



Martin Beckerman

Molecular and Cellular Signaling



Springer

BIOLOGICAL AND MEDICAL PHYSICS
BIOMEDICAL ENGINEERING

Contents

Series Preface	v
Preface	vii
Guide to Acronyms	xxv
1. Introduction	1
1.1 Prokaryotes and Eukaryotes	1
1.2 The Cytoskeleton and Extracellular Matrix	2
1.3 Core Cellular Functions in Organelles	3
1.4 Metabolic Processes in Mitochondria and Chloroplasts	4
1.5 Cellular DNA to Chromatin	5
1.6 Protein Activities in the Endoplasmic Reticulum and Golgi Apparatus	6
1.7 Digestion and Recycling of Macromolecules	8
1.8 Genomes of Bacteria Reveal Importance of Signaling	9
1.9 Organization and Signaling of Eukaryotic Cell	10
1.10 Fixed Infrastructure and the Control Layer	12
1.11 Eukaryotic Gene and Protein Regulation	13
1.12 Signaling Malfunction Central to Human Disease	15
1.13 Organization of Text	16
2. The Control Layer	21
2.1 Eukaryotic Chromosomes Are Built from Nucleosomes	22
2.2 The Highly Organized Interphase Nucleus	23
2.3 Covalent Bonds Define the Primary Structure of a Protein	26
2.4 Hydrogen Bonds Shape the Secondary Structure	27
2.5 Structural Motifs and Domain Folds: Semi-Independent Protein Modules	29

2.6	Arrangement of Protein Secondary Structure Elements and Chain Topology	29
2.7	Tertiary Structure of a Protein: Motifs and Domains	30
2.8	Quaternary Structure: The Arrangement of Subunits	32
2.9	Many Signaling Proteins Undergo Covalent Modifications	33
2.10	Anchors Enable Proteins to Attach to Membranes	34
2.11	Glycosylation Produces Mature Glycoproteins	36
2.12	Proteolytic Processing Is Widely Used in Signaling	36
2.13	Reversible Addition and Removal of Phosphoryl Groups	37
2.14	Reversible Addition and Removal of Methyl and Acetyl Groups	38
2.15	Reversible Addition and Removal of SUMO Groups	39
2.16	Post-Translational Modifications to Histones	40
3.	Exploring Protein Structure and Function	45
3.1	Interaction of Electromagnetic Radiation with Matter	46
3.2	Biomolecule Absorption and Emission Spectra	49
3.3	Protein Structure via X-Ray Crystallography	49
3.4	Membrane Protein 3-D Structure via Electron and Cryoelectron Crystallography	53
3.5	Determining Protein Structure Through NMR	53
3.6	Intrinsic Magnetic Dipole Moment of Protons and Neutrons	56
3.7	Using Protein Fluorescence to Probe Control Layer	57
3.8	Exploring Signaling with FRET	58
3.9	Exploring Protein Structure with Circular Dichroism	60
3.10	Infrared and Raman Spectroscopy to Probe Vibrational States	61
3.11	A Genetic Method for Detecting Protein Interactions	61
3.12	DNA and Oligonucleotide Arrays Provide Information on Genes	62
3.13	Gel Electrophoresis of Proteins	63
3.14	Mass Spectroscopy of Proteins	64

4.	Macromolecular Forces	71
4.1	Amino Acids Vary in Size and Shape	71
4.2	Amino Acids Behavior in Aqueous Environments	72
4.3	Formation of H-Bonded Atom Networks	74
4.4	Forces that Stabilize Proteins	74
4.5	Atomic Radii of Macromolecular Forces	75
4.6	Osmophobic Forces Stabilize Stressed Cells	76
4.7	Protein Interfaces Aid Intra- and Intermolecular Communication	77
4.8	Interfaces Utilize Shape and Electrostatic Complementarity	78
4.9	Macromolecular Forces Hold Macromolecules Together	79
4.10	Motion Models of Covalently Bonded Atoms	79
4.11	Modeling van der Waals Forces	81
4.12	Molecular Dynamics in the Study of System Evolution	83
4.13	Importance of Water Molecules in Cellular Function	84
4.14	Essential Nature of Protein Dynamics	85
5.	Protein Folding and Binding	89
5.1	The First Law of Thermodynamics: Energy Is Conserved	90
5.2	Heat Flows from a Hotter to a Cooler Body	91
5.3	Direction of Heat Flow: Second Law of Thermodynamics	92
5.4	Order-Creating Processes Occur Spontaneously as Gibbs Free Energy Decreases	93
5.5	Spontaneous Folding of New Proteins	94
5.6	The Folding Process: An Energy Landscape Picture	96
5.7	Misfolded Proteins Can Cause Disease	98
5.8	Protein Problems and Alzheimer's Disease	99
5.9	Amyloid Buildup in Neurological Disorders	100
5.10	Molecular Chaperones Assist in Protein Folding in the Crowded Cell	101
5.11	Role of Chaperonins in Protein Folding	102
5.12	Hsp 90 Chaperones Help Maintain Signal Transduction Pathways	103
5.13	Proteins: Dynamic, Flexible, and Ready to Change	104

6.	Stress and Pheromone Responses in Yeast	111
6.1	How Signaling Begins	112
6.2	Signaling Complexes Form in Response to Receptor-Ligand Binding	113
6.3	Role of Protein Kinases, Phosphatases, and GTPases	115
6.4	Role of Proteolytic Enzymes	116
6.5	End Points Are Contact Points to Fixed Infrastructure	117
6.6	Transcription Factors Combine to Alter Genes	118
6.7	Protein Kinases Are Key Signal Transducers	119
6.8	Kinases Often Require Second Messenger Costimulation	121
6.9	Flanking Residues Direct Phosphorylation of Target Residues	122
6.10	Docking Sites and Substrate Specificity	123
6.11	Protein Phosphatases Are Prominent Components of Signaling Pathways	123
6.12	Scaffold and Anchor Protein Role in Signaling and Specificity	124
6.13	GTPases Regulate Protein Trafficking in the Cell	125
6.14	Pheromone Response Pathway Is Activated by Pheromones	125
6.15	Osmotic Stresses Activate Glycerol Response Pathway	128
6.16	Yeasts Have a General Stress Response	129
6.17	Target of Rapamycin (TOR) Adjusts Protein Synthesis	131
6.18	TOR Adjusts Gene Transcription	133
6.19	Signaling Proteins Move by Diffusion	134
7.	Two-Component Signaling Systems	139
7.1	Prokaryotic Signaling Pathways	140
7.2	Catalytic Action by Histidine Kinases	141
7.3	The Catalytic Activity of HK Occurs at the Active Site	143
7.4	The GHKL Superfamily	144
7.5	Activation of Response Regulators by Phosphorylation	145
7.6	Response Regulators Are Switches Thrown at Transcriptional Control Points	146
7.7	Structure and Domain Organization of Bacterial Receptors	147
7.8	Bacterial Receptors Form Signaling Clusters	148

7.9	Bacteria with High Sensitivity and Mobility	149
7.10	Feedback Loop in the Chemotactic Pathway	150
7.11	How Plants Sense and Respond to Hormones	152
7.12	Role of Growth Plasticity in Plants	154
7.13	Role of Phytochromes in Plant Cell Growth	154
7.14	Cryptochromes Help Regulate Circadian Rhythms	156
8.	Organization of Signal Complexes by Lipids, Calcium, and Cyclic AMP	161
8.1	Composition of Biological Membranes	162
8.2	Microdomains and Caveolae in Membranes	163
8.3	Lipid Kinases Phosphorylate Plasma Membrane Phosphoglycerides	165
8.4	Generation of Lipid Second Messengers from PIP ₂	165
8.5	Regulation of Cellular Processes by PI3K	167
8.6	PIPs Regulate Lipid Signaling	168
8.7	Role of Lipid-Binding Domains	169
8.8	Role of Intracellular Calcium Level Elevations	170
8.9	Role of Calmodulin in Signaling	171
8.10	Adenylyl Cyclases and Phosphodiesterases Produce and Regulate cAMP Second Messengers	172
8.11	Second Messengers Activate Certain Serine/ Threonine Kinases	173
8.12	Lipids and Upstream Kinases Activate PKB	174
8.13	PKB Supplies a Signal Necessary for Cell Survival	176
8.14	Phospholipids and Ca ²⁺ Activate Protein Kinase C	177
8.15	Anchoring Proteins Help Localize PKA and PKC Near Substrates	178
8.16	PKC Regulates Response of Cardiac Cells to Oxygen Deprivation	179
8.17	cAMP Activates PKA, Which Regulates Ion Channel Activities	180
8.18	PKs Facilitate the Transfer of Phosphoryl Groups from ATPs to Substrates	182
9.	Signaling by Cells of the Immune System	187
9.1	Leukocytes Mediate Immune Responses	188
9.2	Leukocytes Signal One Another Using Cytokines	190
9.3	APC and Naïve T Cell Signals Guide Differentiation into Helper T Cells	192

9.4	Five Families of Cytokines and Cytokine Receptors	193
9.5	Role of NF- κ B/Rel in Adaptive Immune Responses	194
9.6	Role of MAP Kinase Modules in Immune Responses	196
9.7	Role of TRAF and DD Adapters	196
9.8	Toll/IL-1R Pathway Mediates Innate Immune Responses	198
9.9	TNF Family Mediates Homeostasis, Death, and Survival	199
9.10	Role of Hematopoietin and Related Receptors	200
9.11	Role of Human Growth Hormone Cytokine	202
9.12	Signal-Transducing Jaks and STATs	203
9.13	Interferon System: First Line of Host Defense in Mammals Against Virus Attacks	205
9.14	Chemokines Provide Navigational Cues for Leukocytes	206
9.15	B and T Cell Receptors Recognize Antigens	207
9.16	MHCs Present Antigens on the Cell Surface	208
9.17	Antigen-Recognizing Receptors Form Signaling Complexes with Coreceptors	209
9.18	Costimulatory Signals Between APCs and T Cells	211
9.19	Role of Lymphocyte-Signaling Molecules	212
9.20	Kinetic Proofreading and Serial Triggering of TCRs	213
10.	Cell Adhesion and Motility	221
10.1	Cell Adhesion Receptors: Long Highly Modular Glycoproteins	221
10.2	Integrins as Bidirectional Signaling Receptors	223
10.3	Role of Leukocyte-Specific Integrin	224
10.4	Most Integrins Bind to Proteins Belonging to the ECM	225
10.5	Cadherins Are Present in Most Cells of the Body	226
10.6	IgCAMs Mediate Cell–Cell and Cell–ECM Adhesion	228
10.7	Selectins Are CAMs Involved in Leukocyte Motility	229
10.8	Leukocytes Roll, Adhere, and Crawl to Reach the Site of an Infection	230
10.9	Bonds Form and Break During Leukocyte Rolling	231

10.10	Bond Dissociation of Rolling Leukocyte as Seen in Microscopy	232
10.11	Slip and Catch Bonds Between Selectins and Their Carbohydrate Ligands	233
10.12	Development in Central Nervous System	234
10.13	Diffusible, Anchored, and Membrane-Bound Glycoproteins in Neurite Outgrowth	235
10.14	Growth Cone Navigation Mechanisms	236
10.15	Molecular Marking by Concentration Gradients of Netrins and Slits	237
10.16	How Semaphorins, Scatter Factors, and Their Receptors Control Invasive Growth	239
10.17	Ephrins and Their Eph Receptors Mediate Contact-Dependent Repulsion	239
11.	Signaling in the Endocrine System	247
11.1	Five Modes of Cell-to-Cell Signaling	248
11.2	Role of Growth Factors in Angiogenesis	249
11.3	Role of EGF Family in Wound Healing	250
11.4	Neurotrophins Control Neuron Growth, Differentiation, and Survival	251
11.5	Role of Receptor Tyrosine Kinases in Signal Transduction	252
11.6	Phosphoprotein Recognition Modules Utilized Widely in Signaling Pathways	254
11.7	Modules that Recognize Proline-Rich Sequences Utilized Widely in Signaling Pathways	256
11.8	Protein-Protein Interaction Domains Utilized Widely in Signaling Pathways	256
11.9	Non-RTKs Central in Metazoan Signaling Processes and Appear in Many Pathways	258
11.10	Src Is a Representative NRTK	259
11.11	Roles of Focal Adhesion Kinase Family of NRTKs	261
11.12	GTPases Are Essential Regulators of Cellular Functions	262
11.13	Signaling by Ras GTPases from Plasma Membrane and Golgi	263
11.14	GTPases Cycle Between GTP- and GDP-Bound States	264
11.15	Role of Rho, Rac, and Cdc42, and Their Isoforms	266
11.16	Ran Family Coordinates Traffic In and Out of the Nucleus	267
11.17	Rab and ARF Families Mediate the Transport of Cargo	268

12.	Signaling in the Endocrine and Nervous Systems	
	Through GPCRs	275
12.1	GPCRs Classification Criteria	276
12.2	Study of Rhodopsin GPCR with Cryoelectron Microscopy and X-Ray Crystallography	278
12.3	Subunits of Heterotrimeric G Proteins	279
12.4	The Four Families of G_{α} Subunits	280
12.5	Adenylyl Cyclases and Phosphodiesterases Key to Second Messenger Signaling	281
12.6	Desensitization Strategy of G Proteins to Maintain Responsiveness to Environment	282
12.7	GPCRs Are Internalized, and Then Recycled or Degraded	284
12.8	Hormone-Sending and Receiving Glands	285
12.9	Functions of Signaling Molecules	288
12.10	Neuromodulators Influence Emotions, Cognition, Pain, and Feeling Well	289
12.11	Ill Effects of Improper Dopamine Levels	291
12.12	Inadequate Serotonin Levels Underlie Mood Disorders	292
12.13	GPCRs' Role in the Somatosensory System Responsible for Sense of Touch and Nociception	292
12.14	Substances that Regulate Pain and Fever Responses	293
12.15	Composition of Rhodopsin Photoreceptor	295
12.16	How G Proteins Regulate Ion Channels	297
12.17	GPCRs Transduce Signals Conveyed by Odorants	297
12.18	GPCRs and Ion Channels Respond to Tastants	299
13.	Cell Fate and Polarity	305
13.1	Notch Signaling Mediates Cell Fate Decision	306
13.2	How Cell Fate Decisions Are Mediated	307
13.3	Proteolytic Processing of Key Signaling Elements	308
13.4	Three Components of TGF- β Signaling	311
13.5	Smad Proteins Convey TGF- β Signals into the Nucleus	313
13.6	Multiple Wnt Signaling Pathways Guide Embryonic Development	314
13.7	Role of Noncanonical Wnt Pathway	317
13.8	Hedgehog Signaling Role During Development	317
13.9	Gli Receives Hh Signals	318

13.10	Stages of Embryonic Development Use Morphogens	320
13.11	Gene Family Hierarchy of Cell Fate Determinants in <i>Drosophila</i>	321
13.12	Egg Development in <i>D. Melanogaster</i>	322
13.13	Gap Genes Help Partition the Body into Bands	323
13.14	Pair-Rule Genes Partition the Body into Segments	324
13.15	Segment Polarity Genes Guide Parasegment Development	325
13.16	Hox Genes Guide Patterning in Axially Symmetric Animals	326
14.	Cancer	331
14.1	Several Critical Mutations Generate a Transformed Cell	332
14.2	Ras Switch Sticks to “On” Under Certain Mutations	334
14.3	Crucial Regulatory Sequence Missing in Oncogenic Forms of Src	336
14.4	Overexpressed GFRs Spontaneously Dimerize in Many Cancers	336
14.5	GFRs and Adhesion Molecules Cooperate to Promote Tumor Growth	337
14.6	Role of Mutated Forms of Proteins in Cancer Development	338
14.7	Translocated and Fused Genes Are Present in Leukemias	339
14.8	Repair of DNA Damage	340
14.9	Double-Strand-Break Repair Machinery	342
14.10	How Breast Cancer (BRCA) Proteins Interact with DNA	344
14.11	PI3K Superfamily Members that Recognize Double-Strand Breaks	345
14.12	Checkpoints Regulate Transition Events in a Network	346
14.13	Cyclin-Dependent Kinases Form the Core of Cell-Cycle Control System	347
14.14	pRb Regulates Cell Cycle in Response to Mitogenic Signals	347
14.15	p53 Halts Cell Cycle While DNA Repairs Are Made	349
14.16	p53 and pRb Controllers Central to Metazoan Cancer Prevention Program	350

14.17	p53 Structure Supports Its Role as a Central Controller	352
14.18	Telomerase Production in Cancer Cells	354
15.	Apoptosis	359
15.1	Caspases and Bcl-2 Proteins Are Key Mediators of Apoptosis	360
15.2	Caspases Are Proteolytic Enzymes Synthesized as Inactive Zymogens	361
15.3	Caspases Are Initiators and Executioners of Apoptosis Programs	362
15.4	There Are Three Kinds of Bcl-2 Proteins	363
15.5	How Caspases Are Activated	365
15.6	Cell-to-Cell Signals Stimulate Formation of the DISC	366
15.7	Death Signals Are Conveyed by the Caspase 8 Pathway	367
15.8	How Pro- and Antiapoptotic Signals Are Relayed	368
15.9	Bcl-2 Proteins Regulate Mitochondrial Membrane Permeability	369
15.10	Mitochondria Release Cytochrome c in Response to Oxidative Stresses	371
15.11	Mitochondria Release Apoptosis-Promoting Agents	372
15.12	Role of Apoptosome in (Mitochondrial Pathway to) Apoptosis	373
15.13	Inhibitors of Apoptosis Proteins Regulate Caspase Activity	374
15.14	Smac/DIABLO and Omi/HtrA2 Regulate IAPs	375
15.15	Feedback Loops Coordinate Actions at Various Control Points	375
15.16	Cells Can Produce Several Different Kinds of Calcium Signals	376
15.17	Excessive $[Ca^{2+}]$ in Mitochondria Can Trigger Apoptosis	377
15.18	p53 Promotes Cell Death in Response to Irreparable DNA Damage	378
15.19	Anti-Cancer Drugs Target the Cell's Apoptosis Machinery	379
16.	Gene Regulation in Eukaryotes	385
16.1	Organization of the Gene Regulatory Region	386
16.2	How Promoters Regulate Genes	387
16.3	TFs Bind DNA Through Their DNA-Binding Domains	389

16.4	Transcriptional Activation Domains Initiate Transcription	392
16.5	Nuclear Hormone Receptors Are Transcription Factors	393
16.6	Composition and Structure of the Basal Transcription Machinery	393
16.7	RNAP II Is Core Module of the Transcription Machinery	394
16.8	Regulation by Chromatin-Modifying Enzymes	395
16.9	Multiprotein Complex Use of Energy of ATP Hydrolysis	397
16.10	Protein Complexes Act as Interfaces Between TFs and RNAP II	398
16.11	Alternative Splicing to Generate Multiple Proteins	399
16.12	Pre-Messenger RNA Molecules Contain Splice Sites	400
16.13	Small Nuclear RNAs (snRNAs)	401
16.14	How Exon Splices Are Determined	403
16.15	Translation Initiation Factors Regulate Start of Translation	404
16.16	eIF2 Interfaces Upstream Regulatory Signals and the Ribosomal Machinery	406
16.17	Critical Control Points for Protein Synthesis	407
17.	Cell Regulation in Bacteria	411
17.1	Cell Regulation in Bacteria Occurs Primarily at Transcription Level	412
17.2	Transcription Is Initiated by RNAP Holoenzymes	412
17.3	Sigma Factors Bind to Regulatory Sequences in Promoters	414
17.4	Bacteria Utilize Sigma Factors to Make Major Changes in Gene Expression	414
17.5	Mechanism of Bacterial Transcription Factors	416
17.6	Many TFs Function as Response Regulators	417
17.7	Organization of Protein-Encoding Regions and Their Regulatory Sequences	418
17.8	The Lac Operon Helps Control Metabolism in <i>E. coli</i>	419
17.9	Flagellar Motors Are Erected in Several Stages	421
17.10	Under Starvation Conditions, <i>B. subtilis</i> Undergoes Sporulation	422
17.11	Cell-Cycle Progression and Differentiation in <i>C. crescentus</i>	424

17.12	Antigenic Variation Counters Adaptive Immune Responses	426
17.13	Bacteria Organize into Communities When Nutrient Conditions Are Favorable	426
17.14	Quorum Sensing Plays a Key Role in Establishing a Colony	428
17.15	Bacteria Form Associations with Other Bacteria on Exposed Surfaces	430
17.16	Horizontal Gene Transfer (HGT)	430
17.17	Pathogenic Species Possess Virulence Cassettes	431
17.18	Bacterial Death Modules	433
17.19	Myxobacteria Exhibit Two Distinct Forms of Social Behavior	434
17.20	Structure Formation by Heterocystous Cyanobacteria	435
17.21	Rhizobia Communicate and Form Symbiotic Associations with Legumes	436
18.	Regulation by Viruses	441
18.1	How Viruses Enter Their Host Cells	442
18.2	Viruses Enter and Exit the Nucleus in Several Ways	442
18.3	Ways that Viruses Exit a Cell	443
18.4	Viruses Produce a Variety of Disorders in Humans	444
18.5	Virus–Host Interactions Underlie Virus Survival and Proliferation	445
18.6	Multilayered Defenses Are Balanced by Multilayered Attacks	446
18.7	Viruses Target TNF Family of Cytokines	447
18.8	Hepatitis C Virus Disables Host Cell’s Interferon System	447
18.9	Human T Lymphotropic Virus Type 1 Can Cause Cancer	449
18.10	DNA and RNA Viruses that Can Cause Cancer	450
18.11	HIV Is a Retrovirus	452
18.12	Role of gp120 Envelope Protein in HIV	453
18.13	Early-Acting tat, rev, and nef Regulatory Genes	454
18.14	Late-Acting vpr, vif, vpu, and vpx Regulatory Genes	456
18.15	Bacteriophages’ Two Lifestyles: Lytic and Lysogenic	457
18.16	Deciding Between Lytic and Lysogenic Lifestyles	458
18.17	Encoding of Shiga Toxin in <i>E. coli</i>	459

19.	Ion Channels	465
19.1	How Membrane Potentials Arise	466
19.2	Membrane and Action Potentials Have Regenerative Properties	468
19.3	Hodgkin-Huxley Equations Describe How Action Potentials Arise	470
19.4	Ion Channels Have Gates that Open and Close	472
19.5	Families of Ion Channels Expressed in Plasma Membrane of Neurons	474
19.6	Assembly of Ion Channels	476
19.7	Design and Function of Ion Channels	478
19.8	Gates and Filters in Potassium Channels	478
19.9	Voltage-Gated Chloride Channels Form a Double-Barreled Pore	479
19.10	Nicotinic Acetylcholine Receptors Are Ligand-Gated Ion Channels	480
19.11	Operation of Glutamate Receptor Ion Channels	483
20.	Neural Rhythms	487
20.1	Heartbeat Is Generated by Pacemaker Cells	487
20.2	HCN Channels' Role in Pacemaker Activities	489
20.3	Synchronous Activity in the Central Nervous System	492
20.4	Role of Low Voltage-Activated Calcium Channels	492
20.5	Neuromodulators Modify the Activities of Voltage-Gated Ion Channels	494
20.6	Gap Junctions Formed by Connexins Mediate Rapid Signaling Between Cells	495
20.7	Synchronization of Neural Firing	497
20.8	How Spindling Patterns Are Generated	498
20.9	Epileptic Seizures and Abnormal Brain Rhythms	498
20.10	Swimming and Digestive Rhythms in Lower Vertebrates	499
20.11	CPGs Have a Number of Common Features	502
20.12	Neural Circuits Are Connected to Other Circuits and Form Systems	504
20.13	A Variety of Neuromodulators Regulate Operation of the Crustacean STG	505
20.14	Motor Systems Adapt to Their Environment and Learn	506
21.	Learning and Memory	511
21.1	Architecture of Brain Neurons by Function	512
21.2	Protein Complexes' Structural and Signaling Bridges Across Synaptic Cleft	514

21.3	The Presynaptic Terminal and the Secretion of Signaling Molecules	515
21.4	PSD Region Is Highly Enriched in Signaling Molecules	518
21.5	The Several Different Forms of Learning and Memory	520
21.6	Signal Integration in Learning and Memory Formation	521
21.7	Hippocampal LTP Is an Experimental Model of Learning and Memory	523
21.8	Initiation and Consolidation Phases of LTP	524
21.9	CREB Is the Control Point at the Terminus of the Learning Pathway	525
21.10	Synapses Respond to Use by Strengthening and Weakening	526
21.11	Neurons Must Maintain Synaptic Homeostasis	528
21.12	Fear Circuits Detect and Respond to Danger	529
21.13	Areas of the Brain Relating to Drug Addiction	529
21.14	Drug-Reward Circuits Mediate Addictive Responses	531
21.15	Drug Addiction May Be an Aberrant Form of Synaptic Plasticity	532
21.16	In Reward-Seeking Behavior, the Organism Predicts Future Events	533
Glossary		539
Index		553