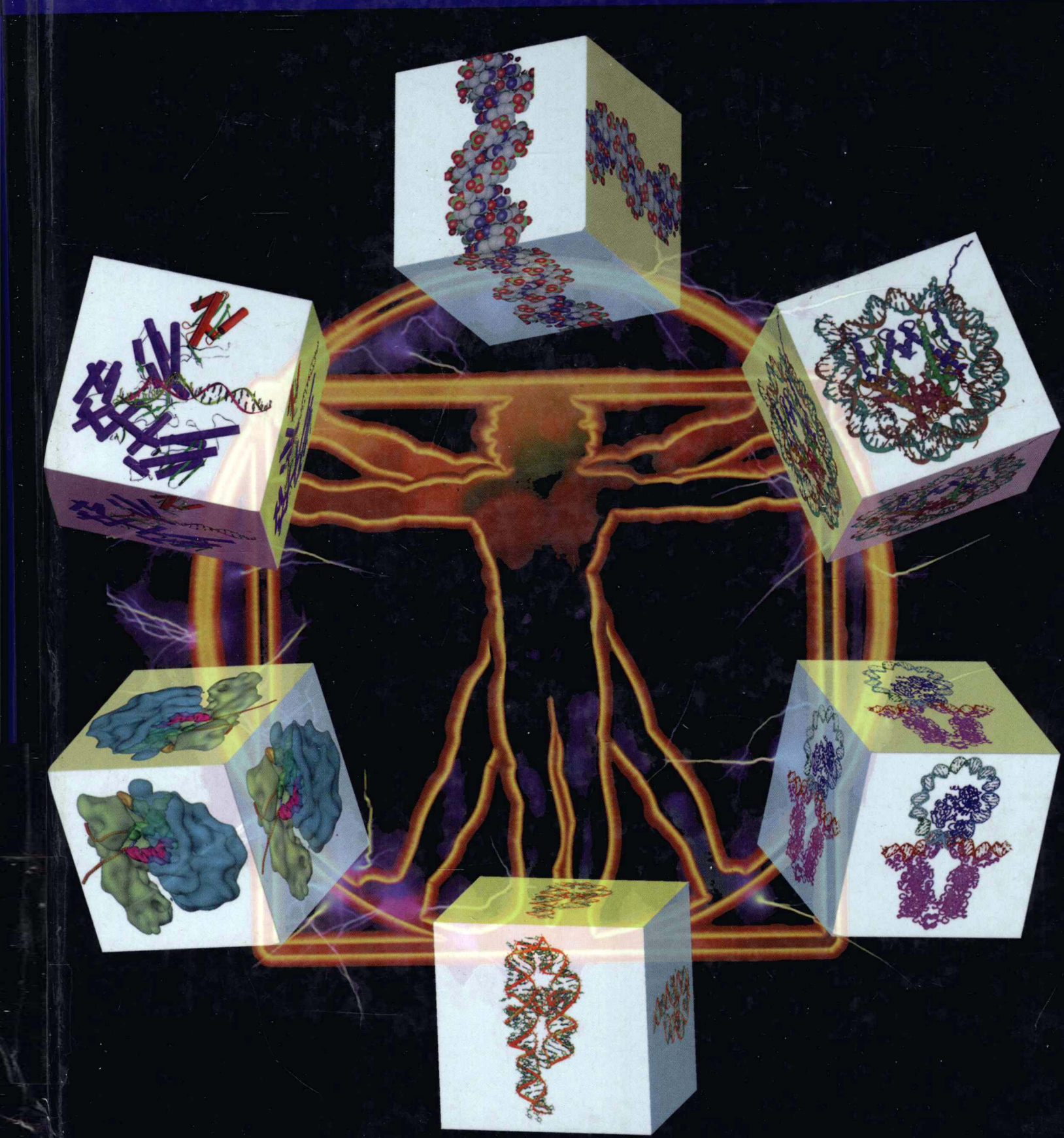
FUNDAMENTALS OF BIOCHEMISTRY

Donald Voet • Judith G. Voet • Charlotte W. Pratt



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The front cover shows some of the molecular assemblies that form the circle of life:
DNA makes RNA makes protein makes DNA.

The images are (*clockwise from the top*):

1. B-DNA, *based on an X-ray structure by Richard Dickerson and Horace Drew.*
2. The nucleosome, *courtesy of Timothy Richmond.*
3. Model of the *lac* repressor in complex with DNA and CAP protein, *courtesy of Ponzy Lu and Mitchell Lewis.*
4. Ribozyme RNA, *based on an X-ray structure by Jennifer Doudna.*
5. The ribosome in complex with tRNAs, *courtesy of Joachim Frank.*
6. DNA polymerase in complex with DNA, *courtesy of Tom Ellenberger.*

The central image is based on Leonardo da Vinci's drawing *Study of Proportions.*
It represents for us the never ending human quest for understanding. (© G. Bartholomew/ Westlight)

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This book is printed on acid-free paper. ♾

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PREFACE

The pleasure of mastering a difficult subject is matched only by the excitement of successfully conveying our knowledge to others. Our objective in writing this textbook therefore was to approach biochemistry as instructors attuned to students' needs. Accordingly, we have constructed a text that is carefully organized, clearly written, and generously illustrated. We sought not to be encyclopedic but instead to present a broad and lucid survey of biochemistry. There is no substitute for a well-crafted text to guide students through an ever-expanding body of knowledge whose relevance and utility is beyond question.

Readers familiar with *Biochemistry* by Donald Voet and Judith G. Voet will be pleased to find that *Fundamentals of Biochemistry* retains the overall philosophy of the larger book but dispenses with the level of detail that some students find overly burdensome. However, *Fundamentals of Biochemistry* is by no means an abridgment of *Biochemistry;* rather, it is an entirely new work with its own organization and style. *Fundamentals of Biochemistry,* like its parent, presents biochemistry with chemical rigor, focusing on the structures of biomolecules, chemical mechanisms, and evolutionary relationships. It is written to impart a sense of the intellectual history of biochemistry, an understanding of the tools and approaches used to solve biochemical puzzles, and a hint of the excitement that accompanies new discoveries. We have also been attentive to the need for up-to-date coverage, particularly regarding human health and disease, since many students of biochemistry subsequently pursue careers in this area. Ultimately, we hope to convey an appreciation for the awe-inspiring beauty of the structure and chemistry of life.

Organization

Fundamentals of Biochemistry is organized into five parts:

1. Two introductory chapters covering the origin of life, evolution, an introduction to thermodynamics, the properties of water, and acid–base chemistry.
2. Eight chapters on biomolecular structure. These cover nucleotides and nucleic acids, amino acids, proteins, carbohydrates, lipids, and biological membranes.
3. Two chapters on enzymes.
4. Ten chapters on metabolism, including an introductory chapter to provide an overview of metabolic pathways, the thermodynamics of "high-energy" compounds, and redox chemistry. A chapter on the integration of metabolism highlights organ specialization and metabolic regulation in mammals.
5. Five chapters to describe the biochemistry of nucleic acids. An introductory chapter includes a unique section on DNA binding proteins to set the stage for understanding many of the proteins that catalyze and regulate replication, transcription, and translation.

We have organized the material in *Fundamentals of Biochemistry* according to the way we would teach it. Yet we recognize that many instructors adhere to different syllabi. The chapters of *Fundamentals of Biochemistry* are therefore divided into sections and subsections that make it easy for instructors and students alike to locate particular subjects and to discern the thematic links among them. We hope that this format allays the anxiety of the reader who "skips around" yet fears missing critical information.

Thermodynamics is introduced in Chapter 1 since it is needed to understand the hydrophobic effect (Chapter 2) and protein structure (Chapter 6). The thermodynamics of metabolic reactions is revisited in Chapter 13, the introduction to metabolism. Here, oxidation–reduction reactions are discussed, although the material on electrochemistry could be deferred until Chapter 17 (Electron Transport and Oxidative Phosphorylation).

Early coverage of nucleotides and nucleic acids (Chapter 3) pays homage to the central role these substances play in biochemistry. Virtually every area of protein chemistry depends on cloning, sequencing, expression, and mutagenesis of genes that encode proteins. Therefore, to comprehend how proteins are studied and how proteins can reveal evolutionary history, students should understand how nucleic acids underlie all of biochemistry. This chapter also serves as a review for students who are already familiar with the biological roles of DNA and RNA and allows better coverage of protein evolution before nucleic acids are covered in detail in the last part of the book. It also provides an introduction to nucleotides such as ATP that play an important role in metabolism. Chapter 3 is designed so that it can also be covered later in the course, after other macromolecules have been presented, or in conjunction with Chapter 23, which takes up the finer points of nucleic acid structure and nucleic acid–protein interactions.

The two chapters on enzymes (Chapters 11 and 12) appear between chapters on molecular structure and chapters on metabolism but could just as easily be covered immediately after protein structure (Chapter 6) or the

chapter on protein function (Chapter 7). A discussion of enzyme mechanisms (Chapter 11) precedes the treatment of enzyme kinetics (Chapter 12) because it is easier for students to see how enzymes work before being presented with the more abstract reaction kinetics.

Similarly, chapters on carbohydrates (Chapter 8), lipids (Chapter 9), and membranes (Chapter 10) can be covered along with other macromolecules (Chapters 3–7), following enzymes (Chapters 11 and 12), or in conjunction with the corresponding chapters in the metabolism section.

Central metabolic pathways are presented in detail (e.g., glycolysis and the citric acid cycle) so that students can appreciate how individual enzymes catalyze reactions and understand how enzymes work in concert to perform complicated biochemical tasks. The regulation of pathways is also a central feature. Not all pathways are described in full detail, particularly some lipid and amino acid biosynthetic pathways. Instead, key enzymatic reactions are highlighted for their interesting chemistry or regulatory properties. The focus is on mammalian metabolism, with mention of interesting variations in other types of organisms. Thus, students can focus on human health and disease.

Virtually all of carbohydrate metabolism is covered in Chapters 14 and 15. The absence of intervening material permits students to develop a better appreciation of the features of opposing metabolic pathways (e.g., glucose or glycogen synthesis and degradation). A chapter on the integration of mammalian metabolism (Chapter 21) highlights such interorgan metabolic processes as the Cori cycle and the development of diabetes, which can be fully comprehended only in this context.

Chapters 24–26 discuss DNA replication, transcription, and translation in somewhat parallel fashion so that students can more easily spot similarities in the initiation, elongation, and termination phases of these processes.

Chapter 27 deals with a variety of regulatory mechanisms that have been collected here so that the chapters on transcription and translation will not contain material that might be considered optional, thereby making it easier to focus on the primary pathways. Material from Chapter 27, of course, can be interspersed with material from Chapters 25 and 26 according to individual instructors' preferences.

Pedagogical Features

We have built several features into the text to guide students, to help them discern the fundamental principles, and to help them study. To begin, each chapter opens with a figure that illustrates a principle that is covered in that chapter. Material within chapters is arranged in **outline form** to help the student understand the relationships among various topics.

The names of biochemical processes, compounds, enzymes, and diseases are highlighted in boldface at their first appearance. A list of **key terms** at the end of each chapter prompts students for definitions or explanations of the most important biochemical terms. Definitions for these and other terms are included in a **glossary** at the end of the book for easy reference. **Key sentences** emphasizing experimental conclusions and major biochemical principles are italicized.

Key figures and tables, focusing on structure, function, and metabolism, are identified for more careful study. Examples are the mechanism of force generation in muscle (Fig. 7-29), the catalytic mechanism of serine proteases (Fig. 11-26), the reactions of the citric acid cycle Fig. 16-2), and the elongation cycle in *E. coli* ribosomes (Fig. 26-28). **Overview figures** at various points in Chapters 13–21 help students follow complicated metabolic processes.

The **illustration program** includes a variety of types of figures, on the premise that students benefit from seeing biomolecules and processes depicted in different ways, in many cases as presented by the investigators who first described them. Accordingly, the text is illustrated with reproductions of figures from the research literature, computer-generated molecular models, electron micrographs, line drawings, tables, and schematic diagrams.

Those figures that are highlighted with a disk icon ( ) are presented as interactive molecular graphics diagrams on the **CD-ROM** that is placed in the back of this textbook. These are in the form of **Interactive Exercises** (Chime™-based images) and **Kinemages** that students can rotate, animate, and otherwise manipulate. The CD-ROM additionally contains a series of computer graphics-animated **Guided Explorations** that deal with a variety of topics.

Optional enrichment material is placed in **boxes** so that the main text contains fewer digressions. Three types of boxes, which in all cases are clearly linked to the text, offer additional information and food for thought. **Biochemistry in Focus** boxes include descriptions of techniques and approaches to biochemical problems as well as upper-level information that might otherwise be beyond the scope of the text (e.g., Box 3-2, Uses of PCR; Box 11-2, Catalytic Antibodies; Box 23-3, Packaging Viral Nucleic Acids). **Biochemistry in Context** boxes are devoted to topics that are of a more theoretical nature and are intended to prompt students to link their biochemical knowledge to other areas of study (e.g., Box 15-1, Optimizing Glycogen Structure; Box 24-5, Why Doesn't DNA Contain Uracil?). **Biochemistry in Health and Disease** boxes include descriptions of diseases resulting from biochemical defects (e.g., Box 6-4, Diseases Related to Protein Folding; Box 20-2, The Porphyrias).

Chapter summaries repeat the chapter's main points for quick review. A set of **study exercises** allows students to identify major themes of each chapter and to check their

mastery of the facts. For example, we ask students to describe the hydrogen bonding pattern of an α helix (Chapter 6), what the metabolic advantage of a substrate cycle is (Chapter 14), and what the functions of the three eukaryotic RNA polymerases are (Chapter 25). Answers to these questions are not provided explicitly but can be found in the text.

Each chapter contains at least 10 thought-provoking **problems.** These are not simple regurgitative exercises but require application of newly mastered principles. **Detailed solutions** to all of these problems are provided at the end of the book.

Sample calculations are included for problems in thermodynamics, pH determination, enzyme kinetics, and redox chemistry.

A few **references,** which are predominantly review articles, are listed at the end of each chapter to provide students with additional information, not to serve as a comprehensive bibliography. Some primary sources of particular importance or historical interest are included. The text also indicates (with URLs provided) how the Internet can be used to access databases on protein and nucleic acid sequences, molecular structures, enzyme classification, and metabolic pathways.

A glossary containing the definitons of many of the biochemical terms used in this textbook is provided at the end of the book.

Supplements

The following supplements to *Fundamentals of Biochemistry* are available:

- The CD-ROM that accompanies this textbook is produced by ScienceMedia, Inc. It contains an extensive series of computer graphics-animated Interactive Exercises and Guided Explorations, all keyed to the textbook as indicated by a disk icon ( ). In addition, the CD contains a set of Kinemages by Donald Voet and Judith G. Voet. These are computer-animated color images of selected proteins and nucleic acids that students can manipulate and which are also keyed to the textbook.
- *Student's Companion to Fundamentals of Biochemistry* by Akif Uzman, Joseph Eichberg, William Widger, Donald Voet, Judith G. Voet, and Charlotte W. Pratt. It contains learning objectives, numerous new problems and their detailed answers, key terms and concepts, and chapter summaries.
- An art notebook, *Take Note,* containing selected figures from the textbook, reproduced in black and white and designed to facilitate student note-taking during lectures.
- A CD-ROM containing nearly all of the illustrations from *Fundamentals of Biochemistry* to be used for computerized classroom projection or from which to print transparencies.
- A Web site (http://www.wiley.com/college/voetfundamentals) containing supplemental material, links to other resources, and a suite of computer-graded quizzes. Students can take these quizzes on their own to test their knowledge or an instructor can assign them and have the grades returned.
- A Listserv site Email discussion forum for instructors. To subscribe to this service, send a message to voetfundamentals@wiley.com with "subscribe" as the subject.

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The atomic coordinates of many of the proteins and nucleic acids that we have drawn for use in this textbook were obtained from the Protein Data Bank at Brookhaven National Laboratory. We created these drawings using the molecular graphics programs RIBBONS by Mike Carson; GRASP by Anthony Nicholls, Kim Sharp, and Barry Honig; and INSIGHT II from BIOSYM Technologies. Many of the drawings generously contributed by others were made using either these programs or MIDAS by Thomas Ferrin, Conrad Huang, Laurie Jarvis, and Robert Langridge; MOLSCRIPT by Per Kraulis; and O by Alwyn Jones.

The interactive computer graphics diagrams that are presented in the CD-ROM that accompanies this textbook are either Chime™ images or Kinemages. Chemscape Chime™, which is based on the program RasMol by Roger Sayle, was developed and generously made publically available by MDL Information Systems, Inc. Kinemages are displayed by the program MAGE, which was written and generously provided by David C. Richardson who also wrote and provided the program PREKIN, which DV and JGV used to help generate the Kinemages.

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BRIEF CONTENTS

A NOTE TO STUDENTS

You are about to embark on a voyage of discovery, that of the chemistry of life. This body of knowledge, compiled by the skilled and dedicated efforts of many tens of thousands of researchers over more than a century, has had an enormous impact on medicine, agriculture, and the way we view ourselves and our world. It forms an epic and awe-inspiring tale that has provided a lifetime of fascination for many of those who study it.

Before you begin your voyage, we have a few words of advice. The vocabulary of biochemistry, to which you will be introduced here, is nearly as rich as that of a foreign language, and many chapters build on their predecessors. Thus, it is important to keep your studies current with the course lectures. The end-of-chapter materials, including Study Exercises and Problems, are designed to aid you in mastering and applying principles. Try to complete the Problems before you look at the Solutions. Avail yourselves of additional information in the supplements, on the Internet, and at your library, using the References as a guide. Biochemistry is a challenging subject that yields to hard work and diligence. The more effort you put into learning the material, the more rewarding these efforts will be. Enjoy meeting the challenge, and bon voyage!

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