pocock, S. J. [1992]. Repeated measures in clinical trials: analysis using summary statistics and its implication for design. *Statistics in Medicine*, **11**: 1685–1704.

Frison, L. J., and Pocock, S. J. [1997]. Linearly divergent treatment effects in clinical trials with repeated measures: efficient analysis using summary statistics. *Statistics in Medicine*, **16**: 2855–2872.

Hanley, J. A., Negassa, A., deB. Edwardes, M. D., and Forrester, J. E. [2003]. Statistical analysis of correlated data using generalized estimating equations: an orientation. *American Journal of Epidemiology*, **157**: 364–375.

Hogan, J. W., and Laird, N. M. [1997a]. Mixture models for the joint distribution of repeated measures and event times. *Statistics in Medicine*, **16**: 239–257.

Hogan, J. W., and Laird, N. M. [1997b]. Model-based approaches to analysing incomplete longitudinal and failure time data. *Statistics in Medicine*, **16**: 259–272.

Kaslow, R. A., Ostrow, D. G., Detels, R., et al. [1987]. The Multicenter AIDS Cohort Study: rationale, organization and selected characteristics of the participants. *American Journal of Epidemiology*, **126**: 310–318.

Koepsell, T. D., and Weiss, N. S. [2003]. *Epidemiological Methods: Studying the Occurrence of Illness*. Oxford University Press, New York.

Koepsell, T. D., Martin, D. C., Diehr, P. H., Psaty, B. M., Wagner, E. H., Perrin, E. B., and Cheadle, A. [1991]. Data analysis and sample size issues in evaluations of community-based health promotion and disease prevention programs: a mixed model analysis of variance approach. *American Journal of Epidemiology*, **44**: 701–713.

Laird, N. M. [1988]. Missing data in longitudinal studies. *Statistics in Medicine*, **7**: 305–315.

Laird, N. M., and Ware, J. H. [1982]. Random-effects models for longitudinal data. *Biometrics*, **38**: 963–974.

Lebowitz, M. D. [1996]. Age, period, and cohort effects. *American Journal of Respiratory Critical Care Medicine*, **154**: S273–S277.

Lee, E. W., Wei, L. J., and Amato, D. A. [1992]. Cox-type regression analysis for large numbers of small groups of correlated failure time observations. In *Survival Analysis: State of the Art*, J. P. Klein and P. K. Joel (eds.). Kluwer Academic Publishers, Dordrecht.

Liang, K.-Y., and Zeger, S. L. [1986]. Longitudinal data analysis using generalised linear models. *Biometrika*, **73**: 13–22.

Liang, K.-Y., and Zeger, S. L. [1993]. Regression analysis for correlated data. *Annual Review of Public Health*, **14**: 43–68.

Lipsitz, S., Laird, N., and Harrington, D. [1991]. Generalized estimating equations for correlated binary data: using odds ratios as a measure of association. *Biometrika*, **78**: 153–160.

Little, R. J. A., and Rubin, D. B. [2002]. *Statistical Analysis with Missing Data*, 2nd ed. Wiley, New York.

McCullagh, P., and Nelder, J. A. [1989]. *Generalized Linear Models, 2nd ed.* Chapman & Hall, New York.

Preisser, J. S., Lohman, K. K., and Rathouz, P. J. [2002]. Performance of weighted estimating equations for longitudinal binary data with drop-outs missing at random. *Statistics in Medicine*, **21**: 3035–3054.

Robins, J. M. [1986]. A new approach to causal inference in mortality studies with sustained exposure periods: application to control of the healthy worker survivor effect. *Mathematical Modelling*, **7**: 1393–1512.

Robins, J. M., Rotnitzky, A., and Zhao, L. P. [1995]. Analysis of semiparametric regression models for repeated outcomes in the presence of missing data. *Journal of the American Statistical Association*, **90**: 106–121.

Robins, J. M., Greenland, S., and Hu, F.-C. [1999]. Estimation of the causal effect of a time-varying exposure on the marginal mean of a repeated binary outcome (with discussion). *Journal of the American Statistical Association*, **94**: 687–712.

Samet, J. M., Dominici, F., Curriero, F. C., Coursac, I., and Zeger, S. L. [2000]. Fine particulate air pollution and mortality in 20 US cities. *New England Journal of Medicine*, **343**(24): 1798–1799.

Schafer, J. L. [1997]. *Analysis of Incomplete Multivariate Data*. Chapman & Hall, New York.

Stram, D. O., and Lee, J. W. [1994]. Variance component testing in the longitudinal mixed model. *Biometrics*, **50**: 1171–1177.

The Childhood Asthma Management Program Research Group [2002]. Long-term effects of budesonide or nedocromil in children with asthma. *New England Journal of Medicine*, **343**(15): 1054–1063.

Verbeke, G., and Molenberghs, G. [2000]. *Linear Mixed Models for Longitudinal Data*. Springer-Verlag, New York.

Wei, L. J., Lin, D., and Weissfeld, L. [1989]. Regression analysis of multivariate incomplete failure time data by modeling marginal distributions. *Journal of the American Statistical Association*, **84**: 1065–1073.

Weiss, S. T., and Ware, J. H. [1996]. Overview of issues in the longitudinal analysis of respiratory data. *American Journal of Respiratory Critical Care Medicine*, **154**: S208–S211.

Yu, O., Sheppard, L., Lumley, T., Koenig, J., and Shapiro, G. [2000]. Effects of ambient air pollution on symptoms of asthma in Seattle-area children enrolled in the CAMP study. *Environmental Health Perspectives*, **108**: 1209–1214.

Zhou, X.-H., and Castelluccio, P. [2004]. Adjusting for non-ignorable verification bias in clinical studies for Alzheimer's disease. *Statistics in Medicine*. **23**: 221–230.

CHAPTER 19

Randomized Clinical Trials

19.1 INTRODUCTION

If Alexander Pope is correct that "the proper study of mankind is man" [Pope, 1733], then the development of new therapeutic and prophylactic measures for humans is one of the more proper uses of biostatistics. In addition, it is one of the most active and highly used areas of biostatistics. In this chapter we consider primarily randomized clinical trials in humans, although we mention other uses of the techniques. The use of *clinical* refers to the evaluation of clinical measures, for example, drug treatments or surgical treatments. If an experiment is randomized—that is, treatment assignments given by some random process—it necessarily implies more than one treatment is being considered or tested. Thus, the trials are comparative. And, of course, the term *trial* means that we test, or try, the treatments considered. The acronym RCT has been used for both a randomized *controlled* trial and a randomized *clinical* trial. Randomized clinical trials are examples of randomized controlled trials, but not necessarily vice versa, as we shall see below. Here we use the abbreviation RCT for both. For the most part we shall be discussing clinical trials, although it will be clear from the context which is referred to.

In addition to the statistical methods we have discussed before there are a number of practical issues in clinical trials that are now accepted as appropriate for the best scientific inference. The issues of trial design to some extent "fall between the cracks" in clinical research. They are not an obvious part of a medical education—not being biological per se—and also not an obvious portion of biostatistics, as they do not explicitly involve the mathematics of probability and statistics. However, the issues are important to successful implementation of good scientific clinical studies (and other studies as well) and are a necessary and appropriate part of biostatistical training. Some of these issues are discussed in less detail in Chapter 2 and in Chapter 8, in which we discuss permutation and randomization tests in Section *8.9. Here we give background on why the design features are needed as well as some discussion of how to implement the design features.

The use of RCTs and new drug development is big business. At the end of 2001, the cost for evaluating an approved new chemical entity was estimated at approximately $800 million [*Wall Street Journal*, 2001], and the time for development is often 10 years or more.

19.2 ETHICS OF EXPERIMENTATION IN HUMANS

The idea of experimenting on humans and other animals is distasteful at first blush. This is especially so in light of the Nazi experiments during the World War II period (see, e.g., Lifton [1986]).

Biostatistics: A Methodology for the Health Sciences, Second Edition, by Gerald van Belle, Lloyd D. Fisher, Patrick J. Heagerty, and Thomas S. Lumley
ISBN 0-471-03185-2

Yet it is clear that if new and improved therapies and treatments are to be developed, they must be tried initially at some point in time on humans and/or animals. Whether designated so or not, such use does constitute experimentation. This being the case, it seems best to acknowledge this fact and to try to make such experiments as appropriate, justified, and useful as possible. Considerable work has been devoted to this end. The ethics of experimentation on humans has been the subject of intense study in recent decades. Ethics was touched on in Section 2.5, and because of its importance, we return to the subject here. A good introduction is Beauchamp and Childress [2001]. They review four principles for biomedical ethics: respect for autonomy, nonmaleficence, beneficence, and justice. Briefly summarized:

- The *principle of autonomy* recognizes a person's right to "hold views, make choices, and take actions based on personal values and beliefs."
- The *principle of nonmaleficence* is not to inflict harm to others.
- The *principle of beneficence* "asserts an obligation to help others further their important and legitimate interests."
- The *principle of justice* is more difficult to characterize briefly and may mean different things to different people. As Beauchamp and Childress note: "The only principle common to all theories of justice is a minimal principle traditionally attributed to Aristotle: Equals must be treated equally, and un-equals must be treated unequally."

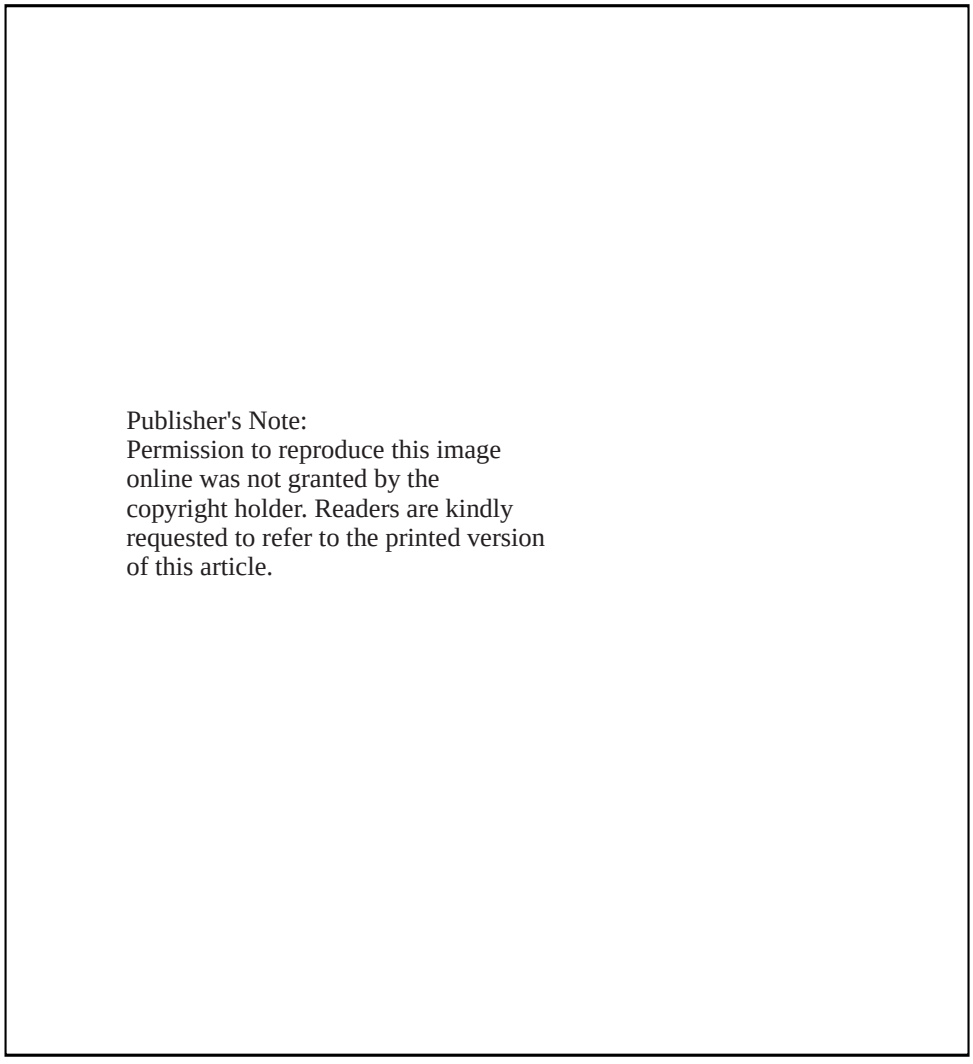
One of the cornerstones of modern clinical research is *informed consent* (consistent with the respect for autonomy). This seemingly simple concept is difficult and complex in application. Can someone near death truly give informed consent? Can prisoners truly give informed consent? Biologically, children are not small adults; drugs may have very different results with children. How can one get informed consent when studying children? Do parents or legal guardians really suffice? How can one do research in emergency settings with unconscious persons who need immediate treatment (e.g., in cardiac arrest)? Do people really understand what they are being told?

The issues have given rise to declarations by professional bodies (e.g., the Declaration of Helsinki, [World Medical Association, 1975], the Nuremberg Code [Reiser et al., 1947], and worldwide regulatory authorities (e.g., Federal Regulations [1988] on Institutional Review Boards). The Health Insurance Portability and Accountability Act (HIPAA) was passed by the U.S. Congress in 1996. The rules resulting from this act have been published and refined since that time. The revised final privacy rules were published in 2002. Much information is protected health information (PHI) and researchers in the United States need to be aware of these regulations and conform to the rules. In the United States, anyone involved in research on humans or animals needs to be familiar with the legal as well as the more general ethical requirements. Without a doubt there is great tension for medical personnel involved in research. Their mandate is to deliver the best possible care to their patients as well as to do good research. See Fisher [1998a] for a brief discussion and some references. In addition, some statistical professional societies have given ethical guidelines for statisticians [Royal Statistical Society, 1993; American Statistical Association, 1999].

All agree that ethical considerations must precede and take precedence over the science. What this means in practice can lead to legitimate differences of opinion. Further continuing scientific advances (such as genetics, cloning, or fetal research) bring up new and important issues that require a societal resolution of what constitutes ethical behavior.

19.3 OBSERVATIONAL AND EXPERIMENTAL STUDIES IN HUMANS

In this section we consider some reasons why randomized studies are usually required by law in the development of new drugs and biologics. Rather than a systematic development, we begin with a few examples and possible lessons to be learned from them.



Example 19.2. If taking a drug helps you survive, it must be effective! During a National Institutes of Health (NIH) Randomized Clinical Trial [Coronary Drug Project Research Group, 1980] a drug was found to have about half the mortality among those who took the drug (defined as taking 80% or more of the assigned medication) vs. those who did not take the drug consistently. The five-year mortality in the men with coronary heart disease was 15.1% of the "good adherers" to drug and 28.2% in the "poor adherers" to drug. Although it certainly seems that the drug is effective (after all counting bodies is not subject to bias), it is possible that those who were good adherers were different when the study started. Fortunately, this was an NIH study with excellent detailed data collected for the known risk factors in this population. There were some differences at baseline between the good and poor adherers. Thus, a multiple linear regression analysis of five-year mortality was run, adjusting for 40 baseline variables in the 2695 patients taking the drug.

The analysis adjusting for these 40 variables led to adjusted five-year mortality of 16.4% for good adherers vs. 25.8% for the poor adherers. This would seem to clearly indicate a survival

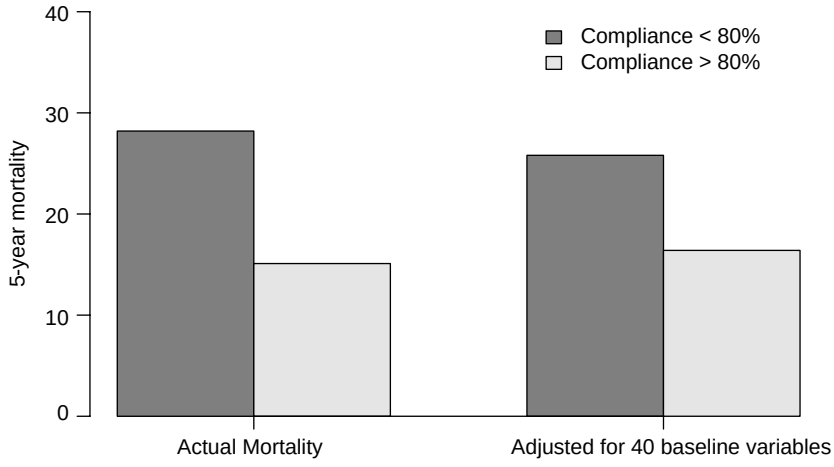


Figure 19.1 Five-year mortality among good and poor adherers to treatment.

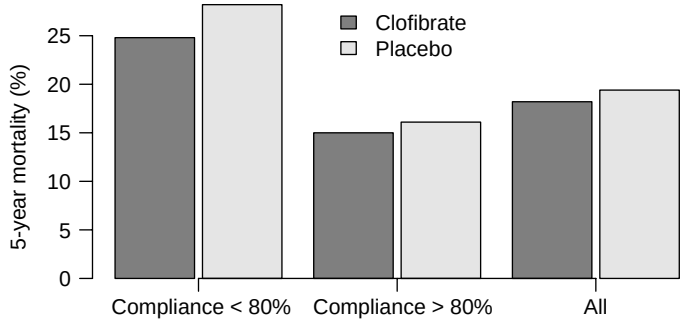


Figure 19.2 Five-year mortality by compliance and treatment in the Coronary Drug Project.

benefit of the drug—thus negating the need for a controlled study, although the data were collected for one arm of a controlled study. The only problem with this result is that the drug above was the placebo! In fact, the good and poor adherers of the active drug, clofibrate, had a very similar pattern. Figures 19.1 and 19.2 give the five-year mortality for the placebo arm of the trial and then for both arms of the trial. The two treatment arms did not differ statistically. The reason for the difference between the placebo mortality for the good and poor adherers was never fully understood.

Results such as this show how difficult it can be to assess a drug effect correctly from observational data. This is one reason why randomized clinical trials are the regulatory gold standard for most drug approvals. This is fine as far as it goes. We are then left with a very difficult consideration. Why, then, does this book give the majority of space to observational data analyses? If we cannot trust such analyses, why bother? The answer is that we do the best we can in any situation. If observational data analyses are the only practical method (due to cost or other feasibility factors), or the only ethical method (as the epidemiology of smoking risk became clear, it would not been considered ethical to randomize to smoking and nonsmoking treatment arms—not to mention the difficulty of execution), observational data must be used.

Example 19.3. If we stop the thing that appears to cause the deaths, we must be prolonging life (or are we?). One of the wonders of the body is our heart; it beats steadily minute

after minute, year after year. If the average number of beats is 60 per minute, there are 86,400 beats/day or 31,536,000 beats/year. In a 65-year-old, the heart may have delivered over 2 billion heartbeats. The contraction of the heart muscle to force blood out into the body is triggered by electrical impulses that depolarize and thus contract the heart in a fixed pattern. As the heart muscle becomes damaged, there can be problems with the electrical trigger that leads to the contraction of the heart. The electrical changes in the heart are monitored when a physician takes an electrocardiogram (ECG) of the heart. If the depolarization starts inappropriately someplace other than the usual trigger point (the sinus atrial node), the heart can contract early; such a resulting irregular heartbeat, or arrhythmic beat, is called a *ventricular premature depolarization* (VPD). Although most people have occasional VPDs, after a heart attack or myocardial infarction (MI), patients may have many more VPDs and complex patterns of irregular heart beats, called *arrhythmias*. The VPDs place patients at an increased risk of sudden cardiac death. To monitor the electrical activity of the heart over longer time periods, ambulatory electrocardiographic monitors (AECGMs) may be used. These units, also called *Holter monitors*, measure and record the electrical activity of the heart over approximately 24-hour periods. In this way, patients' arrhythmic patterns may be monitored over time. Patients have suffered sudden cardiac death, or sudden death, while wearing these monitors, and the electrical sequence of events is usually the following: Patients experience numerous VPDs and then a run of VPDs that occur rapidly in succession (say, at a rate greater than or equal to 120 beats/min); the runs are called *ventricular tachycardia* (VT). Now many coronary patients have runs of VT; however, before death, the VT leads to rapid, irregular, continuous electrical activity of the heart called *ventricular fibrillation* (VF). Observed in a cardiac operation, VF is a fluttering, or quivering, of the heart. This irregular activity interrupts the blood flow and the patient blacks out and if not resuscitated, invariably dies. In hospital monitoring settings and cities with emergency rescue systems, the institution of *cardiopulmonary resuscitation* (CPR) has led to the misnomer of *sudden death survivors*. In a hospital setting and when emergency vehicles arrive, electrical defibrillation with paddles that transmit an electrical shock is used. Individuals with high VPD counts on AECGMs are known to be at increased risk of sudden death, with the risk increasing with the amount and type of arrhythmia.

This being the case, it was natural to try to find drugs that reduced, or even abolished, the arrhythmia in many or most patients. A number of such compounds have been developed. In patients with severe life-threatening arrhythmia, if an antiarrhythmic drug can be found that controls the arrhythmia, the survival is greatly superior to the survival if the arrhythmia cannot be controlled [Graboys et al., 1982]. Graboys and colleagues examined the survival of patients with severe arrhythmia defined as VF (outside the period of an MI) or VT that compromised the blood flow of the heart to the degree that the patients were symptomatic. Figure 19.3 gives the survival from cardiac deaths in 98 patients with the arrhythmia controlled and 25 patients in whom the arrhythmia was not controlled.

Thus, there was a very compelling biological scenario. Arrhythmia leads to runs of VT, which leads to VF and sudden death. Drugs were developed, and could be evaluated using AECGMs, that reduced the amount of arrhythmia and even abolished arrhythmia on AECGMs in many patients. Thus, these people with the reduced or abolished arrhythmia should live longer. One would then rely on the *surrogate endpoint* of the arrhythmia evaluation from an AECGM. A surrogate endpoint is a measurement or event that is thought to be closely associated with the real endpoint of interest such that inducing changes in the surrogate endpoint would imply similar changes in the "real" endpoint of interest. Usually, the surrogate endpoint is a measurement or event that is not of direct benefit to a patient or subject, but that is presumably related to direct benefit and can be used to establish benefit. Prentice [1989] defines the issue statistically: "I define a surrogate endpoint to be *a response variable for which a test of the null hypothesis of no relationship to the treatment groups under comparison is also a valid test of the corresponding null hypothesis based on the true endpoint*." Antiarrhythmic drugs were approved by the U.S. Food and Drug Administration (FDA) based on this surrogate endpoint. It is important to point out that antiarrhythmic drugs may have other benefits than preventing sudden death.

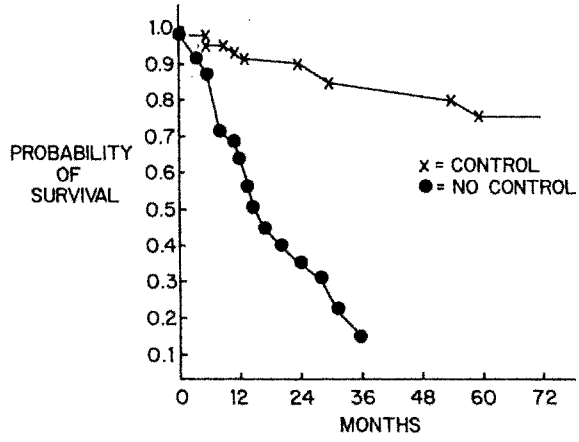


Figure 19.3 Survival free 17 cardiac mortality in patients with severe arrhythmia. The curves are for those whose arrhythmia was controlled by antiarrhythmic drugs and for those in whom the arrhythmia was not controlled by antiarrhythmic drugs.

For example, some patients have such severe runs of VT that they faint. Prevention of fainting spells is of direct benefit to the patient. However, asymptomatic or mildly symptomatic patients with arrhythmia were being prescribed antiarrhythmics with the faith(?), hope(?) that the drugs would prolong their life.

Why, then, would anyone want to perform a randomized survival trial in patients with arrhythmia? How could one perform such a trial ethically? There were a number of reasons: (1) the patients for whom arrhythmia could be controlled by drugs have selected themselves out as biologically different; thus, the survival *even without antiarrhythmic therapy* might naturally be much better than patients for whom no drug worked. That is, modification of the surrogate endpoint of arrhythmia had never been shown to improve the results of the real endpoint of interest (sudden death). (2) Some trials had disturbing results, with adverse trends in mortality on antiarrhythmic drugs [IMPACT Research Group, 1984; Furberg, 1983]. (3) All antiarrhythmic drugs actually produce more arrhythmia in some patients, a *proarrhythmic effect*.

The National Heart, Lung and Blood Institute decided to study the survival benefit of antiarrhythmic drugs in survivors of a myocardial infarction (MI). The study began with a pilot phase to see if antiarrhythmic drugs could be found that reduced arrhythmia by a satisfactory amount. If this could be done, the randomized survival trial would begin. The first study, by the Cardiac Arrhythmia Pilot Study (CAPS) Investigators [1988], showed that three of the drugs studied—encainide, flecainide, and moricizine—suppressed arrhythmias adequately to allow proceeding with the primary survival trial, the Cardiac Arrhythmia Suppression Trial (CAST). Patients within six weeks to two years of an MI needed six VPDs per hour to be eligible for the study. There was an open label, dose titration period where drugs were required to reduce VPDs by at least 80% and runs of VT by at least 90%. (For more detail, see the Cardiac Arrhythmia Suppression Trial (CAST) Investigators [1989] and Echt et al. [1991].) Patients for whom an effective drug was found were then randomized to placebo or to the effective drug (Figure 19.4). Such was the confidence of the investigators that the drugs at least were doing no harm that the test statistic was one-sided to stop for a drug benefit at the 0.025 significance level. The trial was not envisioned as stopping early for excess mortality in the antiarrhythmic drug groups.

The first results to appear were a tremendous shock to the cardiology community. The encainide and flecainide arms were dropped from the study because of excess mortality! Strictly speaking, the investigators could not conclude this with their one-sided design. However, the

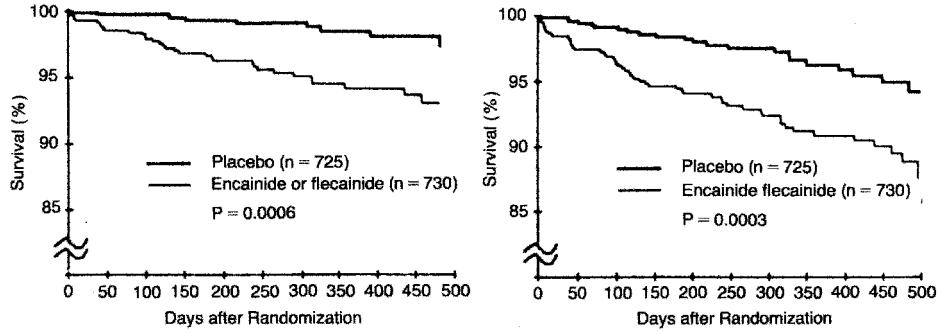


Figure 19.4 The panel on the left shows the survival, free of an arrhythmic death, among 1455 patients randomized to either placebo or one of encainide or flecainide. The second panel is based on all-cause mortality. (From the Cardiac Arrhythmia Suppression Trial (CAST) Investigators [1989].)

evidence was so strong that the investigators, and almost everyone else, were convinced of the harmful effects of these two antiarrhythmic drugs as used in this patient population.

The results of the study have been addressed by Pratt et al. [1990] and Pratt [1990]; the timing of the announcement of the results is described in Bigger [1990]; this paper gives a feeling for the ethical pressure of quickly promulgating the results. Ruskin [1989] conveys some of the impact of the trial results: "The preliminary results ... have astounded most observers and challenge much of the conventional wisdom about antiarrhythmic drugs and some of the arrhythmias they are used to treat. ... Although its basis is not entirely clear, this unexpected outcome is best explained as the result of the induction of lethal ventricular arrhythmias (i.e., a proarrhythmic effect) by encainide and flecainide."

This trial has saved, and will continue to save lives by virtue of changed physician behavior. In addition, it clearly illustrates that consistent, plausible theories and changes in surrogate endpoints cannot be used to replace trials involving the endpoints of importance to the patient, at least not initially. Finally, it is important to note that one should not overextrapolate the results of a trial; the study does not apply directly to patients with characteristics other than those in the trial; it does not imply that other antiarrhythmic drugs have the same effect in this population. However, it does make one more suspicious about the role of antiarrhythmic therapy, with a resulting need for even more well-controlled randomized data for other patient populations and/or drugs.

The trial illustrates the difficulty of relying on very plausible biological theories to generate new drug therapy. New therapies should be tested systematically in a controlled fashion on humans following ethical guidelines and laws. Note also that the arrhythmia itself is not the true focus of the therapy. It was thought to be a good "surrogate" for survival. The use of surrogate endpoints as a guide to approving new therapies is very risky, as the example shows [Temple, 1995; Fleming and DeMets, 1996].

Example 19.4. Epidemiological studies have shown that higher than normal blood pressure in humans is associated with shorter life span [Kesteloot and Joosens, 1980]. The decrease is due especially to increased cardiovascular events, such as a heart attack, stroke, or sudden death due to arrhythmia. Early clinical trials showed that lowering blood pressure by drug therapy resulted in fewer heart attacks, strokes, and cardiovascular deaths. Subsequently, it was considered unethical to treat persons with high blood pressure, called *hypertensive individuals*, with a placebo or sham treatment for a long period of time. Thus blood pressure–lowering drugs, *antihypertensive drugs*, were studied for relatively short periods, six to 12 weeks, in subjects with mild to moderate hypertension. The surrogate endpoint of blood pressure reduction is used for approval of antihypertensive drugs. As blood pressure tends to rise with physical or emotional

stress it is subject to change in response to subtle clues in the environment. For this reason trials use placebo (*inactive*) pills or capsules that are in appearance, smell, and so on, the same as tested *active treatment* pills or capsules, as discussed in Chapter 1. In addition, to prevent the transmission of clues that might affect blood pressure, the subject is not informed if she or he is taking the active drug or the placebo drug. If only the subject does not know the treatment, the trial is a *single-blind trial*.

However, since subtle clues by those treating and/or evaluating the subjects could affect blood pressure, those treating and/or evaluating the subjects also are not told if the subject is getting the active or placebo treatment. A study with both the subject and medical personnel blinded is called a *double-blind study*.

At the beginning of the study, subjects are usually all started on placebo during an initial single-blind period. This period serves multiple purposes: (1) it allows the effect of prior therapy to *wash out* or disappear; (2) it allows identification of subjects who will take their medication to be used in the comparative part of the trial; (3) it lessens the effect of raised blood pressure due to the unsettling medical setting (the *white coat hypertension* effect); (4) it helps to remove a regression to the mean effect of patient selection; and (5) multiple readings can assure relative stability of and measurement of the baseline blood pressure.

Figure 19.5 shows the data of the placebo arm in such a trial. Since subjects were on placebo the entire time, the explanation for the stable mean pressure during the single-blind *run-in period* and the drop during the double-blind portion of the trial was thought to be subtle clues being given to the patients by the medical personnel when they knew that some patients would be getting active therapy. It should be emphasized that subjects were never told in the single-blind portion of the trial that they were not potentially receiving active therapy. (The subjects did sign an informed consent and knew that they might receive placebo or active therapy during portions of the trial.) This figure illustrates the need for blinding in some clinical trials.

Figure 19.6 shows data from a second trial of an antihypertensive drug. The trial was a dose escalation study. That is, the dose of a drug was increased in individual patients until they had a satisfactory blood pressure response. Again the data are from the placebo arm of the trial. The increasing "benefit" observed as the "dose" of placebo escalates illustrates the need for a control group.

Example 19.5. In the United States, the National Institutes of Health (NIH) administers most federal funds for health sciences research as well as having its own (intramural) programs of research. Most of its employees thus value and are aware of the importance of well-conducted medical research. Thus, the NIH population would seem the ideal place to study an intervention

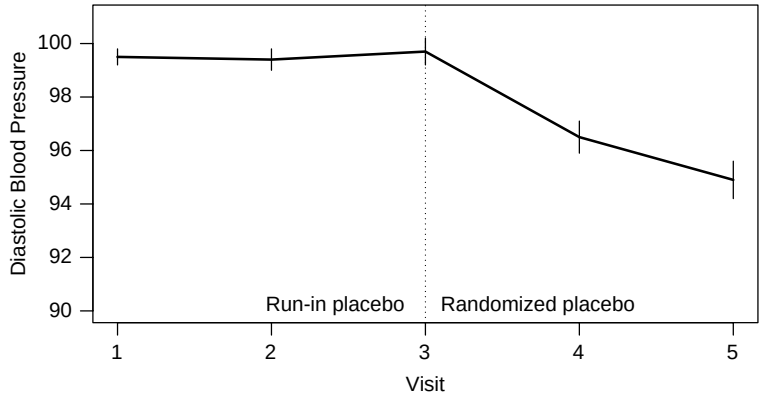


Figure 19.5 Average diastolic blood pressure (±1 standard error) during single-blind run-in and double-blind treatment with placebo.

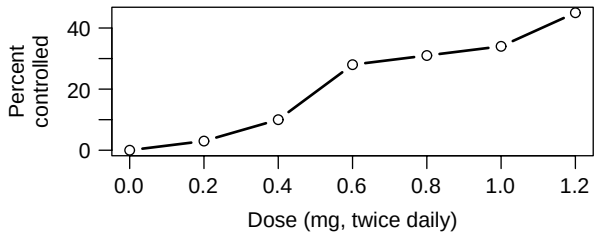


Figure 19.6 Response to escalating doses of placebo antihypertensive.

if there were sufficient numbers of NIH employees experiencing the malady in question. The results of a study on the use of ascorbic acid (vitamin C) for the common cold were published by Karlowski et al. [1975]. Most aspects of the study will not be presented here, in order to concentrate on the difficulty of performing a good experiment. There were four groups in the study. As a preventive (prophylactic) measure there was random assignment to either ascorbic acid or placebo (with capsules containing the study medication), and when a cold was thought to occur (with a clear definition), the study participants were assigned at random (the same for all colds if multiple colds occurred) to either ascorbic acid or placebo. Thus, there were four groups. Three hundred and eleven persons were randomized to therapy (discounting 12 subjects who dropped out early "before taking an appreciable number of capsules"). During the study the investigators learned that some subjects had opened the capsules and tasted the contents to see if they were taking ascorbic acid or placebo. More prophylactic placebo subjects (69) dropped out than ascorbic acid prophylactic subjects (52). At the end of the study the investigators queried the subjects about whether they thought they knew their study drug; of 102 subjects who thought they knew, 79 (77%) guessed correctly. The study results showed no statistical difference in the number of colds, but there was a trend for less severity of a cold if one took ascorbic acid. Unfortunately, this trend disappeared if one took into account those who knew their therapy. The NIH investigators comment under the heading the *power of suggestion*: "Depending upon one's point of view, it is either an unfortunate or fortunate aspect of the study. It would have been gratifying to have performed a flawless clinical trial; on the other hand, it has turned out to be a unique opportunity to gain some insight into the importance of perfect blinding in trials with subjective endpoints. An association between severity and duration of symptoms and knowledge of the medication taken seems to have been clearly established."

These examples above illustrate:

1. The need for a control group to be compared with an active therapy
2. The need for a "fair" or unbiased control, or comparison, group or appropriate mathematical adjustment to make a fair comparison. Appropriate mathematical adjustment is very difficult to do in this setting (as Example 19.2 illustrates)
3. The need for blinding to avoid introducing bias into clinical trials
4. The need for an endpoint of a trial that has clinical relevance (e.g., Temple [1995])

19.4 OBTAINING A FAIR OR UNBIASED COMPARISON: RANDOMIZED CLINICAL TRIAL

We now turn to two aspects of the clinical trial. The first is summarized by the question: How can we assign subjects to unbiased, or comparable, groups at the start of a clinical trial? The idea of random selection to get a "fair" choice or comparison goes back a long time in human history. Lots were used in Old Testament times, the idea of "drawing the short straw," taking a card from a well-shuffled pack, and so on, all show the intuitive appeal of this type of

procedure. However, the formal introduction of *randomization* was made in the 1930s by the British statistician and geneticist Sir Ronald Aylmer Fisher [Box, 1978]. In one of the great intellectual advances of the twentieth century, he combined the methodology of probability theory with the intuitive appeal of randomization to begin the *randomized experiment*. The idea is in some ways counterintuitive. As seen previously in this book, a theme of good observational data analysis or experimentation is to eliminate variability in order to make comparisons as precise as possible. Randomness, or "unexplained noise," does just the opposite. Think of the simplest type of random assignment between two treatments: Each eligible patient has her or his therapy determined (after informed consent) by the flip of an unbiased coin (i.e., the probability of each treatment is $\frac{1}{2}$). The different flips are statistically independent, and if there are n assignments, the number on treatment A, or B for that matter, is a binomial variable. Further, any particular pattern of assignment is equally likely ($1/2^n$).

What are the benefits of this random assignment? First, the assignment to treatment is fair. Human biases, whether conscious or unconscious, are eliminated. Second, on average, the two assignments have the same number of easy or difficult-to-treat assignments; that is, patient characteristics are balanced (statistically). Third, if we assume that treatment is unrelated to our outcome, we can assume that the outcomes were preordained to be good or bad. We can find the probability under this random assignment that each treatment arm had outcomes as extreme or more extreme than that actually observed with the actual assignments because we know that each assignment of cases is equally likely. (see Chapter 8). That is, we can compute a p-value that is not dependent on assumptions about the population we are observing. This is called using the *randomization distribution* (see Edgington [1995]). We do, however, need to be sure that the randomization is done appropriately.

The benefits of the randomized trial are so widely recognized that by law and regulation, in most countries new drugs or biologics need to be evaluated by a randomized clinical trial in order to gain regulatory approval to market the new advance legally. See Note 19.4 for a few references on the need for and benefits of the RCT.

19.4.1 Intent to Treat

There are complications to RCTs in practice. Suppose, in fact, that many patients assigned to one, or both, of the treatments do *not* get the assigned therapy? Does it make sense to compare the treatments as randomized? How can patients who do not receive a therapy benefit from it? Thus, does it not seem odd to keep such patients in a comparison of two therapies? This sticking point has led to some difficult considerations: If we consider only patients who received their assigned or randomized therapy, we can introduce bias since those who do not receive their therapy are usually different (and unfortunately, possibly in unknown ways) from those who do receive their assigned therapy. The issue then becomes one of avoiding bias (include all patients who are randomized into their assigned group) vs. biological plausibility (only count those who actually receive a treatment). At its worst this might pit biostatisticians vs. clinicians. At this point in time, including all subjects in the analysis into the group to which they are randomized is considered standard; such analyses are called *intent-to-treat* (ITT) *analyses*. The name arises from the fact that under the randomized assignment there is an implied initial intent to treat the subject in the manner to which he or she was randomized. The best way to avoid the conflict between bias and biology is to perform an excellent experiment where those randomized to a treatment do receive the treatment. For this reason the assignment to randomization should be accomplished at the last possible moment.

If those subjects who do not begin treatment do so for reasons that cannot have been due to the randomized assignment (e.g., nonbreakable double blinding), the subjects who at least begin therapy can be included into the analysis with all the benefits of the randomization process listed above. Such analyses are called *modified intent to treat* (mITT) and are acceptable provided that one can be assured that the lack of therapeutic delivery *cannot* have been related to the treatment assignment. In practice, modified intent-to-treat analyses are often also called intent to treat.

19.4.2 Blinding

We have seen above that using a randomized assignment does not accomplish the full task of assuring a fair comparison. If the outcome is affected by biased behavior due to the treatment assignment, we can have misleading results despite the fact that the treatments were assigned at random. Bias can still ruin an RCT. We have seen this in both the blood pressure and vitamin C examples above. Wherever possible, double blinding should be used. The more subjective the endpoint, the more important blinding is to a trial. However, even with very "hard" endpoints that would not seem to need blinding (e.g., mortality), blinding can be important. The reason is that if the blinding is not effective, there may be treatment biases that change the way subjects in the assigned groups are treated (e.g., hospitalized, given other medications) and this may affect even hard endpoints such as mortality. It is difficult to blind in many trials [e.g., a drug may induce physiologic changes (in heart rate or blood pressure)] and those seeing and treating a patient may have reasonable guesses as to the therapy. Added steps can be taken. For example, those involved in evaluating a patient for outcome might be required to be different from those treating a patient. Often, outcomes for a trial are evaluated by an external classification committee to reduce bias in the determination of events.

19.4.3 Missing Data

Missing data are one of the most common and difficult issues in the analysis of RCTs. Even a modest discussion of the ways to approach and handle missing data in RTCs goes beyond the scope of this book. However, a few partial solutions, based on the concepts introduced in Section 10.5.2 and Chapter 18 are presented here.

The first and most important thing to understand is that there is no totally satisfactory method of dealing with the issue. The best course is not to have any missing data, but often, that wonderful counsel cannot possibly be implemented. For example, in studies performed in a population of street people with illicit drug use, complete data are virtually unknown if the study requires patient cooperation over a moderate length of time. Subjects simply disappear and are extremely difficult to find. Some turn up in jail or hospitals, but follow-up is difficult. It they are to return for follow-up visits, adherence can be quite low. What are those running such a trial, as well as the general society, with its interest in the outcome, to do? We do the best we can but realize that there will be many missing data. Another example: One studies treadmill walking time in a population of congestive heart failure patients. The primary study endpoint is the change in treadmill time from the baseline measurement to the final visit (at some fixed interval from the time the subject was randomized). Some subjects will die: How should their data be treated in the final analysis? Clearly, the missing information (the impossible final treadmill test) is not independent of patient status. This is known as *informative censoring*. Others may have their heart failure progress to a stage where it is too difficult to come in for the test or to perform the test. Other subjects may become discouraged and exercise their right to withdraw from the study. Others may go on vacation and not be around at the correct time for their evaluation. The possibilities go on and on.

First, one might assume that the missing data do not bias the conclusions and analyze only those who have all appropriate data. This is usually not an acceptable approach unless there are only minimal missing data. However, it is often used as an additional analysis. Data may also be "missing" for legitimate medical reasons. In a trial of blood-pressure-lowering medication, patients may present with greatly elevated blood pressures that require immediate, or perhaps after a week's delay, treatment with known effective drug or drugs. In many trials there are more such subjects in the placebo group. If their data are not taken into account, there is a bias against the active therapy. Further, their data at the end of the scheduled therapy period are not unbiased, as strong active therapy is used to lower blood pressure. In this case the endpoint used is the last observation on the assigned randomized therapy. In effect, the last observation is carried forward to the time for final evaluation. Not surprisingly, such analyses are called *last observation carried*

forward (LOCF). This is often used as a method of analysis when the primary parameter of the study is collected at regularly scheduled visits. Sometimes the missing data are replaced by the mean of the known values for the study. In other cases, more sophisticated methods are used to estimate, *impute*, the missing values. Such strategies can be quite complex. For a discussion of the implications of different reasons that data are missing, the implications for missing data, and analysis methods, see Little and Rubin [2002] and Section 18.6.

If the data are extremely strong, a *worst-case analysis* can be used and an effect still established. For example, in a survival analysis study that is placebo controlled, the comparison to a new therapy, the worst case (for establishing the new therapy), would assume that placebo patients not observed for the full observation period lived to the end of the follow-up period and that those assigned to the new active therapy died immediately after the last time they were known to be alive before being lost to follow-up.

The robustness of the study data to the missing data is sometimes assessed with some type of *sensitivity analysis*. Such analyses make a variety of assumptions about the actual pattern of the missing data and see how extreme it must be to change the study results in some important manner.

19.5 PLANNING AN RCT

19.5.1 Selection of the Study Population

In clinical studies the selection of the study population is critical. The understanding of the drug, biologic, or device mechanism will suggest a population of subjects where efficacy is to be shown. Selection of the highest-risk population is often the most logical choice to demonstrate the effect; however, if only such subjects are studied, the approval for use will usually be limited to such subjects. This may limit use of the new treatment. As a result, this may narrow the range of subjects getting a benefit, as well as lowering the sales potential for the sponsor developing the new therapy.

19.5.2 Special Populations

Historically, many important special populations either were not investigated at all or had very limited data—despite the fact that any realistic appraisal of usage patterns would anticipate such use. For example, women of childbearing potential were avoided; in large part, this was to avoid law suits if there were any birth defects in the children conceived, developing, or born during or close to the trial. The expense of a lifetime of care was avoided by not studying such women. The most infamous example of a drug causing birth defects was thalidomide in Europe and the United States. Nevertheless, many medications are used by pregnant women. Over-the-counter (OTC) products are the most obvious; analgesics (i.e., pain relievers) are one clear class. Now the FDA strongly recommends, and sometimes requires, such studies. Another underevaluated population was children. One might think that from a pharmacological point of view, children are merely small adults and that smaller doses would clearly work if the drug worked in adults. Unfortunately, this idea is simply not true. Children differ in many important ways in addition to size, and care is needed in extrapolating adult results to children. Historically, minorities, especially African-Americans, had limited experimental results in drug development (except in obvious special cases such as sickle cell anemia). In part, this was related to limited access to health care. There are genetic differences in the way that drugs affect humans, and minorities are now studied more systematically. Often, some clinical sites in studies are selected to test a therapy on a more diverse population. The elderly were also underrepresented in RCTs. In part, this is because the elderly have more trouble showing up for clinic visits and complying with their therapy (as they may forget to take their medication). However, the elderly are a particularly important population to study because (1) they take many medications, and drug–drug interactions that cause trouble are more likely to occur in this population; (2) drugs

are often metabolized in the liver, so poor liver function can cause problems (the elderly have more liver impairment); (3) elimination is often through the kidneys, and the elderly are more likely to have kidney problems; and (4) the changing world demography shows that a larger proportion of the world population will be elderly in the next few decades.

19.5.3 Multicenter Clinical Trials

Many clinical trials use multiple clinical centers to enroll patients or subjects. There are several reasons for this. The most obvious is the need to enroll many patients in a timely fashion. There are also other reasons, perhaps not as obvious. Most new drugs are developed to be registered (approved for marketing) in many markets around the world: the United States, the European Union, Japan, and Canada, among others. Thus, the studies often have clinical sites from around the world to aid in approval under the various regulatory authorities. Using "influential" physicians at different centers as investigating clinicians in the research program can also be an aid to marketing when approval is granted. Other benefits of using multiple clinics include (1) showing that there is a benefit in different settings, and (2) assessing therapy under a variety of concomitant medical therapeutic settings.

In addition to the benefits, there are numerous additional challenges to multicenter clinical trials. Standardization of treatment and data recording often require extensive education and monitoring. The randomization process needs to be available over a wide range of times if subjects are enrolled around the world. Forms and data collection may be complicated by the number of languages and cultures involved. Data are analyzed for clinical site heterogeneity in response; often, this is done for different delivery settings (e.g., North America, Europe, and the rest of the world). Security of data, monitoring of the raw data (often in clinical files), and investigator and staff training are all quite complicated.

19.5.4 Practical Aspects of Randomization

The process of randomizing subjects in an RCT involves choices. To simplify the discussion we consider only *two-arm trials*, but similar considerations can be used with more than two treatment arms. The simplest random allocation is a fair coin flip, allocating each subject to one arm or the other. (In practice, the "flips" are done using a *pseudorandom number generator* on a computer.) There are drawbacks to the coin-flip approach. If there are clinical sites, each enrolling a small number of subjects, a number of such sites may involve only one treatment. This makes it impossible to see the variability in treatment effect within such sites. Therefore, the randomization is done using randomized blocks. If the ratio of subjects randomized to each arm is to be the same, even-numbered blocks are used. If the size is $2n$, then among each $2n$ randomizations, n will be to one arm and n to the other. Potentially, this can lead to bias, since if the study is unblinded or one can unblind with a reasonable probability, the probabilities for subsequent patients is no longer $\frac{1}{2}$ to $\frac{1}{2}$. To see this, consider an unblinded study: If we know the first $2n - 1$ treatment assignments, we know what the next subject will receive as a treatment. To get around this problem partially, blocks of different size are sometimes used, being chosen with some probability. For example, one might choose a block of size 4 half the time and a block of size 6 half the time.

Often, the blocks are not used to get balance within a site. If there is an important factor that determines the risk of the trial outcome, blocks with some strata for the risk factor may be used. This "forces" some balance with respect to the important prognostic factor. If more than one factor exists, combinations of two or more factors might be used. There is a limitation, however; if one had five factors, each of which had three levels, and we took all combinations, there would be $5^3 = 125$ possible strata. As the number goes up, we tend to get cells with zero or one subject actually randomized within a cell. When we are using only the first element of each block, randomization is the same as if we did not block at all! For this reason, more complex schemes have been developed for forcing balance on a number of factors; this technique

is known as *adaptive randomization*. For blocking and adaptive randomization, one needs to know selected information about a subject before an assignment can be given. This is often done through either an interactive voice randomization system that uses touchtone phones or through the Internet. In either case, the needed information will be entered, eligibility may be checked, and the database is quickly informed of the randomization, and may check for subsequently expected data. See Efron [1971], Friedman et al. [1999, Chap. 5], or Meinert [1986, Sec. 10.2].

19.5.5 Data Management and Processing

Data management of randomized clinical trials is challenging, particularly so for international multicenter trials. In most instances, data are entered on *case report forms* (CRFs). Often, clinical sites are visited to compare the forms with the official medical records for consistency and documentation. Inspections are made by those sponsoring a study as well as by regulatory authorities if the trial aims to register a drug. Forms are usually submitted to a central data processing unit. They may be carried by hand using monitors, faxed after data entry at the clinical site (*remote data entry*), transferred electronically, entered via the Internet, or (more and more rarely) mailed in batches. To minimize data-entry errors, the data are often entered twice by two different people, and the entries compared for consistency with resolution in the case of disagreement. Entered files usually undergo extensive *consistency checks* [e.g., are the dates possible? Is a datum plausible (in that it is in a reasonable range)? If a discrete variable, is the code a legal one?] One of the worst errors is to have an incorrect patient identifier for a form or forms; for this reason, patient-identifying information (which only identifies the patient uniquely, not allowing the actual person to be identified) often has redundant checking information. When an entry fails a check, a process is instituted to resolve the problem. Tracking the resolution and any changes is documented for possible subsequent review. Problem resolution can be quite extensive and time consuming.

The database often allows identification of the timing of needed follow-up visits, examinations, or contact. For complex studies the database is sometimes used for notifying clinical sites of the expected upcoming data collection. Missing forms (i.e., those expected from subsequent visits) are asked for after some time interval. Some possible inconsistencies may arise externally (e.g., from a blinded committee used to classify endpoints that need resolution), and these are also tracked and recorded. Before a study is analyzed, or unblinded, all outstanding data issues are resolved to the extent possible, and the data file is then *frozen* for the analysis and interpretation of data. In studies that need ongoing monitoring for ethical reasons, there may be an independent *data and safety monitoring board* to review interim data (see Ellenberg et al. [2002]). To avoid introducing bias into the study, a group, independent of the sponsor, often provides tables, lists, and materials. The complexity and effort needed for such processes is hard to appreciate unless one has been through it. (See also Sections 2.6 to 2.9.)

19.6 ANALYSIS OF AN RCT

19.6.1 Preservation of the Validity of Type I Error

Because drug development costs so much and because the financial reward for a successful new drug in the right setting is so great, there is an apparent conflict between the sponsors and regulators. Stated statistically, the sponsors want to maximize the power of a study (i.e., minimize Type II error), and the regulators want to minimize and preserve the appropriateness and interpretability of the Type I error or p-value. Some areas of particular related concern are discussed below.

19.6.2 Interim Analysis of an Ongoing Clinical Trial

New investigational therapies hold potential for both benefit and harm. Experience has shown that no matter how thorough the prior work in other animal species, the results in humans may

differ in unexpected ways. This is especially true with respect to adverse events. This requires looking at outcomes during the study—carrying out *interim analyses*. Similarly, when serious irreversible endpoints, such as death or permanent disability, are being considered, if a therapy is beneficial, there is an ethical requirement to stop the trial. But repeated interim analyses inflate the Type I error. This problem has been dealt with extensively in the biostatistical literature under the rubric of *sequential analysis*. Boundaries for values of a test statistic that would stop the trial at different times have been studied extensively (e.g., O'Brien and Fleming [1979]; Whitehead [1983]; Jennison and Turnbull [2000]; Lan and DeMets [1983]). In recent years, methods have been developed that allow examination of the results by treatment arm, with resulting modifications of the trial that still preserve the Type I error (e.g., Fisher [1998b]; Cui et al. [1999]). A basic strategy is to parcel out the Type I error over the trial. For example, suppose that two interim analyses are planned during the course of a study. Then test the results for the two interim analyses at the 0.001 level and the final analysis at the 0.048 level. This still ensures an overall level of 0.05.

19.6.3 Multiple Endpoints, Multivariate Endpoints, and Composite Endpoints

In some situations, multiple endpoints may be used to demonstrate the benefit of a new therapy. Of course, one cannot simply look at all of them and claim success if any one of them meets the significance level used in the RCT because the multiple comparisons inflate the Type I error. Several strategies have been used:

1. Select one of the possible beneficial endpoints to be the primary analysis for trial.
2. Adjust the p-value to account for the multiple comparisons. A conservative adjustment is to use the Bonferroni inequality and its refinements (Chapter 12) [Wright, 1992]. If the possible endpoints are positively correlated, as is usually the case, less severe adjustments are possible using the randomization distribution for the RCT.
3. The various components of possible endpoints can be considered to be a vector (i.e., arranged in sequence), and methods are available to test all the endpoints at once.
4. Sometimes an index, a weighted sum of the endpoints, is used as the one primary endpoint (see Schouten [2000]).
5. When a number of endpoints occur as distinct events in time, the first occurrence of any of them can be used as one event. Comparisons may be made using the methods of survival, or time to event, analysis (Chapter 16).

These issues are discussed in more detail in Chapter 12.

19.7 DRUG DEVELOPMENT PARADIGM

The following points introduce some of the ideas and terminology used in the development of drugs and biologics (see Mathieu [2002] for more). The first step is to identify a potential drug (a molecule). This used to be accomplished largely by chance (e.g., the discovery of penicillin) or through large screening programs, but because of recent substantial advances in genetics, molecular biology, and computer modeling, more and more compounds are being designed for specific purposes. Compounds may be screened for *in vitro* (i.e., "in glass") reaction with known molecules to identify candidates.

The first testing is carried out in several animal species. This *preclinical phase* of drug development accomplishes several purposes. Among the purposes are the following: The first is to identify if a drug is toxic at most possible doses (both short-term and longer-term studies in at least two species are done). Second, a range of doses can be evaluated. Are there doses that are not toxic (that have efficacy at the lower doses)? Third, use of an animal species will sometimes allow examination of an efficacy assessment vs. toxicity as a function of the dose. Other tasks

performed are to look for the formation of fetal and birth abnormalities (*teratogenicity studies*), to see if drugs cause cancer (*carcinogenicity*, as a function of animal species and dose), and to see if gene abnormality results (*mutagenicity testing*). Of course, usually, the more drug one takes, the greater the amount that enters the body. One studies the time course of the drug [whether administered as a pill or capsule, by injection (intravenously or intramuscularly), by inhalation, etc.] within the body. Almost all drugs change into other molecules (metabolites) when in the body. Study of the time course of adsorption, distribution, metabolism, and elimination of the drug molecule and its metabolites comprises the field of drug *pharmacokinetics*. The relationship of the drug time–concentration value to the magnitude of effect is the field of *pharmacodynamics*.

After the preclinical data have been reviewed (in the United States) and approved by appropriate authorities, testing may begin in humans. *Phase I* of drug development is initial use of the drug in humans. Unfortunately, the preclinical animal testing gives only a rough idea of possible appropriate doses in humans. The animal data are often predictive only to an order of magnitude, so testing in humans usually begins at a very low dose and is slowly escalated. If the drug is anticipated to be well tolerated by normal subjects, the initial testing is usually done in healthy, normal volunteers. Drugs that are harmful by their nature [e.g., cancer (oncology) drugs that kill cells] are tested initially in patients. Some idea of activity may be gained in this initial phase. Slow escalation of the dose given helps to establish a preliminary dose range for the compound.

Phase II studies are reasonably large studies that give preliminary evidence of the efficacy of a drug in humans, to determine reasonable doses, and to get evidence on safety and tolerability in a patient population. These studies are often not blinded.

Phase III studies are large, randomized clinical trials to establish efficacy and safety. For most drugs it is expected that there will be at least two independent RCTs, double-blinded where possible, that establish efficacy at the 0.05 significance level. An increasing number of active control trials are being conducted in which noninferiority is established by showing that the new compound does not differ from the active control by more than a small equivalence margin (see, e.g., Temple and Ellenberg [2000]; Ellenberg and Temple [2000]). Often, the Phase III trials for efficacy do not provide adequate experience to evaluate patient safety. There often are *open label* (i.e., patient and physician know what treatment the subject is getting) extensions, where all patients get the new therapy if they consent to continue in the study. These trials may enroll more subjects, to get additional safety data.

After drugs are approved, *postmarketing*, or *Phase IV*, studies are sometimes performed for a variety of purposes: to collect more safety data, to do additional evaluation of efficacy (sometimes using a different endpoint), or to study efficacy in a broader, representative population.

19.8 SUMMARY

RCTs are difficult, expensive, ethically challenging, and require great attention to planning and monitoring operationally. Still the benefits are generally agreed to be worth the effort. This type of human experimentation gives the most cogent and convincing proof of the benefit of a new therapy. Further, the control group (whether a placebo or a proven active therapy) provides a better comparison of the safety of a new therapy. The benefit and risk must be traded off in the approval of new therapies.

NOTES

19.1 Interventions Other Than Drugs

In the discussion above we have discussed RCTs primarily as if they were for new drugs or biologics. Many interventions, such as medical devices, have been and/or could be investigated using RCTs or analogs. A variety of surgical interventions have been investigated by RCTs.

Prevention programs, such as smoking-cessation programs, can be investigated by randomizing larger experimental units. For example, in an NIH study of smoking prevention, the school district was the unit of randomization [Peterson et al., 2000]. One could randomize to different health care strategies, different modes of psychotherapy, and so on. In these studies the unit of randomization may be much larger; such group randomization is discussed by Feng et al. [2001].

19.2 Drug Approval and Physician Use of Drugs

In the United States, drugs are approved by the Food and Drug Administration. The approval includes labeling that specifies the population the drug is to benefit (i.e., the *indication*) as well as dosing information and warnings about safety, interactions with other drugs, and so on. Physicians may then legally use the drug for other indications (other diseases or patient populations) without violating the law (*off-label use*). If this use is in accord with the practice norms of the community, adequate malpractice defense can often be established. Drug companies selling the drugs are prohibited by law from advertising such off-label use of their product. One suspects that implied off-label uses are sometimes promoted.

19.3 Generic Drugs

In the United States, from the time that human experimentation begins, a sponsor has exclusive rights to sell the drug (assuming approval) for a limited period of time. The rights are for 17 years from the time the application is approved for experimentation on humans. Thus, there is a limited time to recoup research costs and make a profit. After this time, others may manufacture and sell the drug provided that they establish that it is the same drug (*bioequivalence*). These are called *generic drugs*. Equivalence is shown by establishing that the pharmacokinetics is the same for the new version and the original approved version. We do not address the topic of bioequivalence further here (see Chow and Liu [2000]).

19.4 Further Reading: Specific Topics

For more information on informed consent see, for example, Faden and Beauchamp [1986]. For a mathematical discussion of what constitutes an appropriate surrogate endpoint, see the paper of Prentice [1989]. For nice discussions of the history of blinding, see the papers by Kaptchuk [1998] and Chalmers [2001]. Some references on the benefits of the randomized clinical trial are Ederer [1975], Green [1982], Greenberg [1951], and Kempthorne [1977].

Since the 1970s, the number of articles and books about RCTs and statistical analysis has grown exponentially (e.g., books on clinical trials: Bulpitt, 1996; Cato and Sutton, 2002; Chow and Liu, 2003; Cleophas et al., 2002; Duley and Farrell, 2002; Friedman et al., 1999; Matthews, 2000; Meinert, 1986; Mulay, 2001; Norleans, 2001; Piantadosi, 1997; Pocock, 1996; Spilker, 1991).

There are numerous books about particular disease areas (e.g., AIDS [Finkelstein and Schoenfeld, 1999]; cardiology and cardiovascular disease [Hennekens and Zorab, 2000; Pitt et al., 1997]; epilepsy [French et al., 1997]; hypertension [Black, 2001]; multiple sclerosis [Goodkin and Rudick, 1998]; neurology [Guilogg, 2001; Porter and Schoenberg, 1990]; oncology [Green et al., 2002]; opthamology [Kertes and Conway, 1998]); and for material for patients [Giffels, 1996; Slevin and Wood, 1996]; aspects of trials, such as quality of life and pharmacoeconomics [Fairclough, 2002; Spilker, 1995]; data management [McFadden, 1997]; combining data from trials (metaanalysis: [Whitehead, 2002]; evaluating the literature [Ascione, 2001]; and dictionary or encyclopedic entries [Day, 1999; Redmond et al., 2001]).

REFERENCES

American Statistical Association [1999]. *Ethical Guidelines for Statistical Practice.* ASA, Alexandria, VI.

Ascione, F. J. [2001]. *Principles of Scientific Literature Evaluation: Critiquing Clinical Drug Trials*. American Pharmaceutical Association, Washington, DC.

Beauchamp, T. L., and Childress, J. F. [2001]. *Principles of Biomedical Ethics*, 5th ed. Oxford University Press, New York.

Bigger, J. T., Jr., [1990]. Editorial: the events surrounding the removal of encainide and flecainide from the Cardiac Arrhythmia Suppression Trial (CAST) and why CAST is continuing with moricizine. *Journal of the American College of Cardiology*, **15**: 243–245.

Black, H. R. [2001]. *Clinical Trials in the Pharmacologic Management of Hypertension*. Marcel Dekker, New York.

Box, J. F. [1978]. *R. A. Fisher: The Life of a Scientist*. Wiley, New York, p. 146.

Bulpitt, C. J. [1996]. *Randomized Controlled Clinical Trials*. Kluwer Academic, New York.

Cardiac Arrhythmia Pilot Study (CAPS) Investigators [1988]. Effect of encainide, flecainide, imipramine and moricizine on ventricular arrhythmias during the year after acute myocardial infarction: the CAPS. *American Journal of Cardiology*, **61**: 501–509.

Cardiac Arrhythmia Suppression Trial (CAST) Investigators [1989]. Preliminary report: effect of encainide and flecainide on mortality in a randomized trial of arrhythmia suppression after myocardial infarction. *New England Journal of Medicine,* **321**: 406–412.

Cato, A. E., and Sutton, L. [2002]. *Clinical Drug Trials and Tribulations*, 2nd ed. Marcel Dekker, New York.

Chalmers, I. [2001]. Comparing like with like: some historical milestones in the evolution of methods to create unbiased groups in therapeutic experiments. *International Journal of Epidemiology*, **30**: 1156–1164.

Chow, S.-C., and Liu, J.-P. [2003]. *Design and Analysis of Clinical Trials: Concepts and Methodologies*, 2nd ed. Wiley, New York.

Chow, S.-C., and Liu, J.-P. [2000]. *Design and Analysis of Bioavailability and Bioequivalence Studies*, rev. ed. Marcel Dekker, New York.

Cleophas, T. J., Zwinderman, A. H., and Cleophas, T. F. [2002]. *Statistics Applied to Clinical Trials*. Kluwer Academic, New York.

Coronary Drug Project Research Group [1980]. Influence of adherence to treatment and response of cholesterol on mortality in the coronary drug project. *New England Journal of Medicine*, **303**: 1038–1041.

Cui, L., Hung, H. M. J., and Wang, S.-J. [1999]. Modification of sample size in group sequential clinical trials. *Biometrics*, **55**: 853–857.

Day, S. [1999]. *Dictionary for Clinical Trials*. Wiley, New York.

Duley, L., and Farrell, B. (eds.) [2002]. *Clinical Trials*. British Medical Association, London.

Echt, D. S., Liebson, P. R., Mitchell, B., Peters, R. W., Obias-Manno, D., Barker, A. H., Arensberg, D., Baker, A. Friedman, L., Greene, H. L., Huther, M. L., Richardson, D. W., and the CAST Investigators [1991]. Mortality and morbidity in patients receiving encainide, flecainide, or placebo: the Cardiac Arrhythmia Suppression Trial. *New England Journal of Medicine*, **324**: 781–788.

Ederer, F. [1975]. Why do we need controls? Why do we need to randomize? *American Journal of Ophthalmology*, **79**: 758–762.

Edgington, E. S. [1995]. *Randomization Tests*, 3rd rev. exp. ed. Marcel Dekker, New York.

Efron, B. [1971]. Forcing a sequential experiment to be balanced. *Biometrika*, **58**: 403–417.

Ellenberg, S. S., and Temple, R. [2000]. Placebo-controlled trials and active-control trials in the evaluation of new treatments: 2. Practical issues and specific cases. *Annals of Internal Medicine*, **133**: 464–470.

Ellenberg, S. S., Fleming, T. R., and DeMets, D. L. [2002]. *Data Monitoring Committees in Clinical Trials*. Wiley, New York.

Faden, R. R., and Beauchamp, T. L. [1986]. *A History and Theory of Informed Consent*. Oxford University Press, New York.

Fairclough, D. L. [2002]. *Design and Analysis of Quality of Life Studies in Clinical Trials*. CRC Press, Boca Raton, FL.

Federal Regulations [1988]. 21 CFR Ch. I, Part 56: Institutional Review Boards (4-1-88 ed.). U.S. Government Printing Office, Washington, DC.

Feng, Z., Diehr, P., Peterson, A., and McLerran, D. [2001]. Selected statistical issues in group randomized trials. *Annual Review of Public Health*, **22**: 167–187.

Finkelstein, D. M., and Schoenfeld, D. A. [1999]. *AIDS Clinical Trials*. Wiley, New York.

Fisher, L. D. [1998a]. Ethics of randomized clinical trials. In *Encyclopedia of Biostatistics*, Vol. 2, P. Armitage and T. Colton (eds.). Wiley, New York, pp. 1394–1398.

Fisher, L. D. [1998b]. Self-designing clinical trials. *Statistics in Medicine,* **17**: 1551–1562.

Fisher, L. D, Dixon, D. O., Herson, J., Frankowski, R. F., Hearron, M. S., and Peace, K. E. [1990]. Intention to treat in clinical trials. In *Statistical Issues in Drug Research and Development*, K. E. Peace (ed.). Marcel Dekker, New York, pp. 331–350.

Fleming, T. R., and DeMets, D. L. [1996]. Surrogate endpoints in clinical trials: are we being mislead? *Annals of Internal Medicine*, **125**: 605–613.

French, J. A., Leppik, I. E., and Dichter, M. A. [1997]. *Antiepileptic Drug Trials*, Vol. 76. Lippincott Williams & Wilkins, Philadelphia.

Friedman, L., Furberg, C., and DeMets, D. L. [1999]. *Fundamentals of Clinical Trials*, 3rd ed. Springer-Verlag, New York.

Furberg, C. D. [1983]. Effect of antiarrhythmic drugs on mortality after myocardial infarction. *American Journal of Cardiology*, **52**: 32C–36C.

Giffels, J. J. [1996]. *Clinical Trials: What You Should Know before Volunteering to Be a Research Subject*. Demos Medical Publishing, New York.

Goodkin, D. E., and Rudick, R. A. [1998]. *Multiple Sclerosis: Advances in Clinical Trial Design, Treatment and Perspectives*. Springer, New York.

Graboys, T. B., Lown, B., Podrid, P. J., and DeSilva, R. [1982]. Long-term survival of patients with malignant ventricular arrhythmia treated with antiarrhythmic drugs. *American Journal of Cardiology*, **50**: 437–443.

Green, S. B. [1982]. Patient heterogeneity and the need for randomized clinical trials. *Controlled Clinical Trials*, **3**: 189–198.

Green, S., Benedetti, J., and Crowley, J. [2002]. *Clinical Trials in Oncology*, 2nd ed. CRC Press, Boca Raton, FL.

Greenberg, B. G. [1951]. Why randomize? *Biometrics*, **7**: 309–322.

Guilogg, R. J. (ed.) [2001]. *Clinical Trials in Neurology*. Springer, New York.

Hennekens, C. H., and Zorab, R. [2000]. *Clinical Trials in Cardiovascular Disease: A Companion to Braunwald's Heart Disease*. W. B. Saunders, Philadelphia.

IMPACT Research Group [1984]. International Mexiletine and placebo antiarrhythmic coronary trial: I. Report on arrhythmias and other findings. *Journal of the American College of Cardiology*, **4**: 1148–1163.

Jennison, C., and Turnbull, B. W. [2000]. *Group Sequential Methods with Applications to Clinical Trials*. Chapman & Hall, New York.

Kaptchuk, T. J. [1998]. Intentional ignorance: a history of blind assessment and placebo controls in medicine. *Bulletin of the History of Medicine*, **72**: 389–433.

Karlowski, T. R., Chalmers, T. C., Frenkel, L. D., Zapikian, A. Z., Lewis, T. L., and Lynch, J. M. [1975]. Ascorbic acid for the common cold: a prophylactic and therapeutic trial. *Journal of the American Medical Association*, **231**: 1038–1042.

Kempthorne, O. [1977]. Why randomize? *Journal of Statistical Planning and Inference*, **1**: 1–25.

Kertes, P. J., and Conway, M. D. [1998]. *Clinical Trials in Opthamology: A Summary and Practice Guide*. Lippincott Williams & Wilkins, Philadelphia.

Kesteloot, H., and Joosens, J. V. [1980]. *Epidemiology of Arterial Blood Pressure: Developments in Cardiovascular Medicine*, Vol. 8. Martinus Nijhoff, Dordrecht, The Netherlands.

Lan, K. K. G., and DeMets, D. L. [1983]. Discrete sequential boundaries for clinical trials. *Biometrika*, **70**: 659–663.

Lifton, R. J. [1986]. *The Nazi Doctors: Medical Killing and the Psychology of Genocide*. Basic Books, New York.

Little, R. J. A., and Rubin, D. B. [2002]. *Statistical Analysis of Missing Data*, 2nd ed. Wiley, New York.

Mathieu, M. [2002]. *New Drug Development: Regulation Overview*. Parexel International Corporation, Cambridge, MA.

Matthews, J. N. [2000]. *Introduction to Randomized Controlled Clinical Trials*. Edward Arnold, London.

McFadden, E. [1997]. *Management of Data in Clinical Trials*. Wiley, New York.

Meinert, C. L. [1986]. *Clinical Trials: Design, Conduct, and Analysis*. Oxford University Press, New York.

Mulay, M. [2001]. *A Step-by-Step Guide to Clinical Trials*. Jones & Bartlett, Boston.

Norleans, M. X. [2001]. *Statistical Methods for Clinical Trials*. Marcel Dekker, New York.

O'Brien, P. C., and Fleming, T. R. [1979]. A multiple testing procedure for clinical trials. *Biometrics*, **35**: 549–556.

Peterson, A. V., Mann, S. L., Kealey, K. A., and Marek, P. M. [2000]. Experimental design and methods for school-based randomized trials: experience from the Hutchinson smoking prevention project (HSPP). *Controlled Clinical Trials*, **21**: 144–165.

Piantadosi, S. [1997]. *Clinical Trials: A Methodologic Perspective*. Wiley, New York.

Pitt, B., Julian, D., and Pocock, S. J. [1997]. *Clinical Trials in Cardiology*. W. B. Saunders, Philadelphia.

Pocock, S. J. [1982]. Interim analyses for randomized clinical trials: the group sequential approach. *Biometrics*, **38**: 153–162.

Pocock, S. J. [1996]. *Clinical Trials: A Practical Approach*. Wiley, New York.

Pope, A. [1733]. *An Essay on Man*. Cited in [1968] *Bartlett's Familiar Quotations*, 14th ed. Little, Brown, Boston.

Porter, R. J., and Schoenberg, B. S. [1990]. *Controlled Clinical Trials in Neurological Disease.* Kluwer Academic, New York.

Pratt, C. M. (ed.) [1990]. A symposium: the Cardiac Arrhythmia Suppression Trial—does it alter our concepts of and approaches to ventricular arrhythmias? *American Journal of Cardiology*, **65**: 1B–42B.

Pratt, C. M., Brater, D. C., Harrell, F. E., Jr., Kowey, P. R., Leier, C. V., Lowenthal, D. T., Messerlie, F., Packer, M., Pritchett, E. L. C., and Ruskin, J. N. [1990]. Clinical and regulatory implications of the Cardiac Arrhythmia Suppression Trial. *American Journal of Cardiology*, **65**: 103–105.

Prentice, R. L. [1989]. Surrogate endpoints in clinical trials: definition and operational criteria. *Statistics in Medicine*, **8**: 431–440.

Redmond, C. K., Colton, T., and Stephenson, J. [2001]. *Biostatistics in Clinical Trials*. Wiley, New York.

Reiser, S. J., Dyck, A. J., and Curran, W. J. (eds.). [1947]. The Nuremberg Code. in *Ethics in Medicine: Historical Perspectives and Contemporary Concerns*. MIT Press, Cambridge, MA, pp. 272–274.

Royal Statistical Society [1993]. *Code of Conduct*. RSS, London.

Ruskin, J. N. [1989]. The cardiac arrhythmia suppression trial (CAST) (editorial). *New England Journal of Medicine*, **321**: 386–388.

Schouten, H. J. A. [2000]. Combined evidence from multiple outcomes in a clinical trial. *Journal of Clinical Epidemiology*, **53**: 1137–1144.

Slevin, M., and Wood, S. [1996]. *Understanding Clinical Trials*. Cancer BACUP, London. *http://www.cancerbacup.org.uk/info/trials.htm.* Accessed June 10, 2003.

Spilker, B. [1991]. *Guide to Clinical Trials*. Lippincott Williams & Wilkins, Philadelphia.

Spilker, B. [1995]. *Quality of Life and Pharmacoeconomics in Clinical Trials*. Lippincott Williams & Wilkins, Philadelphia.

Student [1931]. The Lanarkshire milk experiment. *Biometrika*, **23**: 398–406.

Temple, R. J. [1995]. A regulatory authority's opinion about surrogate endpoints. In *Clinical Measurement in Drug Evaluation,* W. S. Nimmo and G. T. Tucker, (eds.). Wiley, New York, pp. 3–22.

Temple, R., and Ellenberg, S. S. [2000]. Placebo-controlled trials and active-control trials in the evaluation of new treatments: 1. Ethical and scientific issues. *Annals of Internal Medicine*, **133**: 455–463.

Thomas, L. [1983]. *The Youngest Science*. pp. 30–31. New York, NY, The Viking Press.

Wall Street Journal [2001]. Cost of drug development found to rise, p. B14, Dec. 3, 2001, taken from the Tufts Center for Drug Development. Also given in Tufts Center for the Study of Drug Development, *Outlook 2002*, Boston.

Whitehead J. [1983]. *The Design and Analysis of Sequential Clinical Trials*. Ellis Horwood, Chichester, West Sussex, England.

Whitehead, A. [2002]. *Meta-analysis of Controlled Clinical Trials*. Wiley, New York.

World Medical Association [1975]. Declaration of Helsinki, revision of original 1964 version. In *Ethics in Medicine: Historical Perspectives and Contemporary Concerns*, S. J., Reiser, A. J. Dyck, and W. J., Curran, (eds.). MIT Press, Cambridge, MA, pp. 328–330.

Wright, S. P. [1992]. Adjusted p-values for simultaneous inference. *Biometrics*, **48**: 1005–1013.

CHAPTER 20

Personal Postscript

20.1 INTRODUCTION

One reviewer of this book felt that it would be desirable to have a final chapter that ended the book with more interesting material than yet another statistical method. This stimulated us to think about all the exciting, satisfying, and interesting things that had occurred in our own careers as biostatisticians. We decided to try to convey some of these feelings through our own experiences. This chapter is unabashedly written from a first-person point of view. The examples do not represent a random sample of our experiences but rather, the most important and/or interesting experiences of our careers. There is some deliberate duplication of background material that appears in other chapters so that this chapter may be self-contained (except for the statistical methods used). We have not made an effort to choose experiences that illustrate the use of many different statistical methods (although this would have been possible). Rather, we want to entertain, and in doing so, show the important collaborative role of biostatistics in biomedical research.

20.2 IS THERE TOO MUCH CORONARY ARTERY SURGERY?

The National Institutes of Health in the United States funds much of the health research in the country. During the late 1960s and early 1970s, an exciting new technique for dealing with anginal chest pain caused by coronary artery disease was developed. Recall that coronary artery disease is caused by fibrous fatty deposits building up within the arteries that supply blood to the heart muscle (i.e., the coronary arteries). As the arteries narrow, the blood supply to the heart is inadequate when there are increased demands because of exercise and/or stress; the resulting pain is called *angina*. Further, the narrowed arteries tend to close with blood clots, which results in the death (infarction) of heart muscle (myocardium), whose oxygen and nutrients are supplied by the blood coming through the artery; these heart attacks are also called *myocardial infarctions* (Mls). *Coronary artery bypass graft* (CABG; pronounced "cabbage") surgery replumbs the system. Either saphenous veins from the leg or the internal mammary arteries already in the chest are used to supply blood beyond the narrowing, that is, bypassing the narrowing. Figure 20.1 shows the results of bypass surgery. A key measure of damaged arteries is the *ejection fraction* (EF), the proportion of blood pushed out of the pumping chamber of the heart, the left ventricle. A normal value is 0.5 or greater. EF values between 0.35 and 0.49 are considered evidence of mild to moderate impairment. When the heart muscle is damaged, say by an MI, or has a limited blood supply, the EF decreases.

Biostatistics: A Methodology for the Health Sciences, Second Edition, by Gerald van Belle, Lloyd D. Fisher, Patrick J. Heagerty, and Thomas S. Lumley
ISBN 0-471-03185-2

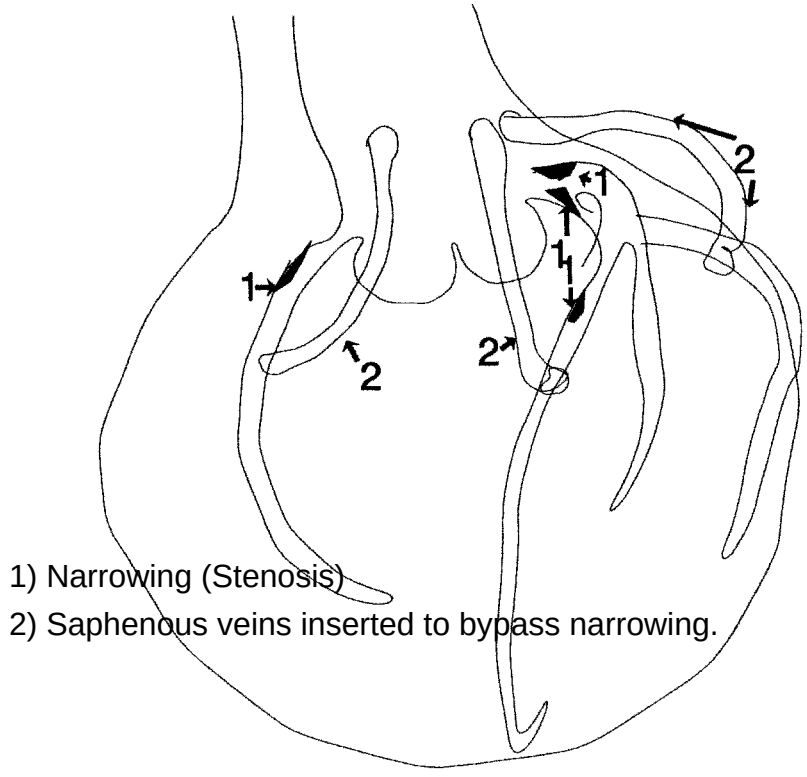


Figure 20.1 Schematic display of coronary artery bypass graft surgery. Here saphenous veins from the leg are sewn into the aorta where the blood is pumped out of the heart and then sewn into coronary arteries beyond narrowings in order to deliver a normal blood supply.

Because the restored blood flow should allow normal function, it was conjectured that surgery would both remove the anginal pain and also prolong life by reducing both the stress on the heart and the number of myocardial infarctions. It became clear early on that surgery did help to relieve angina pain (although even this has been debated; see Preston [1977]). However, the issue of prolonging life was more debatable. The amount of surgery had important implications for the health care budget, since in the early 1970s the cost per operation ranged between $12,000 and $50,000, depending on the location of the clinic, complexity of the surgery, and a variety of other factors. The number of surgeries by year up to 1972 is shown in Figure 20.2.

Because of the potential savings in lives and the large health resources requirements, the National Heart, Lung and Blood Institute (NHLBI; at that time the National Heart Institute) decided that it was appropriate to obtain firm information about which patients have improved survival with CABG surgery. Such therapeutic comparisons are best addressed through a randomized clinical trial, and that was the approach taken here with randomization to early surgery or early medical treatment. However, because not all patients could ethically be randomized, it was also decided to have a registry of patients studied with coronary angiography so that observational data analyses could be performed on other subsets of patients to compare medical and surgical therapy. When the NHLBI has internally sponsored initiatives, they are developed through a request for proposals (RFP), which recruits investigators to perform the collaborative research. This trial and registry, called the Coronary Artery Surgery Study (CASS), had two RFPs; one was for clinical sites and the other for a coordinating center. The RFP for the

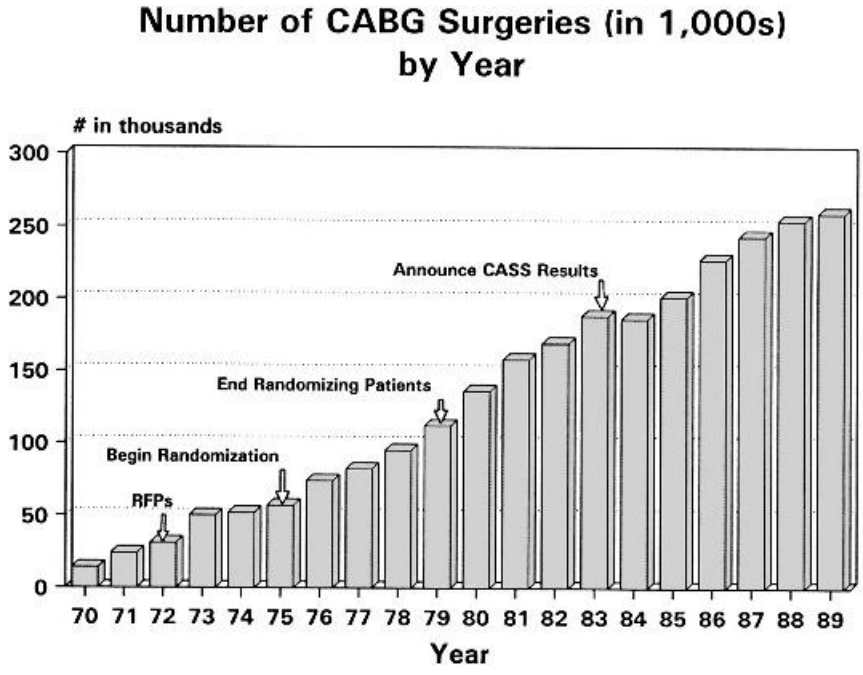


Figure 20.2 Number of coronary artery bypass graft surgeries in thousands of operations by year, 1970–1989. Marked are some of the key time points in the Coronary Artery Surgery Study. (Data courtesy of the cardiac diseases branch of the National Heart, Lung and Blood Institute from the National Hospital Discharge Survey, National Center for Health Services.)

clinical sites was issued in November 1972 and described the proposed study, both randomized and registry components, and asked for clinics to help complete the design and to enroll patients in the randomized and registry components of the study. The coordinating center RFP requested applications for a center to help with the statistical design and analysis of the study, to receive and process the study forms with a resultant database, to produce reports for monitoring the progress of the study and to otherwise participate in the quality assurance of the study, and finally, to collaborate in the analysis and publication of the randomized study and registry results. The organization of such a large multicenter study had a number of components: The NHLBI had a program office with medical, biostatistical, and financial expertise to oversee operation of the study; there were 15 cooperating clinical sites in the United States and Canada; the Coordinating Center was at the University of Washington under the joint direction of Lloyd Fisher and Richard Kronmal; a laboratory to read electrocardiograms (ECG lab) was established at the University of Alabama.

The randomized study enrolled 780 cases with mild angina or no angina with a prior MI, and significant disease (defined as a 70% or greater narrowing of the internal diameter of a coronary artery that was suitable for bypass surgery). There were a variety of other criteria for eligibility for randomization. The registry, including the patients randomized, enrolled 24,959 patients. Extensive data were collected on all patients. The first patients were enrolled in July 1974, with randomization beginning in August 1975 [CASS Principal Investigators and Their Associates, 1981]. Follow-up of patients within the randomized study ended in 1992. Needless to say, such a large effort cost a considerable amount of money, over $30,000,000. It will be shown that the investment was very cost-effective.

Results of the survival analysis and indicators of the quality of life were made public in 1983 [CASS Investigators, 1983a,b, 1984b]. The survival estimates for the subjects randomized to

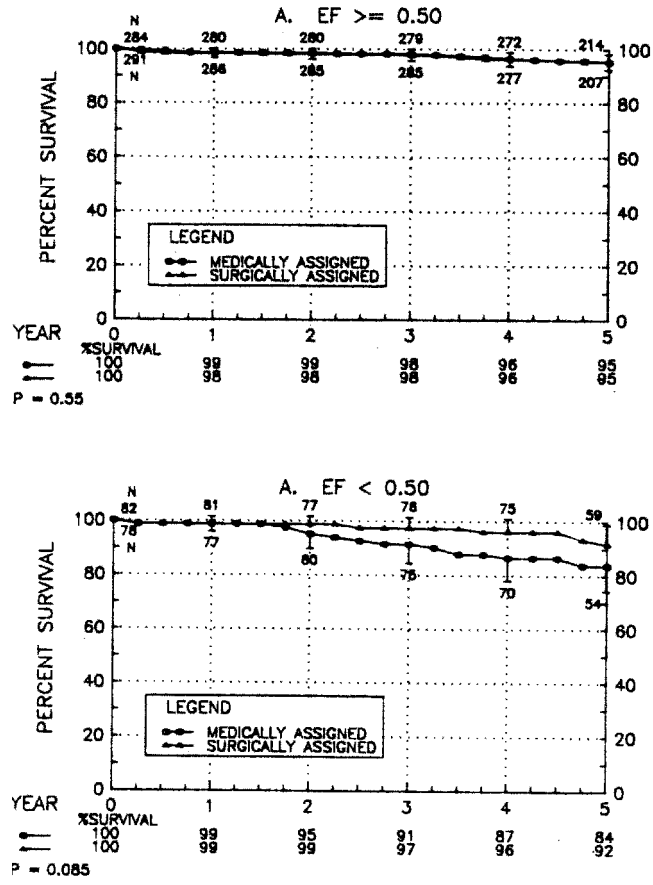


Figure 20.3 Data from the CASS randomized clinical trial; the bottom panel is for patients with ejection fractions less than 0.50; the top panel is for patients with ejection fractions of 0.50 or above. The p-values are the log-rank statistic for the comparison.

initial medical and surgical treatment are given in Figure 20.3. For patients with an EF of 0.5 or more, the survival curves were virtually identical; for subjects with lower EF values, there was a trend toward favorable mortality in the surgery group ($p = 0.085$ by the log-rank test).

A number of points were important in interpreting these data:

1. The CASS investigators agreed before the study started that the surgery was efficacious in relieving angina. Thus, if a patient started to have severe angina that could not be controlled by medication, the patient was allowed to "cross over" to surgery. By year 5, 24% of the patients assigned to initial medical therapy had crossed over to the CABG surgery group. If surgery is, in fact, having a beneficial effect and there is much crossover, the statistical power of the comparison is reduced. Is this a bad thing? The issue is a complex one (see Peto et al. [1977]; Weinstein and Levin [1989]; Fisher et al. [1989, 1990]). We know that one of the benefits of randomization is that we are assured of comparable groups (on average) even with respect to unrecorded and unknown variables. If we manipulated people, or parts of their experience, between groups by using events that occurred after the time of randomization, bias can enter the analysis. Thus, people should be included only in the group to which they are randomized; this is called an *intent-to-treat analysis* since they are counted with the group whose treatment

was intended. (Does such an approach avoid bias? Does it always make biological sense?) The CASS investigators favored an intent-to-treat analysis not only because it avoided possible bias but also because of the ethical imperative to perform CABG surgery for pain relief when the pain became intractable under medical treatment. Thus, including all the experience of those assigned to initial medical treatment, including CABG surgery and subsequent events, mirrored what would happen to such a group in real life. This is the question that the trial should answer: Is early surgery helpful when patients will receive it anyway when the pain becomes too severe? However, the power of such a comparison will be diminished by the crossovers. The interpretation of such intent-to-treat analyses must acknowledge that without the crossover, the results could have been substantially different.

2. Because bypass surgery is such a big industry (e.g., 200,000 surgeries per year at $30,000 per operation adds up to $6 billion per year), with many careers and much professional prestige committed to the field, one could expect a counter reaction if surgery did not look beneficial. Such reactions did occur, and a number of editorials, reviews, and sessions at professional meetings were given to consideration of the results. One of the authors (LF) appeared on the CBS national news as well as going to New York City to be interviewed by Mike Wallace and appearing on the TV program *60-minutes*. Based largely on the CASS results, the program suggested that there was too much CABG surgery.

3. It is important to keep the findings in context. They did not apply to all, or even most, patients. The CASS was one of three major randomized trials of CABG surgery. One study showed definitively that the surgery prolonged life in patients with left main disease [Takaro et al., 1976]. This study excluded patients with severe angina and thus had nothing to say about differential survival in such patients. In fact, there is observational data to suggest that early elective CABG surgery prolonged life in such patients [Kaiser et al., 1985; Myers et al., 1989].

4. Even though the findings may apply to a *relatively* small number of patients, the results could have a very substantial impact on the national health scene. Subsequent CASS papers showed that the trend toward increased survival with surgery in the low ejection fraction patients was real [Passamani et al., 1985; Alderman et al., 1990]. Thus, suppose that we restrict ourselves to those patients with EFs of at least 0.5. This accounted for 575 of the 780 randomized patients. Suppose that the randomized study had not been in effect; how many of these patients might have received early surgery? In the CASS study, there were 1315 patients who met the eligibility criteria and might have been randomized but in fact were not randomized [CASS Principal Investigators, 1984a; Chaitman et al., 1990]; these patients were called the *randomizable patients*. In this group, 43% (570/1315) received early elective surgery. Of those who did not receive early surgery and had good ejection fractions, by 10 years, 38% had received surgery. That is, 60% or so did not receive surgery. Assuming that the CASS clinics were representative of the surgical practice in the country (they may have been more conservative than many centers because they were willing to participate in research to assess the appropriate role of bypass surgery), about 4.4% of the surgery in the United States might be prevented by applying the results of the study. In a year with 188,000 CABGs costing $30,000 each, this would lead to a savings of over $245 million. Over a 4-year period over $1 billion could be saved in surgical costs. However, because the patients treated medically have more anginal pain, they have higher drug costs; they might have higher hospitalization costs (but they do not; see CASS Principal Investigators [1983b] and Rogers et al. [1990]). Without going into detail, it is my (L.F.) opinion that the study saved several billion dollars in health care costs without added risk to patient lives.

5. The issues are more complex than presented here; we have not discussed the findings and integration of results with the other major randomized studies of CABG surgery. Further, it is important to note that a number of other proven and/or promising techniques for dealing with coronary artery disease (CAD) have been developed. These include drug and/or dietary therapy; blowing up balloons in the artery to "squish" the narrowing into the walls of the artery [**p**ercutaneous **t**ransluminal **c**oronary **a**ngioplasty (PTCA)]; introducing lasers into the coronary

arteries to disintegrate the plaques that narrow the arteries; using a roto-rooter in the arteries to replumb by grinding up the plaques; and stents. Although all of these alternatives have been or are being used, the number of CABG surgeries did not decrease but leveled off up to 1989.

6. The surgery may improve with time as techniques and skills improve. Further, it became apparent that the results of the surgery deteriorated at 10 to 12 years or so. The disease process at work in the coronary arteries also was at work in the grafts that bypassed the narrowed areas; thus the grafts themselves narrow and close, often requiring repeat CABG surgery. Internal mammary grafts have a longer lifetime and are now used more often, suggesting that current long-term results will be better.

In summary, the CASS study showed that in patients with selected characteristics, CABG surgery is not needed immediately to prolong life and can often be avoided. The study was a bargain both in human and economic terms, illustrating the need and benefits of careful evaluation of important health care procedures.

20.3 SCIENCE, REGULATION, AND THE STOCK MARKET

In the United States, foods, drugs, biologics, devices, and cosmetics are regulated by the Food and Drug Administration (FDA). To get a new drug or biologic approved for marketing within the United States, the sponsor (usually, a pharmaceutical company or biotechnology company) must perform adequate and well-controlled clinical trials that show the efficacy and safety of the product. The FDA is staffed with personnel who have expertise in a number of areas, including pharmacology, medicine, and biostatistics. The FDA staff reviews materials submitted and rules on the approval or nonapproval of a product. The FDA also regulates marketing of the compounds. Marketing before approval is not allowed. The FDA uses the services of a number of advisory committees composed of experts in the areas considered. The deliberations of the advisory committees are carried out in public, often with large audiences in attendance. At the meetings, the sponsor makes a presentation, usually with both company and clinical experts, and answers questions from the committee. The FDA has a presence, asks questions, particularly of the advisory committee, but usually does not play a dominant role. At the end of its deliberations the committee votes on whether the drug or biologic should be approved, should be disapproved, or should be disapproved at least temporarily because further information is needed before final approval or disapproval is appropriate.

Two of the authors have been members of FDA advisory committees, G.vB. with the peripheral and central nervous system drugs advisory committee and L.F. with the cardiovascular and renal drugs advisory committee. Here we discuss the consideration of one biologic: tissue plasminogen activator (tPA). A *biologic* is a compound that occurs naturally in the human body, whereas a *drug* is a compound that does not occur naturally but is introduced artificially, solely for therapeutic purposes. For example, insulin is a biologic, whereas aspirin is a drug. Here we will use the term *drug* for tPA because that is the more common usage, although within the FDA, drugs and biologics go to different divisions. We turn next to the background and rationale for the use of tPA.

As discussed above, when coronary artery disease occurs, it narrows the arteries, changing the fluid flow properties of the blood, leading to clotting within the coronary arteries. These clots then block the blood supply to the heart muscle, resulting in heart attacks, or myocardial infarctions (MIs), as discussed above. The clot is composed largely of fibrin. When converted to plasmin, plasminogen converts insoluble fibrin into soluble fragments. One conceptual way to treat a heart attack would be to dissolve the blood clot, thus reestablishing blood flow to the heart muscle and preventing the death of the muscle, saving the heart and often saving the life. Should a drug be approved for dissolving blood clots alone? Although biologically plausible, does this assure that the drug will work? In other words, is this an acceptable surrogate endpoint?

Returning to the thrombolytic (i.e., to *lyse*, or break up, the blood clot, the thrombosis) tPA therapy, it is clear that lysing the coronary arterial blood clot is a surrogate endpoint. Should this surrogate endpoint be appropriate for approving the drug? After all, there is such a clearcut biological rationale: Coronary artery clots cause heart attacks; heart attacks damage the heart, often either impairing the heart function, and thus lowering exercise capacity, or killing the person directly. But experience has shown that very convincing biological scenarios do not always deliver the benefits expected; below we present an important example of a situation where an obvious surrogate endpoint did not work out.

Let us return now to the tPA cardiorenal advisory committee meeting and decision. In addition to tPA, another older thrombolytic drug, streptokinase, was also being presented for approval for the same indication. Prior to the meeting, there was considerable publicity over the upcoming meeting and possible approval of the drug tPA. The advisory committee meeting was to take place on Friday, May 29, 1987. On Thursday, May 28, 1987, the *Wall Street Journal* published an editorial entitled "The TPA Decision." The editorial read as follows:

> Profile of a heart-attack victim: 49 years old, three children, middle-manager, in seemingly good health. Cutting the grass on a Saturday afternoon, he is suddenly driven to the ground with severe chest pain. An ambulance takes him to the nearest emergency room, where he receives drugs to reduce shock and pain.
>
> At this point, he is one of approximately 4000 people who suffer a heart attack each day. If he has indeed had a heart attack, he will experience one of two possible outcomes. Either he will be dead, joining the 500,000 Americans killed each year by heart attack. Or, if he's lucky, he will join the one million others who go on to receive some form of therapy for his heart disease.
>
> Chances of survival will depend in great part on the condition of the victim's heart, that is, how much permanent muscular damage the heart sustained during the time a clot prevented the normal flow of blood into the organ. Heart researchers have long understood that if these clots can be broken up early after a seizure's onset, the victim's chances of staying alive increase significantly. Dissolving the clot early enhances the potential benefits of such post-attack therapies as coronary bypass surgery or balloon angioplasty.
>
> Tomorrow morning, a panel of the Food and Drug Administration will review the data on a blood-clot dissolver called TPA, for tissue-type plasminogen activator. In our mind, TPA—not any of the pharmaceutical treatments for AIDS—is the most noteworthy, unavailable drug therapy in the United States. Put another way, the FDA's new rules permitting the distribution of experimental drugs for life-threatening diseases came under pressure to do something about the AIDS epidemic. But isn't it as important for the government to move with equal speed on the epidemic of heart attacks already upon us?
>
> This isn't to say that TPA is more important than AIDS treatments. Both have a common goal: keeping people alive. The difference is that while the first AIDS drug received final approval in about six months, TPA remains unapproved and unavailable to heart-attack victims despite the fact that the medical community has known for more than two years that it can save lives.
>
> How many lives? Obviously no precise projection is possible, but the death toll is staggering, with about 41,000 individuals killed monthly by heart attacks.
>
> In its April 4, 1985, issue, the *New England Journal of Medicine* carried the first report on the results of the National Institutes of Health's TIMI study comparing TPA's clot dissolving abilities with a drug already approved by the FDA. NIH prematurely ended that trial because TPA's results were so significantly better than the other drug.
>
> In an accompanying editorial, the *Journal*'s editor, Dr. Arnold Relman, said a safe and effective thrombolytic "might be of immense clinical value." In October 1985, a medical-policy committee of California's Blue Shield recommended that TPA be recognized "as acceptable medical practice." The following month at the American Heart Association's meeting, Dr. Eugene Braunwald, chairman of the department of medicine at Harvard Medical School, said, "If R-TPA were available on a wide basis, I would select that drug today." In its original TIMI report, the NIH said TPA would next be

> tested against a placebo; later, citing ethical reasons, the researchers dropped the placebo and now all heart patients in the TIMI trial are receiving TPA.
>
> It is for these reasons that we call TPA the most noteworthy unavailable drug in the U.S. The FDA may believe it is already moving faster than usual with the manufacturer's new-drug application. Nonetheless, bureaucratic progress [*sic*] must be measured against the real-world costs of keeping this substance out of the nation's emergency rooms. The personal, social and economic consequences of heart disease in this country are immense. The American Heart Association estimates the total costs of providing medical services for all cardiovascular disease at $71 billion annually.
>
> By now more than 4,000 patients have been treated with TPA in clinical trials. With well over a thousand Americans going to their deaths each day from heart attack, it is hard to see what additional data can justify the government's further delay in making a decision about this drug. If tomorrow's meeting of the FDA's cardio-renal advisory committee only results in more temporizing, some in Congress or at the White House should get on the phone and demand that the American public be given a reason for this delay.

The publicity before the meeting of the advisory committee was quite unusual since companies are prohibited from preapproval advertising; thus the impetus presumably came from other sources.

The cardiorenal advisory committee members met and considered the two thrombolytic drugs, streptokinase and tPA. They voted to recommend approval of streptokinase but felt that further data were needed before tPA could be approved. The reactions to the decision were extreme, but probably predictable given the positions expressed prior to the meeting.

The *Wall Street Journal* responded with an editorial on Tuesday, June 2, 1987, entitled "Human Sacrifice." It follows in its entirety:

> Last Friday an advisory panel of the Food and Drug Administration decided to sacrifice thousands of American lives on an altar of pedantry.
>
> Under the klieg lights of a packed hearing room at the FDA, an advisory panel picked by the agency's Center for Drugs and Biologics declined to recommend approval of TPA, a drug that dissolves blood clots after heart attacks. In a 1985 multicenter study conducted by the U.S. National Heart, Lung and Blood Institute, TPA was so conclusively effective at this that the trial was stopped. The decision to withhold it from patients should be properly viewed as throwing U.S. medical research into a major crisis.
>
> Heart disease dwarfs all other causes of death in the industrialized world, with some 500,000 Americans killed annually; by comparison, some 20,000 have died of AIDS. More than a thousand lives are being destroyed by heart attacks every day. In turning down treatment with TPA, the committee didn't dispute that TPA breaks up the blood clots impeding blood flow to the heart. But the committee asked that Genentech, which makes the genetically engineered drug, collect some more mortality data. Its submission didn't include enough statistics to prove to the panel that dissolving blood clots actually helps people with heart attacks.
>
> Yet on Friday, the panel also approved a new procedure for streptokinase, the less effective clot dissolver—or thrombolytic agent—currently in use. Streptokinase previously had been approved for use in an expensive, specialized procedure called intracoronary infusion. An Italian study, involving 11,712 randomized heart patients at 176 coronary-care units in 1984–1985, concluded that administering streptokinase intravenously reduced deaths by 18%. So the advisory panel decided to approve intravenous streptokinase, but not approve the superior thrombolytic TPA. This is absurd.
>
> Indeed, the panel's suggestion that it is necessary to establish the efficacy of thrombolysis stunned specialists in heart disease. Asked about the committee's justification for its decision, Dr. Eugene Braunwald, chairman of Harvard Medical School's department of medicine, told us: "The real question is, do you accept the proposition that the proximate cause of a heart attack is a blood clot in the coronary artery? The evidence is overwhelming, *overwhelming*. It is sound, basic medical knowledge. It is in every textbook of medicine. It has been firmly established in the past decade beyond any reasonable question. If you accept the fact that a drug [TPA] is twice as effective as

> streptokinase in opening closed vessels, and has a good safety profile, then I find it baffling how that drug was not recommended for approval."
>
> Patients will die who would otherwise live longer. Medical research has allowed statistics to become the supreme judge of its inventions. The FDA, in particular its bureau of drugs under Robert Temple, has driven that system to its absurd extreme. The system now serves itself first and people later. Data supersede the dying.
>
> The advisory panel's suggestion that TPA's sponsor conduct further mortality studies poses grave ethical questions. On the basis of what medicine already knows about TPA, what U.S. doctor will give a randomized placebo or even streptokinase? We'll put it bluntly: Are American doctors going to let people die to satisfy the bureau of drugs' chi-square studies?
>
> Friday's TPA decision should finally alert policy makers in Washington and the medical-research community that the theories and practices now controlling drug approval in this country are significantly flawed and need to be rethought. Something has gone grievously wrong in the FDA bureaucracy. As an interim measure FDA Commissioner Frank Young, with Genentech's assent, could approve TPA under the agency's new experimental drug rules. Better still, Dr. Young should take the matter in hand, repudiate the panel's finding and force an immediate reconsideration. Moreover, it is about time Dr. Young received the clear, public support of Health and Human Services Secretary Dr. Otis Bowen in his efforts to fix the FDA.
>
> If on the other hand Drs. Young and Bowen insist that the actions of bureaucrats are beyond challenge, then perhaps each of them should volunteer to personally administer the first randomized mortality trials of heart-attack victims receiving the TPA clot buster or nothing. Alternatively, coronary-care units receiving heart-attack victims might use a telephone hotline to ask Dr. Temple to randomize the trial himself by flipping a coin for each patient. The gods of pedantry are demanding more sacrifice.

Soon after joining the Cardiovascular and Renal Drugs Advisory Committee, L.F. noticed that a number of people left the room at what seemed inappropriate times, near the end of some advisory deliberations. I was informed that often, stock analysts with expertise in the pharmaceutical industry attended meetings about key drugs; when the analysts thought they knew how the vote was going to turn out, they went out to the phones to send instructions. That was the case during the tPA deliberations (and made it particularly appropriate that the *Wall Street Journal* take an interest in the result). Again we convey the effect of the deliberations through quotations taken from the press. On June 1, 1978, the *Wall Street Journal* had an article under the heading "FDA Panel Rejection of Anti-Clot Drug Set Genentech Back Months, Perils Stock." The article said in part:

> A Food and Drug Administration advisory panel rejected licensing the medication TPA, spoiling the summer debut of what was touted as biotechnology's first billion-dollar drug. . . . Genentech's stock—which reached a high in March of $64.50 following a 2-for-1 split—closed Friday at $48.25, off $2.75, in national over-the-counter trading, even before the close of the FDA panel hearing attended by more than 400 watchful analysts, scientists and competitors. Some analysts expect the shares to drop today. . . . Wall Street bulls will also be rethinking their forecasts. For example, Kidder Peabody & Co.'s Peter Drake, confident of TPA's approval, last week predicted sales of $51 million in the second half of 1987, rising steeply to $205 million in 1988, $490 million in 1989 and $850 million in 1990.

USA Today, on Tuesday, June 2, 1987, on the first page of the Money section, had an article headed "Biotechs Hit a Roadblock, Investors Sell." The article began:

> Biotechnology stocks, buoyed more by promise than products, took one of their worst beatings Monday. Leading the bad-news pack: Biotech giant Genentech Inc., dealt a blow when its first blockbuster drug failed to get federal approval Friday. Its stock plummeted $11\frac{1}{2}$ points to $\$36\frac{3}{4}$, on 14.2 million shares traded—a one-day record for Genentech. "This is very serious, dramatically serious," said analyst Peter Drake, of Kidder, Peabody & Co., who Monday changed his recommendations for the

group from buy to "unattractive." His reasoning: The stocks are driven by "a blend of psychology and product possibilities. And right now, the psychology is terrible."

Biotechnology stocks as a group dropped with the Genentech panel vote. This seemed strange to me because the panel had not indicated that the drug, tPA, was bad but only that in a number of areas the data needed to be gathered and analyzed more appropriately (as described below). The panel was certainly not down on thrombolysis (as the streptokinase approval showed); it felt that the risk/benefit ratio of tPA needed to be clarified before approval could be made.

The advisory committee members replied to the *Wall Street Journal* editorials both individually and in groups, explaining the reasons for the decision [Borer, 1987; Kowey et al., 1988; Fisher et al., 1987]. This last response to the *Wall Street Journal* was submitted with the title "The Prolongation of Human Life"; however, after the review of the article by the editor, the title was changed by the *Wall Street Journal* to "The FDA Cardio-Renal Committee Replies." The reply:

The evaluation and licensing of new drugs is a topic of legitimate concern to not only the medical profession but our entire populace. Thus it is appropriate when the media, such as the *Wall Street Journal*, take an interest in these matters. The Food and Drug Administration recognizes the public interest by holding open meetings of advisory committees that review material presented by pharmaceutical companies, listen to expert opinions, listen to public comment from the floor and then give advice to the FDA. The Cardiovascular and Renal Drugs Advisory Committee met on May 29 to consider two drugs to dissolve blood clots causing heart attacks. The *Journal* published editorials prior to the meeting ("The TPA Decision," May 28) and after the meeting ("Human Sacrifice," June 2 and "The Flat Earth Committee," July 13). The second editorial began with the sentence: "Last Friday an advisory committee of the Food and Drug Administration decided to sacrifice thousands of American lives on an altar of pedantry." How can such decisions occur in our time? This reply by members of the advisory panel presents another side to the story. In part the reply is technical, although we have tried to simplify it. We first discuss drug evaluation in general and then turn to the specific issues involved in the evaluation of the thrombolytic drugs streptokinase and TPA.

The history of medicine has numerous instances of well-meaning physicians giving drugs and treatments that were harmful rather than beneficial. For example, the drug thalidomide was widely marketed in many countries—and in West Germany without a prescription—in the late 1950s and early 1960s. The drug was considered a safe and effective sleeping pill and tranquilizer. Marketing was delayed in the U.S. despite considerable pressure from the manufacturer upon the FDA. The drug was subsequently shown to cause birth defects and thousands of babies world-wide were born with grotesque malformations, including seal-like appendages and lack of limbs. The FDA physician who did not approve the drug in the U.S. received an award from President Kennedy. One can hardly argue with the benefit of careful evaluation in this case. We present this, not as a parallel to TPA, but to point out that there are two sides to the approval coin—early approval of a good drug, with minimal supporting data, looks wise in retrospect; early approval, with minimal supporting data, of a poor drug appears extremely unwise in retrospect. Without adequate and well-controlled data one cannot distinguish between the two cases. Even with the best available data, drugs are sometimes found to have adverse effects that were not anticipated. Acceptance of unusually modest amounts of data, based on assumptions and expectations rather than actual observation is very risky. As will be explained below, the committee concluded there were major gaps in the data available to evaluate TPA.

The second editorial states that "Medical research has allowed statistics to become the supreme judge of its inventions." If this means that data are required, we agree; people evaluate new therapies with the hope that they are effective—again, before licensing, proof of effectiveness and efficacy is needed. If the editorial meant that the TPA decision turned on some arcane mathematical issue, it is incorrect. Review of the transcript shows that statistical issues played no substantial role.

We now turn to the drug of discussion, TPA. Heart attacks are usually caused by a "blood clot in an artery supplying the heart muscle with blood." The editorial quotes Dr. Eugene Braunwald, "The real question is, do you accept the proposition that the proximate cause of a heart attack is a blood clot in the coronary artery?" We accept the statement, but there is still a significant question: "What can one then do to benefit the victim?" It is not obvious that modifying the cause after the event

occurs is in the patient's best interest, especially when the intervention has toxicity of its own. Blood clots cause pulmonary embolism; it is the unusual patient who requires dissolution of the clot by streptokinase. Several trials show the benefit does not outweigh the risk.

On May 29 the Cardiovascular and Renal Drugs Advisory Committee reviewed two drugs that "dissolve" blood clots. The drug streptokinase had been tested in a randomized clinical trial in Italy involving 11,806 patients. The death rate in those treated with streptokinase was 18% lower than in patients not given streptokinase; patients treated within six hours did even better. Review of 10 smaller studies, and early results of a large international study, also showed improved survival. It is important to know that the 18% reduction in death rate is a reduction of a few percent of the patients studied. The second drug considered—recombinant tissue plasminogen activator (TPA)—which also was clearly shown to dissolve blood clots, was not approved. Why? At least five issues contributed, to a greater or lesser amount, to the vote not to recommend approval for TPA at this time. These issues were: the safety of the drug, the completeness and adequacy of the data presented, the dose to be used, and the mechanism of action by which streptokinase (and hopefully TPA) saves lives.

Safety was the first and most important issue concerning TPA. Two formulations of TPA were studied at various doses; the highest dose was 150 milligrams. At this dose there was an unacceptable incidence of cerebral hemorrhage (that is, bleeding in the brain), in many case leading to both severe stroke and death. The incidence may be as high as 4% or as low as 1.5% to 2% (incomplete data at the meeting made it difficult to be sure of the exact figure), but in either case it is disturbingly high; this death rate due to side effects is of the same magnitude as the lives saved by streptokinase. This finding led the National Heart, Lung and Blood Institute to stop the 150-milligram treatment in a clinical trial. It is important to realize that this finding was unexpected, as TPA was thought to be relatively unlikely to cause such bleeding. Because of bleeding, the dose of TPA recommended by Genentech was reduced to 100 milligrams. The safety profile at doses of 100 milligrams looks better, but there were questions of exactly how many patients had been treated and evaluated fully. Relatively few patients getting this dose had been reported in full. Without complete reports from the studies there could be smaller strokes not reported and uncertainty as to how patients were examined. The committee felt a substantially larger database was needed to show safety.

The TPA used to evaluate the drug was manufactured by two processes. Early studies used the double-stranded (roller bottle) form of the drug; the sponsor then changed to a predominantly single-stranded form (suspension culture method) for marketing and production reasons. The second drug differed from the first in how long the drug remained in the blood, in peak effect, in the effect on fibrinogen and in the dose needed to cause lysis of clots. Much of the data was from the early form; these data were not considered very helpful with respect to the safety of the recommended dose of the suspension method drug. This could perhaps be debated, but the intracranial bleeding makes the issue an important one. The excessive bleeding may well prove to be a simple matter of excessive dose, but this is not yet known unequivocally.

Data were incomplete in that many of the patients' data had not been submitted yet and much of the data came from treatment with TPA made by the early method of manufacture. There was uncertainty about the data used to choose the 100-milligram dose, i.e., perhaps a lower dose is adequate. When there is a serious dose-related side effect it is crucial that the dose needed for effectiveness has been well-defined and has acceptable toxicity.

Let us turn to the mechanism of action, the means by which the beneficial effect occurs. There may be a number of mechanisms. The most compelling is clot lysis (dissolution). However, experts presented data that streptokinase changes the viscosity of the blood that could improve the blood flow; the importance is uncertain. Streptokinase also lowers blood pressure, which may decrease tissue damage during a heart attack. While there is convincing evidence that TPA (at least by the first method of manufacture) dissolves clots faster than streptokinase (at least after a few hours from the onset of the heart attack), we do not have adequate knowledge to know what portion of the benefit of streptokinase comes from dissolving the clot. TPA, thus, may differ in its effect on the heart or on survival. The drugs could differ in other respects, such as how often after opening a vessel they allow reclosure, and, of course, the frequency of important adverse effects.

These issues delay possible approval. Fortunately, more data are being collected. It is our sincere hope that the drug lives up to its promise, but should the drug prove as valuable as hoped, that would

not imply the decision was wrong. The decision must be evaluated as part of the overall process of drug approval.

The second editorial suggests that if the drug is not approved, Dr. Temple (director of the Bureau of Drugs, FDA), Dr. Young (FDA commissioner) and Dr. Bowen (secretary of health and human services) should administer "randomized mortality trials of heart-attack victims receiving the TPA clot buster or nothing." This indignant rhetoric seems inappropriate on several counts. First, the advisory committee has no FDA members; our votes are independent and in the past, on occasion, we have voted against the FDA's position. It is particularly inappropriate to criticize Drs. Temple and Young for the action of an independent group. The decision (by a vote of eight against approval, one for and two abstaining) was made by an independent panel of experts in cardiovascular medicine and research from excellent institutions. These unbiased experts reviewed the data presented and arrived at this decision; the FDA deserves no credit or blame. Second, we recommend approval of streptokinase; we are convinced that the drug saves lives of heart-attack victims (at least in the short term). To us it would be questionable to participate in a trial without some treatment in patients of the type shown to benefit from streptokinase. A better approach is to use streptokinase as an active control drug in a randomized trial. If it is as efficacious or better than streptokinase, we will rejoice. We have spent our adult lives in the care of patients and/or research to develop better methods for treatment. Both for our patients and our friends, our families and ourselves, we want proven beneficial drugs available.

In summary, with all good therapeutic modalities the benefits must surely outweigh the risks of treatment. In interpreting the data presented by Genentech in May 1987 the majority of the Cardiovascular and Renal Drugs Advisory Committee members could not confidently identify significant benefits without concomitant significant risk. The review was clouded by issues of safety, manufacturing process, dose size and the mechanism of action. We are hopeful these issues will be addressed quickly, allowing more accurate assessment of TPA's risk-benefit ratio with conclusive evidence that treatment can be recommended that allows us to uphold the physician's credo, *primum non nocere* (first do no harm).

The July 28 1987, *USA Today's* Life section carried an article on the first page entitled "FDA Speeds Approval of Heart Drug." The article mentioned that the FDA commissioner Frank Young was involved in the data gathering. Within a few months of the advisory committee meeting, tPA was approved for use in treating myocardial infarctions. The drug was 5 to 10 times more expensive than streptokinase; however, it opened arteries faster and that was thought to be a potential advantage. A large randomized comparison of streptokinase and tPA was performed (ISIS 3); the preliminary results were presented at the November 1990 American Heart Association meeting. The conclusion was that the efficacy of the two drugs was essentially equivalent. Thus by approving streptokinase, even in retrospect, no period of the lack of availability of a clearly superior drug occurred because of the time delay needed to clear up the questions about tPA. This experience shows that biostatistical collaboration has consequences above and beyond the scientific and humanitarian aspects; large political and financial issues also are often involved.

20.4 OH, MY ACHING BACK!

One of the most common maladies in the industrialized world is the occurrence of low-back problems. By the age of 50, nearly 85% of humans can recall back symptoms; and as someone has said, the other 15% probably forgot. Among persons in the United States, back and spine impairment are the chronic conditions that most frequently cause activity limitation. The occurrence of industrial back disability is one of the most expensive health problems afflicting industry and its employees. The cost associated with back injury in 1976 was $14 billion; the costs are greatly skewed, with a relatively low percent of the cost accrued by a few chronic back injury cases [Spengler et al., 1986]. The costs and human price associated with industrial back injury prompted the Boeing Company to contact the orthopedics department at the University of Washington to institute a collaborative study of back injury at a Boeing factory in western Washington

State. Collaboration was obtained from the Boeing company management, the workers and their unions, and a research group at the University of Washington (including one of the authors, L.F.). The study was supported financially by the National Institutes of Health, the National Institute for Occupational Safety and Health, the Volvo Foundation, and the Boeing Company. The study was designed in two phases. The first phase was a retrospective analysis of past back injury reports and insurance costs from already existing Boeing records; the second phase was a prospective study looking at a variety of possible predictors (to be described below) of industrial back injury.

The retrospective Boeing data were analyzed and presented in a series of three papers [Spengler et al., 1986; Bigos et al., 1986a,b]. The analysis covered 31,200 employees who reported 900 back injuries among 4645 claims filed by 3958 different employees. The data emphasized the cost to Boeing of this malady, and as in previous studies, showed that a small percentage of the back injury reports lead to most of the cost; for example, 10% of the cases accounted for 79% of the cost. The incurred costs of back injury claims was 41% of the Boeing total, although only 19% of the claims were for the back. The most expensive 10% of the back injury claims accounted for 32% of all the Boeing injury claims. Workers were more likely to have reported an acute back injury if they had a poor employee appraisal rating from their supervisor within 6 months prior to the injury.

The prospective study was unique and had some very interesting findings (the investigators were awarded the highest award of the American Academy of Orthopedic Surgeons, the Kappa Delta award, for excellence in orthopedic research). Based on previously published results and investigator conjectures, data were collected in a number of areas with potential ability to predict reports of industrial back injury. Among the information obtained prospectively from the 3020 aircraft employees who volunteered to participate in the study were the following:

- *Demographics:* race, age, gender, total education, marital status, number in family, method, and time spent in commuting to work.
- *Medical history:* questions about treatment for back pain by physicians and by chiropractors; hospitalization for back pain; surgery for back injury; smoking status.
- *Physical examination:* flexibility; spinal canal size by ultrasonography; and anthropometric measures such as height and weight.
- *Physical capacities:* arm strength; leg strength; and aerobic capacity measured by a submaximal treadmill test.
- *Psychological testing:* the MMPI (Minnesota Multiphasic Inventory and its subscales); a schedule of recent life change events; a family questionnaire about interactions at home; a health locus of control questionnaire.
- *Job satisfaction:* subjects were asked a number of questions about their job: did they enjoy their job almost always, some of the time, hardly ever; do they get along well with their supervisor; do they get along well with their fellow employees, etc.

The details of the design and many of the study results may be found in Battie et al. [1989, 1990a,b] and Bigos et al. [1991, 1992a,b]. The extensive psychological questionnaires were given to the employees to be taken home and filled out; 54% of the 3020 employees returned completed questionnaires, and some data analyses were necessarily restricted to those who completed the questionnaire(s). Figure 20.4 summarizes graphically some of the important predictive results.

The results of several stepwise, step-up multivariate Cox models are presented in Table 20.1. There are some substantial risk gradients among the employees. However, the predictive power is not such that one can conclusively identify employees likely to report an acute industrial back injury report. Of more importance, given the traditional approaches to this field, which have been largely biomechanical, work perception and psychological variables are important predictors, and the problem cannot be addressed effectively with only one factor in mind. This is emphasized in Figure 20.5, which represents the amount of information (in a formal sense)

in each of the categories of variables as given above. The figure is a Venn diagram of the estimated amount of predictive information for variables in each of the data collection areas [Fisher and Zeh, 1991]. The job perception and psychological areas are about as important as the medical history and physical examination areas. To truly understand industrial back injury, a multifactorial approach must be used.

Among the more interesting aspects of the study is speculation on the meaning and implications of the findings. Since, as mentioned above, most people experience back problems at

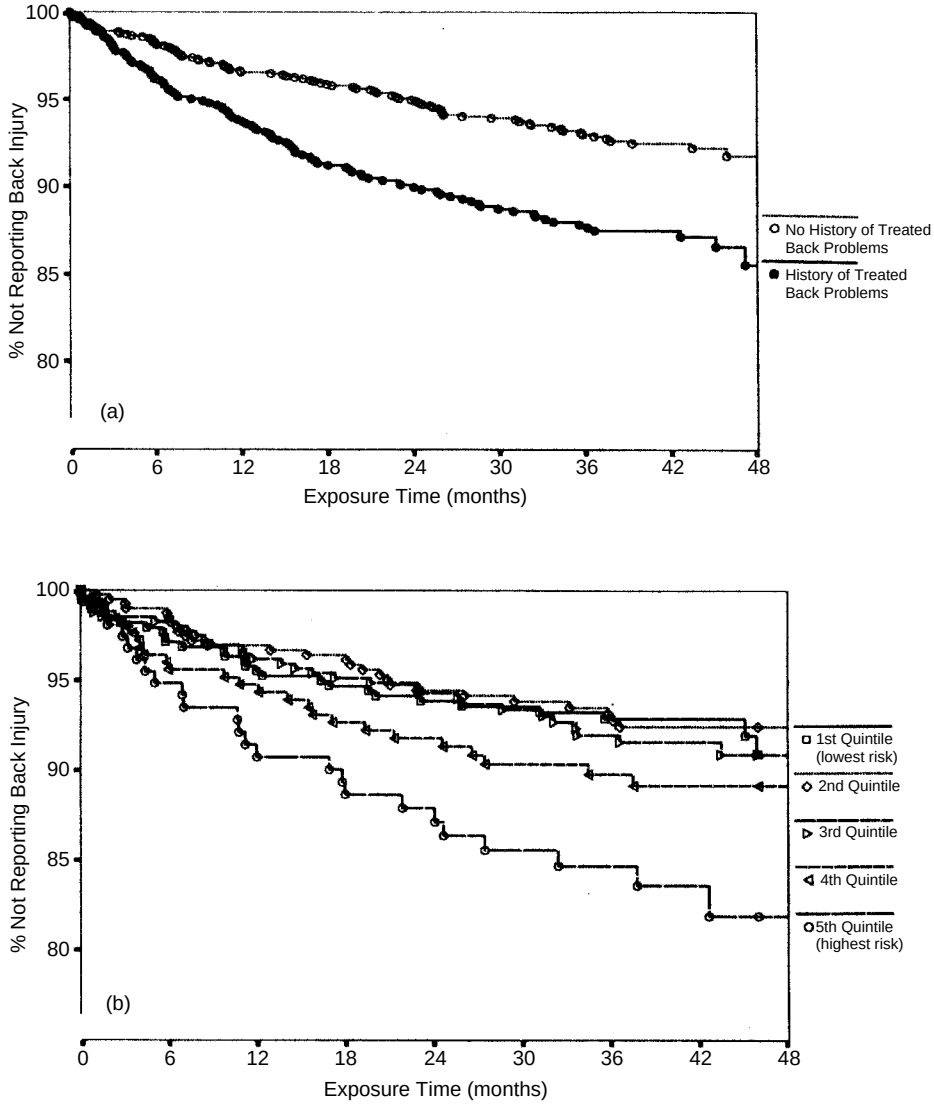


Figure 20.4 Panel (*a*) shows the product limit curves for the time to a subsequent back injury report for those reporting previous back problems and those who did not report such problems. Panel (*b*) divides the MMPI scale 3 (hysteria) values by cut points taken from the quintiles of those actually reporting events. Panel (*c*) divides the subjects by their response to the question: "Do you enjoy your job (1) almost always; (2) some of the time; or (3) hardly ever?" Panel (*d*) gives the results of the multivariate Cox model of Table 20.1; the predictive equation uses the variables from the first three panels. (From Bigos et al. [1991].)

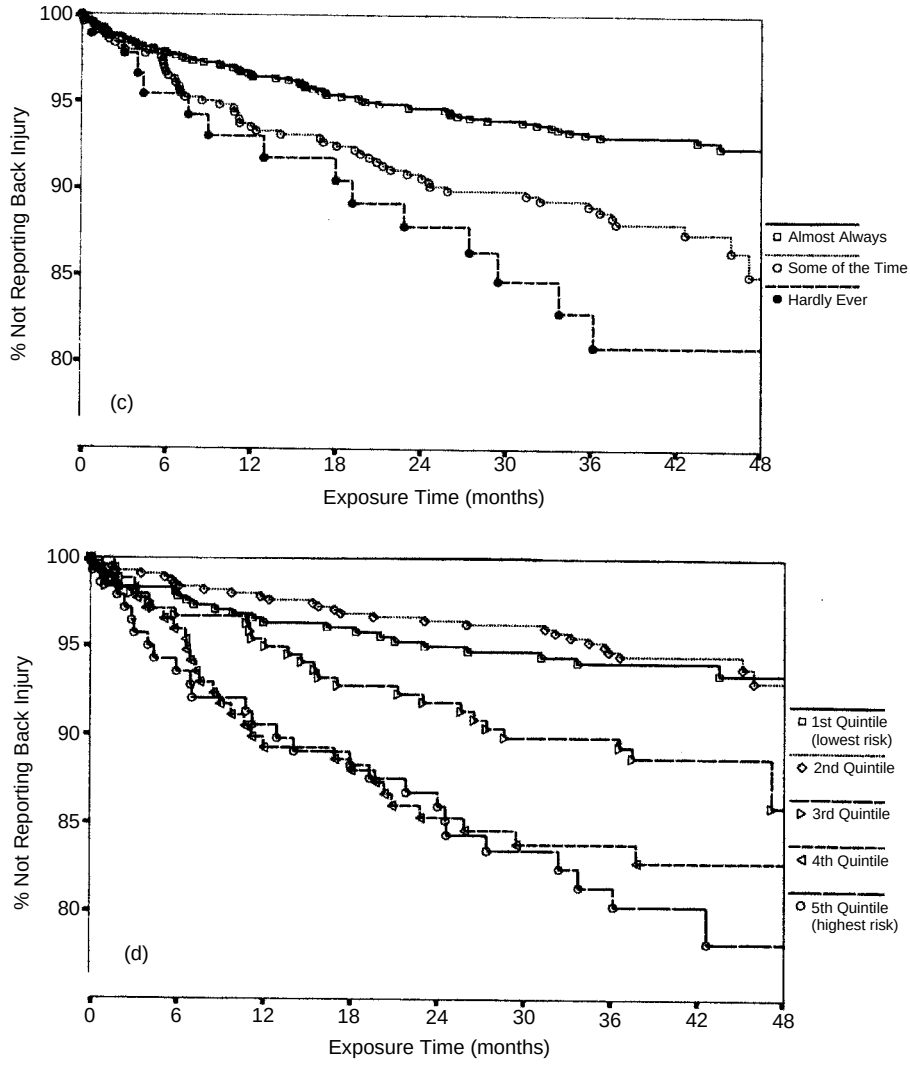


Figure 20.4 *(continued)*

some time in their lives, could legitimate back discomfort be used as an escape if one does not enjoy his or her job? Can the problem be reduced by taking measures to make workers more satisfied with their employment, or do a number of people tend to be unhappy no matter what? Is the problem a mixture of these? The results invite systematic, randomized intervention studies. Because of the magnitude of the problem, such approaches may be effective in both human and financial terms; however, this remains for the future.

20.5 SYNTHESIZING INFORMATION ABOUT MANY COMPETING TREATMENTS

Randomized controlled trials, discussed in Chapter 19, are the gold standard for deciding if a drug is effective and are required before new drugs are marketed. These trials may compare a

Table 20.1 Predicting Acute Back Injury Reports[a]

Variable	Univariate Analysis *p*-Value	Multivariate Analysis *p*-Value	Relative Risk	(95% Confidence Interval)
Entire Population (n = 1326, injury = 117)				
Enjoy job[b]	0.0001	0.0001	1.70	(1.31, 2.21)
MMPI 3[c]	0.0003	0.0032	1.37	(1.11, 1.68)
Prior back pain[d]	0.0010	0.0050	1.70	(1.17, 2.46)
Those with a History of Prior Back Injury (n = 518, injury = 63)				
Enjoy job[b]	0.0003	0.0006	1.85	(1.30, 2.62)
MMPI 3[c]	0.0195	0.0286	1.34	(1.17, 1.54)
Those without a History of Prior Back Pain (n = 808, injury = 54)				
Enjoy jobs[b]	0.0220	0.0353	1.53	(1.09, 2.29)
MMPI 3[c]	0.0334	0.0475	1.41	(1.19, 1.68)

[a]Using the Cox proportional hazards regression model.
[b]Only subjects with complete information on the enjoy job question, MMPI, and history of back pain were included in these analyses.
[c]For an increase of one unit.
[d]For an increase of 10 units.

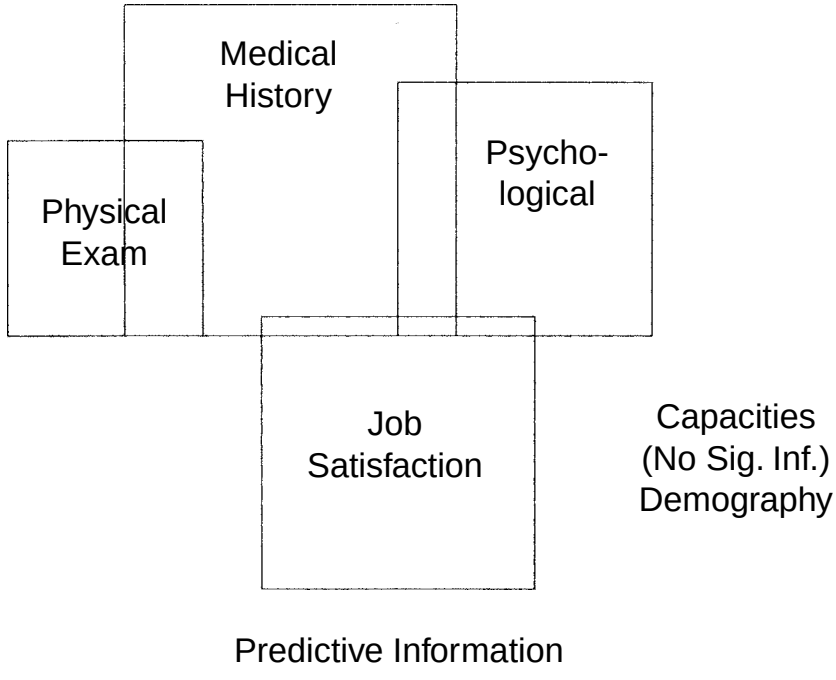


Figure 20.5 Predictive information by type of variable collected. Note that the job satisfaction and psychological areas contribute the same order of magnitude as the more classical medical history and physical examination variables. The relative lack of overlap in predictive information means that at least these areas must be considered if the problem is to be fully characterized. Capacities and demography variables added no information and so have no boxes.

new treatment to a placebo or to an accepted treatment. When many different treatments are available, however, it is not enough to know that they are all better than nothing, and it is often not feasible to compare all possible pairs of treatments in large randomized trials.

Clinicians would find it helpful to be able to use information from "indirect" comparisons. For example, if drug A reduces mortality by 20% compared to placebo, and drug B reduces mortality by 10% compared to drug A, it would be useful to conclude that B was better than placebo. However, indirect comparisons may not be reliable. The International Conference on Harmonisation, a project of European, Japanese, and U.S. regulators and industry experts, says in its document E10 on choice of control groups [2000, Sec. 2.1.7.4]

> "Placebo-controlled trials lacking an active control give little useful information about comparative effectiveness, information that is of interest and importance in many circumstances. Such information cannot reliably be obtained from cross-study comparisons, as the conditions of the studies may have been quite different."

The major concern with cross-study comparisons is that the populations being studied may be importantly different. People who participate in a trial of drug A when no other treatment is available may be very different from those who participate in a trial comparing drug A as an established treatment with a new experimental drug, B. For example, people for whom drug A is less effective may be more likely to participate in the hope of getting a better treatment. The ICH participants are certainly correct that cross-study comparisons *may* be misleading, but it would be very useful to know if they *are* actually misleading in a particular case.

An important example of this comes from the treatment of high blood pressure. There are many classes of drugs to treat high blood pressure, working in different ways on the heart, the blood vessels, and the kidneys. These include α-blockers, β-blockers, calcium channel blockers, angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers, and diuretics. The availability of multiple treatments is useful because they have different side effects and because a single drug may not reduce blood pressure sufficiently. Some of the drug classes have the advantage of also treating other conditions that may be present in some people (β-blockers or calcium channel blockers for angina, α-blockers for the symptoms of prostatic hyperplasia). However, in many cases it is not obvious which drug class to try first.

Many clinical trials have been done, but these usually compare a single pair of treatments, and many important comparisons have not been done. For example, until late 2002, there had been only one trial in previously healthy people designed to measure clinical outcomes comparing ACE inhibitors with diuretics, although these drug classes are both useful in congestive heart failure and so seem a natural comparison. In a situation such as this, where there is reliable information from within-study comparisons of many, but not all, pairs of drugs, it should be possible to assess the reliability of cross-study comparisons and decide whether they can be used. That is, the possible cross-study comparisons of, say, ACE inhibitors and calcium channel blockers can be compared with each other and with any direct within-study comparisons. The better the agreement, the more confidence we will have in the cross-study comparisons. This technique is called *network metaanalysis* [Lumley, 2002]. The name comes from thinking of each randomized trial as a link connecting two treatments. A cross-study comparison is a path between two treatments composed of two or more links. If there are many possible paths joining two treatments, we can obtain an estimate along each path and see how well they agree.

The statistical model behind network metaanalysis is similar to the random-effects models discussed in Chapter 18. Write Y_{ijk} for a summary of the treatment difference in trial k of drugs i and j, for example, the logarithm of the estimated relative risk. If we could simply assume that trials were comparable, we could model this log relative risk by

$$Y_{ijk} = \beta_i - \beta_j + \epsilon_{ijk}$$

where β_i and β_j measure the effectiveness of drugs i and j, and ϵ_{ijk} represents the random sampling error.

When we say that trials of different sets of treatments are not comparable, we mean precisely that the average log relative risk when comparing drugs i and j is not simply given by $\beta_i - \beta_j$: there is some extra systematic difference. These differences can be modeled as random intercepts belonging to each pair of drugs:

$$Y_{ijk} = \beta_i - \beta_j + \xi_{ij} + \epsilon_{ijk}$$
$$\xi \sim N(0, \omega^2)$$

So, comparing two drugs i and j gives on average $\beta_i - \beta_j - \xi_{ij}$. If ξ_{ij} is large, the metaanalysis is useless, since the true differences between treatments $(\beta_i - \beta_j)$ are masked by the biases ξ_{ij}. The random effects standard deviation, ω, also called the *incoherence*, measures how large these biases are, averaged over all the trials. If the incoherence is large, the metaanalysis should not be done. If the incoherence is small, the metaanalysis may be worthwhile. Confidence intervals for $\beta_i - \beta_j$ will be longer because of the uncertainty in ξ_{ij}, slightly longer if the incoherence is very small, and substantially longer if the incoherence is moderately large.

Clearly, it would be better to have a single large trial that compared all the treatments, but this may not be feasible. There is no particular financial incentive for the pharmaceutical companies to conduct such a trial, and the cost would make even the National Institutes of Health think twice. In the case of antihypertensive treatments, a trial of many of the competing treatments was eventually done. This trial, ALLHAT [ALLHAT, 2002] compared a diuretic, a calcium channel blocker, an ACE inhibitor, and an α-blocker. It found that α-blockers were distinctly inferior (that portion of the trial was stopped early), and that diuretics were perhaps slightly superior to the other treatments.

Before the results of ALLHAT were available, Psaty et al. performed a network metaanalysis of the available randomized trials, giving much the same conclusions but also including comparisons with β-blockers, placebo, and angiotensin receptor blockers. This analysis, updated to include the results of ALLHAT, strengthens the conclusion that diuretics are probably slightly superior to the other options in preventing serious cardiovascular events [Psaty et al., 2003]. The cross-study comparisons showed good agreement except for the outcome of congestive heart failure, where there seemed to be substantial disagreement (perhaps due to different definitions over time). The network metaanalysis methodology incorporates this disagreement into confidence intervals, so the conclusions are weaker than they would otherwise be, but still valid.

The most important limitation of network metaanalysis is that it requires many paths and many links to assess the reliability of the cross-study comparisons. If each new antihypertensive drug had been compared only to placebo, there would be only a single path between any two treatments, and no cross-checking would be possible. Reliability of cross-study comparisons would then be an unsupported (and unsupportable) assumption.

20.6 SOMETHING IN THE AIR?

Fine particles in the air have long been known to be toxic in sufficiently high doses. Recently, there has been concern that even the relatively low exposures permitted by European and U.S. law may be dangerous to sensitive individuals. These fine particles come from smoke (wood smoke, car exhaust, power stations), dust from roads or fields, and haze formed by chemical reactions in the air. They have widely varying physical and chemical characteristics, which are incompletely understood, but the legal limits are based simply on the total mass per cubic meter of air.

Most of the recent concern has come from *time-series studies*, which are relatively easy and inexpensive to carry out. These studies examine the associations between total number of deaths, hospital admissions, or emergency room visits in a city with the average pollution levels.

As the EPA requires regular monitoring of air pollution and other government agencies collect information on deaths and hospital attendance, the data merely need to be extracted from the relevant databases.

This description glosses over some important statistical issues, many of which were pointed out by epidemiologists when the first studies were published:

1. There is a lot of variation in exposure among a group of people.
2. The monitors may be deliberately located in dirty areas to detect problems (or in clean areas so as not to detect problems).
3. The day-to-day outcome measurements are not independent.
4. There is a large seasonal variation in both exposure and outcome, potentially confounding the results.
5. We don't know how much time should be expected between exposure to fine particles and death or illness.

You should be able to think of several other potential problems, but a more useful exercise for the statistician is to classify the problems by whether they are important and whether they are soluble. It turns out that the first two are not important because they are more or less constant from day to day and so cancel out of our comparisons. The third problem is potentially important and led to some interesting statistical research, but it turns out that addressing it does not alter the results.

The fourth problem, seasonal variation, is important, as Figure 20.6 shows. In Seattle, mortality and air pollution peak in the winter. In many other cities the pattern is slightly different, with double peaks in winter and summer, but some form of strong seasonality is the rule. The

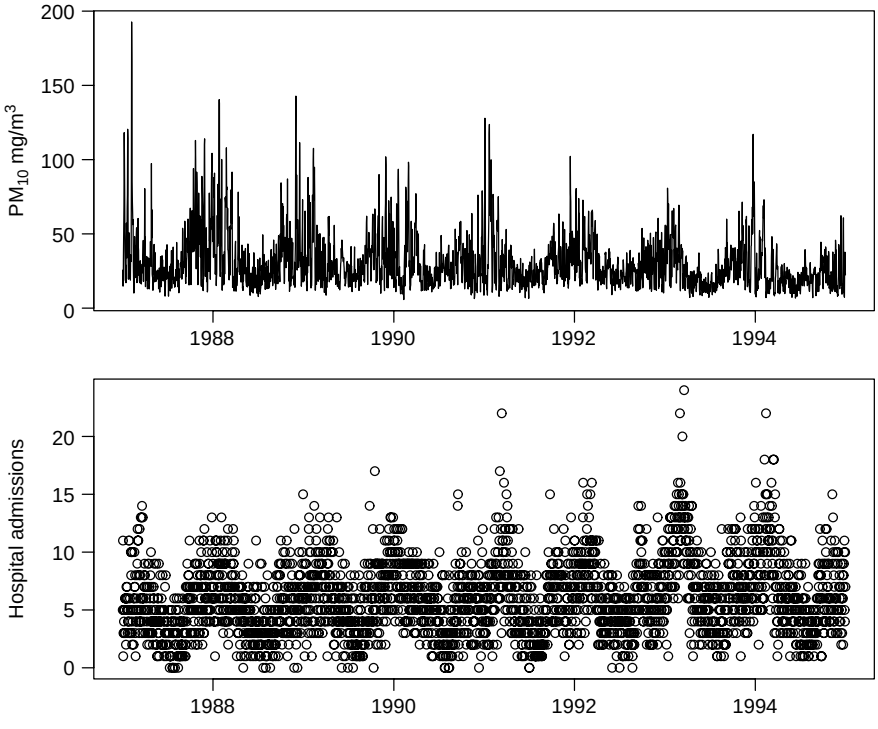


Figure 20.6 Particulate air pollution concentrations and hospital admissions for respiratory disease in Seattle.

solution to this confounding problem is to include these seasonal effects in our regression model. This is complicated: As gardeners and skiers well know, the seasons are not perfectly regular from year to year. Epidemiologists found a statistical solution, the generalized additive model (GAM), which had been developed for completely different problems, and adapted it to these time series. The GAM models allow the seasonal variation to be modeled simply by saying how smooth it should be:

$$\log(\text{mortality rate on day } t) = \alpha(t) + \beta \times \text{fine-particle concentration}$$

The smooth function $\alpha(t)$ absorbs all the seasonal variation and leaves only the short-term day-to-day fluctuations for evaluating the relationship between air pollution and mortality summarized by the log relative risk β. Computationally, $\alpha(t)$ is similar to the scatter plot smoothers discussed in Chapter 3.

With the problem of seasonal variation classified as important but soluble, analyses proceeded using data from many different U.S. cities and cities around the world. Shortly after the EPA had compiled a review of all the relevant research as a prelude to setting new standards, some bad news was revealed. Researchers at Johns Hopkins School of Public Health, who had compiled the largest and most systematic set of time-series studies, reported that they and everyone else had been using the GAM software incorrectly. The software had been written many years before, when computers were much slower, and had been intended for simpler examples than these time-series studies. The computations for a GAM involve iterative improvements to an estimate until it stops changing, and the default criterion for "stops changing" was not tight enough for the air pollution time-series models. At about the same time, researchers in Canada noticed that one of the approximations used in calculating confidence intervals and p-values was also not quite good enough in these time-series models [Ramsay et al., 2003]. When the dust settled, it became clear that the problem of seasonal variation was still soluble—fixes were found for these two problems, many studies were reanalyzed, and the conclusions remained qualitatively the same.

The final problem, the fact that the latency is not known, is just one special case of the problem of model uncertainty—choosing a regression model is much harder than fitting it. It is easy to estimate the association between mortality and today's pollution, or yesterday's pollution, or the previous day's, or the average of the past week, or any other choice. It is very hard to choose between these models. Simply reporting the best results is clearly biased, but is sometimes done. Fitting all the possible models may obscure the true associations among all the random noise. Specifying a particular model a priori allows valid inference but risks missing the true association. This final problem is important, but there is no simple mathematical solution.

20.7 ARE TECHNICIANS AS GOOD AS PHYSICIANS?

The neuropathological diagnosis of Alzheimer's disease (AD) is time consuming and difficult, even for experienced neuropathologists. Work in the late 1960s and early 1970s found that the presence of senile neuritic plaques in the neocortex and hippocampus justified a neuropathological diagnosis of Alzheimer's disease [Tomlinson et al., 1968, 1970]. Plaques are proteins associated with degenerating nerve cells in the brain; they tend to be located near the points of contact between cells. Typically, they are found in the brains of older persons.

These studies also found that large numbers of neurofibrillary tangles were often present in the neocortex and the hippocampus of brains from Alzheimer's disease victims. A tangle is another protein in the shape of a paired helical fragment found in the nerve cell. Neurofibrillary tangles are also found in other diseases. Later studies showed that plaques and tangles could be found in the brains of elderly persons with preserved mental status. Thus, the quantity and distribution of plaques and tangles, rather than their mere presence, are important in distinguishing Alzheimer's brains from the brains of normal aging persons.

A joint conference of 1985 [Khachaturian, 1985] stressed the need for standardized clinical and neuropathological diagnoses for Alzheimer's disease. We wanted to find out whether subjects with minimal training can count plaques and tangles in histological specimens of patients with Alzheimer's disease and controls [van Belle et al., 1997]. Two experienced neuropathologists trained three student helpers to recognize plaques and tangles in slides obtained from autopsy material. After training, the students and pathologists examined coded slides from patients with Alzheimer's disease and controls. Some of the slides were repeated to provide an estimate of reproducibility. Each reader read four fields, which were then averaged.

Ten sequential cases with a primary clinical and neuropathological diagnosis of Alzheimer's disease were chosen from the Alzheimer's Disease Research Center's (ADRC) brain autopsy registry. Age at death ranged from 67 years to 88 years, with a mean of 75.7 years and a standard deviation of 5.9 years.

Ten controls were examined for this study. Nine controls were selected from the ADRC registry of patients with brain autopsy, representing all subjects in the registry with no neuropathological evidence of AD. Four of these did have a clinical diagnosis of Alzheimer's disease, however. One additional control was drawn from files at the University of Washington's Department of Neuropathology. This control, aged 65 years at death, had no clinical history of Alzheimer's disease.

For each case and control, sections from the hippocampus and from the temporal, parietal, and frontal lobes were viewed by two neuropathologists and three technicians. The three technicians were a first-year medical school student, a graduate student in biostatistics with previous histological experience, and a premedical student. The technicians were briefly trained (for several hours) by a neuropathologist. The training consisted of looking at brain tissue (both Alzheimer's cases and normal brains) with a double-headed microscope and at photographs of tissue. The neuropathologist trained the technicians to identify plaques and tangles in the tissue samples viewed. The training ended when the neuropathologist was satisfied that the technicians would be able to identify plaques and tangles in brain tissue samples on their own for the purposes of this study. The slides were masked to hide patient identity and were arbitrarily divided into batches of five subjects, with cases and controls mixed. Each viewer was asked to scan the entire slide to find the areas of the slide with the highest density of plaques and tangles (implied by Khachaturian [1985]). The viewer then chose the four fields on the slide that appeared to contain the highest density of plaques and tangles when viewed at 25×. Neurofibrillary tangles and senile plaques were counted in these four fields at 200×. If the field contained more than 30 plaques or tangles, the viewer scored the number of lesions in that field as 30.

The most important area in the brain for the diagnosis of Alzheimer's is the hippocampus, and the results are presented for that region. Results for other regions were similar. In addition, we deal here only with cases and plaques. Table 20.2 contains results for the estimated number of plaques per field for cases; each reading is the average of readings from four fields. The estimated number of plaques varied considerably, ranging from zero to more than 20. Inspection of Table 20.2 suggests that technician 3 tends to read higher than the other technicians and the neuropathologists, that is, tends to see more plaques. An analysis of variance confirms this impression:

Source of Variation	d.f.	Mean Square	*F*-Ratio
Patients	9	102.256	—
Observers	4	—	—
Technicians vs. neuropathologists	1	21.31	2.70
Within technicians	2	42.53	5.39
Neuropathologist A vs. neuropathologist B	1	2.556	0.32
Patients × observers	36	7.888	—

Table 20.2 Average Number of Plaques per Field in the Hippocampus as Estimated by Three Technicians and Two Neuropathologists[a]

						Correlations:			
	Technician			Neuropathologist		Technician		Neuropathologist	
Case	1	2	3	A	B		2	3	A	B
1	0.75	0.00	0.00	0.00	0.00	1	0.69	0.63	0.65	0.76
2	7.25	6.50	7.50	4.75	3.75	2		0.77	0.79	0.84
3	5.50	7.25	5.50	5.75	8.75	3			0.91	0.67
4	5.25	8.00	14.30	5.75	6.50	A				0.82
5	10.00	8.25	9.00	3.50	7.75					
6	7.25	7.00	21.30	13.00	8.50					
7	5.75	15.30	18.80	10.30	8.00					
8	1.25	4.75	3.25	3.25	4.00					
9	1.75	5.00	7.25	2.50	3.50					
10	10.50	16.00	18.30	13.80	19.00					
Mean	5.25	7.80	10.50	6.26	6.98					
SD	3.44	4.76	7.21	4.60	5.08					

[a] Averages are over four fields.

You will recognize from Chapter 10 the idea of partitioning the variance attributable to observers into three components; there are many ways of partitioning this variance. The table above contains one useful way of doing this. The analysis suggests that the average levels of response do not vary within neuropathologists. There is a highly significant difference among technicians. We would conclude that technician 3 is high, rather than technician 1 being low, because of the values obtained by the two neuropathologists. Note also that the residual variability is estimated to be $\sqrt{7.888} = 2.81$ plaques per patient. This represents considerable variability since the values represent averages of four readings. Using a single reading as a basis produces an estimated standard deviation of $(\sqrt{4})(2.81) = 5.6$ plaques per reading.

But how shall agreement be measured or evaluated? Equality of the mean levels suggests only that the raters tended to count the same number of plaques on average. We need a more precise formulation of the issue. A correlation between the technicians and the neuropathologists will provide some information but is not sufficient because the correlation is invariant under changes in location and scale. In Chapter 4 we distinguished between precision and accuracy. *Precision* is the degree to which the observations cluster around a line; *accuracy* is the degree to which the observations are close to some standard. In this case the standard is the score of the neuropathologist and accuracy can be measured by the extent to which a technician's readings are from a 45° line. A paper by Lin [1989] nicely provides a framework for analyzing these data. In our case, the data are analyzed according to five criteria: location shift, scale shift, precision, accuracy, and concordance. *Location shift* refers to the degree to which the means of the data differ between technician and neuropathologist. A *scale shift* measures the differences in variability. *Precision* is quantified by a measure of correlation (Pearson's in our case). *Accuracy* is estimated by the distance that the observations are from the 45° line. *Concordance* is defined as the product of the precision and the accuracy. In symbols, denote two raters by subscripts 1 and 2. Then we define

$$\text{location shift} = u = \frac{\mu_1 - \mu_2}{\sqrt{\sigma_1 \sigma_2}}$$

$$\text{scale shift} = v = \frac{\sigma_1}{\sigma_2}$$

Table 20.3 Characteristics of Ratings of Three Technicians and Two Neuropathologists[a]

Technician	Pathologist	Location Shift	Scale Shift	Precision	Accuracy	Concordance
1	A	−0.18	0.75	0.95	0.94	0.89
	B	−0.35	0.68	0.76	0.88	0.67
2	A	0.33	1.03	0.79	0.95	0.75
	B	0.17	0.94	0.84	0.98	0.83
3	A	0.74	1.57	0.91	0.73	0.66
	B	0.58	1.42	0.67	0.81	0.55
A	B	−0.14	0.98	0.82	0.99	0.81

[a]Estimated numbers of plaques in the hippocampus of 10 cases, based on data from Table 20.2.

$$\text{precision} = r$$

$$\text{accuracy} = A = \left(\frac{v + 1/v + u^2}{2}\right)^{-1}$$

$$\text{concordance} = rA$$

We discuss these briefly. The location shift is a standardized estimate of the difference between the two raters. The quantity $\sqrt{\sigma_1 \sigma_2}$ is the geometric mean of the two standard deviations. If there is no location difference between the two raters, this quantity is centered around zero. The scale shift is a ratio; if there is no scale shift, this quantity is centered around 1. The precision is the usual correlation coefficient; if the paired data fall on a straight line, the correlation is 1. The accuracy is made up of a mixture of the means and the standard deviations. Note that if there is no location or scale shift, the accuracy is 1, the upper limit for this statistic. The concordance is the product of the accuracy and the precision; it is also bounded by 1. The data in Table 20.2 are analyzed according to the criteria above and displayed in Table 20.3. This table suggests that all the associations between technicians and neuropathologists are comparable. In addition, the comparisons between neuropathologists provide an internal measure of consistency. The "location shift" column indicates that, indeed, technician 3 tended to see more plaques than the neuropathologists. Technician 3 was also more variable, as indicated in the "scale shift" column. Technician 1 tended to be less variable than the neuropathologists. The precision of the technicians was comparable to that of the two neuropathologists compared with each other. The neuropathologists also displayed very high accuracy, almost matched by technician 1 and 2. The concordance, the product of the precision and the accuracy, averaged over the two neuropathologists is comparable to their concordance. As usual, it is very important to graph the data to confirm these analytical results by a graphical display. Figure 20.7 displays the seven possible graphs.

In summary, we conclude that it is possible to train relatively naive observers to count plaques in a manner comparable to that of experienced neuropathologists, as defined by the measures above. By this methodology, we have also been able to isolate the strengths and weaknesses of each technician.

20.8 RISKY BUSINESS

Every day of our lives we meet many risks: the risk of being struck by lightning, getting into a car accident on the way to work, eating contaminated food, and getting hepatitis. Many risks have associated moral and societal values. For example, what is the risk of being infected by AIDS through an HIV-positive health practitioner? How does this risk compare with getting infectious hepatitis from an infected worker? What is the risk to the health practitioner in being identified as HIV positive? As we evaluate risks, we may ignore them, despite their being real

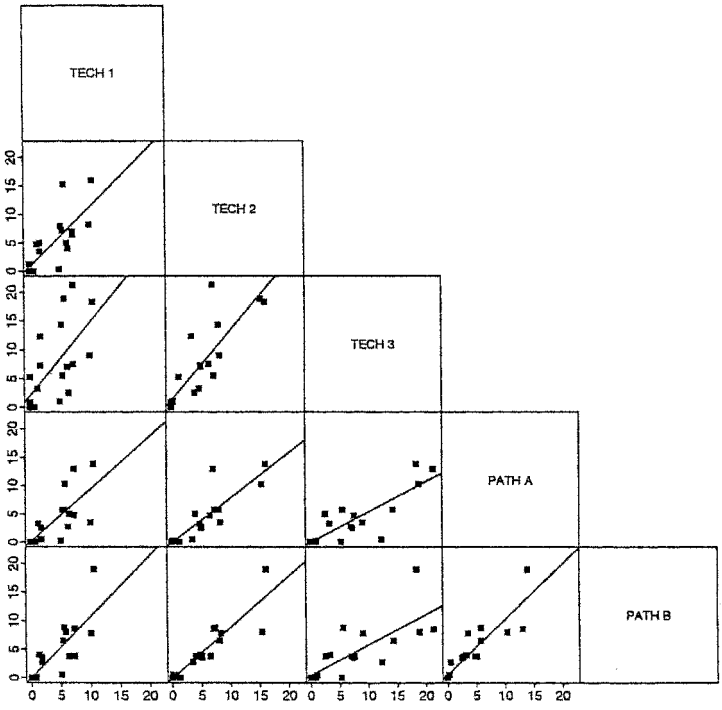


Figure 20.7 Seven possible graphs for the data in Table 20.3, prepared by SYSTAT, a very comprehensive software package. (From Wilkinson [1989].)

and substantial: for example, smoking in the face of the evidence in the Surgeon General's reports. Or we may react to risks even though they are small: for example, worry about being hit by a falling airplane.

What is a risk? A *risk* is usually an event or the probability of the event. Thus, the risk of being hit by lightning is defined to be the probability of this event. The word *risk* has an unfavorable connotation. We usually do not speak of the risk of winning the lottery. For purposes of this chapter, we relate the risk of an event to the probability of the occurrence of the event. In Chapter 3 we stated that all probabilities are conditional probabilities. When we talk about the risk of breast cancer, we usually refer to its occurrence among women. Probabilities are modified as we define different groups at risk. R. A. Fisher talked about *relevant subsets*, that is, what group or set of events is intended when a probability is specified.

In the course of thinking about environmental and occupational risks, one of us (G.vB.) wanted to develop a scale of risks similar to the Richter scale for earthquakes. The advantages of such a scale is to present risks numerically in such a way that the public would have an intuitive understanding of the risks. This, despite not understanding the full basis of the scale (it turns out to be fairly difficult to find a complete description of the Richter scale).

What should be the characteristics of such a scale? It became clear very quickly that the scale would have to be logarithmic. Second, it seemed that increasing risks should be associated with increasing values of the scale. It would also be nice to have the scale have roughly the same numerical range as the Richter scale. Most of its values are in the range 3 to 7. The *risk scale* for events is defined as follows: Let $P(E)$ be the probability of an event; then the risk units, $\mathrm{RU}(E)$, for this event are defined to be

$$\mathrm{RU}(E) = 10 + \log_{10}[P(E)]$$

Table 20.4 Relationship of Risk Units to Probabilities

Probability of Event	Risk Units
1	10
1/10	9
1/100	8
1/1000	7
1/10,000	6
1/100,000	5
1/1,000,000	4
1/10,000,000	3
1/100,000,000	2
1/1,000,000,000	1
1/10,000,000,000	0
1/100,000,000,000	−1

This scale has several nice properties. First, the scale is logarithmic. Second, if the event is certain, $P(E) = 1$ and $\mathrm{RU}(E) = 10$. Given two independent events, E_1 and E_2, the difference in their risks is

$$\mathrm{RU}(E_1) - \mathrm{RU}(E_2) = \log_{10} \frac{P(E_1)}{P(E_2)}$$

that is, the difference in the risk units is related to the relative risk of the events in a logarithmic fashion, that is, a logarithm of the odds (see Table 20.4). Third, the progression is terms of powers of 10 is very simple; and so on. So a shift of 2 risk units represents a 100-fold change in probabilities. Events with risk units of the order of 1 to 4 are associated with relatively rare events. Note that the scale can go below zero.

As with the Richter scale, familiarity with common events will help you get a feeling for the scale. Let us start by considering some random events; next we deal with some common risks and locate them on the scale; finally, we give you some risks and ask you to place them on the scale (the answers are given at the end of the chapter). The simplest case is the coin toss. The probability of, say, a head is 0.5. Hence the risk units associated with observing a head with a single toss of a coin is $\mathrm{RU}(\text{heads}) = 10 - \log_{10}(0.5) = 9.7$ (expressing risk units to one decimal place is usually enough). For a second example, the risk units of drawing at random a specified integer from the digits 0, 1, 2, 3, . . . , 9 is 1/10 and the RU value is 9. Rolling a pair of sevens with two dice has a probability of 1/36 and are RU value of 8.4. Now consider some very small probabilities. Suppose that you dial at random; what is the chance of dialing your own phone number? Assume that we are talking about the seven-digit code and we allow all zeros as a possible number. The RU value is 3. If you throw in the area code as well, you must deduct three more units to get the value $\mathrm{RU} = 0$. There are clearly more efficient ways to make phone calls.

The idea of a logarithmiclike scale for probabilities appears in the literature quite frequently. In a delightful, little-noticed book, *Risk Watch*, Urquhart and Heilmann [1984] defined the safety unit of an event, E, as

$$\text{safety unit of } E = -\log_{10}[P(E)]$$

The drawback of this definition is that it calibrates events in terms of safety rather than risk. People are more inclined to think in terms of risk; they are "risk avoiders" rather than safety

Table 20.5 The Risk Unit Scale and Some Associated Risks

Risk Unit	Event
10	Certain event
9	Pick number 3 at random from 0 to 3
8	Car accident with injury (annual)
7	Killed in hang gliding (annual)
6	EPA action (life time risk)
5	Cancer from 4 tbsp peanut butter/day (annual)
4	Cancer from one transcontinental trip
3	Killed by falling aircraft
2	Dollar bill has specified set of eight numbers
1	Pick spot on earth at random and land within $\frac{1}{4}$ mile of your house
0	Your phone number picked at random (+ area code)
−0.5	Killed by falling meteorite (annual)

Table 20.6 Events to Be Ranked and Placed on Risk Units Scale[a]

a.	Accidental drowning
b.	Amateur pilot death
c.	Appear on the *Johnny Carson Show* (1991)
d.	Death due to smoking
e.	Die in mountain climbing accident
f.	Fatality due to insect bite or sting
g.	Hit by lightning (in lifetime)
h.	Killed in college football
i.	Lifetime risk of cancer due to chlorination
j.	Cancer from one diet cola per day with saccharin
k.	Ace of spades in one draw from 52-card deck
l.	Win the *Reader's Digest* Sweepstakes
m.	Win the Washington State lottery grand prize (with one ticket)

[a] All risks are annual unless otherwise indicated. Events not ordered by risk.

seekers. But it is clear that risk units and safety units very simply related:

$$\mathrm{RU}(E) = 10 - \mathrm{SU}(E)$$

Table 20.5 lists the risk units for a series of events. Most of these probabilities were gleaned from the risk literature. Beside the events mentioned already, the risk unit for a car accident with injury in a 1-year time interval has a value of 8. This corresponds to a probability of 0.01, or 1/100. The Environmental Protection Agency takes action on lifetime risks of risk unit 6. That is, if the lifetime probability of death is 1/10,000, the agency will take some action. This may seem rather anticonservative, but there are many risks, and some selection has to be made. All these probabilities are estimates with varying degrees of precision. Crouch and Wilson [1982] include references to the data set upon which the estimate is based and also indicate whether the risk is changing. Table 20.6 describes some events for which you are asked to estimate the risk units. The answers are given in Table 20.7, preceding the References.

Table 20.7 Activities Estimated to Increase the Annual Probability of Death by One in a Million[a]

Activity	Cause of Death
Smoking 1.4 cigarettes	Cancer, heart disease
Drinking 0.5 liter of wine	Cirrhosis of the liver
Living 2 days in New York or Boston	Air pollution
Traveling 10 miles by bicycle	Accident
Living 2 months with a cigarette smoker	Cancer, heart disease
Drinking Miami drinking water for 1 year	Cancer from chloroform
Living 150 years within 5 miles of a nuclear power plant	Cancer from radiation
Eating 100 charcoal-broiled steaks	Cancer from benzopyrene

Source: Condensed from Wynne [1991].
[a]All events have a risk unit value of 4.

How do we evaluate risks? Why do we take action on some risks but not on others? The study of risks has been become a separate science with its own journals and society. The Borgen [1990] and Slovic [1986] articles in the journal *Risk Analysis* are worth examining. The following dimensions about evaluating risks have been mentioned in the literature:

Voluntary	Involuntary
Immediate effect	Delayed effect
Exposure essential	Exposure a luxury
Common hazard	"Dread" hazard
Affects average person	Affects special group
Reversible	Irreversible

We discuss these briefly. Recreational scuba diving has an annual probability of death of 4/10,000, or a risk unit of 6.6 [Crouch and Wilson, 1982, Table 7.4]. Compare this with some of the risks in Table 20.5. Another dimension is the timing of the effect. If the effect is delayed, we are usually willing to take a bigger risk; the most obvious example is smoking (which also is a voluntary behavior). If the exposure is essential, as part of one's occupation, then again, larger risks are acceptable. A "dread" hazard is often perceived as of greater risk than a common hazard. The most conspicuous example is an airplane crash vs. an automobile accident. But perversely, we are less likely to be concerned about hazards that affect special groups to which we are not immediately linked. For example, migrant workers have high exposures to pesticides and resulting increased immediate risks of neurological damage and long-term risks of cancer. As a society, we are not vigorous in reducing those risks. Finally, if the effects of a risk are reversible, we are willing to take larger risks.

Table 20.7 lists some risks with the same estimated value: Each one increases the annual risk of death by 1 in a million; that is, all events have a risk unit value of 4. These examples illustrate that we do not judge risks to be the same even though the probabilities are equal. Some of the risks are avoidable; others may not be. It may be possible to avoid drinking Miami drinking water by drinking bottled water or by moving to Alaska. Most of the people who live in New York or Boston are not aware of the risk of living in those cities. But even if they did, it is unlikely that they would move. A risk of 1 in a million is too small to act on.

How can risks be ranked? There are many ways. The primary one is by the probability of occurrence as we have discussed so far. Another is by the expected loss (or gain). For example, the probability of a fire destroying your home is fairly small but the loss is so great that it pays to make the unfair bet with the insurance company. An unfair bet is one where the expected gain is negative. Another example is the lottery. A typical state lottery takes more than 50 cents from every dollar that is bet (compared to about 4 cents for roulette play in a casino). But the reward is so large (and the investment apparently small) that many people gladly play this unfair game.

Table 20.8 Answers to Evaluation of Risks in Table 20.5

	Risk Units	Source/Comments
a.	5.6	Crouch and Wilson [1982, Table 7.2]
b.	7.0	Crouch and Wilson [1982, Table 7.4]
c.	4.3	Siskin et al. [1990]
d.	7.5	Slovic [1986, Table 1]
e.	6.8	Crouch and Wilson [1982, Table 7.4]
f.	3.4	Crouch and Wilson [1982, Table 7.2]
g.	4.2	Siskin et al. [1990]
h.	5.5	Crouch and Wilson [1982, Table 7.4]
i.	4.0	Crouch and Wilson [1982, Table 7.5 and pp. 186–187]
j.	5.0	Slovic [1986, Table 1]
k.	8.3	$10 + \log(1/52)$
l.	1.6	From back of announcement; $10 + \log(1/250{,}000{,}000)$
m.	3.0	From back of lottery ticket; $10 + \log(1/10{,}000{,}000)$

How can risks be changed? It is clearly possible to stop smoking, to give up scuba diving, quit the police force, never drive a car. Many risks are associated with specific behaviors and changing those behaviors will change the risks. In the language of probability we have moved to another subset. Some changes will not completely remove the risks because of lingering effects of the behavior. But a great deal of risk reduction can be effected by changes in behavior. It behooves each one of us to assess the risks we take and to decide whether they are worth it.

The *Journal of the Royal Statistical Society*, Series A devoted the June 2003 issue (Volume 166) to statistical issues in risk communication. The journal *Risk Analysis* address risk analysis, risk assessment, and risk communication.

REFERENCES

Alderman, E. L., Bourassa, M. G., Cohen, L. S., Davis, K. B., Kaiser, G. C., Killip, T., Mock, M. B., Pettinger, M., and Robertson, T. L. [1990]. Ten-year follow-up of survival and myocardial infarction in the randomized Coronary Artery Surgery Study. *Circulation*, **82**: 1629–1646.

ALLHAT Officers and Coordinators [2002]. Major outcomes in high-risk hypertensive patients randomized to angiotensin-converting enzyme inhibitor or calcium channel blocker vs diuretic. The antihypertensive and lipid-lowering treatment to prevent heart attach trial (ALLHAT). *JAMA*, **288**: 2981–2997.

Battie, M. C., Bigos, S. J., Fisher, L. D., Hansson, T. H., Nachemson, A. L., Spengler, D. M., Wortley, M. D., and Zeh, J. [1989]. A prospective study of the role of cardiovascular risk factors and fitness in industrial back pain complaints. *Spine*, **14**: 141–147.

Battie, M. C., Bigos, S. J., Fisher, L. D., Spengler, D. M., Hansson, T. H., Nachemson, A. L., and Wortley, M. D. [1990a]. Anthropometric and clinical measures as predictors of back pain complaints in industry: a prospective study. *Journal of Spinal Disorders*, **3**: 195–204.

Battie, M. C., Bigos, S. J., Fisher, L. D., Spengler, D. M., Hansson, T. H., Nachemson, A. L., and Wortley, M. D. [1990b]. The role of spinal flexibility in back pain complaints within industry: a prospective study. *Spine*, **15**: 768–773.

Bigos, S. J., Spengler, D. M., Martin, N. A., Zeh, J., Fisher, L., Nachemson, A., and Wang, M. H. [1986a]. Back injuries in industry—a retrospective study: II. Injury factors. *Spine*, **11**: 246–251.

Bigos, S. J., Spengler, D. M., Martin, N. A., Zeh, J., Fisher, L., Nachemson, A., and Wang, M. H. [1986b]. Back injuries in industry—a retrospective study: III. Employee-related factors. *Spine*, **11**: 252–256.

Bigos, S. J., Battie, M. C., Spengler, D. M., Fisher, L. D., Fordyce, W. E., Hansson, T. H., Nachemson, A. L., and Wortley, M. D. [1991]. A prospective study of work perceptions and psychosocial factors affecting the report of back injury. *Spine*, **16**: 1–6.

Bigos, S. J., Battie, M. C., Fisher, L. D., Fordyce, W. E., Hansson, T. H., Nachemson, A. L., and Spengler, D. M. [1992a]. A longitudinal, prospective study of industrial back injury reporting in industry. *Clinical Orthopaedics*, **279**: 21–34.

Bigos, S. J., Battie, M. C., Fisher, L. D., Hansson, T. H., Spengler, D. M., and Nachemson, A. L. [1992b]. A prospective evaluation of commonly used pre-employment screening tools for acute industrial back pain. *Spine*, **17**: 922–926.

Borer, J. S. [1987]. t-PA and the principles of drug approval (editorial). *New England Journal of Medicine*, **317**: 1659–1661.

Borgen, K. T. [1990]. Of apples, alcohol, and unacceptable risks. *Risk Analysis*, **10**: 199–200.

CASS Principal Investigators and Their Associates [1981]. *National Heart, Lung, Blood Institute Coronary Artery Surgery Study*, T. Killip, L. D. Fisher, and M. B. Mock (eds.). American Heart Association Monograph 79. *Circulation*, **63**(p. II): I-1 to I-81.

CASS Principal Investigators and Their Associates: Coronary Artery Surgery Study (CASS) [1983a]. A randomized trial of coronary artery bypass surgery: survival data. *Circulation*, **68**: 939–950.

CASS Principal Investigators and Their Associates: Coronary Artery Surgery Study (CASS) [1983b]. A randomized trial of coronary artery bypass surgery: quality of life in patients randomly assigned to treatment groups. *Circulation*, **68**: 951–960.

CASS Principal Investigators and Their Associates: Coronary Artery Surgery Study (CASS) [1984a]. A randomized trial of coronary artery bypass surgery: comparability of entry characteristics and survival in randomized patients and nonrandomized patient meeting randomization criteria. *Journal of the American College of Cardiology*, **3**: 114–128.

CASS Principal Investigators and Their Associates [1984b]. Myocardial infarction and mortality in the Coronary Artery Surgery Study (CASS) randomized trial. *New England Journal of Medicine*, **310**: 750–758.

Chaitman, B. R., Ryan, T. J., Kronmal, R. A., Foster, E. D., Frommer, P. L., Killip, T., and the CASS Investigators [1990]. Coronary Artery Surgery Study (CASS): comparability of 10 year survival in randomized and randomizable patients. *Journal of the American College of Cardiology*, **16**: 1071–1078.

Crouch, E. A. C., and Wilson, R. [1982]. *Risk Benefit Analysis*. Ballinger, Cambridge, MA.

Fisher, L. D., Giardina, E.-G., Kowy, P. R., Leier, C. V., Lowenthal, D. T., Messerli, F. H., Pratt, C. M., and Ruskin, J. [1987]. The FDA Cardio-Renal Committee replies (letter to the editor). *Wall Street Journal*, Wed., Aug. 12, p. 19.

Fisher, L. D., Kaiser, G. C., Davis, K. B., and Mock, M. [1989]. Crossovers in coronary bypass grafting trials: desirable, undesirable, or both? *Annals of Thoracic Surgery*, **48**: 465–466.

Fisher, L. D., Dixon, D. O., Herson, J., and Frankowski, R. F. [1990]. Analysis of randomized clinical trials: intention to treat. In *Statistical Issues in Drug Research and Development*, K. E. Peace (ed.). Marcel Dekker, New York, pp. 331–344.

Fisher, L. D., and Zeh, J. [1991]. An information theory approach to presenting predictive value in the Cox proportional hazards regression model (unpublished).

International Conference on Harmonisation [2000]. *ICH Harmonised Tripartite Guideline: E10. Choice of Control Group and Related Issues in Clinical Trials. http://www.ich.org*

Kaiser, G. C., Davis, K. B., Fisher, L. D., Myers, W. O., Foster, E. D., Passamani, E. R., and Gillespie, M. J. [1985]. Survival following coronary artery bypass grafting in patients with severe angina pectoris (CASS) (with discussion). *Journal of Thoracic and Cardiovascular Surgery*, **89**: 513–524.

Khachaturian, Z. S. [1985]. Diagnosis of Alzheimer's disease. *Archives of Neurology*, **42**: 1097–1105.

Kowey, P. R., Fisher, L. D., Giardina, E.-G., Leier, C. V., Lowenthal, D. T., Messerli, F. H., and Pratt, C. M. [1988]. The TPA controversy and the drug approval process: the view of the Cardiovascular and Renal Drugs Advisory Committee. *Journal of the American Medical Association*, **260**: 2250–2252.

Lin, L. I. [1989]. A concordance correlation coefficient to evaluate reproducibility. *Biometrics*, **45**: 255–268.

Lumley, T. [2002]. Network meta-analysis for indirect treatment comparisons. *Statistics in Medicine*, **21**: 2313–2324

Myers, W. O., Schaff, H. V., Gersh, B. J., Fisher, L. D., Kosinski, A. S., Mock, M. B., Holmes, D. R., Ryan, T. J., Kaiser, G. C., and CASS Investigators [1989]. Improved survival of surgically treated patients with triple vessel coronary disease and severe angina pectoris: a report from the Coronary Artery Surgery Study (CASS) registry. *Journal of Thoracic and Cardiovascular Surgery*, **97**: 487–495.

Passamani, E., Davis, K. B., Gillespie, M. J., Killip, T., and the CASS Principal Investigators and Their Associates [1985]. A randomized trial of coronary artery bypass surgery: survival of patients with a low ejection fraction. *New England Journal of Medicine*, **312**: 1665–1671.

Peto, R., Pike, M. C., Armitage, P., Breslow, N. L., Cox, D. R., Howard, S. V., Mantel, N., McPherson, K., Peto, J., and Smith, P. G. [1977]. Design and analysis of randomized clinical trials requiring prolonged observation of each patient: II. Analysis and examples. *British Journal of Cancer*, **35**: 1–39.

Preston, T. A. [1977]. *Coronary Artery Surgery: A Critical Review*. Raven Press, New York.

Psaty, B., Lumley, T., Furberg, C., Schellenbaum, G., Pahor, M., Alderman, M. H., and Weiss, N. S. [2003]. Health outcomes associated with various anti-hypertensive therapies used as first-line agents: a network meta-analysis. *Journal of the American Medical Association*, **289**: 2532–2542.

Ramsay, T. O., Burnett, R. T., and Krewski, D. [2003]. The effect of concurvity in generalized additive models linking mortality to ambient particulate matter. *Epidemiology*, **14**: 18–23.

Rogers, W. J., Coggin, C. J., Gersh, B. J., Fisher, L. D., Myers, W. O., Oberman, A., and Sheffield, L. T. [1990]. Ten-year follow-up of quality of life in patients randomized to receive medical therapy or coronary artery bypass graft surgery. *Circulation*, **82**: 1647–1658.

Siskin, B., Staller, J., and Rornik, D. [1990]. *What Are the Chances? Risk, Odds and Likelihood in Everyday Life*. Crown Publishers, New York.

Slovic, P. [1986]. Informing and educating the public about risk. *Risk Analysis*, **6**: 403–415.

Spengler, D. M., Bigos, S. J., Martin, N. A., Zeh, J., Fisher, L. D., and Nachemson, A. [1986]. Back injuries in industry: a retrospective study: I. Overview and cost analysis. *Spine*, **11**: 241–245.

Takaro, T., Hultgren, H., Lipton, M., Detre, K., and participants in the Veterans Administration Cooperative Study Group [1976]. VA cooperative randomized study for coronary arterial occlusive disease: II. Left main disease. *Circulation*, **54**(suppl. 3): III-107.

Tomlinson, B. E., Blessed, G., and Roth, M. [1968]. Observations on the brains of non-demented old people. *Journal of Neurological Science*, **7**: 331–356.

Tomlinson, B. E., Blessed, G., and Roth, M. [1970]. Observations on the brains of demented old people. *Journal of Neurological Science*, **11**: 205–242.

Urquhart, J., and Heilmann, K. [1984]. *Risk Watch: The Odds of Life*. Facts on File Publications, New York.

van Belle, G., Gibson, K., Nochlin, D., Sumi, M., and Larson, E. B. [1997]. Counting plaques and tangles in Alzheimer's disease: concordance of technicians and pathologists. *Journal of neurological Science*, **145**: 141–146.

Wall Street Journal [1987a]. The TPA decision (editorial). *Wall Street Journal*, Thurs., May 28, p. 26.

Wall Street Journal [1987b]. Human sacrifice (editorial). *Wall Street Journal*, Tues., June 2, p. 30.

Weinstein, G. S., and Levin, B. [1989]. Effect of crossover on the statistical power of randomized studies. *Annals of Thoracic Surgery*, **48**: 490–495.

Wilkinson, L. [1989]. *SYGRAPH: The System for Graphics*. SYSTAT, Inc., Evanston, IL.

Wynne, B. [1991]. Public perception and communication of risk: what do we know? *NIH Journal of Health*, **3**: 65–71.

Appendix

Biostatistics: A Methodology for the Health Sciences, Second Edition, by Gerald van Belle, Lloyd D. Fisher, Patrick J. Heagerty, and Thomas S. Lumley
ISBN 0-471-03185-2

Table A.1 Standard Normal Distribution

Let Z be a normal random variable with mean zero and variance 1. For selected values of Z, three values are tabled: (1) the two-sided p-value, or $P[|Z| \geq z]$; (2) the one-sided p-value, or $P[Z \geq z]$; and (3) the cumulative distribution function at Z, or $P[Z \leq z]$.

z	Two-sided	One-sided	Cum-dist.	z	Two-sided	One-sided	Cum-dist.	z	Two-sided	One-sided	Cum-dist.
0.00	1.0000	.5000	.5000	1.30	.1936	.0968	.9032	1.80	.0719	.0359	.9641
0.05	.9601	.4801	.5199	1.31	.1902	.0951	.9049	1.81	.0703	.0351	.9649
0.10	.9203	.4602	.5398	1.32	.1868	.0934	.9066	1.82	.0688	.0344	.9656
0.15	.8808	.4404	.5596	1.33	.1835	.0918	.9082	1.83	.0673	.0336	.9664
0.20	.8415	.4207	.5793	1.34	.1802	.0901	.9099	1.84	.0658	.0329	.9671
0.25	.8026	.4013	.5987	1.35	.1770	.0885	.9115	1.85	.0643	.0322	.9678
0.30	.7642	.3821	.6179	1.36	.1738	.0869	.9131	1.86	.0629	.0314	.9686
0.35	.7263	.3632	.6368	1.37	.1707	.0853	.9147	1.87	.0615	.0307	.9693
0.40	.6892	.3446	.6554	1.38	.1676	.0838	.9162	1.88	.0601	.0301	.9699
0.45	.6527	.3264	.6736	1.39	.1645	.0823	.9177	1.89	.0588	.0294	.9706
0.50	.6171	.3085	.6915	1.40	.1615	.0808	.9192	1.90	.0574	.0287	.9713
0.55	.5823	.2912	.7088	1.41	.1585	.0793	.9207	1.91	.0561	.0281	.9719
0.60	.5485	.2743	.7257	1.42	.1556	.0778	.9222	1.92	.0549	.0274	.9726
0.65	.5157	.2578	.7422	1.43	.1527	.0764	.9236	1.93	.0536	.0268	.9732
0.70	.4839	.2420	.7580	1.44	.1499	.0749	.9251	1.94	.0524	.0262	.9738
0.75	.4533	.2266	.7734	1.45	.1471	.0735	.9265	1.95	.0512	.0256	.9744
0.80	.4237	.2119	.7881	1.46	.1443	.0721	.9279	1.96	.0500	.0250	.9750
0.85	.3953	.1977	.8023	1.47	.1416	.0708	.9292	1.97	.0488	.0244	.9756
0.90	.3681	.1841	.8159	1.48	.1389	.0694	.9306	1.98	.0477	.0239	.9761
0.95	.3421	.1711	.8289	1.49	.1362	.0681	.9319	1.99	.0466	.0233	.9767
1.00	.3173	.1587	.8413	1.50	.1336	.0668	.9332	2.00	.0455	.0228	.9772
1.01	.3125	.1562	.8438	1.51	.1310	.0655	.9345	2.01	.0444	.0222	.9778
1.02	.3077	.1539	.8461	1.52	.1285	.0643	.9357	2.02	.0434	.0217	.9783
1.03	.3030	.1515	.8485	1.53	.1260	.0630	.9370	2.03	.0424	.0212	.9788
1.04	.2983	.1492	.8508	1.54	.1236	.0618	.9382	2.04	.0414	.0207	.9793
1.05	.2937	.1469	.8531	1.55	.1211	.0606	.9394	2.05	.0404	.0202	.9798
1.06	.2891	.1446	.8554	1.56	.1188	.0594	.9406	2.06	.0394	.0197	.9803
1.07	.2846	.1423	.8577	1.57	.1164	.0582	.9418	2.07	.0385	.0192	.9808
1.08	.2801	.1401	.8599	1.58	.1141	.0571	.9429	2.08	.0375	.0188	.9812
1.09	.2757	.1379	.8621	1.59	.1118	.0559	.9441	2.09	.0366	.0183	.9817
1.10	.2713	.1357	.8643	1.60	.1096	.0548	.9452	2.10	.0357	.0179	.9821
1.11	.2670	.1335	.8665	1.61	.1074	.0537	.9463	2.11	.0349	.0174	.9826
1.12	.2627	.1314	.8686	1.62	.1052	.0526	.9474	2.12	.0340	.0170	.9830
1.13	.2585	.1292	.8708	1.63	.1031	.0516	.9484	2.13	.0332	.0166	.9834
1.14	.2543	.1271	.8729	1.64	.1010	.0505	.9495	2.14	.0324	.0162	.9838
1.15	.2501	.1251	.8749	1.65	.0989	.0495	.9505	2.15	.0316	.0158	.9842
1.16	.2460	.1230	.8770	1.66	.0969	.0485	.9515	2.16	.0308	.0154	.9846
1.17	.2420	.1210	.8790	1.67	.0949	.0475	.9525	2.17	.0300	.0150	.9850
1.18	.2380	.1190	.8810	1.68	.0930	.0465	.9535	2.18	.0293	.0146	.9854
1.19	.2340	.1170	.8830	1.69	.0910	.0455	.9545	2.19	.0285	.0143	.9857
1.20	.2301	.1151	.8849	1.70	.0891	.0446	.9554	2.20	.0278	.0139	.9861
1.21	.2263	.1131	.8869	1.71	.0873	.0436	.9564	2.21	.0271	.0136	.9864
1.22	.2225	.1112	.8888	1.72	.0854	.0427	.9573	2.22	.0264	.0132	.9868
1.23	.2187	.1093	.8907	1.73	.0836	.0418	.9582	2.23	.0257	.0129	.9871
1.24	.2150	.1075	.8925	1.74	.0819	.0409	.9591	2.24	.0251	.0125	.9875
1.25	.2113	.1056	.8944	1.75	.0801	.0401	.9599	2.25	.0244	.0122	.9878
1.26	.2077	.1038	.8962	1.76	.0784	.0392	.9608	2.26	.0238	.0119	.9881
1.27	.2041	.1020	.8980	1.77	.0767	.0384	.9616	2.27	.0232	.0116	.9884
1.28	.2005	.1003	.8997	1.78	.0751	.0375	.9625	2.28	.0226	.0113	.9887
1.29	.1971	.0985	.9015	1.79	.0735	.0367	.9633	2.29	.0220	.0110	.9890

Table A.1 (***continued***)

z	Two-sided	One-sided	Cum-dist.	z	Two-sided	One-sided	Cum-dist.	z	Two-sided	One-sided	Cum-dist.
2.30	.0214	.0107	.9893	2.80	.0051	.0026	.9974	3.30	.0010	.0005	.9995
2.31	.0209	.0104	.9896	2.81	.0050	.0025	.9975	3.31	.0009	.0005	.9995
2.32	.0203	.0102	.9898	2.82	.0048	.0024	.9976	3.32	.0009	.0005	.9995
2.33	.0198	.0099	.9901	2.83	.0047	.0023	.9977	3.33	.0009	.0004	.9996
2.34	.0193	.0096	.9904	2.84	.0045	.0023	.9977	3.34	.0008	.0004	.9996
2.35	.0188	.0094	.9906	2.85	.0044	.0022	.9978	3.35	.0008	.0004	.9996
2.36	.0183	.0091	.9909	2.86	.0042	.0021	.9979	3.36	.0008	.0004	.9996
2.37	.0178	.0089	.9911	2.87	.0041	.0021	.9979	3.37	.0008	.0004	.9996
2.38	.0173	.0087	.9913	2.88	.0040	.0020	.9980	3.38	.0007	.0004	.9996
2.39	.0168	.0084	.9916	2.89	.0039	.0019	.9981	3.39	.0007	.0003	.9997
2.40	.0164	.0082	.9918	2.90	.0037	.0019	.9981	3.40	.0007	.0003	.9997
2.41	.0160	.0080	.9920	2.91	.0036	.0018	.9982	3.41	.0006	.0003	.9997
2.42	.0155	.0078	.9922	2.92	.0035	.0018	.9982	3.42	.0006	.0003	.9997
2.43	.0151	.0075	.9925	2.93	.0034	.0017	.9983	3.43	.0006	.0003	.9997
2.44	.0147	.0073	.9927	2.94	.0033	.0016	.9984	3.44	.0006	.0003	.9997
2.45	.0143	.0071	.9929	2.95	.0032	.0016	.9984	3.45	.0006	.0003	.9997
2.46	.0139	.0069	.9931	2.96	.0031	.0015	.9985	3.46	.0005	.0003	.9997
2.47	.0135	.0068	.9932	2.97	.0030	.0015	.9985	3.47	.0005	.0003	.9997
2.48	.0131	.0066	.9934	2.98	.0029	.0014	.9986	3.48	.0005	.0003	.9997
2.49	.0128	.0064	.9936	2.99	.0028	.0014	.9986	3.49	.0005	.0002	.9998
2.50	.0124	.0062	.9938	3.00	.0027	.0013	.9987	3.50	.0005	.0002	.9998
2.51	.0121	.0060	.9940	3.01	.0026	.0013	.9987	3.51	.0004	.0002	.9998
2.52	.0117	.0059	.9941	3.02	.0025	.0013	.9987	3.52	.0004	.0002	.9998
2.53	.0114	.0057	.9943	3.03	.0024	.0012	.9988	3.53	.0004	.0002	.9998
2.54	.0111	.0055	.9945	3.04	.0024	.0012	.9988	3.54	.0004	.0002	.9998
2.55	.0108	.0054	.9946	3.05	.0023	.0011	.9989	3.55	.0004	.0002	.9998
2.56	.0105	.0052	.9948	3.06	.0022	.0011	.9989	3.56	.0004	.0002	.9998
2.57	.0102	.0051	.9949	3.07	.0021	.0011	.9989	3.57	.0004	.0002	.9998
2.58	.0099	.0049	.9951	3.08	.0021	.0010	.9990	3.58	.0003	.0002	.9998
2.59	.0096	.0048	.9952	3.09	.0020	.0010	.9990	3.59	.0003	.0002	.9998
2.60	.0093	.0047	.9953	3.10	.0019	.0010	.9990	3.60	.0003	.0002	.9998
2.61	.0091	.0045	.9955	3.11	.0019	.0009	.9991	3.61	.0003	.0002	.9998
2.62	.0088	.0044	.9956	3.12	.0018	.0009	.9991	3.62	.0003	.0001	.9999
2.63	.0085	.0043	.9957	3.13	.0017	.0009	.9991	3.63	.0003	.0001	.9999
2.64	.0083	.0041	.9959	3.14	.0017	.0008	.9992	3.64	.0003	.0001	.9999
2.65	.0080	.0040	.9960	3.15	.0016	.0008	.9992	3.65	.0003	.0001	.9999
2.66	.0078	.0039	.9961	3.16	.0016	.0008	.9992	3.66	.0003	.0001	.9999
2.67	.0076	.0038	.9962	3.17	.0015	.0008	.9992	3.67	.0002	.0001	.9999
2.68	.0074	.0037	.9963	3.18	.0015	.0007	.9993	3.68	.0002	.0001	.9999
2.69	.0071	.0036	.9964	3.19	.0014	.0007	.9993	3.69	.0002	.0001	.9999
2.70	.0069	.0035	.9965	3.20	.0014	.0007	.9993	3.70	.0002	.0001	.9999
2.71	.0067	.0034	.9966	3.21	.0013	.0007	.9993	3.71	.0002	.0001	.9999
2.72	.0065	.0033	.9967	3.22	.0013	.0006	.9994	3.72	.0002	.0001	.9999
2.73	.0063	.0032	.9968	3.23	.0012	.0006	.9994	3.73	.0002	.0001	.9999
2.74	.0061	.0031	.9969	3.24	.0012	.0006	.9994	3.74	.0002	.0001	.9999
2.75	.0060	.0030	.9970	3.25	.0012	.0006	.9994	3.75	.0002	.0001	.9999
2.76	.0058	.0029	.9971	3.26	.0011	.0006	.9994	3.76	.0002	.0001	.9999
2.77	.0056	.0028	.9972	3.27	.0011	.0005	.9995	3.77	.0002	.0001	.9999
2.78	.0054	.0027	.9973	3.28	.0010	.0005	.9995	3.78	.0002	.0001	.9999
2.79	.0053	.0026	.9974	3.29	.0010	.0005	.9995	3.79	.0002	.0001	.9999

Table A.2 Critical Values (Percentiles) for the Standard Normal Distribution
The fourth column is the $N(0, 1)$ percentile for the percent given in column one. It is also the upper one-sided $N(0, 1)$ critical value and two-sided $N(0, 1)$ critical value for the significance levels given in columns two and three, respectively.

Percent	One-sided	Two-sided	z	Percent	One-sided	Two-sided	z
50	.50	1.00	0.00	99.59	.0041	.0082	2.64
55	.45	.90	0.13	99.60	.0040	.0080	2.65
60	.40	.80	0.25	99.61	.0039	.0078	2.66
65	.35	.70	0.39	99.62	.0038	.0076	2.67
70	.30	.60	0.52	99.63	.0037	.0074	2.68
75	.25	.50	0.67	99.64	.0036	.0072	2.69
80	.20	.40	0.84	99.65	.0035	.0070	2.70
85	.15	.30	1.04	99.66	.0034	.0068	2.71
90	.10	.20	1.28	99.67	.0033	.0066	2.72
91	.09	.18	1.34	99.68	.0032	.0064	2.73
92	.08	.16	1.41	99.69	.0031	.0062	2.74
93	.07	.14	1.48	99.70	.0030	.0060	2.75
94	.06	.12	1.55	99.71	.0029	.0058	2.76
95	.05	.10	1.64	99.72	.0028	.0056	2.77
95.5	.045	.090	1.70	99.73	.0027	.0054	2.78
96.0	.040	.080	1.75	99.74	.0026	.0052	2.79
96.5	.035	.070	1.81	99.75	.0025	.0050	2.81
97.0	.030	.060	1.88	99.76	.0024	.0048	2.82
97.5	.025	.050	1.96	99.77	.0023	.0046	2.83
98.0	.020	.040	2.05	99.78	.0022	.0044	2.85
98.5	.015	.030	2.17	99.79	.0021	.0042	2.86
99.0	.010	.020	2.33	99.80	.0020	.0040	2.88
99.05	.0095	.0190	2.35	99.81	.0019	.0038	2.89
99.10	.0090	.0180	2.37	99.82	.0018	.0036	2.91
99.15	.0085	.0170	2.39	99.83	.0017	.0034	2.93
99.20	.0080	.0160	2.41	99.84	.0016	.0032	2.95
99.25	.0075	.0150	2.43	99.85	.0015	.0030	2.97
99.30	.0070	.0140	2.46	99.86	.0014	.0028	2.99
99.35	.0065	.0130	2.48	99.87	.0013	.0026	3.01
99.40	.0060	.0120	2.51	99.88	.0012	.0024	3.04
99.45	.0055	.0110	2.54	99.89	.0011	.0022	3.06
99.50	.0050	.0100	2.58	99.90	.0010	.0020	3.09
99.51	.0049	.0098	2.58	99.91	.0009	.0018	3.12
99.52	.0048	.0096	2.59	99.92	.0008	.0016	3.16
99.53	.0047	.0094	2.60	99.93	.0007	.0014	3.19
99.54	.0046	.0092	2.60	99.94	.0006	.0012	3.24
99.55	.0045	.0090	2.61	99.95	.0005	.0010	3.29
99.56	.0044	.0088	2.62	99.96	.0004	.0008	3.35
99.57	.0043	.0086	2.63	99.97	.0003	.0006	3.43
99.58	.0042	.0084	2.64	99.98	.0002	.0004	3.54
				99.99	.0001	.0002	3.72

Table A.3 Critical Values (Percentiles) for the Chi-Square Distribution

For each degree of freedom (d.f.) in the first column, the table entries are the critical values for the upper one-sided significance levels in the column headings or, equivalently, the percentiles for the corresponding percentages.

	Percentage								
	2.5	5	50	75	90	95	97.5	99	99.9
	Upper One-Sided α								
d.f.	.975	.95	.50	.25	.10	.05	.025	.01	.001
1	.001	.004	.455	1.32	2.71	3.84	5.02	6.63	10.83
2	.051	.103	1.39	2.77	4.61	5.99	7.38	9.21	13.82
3	.216	.352	2.37	4.11	6.25	7.82	9.35	11.34	16.27
4	.484	.711	3.36	5.39	7.78	9.49	11.14	13.28	18.47
5	.831	1.15	4.35	6.63	9.24	11.07	12.83	15.09	20.52
6	1.24	1.64	5.35	7.84	10.64	12.59	14.45	16.81	22.46
7	1.69	2.17	6.35	9.04	12.02	14.07	16.01	18.47	24.32
8	2.18	2.73	7.34	10.22	13.36	15.51	17.53	20.09	26.12
9	2.70	3.33	8.34	11.39	14.68	16.92	19.02	21.67	27.88
10	3.25	3.94	9.34	12.55	15.99	18.31	20.48	23.21	29.59
11	3.82	4.57	10.34	13.70	17.27	19.68	21.92	24.72	31.26
12	4.40	5.23	11.34	14.85	18.55	21.03	23.34	26.22	32.91
13	5.01	5.89	12.34	15.98	19.81	22.36	24.74	27.69	34.53
14	5.63	6.57	13.34	17.12	21.06	23.68	26.12	29.14	36.12
15	6.26	7.26	14.34	18.25	22.31	25.00	27.49	30.58	37.70
16	6.91	7.96	15.34	19.37	23.54	26.30	28.85	32.00	39.25
17	7.56	8.67	16.34	20.49	24.77	27.59	30.19	33.41	40.79
18	8.23	9.39	17.34	21.60	25.99	28.87	31.53	34.81	42.31
19	8.91	10.12	18.34	22.72	27.20	30.14	32.85	36.19	43.82
20	9.59	10.85	19.34	23.83	28.41	31.41	34.17	37.57	45.31
21	10.28	11.59	20.34	24.93	29.62	32.67	35.48	38.93	46.80
22	10.98	12.34	21.34	26.04	30.81	33.92	36.78	40.29	48.27
23	11.69	13.09	22.34	27.14	32.01	35.17	38.08	41.64	49.73
24	12.40	13.85	23.34	28.24	33.20	36.42	39.36	42.98	51.18
25	13.12	14.61	24.34	29.34	34.38	37.65	40.65	44.31	52.62
26	13.84	15.38	25.34	30.43	35.56	38.89	41.92	45.64	54.05
27	14.57	16.15	26.34	31.53	36.74	40.11	43.19	46.96	55.48
28	15.31	16.93	27.34	32.62	37.92	41.34	44.46	48.28	56.89
29	16.05	17.71	28.34	33.71	39.09	42.56	45.72	49.59	58.30
30	16.79	18.49	29.34	34.80	40.26	43.77	46.98	50.89	59.70
35	20.57	22.47	34.34	40.22	46.06	49.80	53.20	57.34	66.62
40	24.43	26.51	39.34	45.62	51.81	55.76	59.34	63.69	73.40
45	28.37	30.61	44.34	50.98	57.51	61.66	65.41	69.96	80.08
50	32.36	34.76	49.33	56.33	63.17	67.50	71.42	76.15	86.66
55	36.40	38.96	54.33	61.66	68.80	73.31	77.38	82.29	93.17
60	40.48	43.19	59.33	66.98	74.40	79.08	83.30	88.38	99.61
65	44.60	47.45	64.33	72.28	79.97	84.82	89.18	94.42	105.99
70	48.76	51.74	69.33	77.58	85.53	90.53	95.02	100.43	112.32
75	52.94	56.05	74.33	82.86	91.06	96.22	100.84	106.39	118.60
80	57.15	60.39	79.33	88.13	96.58	101.88	106.63	112.33	124.84
85	61.39	64.75	84.33	93.39	102.08	107.52	112.39	118.24	131.04
90	65.65	69.13	89.33	98.65	107.57	113.15	118.14	124.12	137.21
95	69.92	73.52	94.33	103.90	113.04	118.75	123.86	129.97	143.34
100	74.22	77.93	99.33	109.14	118.50	124.34	129.56	135.81	149.45

For more than 100 degrees of freedom chi-square critical values may be found in terms of the degrees of freedom and the corresponding two-sided critical value for a standard normal deviate Z by the equation $X^2 = 0.5 \cdot (Z + \sqrt{2 \cdot D - 1})^2$.

Table A.4 Critical Values (Percentiles) for the t-Distribution

The table entries are the critical values (percentiles) for the t-distribution. The column headed d.f. (degrees of freedom) gives the degrees of freedom for the values in that row. The columns are labeled by "percent," "one-sided," and "two-sided." "Percent" is 100 × cumulative distribution function—the table entry is the corresponding percentile. "One-sided" is the significance level for the one-sided upper critical value—the table entry is the critical value. "Two-sided" gives the two-sided significance level—the table entry is the corresponding two-sided critical value.

	Percent											
	75	90	95	97.5	99	99.5	99.75	99.9	99.95	99.975	99.99	99.995
	One-Sided α											
	.25	.10	.05	.025	.01	.005	.0025	.001	.0005	.00025	.0001	.00005
	Two-Sided α											
	.50	.20	.10	.05	.02	.01	.005	.002	.001	.0005	.0002	.0001
d.f.												
1	1.00	3.08	6.31	12.71	31.82	63.66	127.32	318.31	636.62	1273.24	3183.10	6366.20
2	.82	1.89	2.92	4.30	6.96	9.22	14.09	22.33	31.60	44.70	70.70	99.99
3	.76	1.64	2.35	3.18	4.54	5.84	7.45	10.21	12.92	16.33	22.20	28.00
4	.74	1.53	2.13	2.78	3.75	4.60	5.60	7.17	8.61	10.31	13.03	15.54
5	.73	1.48	2.02	2.57	3.37	4.03	4.77	5.89	6.87	7.98	9.68	11.18
6	.72	1.44	1.94	2.45	3.14	3.71	4.32	5.21	5.96	6.79	8.02	9.08
7	.71	1.42	1.90	2.37	3.00	3.50	4.03	4.79	5.41	6.08	7.06	7.88
8	.71	1.40	1.86	2.31	2.90	3.36	3.83	4.50	5.04	5.62	6.44	7.12
9	.70	1.38	1.83	2.26	2.82	3.25	3.69	4.30	4.78	5.29	6.01	6.59
10	.70	1.37	1.81	2.23	2.76	3.17	3.58	4.14	4.59	5.05	5.69	6.21
11	.70	1.36	1.80	2.20	2.72	3.11	3.50	4.03	4.44	4.86	5.45	5.92
12	.70	1.36	1.78	2.18	2.68	3.06	3.43	3.93	4.32	4.72	5.26	5.69
13	.69	1.35	1.77	2.16	2.65	3.01	3.37	3.85	4.22	4.60	5.11	5.51
14	.69	1.35	1.76	2.15	2.63	2.98	3.33	3.79	4.14	4.50	4.99	5.36
15	.69	1.34	1.75	2.13	2.60	2.95	3.29	3.73	4.07	4.42	4.88	5.24
16	.69	1.34	1.75	2.12	2.58	2.92	3.25	3.69	4.02	4.35	4.79	5.13
17	.69	1.33	1.74	2.11	2.57	2.90	3.22	3.65	3.97	4.29	4.71	5.04
18	.69	1.33	1.73	2.10	2.55	2.88	3.20	3.61	3.92	4.23	4.65	4.97
19	.69	1.33	1.73	2.09	2.54	2.86	3.17	3.58	3.88	4.19	4.59	4.90
20	.69	1.33	1.73	2.09	2.53	2.85	3.15	3.55	3.85	4.15	4.54	4.84
21	.69	1.32	1.72	2.08	2.52	2.83	3.14	3.53	3.82	4.11	4.49	4.78
22	.69	1.32	1.72	2.07	2.51	2.82	3.12	3.51	3.79	4.08	4.45	4.74
23	.68	1.32	1.71	2.07	2.50	2.81	3.10	3.49	3.77	4.05	4.42	4.69
24	.68	1.32	1.71	2.06	2.49	2.80	3.09	3.47	3.75	4.02	4.38	4.65
25	.68	1.32	1.71	2.06	2.49	2.79	3.08	3.45	3.73	4.00	4.35	4.62
26	.68	1.32	1.71	2.06	2.48	2.78	3.07	3.44	3.71	3.97	4.32	4.59
27	.68	1.31	1.70	2.05	2.47	2.77	3.06	3.42	3.69	3.95	4.30	4.56
28	.68	1.31	1.70	2.05	2.47	2.76	3.05	3.41	3.67	3.94	4.28	4.53
29	.68	1.31	1.70	2.05	2.46	2.76	3.04	3.40	3.66	3.92	4.25	4.51
30	.68	1.31	1.70	2.04	2.46	2.75	3.03	3.39	3.65	3.90	4.23	4.48
35	.68	1.31	1.69	2.03	2.44	2.72	3.00	3.34	3.59	3.84	4.15	4.39
40	.68	1.30	1.68	2.02	2.42	2.70	2.97	3.31	3.55	3.79	4.09	4.32
45	.68	1.30	1.68	2.01	2.41	2.69	2.95	3.28	3.52	3.75	4.05	4.27
50	.68	1.30	1.68	2.01	2.40	2.68	2.94	3.26	3.50	3.72	4.01	4.23
55	.68	1.30	1.67	2.00	2.40	2.67	2.93	3.25	3.48	3.70	3.99	4.20
60	.68	1.30	1.67	2.00	2.39	2.66	2.91	3.23	3.46	3.68	3.96	4.17
65	.68	1.29	1.67	2.00	2.39	2.65	2.91	3.22	3.45	3.66	3.94	4.15
70	.68	1.29	1.67	1.99	2.38	2.65	2.90	3.21	3.44	3.65	3.93	4.13
75	.68	1.29	1.67	1.99	2.38	2.64	2.89	3.20	3.43	3.64	3.91	4.11
80	.68	1.29	1.66	1.99	2.37	2.64	2.89	3.20	3.42	3.63	3.90	4.10
85	.68	1.29	1.66	1.99	2.37	2.64	2.88	3.19	3.41	3.62	3.89	4.08
90	.68	1.29	1.66	1.99	2.37	2.63	2.88	3.18	3.40	3.61	3.88	4.07
95	.68	1.29	1.66	1.99	2.37	2.63	2.87	3.18	3.40	3.60	3.87	4.06
100	.68	1.29	1.66	1.98	2.36	2.63	2.87	3.17	3.39	3.60	3.86	4.05
200	.68	1.29	1.65	1.97	2.35	2.60	2.84	3.13	3.34	3.54	3.79	3.97
500	.68	1.28	1.65	1.97	2.33	2.59	2.82	3.11	3.31	3.50	3.75	3.92
∞	.67	1.28	1.65	1.96	2.33	2.58	2.81	3.10	3.30	3.49	3.73	3.91

Table A.5 Critical Values (Percentiles) for the F-Distribution

Upper one-sided 0.05 significance levels; two-sided 0.10 significance levels; 95% percentiles. Tabulated are critical values for the F-distribution. The column headings give the numerator degrees of freedom and the row headings the denominator degrees of freedom. Lower one-sided critical values may be found from these tables by reversing the degrees of freedom and using the reciprocal of the tabled value at the same significance level (100 minus the percent for the percentile).

	Numerator Degrees of Freedom																		
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19
1	161.4	199.5	215.7	224.6	230.2	234.0	236.8	238.9	240.5	241.9	243.9	245.9	248.0	249.1	250.1	251.1	252.2	253.3	254.3
2	18.51	19.00	19.16	19.25	19.30	19.33	19.35	19.37	19.38	19.40	19.41	19.43	19.45	19.45	19.46	19.47	19.48	19.49	19.50
3	10.13	9.55	9.28	9.12	9.01	8.94	8.89	8.85	8.81	8.79	8.74	8.70	8.66	8.64	8.62	8.59	8.57	8.55	8.53
4	7.71	6.94	6.59	6.39	6.26	6.16	6.09	6.04	6.00	5.96	5.91	5.86	5.80	5.77	5.75	5.72	5.69	5.66	5.63
5	6.61	5.79	5.41	5.19	5.05	4.95	4.88	4.82	4.77	4.74	4.68	4.62	4.56	4.53	4.50	4.46	4.43	4.40	4.36
6	6.99	5.14	4.76	4.53	4.39	4.28	4.21	4.15	4.10	4.06	4.00	3.94	3.87	3.84	3.81	3.77	3.74	3.70	3.67
7	5.59	4.74	4.35	4.12	3.97	3.87	3.79	3.73	3.68	3.64	3.57	3.51	3.44	3.41	3.38	3.34	3.30	3.27	3.23
8	5.32	4.46	4.07	3.84	3.69	3.58	3.50	3.44	3.39	3.35	3.28	3.22	3.15	3.12	3.08	3.04	3.01	2.97	2.93
9	5.12	4.26	3.86	3.63	3.48	3.37	3.29	3.23	3.18	3.14	3.07	3.01	2.94	2.90	2.86	2.83	2.79	2.75	2.71
10	4.96	4.10	3.71	3.48	3.33	3.22	3.14	3.07	3.02	2.98	2.91	2.85	2.77	2.74	2.70	2.66	2.62	2.58	2.54
11	4.84	3.98	3.59	3.36	3.20	3.09	3.01	2.95	2.90	2.85	2.79	2.72	2.65	2.61	2.57	2.53	2.49	2.45	2.40
12	4.75	3.89	3.49	3.26	3.11	3.00	2.91	2.85	2.80	2.75	2.69	2.62	2.54	2.51	2.47	2.43	2.38	2.34	2.30
13	4.67	3.81	3.41	3.18	3.03	2.92	2.83	2.77	2.71	2.67	2.60	2.53	2.46	2.42	2.38	2.34	2.30	2.25	2.21
14	4.60	3.74	3.34	3.11	2.96	2.85	2.76	2.70	2.65	2.60	2.53	2.46	2.39	2.35	2.31	2.27	2.22	2.18	2.13
15	4.54	3.68	3.29	3.06	2.90	2.79	2.71	2.64	2.59	2.54	2.48	2.40	2.33	2.29	2.25	2.20	2.16	2.11	2.07
16	4.49	3.63	3.24	3.01	2.85	2.74	2.66	2.59	2.54	2.49	2.42	2.35	2.28	2.24	2.19	2.15	2.11	2.06	2.01
17	4.45	3.59	3.20	2.96	2.81	2.70	2.61	2.55	2.49	2.45	2.38	2.31	2.23	2.19	2.15	2.10	2.06	2.01	1.96

(*continued overleaf*)

Table A.5 (*continued*)

	Numerator Degrees of Freedom																		
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19
18	4.41	3.55	3.16	2.93	2.77	2.66	2.58	2.51	2.46	2.41	2.34	2.27	2.19	2.15	2.11	2.06	2.02	1.97	1.92
19	4.38	3.52	3.13	2.90	2.74	2.63	2.54	2.48	2.42	2.38	2.31	2.23	2.16	2.11	2.07	2.03	1.98	1.93	1.88
20	4.35	3.49	3.10	2.87	2.71	2.60	2.51	2.45	2.39	2.35	2.28	2.20	2.12	2.08	2.04	1.99	1.95	1.90	1.84
21	4.32	3.47	3.07	2.84	2.68	2.57	2.49	2.42	2.37	2.32	2.25	2.18	2.10	2.05	2.01	1.96	1.92	1.87	1.81
22	4.30	3.44	3.05	2.82	2.66	2.55	2.46	2.40	2.34	2.30	2.23	2.15	2.07	2.03	1.98	1.94	1.89	1.84	1.78
23	4.28	3.42	3.03	2.80	2.64	2.53	2.44	2.37	2.32	2.27	2.20	2.13	2.05	2.01	1.96	1.91	1.86	1.81	1.76
24	4.26	3.40	3.01	2.78	2.62	2.51	2.42	2.36	2.30	2.25	2.18	2.11	2.03	1.98	1.94	1.89	1.84	1.79	1.73
25	4.24	3.39	2.99	2.76	2.60	2.49	2.40	2.34	2.28	2.24	2.16	2.09	2.01	1.96	1.92	1.87	1.82	1.77	1.71
26	4.23	3.37	2.98	2.74	2.59	2.47	2.39	2.32	2.27	2.22	2.15	2.07	1.99	1.95	1.90	1.85	1.80	1.75	1.69
27	4.21	3.35	2.96	2.73	2.57	2.46	2.37	2.31	2.25	2.20	2.13	2.06	1.97	1.93	1.88	1.84	1.79	1.73	1.67
28	4.20	3.34	2.95	2.71	2.56	2.45	2.36	2.29	2.24	2.19	2.12	2.04	1.96	1.91	1.87	1.82	1.77	1.71	1.65
29	4.18	3.33	2.93	2.70	2.55	2.43	2.35	2.28	2.22	2.18	2.10	2.03	1.94	1.90	1.85	1.81	1.75	1.70	1.64
30	4.17	3.32	2.92	2.69	2.53	2.42	2.33	2.27	2.21	2.16	2.09	2.01	1.93	1.89	1.84	1.79	1.74	1.68	1.62
40	4.08	3.23	2.84	2.61	2.45	2.34	2.25	2.18	2.12	2.08	2.00	1.92	1.84	1.79	1.74	1.69	1.64	1.58	1.51
60	4.00	3.15	2.76	2.53	2.37	2.25	2.17	2.10	2.04	1.99	1.92	1.84	1.75	1.70	1.65	1.59	1.53	1.47	1.39
120	3.92	3.07	2.68	2.45	2.29	2.17	2.09	2.02	1.96	1.91	1.83	1.75	1.66	1.61	1.55	1.50	1.43	1.35	1.25
∞	3.84	3.00	2.60	2.37	2.21	2.10	2.01	1.94	1.88	1.83	1.75	1.67	1.57	1.52	1.46	1.39	1.32	1.22	1.00

Table A.6 Critical Values (Percentiles) for the F-Distribution

Upper one-sided 0.01 significance levels; two-sided 0.02 significance levels; 99% percentiles.

	Numerator Degrees of Freedom																		
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19
1	4052	5000	5403	5625	5764	5859	5928	5982	6022	6056	6106	6157	6209	6235	6261	6287	6313	6339	6366
2	98.50	99.00	99.17	99.25	99.30	99.33	99.36	99.37	99.39	99.40	99.42	99.43	99.45	99.46	99.47	99.47	99.48	99.49	99.50
3	34.12	30.82	29.46	28.71	28.24	27.91	27.67	27.49	27.35	27.23	27.05	26.87	26.69	26.60	26.50	26.41	26.32	26.22	26.13
4	21.20	18.00	16.69	15.98	15.52	15.21	14.98	14.80	14.66	14.55	14.37	14.20	14.02	13.93	13.84	13.75	13.65	13.56	13.46
5	16.26	13.27	12.06	11.39	10.97	10.67	10.46	10.29	10.16	10.05	9.89	9.72	9.55	9.47	9.38	9.29	9.20	9.11	9.02
6	13.75	10.92	9.78	9.15	8.75	8.47	8.26	8.10	7.98	7.87	7.72	7.56	7.40	7.31	7.23	7.14	7.06	6.97	6.88
7	12.25	9.55	8.45	7.85	7.46	7.19	6.99	6.84	6.72	6.62	6.47	6.31	6.16	6.07	5.99	5.91	5.82	5.74	5.65
8	11.26	8.65	7.59	7.01	6.63	6.37	6.18	6.03	5.91	5.81	5.67	5.52	5.36	5.28	5.20	5.12	5.03	4.95	4.86
9	10.56	8.02	6.99	6.42	6.06	5.80	5.61	5.47	5.35	5.26	5.11	4.96	4.81	4.73	4.65	4.57	4.48	4.40	4.31
10	10.04	7.56	6.55	5.99	5.64	5.39	5.20	5.06	4.94	4.85	4.71	4.56	4.41	4.33	4.25	4.17	4.08	4.00	3.91
11	9.65	7.21	6.22	5.67	5.32	5.07	4.89	4.74	4.63	4.54	4.40	4.25	4.10	4.02	3.94	3.86	3.78	3.69	3.60
12	9.33	6.93	5.95	5.41	5.06	4.82	4.64	4.50	4.39	4.30	4.16	4.01	3.86	3.78	3.70	3.62	3.54	3.45	3.36
13	9.07	6.70	5.74	5.21	4.86	4.62	4.44	4.30	4.19	4.10	3.96	3.82	3.66	3.59	3.51	3.43	3.34	3.25	3.17
14	8.86	6.51	5.56	5.04	4.69	4.46	4.28	4.14	4.03	3.94	3.80	3.66	3.51	3.43	3.35	3.27	3.18	3.09	3.00
15	8.68	6.36	5.42	4.89	4.56	4.32	4.14	4.00	3.89	3.80	3.67	3.52	3.37	3.29	3.21	3.13	3.05	2.96	2.87
16	8.53	6.23	5.29	4.77	4.44	4.20	4.03	3.89	3.78	3.69	3.55	3.41	3.26	3.18	3.10	3.02	2.93	2.84	2.75
17	8.40	6.11	5.18	4.67	4.34	4.10	3.93	3.79	3.68	3.59	3.46	3.31	3.16	3.08	3.00	2.92	2.83	2.75	2.65

(*continued overleaf*)

Table A.6 (***continued***)

	Numerator Degrees of Freedom																		
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19
18	8.29	6.01	5.09	4.58	4.25	4.01	3.84	3.71	3.60	3.51	3.37	3.23	3.08	3.00	2.92	2.84	2.75	2.66	2.57
19	8.18	5.93	5.01	4.50	4.17	3.94	3.77	3.63	3.52	3.43	3.30	3.15	3.00	2.92	2.84	2.76	2.67	2.58	2.49
20	8.10	5.85	4.94	4.43	4.10	3.87	3.70	3.56	3.46	3.37	3.23	3.09	2.94	2.86	2.78	2.69	2.61	2.52	2.42
21	8.02	5.78	4.87	4.37	4.04	3.81	3.64	3.51	3.40	3.31	3.17	3.03	2.88	2.80	2.72	2.64	2.55	2.46	2.36
22	7.95	5.72	4.82	4.31	3.99	3.76	3.59	3.45	3.35	3.26	3.12	2.98	2.83	2.75	2.67	2.58	2.50	2.40	2.31
23	7.88	5.66	4.76	4.26	3.94	3.71	3.54	3.41	3.30	3.21	3.07	2.93	2.78	2.70	2.62	2.54	2.45	2.35	2.26
24	7.82	5.61	4.72	4.22	3.90	3.67	3.50	3.36	3.26	3.17	3.03	2.89	2.74	2.66	2.58	2.49	2.40	2.31	2.21
25	7.77	5.57	4.68	4.18	3.85	3.63	3.46	3.32	3.22	3.13	2.99	2.85	2.70	2.62	2.54	2.45	2.36	2.27	2.17
26	7.72	5.53	4.64	4.14	3.82	3.59	3.42	3.29	3.18	3.09	2.96	2.81	2.66	2.58	2.50	2.42	2.33	2.23	2.13
27	7.68	5.49	4.60	4.11	3.78	3.56	3.39	3.26	3.15	3.06	2.93	2.78	2.63	2.55	2.47	2.38	2.29	2.20	2.10
28	7.64	5.45	4.57	4.07	3.75	3.53	3.36	3.23	3.12	3.03	2.90	2.75	2.60	2.52	2.44	2.35	2.26	2.17	2.06
29	7.60	5.42	4.54	4.04	3.73	3.50	3.33	3.20	3.09	3.00	2.87	2.73	2.57	2.49	2.41	2.33	2.23	2.14	2.03
30	7.56	5.39	4.51	4.02	3.70	3.47	3.30	3.17	3.07	2.98	2.84	2.70	2.55	2.47	2.39	2.30	2.21	2.11	2.01
40	7.31	5.18	4.31	3.83	3.51	3.29	3.12	2.99	2.89	2.80	2.66	2.52	2.37	2.29	2.20	2.11	2.02	1.92	1.80
60	7.08	4.98	4.13	3.65	3.34	3.12	2.95	2.82	2.72	2.63	2.50	2.35	2.20	2.12	2.03	1.94	1.84	1.73	1.60
120	6.85	4.79	3.95	3.48	3.17	2.96	2.79	2.66	2.56	2.47	2.34	2.19	2.03	1.95	1.86	1.76	1.66	1.53	1.38
∞	6.63	4.61	3.78	3.32	3.02	2.80	2.64	2.51	2.41	2.32	2.18	2.04	1.88	1.79	1.70	1.59	1.47	1.32	1.00

Table A.7 Fisher's Exact Test for 2 × 2 Tables

Consider a 2 × 2 table: $\begin{matrix} aA-a|A \\ bB-b|B \end{matrix}$ with rows and/or columns exchanged so that (1) $A \geq B$ and (2) $(a/A) \geq (b/B)$. The table entries are ordered lexicographically by A (ascending). B (descending) and a (descending). For each triple (A, B, a) the table presents critical values for one-sided tests of the hypothesis that the true proportion corresponding to a/A is greater than the true proportion corresponding to b/B. Significance levels of 0.05, 0.025, and 0.01 are considered. For $A \leq 15$ all values where critical values exist are tabulated. For each significance level two columns give (1) the nominal critical value for b (i.e., reject the null hypothesis if the observed b is less than or equal to the table entry) and (2) the p-value corresponding to the critical value (this is less than the nominal significance level in most cases due to the discreteness of the distribution).

A	B	a	b	p	b	p	b	p	A	B	a	b	p	b	p	b	p
3	3	3	0	.050	—	—	—	—	8	7	5	0	.019	0	.019	—	—
4	4	4	0	.014	0	.014	—	—	8	6	8	2	.015	2	.015	1	.003
4	3	4	0	.029	—	—	—	—	8	6	7	1	.016	1	.016	0	.002
5	5	5	1	.024	1	.024	0	.004	8	6	6	0	.009	0	.009	0	.009
5	5	4	0	.024	0	.024	—	—	8	6	5	0	.028	—	—	—	—
5	4	5	1	.048	0	.008	0	.008	8	5	8	2	.035	1	.007	1	.007
5	4	4	0	.040	—	—	—	—	8	5	7	1	.032	0	.005	0	.005
5	3	5	0	.018	0	.018	—	—	8	5	6	0	.016	0	.016	—	—
5	2	5	0	.048	—	—	—	—	8	5	5	0	.044	—	—	—	—
6	6	6	2	.030	1	.008	1	.008	8	4	8	1	.018	1	.018	0	.002
6	6	5	1	.040	0	.008	0	.008	8	4	7	0	.010	0	.010	—	—
6	6	4	0	.030	—	—	—	—	8	4	6	0	.030	—	—	—	—
6	5	6	1	.015	1	.015	0	.002	8	3	8	0	.006	0	.006	0	.006
6	5	5	0	.013	0	.013	—	—	8	3	7	0	.024	0	.024	—	—
6	5	4	0	.045	—	—	—	—	8	2	8	0	.022	0	.022	—	—
6	4	6	1	.033	0	.005	0	.005	9	9	9	5	.041	4	.015	3	.005
6	4	5	0	.024	0	.024	—	—	9	9	8	3	.025	3	.025	2	.008
6	3	6	0	.012	0	.012	—	—	9	9	7	2	.028	1	.008	1	.008
6	3	5	0	.048	—	—	—	—	9	9	6	1	.025	1	.025	0	.005
6	2	6	0	.036	—	—	—	—	9	9	5	0	.015	0	.015	—	—
7	7	7	3	.035	2	.010	1	.002	9	9	4	0	.041	—	—	—	—
7	7	6	1	.015	1	.015	0	.002	9	8	9	4	.029	3	.009	3	.009
7	7	5	0	.010	0	.010	—	—	9	8	8	3	.043	2	.013	1	.003
7	7	4	0	.035	—	—	—	—	9	8	7	2	.044	1	.012	0	.002
7	6	7	2	.021	2	.021	1	.005	9	8	6	1	.036	0	.007	0	.007
7	6	6	1	.025	0	.004	0	.004	9	8	5	0	.020	0	.020	—	—
7	6	5	0	.016	0	.016	—	—	9	7	9	3	.019	3	.019	2	.005
7	6	4	0	.049	—	—	—	—	9	7	8	2	.024	2	.024	1	.006
7	5	7	2	.045	1	.010	0	.001	9	7	7	1	.020	1	.020	0	.003
7	5	6	1	.045	0	.008	0	.008	9	7	6	0	.010	0	.010	—	—
7	5	5	0	.027	—	—	—	—	9	7	5	0	.029	—	—	—	—
7	4	7	1	.024	1	.024	0	.003	9	6	9	3	.044	2	.011	1	.002
7	4	6	0	.015	0	.015	—	—	9	6	8	2	.047	1	.011	0	.001
7	4	5	0	.045	—	—	—	—	9	6	7	1	.035	0	.006	0	.006
7	3	7	0	.008	0	.008	0	.008	9	6	6	0	.017	0	.017	—	—
7	3	6	0	.033	—	—	—	—	9	6	5	0	.042	—	—	—	—
7	2	7	0	.028	—	—	—	—	9	5	9	2	.027	1	.005	1	.005
8	8	8	4	.038	3	.013	2	.003	9	5	8	1	.023	1	.023	0	.003
8	8	7	2	.020	2	.020	1	.005	9	5	7	0	.010	0	.010	—	—
8	8	6	1	.020	1	.020	0	.003	9	5	6	0	.028	—	—	—	—
8	8	5	0	.013	0	.013	—	—	9	4	9	1	.014	1	.014	0	.001
8	8	4	0	.038	—	—	—	—	9	4	8	0	.007	0	.007	0	.007
8	7	8	3	.026	2	.007	2	.007	9	4	7	0	.021	0	.021	—	—
8	7	7	2	.035	1	.009	1	.009	9	4	6	0	.049	—	—	—	—
8	7	6	1	.032	0	.006	0	.006	9	3	9	1	.045	0	.005	0	.005

(*continued overleaf*)

Table A.7 (***continued***)

A	*B*	*a*	*b*	*p*	*b*	*p*	*b*	*p*	*A*	*B*	*a*	*b*	*p*	*b*	*p*	*b*	*p*
9	3	8	0	.018	0	.018	—	—	11	11	8	3	.043	2	.015	1	.004
9	3	7	0	.045	—	—	—	—	11	11	7	2	.040	1	.012	0	.002
9	2	9	0	.018	0	.018	—	—	11	11	6	1	.032	0	.006	0	.006
10	10	10	6	.043	5	.016	4	.005	11	11	5	0	.018	0	.018	—	—
10	10	9	4	.029	3	.010	3	.010	11	11	4	0	.045	—	—	—	—
10	10	8	3	.035	2	.012	1	.003	11	10	11	6	.035	5	.012	4	.004
10	10	7	2	.035	1	.010	1	.010	11	10	10	4	.021	4	.021	3	.007
10	10	6	1	.029	0	.005	0	.005	11	10	9	3	.024	3	.024	2	.007
10	10	5	0	.016	0	.016	—	—	11	10	8	2	.023	2	.023	1	.006
10	10	4	0	.043	—	—	—	—	11	10	7	1	.017	1	.017	0	.003
10	9	10	5	.033	4	.011	3	.003	11	10	6	1	.043	0	.009	0	.009
10	9	9	4	.050	3	.017	2	.005	11	10	5	0	.023	0	.023	—	—
10	9	8	2	.019	2	.019	1	.004	11	9	11	5	.026	4	.008	4	.008
10	9	7	1	.015	1	.015	0	.002	11	9	10	4	.038	3	.012	2	.003
10	9	6	1	.040	0	.008	0	.008	11	9	9	3	.040	2	.012	1	.003
10	9	5	0	.022	0	.022	—	—	11	9	8	2	.035	1	.009	1	.009
10	8	10	4	.023	4	.023	3	.007	11	9	7	1	.025	1	.025	0	.004
10	8	9	3	.032	2	.009	2	.009	11	9	6	0	.012	0	.012	—	—
10	8	8	2	.031	1	.008	1	.008	11	9	5	0	.030	—	—	—	—
10	8	7	1	.023	1	.023	0	.004	11	8	11	4	.018	4	.018	3	.005
10	8	6	0	.011	0	.011	—	—	11	8	10	3	.024	3	.024	2	.006
10	8	5	0	.029	—	—	—	—	11	8	9	2	.022	2	.022	1	.005
10	7	10	3	.015	3	.015	2	.003	11	8	8	1	.015	1	.015	0	.002
10	7	9	2	.018	2	.018	1	.004	11	8	7	1	.037	0	.007	0	.007
10	7	8	1	.013	1	.013	0	.002	11	8	6	0	.017	0	.017	—	—
10	7	7	1	.036	0	.006	0	.006	11	8	5	0	.040	—	—	—	—
10	7	6	0	.017	0	.017	—	—	11	7	11	4	.043	3	.011	2	.002
10	7	5	0	.041	—	—	—	—	11	7	10	3	.047	2	.013	1	.002
10	6	10	3	.036	2	.008	2	.008	11	7	9	2	.039	1	.009	1	.009
10	6	9	2	.036	1	.008	1	.008	11	7	8	1	.025	1	.025	0	.004
10	6	8	1	.024	1	.024	0	.003	11	7	7	0	.010	0	.010	—	—
10	6	7	0	.010	0	.010	—	—	11	7	6	0	.025	0	.025	—	—
10	6	6	0	.026	—	—	—	—	11	6	11	3	.029	2	.006	2	.006
10	5	10	2	.022	2	.022	1	.004	11	6	10	2	.028	1	.005	1	.005
10	5	9	1	.017	1	.017	0	.002	11	6	9	1	.018	1	.018	0	.002
10	5	8	1	.047	0	.007	0	.007	11	6	8	1	.043	0	.007	0	.007
10	5	7	0	.019	0	.019	—	—	11	6	7	0	.017	0	.017	—	—
10	5	6	0	.042	—	—	—	—	11	6	6	0	.037	—	—	—	—
10	4	10	1	.011	1	.011	0	.001	11	5	11	2	.018	2	.018	1	.003
10	4	9	1	.041	0	.005	0	.005	11	5	10	1	.013	1	.013	0	.001
10	4	8	0	.015	0	.015	—	—	11	5	9	1	.036	0	.005	0	.005
10	4	7	0	.035	—	—	—	—	11	5	8	0	.013	0	.013	—	—
10	3	10	1	.038	0	.003	0	.003	11	5	7	0	.029	—	—	—	—
10	3	9	0	.014	0	.014	—	—	11	4	11	1	.009	1	.009	1	.009
10	3	8	0	.035	—	—	—	—	11	4	10	1	.033	0	.004	0	.004
10	2	10	0	.015	0	.015	—	—	11	4	9	0	.011	0	.011	—	—
10	2	9	0	.045	—	—	—	—	11	4	8	0	.026	—	—	—	—
11	11	11	7	.045	6	.018	5	.006	11	3	11	1	.033	0	.003	0	.003
11	11	10	5	.032	4	.012	3	.004	11	3	10	0	.011	0	.011	—	—
11	11	9	4	.040	3	.015	2	.004	11	3	9	0	.027	—	—	—	—

Table A.7 (***continued***)

A	*B*	*a*	*b*	*p*	*b*	*p*	*b*	*p*	*A*	*B*	*a*	*b*	*p*	*b*	*p*	*b*	*p*
11	2	11	0	.013	0	.013	—	—	12	6	11	2	.022	2	.022	1	.004
11	2	10	0	.038	—	—	—	—	12	6	10	1	.013	1	.013	0	.002
12	12	12	8	.047	7	.019	6	.007	12	6	9	1	.032	0	.005	0	.005
12	12	11	6	.034	5	.014	4	.005	12	6	8	0	.011	0	.011	—	—
12	12	10	5	.045	4	.018	3	.006	12	6	7	0	.025	0	.025	—	—
12	12	9	4	.050	3	.020	2	.006	12	6	6	0	.050	—	—	—	—
12	12	8	3	.050	2	.018	1	.005	12	5	12	2	.015	2	.015	1	.002
12	12	7	2	.045	1	.014	0	.002	12	5	11	1	.010	1	.010	1	.010
12	12	6	1	.034	0	.007	0	.007	12	5	10	1	.028	0	.003	0	.003
12	12	5	0	.019	0	.019	—	—	12	5	9	0	.009	0	.009	0	.009
12	12	4	0	.047	—	—	—	—	12	5	8	0	.020	0	.020	—	—
12	11	12	7	.037	6	.014	5	.005	12	5	7	0	.041	—	—	—	—
12	11	11	5	.024	5	.024	4	.008	12	4	12	2	.050	1	.007	1	.007
12	11	10	4	.029	3	.010	2	.003	12	4	11	1	.027	0	.003	0	.003
12	11	9	3	.030	2	.009	2	.009	12	4	10	0	.008	0	.008	0	.008
12	11	8	2	.026	1	.007	1	.007	12	4	9	0	.019	0	.019	—	—
12	11	7	1	.019	1	.019	0	.003	12	4	8	0	.038	—	—	—	—
12	11	6	1	.045	0	.009	0	.009	12	3	12	1	.029	0	.002	0	.002
12	11	5	0	.024	0	.024	—	—	12	3	11	0	.009	0	.009	0	.009
12	10	12	6	.029	5	.010	5	.010	12	3	10	0	.022	0	.022	—	—
12	10	11	5	.043	4	.015	3	.005	12	3	9	0	.044	—	—	—	—
12	10	10	4	.048	3	.017	2	.005	12	2	12	0	.011	0	.011	—	—
12	10	9	3	.046	2	.015	1	.004	12	2	11	0	.033	—	—	—	—
12	10	8	2	.038	1	.010	0	.002	13	13	13	9	.048	8	.020	7	.007
12	10	7	1	.026	0	.005	0	.005	13	13	12	7	.037	6	.015	5	.006
12	10	6	0	.012	0	.012	—	—	13	13	11	6	.048	5	.021	4	.008
12	10	5	0	.030	—	—	—	—	13	13	10	4	.024	4	.024	3	.008
12	9	12	5	.021	5	.021	4	.006	13	13	9	3	.024	3	.024	2	.008
12	9	11	4	.029	3	.009	3	.009	13	13	8	2	.021	2	.021	1	.006
12	9	10	3	.029	2	.008	2	.008	13	13	7	2	.048	1	.015	0	.003
12	9	9	2	.024	2	.024	1	.006	13	13	6	1	.037	0	.007	0	.007
12	9	8	1	.016	1	.016	0	.002	13	13	5	0	.020	0	.020	—	—
12	9	7	1	.037	0	.007	0	.007	13	13	4	0	.048	—	—	—	—
12	9	6	0	.017	0	.017	—	—	13	12	13	8	.039	7	.015	6	.005
12	9	5	0	.039	—	—	—	—	13	12	12	6	.027	5	.010	5	.010
12	8	12	5	.049	4	.014	3	.004	13	12	11	5	.033	4	.013	3	.004
12	8	11	3	.018	3	.018	2	.004	13	12	10	4	.036	3	.013	2	.004
12	8	10	2	.015	2	.015	1	.003	13	12	9	3	.034	2	.011	1	.003
12	8	9	2	.040	1	.010	1	.010	13	12	8	2	.029	1	.008	1	.008
12	8	8	1	.025	1	.025	0	.004	13	12	7	1	.020	1	.020	0	.004
12	8	7	0	.010	0	.010	—	—	13	12	6	1	.046	0	.010	0	.010
12	8	6	0	.024	0	.024	—	—	13	12	5	0	.024	0	.024	—	—
12	7	12	4	.036	3	.009	3	.009	13	11	13	7	.031	6	.011	5	.003
12	7	11	3	.038	2	.010	2	.010	13	11	12	6	.048	5	.018	4	.006
12	7	10	2	.029	1	.006	1	.006	13	11	11	4	.021	4	.021	3	.007
12	7	9	1	.017	1	.017	0	.002	13	11	10	3	.021	3	.021	2	.006
12	7	8	1	.040	0	.007	0	.007	13	11	9	3	.050	2	.017	1	.004
12	7	7	0	.016	0	.016	—	—	13	11	8	2	.040	1	.011	0	.002
12	7	6	0	.034	—	—	—	—	13	11	7	1	.027	0	.005	0	.005
12	6	12	3	.025	3	.025	2	.005	13	11	6	0	.013	0	.013	—	—

(*continued overleaf*)

Table A.7 (*continued*)

A	*B*	*a*	*b*	*p*	*b*	*p*	*b*	*p*	*A*	*B*	*a*	*b*	*p*	*b*	*p*	*b*	*p*
13	11	5	0	.030	—	—	—	—	13	4	11	0	.006	0	.006	0	.006
13	10	13	6	.024	6	.024	5	.007	13	4	10	0	.015	0	.015	—	—
13	10	12	5	.035	4	.012	3	.003	13	4	9	0	.029	—	—	—	—
13	10	11	4	.037	3	.012	2	.003	13	3	13	1	.025	1	.025	0	.002
13	10	10	3	.033	2	.010	1	.002	13	3	12	0	.007	0	.007	0	.007
13	10	9	2	.026	1	.006	1	.006	13	3	11	0	.018	0	.018	—	—
13	10	8	1	.017	1	.017	0	.003	13	3	10	0	.036	—	—	—	—
13	10	7	1	.038	0	.007	0	.007	13	2	13	0	.010	0	.010	0	.010
13	10	6	0	.017	0	.017	—	—	13	2	12	0	.029	—	—	—	—
13	10	5	0	.038	—	—	—	—	14	14	14	10	.049	9	.020	8	.008
13	9	13	5	.017	5	.017	4	.005	14	14	13	8	.038	7	.016	6	.006
13	9	12	4	.023	4	.023	3	.007	14	14	12	6	.023	6	.023	5	.009
13	9	11	3	.022	3	.022	2	.006	14	14	11	5	.027	4	.011	3	.004
13	9	10	2	.017	2	.017	1	.004	14	14	10	4	.028	3	.011	2	.003
13	9	9	2	.040	1	.010	0	.001	14	14	9	3	.027	2	.009	2	.009
13	9	8	1	.025	1	.025	0	.004	14	14	8	2	.023	2	.023	1	.006
13	9	7	0	.010	0	.010	—	—	14	14	7	1	.016	1	.016	0	.003
13	9	6	0	.023	0	.023	—	—	14	14	6	1	.038	0	.008	0	.008
13	9	5	0	.049	—	—	—	—	14	14	5	0	.020	0	.020	—	—
13	8	13	5	.042	4	.012	3	.003	14	14	4	0	.049	—	—	—	—
13	8	12	4	.047	3	.014	2	.003	14	13	14	9	.041	8	.016	7	.006
13	8	11	3	.041	2	.011	1	.002	14	13	13	7	.029	6	.011	5	.004
13	8	10	2	.029	1	.007	1	.007	14	13	12	6	.037	5	.015	4	.005
13	8	9	1	.017	1	.017	0	.002	14	13	11	5	.041	4	.017	3	.006
13	8	8	1	.037	0	.006	0	.006	14	13	10	4	.041	3	.016	2	.005
13	8	7	0	.015	0	.015	—	—	14	13	9	3	.038	2	.013	1	.003
13	8	6	0	.032	—	—	—	—	14	13	8	2	.031	1	.009	1	.009
13	7	13	4	.031	3	.007	3	.007	14	13	7	1	.021	1	.021	0	.004
13	7	12	3	.031	2	.007	2	.007	14	13	6	1	.048	0	.010	—	—
13	7	11	2	.022	2	.022	1	.004	14	13	5	0	.025	0	.025	—	—
13	7	10	1	.012	1	.012	0	.002	14	12	14	8	.033	7	.012	6	.004
13	7	9	1	.029	0	.004	0	.004	14	12	13	6	.021	6	.021	5	.007
13	7	8	0	.010	0	.010	—	—	14	12	12	5	.025	4	.009	4	.009
13	7	7	0	.022	0	.022	—	—	14	12	11	4	.026	3	.009	3	.009
13	7	6	0	.044	—	—	—	—	14	12	10	3	.024	3	.024	2	.007
13	6	13	3	.021	3	.021	2	.004	14	12	9	2	.019	2	.019	1	.005
13	6	12	2	.017	2	.017	1	.003	14	12	8	2	.042	1	.012	0	.002
13	6	11	2	.046	1	.010	1	.010	14	12	7	1	.028	0	.005	0	.005
13	6	10	1	.024	1	.024	0	.003	14	12	6	0	.013	0	.013	—	—
13	6	9	1	.050	0	.008	0	.008	14	12	5	0	.030	—	—	—	—
13	6	8	0	.017	0	.017	—	—	14	11	14	7	.026	6	.009	6	.009
13	6	7	0	.034	—	—	—	—	14	11	13	6	.039	5	.014	4	.004
13	5	13	2	.012	2	.012	1	.002	14	11	12	5	.043	4	.016	3	.005
13	5	12	2	.044	1	.008	1	.008	14	11	11	4	.042	3	.015	2	.004
13	5	11	1	.022	1	.022	0	.002	14	11	10	3	.036	2	.011	1	.003
13	5	10	1	.047	0	.007	0	.007	14	11	9	2	.027	1	.007	1	.007
13	5	9	0	.015	0	.015	—	—	14	11	8	1	.017	1	.017	0	.003
13	5	8	0	.029	—	—	—	—	14	11	7	1	.038	0	.007	0	.007
13	4	13	2	.044	1	.006	1	.006	14	11	6	0	.017	0	.017	—	—
13	4	12	1	.022	1	.022	0	.002	14	11	5	0	.038	—	—	—	—

Table A.7 (***continued***)

A	*B*	*a*	*b*	*p*	*b*	*p*	*b*	*p*	*A*	*B*	*a*	*b*	*p*	*b*	*p*	*b*	*p*
14	10	14	6	.020	6	.020	5	.006	14	5	8	0	.040	—	—	—	—
14	10	13	5	.028	4	.009	4	.009	14	4	14	2	.039	1	.005	1	.005
14	10	12	4	.028	3	.009	3	.009	14	4	13	1	.019	1	.019	0	.002
14	10	11	3	.024	3	.024	2	.007	14	4	12	1	.044	0	.005	0	.005
14	10	10	2	.018	2	.018	1	.004	14	4	11	0	.011	0	.011	—	—
14	10	9	2	.040	1	.011	0	.002	14	4	10	0	.023	0	.023	—	—
14	10	8	1	.024	1	.024	0	.004	14	4	9	0	.041	—	—	—	—
14	10	7	0	.010	0	.010	0	.010	14	3	14	1	.022	1	.022	0	.001
14	10	6	0	.022	0	.022	—	—	14	3	13	0	.006	0	.006	0	.006
14	10	5	0	.047	—	—	—	—	14	3	12	0	.015	0	.015	—	—
14	9	14	6	.047	5	.014	4	.004	14	3	11	0	.029	—	—	—	—
14	9	13	4	.018	4	.018	3	.005	14	2	14	0	.008	0	.008	0	.008
14	9	12	3	.017	3	.017	2	.004	14	2	13	0	.025	0	.025	—	—
14	9	11	3	.042	2	.012	1	.002	14	2	12	0	.050	—	—	—	—
14	9	10	2	.029	1	.007	1	.007	15	15	15	11	.050	10	.021	9	.008
14	9	9	1	.017	1	.017	0	.002	15	15	14	9	.040	8	.018	7	.007
14	9	8	1	.036	0	.006	0	.006	15	15	13	7	.025	6	.010	5	.004
14	9	7	0	.014	0	.014	—	—	15	15	12	6	.030	5	.013	4	.005
14	9	6	0	.030	—	—	—	—	15	15	11	5	.033	4	.013	3	.005
14	8	14	5	.036	4	.010	4	.010	15	15	10	4	.033	3	.013	2	.004
14	8	13	4	.039	3	.011	2	.002	15	15	9	3	.030	2	.010	1	.003
14	8	12	3	.032	2	.008	2	.008	15	15	8	2	.025	1	.007	1	.007
14	8	11	2	.022	2	.022	1	.005	15	15	7	1	.018	1	.018	0	.003
14	8	10	2	.048	1	.012	0	.002	15	15	6	1	.040	0	.008	0	.008
14	8	9	1	.026	0	.004	0	.004	15	15	5	0	.021	0	.021	—	—
14	8	8	0	.009	0	.009	0	.009	15	15	4	0	.050	—	—	—	—
14	8	7	0	.020	0	.020	—	—	15	14	15	10	.042	9	.017	8	.006
14	8	6	0	.040	—	—	—	—	15	14	14	8	.031	7	.013	6	.005
14	7	14	4	.026	3	.006	3	.006	15	14	13	7	.041	6	.017	5	.007
14	7	13	3	.025	2	.006	2	.006	15	14	12	6	.046	5	.020	4	.007
14	7	12	2	.017	2	.017	1	.003	15	14	11	5	.048	4	.020	3	.007
14	7	11	2	.041	1	.009	1	.009	15	14	10	4	.046	3	.018	2	.006
14	7	10	1	.021	1	.021	0	.003	15	14	9	3	.041	2	.014	1	.004
14	7	9	1	.043	0	.007	0	.007	15	14	8	2	.033	1	.009	1	.009
14	7	8	0	.015	0	.015	—	—	15	14	7	1	.022	1	.022	0	.004
14	7	7	0	.030	—	—	—	—	15	14	6	1	.049	0	.011	—	—
14	6	14	3	.018	3	.018	2	.003	15	14	5	0	.025	—	—	—	—
14	6	13	2	.014	2	.014	1	.002	15	13	15	9	.035	8	.013	7	.005
14	6	12	2	.037	1	.007	1	.007	15	13	14	7	.023	7	.023	6	.009
14	6	11	1	.018	1	.018	0	.002	15	13	13	6	.029	5	.011	4	.004
14	6	10	1	.038	0	.005	0	.005	15	13	12	5	.031	4	.012	3	.004
14	6	9	0	.012	0	.012	—	—	15	13	11	4	.030	3	.011	2	.003
14	6	8	0	.024	0	.024	—	—	15	13	10	3	.026	2	.008	2	.008
14	6	7	0	.044	—	—	—	—	15	13	9	2	.020	2	.020	1	.005
14	5	14	2	.010	2	.010	1	.001	15	13	8	2	.043	1	.013	0	.002
14	5	13	2	.037	1	.006	1	.006	15	13	7	1	.029	0	.005	0	.005
14	5	12	1	.017	1	.017	0	.002	15	13	6	0	.013	0	.013	—	—
14	5	11	1	.038	0	.005	0	.005	15	13	5	0	.031	—	—	—	—
14	5	10	0	.011	0	.011	—	—	15	12	15	8	.028	7	.010	7	.010
14	5	9	0	.022	0	.022	—	—	15	12	14	7	.043	6	.016	5	.006

(*continued overleaf*)

Table A.7 (***continued***)

A	*B*	*a*	*b*	*p*	*b*	*p*	*b*	*p*	*A*	*B*	*a*	*b*	*p*	*b*	*p*	*b*	*p*
15	12	13	6	.049	5	.019	4	.007	15	8	10	1	.019	1	.019	0	.003
15	12	12	5	.049	4	.019	3	.006	15	8	9	1	.038	0	.006	0	.006
15	12	11	4	.045	3	.017	2	.005	15	8	8	0	.013	0	.013	—	—
15	12	10	3	.038	2	.012	1	.003	15	8	7	0	.026	—	—	—	—
15	12	9	2	.028	1	.007	1	.007	15	8	6	0	.050	—	—	—	—
15	12	8	1	.018	1	.018	0	.003	15	7	15	4	.023	4	.023	3	.005
15	12	7	1	.038	0	.007	0	.007	15	7	14	3	.021	3	.021	2	.004
15	12	6	0	.017	0	.017	—	—	15	7	13	2	.014	2	.014	1	.002
15	12	5	0	.037	—	—	—	—	15	7	12	2	.032	1	.007	1	.007
15	11	15	7	.022	7	.022	6	.007	15	7	11	1	.015	1	.015	0	.002
15	11	14	6	.032	5	.011	4	.003	15	7	10	1	.032	0	.005	0	.005
15	11	13	5	.034	4	.012	3	.003	15	7	9	0	.010	0	.010	—	—
15	11	12	4	.032	3	.010	2	.003	15	7	8	0	.020	0	.020	—	—
15	11	11	3	.026	2	.008	2	.008	15	7	7	0	.038	—	—	—	—
15	11	10	2	.019	2	.019	1	.004	15	6	15	3	.015	3	.015	2	.003
15	11	9	2	.040	1	.011	0	.002	15	6	14	2	.011	2	.011	1	.002
15	11	8	1	.024	1	.024	0	.004	15	6	13	2	.031	1	.006	1	.006
15	11	7	1	.049	0	.010	0	.010	15	6	12	1	.014	1	.014	0	.002
15	11	6	0	.022	0	.022	—	—	15	6	11	1	.029	0	.004	0	.004
15	11	5	0	.046	—	—	—	—	15	6	10	0	.009	0	.009	0	.009
15	10	15	6	.017	6	.017	5	.005	15	6	9	0	.017	0	.017	—	—
15	10	14	5	.023	5	.023	4	.007	15	6	8	0	.032	—	—	—	—
15	10	13	4	.022	4	.022	3	.007	15	5	15	2	.009	2	.009	2	.009
15	10	12	3	.018	3	.018	2	.005	15	5	14	2	.032	1	.005	1	.005
15	10	11	3	.042	2	.013	1	.003	15	5	13	1	.014	1	.014	0	.001
15	10	10	2	.029	1	.007	1	.007	15	5	12	1	.031	0	.004	0	.004
15	10	9	1	.016	1	.016	0	.002	15	5	11	0	.008	0	.008	0	.008
15	10	8	1	.034	0	.006	0	.006	15	5	10	0	.016	0	.016	—	—
15	10	7	0	.013	0	.013	—	—	15	5	9	0	.030	—	—	—	—
15	10	6	0	.028	—	—	—	—	15	4	15	2	.035	1	.004	1	.004
15	9	15	6	.042	5	.012	4	.003	15	4	14	1	.016	1	.016	0	.001
15	9	14	5	.047	4	.015	3	.004	15	4	13	1	.037	0	.004	0	.004
15	9	13	4	.042	3	.013	2	.003	15	4	12	0	.009	0	.009	0	.009
15	9	12	3	.032	2	.009	2	.009	15	4	11	0	.018	0	.018	—	—
15	9	11	2	.021	2	.021	1	.005	15	4	10	0	.033	—	—	—	—
15	9	10	2	.045	1	.011	0	.002	15	3	15	1	.020	1	.020	0	.001
15	9	9	1	.024	1	.024	0	.004	15	3	14	0	.005	0	.005	0	.005
15	9	8	1	.048	0	.009	0	.009	15	3	13	0	.012	0	.012	—	—
15	9	7	0	.019	0	.019	—	—	15	3	12	0	.025	0	.025	—	—
15	9	6	0	.037	—	—	—	—	15	3	11	0	.043	—	—	—	—
15	8	15	5	.032	4	.008	4	.008	15	2	15	0	.007	0	.007	0	.007
15	8	14	4	.033	3	.009	3	.009	15	2	14	0	.022	0	.022	—	—
15	8	13	3	.026	2	.006	2	.006	15	2	13	0	.044	—	—	—	—
15	8	12	2	.017	2	.017	1	.003									
15	8	11	2	.037	1	.008	1	.008	23	10	21	5	.016	5	.016	4	.004
									32	13	32	10	.020	10	.020	9	.005

Table A.8 Sample Sizes for Comparing Two Proportions with a One-Sided Fisher's Exact Test in 2 × 2 Tables

Let P_A and P_B be the true proportions in two populations. The sample size, N, for two equally sized groups is tabulated for one-sided significance level α and probability β of not rejecting the null hypothesis. Each rectangular portion of the table contains sample sizes for *two* pairs of α and β values, one above the diagonal and one below it. The arcsine approximation was used to estimate N.

P_A	P_B							$\alpha = .01$ and $\beta = .01$						
	.001	.01	.05	.10	.15	.20	.25	.30	.40	.50	.60	.70	.80	.90
.001	—	2305	288	129	81	58	45	37	26	20	15	12	10	8
.01	1679	—	689	221	123	82	61	48	32	24	18	14	11	9
.05	210	502	—	1169	366	191	122	87	52	35	25	19	14	11
.10	94	161	852	—	1877	538	266	163	83	51	34	25	18	13
.15	59	90	266	1368	—	2489	683	327	132	73	46	31	22	15
.20	43	60	140	392	1814	—	3012	805	222	105	61	39	27	18
.25	33	44	89	194	498	2194	—	3447	417	158	83	50	32	21
.30	27	35	63	119	239	587	2511	—	981	256	116	64	39	25
.40	19	24	38	60	96	162	304	715	—	1068	267	116	61	34
.50	14	17	26	37	53	77	116	187	778	—	1068	256	105	51
.60	11	13	19	25	34	45	61	84	195	778	—	981	222	83
.70	9	10	14	18	23	29	37	47	84	187	715	—	805	163
.80	7	8	11	13	16	20	24	29	45	77	162	587	—	538
.90	6	6	8	10	11	13	15	18	25	37	60	119	392	—
							$\alpha = .01$ and $\beta = .05$ (or $\alpha = .05$ and $\beta = .01$)							

P_A	P_B						$\alpha = .025$ and $\beta = .05$ (or $\alpha = .05$ and $\beta = .025$)							
	.001	.01	.05	.10	.15	.20	.25	.30	.40	.50	.60	.70	.80	.90
.001	—	1384	173	78	49	35	27	22	16	12	9	8	6	5
.01	1119	—	414	133	74	50	37	29	20	14	11	9	7	5
.05	140	335	—	702	220	115	74	52	31	21	15	12	9	7
.10	63	108	568	—	1127	323	160	98	50	31	21	15	11	8
.15	40	60	178	911	—	1494	410	197	79	44	28	19	13	9
.20	29	40	93	261	1208	—	1808	483	133	63	37	24	16	11
.25	22	30	60	129	332	1462	—	2069	251	95	50	30	20	13
.30	18	23	42	79	159	391	1673	—	589	154	70	39	24	15
.40	13	16	25	40	64	108	203	476	—	641	161	70	37	21
.50	10	12	17	25	35	51	77	125	519	—	641	154	63	31
.60	8	9	13	17	23	30	40	56	130	519	—	589	133	50
.70	6	7	9	12	15	19	25	32	56	125	476	—	483	98
.80	5	6	7	9	11	13	16	19	30	51	108	391	—	323
.90	4	4	6	7	8	9	10	12	17	25	40	79	261	—
							$\alpha = .025$ and $\beta = .10$ (or $\alpha = .10$ and $\beta = .025$)							

P_A	P_B							$\alpha = .05$ and $\beta = .05$						
	.001	.01	.05	.10	.15	.20	.25	.30	.40	.50	.60	.70	.80	.90
.001	—	1152	144	65	41	29	23	19	13	10	8	6	5	4
.01	912	—	345	111	62	41	31	24	16	12	9	7	6	5
.05	114	273	—	585	183	96	61	44	26	18	13	10	7	6
.10	51	88	463	—	939	269	133	82	42	26	17	13	9	7
.15	32	49	145	743	—	1245	342	164	66	36	23	16	11	8
.20	23	33	76	213	985	—	1506	403	111	53	31	20	14	9
.25	18	24	49	106	271	1192	—	1723	209	79	42	25	16	11
.30	15	19	35	65	130	319	1364	—	491	128	58	32	20	13
.40	11	13	21	33	52	88	165	388	—	534	134	58	31	17
.50	8	10	14	20	29	42	63	102	423	—	534	128	53	26
.60	6	7	10	14	18	24	33	46	106	423	—	491	111	42
.70	5	6	8	10	13	16	20	26	46	102	388	—	403	82
.80	4	5	6	7	9	11	13	16	24	42	88	319	—	269
.90	3	4	5	5	6	7	9	10	14	20	33	65	213	—
							$\alpha = .05$ and $\beta = .10$ (or $\alpha = .10$ and $\beta = .05$)							

(*continued overleaf*)

Table A.8 (*continued*)

P_A	P_B	$\alpha = .10$ and $\beta = .10$												
	.001	.01	.05	.10	.15	.20	.25	.30	.40	.50	.60	.70	.80	.90
.001	—	700	88	40	25	18	14	11	8	6	5	4	3	3
.01	480	—	210	67	38	25	19	15	10	7	6	5	4	3
.05	60	144	—	355	111	58	37	27	16	11	8	6	5	4
.10	27	46	244	—	570	164	81	50	25	16	11	8	6	4
.15	17	26	77	391	—	756	208	100	40	22	14	10	7	5
.20	13	18	40	112	519	—	914	245	68	32	19	12	8	6
.25	10	13	26	56	143	628	—	1046	127	48	25	16	10	7
.30	8	10	18	34	69	168	718	—	298	78	35	20	12	8
.40	6	7	11	18	28	47	87	205	—	325	82	35	19	11
.50	4	5	8	11	15	22	33	54	223	—	325	78	32	16
.60	4	4	6	8	10	13	18	25	56	223	—	298	68	25
.70	3	3	4	6	7	9	11	14	25	54	205	—	245	50
.80	2	3	3	4	5	6	7	9	13	22	47	168	—	164
.90	2	2	3	3	4	4	5	6	8	11	18	34	112	—
	$\alpha = .10$ and $\beta = .20$ (or $\alpha = .20$ and $\beta = .10$)													

Table A.9 Critical Values for the Signed Ranks Test

For the given n, critical values for the signed ranks test are tabled corresponding to the upper one- and two-sided significance levels in the column headings.

	One-Sided α												
	.05	.025	.01	.005	.05	.025	.01	.005	.05	.025	.01	.005
	Two-Sided α												
	.10	.05	.02	.01	.10	.05	.02	.01	.10	.05	.02	.01
n					n				n				
5	1	—	—	—	20	60	52	43	37	35	214	195	174	160
6	2	1	—	—	21	68	59	49	43	36	228	208	186	171
7	4	2	0	—	22	75	66	56	49	37	242	222	198	183
8	6	4	2	0	23	83	73	62	55	38	256	235	211	195
9	8	6	3	2	24	92	81	69	61	39	271	250	224	208
10	11	8	5	3	25	101	90	77	68	40	287	264	238	221
11	14	11	7	5	26	110	98	85	76	41	303	279	252	234
12	17	14	10	7	27	120	107	93	84	42	319	295	267	248
13	21	17	13	10	28	130	117	102	92	43	336	311	281	262
14	26	21	16	13	29	141	127	111	100	44	353	327	297	277
15	30	25	20	16	30	152	137	120	109	45	371	344	313	292
16	36	30	24	19	31	163	148	130	118	46	389	361	329	307
17	41	35	28	23	32	175	159	141	128	47	408	379	345	323
18	47	40	33	28	33	188	171	151	138	48	427	397	362	339
19	54	46	38	32	34	201	183	162	149	49	446	415	380	356
										50	466	434	398	373

Table A.10 Critical Values for the Mann–Whitney (Wilcoxon) Statistic

This table presents upper one- and two-sided critical values for the Mann–Whitney U statistic. Lower one-sided critical values are computed from the upper one-sided critical value (at the same significance level) as $(M \cdot N) - U$. The Wilcoxon two-sample statistic, W, is related to U by the equation $W = (M \cdot N) + (M \cdot (M + 1)/2) - U$, where W is the sum of the ranks of the sample of size M in the combined sample.

		One-Sided α								*One-Sided α*					
		.10	.05	.025	.01	.005	.001			.10	.05	.025	.01	.005	.001
		Two-Sided α								*Two-Sided α*					
		.20	.10	.05	.02	.01	.002			.20	.10	.05	.02	.01	.002
n	*m*							*n*	*m*						
3	2	6	—	—	—	—	—	10	1	10	—	—	—	—	—
3	3	8	9	—	—	—	—	10	2	17	19	20	—	—	—
								10	3	24	26	27	29	30	—
4	2	8	—	—	—	—	—	10	4	30	33	35	37	38	40
4	3	11	12	—	—	—	—	10	5	37	39	42	44	46	49
4	4	13	15	16	—	—	—	10	6	43	46	49	52	54	57
								10	7	49	53	56	59	61	65
5	2	9	10	—	—	—	—	10	8	56	60	63	67	69	74
5	3	13	14	15	—	—	—	10	9	62	66	70	74	77	82
5	4	16	18	19	20	—	—	10	10	68	73	77	81	84	90
5	5	20	21	23	24	25	—								
								11	1	11	—	—	—	—	—
6	2	11	12	—	—	—	—	11	2	19	21	22	—	—	—
6	3	15	16	17	—	—	—	11	3	26	28	30	32	33	—
6	4	19	21	22	23	24	—	11	4	33	36	38	40	42	44
6	5	23	25	27	28	29	—	11	5	40	43	46	48	50	53
6	6	27	29	31	33	34	—	11	6	47	50	53	57	59	62
								11	7	54	58	61	65	67	71
7	2	13	14	—	—	—	—	11	8	61	65	69	73	75	80
7	3	17	19	20	21	—	—	11	9	68	72	76	81	83	89
7	4	22	24	25	27	28	—	11	10	74	79	84	88	92	98
7	5	27	29	30	32	34	—	11	11	81	87	91	96	100	106
7	6	31	34	36	38	39	42								
7	7	36	38	41	43	45	48	12	1	12	—	—	—	—	—
								12	2	20	22	23	—	—	—
8	2	14	15	16	—	—	—	12	3	28	31	32	34	35	—
8	3	19	21	22	24	—	—	12	4	36	39	41	43	45	48
8	4	25	27	28	30	31	—	12	5	43	47	49	52	54	58
8	5	30	32	34	36	38	40	12	6	51	55	58	61	63	68
8	6	35	38	40	42	44	47	12	7	58	63	66	70	72	77
8	7	40	43	46	49	50	54	12	8	66	70	74	79	81	87
8	8	45	49	51	55	57	60	12	9	73	78	82	87	90	96
								12	10	81	86	91	96	99	106
9	1	9	—	—	—	—	—	12	11	88	94	99	104	108	115
9	2	16	17	18	—	—	—	12	12	95	102	107	113	117	124
9	3	22	23	25	26	27	—								
9	4	27	30	32	33	35	—	13	1	13	—	—	—	—	—
9	5	33	36	38	40	42	44	13	2	22	24	25	26	—	—
9	6	39	42	44	47	49	52	13	3	30	33	35	37	38	—
9	7	45	48	51	54	56	60	13	4	39	42	44	47	49	51
9	8	50	54	57	61	63	67	13	5	47	50	53	56	58	62
9	9	56	60	64	67	70	74	13	6	55	59	62	66	68	73

(*continued overleaf*)

Table A.10 (***continued***)

		One-Sided α												
		.10	.05	.025	.01	.005	.001		.10	.05	.025	.01	.005	.001
		Two-Sided α												
		.20	.10	.05	.02	.01	.002		.20	.10	.05	.02	.01	.002
n	*m*							*n*	*m*					
13	7	63	67	71	75	78	83	16	12	125	132	139	146	151	161
13	8	71	76	80	84	87	93	16	13	134	143	149	157	163	173
13	9	79	84	89	94	97	103	16	14	144	153	160	168	174	185
13	10	87	93	97	103	106	113	16	15	154	163	170	179	185	197
13	11	95	101	106	112	116	123	16	16	163	173	181	190	196	208
13	12	103	109	115	121	125	133								
13	13	111	118	124	130	135	143	17	1	17	—	—	—	—	—
								17	2	28	31	32	34	—	—
14	1	14	—	—	—	—	—	17	3	39	42	45	47	49	51
14	2	23	25	27	28	—	—	17	4	50	53	57	60	62	66
14	3	32	35	37	40	41	—	17	5	60	65	68	72	75	80
14	4	41	45	47	50	52	55	17	6	71	76	80	84	87	93
14	5	50	54	57	60	63	67	17	7	81	86	91	96	100	106
14	6	59	63	67	71	73	78	17	8	91	97	102	108	112	119
14	7	67	72	76	81	83	89	17	9	101	108	114	120	124	132
14	8	76	81	86	90	94	100	17	10	112	119	125	132	136	145
14	9	85	90	95	100	104	111	17	11	122	130	136	143	148	158
14	10	93	99	104	110	114	121	17	12	132	140	147	155	160	170
14	11	102	108	114	120	124	132	17	13	142	151	158	166	172	183
14	12	110	117	123	130	134	143	17	14	153	161	169	178	184	195
14	13	119	126	132	139	144	153	17	15	163	172	180	189	195	208
14	14	127	135	141	149	154	164	17	16	173	183	191	201	207	220
								17	17	183	193	202	212	219	232
15	1	15	—	—	—	—	—								
15	2	25	27	29	30	—	—	18	1	18	—	—	—	—	—
15	3	35	38	40	42	43	—	18	2	30	32	34	36	—	—
15	4	44	48	50	53	55	59	18	3	41	45	47	50	52	54
15	5	53	57	61	64	67	71	18	4	52	56	60	63	66	69
15	6	63	67	71	75	78	83	18	5	63	68	72	76	79	84
15	7	72	77	81	86	89	95								
15	8	81	87	91	96	100	106	18	6	74	80	84	89	92	98
15	9	90	96	101	107	111	118	18	7	85	91	96	102	105	112
15	10	99	106	111	117	121	129	18	8	96	103	108	114	118	126
15	11	108	115	121	128	132	141	18	9	107	114	120	126	131	139
15	12	117	125	131	138	143	152	18	10	118	125	132	139	143	153
15	13	127	134	141	148	153	163								
15	14	136	144	151	159	164	174	18	11	129	137	143	151	156	166
15	15	145	153	161	169	174	185	18	12	139	148	155	163	169	179
								18	13	150	159	167	175	181	192
16	1	16	—	—	—	—	—	18	14	161	170	178	187	194	206
16	2	27	29	31	32	—	—	18	15	172	182	190	200	206	219
16	3	37	40	42	45	46	—	18	16	182	193	202	212	218	232
16	4	47	50	53	57	59	62	18	17	193	204	213	224	231	245
16	5	57	61	65	68	71	75	18	18	204	215	225	236	243	258
16	6	67	71	75	80	83	88								
16	7	76	82	86	91	94	101	19	1	18	19	—	—	—	—
16	8	86	92	97	102	106	113	19	2	31	34	36	37	38	—
16	9	96	102	107	113	117	125	19	3	43	47	50	53	54	57
16	10	106	112	118	124	129	137	19	4	55	59	63	67	69	73
16	11	115	122	129	135	140	149	19	5	67	72	76	80	83	88

Table A.10 (*continued*)

		One-Sided α												
		.10	.05	.025	.01	.005	.001		.10	.05	.025	.01	.005	.001
		Two-Sided α												
		.20	.10	.05	.02	.01	.002		.20	.10	.05	.02	.01	.002
n	m							n	m					
19	6	78	84	89	94	97	103	20	4	58	62	66	70	72	77
19	7	90	96	101	107	111	118	20	5	70	75	80	84	87	93
19	8	101	108	114	120	124	132	20	6	82	88	93	98	102	108
19	9	113	120	126	133	138	146	20	7	94	101	106	112	116	124
19	10	124	132	138	146	151	161	20	8	106	113	119	126	130	139
19	11	136	144	151	159	164	175	20	9	118	126	132	140	144	154
19	12	147	156	163	172	177	188	20	10	130	138	145	153	158	168
19	13	158	167	175	184	190	202	20	11	142	151	158	167	172	183
19	14	169	179	188	197	203	216	20	12	154	163	171	180	186	198
19	15	181	191	200	210	216	230	20	13	166	176	184	193	200	212
19	16	192	203	212	222	230	244	20	14	178	188	197	207	213	226
19	17	203	214	224	235	242	257	20	15	190	200	210	220	227	241
19	18	214	226	236	248	255	271	20	16	201	213	222	233	241	255
19	19	226	238	248	260	268	284	20	17	213	225	235	247	254	270
20	1	19	20	—	—	—	—	20	18	225	237	248	260	268	284
20	2	33	36	38	39	40	—	20	19	237	250	261	273	281	298
20	3	45	49	52	55	57	60	20	20	249	262	273	286	295	312

Table A.11 Critical Values of the Bivariate Normal Sample Correlation Coefficient ρ

When $\rho = 0$, the distribution is symmetric about zero; thus, one-sided lower critical values are -1 times the tabled one-sided upper critical values. Column headings are also labeled for the corresponding two-sided significance level and the percentage of the distribution less than the tabled value. N is the number of observations; the degrees of freedom is two less than this.

	Percent								Percent						
	90	95	97.5	99	99.5	99.9	99.95		90	95	97.5	99	99.5	99.9	99.95
	One-Sided α								One-Sided α						
	.10	.05	.025	.01	.005	.001	.0005		.10	.05	.025	.01	.005	.001	.0005
	Two-Sided α								Two-Sided α						
	.20	.10	.05	.02	.01	.002	.001		.20	.10	.05	.02	.01	.002	.001
N								N							
3	.951	.988	.997	1.000	1.000	1.000	1.000	20	.299	.378	.444	.516	.562	.648	.679
4	.800	.900	.950	.980	.990	.998	.999	25	.265	.337	.396	.462	.505	.588	.618
5	.687	.805	.878	.934	.959	.986	.991	30	.241	.306	.361	.423	.463	.542	.570
6	.608	.729	.811	.882	.917	.963	.974								
7	.551	.669	.755	.833	.875	.935	.951	35	.222	.283	.334	.392	.430	.505	.532
								40	.207	.264	.312	.367	.403	.474	.501
8	.507	.622	.707	.789	.834	.905	.925	45	.195	.248	.294	.346	.380	.449	.474
9	.472	.582	.666	.750	.798	.875	.898	50	.184	.235	.279	.328	.361	.427	.451
10	.443	.549	.632	.716	.765	.847	.872	55	.176	.224	.266	.313	.345	.408	.432
11	.419	.522	.602	.685	.735	.820	.847								
12	.398	.497	.576	.658	.708	.795	.823	60	.168	.214	.254	.300	.330	.391	.414
								65	.161	.206	.244	.288	.317	.376	.399
13	.380	.476	.553	.634	.684	.772	.801	70	.155	.198	.235	.278	.306	.363	.385
14	.365	.458	.533	.612	.661	.750	.780	75	.150	.191	.227	.268	.296	.351	.372
15	.351	.441	.514	.592	.641	.730	.760	80	.145	.185	.220	.260	.286	.341	.361
16	.338	.426	.497	.574	.623	.711	.742								
17	.327	.412	.482	.558	.606	.694	.725	85	.140	.180	.213	.252	.278	.331	.351
								90	.136	.175	.207	.245	.270	.322	.341
18	.317	.400	.468	.543	.590	.678	.708	95	.133	.170	.202	.238	.263	.313	.332
19	.308	.389	.456	.529	.575	.662	.693	100	.129	.165	.197	.232	.257	.305	.324

Table A.12 Critical Values for Spearman's Rank Correlation Coefficient

For a sample of size n, two-sided critical values are given for significance levels .10, .05, and .01. Reject the null hypothesis of independence if the absolute value of the sample Spearman correlation coefficient exceeds the tabled value.

	Two-Sided α		
	.10	.05	.01
n			
5	.900	—	—
6	.829	.886	—
7	.714	.786	.929
8	.643	.738	.881
9	.600	.700	.833
10	.564	.648	.794
11	.536	.618	.818
12	.497	.591	.780
13	.475	.566	.745
14	.457	.545	.716
15	.441	.525	.689
16	.425	.507	.666
17	.412	.490	.645
18	.399	.476	.625
19	.388	.462	.608
20	.377	.450	.591
21	.368	.438	.576
22	.359	.428	.562
23	.351	.418	.549
24	.343	.409	.537
25	.336	.400	.526
26	.329	.392	.515
27	.323	.385	.505
28	.317	.377	.496
29	.311	.370	.487
30	.305	.364	.478

Table A.13 Expected Values of Normal Order Statistics

A sample of $NN(0, 1)$ observations is ranked from largest (rank 1) to smallest (rank N). The expected values of the order statistics (the ranked values) are given. Only the expected values for the upper half of the order statistics are given since the expected values are symmetric about zero. The column headings give the size of the sample and the row headings the rank of the order statistic.

	Sample Size												
Rank	2	3	4	5	6	7	8	9	10	11	12	13	14
1	.56419	.34628	1.02938	1.16296	1.26721	1.35218	1.42360	1.48501	1.53875	1.58644	1.62923	1.66799	1.70338
2		.00000	.29701	.49502	.64176	.75737	.85222	.93230	1.00136	1.06192	1.11573	1.16408	1.20790
3				.00000	.20155	.35271	.47282	.57197	.65606	.72884	.79284	.84983	.90113
4						.00000	.15251	.27453	.37576	.46198	.53684	.60285	.66176
5								.00000	.12267	.22489	.31225	.38833	.45557
6										.00000	.10259	.19052	.26730
7												.00000	.08816

	Sample Size												
Rank	15	16	17	18	19	20	21	22	23	24	25	26	27
1	1.73591	1.76599	1.79394	1.82003	1.84448	1.86748	1.88917	1.90969	1.92916	1.94767	1.96531	1.98216	1.99827
2	1.24794	1.28474	1.31878	1.35041	1.37994	1.40760	1.43362	1.45816	1.48137	1.50338	1.52430	1.54423	1.56326
3	.94769	.99027	1.02946	1.06573	1.09945	1.13095	1.16047	1.18824	1.21445	1.23924	1.26275	1.28511	1.30641
4	.71488	.76317	.80738	.84812	.88586	.92098	.95380	.98459	1.01356	1.04091	1.06679	1.09135	1.11471
5	.51570	.57001	.61946	.66479	.70661	.74538	.78150	.81527	.84697	.87682	.90501	.93171	.95705
6	.33530	.39622	.45133	.50158	.54771	.59030	.62982	.66667	.70115	.73354	.76405	.79289	.82021
7	.16530	.23375	.29519	.35084	.40164	.44833	.49148	.53157	.56896	.60299	.63690	.66794	.69727
8	.00000	.07729	.14599	.20774	.26374	.31493	.36203	.40559	.44609	.48391	.51935	.55267	.58411
9			.00000	.06880	.13072	.18696	.23841	.28579	.32965	.37047	.40860	.44436	.47801
10					.00000	.06200	.11836	.16997	.21755	.26163	.30268	.34105	.37706
11							.00000	.05642	.10813	.15583	.20006	.24128	.27983
12									.00000	.05176	.09953	.14387	.18520
13											.00000	.04781	.09220
14													.00000

(*continued overleaf*)

Table A.13 (*continued*)

	Sample Size											
Rank	28	29	30	31	32	33	34	35	36	37	38	39
1	2.01371	2.02852	2.04276	2.05646	2.06967	2.08241	2.09471	2.10661	2.11812	2.12928	2.14009	2.15059
2	1.58145	1.59888	1.61560	1.63166	1.64712	1.66200	1.67636	1.69023	1.70362	1.71659	1.72914	1.74131
3	1.32674	1.34619	1.36481	1.38268	1.39985	1.41637	1.43228	1.44762	1.46244	1.47676	1.49061	1.50402
4	1.13697	1.15822	1.17855	1.19803	1.21672	1.23468	1.25196	1.26860	1.28466	1.30016	1.31514	1.32964
5	.98115	1.00414	1.02609	1.04709	1.06721	1.08652	1.10509	1.12295	1.14016	1.15677	1.17280	1.18830
6	.84615	.87084	.89439	.91688	.93841	.95905	.97886	.99790	1.01624	1.03390	1.05095	1.06741
7	.72508	.75150	.77666	.80066	.82359	.84555	.86660	.88681	.90625	.92496	.94300	.96041
8	.61385	.64205	.66885	.69438	.71875	.74204	.76435	.78574	.80629	.82605	.84508	.86343
9	.50977	.53982	.56834	.59545	.62129	.64596	.66954	.69214	.71382	.73465	.75468	.77398
10	.41096	.44298	.47329	.50206	.52943	.55552	.58043	.60427	.62710	.64902	.67009	.69035
11	.31603	.35013	.38235	.41287	.44185	.46942	.49572	.52084	.54488	.56793	.59005	.61131
12	.22389	.26023	.29449	.32686	.35755	.38669	.41444	.44091	.46620	.49042	.51363	.53592
13	.13361	.17240	.20885	.24322	.27573	.30654	.33582	.36371	.39032	.41576	.44012	.46348
14	.04442	.08588	.12473	.16126	.19572	.22832	.25924	.28863	.31663	.34336	.36892	.39340
15		.00000	.04148	.08037	.11695	.15147	.18415	.21515	.24463	.27272	.29954	.32520
16				.00000	.03890	.07552	.11009	.14282	.17388	.20342	.23159	.25849
17						.00000	.03663	.07123	.10399	.13509	.16469	.19292
18								.00000	.03461	.06739	.09853	.12817
19										.00000	.03280	.06395
20												.00000

Author Index

Biostatistics: A Methodology for the Health Sciences, Second Edition, by Gerald van Belle, Lloyd D. Fisher, Patrick J. Heagerty, and Thomas S. Lumley
ISBN 0-471-03185-2

Subject Index

Biostatistics: A Methodology for the Health Sciences, Second Edition, by Gerald van Belle, Lloyd D. Fisher, Patrick J. Heagerty, and Thomas S. Lumley
ISBN 0-471-03185-2

Symbol Index

Biostatistics: A Methodology for the Health Sciences, Second Edition, by Gerald van Belle, Lloyd D. Fisher, Patrick J. Heagerty, and Thomas S. Lumley
ISBN 0-471-03185-2

WILEY SERIES IN PROBABILITY AND STATISTICS

Established by WALTER A. SHEWHART and SAMUEL S. WILKS

Editors: *David J. Balding, Noel A. C. Cressie, Nicholas I. Fisher, Iain M. Johnstone, J. B. Kadane, Geert Molenberghs, Louise M. Ryan, David W. Scott, Adrian F. M. Smith, Jozef L. Teugels*
Editors Emeriti: *Vic Barnett, J. Stuart Hunter, David G. Kendall*

A complete list of the titles in this series appears at the end of this volume.

Biostatistics: A Methodology for the Health Sciences, Second Edition, by Gerald van Belle, Lloyd D. Fisher, Patrick J. Heagerty, and Thomas S. Lumley
ISBN 0-471-03185-2

WILEY SERIES IN PROBABILITY AND STATISTICS

ESTABLISHED BY WALTER A. SHEWHART AND SAMUEL S. WILKS

The ***Wiley Series in Probability and Statistics*** is well established and authoritative. It covers many topics of current research interest in both pure and applied statistics and probability theory. Written by leading statisticians and institutions, the titles span both state-of-the-art developments in the field and classical methods.

Reflecting the wide range of current research in statistics, the series encompasses applied, methodological and theoretical statistics, ranging from applications and new techniques made possible by advances in computerized practice to rigorous treatment of theoretical approaches.

This series provides essential and invaluable reading for all statisticians, whether in academia, industry, government, or research.

*Now available in a lower priced paperback edition in the Wiley Classics Library.

BELSLEY, KUH, and WELSCH · Regression Diagnostics: Identifying Influential Data and Sources of Collinearity
BENDAT and PIERSOL · Random Data: Analysis and Measurement Procedures, *Third Edition*
BERRY, CHALONER, and GEWEKE · Bayesian Analysis in Statistics and Econometrics: Essays in Honor of Arnold Zellner
BERNARDO and SMITH · Bayesian Theory
BHAT and MILLER · Elements of Applied Stochastic Processes, *Third Edition*
BHATTACHARYA and WAYMIRE · Stochastic Processes with Applications
BILLINGSLEY · Convergence of Probability Measures, *Second Edition*
BILLINGSLEY · Probability and Measure, *Third Edition*
BIRKES and DODGE · Alternative Methods of Regression
BLISCHKE AND MURTHY (editors) · Case Studies in Reliability and Maintenance
BLISCHKE AND MURTHY · Reliability: Modeling, Prediction, and Optimization
BLOOMFIELD · Fourier Analysis of Time Series: An Introduction, *Second Edition*
BOLLEN · Structural Equations with Latent Variables
BOROVKOV · Ergodicity and Stability of Stochastic Processes
BOULEAU · Numerical Methods for Stochastic Processes
BOX · Bayesian Inference in Statistical Analysis
BOX · R. A. Fisher, the Life of a Scientist
BOX and DRAPER · Empirical Model-Building and Response Surfaces
*BOX and DRAPER · Evolutionary Operation: A Statistical Method for Process Improvement
BOX, HUNTER, and HUNTER · Statistics for Experimenters: An Introduction to Design, Data Analysis, and Model Building
BOX and LUCEÑO · Statistical Control by Monitoring and Feedback Adjustment
BRANDIMARTE · Numerical Methods in Finance: A MATLAB-Based Introduction
BROWN and HOLLANDER · Statistics: A Biomedical Introduction
BRUNNER, DOMHOF, and LANGER · Nonparametric Analysis of Longitudinal Data in Factorial Experiments
BUCKLEW · Large Deviation Techniques in Decision, Simulation, and Estimation
CAIROLI and DALANG · Sequential Stochastic Optimization
CHAN · Time Series: Applications to Finance
CHATTERJEE and HADI · Sensitivity Analysis in Linear Regression
CHATTERJEE and PRICE · Regression Analysis by Example, *Third Edition*
CHERNICK · Bootstrap Methods: A Practitioner's Guide
CHERNICK and FRIIS · Introductory Biostatistics for the Health Sciences
CHILÈS and DELFINER · Geostatistics: Modeling Spatial Uncertainty
CHOW and LIU · Design and Analysis of Clinical Trials: Concepts and Methodologies, *Second Edition*
CLARKE and DISNEY · Probability and Random Processes: A First Course with Applications, *Second Edition*
*COCHRAN and COX · Experimental Designs, *Second Edition*
CONGDON · Applied Bayesian Modelling
CONGDON · Bayesian Statistical Modelling
CONOVER · Practical Nonparametric Statistics, *Third Edition*
COOK · Regression Graphics
COOK and WEISBERG · Applied Regression Including Computing and Graphics
COOK and WEISBERG · An Introduction to Regression Graphics
CORNELL · Experiments with Mixtures, Designs, Models, and the Analysis of Mixture Data, *Third Edition*
COVER and THOMAS · Elements of Information Theory
COX · A Handbook of Introductory Statistical Methods

*Now available in a lower priced paperback edition in the Wiley Classics Library.

*COX · Planning of Experiments
CRESSIE · Statistics for Spatial Data, *Revised Edition*
CSÖRGŐ and HORVÁTH · Limit Theorems in Change Point Analysis
DANIEL · Applications of Statistics to Industrial Experimentation
DANIEL · Biostatistics: A Foundation for Analysis in the Health Sciences, *Eighth Edition*
*DANIEL · Fitting Equations to Data: Computer Analysis of Multifactor Data, *Second Edition*
DASU and JOHNSON · Exploratory Data Mining and Data Cleaning
DAVID and NAGARAJA · Order Statistics, *Third Edition*
*DEGROOT, FIENBERG, and KADANE · Statistics and the Law
DEL CASTILLO · Statistical Process Adjustment for Quality Control
DEMARIS · Regression with Social Data: Modeling Continuous and Limited Response Variables
DEMIDENKO · Mixed Models: Theory and Applications
DENISON, HOLMES, MALLICK and SMITH · Bayesian Methods for Nonlinear Classification and Regression
DETTE and STUDDEN · The Theory of Canonical Moments with Applications in Statistics, Probability, and Analysis
DEY and MUKERJEE · Fractional Factorial Plans
DILLON and GOLDSTEIN · Multivariate Analysis: Methods and Applications
DODGE · Alternative Methods of Regression
*DODGE and ROMIG · Sampling Inspection Tables, *Second Edition*
*DOOB · Stochastic Processes
DOWDY, WEARDEN, and CHILKO · Statistics for Research, *Third Edition*
DRAPER and SMITH · Applied Regression Analysis, *Third Edition*
DRYDEN and MARDIA · Statistical Shape Analysis
DUDEWICZ and MISHRA · Modern Mathematical Statistics
DUNN and CLARK · Basic Statistics: A Primer for the Biomedical Sciences, *Third Edition*
DUPUIS and ELLIS · A Weak Convergence Approach to the Theory of Large Deviations
*ELANDT-JOHNSON and JOHNSON · Survival Models and Data Analysis
ENDERS · Applied Econometric Time Series
ETHIER and KURTZ · Markov Processes: Characterization and Convergence
EVANS, HASTINGS, and PEACOCK · Statistical Distributions, *Third Edition*
FELLER · An Introduction to Probability Theory and Its Applications, Volume I, *Third Edition,* Revised; Volume II, *Second Edition*
FISHER and VAN BELLE · Biostatistics: A Methodology for the Health Sciences
FITZMAURICE, LAIRD, and WARE · Applied Longitudinal Analysis
*FLEISS · The Design and Analysis of Clinical Experiments
FLEISS · Statistical Methods for Rates and Proportions, *Third Edition*
FLEMING and HARRINGTON · Counting Processes and Survival Analysis
FULLER · Introduction to Statistical Time Series, *Second Edition*
FULLER · Measurement Error Models
GALLANT · Nonlinear Statistical Models
GHOSH, MUKHOPADHYAY, and SEN · Sequential Estimation
GIESBRECHT and GUMPERTZ · Planning, Construction, and Statistical Analysis of Comparative Experiments
GIFI · Nonlinear Multivariate Analysis
GLASSERMAN and YAO · Monotone Structure in Discrete-Event Systems
GNANADESIKAN · Methods for Statistical Data Analysis of Multivariate Observations, *Second Edition*
GOLDSTEIN and LEWIS · Assessment: Problems, Development, and Statistical Issues
GREENWOOD and NIKULIN · A Guide to Chi-Squared Testing

*Now available in a lower priced paperback edition in the Wiley Classics Library.

GROSS and HARRIS · Fundamentals of Queueing Theory, *Third Edition*
*HAHN and SHAPIRO · Statistical Models in Engineering
HAHN and MEEKER · Statistical Intervals: A Guide for Practitioners
HALD · A History of Probability and Statistics and their Applications Before 1750
HALD · A History of Mathematical Statistics from 1750 to 1930
HAMPEL · Robust Statistics: The Approach Based on Influence Functions
HANNAN and DEISTLER · The Statistical Theory of Linear Systems
HEIBERGER · Computation for the Analysis of Designed Experiments
HEDAYAT and SINHA · Design and Inference in Finite Population Sampling
HELLER · MACSYMA for Statisticians
HINKELMAN and KEMPTHORNE: · Design and Analysis of Experiments, Volume 1: Introduction to Experimental Design
HOAGLIN, MOSTELLER, and TUKEY · Exploratory Approach to Analysis of Variance
HOAGLIN, MOSTELLER, and TUKEY · Exploring Data Tables, Trends and Shapes
*HOAGLIN, MOSTELLER, and TUKEY · Understanding Robust and Exploratory Data Analysis
HOCHBERG and TAMHANE · Multiple Comparison Procedures
HOCKING · Methods and Applications of Linear Models: Regression and the Analysis of Variance, *Second Edition*
HOEL · Introduction to Mathematical Statistics, *Fifth Edition*
HOGG and KLUGMAN · Loss Distributions
HOLLANDER and WOLFE · Nonparametric Statistical Methods, *Second Edition*
HOSMER and LEMESHOW · Applied Logistic Regression, *Second Edition*
HOSMER and LEMESHOW · Applied Survival Analysis: Regression Modeling of Time to Event Data
HUBER · Robust Statistics
HUBERTY · Applied Discriminant Analysis
HUNT and KENNEDY · Financial Derivatives in Theory and Practice
HUSKOVA, BERAN, and DUPAC · Collected Works of Jaroslav Hajek—with Commentary
HUZURBAZAR · Flowgraph Models for Multistate Time-to-Event Data
IMAN and CONOVER · A Modern Approach to Statistics
JACKSON · A User's Guide to Principle Components
JOHN · Statistical Methods in Engineering and Quality Assurance
JOHNSON · Multivariate Statistical Simulation
JOHNSON and BALAKRISHNAN · Advances in the Theory and Practice of Statistics: A Volume in Honor of Samuel Kotz
JOHNSON and BHATTACHARYYA · Statistics: Principles and Methods, *Fifth Edition*
JOHNSON and KOTZ · Distributions in Statistics
JOHNSON and KOTZ (editors) · Leading Personalities in Statistical Sciences: From the Seventeenth Century to the Present
JOHNSON, KOTZ, and BALAKRISHNAN · Continuous Univariate Distributions, Volume 1, *Second Edition*
JOHNSON, KOTZ, and BALAKRISHNAN · Continuous Univariate Distributions, Volume 2, *Second Edition*
JOHNSON, KOTZ, and BALAKRISHNAN · Discrete Multivariate Distributions
JOHNSON, KOTZ, and KEMP · Univariate Discrete Distributions, *Second Edition*
JUDGE, GRIFFITHS, HILL, LÜTKEPOHL, and LEE · The Theory and Practice of Econometrics, *Second Edition*
JUREČKOVÁ and SEN · Robust Statistical Procedures: Aymptotics and Interrelations
JUREK and MASON · Operator-Limit Distributions in Probability Theory
KADANE · Bayesian Methods and Ethics in a Clinical Trial Design

*Now available in a lower priced paperback edition in the Wiley Classics Library.

KADANE AND SCHUM · A Probabilistic Analysis of the Sacco and Vanzetti Evidence
KALBFLEISCH and PRENTICE · The Statistical Analysis of Failure Time Data, *Second Edition*
KASS and VOS · Geometrical Foundations of Asymptotic Inference
KAUFMAN and ROUSSEEUW · Finding Groups in Data: An Introduction to Cluster Analysis
KEDEM and FOKIANOS · Regression Models for Time Series Analysis
KENDALL, BARDEN, CARNE, and LE · Shape and Shape Theory
KHURI · Advanced Calculus with Applications in Statistics, *Second Edition*
KHURI, MATHEW, and SINHA · Statistical Tests for Mixed Linear Models
KLEIBER and KOTZ · Statistical Size Distributions in Economics and Actuarial Sciences
KLUGMAN, PANJER, and WILLMOT · Loss Models: From Data to Decisions
KLUGMAN, PANJER, and WILLMOT · Solutions Manual to Accompany Loss Models: From Data to Decisions
KOTZ, BALAKRISHNAN, and JOHNSON · Continuous Multivariate Distributions, Volume 1, *Second Edition*
KOTZ and JOHNSON (editors) · Encyclopedia of Statistical Sciences: Volumes 1 to 9 with Index
KOTZ and JOHNSON (editors) · Encyclopedia of Statistical Sciences: Supplement Volume
KOTZ, READ, and BANKS (editors) · Encyclopedia of Statistical Sciences: Update Volume 1
KOTZ, READ, and BANKS (editors) · Encyclopedia of Statistical Sciences: Update Volume 2
KOVALENKO, KUZNETZOV, and PEGG · Mathematical Theory of Reliability of Time-Dependent Systems with Practical Applications
LACHIN · Biostatistical Methods: The Assessment of Relative Risks
LAD · Operational Subjective Statistical Methods: A Mathematical, Philosophical, and Historical Introduction
LAMPERTI · Probability: A Survey of the Mathematical Theory, *Second Edition*
LANGE, RYAN, BILLARD, BRILLINGER, CONQUEST, and GREENHOUSE · Case Studies in Biometry
LARSON · Introduction to Probability Theory and Statistical Inference, *Third Edition*
LAWLESS · Statistical Models and Methods for Lifetime Data, *Second Edition*
LAWSON · Statistical Methods in Spatial Epidemiology
LE · Applied Categorical Data Analysis
LE · Applied Survival Analysis
LEE and WANG · Statistical Methods for Survival Data Analysis, *Third Edition*
LEPAGE and BILLARD · Exploring the Limits of Bootstrap
LEYLAND and GOLDSTEIN (editors) · Multilevel Modelling of Health Statistics
LIAO · Statistical Group Comparison
LINDVALL · Lectures on the Coupling Method
LINHART and ZUCCHINI · Model Selection
LITTLE and RUBIN · Statistical Analysis with Missing Data, *Second Edition*
LLOYD · The Statistical Analysis of Categorical Data
MAGNUS and NEUDECKER · Matrix Differential Calculus with Applications in Statistics and Econometrics, *Revised Edition*
MALLER and ZHOU · Survival Analysis with Long Term Survivors
MALLOWS · Design, Data, and Analysis by Some Friends of Cuthbert Daniel
MANN, SCHAFER, and SINGPURWALLA · Methods for Statistical Analysis of Reliability and Life Data
MANTON, WOODBURY, and TOLLEY · Statistical Applications Using Fuzzy Sets
MARCHETTE · Random Graphs for Statistical Pattern Recognition
MARDIA and JUPP · Directional Statistics

*Now available in a lower priced paperback edition in the Wiley Classics Library.

MASON, GUNST, and HESS · Statistical Design and Analysis of Experiments with Applications to Engineering and Science, *Second Edition*
McCULLOCH and SEARLE · Generalized, Linear, and Mixed Models
McFADDEN · Management of Data in Clinical Trials
McLACHLAN · Discriminant Analysis and Statistical Pattern Recognition
McLACHLAN and KRISHNAN · The EM Algorithm and Extensions
McLACHLAN and PEEL · Finite Mixture Models
McNEIL · Epidemiological Research Methods
MEEKER and ESCOBAR · Statistical Methods for Reliability Data
MEERSCHAERT and SCHEFFLER · Limit Distributions for Sums of Independent Random Vectors: Heavy Tails in Theory and Practice
MICKEY, DUNN, and CLARK · Applied Statistics: Analysis of Variance and Regression, *Third Edition*
*MILLER · Survival Analysis, *Second Edition*
MONTGOMERY, PECK, and VINING · Introduction to Linear Regression Analysis, *Third Edition*
MORGENTHALER and TUKEY · Configural Polysampling: A Route to Practical Robustness
MUIRHEAD · Aspects of Multivariate Statistical Theory
MULLER and STOYAN · Comparison Methods for Stochastic Models and Risks
MURRAY · X-STAT 2.0 Statistical Experimentation, Design Data Analysis, and Nonlinear Optimization
MURTHY, XIE, and JIANG · Weibull Models
MYERS and MONTGOMERY · Response Surface Methodology: Process and Product Optimization Using Designed Experiments, *Second Edition*
MYERS, MONTGOMERY, and VINING · Generalized Linear Models. With Applications in Engineering and the Sciences
NELSON · Accelerated Testing, Statistical Models, Test Plans, and Data Analyses
NELSON · Applied Life Data Analysis
NEWMAN · Biostatistical Methods in Epidemiology
OCHI · Applied Probability and Stochastic Processes in Engineering and Physical Sciences
OKABE, BOOTS, SUGIHARA, and CHIU · Spatial Tesselations: Concepts and Applications of Voronoi Diagrams, *Second Edition*
OLIVER and SMITH · Influence Diagrams, Belief Nets and Decision Analysis
PALTA · Quantitative Methods in Population Health: Extensions of Ordinary Regressions
PANKRATZ · Forecasting with Dynamic Regression Models
PANKRATZ · Forecasting with Univariate Box-Jenkins Models: Concepts and Cases
*PARZEN · Modern Probability Theory and Its Applications
PEÑA, TIAO, and TSAY · A Course in Time Series Analysis
PIANTADOSI · Clinical Trials: A Methodologic Perspective
PORT · Theoretical Probability for Applications
POURAHMADI · Foundations of Time Series Analysis and Prediction Theory
PRESS · Bayesian Statistics: Principles, Models, and Applications
PRESS · Subjective and Objective Bayesian Statistics, *Second Edition*
PRESS and TANUR · The Subjectivity of Scientists and the Bayesian Approach
PUKELSHEIM · Optimal Experimental Design
PURI, VILAPLANA, and WERTZ · New Perspectives in Theoretical and Applied Statistics
PUTERMAN · Markov Decision Processes: Discrete Stochastic Dynamic Programming
*RAO · Linear Statistical Inference and Its Applications, *Second Edition*
RAUSAND and HØYLAND · System Reliability Theory: Models, Statistical Methods, and Applications, *Second Edition*
RENCHER · Linear Models in Statistics

*Now available in a lower priced paperback edition in the Wiley Classics Library.

RENCHER · Methods of Multivariate Analysis, *Second Edition*
RENCHER · Multivariate Statistical Inference with Applications
RIPLEY · Spatial Statistics
RIPLEY · Stochastic Simulation
ROBINSON · Practical Strategies for Experimenting
ROHATGI and SALEH · An Introduction to Probability and Statistics, *Second Edition*
ROLSKI, SCHMIDLI, SCHMIDT, and TEUGELS · Stochastic Processes for Insurance and Finance
ROSENBERGER and LACHIN · Randomization in Clinical Trials: Theory and Practice
ROSS · Introduction to Probability and Statistics for Engineers and Scientists
ROUSSEEUW and LEROY · Robust Regression and Outlier Detection
RUBIN · Multiple Imputation for Nonresponse in Surveys
RUBINSTEIN · Simulation and the Monte Carlo Method
RUBINSTEIN and MELAMED · Modern Simulation and Modeling
RYAN · Modern Regression Methods
RYAN · Statistical Methods for Quality Improvement, *Second Edition*
SALTELLI, CHAN, and SCOTT (editors) · Sensitivity Analysis
*SCHEFFE · The Analysis of Variance
SCHIMEK · Smoothing and Regression: Approaches, Computation, and Application
SCHOTT · Matrix Analysis for Statistics
SCHOUTENS · Levy Processes in Finance: Pricing Financial Derivatives
SCHUSS · Theory and Applications of Stochastic Differential Equations
SCOTT · Multivariate Density Estimation: Theory, Practice, and Visualization
*SEARLE · Linear Models
SEARLE · Linear Models for Unbalanced Data
SEARLE · Matrix Algebra Useful for Statistics
SEARLE, CASELLA, and McCULLOCH · Variance Components
SEARLE and WILLETT · Matrix Algebra for Applied Economics
SEBER and LEE · Linear Regression Analysis, *Second Edition*
SEBER · Multivariate Observations
SEBER and WILD · Nonlinear Regression
SENNOTT · Stochastic Dynamic Programming and the Control of Queueing Systems
*SERFLING · Approximation Theorems of Mathematical Statistics
SHAFER and VOVK · Probability and Finance: It's Only a Game!
SMALL and McLEISH · Hilbert Space Methods in Probability and Statistical Inference
SRIVASTAVA · Methods of Multivariate Statistics
STAPLETON · Linear Statistical Models
STAUDTE and SHEATHER · Robust Estimation and Testing
STOYAN, KENDALL, and MECKE · Stochastic Geometry and Its Applications, *Second Edition*
STOYAN and STOYAN · Fractals, Random Shapes and Point Fields: Methods of Geometrical Statistics
STYAN · The Collected Papers of T. W. Anderson: 1943–1985
SUTTON, ABRAMS, JONES, SHELDON, and SONG · Methods for Meta-Analysis in Medical Research
TANAKA · Time Series Analysis: Nonstationary and Noninvertible Distribution Theory
THOMPSON · Empirical Model Building
THOMPSON · Sampling, *Second Edition*
THOMPSON · Simulation: A Modeler's Approach
THOMPSON and SEBER · Adaptive Sampling
THOMPSON, WILLIAMS, and FINDLAY · Models for Investors in Real World Markets
TIAO, BISGAARD, HILL, PEÑA, and STIGLER (editors) · Box on Quality and Discovery: with Design, Control, and Robustness
TIERNEY · LISP-STAT: An Object-Oriented Environment for Statistical Computing and Dynamic Graphics

*Now available in a lower priced paperback edition in the Wiley Classics Library.

TSAY · Analysis of Financial Time Series
UPTON and FINGLETON · Spatial Data Analysis by Example, Volume II: Categorical and Directional Data
VAN BELLE · Statistical Rules of Thumb
VAN BELLE, FISHER, HEAGERTY, and LUMLEY · Biostatistics: A Methodology for the Health Sciences, *Second Edition*
VESTRUP · The Theory of Measures and Integration
VIDAKOVIC · Statistical Modeling by Wavelets
WALLER and GOTWAY · Applied Spatial Statistics for Public Health Data
WEISBERG · Applied Linear Regression, *Second Edition*
WELSH · Aspects of Statistical Inference
WESTFALL and YOUNG · Resampling-Based Multiple Testing: Examples and Methods for *p*-Value Adjustment
WHITTAKER · Graphical Models in Applied Multivariate Statistics
WINKER · Optimization Heuristics in Economics: Applications of Threshold Accepting
WONNACOTT and WONNACOTT · Econometrics, *Second Edition*
WOODING · Planning Pharmaceutical Clinical Trials: Basic Statistical Principles
WOOLSON and CLARKE · Statistical Methods for the Analysis of Biomedical Data, *Second Edition*
WU and HAMADA · Experiments: Planning, Analysis, and Parameter Design Optimization
YANG · The Construction Theory of Denumerable Markov Processes
*ZELLNER · An Introduction to Bayesian Inference in Econometrics
ZHOU, OBUCHOWSKI, and MCCLISH · Statistical Methods in Diagnostic Medicine