Martin Beckerman

Molecular and Cellular Signaling

Springer

BIOLOGICAL AND MEDICAL PHYSICS
BIOMEDICAL ENGINEERING

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With 227 Figures

AIP PRESS

Springer

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Library of Congress Cataloging-in-Publication Data
Beckerman, Martin.
Molecular and cellular signaling/Martin Beckerman.
p. cm.—(Biological and medical physics, biomedical engineering, ISSN 1618-7210)
Includes bibliographical references and index.
ISBN 0-387-22130-1 (alk. paper)
1. Cellular signal transduction. I. Title. II. Series.
QP517.C45B43 2005
571.7′4—dc22 2004052556

ISBN-10: 0-387-22130-1 Printed on acid-free paper.
ISBN-13: 978-0387-22130-4

Printed in the United States of America. (BS/EB)

9 8 7 6 5 4 3 2 1 SPIN 10948309

springeronline.com

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The fields of biological and medical physics and biomedical engineering are broad, multidisciplinary, and dynamic. They lie at the crossroads of frontier research in physics, biology, chemistry, and medicine. The Biological and Medical Physics/Biomedical Engineering series is intended to be comprehensive, covering a broad range of topics important to the study of the physical, chemical, and biological sciences. Its goal is to provide scientists and engineers with textbooks, monographs, and reference works to address the growing need for information.

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Series Preface

The fields of biological and medical physics and biomedical engineering are broad, multidisciplinary, and dynamic. They lie at the crossroads of frontier research in physics, biology, chemistry, and medicine. The Biological and Medical Physics/Biomedical Engineering series is intended to be comprehensive, covering a broad range of topics important to the study of the physical, chemical, and biological sciences. Its goal is to provide scientists and engineers with textbooks, monographs, and reference works to address the growing need for information.

Books in the series emphasize established and emergent areas of science including molecular, membrane, and mathematical biophysics; photosynthetic energy harvesting and conversion; information processing; physical principles of genetics; sensory communications; and automata networks, neural networks, and cellular automata. Equally important will be coverage of applied aspects of biological and medical physics and biomedical engineering, such as molecular electronic components and devices, biosensors, medicine, imaging, physical principles of renewable energy production, advanced prostheses, and environmental control and engineering.

Oak Ridge, Tennessee

ELIAS GREENBAUM
Series Editor-in-Chief

Preface

This text provides an introduction to molecular and cellular signaling in biological systems. Cells partition their core cellular processes into a fixed infrastructure and a control layer. Proteins in the control layer, the subject of this textbook, function as signals, as receptors of the signals, as transcription factors that turn genes on and off, and as signaling transducers and intermediaries. The signaling and regulatory proteins and associated small molecules make contact with the fixed infrastructure responsible for metabolism, growth, replication, and reproduction at well-defined control points, where the signals are converted into cellular responses.

The text is aimed at a broad audience of students and other individuals interested in furthering their understanding of how cells regulate and coordinate their core activities. Malfunction in the control layer is responsible for a host of human disorders ranging from neurological disorders to cancers. Most drugs target components in the control layer, and difficulties in drug design are intimately related to the architecture of the control layer. The text will assist students and individuals in medicine and pharmacology interested in broadening their understanding of how the control layer works. To further that goal, there are chapters on cancers and apoptosis, and on bacteria and viruses. In those chapters not specifically devoted to pathogens, connections between diseases, drugs, and signaling are made.

The target audience for this text includes students in chemistry, physics, and computer science who intend to work in biological and medical physics, and bioinformatics and systems biology. To assist them, the textbook includes a fair amount of background information on the main points of these areas. The first five chapters of the book are mainly background and review chapters. Signaling in the immune, endocrine (hormonal), and nervous systems is covered, along with cancer, apoptosis, and gene regulation.

Biological systems are stunningly well engineered. Proof of this is all around us. It can be seen in the sheer variety of life on Earth, all built pretty much from the same building blocks and according to the same assembly rules, but arranged in myriad different ways. It can be seen in the relatively modest sizes of the genomes of even the most complex organisms, such as

ourselves. The genomes of worms, flies, mice, and humans are roughly comparable, and only a factor of two or three larger than those of some bacteria. The good engineering of biological systems is exemplified by the above-mentioned partition of cellular processes into the fixed infrastructure and the control layer. This makes possible machinery that always works the same way in any cell at any time, and whose interactions can be exactly known, while allowing for the machinery's regulation by the variable control layer at well-defined control points.

Another example of good engineering design is that of modularity of design. Proteins, especially signaling proteins, are modular in design and their components can be transferred, arranged, and rearranged to make many different proteins. The protein components interact with one another through their interfaces. There are interfaces for interactions with other proteins and with lipids DNA and RNA. Modularity is encountered not only in the largely independent components, but also in the DNA regulatory sequences. These sequences serve as control points for the networks that regulate gene expression. The DNA regulatory sequences can also be rearranged in a multitude of ways along the chromosomes, and these rearrangements, rather than the genes themselves, are largely responsible for the richness of life on Earth. Two of the key objectives of the text are to examine how modularity in design is used and how interfaces are exploited. X-ray crystal structures and nuclear magnetic resonance (NMR) solution structures provide insights at the atomic level of how the interfaces between modules operate, and these will be looked at throughout the text.

One of the great conceptual breakthroughs in explorations of the control layer was the idea that signaling proteins involved in cell-to-cell communication are organized into signaling pathways. In a signaling pathway, there is a starting point, usually a receptor at the plasma membrane, and an endpoint (control point), more often than not a transcription regulatory site in the nucleus, and there is a linear route leading from one to the other. In spite of the enormous complexity of metazoans, there are only about a dozen or so such pathways. These will be explored in the context of where they are most strongly associated. For example, some pathways are prominent during development and are best understood in that context. Other pathways are associated with stress responses and are best understood within that framework, and still others are associated with immune responses.

Signaling and the cellular responses to signals are complex. The responses are controlled by a plethora of positive and negative feedback loops. The presence of feedback complicates the simple picture of a linear pathway, but this aspect is an essential part of the signaling process. Positive feedback ensures that once the appropriate thresholds are passed there will be a firm commitment to a specific action and the system will not jump back and forth between alternative responses. Negative feedback generates the thresholds that ensure random excursions and perturbations do not unnec-

essarily commit the cell to some irreversible response when it ought not to, and it permits the cells to turn off the signaling once it has served its purpose. These feedback loops will be examined along with the discussions of the linear signaling pathways.

The goal of this textbook is to provide an introduction to the molecular and cellular signaling processing comprising the control layer. The topic is a vast one, and it is not possible to cover every possible aspect and still keep the text concise and readable. To achieve the stated goal, material of a historical nature has been omitted, as have lengthy descriptions of all proteins identified as being involved in the particular aspect of signaling being considered. In place of such an encyclopedic approach, selected processes are presented step-by-step from start to end. These examples serve as simple models of how the control process is carried out.

Oak Ridge, Tennessee MARTIN BECKERMAN

Guide to Acronyms

This Guide to Acronyms contains a list arranged alphabetically of commonly encountered acronyms all of which are discussed in the text. There are a number of instances where the same acronym has more than one usage. In some cases, the correct meaning can be discerned from the way the acronym is denoted, but in other cases, the correct usage must be deduced from the context. In the text, proteins are written starting with a capital letter, while the genes encoding the proteins are written all in lowercase letters. Protein names are, for the most part, not included in the list of acronyms. Proteins appearing in the list with names ending in numerals such as Ste2 are entered once; names of proteins of the same spelling with different numerals (e.g., Ste7, Ste11 in the case of Ste2) can be readily deduced.

5-HT	5-hydroxytryptamine (serotonin)
AA	arachidonic acid
AC	adenylyl cyclase
ACE	angiotensin-converting enzyme
ACF	ATP-dependent chromatin assembly and remodeling factor
ACh	acetylcholine
ACTH	adrenocorticotropic hormone
ADAM	a disintegrin and metalloprotease
ADHD	attention-deficit hyperactivity disorder
ADP	adenosine diphosphate
AFM	atomic force microscopy
AGC	PKA, PKG, PKC family
AHL	acetyl homoserine lactase
AIDS	acquired immunodeficiency syndrome
AIF	apoptosis inducing factor
AIP	autoinducing peptides
AKAP	A-kinase anchoring protein
ALK	activin receptor-like kinase
ALS	amytrophic lateral sclerosis

AMP	adenosine monophosphate
AMPA	α-amino-3-hydroxyl-5-methyl-4-isoxazole propionate acid
AMPK	AMP-dependent protein kinase
ANT	adenosine nucleotide translocator
APC	adenomatous polyposis coli
APC	antigen-presenting cell
APP	amyloid β protein precursor
ARC-L	activation-recruited coactivator-large
Arf	ADP-ribosylation factor
ARF	alternative reading frame (of exon 2)
ARR	Arabidopsis response regulator
ATM	ataxia-telangeictasia mutated
ATP	adenosine triphosphate
ATR	ATM and Rad3-related
AVN	atrioventricular node
AVP	vasopressin
Bcl-2	B cell leukemia 2
BCR	B-cell receptor
BDNF	brain-derived neurotrophic factor
BER	base excision repair
BFGF	basic fibroblast growth factor
BIR	baculoviral IAP repeat
BLV	bovine leukemia virus
BMP	bone morphogenetic protein
BRCA1	breast cancer 1
BRCT	BRCA1 C-terminal
BRE	TFIIB recognition element
bZIP	basic region leucine zipper
C1	protein kinase C homology-1
CAD	caspase-activated deoxyribonuclease
CaM	calmodulin
CaMKII	calcium/calmodulin-dependent protein kinase II
cAMP	cyclic AMP
CAP	catabolite activator protein
CAPRI	calcium-promoted Ras inactivator
CaR	extracellular calcium receptor
CARD	caspase recruitment domain
CASK	CaMK/SH3/guanylate kinase domain protein
CB	Cajal body
CBP	complement binding protein
CBP	CREB binding protein
CD	cluster of differentiation
Cdc25	cell division cycle (protein) 25
Cdk	cyclin-dependent kinase

cDNA	complementary DNA
CFP	cyan fluorescent protein
CFTR	cystic fibrosis transmembrane conductance regulator
cGMP	cyclic guanosine monophosphate
CHRAC	chromatin accessibility complex
Chromo	chromatin organization modifier
Ci	cubitus interruptus
Ck2	casein kinase-2
ClC	chloride channel of the CLC family
Clk	cyclin-dependent kinase-like kinase
CMGC	CDK, MAPK, GSK-3 CLK, CK2
CNG	cyclic nucleotide-gated
CNS	central nervous system
CNTF	ciliary neurotrophic factor
CoA	acetyl coenzyme A
COX	cyclo-oxygenase
CPG	central pattern generator
CR	consensus repeat
CRD	cysteine-rich domain
CRE	cAMP response element
CREB	cAMP response element-binding protein
CRF	corticotropin-releasing factor
CRH	corticotropin-releasing hormone
CRSP	coactivator required for Sp1 activation
CSF	cerebrospinal fluid
cSMAC	central supramolecular activation cluster
CST	cortistatin
DA	dopamine
DAG	diacylglycerol
DAT	dopamine transporter
dATP	deoxyadenosine triphosphate
DC	dendritic cell
DCC	deleted in colorectal cancer
DD	death domain
DED	death effector domain
DEP	disheveled, egl-10, and pleckstrin
DFF	DNA fragmentation factor
Dhh	desert hedgehog
DIABLO	direct IAP binding protein with low pI
DISC	death-inducing signaling complex
DIX	disheveled and axin
DLG	discs large
DNA	deoxyribonucleic acid
DNA-PK	DNA-dependent protein kinase
DPE	downstream promoter element

DR	death receptor
DSB	double-strand break
DSL	delta/serrate/lin
dsRNA	double-stranded RNA
E	epinephrine (adrenaline)
ECF	extracytoplasmic function
ECM	extracellular matrix
EEG	electroencephalographic
EGF	epidermal growth factor
EGFR	epidermal growth factor receptor
eIF	eukaryotic initiation factors
EPEC	enteropathogenic *E. coli*
ER	endoplasmic reticulum
ERK	extracellular signal-regulated kinase
ESCRT	endosomal-sorting complexes required for transport
ESE	exonic splice enhancer
ESI	electrospray ionization
ESS	exonic splice silencer
EVH1	enabled/vasodilator-stimulated phosphoprotein homology-1
FA	focal adhesion
FADD	Fas-associated death domain
FAK	focal adhesion kinase
FAT	focal adhesion targeting
FH	forkhead
FHA	forkhead associated
FNIII	fibronectin type III
FRAP	fluorescence recovery following photobleaching
FSH	follicle-stimulating hormone
FYVE	Fab1p, YOTB, Vac1p, Eea1
GABA	γ-aminobutyric acid
GAP	GTPase-activating protein
GAS	group A streptococcus
GAS	interferon-gamma activated site
GDI	GDP dissociation inhibitors
GDNF	glial-derived neurotrophic factor
GDP	guanosine diphosphate
GEF	guanine nucleotide exchange factor
GFP	green fluorescent protein
GFR	growth factor receptor
GH	growth hormone
GHIH	growth hormone-inhibiting hormone
GHRH	growth hormone-releasing hormone

GIRK	G protein-linked inward rectified K^+ channels
GKAP	guanylate kinase-associated protein
GPCR	G protein-coupled receptor
GPI	glycosyl phosphatidyl inositol
GRH	gonadotropin-releasing hormone
GRIP	glutamate receptor interacting protein
GRK	G protein-coupled receptor kinase
GSK-3	glycogen synthase kinase-3
GTP	guanosine triphosphate
HA	histamine
HAT	histone acetyltransferase
HDAC	histone deacetylase
hGH	human growth hormone
HGT	horizontal gene transfer
Hh	hedgehog
HHV	human herpesvirus
HIV	human immunodeficiency virus
HK	histidine kinase
HLH	helix-loop-helix
HNC	hyperpolarization-activated cyclic nucleotide gated
hnRNP	heterogeneous nuclear RNP
HOG	high osmolarity glycerol
HPt	histidine phosphotransfer
HR	homologous recombination
Hsp	heat shock protein
HSV-1	herpes simplex virus type 1
hTERT	human telomerase reverse transcriptase
HTH	helix-turn-helix
HTLV-1	human T lymphotropic virus type 1
hTR	human telomerase RNA
HtrA2	high temperature requirement factor A2
IAP	inhibitor of apoptosis
ICAD	inhibitor of CAD
ICAM	intercellular cell adhesion molecule
ICE	interleukin-1β converting enzyme
IEG	immediate early gene
IFN	interferon
Ig	immunoglobulin
IGC	interchromatin granule clusters
IgCAM	immunoglobulin cell adhesion molecule
IGluR	inhibitory glutamate receptor ion channel
IGluR	ionotropic glutamate receptor
Ihh	Indian hedgehog

IL	interleukin
ILP	IAP-like protein
IN	integrase
Inr	initiator
$InsP_3R$	inositol (1,4,5) triphosphate receptor
IP	Ischemic preconditioning
IPSP	inhibitory postsynaptic potential
IRAK	IL-1R-associated kinase
IRES	internal ribosomal entry site
IRF	interferon regulatory factor
IS	immunological synapse
IS	intracellular stores
ISE	intronic splice enhancer
ISRE	interferon stimulated response element
ISS	intronic splice silencer
ISWI	imitation SWI
ITAM	immunoreceptor tyrosine-based activation motif
Jak	Janus kinase
JNK	c-Jun N-terminal kinase
KSHV	Kaposi's sarcoma-associated herpesvirus
L	late (domain)
LAMP	latency-associated membrane protein
LANA-1	latency-associated nuclear antigen type 1
LH	luteinizing hormone
LNR	lin/notch repeat
LNS	laminin, neurexin, sex hormone-binding globulin
LPS	lipopolysaccharides
LRR	leucine-rich repeat
LTD	long-term depression
LTP	long-term potentiation
LTR	long terminal repeat
LZ	leucine zipper
MA	matrix
MAGE	melanoma-associated antigen
MALDI	matrix-assisted laser desorption ionization
MAOI	monoamine oxidase inhibitor
MAP	mitogen-activated protein
MAPK	mitogen-activated protein kinase
MCP	methyl-accepting chemotaxis protein
MD	molecular dynamics
MH1	mad homology-1
MHC	major histocompatibility complex

MIP	macrophage inflammatory protein
MM	molecular mechanics
MMP	matrix metalloproteinase
MMR	mismatch repair
MRI	magnetic resonance imaging
mRNA	messenger RNA
MSH	melanocyte-stimulating hormone
MVB	multivesicular body
NAc	nucleus accumbens
nAChR	nicotinic acetylcholine receptor
NADE	p75-associated cell death executioner
NAIP	neuronal inhibitory apoptosis protein
NBS	Nijmegem breakage syndrome
NC	nucleocapsid
NCAM	neural cell adhesion molecule
NE	norepinephrine (noradrenaline)
NER	nucleotide excision repair
NES	nuclear export signal (sequence)
NFAT	nuclear factor of activated T cells
NF-κB	nuclear factor kappa B
NGF	nerve growth factor
NH	amide (molecule)
NHEJ	nonhomologous end joining
NICD	notch intracellular domain
NKA	neurokinin A
NKB	neurokinin B
NLS	nuclear localization signal (sequence)
NMDA	*N*-methyl-D-aspartate
NMR	nuclear magnetic resonance
NPC	nuclear pore complex
NRAGE	neurotrophin receptor-interacting MAGE homolog
NRIF	neurotrophin receptor-interacting factor
NSAID	nonsteroidal anti-inflammatory drug
NSF	*N*-ethylmaleimide-sensitive fusion protein
NURF	nucleosome remodeling factor
OCT	octopamine
OPR	octicopeptide repeat
OT	oxytocin
PACAP	pituitary adenylate cyclase-activating polypeptide
PAGE	polyacrylamide gel electrophoresis
PBP	periplasmic binding protein
PCP	planar cell polarity
PCR	polymerase chain reaction

PDB	protein data bank
PDE	phosphodiesterase
PDGF	platelet-derived growth factor
PDK	phosphoinositide-dependent protein kinase
PDZ	PSD-95, DLG, ZO-1
PGHS	endoperoxide H synthase
PH	pleckstrin homology
PIC	pre-initiation complex
PIH	prolactin-inhibiting hormone
PIKK	phosphoinositide 3-kinase related kinase
PIP	phosphatidylinositol phosphatase
PKA	protein kinase A
PKB	protein kinase B
PKC	protein kinase C
PKG	protein kinase G
PKR	protein kinase R
PLA_2	phospholipase A_2
PLC	phospholipase C
PMCA	plasma membrane calcium ATPase
PNS	peripheral nervous system
POMC	pro-opiomelanocortin
PP-II	polyproline (helix)
PRH	prolactin-releasing hormone
PRL	prolactin
PS	pseudosubstrate
PSD	postsynaptic density
PSD-95	postsynaptic density protein of 95 kDa
pSMAC	peripheral supramolecular activation cluster
PTB	phosphotyrosine binding
PTH	parathyroid hormone
PTHrH	parathyroid hormone related protein
PTPC	permeability transition pore complex
PYD	pyrin domain
QM	quantum mechanics
RACK	receptor for activated C-kinase
RAIP	Arg-Ala-Ile-Pro (motif)
RE	responsive (response) element
REM	rapid eye movement
RF	radiofrequency
RGS	regulator-of-G-protein signaling
RH	RGS homology
RHD	rel homology domain
RIP	receptor-interacting protein