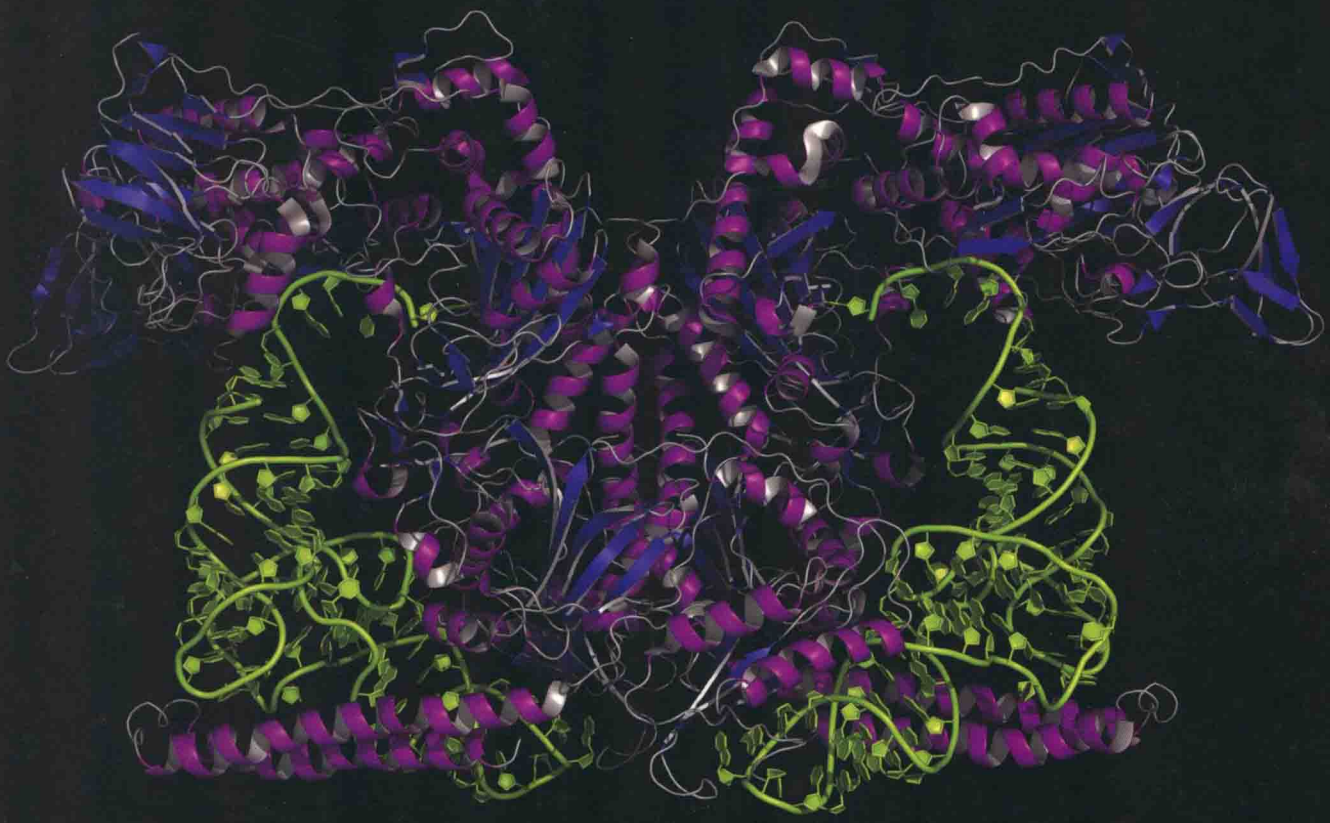

BIOCHEMISTRY & MOLECULAR BIOLOGY

DESPO PAPACHRISTODOULOU | ALISON SNAPE
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5TH EDITION

OXFORD

Biochemistry and Molecular Biology

Fifth edition

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OXFORD
UNIVERSITY PRESS

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Great Clarendon Street, Oxford, OX2 6DP,
United Kingdom

Oxford University Press is a department of the University of Oxford.
It furthers the University's objective of excellence in research, scholarship,
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Impression: 1

British Library Cataloguing in Publication Data
Data available

Library of Congress Control Number: 2013956989

ISBN 978–0–19–960949–9
Printed in Italy by L.E.G.O. S.p.A. —Lavis TN

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

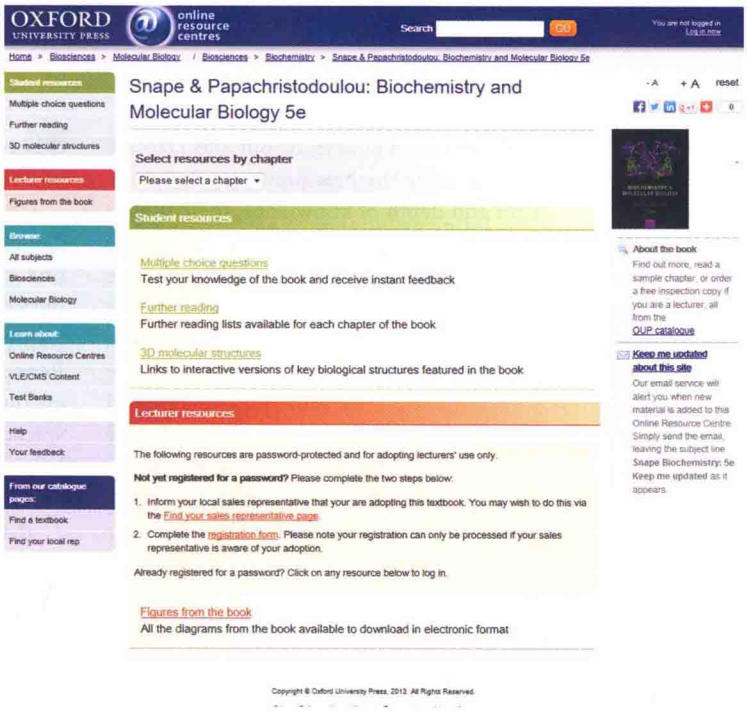
The Online Resource Centre, which has been built to accompany this text, contains a number of useful teaching and learning resources for lecturers and students. Visit the site at **www.oxfordtextbooks.co.uk/orc/snape_biochemistry5e/**

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.



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.

Finally we would like to thank staff and students at King's College London. Our colleagues have contributed greatly to our knowledge and understanding of numerous topics, in particular Dr Liz Andrew, who reviewed Chapter 33 on the immune system. Professor Guy Tear, Dr Paul Brown, Dr Renee Tata and others have provided invaluable support and encouragement. Our students have persistently, and often perspicaciously, made comments and asked questions that have helped us develop our ability to teach.

> 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*

Brief contents

Diseases and medically relevant topics

Abbreviations

A	adenine
AA	aminoacyl group
ABC	ATP-binding cassette
ACAT	acyl-CoA:cholesterol acyltransferase
ACP	acyl carrier protein
ACTH	adrenocorticotrophic hormone (also called corticotrophin)
ADH	antidiuretic hormone (also called vasopressin)
ADP	adenosine diphosphate
AgAp	agouti-related appetite stimulant
Akt	protein kinase (*see also* PKB)
AIDS	acquired immunodeficiency syndrome
ALA	5-aminolevulinic acid
ALA-S	aminolevulinate synthase
ALT	alternative mechanism of lengthening telomeres
AMP	adenosine monophosphate
AMPK	AMP-activated protein kinase
AP	apurine or apyrimidine
APC	antigen-presenting cell
APR	anaphase promoting complex
Apaf-1	apoptopic protease mediating factor
A site	acceptor site (or amino acyl site) of ribosome
ATCase	aspartyl transcarbamylase
ATM	ataxia telangiectasia mutated
ATP	adenosine triphosphate
ARE	AU-rich element (in mRNA)
AZT	azidothymidine
BAC	bacterial artificial chromosome
bp	base pair
BPG	2,3-bisphosphoglycerate
BSE	bovine spongiform encephalopathy (mad cow disease)
C	cytosine
c-	'cellular', denotes protooncogene (c-*ras*, c-*myc*, etc.)
cal	calorie
CAM	calmodulin
cAMP	adenosine-3′,5′-cyclic monophosphate
CAK	Cdk activating kinase
CAP	catabolite gene-activator protein
CBP	CREB-binding protein
CD	cluster of differentiation (proteins)
Cdk	cyclin-dependent kinase
cDNA	complementary DNA
CETP	cholesterol ester transfer protein
CGRP	calcitonin gene related peptide
CJD	Creutzfeldt-Jakob disease
CDP	cytidine diphosphate
Cki	Cdk inhibitor protein
COP	coat protein (of transport vesicles)
CoA	coenzyme A (A = acyl)
CoQ	ubiquinone (*see also* Q, UQ)
COX	cyclooxygenase
CRE	cAMP-response element
CREB	CRE-binding protein
CSF	colony-stimulating factor
CTD	carboxy-terminal domain (of eukaryotic RNA polymerase)
CTP	cytidine triphosphate
CVD	cardiovascular disease
d-	deoxy (as in deoxyribonucleotides: dATP, dCTP etc.)
DAG	diacylglycerol
Da	Dalton (unit of atomic or molecular mass: one twelfth of the mass of a carbon 12 atom)
dd-	dideoxy (as in dideoxyribonucleotides: ddATP, ddCTP etc.)
DHAP	dihydroxyacetone phosphate
DNA	deoxyribonucleic acid
DNase	deoxyribonuclease
DPE	downstream promoter element
ds	double stranded (DNA, RNA)
DNP	dinitrophenol
DSB	double stranded break
E_0'	redox potential value at pH 7.0
ECM	extracellular matrix
EF	elongation factor (in translation)
EF_2	elongation factor 2 (eukaryotic ribosomal translocase)
EF-G	elongation factor-G (*E. coli* ribosomal translocase)
EF-Tu	elongation factor temperature unstable
EGF	epidermal growth factor
eIF	eukaryotic initiation factor (in translation)
ELISA	enzyme-linked immunoabsorbent assay

ENCODE	Encyclopoedia of DNA elements (project)
ER	endoplasmic reticulum
ES cell	embryonic stem cell
ESI	electrospray ionization
E site	exit site of ribosome
F_o	membrane rotary subunit of ATP synthase
F_1	catalytic subunit of ATP synthase
F	Faraday constant (96.5 kJ V^{-1} mol^{-1})
FAD	flavin adenine dinucleotide
FADD	Fas-associated protein with a death domain
$FADH_2$	reduced form of FAD
Fd	ferredoxin
FFA	free fatty acid
FH_2	dihydrofolate
FH_4	tetrahydrofolate
fMet	formylmethionine
FMN	flavin mononucleotide
FSH	follicle-stimulating hormone
G_1 *or* G_2	'gap' phases of cell cycle
G	guanine
G	free energy (Gibbs)
$G^{0\prime}$	standard free energy (Gibbs) at pH 7.0
G-1-P	glucose-1-phosphate
G-6-P	glucose-6-phosphate
G6PD or G6PDH	glucose-6-phosphate dehydrogenase
GAG	glycosaminoglycan
GAP	GTPase-activating protein
GDP	guanosine diphosphate
GEF	guanine nucleotide exchange factor
GLUT	glucose transporter
GMO	genetically modified organism
GroEL	multisubunit molecular chaperone (chaperonin) of Hsp 60 class
GroES	'lid' structure of groEL chaperonin complex
GRB	growth receptor-binding protein
GRK	G-protein receptor kinase
GSH	reduced glutathione
GSK3	glycogen synthase kinase 3
GSSG	oxidized glutathione
GTP	guanosine triphosphate
H	enthalpy
HAT	histone acetyltransferase
Hb	haemoglobin
HbO_2	oxyhaemoglobin
HDAC	histone deacetylase
HDL	high-density lipoprotein
hESC	human embryonic stem cell
HGPRT	hypoxanthine–guanine phosphoribosyltransferase
HIF	hypoxia-inducible factor
HIV	human immunodeficiency virus
HLH	helix-loop-helix
HMG-CoA	3-hydroxy-3-methylglutaryl-CoA
HNPCC	hereditary nonpolyposis colorectal cancer
hnRNP	hetero-ribonucleoprotein complex
HPLC	high-pressure (or high performance) liquid chromatography
Hsp	heat-shock protein
HTH	helix–turn–helix (DNA-recognition motif)
I	inosine
IDL	intermediate-density lipoprotein
IF	initiation factor (e.g. IF1, IF2, IF3) in translation
IF	intermediate filament
Ig	immunoglobulin (IgG, IgG1, IgA, etc.)
IGF	insulin-like growth factor (IGFI, IGFII)
Il	interleukin
Inr	initiator (eukaryotic transcription)
IP_3	inositol trisphosphate
iPSC	induced pluripotent stem cell
IRE	iron-responsive element
IRP	IRE-binding protein
IRS	insulin receptor substrate
JAK	type of tyrosine kinase (*Janus kinase*)
J	Joule
K	Kelvin
K_a	acid dissociation constant
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)
K_{eq}	equilibrium constant of a reaction
K'_{eq}	equilibrium constant at pH 7.0
K_m	Michaelis constant:the substrate concentration at which a Michaelis–Menten enzyme works at half-maximal velocity
kb	kilobase
LCAT	lecithin:cholesterol acyltransferase
LDL	low-density lipoprotein
LINES	long interspersed elements
LTR	long terminal repeat (sequences in retroviruses and certain retrotransposons)
M	Molar (moles dm^{-3} or moles $litre^{-1}$)
MALDI	matrix-assisted laser-desorption ionization

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

SCID	severe combined immunodeficiency disease
SCNT	somatic cell-nuclear transfer
SECIS	selenocysteine insertion sequence
SDS	sodium dodecylsulfate
SDS-PAGE	SDS polyacrylamide gel electrophoresis
SH2	Src homology region 2
SINES	short interspersed elements
siRNA	small interfering RNA
Sn	stereospecific numbering
SNP	single nucleotide polymorphism
snRNAs	small nuclear RNAs
snoRNA	small nucleolar RNA
SOCS	suppressors of cytokine signalling
SOS	'son of sevenless'
SR	sarcoplasmic reticulum
SRP	signal-recognition particle
Ss	single-stranded (DNA or RNA)
SSB	single-strand binding protein
STAT	signal transducer and activator of transcription
STR	short tandem repeats (microsatellites)
T	thymine
T_3	triiodothyronine
T_4	thyroxine
TAF	TBP-associated factor
TAG	triacylglycerol
TBP	TATA-binding protein
TCA	tricarboxylic acid
TCR	T cell receptor
TF	transcription factor
TFIID	transcription factor D for RNA polymerase II
TIM	translocator of the inner mitochondrial membrane
TNF-α	tumour necrosis factor-α
TOF	time of flight
TOM	translocator of the outer mitochondrial membrane
TPA (t-pa)	tissue plasminogen activator
TPP	thiamin pyrophosphate
tRNA	transfer RNA
$tRNA^{phe}$	tRNA specific for phenylalanine (by analogy, $tRNA^{Leu}$, $tRNA^{Met}$, etc.)
$tRNA_f$	tRNA formyl (bacterial translation initiation)
$tRNA_i$	tRNA for eukaryote translation initiation
TSH	thyroid-stimulating hormone
U	uracil
UDP	uridine diphosphate
UDPG	uridine diphosphoglucose
UDP-Gal	uridine diphosphogalactose
UTP	uridine triphosphate
UQ	ubiquinone (*see also* CoQ, Q)
UTR	untranslated region (of mRNA)
UV	ultraviolet (light)
v-	'viral', denotes oncogene (v-*ras*, v-*myc*, etc.)
V	velocity of reaction
V0	initial velocity of reaction
V_{max}	maximum velocity of reaction
VLDL	very-low-density lipoprotein
VNTR	variable number of tandem repeats
X-5-P	xylulose-5-phosphate
YAC	yeast artificial chromosome

Contents

Part 2 Structure and function of proteins and membranes

Part 3 Metabolism and nutrition