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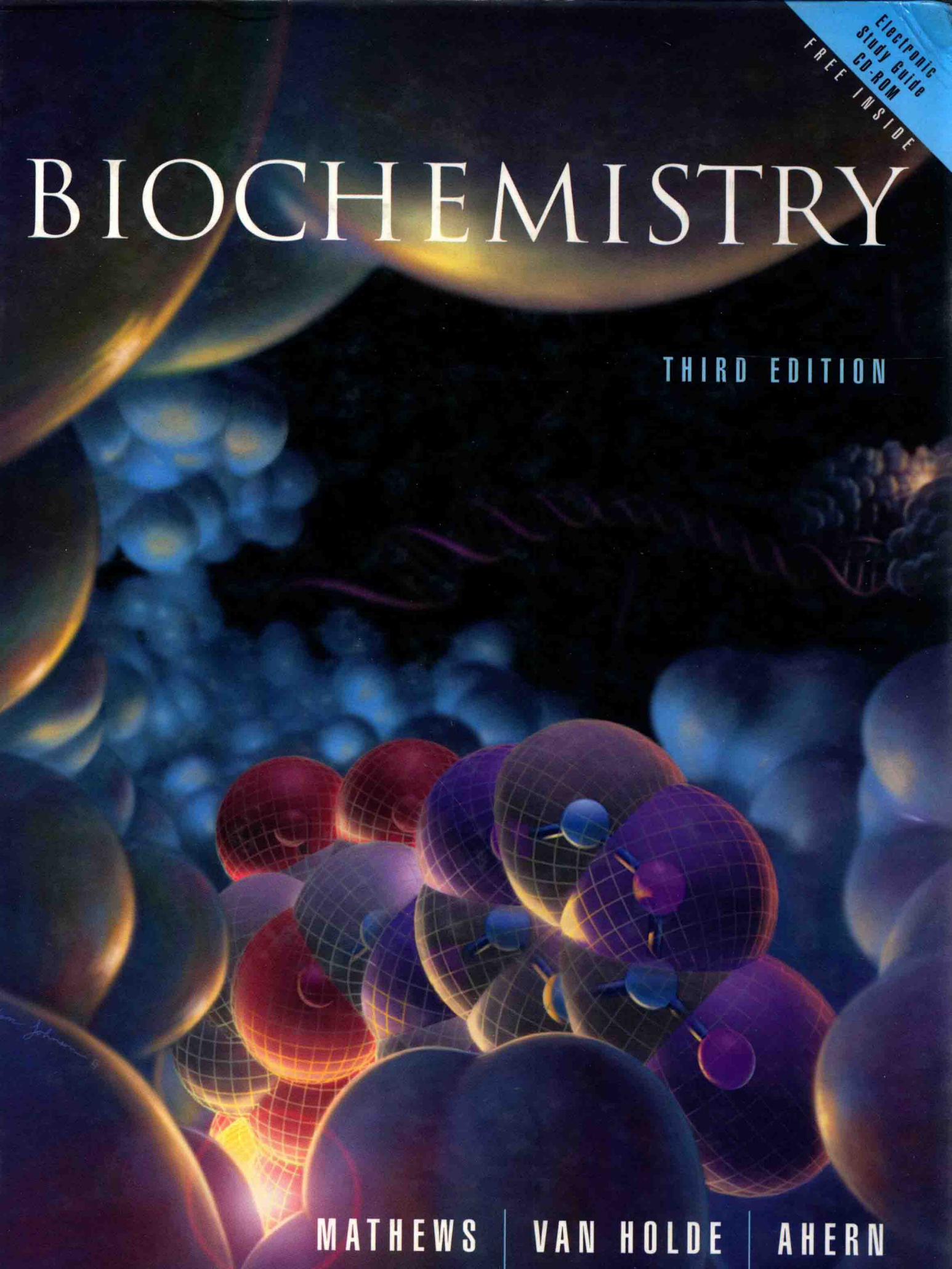
BIOCHEMISTRY

THIRD EDITION



MATHEWS | VAN HOLDE | AHERN

Biochemistry

THIRD EDITION

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An Imprint of Addison Wesley Longman, Inc.

San Francisco • Reading, Massachusetts • New York • Harlow, England
Don Mills, Ontario • Sydney • Madrid • Amsterdam

Publisher: Robin Heyden
Sponsoring Editor: Ben Roberts
Production Editor, Art Coordinator: Lisa Weber
Managing Editor: Joan Marsh
Marketing Manager: Jennifer Schmidt
Director of Marketing: Stacy Treco
Prepress and Manufacturing Supervisor: Lillian Hom
Publishing Assistant: Anthony J. Asaro
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Developmental Editor: John Murdzek
Copyeditor: Mary Prescott
Proofreader: Anita Wagner
Indexer: Shane-Armstrong Information Systems
Text Designers: Bruce Kortebein, Kathleen Cunningham
Developmental Artist (Second Edition): Darwen Hennings
Artists: Graham Johnson, Precision Graphics, Karl Miyajima, Thompson Type
Permissions Editors: Marcy Lunetta, Charles Morris
Photo Editor: Roberta Spieckerman Associates
Compositor: Thompson Type
Cover Designer: Yvo Riezebos Design
Cover Artist: Graham Johnson

Library of Congress Cataloging-in-Publication Data
Mathews, Christopher K., 1937–
Biochemistry / Christopher K. Mathews, K. E. van Holde, Kevin G. Ahern.—3rd ed.
p. cm.
Includes bibliographical references and index.
ISBN 0-8053-3066-6
1. Biochemistry. I. Title. II. Van Holde, K. E. (Kensal Edward), 1928–
III. Ahern, Kevin G.

QD415 .M34 1999
572 21—dc21 99-043683

3 4 5 6 7 8 9 10—VH—03 02

Benjamin/Cummings, an imprint of Addison Wesley Longman
1301 Sansome Street
San Francisco, CA 94111

Credits and Acknowledgments
Figures 1.6, 2.5, 2.8, 2.10, 2.11, 2.13, 2.14, 4.15, 4.16, 4.20, 5.12, 6.2, 6.5, 6.13, 7.5, 7.7, 7.10, 7.20, 7.33, 9.19, 9.20, 9.21, 10.22, 10.23, and 11.11 were rendered by Graham Johnson.

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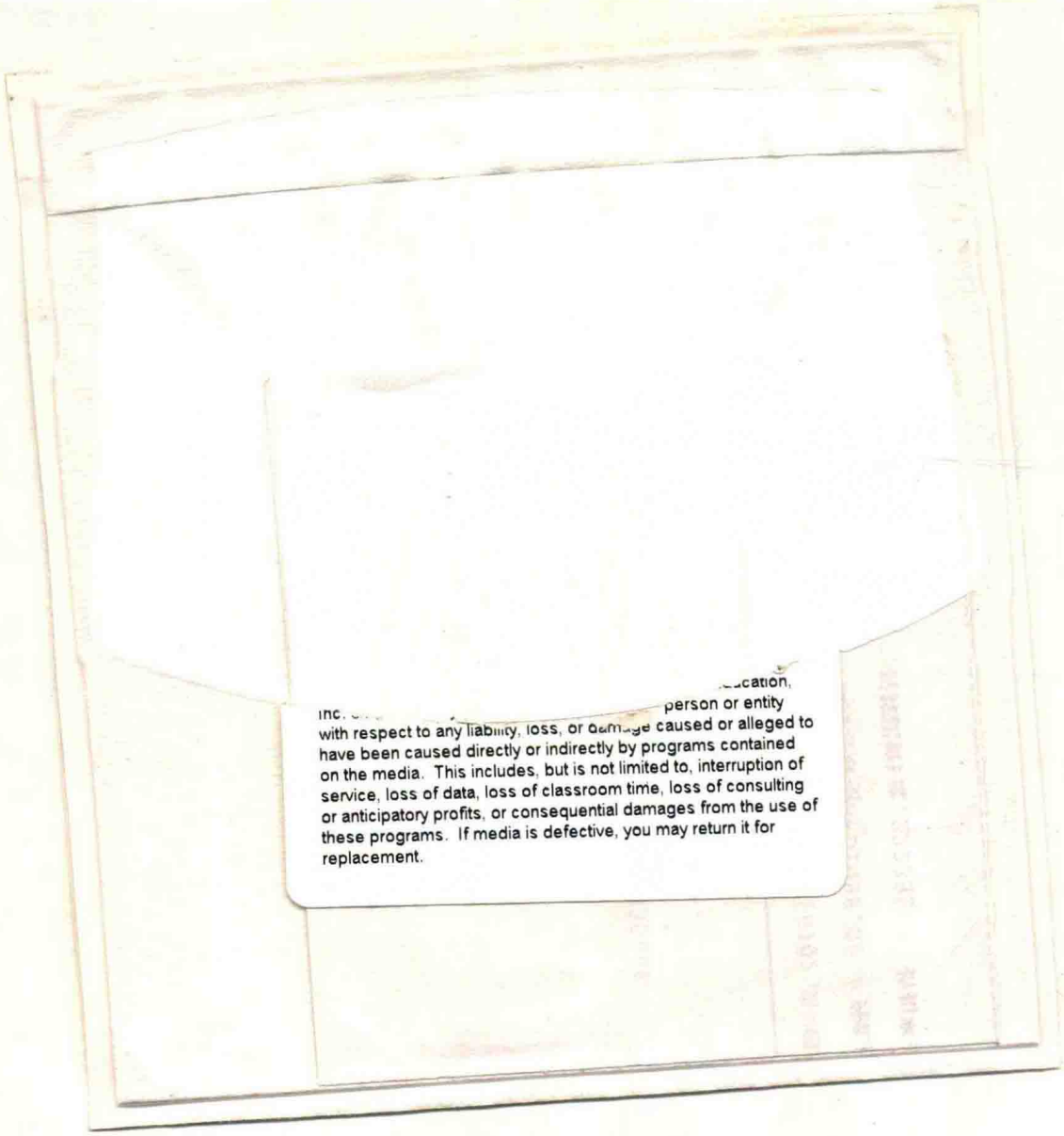

AMINO ACIDS

Name	Symbol		Genetic Code Words					
Alanine	Ala	A	GCA	GCC	GCG	GCU		
Arginine	Arg	R	AGA	AGG	CGA	CGC	CGG	CGU
Asparagine	Asn	N	AAC	AAU				
Aspartic acid	Asp	D	GAC	GAU				
Cysteine	Cys	C	UGC	UGU				
Glutamic acid	Glu	E	GAA	GAG				
Glutamine	Gln	Q	CAA	CAG				
Glycine	Gly	G	GGA	GGC	GGG	GGU		
Histidine	His	H	CAC	CAU				
Isoleucine	Ile	I	AUA	AUC	AUU			
Leucine	Leu	L	CUA	CUC	CUG	CUU	UUA	UUG
Lysine	Lys	K	AAA	AAG				
Methionine	Met	M	AUG					
Phenylalanine	Phe	F	UUC	UUU				
Proline	Pro	P	CCA	CCC	CCG	CCU		
Serine	Ser	S	AGC	AGU	UCA	UCC	UCG	UCU
Threonine	Thr	T	ACA	ACC	ACG	ACU		
Tryptophan	Trp	W	UGG					
Tyrosine	Tyr	Y	UAC	UAU				
Valine	Val	V	GUA	GUC	GUG	GUU		

THE GENETIC CODE (mRNA)

First position	Second position: U	Second position: C	Second position: A	Second position: G	Third position
U	UUU Phe	UCU Ser	UAU Tyr	UGU Cys	U
	UUC Phe	UCC Ser	UAC Tyr	UGC Cys	C
	UUA Leu	UCA Ser	UAA Stop	UGA Stop	A
	UUG Leu	UCG Ser	UAG Stop	UGG Trp	G
C	CUU Leu	CCU Pro	CAU His	CGU Arg	U
	CUC Leu	CCC Pro	CAC His	CGC Arg	C
	CUA Leu	CCA Pro	CAA Gln	CGA Arg	A
	CUG Leu	CCG Pro	CAG Gln	CGG Arg	G
A	AUU Ile	ACU Thr	AAU Asn	AGU Ser	U
	AUC Ile	ACC Thr	AAC Asn	AGC Ser	C
	AUA Ile	ACA Thr	AAA Lys	AGA Arg	A
	AUG Met/start	ACG Thr	AAG Lys	AGG Arg	G
G	GUU Val	GCU Ala	GAU Asp	GGU Gly	U
	GUC Val	GCC Ala	GAC Asp	GGC Gly	C
	GUA Val	GCA Ala	GAA Glu	GGA Gly	A
	GUG Val	GCG Ala	GAG Glu	GGG Gly	G

SOME PREFIXES USED IN THE INTERNATIONAL SYSTEM OF UNITS

10^{9}	giga	G
10^{6}	mega	M
10^{3}	kilo	k
10^{-1}	deci	d
10^{-2}	centi	c
10^{-3}	milli	m
10^{-6}	micro	μ
10^{-9}	nano	n
10^{-12}	pico	p
10^{-15}	femto	f

CONVERSION FACTORS

Energy: 1 joule = 10^7 ergs = 0.239 cal
1 cal = 4.184 joule

Length: 1 nm = 10 Å = 1×10^{-7} cm = 1×10^{-9} m

Mass: 1 kg = 1000 g = 2.2 lb
1 lb = 453.6 g

Pressure: 1 atm = 760 torr = 14.696 psi
1 torr = 1 mm Hg

Temperature: °K = °C + 273
°C = (5/9)(°F − 32)

Volume: 1 L = 1×10^{-3} m^3 = 1000 cm^3

PHYSICAL CONSTANTS

Name	Symbol	SI Units	cgs Units
Avogadro's number	N	6.022137×10^{23}/mol	6.022137×10^{23}/mol
Boltzmann constant	k	1.38066×10^{-23}J/°K	1.38066×10^{-16} erg/°K
Curie	Ci	3.7×10^{10} d/s	3.7×10^{10} d/s
Electron charge	e	1.602177×10^{-19} coulomb[b]	4.80321×10^{-10} esu
Faraday constant	F	96485 J/V · mol	9.6485×10^{11} erg/V · m
Gas constant[a]	R	8.31451 J/°K · mol	8.31451×10^{7} erg/°K · m
Light speed (vacuum)	c	2.99792×10^{8} m/s	2.99792×10^{10} cm/s
Planck's constant	h	6.626075×10^{-34} J · s	6.626075×10^{-27} erg · s

[a]Other values of R: 1.9872 cal/K · mol = 0.082 L · atm/°K · mol
[b]1 coulomb = 1 J/V

USEFUL EQUATIONS

Henderson–Hasselbalch equation	$pH = pK_a + \log([A^-]/[HA])$
Michaelis–Menten equation	$V = V_{max}[S]/(K_M + [S])$
Free energy change under non-standard-state conditions	$\Delta G = \Delta G° + RT \ln([C][D]/[A][B])$
Free energy change and standard reduction potential	$\Delta G°' = -nF\Delta E'_0$
Reduction potentials in a redox reaction	$\Delta E'_0 = E'_0(\text{acceptor}) - E'_0(\text{donor})$
Proton motive force	$\Delta p = \Delta\Psi - 2.3RT\,\Delta pH/F$
Passive diffusion of a charged species	$\Delta G = G_2 - G_1 = RT \ln(C_2/C_1) + ZF\Delta\Psi$

Ab	antibody
Ac-CoA	acetyl-coenzyme A
ACP	acyl carrier protein
ADH	alcohol dehydrogenase
AdoMet	*S*-adenosylmethionine
ADP	adenosine diphosphate
Ag	antigen
AIDS	acquired immune deficiency syndrome
Ala	alanine
AMP	adenosine monophosphate
Arg	arginine
ARS	autonomously replicating sequence
Asn	asparagine
Asp	aspartic acid
atm	atmosphere
ATP	adenosine triphosphate
bp	base pair
BPG	bisphosphoglycerate
cal	calorie
cAMP	cyclic 3′,5′-adenosine monophosphate
CD	circular dichroism
cDNA	complementary DNA
CDP	cytidine diphosphate
Chl	chlorophyll
CMP	cytidine monophosphate
CoA or CoA-SH	coenzyme A
CoQ	coenzyme Q
cpm	counts per minute
CRP	cAMP receptor protein (catabolite activator protein)
CTP	cytidine triphosphate
Cys	cysteine
d	deoxy
Da	dalton
dd	dideoxy
DEAE	diethylaminoethyl
DHAP	dihydroxyacetone phosphate
DHF	dihydrofolate
DHFR	dihydrofolate reductase
DNA	deoxyribonucleic acid
DNP	dinitrophenol
dopa	dihydroxyphenylalanine
dTDP	thymidine diphosphate
dTMP	thymidine monophosphate
dTTP	thymidine triphosphate
E	reduction potential
EF	elongation factor
EGF	epidermal growth factor
EPR	electron paramagnetic resonance
ER	endoplasmic reticulum
F	phenylalanine
F	Faraday constant
F_{AB}	antibody molecule fragment that binds antigen
FAD	flavin adenine dinucleotide
$FADH_2$	reduced flavin adenine dinucleotide
FBP	fructose-1,6-bisphosphate
FBPase	fructose bisphosphatase
Fd	ferredoxin
fMet	*N*-formylmethionine
FMN	flavin mononucleotide
F1P	fructose-1-phosphate
F6P	fructose-6-phosphate
G	Gibbs free energy
GABA	γ-aminobutyric acid
Gal	galactose
GDP	guanosine diphosphate
GLC	gas–liquid chromatography
Glc	glucose
Gln	glutamine
Glu	glutamic acid
Gly	glycine
GMP	guanosine monophosphate
G1P	glucose-1-phosphate
GS	glutamine synthetase
GSH	glutathione (reduced glutatione)
G6P	glucose-6-phosphate
GSSG	glutathione disulfide (oxidized glutathione)
G3P	glyceraldehyde-3-phosphate
GTP	guanosine triphosphate
h	hour
h	Planck's constant
Hb	hemoglobin
HDL	high-density lipoprotein
HIV	human immunodeficiency virus
hnRNA	heterogeneous nuclear RNA
HPLC	high-pressure (or high-performance) liquid chromatography
HX	hypoxanthine
Hyl	hydroxylysine
Hyp	hydroxyproline
IDL	intermediate-density lipoprotein
IF	initiation factor
IgG	immunoglobulin G
Ile	isoleucine
IMP	inosine monophosphate
$InsP_3$	inositol 1,4,5-trisphosphate
IPTG	isopropylthiogalactoside
IR	infrared
ITP	inosine triphosphate
J	joule

k	kilo (10^3)
k_{cat}	turnover number
K_M	Michaelis constant
kb	kilobase
kDa	kilodalton
L	liter
LDH	lactate dehydrogenase
LDL	low-density lipoprotein
Leu	leucine
Lys	lysine
M	molar (mol/L)
m	milli (10^{-3})
Man	mannose
Mb	myoglobin
Met	methionine
mL	milliliter
mm	millimeter
mM	millimolar (mmol/L)
mmol	millimole
μ	micro (10^{-6})
μm	micrometer
μM	micromolar (μmol/L)
μmol	micromole
mol	mole
mRNA	messenger RNA
mV	millivolt
N	Avogadro's number
n	nano (10^{-9})
NAD^+	nicotinamide adenine dinucleotide
NADH	reduced nicotinamide adenine dinucleotide
$NADP^+$	nicotinamide adenine dinucleotide phosphate
NADPH	reduced nicotinamide adenine dinucleotide phosphate
nm	nanometer
NMR	nuclear magnetic resonance
P	phosphate
p	pico (10^{-12})
P_i	inorganic phosphate
PAGE	polyacrylamide gel electrophoresis
PBG	porphobilinogen
PC	phosphatidylcholine
PCR	polymerase chain reaction
PE	phosphatidylethanolamine
PEP	phosphoenolpyruvate
PG	prostaglandin
Phe	phenylalanine
PI	phosphatidyl-inositol
PK	pyruvate kinase
PKU	phenylketonuria
PLP	pyridoxal-5-phosphate
Pol	polymerase
PP_i	pyrophosphate ion
PQ	plastoquinone
Pro	proline
PRPP	5-phosphoribosyl-1-pyrophosphate
PS	phosphatidylserine
PTH	phenylthiohydantoin
QH_2	reduced coenzyme Q (ubiquinol)
R	gas constant
rpm	revolutions per minute
RER	rough endoplasmic reticulum
RF	release factor
R5P	ribose-5-phosphate
RFLP	restriction fragment length polymorphism
RNA	ribonucleic acid
rRNA	ribosomal RNA
RuBP	ribulose-1,5-bisphosphate
S	Svedberg unit
S	sedimentation coefficient
s	second
SDS	sodium dodecylsulfate
Ser	serine
snRNA	small nuclear RNA
snRNP	small nuclear ribonucleoprotein
SRP	signal recognition particle
T	absolute temperature
TCA	tricarboxylic acid cycle
THF	tetrahydrofolate
Thr	threonine
3PG	3-phosphoglycerate
TMV	tobacco mosaic virus
TPP	thiamine pyrophosphate
tRNA	transfer RNA
Trp	tryptophan
2PG	2-phosphoglycerate
Tyr	tyrosine
UDP	uridine diphosphate
UDPG	UDP-glucose
UMP	uridine monophosphate
UTP	uridine triphosphate
UV	ultraviolet
V	volt
V_{max}	maximal velocity
Val	valine
VLDL	very low-density lipoprotein
XMP	xanthosine monophosphate
YAC	yeast artificial chromosome
yr	year

Biochemistry

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To our students,
who continue to teach us biochemistry
by showing us that the best way
to learn a subject is to teach it.

About the Authors

CHRISTOPHER K. MATHEWS is Distinguished Professor and Chairman of the Department of Biochemistry and Biophysics at Oregon State University. He holds a B.A. from Reed College (1958) and a Ph.D. from The University of Washington (1962). He served on the faculties of Yale University and The University of Arizona before assuming his present position in 1978. His major research interest is the coordination between DNA precursor biosynthesis and DNA replication. Dr. Mathews was an Eleanor Roosevelt International Cancer Fellow at the Karolinska Institute in Stockholm in 1984–85 and Tage Erlander Guest Professor at Stockholm University in 1994–95. Dr. Mathews has published over 150 scientific papers dealing with molecular virology, metabolic regulation, nucleotide enzymology, and biochemical genetics. He is the author of *Bacteriophage Biochemistry* (1971) and coeditor of *Bacteriophage T4* (1983) and *Structural and Organizational Aspects of Metabolic Regulation* (1990). His teaching experience includes undergraduate, graduate, and medical school biochemistry courses.

K. E. VAN HOLDE is Distinguished Professor Emeritus of Biophysics and Biochemistry at Oregon State University. He earned his B.A. (1949) and Ph.D. (1952) from the University of Wisconsin. Over many years, Dr. van Holde's major research interest has been the structure of chromatin; his work resulted in the award of an American Cancer Society Research Professorship in 1977. He has been at Oregon State University since 1967, and was named Distinguished Professor in 1988. He is a member of the National Academy of Sciences and the American Academy of Arts and Sciences, and has received Guggenheim, NSF, and EMBO fellowships. He is the author of over 200 scientific papers and three books in addition to this volume: *Physical Biochemistry* (1971, 1985), *Chromatin* (1988), and *Principles of Physical Biochemistry* (1998). He was also coeditor of *The Origins of Life and Evolution* (1981). His teaching experience includes undergraduate and graduate chemistry, biochemistry and biophysics, and also the Physiology and Molecular Biology Course at The Marine Biological Laboratory at Woods Hole.

KEVIN G. AHERN is a Senior Instructor in the Department of Biochemistry and Biophysics at Oregon State University. He received his B.S (1976) and M.S. (1981) degrees from Oklahoma State University and his Ph.D. (1986) from Oregon State University. His interests include the use of computers in scientific research and teaching. Since 1994, Dr. Ahern has been on the faculty at Oregon State University, where he pioneered the development of Web-based courses for teaching biochemistry. He is a contributing editor to *Science* magazine, a columnist for *Genetic*

Engineering News, and a freelance writer for numerous online and printed publications. Dr. Ahern served as editor of *Biotechnology Software and Internet Journal* from 1987 to 1998 and is the founder of DaVinci Press Ink (www.davincipress.com), a scientific software consulting firm. He has edited two books, *Biotechnology Software Reports—Computer Applications for Molecular Biologists* and *The Biotechnology Software Directory, A Buyer's Guide.* Dr. Ahern's teaching experience includes undergraduate and graduate biochemistry courses.

Preface

PLANNING THE THIRD EDITION OF A WELL-RECEIVED BIOCHEMISTRY TEXTBOOK would seem a simple matter. Certainly, improvements are needed: those suggested by users of the text, as well as essential changes identified by the authors. Despite the greatest care, the inevitable pesky errors have come to light and must be corrected. But surely, if the text has worked well, the chief task should be updating. So we thought—until we began to contemplate the explosive expansion of biochemical knowledge in the few years since the second edition of *Biochemistry* appeared. How can this new information be accommodated without producing a textbook so densely packed with information as to be unusable by students, most of whom are taking a first course in biochemistry?

It became apparent that a qualitatively different approach was required. Without doubt, this approach must harness the power of the computer to access and organize the vast information on genomics, proteomics, gene sequences, and protein structures present in ever-expanding databases. It is crucial that the text form a seamless whole with the auxiliary information resources and that these resources be closely keyed to the text. Furthermore, these resources must be designed and produced in collaboration with one who has not only the technical skills but also experience in teaching biochemistry, ideally from previous editions of our textbook. In other words, to realize our goals, it was essential to recruit a third author.

The two of us involved in the first two editions (i.e., van Holde and Mathews) were extraordinarily fortunate to enlist Dr. Kevin Ahern as our third author. Dr. Ahern has a broad and deep knowledge of bioinformatics, honed by experience as the Editor of the journal *Biotechnology Software & Internet Journal* and as a Contributing Editor for *Science* with particular responsibility for computer applications in biological sciences. Of equal importance, Dr. Ahern teaches biochemistry courses in our department using this textbook.

Dr. Ahern's participation makes the third edition of *Biochemistry* quite a new enterprise, even though the book itself resembles the earlier editions in essential ways. We think of the text as serving two functions. As in the past, we have tried to create a readable and usable text, to guide students through an introductory biochemistry course that is usually, but not always, of one year's duration. But, in combination with the Electronic Study Guide designed by Dr. Ahern, the text has become a doorway to the vast and continuously evolving world of biochemistry. Our goal has been to create a media resource that will help and guide students long after they have completed their first course in biochemistry.

MEDIA RESOURCES

The Electronic Study Guide must serve two primary purposes. (1) It must enhance the ability of students to understand biochemistry, and (2) it must provide access to a body of knowledge far greater than could be covered in the printed pages of the textbook. To maximize accessibility and ease of use, we chose to provide all materials in a common hypertext format (HTML) and programming language (Java) that could be accessed easily via any of the common browsers, such as Netscape Navigator or Microsoft Internet Explorer, on virtually any personal computer. Our Electronic Study Guide has two parts: one stored on fixed media, namely the CD-ROM accompanying this text, and the other on a dynamic, continually updated Web site. Thus, items that we expect will require little or no updating over the life of the textbook are provided on the CD-ROM, but items that require more frequent updating will be kept on the Addison Wesley Longman Web site at www.awlonline.com/mathews.

The Electronic Study Guide CD-ROM that is packaged with each new copy of this text contains Outline, Concepts, Terminology and Quizzing sections. The Outline section follows the chapter organization of the text and contains hyperlinks to lead students at the click of a button to other points of relevant information, such as chemical structures and enzymatic reactions. The Concepts sections provide short, hyperlinked summaries of the important ideas of each chapter. The Terminology section contains summaries and definitions of all of the important terms in each chapter. The Quizzing section, organized by chapter, employs a database of questions and answers to enable students to test their knowledge of biochemical structures, names, enzymes, reactions, terms, and concepts.

The Benjamin/Cummings Science Digital Library for Biochemistry is a CD-ROM for faculty, designed to enhance teaching from the textbook. The figures on this CD can be used to create transparencies and slides and to build PowerPoint presentations and personal Web pages. The Science Digital Library CD is available to qualified adopters of this book. For more information, please contact your Benjamin/Cummings sales representative.

To keep pace with the development of biochemical knowledge, we have created a dynamic Web site that will be continually updated throughout the lifetime of the textbook. In this way we can keep users of our text abreast of exciting developments as they happen. Our Web site incorporates all of the essential features of both the student and faculty CD-ROMs, as well as Current News in biochemistry and biotechnology, a search engine for locating pages via user entry of keywords, and a Links section containing a vast collection of hyperlinks.

EVOLUTION OF THE TEXT

Within the text, our overall organization remains the same—that is, we begin with structure and mechanism, followed by intermediary metabolism and then biological information processing. Nevertheless, a few significant changes have been made. Chapter 3 (Bioenergetics) was shortened by transferring one section (ATP as Energy Currency) to Chapter 12 (Introduction to Metabolism). This change removed some redundancy and placed this material in appropriate juxtaposition with metabolism.

Many sections were either created or rewritten to amplify new concepts and discoveries. Examples include expanded discussions of protein folding and chaperone proteins (Chapter 6), molecular motors (Chapter 8), structures of mitochondrial respiratory complexes (Chapter 15), reactive oxygen species and human disease (Chapter 15), biochemical insights into obesity (Chapter 18), folic acid and the heart (Chapter 20), neurotransmitters and psychopharmacology (Chapter 21), new signal transduction pathways (Chapter 23), structures and mechanisms of

DNA polymerases (Chapter 24), genetic recombination mechanisms (Chapter 25), and eukaryotic gene expression (Chapter 28). This new material has been folded into the format that has worked well in previous editions, namely an early introduction of nucleic acid structure (to clarify presentations of protein structure and function), an emphasis on the experimental roots of biochemistry, a continual emphasis on energy relationships in biochemistry, and a stepwise approach to complex metabolic pathways (introduction, followed by overview and then details, and ending with reiteration of overview and discussion of regulation).

TOOLS OF BIOCHEMISTRY

Because the methods used by biochemists are continually evolving, in each edition we add new techniques in this section and delete those that are no longer of major use. In the Third Edition we have added one new Tools section, "Methods for Detecting and Analyzing Protein–Protein Interactions." We have deleted the section on Maxam–Gilbert DNA sequencing (although this historically important technique is outlined where we present transcript mapping techniques in Chapter 26), and we have also deleted a section that describes identification of N- and C-termini of polypeptides. The section on protein sequence analysis (Chapter 5) still indicates how N-termini are identified as part of automated sequencing protocols.

We have expanded other Tools sections to include new variants of older techniques, such as laser scanning confocal microscopy (Chapter 1) and the synthesis of combinatorial arrays of peptides (Chapter 5). The section on mass spectrometry (Chapter 6) has also been expanded to reflect the growing importance and versatility of this technique.

END-OF-CHAPTER PROBLEMS

Quantitative problems and discussion-type questions are among the most valuable learning resources in a text, and users consistently ask for more problems and complete answers. Most chapters in the Third Edition have two to four new problems each, with brief answers to all problems given at the end of the book.

ADDITIONAL SUPPLEMENTS

Along with the CD-ROM and Web site, another important learning aid is the *Complete Solutions Manual* (0-8053-3074-7), written by Joshua Hicks and Christopher Stoner, two graduate students in our department at Oregon State University. This printed manual contains fully worked solutions to all end-of-chapter problems in the text. Also, a set of 107 full-color *Transparency Acetates* (0-8053-3068-2) provides representative samples of illustrations from the text and can be used as lecture aids. The *Complete Solutions Manual* and the *Transparency Acetates* are available to qualified adopters of this book. For more information about these supplements or any of the media resources, please contact your Benjamin/Cummings sales representative or our customer service department at (800) 282-0693.

ACKNOWLEDGMENTS

Each of the three editions of this book has found us working with a completely different editorial and production team at Addison Wesley Longman. We have particularly enjoyed working with this team. Their professionalism and commitment to the project made it a pleasure to work with them and allowed us to write this text, create the media resources, and see the project to completion in nearly

one year less than the time originally envisaged. Heading the team was Ben Roberts, Chemistry Editor, who oversaw both editorial and production phases of the work. Ben's consistent enthusiasm for the project was a powerful motivating force. Dr. John Murdzek, Developmental Editor, was a perceptive and persistent critic. John holds a Ph.D. in chemistry, which allowed him to interact with us as a fellow scientist and helped him to detect errors and ambiguities that would certainly have been missed by an editor less well trained in contemporary science.

Claudia Herman, Publishing Associate, helped in many ways to keep the project moving forward, including lining up all of the reviewers and making sure that we received the reviews in timely fashion. Once the text went into production, we had the pleasure of working with Lisa Weber, Production Editor. In her ability to keep abreast of myriad details and to coordinate all phases of the production process, Lisa reminded us of a chess player who can play twenty games simultaneously and win all of them. Lisa was assisted by Photo Researcher Roberta Spieckerman, who saved us an enormous amount of work by contacting authors and copyright holders of the numerous figures that we reproduced or adapted from published sources. Anita Wagner, our proofreader, made us aware of many substantive issues, as well as typographical errors, during her perceptive reading of the page proofs. We are grateful to many colleagues, acknowledged in the appropriate figure legends, who interacted with the authors directly in providing molecular graphics and artwork. We are grateful also to Copy Editor Mary Prescott, the only team member to have worked also on the First Edition of this text. Thanks also to Lynn Armstrong and Charlotte Shane for preparing the index.

Special thanks go to artist Graham Johnson, who designed a strikingly beautiful and original cover illustration and who brilliantly turned many of our sketched ideas into attractive and informative figures. Thanks also to many biochemists, acknowledged individually on pages xii–xiv, who were engaged by the publisher to review early drafts of our manuscripts. All of their suggestions were appreciated, even those that we were unable to follow.

Special thanks are due to two reviewers, Drs. Kimberley Waldron (Regis College) and Robert Ludwig (University of California, Santa Cruz), both of whom read the entire text at the page proof stage, catching errors and ambiguities that had been unaccountably missed by all the authors and other reviewers.

Kevin Ahern's efforts in developing the Electronic Study Guide depended heavily upon Oregon State University student Jody Franke, who assisted with linking and HTML issues; Heather Wycoff, who helped with graphics; and Hamid Ghanadan, for consultation regarding HTML issues. Thanks to these three from the three of us.

As always, our most persistent critics and supporters were our wives—Kate Mathews, Barbara van Holde, and Indira Rajagopal. The love and support that they consistently offered were the most important elements in seeing this project to a timely and satisfying conclusion.

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