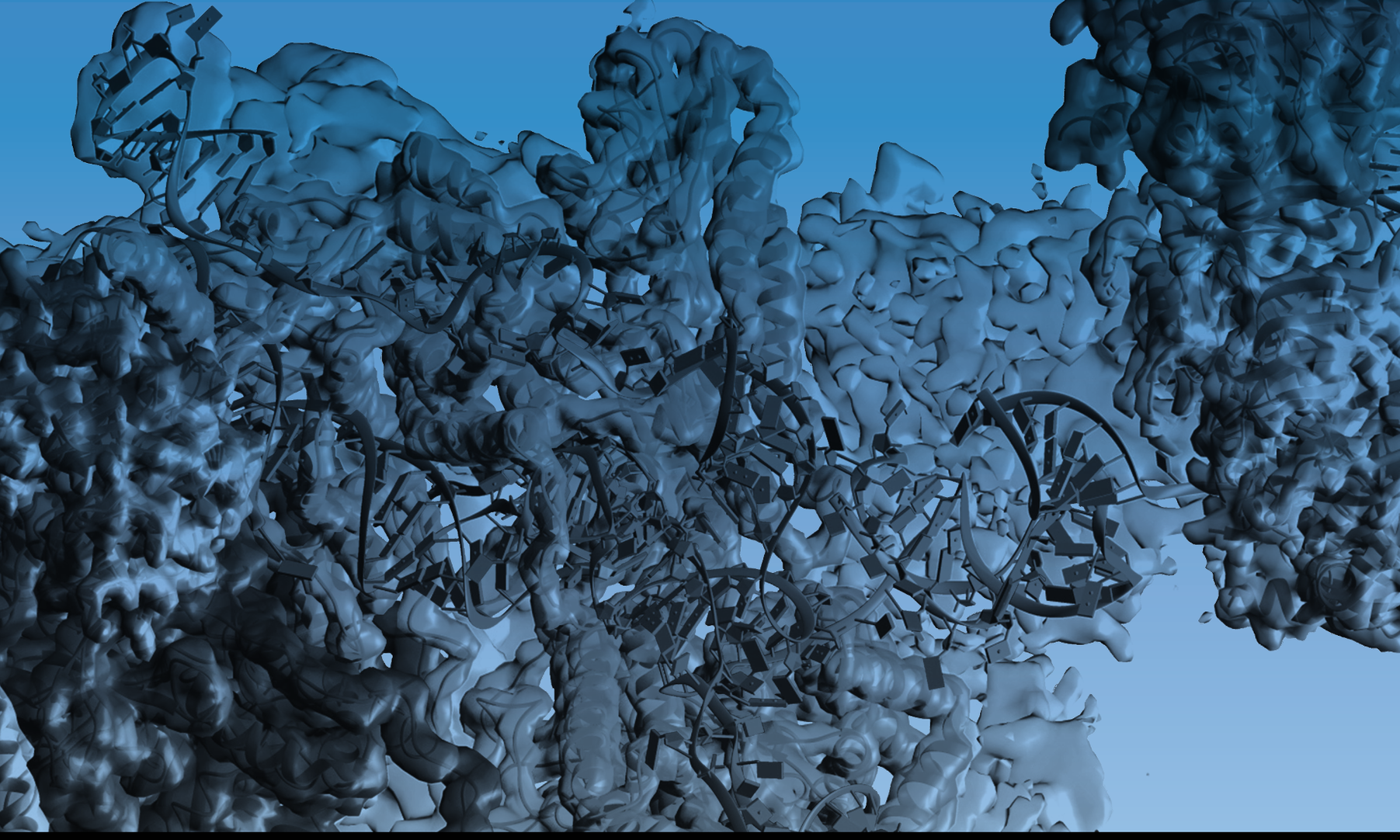


BIOCHEMISTRY

Concepts & Connections

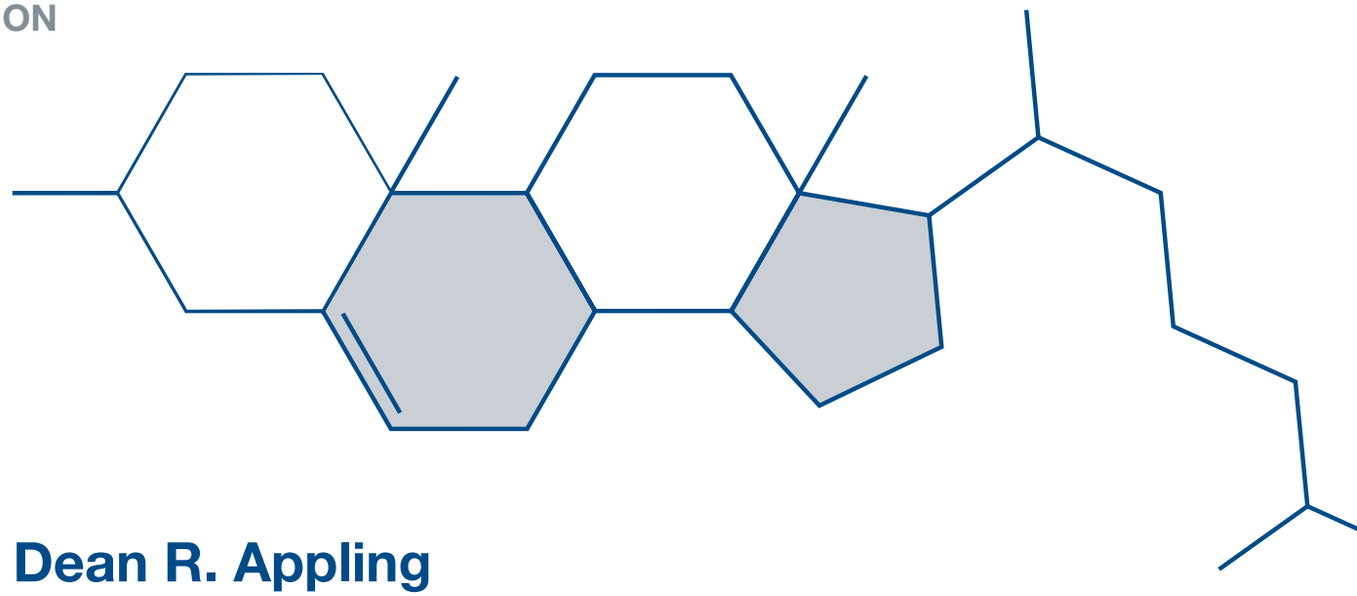
SECOND EDITION

Appling
Anthony-Cahill
Mathews

Biochemistry

CONCEPTS AND CONNECTIONS

SECOND EDITION



Dean R. Appling

THE UNIVERSITY OF TEXAS AT AUSTIN

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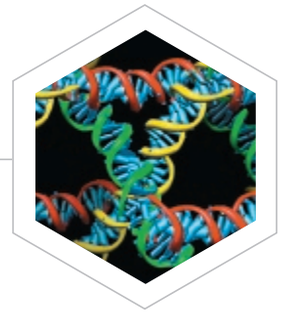

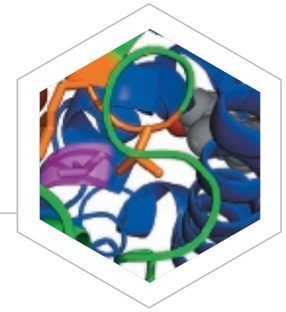

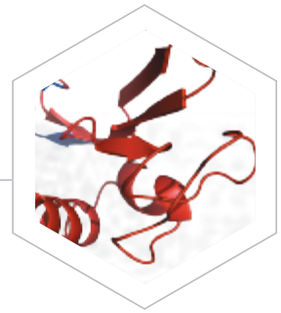

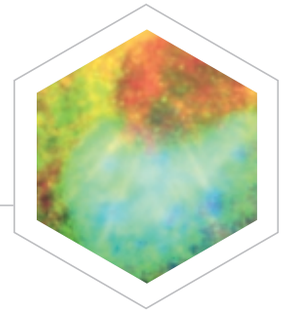

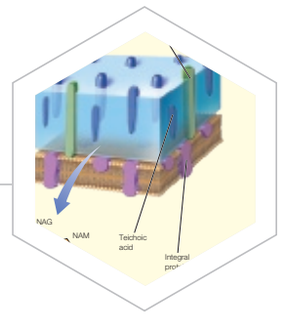

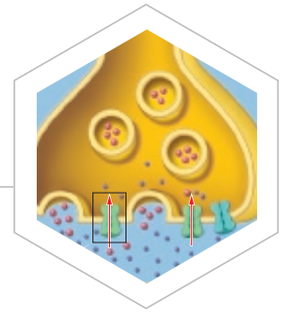

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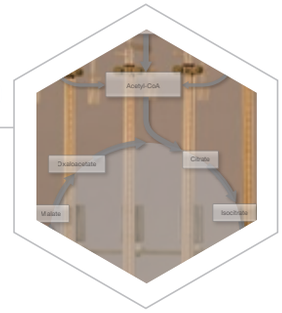

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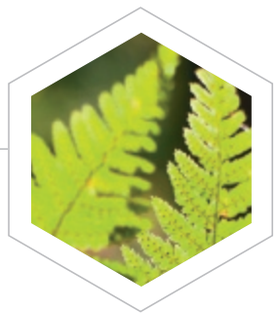

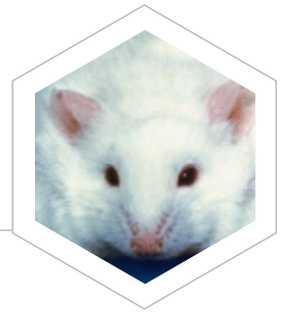

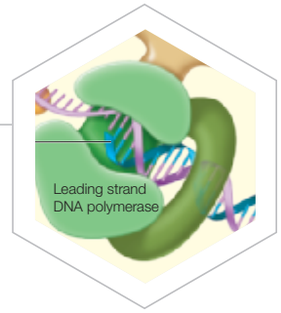

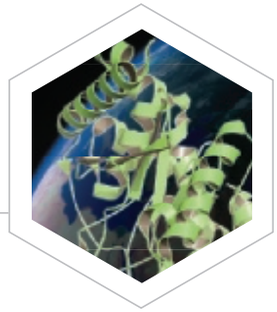

Preface

Biochemistry: Concepts and Connections

As genomics and informatics revolutionize biomedical science and health care, we must prepare students for the challenges of the twenty-first century and ensure their ability to apply quantitative reasoning skills to the science most fundamental to medicine: biochemistry.

We have written *Biochemistry: Concepts and Connections* to provide students with a clear understanding of the chemical logic underlying the mechanisms, pathways, and processes in living cells. The title reinforces our vision for this book—twin emphases upon fundamental *concepts* at the expense of lengthy descriptive information, and upon *connections,* showing how biochemistry relates to all other life sciences and to practical applications in medicine, agricultural sciences, environmental sciences, and forensics.

Inspired by our experience as authors of the biochemistry majors' text, *Biochemistry, Fourth Edition* and the first edition of this book, and as teachers of biochemistry majors' and mixed-science-majors' courses, we believe there are several requirements that a textbook for the mixed-majors' course must address:

- The need for students to understand the structure and function of biological molecules before moving into metabolism and dynamic aspects of biochemistry.
- The need for students to understand that biochemical concepts derive from experimental evidence, meaning that the principles of biochemical techniques must be presented to the greatest extent possible.
- The need for students to encounter many and diverse real-world applications of biochemical concepts.
- The need for students to understand the quantitative basis for biochemical concepts. The Henderson–Hasselbalch equation, the quantitative expressions of thermodynamic laws, and the Michaelis–Menten equation, for example, are not equations to be memorized and forgotten when the course moves on. The basis for these and other quantitative statements must be understood and constantly repeated as biochemical concepts, such as mechanisms of enzyme action, are developed. They are essential to help students grasp the concepts.

In designing *Biochemistry: Concepts and Connections,* we have stayed with the organization that serves us well in our own classroom experience. The first 10 chapters cover structure and function of biological molecules, the next 10 deal with intermediary metabolism, and the final 6 with genetic biochemistry. Our emphasis on biochemistry as a quantitative science can be seen in Chapters 2 and 3, where we focus on water, the matrix of life, and bioenergetics. Chapter 4 introduces nucleic acid structure, with a brief introduction to nucleic acid and protein synthesis—topics covered in much more detail at the end of the book.

Chapters 11 through 20 deal primarily with intermediary metabolism. We cover the major topics in carbohydrate metabolism, lipid metabolism, and amino acid metabolism in one chapter each (12, 16, and 18, respectively). Our treatment of cell signaling is a bit unconventional, since it appears in Chapter 20, well after we present hormonal control of carbohydrate and lipid metabolism. However, this treatment allows more extended presentation of receptors, G proteins, oncogenes, and neurotransmission. In addition, because cancer often results from aberrant signaling processes, our placement of the signaling chapter leads fairly naturally into genetic biochemistry, which follows, beginning in Chapter 21.

With assistance from talented artists, we have built a compelling visual narrative from the ground up, composed of a wide range of graphic representations, from macromolecules to cellular structures as well as reaction mechanisms and metabolic pathways that highlight and reinforce overarching themes (chemical logic, regulation, interface between chemistry and biology). In addition, we have added two new **Foundation Figures** to the Second Edition, bringing the total number to 10. These novel Foundation Figures integrate core chemical and biological connections visually, providing a way to organize the complex and detailed material intellectually, thus making relationships among key concepts clear and easier to study. The "**CONCEPT**" and "**CONNECTION**" statements within the narrative, which highlight fundamental concepts and real-world applications of biochemistry, have been reviewed and revised for the Second Edition.

In *Biochemistry: Concepts and Connections,* we emphasize our field as an experimental science by including 17 separate sections, called **Tools of Biochemistry,** that highlight the most important research techniques. We also provide students with references (about 12 per chapter), choosing those that would be most appropriate for our target audience, such as links to Nobel Prize lectures.

We consider end-of-chapter problems to be an indispensable learning tool and provide 15 to 25 problems for each chapter. (In the Second Edition we have added 3 to 4 new end-of-chapter problems to each chapter.) About half of the problems have brief answers at the end of the book, with complete answers provided in a separate solutions manual. Additional tutorials in Mastering Chemistry will help students with some of the most basic concepts and operations. See the table of Instructor and Student Resources on the following page.

Producing a book of this magnitude involves the efforts of dedicated editorial and production teams. We have not had the pleasure of meeting all of these talented individuals, but we consider them close colleagues nonetheless. First, of course, is Jeanne Zalesky, our sponsoring editor, now Editor-in-Chief, Physical Sciences, who always found a way to keep us focused on our goal. Susan Malloy, Program Manager, kept us organized and on schedule, juggling disparate elements in this complex project—later replaced by Anastasia Slesareva. Jay McElroy, Art Development Editor, was our intermediary with the talented artists at Imagineering, Inc., and displayed considerable artistic and editorial gifts in his own right. We also worked with an experienced development editor, Matt Walker. His suggested edits, insights, and attention to detail were invaluable. Beth Sweeten, Senior Project Manager, coordinated the production of the main text and preparation of the Solutions Manual for the end-of-chapter problems. Gary Carlton provided great assistance with many of the illustrations. Chris Hess provided the inspiration for our cover illustration, and Mo Spuhler helped us locate much excellent illustrative material. Once the book was in production, Mary Tindle skillfully kept us all on a complex schedule.

Instructor and Student Resources

Resource	Instructor or Student Resource	Description
Solutions Manual ISBN: 0134814800	Instructor	Prepared by Dean Appling, Spencer Anthony-Cahill, and Christopher Mathews, the solutions manual includes worked-out answers and solutions for problems in the text.
Mastering™ Chemistry pearson.com/mastering/chemistry ISBN: 0134787250	Student & Instructor	Mastering™ Chemistry is the leading online homework, tutorial, and assessment platform, designed to improve results by engaging students with powerful content. Instructors ensure students arrive ready to learn by assigning educationally effective content before class, and encourage critical thinking and retention with in-class resources such as Learning Catalytics. Learn more about Mastering Chemistry. **Mastering Chemistry for *Biochemistry: Concepts and Connections,* 2/e** now has hundreds of more biochemistry-specific assets to help students tackle threshold concepts, connect course materials to real world applications, and build the problem solving skills they need to succeed in future courses and careers.
Pearson eText ISBN: 0134763025	Student	*Biochemistry: Concepts and Connections* 2/e now offers **Pearson eText, optimized for mobile,** which seamlessly integrates videos and other rich media with the text and gives students access to their textbook anytime, anywhere. Pearson eText is available with Mastering Chemistry when packaged with new books, or as an upgrade students can purchase online. The Pearson eText mobile app offers: • Offline access on most iOS and Android phones/tablets. • Accessibility (screen-reader ready) • Configurable reading settings, including resizable type and night reading mode • Instructor and student note-taking, highlighting, bookmarking, and search tools • Embedded videos for a more interactive learning experience
TestGen Test Bank ISBN: 0134814827	Instructor	This resource includes more than 2000 questions in multiple-choice answer format. Test bank problems are linked to textbook-specific learning outcomes as well as MCAT-associated outcomes. Available for download on the Pearson catalog page for *Biochemistry: Concepts and Connections* at www.pearson.com
Instructor Resource Materials ISBN: 0134814843 ISBN: 0134814835	Instructor	Includes all the art, photos, and tables from the book in JPEG format, as well as Lecture Powerpoint slides, for use in classroom projection or when creating study materials and tests. Available for download on the Pearson catalog page for *Biochemistry: Concepts and Connections* at www.pearson.com

The three of us give special thanks to friends and colleagues who provided unpublished material for us to use as illustrations. These contributors include John S. Olson (Rice University), Jack Benner (New England BioLabs), Andrew Karplus (Oregon State University), Scott Delbecq and Rachel Klevit (University of Washington), William Horton (Oregon Health and Science University), Cory Hamada (Western Washington University), Nadrian C. Seaman (New York University), P. Shing Ho (Colorado State University), Catherine Drennan and Edward Brignole (MIT), John G. Tesmer (University of Michigan), Katsuhiko Murakami (Penn State University), Alan Cheung (University College London), Joyce Hamlin (University of Virginia), Stefano Tiziani, Edward Marcotte, David Hoffman, and Robin Gutell (University of Texas at Austin), Dean Sherry and Craig Malloy (University of Texas-Southwestern Medical Center), and Stephen C. Kowalczykowski (University of California, Davis). The cover image, representing in part the structure of the human splicesome, was kindly provided by Karl Bertram (University of Göttingen, Germany).

We are also grateful to the numerous talented biochemists retained by our editors to review our outline, prospectus, chapter drafts, and solutions to our end-of-chapter problems. Their names and affiliations are listed separately.

Our team—authors and editors—put forth great effort to detect and root out errors and ambiguities. We undertook an arduous process of editing and revising several drafts of each chapter in manuscript stage, as well as copyediting, proofreading, and accuracy, reviewing multiple rounds of page proofs in an effort to ensure the highest level of quality control.

Throughout this process, as in our previous writing, we have been most grateful for the patience, good judgment, and emotional support provided by our wives—Maureen Appling, Yvonne Anthony-Cahill, and Kate Mathews. We expect them to be as relieved as we are to see this project draw to a close, and hope that they can share our pleasure at the completed product.

Dean R. Appling
Spencer J. Anthony-Cahill
Christopher K. Mathews

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Dean R. Appling is the Lester J. Reed Professor of Biochemistry and the Associate Dean for Research and Facilities for the College of Natural Sciences at the University of Texas at Austin, where he has taught and done research for the past 32 years. Dean earned his B.S. in Biology from Texas A&M University (1977) and his Ph.D. in Biochemistry from Vanderbilt University (1981). The Appling laboratory studies the organization and regulation of metabolic pathways in eukaryotes, focusing on folate-mediated one-carbon metabolism. The lab is particularly interested in understanding how one-carbon metabolism is organized in mitochondria, as these organelles are central players in many human diseases. In addition to coauthoring *Biochemistry, Fourth Edition,* a textbook for majors and graduate students, Dean has published over 65 scientific papers and book chapters.

As much fun as writing a textbook might be, Dean would rather be outdoors. He is an avid fisherman and hiker. Recently, Dean and his wife, Maureen, have become entranced by the birds on the Texas coast. They were introduced to bird-watching by coauthor Chris Mathews and his wife Kate—an unintended consequence of writing textbooks!

Spencer J. Anthony-Cahill is a Professor and chair of the Department of Chemistry at Western Washington University (WWU), Bellingham, WA. Spencer earned his B.A. in chemistry from Whitman College and his Ph.D. in bioorganic chemistry from the University of California, Berkeley. His graduate work, in the laboratory of Peter Schultz, focused on the biosynthetic incorporation of unnatural amino acids into proteins. Spencer was an NIH postdoctoral fellow in the laboratory of Bill DeGrado (then at DuPont Central Research), where he worked on *de novo* peptide design and the prediction of the tertiary structure of the HLH DNA-binding motif. He then worked for five years as a research scientist in the biotechnology industry, developing recombinant hemoglobin as a treatment for acute blood loss. In 1997, Spencer decided to pursue his long-standing interest in teaching and moved to WWU, where he is today. In 2012, Spencer was recognized by WWU with the Peter J. Elich Award for Excellence in Teaching.

Research in the Anthony-Cahill laboratory is directed at the protein engineering and structural biology of oxygen-binding proteins. The primary focus is on the design of polymeric human hemoglobins with desirable therapeutic properties as a blood replacement.

Outside the classroom and laboratory, Spencer is a great fan of the outdoors—especially the North Cascades and southeastern Utah, where he has often backpacked, camped, climbed, and mountain biked. He also plays electric bass (poorly) in a local blues–rock band and teaches Aikido in Bellingham.

Christopher K. Mathews is Distinguished Professor Emeritus of Biochemistry at Oregon State University. He earned his B.A. in chemistry from Reed College (1958) and his Ph.D. in biochemistry from the University of Washington (1962). He served on the faculties of Yale University and the University of Arizona from 1963 until 1978, when he moved to Oregon State University as Chair of the Department of Biochemistry and Biophysics, a position he held until 2002. His major research interests are the enzymology and regulation of DNA precursor metabolism and the intracellular coordination between deoxyribonucleotide synthesis and DNA replication. From 1984 to 1985, Dr. Mathews was an Eleanor Roosevelt International Cancer Fellow at the Karolinska Institute in Stockholm, and in 1994–1995, he held the Tage Erlander Guest Professorship at Stockholm University. Dr. Mathews has published about 190 research papers, book chapters, and reviews dealing with molecular virology, metabolic regulation, nucleotide enzymology, and biochemical genetics. From 1964 until 2012, he was principal investigator on grants from the National Institutes of Health, the National Science Foundation, and the Army Research Office. He is the author of *Bacteriophage Biochemistry* (1971) and coeditor of *Bacteriophage T4* (1983) and *Structural and Organizational Aspects of Metabolic Regulation* (1990). He was lead author of four editions of *Biochemistry,* a textbook for majors and graduate students. His teaching experience includes undergraduate, graduate, and medical school biochemistry courses.

He has backpacked and floated the mountains and rivers, respectively, of Oregon and the Northwest. As an enthusiastic birder, he is serving as President of the Audubon Society of Corvallis.

Tools of Biochemistry

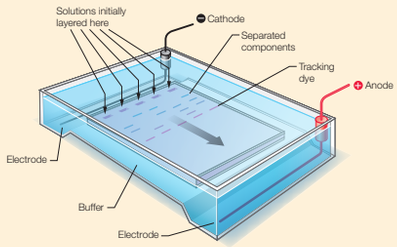
TOOLS OF BIOCHEMISTRY 2A Electrophoresis and Isoelectric Focusing

When an electric field is applied to a solution, solute molecules with a net positive charge migrate toward the cathode, and molecules with a net negative charge move toward the anode. This migration is called **electrophoresis.** Although electrophoresis can be carried out free in solution, it is more convenient to use some kind of *supporting medium* through which the charged molecules move. The supporting medium could be paper or, most typically, a gel composed of the polysaccharide agarose (commonly used to separate nucleic acids; see FIGURE 2A.1) or crosslinked polyacrylamide (commonly used to separate proteins).

The velocity, or **electrophoretic mobility (μ),** of the molecule in the field is defined as the ratio between two opposing factors: the force exerted by the electric field on the charged particle, and the frictional force exerted on the particle by the medium:

$$\mu = \frac{Ze}{f} \qquad (2A.1)^3$$

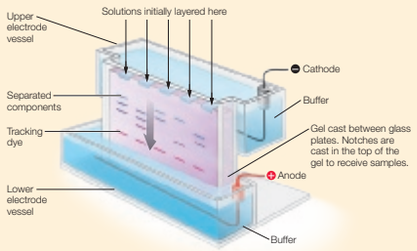
The numerator equals the product of the negative (or positive) charge (e) times the number of unit charges, Z (a positive or negative integer). The greater the overall charge on the molecule, the greater the force it experiences in the electric field. The denominator f is the **frictional coefficient,** which depends on the size and shape of the molecule. Large or asymmetric molecules encounter more frictional resistance than small or compact ones and consequently have larger frictional coefficients. Equation 2A.1 tells us that the mobility of a molecule depends on its charge and on its molecular dimensions.[‡] Because ions and macroions differ in both respects, electrophoresis provides a powerful way of separating them.



▲ FIGURE 2A.1 **Electrophoresis.** A molecule with a net positive charge will migrate toward the cathode, whereas a molecule with a net negative charge will migrate toward the anode.

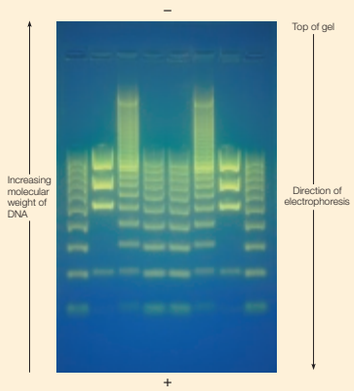
Gel Electrophoresis

In **gel electrophoresis,** a gel containing the appropriate buffer solution is cast in a mold (for agarose gel electrophoresis, shown in Figure 2A.1) or as a thin slab between glass plates (for polyacrylamide gel electrophoresis, shown in FIGURE 2A.2). The gel is placed between electrode compartments, and the samples to be analyzed are carefully pipetted into precast notches in the gel, called wells. Usually, glycerol and a water-soluble anionic "tracking" dye (such as bromophenol blue) are added to the samples. The glycerol makes the sample solution dense, so that it sinks into the well and does not mix into the buffer solution. The dye migrates faster than most macroions, so the experimenter is able to follow the progress of the experiment. The current is turned on until the tracking dye band is near the side of the gel opposite the wells. The gel is then removed from the apparatus and is usually stained with a dye that binds to proteins or nucleic acids. Because the protein or nucleic acid mixture was applied as a narrow band in the well of the gel, components migrating with different electrophoretic mobilities appear as separated bands on the gel. FIGURE 2A.3 shows an example of separation of DNA fragments by this method using an agarose gel. An example of the electrophoretic separation of proteins using a polyacrylamide gel is shown in Chapter 5 (see Figure 5A.9).



▲ FIGURE 2A.2 **Gel electrophoresis.** An apparatus for polyacrylamide gel electrophoresis is shown schematically. The gel is cast between plates. The gel is in contact with buffer in the upper (cathode) and lower (anode) reservoirs. A sample is loaded into one or more wells cast into the top of the gel, and then current is applied to achieve separation of the components in the sample.

[‡]Equation 2A.1 is an approximation which neglects the effects of the ion atmosphere. See van Holde, Johnson, and Ho in Appendix II for more detail.



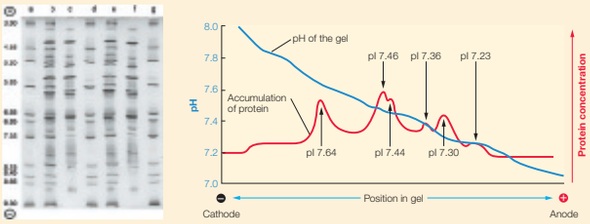
▲ FIGURE 2A.3 **Gel showing separation of DNA fragments.** Following electrophoretic separation of the different-length DNA molecules, the gel is mixed with a fluorescent dye that binds DNA. The unbound dye is then washed off, and the stained DNA molecules are visualized under ultraviolet light.

Polyelectrolytes like DNA or polylysine have one unit charge on each residue, so each molecule has a charge (Ze) proportional to its molecular length. But the frictional coefficient (f) also increases with molecular length, so to a first approximation, a macroion whose charge is proportional to its length has an electrophoretic mobility almost independent of its size. However, gel electrophoresis introduces additional frictional forces that allow the separation of molecules based on size. For linear molecules like the nucleic acid fragments in Figure 2A.3, the relative mobility in an agarose gel is a pproximately a linear function of the logarithm of the molecular weight. Usually, standards of known molecular weight are electrophoresed in one or more lanes on the gel. The molecular weight of the sample can then be estimated by comparing its migration in the gel to those of the standards. For proteins, a similar separation in a polyacrylamide gel is achieved by coating the denatured protein molecule with the anionic detergent sodium dodecylsulfate (SDS) before electrophoresis. This important technique is discussed further in Chapter 5.

Isoelectric Focusing

Proteins are polyampholytes; thus, a protein will migrate in an electric field like other ions if it has a net positive or negative charge. At its isoelectric point, however, its net charge is zero, and it is attracted to neither the anode nor the cathode. If we use a gel with a stable pH gradient covering a wide pH range, each protein molecule in a complex mixture of proteins migrates to the position of its isoelectric point and accumulates there. This method of separation, called **isoelectric focusing,** produces distinct bands of accumulated proteins and can separate proteins with very small differences in the isoelectric point (FIGURE 2A.4). Since the pH of each portion of the gel is known, isoelectric focusing can also be used to determine experimentally the isoelectric point of a particular protein.

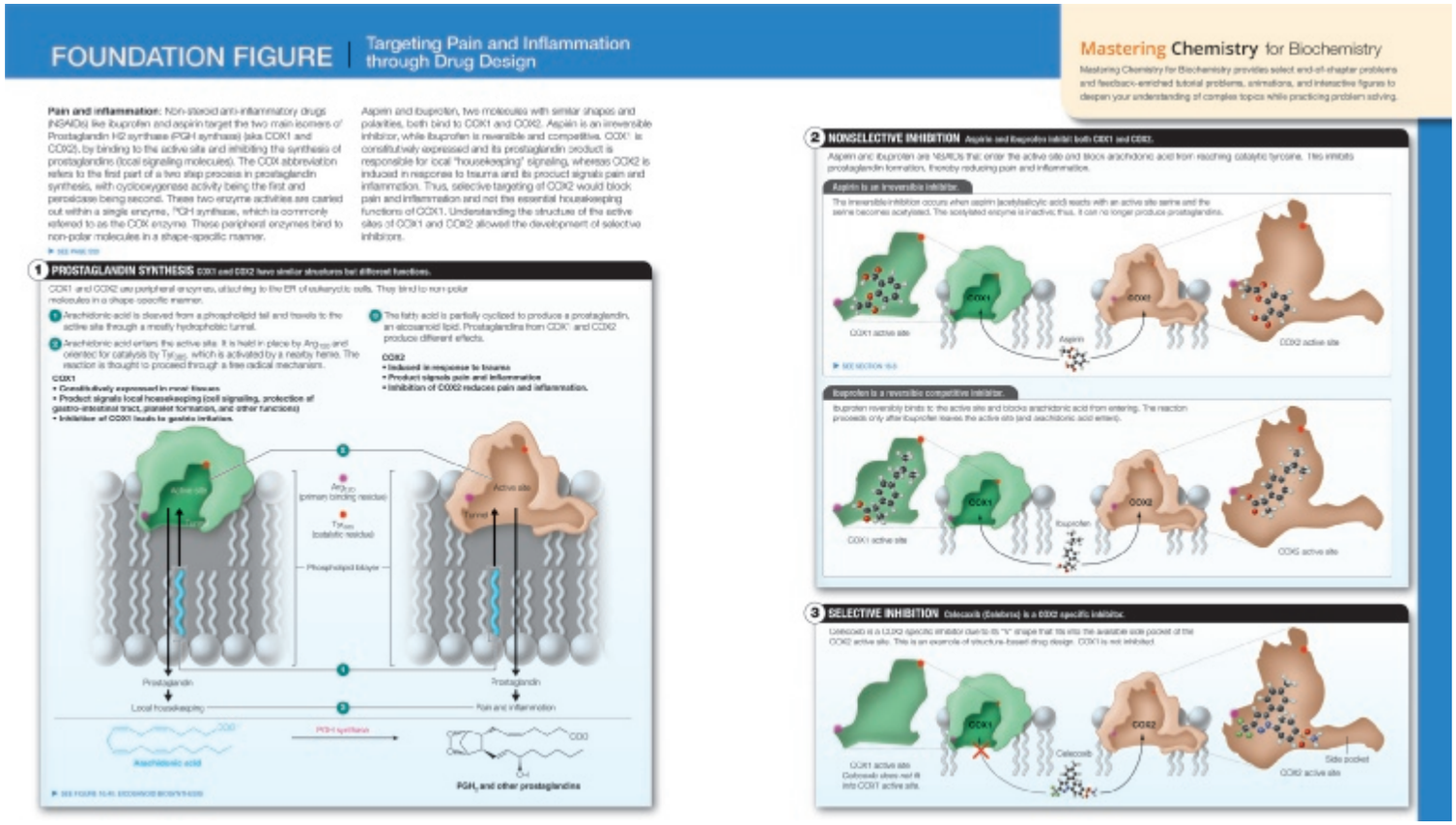
What we have presented here is only a brief overview of a widely applied technique. Additional information on electrophoresis and isoelectric focusing can be found in Appendix II.



▲ FIGURE 2A.4 **Isoelectric focusing of proteins.** **(a)** An isoelectric focusing gel with a pH gradient from 3.50 (anode end) to 9.30 (cathode end). **(b)** A schematic showing where proteins of the indicated pIs would accumulate (peaks shown in red) in a pH gradient gel.

TOOLS OF BIOCHEMISTRY emphasize our field as an experimental science and highlight the most important research techniques relevant to students today.

Foundation Figures



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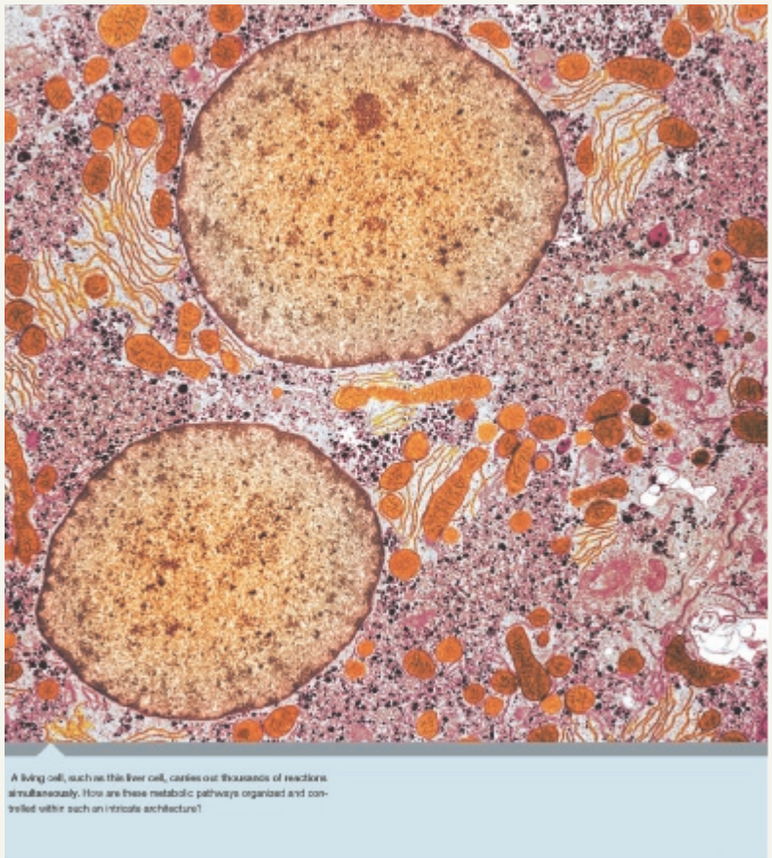
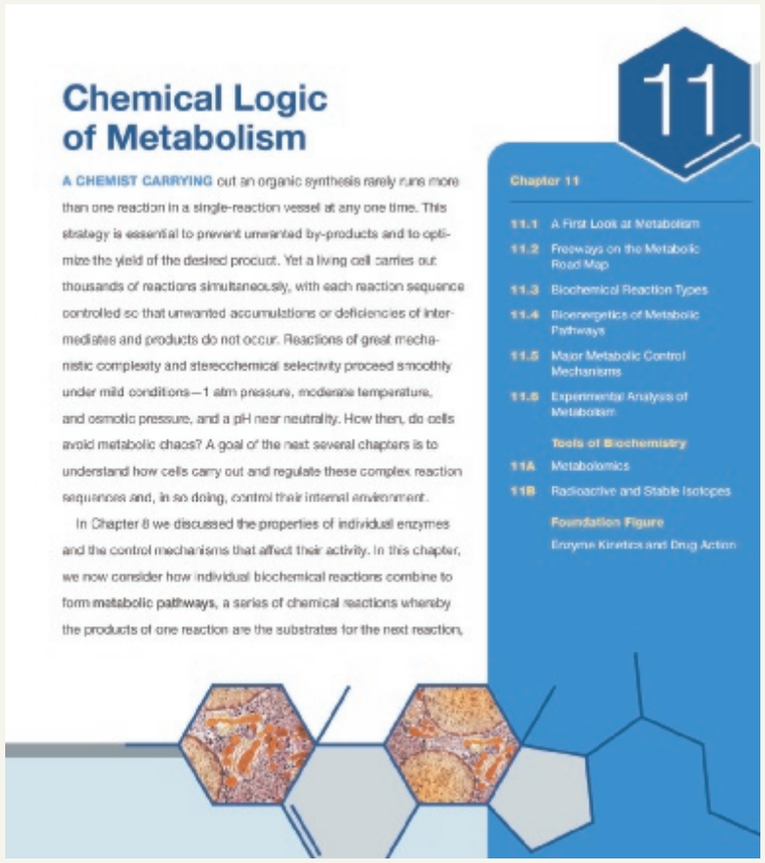


A living cell, such as this liver cell, carries out thousands of reactions simultaneously. How are these metabolic pathways organized and controlled within such an intricate architecture?



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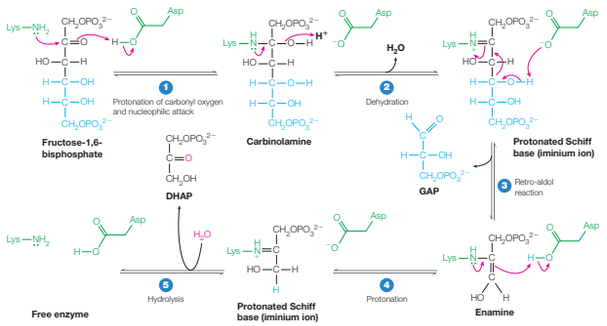


▲ **FIGURE 12.5 Reaction mechanism for fructose-1,6-bisphosphate aldolase.** The Figure shows the protonated Schiff base intermediate (iminium ion) between the substrate and an active site lysine residue. An aspartate residue facilitates the reaction via general acid–base catalysis.

● **CONCEPT** Aldolase cleaves fructose-1,6-bisphosphate under intracellular conditions, even though the equilibrium lies far toward fructose-1,6-bisphosphate under standard conditions.

Reaction 4 is so strongly endergonic under standard conditions that the formation of fructose-1,6-bisphosphate is highly favored. However, from the actual intracellular concentrations of the reactant and products, ΔG is estimated to be approximately -1.3 kJ/mol, consistent with the observation that the reaction proceeds as written in vivo. Reaction 4 demonstrates the importance of considering the conditions *in the cell* (ΔG) rather than standard state conditions ($\Delta G^{\circ\prime}$) when deciding in which direction a reaction is favored.

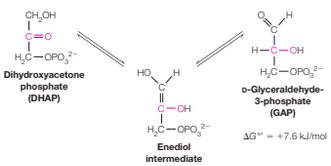
Aldolase activates the substrate for cleavage by nucleophilic attack on the keto carbon at position 2 with a lysine ε-amino group in the active site, as shown in **FIGURE 12.5.** This is facilitated by protonation of the carbonyl oxygen by an active site acid (aspartate) 1. The resulting carbinolamine undergoes dehydration to give an iminium ion, or protonated **Schiff base** 2. A Schiff base is a nucleophilic addition product between an amino group and a carbonyl group. A retro-aldol reaction then cleaves the protonated Schiff base into an enamine plus GAP 3. The enamine is protonated to give another iminium ion (protonated Schiff base) 4, which is then hydrolyzed off the enzyme to give the second product, DHAP 5.

The Schiff base intermediate is advantageous in this reaction because it can delocalize electrons. The positively charged iminium ion is thus a better electron acceptor than a ketone carbonyl, facilitating retro-aldol reactions like this one and, as we shall see, many other biological conversions. This mechanism also demonstrates why it was important to isomerize G6P to F6P in reaction 2. If glucose had not been isomerized to fructose (moving the carbonyl from C-1 to C-2), then the aldolase reaction would have given two- and four-carbon fragments, instead of the metabolically equivalent three-carbon fragments.

Reaction 5: Isomerization of Dihydroxyacetone Phosphate

In reaction 5, **triose phosphate isomerase (TIM)** catalyzes the isomerization of dihydroxyacetone phosphate (DHAP) to glyceraldehyde-3-phosphate (GAP) via an enediol intermediate.

Reaction 5: Triose phosphate isomerase (TIM)



Like reaction 4, reaction 5 is weakly endergonic under standard conditions, but the intracellular concentration of GAP is low because it is consumed in subsequent reactions. Thus, reaction 5 is drawn toward the right.

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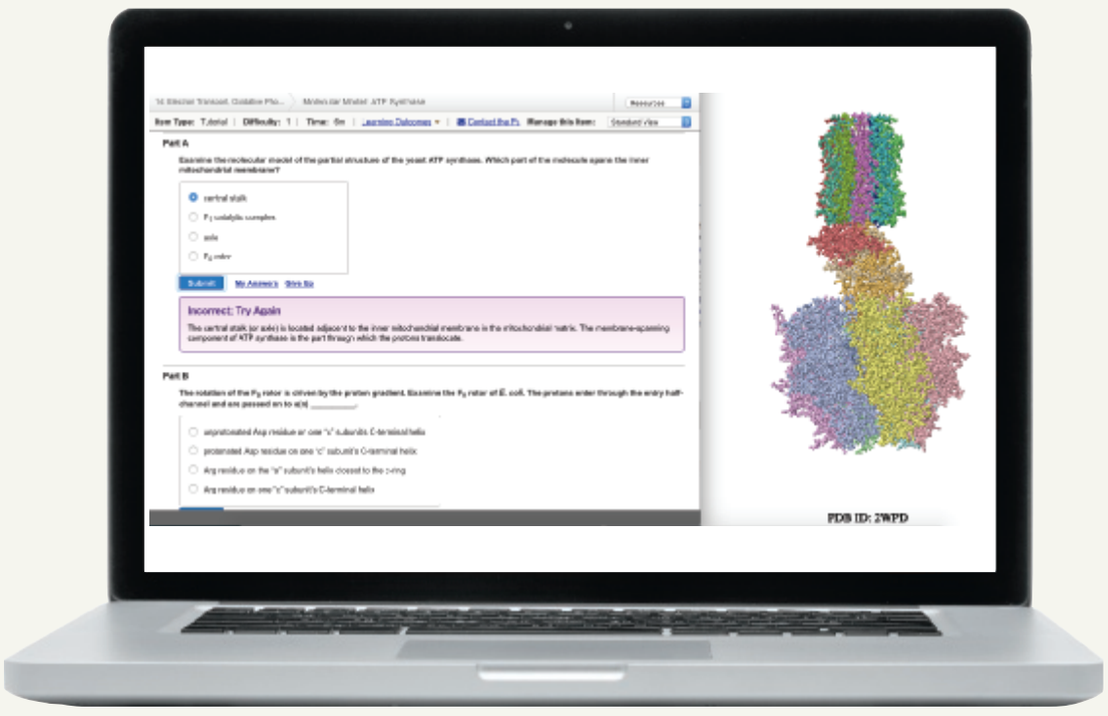
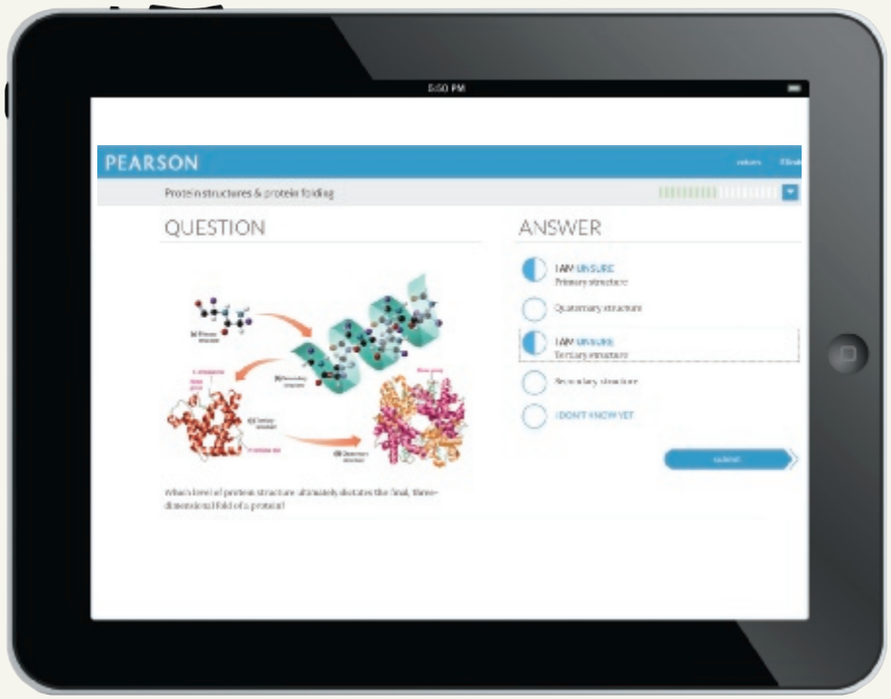


and understand what's happening on the cellular level



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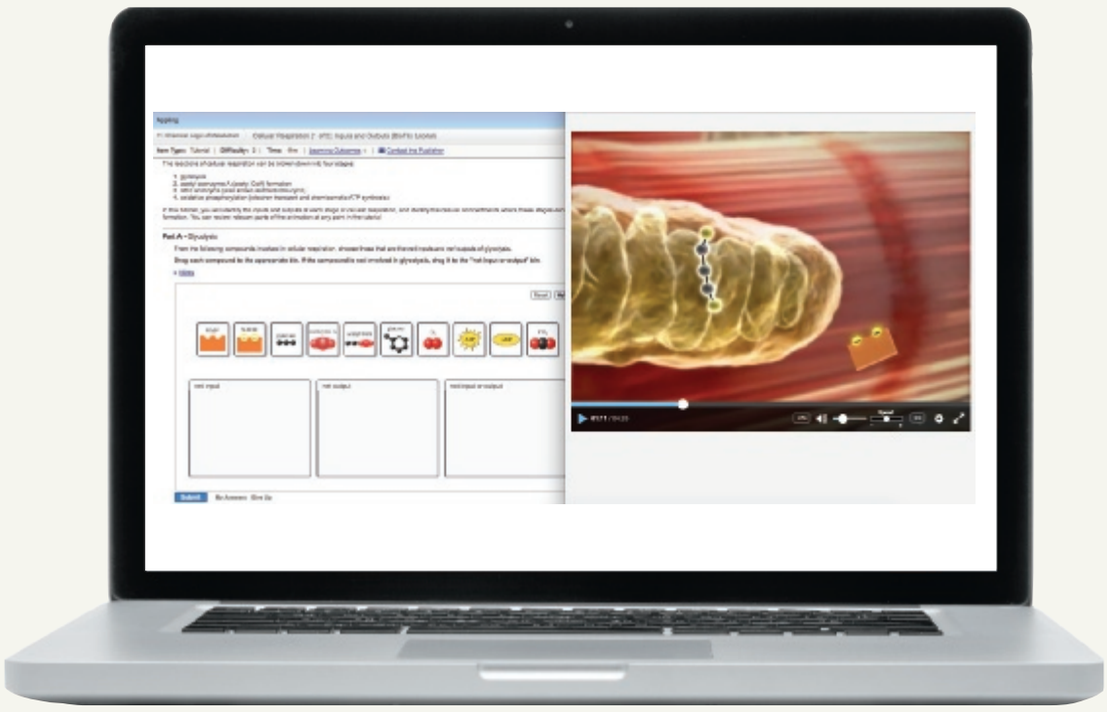
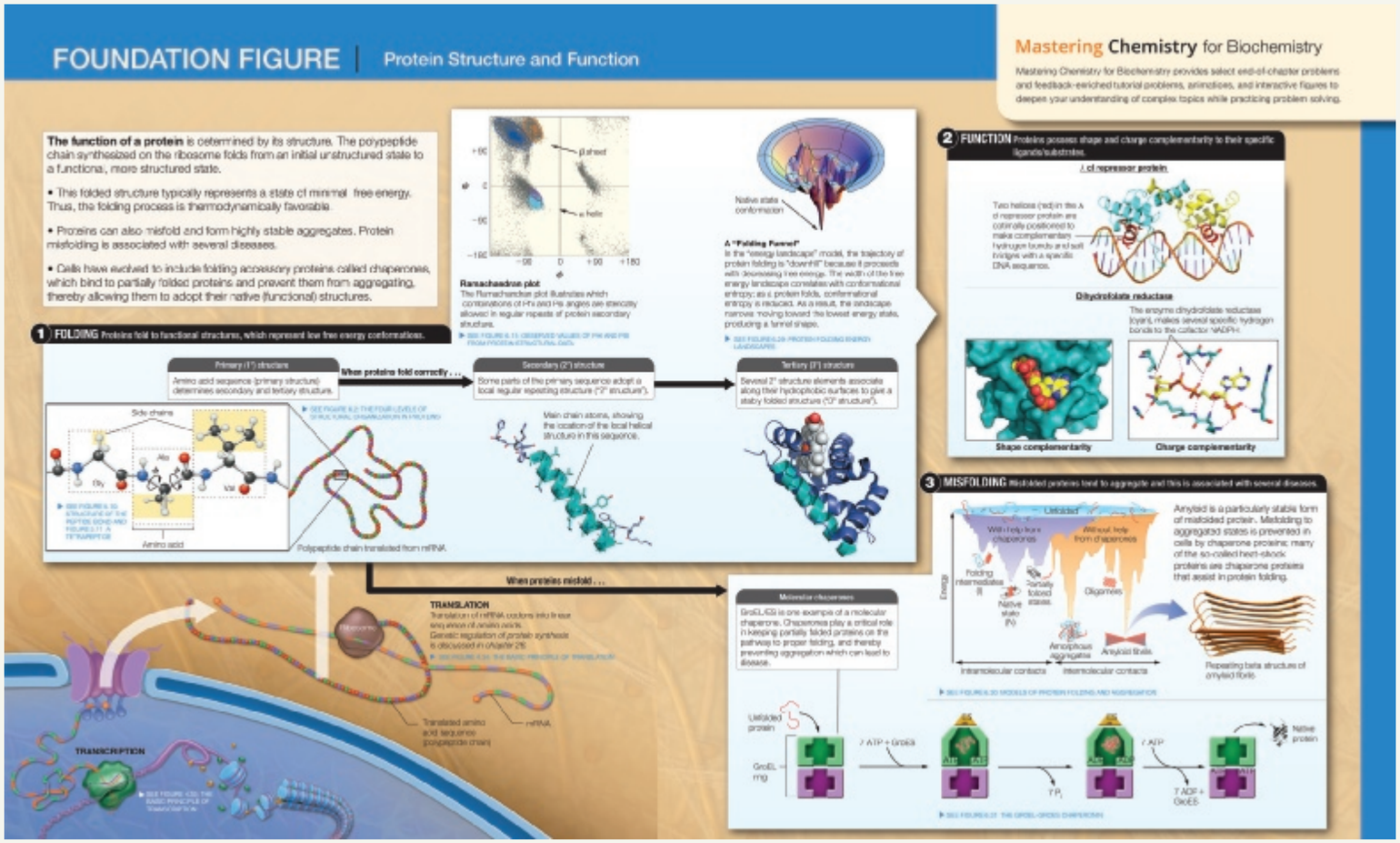


Synthesis of information is simplified through features



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that help students connect complex concepts

Note that we have expressed concentrations of all solutes in units of molarity, then divided by the proper standard state concentration (also in units of molarity). These steps ensure that the terms in Q are of the proper magnitude and stripped of units:

$$\Delta G = -32.2\,\frac{\text{kJ}}{\text{mol}} + \left(2.478\,\frac{\text{kJ}}{\text{mol}}\right) \ln\left(\frac{(0.0001)(0.035)(0.398)}{(0.005)}\right) \quad (3.31b)$$

or

$$\Delta G = -32.2\,\frac{\text{kJ}}{\text{mol}} + -20.3\,\frac{\text{kJ}}{\text{mol}} = -52.5\,\frac{\text{kJ}}{\text{mol}} \quad (3.31c)$$

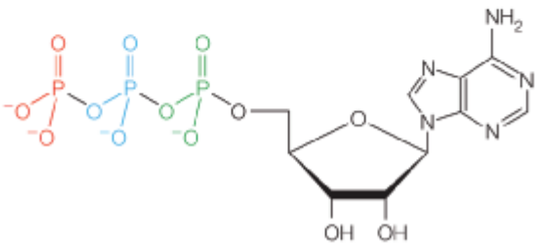
Note that the value calculated for ΔG is much more negative (i.e., more favorable) than the standard free energy change $\Delta G^{\circ\prime}$. This last point underscores the fact that it is ΔG and not $\Delta G^{\circ\prime}$ that determines the driving force for a reaction. However, to evaluate ΔG using Equation 3.19, we must be given, or be able to calculate, $\Delta G^{\circ\prime}$ for the reaction of interest. Recall that $\Delta G^{\circ\prime}$ can be calculated from K using Equation 3.22. In the remaining pages of this chapter, we will use examples relevant to biochemistry to illustrate two alternative methods for calculating $\Delta G^{\circ\prime}$.

3.4 Free Energy in Biological Systems

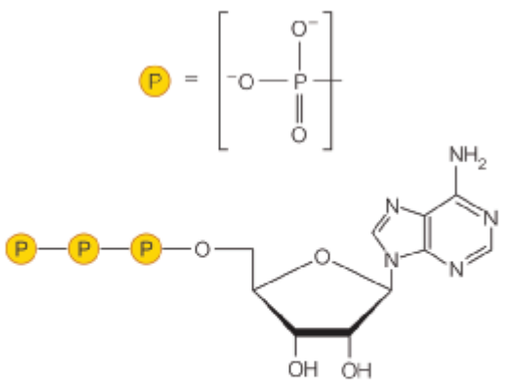
Understanding the central role of free energy changes in determining the favorable directions for chemical reactions is important in the study of biochemistry because every biochemical process (such as protein folding, metabolic reactions, DNA replication, or muscle contraction) must, overall, be a thermodynamically favorable process. Very often, a particular reaction or process that is necessary for life is in itself endergonic. Such intrinsically unfavorable processes can be made thermodynamically favorable by *coupling* them to strongly favorable reactions. Suppose, for example, we have a reaction A ⟶ B that is part of an essential pathway but is endergonic under standard conditions:

$$\text{A} \rightleftharpoons \text{B} \qquad \Delta G^{\circ\prime} = +10\ \text{kJ/mol}$$

C in our previous example) that can undergo reactions with large negative free energy changes. Such substances can be thought of as energy transducers in the cell. Many of these energy-transducing compounds are organic phosphates such as ATP (FIGURE 3.5), which can transfer a phosphoryl group ($-PO_3^{2-}$) to an acceptor molecule. You will see many examples of phosphoryl group transfer reactions in this text. As shown in Figure 3.5, we will use a common shorthand notation, Ⓟ, to represent the phosphoryl group when describing these processes.



Adenosine triphosphate (ATP)



▲ **FIGURE 3.5 The phosphoryl groups in ATP.** Top: The three phosphoryl groups in ATP are shown in red, blue, and green. Middle: A commonly used shorthand for a phosphoryl group is the symbol Ⓟ. Bottom: The three phosphoryl groups in ATP are represented by this symbol.

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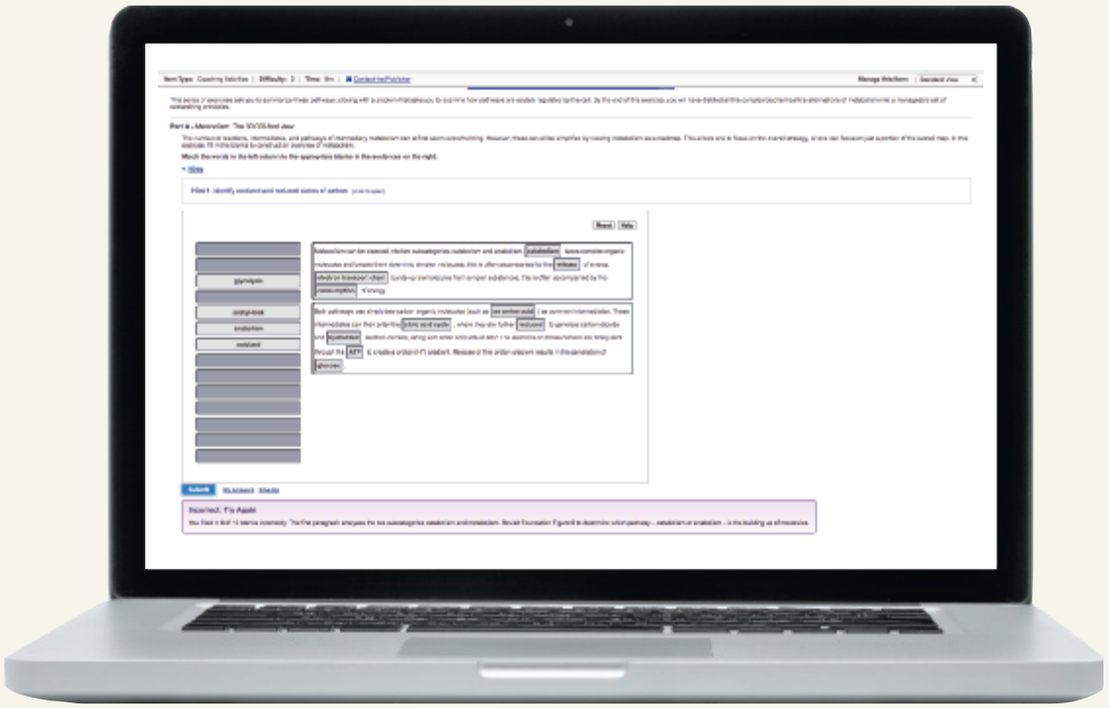

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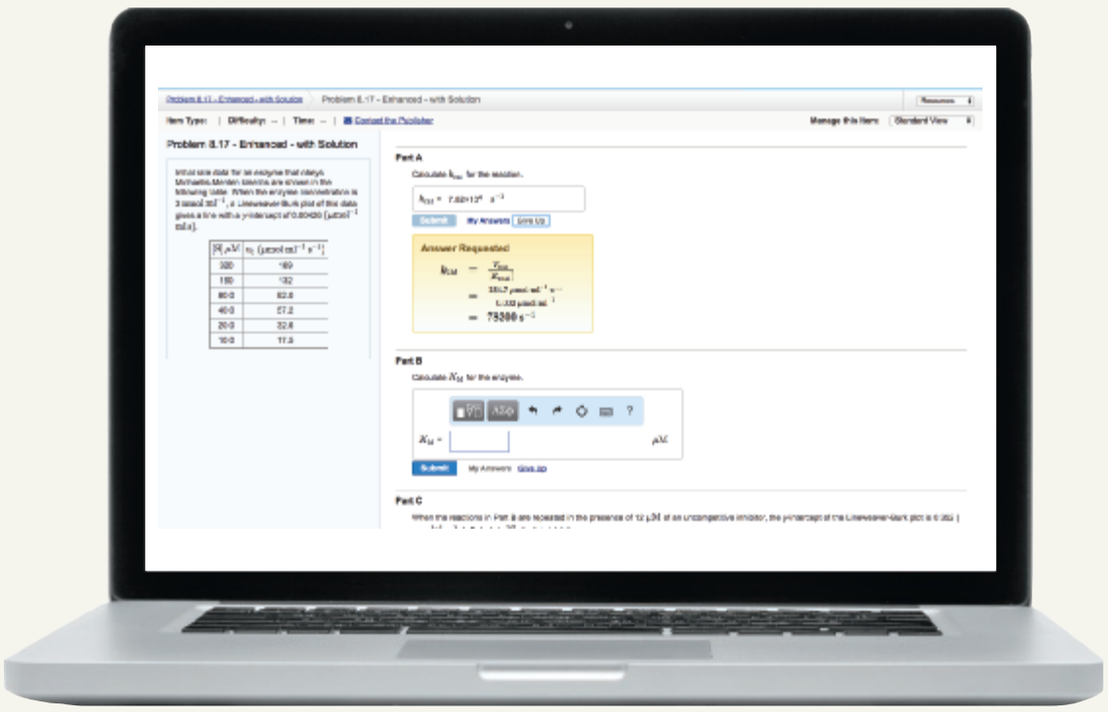

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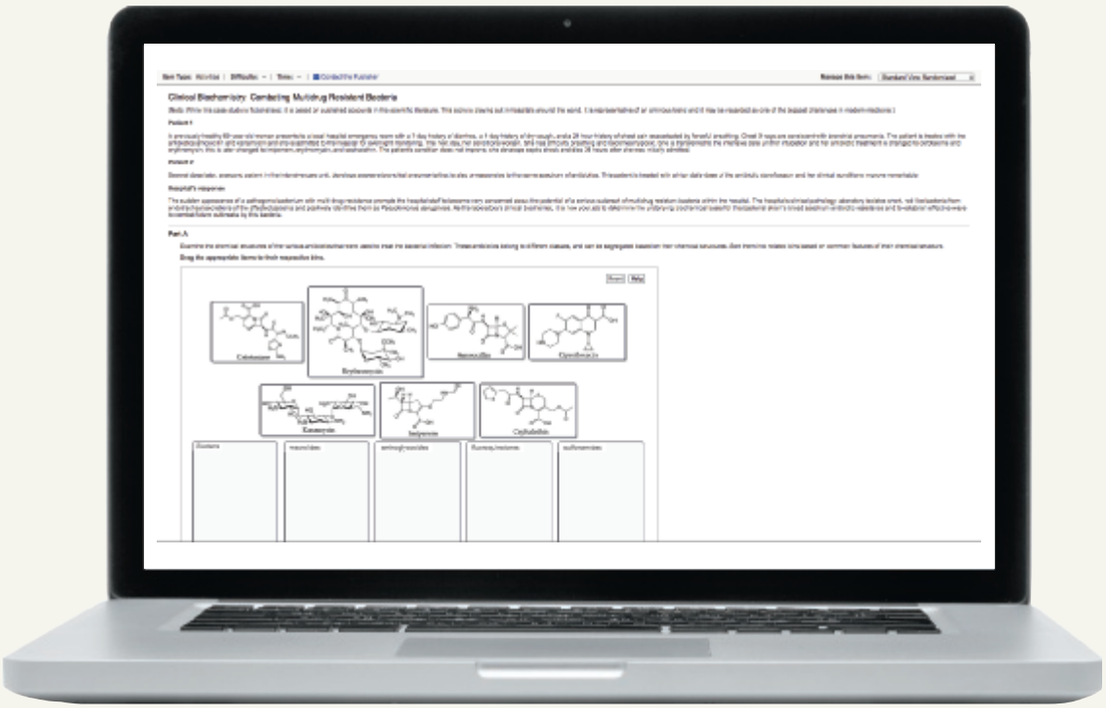

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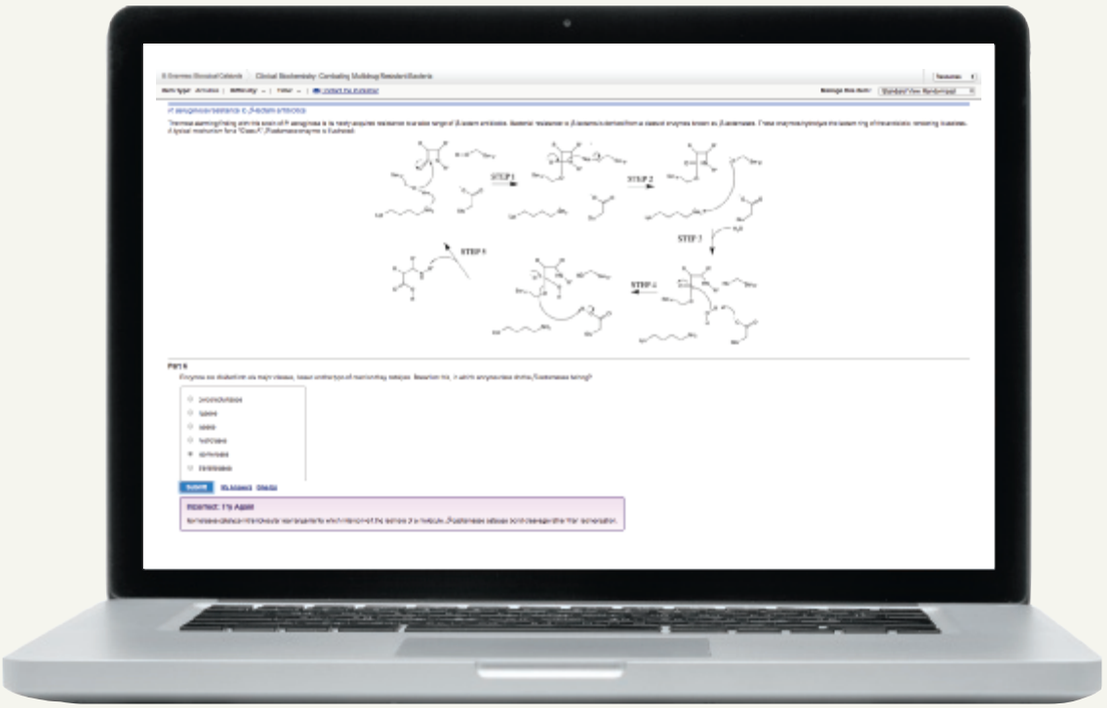

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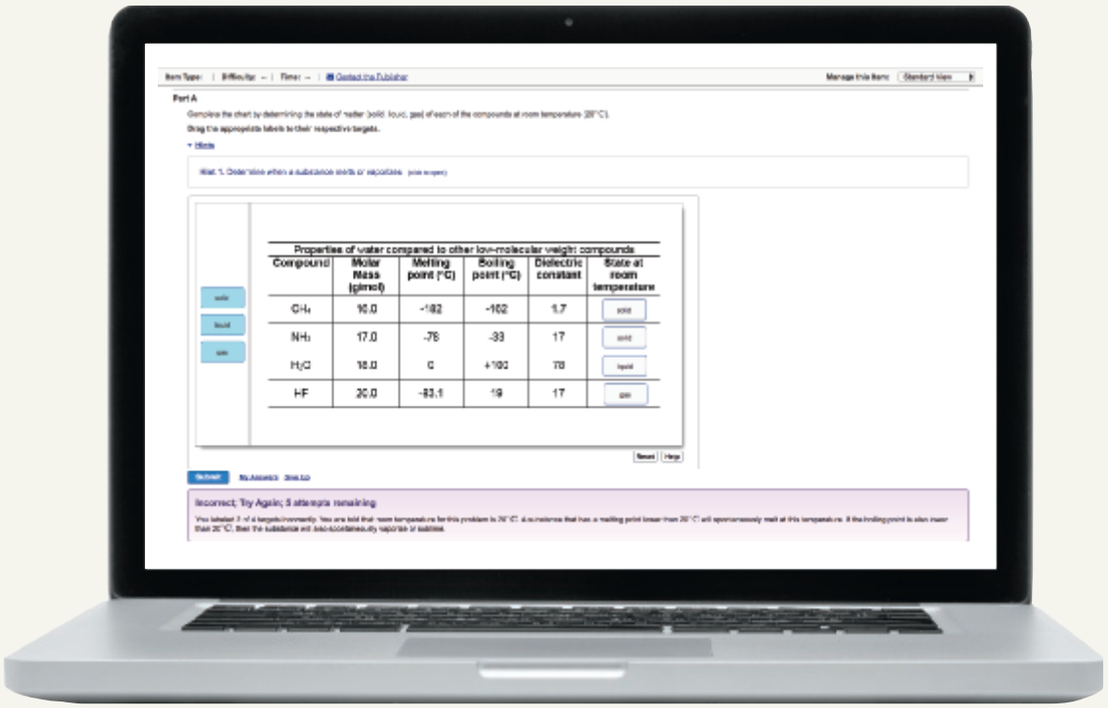

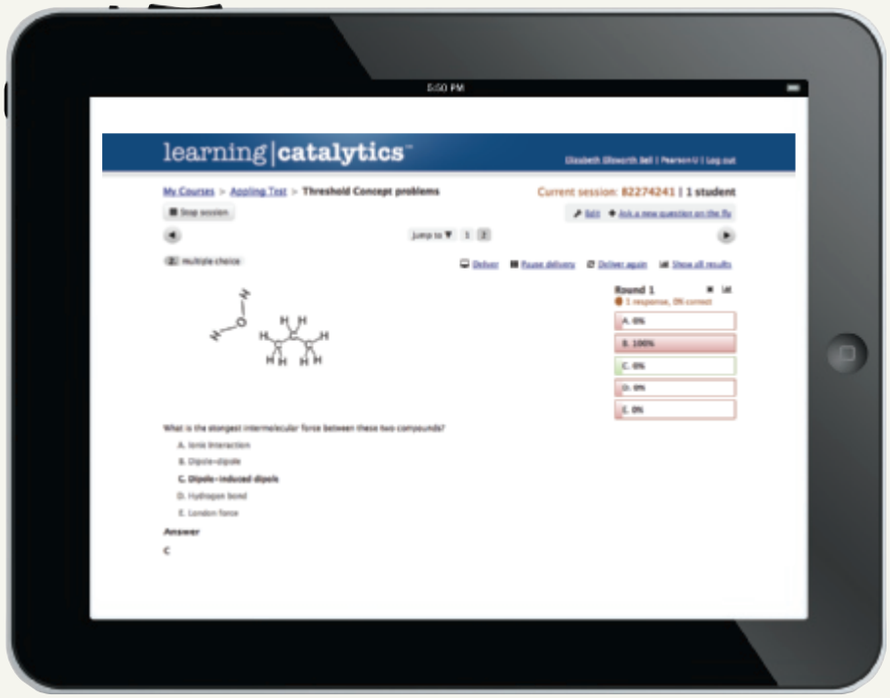

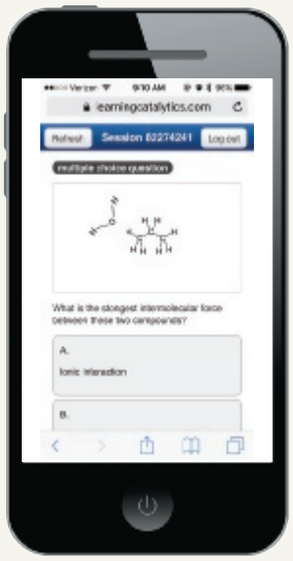

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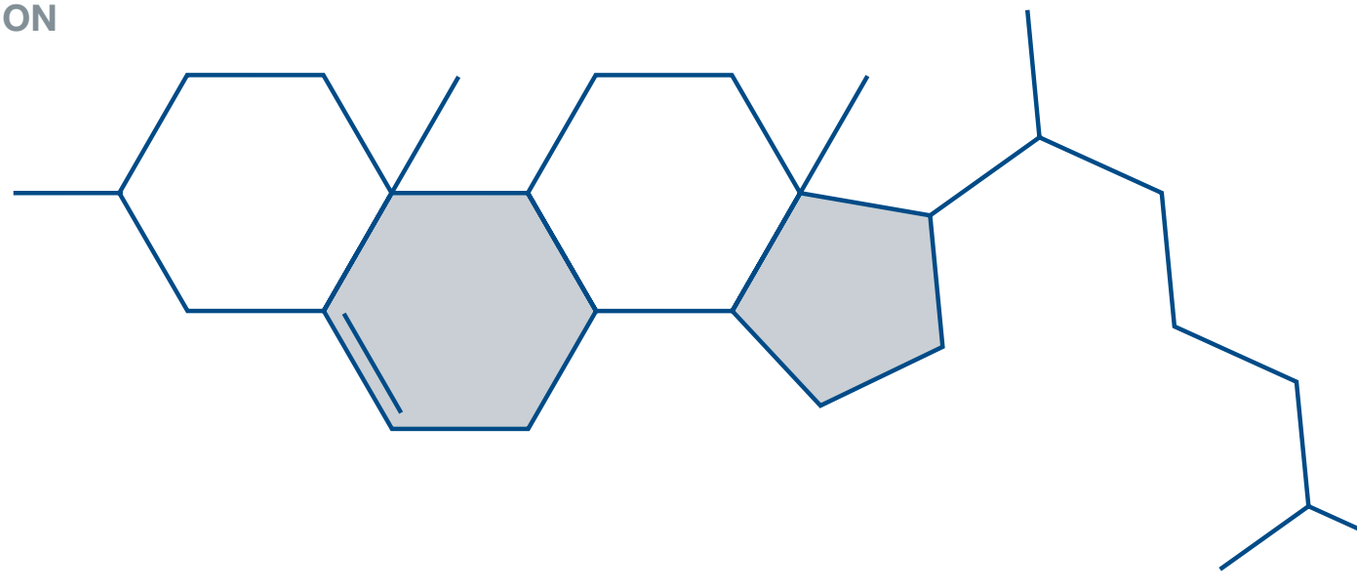


Discovering new medicines requires comprehension of the structure and function of the drug target, whether that be an enzyme, a gene, or a signaling molecule. Success in drug discovery requires deep understanding of biochemistry and its allied disciplines.

Biochemistry and the Language of Chemistry

1

"MUCH OF LIFE can be understood in rational terms if expressed in the language of chemistry. It is an international language, a language for all of time, and a language that explains where we came from, what we are, and where the physical world will allow us to go." These words were written in 1987 by Arthur Kornberg (1918–2007), one of the greatest biochemists of the twentieth century, and they provide a backdrop for our study of biochemistry. Because it seeks to understand the chemical basis for all life processes, biochemistry is at once a biological science and a chemical science. Indeed, all of the traditional disciplines within biology—including physiology, genetics, evolution, and ecology, to name a few—now use the language and techniques of chemistry. Many of you who are using this book are planning careers in life sciences—in teaching, basic research, health sciences, science journalism, drug discovery, environmental science, bioengineering, agriculture, science policy, and more. You will find biochemistry at the heart of all fields within the biological sciences.

Chapter 1

As we proceed through our study of biochemistry, think about "the language of chemistry." To understand a language, we must become familiar with the words and how to incorporate them into sentences. In this text we will be faced with numerous chemical names and structures that must be learned, such as the amino acids in proteins or the sugars in starch or cellulose. These are the *words* in the biochemical language, and learning them will occupy much of the first several chapters of this book. Next, we begin putting these words into *sentences*—chemical reactions—and *paragraphs*—metabolic pathways, which are made up of linked sequences of two or more individual reactions. Reading the sentences and paragraphs will require that we learn about enzymes and catalysis of biochemical reactions. Later we move from paragraphs to pages and chapters, as we explore how metabolic processes in different tissues interrelate to explain, for example, the adaptation of an animal to starvation, or the possible effects of calorie restriction on life-span extension. We will also learn what regulates expression of the biochemical language when we explore chromosomes, genomes, and genes—and how the controlled expression of genes dictates which sentences will be printed and in which cells, and how instructions in the language are transmitted from generation to generation.

As we discuss the biochemical language and its expression, three themes will dominate our discussion—*metabolism, energy,* and *regulation.* What are the chemical reactions? How is metabolic work done? How is expression of the language controlled?

● **CONCEPT** All of the life sciences require an understanding of the language of chemistry.

In order to apply the language of chemistry to learning biochemistry, you will need to recall much of what you learned in organic chemistry—the structures and properties of the principal functional groups, for example. Chapter 2 provides a brief review of the major functional groups, and Chapter 11 describes those reaction mechanisms most directly involved in biochemistry.

Because most of you are learning the biochemical language for the first time, our initial emphasis must be on individual reactions and pathways, operating to some extent in isolation. Be aware, however, that plucking individual reactions out of a cell for investigation is artificial and that a chemical reaction within a cell is but one in a coordinated system of hundreds or thousands of individual reactions, all occurring in the same time and space. In the past two decades, techniques have been developed that allow analysis of a true *systems biology*—chemical reactions as they occur within a complex system rather than in isolation. In time, we will discuss these techniques and what they teach us, but the emphasis in a first course in biochemistry is on elements and expression of the biochemical language.

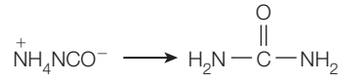
1.1 The Science of Biochemistry

Humankind has harvested the fruits of biochemistry for thousands of years, perhaps beginning some 8000 years ago with the fermentation of grapes into wine. **FIGURE 1.1** illustrates winemaking as it was carried out in Egypt in about 1500 B.C. However, the science behind winemaking and many other biochemical applications, such as medicinal folk remedies or the tanning of leather, remained obscure until the past three centuries or so, with the birth of biochemistry as a science. With respect to winemaking, see Chapter 12 for a presentation of **glycolysis,** the fundamental process for the breakdown of sugars, which in yeast and other microorganisms converts the sugar to ethanol.

The Origins of Biochemistry

Biochemistry as a science can be said to have originated early in the nineteenth century, with the pioneering work of Friedrich Wöhler (1800–1882) in Germany. Prior to Wöhler's time, it was believed that the substances in living cells and organisms were somehow qualitatively different from those in nonliving matter and did not behave according to the known laws of physics and chemistry. In 1828 Wöhler showed that urea, a substance of biological origin, could be synthesized in the laboratory from the inorganic compound, ammonium cyanate. As Wöhler phrased it in a letter to a colleague, "I must tell you that I can prepare urea without requiring a kidney or an animal, either man or dog." This was a shocking statement in its time, for it breached the presumed barrier between the living and nonliving.

Wöhler's synthesis of urea from ammonium cyanate:



Ammonium cyanate **Urea**

Another landmark in the history of biochemistry occurred in the mid-nineteenth century when the great French chemist Louis

▲ **FIGURE 1.1 An ancient application of biochemistry.** Manufacture of wine in Egypt, around 1500 B.C.

Pasteur (1822–1895) turned his attention to fermentation in order to help the French wine industry. Pasteur recognized that wine could be spoiled by the accidental introduction of bacteria during the fermentation process and that yeast cells alone possess the ability to convert the sugars in grapes to ethanol in wine. Following this discovery, he devised ways to exclude bacteria from fermentation mixtures.

● **CONCEPT** Early biochemists had to overcome the doctrine of vitalism, which claimed that living matter and nonliving matter were fundamentally different.

Although Pasteur demonstrated that yeast cells in culture could ferment sugar to alcohol, he adhered to the prevailing view known as *vitalism,* which held that biological reactions took place only through the action of a mysterious "life force" rather than physical or chemical processes. In other words, the fermentation of sugar into ethanol could occur only in whole, living cells.

The vitalist dogma was shattered in 1897 when two German brothers, Eduard (1860–1917) and Hans Buchner (1850–1902), found that extracts from broken and thoroughly dead yeast cells could carry out the entire process of fermentation of sugar into ethanol. This discovery opened the door to analysis of biochemical reactions and processes **in vitro** (Latin, "in glass"), meaning in a test tube—or, more generally, outside of a living organism or cell, rather than **in vivo,** in living cells or organisms. In the following decades, other metabolic reactions and reaction pathways were reproduced in vitro, allowing identification of reactants and products and of the biological catalysts, known as **enzymes,** that promoted each biochemical reaction. The name "enzyme," coined in 1878, comes from the Greek *en zyme* (meaning "in yeast"), reflecting the fact that the chemical nature of these catalysts did not become known until some time later, as described below.

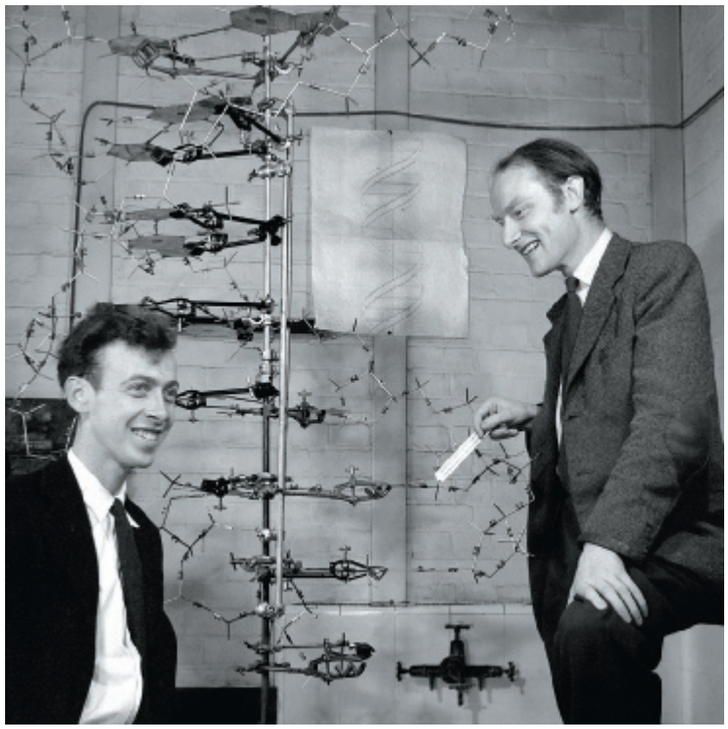
The nature of biological catalysis remained the last refuge of the vitalists, who held that the structures of enzymes were far too complex to be described in chemical terms. But in 1926, James B. Sumner (1887–1955) showed that an enzyme from jack beans, called **urease,** could be crystallized like any organic compound and that it consisted entirely of protein. Although proteins have large and complex structures, they are just organic compounds, and their structures can be determined by the methods of chemistry and physics. This discovery marked the final fall of vitalism.

Although developments in the first half of the twentieth century revealed in broad outline the chemical structures of biological materials, identified the reactions in many metabolic pathways, and localized these reactions within the cell, biochemistry remained an incomplete science. We knew that the uniqueness of an organism is determined by the totality of its chemical reactions. However, we had little understanding of how those reactions are controlled in living tissue or of how the information that regulates those reactions is stored, transmitted when cells divide, and processed when cells differentiate.

What factors determine why yeast cells might ferment sugars to ethanol, while bacteria contaminating a wine culture might convert the sugars to acetic acid and turn the wine culture to vinegar? To answer this question, we must understand expression of **genes,** which control synthesis of the enzymes involved. The idea of the gene, a unit of hereditary information, was first proposed in the mid-nineteenth century by Gregor Mendel (1882–1894), an Austrian monk, from his studies on the genetics of pea plants. By about 1900, cell biologists realized that genes must be found in chromosomes, which are composed of proteins and nucleic acids. Subsequently, the new science of genetics provided increasingly detailed knowledge of patterns of inheritance and development. However, until the mid-twentieth century no one had isolated a gene or determined its chemical composition. Nucleic acids had been recognized as cellular constituents since their discovery in 1869 by Friedrich Miescher (1844–1895). But their chemical structures were poorly understood, and in the early 1900s nucleic acids were thought to be simple substances, fit only for structural roles in the cell. Most biochemists believed that only proteins were sufficiently complex to carry genetic information.

That belief turned out to be incorrect. Experiments in the 1940s and early 1950s proved conclusively that **deoxyribonucleic acid (DNA)** is the primary bearer of genetic information (**ribonucleic acid, RNA,** is also an informational molecule). The year 1953 was a landmark year, when James Watson (1928–) and Francis Crick (1916–2004) described the double-helical structure of DNA. This concept immediately suggested ways in which information could be encoded in the structure of molecules and transmitted intact from one generation to the next. The discovery of DNA structure, which we describe more fully in Chapter 4, represents one of the most important scientific developments of the twentieth century (**FIGURE 1.2**).

● **CONCEPT** Biology was transformed in 1953, when Watson and Crick proposed the double-helical model for DNA structure.



▲ **FIGURE 1.2** James Watson and Francis Crick with their hand-assembled wire model of the structure of DNA.

Although Watson and Crick made their landmark discovery over six decades ago, the revolution ushered in by that discovery is still underway, as seen by some of the major advances that have occurred since 1953. By the early 1960s, we knew much about the functions of RNA in gene expression, and the genetic code had been deciphered (see Chapters 24 and 25). By the early 1970s, the first recombinant DNA molecules were produced in the laboratory (see Chapter 4), opening the door, as no other discovery had done, to practical applications of biological information in health, agriculture, forensics, and environmental science. By the next decade, scientists had learned how to amplify minute amounts of DNA (see Chapter 21) so that any gene could be isolated by cloning (Chapter 4), allowing any desired change to be made in the structure of a gene. After another decade, by the early 1990s, scientists had learned not only how to introduce new genes into the germ line of plants and animals, but also how to disrupt or delete any gene, allowing analysis of the biochemical function of any gene product (see Chapter 23). A decade later, the nearly complete nucleotide sequence of the human genome was announced—2.9×10^9 base pairs of DNA, representing more than 20,000 different genes. At about the same time came discoveries regarding noncoding properties of RNA, in catalysis and gene regulation (Chapters 7, 25, and 26). The 20-teens saw development of CRISPR **(clustered regularly interspersed short palindromic repeats)** technology, which allowed unprecedented opportunities for editing genes in living organisms (Chapter 23). The wealth of information from genomic sequence analysis and gene regulation by RNA continues to transform the biochemical landscape well into the twenty-first century.

The Tools of Biochemistry

The advances in biochemistry discussed in the previous section and described throughout this book would not have been possible without the development of new technologies for studying biological molecules and processes. Biochemistry is an experimental science—more so, for example, than physics, with its large theoretical component. To understand the key biochemical concepts and processes, we must have some understanding of the experiments that helped us elucidate them. We will describe the experimental basis for much of our understanding of biochemistry in this book. In some cases, the description of experimental techniques will be set apart in end-of-chapter segments called "Tools of Biochemistry."

In the case of DNA structural analysis, the needed technology came from X-ray diffraction. Physicists and chemists had learned that the molecular structures of small crystals could be determined by analyzing patterns showing how X-rays are deflected upon striking atoms in a crystal. Stretched DNA fibers yield comparable data, and these patterns (obtained by Rosalind Franklin, 1920–1958; see Chapter 4), along with the chemical structures of the individual nucleotide units in DNA, led Watson and Crick to their leap of intuition.

FIGURE 1.3 shows a timeline for introduction of methods related to biochemistry beginning at the end of World War II (1945) with the introduction of radioisotopes; these are used to tag biomolecules so that they can be followed through reactions and pathways. Other notable developments include gel electrophoresis (early 1960s), which allows separation and analysis of nucleic acids and proteins. By the early 1970s, restriction enzymes (Chapter 21) had been shown to cut DNA strands at particular sequences in DNA molecules; this finding opened the door to isolating individual genes by recombinant DNA technology. Polymerase chain reaction (Chapter 21) allowed the amplification of selected DNA sequences from minute tissue samples. CRISPR technology (Chapter 23), introduced in 2013, allowed unprecedented opportunities for genome editing in living cells. Throughout this book we will be describing these and other benchmark technologies, and you may wish to refer back to this figure.

● **CONCEPT** Powerful new chemical and physical techniques have accelerated the pace at which biological processes have become understood in molecular terms.

Biochemistry as a Discipline and an Interdisciplinary Science

In trying to define biochemistry, we must consider it both as an interdisciplinary field and as a distinct discipline. Biochemistry shares its major concepts and techniques with many disciplines—with organic chemistry, which describes the properties and reactions of carbon-containing molecules; with physical chemistry, which describes thermodynamics, reaction kinetics, and electrical parameters of oxidation–reduction reactions; with biophysics, which applies the techniques of physics to study the structures of biomolecules; with medical science, which increasingly seeks to understand disease states in molecular terms; with nutrition, which has illuminated metabolism by describing the dietary requirements for maintenance of health; with microbiology, which has shown that single-celled organisms and viruses are ideally suited for the elucidation of many metabolic pathways and regulatory mechanisms; with physiology, which investigates life processes at the tissue and organism levels; with cell biology, which describes the metabolic and mechanical division of labor within a cell; and with genetics, which analyzes mechanisms that give a particular cell or organism its biochemical identity. Biochemistry draws strength from all of these disciplines, and it nourishes them in return; it is truly an interdisciplinary science.

2015
- Cryo-electron microscopy
- CRISPR-Cas9 technology

- Synthetic biology

2010
- RNA-sequence analysis
- Chromatin immunoprecipitation/ sequencing
- Induced pluripotent cells
- Second generation DNA sequence analysis

2005
- Proteomic analysis with mass spectrometry

2000
- Genetic code expansion
- Gene analysis on microchips

- Single-molecule dynamics

1995
- Targeted gene disruption

- In vivo NMR
- Atomic force microscopy

1990
- Scanning tunneling microscopy

1985
- Pulsed field electrophoresis
- Transgenic animals
- Amplification of DNA: polymerase chain reaction
- Automated oligonucleotide synthesis

1980
- Site-directed mutagenesis of cloned genes
- Automated micro-scale protein sequencing
- Rapid DNA sequence determination
- Monoclonal antibodies

1975
- Southern blotting
- Two-dimensional gel electrophoresis
- Gene cloning

1970
- Restriction cleavage mapping of DNA molecules

- Rapid methods for enzyme kinetics

1965
- High-performance liquid chromatography
- Polyacrylamide gel electrophoresis
- Solution hybridization of nucleic acids

1960
- X-ray crystallographic protein structure determination
- Zone sedimentation velocity centrifugation
- Equilibrium gradient centrifugation
- Liquid scintillation counting

1955
- First determination of the amino acid sequence of a protein
- X-ray diffraction of DNA fibers

1950

1945
- Radioisotopic tracers used to elucidate reactions

◀ **FIGURE 1.3 The recent history of biochemistry as shown by the introduction of new research techniques.** The timeline begins with the introduction of radioisotopes as biochemical reagents, immediately following World War II.

You may wonder about the distinction between biochemistry and *molecular biology,* because both fields take as their ultimate aim the complete definition of life in molecular terms. The term *molecular biology* is often used in a narrower sense to denote the study of nucleic acid structure and function and the genetic aspects of biochemistry—an area we might more properly call *molecular genetics* or *genetic biochemistry*.

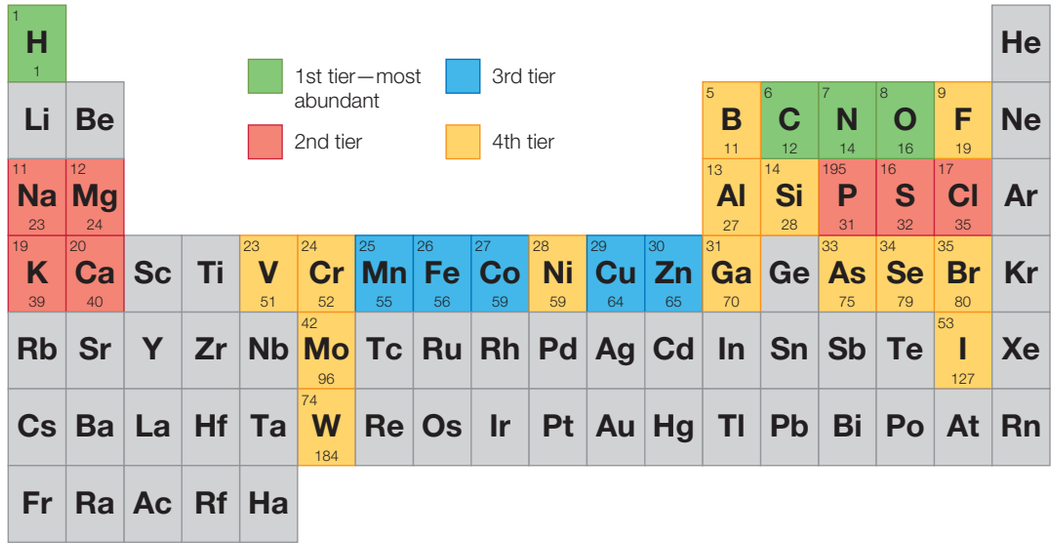
Regardless of uncertainty in terminology, biochemistry is a distinct discipline, with its own identity. It is distinctive in its emphasis on the structures and reactions of biomolecules, particularly on enzymes and biological catalysis and on the elucidation of metabolic pathways and their control. As you read this book, keep in mind both the uniqueness of biochemistry as a separate discipline and the absolute interdependence of biochemistry and other physical and life sciences.

1.2 The Elements and Molecules of Living Systems

All forms of life, from the smallest bacterial cell to a human being, are constructed from the same chemical elements, which in turn make up the same types of molecules. The chemistry of living systems is similar throughout the biological world; the reactions and pathways that will concern us involve fewer than 200 different molecules. Undoubtedly, this continuity in biochemical processes reflects the common evolutionary ancestry of all cells and organisms. Let us begin to examine the composition of living systems, starting with the chemical elements and then moving to biological molecules.

The Chemical Elements of Cells and Organisms

Life is a phenomenon of the second generation of stars. This rather strange-sounding statement is based on the fact that life, as we conceive it, could come into being only when certain elements—carbon, hydrogen, oxygen, nitrogen, phosphorus, and sulfur (C, H, O, N, P, and S)—were abundant (**FIGURE 1.4**). The primordial universe was made up almost entirely of hydrogen (H) and helium (He), for only these simplest elements were produced in the condensation of matter following the primeval explosion, or "big bang," which we think created the universe. The first generation of stars contained no heavier elements from which to form planets. As these early stars matured over the next seven to eight billion years, they burned their hydrogen and helium in thermonuclear reactions. These reactions produced heavier elements—first carbon, nitrogen, and oxygen, and eventually all the other members of the periodic table. As large stars matured, they became unstable and exploded as novas and supernovas, spreading the heavier elements through the cosmic surroundings. This matter condensed again to form



▲ **FIGURE 1.4 Periodic table pertinent to biochemistry.** The four tiers of chemical elements, grouped in order of their abundance in living systems, are highlighted in separate colors.

CONCEPT Life depends primarily on a few elements (C, H, O, N, S, and P), although many others have essential functions as well.

second-generation stars, at least some of which (like our sun) have planetary systems incorporating these heavier elements. Our universe, which is now rich in second-generation stars, has an elemental composition compatible with life as we know it.

Relatively few elements are involved in the creation of living systems. Living creatures on Earth are composed primarily of just four elements—carbon, hydrogen, oxygen, and nitrogen. These are also the most abundant elements in the universe, along with helium and neon. Helium and neon, inert gases, are not equipped for a role in life processes; they do not form stable compounds, and they are readily lost from planetary atmospheres.

The abundance of oxygen and hydrogen in organisms is explained partly by the major role of water in life on Earth. We live in a highly aqueous world, and, as we will see in Chapter 2, the solvent properties of water are indispensable in biochemical processes. The human body, in fact, is about 70% water. The elements C, H, O, and N are important to life because of their strong tendencies to form covalent bonds. In particular, the stability of carbon–carbon bonds and the possibility of forming single, double, or triple bonds give carbon the versatility to be part of an enormous diversity of chemical compounds.

But life is not built on these four elements alone. Many other elements are necessary for organisms on Earth, as you can see in Figure 1.4. A "second tier" of essential elements includes sulfur and phosphorus, which form covalent bonds, and the ions Na^+, K^+, Mg^{2+}, Ca^{2+}, and Cl^-. Sulfur is a constituent of nearly all proteins, and phosphorus plays essential roles in energy metabolism and the structure of nucleic acids. Beyond the first two tiers of elements (which correspond roughly to the most abundant elements in the first two rows of the periodic table), we come to those that play quantitatively minor—but often indispensable—roles. As Figure 1.4 shows, most of these third- and fourth-tier elements are metals, some of which serve as aids to the catalysis of biochemical reactions.In succeeding chapters we shall encounter many examples of the importance of these trace elements to life. Molybdenum, for example, is essential in nitrogen fixation—the reduction of nitrogen gas in the atmosphere to ammonia, for synthesis of nucleic acids and proteins (see Chapter 18).

The Origin of Biomolecules and Cells

Once the chemical elements had formed, during cooling of the second-generation stars, how did the complex molecules that we associate with living systems come into being on Earth? An educated guess is that they arose as part of a "primordial soup" within the oceans. Because the strong oxidant, oxygen, was absent from Earth's atmosphere, scientists hypothesize that a highly reducing environment prevailed within the primordial atmosphere, a condition that tends to promote joining reactions of atoms and molecules. Moreover, high-energy discharges were thought to occur through lightning or volcanic eruptions, providing sufficient energy to drive atoms and small molecules together.

In 1953, Stanley Miller tested this hypothesis by simulating the presumed primordial environment. Miller mixed ammonia, methane, water, and hydrogen in a closed system subject to continuous electric discharge. After several days, the system was analyzed and shown to contain several amino acids, as well as other simple compounds, including carbon monoxide, carbon dioxide, and hydrogen cyanide. Thus, it was established that biological compounds could have been produced abiotically (without living systems). Refinements of the Miller experiment have shown that much more complex organic molecules can also arise under similar conditions.

How we went from the primordial soup, rich in potential biomolecules, to primitive living systems is still a matter of conjecture. Many biochemists believe that the earliest primitive systems, capable of self-replication and some form of metabolism, were based on ribonucleic acid (RNA). RNA is a more versatile molecule than DNA, as we discuss in Chapters 4 and 8, and it is capable of catalyzing chemical reactions as well as storing information. Thus, biochemists speak of an ancient "RNA world," in which simple self-replicating cellular structures, surrounded by crude, lipid-rich membranes, might have existed. Eventually, because DNA is more stable than RNA, this presumed chemical evolution would have led to processes by which RNA or its component nucleotides could give rise to DNA-based life forms.

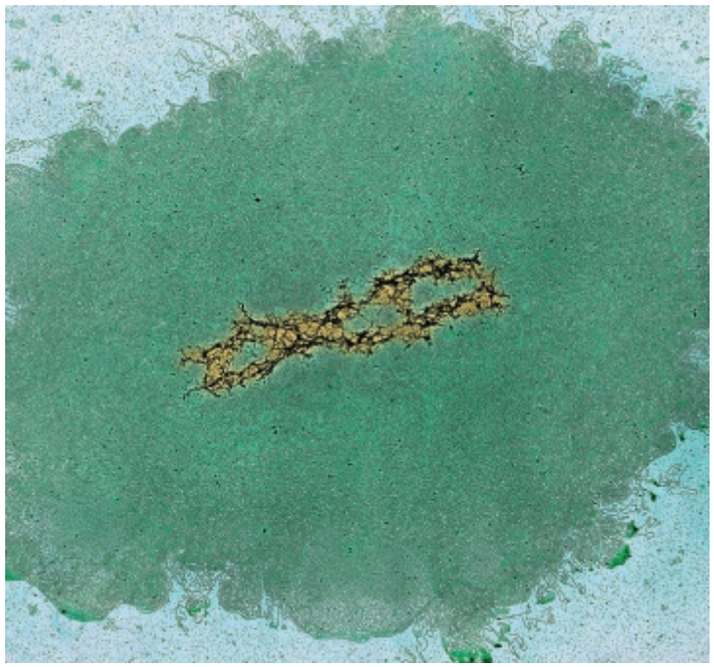
The earliest living systems would almost certainly have been anaerobic because of the absence of oxygen in the atmosphere. Energy was probably obtained from coupled oxidation–reduction reactions involving inorganic compounds of sulfur and iron. Over time, photosynthetic capability would have arisen, as some organisms evolved the ability to harness light energy from the sun to drive the reduction of inorganic compounds, notably CO_2, to reduced organic compounds. Eventually, organisms would have developed the ability to use water as an electron donor, thereby creating enough oxygen over time to enrich the atmosphere with oxygen. Because much more energy can be derived through complete oxidation of organic compounds than from anaerobic processes (see Chapter 11), aerobic organisms would have had a large evolutionary advantage.

As primitive bacteria underwent the numerous changes leading to characteristic features of eukaryotic cells—condensation of genes into chromosomes, development of intracellular membranous structures—some eukaryotic cells acquired new metabolic capabilities through infection with aerobic bacteria or photosynthetic bacteria. Over time, the intracellular organisms living in this symbiotic relationship underwent their own evolution, eventually becoming what we now recognize as mitochondria and chloroplasts in present-day cells.

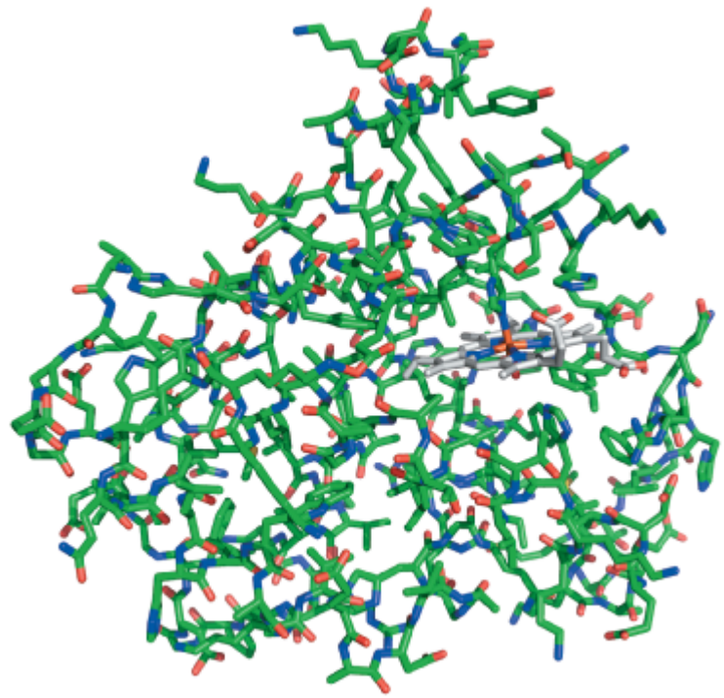
How long might this process have taken? Geologists tell us that Earth was formed about 4.6 billion years ago. Rocks containing carbon of likely biological origin have been dated to more than 3.5 billion years ago. Evidence for aerobic bacteria and an oxygen-rich atmosphere dates to about 2.5 billion years ago, with the first eukaryotic microorganisms following about one billion years later. The earliest multicellular eukaryotes are 400 to 500 million years old. Although we understand the forces that have shaped life since it arose—and these will be described as we proceed through our study of biochemistry—our understanding of the origin of life is conjectural. Although the spontaneous generation of self-replicating entities seems highly improbable, the enormous amount of time during which this could have occurred changes the almost impossible to highly likely, and perhaps inevitable.

The Complexity and Size of Biological Molecules

The complexity of life processes requires that many of the molecules governing them be enormous. Consider, for instance, the DNA molecules released from one human chromosome, as shown in **FIGURE 1.5**. The long, looped thread you see corresponds to a small part of a huge molecule, with a molecular mass of about 20 billion daltons. (A dalton, Da, is 1/12 the mass of a carbon-12 atom, 1.66×10^{-24} g.) Even a simple organism such as the single-celled bacterium *Escherichia coli* contains a DNA molecule with a molecular mass of about 2 billion Da—more than one millimeter long. Protein molecules are generally much smaller than DNA molecules,



▲ **FIGURE 1.5 Part of the DNA from a single human chromosome.** Most of the chromosomal proteins have been removed in this color-enhanced electron micrograph, leaving only a protein "skeleton" from which enormous loops of DNA emerge.



▲ **FIGURE 1.6 The three-dimensional structure of myoglobin.** This computer-generated stick model portrays sperm whale myoglobin, the first protein whose structure was deduced by X-ray diffraction. It depicts, therefore, our first indication of the complexity and specificity of the three-dimensional structure of proteins. PDB ID: 1mbn.

but they are still large, with molecular masses ranging from about 10,000 to one million Da. The complexity of these molecules is seen from the three-dimensional structure of even a fairly small protein. **FIGURE 1.6** illustrates the structure of myoglobin, an oxygen-carrying protein of muscle, which has a molecular mass of about 17,000 Da.

Biological **macromolecules** are giant molecules made up of smaller organic molecule subunits. In living organisms, there are four major classes of macromolecules, all essential to the structure and function of cells: proteins, nucleic acids, carbohydrates, and lipids. As we shall see throughout this text, there are good reasons for some biological materials to be so large. DNA molecules, for example, can be thought of as tapes from which genetic information is read out in a linear fashion. Because the amount of information needed to specify the structure of a multicellular organism is enormous, these tapes must be extremely long. In fact, if the DNA molecules in a single human cell were stretched end to end, they would reach a length of about 2 meters. As revealed in the early twenty-first century through the Human Genome Project, the information encoded in this DNA is sufficient to encode about 100,000 proteins, although the actual number of genes is far smaller.

The Biopolymers: Proteins, Nucleic Acids, and Carbohydrates

The synthesis of such large molecules poses an interesting challenge to the cell. If the cell functioned like an organic chemist carrying out a complex laboratory synthesis bit by bit, millions of different types of reactions would be involved, and thousands of intermediates would accumulate. Instead, cells use a modular approach for constructing large polymeric molecules. These **biopolymers** are made by joining together prefabricated units, or **monomers.** Of the four classes of macromolecules, three of them are biopolymers: proteins, nucleic acids, and carbohydrates. Lipids, the fourth class of macromolecule, are not considered polymers and are discussed in the next section.

● **CONCEPT** Cells use a modular approach for constructing large molecules.

The monomers of a given type of macromolecule are of limited diversity and are linked together, or **polymerized,** by identical mechanisms. Each process involves **condensation,** or removal of a molecule of water in the joining reaction. A simple example is the carbohydrate **cellulose** (**FIGURE 1.7(a)**), a major constituent of the cell walls of plants. Cellulose is a polymer made by joining thousands of molecules of glucose, a simple sugar. In this polymer, all of the chemical linkages between the monomers are identical. Covalent links between glucose units are formed by removing a water molecule between two adjoining glucose molecules; the portion of each glucose molecule remaining in the chain is called a glucose **residue.** Because cellulose is a polymer of a simple sugar, or **saccharide,** it is called a **polysaccharide.** This particular polymer is constructed from identical monomeric units, so it is called a **homopolymer.** In contrast, many polysaccharides—and all nucleic acids and proteins—are **heteropolymers,** polymers constructed from a number of different kinds of monomer units.

Nucleic acids (Figure 1.7(b)) are polymers made up of four **nucleotides,** so nucleic acids are also called **polynucleotides.** Similarly, proteins (Figure 1.7(c)) are assembled from combinations of 20 different **amino acids.** Protein chains are called **polypeptides,** a term derived from the **peptide bond** that joins two amino acids together.

Polymers form much of the structural and functional machinery of the cell. Polysaccharides serve both as structural components, such as cellulose, and as reserves of biological energy, such as **starch,** another type of glucose polymer found in plants. The nucleic acids, DNA and RNA,