



BIOCHEMISTRY & MOLECULAR BIOLOGY

DESPO PAPACHRISTODOULOU | ALISON SNAPE
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5TH EDITION

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Biochemistry and Molecular Biology

Fifth edition

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Preface

Though perhaps not as intimidating as writing a book from scratch, taking on a new edition of an established text is a daunting task. William and Daphne Elliott, in their preface to the fourth edition, described this as a book ‘designed for undergraduates taking science and health-related courses in biochemistry and molecular biology’ and said that their aim was ‘to provide a text suitable for students meeting those subjects for the first time, but of sufficient depth to be intellectually satisfying ... written in an approachable style, but with lots of explanation to promote understanding.’ Our experience of using this book for undergraduate courses is that they succeeded in their aim, achieving what one reviewer has described as a style that is ‘refreshingly different more personal and more direct’ that ‘seems to take the reader on a one-to-one tutorial’. It is this admirable quality of the earlier editions that we have sought to retain. The book is aimed at students in the early years of their undergraduate programmes. It assumes little prior knowledge, and seeks to provide accessible explanations of terms and concepts that may be unfamiliar, while building up to a level that should enable students to tackle short review articles of the kind found in many journals. It also avoids giving the impression that biochemistry and molecular biology are closed subjects. Undergraduates at the beginning of their course are sometimes uncomfortable with the notion of uncertainty and ask to be given ‘just the facts’. However, by emphasizing the relevance of this material to current medical and biological research and pointing out areas where our knowledge is still imperfect, we hope to give students an appreciation of the interest and importance of continuing developments and to inspire some of them to pursue their studies to a higher level.

It has been noted many times that adding new material to a textbook creates the dilemma of which older material should be discarded in order to keep the size of the book manageable. While we have tried to be up to date we have been relatively cautious about leaving anything out that was covered in previous editions, recent developments in metabolomics and cancer research having shown that those who suggested that certain metabolic topics or even the whole of metabolism were no longer worth learning were speaking prematurely. In genomics and molecular biology the vast quantity of new data and novel methodology presents particular challenges, and we have included some new material in that area. However, we have considered it worthwhile to retain coverage of techniques such as Southern blotting and library screening for now, even though they may be rarely used in modern laboratories, because we feel that knowledge of these methods provides an

historic framework that allows students to build up a thorough understanding of our present position. In order to save space and allow for these additions and retentions we have taken the step of moving online the suggestions for further reading and the web based bioinformatics exercise. This has the added advantage that these resources can be more easily updated.

About the book

The book is organized into six main parts:

- 1 Basic concepts of life
- 2 Structure and function of proteins and membranes
- 3 Metabolism and nutrition
- 4 Information storage and utilization
- 5 Cells and tissues
- 6 Protective mechanisms against disease.

The chapters are arranged to give a seamless progression through the subject but we recognize that the order in which topics are taught varies with the teacher. There is, therefore, extensive cross-referencing between chapters in order to help students with their learning.

What is new in this edition?

- All the chapters have been reviewed to update them. The extent of the update varies in the different chapters from extensive rewriting and major additions to minor changes. A number of complex areas, which some students find difficult, have been rewritten for increased clarity. These include X-ray crystallography and nuclear magnetic resonance (Chapter 5); mechanisms of transport, storage and mobilization of dietary components (Chapter 11); mechanisms of metabolic control and their applications to metabolic integration (Chapter 20); homologous recombination (Chapter 23); cell signalling, particularly the insulin receptor and insulin signalling (Chapter 29); and vesicle transport of proteins (Chapter 27).
- A new chapter has been added, General principles of nutrition (Chapter 9) to introduce the subject and the terminology before dealing with the handling of dietary components.

- Material on regulation of gene expression, both transcriptional and post-transcriptional, has been reorganized and moved into a single new chapter (Chapter 26). This chapter includes an updated section on the role of chromatin in eukaryotic gene control with a new box on Genomic imprinting disorders (Box 26.1). It also incorporates material on microRNAs and RNA interference, which was given a separate chapter in the previous edition.
- The last section of the book has been reorganized. Part 5, *Cells and tissues*, is designed to illustrate how cell communication and coordination of cell division and cell death take place in eukaryotes, and then to illustrate how perturbation of these processes may lead to cancer. Part 6 then deals briefly with some special topics relating to protective mechanisms against disease.
- Cell division (mitosis and meiosis) is dealt with in the same chapter as the cell cycle (Chapter 30), which also includes cell death (apoptosis).

In metabolism, attention has been paid to the clinical relevance of the biochemical events. New material includes:

- Lipid transport, including cholesterol homeostasis and the hyperlipoproteinaemias.
- An extensive review of the regulation of metabolism in the fed state, fasting state, starvation and diabetes mellitus.
- New boxes: The Warburg effect (Box 13.1); Glucose-6-phosphate dehydrogenase deficiency (Box 15.1); Alcohol and the oriental flushing syndrome (Box 16.1); The alpha and the omega of fatty acids and diet (Box 17.1).

Important developments covered in Chapter 28 on DNA manipulation include the following:

- An introduction to Next Generation Sequencing methods for DNA and the potential medical application of rapid sequencing. No doubt these topics will gain still greater prominence in future editions.

- The principle of Genome Wide Association Studies used for elucidation of genetic causes for common complex diseases such as type 2 diabetes and coronary heart disease.
- Recent promising clinical trials using human embryonic stem cells, and the production of induced pluripotent stem cells from patients and their use to model diseases.

Using the book

This book includes a number of features to help make it easy to use, and to make learning from it as effective as possible.

- Index of diseases. A separate index of diseases and medically relevant topics helps students on health-related courses to identify relevant topics.
- Medical boxes. These illustrate the direct relevance of biochemistry and molecular biology to medicine and health-related issues. A separate list of these boxes is shown on the Contents pages.
- Questions and answers. Questions at the end of each chapter (with answers at the back of the book) are designed to support student learning.
- Chapter summaries. Summaries at the end of each chapter highlight the key concepts presented and aid revision.
- Further reading references. References online direct the reader mainly to review articles of the shorter type found in Trends journals. References can be accessed by scanning the QR code image at the end of each chapter. QR Code images are used throughout this book. QR Code is a registered trademark of DENSO WAVE INCORPORATED. If your mobile device does not have a QR Code reader try this website for advice www.mobile-barcodes.com/qr-code-software.

Online Resource Centre

The Online Resource Centre, which has been built to accompany this text, contains a number of useful teaching and learning resources for lecturers and students. Visit the site at www.oxfordtextbooks.co.uk/orc/snape_biochemistry5e/

For registered adopters of the book:

- Figures from the book available to download, for use in lectures and presentations.

For students:

- Comprehensive further reading lists, organized by chapter, and linked to relevant sections in the book via QR codes.
- An extensive bank of multiple-choice questions for self-directed learning. Each question has feedback keyed to the book so that students can review the relevant concepts easily.
- Links to three-dimensional structures of key biological molecules featured in the book.

The screenshot shows the Oxford University Press Online Resource Centre for the textbook 'Snape & Papachristodoulou: Biochemistry and Molecular Biology 5e'. The page is organized into several sections:

- Navigation Bar:** Includes the Oxford University Press logo, the title 'online resource centres', a search bar, and a user login status 'You are not logged in (last 2.20s)'.
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Acknowledgements

Our first and enormous debt is, of course, to Bill and Daphne Elliott, who developed and wrote the four previous editions of this book. Their breadth and depth of knowledge, their skill in organizing and explaining complex material in an accessible way, and their enthusiasm and capacity for keeping up to date with new developments across a range of subject areas are truly inspirational. They wrote to us most generously on hearing that we would take on the fifth edition, and we can only hope that we have learned from them sufficiently to maintain the standard they set. It was especially sad to hear that Bill Elliott died in July 2012, before we had a chance to meet, particularly since it turns out that he and AS also have their native county, Durham (UK) in common. The Elliotts acknowledged several colleagues for help with previous editions, and as we have retained much of the earlier structure and material, we have also without knowing them personally benefitted from their expertise and advice.

Our second major thanks go to the staff at Oxford University Press, Jonathan Crowe, who decided to let us loose on the book, and our editors, Holly Edmundson and Alice Mumford, who have guided us with patience, firmness, and good humour. We would also like to thank the members of the advisory and reviewing panels appointed by OUP who made many constructive suggestions for the development of

this edition and helpful comments on draft versions of some of our chapters.

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It may metaphorically be said that natural selection is daily and hourly scrutinising, throughout the world, the slightest variations; rejecting those that are bad and adding up all that are good; silently and insensibly working, whenever and wherever opportunity offers, at the improvement of each organic being in relations to its organic and inorganic conditions of life.

Charles Darwin

Evolution is a tinkerer.

Francois Jacob

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Diseases and medically relevant topics

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Abbreviations

A	adenine	Cdk	cyclin-dependent kinase
AA	aminoacyl group	cDNA	complementary DNA
ABC	ATP-binding cassette	CETP	cholesterol ester transfer protein
ACAT	acyl-CoA:cholesterol acyltransferase	CGRP	calcitonin gene related peptide
ACP	acyl carrier protein	CJD	Creutzfeldt-Jakob disease
ACTH	adrenocorticotrophic hormone (also called corticotrophin)	CDP	cytidine diphosphate
ADH	antidiuretic hormone (also called vasopressin)	Cki	Cdk inhibitor protein
ADP	adenosine diphosphate	COP	coat protein (of transport vesicles)
AgAp	agouti-related appetite stimulant	CoA	coenzyme A (A = acyl)
Akt	protein kinase (<i>see also</i> PKB)	CoQ	ubiquinone (<i>see also</i> Q, UQ)
AIDS	acquired immunodeficiency syndrome	COX	cyclooxygenase
ALA	5-aminolevulinic acid	CRE	cAMP-response element
ALA-S	aminolevulinate synthase	CREB	CRE-binding protein
ALT	alternative mechanism of lengthening telomeres	CSF	colony-stimulating factor
AMP	adenosine monophosphate	CTD	carboxy-terminal domain (of eukaryotic RNA polymerase)
AMPK	AMP-activated protein kinase	CTP	cytidine triphosphate
AP	apurine or apyrimidine	CVD	cardiovascular disease
APC	antigen-presenting cell	d-	deoxy (as in deoxyribonucleotides: dATP, dCTP etc.)
APR	anaphase promoting complex	DAG	diacylglycerol
Apaf-1	apoptotic protease mediating factor	Da	Dalton (unit of atomic or molecular mass: one twelfth of the mass of a carbon 12 atom)
A site	acceptor site (or amino acyl site) of ribosome	dd-	dideoxy (as in dideoxyribonucleotides: ddATP, ddCTP etc.)
ATCase	aspartyl transcarbamylase	DHAP	dihydroxyacetone phosphate
ATM	ataxia telangiectasia mutated	DNA	deoxyribonucleic acid
ATP	adenosine triphosphate	DNase	deoxyribonuclease
ARE	AU-rich element (in mRNA)	DPE	downstream promoter element
AZT	azidothymidine	ds	double stranded (DNA, RNA)
BAC	bacterial artificial chromosome	DNP	dinitrophenol
bp	base pair	DSB	double stranded break
BPG	2,3-bisphosphoglycerate	E ₀ '	redox potential value at pH 7.0
BSE	bovine spongiform encephalopathy (mad cow disease)	ECM	extracellular matrix
C	cytosine	EF	elongation factor (in translation)
c-	'cellular', denotes protooncogene (<i>c-ras</i> , <i>c-myc</i> , etc.)	EF ₂	elongation factor 2 (eukaryotic ribosomal translocase)
cal	calorie	EF-G	elongation factor-G (<i>E. coli</i> ribosomal translocase)
CAM	calmodulin	EF-Tu	elongation factor temperature unstable
cAMP	adenosine-3',5'-cyclic monophosphate	EGF	epidermal growth factor
CAK	Cdk activating kinase	eIF	eukaryotic initiation factor (in translation)
CAP	catabolite gene-activator protein	ELISA	enzyme-linked immunoabsorbent assay
CBP	CREB-binding protein		
CD	cluster of differentiation (proteins)		

ENCODE	Encyclopaedia of DNA elements (project)	HIF	hypoxia-inducible factor
ER	endoplasmic reticulum	HIV	human immunodeficiency virus
ES cell	embryonic stem cell	HLH	helix-loop-helix
ESI	electrospray ionization	HMG-CoA	3-hydroxy-3-methylglutaryl-CoA
E site	exit site of ribosome	HNPCC	hereditary nonpolyposis colorectal cancer
		hnRNP	hetero-ribonucleoprotein complex
F ₀	membrane rotary subunit of ATP synthase	HPLC	high-pressure (or high performance) liquid chromatography
F ₁	catalytic subunit of ATP synthase		
F	Faraday constant (96.5 kJ V ⁻¹ mol ⁻¹)	Hsp	heat-shock protein
FAD	flavin adenine dinucleotide	HTH	helix-turn-helix (DNA-recognition motif)
FADD	Fas-associated protein with a death domain		
FADH ₂	reduced form of FAD	I	inosine
Fd	ferredoxin	IDL	intermediate-density lipoprotein
FFA	free fatty acid	IF	initiation factor (e.g. IF1, IF2, IF3) in translation
FH ₂	dihydrofolate	IF	intermediate filament
FH ₄	tetrahydrofolate	Ig	immunoglobulin (IgG, IgG1, IgA, etc.)
fMet	formylmethionine	IGF	insulin-like growth factor (IGFI, IGFII)
FMN	flavin mononucleotide	Il	interleukin
FSH	follicle-stimulating hormone	Inr	initiator (eukaryotic transcription)
		IP ₃	inositol trisphosphate
G ₁ or G ₂	'gap' phases of cell cycle	iPSC	induced pluripotent stem cell
G	guanine	IRE	iron-responsive element
G	free energy (Gibbs)	IRP	IRE-binding protein
G ^o	standard free energy (Gibbs) at pH 7.0	IRS	insulin receptor substrate
G-1-P	glucose-1-phosphate		
G-6-P	glucose-6-phosphate	JAK	type of tyrosine kinase (Janus kinase)
G6PD or G6PDH	glucose-6-phosphate dehydrogenase	J	Joule
GAG	glycosaminoglycan		
GAP	GTPase-activating protein	K	Kelvin
GDP	guanosine diphosphate	K _a	acid dissociation constant
GEF	guanine nucleotide exchange factor	K _{cat}	turnover number of an enzyme (number of molecules of substrate converted to product by a molecule of enzyme at saturating levels of substrate per second)
GLUT	glucose transporter	K _{eq}	equilibrium constant of a reaction
GMO	genetically modified organism	K' _{eq}	equilibrium constant at pH 7.0
GroEL	multisubunit molecular chaperone (chaperonin) of Hsp 60 class	K _m	Michaelis constant: the substrate concentration at which a Michaelis-Menten enzyme works at half-maximal velocity
GroES	'lid' structure of groEL chaperonin complex	kb	kilobase
GRB	growth receptor-binding protein		
GRK	G-protein receptor kinase	LCAT	lecithin:cholesterol acyltransferase
GSH	reduced glutathione	LDL	low-density lipoprotein
GSK3	glycogen synthase kinase 3	LINES	long interspersed elements
GSSG	oxidized glutathione	LTR	long terminal repeat (sequences in retroviruses and certain retrotransposons)
GTP	guanosine triphosphate		
		M	Molar (moles dm ⁻³ or moles litre ⁻¹)
H	enthalpy	MALDI	matrix-assisted laser-desorption ionization
HAT	histone acetyltransferase		
Hb	haemoglobin		
HbO ₂	oxyhaemoglobin		
HDAC	histone deacetylase		
HDL	high-density lipoprotein		
hESC	human embryonic stem cell		
HGPRT	hypoxanthine-guanine phosphoribosyltransferase		

MAP	mitogen-activated protein (kinase)	PI 3-kinase	phosphatidylinositol 3-kinase
MHC	major histocompatibility complex	piRNA	piwi-interacting RNA
miRNA	microRNA	PK	protein kinase (PKA, PKB, PKC, etc.)
mRNA	messenger RNA	PK	pyruvate kinase
MS	mass spectrometry	pK _a	the pH at which there is 50% dissociation of an acid
MTOC	microtubule-organizing centre	PKB	mammalian homologue of Akt
m/z	mass-to-charge ratio	PKU	phenylketonuria
N	unspecified base in a nucleotide (e.g. NTP)	PLC	phospholipase C
NAD ⁺	nicotinamide adenine dinucleotide (oxidized form)	PLP	pyridoxal-5'-phosphate
NADH	reduced form of NAD	Pol	DNA or RNA polymerase
NADP ⁺	nicotinamide adenine dinucleotide phosphate (oxidized form)	POMC	pro-opiomelanocortin; appetite repressor
NADPH	reduced form of NADP	PP _i	inorganic pyrophosphate
N-CAMS	nerve cell adhesion proteins	PPI	peptidylproline isomerase
NEFA	non-esterified fatty acid	Pq	plasto-quinone
NES	nuclear export signal	PRE	polypyrimidine (C-rich) element (in mRNA)
NF-κB	nuclear factor family of eukaryotic transcription factors	pri-miRNA	primary microRNA
NGS	next generation sequencing	PrP ^c	prion protein (constitutive)
NK	natural killer cells	PrP ^{sc}	prion protein (scrapie)
NLS	nuclear localization signal	PRPP	5-phosphoribosyl-1-pyrophosphate
nm	nanometer (10 ⁻⁹ metres)	PS	phosphatidylserine
NMR	nuclear magnetic resonance spectroscopy	PS	photosystem (PSI, PSII)
NPY	neuropeptide Y; appetite stimulant	P site	peptidyl site (of ribosome)
NSAID	nonsteroidal anti-inflammatory drugs	PTGS	posttranscriptional silencing (plants)
NTF	nuclear transport factor	PTS	peroxisome-targeting signal
—Ⓢ	high-energy phosphoryl group	PYY-3–36	neuropeptide appetite inhibitor
P450	cytochrome P450	Q	ubiquinone (<i>see also</i> CoQ, UQ)
PAGE	polyacrylamide gel electrophoresis	Q	quadrupole (in mass spectrometry)
PBG	porphobilinogen	qPCR	quantitative PCR (polymerase chain reaction)
PC	phosphatidylcholine (lecithin)	R	gas constant (8.315 J mol ⁻¹ K ⁻¹)
Pc	plastocyanin	Rb	retinoblastoma
PCNA	proliferating cell nuclear antigen (eukaryotic sliding clamp protein)	RFLP	restriction fragment length polymorphism
PCR	polymerase chain reaction	RF	release factor (in translation)
PDB	protein database	RISC	RNA-induced silencing complex
PDGF	platelet-derived growth factor	RNA	ribonucleic acid
PDH	pyruvate dehydrogenase	RNase	ribonuclease
PDI	protein disulfide isomerase	RNAi	RNA interference
PE	phosphatidylethanolamine (cephalin)	ROS	reactive oxygen species
PEP	phosphoenolpyruvate	R-5-P	ribose-5-phosphate
PEP-CK	PEP carboxykinase	RPA	replication protein A (detects single-stranded DNA)
PET	positron emitting tomography	rRNA	ribosomal RNA
PFK	phosphofructokinase (PFK1, PFK2)	Rubisco	ribulose-1,5-bisphosphate carboxylase
PG	prostaglandin	S	Svedberg unit
3-PGA	3-phosphoglycerate	S	'synthesis' (DNA replication) phase of cell cycle
PH	pleckstrin homology (domain)	S	entropy
P _i	inorganic phosphate	SAM	S-adenosylmethionine
pI	isoelectric point		
PIAS	protein inhibitor of activated STATS		
PIC	preinitiation complex		

SCID	severe combined immunodeficiency disease	TNF- α	tumour necrosis factor- α
SCNT	somatic cell-nuclear transfer	TOF	time of flight
SECIS	selenocysteine insertion sequence	TOM	translocator of the outer mitochondrial membrane
SDS	sodium dodecylsulfate	TPA (t-pa)	tissue plasminogen activator
SDS-PAGE	SDS polyacrylamide gel electrophoresis	TPP	thiamin pyrophosphate
SH2	Src homology region 2	tRNA	transfer RNA
SINES	short interspersed elements	tRNA ^{phe}	tRNA specific for phenylalanine (by analogy, tRNA ^{Leu} , tRNA ^{Met} , etc.)
siRNA	small interfering RNA	tRNA _f	tRNA formyl (bacterial translation initiation)
Sn	stereospecific numbering	tRNA _i	tRNA for eukaryote translation initiation
SNP	single nucleotide polymorphism	TSH	thyroid-stimulating hormone
snRNAs	small nuclear RNAs		
snoRNA	small nucleolar RNA		
SOCS	suppressors of cytokine signalling		
SOS	'son of sevenless'	U	uracil
SR	sarcoplasmic reticulum	UDP	uridine diphosphate
SRP	signal-recognition particle	UDPG	uridine diphosphoglucose
Ss	single-stranded (DNA or RNA)	UDP-Gal	uridine diphosphogalactose
SSB	single-strand binding protein	UTP	uridine triphosphate
STAT	signal transducer and activator of transcription	UQ	ubiquinone (<i>see also</i> CoQ, Q)
STR	short tandem repeats (microsatellites)	UTR	untranslated region (of mRNA)
		UV	ultraviolet (light)
T	thymine		
T ₃	triiodothyronine	v-	'viral', denotes oncogene (<i>v-ras</i> , <i>v-myc</i> , etc.)
T ₄	thyroxine	V	velocity of reaction
TAF	TBP-associated factor	V ₀	initial velocity of reaction
TAG	triacylglycerol	V _{max}	maximum velocity of reaction
TBP	TATA-binding protein	VLDL	very-low-density lipoprotein
TCA	tricarboxylic acid	VNTR	variable number of tandem repeats
TCR	T cell receptor		
TF	transcription factor	X-5-P	xylulose-5-phosphate
TFIID	transcription factor D for RNA polymerase II	YAC	yeast artificial chromosome
TIM	translocator of the inner mitochondrial membrane		

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Part 1 Basic concepts of life

Chapter 1 The basic molecular themes of life

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All life forms are similar at the molecular level

3

The energy cycle in life

4

The laws of thermodynamics deal with energy

4

Energy can be transformed from one state to another

5

- ATP (adenosine triphosphate) is the universal energy currency in life

5

Types of molecules found in living cells

5

- Small molecules
- Macromolecules are made by polymerization of smaller units
- Protein and nucleic acid molecules have information content

6

7

7

Proteins

8

- Catalysis of reactions by enzyme proteins is central to the existence of life
- What is the function of enzymes?

8

8

Proteins work by molecular recognition

9

- Life is self-assembling due to molecular recognition by proteins
- Many proteins are molecular machines
- How can one class of molecule carry out so many tasks?

9

9

9

Evolution of proteins

9

- Development of new genes

9

DNA (deoxyribonucleic acid)

10

- DNA directs its own replication
- Genetic code

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- Membrane proteins
- Conjugated proteins and post-translational modifications of proteins

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- Molecular weight determination of proteins
- Identification of proteins using mass spectrometry without sequencing
- Identification of proteins by limited sequencing and database searching
- Analysis of post-translational modification of proteins

Methods of sequencing protein

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- Sequence prediction of proteins from gene DNA sequences
- Sequencing by mass spectrometry

Determination of the three-dimensional structure of proteins

- X-ray diffraction
- Nuclear magnetic resonance spectroscopy
- Homology modelling
- An exercise in obtaining a 3-D structure from a protein database

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