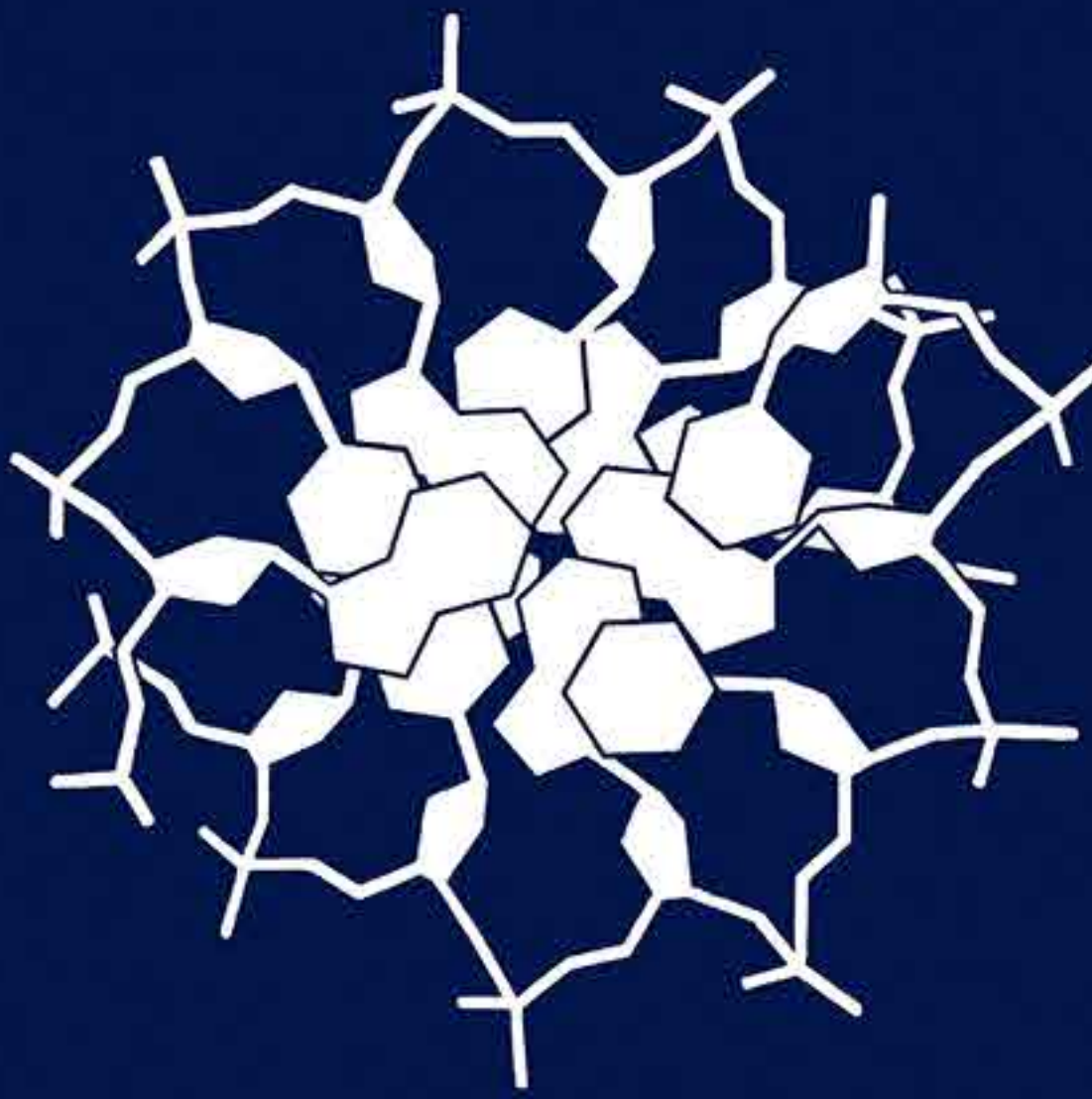
Biochemistry

EIGHTH EDITION



Jeremy M. Berg
John L. Tymoczko
Gregory J. Gatto, Jr
Lubert Stryer

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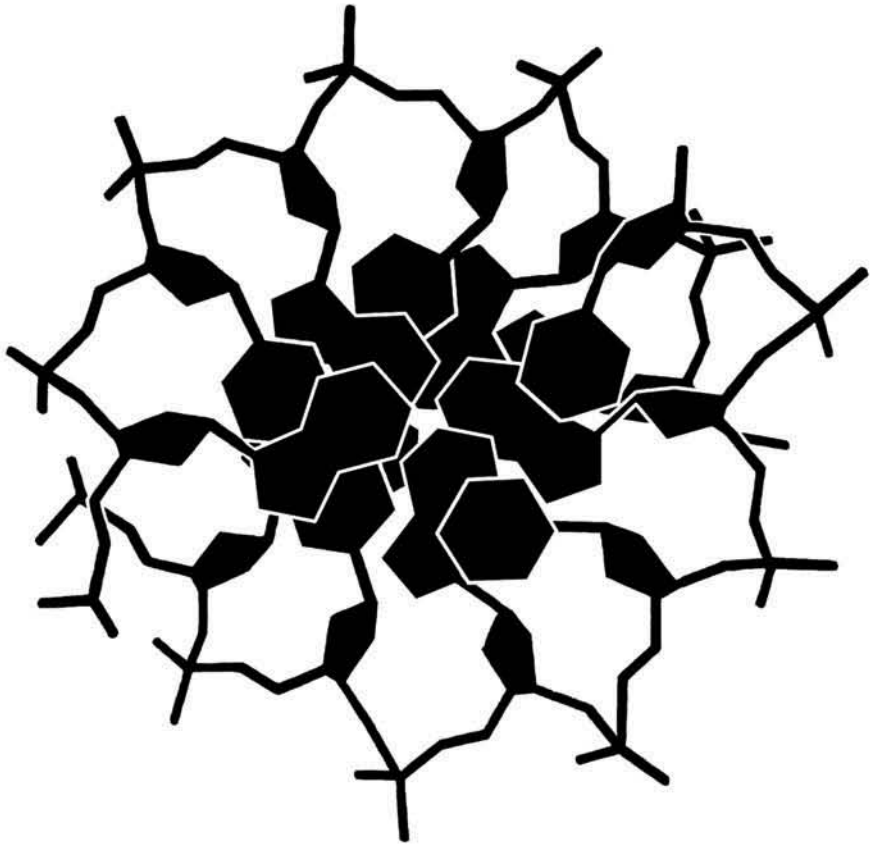

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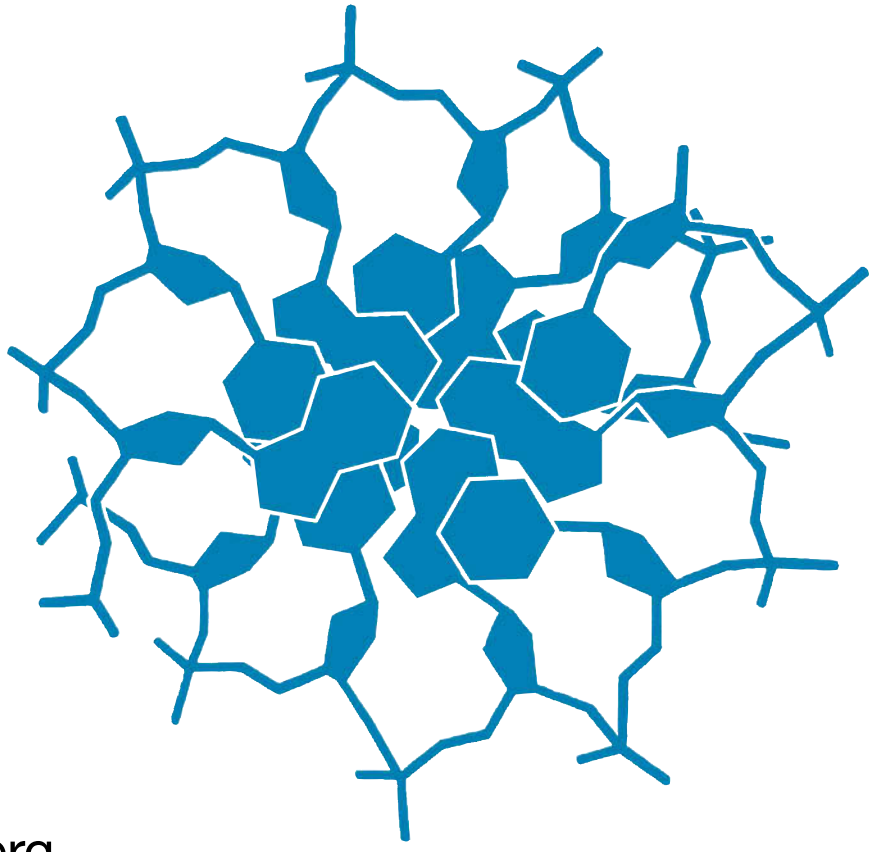

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W. H. Freeman & Company
A Macmillan Education Imprint

Publisher: Kate Ahr Parker
Senior Acquisitions Editor: Lauren Schultz
Developmental Editor: Irene Pech
Editorial Assistants: Shannon Moloney and Nandini Ahuja
Senior Project Editor: Denise Showers with Sherrill Redd
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Media Editor: Donna Brodman
Executive Marketing Manager: Sandy Lindelof
Composition: Aptara®, Inc.
Printing and Binding: RR Donnelley

Library of Congress Control Number: 2014950359

Gregory J. Gatto, Jr., is an employee of GlaxoSmithKline (GSK), which has not supported or funded this work in any way. Any views expressed herein do not necessarily represent the views of GSK.

ISBN-13: 978-1-4641-2610-9
ISBN-10: 1-4641-2610-0

Printed in the United States of America

First printing

W. H. Freeman and Company
41 Madison Avenue
New York, NY 10010

www.whfreeman.com

To our teachers and our students

ABOUT THE AUTHORS

JEREMY M. BERG received his B.S. and M.S. degrees in Chemistry from Stanford (where he did research with Keith Hodgson and Lubert Stryer) and his Ph.D. in Chemistry from Harvard with Richard Holm. He then completed a postdoctoral fellowship with Carl Pabo in Biophysics at Johns Hopkins University School of Medicine. He was an Assistant Professor in the Department of Chemistry at Johns Hopkins from 1986 to 1990. He then moved to Johns Hopkins University School of Medicine as Professor and Director of the Department of Biophysics and Biophysical Chemistry, where he remained until 2003. He then became Director of the National Institute of General Medical Sciences at the National Institutes of Health. In 2011, he moved to the University of Pittsburgh where he is now Professor of Computational and Systems Biology and Pittsburgh Foundation Professor and Director of the Institute for Personalized Medicine. He served as President of the American Society for Biochemistry and Molecular Biology from 2011–2013. He is a Fellow of the American Association for the Advancement of Science and a member of the Institute of Medicine of the National Academy of Sciences. He received the American Chemical Society Award in Pure Chemistry (1994) and the Eli Lilly Award for Fundamental Research in Biological Chemistry (1995), was named Maryland Outstanding Young Scientist of the Year (1995), received the Harrison Howe Award (1997), and received public service awards from the Biophysical Society, the American Society for Biochemistry and Molecular Biology, the American Chemical Society, and the American Society for Cell Biology. He also received numerous teaching awards, including the W. Barry Wood Teaching Award (selected by medical students), the Graduate Student Teaching Award, and the Professor's Teaching Award for the Preclinical Sciences. He is coauthor, with Stephen J. Lippard, of the textbook *Principles of Bioinorganic Chemistry.*

JOHN L. TYMOCZKO is Towsley Professor of Biology at Carleton College, where he has taught since 1976. He currently teaches Biochemistry, Biochemistry Laboratory, Oncogenes and the Molecular Biology of Cancer, and Exercise Biochemistry and coteaches an introductory course, Energy Flow in Biological Systems. Professor Tymoczko received his B.A. from the University of Chicago in 1970 and his Ph.D. in Biochemistry from the University of Chicago with Shutsung Liao at the Ben May Institute for Cancer Research. He then had a postdoctoral position with Hewson Swift of the Department of Biology at the University of Chicago. The focus of his research has been on steroid receptors, ribonucleoprotein particles, and proteolytic processing enzymes.

GREGORY J. GATTO, JR., received his A.B. degree in Chemistry from Princeton University, where he worked with Martin F. Semmelhack and was awarded the Everett S. Wallis Prize in Organic Chemistry. In 2003, he received his M.D. and Ph.D. degrees from the Johns Hopkins University School of Medicine, where he studied the structural biology of peroxisomal targeting signal recognition with Jeremy M. Berg and received the Michael A. Shanoff Young Investigator Research Award. He completed a postdoctoral fellowship in 2006 with Christopher T. Walsh at Harvard Medical School, where he studied the biosynthesis of the macrolide immunosuppressants. He is currently a Senior Scientific Investigator in the Heart Failure Discovery Performance Unit at GlaxoSmithKline.

LUBERT STRYER is Winzer Professor of Cell Biology, Emeritus, in the School of Medicine and Professor of Neurobiology, Emeritus, at Stanford University, where he has been on the faculty since 1976. He received his M.D. from Harvard Medical School. Professor Stryer has received many awards for his research on the interplay of light and life, including the Eli Lilly Award for Fundamental Research in Biological Chemistry, the Distinguished Inventors Award of the Intellectual Property Owners' Association, and election to the National Academy of Sciences and the American Philosophical Society. He was awarded the National Medal of Science in 2006. The publication of his first edition of *Biochemistry* in 1975 transformed the teaching of biochemistry.

PREFACE

For several generations of students and teachers, *Biochemistry* has been an invaluable resource, presenting the concepts and details of molecular structure, metabolism, and laboratory techniques in a streamlined and engaging way. *Biochemistry*'s success in helping students learn the subject for the first time is built on a number of hallmark features:

- **Clear writing and simple illustrations**. The language of biochemistry is made as accessible as possible for students learning the subject for the first time. To complement the straightforward language and organization of concepts in the text, figures illustrate a single concept at a time to help students see main points without the distraction of excess detail.
- **Physiological relevance**. It has always been our goal to help students connect biochemistry to their own lives on a variety of scales. Pathways and processes are presented in a physiological context so students can see how biochemistry works in the body and under different conditions, and Clinical Application sections in every chapter show students how the concepts they are studying impact human health. The eighth edition includes a number of new Clinical Application sections based on recent discoveries in biochemistry and health. (For a full list, see p. xi)
- **Evolutionary perspective**. Discussions of evolution are woven into the narrative of the text, just as evolution shapes every pathway and molecular structure described in the text. Molecular Evolution sections highlight important milestones in the evolution of life as a way to provide context for the processes and molecules being discussed. (For a full list, see p. x)
- **Problem-solving practice**. Every chapter of *Biochemistry* provides numerous opportunities for students to practice problem-solving skills and apply the concepts described in the text. End-of-chapter problems are divided into three categories to address different problem-solving skills: Mechanism problems ask students to suggest or describe a chemical mechanism; Data interpretation problems ask students to draw conclusions from data taken from real research papers; and chapter integration problems require students to connect concepts from across chapters. Further problem-solving practice is provided online, on the *Biochemistry* LaunchPad. (For more details on LaunchPad resources, see p. viii)
- **A variety of molecular structures**. All molecular structures in the book, with few exceptions, have been selected and rendered by Jeremy Berg and Gregory Gatto to emphasize the aspect of structure most important to the topic at hand. Students are introduced to realistic renderings of molecules through a molecular model "primer" in the appendices to Chapters 1 and 2 so they are well-equipped to recognize and interpret the structures throughout the book. Figure legends direct students explicitly to the key features of a model, and often include PDB numbers so the reader can access the file used in generating the structure from the Protein Data Bank website (www.pdb.org). Students

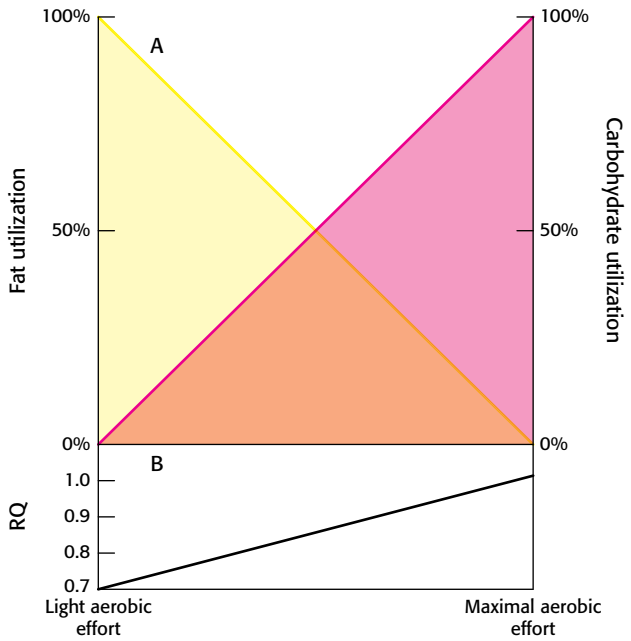

Figure 27.12 An idealized representation of fuels use as a function of aerobic exercise intensity. (A) With increased exercise intensity, the use of fats as fuels falls as the utilization of glucose increases. (B) The respiratory quotient (RQ) measures the alteration in fuel use.

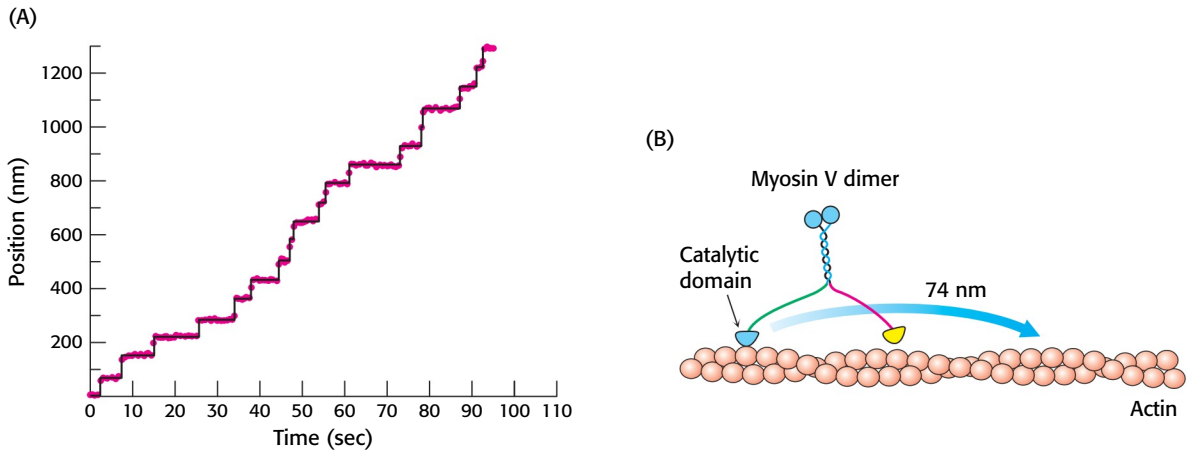

Figure 9.48 Single molecule motion. (A) A trace of the position of a single dimeric myosin V molecule as it moves across a surface coated with actin filaments. (B) A model of how the dimeric molecule moves in discrete steps with an average size of 74 ± 5 nm. [Data from A. Yildiz et al., Science 300(5628)2061–2065, 2003.]

can explore molecular structures further online through the Living Figures, in which they can rotate 3D models of molecules and view alternative renderings.

In this revision of *Biochemistry*, we focused on building on the strengths of the previous editions to present biochemistry in an even more clear and streamlined manner, as well as incorporating exciting new advances from the field. Throughout the book, we have updated explanations of basic concepts and bolstered them with examples from new research. Some new topics that we present in the eighth edition include:

- Environmental factors that influence human biochemistry (Chapter 1)
- Genome editing (Chapter 5)
- Horizontal gene transfer events that may explain unexpected branches of the evolutionary tree (Chapter 6)
- Penicillin irreversibly inactivating a key enzyme in bacterial cell-wall synthesis (Chapter 8)
- Scientists watching single molecules of myosin move (Chapter 9)
- Glycosylation functions in nutrient sensing (Chapter 11)
- The structure of a SNARE complex (Chapter 12)
- The mechanism of ABC transporters (Chapter 13)
- The structure of the gap junction (Chapter 13)
- The structural basis for activation of the β-adrenergic receptor (Chapter 14)
- Excessive fructose consumption can lead to pathological conditions (Chapter 16)
- Alterations in the glycolytic pathway by cancer cells (Chapter 16)
- Regulation of mitochondrial ATP synthase (Chapter 18)
- Control of chloroplast ATP synthase (Chapter 19)
- Activation of rubisco by rubisco activase (Chapter 20)

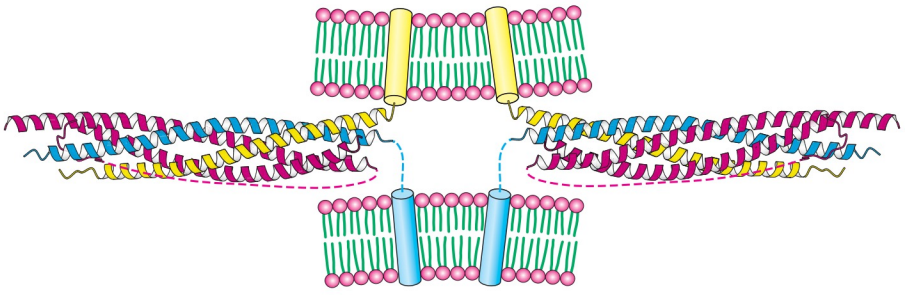

Figure 12.39 SNARE complexes initiate membrane fusion. The SNARE protein synaptobrevin (yellow) from one membrane forms a tight four-helical bundle with the corresponding SNARE proteins syntaxin-1 (blue) and SNAP25 (red) from a second membrane. The complex brings the membranes close together, initiating the fusion event. [Drawn from 1SFC.pdb.]

- The role of the pentose phosphate pathway in rapid cell growth (Chapter 20)
- Biochemical characteristics of muscle fiber types (Chapter 21)
- Alteration of fatty acid metabolism in tumor cells (Chapter 22)
- Biochemical basis of neurological symptoms of phenylketonuria (Chapter 24)
- Ribonucleotide reductase as a chemotherapeutic target (Chapter 25)
- The role of excess choline in the development of heart disease (Chapter 26)
- Cycling of the LDL receptor is regulated (Chapter 26)
- The role of ceramide metabolism in stimulating tumor growth (Chapter 26)
- The extraordinary power of DNA repair systems illustrated by *Deinococcus radiodurans* (Chapter 28)
- The structural details of ligand binding by TLRs (Chapter 34)

LaunchPad

All of the new media resources for *Biochemistry* will be available in our new system.

www.macmillanhighered.com/launchpad/berg8e

LaunchPad is a dynamic, fully integrated learning environment that brings together all of our teaching and learning resources in one place. It also contains the fully interactive **e-Book** and other newly updated resources for students and instructors, including the following:

- **NEW Case Studies** are a series of biochemistry case studies you can integrate into your course. Each case study gives students practice in working with data, developing critical thinking skills, connecting topics, and applying knowledge to real scenarios. We also provide instructional guidance with each case study (with suggestions on how to use the case in the classroom) and aligned assessment questions for quizzes and exams.
- **Newly Updated Clicker Questions** allow instructors to integrate active learning in the classroom and to assess students' understanding of key concepts during lectures. Available in Microsoft Word and PowerPoint (PPT).
- **Newly Updated Lecture PowerPoints** have been developed to minimize preparation time for new users of the book. These files offer suggested lectures including key illustrations and summaries that instructors can adapt to their teaching styles.
  - **Updated Layered PPTs** deconstruct key concepts, sequences, and processes from the textbook images, allowing instructors to present complex ideas step-by-step.
  - **Updated Textbook Images and Tables** are offered as high-resolution JPEG files. Each image has been fully optimized to increase type sizes and adjust color saturation. These images have been tested in a large lecture hall to ensure maximum clarity and visibility.
  - **The Clinical Companion**, by Gregory Raner, The University of North Carolina at Greensboro and Douglas Root, University of North Texas, applies concepts that students have learned in the book to novel medical situations. Students read clinical case studies and use basic biochemistry concepts to solve the medical mysteries, applying and reinforcing what they learn in lecture and from the book.
  - **Hundreds of self-graded practice problems** allow students to test their understanding of concepts explained in the text, with immediate feedback.
  - **The Metabolic Map** helps students understand the principles and applications of the core metabolic pathways. Students can work through guided tutorials with embedded assessment questions, or explore the Metabolic Map on their own using the dragging and zooming functionality of the map.
  - **Jmol tutorials** by Jeffrey Cohlberg, California State University at Long Beach, teach students

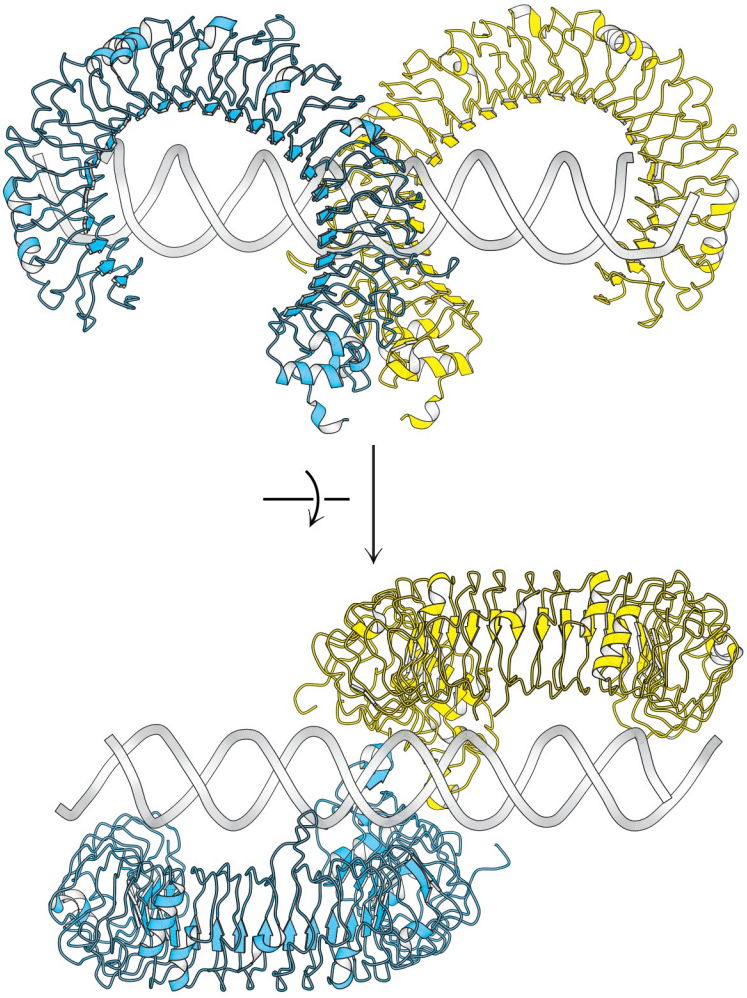

Figure 34.3 Recognition of a PAMP by a Toll-like receptor. The structure of TLR3 bound to its PAMP, a fragment of double-stranded RNA, as seen from the side (top) and from above (bottom). *Notice* that the PAMP induces receptor dimerization by binding the surfaces on the side of each of the extracellular domains. [Drawn from 3CIY.pdb].

how to create models of proteins in Jmol based on data from the Protein Data Bank. By working through the tutorial and answering assessment questions at the end of each exercise, students learn to use this important database and fully realize the relationships between the structure and function of enzymes.

- **Living figures** allow students to explore protein structure in 3-D. Students can zoom and rotate the "live" structures to get a better understanding of their three-dimensional nature and can experiment with different display styles (space-filling, ball-and-stick, ribbon, backbone) by means of a user-friendly interface.
- **Concept-based tutorials** by Neil D. Clarke help students build an intuitive understanding of some of the more difficult concepts covered in the textbook.
- **Animated techniques** help students grasp experimental techniques used for exploring genes and proteins.
- **NEW animations** show students biochemical processes in motion. The eighth edition includes many new animations.
- **Online end-of-chapter questions** are assignable and self-graded multiple-choice versions of the end-of-chapter questions in the book, giving students a way to practice applying chapter content in an online environment.
- **Flashcards** are an interactive tool that allows students to study key terms from the book.
- **LearningCurve** is a self-assessment tool that helps students evaluate their progress. Students can test their understanding by taking an online multiple-choice quiz provided for each chapter, as well as a general chemistry review.

Updated Student Companion

[1-4641-8803-3]

For each chapter of the textbook, the *Student Companion* includes:

- **Chapter Learning Objectives and Summary**
- **Self-Assessment Problems,** including multiple-choice, short-answer, matching questions, and challenge problems, and their answers
- **Expanded Solutions** to end-of-chapter problems in the textbook

MOLECULAR EVOLUTION

This icon signals the start of the many discussions that highlight protein commonalities or other molecular evolutionary insights.

Only L amino acids make up proteins (p. 29)

Why this set of 20 amino acids? (p. 35)

Sickle-cell trait and malaria (p. 206)

Additional human globin genes (p. 208)

Catalytic triads in hydrolytic enzymes (p. 258)

Major classes of peptide-cleaving enzymes (p. 260)

Common catalytic core in type II restriction enzymes (p. 275)

P-loop NTPase domains (p. 280)

Conserved catalytic core in protein kinases (p. 298)

Why do different human blood types exist? (p. 331)

Archaeal membranes (p. 346)

Ion pumps (p. 370)

P-type ATPases (p. 374)

ATP-binding cassettes (p. 374)

Sequence comparisons of Na^+ and Ca^{2+} channels (p. 382)

Small G proteins (p. 414)

Metabolism in the RNA world (p. 444)

Why is glucose a prominent fuel? (p. 451)

NAD^+ binding sites in dehydrogenases (p. 465)

Isozymic forms of lactate dehydrogenase (p. 487)

Evolution of glycolysis and gluconeogenesis (p. 487)

The α-ketoglutarate dehydrogenase complex (p. 505)

Domains of succinyl CoA synthetase (p. 507)

Evolution of the citric acid cycle (p. 516)

Mitochondrial evolution (p. 525)

Conserved structure of cytochrome *c* (p. 541)

Common features of ATP synthase and G proteins (p. 548)

Pigs lack uncoupling protein 1 (UCP-1) and brown fat (p. 556)

Related uncoupling proteins (p. 556)

Chloroplast evolution (p. 568)

Evolutionary origins of photosynthesis (p. 584)

Evolution of the C4 pathway (p. 601)

The relationship of the Calvin cycle and the pentose phosphate pathway (p. 610)

Increasing sophistication of glycogen phosphorylase regulation (p. 629)

Glycogen synthase is homologous to glycogen phosphorylase (p. 631)

A recurring motif in the activation of carboxyl groups (p. 649)

Prokaryotic counterparts of the ubiquitin pathway and the proteasome (p. 686)

A family of pyridoxal-dependent enzymes (p. 692)

Evolution of the urea cycle (p. 696)

The P-loop NTPase domain in nitrogenase (p. 716)

Conserved amino acids in transaminases determine amino acid chirality (p. 721)

Feedback inhibition (p. 731)

Recurring steps in purine ring synthesis (p. 749)

Ribonucleotide reductases (p. 755)

Increase in urate levels during primate evolution (p. 761)

Deinococcus radiodurans illustrates the power of DNA repair systems (p. 828)

DNA polymerases (p. 829)

Thymine and the fidelity of the genetic message (p. 849)

Sigma factors in bacterial transcription (p. 865)

Similarities in transcription between archaea and eukaryotes (p. 876)

Evolution of spliceosome-catalyzed splicing (p. 888)

Classes of aminoacyl-tRNA synthetases (p. 901)

Composition of the primordial ribosome (p. 903)

Homologous G proteins (p. 908)

A family of proteins with common ligand-binding domains (p. 930)

The independent evolution of DNA-binding sites of regulatory proteins (p. 931)

Key principles of gene regulation are similar in bacteria and archaea (p. 937)

CpG islands (p. 949)

Iron-response elements (p. 955)

miRNAs in gene evolution (p. 957)

The odorant-receptor family (p. 963)

Photoreceptor evolution (p. 973)

The immunoglobulin fold (p. 988)

Relationship of tubulin to prokaryotic proteins (p. 1023)

CLINICAL APPLICATIONS

This icon signals the start of a clinical application in the text. Additional, briefer clinical correlations appear in the text as appropriate.

Osteogenesis imperfecta (p. 46)
Protein-misfolding diseases (p. 56)
Protein modification and scurvy (p. 57)
Antigen/antibody detection with ELISA (p. 82)
Synthetic peptides as drugs (p. 92)
PCR in diagnostics and forensics (p.142)
Gene therapy (p. 164)
Aptamers in biotechnology and medicine (p. 187)
Functional magnetic resonance imaging (p. 193)
2,3-BPG and fetal hemoglobin (p. 201)
Carbon monoxide poisoning (p. 201)
Sickle-cell anemia (p. 205)
Thalassemia (p. 207)
Aldehyde dehydrogenase deficiency (p. 228)
Action of penicillin (p. 239)
Protease inhibitors (p. 263)
Carbonic anhydrase and osteopetrosis (p. 264)
Isozymes as a sign of tissue damage (p. 293)
Trypsin inhibitor helps prevent pancreatic damage (p. 302)
Emphysema (p. 303)
Blood clotting involves a cascade of zymogen activations (p. 303)
Vitamin K (p. 306)
Antithrombin and hemorrhage (p. 307)
Hemophilia (p.308)
Monitoring changes in glycosylated hemoglobin (p. 321)
Erythropoietin (p. 327)
Hurler disease (p. 327)
Mucins (p. 329)
Blood groups (p. 331)
I-cell disease (p. 332)
Influenza virus binding (p. 335)
Clinical applications of liposomes (p. 349)
Aspirin and ibuprofen (p. 353)
Digitalis and congestive heart failure (p. 373)
Multidrug resistance (p. 374)
Long QT syndrome (p. 388)
Signal-transduction pathways and cancer (p. 416)
Monoclonal antibodies as anticancer drugs (p. 416)
Protein kinase inhibitors as anticancer drugs (p. 417)
G-proteins, cholera and whooping cough (p. 417)
Vitamins (p. 438)
Triose phosphate isomerase deficiency (p. 454)
Excessive fructose consumption (p. 466)
Lactose intolerance (p. 467)
Galactosemia (p. 468)
Aerobic glycolysis and cancer (p. 474)
Phosphatase deficiency (p. 512)
Defects in the citric acid cycle and the development of cancer (p. 513)
Beriberi and mercury poisoning (p. 515)
Frataxin mutations cause Friedreich's ataxia (p. 531)
Reactive oxygen species (ROS) are implicated in a variety of diseases (p. 539)
ROS may be important in signal transduction (p. 540)
IF1 overexpression and cancer (p. 554)
Brown adipose tissue (p. 555)
Mild uncouplers sought as drugs (p.557)
Mitochondrial diseases (p. 557)
Glucose 6-phosphate dehydrogenase deficiency causes drug-induced hemolytic anemia (p. 610)
Glucose 6-phosphate dehydrogenase deficiency protects against malaria (p. 612)
Developing drugs for type 2 diabetes (p. 636)
Glycogen-storage diseases (p. 637)
Chanarin-Dorfman syndrome (p. 648)
Carnitine deficiency (p. 650)
Zellweger syndrome (p. 657)
Diabetic ketosis (p. 659)
Ketogenic diets to treat epilepsy (p. 660)
Some fatty acids may contribute to pathological conditions (p. 661)
The use of fatty acid synthase inhibitors as drugs (p. 667)
Effects of aspirin on signaling pathways (p. 669)
Diseases resulting from defects in transporters of amino acids (p. 682)
Diseases resulting from defects in E3 proteins (p. 685)
Drugs target the ubiquitin-proteasome system (p.687)
Using proteasome inhibitors to treat tuberculosis (p. 687)
Blood levels of aminotransferases indicate liver damage (p. 691)
Inherited defects of the urea cycle (hyperammonemia) (p. 697)
Alcaptonuria, maple syrup urine disease, and phenylketonuria (p. 705)

High homocysteine levels and vascular disease (p. 726)
Inherited disorders of porphyrin metabolism (p. 737)
Anticancer drugs that block the synthesis of thymidylate (p. 757)
Ribonucleotide reductase is a target for cancer therapy (p. 759)
Adenosine deaminase and severe combined immunodeficiency (p. 760)
Gout (p. 761)
Lesch–Nyhan syndrome (p. 761)
Folic acid and spina bifida (p. 762)
Enzyme activation in some cancers to generate phosphocholine (p. 770)
Excess choline and heart disease (p. 771)
Gangliosides and cholera (p. 773)
Second messengers derived from sphingolipids and diabetes (p. 773)
Respiratory distress syndrome and Tay–Sachs disease (p. 774)
Ceramide metabolism stimulates tumor growth (p. 775)
Phosphatidic acid phosphatase and lipodystrophy (p. 776)
Hypercholesterolemia and atherosclerosis (p. 784)
Mutations in the LDL receptor (p. 785)
LDL receptor cycling is regulated (p. 787)
The role of HDL in protecting against arteriosclerosis (p. 787)
Clinical management of cholesterol levels (p. 788)
Bile salts are derivatives of cholesterol (p. 789)
The cytochrome P450 system is protective (p. 791)
A new protease inhibitor also inhibits a cytochrome P450 enzyme (p. 792)
Aromatase inhibitors in the treatment of breast and ovarian cancer (p. 794)
Rickets and vitamin D (p. 795)
Caloric homeostasis is a means of regulating body weight (p. 802)
The brain plays a key role in caloric homeostasis (p. 804)
Diabetes is a common metabolic disease often resulting from obesity (p. 807)
Exercise beneficially alters the biochemistry of cells (p. 813)
Food intake and starvation induce metabolic changes (p. 816)
Ethanol alters energy metabolism in the liver (p. 819)
Antibiotics that target DNA gyrase (p. 839)
Blocking telomerase to treat cancer (p. 845)
Huntington disease (p. 850)
Defective repair of DNA and cancer (p. 850)
Detection of carcinogens (Ames test) (p. 852)
Translocations can result in diseases (p. 855)
Antibiotic inhibitors of transcription (p. 869)
Burkitt lymphoma and B-cell leukemia (p. 876)
Diseases of defective RNA splicing (p. 884)
Vanishing white matter disease (p. 913)
Antibiotics that inhibit protein synthesis (p. 914)
Diphtheria (p. 914)
Ricin, a lethal protein-synthesis inhibitor (p. 915)
Induced pluripotent stem cells (p. 947)
Anabolic steroids (p. 951)
Color blindness (p. 974)
The use of capsaicin in pain management (p. 978)
Immune-system suppressants (p. 994)
MHC and transplantation rejection (p. 1002)
AIDS (p. 1003)
Autoimmune diseases (p. 1005)
Immune system and cancer (p. 1005)
Vaccines (p. 1006)
Charcot-Marie-Tooth disease (p. 1022)
Taxol (p. 1023)

ACKNOWLEDGMENTS

Writing a popular textbook is both a challenge and an honor. Our goal is to convey to our students our enthusiasm and understanding of a discipline to which we are devoted. They are our inspiration. Consequently, not a word was written or an illustration constructed without the knowledge that bright, engaged students would immediately detect vagueness and ambiguity. We also thank our colleagues who supported, advised, instructed, and simply bore with us during this arduous task. We are grateful to our colleagues throughout the world who patiently answered our questions and shared their insights into recent developments.

We also especially thank those who served as reviewers for this new edition. Their thoughtful comments, suggestions, and encouragement have been of immense help to us in maintaining the excellence of the preceding editions. These reviewers are:

Paul Adams
University of Arkansas, Fayetteville

Kevin Ahern
Oregon State University

Zulfiqar Ahmad
A.T. Still University of Health Sciences

Young-Hoon An
Wayne State University

Richard Amasino
University of Wisconsin

Kenneth Balazovich
University of Michigan

Donald Beitz
Iowa State University

Matthew Berezuk
Azusa Pacific University

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We have been working with the people at W. H. Freeman/Macmillan Higher Education for many years now, and our experiences have always been enjoyable and rewarding. Writing and producing the eighth edition of *Biochemistry* confirmed our belief that they are a wonderful publishing team and we are honored to work with them. Our Macmillan colleagues have a knack for undertaking stressful, but exhilarating, projects and reducing the stress without reducing the exhilaration and a remarkable ability to coax without ever nagging. We have many people to thank for this experience, some of whom are first timers to the *Biochemistry* project.

We are delighted to work with Senior Acquisitions Editor, Lauren Schultz, for the first time. She was unfailing in her enthusiasm and generous with her support. Another new member of the team was our developmental editor, Irene Pech. We have had the pleasure of working with a number of outstanding developmental editors over the years, and Irene continues this tradition. Irene is thoughtful, insightful, and very efficient at identifying aspects of our writing and figures that were less than clear. Lisa Samols, a former developmental editor, served as a consultant, archivist for previous editions, and a general source of publishing knowledge. Senior Project Editor Deni Showers, with Sherrill Redd, managed the flow of the entire project, from copyediting through bound book, with admirable efficiency. Irene Vartanoff and Mercy Heston, our manuscript editors, enhanced the literary consistency and clarity of the text. Vicki Tomaselli, Design Manager, produced a design and layout that makes the book uniquely attractive while still emphasizing its ties to past editions. Photo Editor Christine Buese and Photo Researcher Jacalyn Wong found the photographs that we hope make the text not only more inviting, but also fun to look through. Janice Donnola, Illustration Coordinator, deftly directed the rendering of new illustrations. Paul Rohloff, Production Coordinator, made sure that the significant difficulties of scheduling, composition, and manufacturing were smoothly overcome. Amanda Dunning and Donna Brodman did a wonderful job in their management of the media program. In addition, Amanda ably coordinated the print supplements plan. Special thanks also to editorial assistants Shannon Moloney and Nandini Ahuja. Sandy Lindelof, Executive Marketing Manager, enthusiastically introduced this newest edition of *Biochemistry* to the academic world. We are deeply appreciative of Craig Bleyer and his sales staff for their support. Without their able and enthusiastic presentation of our text to the academic community, all of our efforts would be in vain. We also wish to thank Kate Ahr Parker, Publisher, for her encouragement and belief in us.

Thanks also to our many colleagues at our own institutions as well as throughout the country who patiently answered our questions and encouraged us on our quest. Finally, we owe a debt of gratitude to our families—our wives, Wendie Berg, Alison Unger, and Megan Williams, and our children, especially Timothy and Mark Gatto. Without their support, comfort, and understanding, this endeavor could never have been undertaken, let alone successfully completed.

BRIEF CONTENTS

Part I THE MOLECULAR DESIGN OF LIFE

1 Biochemistry: An Evolving Science 1
2 Protein Composition and Structure 27
3 Exploring Proteins and Proteomes 65
4 DNA, RNA, and the Flow of Genetic Information 105
5 Exploring Genes and Genomes 135
6 Exploring Evolution and Bioinformatics 169
7 Hemoglobin: Portrait of a Protein in Action 191
8 Enzymes: Basic Concepts and Kinetics 215
9 Catalytic Strategies 251
10 Regulatory Strategies 285
11 Carbohydrates 315
12 Lipids and Cell Membranes 341
13 Membrane Channels and Pumps 367
14 Signal-Transduction Pathways 397

Part II TRANSDUCING AND STORING ENERGY

15 Metabolism: Basic Concepts and Design 423
16 Glycolysis and Gluconeogenesis 449
17 The Citric Acid Cycle 495
18 Oxidative Phosphorylation 523
19 The Light Reactions of Photosynthesis 565
20 The Calvin Cycle and the Pentose Phosphate Pathway 589
21 Glycogen Metabolism 617
22 Fatty Acid Metabolism 643
23 Protein Turnover and Amino Acid Catabolism 681

Part III SYNTHESIZING THE MOLECULES OF LIFE

24 The Biosynthesis of Amino Acids 713
25 Nucleotide Biosynthesis 743
26 The Biosynthesis of Membrane Lipids and Steroids 767
27 The Integration of Metabolism 801
28 DNA Replication, Repair, and Recombination 827
29 RNA Synthesis and Processing 859
30 Protein Synthesis 893
31 The Control of Gene Expression in Prokaryotes 925
32 The Control of Gene Expression in Eukaryotes 941

Part IV RESPONDING TO ENVIRONMENTAL CHANGES

33 Sensory Systems 961
34 The Immune System 981
35 Molecular Motors 1011
36 Drug Development 1033

CONTENTS

Preface v

Part I THE MOLECULAR DESIGN OF LIFE 1

CHAPTER 1 Biochemistry: An Evolving Science 1

1.1 Biochemical Unity Underlies Biological Diversity 1
1.2 DNA Illustrates the Interplay Between Form and Function 4
DNA is constructed from four building blocks 4
Two single strands of DNA combine to form a double helix 5
DNA structure explains heredity and the storage of information 5
1.3 Concepts from Chemistry Explain the Properties of Biological Molecules 6
The formation of the DNA double helix as a key example 6
The double helix can form from its component strands 6
Covalent and noncovalent bonds are important for the structure and stability of biological molecules 6
The double helix is an expression of the rules of chemistry 9
The laws of thermodynamics govern the behavior of biochemical systems 10
Heat is released in the formation of the double helix 12
Acid–base reactions are central in many biochemical processes 13
Acid–base reactions can disrupt the double helix 14
Buffers regulate pH in organisms and in the laboratory 15
1.4 The Genomic Revolution Is Transforming Biochemistry, Medicine, and Other Fields 17
Genome sequencing has transformed biochemistry and other fields 17
Environmental factors influence human biochemistry 20
Genome sequences encode proteins and patterns of expression 21
APPENDIX: Visualizing Molecular Structures I: Small Molecules 22

CHAPTER 2 Protein Composition and Structure 27

2.1 Proteins Are Built from a Repertoire of 20 Amino Acids 29
2.2 Primary Structure: Amino Acids Are Linked by Peptide Bonds to Form Polypeptide Chains 35
Proteins have unique amino acid sequences specified by genes 37
Polypeptide chains are flexible yet conformationally restricted 38
2.3 Secondary Structure: Polypeptide Chains Can Fold into Regular Structures Such As the Alpha Helix, the Beta Sheet, and Turns and Loops 40
The alpha helix is a coiled structure stabilized by intrachain hydrogen bonds 40
Beta sheets are stabilized by hydrogen bonding between polypeptide strands 42

Polypeptide chains can change direction by making reverse turns and loops 44
Fibrous proteins provide structural support for cells and tissues 44
2.4 Tertiary Structure: Water-Soluble Proteins Fold into Compact Structures with Nonpolar Cores 46
2.5 Quaternary Structure: Polypeptide Chains Can Assemble into Multisubunit Structures 48
2.6 The Amino Acid Sequence of a Protein Determines Its Three-Dimensional Structure 49
Amino acids have different propensities for forming α helices, β sheets, and turns 51
Protein folding is a highly cooperative process 52
Proteins fold by progressive stabilization of intermediates rather than by random search 53
Prediction of three-dimensional structure from sequence remains a great challenge 54
Some proteins are inherently unstructured and can exist in multiple conformations 55
Protein misfolding and aggregation are associated with some neurological diseases 56
Protein modification and cleavage confer new capabilities 57
APPENDIX: Visualizing Molecular Structures II: Proteins 61

CHAPTER 3 Exploring Proteins and Proteomes 65

The proteome is the functional representation of the genome 66
3.1 The Purification of Proteins Is an Essential First Step in Understanding Their Function 66
The assay: How do we recognize the protein that we are looking for? 67
Proteins must be released from the cell to be purified 67
Proteins can be purified according to solubility, size, charge, and binding affinity 68
Proteins can be separated by gel electrophoresis and displayed 71
A protein purification scheme can be quantitatively evaluated 75
Ultracentrifugation is valuable for separating biomolecules and determining their masses 76
Protein purification can be made easier with the use of recombinant DNA technology 78
3.2 Immunology Provides Important Techniques with Which to Investigate Proteins 79
Antibodies to specific proteins can be generated 79
Monoclonal antibodies with virtually any desired specificity can be readily prepared 80
Proteins can be detected and quantified by using an enzyme-linked immunosorbent assay 82
Western blotting permits the detection of proteins separated by gel electrophoresis 83
Fluorescent markers make the visualization of proteins in the cell possible 84
3.3 Mass Spectrometry Is a Powerful Technique for the Identification of Peptides and Proteins 85
Peptides can be sequenced by mass spectrometry 87
Proteins can be specifically cleaved into small peptides to facilitate analysis 88
Genomic and proteomic methods are complementary 89
The amino acid sequence of a protein provides valuable information 90
Individual proteins can be identified by mass spectrometry 91
3.4 Peptides Can Be Synthesized by Automated Solid-Phase Methods 92
3.5 Three-Dimensional Protein Structure Can Be Determined by X-ray Crystallography and NMR Spectroscopy 95
X-ray crystallography reveals three-dimensional structure in atomic detail 95
Nuclear magnetic resonance spectroscopy can reveal the structures of proteins in solution 97

CHAPTER 4 DNA, RNA, and the Flow of Genetic Information 105

4.1 A Nucleic Acid Consists of Four Kinds of Bases Linked to a Sugar–Phosphate Backbone 106
RNA and DNA differ in the sugar component and one of the bases 106
Nucleotides are the monomeric units of nucleic acids 107
DNA molecules are very long and have directionality 108
4.2 A Pair of Nucleic Acid Strands with Complementary Sequences Can Form a Double-Helical Structure 109
The double helix is stabilized by hydrogen bonds and van der Waals interactions 109
DNA can assume a variety of structural forms 111
Z-DNA is a left-handed double helix in which backbone phosphates zigzag 112
Some DNA molecules are circular and supercoiled 113
Single-stranded nucleic acids can adopt elaborate structures 113
4.3 The Double Helix Facilitates the Accurate Transmission of Hereditary Information 114
Differences in DNA density established the validity of the semiconservative replication hypothesis 115
The double helix can be reversibly melted 116
4.4 DNA Is Replicated by Polymerases That Take Instructions from Templates 117
DNA polymerase catalyzes phosphodiester-bridge formation 117
The genes of some viruses are made of RNA 118
4.5 Gene Expression Is the Transformation of DNA Information into Functional Molecules 119
Several kinds of RNA play key roles in gene expression 119

All cellular RNA is synthesized by RNA polymerases 120
RNA polymerases take instructions from DNA templates 121
Transcription begins near promoter sites and ends at terminator sites 122
Transfer RNAs are the adaptor molecules in protein synthesis 123

4.6 Amino Acids Are Encoded by Groups of Three Bases Starting from a Fixed Point 124
Major features of the genetic code 125
Messenger RNA contains start and stop signals for protein synthesis 126
The genetic code is nearly universal 126

4.7 Most Eukaryotic Genes Are Mosaics of Introns and Exons 127
RNA processing generates mature RNA 127
Many exons encode protein domains 128

CHAPTER 5 Exploring Genes and Genomes 135

5.1 The Exploration of Genes Relies on Key Tools 136
Restriction enzymes split DNA into specific fragments 137
Restriction fragments can be separated by gel electrophoresis and visualized 137
DNA can be sequenced by controlled termination of replication 138
DNA probes and genes can be synthesized by automated solid-phase methods 139
Selected DNA sequences can be greatly amplified by the polymerase chain reaction 141
PCR is a powerful technique in medical diagnostics, forensics, and studies of molecular evolution 142
The tools for recombinant DNA technology have been used to identify disease-causing mutations 143

5.2 Recombinant DNA Technology Has Revolutionized All Aspects of Biology 143
Restriction enzymes and DNA ligase are key tools in forming recombinant DNA molecules 143
Plasmids and λ phage are choice vectors for DNA cloning in bacteria 144
Bacterial and yeast artificial chromosomes 147
Specific genes can be cloned from digests of genomic DNA 147
Complementary DNA prepared from mRNA can be expressed in host cells 149
Proteins with new functions can be created through directed changes in DNA 150
Recombinant methods enable the exploration of the functional effects of disease-causing mutations 152

5.3 Complete Genomes Have Been Sequenced and Analyzed 152
The genomes of organisms ranging from bacteria to multicellular eukaryotes have been sequenced 153
The sequence of the human genome has been completed 154
Next-generation sequencing methods enable the rapid determination of a complete genome sequence 155
Comparative genomics has become a powerful research tool 156

5.4 Eukaryotic Genes Can Be Quantitated and Manipulated with Considerable Precision 157
Gene-expression levels can be comprehensively examined 157
New genes inserted into eukaryotic cells can be efficiently expressed 159
Transgenic animals harbor and express genes introduced into their germ lines 160
Gene disruption and genome editing provide clues to gene function and opportunities for new therapies 160
RNA interference provides an additional tool for disrupting gene expression 162
Tumor-inducing plasmids can be used to introduce new genes into plant cells 163
Human gene therapy holds great promise for medicine 164

CHAPTER 6 Exploring Evolution and Bioinformatics 169

6.1 Homologs Are Descended from a Common Ancestor 170

6.2 Statistical Analysis of Sequence Alignments Can Detect Homology 171
The statistical significance of alignments can be estimated by shuffling 173
Distant evolutionary relationships can be detected through the use of substitution matrices 174
Databases can be searched to identify homologous sequences 177

6.3 Examination of Three-Dimensional Structure Enhances Our Understanding of Evolutionary Relationships 177
Tertiary structure is more conserved than primary structure 178
Knowledge of three-dimensional structures can aid in the evaluation of sequence alignments 179
Repeated motifs can be detected by aligning sequences with themselves 180
Convergent evolution illustrates common solutions to biochemical challenges 181
Comparison of RNA sequences can be a source of insight into RNA secondary structures 182

6.4 Evolutionary Trees Can Be Constructed on the Basis of Sequence Information 183
Horizontal gene transfer events may explain unexpected branches of the evolutionary tree 184

6.5 Modern Techniques Make the Experimental Exploration of Evolution Possible 185
Ancient DNA can sometimes be amplified and sequenced 185
Molecular evolution can be examined experimentally 185

CHAPTER 7 Hemoglobin: Portrait of a Protein in Action 191

7.1 Myoglobin and Hemoglobin Bind Oxygen at Iron Atoms in Heme 192
- Changes in heme electronic structure upon oxygen binding are the basis for functional imaging studies 193
- The structure of myoglobin prevents the release of reactive oxygen species 194
- Human hemoglobin is an assembly of four myoglobin-like subunits 195

7.2 Hemoglobin Binds Oxygen Cooperatively 195
- Oxygen binding markedly changes the quaternary structure of hemoglobin 197
- Hemoglobin cooperativity can be potentially explained by several models 198
- Structural changes at the heme groups are transmitted to the $\alpha_1\beta_1$–$\alpha_2\beta_2$ interface 200
- 2,3-Bisphosphoglycerate in red cells is crucial in determining the oxygen affinity of hemoglobin 200
- Carbon monoxide can disrupt oxygen transport by hemoglobin 201

7.3 Hydrogen Ions and Carbon Dioxide Promote the Release of Oxygen: The Bohr Effect 202

7.4 Mutations in Genes Encoding Hemoglobin Subunits Can Result in Disease 204
- Sickle-cell anemia results from the aggregation of mutated deoxyhemoglobin molecules 205
- Thalassemia is caused by an imbalanced production of hemoglobin chains 207
- The accumulation of free alpha-hemoglobin chains is prevented 207
- Additional globins are encoded in the human genome 208

APPENDIX: Binding Models Can Be Formulated in Quantitative Terms: The Hill Plot and the Concerted Model 210

CHAPTER 8 Enzymes: Basic Concepts and Kinetics 215

8.1 Enzymes are Powerful and Highly Specific Catalysts 216
- Many enzymes require cofactors for activity 217
- Enzymes can transform energy from one form into another 217

8.2 Gibbs Free Energy Is a Useful Thermodynamic Function for Understanding Enzymes 218
- The free-energy change provides information about the spontaneity but not the rate of a reaction 218
- The standard free-energy change of a reaction is related to the equilibrium constant 219
- Enzymes alter only the reaction rate and not the reaction equilibrium 220

8.3 Enzymes Accelerate Reactions by Facilitating the Formation of the Transition State 221
- The formation of an enzyme–substrate complex is the first step in enzymatic catalysis 222
- The active sites of enzymes have some common features 223
- The binding energy between enzyme and substrate is important for catalysis 225

8.4 The Michaelis–Menten Model Accounts for the Kinetic Properties of Many Enzymes 225
- Kinetics is the study of reaction rates 225
- The steady-state assumption facilitates a description of enzyme kinetics 226
- Variations in K_M can have physiological consequences 228
- K_M and V_{max} values can be determined by several means 228
- K_M and V_{max} values are important enzyme characteristics 229
- k_{cat}/K_M is a measure of catalytic efficiency 230
- Most biochemical reactions include multiple substrates 231
- Allosteric enzymes do not obey Michaelis–Menten kinetics 233

8.5 Enzymes Can Be Inhibited by Specific Molecules 234
- The different types of reversible inhibitors are kinetically distinguishable 235
- Irreversible inhibitors can be used to map the active site 237
- Penicillin irreversibly inactivates a key enzyme in bacterial cell-wall synthesis 239
- Transition-state analogs are potent inhibitors of enzymes 240
- Catalytic antibodies demonstrate the importance of selective binding of the transition state to enzymatic activity 241

8.6 Enzymes Can Be Studied One Molecule at a Time 242

APPENDIX: Enzymes are Classified on the Basis of the Types of Reactions That They Catalyze 245

CHAPTER 9 Catalytic Strategies 251
- A few basic catalytic principles are used by many enzymes 252

9.1 Proteases Facilitate a Fundamentally Difficult Reaction 253
- Chymotrypsin possesses a highly reactive serine residue 253
- Chymotrypsin action proceeds in two steps linked by a covalently bound intermediate 254
- Serine is part of a catalytic triad that also includes histidine and aspartate 255
- Catalytic triads are found in other hydrolytic enzymes 258
- The catalytic triad has been dissected by site-directed mutagenesis 260
- Cysteine, aspartyl, and metalloproteases are other major classes of peptide-cleaving enzymes 260
- Protease inhibitors are important drugs 263

9.2 Carbonic Anhydrases Make a Fast Reaction Faster 264
Carbonic anhydrase contains a bound zinc ion essential for catalytic activity 265
Catalysis entails zinc activation of a water molecule 265
A proton shuttle facilitates rapid regeneration of the active form of the enzyme 267

9.3 Restriction Enzymes Catalyze Highly Specific DNA-Cleavage Reactions 269
Cleavage is by in-line displacement of 3′-oxygen from phosphorus by magnesium-activated water 269
Restriction enzymes require magnesium for catalytic activity 271
The complete catalytic apparatus is assembled only within complexes of cognate DNA molecules, ensuring specificity 272
Host-cell DNA is protected by the addition of methyl groups to specific bases 274
Type II restriction enzymes have a catalytic core in common and are probably related by horizontal gene transfer 275

9.4 Myosins Harness Changes in Enzyme Conformation to Couple ATP Hydrolysis to Mechanical Work 275
ATP hydrolysis proceeds by the attack of water on the gamma-phosphoryl group 276
Formation of the transition state for ATP hydrolysis is associated with a substantial conformational change 277
The altered conformation of myosin persists for a substantial period of time 278
Scientists can watch single molecules of myosin move 279
Myosins are a family of enzymes containing P-loop structures 280

CHAPTER 10 Regulatory Strategies 285

10.1 Aspartate Transcarbamoylase Is Allosterically Inhibited by the End Product of Its Pathway 286
Allosterically regulated enzymes do not follow Michaelis–Menten kinetics 287
ATCase consists of separable catalytic and regulatory subunits 287
Allosteric interactions in ATCase are mediated by large changes in quaternary structure 288
Allosteric regulators modulate the T-to-R equilibrium 291

10.2 Isozymes Provide a Means of Regulation Specific to Distinct Tissues and Developmental Stages 292

10.3 Covalent Modification Is a Means of Regulating Enzyme Activity 293
Kinases and phosphatases control the extent of protein phosphorylation 294
Phosphorylation is a highly effective means of regulating the activities of target proteins 296
Cyclic AMP activates protein kinase A by altering the quaternary structure 297
ATP and the target protein bind to a deep cleft in the catalytic subunit of protein kinase A 298

10.4 Many Enzymes Are Activated by Specific Proteolytic Cleavage 299
Chymotrypsinogen is activated by specific cleavage of a single peptide bond 299
Proteolytic activation of chymotrypsinogen leads to the formation of a substrate-binding site 300
The generation of trypsin from trypsinogen leads to the activation of other zymogens 301
Some proteolytic enzymes have specific inhibitors 302
Blood clotting is accomplished by a cascade of zymogen activations 303
Prothrombin requires a vitamin K-dependent modification for activation 304
Fibrinogen is converted by thrombin into a fibrin clot 304
Vitamin K is required for the formation of γ-carboxyglutamate 306
The clotting process must be precisely regulated 307
Hemophilia revealed an early step in clotting 308

CHAPTER 11 Carbohydrates 315

11.1 Monosaccharides Are the Simplest Carbohydrates 316
Many common sugars exist in cyclic forms 318
Pyranose and furanose rings can assume different conformations 320
Glucose is a reducing sugar 321
Monosaccharides are joined to alcohols and amines through glycosidic bonds 322
Phosphorylated sugars are key intermediates in energy generation and biosyntheses 322

11.2 Monosaccharides Are Linked to Form Complex Carbohydrates 323
Sucrose, lactose, and maltose are the common disaccharides 323
Glycogen and starch are storage forms of glucose 324
Cellulose, a structural component of plants, is made of chains of glucose 324

11.3 Carbohydrates Can Be Linked to Proteins to Form Glycoproteins 325
Carbohydrates can be linked to proteins through asparagine (*N*-linked) or through serine or threonine (*O*-linked) residues 326
The glycoprotein erythropoietin is a vital hormone 327
Glycosylation functions in nutrient sensing 327
Proteoglycans, composed of polysaccharides and protein, have important structural roles 327
Proteoglycans are important components of cartilage 328
Mucins are glycoprotein components of mucus 329
Protein glycosylation takes place in the lumen of the endoplasmic reticulum and in the Golgi complex 330

Specific enzymes are responsible for oligosaccharide assembly 331
Blood groups are based on protein glycosylation patterns 331
Errors in glycosylation can result in pathological conditions 332
Oligosaccharides can be "sequenced" 332
11.4 Lectins Are Specific Carbohydrate-Binding Proteins 333
Lectins promote interactions between cells 334
Lectins are organized into different classes 334
Influenza virus binds to sialic acid residues 335

CHAPTER 12 Lipids and Cell Membranes 341

Many common features underlie the diversity of biological membranes 342
12.1 Fatty Acids Are Key Constituents of Lipids 342
Fatty acid names are based on their parent hydrocarbons 342
Fatty acids vary in chain length and degree of unsaturation 343
12.2 There Are Three Common Types of Membrane Lipids 344
Phospholipids are the major class of membrane lipids 344
Membrane lipids can include carbohydrate moieties 345
Cholesterol is a lipid based on a steroid nucleus 346
Archaeal membranes are built from ether lipids with branched chains 346
A membrane lipid is an amphipathic molecule containing a hydrophilic and a hydrophobic moiety 347
12.3 Phospholipids and Glycolipids Readily Form Bimolecular Sheets in Aqueous Media 348
Lipid vesicles can be formed from phospholipids 348
Lipid bilayers are highly impermeable to ions and most polar molecules 349
12.4 Proteins Carry Out Most Membrane Processes 350
Proteins associate with the lipid bilayer in a variety of ways 351
Proteins interact with membranes in a variety of ways 351
Some proteins associate with membranes through covalently attached hydrophobic groups 354
Transmembrane helices can be accurately predicted from amino acid sequences 354
12.5 Lipids and Many Membrane Proteins Diffuse Rapidly in the Plane of the Membrane 356
The fluid mosaic model allows lateral movement but not rotation through the membrane 357
Membrane fluidity is controlled by fatty acid composition and cholesterol content 357
Lipid rafts are highly dynamic complexes formed between cholesterol and specific lipids 358
All biological membranes are asymmetric 358
12.6 Eukaryotic Cells Contain Compartments Bounded by Internal Membranes 359

CHAPTER 13 Membrane Channels and Pumps 367

The expression of transporters largely defines the metabolic activities of a given cell type 368
13.1 The Transport of Molecules Across a Membrane May Be Active or Passive 368
Many molecules require protein transporters to cross membranes 368
Free energy stored in concentration gradients can be quantified 369
13.2 Two Families of Membrane Proteins Use ATP Hydrolysis to Pump Ions and Molecules Across Membranes 370
P-type ATPases couple phosphorylation and conformational changes to pump calcium ions across membranes 370
Digitalis specifically inhibits the Na^+–K^+ pump by blocking its dephosphorylation 373
P-type ATPases are evolutionarily conserved and play a wide range of roles 374
Multidrug resistance highlights a family of membrane pumps with ATP-binding cassette domains 374
13.3 Lactose Permease Is an Archetype of Secondary Transporters That Use One Concentration Gradient to Power the Formation of Another 376
13.4 Specific Channels Can Rapidly Transport Ions Across Membranes 378
Action potentials are mediated by transient changes in Na^+ and K^+ permeability 378
Patch-clamp conductance measurements reveal the activities of single channels 379
The structure of a potassium ion channel is an archetype for many ion-channel structures 379
The structure of the potassium ion channel reveals the basis of ion specificity 380
The structure of the potassium ion channel explains its rapid rate of transport 383
Voltage gating requires substantial conformational changes in specific ion-channel domains 383
A channel can be inactivated by occlusion of the pore: the ball-and-chain model 384
The acetylcholine receptor is an archetype for ligand-gated ion channels 385
Action potentials integrate the activities of several ion channels working in concert 387
Disruption of ion channels by mutations or chemicals can be potentially life-threatening 388
13.5 Gap Junctions Allow Ions and Small Molecules to Flow Between Communicating Cells 389
13.6 Specific Channels Increase the Permeability of Some Membranes to Water 390

CHAPTER 14 Signal-Transduction Pathways 397

Signal transduction depends on molecular circuits 398

14.1 Heterotrimeric G Proteins Transmit Signals and Reset Themselves 399

Ligand binding to 7TM receptors leads to the activation of heterotrimeric G proteins 400

Activated G proteins transmit signals by binding to other proteins 402

Cyclic AMP stimulates the phosphorylation of many target proteins by activating protein kinase A 403

G proteins spontaneously reset themselves through GTP hydrolysis 403

Some 7TM receptors activate the phosphoinositide cascade 404

Calcium ion is a widely used second messenger 405

Calcium ion often activates the regulatory protein calmodulin 407

14.2 Insulin Signaling: Phosphorylation Cascades Are Central to Many Signal-Transduction Processes 407

The insulin receptor is a dimer that closes around a bound insulin molecule 408

Insulin binding results in the cross-phosphorylation and activation of the insulin receptor 408

The activated insulin-receptor kinase initiates a kinase cascade 409

Insulin signaling is terminated by the action of phosphatases 411

14.3 EGF Signaling: Signal-Transduction Pathways Are Poised to Respond 411

EGF binding results in the dimerization of the EGF receptor 411

The EGF receptor undergoes phosphorylation of its carboxyl-terminal tail 413

EGF signaling leads to the activation of Ras, a small G protein 413

Activated Ras initiates a protein kinase cascade 414

EGF signaling is terminated by protein phosphatases and the intrinsic GTPase activity of Ras 414

14.4 Many Elements Recur with Variation in Different Signal-Transduction Pathways 415

14.5 Defects in Signal-Transduction Pathways Can Lead to Cancer and Other Diseases 416

Monoclonal antibodies can be used to inhibit signal-transduction pathways activated in tumors 416

Protein kinase inhibitors can be effective anticancer drugs 417

Cholera and whooping cough are the result of altered G-protein activity 417

Part II TRANSDUCING AND STORING ENERGY

CHAPTER 15 Metabolism: Basic Concepts and Design 423

15.1 Metabolism Is Composed of Many Coupled, Interconnecting Reactions 424

Metabolism consists of energy-yielding and energy-requiring reactions 424

A thermodynamically unfavorable reaction can be driven by a favorable reaction 425

15.2 ATP Is the Universal Currency of Free Energy in Biological Systems 426

ATP hydrolysis is exergonic 426

ATP hydrolysis drives metabolism by shifting the equilibrium of coupled reactions 427

The high phosphoryl potential of ATP results from structural differences between ATP and its hydrolysis products 429

Phosphoryl-transfer potential is an important form of cellular energy transformation 430

15.3 The Oxidation of Carbon Fuels Is an Important Source of Cellular Energy 432

Compounds with high phosphoryl-transfer potential can couple carbon oxidation to ATP synthesis 432

Ion gradients across membranes provide an important form of cellular energy that can be coupled to ATP synthesis 433

Phosphates play a prominent role in biochemical processes 434

Energy from foodstuffs is extracted in three stages 434

15.4 Metabolic Pathways Contain Many Recurring Motifs 435

Activated carriers exemplify the modular design and economy of metabolism 435

Many activated carriers are derived from vitamins 438

Key reactions are reiterated throughout metabolism 440

Metabolic processes are regulated in three principal ways 442

Aspects of metabolism may have evolved from an RNA world 444

CHAPTER 16 Glycolysis and Gluconeogenesis 449

Glucose is generated from dietary carbohydrates 450

Glucose is an important fuel for most organisms 451

16.1 Glycolysis Is an Energy-Conversion Pathway in Many Organisms 451

Hexokinase traps glucose in the cell and begins glycolysis 451

Fructose 1,6-bisphosphate is generated from glucose 6-phosphate 453

The six-carbon sugar is cleaved into two three-carbon fragments 454

Mechanism: Triose phosphate isomerase salvages a three-carbon fragment 455

The oxidation of an aldehyde to an acid powers the formation of a compound with high phosphoryl-transfer potential 457

Mechanism: Phosphorylation is coupled to the oxidation of glyceraldehyde 3-phosphate by a thioester intermediate 458

ATP is formed by phosphoryl transfer from 1,3-bisphosphoglycerate 459

Additional ATP is generated with the formation of pyruvate 460

Two ATP molecules are formed in the conversion of glucose into pyruvate 461

NAD^+ is regenerated from the metabolism of pyruvate 462
Fermentations provide usable energy in the absence of oxygen 464
The binding site for NAD^+ is similar in many dehydrogenases 465
Fructose is converted into glycolytic intermediates by fructokinase 465
Excessive fructose consumption can lead to pathological conditions 466
Galactose is converted into glucose 6-phosphate 466
Many adults are intolerant of milk because they are deficient in lactase 467
Galactose is highly toxic if the transferase is missing 468

16.2 The Glycolytic Pathway Is Tightly Controlled 469
Glycolysis in muscle is regulated to meet the need for ATP 469
The regulation of glycolysis in the liver illustrates the biochemical versatility of the liver 472
A family of transporters enables glucose to enter and leave animal cells 473
Aerobic glycolysis is a property of rapidly growing cells 474
Cancer and endurance training affect glycolysis in a similar fashion 476

16.3 Glucose Can Be Synthesized from Noncarbohydrate Precursors 476
Gluconeogenesis is not a reversal of glycolysis 478
The conversion of pyruvate into phosphoenolpyruvate begins with the formation of oxaloacetate 478
Oxaloacetate is shuttled into the cytoplasm and converted into phosphoenolpyruvate 480
The conversion of fructose 1,6-bisphosphate into fructose 6-phosphate and orthophosphate is an irreversible step 480
The generation of free glucose is an important control point 481
Six high-transfer-potential phosphoryl groups are spent in synthesizing glucose from pyruvate 481

16.4 Gluconeogenesis and Glycolysis Are Reciprocally Regulated 482
Energy charge determines whether glycolysis or gluconeogenesis will be most active 482
The balance between glycolysis and gluconeogenesis in the liver is sensitive to blood-glucose concentration 483
Substrate cycles amplify metabolic signals and produce heat 485
Lactate and alanine formed by contracting muscle are used by other organs 485
Glycolysis and gluconeogenesis are evolutionarily intertwined 487

CHAPTER 17 The Citric Acid Cycle 495

The citric acid cycle harvests high-energy electrons 496

17.1 The Pyruvate Dehydrogenase Complex Links Glycolysis to the Citric Acid Cycle 497
Mechanism: The synthesis of acetyl coenzyme A from pyruvate requires three enzymes and five coenzymes 498
Flexible linkages allow lipoamide to move between different active sites 500

17.2 The Citric Acid Cycle Oxidizes Two-Carbon Units 501
Citrate synthase forms citrate from oxaloacetate and acetyl coenzyme A 502
Mechanism: The mechanism of citrate synthase prevents undesirable reactions 502
Citrate is isomerized into isocitrate 504
Isocitrate is oxidized and decarboxylated to alpha-ketoglutarate 504
Succinyl coenzyme A is formed by the oxidative decarboxylation of alpha-ketoglutarate 505
A compound with high phosphoryl-transfer potential is generated from succinyl coenzyme A 505
Mechanism: Succinyl coenzyme A synthetase transforms types of biochemical energy 506
Oxaloacetate is regenerated by the oxidation of succinate 507
The citric acid cycle produces high-transfer-potential electrons, ATP, and CO_2 508

17.3 Entry to the Citric Acid Cycle and Metabolism Through It Are Controlled 510
The pyruvate dehydrogenase complex is regulated allosterically and by reversible phosphorylation 511
The citric acid cycle is controlled at several points 512
Defects in the citric acid cycle contribute to the development of cancer 513

17.4 The Citric Acid Cycle Is a Source of Biosynthetic Precursors 514
The citric acid cycle must be capable of being rapidly replenished 514
The disruption of pyruvate metabolism is the cause of beriberi and poisoning by mercury and arsenic 515
The citric acid cycle may have evolved from preexisting pathways 516

17.5 The Glyoxylate Cycle Enables Plants and Bacteria to Grow on Acetate 516

CHAPTER 18 Oxidative Phosphorylation 523

18.1 Eukaryotic Oxidative Phosphorylation Takes Place in Mitochondria 524
Mitochondria are bounded by a double membrane 524
Mitochondria are the result of an endosymbiotic event 525

18.2 Oxidative Phosphorylation Depends on Electron Transfer 526
The electron-transfer potential of an electron is measured as redox potential 526
A 1.14-volt potential difference between NADH and molecular oxygen drives electron transport through the chain and favors the formation of a proton gradient 528

18.3 The Respiratory Chain Consists of Four Complexes: Three Proton Pumps and a Physical Link to the Citric Acid Cycle 529
Iron–sulfur clusters are common components of the electron transport chain 531

The high-potential electrons of NADH enter the respiratory chain at NADH-Q oxidoreductase 532
Ubiquinol is the entry point for electrons from $FADH_2$ of flavoproteins 533
Electrons flow from ubiquinol to cytochrome *c* through Q-cytochrome *c* oxidoreductase 533
The Q cycle funnels electrons from a two-electron carrier to a one-electron carrier and pumps protons 535
Cytochrome *c* oxidase catalyzes the reduction of molecular oxygen to water 535
Toxic derivatives of molecular oxygen such as superoxide radicals are scavenged by protective enzymes 538
Electrons can be transferred between groups that are not in contact 540
The conformation of cytochrome *c* has remained essentially constant for more than a billion years 541

18.4 A Proton Gradient Powers the Synthesis of ATP 541
ATP synthase is composed of a proton-conducting unit and a catalytic unit 543
Proton flow through ATP synthase leads to the release of tightly bound ATP: The binding-change mechanism 544
Rotational catalysis is the world's smallest molecular motor 546
Proton flow around the **c** ring powers ATP synthesis 546
ATP synthase and G proteins have several common features 548

18.5 Many Shuttles Allow Movement Across Mitochondrial Membranes 549
Electrons from cytoplasmic NADH enter mitochondria by shuttles 549
The entry of ADP into mitochondria is coupled to the exit of ATP by ATP-ADP translocase 550
Mitochondrial transporters for metabolites have a common tripartite structure 551

18.6 The Regulation of Cellular Respiration Is Governed Primarily by the Need for ATP 552
The complete oxidation of glucose yields about 30 molecules of ATP 552
The rate of oxidative phosphorylation is determined by the need for ATP 553
ATP synthase can be regulated 554
Regulated uncoupling leads to the generation of heat 554
Oxidative phosphorylation can be inhibited at many stages 556
Mitochondrial diseases are being discovered 557
Mitochondria play a key role in apoptosis 557
Power transmission by proton gradients is a central motif of bioenergetics 558

CHAPTER 19 The Light Reactions of Photosynthesis 565
Photosynthesis converts light energy into chemical energy 566

19.1 Photosynthesis Takes Place in Chloroplasts 567
The primary events of photosynthesis take place in thylakoid membranes 567
Chloroplasts arose from an endosymbiotic event 568

19.2 Light Absorption by Chlorophyll Induces Electron Transfer 568
A special pair of chlorophylls initiate charge separation 569
Cyclic electron flow reduces the cytochrome of the reaction center 572

19.3 Two Photosystems Generate a Proton Gradient and NADPH in Oxygenic Photosynthesis 572
Photosystem II transfers electrons from water to plastoquinone and generates a proton gradient 572
Cytochrome *bf* links photosystem II to photosystem I 575
Photosystem I uses light energy to generate reduced ferredoxin, a powerful reductant 575
Ferredoxin–$NADP^+$ reductase converts $NADP^+$ into NADPH 576

19.4 A Proton Gradient across the Thylakoid Membrane Drives ATP Synthesis 578
The ATP synthase of chloroplasts closely resembles those of mitochondria and prokaryotes 578
The activity of chloroplast ATP synthase is regulated 579
Cyclic electron flow through photosystem I leads to the production of ATP instead of NADPH 580
The absorption of eight photons yields one O_2, two NADPH, and three ATP molecules 581

19.5 Accessory Pigments Funnel Energy into Reaction Centers 581
Resonance energy transfer allows energy to move from the site of initial absorbance to the reaction center 582
The components of photosynthesis are highly organized 583
Many herbicides inhibit the light reactions of photosynthesis 584

19.6 The Ability to Convert Light into Chemical Energy Is Ancient 584
Artificial photosynthetic systems may provide clean, renewable energy 585

CHAPTER 20 The Calvin Cycle and the Pentose Phosphate Pathway 589

20.1 The Calvin Cycle Synthesizes Hexoses from Carbon Dioxide and Water 590
Carbon dioxide reacts with ribulose 1,5-bisphosphate to form two molecules of 3-phosphoglycerate 591
Rubisco activity depends on magnesium and carbamate 592
Rubisco activase is essential for rubisco activity 593
Rubisco also catalyzes a wasteful oxygenase reaction: Catalytic imperfection 593
Hexose phosphates are made from phosphoglycerate, and ribulose 1,5-bisphosphate is regenerated 594
Three ATP and two NADPH molecules are used to bring carbon dioxide to the level of a hexose 597
Starch and sucrose are the major carbohydrate stores in plants 597

20.2 The Activity of the Calvin Cycle Depends on Environmental Conditions 598

Rubisco is activated by light-driven changes in proton and magnesium ion concentrations 598
Thioredoxin plays a key role in regulating the Calvin cycle 599
The C_4 pathway of tropical plants accelerates photosynthesis by concentrating carbon dioxide 599
Crassulacean acid metabolism permits growth in arid ecosystems 601

20.3 The Pentose Phosphate Pathway Generates NADPH and Synthesizes Five-Carbon Sugars 601
Two molecules of NADPH are generated in the conversion of glucose 6-phosphate into ribulose 5-phosphate 602
The pentose phosphate pathway and glycolysis are linked by transketolase and transaldolase 602
Mechanism: Transketolase and transaldolase stabilize carbanionic intermediates by different mechanisms 605

20.4 The Metabolism of Glucose 6-Phosphate by the Pentose Phosphate Pathway Is Coordinated with Glycolysis 607
The rate of the pentose phosphate pathway is controlled by the level of $NADP^+$ 607
The flow of glucose 6-phosphate depends on the need for NADPH, ribose 5-phosphate, and ATP 608
The pentose phosphate pathway is required for rapid cell growth 610
Through the looking-glass: The Calvin cycle and the pentose phosphate pathway are mirror images 610

20.5 Glucose 6-Phosphate Dehydrogenase Plays a Key Role in Protection Against Reactive Oxygen Species 610
Glucose 6-phosphate dehydrogenase deficiency causes a drug-induced hemolytic anemia 610
A deficiency of glucose 6-phosphate dehydrogenase confers an evolutionary advantage in some circumstances 612

CHAPTER 21 Glycogen Metabolism 617
Glycogen metabolism is the regulated release and storage of glucose 618

21.1 Glycogen Breakdown Requires the Interplay of Several Enzymes 619
Phosphorylase catalyzes the phosphorolytic cleavage of glycogen to release glucose 1-phosphate 619
Mechanism: Pyridoxal phosphate participates in the phosphorolytic cleavage of glycogen 620
A debranching enzyme also is needed for the breakdown of glycogen 621
Phosphoglucomutase converts glucose 1-phosphate into glucose 6-phosphate 622
The liver contains glucose 6-phosphatase, a hydrolytic enzyme absent from muscle 622

21.2 Phosphorylase Is Regulated by Allosteric Interactions and Reversible Phosphorylation 623
Liver phosphorylase produces glucose for use by other tissues 623
Muscle phosphorylase is regulated by the intracellular energy charge 625
Biochemical characteristics of muscle fiber types differ 625
Phosphorylation promotes the conversion of phosphorylase *b* to phosphorylase *a* 626
Phosphorylase kinase is activated by phosphorylation and calcium ions 626

21.3 Epinephrine and Glucagon Signal the Need for Glycogen Breakdown 627
G proteins transmit the signal for the initiation of glycogen breakdown 627
Glycogen breakdown must be rapidly turned off when necessary 629
The regulation of glycogen phosphorylase became more sophisticated as the enzyme evolved 629

21.4 Glycogen Is Synthesized and Degraded by Different Pathways 630
UDP-glucose is an activated form of glucose 630
Glycogen synthase catalyzes the transfer of glucose from UDP-glucose to a growing chain 630
A branching enzyme forms α-1,6 linkages 631
Glycogen synthase is the key regulatory enzyme in glycogen synthesis 632
Glycogen is an efficient storage form of glucose 632

21.5 Glycogen Breakdown and Synthesis Are Reciprocally Regulated 632
Protein phosphatase 1 reverses the regulatory effects of kinases on glycogen metabolism 633
Insulin stimulates glycogen synthesis by inactivating glycogen synthase kinase 635
Glycogen metabolism in the liver regulates the blood-glucose level 635
A biochemical understanding of glycogen-storage diseases is possible 637

CHAPTER 22 Fatty Acid Metabolism 643
Fatty acid degradation and synthesis mirror each other in their chemical reactions 644

22.1 Triacylglycerols Are Highly Concentrated Energy Stores 645
Dietary lipids are digested by pancreatic lipases 645
Dietary lipids are transported in chylomicrons 646

22.2 The Use of Fatty Acids as Fuel Requires Three Stages of Processing 647
Triacylglycerols are hydrolyzed by hormone-stimulated lipases 647
Free fatty acids and glycerol are released into the blood 648
Fatty acids are linked to coenzyme A before they are oxidized 648
Carnitine carries long-chain activated fatty acids into the mitochondrial matrix 649
Acetyl CoA, NADH, and $FADH_2$ are generated in each round of fatty acid oxidation 650

The complete oxidation of palmitate yields 106 molecules of ATP 652

22.3 Unsaturated and Odd-Chain Fatty Acids Require Additional Steps for Degradation 652

An isomerase and a reductase are required for the oxidation of unsaturated fatty acids 652
Odd-chain fatty acids yield propionyl CoA in the final thiolysis step 654
Vitamin B_{12} contains a corrin ring and a cobalt atom 654
Mechanism: Methylmalonyl CoA mutase catalyzes a rearrangement to form succinyl CoA 655
Fatty acids are also oxidized in peroxisomes 656
Ketone bodies are formed from acetyl CoA when fat breakdown predominates 657
Ketone bodies are a major fuel in some tissues 658
Animals cannot convert fatty acids into glucose 660
Some fatty acids may contribute to the development of pathological conditions 661

22.4 Fatty Acids Are Synthesized by Fatty Acid Synthase 661

Fatty acids are synthesized and degraded by different pathways 661
The formation of malonyl CoA is the committed step in fatty acid synthesis 662
Intermediates in fatty acid synthesis are attached to an acyl carrier protein 662
Fatty acid synthesis consists of a series of condensation, reduction, dehydration, and reduction reactions 662
Fatty acids are synthesized by a multifunctional enzyme complex in animals 664
The synthesis of palmitate requires 8 molecules of acetyl CoA, 14 molecules of NADPH, and 7 molecules of ATP 666
Citrate carries acetyl groups from mitochondria to the cytoplasm for fatty acid synthesis 666
Several sources supply NADPH for fatty acid synthesis 667
Fatty acid metabolism is altered in tumor cells 667

22.5 The Elongation and Unsaturation of Fatty Acids are Accomplished by Accessory Enzyme Systems 668

Membrane-bound enzymes generate unsaturated fatty acids 668
Eicosanoid hormones are derived from polyunsaturated fatty acids 669
Variations on a theme: Polyketide and nonribosomal peptide synthetases resemble fatty acid synthase 670

22.6 Acetyl CoA Carboxylase Plays a Key Role in Controlling Fatty Acid Metabolism 670

Acetyl CoA carboxylase is regulated by conditions in the cell 671
Acetyl CoA carboxylase is regulated by a variety of hormones 671

CHAPTER 23 Protein Turnover and Amino Acid Catabolism 681

23.1 Proteins are Degraded to Amino Acids 682

The digestion of dietary proteins begins in the stomach and is completed in the intestine 682
Cellular proteins are degraded at different rates 682

23.2 Protein Turnover Is Tightly Regulated 683

Ubiquitin tags proteins for destruction 683
The proteasome digests the ubiquitin-tagged proteins 685
The ubiquitin pathway and the proteasome have prokaryotic counterparts 686
Protein degradation can be used to regulate biological function 687

23.3 The First Step in Amino Acid Degradation Is the Removal of Nitrogen 687

Alpha-amino groups are converted into ammonium ions by the oxidative deamination of glutamate 687
Mechanism: Pyridoxal phosphate forms Schiff-base intermediates in aminotransferases 689
Aspartate aminotransferase is an archetypal pyridoxal-dependent transaminase 690
Blood levels of aminotransferases serve a diagnostic function 691
Pyridoxal phosphate enzymes catalyze a wide array of reactions 691
Serine and threonine can be directly deaminated 692
Peripheral tissues transport nitrogen to the liver 692

23.4 Ammonium Ion Is Converted into Urea in Most Terrestrial Vertebrates 693

The urea cycle begins with the formation of carbamoyl phosphate 693
Carbamoyl phosphate synthetase is the key regulatory enzyme for urea synthesis 694
Carbamoyl phosphate reacts with ornithine to begin the urea cycle 694
The urea cycle is linked to gluconeogenesis 696
Urea-cycle enzymes are evolutionarily related to enzymes in other metabolic pathways 696
Inherited defects of the urea cycle cause hyperammonemia and can lead to brain damage 697
Urea is not the only means of disposing of excess nitrogen 698

23.5 Carbon Atoms of Degraded Amino Acids Emerge as Major Metabolic Intermediates 698

Pyruvate is an entry point into metabolism for a number of amino acids 699
Oxaloacetate is an entry point into metabolism for aspartate and asparagine 700
Alpha-ketoglutarate is an entry point into metabolism for five-carbon amino acids 700
Succinyl coenzyme A is a point of entry for several nonpolar amino acids 701
Methionine degradation requires the formation of a key methyl donor, *S*-adenosylmethionine 701
The branched-chain amino acids yield acetyl CoA, acetoacetate, or propionyl CoA 701
Oxygenases are required for the degradation of aromatic amino acids 703

23.6 Inborn Errors of Metabolism Can Disrupt Amino Acid Degradation 705

Phenylketonuria is one of the most common metabolic disorders 706
Determining the basis of the neurological symptoms of phenylketonuria is an active area of research 706

Part III SYNTHESIZING THE MOLECULES OF LIFE

CHAPTER 24 The Biosynthesis of Amino Acids 713

Amino acid synthesis requires solutions to three key biochemical problems 714

24.1 Nitrogen Fixation: Microorganisms Use ATP and a Powerful Reductant to Reduce Atmospheric Nitrogen to Ammonia 714

The iron–molybdenum cofactor of nitrogenase binds and reduces atmospheric nitrogen 715

Ammonium ion is assimilated into an amino acid through glutamate and glutamine 717

24.2 Amino Acids Are Made from Intermediates of the Citric Acid Cycle and Other Major Pathways 719

Human beings can synthesize some amino acids but must obtain others from their diet 719

Aspartate, alanine, and glutamate are formed by the addition of an amino group to an alpha-ketoacid 720

A common step determines the chirality of all amino acids 721

The formation of asparagine from aspartate requires an adenylated intermediate 721

Glutamate is the precursor of glutamine, proline, and arginine 722

3-Phosphoglycerate is the precursor of serine, cysteine, and glycine 722

Tetrahydrofolate carries activated one-carbon units at several oxidation levels 723

S-Adenosylmethionine is the major donor of methyl groups 724

Cysteine is synthesized from serine and homocysteine 726

High homocysteine levels correlate with vascular disease 726

Shikimate and chorismate are intermediates in the biosynthesis of aromatic amino acids 727

Tryptophan synthase illustrates substrate channeling in enzymatic catalysis 729

24.3 Feedback Inhibition Regulates Amino Acid Biosynthesis 730

Branched pathways require sophisticated regulation 731

The sensitivity of glutamine synthetase to allosteric regulation is altered by covalent modification 732

24.4 Amino Acids Are Precursors of Many Biomolecules 734

Glutathione, a gamma-glutamyl peptide, serves as a sulfhydryl buffer and an antioxidant 734

Nitric oxide, a short-lived signal molecule, is formed from arginine 735

Porphyrins are synthesized from glycine and succinyl coenzyme A 736

Porphyrins accumulate in some inherited disorders of porphyrin metabolism 737

CHAPTER 25 Nucleotide Biosynthesis 743

Nucleotides can be synthesized by de novo or salvage pathways 744

25.1 The Pyrimidine Ring Is Assembled de Novo or Recovered by Salvage Pathways 744

Bicarbonate and other oxygenated carbon compounds are activated by phosphorylation 745

The side chain of glutamine can be hydrolyzed to generate ammonia 745

Intermediates can move between active sites by channeling 745

Orotate acquires a ribose ring from PRPP to form a pyrimidine nucleotide and is converted into uridylate 746

Nucleotide mono-, di-, and triphosphates are interconvertible 747

CTP is formed by amination of UTP 747

Salvage pathways recycle pyrimidine bases 748

25.2 Purine Bases Can Be Synthesized de Novo or Recycled by Salvage Pathways 748

The purine ring system is assembled on ribose phosphate 749

The purine ring is assembled by successive steps of activation by phosphorylation followed by displacement 749

AMP and GMP are formed from IMP 751

Enzymes of the purine synthesis pathway associate with one another in vivo 752

Salvage pathways economize intracellular energy expenditure 752

25.3 Deoxyribonucleotides Are Synthesized by the Reduction of Ribonucleotides Through a Radical Mechanism 753

Mechanism: A tyrosyl radical is critical to the action of ribonucleotide reductase 753

Stable radicals other than tyrosyl radical are employed by other ribonucleotide reductases 755

Thymidylate is formed by the methylation of deoxyuridylate 755

Dihydrofolate reductase catalyzes the regeneration of tetrahydrofolate, a one-carbon carrier 756

Several valuable anticancer drugs block the synthesis of thymidylate 757

25.4 Key Steps in Nucleotide Biosynthesis Are Regulated by Feedback Inhibition 758

Pyrimidine biosynthesis is regulated by aspartate transcarbamoylase 758

The synthesis of purine nucleotides is controlled by feedback inhibition at several sites 758

The synthesis of deoxyribonucleotides is controlled by the regulation of ribonucleotide reductase 759

25.5 Disruptions in Nucleotide Metabolism Can Cause Pathological Conditions 760

The loss of adenosine deaminase activity results in severe combined immunodeficiency 760

Gout is induced by high serum levels of urate 761

Lesch–Nyhan syndrome is a dramatic consequence of mutations in a salvage-pathway enzyme 761

Folic acid deficiency promotes birth defects such as spina bifida 762

CHAPTER 26 The Biosynthesis of Membrane Lipids and Steroids 767

26.1 Phosphatidate Is a Common Intermediate in the Synthesis of Phospholipids and Triacylglycerols 768
- The synthesis of phospholipids requires an activated intermediate 769
- Some phospholipids are synthesized from an activated alcohol 770
- Phosphatidylcholine is an abundant phospholipid 770
- Excess choline is implicated in the development of heart disease 771
- Base-exchange reactions can generate phospholipids 771
- Sphingolipids are synthesized from ceramide 772
- Gangliosides are carbohydrate-rich sphingolipids that contain acidic sugars 772
- Sphingolipids confer diversity on lipid structure and function 773
- Respiratory distress syndrome and Tay–Sachs disease result from the disruption of lipid metabolism 774
- Ceramide metabolism stimulates tumor growth 774
- Phosphatidic acid phosphatase is a key regulatory enzyme in lipid metabolism 775

26.2 Cholesterol Is Synthesized from Acetyl Coenzyme A in Three Stages 776
- The synthesis of mevalonate, which is activated as isopentenyl pyrophosphate, initiates the synthesis of cholesterol 776
- Squalene (C_{30}) is synthesized from six molecules of isopentenyl pyrophosphate (C_5) 777
- Squalene cyclizes to form cholesterol 778

26.3 The Complex Regulation of Cholesterol Biosynthesis Takes Place at Several Levels 779
- Lipoproteins transport cholesterol and triacylglycerols throughout the organism 782
- Low-density lipoproteins play a central role in cholesterol metabolism 784
- The absence of the LDL receptor leads to hypercholesterolemia and atherosclerosis 784
- Mutations in the LDL receptor prevent LDL release and result in receptor destruction 785
- Cycling of the LDL receptor is regulated 787
- HDL appears to protect against atherosclerosis 787
- The clinical management of cholesterol levels can be understood at a biochemical level 788

26.4 Important Derivatives of Cholesterol Include Bile Salts and Steroid Hormones 788
- Letters identify the steroid rings and numbers identify the carbon atoms 790
- Steroids are hydroxylated by cytochrome P450 monooxygenases that use NADPH and O_2 790
- The cytochrome P450 system is widespread and performs a protective function 791
- Pregnenolone, a precursor of many other steroids, is formed from cholesterol by cleavage of its side chain 792
- Progesterone and corticosteroids are synthesized from pregnenolone 792
- Androgens and estrogens are synthesized from pregnenolone 792
- Vitamin D is derived from cholesterol by the ring-splitting activity of light 794

CHAPTER 27 The Integration of Metabolism 801

27.1 Caloric Homeostasis Is a Means of Regulating Body Weight 802

27.2 The Brain Plays a Key Role in Caloric Homeostasis 804
- Signals from the gastrointestinal tract induce feelings of satiety 804
- Leptin and insulin regulate long-term control over caloric homeostasis 805
- Leptin is one of several hormones secreted by adipose tissue 806
- Leptin resistance may be a contributing factor to obesity 806
- Dieting is used to combat obesity 807

27.3 Diabetes Is a Common Metabolic Disease Often Resulting from Obesity 807
- Insulin initiates a complex signal-transduction pathway in muscle 808
- Metabolic syndrome often precedes type 2 diabetes 809
- Excess fatty acids in muscle modify metabolism 810
- Insulin resistance in muscle facilitates pancreatic failure 810
- Metabolic derangements in type 1 diabetes result from insulin insufficiency and glucagon excess 812

27.4 Exercise Beneficially Alters the Biochemistry of Cells 813
- Mitochondrial biogenesis is stimulated by muscular activity 813
- Fuel choice during exercise is determined by the intensity and duration of activity 813

27.5 Food Intake and Starvation Induce Metabolic Changes 816
- The starved–fed cycle is the physiological response to a fast 816
- Metabolic adaptations in prolonged starvation minimize protein degradation 818

27.6 Ethanol Alters Energy Metabolism in the Liver 819
- Ethanol metabolism leads to an excess of NADH 820
- Excess ethanol consumption disrupts vitamin metabolism 821

CHAPTER 28 DNA Replication, Repair, and Recombination 827

28.1 DNA Replication Proceeds by the Polymerization of Deoxyribonucleoside Triphosphates Along a Template 828

DNA polymerases require a template and a primer 829
All DNA polymerases have structural features in common 829
Two bound metal ions participate in the polymerase reaction 829
The specificity of replication is dictated by complementarity of shape between bases 830
An RNA primer synthesized by primase enables DNA synthesis to begin 831
One strand of DNA is made continuously, whereas the other strand is synthesized in fragments 831
DNA ligase joins ends of DNA in duplex regions 832
The separation of DNA strands requires specific helicases and ATP hydrolysis 832

28.2 DNA Unwinding and Supercoiling Are Controlled by Topoisomerases 833
The linking number of DNA, a topological property, determines the degree of supercoiling 835
Topoisomerases prepare the double helix for unwinding 836
Type I topoisomerases relax supercoiled structures 836
Type II topoisomerases can introduce negative supercoils through coupling to ATP hydrolysis 837

28.3 DNA Replication Is Highly Coordinated 839
DNA replication requires highly processive polymerases 839
The leading and lagging strands are synthesized in a coordinated fashion 840
DNA replication in *Escherichia coli* begins at a unique site 842
DNA synthesis in eukaryotes is initiated at multiple sites 843
Telomeres are unique structures at the ends of linear chromosomes 844
Telomeres are replicated by telomerase, a specialized polymerase that carries its own RNA template 845

28.4 Many Types of DNA Damage Can Be Repaired 845
Errors can arise in DNA replication 846
Bases can be damaged by oxidizing agents, alkylating agents, and light 846
DNA damage can be detected and repaired by a variety of systems 847
The presence of thymine instead of uracil in DNA permits the repair of deaminated cytosine 849
Some genetic diseases are caused by the expansion of repeats of three nucleotides 850
Many cancers are caused by the defective repair of DNA 850
Many potential carcinogens can be detected by their mutagenic action on bacteria 852

28.5 DNA Recombination Plays Important Roles in Replication, Repair, and Other Processes 852
RecA can initiate recombination by promoting strand invasion 853
Some recombination reactions proceed through Holliday-junction intermediates 854

CHAPTER 29 RNA Synthesis and Processing 859
RNA synthesis comprises three stages: Initiation, elongation, and termination 860

29.1 RNA Polymerases Catalyze Transcription 861
RNA chains are formed de novo and grow in the 5′-to-3′ direction 862
RNA polymerases backtrack and correct errors 863
RNA polymerase binds to promoter sites on the DNA template to initiate transcription 864
Sigma subunits of RNA polymerase recognize promoter sites 865
RNA polymerases must unwind the template double helix for transcription to take place 865
Elongation takes place at transcription bubbles that move along the DNA template 866
Sequences within the newly transcribed RNA signal termination 866
Some messenger RNAs directly sense metabolite concentrations 867
The *rho* protein helps to terminate the transcription of some genes 868
Some antibiotics inhibit transcription 869
Precursors of transfer and ribosomal RNA are cleaved and chemically modified after transcription in prokaryotes 870

29.2 Transcription in Eukaryotes Is Highly Regulated 871
Three types of RNA polymerase synthesize RNA in eukaryotic cells 872
Three common elements can be found in the RNA polymerase II promoter region 874
The TFIID protein complex initiates the assembly of the active transcription complex 874
Multiple transcription factors interact with eukaryotic promoters 875
Enhancer sequences can stimulate transcription at start sites thousands of bases away 876

29.3 The Transcription Products of Eukaryotic Polymerases Are Processed 876
RNA polymerase I produces three ribosomal RNAs 877
RNA polymerase III produces transfer RNA 877
The product of RNA polymerase II, the pre-mRNA transcript, acquires a 5′ cap and a 3′ poly(A) tail 878
Small regulatory RNAs are cleaved from larger precursors 879
RNA editing changes the proteins encoded by mRNA 879
Sequences at the ends of introns specify splice sites in mRNA precursors 880
Splicing consists of two sequential transesterification reactions 881
Small nuclear RNAs in spliceosomes catalyze the splicing of mRNA precursors 882
Transcription and processing of mRNA are coupled 883
Mutations that affect pre-mRNA splicing cause disease 884
Most human pre-mRNAS can be spliced in alternative ways to yield different proteins 885

29.4 The Discovery of Catalytic RNA was Revealing in Regard to Both Mechanism and Evolution 886

CHAPTER 30 Protein Synthesis 893

30.1 Protein Synthesis Requires the Translation of Nucleotide Sequences into Amino Acid Sequences 894
The synthesis of long proteins requires a low error frequency 894
Transfer RNA molecules have a common design 895
Some transfer RNA molecules recognize more than one codon because of wobble in base-pairing 897

30.2 Aminoacyl Transfer RNA Synthetases Read the Genetic Code 898
Amino acids are first activated by adenylation 898
Aminoacyl-tRNA synthetases have highly discriminating amino acid activation sites 899
Proofreading by aminoacyl-tRNA synthetases increases the fidelity of protein synthesis 900
Synthetases recognize various features of transfer RNA molecules 901
Aminoacyl-tRNA synthetases can be divided into two classes 901

30.3 The Ribosome Is the Site of Protein Synthesis 902
Ribosomal RNAs (5S, 16S, and 23S rRNA) play a central role in protein synthesis 903
Ribosomes have three tRNA-binding sites that bridge the 30s and 50s subunits 905
The start signal is usually AUG preceded by several bases that pair with 16S rRNA 905
Bacterial protein synthesis is initiated by formylmethionyl transfer RNA 906
Formylmethionyl-tRNA$_f$ is placed in the P site of the ribosome in the formation of the 70S initiation complex 907
Elongation factors deliver aminoacyl-tRNA to the ribosome 907
Peptidyl transferase catalyzes peptide-bond synthesis 908
The formation of a peptide bond is followed by the GTP-driven translocation of tRNAs and mRNA 909
Protein synthesis is terminated by release factors that read stop codons 910

30.4 Eukaryotic Protein Synthesis Differs from Bacterial Protein Synthesis Primarily in Translation Initiation 911
Mutations in initiation factor 2 cause a curious pathological condition 913

30.5 A Variety of Antibiotics and Toxins Can Inhibit Protein Synthesis 913
Some antibiotics inhibit protein synthesis 914
Diphtheria toxin blocks protein synthesis in eukaryotes by inhibiting translocation 914
Ricin fatally modifies 28S ribosomal RNA 915

30.6 Ribosomes Bound to the Endoplasmic Reticulum Manufacture Secretory and Membrane Proteins 915
Protein synthesis begins on ribosomes that are free in the cytoplasm 916
Signal sequences mark proteins for translocation across the endoplasmic reticulum membrane 916
Transport vesicles carry cargo proteins to their final destination 918

CHAPTER 31 The Control of Gene Expression in Prokaryotes 925

31.1 Many DNA-Binding Proteins Recognize Specific DNA Sequences 926
The helix-turn-helix motif is common to many prokaryotic DNA-binding proteins 927

31.2 Prokaryotic DNA-Binding Proteins Bind Specifically to Regulatory Sites in Operons 927
An operon consists of regulatory elements and protein-encoding genes 928
The *lac* repressor protein in the absence of lactose binds to the operator and blocks transcription 929
Ligand binding can induce structural changes in regulatory proteins 930
The operon is a common regulatory unit in prokaryotes 930
Transcription can be stimulated by proteins that contact RNA polymerase 931

31.3 Regulatory Circuits Can Result in Switching Between Patterns of Gene Expression 932
The λ repressor regulates its own expression 932
A circuit based on the λ repressor and Cro forms a genetic switch 933
Many prokaryotic cells release chemical signals that regulate gene expression in other cells 933
Biofilms are complex communities of prokaryotes 934

31.4 Gene Expression Can Be Controlled at Posttranscriptional Levels 935
Attenuation is a prokaryotic mechanism for regulating transcription through the modulation of nascent RNA secondary structure 935

CHAPTER 32 The Control of Gene Expression in Eukaryotes 941

32.1 Eukaryotic DNA Is Organized into Chromatin 943
Nucleosomes are complexes of DNA and histones 943
DNA wraps around histone octamers to form nucleosomes 943

32.2 Transcription Factors Bind DNA and Regulate Transcription Initiation 945
A range of DNA-binding structures are employed by eukaryotic DNA-binding proteins 945
Activation domains interact with other proteins 946
Multiple transcription factors interact with eukaryotic regulatory regions 946
Enhancers can stimulate transcription in specific cell types 946
Induced pluripotent stem cells can be generated by introducing four transcription factors into differentiated cells 947

32.3 The Control of Gene Expression Can Require Chromatin Remodeling 948

The methylation of DNA can alter patterns of gene expression 949
Steroids and related hydrophobic molecules pass through membranes and bind to DNA-binding receptors 949
Nuclear hormone receptors regulate transcription by recruiting coactivators to the transcription complex 950
Steroid-hormone receptors are targets for drugs 951
Chromatin structure is modulated through covalent modifications of histone tails 952
Histone deacetylases contribute to transcriptional repression 953

32.4 Eukaryotic Gene Expression Can Be Controlled at Posttranscriptional Levels 954
Genes associated with iron metabolism are translationally regulated in animals 954
Small RNAs regulate the expression of many eukaryotic genes 956

Part IV RESPONDING TO ENVIRONMENTAL CHANGES

CHAPTER 33 Sensory Systems 961

33.1 A Wide Variety of Organic Compounds Are Detected by Olfaction 962
Olfaction is mediated by an enormous family of seven-transmembrane-helix receptors 962
Odorants are decoded by a combinatorial mechanism 964

33.2 Taste Is a Combination of Senses That Function by Different Mechanisms 966
Sequencing of the human genome led to the discovery of a large family of 7TM bitter receptors 967
A heterodimeric 7TM receptor responds to sweet compounds 968
Umami, the taste of glutamate and aspartate, is mediated by a heterodimeric receptor related to the sweet receptor 969
Salty tastes are detected primarily by the passage of sodium ions through channels 969
Sour tastes arise from the effects of hydrogen ions (acids) on channels 969

33.3 Photoreceptor Molecules in the Eye Detect Visible Light 970
Rhodopsin, a specialized 7TM receptor, absorbs visible light 970
Light absorption induces a specific isomerization of bound 11-*cis*-retinal 971
Light-induced lowering of the calcium level coordinates recovery 972
Color vision is mediated by three cone receptors that are homologs of rhodopsin 973
Rearrangements in the genes for the green and red pigments lead to "color blindness" 974

33.4 Hearing Depends on the Speedy Detection of Mechanical Stimuli 975
Hair cells use a connected bundle of stereocilia to detect tiny motions 975
Mechanosensory channels have been identified in *Drosophila* and vertebrates 976

33.5 Touch Includes the Sensing of Pressure, Temperature, and Other Factors 977
Studies of capsaicin reveal a receptor for sensing high temperatures and other painful stimuli 977

CHAPTER 34 The Immune System 981

Innate immunity is an evolutionarily ancient defense system 982
The adaptive immune system responds by using the principles of evolution 984

34.1 Antibodies Possess Distinct Antigen-Binding and Effector Units 985

34.2 Antibodies Bind Specific Molecules Through Hypervariable Loops 988
The immunoglobulin fold consists of a beta-sandwich framework with hypervariable loops 988
X-ray analyses have revealed how antibodies bind antigens 989
Large antigens bind antibodies with numerous interactions 990

34.3 Diversity Is Generated by Gene Rearrangements 991
J (joining) genes and D (diversity) genes increase antibody diversity 991
More than 10^8 antibodies can be formed by combinatorial association and somatic mutation 992
The oligomerization of antibodies expressed on the surfaces of immature B cells triggers antibody secretion 993
Different classes of antibodies are formed by the hopping of V_H genes 994

34.4 Major-Histocompatibility-Complex Proteins Present Peptide Antigens on Cell Surfaces for Recognition by T-Cell Receptors 995
Peptides presented by MHC proteins occupy a deep groove flanked by alpha helices 996
T-cell receptors are antibody-like proteins containing variable and constant regions 998
CD8 on cytotoxic T cells acts in concert with T-cell receptors 998
Helper T cells stimulate cells that display foreign peptides bound to class II MHC proteins 1000
Helper T cells rely on the T-cell receptor and CD4 to recognize foreign peptides on antigen-presenting cells 1000
MHC proteins are highly diverse 1002
Human immunodeficiency viruses subvert the immune system by destroying helper T cells 1003

34.5 The Immune System Contributes to the Prevention and the Development of Human Diseases 1004
T cells are subjected to positive and negative selection in the thymus 1004
Autoimmune diseases result from the generation of immune responses against self-antigens 1005

The immune system plays a role in cancer prevention 1005
Vaccines are a powerful means to prevent and eradicate disease 1006

CHAPTER 35 Molecular Motors 1011

35.1 Most Molecular-Motor Proteins Are Members of the P-Loop NTPase Superfamily 1012
Molecular motors are generally oligomeric proteins with an ATPase core and an extended structure 1012
ATP binding and hydrolysis induce changes in the conformation and binding affinity of motor proteins 1014
35.2 Myosins Move Along Actin Filaments 1016
Actin is a polar, self-assembling, dynamic polymer 1016
Myosin head domains bind to actin filaments 1018
Motions of single motor proteins can be directly observed 1018
Phosphate release triggers the myosin power stroke 1019
Muscle is a complex of myosin and actin 1019
The length of the lever arm determines motor velocity 1022
35.3 Kinesin and Dynein Move Along Microtubules 1022
Microtubules are hollow cylindrical polymers 1022
Kinesin motion is highly processive 1024
35.4 A Rotary Motor Drives Bacterial Motion 1026
Bacteria swim by rotating their flagella 1026
Proton flow drives bacterial flagellar rotation 1026
Bacterial chemotaxis depends on reversal of the direction of flagellar rotation 1028

CHAPTER 36 Drug Development 1033

36.1 The Development of Drugs Presents Huge Challenges 1034
Drug candidates must be potent and selective modulators of their targets 1035
Drugs must have suitable properties to reach their targets 1036
Toxicity can limit drug effectiveness 1040
36.2 Drug Candidates Can Be Discovered by Serendipity, Screening, or Design 1041
Serendipitous observations can drive drug development 1041
Natural products are a valuable source of drugs and drug leads 1043
Screening libraries of synthetic compounds expands the opportunity for identification of drug leads 1044
Drugs can be designed on the basis of three-dimensional structural information about their targets 1046
36.3 Analyses of Genomes Hold Great Promise for Drug Discovery 1048
Potential targets can be identified in the human proteome 1048
Animal models can be developed to test the validity of potential drug targets 1049
Potential targets can be identified in the genomes of pathogens 1050
Genetic differences influence individual responses to drugs 1050
36.4 The Clinical Development of Drugs Proceeds Through Several Phases 1051
Clinical trials are time consuming and expensive 1052
The evolution of drug resistance can limit the utility of drugs for infectious agents and cancer 1053

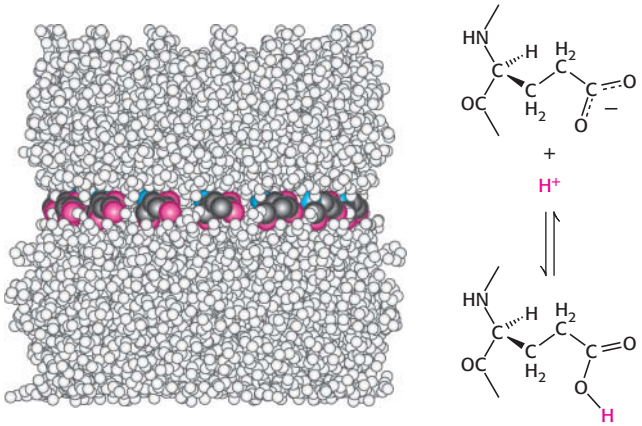
Answers to Problems A1

Selected Readings B1

Index C1

CHAPTER

1 Biochemistry: An Evolving Science



Chemistry in action. Human activities require energy. The interconversion of different forms of energy requires large biochemical machines comprising many thousands of atoms such as the complex shown above. Yet, the functions of these elaborate assemblies depend on simple chemical processes such as the protonation and deprotonation of the carboxylic acid groups shown on the right. The photograph is of Nobel Prize winners Peter Agre, M.D., and Carol Greider, Ph.D., who used, respectively, biochemical techniques to reveal key mechanisms of how water is transported into and out of cells, and how chromosomes are replicated faithfully. [Keith Weller for Johns Hopkins Medicine.]

Biochemistry is the study of the chemistry of life processes. Since the discovery that biological molecules such as urea could be synthesized from nonliving components in 1828, scientists have explored the chemistry of life with great intensity. Through these investigations, many of the most fundamental mysteries of how living things function at a biochemical level have now been solved. However, much remains to be investigated. As is often the case, each discovery raises at least as many new questions as it answers. Furthermore, we are now in an age of unprecedented opportunity for the application of our tremendous knowledge of biochemistry to problems in medicine, dentistry, agriculture, forensics, anthropology, environmental sciences, alternative energy, and many other fields. We begin our journey into biochemistry with one of the most startling discoveries of the past century: namely, the great unity of all living things at the biochemical level.

OUTLINE

1.1 Biochemical Unity Underlies Biological Diversity

1.2 DNA Illustrates the Interplay Between Form and Function

1.3 Concepts from Chemistry Explain the Properties of Biological Molecules

1.4 The Genomic Revolution Is Transforming Biochemistry, Medicine, and Other Fields

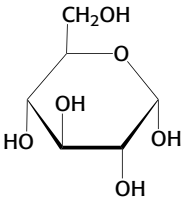
1.1 Biochemical Unity Underlies Biological Diversity

The biological world is magnificently diverse. The animal kingdom is rich with species ranging from nearly microscopic insects to elephants and whales. The plant kingdom includes species as small and relatively

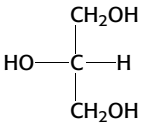
simple as algae and as large and complex as giant sequoias. This diversity extends further when we descend into the microscopic world. Organisms such as protozoa, yeast, and bacteria are present with great diversity in water, in soil, and on or within larger organisms. Some organisms can survive and even thrive in seemingly hostile environments such as hot springs and glaciers.

The development of the microscope revealed a key unifying feature that underlies this diversity. Large organisms are built up of *cells,* resembling, to some extent, single-celled microscopic organisms. The construction of animals, plants, and microorganisms from cells suggested that these diverse organisms might have more in common than is apparent from their outward appearance. With the development of biochemistry, this suggestion has been tremendously supported and expanded. At the biochemical level, all organisms have many common features (Figure 1.1).

As mentioned earlier, biochemistry is the study of the chemistry of life processes. These processes entail the interplay of two different classes of molecules: large molecules such as proteins and nucleic acids, referred to as *biological macromolecules,* and low-molecular-weight molecules such as glucose and glycerol, referred to as *metabolites,* that are chemically transformed in biological processes.

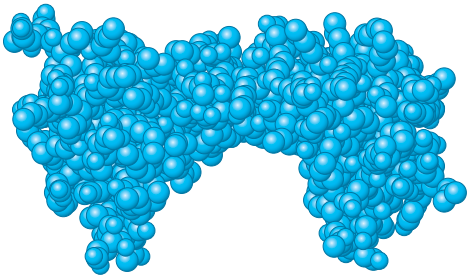


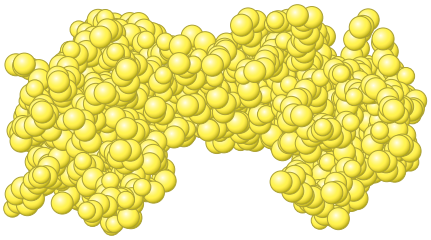
Glucose

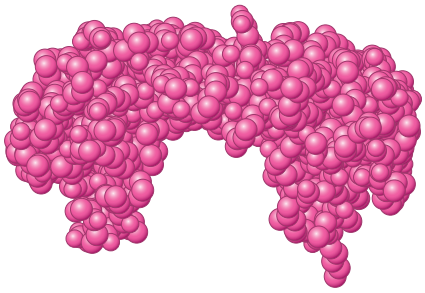


Glycerol

Members of both these classes of molecules are common, with minor variations, to all living things. For example, *deoxyribonucleic acid* (DNA) stores genetic information in all cellular organisms. *Proteins,* the macromolecules that are key participants in most biological processes, are built from the same set of 20 building blocks in all organisms. Furthermore, proteins that play similar roles in different organisms often have very similar three-dimensional structures (Figure 1.1).


Sulfolobus archaea


Arabidopsis thaliana


Homo sapiens

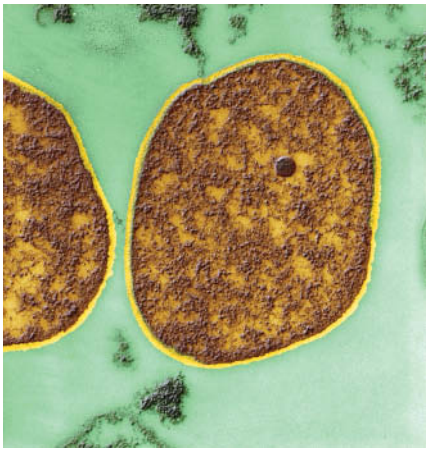


FIGURE 1.1 Biological diversity and similarity. The shape of a key molecule in gene regulation (the TATA-box-binding protein) is similar in three very different organisms that are separated from one another by billions of years of evolution. [(Left) Eye of Science/Science Source; (middle) Holt Studios/Photo Researchers; (right) Time Life Pictures/Getty Images.]

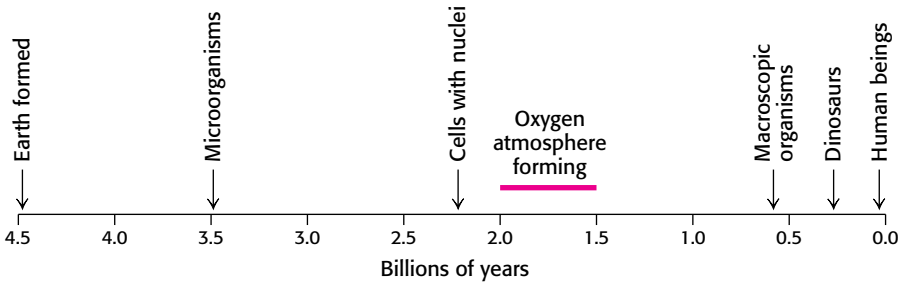


FIGURE 1.2 A possible time line for biochemical evolution. Selected key events are indicated. Note that life on Earth began approximately 3.5 billion years ago, whereas human beings emerged quite recently.

Key metabolic processes also are common to many organisms. For example, the set of chemical transformations that converts glucose and oxygen into carbon dioxide and water is essentially identical in simple bacteria such as *Escherichia coli (E. coli)* and human beings. Even processes that appear to be quite distinct often have common features at the biochemical level. Remarkably, the biochemical processes by which plants capture light energy and convert it into more-useful forms are strikingly similar to steps used in animals to capture energy released from the breakdown of glucose.

These observations overwhelmingly suggest that all living things on Earth have a common ancestor and that modern organisms have evolved from this ancestor into their present forms. Geological and biochemical findings support a time line for this evolutionary path (Figure 1.2). On the basis of their biochemical characteristics, the diverse organisms of the modern world can be divided into three fundamental groups called *domains: Eukarya* (eukaryotes), *Bacteria*, and *Archaea*. Domain Eukarya comprises all multicellular organisms, including human beings as well as many microscopic unicellular organisms such as yeast. The defining characteristic of *eukaryotes* is the presence of a well-defined nucleus within each cell. Unicellular organisms such as bacteria, which lack a nucleus, are referred to as *prokaryotes*. The prokaryotes were reclassified as two separate domains in response to Carl Woese's discovery in 1977 that certain bacteria-like organisms are biochemically quite distinct from other previously characterized bacterial species. These organisms, now recognized as having diverged from bacteria early in evolution, are the *archaea*. Evolutionary paths from a common ancestor to modern organisms can be deduced on the basis of biochemical information. One such path is shown in Figure 1.3.

Much of this book will explore the chemical reactions and the associated biological macromolecules and metabolites that are found in biological processes common to all organisms. The unity of life at the biochemical level makes this approach possible. At the same time, different organisms have specific needs, depending on the particular biological niche in which they evolved and live. By comparing and contrasting details of particular biochemical pathways in different organisms, we can learn how biological challenges are solved at the biochemical level. In most cases, these challenges are addressed by the adaptation of existing macromolecules to new roles rather than by the evolution of entirely new ones.

Biochemistry has been greatly enriched by our ability to examine the three-dimensional structures of biological macromolecules in great detail. Some of these structures

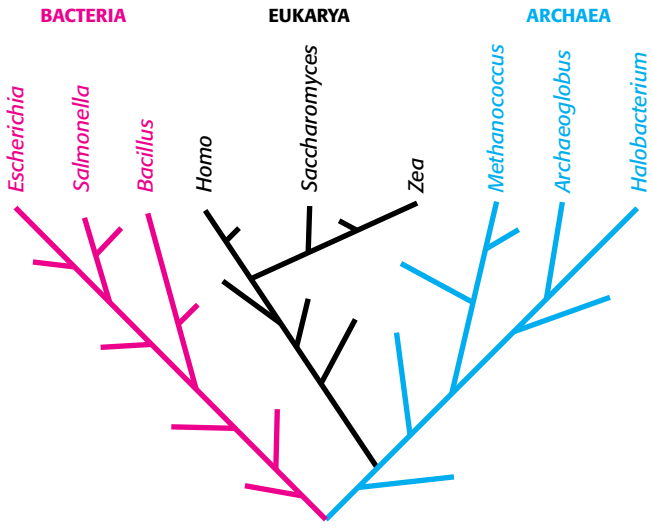


FIGURE 1.3 The tree of life. A possible evolutionary path from a common ancestor approximately 3.5 billion years ago at the bottom of the tree to organisms found in the modern world at the top.

are simple and elegant, whereas others are incredibly complicated. In any case, these structures provide an essential framework for understanding function. We begin our exploration of the interplay between structure and function with the genetic material, DNA.

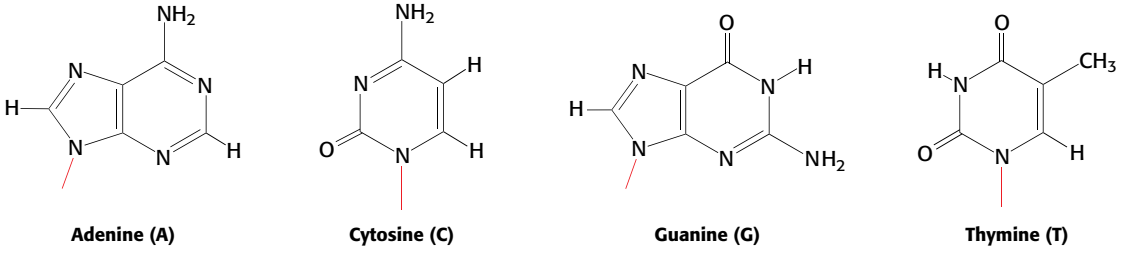
1.2 DNA Illustrates the Interplay Between Form and Function

A fundamental biochemical feature common to all cellular organisms is the use of DNA for the storage of genetic information. The discovery that DNA plays this central role was first made in studies of bacteria in the 1940s. This discovery was followed by a compelling proposal for the three-dimensional structure of DNA in 1953, an event that set the stage for many of the advances in biochemistry and many other fields, extending to the present.

The structure of DNA powerfully illustrates a basic principle common to all biological macromolecules: the intimate relation between structure and function. The remarkable properties of this chemical substance allow it to function as a very efficient and robust vehicle for storing information. We start with an examination of the covalent structure of DNA and its extension into three dimensions.

DNA is constructed from four building blocks

DNA is a *linear polymer* made up of four different types of monomers. It has a fixed backbone from which protrude variable substituents, referred to as bases (Figure 1.4). The backbone is built of repeating sugar–phosphate units. The sugars are molecules of *deoxyribose* from which DNA receives its name. Each sugar is connected to two phosphate groups through different linkages. Moreover, each sugar is oriented in the same way, and so each DNA strand has directionality, with one end distinguishable from the other. Joined to each deoxyribose is one of four possible bases: adenine (A), cytosine (C), guanine (G), and thymine (T).



These bases are connected to the sugar components in the DNA backbone through the bonds shown in black in Figure 1.4. All four bases are planar but differ significantly in other respects. Thus, each monomer of DNA consists of a sugar–phosphate unit and one of four bases attached to the sugar. These bases can be arranged in any order along a strand of DNA.

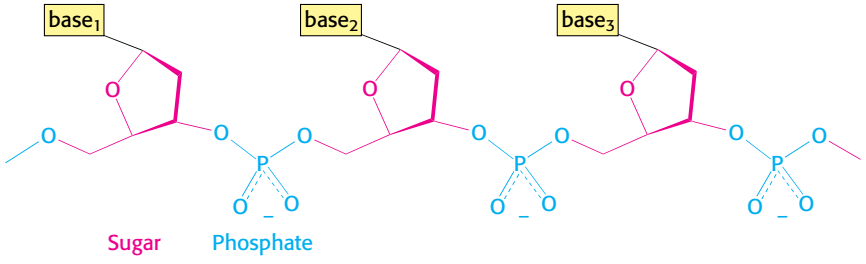


FIGURE 1.4 Covalent structure of DNA. Each unit of the polymeric structure is composed of a sugar (deoxyribose), a phosphate, and a variable base that protrudes from the sugar–phosphate backbone.

Two single strands of DNA combine to form a double helix

Most DNA molecules consist of not one but two strands (Figure 1.5). In 1953, James Watson and Francis Crick deduced the arrangement of these strands and proposed a three-dimensional structure for DNA molecules. This structure is a *double helix* composed of two intertwined strands arranged such that the sugar–phosphate backbone lies on the outside and the bases on the inside. The key to this structure is that the bases form *specific base pairs* (bp) held together by *hydrogen bonds* (Section 1.3): adenine pairs with thymine (A–T) and guanine pairs with cytosine (G–C), as shown in Figure 1.6. Hydrogen bonds are much weaker than *covalent bonds* such as the carbon–carbon or carbon–nitrogen bonds that define the structures of the bases themselves. Such weak bonds are crucial to biochemical systems; they are weak enough to be reversibly broken in biochemical processes, yet they are strong enough, particularly when many form simultaneously, to help stabilize specific structures such as the double helix.

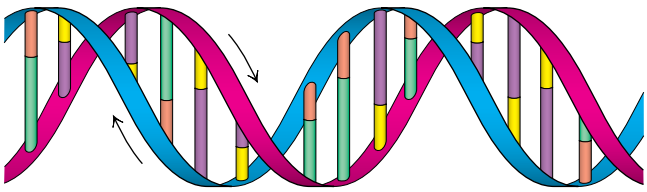


FIGURE 1.5 The double helix. The double-helical structure of DNA proposed by Watson and Crick. The sugar–phosphate backbones of the two chains are shown in red and blue, and the bases are shown in green, purple, orange, and yellow. The two strands are antiparallel, running in opposite directions with respect to the axis of the double helix, as indicated by the arrows.

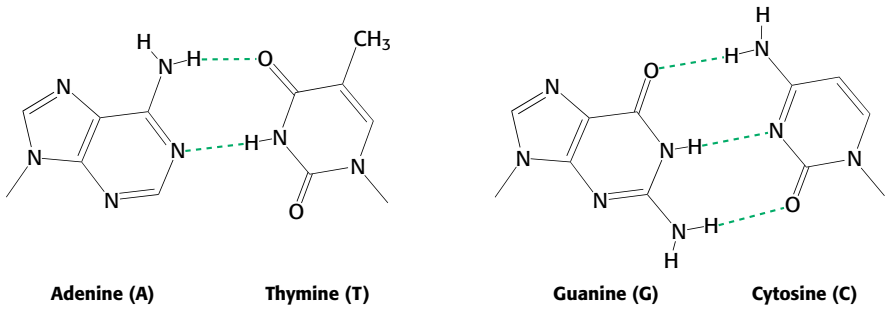


FIGURE 1.6 Watson–Crick base pairs. Adenine pairs with thymine (A–T), and guanine with cytosine (G–C). The dashed green lines represent hydrogen bonds.

DNA structure explains heredity and the storage of information

The structure proposed by Watson and Crick has two properties of central importance to the role of DNA as the hereditary material. First, the structure is compatible with any sequence of bases. While the bases are distinct in structure, the base pairs have essentially the same shape (Figure 1.6) and thus fit equally well into the center of the double-helical structure of any sequence. Without any constraints, the sequence of bases along a DNA strand can act as an efficient means of storing information. Indeed, the sequence of bases along DNA strands is how genetic information is stored. The DNA sequence determines the sequences of the ribonucleic acid (RNA) and protein molecules that carry out most of the activities within cells.

Second, because of base-pairing, the sequence of bases along one strand completely determines the sequence along the other strand. As Watson and Crick so coyly wrote: "It has not escaped our notice that the specific pairing we have postulated immediately suggests a possible copying mechanism for the genetic material." Thus, if the DNA double helix is separated into two single strands, each strand can act as a template for the generation of its partner strand through specific base-pair formation (Figure 1.7). The three-dimensional structure of DNA beautifully illustrates the close connection between molecular form and function.

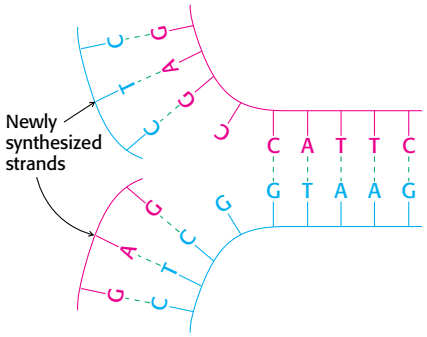


FIGURE 1.7 DNA replication. If a DNA molecule is separated into two strands, each strand can act as the template for the generation of its partner strand.

1.3 Concepts from Chemistry Explain the Properties of Biological Molecules

We have seen how a chemical insight into the hydrogen-bonding capabilities of the bases of DNA led to a deep understanding of a fundamental biological process. To lay the groundwork for the rest of the book, we begin our study of biochemistry by examining selected concepts from chemistry and showing how these concepts apply to biological systems. The concepts include the types of chemical bonds; the structure of water, the solvent in which most biochemical processes take place; the First and Second Laws of Thermodynamics; and the principles of acid–base chemistry.

The formation of the DNA double helix as a key example

We will use these concepts to examine an archetypical biochemical process—namely, the formation of a DNA double helix from its two component strands. The process is but one of many examples that could have been chosen to illustrate these topics. Keep in mind that, although the specific discussion is about DNA and double-helix formation, the concepts considered are quite general and will apply to many other classes of molecules and processes that will be discussed in the remainder of the book. In the course of these discussions, we will touch on the properties of water and the concepts of pK_a and buffers that are of great importance to many aspects of biochemistry.

The double helix can form from its component strands

The discovery that DNA from natural sources exists in a double-helical form with Watson–Crick base pairs suggested, but did not prove, that such double helices would form spontaneously outside biological systems. Suppose that two short strands of DNA were chemically synthesized to have complementary sequences so that they could, in principle, form a double helix with Watson–Crick base pairs. Two such sequences are CGATTAAT and ATTAATCG. The structures of these molecules in solution can be examined by a variety of techniques. In isolation, each sequence exists almost exclusively as a single-stranded molecule. However, when the two sequences are mixed, a double helix with Watson–Crick base pairs does form (Figure 1.8). This reaction proceeds nearly to completion.

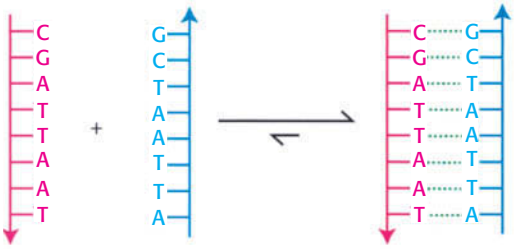


FIGURE 1.8 Formation of a double helix. When two DNA strands with appropriate, complementary sequences are mixed, they spontaneously assemble to form a double helix.

What forces cause the two strands of DNA to bind to each other? To analyze this binding reaction, we must consider several factors: the types of interactions and bonds in biochemical systems and the energetic favorability of the reaction. We must also consider the influence of the solution conditions—in particular, the consequences of acid–base reactions.

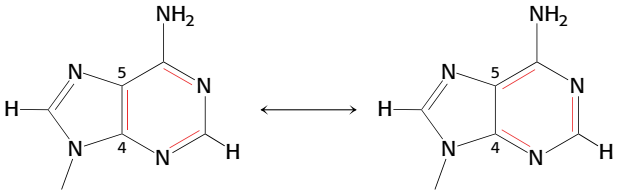
Covalent and noncovalent bonds are important for the structure and stability of biological molecules

Atoms interact with one another through chemical bonds. These bonds include the covalent bonds that define the structure of molecules as well as a variety of noncovalent bonds that are of great importance to biochemistry.

Covalent bonds. The strongest bonds are covalent bonds, such as the bonds that hold the atoms together within the individual bases shown on page 4. A covalent bond is formed by the sharing of a pair of electrons between adjacent atoms. A typical carbon–carbon (C—C) covalent bond has

a bond length of 1.54 Å and bond energy of 355 kJ mol^{-1} (85 kcal mol^{-1}). Because covalent bonds are so strong, considerable energy must be expended to break them. More than one electron pair can be shared between two atoms to form a multiple covalent bond. For example, three of the bases in Figure 1.6 include carbon–oxygen (C═O) double bonds. These bonds are even stronger than C—C single bonds, with energies near 730 kJ mol^{-1} (175 kcal mol^{-1}) and are somewhat shorter.

For some molecules, more than one pattern of covalent bonding can be written. For example, adenine can be written in two nearly equivalent ways called *resonance structures.*

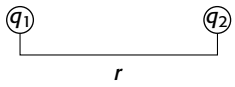


These adenine structures depict alternative arrangements of single and double bonds that are possible within the same structural framework. Resonance structures are shown connected by a double-headed arrow. Adenine's true structure is a composite of its two resonance structures. The composite structure is manifested in the bond lengths such as that for the bond joining carbon atoms C-4 and C-5. The observed bond length of 1.40 Å is between that expected for a C—C single bond (1.54 Å) and a C═C double bond (1.34 Å). A molecule that can be written as several resonance structures of approximately equal energies has greater stability than does a molecule without multiple resonance structures.

Noncovalent bonds. Noncovalent bonds are weaker than covalent bonds but are crucial for biochemical processes such as the formation of a double helix. Four fundamental noncovalent bond types are *ionic interactions, hydrogen bonds, van der Waals interactions,* and *hydrophobic interactions*. They differ in geometry, strength, and specificity. Furthermore, these bonds are affected in vastly different ways by the presence of water. Let us consider the characteristics of each type:

1. *Ionic Interactions*. A charged group on one molecule can attract an oppositely charged group on the same or another molecule. The energy of an ionic interaction (sometimes called an electrostatic interaction) is given by the *Coulomb energy:*

$$E = kq_1q_2/Dr$$



where E is the energy, q_1 and q_2 are the charges on the two atoms (in units of the electronic charge), r is the distance between the two atoms (in angstroms), D is the dielectric constant (which decreases the strength of the Coulomb depending on the intervening solvent or medium), and k is a proportionality constant ($k = 1389$, for energies in units of kilojoules per mole, or 332 for energies in kilocalories per mole).

By convention, an attractive interaction has a negative energy. The ionic interaction between two ions bearing single opposite charges separated by 3 Å in water (which has a dielectric constant of 80) has an energy of −5.8 kJ mol^{-1} (−1.4 kcal mol^{-1}). Note how important the dielectric constant of the medium is. For the same ions separated by 3 Å in a nonpolar solvent such as hexane (which has a dielectric constant of 2), the energy of this interaction is −232 kJ mol^{-1} (−55 kcal mol^{-1}).

Distance and energy units

Interatomic distances and bond lengths are usually measured in angstrom (Å) units:

$$1\ Å = 10^{-10}\ m = 10^{-8}\ cm = 0.1\ nm$$

Several energy units are in common use. One joule (J) is the amount of energy required to move 1 meter against a force of 1 newton. A kilojoule (kJ) is 1000 joules. One calorie is the amount of energy required to raise the temperature of 1 gram of water 1 degree Celsius. A kilocalorie (kcal) is 1000 calories. One joule is equal to 0.239 cal.

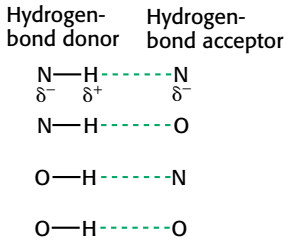
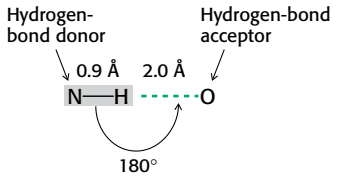


FIGURE 1.9 Hydrogen bonds. Hydrogen bonds are depicted by dashed green lines. The positions of the partial charges (δ^+ and δ^-) are shown.



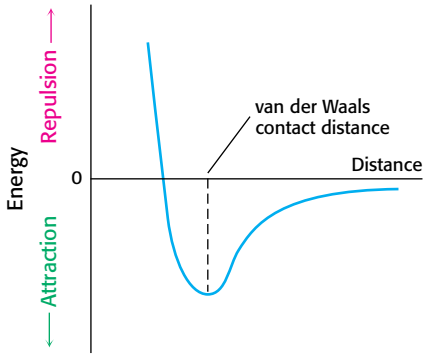
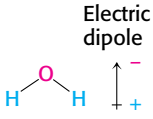


FIGURE 1.10 Energy of a van der Waals interaction as two atoms approach each other. The energy is most favorable at the van der Waals contact distance. Owing to electron–electron repulsion, the energy rises rapidly as the distance between the atoms becomes shorter than the contact distance.



2. *Hydrogen Bonds*. These interactions are largely ionic interactions, with partial charges on nearby atoms attracting one another. Hydrogen bonds are responsible for specific base-pair formation in the DNA double helix. The hydrogen atom in a hydrogen bond is partially shared by two electronegative atoms such as nitrogen or oxygen. The *hydrogen-bond donor* is the group that includes both the atom to which the hydrogen atom is more tightly linked and the hydrogen atom itself, whereas the *hydrogen-bond acceptor* is the atom less tightly linked to the hydrogen atom (Figure 1.9). The electronegative atom to which the hydrogen atom is covalently bonded pulls electron density away from the hydrogen atom, which thus develops a partial positive charge (δ^+). Thus, the hydrogen atom with a partial positive charge can interact with an atom having a partial negative charge (δ^-) through an ionic interaction.

Hydrogen bonds are much weaker than covalent bonds. They have energies ranging from 4 to 20 kJ mol^{-1} (from 1 to 5 kcal mol^{-1}). Hydrogen bonds are also somewhat longer than covalent bonds; their bond lengths (measured from the hydrogen atom) range from 1.5 Å to 2.6 Å; hence, a distance ranging from 2.4 Å to 3.5 Å separates the two nonhydrogen atoms in a hydrogen bond.

The strongest hydrogen bonds have a tendency to be approximately straight, such that the hydrogen-bond donor, the hydrogen atom, and the hydrogen-bond acceptor lie along a straight line. This tendency toward linearity can be important for orienting interacting molecules with respect to one another. Hydrogen-bonding interactions are responsible for many of the properties of water that make it such a special solvent, as will be described shortly.

3. *van der Waals Interactions*. The basis of a van der Waals interaction is that the distribution of electronic charge around an atom fluctuates with time. At any instant, the charge distribution is not perfectly symmetric. This transient asymmetry in the electronic charge about an atom acts through ionic interactions to induce a complementary asymmetry in the electron distribution within its neighboring atoms. The atom and its neighbors then attract one another. This attraction increases as two atoms come closer to each other, until they are separated by the van der Waals *contact distance* (Figure 1.10). At distances shorter than the van der Waals contact distance, very strong repulsive forces become dominant because the outer electron clouds of the two atoms overlap.

Energies associated with van der Waals interactions are quite small; typical interactions contribute from 2 to 4 kJ mol^{-1} (from 0.5 to 1 kcal mol^{-1}) per atom pair. When the surfaces of two large molecules come together, however, a large number of atoms are in van der Waals contact, and the net effect, summed over many atom pairs, can be substantial.

We will cover the fourth noncovalent interaction, the hydrophobic interaction, after we examine the characteristics of water; these characteristics are essential to understanding the hydrophobic interaction.

Properties of water. Water is the solvent in which most biochemical reactions take place, and its properties are essential to the formation of macromolecular structures and the progress of chemical reactions. Two properties of water are especially relevant:

1. *Water is a polar molecule*. The water molecule is bent, not linear, and so the distribution of charge is asymmetric. The oxygen nucleus draws electrons away from the two hydrogen nuclei, which leaves the region around

each hydrogen atom with a net positive charge. The water molecule is thus an electrically polar structure.

2. *Water is highly cohesive*. Water molecules interact strongly with one another through hydrogen bonds. These interactions are apparent in the structure of ice (Figure 1.11). Networks of hydrogen bonds hold the structure together; similar interactions link molecules in liquid water and account for many of the properties of water. In the liquid state, approximately one in four of the hydrogen bonds present in ice are broken. The polar nature of water is responsible for its high dielectric constant of 80. Molecules in aqueous solution interact with water molecules through the formation of hydrogen bonds and through ionic interactions. These interactions make water a versatile solvent, able to readily dissolve many species, especially polar and charged compounds that can participate in these interactions.

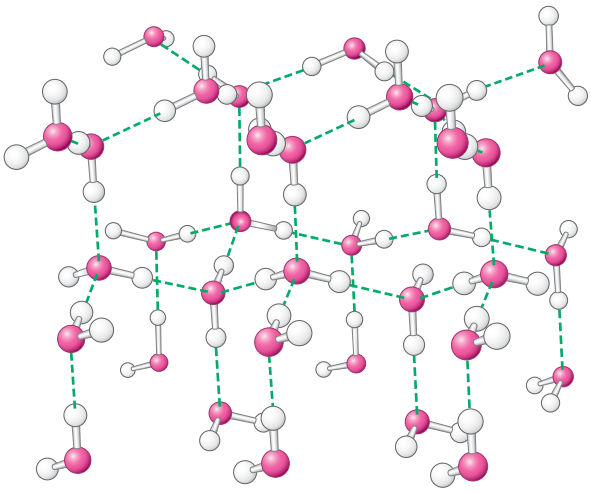


FIGURE 1.11 Structure of ice. Hydrogen bonds (shown as dashed green lines) are formed between water molecules to produce a highly ordered and open structure.

The hydrophobic effect. A final fundamental interaction called the *hydrophobic effect* is a manifestation of the properties of water. Some molecules (termed *nonpolar molecules*) cannot participate in hydrogen bonding or ionic interactions. The interactions of nonpolar molecules with water molecules are not as favorable as are interactions between the water molecules themselves. The water molecules in contact with these nonpolar molecules form "cages" around them, becoming more well ordered than water molecules free in solution. However, when two such nonpolar molecules come together, some of the water molecules are released, allowing them to interact freely with bulk water (Figure 1.12). The release of water from such cages is favorable for reasons to be considered shortly. The result is that nonpolar molecules show an increased tendency to associate with one another in water compared with other, less polar and less self-associating, solvents. This tendency is called the hydrophobic effect and the associated interactions are called *hydrophobic interactions*.

The double helix is an expression of the rules of chemistry

Let us now see how these four noncovalent interactions work together in driving the association of two strands of DNA to form a double helix. First, each phosphate group in a DNA strand carries a negative charge. These negatively charged groups interact unfavorably with one another over distances. Thus, unfavorable ionic interactions take place when two strands of

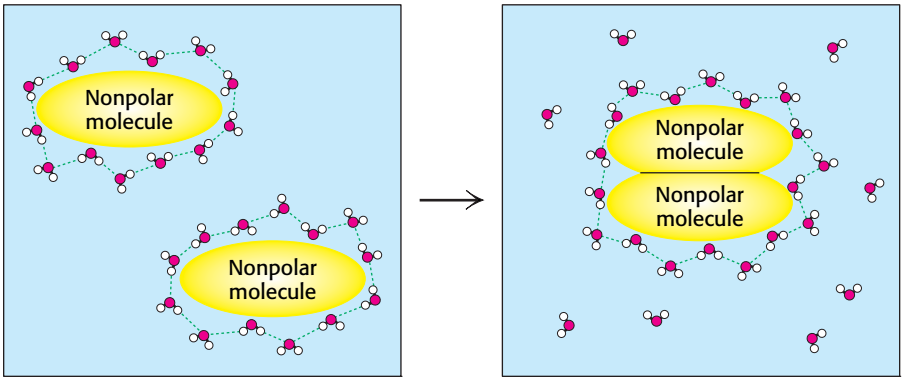


FIGURE 1.12 The hydrophobic effect. The aggregation of nonpolar groups in water leads to the release of water molecules, initially interacting with the nonpolar surface, into bulk water. The release of water molecules into solution makes the aggregation of nonpolar groups favorable.