

# Contents

<i>Preface</i>	vii
<i>Acknowledgments</i>	xiii
<i>Special Sections</i>	xxix
<i>Map of the Maps</i>	xxx

## PART 1 THE FACTS OF LIFE

<b>Chapter 1:</b>	Why: Biology by the Numbers	3
<b>Chapter 2:</b>	What and Where: Construction Plans for Cells and Organisms	35
<b>Chapter 3:</b>	When: Stopwatches at Many Scales	87
<b>Chapter 4:</b>	Who: “Bless the Little Beasties”	137

## PART 2 LIFE AT REST

<b>Chapter 5:</b>	Mechanical and Chemical Equilibrium in the Living Cell	187
<b>Chapter 6:</b>	Entropy Rules!	237
<b>Chapter 7:</b>	Two-State Systems: From Ion Channels to Cooperative Binding	281
<b>Chapter 8:</b>	Random Walks and the Structure of Macromolecules	311
<b>Chapter 9:</b>	Electrostatics for Salty Solutions	355
<b>Chapter 10:</b>	Beam Theory: Architecture for Cells and Skeletons	383
<b>Chapter 11:</b>	Biological Membranes: Life in Two Dimensions	427

## PART 3 LIFE IN MOTION

<b>Chapter 12:</b>	The Mathematics of Water	483
<b>Chapter 13:</b>	A Statistical View of Biological Dynamics	509
<b>Chapter 14:</b>	Life in Crowded and Disordered Environments	543
<b>Chapter 15:</b>	Rate Equations and Dynamics in the Cell	573
<b>Chapter 16:</b>	Dynamics of Molecular Motors	623
<b>Chapter 17:</b>	Biological Electricity and the Hodgkin–Huxley Model	681
<b>Chapter 18:</b>	Light and Life	717

<b>Chapter 19:</b>	Organization of Biological Networks	801
<b>Chapter 20:</b>	Biological Patterns: Order in Space and Time	893
<b>Chapter 21:</b>	Sequences, Specificity, and Evolution	951
<b>Chapter 22:</b>	Whither Physical Biology?	1023
	<i>Index</i>	1039

# Contents in Detail

Preface	vii
Acknowledgments	xiii
Special Sections	xxix
Map of the Maps	xxx

## PART 1 THE FACTS OF LIFE 1

<b>Chapter 1 Why: Biology by the Numbers</b>	<b>3</b>
1.1 BIOLOGICAL CARTOGRAPHY	3
1.2 PHYSICAL BIOLOGY OF THE CELL Model Building Requires a Substrate of Biological Facts and Physical (or Chemical) Principles	4 5
1.3 THE STUFF OF LIFE Organisms Are Constructed from Four Great Classes of Macromolecules Nucleic Acids and Proteins Are Polymer Languages with Different Alphabets	5 6 7
1.4 MODEL BUILDING IN BIOLOGY	9
1.4.1 Models as Idealizations Biological Stuff Can Be Idealized Using Many Different Physical Models	9 11
1.4.2 Cartoons and Models Biological Cartoons Select Those Features of the Problem Thought to Be Essential Quantitative Models Can Be Built by Mathematicizing the Cartoons	16 16 19
1.5 QUANTITATIVE MODELS AND THE POWER OF IDEALIZATION	20
1.5.1 On the Springiness of Stuff	21
1.5.2 The Toolbox of Fundamental Physical Models	22
1.5.3 The Unifying Ideas of Biology	23
1.5.4 Mathematical Toolkit	25
1.5.5 The Role of Estimates	26
1.5.6 On Being Wrong	29
1.5.7 Rules of Thumb: Biology by the Numbers	30
1.6 SUMMARY AND CONCLUSIONS	32
1.7 FURTHER READING	32
1.8 REFERENCES	33

## Chapter 2 What and Where: Construction Plans for Cells and Organisms 35

2.1 AN ODE TO <i>E. COLI</i>	35
2.1.1 The Bacterial Standard Ruler The Bacterium <i>E. coli</i> Will Serve as Our Standard Ruler	37 37
2.1.2 Taking the Molecular Census The Cellular Interior Is Highly Crowded, with Mean Spacings Between Molecules That Are Comparable to Molecular Dimensions	38 48
2.1.3 Looking Inside Cells	49
2.1.4 Where Does <i>E. coli</i> Fit? Biological Structures Exist Over a Huge Range of Scales	51 51

2.2 CELLS AND STRUCTURES WITHIN THEM	52
2.2.1 Cells: A Rogue's Gallery Cells Come in a Wide Variety of Shapes and Sizes and with a Huge Range of Functions Cells from Humans Have a Huge Diversity of Structure and Function	52 57
2.2.2 The Cellular Interior: Organelles	59
2.2.3 Macromolecular Assemblies: The Whole is Greater than the Sum of the Parts Macromolecules Come Together to Form Assemblies Helical Motifs Are Seen Repeatedly in Molecular Assemblies Macromolecular Assemblies Are Arranged in Superstructures	63 63 64 65
2.2.4 Viruses as Assemblies	66
2.2.5 The Molecular Architecture of Cells: From Protein Data Bank (PDB) Files to Ribbon Diagrams Macromolecular Structure Is Characterized Fundamentally by Atomic Coordinates Chemical Groups Allow Us to Classify Parts of the Structure of Macromolecules	69 69 70
2.3 TELESCOPING UP IN SCALE: CELLS DON'T GO IT ALONE	72
2.3.1 Multicellularity as One of Evolution's Great Inventions Bacteria Interact to Form Colonies such as Biofilms Teaming Up in a Crisis: Lifestyle of <i>Dictyostelium discoideum</i> Multicellular Organisms Have Many Distinct Communities of Cells	73 73 75 76
2.3.2 Cellular Structures from Tissues to Nerve Networks One Class of Multicellular Structures is the Epithelial Sheets Tissues Are Collections of Cells and Extracellular Matrix Nerve Cells Form Complex, Multicellular Complexes	77 77 77 78
2.3.3 Multicellular Organisms Cells Differentiate During Development Leading to Entire Organisms The Cells of the Nematode Worm, <i>Caenorhabditis Elegans</i> , Have Been Charted, Yielding a Cell-by-Cell Picture of the Organism Higher-Level Structures Exist as Colonies of Organisms	78 78 80 82
2.4 SUMMARY AND CONCLUSIONS	83
2.5 PROBLEMS	83
2.6 FURTHER READING	84
2.7 REFERENCES	85

## Chapter 3 When: Stopwatches at Many Scales 87

3.1 THE HIERARCHY OF TEMPORAL SCALES	87
3.1.1 The Pageant of Biological Processes Biological Processes Are Characterized by a Huge Diversity of Time Scales	89 89
3.1.2 The Evolutionary Stopwatch	95

3.1.3	The Cell Cycle and the Standard Clock The <i>E. coli</i> Cell Cycle Will Serve as Our Standard Stopwatch	99			Structural Biology Has Its Roots in the Determination of the Structure of Hemoglobin	145
3.1.4	Three Views of Time in Biology	105	4.2.3	Hemoglobin and Molecular Models of Disease	146	
			4.2.4	The Rise of Allosterity and Cooperativity	146	
3.2	PROCEDURAL TIME	106	4.3	BACTERIOPHAGES AND MOLECULAR BIOLOGY	147	
3.2.1	The Machines (or Processes) of the Central Dogma The Central Dogma Describes the Processes Whereby the Genetic Information Is Expressed Chemically	107	4.3.1	Bacteriophages and the Origins of Molecular Biology Bacteriophages Have Sometimes Been Called the "Hydrogen Atoms of Biology"	148	
	The Processes of the Central Dogma Are Carried Out by Sophisticated Molecular Machines	108		Experiments on Phages and Their Bacterial Hosts Demonstrated That Natural Selection Is Operative in Microscopic Organisms	148	
3.2.2	Clocks and Oscillators Developing Embryos Divide on a Regular Schedule Dictated by an Internal Clock	111		The Hershey–Chase Experiment Both Confirmed the Nature of Genetic Material and Elucidated One of the Mechanisms of Viral DNA Entry into Cells	149	
	Diurnal Clocks Allow Cells and Organisms to Be on Time Everyday	111		Experiments on Phage T4 Demonstrated the Sequence Hypothesis of Collinearity of DNA and Proteins	150	
3.3	RELATIVE TIME	114		The Triplet Nature of the Genetic Code and DNA Sequencing Were Carried Out on Phage Systems	150	
3.3.1	Checkpoints and the Cell Cycle The Eukaryotic Cell Cycle Consists of Four Phases Involving Molecular Synthesis and Organization	115		Phages Were Instrumental in Elucidating the Existence of mRNA	151	
3.3.2	Measuring Relative Time Genetic Networks Are Collections of Genes Whose Expression Is Interrelated	117	4.3.2	Bacteriophages and Modern Biophysics Many Single- Molecule Studies of Molecular Motors Have Been Performed on Motors from Bacteriophages	154	
	The Formation of the Bacterial Flagellum Is Intricately Organized in Space and Time	119				
3.3.3	Killing the Cell: The Life Cycles of Viruses Viral Life Cycles Include a Series of Self-Assembly Processes	121	4.4	A TALE OF TWO CELLS: <i>E. COLI</i> AS A MODEL SYSTEM	154	
3.3.4	The Process of Development	122	4.4.1	Bacteria and Molecular Biology	154	
			4.4.2	<i>E. coli</i> and the Central Dogma The Hypothesis of Conservative Replication Has Falsifiable Consequences	156	
3.4	MANIPULATED TIME	125		Extracts from <i>E. coli</i> Were Used to Perform <i>In Vitro</i> Synthesis of DNA, mRNA, and Proteins	157	
3.4.1	Chemical Kinetics and Enzyme Turnover	125	4.4.3	The <i>lac</i> Operon as the "Hydrogen Atom" of Genetic Circuits	157	
3.4.2	Beating the Diffusive Speed Limit Diffusion Is the Random Motion of Microscopic Particles in Solution	127		Gene Regulation in <i>E. coli</i> Serves as a Model for Genetic Circuits in General	157	
	Diffusion Times Depend upon the Length Scale	127		The <i>lac</i> Operon Is a Genetic Network That Controls the Production of the Enzymes Responsible for Digesting the Sugar Lactose	158	
	Diffusive Transport at the Synaptic Junction Is the Dynamical Mechanism for Neuronal Communication	128	4.4.4	Signaling and Motility: The Case of Bacterial Chemotaxis	159	
	Molecular Motors Move Cargo over Large Distances in a Directed Way	129		<i>E. coli</i> Has Served as a Model System for the Analysis of Cell Motility	159	
	Membrane-Bound Proteins Transport Molecules from One Side of a Membrane to the Other	130	4.5	YEAST: FROM BIOCHEMISTRY TO THE CELL CYCLE	161	
3.4.3	Beating the Replication Limit	131		Yeast Has Served as a Model System Leading to Insights in Contexts Ranging from Vitalism to the Functioning of Enzymes to Eukaryotic Gene Regulation	161	
3.4.4	Eggs and Spores: Planning for the Next Generation	132	4.5.1	Yeast and the Rise of Biochemistry	162	
			4.5.2	Dissecting the Cell Cycle	162	
3.5	SUMMARY AND CONCLUSIONS	133	4.5.3	Deciding Which Way Is Up: Yeast and Polarity	164	
3.6	PROBLEMS	133	4.5.4	Dissecting Membrane Traffic	166	
3.7	FURTHER READING	136	4.5.5	Genomics and Proteomics	167	
3.8	REFERENCES	136	4.6	FLIES AND MODERN BIOLOGY	170	
<b>Chapter 4</b>	<b>Who: "Bless the Little Beasties"</b>	<b>137</b>	4.6.1	Flies and the Rise of Modern Genetics <i>Drosophila melanogaster</i> Has Served as a Model System for Studies Ranging from Genetics to Development to the Functioning of the Brain and Even Behavior	170	
4.1	CHOOSING A GRAIN OF SAND Modern Genetics Began with the Use of Peas as a Model System	138	4.6.2	How the Fly Got His Stripes	171	
4.1.1	Biochemistry and Genetics	138	4.7	OF MICE AND MEN	173	
4.2	HEMOGLOBIN AS A MODEL PROTEIN	143	4.8	THE CASE FOR EXOTICA	174	
4.2.1	Hemoglobin, Receptor–Ligand Binding, and the Other Bohr The Binding of Oxygen to Hemoglobin Has Served as a Model System for Ligand–Receptor Interactions More Generally	143	4.8.1	Specialists and Experts	174	
	Quantitative Analysis of Hemoglobin Is Based upon Measuring the Fractional Occupancy of the Oxygen-Binding Sites as a Function of Oxygen Pressure	144	4.8.2	The Squid Giant Axon and Biological Electricity There Is a Steady-State Potential Difference Across the Membrane of Nerve Cells	176	
4.2.2	Hemoglobin and the Origins of Structural Biology The Study of the Mass of Hemoglobin Was Central in the Development of Centrifugation	145	4.8.3	Nerve Cells Propagate Electrical Signals and Use Them to Communicate with Each Other	176	
				Exotica Toolkit	178	

4.9	SUMMARY AND CONCLUSIONS	179
4.10	PROBLEMS	179
4.11	FURTHER READING	181
4.12	REFERENCES	183

## PART 2 LIFE AT REST

185

### Chapter 5 Mechanical and Chemical Equilibrium in the Living Cell 187

5.1	ENERGY AND THE LIFE OF CELLS	187
5.1.1	The Interplay of Deterministic and Thermal Forces	189
	Thermal Jostling of Particles Must Be Accounted for in Biological Systems	189
5.1.2	Constructing the Cell: Managing the Mass and Energy Budget of the Cell	190
5.2	BIOLOGICAL SYSTEMS AS MINIMIZERS	200
5.2.1	Equilibrium Models for Out of Equilibrium Systems	200
	Equilibrium Models Can Be Used for Nonequilibrium Problems if Certain Processes Happen Much Faster Than Others	201
5.2.2	Proteins in "Equilibrium"	202
	Protein Structures are Free-Energy Minimizers	203
5.2.3	Cells in "Equilibrium"	204
5.2.4	Mechanical Equilibrium from a Minimization Perspective	204
	The Mechanical Equilibrium State is Obtained by Minimizing the Potential Energy	204
5.3	THE MATHEMATICS OF SUPERLATIVES	209
5.3.1	The Mathematization of Judgement: Functions and Functionals	209
	Functionals Deliver a Number for Every Function They Are Given	210
5.3.2	The Calculus of Superlatives	211
	Finding the Maximum and Minimum Values of a Function Requires That We Find Where the Slope of the Function Equals Zero	211
5.4	CONFIGURATIONAL ENERGY	214
	In Mechanical Problems, Potential Energy Determines the Equilibrium Structure	214
5.4.1	Hooke's Law: Actin to Lipids	216
	There is a Linear Relation Between Force and Extension of a Beam	216
	The Energy to Deform an Elastic Material is a Quadratic Function of the Strain	217
5.5	STRUCTURES AS FREE-ENERGY MINIMIZERS	219
	The Entropy is a Measure of the Microscopic Degeneracy of a Macroscopic State	219
5.5.1	Entropy and Hydrophobicity	222
	Hydrophobicity Results from Depriving Water Molecules of Some of Their Configurational Entropy	222
	Amino Acids Can Be Classified According to Their Hydrophobicity	224
	When in Water, Hydrocarbon Tails on Lipids Have an Entropy Cost	225
5.5.2	Gibbs and the Calculus of Equilibrium	225
	Thermal and Chemical Equilibrium are Obtained by Maximizing the Entropy	225
5.5.3	Departure from Equilibrium and Fluxes	227
5.5.4	Structure as a Competition	228
	Free Energy Minimization Can Be Thought of as an Alternative Formulation of Entropy Maximization	228
5.5.5	An Ode to $\Delta G$	230
	The Free Energy Reflects a Competition Between Energy and Entropy	230

5.6	SUMMARY AND CONCLUSIONS	231
5.7	APPENDIX: THE EULER-LAGRANGE EQUATIONS, FINDING THE SUPERLATIVE	232
	Finding the Extrema of Functionals Is Carried Out Using the Calculus of Variations	232
	The Euler-Lagrange Equations Let Us Minimize Functionals by Solving Differential Equations	232
5.8	PROBLEMS	233
5.9	FURTHER READING	235
5.10	REFERENCES	236

### Chapter 6 Entropy Rules! 237

6.1	THE ANALYTICAL ENGINE OF STATISTICAL MECHANICS	237
	The Probability of Different Microstates Is Determined by Their Energy	240
6.1.1	A First Look at Ligand-Receptor Binding	241
6.1.2	The Statistical Mechanics of Gene Expression: RNA Polymerase and the Promoter	244
	A Simple Model of Gene Expression Is to Consider the Probability of RNA Polymerase Binding at the Promoter	245
	Most Cellular RNA Polymerase Molecules Are Bound to DNA	245
	The Binding Probability of RNA Polymerase to Its Promoter Is a Simple Function of the Number of Polymerase Molecules and the Binding Energy	247
6.1.3	Classic Derivation of the Boltzmann Distribution	248
	The Boltzmann Distribution Gives the Probability of Microstates for a System in Contact with a Thermal Reservoir	248
6.1.4	Boltzmann Distribution by Counting	250
	Different Ways of Partitioning Energy Among Particles Have Different Degeneracies	250
6.1.5	Boltzmann Distribution by Guessing	253
	Maximizing the Entropy Corresponds to Making a Best Guess When Faced with Limited Information	253
	Entropy Maximization Can Be Used as a Tool for Statistical Inference	255
	The Boltzmann Distribution is the Maximum Entropy Distribution in Which the Average Energy is Prescribed as a Constraint	258
6.2	ON BEING IDEAL	259
6.2.1	Average Energy of a Molecule in a Gas	259
	The Ideal Gas Entropy Reflects the Freedom to Rearrange Molecular Positions and Velocities	259
6.2.2	Free Energy of Dilute Solutions	262
	The Chemical Potential of a Dilute Solution Is a Simple Logarithmic Function of the Concentration	262
6.2.3	Osmotic Pressure as an Entropic Spring	264
	Osmotic Pressure Arises from Entropic Effects	264
	Viruses, Membrane-Bound Organelles, and Cells Are Subject to Osmotic Pressure	265
	Osmotic Forces Have Been Used to Measure the Interstrand Interactions of DNA	266
6.3	THE CALCULUS OF EQUILIBRIUM APPLIED: LAW OF MASS ACTION	267
6.3.1	Law of Mass Action and Equilibrium Constants	267
	Equilibrium Constants are Determined by Entropy Maximization	267
6.4	APPLICATIONS OF THE CALCULUS OF EQUILIBRIUM	270
6.4.1	A Second Look at Ligand-Receptor Binding	270
6.4.2	Measuring Ligand-Receptor Binding	272
6.4.3	Beyond Simple Ligand-Receptor Binding: The Hill Function	273
6.4.4	ATP Power	274
	The Energy Released in ATP Hydrolysis Depends Upon the Concentrations of Reactants and Products	275

6.5	SUMMARY AND CONCLUSIONS	276			
6.6	PROBLEMS	276			
6.7	FURTHER READING	278			
6.8	REFERENCES	278			
<b>Chapter 7 Two-State Systems: From Ion Channels to Cooperative Binding</b>			<b>281</b>		
7.1	MACROMOLECULES WITH MULTIPLE STATES	281			
7.1.1	The Internal State Variable Idea	281			
	The State of a Protein or Nucleic Acid Can Be Characterized Mathematically Using a State Variable	282			
7.1.2	Ion Channels as an Example of Internal State Variables	286			
	The Open Probability ( $\sigma$ ) of an Ion Channel Can Be Computed Using Statistical Mechanics	287			
7.2	STATE VARIABLE DESCRIPTION OF BINDING	289			
7.2.1	The Gibbs Distribution: Contact with a Particle Reservoir	289			
	The Gibbs Distribution Gives the Probability of Microstates for a System in Contact with a Thermal and Particle Reservoir	289			
7.2.2	Simple Ligand–Receptor Binding Revisited	291			
7.2.3	Phosphorylation as an Example of Two Internal State Variables	292			
	Phosphorylation Can Change the Energy Balance Between Active and Inactive States	293			
	Two-Component Systems Exemplify the Use of Phosphorylation in Signal Transduction	295			
7.2.4	Hemoglobin as a Case Study in Cooperativity	298			
	The Binding Affinity of Oxygen for Hemoglobin Depends upon Whether or Not Other Oxygens Are Already Bound	298			
	A Toy Model of a Dimeric Hemoglobin (Dimoglobin) Illustrate the Idea of Cooperativity	298			
	The Monod–Wyman–Changeux (MWC) Model Provides a Simple Example of Cooperative Binding	300			
	Statistical Models of the Occupancy of Hemoglobin Can Be Written Using Occupation Variables	301			
	There is a Logical Progression of Increasingly Complex Binding Models for Hemoglobin	301			
7.3	ION CHANNELS REVISITED: LIGAND-GATED CHANNELS AND THE MWC MODEL	305			
7.4	SUMMARY AND CONCLUSIONS	308			
7.5	PROBLEMS	308			
7.6	FURTHER READING	310			
7.7	REFERENCES	310			
<b>Chapter 8 Random Walks and the Structure of Macromolecules</b>			<b>311</b>		
8.1	WHAT IS A STRUCTURE: PDB OR $R_G$ ?	311			
8.1.1	Deterministic versus Statistical Descriptions of Structure	312			
	PDB Files Reflect a Deterministic Description of Macromolecular Structure	312			
	Statistical Descriptions of Structure Emphasize Average Size and Shape Rather Than Atomic Coordinates	312			
8.2	MACROMOLECULES AS RANDOM WALKS	312			
	Random Walk Models of Macromolecules View Them as Rigid Segments Connected by Hinges	312			
8.2.1	A Mathematical Stupor	313			
	In Random Walk Models of Polymers, Every Macromolecular Configuration Is Equally Probable	313			
	The Mean Size of a Random Walk Macromolecule Scales as the Square Root of the Number of Segments, $\sqrt{N}$	314			
	The Probability of a Given Macromolecular State Depends Upon Its Microscopic Degeneracy	315			
	Entropy Determines the Elastic Properties of Polymer Chains	316			
	The Persistence Length Is a Measure of the Length Scale Over Which a Polymer Remains Roughly Straight	319			
8.2.2	How Big Is a Genome?	321			
8.2.3	The Geography of Chromosomes	322			
	Genetic Maps and Physical Maps of Chromosomes Describe Different Aspects of Chromosome Structure	322			
	Different Structural Models of Chromatin Are Characterized by the Linear Packing Density of DNA	323			
	Spatial Organization of Chromosomes Shows Elements of Both Randomness and Order	324			
	Chromosomes Are Tethered at Different Locations	325			
	Chromosome Territories Have Been Observed in Bacterial Cells	327			
	Chromosome Territories in <i>Vibrio cholerae</i> Can Be Explored Using Models of Polymer Confinement and Tethering	328			
8.2.4	DNA Looping: From Chromosomes to Gene Regulation	333			
	The Lac Repressor Molecule Acts Mechanistically by Forming a Sequestered Loop in DNA	334			
	Looping of Large DNA Fragments Is Dictated by the Difficulty of Distant Ends Finding Each Other	334			
	Chromosome Conformation Capture Reveals the Geometry of Packing of Entire Genomes in Cells	336			
8.3	THE NEW WORLD OF SINGLE-MOLECULE MECHANICS	337			
	Single-Molecule Measurement Techniques Lead to Force Spectroscopy	337			
8.3.1	Force–Extension Curves: A New Spectroscopy	339			
	Different Macromolecules Have Different Force Signatures When Subjected to Loading	339			
8.3.2	Random Walk Models for Force–Extension Curves	340			
	The Low-Force Regime in Force–Extension Curves Can Be Understood Using the Random Walk Model	340			
8.4	PROTEINS AS RANDOM WALKS	344			
8.4.1	Compact Random Walks and the Size of Proteins	345			
	The Compact Nature of Proteins Leads to an Estimate of Their Size	345			
8.4.2	Hydrophobic and Polar Residues: The HP Model	346			
	The HP Model Divides Amino Acids into Two Classes: Hydrophobic and Polar	346			
8.4.3	HP Models of Protein Folding	348			
8.5	SUMMARY AND CONCLUSIONS	351			
8.6	PROBLEMS	351			
8.7	FURTHER READING	353			
8.8	REFERENCES	353			
<b>Chapter 9 Electrostatics for Salty Solutions</b>			<b>355</b>		
9.1	WATER AS LIFE'S AETHER	355			
9.2	THE CHEMISTRY OF WATER	358			
9.2.1	pH and the Equilibrium Constant	358			
	Dissociation of Water Molecules Reflects a Competition Between the Energetics of Binding and the Entropy of Charge Liberation	358			
9.2.2	The Charge on DNA and Proteins	359			
	The Charge State of Biopolymers Depends upon the pH of the Solution	359			
	Different Amino Acids Have Different Charge States	359			
9.2.3	Salt and Binding	360			
<b>xxii</b>	<b>CONTENTS IN DETAIL</b>				





13.6	FURTHER READING	540
13.7	REFERENCES	540

## Chapter 14 Life in Crowded and Disordered Environments **543**

14.1	CROWDING, LINKAGE, AND ENTANGLEMENT	543
14.1.1	The Cell Is Crowded	544
14.1.2	Macromolecular Networks: The Cytoskeleton and Beyond	545
14.1.3	Crowding on Membranes	546
14.1.4	Consequences of Crowding	547
	Crowding Alters Biochemical Equilibria	548
	Crowding Alters the Kinetics within Cells	548
14.2	EQUILIBRIA IN CROWDED ENVIRONMENTS	550
14.2.1	Crowding and Binding	550
	Lattice Models of Solution Provide a Simple Picture of the Role of Crowding in Biochemical Equilibria	550
14.2.2	Osmotic Pressures in Crowded Solutions	552
	Osmotic Pressure Reveals Crowding Effects	552
14.2.3	Depletion Forces: Order from Disorder	554
	The Close Approach of Large Particles Excludes Smaller Particles Between Them, Resulting in an Entropic Force	554
	Depletion Forces Can Induce Entropic Ordering!	559
14.2.4	Excluded Volume and Polymers	559
	Excluded Volume Leads to an Effective Repulsion Between Molecules	559
	Self-avoidance Between the Monomers of a Polymer Leads to Polymer Swelling	561
14.2.5	Case Study in Crowding: How to Make a Helix	563
14.2.6	Crowding at Membranes	565
14.3	CROWDED DYNAMICS	566
14.3.1	Crowding and Reaction Rates	566
	Enzymatic Reactions in Cells Can Proceed Faster than the Diffusion Limit Using Substrate Channeling	566
	Protein Folding Is Facilitated by Chaperones	567
14.3.2	Diffusion in Crowded Environments	567
14.4	SUMMARY AND CONCLUSIONS	569
14.5	PROBLEMS	569
14.6	FURTHER READING	570
14.7	REFERENCES	571

## Chapter 15 Rate Equations and Dynamics in the Cell **573**

15.1	BIOLOGICAL STATISTICAL DYNAMICS: A FIRST LOOK	573
15.1.1	Cells as Chemical Factories	574
15.1.2	Dynamics of the Cytoskeleton	575
15.2	A CHEMICAL PICTURE OF BIOLOGICAL DYNAMICS	579
15.2.1	The Rate Equation Paradigm	579
	Chemical Concentrations Vary in Both Space and Time	580
	Rate Equations Describe the Time Evolution of Concentrations	580
15.2.2	All Good Things Must End	581
	Macromolecular Decay Can Be Described by a Simple, First-Order Differential Equation	581
15.2.3	A Single-Molecule View of Degradation: Statistical Mechanics Over Trajectories	582
	Molecules Fall Apart with a Characteristic Lifetime	582
	Decay Processes Can Be Described with Two-State Trajectories	583

	Decay of One Species Corresponds to Growth in the Number of a Second Species	585
15.2.4	Bimolecular Reactions	586
	Chemical Reactions Can Increase the Concentration of a Given Species	586
	Equilibrium Constants Have a Dynamical Interpretation in Terms of Reaction Rates	588
15.2.5	Dynamics of Ion Channels as a Case Study	589
	Rate Equations for Ion Channels Characterize the Time Evolution of the Open and Closed Probability	590
15.2.6	Rapid Equilibrium	591
15.2.7	Michaelis–Menten and Enzyme Kinetics	596
15.3	THE CYTOSKELETON IS ALWAYS UNDER CONSTRUCTION	599
15.3.1	The Eukaryotic Cytoskeleton	599
	The Cytoskeleton Is a Dynamical Structure That Is Always Under Construction	599
15.3.2	The Curious Case of the Bacterial Cytoskeleton	600
15.4	SIMPLE MODELS OF CYTOSKELETAL POLYMERIZATION	602
	The Dynamics of Polymerization Can Involve Many Distinct Physical and Chemical Effects	603
15.4.1	The Equilibrium Polymer	604
	Equilibrium Models of Cytoskeletal Filaments Describe the Distribution of Polymer Lengths for Simple Polymers	604
	An Equilibrium Polymer Fluctuates in Time	606
15.4.2	Rate Equation Description of Cytoskeletal Polymerization	609
	Polymerization Reactions Can Be Described by Rate Equations	609
	The Time Evolution of the Probability Distribution $P_n(t)$ Can Be Written Using a Rate Equation	610
	Rates of Addition and Removal of Monomers Are Often Different on the Two Ends of Cytoskeletal Filaments	612
15.4.3	Nucleotide Hydrolysis and Cytoskeletal Polymerization	614
	ATP Hydrolysis Sculpts the Molecular Interface, Resulting in Distinct Rates at the Ends of Cytoskeletal Filaments	614
15.4.4	Dynamic Instability: A Toy Model of the Cap	615
	A Toy Model of Dynamic Instability Assumes That Catastrophe Occurs When Hydrolyzed Nucleotides Are Present at the Growth Front	616
15.5	SUMMARY AND CONCLUSIONS	618
15.6	PROBLEMS	619
15.7	FURTHER READING	621
15.8	REFERENCES	621

## Chapter 16 Dynamics of Molecular Motors **623**

16.1	THE DYNAMICS OF MOLECULAR MOTORS: LIFE IN THE NOISY LANE	623
16.1.1	Translational Motors: Beating the Diffusive Speed Limit	625
	The Motion of Eukaryotic Cilia and Flagella Is Driven by Translational Motors	628
	Muscle Contraction Is Mediated by Myosin Motors	630
16.1.2	Rotary Motors	634
16.1.3	Polymerization Motors: Pushing by Growing	637
16.1.4	Translocation Motors: Pushing by Pulling	638
16.2	RECTIFIED BROWNIAN MOTION AND MOLECULAR MOTORS	639
16.2.1	The Random Walk Yet Again	640
	Molecular Motors Can Be Thought of as Random Walkers	640

16.2.2	The One-State Model	641	Voltage-Gated Channels Result in a Nonlinear Current-Voltage Relation for the Cell Membrane	699
	The Dynamics of a Molecular Motor Can Be Written Using a Master Equation	642	A Patch of Membrane Acts as a Bistable Switch	700
	The Driven Diffusion Equation Can Be Transformed into an Ordinary Diffusion Equation	644	The Dynamics of Voltage Relaxation Can Be Modeled Using an RC Circuit	702
16.2.3	Motor Stepping from a Free-Energy Perspective	647	17.4.2 The Cable Equation	703
16.2.4	The Two-State Model	651	17.4.3 Depolarization Waves	705
	The Dynamics of a Two-State Motor Is Described by Two Coupled Rate Equations	651	Waves of Membrane Depolarization Rely on Sodium Channels Switching into the Open State	705
	Internal States Reveal Themselves in the Form of the Waiting Time Distribution	654	17.4.4 Spikes	710
16.2.5	More General Motor Models	656	17.4.5 Hodgkin-Huxley and Membrane Transport	712
16.2.6	Coordination of Motor Protein Activity	658	Inactivation of Sodium Channels Leads to Propagating Spikes	712
16.2.7	Rotary Motors	660	17.5 SUMMARY AND CONCLUSIONS	714
16.3	POLYMERIZATION AND TRANSLOCATION AS MOTOR ACTION	663	17.6 PROBLEMS	714
16.3.1	The Polymerization Ratchet	663	17.7 FURTHER READING	715
	The Polymerization Ratchet Is Based on a Polymerization Reaction That Is Maintained Out of Equilibrium	666	17.8 REFERENCES	715
	The Polymerization Ratchet Force-Velocity Can Be Obtained by Solving a Driven Diffusion Equation	668	<b>Chapter 18 Light and Life</b>	<b>717</b>
16.3.2	Force Generation by Growth	670	18.1 INTRODUCTION	718
	Polymerization Forces Can Be Measured Directly	670	18.2 PHOTOSYNTHESIS	719
	Polymerization Forces Are Used to Center Cellular Structures	672	Organisms From All Three of the Great Domains of Life Perform Photosynthesis	720
16.3.3	The Translocation Ratchet	673	18.2.1 Quantum Mechanics for Biology	724
	Protein Binding Can Speed Up Translocation through a Ratcheting Mechanism	674	Quantum Mechanical Kinematics Describes States of the System in Terms of Wave Functions	725
	The Translocation Time Can Be Estimated by Solving a Driven Diffusion Equation	676	Quantum Mechanical Observables Are Represented by Operators	728
16.4	SUMMARY AND CONCLUSIONS	677	The Time Evolution of Quantum States Can Be Determined Using the Schrödinger Equation	729
16.5	PROBLEMS	677	18.2.2 The Particle-in-a-Box Model	730
16.6	FURTHER READING	679	Solutions for the Box of Finite Depth Do Not Vanish at the Box Edges	731
16.7	REFERENCES	679	18.2.3 Exciting Electrons With Light	733
			Absorption Wavelengths Depend Upon Molecular Size and Shape	735
			18.2.4 Moving Electrons From Hither to Yon	737
			Excited Electrons Can Suffer Multiple Fates	737
			Electron Transfer in Photosynthesis Proceeds by Tunneling	739
			Electron Transfer Between Donor and Acceptor Is Gated by Fluctuations of the Environment	745
			Resonant Transfer Processes in the Antenna Complex Efficiently Deliver Energy to the Reaction Center	747
			18.2.5 Bioenergetics of Photosynthesis	748
			Electrons Are Transferred from Donors to Acceptors Within and Around the Cell Membrane	748
			Water, Water Everywhere, and Not an Electron to Drink	750
			Charge Separation across Membranes Results in a Proton-Motive Force	751
			18.2.6 Making Sugar	752
			18.2.7 Destroying Sugar	757
			18.2.8 Photosynthesis in Perspective	758
			18.3 THE VISION THING	759
			18.3.1 Bacterial "Vision"	760
			18.3.2 Microbial Phototaxis and Manipulating Cells with Light	763
			18.3.3 Animal Vision	763
			There Is a Simple Relationship between Eye Geometry and Resolution	765
			The Resolution of Insect Eyes Is Governed by Both the Number of Ommatidia and Diffraction Effects	768
			The Light-Driven Conformational Change of Retinal Underlies Animal Vision	769
			Information from Photon Detection Is Amplified by a Signal Transduction Cascade in the Photoreceptor Cell	773
<b>Chapter 17 Biological Electricity and the Hodgkin-Huxley Model</b>	<b>681</b>			
17.1	THE ROLE OF ELECTRICITY IN CELLS	681		
17.2	THE CHARGE STATE OF THE CELL	682		
17.2.1	The Electrical Status of Cells and Their Membranes	682		
17.2.2	Electrochemical Equilibrium and the Nernst Equation	683		
	Ion Concentration Differences Across Membranes Lead to Potential Differences	683		
17.3	MEMBRANE PERMEABILITY: PUMPS AND CHANNELS	685		
	A Nonequilibrium Charge Distribution Is Set Up Between the Cell Interior and the External World	685		
	Signals in Cells Are Often Mediated by the Presence of Electrical Spikes Called Action Potentials	686		
17.3.1	Ion Channels and Membrane Permeability	688		
	Ion Permeability Across Membranes Is Mediated by Ion Channels	688		
	A Simple Two-State Model Can Describe Many of the Features of Voltage Gating of Ion Channels	689		
17.3.2	Maintaining a Nonequilibrium Charge State	691		
	Ions Are Pumped Across the Cell Membrane Against an Electrochemical Gradient	691		
17.4	THE ACTION POTENTIAL	693		
17.4.1	Membrane Depolarization: The Membrane as a Bistable Switch	693		
	Coordinated Muscle Contraction Depends Upon Membrane Depolarization	694		
	A Patch of Cell Membrane Can Be Modeled as an Electrical Circuit	696		
	The Difference Between the Membrane Potential and the Nernst Potential Leads to an Ionic Current Across the Cell Membrane	698		

	The Vertebrate Visual System Is Capable of Detecting Single Photons	776
18.3.4	Sex, Death, and Quantum Mechanics Let There Be Light: Chemical Reactions Can Be Used to Make Light	781 784
18.4	SUMMARY AND CONCLUSIONS	785
18.5	APPENDIX: SIMPLE MODEL OF ELECTRON TUNNELING	785
18.6	PROBLEMS	793
18.7	FURTHER READING	795
18.8	REFERENCES	796

**PART 4 THE MEANING OF LIFE 799**

**Chapter 19 Organization of Biological Networks 801**

19.1	CHEMICAL AND INFORMATIONAL ORGANIZATION IN THE CELL	801
	Many Chemical Reactions in the Cell are Linked in Complex Networks	801
	Genetic Networks Describe the Linkages Between Different Genes and Their Products	802
	Developmental Decisions Are Made by Regulating Genes	802
	Gene Expression Is Measured Quantitatively in Terms of How Much, When, and Where	804
19.2	GENETIC NETWORKS: DOING THE RIGHT THING AT THE RIGHT TIME	807
	Promoter Occupancy Is Dictated by the Presence of Regulatory Proteins Called Transcription Factors	808
19.2.1	The Molecular Implementation of Regulation: Promoters, Activators, and Repressors	808
	Repressor Molecules Are the Proteins That Implement Negative Control	808
	Activators Are the Proteins That Implement Positive Control	809
	Genes Can Be Regulated During Processes Other Than Transcription	809
19.2.2	The Mathematics of Recruitment and Rejection	810
	Recruitment of Proteins Reflects Cooperativity Between Different DNA-Binding Proteins	810
	The Regulation Factor Dictates How the Bare RNA Polymerase Binding Probability Is Altered by Transcription Factors	812
	Activator Bypass Experiments Show That Activators Work by Recruitment	813
	Repressor Molecules Reduce the Probability Polymerase Will Bind to the Promoter	814
19.2.3	Transcriptional Regulation by the Numbers: Binding Energies and Equilibrium Constants	819
	Equilibrium Constants Can Be Used To Determine Regulation Factors	819
19.2.4	A Simple Statistical Mechanical Model of Positive and Negative Regulation	820
19.2.5	The <i>lac</i> Operon	822
	The <i>lac</i> Operon Has Features of Both Negative and Positive Regulation	822
	The Free Energy of DNA Looping Affects the Repression of the <i>lac</i> Operon	824
	Inducers Tune the Level of Regulatory Response	829
19.2.6	Other Regulatory Architectures	829
	The Fold-Change for Different Regulatory Motifs Depends Upon Experimentally Accessible Control Parameters	830
	Quantitative Analysis of Gene Expression in Eukaryotes Can Also Be Analyzed Using Thermodynamic Models	832

19.3	REGULATORY DYNAMICS	835
19.3.1	The Dynamics of RNA Polymerase and the Promoter	835
	The Concentrations of Both RNA and Protein Can Be Described Using Rate Equations	835
19.3.2	Dynamics of mRNA Distributions	838
	Unregulated Promoters Can Be Described By a Poisson Distribution	841
19.3.3	Dynamics of Regulated Promoters	843
	The Two-State Promoter Has a Fano Factor Greater Than One	844
	Different Regulatory Architectures Have Different Fano Factors	849
19.3.4	Dynamics of Protein Translation	854
19.3.5	Genetic Switches: Natural and Synthetic	861
19.3.6	Genetic Networks That Oscillate	870
19.4	CELLULAR FAST RESPONSE: SIGNALING	872
19.4.1	Bacterial Chemotaxis	873
	The MWC Model Can Be Used to Describe Bacterial Chemotaxis	878
	Precise Adaptation Can Be Described by a Simple Balance Between Methylation and Demethylation	881
19.4.2	Biochemistry on a Leash	883
	Tethering Increases the Local Concentration of a Ligand	884
	Signaling Networks Help Cells Decide When and Where to Grow Their Actin Filaments for Motility	884
	Synthetic Signaling Networks Permit a Dissection of Signaling Pathways	885
19.5	SUMMARY AND CONCLUSIONS	888
19.6	PROBLEMS	889
19.7	FURTHER READING	891
19.8	REFERENCES	892

**Chapter 20 Biological Patterns: Order in Space and Time 893**

20.1	INTRODUCTION: MAKING PATTERNS	893
20.1.1	Patterns in Space and Time	894
20.1.2	Rules for Pattern-Making	895
20.2	MORPHOGEN GRADIENTS	896
20.2.1	The French Flag Model	896
20.2.2	How the Fly Got His Stripes	898
	Bicoid Exhibits an Exponential Concentration Gradient Along the Anterior–Posterior Axis of Fly Embryos	898
	A Reaction–Diffusion Mechanism Can Give Rise to an Exponential Concentration Gradient	899
20.2.3	Precision and Scaling	905
20.2.4	Morphogen Patterning with Growth in <i>Anabaena</i>	912
20.3	REACTION–DIFFUSION AND SPATIAL PATTERNS	914
20.3.1	Putting Chemistry and Diffusion Together: Turing Patterns	914
20.3.2	How Bacteria Lay Down a Coordinate System	920
20.3.3	Phyllotaxis: The Art of Flower Arrangement	926
20.4	TURNING TIME INTO SPACE: TEMPORAL OSCILLATIONS IN CELL FATE SPECIFICATION	931
20.4.1	Somitogenesis	932
20.4.2	Seashells Forming Patterns in Space and Time	935
20.5	PATTERN FORMATION AS A CONTACT SPORT	939
20.5.1	The Notch–Delta Concept	939
20.5.2	<i>Drosophila</i> Eyes	944
20.6	SUMMARY AND CONCLUSIONS	947
20.7	PROBLEMS	948
20.8	FURTHER READING	949
20.9	REFERENCES	950

