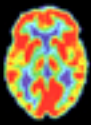
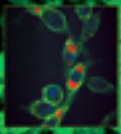
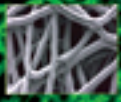
CAMBRIDGE TEXTS IN
BIOMEDICAL
ENGINEERING



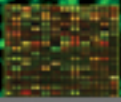
BIOMEDICAL ENGINEERING



Bridging Medicine and Technology



W. MARK SALTZMAN



CAMBRIDGE www.cambridge.org/9780521840996

This page intentionally left blank

BIOMEDICAL ENGINEERING

Bridging Medicine and Technology

This is an ideal text for an introduction to biomedical engineering. The book presents the basic science knowledge used by biomedical engineers at a level accessible to all students and illustrates the first steps in applying this knowledge to solve problems in human medicine.

Biomedical engineering now encompasses a range of fields of specialization including bioinstrumentation, bioimaging, biomechanics, biomaterials, and biomolecular engineering. This introduction to bioengineering assembles foundational resources from molecular and cellular biology and physiology and relates them to various subspecialties of biomedical engineering.

The first two parts of the book present basic information in molecular/cellular biology and human physiology; quantitative concepts are stressed in these sections. Comprehension of these basic life science principles provides the context in which biomedical engineers interact. The third part of the book introduces the subspecialties in biomedical engineering and emphasizes – through examples and profiles of people in the field – the types of problems biomedical engineers solve.

W. Mark Saltzman is the Goizueta Foundation Professor of Chemical and Biomedical Engineering at Yale University. His research interests include materials for controlled drug delivery, drug delivery to the brain, and tissue engineering. He has taught at Johns Hopkins University and Cornell University and, after joining the Yale faculty in 2002, was named the first Chair of the Department of Biomedical Engineering.

Professor Saltzman has published more than 150 research papers, 3 authored books, and 2 edited books, and he is an inventor on more than 10 patents. His many honors and awards include a Camille and Henry Dreyfus Foundation Teacher-Scholar Award (1990), the Allan C. Davis Medal as Maryland's Outstanding Young Engineer (1995), the Controlled Release Society Young Investigator Award (1996), Fellow of the American Institute of Biological and Medical Engineers (1997), the Professional Progress in Engineering Award from Iowa State University (2000), Britton Chance Distinguished Lecturer in Engineering and Medicine at the University of Pennsylvania (2000), and Distinguished Lecturer of the Biomedical Engineering Society (2004).

CAMBRIDGE TEXTS IN BIOMEDICAL ENGINEERING

The *Cambridge Texts in Biomedical Engineering* series provides a forum for high-quality, accessible textbooks targeted at undergraduate and graduate courses in biomedical engineering. It covers a broad range of biomedical engineering topics from introductory texts to advanced topics, including, but not limited to, biomechanics, physiology, biomedical instrumentation, imaging, signals and systems, cell engineering, and bioinformatics. The series blends theory and practice and is aimed primarily at biomedical engineering students, but it is suitable for broader courses in engineering, life science, and medicine.

BIOMEDICAL ENGINEERING

Bridging Medicine and Technology

W. Mark Saltzman
Yale University

CAMBRIDGE
UNIVERSITY PRESS

CAMBRIDGE UNIVERSITY PRESS
Cambridge, New York, Melbourne, Madrid, Cape Town, Singapore,
São Paulo, Delhi, Dubai, Tokyo

Cambridge University Press
The Edinburgh Building, Cambridge CB2 8RU, UK

Published in the United States of America by Cambridge University Press, New York

www.cambridge.org
Information on this title: www.cambridge.org/9780521840996

First published in print format 2009

ISBN-13 978-0-511-57764-2 eBook (Adobe Reader)

ISBN-13 978-0-521-84099-6 Hardback

To Zach and Alex
There is no luckier, happier father on earth than I.

Contents

PART 3. BIOMEDICAL ENGINEERING

Color plates follow page 298

Preface

The field of biomedical engineering has expanded markedly in the past ten years. This growth is supported by advances in biological science, which have created new opportunities for development of tools for diagnosis of and therapy for human disease. This book is designed as a textbook for an introductory course in biomedical engineering. The text was written to be accessible for most entering college students. In short, the book presents some of the basic science knowledge used by biomedical engineers and illustrates the first steps in applying this knowledge to solve problems in human medicine.

Biomedical engineering now encompasses a range of fields of specialization including bioinstrumentation, bioimaging, biomechanics, biomaterials, and biomolecular engineering. Most undergraduate students majoring in biomedical engineering are faced with a decision, early in their program of study, regarding the field in which they would like to specialize. Each chosen specialty has a specific set of course requirements and is supplemented by wise selection of elective and supporting coursework. Also, many young students of biomedical engineering use independent research projects as a source of inspiration and preparation but have difficulty identifying research areas that are right for them. Therefore, a second goal of this book is to link knowledge of basic science and engineering to fields of specialization and current research.

As a general introduction to the field, this textbook assembles foundational resources from molecular and cellular biology and physiology and relates this science to various subspecialties of biomedical engineering. The first two parts of the book present basic information in molecular/cellular biology and human physiology; quantitative concepts are stressed in these sections. Comprehension of these basic life science principles provides the context in which biomedical engineers interact. The third part of the book introduces the subspecialties in biomedical engineering and emphasizes—through examples and profiles of people in the field—the types of problems biomedical engineers solve. Organization of the chapters into these three major parts allows course instructors and students to customize their usage of some or all of the chapters depending on the background of the students and the availability of other course offerings in the curriculum.

WHICH STUDENTS PROFIT FROM THIS BOOK?

A significant number of students come to college with a clear idea of pursuing a career in biomedical engineering. Of course, these students benefit tremendously from a rigorous overview of the field, ideally provided in their first year. Most of these students leave the course even more certain about their choice of career. Many of them jump right into independent study or research projects: This overview of the diverse applications of biomedical engineering provides them with the information that they need to select research projects—or future courses—that will move them in the right direction.

I have also found this material to be interesting to engineering students who are trying to decide which of the engineering degree programs is right for them. The material in this textbook might also be used to introduce undeclared or undecided engineering majors to the field of biomedical engineering. Students enter college with varying degrees of competence in science and math. Some do not know what biomedical engineering encompasses and whether they have the adequate secondary education training to succeed. Exposure to the topics presented here may inspire some of these students to further their studies in biomedical engineering.

Also, I encourage instructors to make their course accessible to students who are not likely to become engineering majors; biomedical technology is increasingly important to the life of all educated citizens. I have taught courses in this subject to freshmen at three different universities over the past 20 years; students with a variety of intended majors always enroll in the course (mathematics, history, economics, English, fine arts, and anthropology majors have participated in the past few years). In fact, it is these students who appear to be most changed by the experience.

TO THE INSTRUCTOR

Teachers of courses directed to early undergraduates in biomedical engineering struggle against competing forces: The diverse backgrounds of the students pull you to start from first principles, and the rapid progress of the field pushes you to cover more and more topics. To address this, I have presented more material than I am capable of covering in a one-semester course for freshmen students. In a typical 13-week semester, I find that only 12–13 of the 16 chapters can be covered comfortably. Assuming that this will be true for your situation as well, I recommend that you assess the level of experience of your students and decide which chapters are most valuable in creating a coherent and satisfying course. Many students arrive at college with a sophisticated understanding of cellular and molecular biology; therefore, I do not cover Part 1 (Chapters 2–5) in detail. Condensing this early material allows me to include almost all of the other chapters. Part 1 is still available to the student, of course, and most of them profit from reading these chapters, as they need as the course progresses, even if the details are not covered in lecture. In courses that emphasize biomedical

engineering, and not the biological sciences, the instructor might want to cover only Part 3 of the book and use the previous parts as reference material.

Some examples of approaches for arranging the chapters into semester-long courses that emphasize different aspects of biomedical engineering are presented in the following table.

Modular approaches to teaching an introductory course in biomedical engineering using this text

Week of the course	Comprehensive approach	Applications emphasis	Physiology emphasis	Cellular engineering emphasis
1	Chap. 1 and 2	Chap. 1	Chap. 1	Chap. 1
2	Chap. 3 and 4	Chap. 2–5 (selected)	Chap. 2–4 (selected)	Chap. 2 and 3
3	Chap. 5	Chap. 10	Chap. 5	Chap. 4
4	Chap. 7	Chap. 10 and 11	Chap. 6	Chap. 5
5	Chap. 8	Chap. 11	Chap. 7	Chap. 6–9 (selected)
6	Chap. 9	Chap. 12	Chap. 8	Chap. 10
7	Midterm review	Midterm review	Midterm review	Midterm review
8	Chap. 10	Chap. 2–5 (selected)	Chap. 9	Chap. 11
9	Chap. 11	Chap. 13	Chap. 10	Chap. 12
10	Chap. 12	Chap. 14	Chap. 11 and 12	Chap. 13
11	Chap. 13 and 14	Chap. 15	Chap. 13	Chap. 14
12	Chap. 15	Chap. 16	Chap. 14	Chap. 15
13	Chap. 16	Chap. 16	Chap. 15	Chap. 16

Acknowledgments

I have many people to thank, for encouragement and direct participation. It is a long list, and undoubtedly incomplete. For the past seven years, I have been immersed in a milieu rich in inspiration, creation, and succor. So I profited from brushes and asides, from long conversations and wisdom overheard.

I thank the Whitaker Foundation for their generous financial support, which made it possible for me to transform notes and notions into text. I am particularly grateful to Jack Linehan, who has been a steady source of inspiration and advice to me over the past decade.

I thank Peter Gordon of Cambridge University Press, who has been the most stalwart supporter of this project. Peter is everything one could hope for in an editor: He is wise, generous with praise, and direct (yet kind) with criticism. Thankfully, he is also patient. I thank Michelle Carey for her brilliant support. What a pleasure, to be an author for Cambridge University Press.

I thank Veronique Tran for her help in the inception of this project, her critical assistance in overall organization of the book, and her work on early versions of Chapters 2, 6, and 11. It was Veronique who urged this project forward at the start, and it would not have happened without her effort and enthusiasm. I thank Lawrence Staib, who co-authored Chapter 12 and shaped it into one of my favorite chapters in the book. I thank Rachael Sirianni, who continues to amaze me with the breadth of her talents: Rachael's photography enhances every chapter.

I burdened generous friends; each of them gave one of the chapters a careful reading and provided thoughtful edits and suggestions, which made each chapter better, more readable. I thank Ian Suydam (Chapter 2), Kim Woodrow (Chapter 3), Michael Caplan (Chapter 5), Michelle Kelly (Chapter 7), Peter Aronson (Chapter 9), Deepak Vashishith (Chapter 10), and Themis Kyriakides (Chapter 15).

I am grateful to my co-instructors in Physiological Systems (BENG 350) at Yale, who have been exceptional colleagues and patient, enthusiastic teachers of physiology. The influence of Michael Caplan, Walter Boron, Emile Boulpaep, and Peter Aronson can be felt in Chapters 5, 7, 8, and 9, respectively. I have profited from their examples as teachers.

A number of people contributed essential administrative and research support—tracking down papers and facts, producing figures, proofreading, and creating and solving homework problems. I thank Tiffanee Green, Michael Henry, Kofi Buaku Atsina, Florence Kwo, and Salvador Joel Nunez Gastelum. Two special people did this and much more: Audrey Lin and Jennifer Saucier-Sawyer proofread, edited, pursued figures (and permissions for figures), and managed to keep binders, drafts, and sticky notes organized. More than this, they smiled at every obstacle, accommodated every idea, and remained positive as I missed deadlines. Without Audrey's expert help in the final push—and her never-say-no generosity—this text would still be in binders.

I thank Caroline, for letting me be me, as she is she. It is a marvel, isn't it, this unexpected shower, rescuing a late summer afternoon? Thanks, Caroline, for sharing it with me.

Abbreviations and Acronyms

3D-	three-dimensional
3DCRT	three-dimensional conformal radiation therapy
Ab	antibody
ADA	adenosine deaminase deficiency
ADH	anti-diuretic hormone
ADP	adenosine diphosphate
AIDS	acquired immune deficiency syndrome
AML	acute myeloid leukemia
APC	antigen presenting cell
ATP	adenosine-5′-triphosphate
AV	atrioventricular
BBB	blood-brain barrier
BCG	Bacillus Calmette-Guérin
BME	biomedical engineering
BMR	basal metabolic rate
BSA	bovine serum albumin
CABG	coronary artery bypass graft
CLL	chronic lymphocytic leukemia
CT	computed tomography
DAG	diacylglycerol
DNA	deoxyribonucleic acid
EBRT	external beam radiation therapy
ECF	extracellular fluid
ECG	electrocardiography, electrocardiogram
ECM	extracellular matrix
EGF	epidermal growth factor
EGFR	epidermal growth factor receptor
EVAc	poly(ethylene-co-vinyl acetate)
FBR	foreign body response
FDA	U.S. Food and Drug Administration
fMRI	functional magnetic resonance imaging
GFR	glomerular filtration rate
GFP	green fluorescent protein

HIV	human immunodeficiency virus
HPV	human papillomavirus
HSC	hematopoietic stem cells
HUVEC	human umbilical vein endothelial cells
ICAM	intercellular adhesion molecule
Ig	immunoglobulin
IL-2	interleukin 2
IMRT	intensity-modulated radiation therapy
IR	infrared
IRS	insulin receptor substrate
ISF	interstitial fluid
LDL	low-density lipoprotein
mAbs	monoclonal antibodies
MHC	major histocompatibility complex
MRI	magnetic resonance imaging
MW	molecular weight
NHL	non-Hodgkin's lymphoma
NMR	nuclear magnetic resonance
PAH	para-aminohippuric acid
PAN	polyacrylonitrile
PCR	polymerase chain reaction
PDMS	polydimethylsiloxane
PE	polyethylene
PEG	poly(ethylene glycol)
PET	positron emission tomography *or* poly(ethylene terephthalate)
PEU	polyurethane
pHEMA	poly(2-hydroxymethacrylate)
PIP3	phosphatidylinositol 3,4,5-trisphosphate
PKB	protein kinase B
PLGA	poly(lactide-co-glycolide)
pMMA	poly(methyl methacrylate)
PP	polypropylene
PS	polystyrene
PSA	prostate specific antigen
PSu	polysulphone
PTFE	poly(tetrafluoroethylene)
PVC	poly(vinyl chloride)
PVP	poly(vinyl pyrrolidone)
RBC	red blood cell
RF	radio frequency
RGD	three peptide sequence of arginine (R), glycine (G), and aspartic acid (D)
RNA	ribonucleic acid
RPF	renal plasma flow
rRNA	ribosomal RNA

RSV	respiratory syncytial virus
RTK	receptor tyrosine kinase
SA	sinoatrial
SARS	Severe Acute Respiratory Syndrome
SGOT	serum glutamic oxaloacetic transaminase
siRNA	small interfering RNA
sMRI	structural magnetic resonance imaging
SPECT	single photon emission computed tomography
TIL	tumor-infiltrating lymphocytes
tRNA	transfer RNA
UV-VIS	ultraviolet-visible spectroscopy
VEGF	vascular endothelial cell growth factor
WBC	white blood cells
WHO	World Health Organization

1 Introduction: What Is Biomedical Engineering?

LEARNING OBJECTIVES

After reading this chapter, you should:

- Be familiar with how changes in medicine have enhanced life span and quality of life.
- Understand a few examples of the role of engineering in defining medical treatments.
- Have developed your own definition of biomedical engineering.
- Understand some of the subdisciplines that are included in biomedical engineering.
- Understand the relationship between the study of biomedical engineering and the study of human physiology.
- Be familiar with the structure of this book, and have developed a plan for using it that fits your needs.

1.1 Prelude

The practice of medicine has changed dramatically since you were born. Consider a few of these changes, some of which have undoubtedly affected your own life: Couples can test for pregnancy in their homes, a new vaccine is available for chicken pox, inexpensive contact lenses provide clear vision, artificial hips allow recipients to walk and run, ultrasound imaging follows the progress of pregnancy, and small reliable pumps administer insulin continuously for diabetics. For your parents, the changes have been even more sweeping. Overall life expectancy—that is, the span of years that people born in a given year are expected to live—increased from 50 in 1900 to almost 80 by 2000 (Figure 1.1). You can expect to live 30 years longer than your great-grandparents; you can also expect to be healthier and more active during all the years of your life.

How has this happened? One answer is obvious. People are living longer because they are not dying in situations that were previously fatal, such as childbirth and bacterial infections. The growth of biomedical engineering is a major factor in this extension of life and improvement of health. Biomedical engineers have contributed to every field of medicine—from radiology to obstetrics to cancer treatment—but in the next few paragraphs this growth is illustrated with examples from emergency medicine.

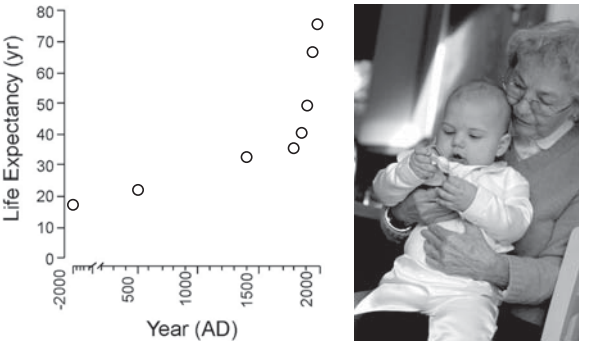


Figure 1.1 **Human life expectancy.** Human life expectancy has increased dramatically in the past 200 years.

Accidents and trauma are major causes of death and disability around the world. In the United States, it is overwhelmingly the leading cause of death among people of college age, and it is ranked fifth among causes of death for all ages (1). Automobile accidents account for many of these deaths: 42,116 people were killed in automobile accidents in the United States in 2001. Victims of trauma often have internal injuries, which are life threatening but not easy to diagnose by visual observation. Many accident victims are rushed to emergency rooms for treatment, and actions performed in the first few minutes after arrival can often mean the difference between life and death. Emergency room treatment has improved enormously over the past few decades, chiefly due to advances in the technology for looking inside of people quickly and accurately (Figure 1.2). Ultrasound imaging, which can provide pictures of internal bleeding within seconds, has replaced exploratory surgery and other slower, more invasive approaches for localization of internal injuries. Old ultrasound imaging machines weighed hundreds of pounds, but new instruments are smaller and lighter—some weighing only a few pounds, making it possible to get them to the patient faster. Other imaging technologies have also improved: Helical computed tomography (CT) scanners produce rapid three-dimensional internal images of the whole body, and new magnetic resonance imaging (MRI) techniques can reveal the chemistry, not just the shape, of internal structures. As a result of faster and better diagnosis of internal injuries, more accident victims are saved today.

In the near future, emergency medicine providers will probably use ultrasound imagers that are small enough to be carried in a pocket and inexpensive enough for every physician to own, like a stethoscope is today. Reduction in size and cost will surely save the lives of more accident victims. A pill-sized sensor is already available that patients can swallow; it continuously reports internal temperature as it passes through the intestinal tract. In the future, similar devices will probably be used to report other internal conditions such as sites of bleeding or abnormal cells. Further in the future, these small devices will be guided to specific locations in the body, where they can initiate repair of disease that is deep within the body.

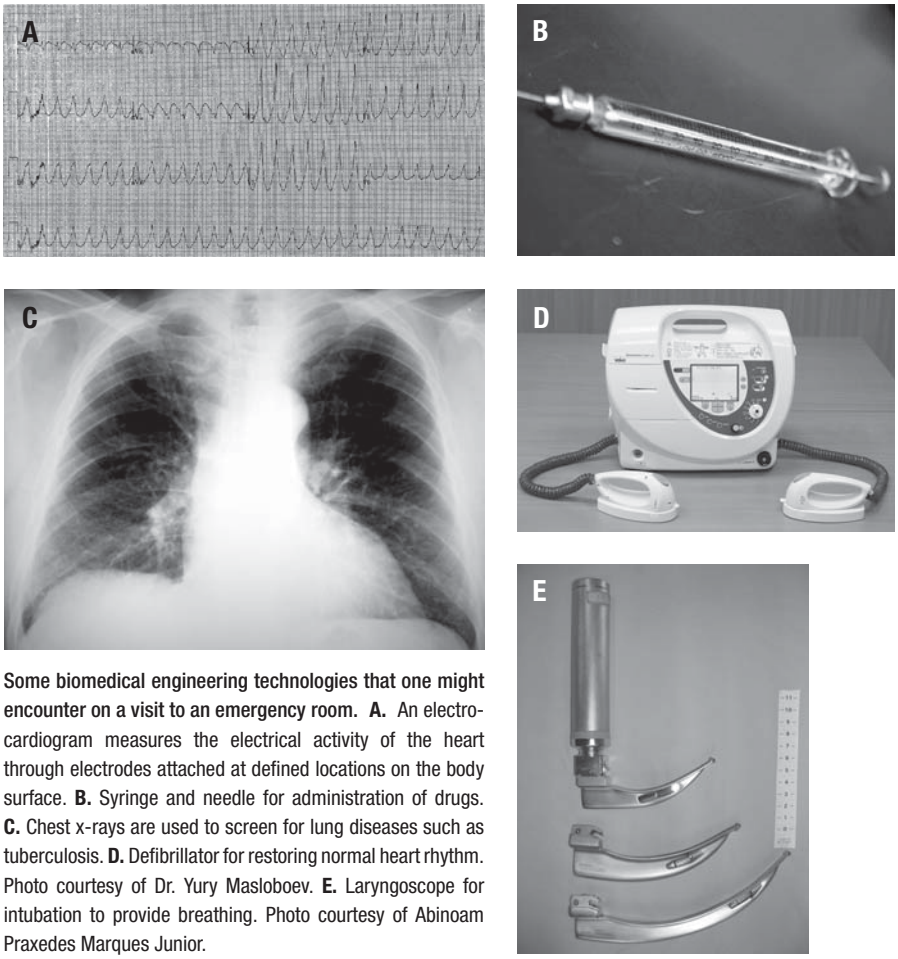


Figure 1.2

Some biomedical engineering technologies that one might encounter on a visit to an emergency room. A. An electrocardiogram measures the electrical activity of the heart through electrodes attached at defined locations on the body surface. **B.** Syringe and needle for administration of drugs. **C.** Chest x-rays are used to screen for lung diseases such as tuberculosis. **D.** Defibrillator for restoring normal heart rhythm. Photo courtesy of Dr. Yury Masloboev. **E.** Laryngoscope for intubation to provide breathing. Photo courtesy of Abinoam Praxedes Marques Junior.

The trends in emergency medicine are not unique. Innovations produced by biomedical engineers are saving lives once lost to kidney failure, improving eyesight lost to disease and aging, and producing artificial hips, knees, and hearts.

Do you want to be a part of this story or similar stories that are changing the conduct of medicine in operating rooms, doctors' offices, emergency vehicles, and homes? Then you want to be a biomedical engineer. This book will introduce you to the field of biomedical engineering and show how your knowledge of math, chemistry, physics, and biology can be used to understand how the human body works. It will show you how biomedical engineers work to develop new methods to diagnose problems with the human machine and new approaches to treat disease efficiently and inexpensively. This book will also show you how biomedical engineering and medicine will grow in the future, and point you in some directions that you can pursue to be part of this future. Biomedical engineering has been performed under different titles throughout history (Box 1.1); this book will help put this development into perspective, so that you can focus on how biomedical engineers will contribute to the future.

Box 1.1 Too many names?

As you read about the subject of biomedical engineering, you will encounter a variety of names that sound similar: bioengineering, biological engineering, biotechnology, biosystems engineering, bioprocess engineering, biomolecular engineering, and biochemical engineering. Some of the differences between these names are important, but unfortunately the terminology is not used consistently. Therefore, students of biomedical engineering need to approach the terminology with care (and without assuming that the person using the terminology has the same definition that they do!).

Biomedical engineering and bioengineering are often used interchangeably [e.g., see ref. (2)]. This is certainly true in the case of names of academic departments at universities. Some departments are called Department of Biomedical Engineering and others Department of Bioengineering, but in most cases the educational mission and research programs associated with these departments are similar. Still, it is wise for prospective students to look closely at the classes that are offered at each university and to decide if the emphasis of the department is the right one for them.

Some of the terms represent subsets of the larger discipline of biomedical engineering. Biomolecular engineering, for example, is now used to describe the contributions of chemical engineering to the larger field of biomedical engineering. In that sense, biochemical engineering and bioprocess engineering, which have historically been used to indicate the use of chemical engineering tools in the development of industrial processing methods for biological systems, are now embraced by the larger subdiscipline of biomolecular engineering. One could argue that all of these are subsets of the larger field of bioengineering or biomedical engineering.

Biotechnology is a trickier term to characterize because it has been used in a variety of different contexts over the past few decades. To many people, biotechnology is the end result of DNA manipulation: for example, transgenic animals, recombinant proteins, and gene therapy. Some common definitions are “the application of the principles of engineering and technology to the life sciences”; “the application of science and engineering to the direct or indirect use of living organisms, or parts or products of living organisms, in their natural or modified forms”; or “the use of biological processes to solve problems or make useful products.” Again, one could argue that these definitions are equivalent to biomedical engineering. Even the technologies most commonly associated with biotechnology (e.g., production of recombinant proteins as pharmaceuticals) are examples of biomedical engineering. They are treated as such in this textbook, and are discussed in Chapters 13 and 14.

1.2 Engineering in modern medicine

Our experience of the world is shaped by engineering and technology. Because of the work of engineers, we can move easily from place to place, communicate with people at distant sites (even on the moon!), live and work in buildings that are safe from natural elements, and obtain affordable and diverse foods. It is

widely, although not universally, accepted that the quality of life on our planet has improved as a result of the proliferation of technology that occurred during the 20th century. There is little doubt that the presence of technology creates constraints on the way that we live, and that the daily choices we make are shaped by the technologies that have infiltrated widely (think about the ways that television, computers, airplanes, cell phones, and ATMs have influenced your progress through this past day). Choices that we make in the future, and maybe even historical trajectories, will be influenced by future technologies such as (perhaps) nanomachines, efficient fuel cells, and small, inexpensive global positioning devices. It is the work of engineers to make technology possible, and then to make that technology reliable and inexpensive enough to influence people throughout the world.

Medical technology is one of the most visible aspects of the modern world; it is impossible to avoid and uniquely compelling. People from all walks of life are eager to hear about new machines, new medicines, and new devices that will uncover hidden disease, treat previously untreatable ailments, and mend weary or broken organs. Evidence for this high interest is everywhere; for example, new medical technology appears routinely on the covers of news magazines such as *Time* and *Newsweek* and in daily newspaper reports. We know that modern medicine is built on steady progress in science, but it is just as heavily dependent on innovations in engineering. It is engineers who transfer scientific knowledge into useful products, devices, and methods; therefore, progress in biomedical engineering is arguably more central to our experience of modern medicine than are advances in science. Some of the most fascinating stories of the 20th century involved the development of new medical technologies (Figure 1.3). Whole-organ transplantation, such as the first heart transplant in 1967, could not occur until there were machines to sustain life during the operation, tools for the surgeons to operate with and repair the wounds they created, and methods for preserving organs during transport. Thousands of transplants are performed annually in the United States today, but the need for organs far exceeds the supply. Biomedical engineers have been working for many decades to create an artificial heart, and there is no doubt that this work will continue until it is successful (see Chapter 15). Clinical testing of the Salk polio vaccine, in which millions of doses were administered to children, could not happen without the engineering methods to cheaply produce the vaccine in large quantity (see Chapter 14). The Human Genome Project would have not been possible without automated machines for deoxyribonucleic acid (DNA) sequencing.

Medical technology has also invaded our homes in surprising and influential ways. Every home has a thermometer, specially designed to permit the recording of body temperature. But we can now also test for pregnancy at home, so that one of the most life-changing medical discoveries can be done in privacy. Blood glucose tests,which are essential for proper treatment of diabetes, have advanced rapidly and now are commonly done at home. Your home can be easily equipped to be a screening center for high blood pressure, high cholesterol, glucose monitoring, and ovulation prediction.

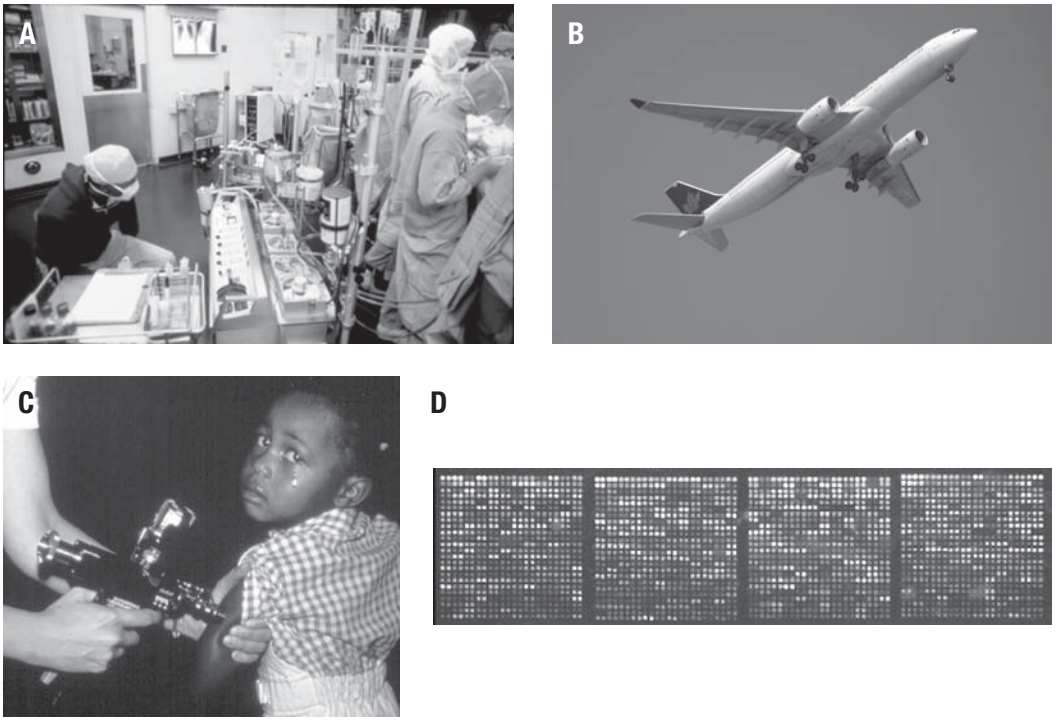


Figure 1.3 **Examples of new technology that permitted medical advances. A.** Heart–lung machine that permits heart transplantation and surgery. Photo courtesy of National Institutes of Health. **B.** Jet airplanes are used for rapid transport of a preserved organ to a distant operating room. **C.** An injector for vaccine delivery. Photo courtesy of The Centers For Disease Control and Prevention. **D.** DNA microarrays can be used to measure the expression of genes in cells and tissues. Photo courtesy of the W.M. Keck Foundation at Yale University. (See color plate.)

In addition, medical technologies have entered our bodies. Many people now elect to use contact lenses instead of eyeglasses; this change has resulted from the development of materials that can remain in contact with the eye for extended periods without causing damage. Artificial joints and limbs are common, as are artificial heart valves; synthetic components, usually metals and polymers, are fashioned into implantable devices that can replace the function of the human skeleton. We are not yet able to reanimate dead tissue (as Shelley predicted in *Frankenstein*), but we are close to the technology required for a 6 million dollar man.

This book supplies an introduction to biomedical engineering, the most rapidly growing of the engineering disciplines. Biomedical engineers invent, design, and build new technologies for diagnosis, treatment, and study of human disease. Usually, they work as a part of a team of engineers, scientists, and physicians, but the role of the engineer is essential. It is the engineer who is responsible for converting new knowledge into a useful form.

1.3 What is biomedical engineering?

New students to the field of biomedical engineering ask versions of this question: "What is biomedical engineering?" Often, they ask the question directly but, just

as often, they ask it in indirect and interesting ways. Some of the forms of this question that I have heard in the past few years are:

- Do biomedical engineers all work in hospitals?
- Do you have to have an MD degree to be a biomedical engineer?
- How can I learn enough biology to understand biomedical engineering and enough engineering to be a real engineer?
- Is biomedical engineering the same as genetic engineering?
- How much of biomedical engineering is biology, chemistry, physics, and mathematics?

Some versions of the question are easy to answer. For example, most biomedical engineers do not work in hospitals and do not hold MD degrees. Other questions can inspire answers that take up whole books (such as this book), and still be incomplete. All of the chapters in this book are designed to address these questions from different perspectives. In this introduction, the overall question is examined from several different angles.

1.3.1 We can learn something about biomedical engineering from standard definitions

Our working definition of biomedical engineering can start in an obvious place. According to the Merriam-Webster Dictionary:

> engineering *noun*: a) the application of science and mathematics by which the properties of matter and the sources of energy in nature are made useful to people; b) the design and manufacture of complex products.

Biomedical engineering is engineering that is applied to human health. Because human health is multifaceted—involving not only our physical bodies but also the things that we put in our bodies (such as foods, pharmaceuticals, and medical devices) and the things that we put on our bodies (such as protective clothing and contact lenses)—biomedical engineers are interested in a wide range of problems. The breadth of modern biomedical engineering is reflected in the table of contents for this book (shown in diagrammatic form in Figure 1.4).

The work of engineers is often hidden from view of the general public, occurring in laboratories, office buildings, construction sites, pilot plants, and testing facilities. This is true for biomedical engineering as well as civil engineering and other engineering disciplines. Although the work might be hidden, the end result is often visible and important (e.g., the Brooklyn Bridge or the artificial heart; see Figure 1.5). Because of this, society has huge expectations for engineers, and engineers have large goals for themselves.

The importance of engineers to human progress is worthy of celebration. Consider this quote about the role of engineers from the president of the American

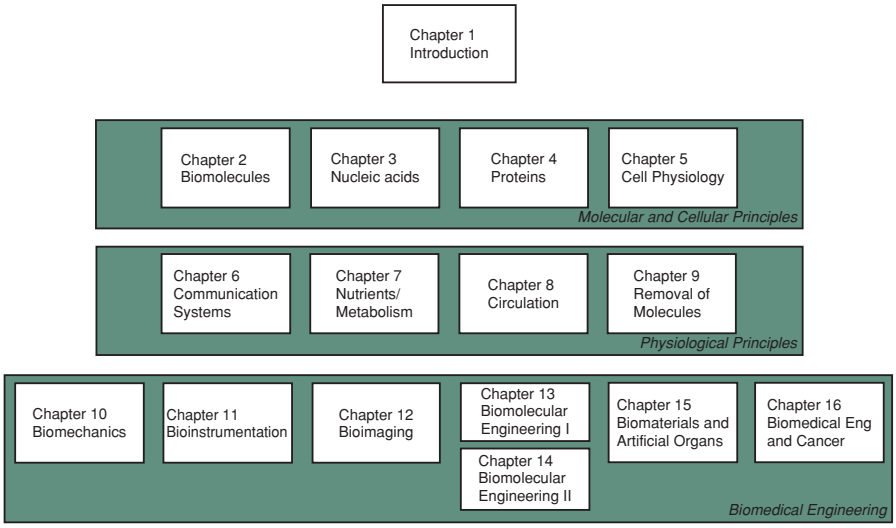


Figure 1.4 Organization of this book.

Society of Civil Engineers, Robert Moore. Mr. Moore, in a speech to the society in May 1902, said [from ref. (3)]:

> And in the future, even more than in the present, will the secrets of power be in his keeping, and more and more will he be a leader and benefactor of men. That his place in the esteem of his fellows and of the world will keep pace with his growing capacity and widening achievement is as certain as that effect follow cause.

Mr. Moore was speaking in the shadow of incredible engineering achievements: The work of engineers to build bridges over large spans of water changed the flow of society, for example. The substance of this quote—although not its selection of pronouns—is relevant today. Engineers of today have ambitious visions for their profession, and they are still called upon to be worthy inheritors of the engineering

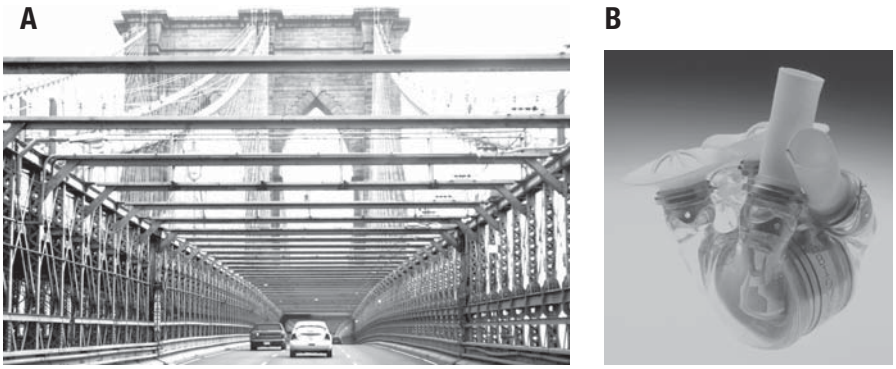


Figure 1.5 **Examples of engineering on the heroic scale.** **A.** Brooklyn Bridge (opened May 24,1883). **B.** AbioCor™ artificial heart (reprinted with permission from Jewish Hospital & St. Mary's HealthCare and the University of Louisville).

tradition to do good works. Imagine the confidence in your profession that is required to suggest that you can build a machine to replace the human heart, which is one of the most durable, reliable, and complex of machines. As we will see in Chapters 13 and 15, biomedical engineers now imagine that the creation of reliable replacement tissues and organs such as the heart is achievable. The success of the Abiomed artificial heart (called AbioCor™, Figure 1.5, which had been implanted into 10 patients as of March 2003), is an example of progress in this heroic effort.

A simple definition of engineering might be this: Engineering is the art of making practical application of the knowledge of pure science (3). Engineering is a creative discipline (like sculpture, poetry, and dance), but the end result is often intended to be durable, useful, abundant, and safe. Engineering art is not produced for museums, but intended to infiltrate the world.

Technology is a broader and more comprehensive term than engineering; in general, technology is the end result of a practical application of knowledge in a particular area. Anyone can produce technology, but engineers—because their training is focused on providing the knowledge tools needed to produce technology—have had the dominant role.

1.3.2 Biomedical engineers seek to understand human physiology and to build devices to improve or repair it

Other textbooks and review articles have described the origins of biomedical engineering, which can be identified even in ancient sources (2). Rather than reviewing this history in detail, we instead offer a schematic, speculative view of progress in biomedical engineering (Figure 1.6). Early humans learned that tools could improve the quality of their life; one might argue that the first engineers were the clever individuals who either recognized the value of wheels, levers, and sharpened rocks or figured out new ways to use these tools. As humans used tools, and as a result found new leisure time for other activities, some curious individuals probably began to use these implements to study themselves. As people learned more about the structure and function of their own bodies (that is, as they learned more about human anatomy and physiology), they were able to apply this knowledge to the creation of improved tools for repair of function (such as splints and sutures).

Observed in this way, the history of biomedical engineering involves a sequential and iterative process of discovery and invention: new tools for studying the human body leading to a deeper understanding of body function leading to the invention of improved tools for repair and study of the human body, and so forth. The dual nature of biomedical engineering is alive today; some biomedical engineers are concerned with careful analysis and study of the operation of body systems, others are concerned with the development of new techniques for the study and repair of the body, and still others do a bit of each.

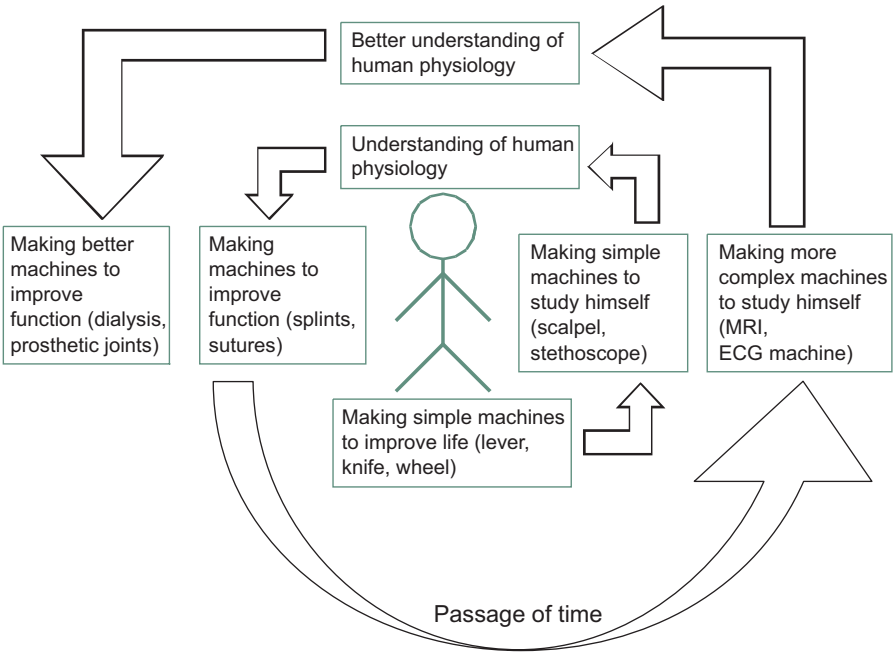


Figure 1.6 **Advances in biomedical engineering.** Figure shows a schematic view of advancement in biomedical engineering, which relies on sequential development of improved tools for studying physiology and the subsequent increased understanding of physiology that results. MRI, magnetic resonance imaging; ECG, electrocardiogram.

This speculative view of biomedical engineering can be confirmed through history; consider the timeline provided in Table 1.1, which shows highlights in the development of contact lenses. Many vision problems can now be corrected in humans; how did we get to this state? It was probably recognized very early in human history that the eye was involved in human vision; placing a hand in front of the eye blocks vision, and injuries to the eye destroy it. This knowledge of the source of vision was eventually translated into efforts to repair faulty vision with lenses (by Bacon in 1249 and Nicholas of Cusa in 1451); these developments could not happen until people (we would later call them engineers) had developed sufficient experience with the optical properties of materials and the construction of the lens. Leonardo da Vinci suggested a lens that was directly applied to the human eye early in the 15th century, but the technical skill required to make polished glass lenses shaped like the eye did not appear until 1887, in the hands of the German glassblower F. E. Muller. These early lenses were difficult to make (and therefore expensive), and they were not well tolerated by the eye. Study of the response of the eye to the presence of these materials revealed new aspects of eye physiology, such as the eye's nonspherical geometry and the circulation pathway for tears. New materials were developed especially for lenses; plastics were particularly valuable (Figure 1.7). Long wear contact lenses required an understanding of the cornea's need for oxygen (which is a wonderful engineering problem that illustrates an aspect of physiology, see Problem 15 in Chapter 2). Today, lenses are

Table 1.1 Development of contact lenses

Year	Event
1249	Roger Bacon writes about convex lens eyeglasses for treating farsightedness
1451	Nicholas of Cusa invents concave lens spectacles to treat nearsightedness
1508	Leonardo da Vinci conceives of a water-filled hemisphere that could be worn directly on the eye
1636	Rene Descartes proposes placing a lens at one end of a water-filled tube with the other end placed on cornea of the eye
1801	English scientist Thomas Young develops a model based on the theories of da Vinci and Descartes
1827	Sir John Herschel studies how to mold lenses for accurate fitting over the cornea
1884	The development of anesthesia allows for molding the cornea
1887	Glassblower F.E. Muller produces the first glass contact lens to protect a diseased eye
1888	A.E. Fick makes the first glass contact lens to correct vision
1889	August Muller creates lenses to correct his myopia by molding the human eye
1936	W. Feinbloom is the first to use plastic in contact lenses
1938	Obrig and Mullen produce the first all-plastic scleral contact lens using Poly(methyl methacrylate) (PMMA). (Scleral lenses covered the entire eye, including the white part of the eye.)
1947	Tuohy develops an all-plastic corneal contact lens, a “hard” lens
1960	Wichterle, Lim, and Dreifus begin to work on making “soft” lenses with hydroxyethyl methacrylate (HEMA) hydrogels
1971	Bausch & Lomb receive U.S. Food and Drug Administration (FDA) approval to sell soft lenses developed by Wichterle
1980s	FDA approves contact lenses for extended wear
1983	CIBA Vision introduces BiSoft, the first FDA-approved soft bifocal contact lens
1987	First disposable extended wear lenses are introduced
1988	Vistakon invents the first soft disposable contact lenses, the ACUVUE brand
1995	Johnson & Johnson launches the first daily disposable contact lens, 1-DAY ACUVUE
2001	FDA approves 30-night continuous wear contact lenses developed by CIBA Vision (Focus Day and Night)
2002	CIBA Vision launches FOCUS Dailies Toric, the first daily disposable contact lens for astigmatism
2002	FDA approves contact lenses for corrective refractive therapy (Paragon CRT) that reshape the cornea during sleep and temporarily correct vision. The lenses are only worn during sleep and provide clear vision when removed the following morning! (http://www.paragoncrt.com)

manufactured from synthetic oxygen-permeable materials using computer-aided techniques; the manufacturing process is inexpensive and reliable enough to render the lenses disposable.

This example also demonstrates the kinds of science that a biomedical engineer must master: physics (e.g., light refraction and mechanics); anatomy; physiology (e.g., tear production and circulation); materials science; immunology (e.g., the body’s response to foreign materials); and mathematics (e.g., evaluation of oxygen diffusion).

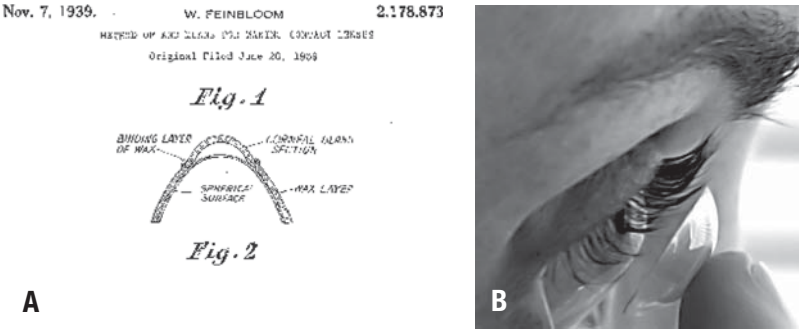


Figure 1.7 **Contact lenses. A.** An early plastic contact lens by Feinbloom. **B.** A modern hydrogel contact lens.

1.3.3 Biomedical engineering has been taught in universities for many decades, but is growing at present

The academic discipline of engineering became defined around the mid-1800s. The teaching of engineering in the United States began in the years before the Civil War. For example, Yale University began offering a course on civil engineering in 1852. In 1863, Yale awarded the first PhD in engineering in the United States to J. Willard Gibbs (whose "free energy" you will encounter in Chapter 2). President Abraham Lincoln signed into law the Land Grant Colleges Act in 1862, which provided land and perpetual endowments to each state for the support of colleges of agriculture and mechanical arts. Some of these land grant colleges became major engineering schools that thrive today including Iowa State University, Massachusetts Institute of Technology, Washington State University, Michigan State University, Texas A & M, Cornell University, California Polytechnic State University, and Purdue University. Engineering education and engineering practice both accelerated during World War II.

Much has been written recently about the history of biomedical engineering; for example, a history of accomplishments of the past 50 years is available (4). A history of the development of the academic field was written by Peter Katona, president of the Whitaker Foundation (5). According to Katona, biomedical engineering began to appear as a subject of study at universities and colleges in the late 1950s and early 1960s. The number of university programs and students has expanded tremendously over the past few decades (Figure 1.8).

Why this recent increase in student interest in biomedical engineering? Is something new happening in the field that contributes to this increase? Biomedical engineering has been a productive area of study for decades, and many life-saving products have emerged from this study including heart pacemakers, kidney dialysis machines, and artificial joints, but our understanding of biology and human medicine has expanded at an explosive rate in the past decade. The Human Genome Project is just one example of newly acquired riches of biological information. Biology has been transformed from a descriptive science

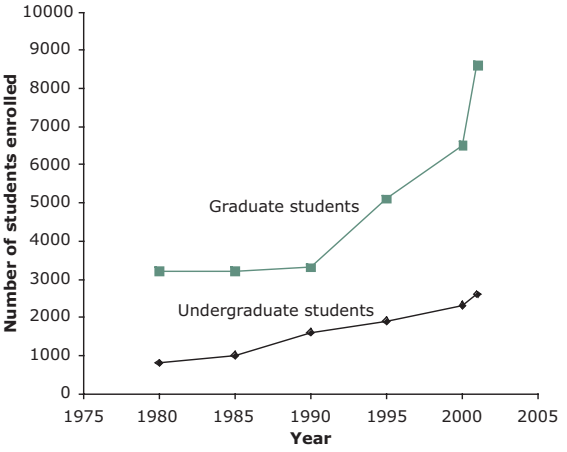


Figure 1.8 Numbers of students enrolled in biomedical engineering degree programs.

into a quantitative science. As such, it now provides an easier point of entry for engineering.

The current growth of biomedical engineering might be similar to expansions that occurred in civil, mechanical, and electrical engineering in the past. As we learned about mechanics and properties of materials during the 20th century, engineers acquired new tools that allowed them to build bridges, buildings, and other physical structures that were unimaginable in 1900. Similarly, the growth of basic knowledge in physics during the 20th century enabled new accomplishments (such as transistors, computers, and telecommunications systems) by electrical engineers. The increase of biological knowledge is already leading to new potentials, but it will be the work of this new and expanded group of biomedical engineers (including you) to convert that knowledge into safe and affordable new products that improve life for future generations.

1.3.4 Biomedical engineering can be divided into subdisciplines

Biomedical engineers study a variety of different kinds of problems related to human health (Table 1.2). Some concepts are important to all biomedical engineers; quantitative human physiology and mathematical analysis are essential to all of biomedical engineering, but some biomedical engineers study systems that are best approached through an understanding of electrical signals and circuits, or mechanics, or chemistry. For this reason, biomedical engineering is conveniently divided into subdivisions that reflect the kinds of tools that are best used to approach the problem of interest and the nature of the problem itself. Understanding each of these subdivisions—and recognizing the similarities and the differences between them—is another way of seeing what biomedical engineering is about. The next few paragraphs describe briefly the subdivisions that we will explore in this book.

Table 1.2 Subdisciplines of biomedical engineering

Subspecialty	Examples	
Systems biology and Bioinformatics	Modeling of cellular networks DNA sequence analysis Microarray technology	Chapters 3 and 16
Physiological modeling	Physiology of excitable cells Dynamics of the microcirculation Models of cellular mechanics Pharmacokinetic models of chemotherapy drugs	Chapters 6–9
Biomechanics	Gait analysis Prosthetic joints and limbs Cellular mechanics	Chapter 10
Biomedical instrumentation and Biomedical sensors	Electrocardiogram Cardiac pacemaker Glucose sensor O_2 sensor pH sensor	Chapter 11
Biomedical imaging	Radiographic imaging Ultrasound imaging Magnetic resonance imaging Optical imaging	Chapter 12
Biomolecular engineering and Biotechnology	Drug-delivery systems Artificial skin (tissue engineering) Protein engineering Chromatography and other separation methods Vaccines	Chapters 13 and 14
Artificial organs	Biomaterials Hemodialysis Artificial heart	Chapter 15

PHYSIOLOGICAL MODELING

Biomedical engineers are experts in physiology and mathematics, so it is not surprising that they have been pioneers in the development of physiological models. Often, biomedical engineers make mathematical models of the systems that they are working on to help them understand and predict system behavior. For example, biomedical engineers that are designing prosthetic hips use mathematical models of hip mechanics to predict the stresses and strains that their artificial hip must endure (Figure 1.9).

Physiological modeling often has long-lasting influences. Mathematical models of blood flow in small vessels is one of the most important results of biomedical engineering, and still guides the development of tissue-engineered blood vessels and cardiovascular biomaterials such as stents. Low velocity flow through a cylindrical conduit is called Hagen-Poiseuille flow in honor of Jean Leonard Marie Poiseuille and Gotthilf Heinrich Ludwig Hagen; Poiseuille (a physiologist) and Hagen (an engineer) independently published the first systematic measurements of pressure drop within flowing fluids in simple tubes in 1839 and 1840

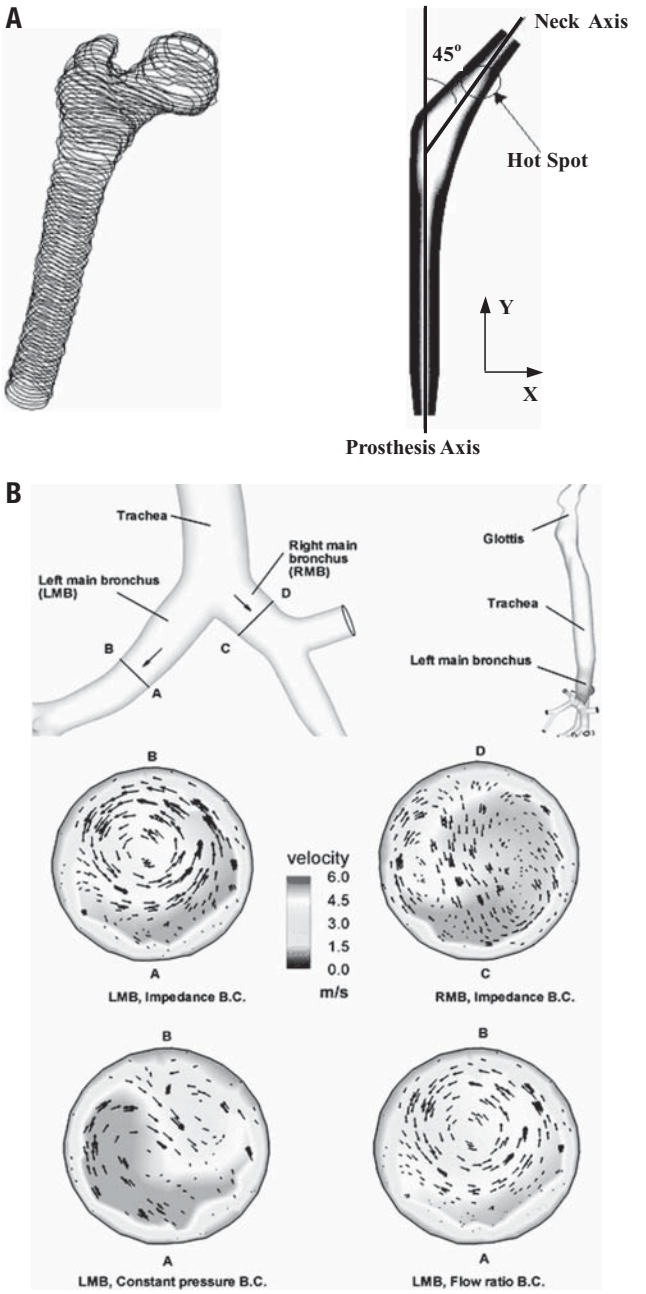


Figure 1.9 **Examples of physiological modeling. A.** Modeling of forces acting on a human hip, from reference (6) with permission. **B.** Modeling of air flows in the left main bronchus and right main bronchus under different conditions within the lung. Models such as this one are useful in evaluating breathing patterns for patients with different lung diseases, and quantifying the extent of disease in a particular patient, from reference (7) with permission. (See color plate.)

(this work is reviewed in more detail in Chapter 8). As we will see in Chapter 16, physiological modeling is becoming even more important in understanding biology; models of the networks of chemical reactions that occur within cells is an essential ingredient of systems biology and bioinformatics. Now, mathematics

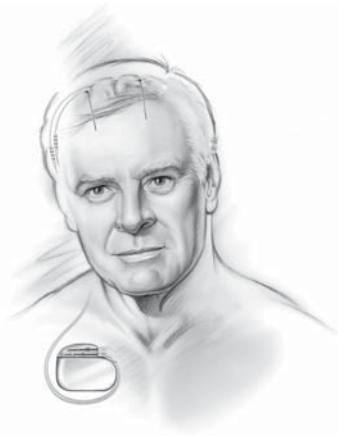


Figure 1.10 **Biomedical instrumentation.** This field is described in detail in Chapter 11. This image shows a deep-brain stimulator (developed by Medtronic), which is now used to treat patients with Parkinson's disease. Image courtesy of Medtronic, Inc.

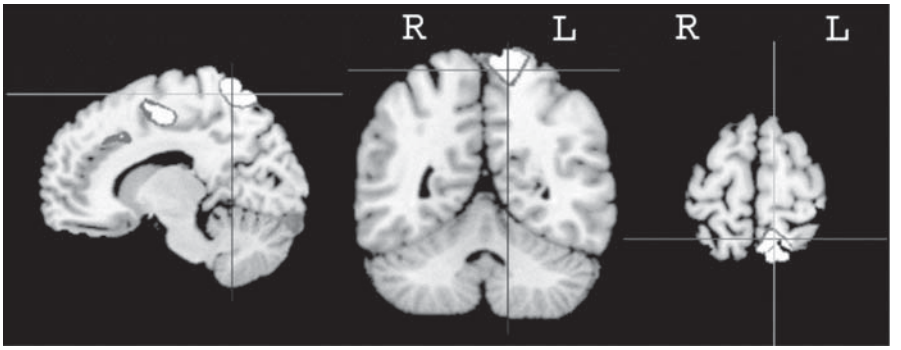
is being used to explore complex physiological responses, such as angiogenesis (Figure 1.9); these models may have profound implications for treatment of cancer, as described in Chapter 16. The influence of biomedical engineers on the biology of the future will be profound.

BIOMEDICAL INSTRUMENTATION

Instrumentation has long been an important component of medicine. Hospitals depend on electronic instruments, such as heart and blood pressure monitors, to provide continuous and reliable feedback on the health status of critically ill patients. As the microelectronics industry has developed more sophisticated materials and techniques over the past 20 years, biomedical instrumentation has become multifaceted. Instruments are more sensitive and smaller; many functions that once required large machines can now be performed on microchips that are small enough to be implanted. Of course, some instruments, such as cardiac pacemakers, have long been implanted. Pacemakers, which are now multifunctional and highly reliable, have created a major advance in human health. Similar devices are now being used to treat Parkinson's disease and other neurological disorders by delivery of electrical stimulation (Figure 1.10). Implantable instruments of the future will deliver drugs, monitor local tissue states, and send detailed information on internal function outside of the body.

BIOMEDICAL IMAGING

Biomedical imaging technology has revolutionized medicine. Physicians all over the world now have access to reliable and safe methods for collecting medical images using technologies such as conventional radiographic imaging, CT, MRI, and ultrasound imaging. The wide availability and safety of these techniques have improved our standards for following the progress of common conditions such as pregnancy and life-threatening ailments such as cancer. Biomedical engineers have been leaders in the design and construction of new imaging machines, the creation of medical imaging approaches using these machines, and the analysis of image data that are acquired from patients. Each year the state of the art in imaging improves; each improvement in image resolution and quality means more accurate diagnosis of disease and improved health care. Most current imaging methods provide information on tissue anatomy, but imaging techniques of the future will also provide information on the function of tissue (Figure 1.11), opening new doors for the study of disease progress and creating opportunities for development of new treatments.



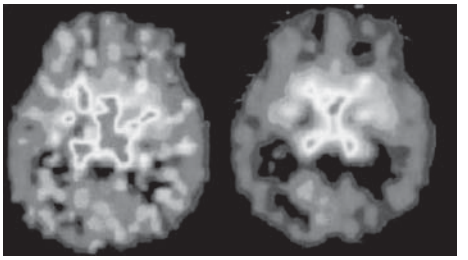


Figure 1.11 **Biomedical imaging.** This field is described in Chapter 12. Functional magnetic resonance (fMRI, top) and positron emission tomography (PET, right) are now providing functional and metabolic information in addition to anatomical information. Top panel provided by Todd Constable, Yale University. Bottom panel reprinted by permission from Macmillan Publishers Ltd: *J Cereb Blood Flow Metab*. 2003;23:1096–1112. (See color plate.)

BIOMECHANICS

Humans live in a physical world. Biomedical engineers have long studied the performance of humans as mechanical objects and determined the role of mechanical forces on human function. Some engineers who are interested in biomechanics study the role of forces (produced by exercise, work conditions, or the activities of normal life) on tissue physiology or human performance. Others are interested in the consequences of mechanical injury and the design of better ways to protect humans from mechanical forces by the design of seat belts or helmets, for example. Still others examine the ways that diseases affect the mechanical performance of tissues such as the heart or the ability of humans to move after loss of mechanical function in their bones or control of muscles. Of course, biomedical engineers have been leaders in the design of mechanical replacements for hips, joints, heart valves, and organs (Figure 1.12).

As biology advances, the role of biomechanical analysis is expanding. Biomedical engineers are studying the mechanical function of cells, for example, by studying the mechanics of cell movement through circulation or cell motility through tissues. Structural proteins within cells, such as the proteins that make muscle cells contract or the proteins that regulate cell division, also operate as mechanical objects, and biomedical engineers are leading the effort to understand how these systems work.

BIOMOLECULAR ENGINEERING

Drugs are chemical substances used to improve health, but they often have unwanted, even deadly, side effects. A major advance in drug therapy over the

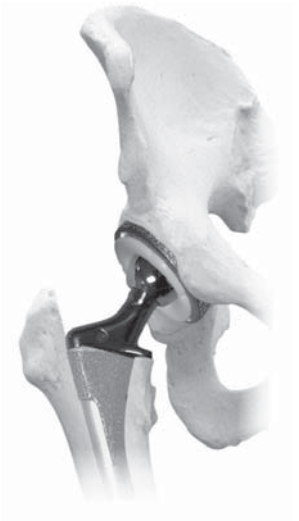


Figure 1.12 **Biomechanics.** This field is described in detail in Chapter 10. This image shows a metal hip implant, with a polyethylene cup to lubricate. Image courtesy of Zimmer, Inc.

past century is the development of pharmacokinetic analysis, which predicts patterns of drug absorption and metabolism (often based on mathematical models), thereby providing tools that can be used to give drugs safely and effectively. Biomedical engineers, especially those trained in chemical engineering, have been pioneers in this area. Similar mathematical tools applied to the design and operation of biological reactors have been enormously important in the large-scale production of drugs. Biomolecular engineering is the branch of biomedical engineering that emphasizes the use of chemical engineering principles for design and analysis.

Today, biomolecular engineers are using similar approaches to design drug-delivery systems and to create new treatments using tissue and cellular engineering (Figure 1.13). Many areas of interest to biomedical engineers can be approached using the tools of chemical engineering such as biomaterials design, nanobiotechnology, and genomic analysis. For this reason, biomolecular engineering is growing and developing as a subdiscipline of biomedical engineering. In fact, it is growing so rapidly that we have divided our

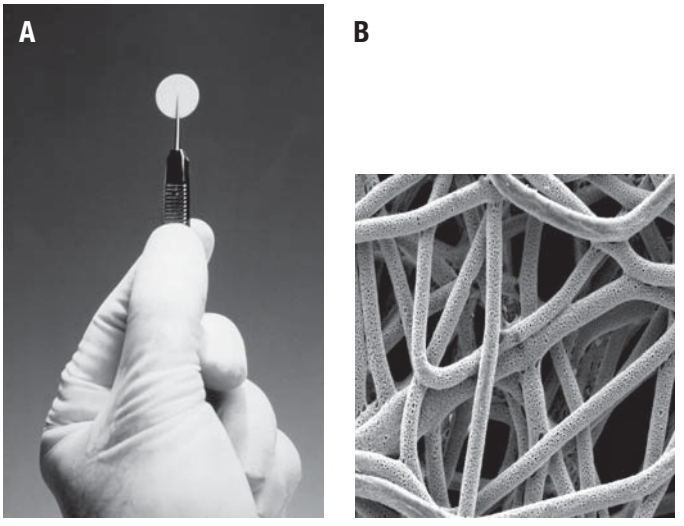


Figure 1.13 **Biomolecular engineering.** This field is described in detail in Chapters 13 and 14. **A.** The GLIADEL® drug-delivery system for treating brain cancer allows surgeons to give a long-lasting dose of chemotherapy directly at the site of the tumor. Photo used with permission. **B.** Polymer scaffolds built by biomolecular engineers are being used for tissue engineering. Each polymer fiber in this electron microscopic image is ~10 microns in diameter.

Figure 1.14 **Artificial organs.** This field is described in detail in Chapter 15. The development of synthetic heart valves, which have provided reliable mechanical function for decades, is a union of artificial organ design and biomechanics analysis. This image shows a bileaflet tilting disk mechanical heart valve (Photo courtesy of St. Jude Medical, Inc.). From Schoen and Padera (8).

description of biomolecular engineering into three sections: a general introduction (Chapter 13), a more specialized treatment concerning applications in the immune system such as vaccines (Chapter 14), and a more detailed description of treatments for cancer (Chapter 16), which combines biomolecular engineering, radiation physics, and imaging.

ARTIFICIAL ORGANS

Synthetic materials can be combined with biological components to produce devices that function like tissues and organs. The use of natural materials—often derived from animal tissues—to repair tissues was described in ancient times. But the development of synthetic materials (metals, ceramics, and polymers) has provided biomedical engineers with tools to expand and improve the design of artificial organs. For example, polymeric materials are routinely used in vascular grafts, and combinations of synthetic polymers and living cells may someday lead to implantable replacement cartilage, liver, or nervous tissue (see Chapter 15).

Synthetic materials are critical components in extracorporeal systems for blood purification (i.e., systems that treat blood by taking it out of the body). Willem Kolff, a Dutch physician, developed the first successful kidney dialysis unit in 1943, using cellophane to remove urea from the blood of diabetics; further work by biomedical engineers has made hemodialysis a life-saving procedure that is widely available. The addition of cells to a dialysis-like machine can make it function as an artificial liver or pancreas. Biomedical engineers design artificial hearts and heart components, such as valves (Figure 1.14), and also design the machines that keep patients alive during cardiac surgery.

SYSTEMS BIOLOGY

Systems biology is a frontier area for biomedical engineers. Engineers, of course, are specialists in the analysis of all kinds of systems; engineers are trained to develop models of complex systems, to learn how to control these systems, modify them, or replicate them in alternate forms. Systems analysis may be the quintessential engineering exercise, and the revolution in modern molecular biology has placed engineers in a position to apply these analytical tools to deep and fundamental biological problems.

Systems biology requires contributions in many areas of strength for biomedical engineers. Of course, the development of models of biological function (usually at the cellular and molecular level) is a key component, as is the development

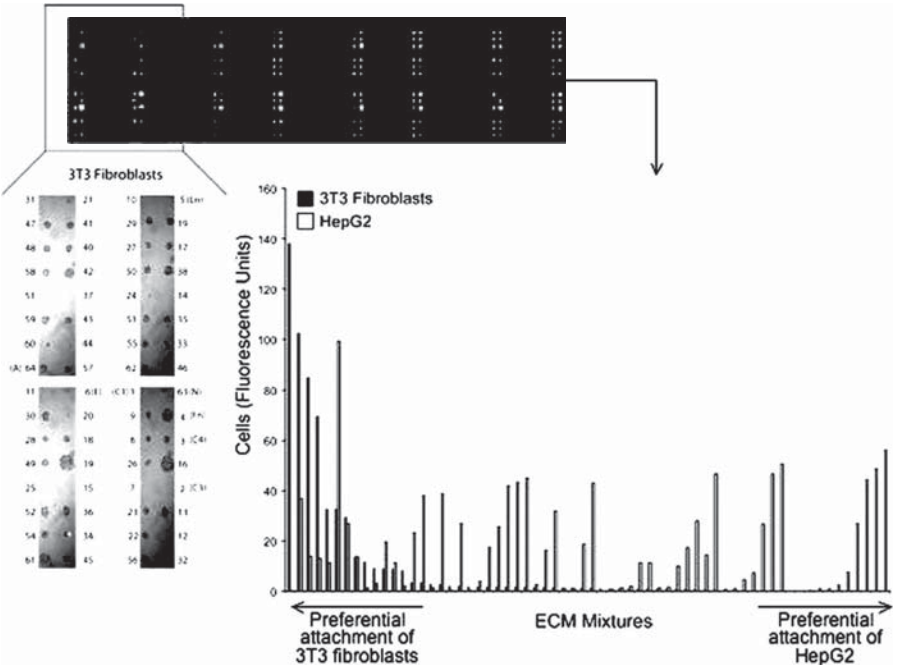


Figure 1.15 **Systems biology.** This field is described in detail in Chapter 16. Here, a protein microarray is used to probe the relative strength of adhesion of hepatocytes and fibroblasts to small spots of differing protein composition (Woodrow K. and Saltzman W.M., unpublished data, 2008).

of efficient computer methods for examining biological databases (such as gene or protein databases) to find or sort new biological information. Biomedical engineers have also created new methods to manipulate cells through genetic and cellular engineering. All of these advances will require new methods for measuring the state of function of individual cells. Biomedical engineers are already contributing to this effort by analyzing the protein composition of living cells (proteomics), creating methods for simultaneous measurement of thousands of genes and proteins within a cell (array technologies), creating arrays of cells and tissues for diagnostic purposes (Figure 1.15), and designing devices that can physically interface with cells and proteins (biomicroelectromechanical systems, see Chapter 11).

1.4 Biomedical engineering in the future

There have been enormous advances in human health care over the past 100 years, and our life expectancy has increased dramatically during this period (remember Figure 1.1). Much of this progress is because of success in the battle with infectious diseases. In London, in 1665, 93% of deaths were the result of infectious disease, whereas in the United States, only 4% of deaths were the result of infectious disease in 1997. Engineers contributed significantly to this effort by developing sanitation methods for cities, large-scale processes for manufacture of vaccines and antibiotics, and delivery methods for drugs.

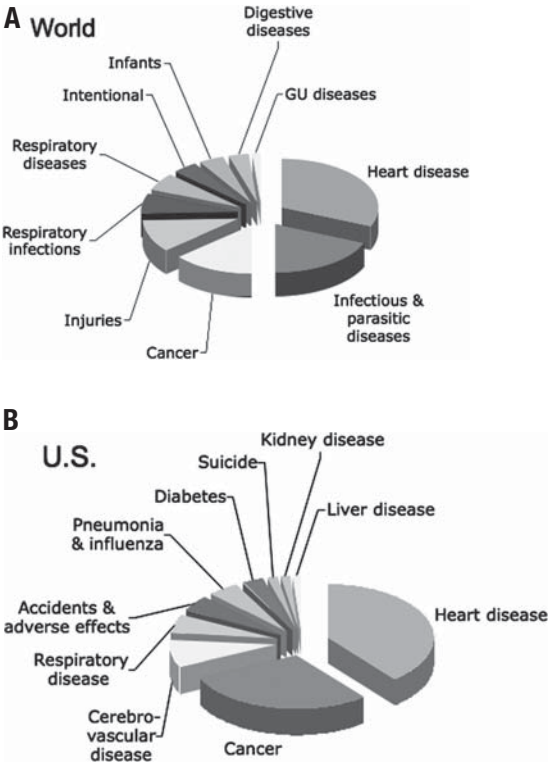


Figure 1.16 **Causes of death in the world and the United States, 1997**. GU, genitourinary.

We have made progress, but the problems are not solved (Figure 1.16). Infectious diseases are still the second leading cause of death in the world and the most important cause of premature death in many developing countries. Current vaccines are not perfect (in fact, some people get chicken pox even after getting an expensive and painful vaccine!). Biomedical engineers can do a better job in making technology that can also be translated to people with limited resources; we need to make vaccines less expensive, easier to administer, and easier to transport. And of course, there are established infectious diseases (such as the ones caused by human immunodeficiency virus [HIV] or hepatitis C) and emerging diseases (such as Severe Acute Respiratory Syndrome [SARS] and West Nile virus infection) that are important health problems in all areas of the world. We will not achieve control of these diseases without the work of biomedical engineers.

Most people die from non-infectious diseases such as cancer and heart disease (Figure 1.16). Chronic diseases such as rheumatoid arthritis, diabetes, and Alzheimer's disease impair quality of life. In the same way that past engineers revolutionized treatment of kidney disease, biomedical engineers are now studying imaging systems, biomaterials, biomechanics, and all of the subdisciplines described earlier to help patients with these incurable ailments. The future of medicine will be shaped by these inventive minds.

Engineers work to improve the human condition, but they must also be aware of the context and potential consequences of their work. We can learn something from the history of the use of technology, but the lessons are not always clear nor can they be easily translated from one field to another. Mechanical engineers have given us the marvel of commercial air travel, but no one could predict that commercial airliners would one day be used as weapons. Today, there is legitimate concern about the possible consequences of stem cell engineering, cloning of organisms, and other technologies on which biomedical engineers will work. Each of us is obliged to look carefully at the relationship between engineering, ethics, and impact on society.

1.5 How to use this book

This book is intended for use with introductory courses in biomedical engineering, for students who have no previous experience with engineering and limited experience with biology. We do assume that most students will be taking the standard freshman courses in physics, chemistry, and mathematics. Most of the mathematical analysis, however, is separated from the main part of the text within colored boxes. All of the necessary biological background material is included in the chapters of the book (Figure 1.4); surveys of molecular and cellular principles (Part 1) and physiological principles (Part 2) are provided. Students and instructors can use these parts of the book as introductory surveys to the biological foundations of biomedical engineering, or they can use these chapters as reference materials, to be consulted as they focus on the major subdivisions of biomedical engineering practice, which is contained in Part 3.

TO THE STUDENT

Within each chapter, I have highlighted two types of information. First, mathematical analysis is a central part of biomedical engineering, but I realize that students taking a first course in biomedical engineering might still be taking their first course in college calculus. Therefore, I have illustrated the use of mathematics in biomedical engineering in a way that (I hope) complements, but does not interfere, with the reading of the main text. Mathematical concepts are presented in boxes that appear alongside the main text. In addition, the problems at the end of each chapter are arranged roughly in order of the level of mathematical sophistication that is required for their solution. I also provide guidance, throughout the book, on developing an approach to problem solving. Box 1.2 contains some initial advice.

Second, I have profited enormously from my personal associations with other biomedical engineers and I realize that many students are searching for a career path that matches their personal strengths with their professional ambitions. To help with this process, I have included profiles of other individuals in biomedical engineering, including pioneers of the field as well as recent graduates. In each

Box 1.2 Solving engineering problems

Good engineers are skilled at making estimates and solving problems. The problems in Chapter 1 were designed to exercise your skill at estimation. As you solve these problems, and those throughout the book, develop a systematic approach for thinking about and presenting your work on each problem.

Here are some guidelines to help in developing and presenting your solutions to engineering problems.

General features

- Use fine-lined paper, preferably lined in grids (like graph paper) to facilitate drawing of diagrams and graphs.
- Include—in the top right hand corner of the first page (and perhaps on every page)—a title block that includes your name, the date of submission, the class number, and so forth.
- Always be clear about the units. Break complex units down into their components (length, mass, time, etc.), using the unit conversion table in Appendix C.

For each problem

- Include a concise statement of the problem you are solving.
- Describe clearly what things you are trying to determine: What is your goal?
- Start each problem by writing down all of your assumptions; leave room so that you can add assumptions as you work through the problem.
- Draw a diagram to help in defining the important variables and clarifying the problem statement.
- Define the key variables in the problem and assign an appropriate symbol for each.
- As you develop equations that relate the variables in the problem, use the symbols for as long as possible, substituting known values only near the end.
- If you estimate values for any of the variables, justify your choices as clearly as you can; if you find values in reference tables, indicate the source clearly.
- Look at your answer and challenge it. Does the answer you found make sense, given what you know?

profile I summarize briefly the career of the individual and then, where possible, I have asked each person to describe his or her own feelings about biomedical engineering, how she or he got started in the field, and how it has impacted her or his life.

Summary

- Life expectancy and quality of life have increased for people in most nations of the world during the last century; the development of reliable, safe, and inexpensive medical technology by biomedical engineers has played an important role in this enhancement.

Profile of the Author: W. Mark Saltzman

I was born in Des Moines, Iowa, and spent my childhood in Iowa and Illinois. I was always interested in biology and medicine, and I started my college career as a premedical student at Drake University in Des Moines. During my freshmen year of college, I discovered physics, math, chemistry, and the pleasure of using quantitative tools to find answers to complex problems. I transferred to the College of Engineering at Iowa State University, where I earned a Bachelor of Science degree in chemical engineering in 1981.

During my senior year at Iowa State, I listened to a lecture on using chemical engineering tools to solve problems in biomedical engineering; Richard Seagrave, one of my Iowa State professors, delivered the lecture elegantly and at the chalkboard. I listened, and it felt as if a door was opening to a previously hidden world that combined my interest in medicine with my new skills as a chemical engineer. I followed this path to the Massachusetts Institute of Technology (MIT), where I entered the MIT/Harvard Division of Health Science and Technology graduate program in medical engineering. At MIT, I earned a master's degree in chemical engineering in 1984 and a doctorate in medical engineering in 1987. I discovered many things during my years at MIT, including the joy of teaching, and I decided to pursue a career that combined biomedical engineering research and teaching. My mentor at MIT was Robert Langer, who is profiled in Chapter 13; Bob has been a bottomless source of inspiration for me for the past 20 years.

After graduating from MIT, I was fortunate to join the faculty at Johns Hopkins University, where I started my own research program and developed new classes at the intersection of chemical and biomedical engineering, including a class for freshmen called "Introduction to Biotechnology." My research program developed quickly—thanks to outstanding students and terrific collaborators at Hopkins such as Henry Brem and Richard Cone—to include projects involving controlled drug delivery to the brain, polymers for supplementing or stimulating the immune system, cell interactions with polymer materials, and tissue engineering. In 1996, I moved to Cornell University, which allowed me to expand my research program into new areas of biomaterials and nanotechnology. I continued developing my course for freshmen students, extending its scope and enhancing its focus on human physiology to become "Introduction to Biomedical Engineering." I joined the faculty of engineering at Yale University, as the Goizueta Foundation Professor of Chemical and Biomedical Engineering, in July of 2002 and became the first chair of Yale's Department of Biomedical Engineering in 2003. I continue to teach my course for freshmen at Yale, which is now called "Frontiers in Biomedical Engineering" and covers the material presented in this book.

I currently live happily in New Haven, Connecticut. I have two sons, Alexander and Zachary, who (so far) are mute on the role of biomedical engineering in their futures.

- Emergency rooms, hospitals, doctors' offices, and homes contain medical instruments and products that resulted from 20th century biomedical engineering.
- Biomedical engineering is the application of science, mathematics, and engineering design principles to improve human health.

- Human physiology is the foundational science that distinguishes biomedical engineering from other forms of engineering; throughout history, advances in our understanding of physiology have led to new biomedical engineering technology.
- Biomedical engineering is growing in interest among students, and opportunities for biomedical engineers to find productive work and contribute to society are increasing rapidly.
- Biomedical engineers often specialize in a variety of subdisciplines or fields such as physiological modeling, biomedical instrumentation, biomedical imaging, biomechanics, biomolecular engineering, artificial organs, and systems biology.
- Emerging human diseases and new discoveries in physiology and human health promise to present new problems for biomedical engineers of the future.

REFERENCES

1. Table 1. Deaths, percent of total deaths, and death rates for the 10 leading causes of death in the selected age groups, by race and sex: United States, 2000. National Vital Statistics Report. 2002;50(16):13–48.
2. Enderle J, Blanchard S, Bronzino J, eds. *Introduction to Biomedical Engineering*. San Diego: Academic Press; second edition, 2005.
3. Florman SC. *The Existential Pleasures of Engineering*. New York: St. Martins Press, Inc.; 1976.
4. Nebeker F. Golden accomplishments in biomedical engineering. *IEEE Eng Med Biol Mag*. 2002;21(3):17–47.
5. Katona PG. The Whitaker Foundation: The end will be just the beginning. *IEEE Trans Med Imaging*. 2002;21(8):845–849.
6. Li C, Granger, C, Schutte, H, Biggers, SB, Kennedy, JM, Latour, RA. Failure analysis of composite femoral components for hip arthroplasty. *J Rehabil Res Dev*. 2003;40(2):131–146.
7. Ma B, Lutchen KR. An anatomically based hybrid computational model of the human lung and its application to low frequency oscillatory mechanics. *Ann Biomed Eng*. 2006;34(11):1691–1704.
8. Schoen FJ, Padera RF. Cardiac surgical pathology. In: Cohn LH, Edmunds LHJ, eds. *Cardiac Surgery in the Adult*. New York: McGraw-Hill; 2003:119–185.

FURTHER READING

Schwan HP. The development of biomedical engineering: Historical comments and early developments. *IEEE Trans Biomed Eng*. 1984;31:730–736.

Schwan HP, ed. The history of biomedical engineering. *IEEE Eng Med Biol Mag*. 1991;10:24–50.

USEFUL LINKS ON THE WORLD WIDE WEB

http://www.bmenet.org/BMEnet/

This site contains a wide collection of information on Biomedical Engineering including information on all of the academic programs that are available in the field, links to research on latest advances, and information on jobs.

http://www.whitaker.org

The Whitaker Foundation is a private philanthropic organization that has been an influential participant in the growth of biomedical engineering as an academic discipline. Their Web site contains information on academic programs in biomedical engineering and reports of research that is supported by the foundation.

http://www.bmes.org/

This is the official site for the Biomedical Engineering Society (BMES), with information about the professional society for biomedical engineers. Information about the BMES annual meeting is also provided here.

http://www.asee.org/precollege/

This site has a guide for precollege students who are interested in careers in engineering. Presented by ASEE (The American Society for Engineering Education), 1818 N Street, N.W., Suite 600, Washington, DC, 20036.

http://www.nibib1.nih.gov/

The National Institute of Biomedical Imaging and Bioengineering (NIBIB) is the newest member of the National Institutes of Health (NIH) in the United States. The mission of the NIBIB is to improve health by promoting fundamental discoveries, design and development, and translation and assessment of technological capabilities. The NIBIB Web site contains information on all aspects of the NIBIB including organization and mission, research and training grant opportunities and related information, breaking news, publications, events, bioimaging and bioengineering information of general interest, interagency activities, and the NIH Bioengineering Consortium (BECON), which is administered by the NIBIB.

http://www.greatachievements.org/greatachievements/

The greatest engineering achievements of the 20th century were assembled by the U.S. National Academy of Engineering. For each broad category of achievement (i.e., #1 is electrification, #2 is the automobile), a history and a timeline of significant events during the century is provided. Biomedical engineers directly impacted both imaging (#14) and health technologies (#16) on the list of top 20 achievements.

http://www.uh.edu/engines

This is the Web site that accompanies the Engines of Our Ingenuity *radio program. Professor John Lienhard provides historical (and entertaining) information on the origins of technological innovation and their impact on society*.

QUESTIONS

1. Write a definition (1–2 sentences) of biomedical engineering in your own words (test yourself by not looking back at any of the definitions in the text when you write your own definition).
2. Make two lists (of at least 10 items each) in response to the following two questions:
   a. What products of biomedical engineering have you personally encountered? Pick three of these products and write a description of what you think is good, and what could be improved in that product.
   b. What products of biomedical engineering do you expect to encounter in the next 50 years?
3. Pick a faculty member who teaches or does research in biomedical engineering from your department for this exercise.
   a. Perform a Medline search with your selected faculty member as the author to find a list of articles that he or she has written in the past two years.
   b. Select one of the articles and find a copy of it in your library (or online if it is available in that format). Read it and write a brief review of the findings for a general audience. In which subdiscipline of biomedical engineering does this research work belong?
4. Interview an older family member (parent, grandparent, aunt, uncle) about an advance in medicine that they remember. Why was this advance memorable to them? How did they find out about it?

PROBLEMS

1. Drugs are often administered in capsules. Some capsules act as containers, which hold many smaller particles that contain the active agent. Administration of the drug is improved by the capsule; when the capsule breaks down in the intestine and the particles are freed from the container, the large surface area of the drug particles allows rapid dissolution of the drug.
   a. Assume that a capsule is approximately 1 cm long and 3 mm in diameter. Calculate the surface-to-volume ratio of the capsule.
   b. Assume that the capsule is filled with particles that are 0.4 mm in diameter. How many of these particles will fit into one capsule?
   c. What is the total surface area of the particles within the capsule?
2. Using only the information provided in Figure 1.1, estimate the following:
   a. Human life expectancy in the year 1250.
   b. Human life expectancy in the year 2050.
3. From Figure 1.8, estimate the fraction of biomedical engineering students who were undergraduates in 1980, 1985, 1990, 1995, and 2000.

4. Figure 1.13 shows a surgeon holding a GLIADEL® wafer. From this photographic evidence only, estimate the following:
   a. The dimensions of the wafer.
   b. The dose of drug that it contains, if the loading of drug is 3.85% by mass (i.e., 3.85% of the wafer mass is due to the drug).
5. Figure 1.14 shows a mechanical artificial heart valve. If this valve opens and closes once during each cycle, or beat, of the heart, how many times will the valve need to open and close during 10 years of continuous use? Measure your own heart rate (describe how you do it) and use this rate in answering this question.
6. Figure 1.15 shows an image of a microscope slide, onto which small spots of protein have been printed. The slide was used to identify protein compositions that provide for good adhesion of cells. If each spot of protein is 300 microns (micrometers) in diameter, and each cell is 15 microns in diameter, what is the maximum number of cells that can fit into each spot?

PART 1

MOLECULAR AND CELLULAR PRINCIPLES

2 Biomolecular Principles

LEARNING OBJECTIVES

After reading this chapter, you should:

- Understand the types of chemical bonds that hold atoms together in molecules.
- Understand the difference between polar and nonpolar molecules, and the important role that polarity plays in interactions of biological molecules.
- Understand the basic concepts of biochemical energetics, including the role of adenosine-5′-triphosphate (ATP) in the transformation of energy into biochemical work.
- Understand the concepts of acids, bases, pH, and buffering.
- Know the major classes of biological polymers: proteins, polysaccharides, and nucleic acids.
- Understand the chemical structure of polysaccharides as polymers of monosaccharides, including the simple sugars glucose, galactose, and fructose.
- Understand the basic structure of nucleic acids as polymers of nucleotides and how that structure is different in deoxyribonucleic acid (DNA) and ribonucleic acid (RNA) polymers.
- Understand the basic structure of proteins, which are polymers of amino acids, and how the diversity of amino acid structure influences protein three-dimensional structure and function.
- Understand how the chemical structure of phospholipids contributes to the properties of biological membranes.
- Understand the basic features of biological membranes, which are lipid bilayers that are decorated with proteins and carbohydrates.
- Understand the mechanisms of diffusion and osmotic pressure generation.

2.1 Prelude

Biomedical engineers are engaged in a great diversity of activities: Chapter 1 described many of the fields in which biomedical engineers make significant contributions. This chapter, together with Chapters 3 and 4, reviews fundamental chemistry concepts that are important for understanding human physiology and biomedical engineering (BME). These chapters introduce several families of

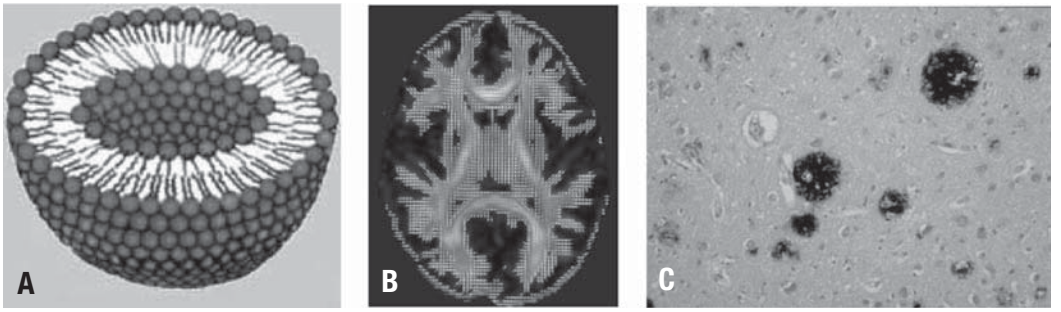


Figure 2.1 **Examples of chemistry in biomedical engineering. A**. Liposomes are synthetic structures produced by assembly of lipids into small sacs or vesicles. **B**. Diffusion tensor imaging (DTI), which maps the diffusion of water in the brain using magnetic resonance imaging (MRI). Photo courtesy of A Brock and L Staib, Yale University. **C**. Collection of proteins that accumulate in the brains of patients with Alzheimer's disease, called an Alzheimer's plaque. Photo credit: BRACE-Alzheimer's Research Registered UK Charity No. 297965. (See color plate.)

biological molecules—proteins, nucleic acids, carbohydrates, and lipids—that will be explored in more detail throughout the rest of the book.

Why should biomedical engineers understand chemistry? Knowing how molecules interact with each other and with their environments helps biomedical engineers to manipulate these molecules to create new tools for treating disease. For example, biomedical engineers have developed methods to synthesize lipid molecules into **liposomes** (Figure 2.1). Liposomes have already found many uses in human health—as carriers of the anticancer drug doxorubicin and as alternate vehicles for gene therapy that do not require the use of viruses. Similarly, biomedical engineers have used their skills in mathematical modeling and their understanding of molecular interactions to understand the formation of molecular complexes, such as the extracellular clumps of protein-rich materials (plaques) that form in Alzheimer's disease (Figure 2.1). A better understanding of the properties of the proteins that form plaque may someday lead to treatments for Alzheimer's disease.

Understanding basic chemical concepts is important in almost every aspect of BME. Artificial hips are made of synthetic materials, usually metals and polymers. Early efforts in creating artificial devices sometimes failed because of unwanted interactions between molecules of the artificial device and molecules of the body. Magnetic resonance imaging (MRI), one of the most powerful methods for non-invasive imaging of the internal structure of humans, is derived from a method that has been used for decades by chemists to understand molecules and their interactions. Even projects that appear to be dominated by physics and mechanics, such as the design of imaging systems, artificial hips, and many others, are based on a deep understanding of molecules and their interactions.

As Chapter 12 will describe in more detail, the images that biomedical engineers create using MRI (Figure 2.1) are based on the chemistry and interactions of water within tissues in the body (Figure 2.2). To understand MR images, it is

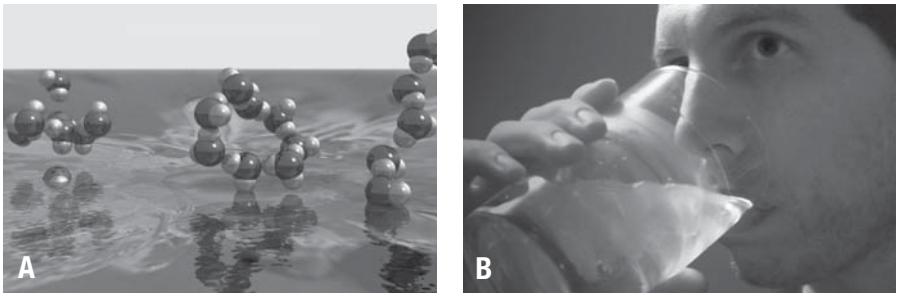


Figure 2.2 **Water. A**. Structure of liquid water. Photo courtesy of Anders Nilsson, Stanford University. **B**. Water is an indispensable part of human health.

helpful to understand the properties of water and how water interacts with other molecules in cells and tissues.

This chapter begins with a brief introduction to bonding in atoms and molecules and builds to include descriptions of proteins and nucleic acids and other large biological molecules. Every chapter in this book attempts to relate chemical, biological, and physiological facts to engineering analysis; an introduction to engineering analysis is provided in Box 2.1.

2.2 Bonding between atoms and molecules

All basic life processes that allow us to digest food, move, and grow involve chemical reactions: reactions that yield energy, build new molecules, or break down unneeded molecules. The molecules in our body are involved in thousands of chemical reactions. Before learning about the function of biological molecules, it is useful to examine the ways they can interact with one another by reviewing key concepts in chemistry.

2.2.1 Atomic bonding

There are two types of bonds that can be formed *between atoms*: ionic and covalent bonds. **Ions** are molecules with a net charge, either positive or negative. **Ionic bonds** are formed when electrons are transferred from one atom to another (e.g., Na^+Cl^-). This transfer results in two ions: a positively charged molecule, or **cation**, caused by the loss of electrons, and a negatively charged molecule, or **anion**, caused by the gain of electrons. **Covalent bonds** result from the sharing of electrons (e.g., H_2). Covalently bonded molecules can further be classified as **polar** or **nonpolar**. Molecules are called "polar" because they have partially negative and partially positive charges at the poles of the molecule. This polarity of charge is caused by unequal sharing of electrons between atoms within a molecule. For example, water (H_2O) is a polar molecule because the oxygen atom within the molecule is slightly negative, whereas the hydrogen atoms are

Box 2.1 Engineering analysis and boxes in this book

Biomedical engineers make extensive use of engineering tools and mathematical models to describe the systems that they study. One of the most valuable and far-reaching aspects of an education in engineering is the development of tools and techniques for solving real-world problems. Box 1.2 provides you with some general techniques for approaching and solving engineering problems. This box, and the others like it that appear throughout the rest of this book, provide more information on engineering analysis. Careful study of these boxes, in conjunction with the main text of the chapters, will provide a thorough introduction to the science and technology of biomedical engineering.

Engineering analysis invariably begins by defining the system under study. The system might be a supporting beam in a bridge, a set of components on an integrated circuit board, the human body, or an individual cell or organ in the body. In describing a system, it is important to pay careful attention to the **system boundaries**, i.e., the physical sites of intersection between the system under study and the rest of the world (Figure Box 2.1).

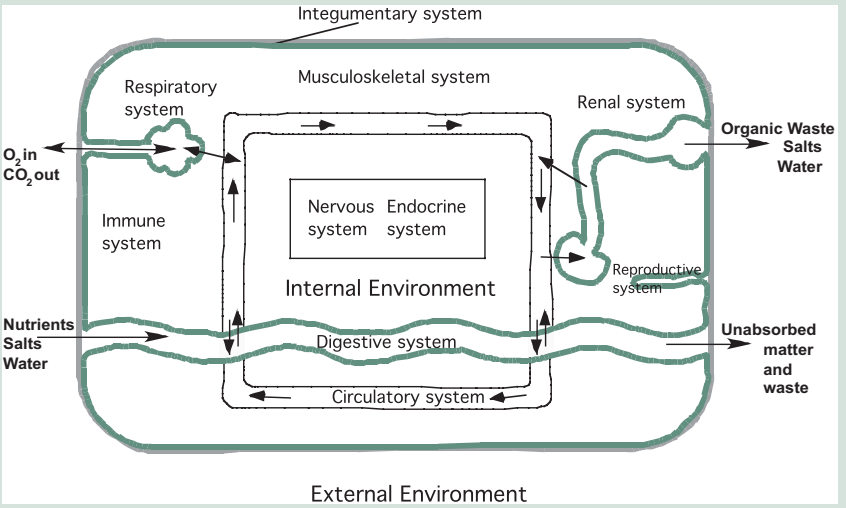
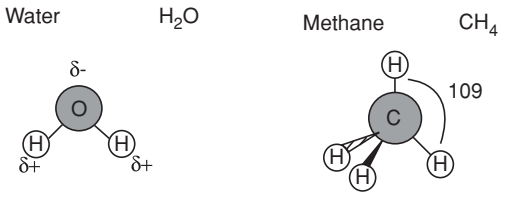


Figure Box 2.1 Schematic diagram of body systems. Notice two methods for defining the system under study: The colored boundary does not include the space inside of the intestinal, reproductive, and urinary systems; the grey boundary does include them. Notice also the arrows, which represent the movement of mass across system boundaries.

Often there are multiple choices for the system boundaries, which lead to alternate descriptions of the system under study. For example, if the system is the human body, the boundary might be defined as the skin and the physical openings between the body and the environment (such as the mouth, nostrils, and urethra). Alternately, the boundary could be the skin and the mucus epithelial surfaces that line the intestinal, respiratory, and reproductive tracts. The engineer is often free to select the system boundary that makes the problem either easier to solve or more interesting. In the first case, the contents of the intestines and lungs would be part of the system; in the second case, they would not be in the system, but instead part of the environment in which the system resides. The boundary selected might depend on the question that the engineer is trying to answer.

This chapter is primarily concerned with chemistry and chemical reactions. When analyzing chemical systems, it is often convenient to define the system as 1 mole of the material of interest. For example, in Box 2.2, the formation of water from atomic hydrogen and oxygen is described. In this example, a convenient system to consider is 1 mole of hydrogen and 1 mole of oxygen.



Polar
Unequal sharing of electrons results in polar distribution of charges

Nonpolar
Charges are distributed symmetrically

Figure 2.3 **Polar and nonpolar molecules.** Water is an example of a polar molecule. The unequal sharing of electrons between oxygen and hydrogen atoms creates a distribution of charge, which creates electrical polarity. The oxygen atom has a partial negative charge ($\delta-$), whereas the two hydrogen atoms are partially positive ($\delta+$). Methane is a nonpolar molecule because the charges are distributed equally; the hydrogens are arranged with equal three-dimensional spacing, each separated by an angle of 109°. The symbol δ indicates a partial charge.

Figure 2.4 **Biomedical engineers design new molecules.** This diagram shows the structure of a polymer built for drug delivery and targeting. A polyamidoamine dendritic polymer (black) with poly(ethylene glycol) arms (blue) attached to the dendrimer via covalent linkages (red). Reproduced from (1) with permission, copyright 2002 American Chemical Society. (See color plate.)

slightly positive (Figure 2.3). This charge difference occurs because oxygen atoms hold on to shared electrons more tightly than do hydrogen atoms. In contrast, a nonpolar molecule, such as methane (CH_4), has uniform and symmetrical charge distribution within the molecule (Figure 2.3).

Biomedical engineers are frequently involved in synthesis of new molecules for medical applications. One example is dendrimers for **gene delivery** (Figure 2.4), which is the act of transferring foreign DNA into a cell. These new agents are created by the formation of new covalent bonds between simple precursor molecules. In the example shown in Figure 2.4, a complex gene delivery molecule is constructed by covalent assembly of a number of simpler starting ingredients. The resulting covalent complex has new properties—such as the ability to bind reversibly to DNA molecules and protect them during entry into a cell—not found in the simpler starting materials.

2.2.2 Molecular bonding

Other types of bonding can occur between molecules (and sometimes between small segments of large molecules, as we will see in Chapter 3, Section 3.3 and Chapter 4, Section 4.2). Two molecules can be weakly attracted to one another through intermolecular forces. These forces may include van der Waals interactions and hydrogen bonding.

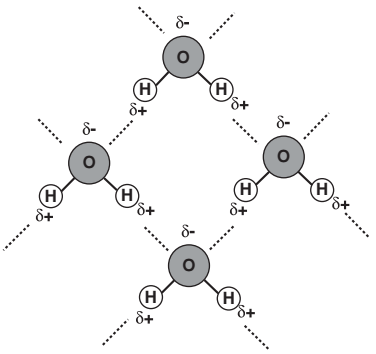


Figure 2.5 **Hydrogen bonding.** Polar water molecules can form hydrogen bonds with each other. Partial positive hydrogen atoms in one water molecule are weakly attracted to partial negative oxygen atoms in another water molecule.

Figure 2.6 **Spider silk.** Spider silk is composed predominantly of proteins. Some spiders make many different kinds of silk, each with a specialized protein composition and unique physical properties. Some spider silks are amazingly strong—stronger than the best man-made materials and more resilient. Hydrogen bonding between parts of the protein contributes to the unusual mechanical properties.

Hydrogen bonding occurs when a partially positive hydrogen atom in a polar molecule is attracted to a slightly negative atom (usually O, N, or F) in a neighboring molecule (Figure 2.5). Hydrogen bonds (1–5 kcal/mol) are much weaker than covalent bonds (50–300 kcal/mol). However, the additive effect of thousands of these weak interactions makes hydrogen bonding an effective glue, which holds molecules—particularly large molecules—together. Chapters 3 and 4 describe the importance of hydrogen bonds in the formation of large molecules—often called **macromolecules** because of their size and their construction from repeated smaller molecular units—such as double-stranded DNA and proteins. Hydrogen bonds are also involved in the formation of **molecular complexes**, or collections of molecules held together often by multiple weak bonds. One such complex occurs in the binding of some molecules to specialized proteins, called **enzymes**, which speed up their chemical conversion to another form (more about enzymes in Chapter 4.4). Spiders are able to manufacture special proteins that form exceptionally strong fibers (Figure 2.6); some forms of spider silk are stronger than steel, but also elastic. Hydrogen bonding interactions between different segments of the spider silk protein appear to be important in creating its unique material properties.

Van der Waals interactions are also weak noncovalent attractions but they are due to temporary and unequal electron distributions around atoms rather than the permanent dipole found in hydrogen-bonded atoms.

2.3 Water: The medium of life

The chemical reactions that drive life occur predominantly in aqueous—or water-rich—environments. For this reason, water is often called "the source of life," but it is also the molecular product of a chemical reaction. Three atoms—two

Figure 2.7 **The unique properties of water.** **A**. Because solid water (ice) is less dense than liquid water, ice floats on the top of water in the ocean, lakes, and streams. **B**. High surface tension of water causes it to bead up on many surfaces (and allows some creatures to walk on water). **C**. Water absorbs a tremendous quantity of heat before it eventually boils.

hydrogens and one oxygen—are held together by covalent bonds to form water. In addition, water can be a product or a reactant in other chemical reactions.

Because the human body is approximately 70% water, it is the ideal environment for these reactions. The extensive hydrogen bonding network that can form between water molecules gives rise to its unique properties. These properties include high melting and boiling temperatures, high surface tension, and a higher density than ice (Figure 2.7).

The ability to form hydrogen bonds also makes water an excellent **solvent**. Water can easily dissolve ions or other polar molecules that are capable of forming hydrogen bonds (Figure 2.5). These water-soluble molecules are referred to as **hydrophilic** ("water loving"). Nonpolar molecules are not easily dissolved in water and are called **hydrophobic** ("water fearing"). Hydrophobic molecules aggregate together to exclude water as best they can: This behavior is often described as the **hydrophobic effect**. As described in Chapter 4, the hydrophobic effect is an important driving force in **protein folding**, the process by which a long macromolecule of amino acids forms a three-dimensional, biologically active protein molecule (Figure 2.8).

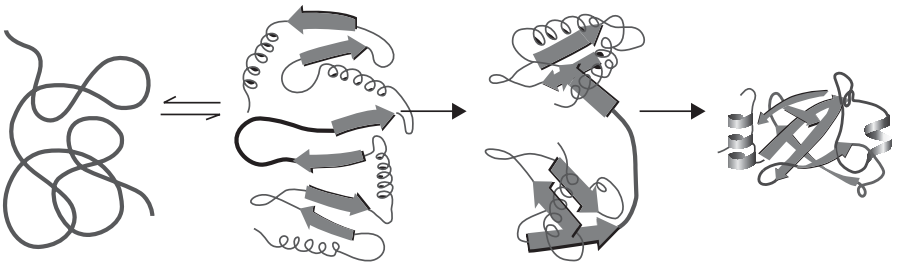


Figure 2.8 **Protein folding.** A polypeptide, which is a macromolecule composed of amino acids, is converted into an active protein by a process known as protein folding, in which the chemical properties of the amino acids within the polymer interact with other amino acids on the chain. The polypeptide is flexible, allowing it to fold into complex three-dimensional shapes. The ultimate shape of the protein depends on interactions between amino acids and their linear sequence along the molecule. Hydrophobic interactions are important in formation of the three-dimensional structure of proteins.

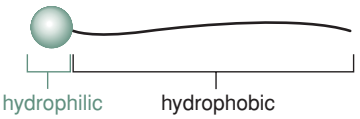


Figure 2.9 **Amphiphilic molecule.** An amphiphilic molecule has both a hydrophilic and a hydrophobic portion within the same molecule.

Molecules that contain both hydrophilic and hydrophobic groups are called **amphiphilic**. For example, phospholipids are amphiphilic molecules (Figure 2.9) that form the plasma membrane surrounding cells (Section 2.7.1). Bioengineers use these kinds of molecules to form complex structures such as the liposomes described earlier (Figure 2.1).

2.4 Biochemical energetics

Humans gain energy through the food that they eat. This energy is stored or expended to sustain life. Running, jumping, and breathing require the activity of muscles; energy must be expended to power these muscles (Figure 2.10). Humans can store energy in the form of molecules such as glycogen and triglycerides within the body. These storage molecules are digested in reactions that release energy when it is needed.

All of the chemical reactions in our bodies result in utilization or accumulation of energy. The factors that determine whether a particular reaction will release energy or require energy are discussed in Box 2.2. It is important to separate the possibility of a reaction occurring (which is considered in Box 2.2) from the rate at which the reaction will proceed (which is considered in Box 2.3). These concepts are related but distinct. Later, in Chapter 4, the rate of biochemical reactions will be considered in more detail. In addition, the role of **enzymes**, which are proteins that are specialized to serve as biological catalysts, or agents that speed up biochemical reactions, will be described.

Figure 2.10 **Human activities require expenditure of energy.** Photo credit: Steve Woltmann, courtesy of Augustana College.

One of the most important chemical reactions for energy utilization in cells involves another molecule, ATP (Figure 2.11). ATP is similar to the nucleotides that make up DNA and RNA, but ATP has three phosphate groups linked together (whereas the nucleotide adenosine of DNA has only one phosphate). The covalent bonds between the phosphate groups are said to be "high energy bonds" because chemical reactions that break these bonds release substantial amounts of energy. A **hydrolysis** reaction is any chemical reaction in which water is a reactant. The hydrolysis of ATP—in which ATP reacts with water to form adenosine

Box 2.2 Thermodynamics of chemical reactions

Water is formed by the reaction of hydrogen atoms and oxygen atoms. The chemical reaction describing the formation of water can be written as:

$$2H_2 + O_2 \rightarrow 2H_2O \qquad \text{(Equation 1)}$$

In this reaction, some covalent bonds are broken and new ones are formed: For example, the bonds that hold the two hydrogen atoms in the stable molecular form of hydrogen (H_2) are broken, and new bonds between O and H are formed. Suppose that a system is defined as 2 moles of hydrogen and 1 mole of oxygen. What is the change in energy of the system, if those 3 moles of hydrogen and oxygen are converted into 2 moles of water? Energy is always released upon formation of a chemical bond, and required for their formation. Therefore, the total energy change for a reaction, such as the reaction in Equation 1, depends on the net energy change for all of the bonds broken and formed. If net energy is released, then the change in bond energy is converted into heat within the system.

Enthalpy is a thermodynamic property of chemicals; the enthalpy of a compound is a measure of the amount of internal energy of the compound.* Therefore, the amount of heat associated with a chemical reaction is equal to the change of internal energy on reaction and depends on the sum of energies released and consumed as bonds are broken and formed in the overall reaction.

The reaction of Equation 1 is an example of a **formation reaction**, in that it describes the formation of the molecule of water from the most stable form of its component atoms. The overall heat of formation—or **enthalpy** change of formation reaction—is a measure of the amount of energy that is either consumed or released when water is formed and is called ΔH_f° (the superscript "o" means that the energy is measured at standard conditions, 25°C and 1 atm). Appendix B contains a table with heats of formation for some compounds: The ΔH_f° is equal to −242 kJ/mole for gaseous water and −286 kJ/mole for liquid water. A negative value of a heat of formation indicates that heat is released when the reaction occurs (the enthalpy of the products is less than the enthalpy of the reactants). The heat of formation for gaseous water indicates that less heat is released to form a gas; this makes sense because some of the heat released by the formation reaction is used to convert the liquid water to the gaseous state.

Heats of formation can be used to calculate the enthalpy change for other kinds of reactions. Consider the more general chemical reaction:

$$aA + bB \rightarrow cC + dD \qquad \text{(Equation 2)}$$

where compounds A and B react to form compounds C and D. The coefficients a, b, c, and d are stoichiometric coefficients, indicating the number of moles of each reactant (or product) consumed (or produced) during the reaction. The overall energy change that occurs in this reaction can be determined from heats of formation (ΔH_f°) (see Figure Box 2.1):

$$\Delta H^\circ = c\Delta H_{f,c}^\circ + d\Delta H_{f,D}^\circ - \left(a\Delta H_{f,A}^\circ + b\Delta H_{f,B}^\circ\right) \qquad \text{(Equation 3)}$$

(continued)

Box 2.2 *(continued)*

The heats of formation ΔH_f° for each of the reactants (A, B) and products (C, D) can be found in tables, such as the one in Appendix B. A negative ΔH° indicates an **exothermic** reaction, in which heat is released as the reaction proceeds. A positive ΔH° means that the reaction absorbs heat, or is **endothermic**.

The **entropy** (S) of a system is a measure of disorder in a system or the amount of energy in a system that cannot be used to do **work**. For any change in state of a system, a change in entropy, or ΔS, can be calculated. The standard entropy change, ΔS°, can be calculated similarly to ΔH° by using standard entropy tables.

The energetics of biochemical reactions are often described in terms of **Gibbs free energy**, G, which is related to both the enthalpy and entropy:

$$\Delta G = \Delta H - T\Delta S \qquad \text{(Equation 4)}$$

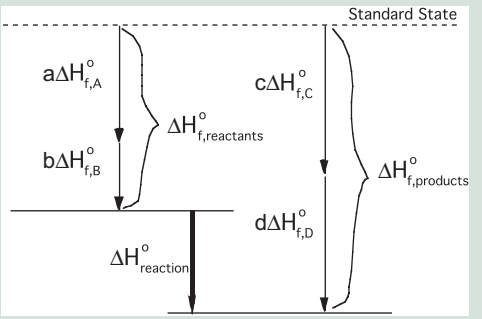
The value of ΔG can be used to predict whether a reaction is favorable under the given conditions:

If ΔG is < 0, the reaction is spontaneous and will proceed.

If ΔG is > 0, the reaction is not favorable and will not proceed without some input of energy.

Consider, for example, a combustion reaction, which is strongly exothermic (i.e., it has a large negative ΔH). Unless $T\Delta S$ is also large and negative—which is unlikely because combustion reactions tend to increase disorder, so ΔS will be positive—the combustion reaction will proceed spontaneously.

Most biological reactions have a positive ΔG, so they do not occur spontaneously. How do the unfavorable reactions proceed? They require an input of energy, which most often comes from the breaking of a high-energy phosphate bond found in a special biochemical called adenosine triphosphate (ATP). ATP hydrolysis, the breakdown by addition of water occurs as follows:



$$ATP + H_2O \rightarrow ADP + P_i \qquad \text{(Equation 5)}$$

This reaction is energetically favorable, with: $\Delta G^\circ = -7.3$ kcal/mol for the reaction in Equation 5. Unfavorable reactions can occur in combination with the ATP hydrolysis reaction (Equation 5); the overall free-energy change is the sum of the ΔG for two reactions. Thus, the negative free energy of ATP hydrolysis can be used to drive a reaction that is energetically unfavorable on its own.

---

* Enthalpy is actually equal to the internal energy of the system plus the product of volume and pressure, which is a measure of the mechanical **work** performed on the systems by the surroundings. For our purposes, it is reasonable to think of enthalpy as a measure of the internal energy.

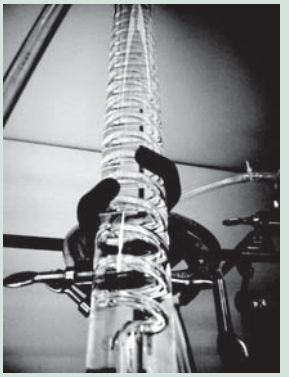
Box 2.3 Kinetics of chemical reactions

Box 2.2 introduced some concepts regarding biochemical reactions, including the amount of heat released or absorbed during reaction, and some methods for determining whether reactions will occur spontaneously. Those concepts are related to the **thermodynamic** behavior of compounds: Thermodynamics is the branch of chemistry that is mainly concerned with states of matter and the ways that they change with pressure, temperature, and volume. The thermodynamic properties described in Box 2.2 indicate changes of state that are possible, how the energy will change as the reaction proceeds, and if a reaction will proceed under certain conditions, but these properties do not indicate the speed or rate of a reaction. Study of rates of reactions or rates of change in chemical systems is called **chemical kinetics**.

To illustrate chemical kinetics, consider the important biochemical reaction between water and carbon dioxide:

$$H_2O + CO_2 \underset{k_r}{\overset{k_f}{\rightleftarrows}} H_2CO_3 \qquad \text{(Equation 1)}$$

Notice that, in Equation 1, a forward reaction (in which carbon dioxide and water react to form carbonic acid) and a reverse reaction (in which carbonic acid dissociates into carbon dioxide and water) are both shown. This notation illustrates that the reaction is **reversible**: It can proceed in either the forward or the reverse direction. In a real system—for example, a closed vessel that was filled with liquid water that contained dissolved carbon dioxide and carbonic acid—both the forward and the reverse reaction would be happening at all times. The net amount of change in the concentration of any of the chemical species would depend on the rate of the forward reaction (which is consuming water and carbon dioxide and generating carbonic acid) and the rate of the reverse reaction (which is doing the opposite).



Rates of chemical reactions are described mathematically by rate constants, usually designated by the symbol k.* In the example of Equation 1, the rate constant for the forward reaction is k_f and the rate constant for the reverse reaction is k_r. The rate of formation of carbonic acid by the forward reaction is determined by the rate constant and the concentrations of the reacting species:

$$Rate_f = k_f\,[H_2O]\,[CO_2] \qquad \text{(Equation 2)}$$

where [X] indicates the concentration of component X. Likewise, the rate of the reverse reaction, which is the rate of formation of water or carbon dioxide by the reverse reaction, can be written:

$$Rate_r = k_r\,[H_2CO_3] \qquad \text{(Equation 3)}$$

To determine the net rate of production of carbonic acid at any given time, one would need to consider both the rate of generation by the forward reaction and the rate of consumption by the reverse reaction:

$$\text{Net Rate of } H_2CO_3 \text{ production} = k_f\,[H_2O]\,[CO_2] - k_r[H_2CO_3] \qquad \text{(Equation 4)}$$

(continued)

Box 2.3 *(continued)*

A reaction reaches **chemical equilibrium** when the forward and reverse reactions are occurring at the same rate; therefore, the concentration of reactants and products stop changing. This phenomenon can be written mathematically; the rate of the forward reaction (Equation 2) is equal to the rate of the reverse reaction (Equation 3), so that $k_f[H_2O][CO_2] = k_r[H_2CO_3]$ or:

$$K = \frac{k_f}{k_r} = \frac{[H_2CO_3]}{[H_2O]\,[CO_2]} \qquad \text{(Equation 5)}$$

This new quantity, the equilibrium constant K, is equal to the ratio of the forward and reverse rate constants. Although this discussion has considered chemical kinetic properties and rates of change, the equilibrium constant is a thermodynamic property: It is a state of matter that represents a stable equilibrium condition. In fact, it can be shown that K is related to the standard free-energy change, ΔG°, for the reaction, which was defined in Box 2.2:

$$\Delta G^\circ = -RT \ln(K) \qquad \text{(Equation 6)}$$

The expression for equilibrium can be written more generally, for the reaction shown in Equation 2 of Box 2.2:

$$K = \frac{k_f}{k_r} = \frac{[C]^c\,[D]^d}{[A]^a\,[B]^b} \qquad \text{(Equation 7)}$$

The equilibrium constant for this more general reaction is still related to the standard free-energy change for the reaction, as described by Equation 6.

* In this example, the reaction rate is assumed to be a **first order reaction**, which means that all of the reaction rates are equal to the rate constant multiplied by the concentration. This assumption is true for many reactions, but not all. The interested reader is referred to other books that discuss reaction rates and rate constants more broadly. When the kinetics of enzyme-catalyzed reactions is considered in Chapter 4, Michaelis Menton kinetics, which is not first order, will be described.

diphosphate (ADP) and an inorganic phosphate—releases 30.5 kJ/mole of energy; that is, the change in Gibbs free energy (defined in Box 2.2) for the reaction shown in Figure 2.11 is $\Delta G^\circ = -30.5$ kJ/mole.

ATP has a number of properties that make it an important and active participant in biochemical energetics. It can be generated efficiently from other energy-rich

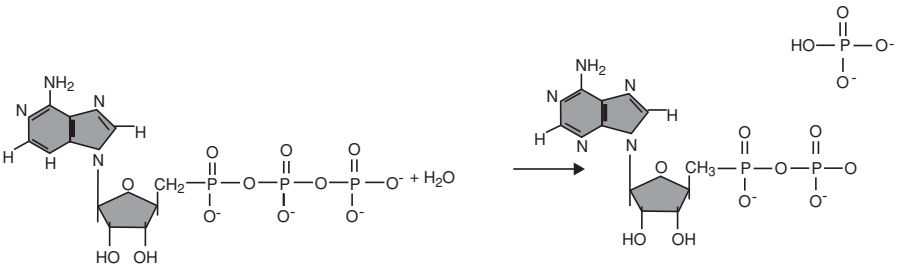


Figure 2.11 Hydrolysis of adenosine-5′-triphosphate (ATP).

Figure 2.12 **Adenosine-5′-triphosphate (ATP) as currency.** It might be helpful to thinking of ATP as the body's instant energy currency. Like cash in your pocket, ATP is ready to be converted into other forms of energy.

substances to serve as a temporary store of energy, and rapidly hydrolyzed to release the stored energy. This ease of conversion makes ATP an excellent currency for efficient, immediate energy exchange. Some people like to think about ATP in analogy to monetary currency, in the sense that the energy stored in macromolecules such as glycogen is similar to money in the bank, whereas ATP is similar to money in your pocket (Figure 2.12).

The generation of inorganic phosphate during ATP hydrolysis is also convenient, in that many biochemical reactions can be coupled to ATP hydrolysis, allowing the energy that is released by ATP conversion to be used to drive an otherwise unfavorable reaction (Figure 2.13). For example, the conversion of glutamic acid to glutamine, an amino acid that is necessary for protein synthesis, does not occur spontaneously:

$$\text{Glutamic acid} + \text{Ammonia} \rightarrow \text{Glutamine} \qquad (2.1)$$

because the change in free energy for the reaction is positive (see Box 2.2). However, if glutamic acid is first converted to an intermediate, glutamyl phosphate, and the phosphate group is provided by an ATP molecule, the conversion of glutamic acid to glutamine can occur in two sequential reactions, both of which do occur spontaneously:

$$\begin{array}{c} \text{Glutamic acid} + \text{ATP} \rightarrow \text{Glutamyl phosphate} + \text{ADP} \\ \text{Glutamyl phosphate} + \text{ammonia} \rightarrow \text{Glutamine} + P_i \\ \hline \text{Glutamic acid} + \text{ATP} + \text{ammonia} \rightarrow \text{Glutamine} + \text{ADP} + P_i \end{array} \qquad (2.2)$$

Equation 2.2 is an example of coupled reactions, in which the energy released by the conversion of ATP to ADP is used to make an energetically unfavorable

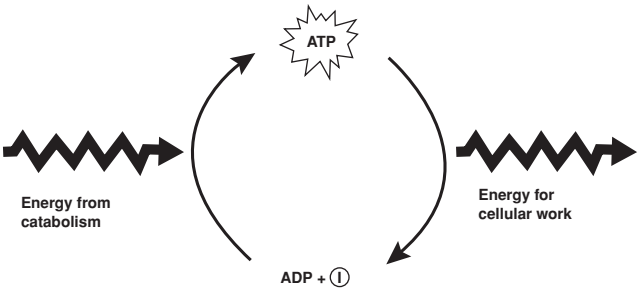


Figure 2.13 **Adenosine-5′-triphosphate (ATP) as an intermediate in metabolism.** ADP, adenosine diphosphate. From http://Fig.cox.miami.edu/~cmallery/150/metab/ATPcycle.jpg.

reaction (one from which the changes in free energy are positive) occur spontaneously. In the rest of this book, there are other examples of reactions that are driven by the hydrolysis of ATP (see Chapter 6, in particular Section 6.2).

For this type of coupling to occur, it is necessary that small amounts of ATP be constantly available in cells throughout the body. In this way, ATP serves as an intermediary in the overall process of conversion of energy from foods to the activities of life. Chapter 7 will describe the generation of ATP from other energy sources derived from food.

SELF-TEST 1 When carbon dioxide dissolves in water, it can react to form carbonic acid according to the reaction: $H_2O(l) + CO_2(aq) \rightarrow H_2CO_3(aq)$. According to the table of standard heats of formation in Appendix B, Table B.2, ΔH_f° for H_2O, CO_2, and H_2CO_3 are -285.8, -393.5, and -699.7 kJ/mole, respectively. Calculate the standard change of enthalpy for this reaction.

ANSWER: $-699.7 - (-285.8 - 393.5)$ kJ/mole $= -20.4$ kJ/mole

2.5 Importance of pH

2.5.1 Hydrogen ions and water

Water dissociates—or breaks down into components—in solution. Dissociation of water produces a hydrogen ion (H^+, which is often called a **proton**, because each hydrogen atom, H, consists of only one proton and one electron, so that H^+—hydrogen without an electron—is a proton), and a hydroxide ion (OH^-):

$$H_2O \rightarrow H^+ + OH^- \tag{2.3}$$

However, free hydrogen ions do not exist in solution; because they are so small and positively charged, protons associate with water (the positively charged proton is attracted to the negative pole of water at the oxygen atom; see Figure 2.5). Equation 2.3a is therefore written:

$$2H_2O \rightarrow H_3O^+ + OH^-, \tag{2.3a}$$

where H_3O^+ is the hydronium ion.

The fraction of water molecules that undergo dissociation is very small. In fact, the concentrations of the dissociated H^+ and OH^- in pure water at 25°C are, respectively, 10^{-7} M and 10^{-7} M. Of course, in pure water, H^+ and OH^- concentration must be the same, because one molecule of each is produced with each water molecule that dissociates. One way to describe the extent of dissociation is to report the number of ions in solution: 10^{-7} M each of H^+ and OH^- in this case. But the use of such small numbers is cumbersome, so an alternate method was developed to report the concentration of H^+ in a solution. A new variable, called pH for "potential of hydrogen," is defined as the negative