Contents in Detail

Preface		vii	2.2	CELLS AND STRUCTURES WITHIN THEM	52
Acknow	ledgments	xiii	2.2.1	Cells: A Rogue's Gallery Cells Come in a Wide Variety of Shapes and Sizes	52
Special	Sections	xxix		and with a Huge Range of Functions	52
Map of	the Maps	XXX		Cells from Humans Have a Huge Diversity of Structure and Function	5 7
			2.2.2	The Cellular Interior: Organelles	59
PAR	T 1 THE FACTS OF LIFE	1	2.2.3	Macromolecular Assemblies: The Whole is Greater than the Sum of the Parts	63
MARCHANICA CONTRACTOR				Macromolecules Come Together to Form	
Chapt	er 1 Why: Biology by the Numbers	3		Assemblies Helical Motifs Are Seen Repeatedly in Molecular	63
1.1	BIOLOGICAL CARTOGRAPHY	3		Assemblies	64
1.2	PHYSICAL BIOLOGY OF THE CELL	4		Macromolecular Assemblies Are Arranged in	
	Model Building Requires a Substrate of Biological Facts and Physical (or Chemical) Principles	5	2.2.4	Superstructures Viruses as Assemblies	65
	racts and rhysical (of Chemical) rimciples	ر	2.2.4	The Molecular Architecture of Cells: From Protein	66
1.3	THE STUFF OF LIFE	5		Data Bank (PDB) Files to Ribbon Diagrams	69
	Organisms Are Constructed from Four Great Classes of Macromolecules	6		Macromolecular Structure Is Characterized Fundamentally by Atomic Coordinates	69
	Nucleic Acids and Proteins Are Polymer Languages	O		Chemical Groups Allow Us to Classify Parts of the	03
	with Different Alphabets	7		Structure of Macromolecules	70
1.4	MODEL BUILDING IN BIOLOGY	9	2.3	TELESCOPING UP IN SCALE: CELLS DON'T GO IT	
1.4.1	Models as Idealizations	9	221	ALONE	72
	Biological Stuff Can Be Idealized Using Many Different Physical Models	11	2.3.1	Multicellularity as One of Evolution's Great Inventions Bacteria Interact to Form Colonies such as Biofilms	73 73
1.4.2	Cartoons and Models	16		Teaming Up in a Crisis: Lifestyle of <i>Dictyostelium</i>	٠.
	Biological Cartoons Select Those Features of the			discoideum	75
	Problem Thought to Be Essential	16		Multicellular Organisms Have Many Distinct	_
	Quantitative Models Can Be Built by Mathematicizing the Cartoons	19	2.3.2	Communities of Cells Cellular Structures from Tissues to Nerve	76
	mathematicizing the Cartoons	19	2.3.2	Networks	7:
1.5	QUANTITATIVE MODELS AND THE POWER			One Class of Multicellular Structures is the Epithelial	
	OF IDEALIZATION	20		Sheets	7
1.5.1 1.5.2	On the Springiness of Stuff The Toolbox of Fundamental Physical Models	21 22		Tissues Are Collections of Cells and Extracellular Matrix	٠,٠
1.5.3	The Unifying Ideas of Biology	23		Nerve Cells Form Complex, Multicellular	7
1.5.4	Mathematical Toolkit	25		Complexes	78
1.5.5	The Role of Estimates	26	2.3.3	Multicellular Organisms	78
1.5.6 1.5.7	On Being Wrong Rules of Thumb: Biology by the Numbers	29 30		Cells Differentiate During Development Leading to	
1.3.7	Rules of Thumb. Biology by the Numbers	30		Entire Organisms	78
1.6	SUMMARY AND CONCLUSIONS	32		The Cells of the Nematode Worm, <i>Caenorhabditis Elegans</i> , Have Been Charted, Yielding a Cell-by-Cell	
1.7	FURTHER READING	32		Picture of the Organism	80
1.8	REFERENCES	33		Higher-Level Structures Exist as Colonies of	
Chans	on 2 What and Whove Construction			Organisms	82
-	er 2 What and Where: Construction	35	2.4	SUMMARY AND CONCLUSIONS	83
	for Cells and Organisms		2.5	PROBLEMS	83
2.1	AN ODE TO E. COLI	35	2.6	FURTHER READING	84
2.1.1	The Bacterial Standard Ruler The Bacterium <i>E. coli</i> Will Serve as Our	37	2.7	REFERENCES	85
	Standard Ruler	37			٠.
2.1.2	Taking the Molecular Census	38	Chap	ter 3 When: Stopwatches at	
	The Cellular Interior Is Highly Crowded, with Mean		Many	⁄ Scales	87
	Spacings Between Molecules That Are Comparable to Molecular Dimensions	48	3.1	THE HIERARCHY OF TEMPORAL SCALES	87
2.1.3	Looking Inside Cells	49	3.1.1	The Pageant of Biological Processes	89
2.1.4	Where Does E. coli Fit?	51		Biological Processes Are Characterized by a Huge	
	Biological Structures Exist Over a Huge Range of	51	3.1.2	Diversity of Time Scales The Evolutionary Stangarch	89
	Scales	31	3.1.2	The Evolutionary Stopwatch	95

3.1.3	The Cell Cycle and the Standard Clock	99		Structural Biology Has Its Roots in the Determination of the Structure of Hemoglobin	145
	The <i>E. coli</i> Cell Cycle Will Serve as Our Standard Stopwatch	99	4.2.3	Hemoglobin and Molecular Models of Disease	145
3.1.4	Three Views of Time in Biology	105	4.2.4	The Rise of Allostery and Cooperativity	146
		106	4.3	BACTERIOPHAGES AND MOLECULAR BIOLOGY	147
3.2 3.2.1	PROCEDURAL TIME The Machines (or Processes) of the Central Dogma	100	4.3.1		148
3.2.1	The Central Dogma Describes the Processes	107		Bacteriophages Have Sometimes Been Called the	
	Whereby the Genetic Information Is Expressed			"Hydrogen Atoms of Biology"	148
	Chemically The Branch of the Control Dooms Are Carried Out	107		Experiments on Phages and Their Bacterial Hosts Demonstrated That Natural Selection Is Operative in	
	The Processes of the Central Dogma Are Carried Out by Sophisticated Molecular Machines	108		Microscopic Organisms	148
3.2.2	Clocks and Oscillators	110		The Hershey-Chase Experiment Both Confirmed the	
	Developing Embryos Divide on a Regular Schedule			Nature of Genetic Material and Elucidated One of the Mechanisms of Viral DNA Entry into Cells	149
	Dictated by an Internal Clock	111		Experiments on Phage T4 Demonstrated the	פדו
	Diurnal Clocks Allow Cells and Organisms to Be on Time Everyday	111		Sequence Hypothesis of Collinearity of DNA and	
	, ,			Proteins State Country Colored BNA	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	115		Phages Were Instrumental in Elucidating the	
	Involving Molecular Synthesis and Organization	115		Existence of mRNA	151
3.3.2	Measuring Relative Time	117		General Ideas about Gene Regulation Were Learned	
	Genetic Networks Are Collections of Genes			from the Study of Viruses as a Model System	152
	Whose Expression Is Interrelated	117	4.3.2	Bacteriophages and Modern Biophysics	153
	The Formation of the Bacterial Flagellum Is	119		Many Single- Molecule Studies of Molecular Motors Have Been Performed on Motors from Bacteriophages	154
3.3.3	Intricately Organized in Space and Time Killing the Cell: The Life Cycles of Viruses	120			
3.3.3	Viral Life Cycles Include a Series of Self-Assembly	120	4.4	7. 17.22 01 1110 022251 27 0027 7 0 7 1 1110 2 2 2 2 1 1 1	154
	Processes	121	4.4.1	Bacteria and Molecular Biology	154 156
3.3.4	The Process of Development	122	4.4.2	E. coli and the Central Dogma The Hypothesis of Conservative Replication Has	130
3.4	MANIPULATED TIME	125		Falsifiable Consequences	156
3.4.1	Chemical Kinetics and Enzyme Turnover	125		Extracts from E. coli Were Used to Perform In Vitro	
3.4.2	Beating the Diffusive Speed Limit	126		Synthesis of DNA, mRNA, and Proteins	157
	Diffusion is the Random Motion of Microscopic		4.4.3	The <i>lac</i> Operon as the "Hydrogen Atom" of Genetic	157
	Particles in Solution	127		Circuits Gene Regulation in <i>E. coli</i> Serves as a Model for	137
	Diffusion Times Depend upon the Length Scale	127 127		Genetic Circuits in General	157
	Diffusive Transport at the Synaptic Junction Is the	127		The lac Operon Is a Genetic Network That Controls	
	Dynamical Mechanism for Neuronal Communication	128		the Production of the Enzymes Responsible for	
	Molecular Motors Move Cargo over Large Distances			Digesting the Sugar Lactose	158
	in a Directed Way	129	4.4.4	Signaling and Motility: The Case of Bacterial Chemotaxis	159
	Membrane-Bound Proteins Transport Molecules from One Side of a Membrane to the Other	120		E. coli Has Served as a Model System for the	
3.4.3	Beating the Replication Limit	130 131		Analysis of Cell Motility	159
3.4.4	Eggs and Spores: Planning for the Next	131	4.5	YEAST: FROM BIOCHEMISTRY TO THE CELL CYCLE	161
	Generation	132	4.3	Yeast Has Served as a Model System Leading to	
3.5	SHAMADY AND CONCLUSIONS	122		Insights in Contexts Ranging from Vitalism to the	
3.6	SUMMARY AND CONCLUSIONS PROBLEMS	133		Functioning of Enzymes to Eukaryotic Gene	
3.7	FURTHER READING	133		Regulation	161
3.8	REFERENCES	136	4.5.1	Yeast and the Rise of Biochemistry	162 162
3.0	ILI EREINCES	136	4.5.2 4.5.3	Dissecting the Cell Cycle Deciding Which Way Is Up: Yeast and Polarity	164
Chapt	ter 4 Who: "Bless the Little Beasties"	137	4.5.4	Dissecting Membrane Traffic	166
4.1	CHOOSING A GRAIN OF SAND		4.5.5	Genomics and Proteomics	167
•••	Modern Genetics Began with the Use of Peas as a	137	4.6	FLIFE AND MODERN BIOLOGY	170
	Model System	138	4.6.1	FLIES AND MODERN BIOLOGY Flies and the Rise of Modern Genetics	170
4.1.1	Biochemistry and Genetics	138	4.0.1	Drosophila melanogaster Has Served as a Model	
4.2	HEMOCLOPIN AS A MODEL PROTEIN			System for Studies Ranging from Genetics to	
4.2.1	HEMOGLOBIN AS A MODEL PROTEIN Hemoglobin, Receptor–Ligand Binding, and the	143		Development to the Functioning of the Brain and	170
	Other Bohr	143	4.6.3	Even Behavior	171
	The Binding of Oxygen to Hemoglobin Has Served	173	4.6.2	How the Fly Got His Stripes	
	as a Model System for Ligand-Receptor Interactions		4.7	OF MICE AND MEN	173
	More Generally	143	4.8	THE CASE FOR EXOTICA	174 174
	Quantitative Analysis of Hemoglobin Is Based upon Measuring the Fractional Occupancy of the		4.8.1	Specialists and Experts The Smith Circumstant Pietricity	175
	Oxygen-Binding Sites as a Function of Oxygen		4.8.2	The Squid Giant Axon and Biological Electricity There Is a Steady-State Potential Difference Across	
	Pressure	144		the Membrane of Nerve Cells	176
4.2.2	Hemoglobin and the Origins of Structural Biology	144		Nerve Cells Propagate Electrical Signals and Use	176
	The Study of the Mass of Hemoglobin Was Central in the Development of Centrifugation			Them to Communicate with Each Other	176 178
	or Centinuyation	145	4.8.3	Exotica Toolkit	, , 0

4.9	SUMMARY AND CONCLUSIONS	179	5.6	SUMMARY AND CONCLUSIONS	231
4.10 4.11	PROBLEMS FURTHER READING	179 181	5.7	APPENDIX: THE EULER–LAGRANGE EQUATIONS, FINDING THE SUPERLATIVE	232
4.12	REFERENCES	183		Finding the Extrema of Functionals Is Carried Out Using the Calculus of Variations	232
DAR	T 2 LIFE AT REST 1	85		The Euler–Lagrange Equations Let Us Minimize Functionals by Solving Differential Equations	232
			5.8	PROBLEMS	233
Chan	ter 5 Mechanical and Chemical		5.9	FURTHER READING	235
			5.10	REFERENCES	236
Equi	ibrium in the Living Cell	187	5.10	REFERENCES	230
5.1 5.1.1	ENERGY AND THE LIFE OF CELLS The Interplay of Deterministic and Thermal	187	•	• •	237
	Forces Thermal Jostling of Particles Must Be Accounted for	189	6.1	THE ANALYTICAL ENGINE OF STATISTICAL MECHANICS	237
5.1.2	in Biological Systems Constructing the Cell: Managing the Mass and	189		The Probability of Different Microstates Is Determined by Their Energy	240
	Energy Budget of the Cell	190	6.1.1 6.1.2	A First Look at Ligand-Receptor Binding The Statistical Mechanics of Gene Expression: RNA	241
5.2 5.2.1	BIOLOGICAL SYSTEMS AS MINIMIZERS Equilibrium Models for Out of Equilibrium Systems Equilibrium Models Can Be Used for Nonequilibrium	200 200		Polymerase and the Promoter A Simple Model of Gene Expression Is to Consider the Probability of RNA Polymerase Binding at the	244
	Problems if Certain Processes Happen Much Faster Than Others	201		Promoter Most Cellular RNA Polymerase Molecules Are Bound	245
5.2.2	Proteins in "Equilibrium"	202		to DNA	245
	Protein Structures are Free-Energy Minimizers	203		The Binding Probability of RNA Polymerase to Its	
5.2.3	Cells in "Equilibrium"	204		Promoter Is a Simple Function of the Number of	
5.2.4	Mechanical Equilibrium from a Minimization			Polymerase Molecules and the Binding Energy	247
	Perspective	204	6.1.3	Classic Derivation of the Boltzmann Distribution	248
	The Mechanical Equilibrium State is Obtained by	204		The Boltzmann Distribution Gives the Probability of	
	Minimizing the Potential Energy	204		Microstates for a System in Contact with a Thermal Reservoir	248
5.3	THE MATHEMATICS OF SUPERLATIVES	209	6.1.4	Boltzmann Distribution by Counting	250
5.3.1	The Mathematization of Judgement: Functions and		0.1.4	Different Ways of Partitioning Energy Among	230
	Functionals	209		Particles Have Different Degeneracies	250
	Functionals Deliver a Number for Every Function		6.1.5	Boltzmann Distribution by Guessing	253
	They Are Given	210		Maximizing the Entropy Corresponds to Making a	
5.3.2	The Calculus of Superlatives Finding the Maximum and Minimum Values of a	211		Best Guess When Faced with Limited Information	253
	Function Requires That We Find Where the Slope of			Entropy Maximization Can Be Used as a Tool for Statistical Inference	255
	the Function Equals Zero	211		The Boltzmann Distribution is the Maximum Entropy	
5.4	CONFIGURATIONAL ENERGY	214		Distribution in Which the Average Energy is Prescribed as a Constraint	258
	In Mechanical Problems, Potential Energy			riescribeu as a Constraint	230
	Determines the Equilibrium Structure	214	6.2	ON BEING IDEAL	259
5.4.1	Hooke's Law: Actin to Lipids	216	6.2.1	Average Energy of a Molecule in a Gas	259
	There is a Linear Relation Between Force and			The Ideal Gas Entropy Reflects the Freedom to	
	Extension of a Beam	216		Rearrange Molecular Positions and Velocities	259
	The Energy to Deform an Elastic Material is a	217	6.2.2	Free Energy of Dilute Solutions	262
	Quadratic Function of the Strain	217		The Chemical Potential of a Dilute Solution Is a	262
5.5	STRUCTURES AS FREE-ENERGY MINIMIZERS	219	6.2.3	Simple Logarithmic Function of the Concentration Osmotic Pressure as an	262
	The Entropy is a Measure of the Microscopic		0.2.3	Entropic Spring	264
	Degeneracy of a Macroscopic State	219		Osmotic Pressure Arises from Entropic Effects	264
5.5.1	Entropy and Hydrophobicity	222		Viruses, Membrane-Bound Organelles, and Cells	
	Hydrophobicity Results from Depriving Water			Are Subject to Osmotic Pressure	265
	Molecules of Some of Their Configurational Entropy	222		Osmotic Forces Have Been Used to Measure the	
	Amino Acids Can Be Classified According to Their	222		Interstrand Interactions of DNA	266
	Hydrophobicity	224	6.3	THE CALCULUS OF EQUILIBRIUM APPLIED: LAW OF	
	When in Water, Hydrocarbon Tails on Lipids Have an		0.5	MASS ACTION	267
	Entropy Cost	225	6.3.1	Law of Mass Action and Equilibrium Constants	267
5.5.2	Gibbs and the Calculus of Equilibrium	225		Equilibrium Constants are Determined by Entropy	
	Thermal and Chemical Equilibrium are Obtained by			Maximization	267
	Maximizing the Entropy	225		APPLICATIONS OF THE CALCULAR OF TOWN	
5.5.3	Departure from Equilibrium and Fluxes	227	6.4	APPLICATIONS OF THE CALCULUS OF EQUILIBRIUM	270
5.5.4	Structure as a Competition Free Energy Minimization Can Be Thought	228	6.4.1	A Second Look at Ligand-Receptor Binding	270
	of as an Alternative Formulation of Entropy		6.4.2 6.4.3	Measuring Ligand-Receptor Binding Beyond Simple Ligand-Receptor Binding: The Hill	272
	Maximization	228	0.7.3	Function	273
5.5.5	An Ode to ΔG	230	6.4.4	ATP Power	274
	The Free Energy Reflects a Competition Between			The Energy Released in ATP Hydrolysis Depends	
	Energy and Entropy	230		Upon the Concentrations of Reactants and Products	275

6.5	SUMMARY AND CONCLUSIONS	276		The Probability of a Given Macromolecular State	
6.6	PROBLEMS	276		Depends Upon Its Microscopic Degeneracy	315
6.7	FURTHER READING	278		Entropy Determines the Elastic Properties of	216
6.8	REFERENCES	278		Polymer Chains	316
•	, <u></u>			The Persistence Length Is a Measure of the Length Scale Over Which a Polymer Remains Roughly	
Chant	er 7 Two-State Systems: From Ion			Straight	319
		281	8.2.2	How Big Is a Genome?	321
Chan	nels to Cooperative Binding	281	8.2.3	The Geography of Chromosomes	322
7.1	MACROMOLECULES WITH MULTIPLE STATES	281		Genetic Maps and Physical Maps of Chromosomes	
7.1.1	The Internal State Variable Idea	281		Describe Different Aspects of Chromosome	322
	The State of a Protein or Nucleic Acid Can Be Characterized Mathematically Using a State			Structure Different Structural Models of Chromatin Are	322
	Variable	282		Characterized by the Linear Packing Density	
7.1.2	Ion Channels as an Example of Internal State			of DNA	323
,,,,,	Variables	286		Spatial Organization of Chromosomes Shows	
	The Open Probability $\langle \sigma \rangle$ of an Ion Channel Can Be			Elements of Both Randomness and Order	324
	Computed Using Statistical Mechanics	287		Chromosomes Are Tethered at Different Locations	325
7.2	STATE VARIABLE DESCRIPTION OF BINDING	289		Chromosome Territories Have Been Observed	227
7.2 7.2.1	The Gibbs Distribution: Contact with a Particle	203		in Bacterial Cells	327
7.2.1	Reservoir	289		Chromosome Territories in <i>Vibrio cholerae</i> Can Be Explored Using Models of Polymer Confinement	
	The Gibbs Distribution Gives the Probability of			and Tethering	328
	Microstates for a System in Contact with a Thermal	222	8.2.4	DNA Looping: From Chromosomes to Gene	
722	and Particle Reservoir	289		Regulation	333
7.2.2 7.2.3	Simple Ligand–Receptor Binding Revisited Phosphorylation as an Example of Two Internal	291		The Lac Repressor Molecule Acts Mechanistically	224
7.2.3	State Variables	292		by Forming a Sequestered Loop in DNA	334
	Phosphorylation Can Change the Energy Balance			Looping of Large DNA Fragments Is Dictated by the Difficulty of Distant Ends Finding Each Other	334
	Between Active and Inactive States	293		Chromosome Conformation Capture Reveals	55.
	Two-Component Systems Exemplify the Use of	205		the Geometry of Packing of Entire Genomes	
7.2.4	Phosphorylation in Signal Transduction	295		in Cells	336
7.2.4	Hemoglobin as a Case Study in Cooperativity The Binding Affinity of Oxygen for Hemoglobin	298			
	Depends upon Whether or Not Other Oxygens Are		8.3	THE NEW WORLD OF SINGLE-MOLECULE MECHANICS	337
	Already Bound	298		Single-Molecule Measurement Techniques Lead to	,,,,
	A Toy Model of a Dimeric Hemoglobin (Dimoglobin)			Force Spectroscopy	337
	Illustrate the Idea of Cooperativity	298	8.3.1	Force-Extension Curves: A New Spectroscopy	339
	The Monod-Wyman-Changeux (MWC) Model Provides a Simple Example of Cooperative Binding	300		Different Macromolecules Have Different Force	
	Statistical Models of the Occupancy of Hemoglobin	300		Signatures When Subjected to Loading	339
	Can Be Written Using Occupation Variables	301	8.3.2	Random Walk Models for Force–Extension Curves	340
	There is a Logical Progression of Increasingly			The Low-Force Regime in Force-Extension Curves Can Be Understood Using the Random Walk Model	340
	Complex Binding Models for Hemoglobin	301		can be orderstood osing the Random Walk Model	
7.3	ION CHANNELS REVISITED: LIGAND-GATED		8.4	PROTEINS AS RANDOM WALKS	344
7.5	CHANNELS AND THE MWC MODEL	305	8.4.1	Compact Random Walks and the Size of Proteins	345
7.4	SUMMARY AND CONCLUSIONS	303		The Compact Nature of Proteins Leads to an	345
7.5	PROBLEMS	308	8.4.2	Estimate of Their Size	346
7.6	FURTHER READING	310	6.4.2	Hydrophobic and Polar Residues: The HP Model The HP Model Divides Amino Acids into Two	5.10
7.7	REFERENCES			Classes: Hydrophobic and Polar	346
		310	8.4.3	HP Models of Protein Folding	348
Char	ter 8 Random Walks and the		0.5		351
Struck	cture of Macromolecules		8.5	SUMMARY AND CONCLUSIONS	351
		311	8.6	PROBLEMS	353
8.1	WHAT IS A STRUCTURE: PDB OR R_{G} ?	311	8.7	FURTHER READING	353
8.1.1	Deterministic versus Statistical Descriptions of Structure		8.8	REFERENCES	555
	PDB Files Reflect a Deterministic Description of	312			
	Macromolecular Structure	312		ter 9 Electrostatics for Salty	
	Statistical Descriptions of Structure Emphasize	312	Solut	tions	355
	Average Size and Shape Rather Than Atomic		9.1	WATER AS LIFE'S AETHER	355
	Coordinates	312			250
8.2	MACROMOLECULES AS RANDOM WALKS	212	9.2	THE CHEMISTRY OF WATER	358
	Random Walk Models of Macromolecules View	312	9.2.1	pH and the Equilibrium Constant	358
	Them as Rigid Segments Connected by Hinges	312		Dissociation of Water Molecules Reflects a	
8.2.1	A Mathematical Stupor	313		Competition Between the Energetics of Binding and the Entropy of Charge Liberation	358
	In Random Walk Models of Polymers, Every	- • •	9.2.2	The Charge on DNA and Proteins	359
	Macromolecular Configuration Is Equally Probable	313		The Charge State of Biopolymers Depends	250
	The Mean Size of a Random Walk Macromolecule Scales as the Square Root of the Number of			upon the pH of the Solution	359 359
	Segments, \sqrt{N}	214		Different Amino Acids Have Different Charge States	360
		314	9.2.3	Salt and Binding	200

9.3	ELECTROSTATICS FOR SALTY SOLUTIONS	360	10.4	DNA PACKING: FROM VIRUSES TO EUKARYOTES	398
9.3.1	An Electrostatics Primer A Charge Distribution Produces an Electric Field	361		The Packing of DNA in Viruses and Cells Requires Enormous Volume Compaction	398
	Throughout Space	362	10.4.1	The Problem of Viral DNA Packing	400
	The Flux of the Electric Field Measures the Density			Structural Biologists Have Determined the Structure	
	of Electric Field Lines	363		of Many Parts in the Viral Parts List	400
	The Electrostatic Potential Is an Alternative Basis	264		The Packing of DNA in Viruses Results in a	402
	for Describing the Electrical State of a System There Is an Energy Cost Associated With Assembling	364		Free-Energy Penalty A Simple Model of DNA Packing in Viruses Uses the	402
	a Collection of Charges	367		Elastic Energy of Circular Hoops	403
	The Energy to Liberate lons from Molecules Can			DNA Self-Interactions Are also Important in	
	Be Comparable to the Thermal Energy	368		Establishing the Free Energy Associated with DNA	
9.3.2	The Charged Life of a Protein	369		Packing in Viruses	404
9.3.3	The Notion of Screening: Electrostatics in Salty Solutions	370		DNA Packing in Viruses Is a Competition Between Elastic and Interaction Energies	406
	Ions in Solution Are Spatially Arranged to Shield	5,0	10.4.2	Constructing the Nucleosome	407
	Charged Molecules Such as DNA	370		Nucleosome Formation Involves Both Elastic	
	The Size of the Screening Cloud Is Determined			Deformation and Interactions Between Histones	400
	by a Balance of Energy and Entropy of the Surrounding Ions	371	10.4.3	and DNA Equilibrium Accessibility of Nucleosomal DNA	408 409
9.3.4	The Poisson-Boltzmann Equation	374	10.4.5	The Equilibrium Accessibility of Sites within the	703
	The Distribution of Screening Ions Can Be Found			Nucleosome Depends upon How Far They Are	
	by Minimizing the Free Energy	374		from the Unwrapped Ends	409
	The Screening Charge Decays Exponentially Around Macromolecules in Solution	376	10.5	THE CYTOSKELETON AND BEAM THEORY	413
9.3.5	Viruses as Charged Spheres	377	10.5	Eukaryotic Cells Are Threaded by Networks	713
3.3.3	viruses as charged spireles			of Filaments	413
9.4	SUMMARY AND CONCLUSION	379	10.5.1	The Cellular Interior: A Structural Perspective	414
9.5	PROBLEMS	380		Prokaryotic Cells Have Proteins Analogous to the Eukaryotic Cytoskeleton	416
9.6	FURTHER READING	382	10.5.2	Stiffness of Cytoskeletal Filaments	416
9.7	REFERENCES	382		The Cytoskeleton Can Be Viewed as a Collection	
				of Elastic Beams	416
	ter 10 Beam Theory: Architecture		10.5.3	Cytoskeletal Buckling	419 419
for Co	ells and Skeletons	383	10.5.4	A Beam Subject to a Large Enough Force Will Buckle Estimate of the Buckling Force	420
10.1	BEAMS ARE EVERYWHERE: FROM FLAGELLA TO THE		10.5.4	Beam Buckling Occurs at Smaller Forces for Longer	720
	CYTOSKELETON	383		Beams	420
	One-Dimensional Structural Elements Are the Basis of Much of Macromolecular and Cellular		10.6	CHAMARY AND CONCLUCIONS	421
	Architecture	383	10.6	SUMMARY AND CONCLUSIONS APPENDIX: THE MATHEMATICS OF THE WORM LIKE	421
			10.7	APPENDIX: THE MATHEMATICS OF THE WORM-LIKE CHAIN	421
10.2	GEOMETRY AND ENERGETICS OF BEAM	205	10.8	PROBLEMS	424
10.2.1	DEFORMATION Stretch, Bend, and Twist	385 385	10.9	FURTHER READING	426
10.2.1	Beam Deformations Result in Stretching, Bending,	303	10.10	REFERENCES	426
	and Twisting	385			
	A Bent Beam Can Be Analyzed as a Collection of	205		ter 11 Biological Membranes: Life in	
	Stretched Beams The Energy Cost to Deform a Beam Is a Quadratic	385	Two E	Dimensions	427
	Function of the Strain	387	11.1	THE NATURE OF BIOLOGICAL MEMBRANES	427
10.2.2	Beam Theory and the Persistence Length: Stiffness		11.1.1	Cells and Membranes	427
	is Relative	389		Cells and Their Organelles Are Bound by Complex Membranes	427
	Thermal Fluctuations Tend to Randomize the	389		Electron Microscopy Provides a Window on Cellular	427
	Orientation of Biological Polymers The Persistence Length Is the Length Over Which a	309		Membrane Structures	429
	Polymer Is Roughly Rigid	390	11.1.2	The Chemistry and Shape of Lipids	431
	The Persistence Length Characterizes the			Membranes Are Built from a Variety of Molecules	421
	Correlations in the Tangent Vectors at Different	200		That Have an Ambivalent Relationship with Water The Shapes of Lipid Molecules Can Induce	431
	Positions Along the Polymer The Positions Along the Polymer	390		Spontaneous Curvature on Membranes	436
	The Persistence Length Is Obtained by Averaging Over All Configurations of the Polymer	391	11.1.3	The Liveliness of Membranes	436
10.2.3	Elasticity and Entropy: The Worm-Like Chain	392		Membrane Proteins Shuttle Mass Across Membranes	437
	The Worm-Like Chain Model Accounts for Both			Membrane Proteins Communicate Information	420
	the Elastic Energy and Entropy of Polymer	202		Across Membranes	439 439
	Chains	392		Specialized Membrane Proteins Generate ATP Membrane Proteins Can Be Reconstituted in Vesicles	
10.3	THE MECHANICS OF TRANSCRIPTIONAL			Wellbrane Proteins can be reconstituted in vesicles	733
	REGULATION: DNA LOOPING REDUX	394	11.2	ON THE SPRINGINESS OF MEMBRANES	440
10.3.1	The lac Operon and Other Looping Systems Transcriptional Pagulation Can Be Effected	394	11.2.1	An Interlude on Membrane Geometry	440
	Transcriptional Regulation Can Be Effected by DNA Looping	395		Membrane Stretching Geometry Can Be Described by a Simple Area Function	441
10.3.2	Energetics of DNA Looping	395		Membrane Bending Geometry Can Be Described by	• • •
10.3.3	Putting It All Together: The J-Factor	396		a Simple Height Function, $h(x, y)$	441

		Membrane Compression Geometry Can Be Described by a Simple Thickness Function, $w(x,y)$ Membrane Shearing Can Be Described by an Angle	444	12.2.1	Though Fluids Are Composed of Molecules It Is Possible to Treat Them as a Continuous Medium	484 484
1	11.2.2	Variable, θ Free Energy of Membrane Deformation	444 445	12.2.2	What Can Newton Tell Us? Gradients in Fluid Velocity Lead to Shear Forces	485 485
		There Is a Free-Energy Penalty Associated with Changing the Area of a Lipid Bilayer	445	12.2.3 12.2.4	F = ma for Fluids The Newtonian Fluid and the Navier-Stokes	486
		There Is a Free-Energy Penalty Associated with Bending a Lipid Bilayer	446	12.2.7	Equations The Velocity of Fluids at Surfaces Is Zero	490 491
		There Is a Free-Energy Penalty for Changing the Thickness of a Lipid Bilayer	446	12.3	THE RIVER WITHIN: FLUID DYNAMICS OF BLOOD	491
		There Is an Energy Cost Associated with the Gaussian Curvature	447	12.3.1	Boats in the River: Leukocyte Rolling and Adhesion	493
	11.3	STRUCTURE, ENERGETICS, AND FUNCTION OF		12.4	THE LOW REYNOLDS NUMBER WORLD	495
		VESICLES	448	12.4.1 12.4.2	Stokes Flow: Consider a Spherical Bacterium Stokes Drag in Single-Molecule Experiments	495 498
	11.3.1	Measuring Membrane Stiffness Membrane Elastic Properties Can Be Measured by	448	12.4.2	Stokes Drag Is Irrelevant for Optical Tweezers	
		Stretching Vesicles	448	1247	Experiments Discipation Time Scales and the Boundles	498
	11.3.2	Membrane Pulling Vesicles in Cells	450 453	12.4.3	Dissipative Time Scales and the Reynolds Number	499
	11.3.3	Vesicles Are Used for a Variety of Cellular Transport		12.4.4	Fish Gotta Swim, Birds Gotta Fly, and Bacteria Gotta Swim Too	500
		Processes There Is a Fixed Free-Energy Cost Associated with	453		Reciprocal Deformation of the Swimmer's Body	300
		Spherical Vesicles of All Sizes	455		Does Not Lead to Net Motion at Low Reynolds Number	502
		Vesicle Formation Is Assisted by Budding Proteins There Is an Energy Cost to Disassemble Coated	456	12.4.5	Centrifugation and Sedimentation: Spin It Down	502
		Vesicles	458	12.5	SUMMARY AND CONCLUSIONS	504
	11.4	FUSION AND FISSION	458	12.6	PROBLEMS	505
	11.4.1	Pinching Vesicles: The Story of Dynamin	459	12.7	FURTHER READING	507
	11.5	MEMBRANES AND SHAPE	462	12.8	REFERENCES	507
	11.5.1	The Shapes of Organelles	462			
		The Surface Area of Membranes Due to Pleating Is So Large That Organelles Can Have Far More Area		_	ter 13 A Statistical View of	509
		than the Plasma Membrane	463		gical Dynamics	509
	11.5.2	The Shapes of Cells The Equilibrium Shapes of Red Blood Cells Can Be	465	13.1 13.1.1	DIFFUSION IN THE CELL Active versus Passive Transport	510
	11.6	Found by Minimizing the Free Energy	466	13.1.2	Biological Distances Measured in Diffusion Times The Time It Takes a Diffusing Molecule to Travel a	511
	11.6 11.6.1	THE ACTIVE MEMBRANE Mechanosensitive Ion Channels and Membrane	467		Distance L Grows as the Square of the Distance	512
		Elasticity	467		Diffusion Is Not Effective Over Large Cellular	512
		Mechanosensitive lon Channels Respond to Membrane Tension	467	13.1.3	Distances Random Walk Redux	514
	11.6.2	Elastic Deformations of Membranes Produced by Proteins	468	13.2	CONCENTRATION FIELDS AND DIFFUSIVE DYNAMICS	515
		Proteins Induce Elastic Deformations in the	700		Fick's Law Tells Us How Mass Transport Currents	7
		Surrounding Membrane Protein-Induced Membrane Bending Has an	468		Arise as a Result of Concentration Gradients The Diffusion Equation Results from Fick's Law and	517
		Associated Free-Energy Cost	469		Conservation of Mass	518
	11.6.3	c.ic.id.id.id.id.id.id.id.id.id.id.id.id.id.	470	13.2.1	Diffusion by Summing Over Microtrajectories	518 524
		Membrane Deformations Can Be Obtained by Minimizing the Membrane Free Energy	470	13.2.2	Solutions and Properties of the Diffusion Equation Concentration Profiles Broaden Over Time in a Very	727
		The Membrane Surrounding a Channel Protein			Precise Way	524 525
		Produces a Line Tension	472	13.2.3 13.2.4	FRAP and FCS Drunks on a Hill: The Smoluchowski Equation	529
	11.7	SUMMARY AND CONCLUSIONS	475	13.2.5	The Einstein Relation	530
	11.8 11.9	PROBLEMS	476	13.3	DIFFUSION TO CAPTURE	532
	11.10	FURTHER READING REFERENCES	479	13.3.1	Modeling the Cell Signaling Problem	532
	•		479		Perfect Receptors Result in a Rate of Uptake $4\pi Dc_0 a$ A Distribution of Receptors Is Almost as Good as a	533
	DAR	T 2 LIFE IN MACHINE			Perfectly Absorbing Sphere	534
	PAR	T 3 LIFE IN MOTION 4	81	1222	Real Receptors Are Not Always Uniformly Distributed	d 536
				13.3.2	A "Universal" Rate for Diffusion-Limited	537
	Chap	ter 12 The Mathematics of Water	482		Chemical Reactions	,,,
	Chap 12.1	ter 12 The Mathematics of Water PUTTING WATER IN ITS PLACE	483	12 4		
		PUTTING WATER IN ITS PLACE HYDRODYNAMICS OF WATER AND OTHER FLUIDS	483 483 484	13.4 13.5	Chemical Reactions SUMMARY AND CONCLUSIONS PROBLEMS	538 539

13.6	FURTHER READING	540		Decay of One Species Corresponds to Growth in the	
13.7	REFERENCES	540	15.2.4	Number of a Second Species Bimolecular Reactions	585 586
			13.2.4	Chemical Reactions Can Increase the Concentration	300
-	ter 14 Life in Crowded and			of a Given Species	586
Disor	dered Environments	543		Equilibrium Constants Have a Dynamical Interpretation in Terms of Reaction Rates	588
14.1	CROWDING, LINKAGE, AND ENTANGLEMENT	543	15.2.5	Dynamics of Ion Channels as a Case Study	589
14.1.1 14.1.2	The Cell Is Crowded Macromolecular Networks: The Cytoskeleton	544		Rate Equations for Ion Channels Characterize the	
14.1.2	and Beyond	545		Time Evolution of the Open and Closed Probability	590
14.1.3	Crowding on Membranes	546	15.2.6 15.2.7	Rapid Equilibrium Michaelis-Menten and Enzyme Kinetics	591 596
14.1.4		547	13.2.7	Michaelis-Menten and Enzyme Kinetics	390
	Crowding Alters Biochemical Equilibria Crowding Alters the Kinetics within Cells	548 548	15.3	THE CYTOSKELETON IS ALWAYS UNDER CONSTRUCTION	599
	FOLUMENT IN COOKER SHOWS ON STATE		15.3.1	The Eukaryotic Cytoskeleton	599
14.2 14.2.1	EQUILIBRIA IN CROWDED ENVIRONMENTS Crowding and Binding	550 550		The Cytoskeleton Is a Dynamical Structure That Is	
14.2.1	Lattice Models of Solution Provide a Simple	000		Always Under Construction	599
	Picture of the Role of Crowding in Biochemical		15.3.2	The Curious Case of the Bacterial Cytoskeleton	600
	Equilibria	550	15.4	SIMPLE MODELS OF CYTOSKELETAL POLYMERIZATION	602
14.2.2	Osmotic Pressures in Crowded Solutions Osmotic Pressure Reveals Crowding Effects	552 552		The Dynamics of Polymerization Can Involve Many	
14.2.3	Depletion Forces: Order from Disorder	554		Distinct Physical and Chemical Effects	603
14.2.3	The Close Approach of Large Particles Excludes	,	15.4.1	The Equilibrium Polymer Equilibrium Models of Cytoskeletal Filaments	604
	Smaller Particles Between Them, Resulting in an			Describe the Distribution of Polymer Lengths for	
	Entropic Force	554		Simple Polymers	604
14.2.4	Depletion Forces Can Induce Entropic Ordering! Excluded Volume and Polymers	559 559		An Equilibrium Polymer Fluctuates in Time	606
14.2.4	Excluded Volume Leads to an Effective Repulsion	223	15.4.2	Rate Equation Description of Cytoskeletal	C00
	Between Molecules	559		Polymerization Polymerization Reactions Can Be Described by Rate	609
	Self-avoidance Between the Monomers of a Polymer			Equations	609
1425	Leads to Polymer Swelling	561		The Time Evolution of the Probability Distribution	
14.2.5 14.2.6	Case Study in Crowding: How to Make a Helix Crowding at Membranes	563 565		$P_n(t)$ Can Be Written Using a Rate Equation	610
11.2.0	crowding at membranes	303		Rates of Addition and Removal of Monomers Are Often Different on the Two Ends of Cytoskeletal	
14.3	CROWDED DYNAMICS	566		Filaments	612
14.3.1	Crowding and Reaction Rates	566	15.4.3	Nucleotide Hydrolysis and Cytoskeletal	•
	Enzymatic Reactions in Cells Can Proceed Faster than the Diffusion Limit Using Substrate			Polymerization	614
	Channeling	566		ATP Hydrolysis Sculpts the Molecular Interface, Resulting in Distinct Rates at the Ends of	
	Protein Folding Is Facilitated by Chaperones	567		Cytoskeletal Filaments	614
14.3.2	Diffusion in Crowded Environments	567	15.4.4	Dynamic Instability: A Toy Model of the Cap	615
14.4	SUMMARY AND CONCLUSIONS	569		A Toy Model of Dynamic Instability Assumes That	
14.5	PROBLEMS	569		Catastrophe Occurs When Hydrolyzed Nucleotides Are Present at the Growth Front	616
14.6	FURTHER READING	570		Are riesent at the Glowth Front	010
14.7	REFERENCES	571	15.5	SUMMARY AND CONCLUSIONS	618
			15.6	PROBLEMS	619
Chapt	ter 15 Rate Equations and		15.7	FURTHER READING	621
Dynai	mics in the Cell	573	15.8	REFERENCES	621
15.1	BIOLOGICAL STATISTICAL DYNAMICS: A FIRST		Chant	ter 16 Dynamics of Molecular	
	LOOK	573	Motor		623
15.1.1		574			023
15.1.2	Dynamics of the Cytoskeleton	575	16.1	THE DYNAMICS OF MOLECULAR MOTORS: LIFE IN THE NOISY LANE	623
15.2	A CHEMICAL PICTURE OF BIOLOGICAL DYNAMICS	579	16.1.1	Translational Motors: Beating the Diffusive Speed	
15.2.1	The Rate Equation Paradigm Chemical Concentrations Vary in Both Space and	579		Limit The Mexicon of Full and Silver and Sharelle to Driver	625
	Time	580		The Motion of Eukaryotic Cilia and Flagella Is Driven by Translational Motors	628
	Rate Equations Describe the Time Evolution of			Muscle Contraction Is Mediated by Myosin Motors	630
	Concentrations	580	16.1.2	Rotary Motors	634
15.2.2		581	16.1.3	, , , , , , , , , , , , , , , , , , , ,	637
	Macromolecular Decay Can Be Described by a Simple, First-Order Differential Equation	581	16.1.4	Translocation Motors: Pushing by Pulling	638
15.2.3	A Single-Molecule View of Degradation: Statistical		16.2	RECTIFIED BROWNIAN MOTION AND	
	Mechanics Over Trajectories	582		MOLECULAR MOTORS	639
	Molecules Fall Apart with a Characteristic Lifetime	582	16.2.1	The Random Walk Yet Again	640
	Decay Processes Can Be Described with Two-State Trajectories	583		Molecular Motors Can Be Thought of as Random Walkers	640
	,, mj. m. m. 1, 100	-			

16.2.2	The One-State Model	641		Voltage-Gated Channels Result in a Nonlinear	
	The Dynamics of a Molecular Motor Can Be Written			Current-Voltage Relation for the Cell Membrane	699
	Using a Master Equation	642		A Patch of Membrane Acts as a Bistable Switch	700
	The Driven Diffusion Equation Can Be Transformed	644		The Dynamics of Voltage Relaxation Can Be Modeled Using an RC Circuit	702
1672	into an Ordinary Diffusion Equation Motor Stepping from a Free-Energy Perspective	647	17/2	The Cable Equation	702
16.2.3 16.2.4	The Two-State Model	651	17.4.2	Depolarization Waves	705
10.2.4	The Dynamics of a Two-State Motor Is Described		17.1.5	Waves of Membrane Depolarization Rely on	
	by Two Coupled Rate Equations	651		Sodium Channels Switching into the Open State	705
	Internal States Reveal Themselves in the Form		17.4.4	Spikes	710
	of the Waiting Time Distribution	654	17.4.5	Hodgkin-Huxley and Membrane Transport	712
16.2.5	More General Motor Models	656		Inactivation of Sodium Channels Leads to	712
16.2.6	Coordination of Motor Protein Activity	658 660		Propagating Spikes	/12
16.2.7	Rotary Motors	000	17.5	SUMMARY AND CONCLUSIONS	714
16.3	POLYMERIZATION AND TRANSLOCATION AS		17.6	PROBLEMS	714
	MOTOR ACTION	663	17.7	FURTHER READING	715
16.3.1	The Polymerization Ratchet	663	17.8	REFERENCES	715
	The Polymerization Ratchet Is Based on a Polymerization Reaction That Is Maintained Out of				
	Equilibrium	666	Chapt	er 18 Light and Life	717
	The Polymerization Ratchet Force-Velocity Can Be		18.1	INTRODUCTION	718
	Obtained by Solving a Driven Diffusion Equation	668	18.2	PHOTOSYNTHESIS	719
16.3.2	Force Generation by Growth	670	10.2	Organisms From All Three of the Great Domains	, , ,
	Polymerization Forces Can Be Measured Directly	670		of Life Perform Photosynthesis	720
	Polymerization Forces Are Used to Center Cellular		18.2.1	Quantum Mechanics for Biology	724
	Structures	672		Quantum Mechanical Kinematics Describes	
16.3.3	The Translocation Ratchet	673		States of the System in Terms of Wave Functions	725
	Protein Binding Can Speed Up Translocation through a Ratcheting Mechanism	674		Quantum Mechanical Observables Are Represented	720
	The Translocation Time Can Be Estimated by	0, 1		by Operators	728
	Solving a Driven Diffusion Equation	676		The Time Evolution of Quantum States Can Be	729
			18.2.2	Determined Using the Schrödinger Equation The Particle-in-a-Box Model	730
16.4	SUMMARY AND CONCLUSIONS	677	10.2.2	Solutions for the Box of Finite Depth Do Not Vanish	, 50
16.5	PROBLEMS	677		at the Box Edges	731
16.6	FURTHER READING	679	18.2.3	Exciting Electrons With Light	733
16.7	REFERENCES	679		Absorption Wavelengths Depend Upon Molecular	-25
				Size and Shape	735
-	ter 17 Biological Electricity		18.2.4		737 737
and t	he Hodgkin-Huxley Model	681		Excited Electrons Can Suffer Multiple Fates Electron Transfer in Photosynthesis Proceeds by	, 5.
17.1	THE ROLE OF ELECTRICITY IN CELLS	681		Tunneling	739
17.2	THE CHARGE STATE OF THE CELL	682		Electron Transfer Between Donor and Acceptor Is	
17.2.1	The Electrical Status of Cells and Their Membranes	682		Gated by Fluctuations of the Environment	745
17.2.2	Electrochemical Equilibrium and the Nernst Equation	683		Resonant Transfer Processes in the Antenna	
	Ion Concentration Differences Across Membranes Lead to Potential Differences	683		Complex Efficiently Deliver Energy to the Reaction	747
	read to rotential Differences	003	1025	Center	748
17.3	MEMBRANE PERMEABILITY: PUMPS AND		18.2.5	Bioenergetics of Photosynthesis Electrons Are Transferred from Donors to Acceptors	, 40
	CHANNELS	685		Within and Around the Cell Membrane	748
	A Nonequilibrium Charge Distribution Is Set Up			Water, Water Everywhere, and Not an Electron to	
	Between the Cell Interior and the External World	685		Drink	750
	Signals in Cells Are Often Mediated by the Presence	505		Charge Separation across Membranes Results in a	
17.3.1	of Electrical Spikes Called Action Potentials Ion Channels and Membrane Permeability	686		Proton-Motive Force	751
17.3.1	Ion Permeability Across Membranes Is Mediated	688	18.2.6		752 757
	by Ion Channels	688	18.2.7	Destroying Sugar	758
	A Simple Two-State Model Can Describe Many		18.2.8	Photosynthesis in Perspective	, 50
	of the Features of Voltage Gating of Ion Channels	689	18.3	THE VISION THING	759
17.3.2		691	18.3.1	Bacterial "Vision"	760
	lons Are Pumped Across the Cell Membrane		18.3.2	Microbial Phototaxis and Manipulating Cells with	763
	Against an Electrochemical Gradient	691		Light	763 763
17.4	THE ACTION POTENTIAL	693	18.3.3	Animal Vision	703
17.4.1	Membrane Depolarization: The Membrane as a	033		There Is a Simple Relationship between Eye Geometry and Resolution	765
	Bistable Switch	693		The Resolution of Insect Eyes Is Governed by	
	Coordinated Muscle Contraction Depends Upon			Both the Number of Ommatidia and Diffraction	
	Membrane Depolarization	694		Effects	768
	A Patch of Cell Membrane Can Be Modeled as an Electrical Circuit			The Light-Driven Conformational Change of Retinal	769
	The Difference Between the Membrane Potential and	696		Underlies Animal Vision	709
	the Nernst Potential Leads to an Ionic Current			Information from Photon Detection Is Amplified	
	Across the Cell Membrane	698	,	by a Signal Transduction Cascade in the Photoreceptor Cell	773
				· ····································	

	The Vertebrate Visual System Is Capable of		19.3	REGULATORY DYNAMICS	835
	Detecting Single Photons	776	19.3.1	The Dynamics of RNA Polymerase and the	
18.3.4	Sex, Death, and Quantum Mechanics	781		Promoter	835
	Let There Be Light: Chemical Reactions Can Be Used			The Concentrations of Both RNA and Protein Can Be	
	to Make Light	784	10.2.2	Described Using Rate Equations	835
18.4	SUMMARY AND CONCLUSIONS	785	19.3.2	Dynamics of mRNA Distributions Unregulated Promoters Can Be Described By a	838
18.5	APPENDIX: SIMPLE MODEL OF ELECTRON TUNNELING			Poisson Distribution	841
18.6	PROBLEMS	703 793	19.3.3		843
18.7	FURTHER READING	795 795	13.3.5	The Two-State Promoter Has a Fano Factor Greater	0,5
				Than One	844
18.8	REFERENCES	796		Different Regulatory Architectures Have Different	
				Fano Factors	849
			19.3.4	Dynamics of Protein Translation	854
PAR	T 4 THE MEANING OF LIFE 79	99		Genetic Switches: Natural and Synthetic Genetic Networks That Oscillate	861 870
Chap	ter 19 Organization of Biological		19.4 19.4.1	CELLULAR FAST RESPONSE: SIGNALING	872
Netw	orks	801	19.4.1	Bacterial Chemotaxis The MWC Model Can Be Used to Describe Bacterial	873
19.1	CHEMICAL AND INFORMATIONAL ORGANIZATION			Chemotaxis	878
	IN THE CELL	801		Precise Adaptation Can Be Described by a Simple	
	Many Chemical Reactions in the Cell are Linked in			Balance Between Methylation and Demethylation	881
	Complex Networks	801	19.4.2	Biochemistry on a Leash	883
	Genetic Networks Describe the Linkages Between			Tethering Increases the Local Concentration of a	
	Different Genes and Their Products	802		Ligand	884
	Developmental Decisions Are Made by Regulating Genes	802		Signaling Networks Help Cells Decide When and	884
	Gene Expression Is Measured Quantitatively in	802		Where to Grow Their Actin Filaments for Motility Synthetic Signaling Networks Permit a Dissection of	
	Terms of How Much, When, and Where	804		Signaling Pathways	885
	,			gg · a, -	000
19.2	GENETIC NETWORKS: DOING THE RIGHT THING AT		19.5	SUMMARY AND CONCLUSIONS	888
	THE RIGHT TIME	807	19.6	PROBLEMS	889
	Promoter Occupancy Is Dictated by the Presence of Regulatory Proteins Called Transcription		19.7	FURTHER READING	891
	Factors	808	19.8	REFERENCES	892
19.2.1	The Molecular Implementation of Regulation:				
	Promoters, Activators, and Repressors	808	Chap	ter 20 Biological Patterns: Order	
	Repressor Molecules Are the Proteins That		in Spa	ace and Time	893
	Implement Negative Control	808	in Spa 20.1	ace and Time INTRODUCTION: MAKING PATTERNS	893 893
	Implement Negative Control Activators Are the Proteins That Implement Positive		•	INTRODUCTION: MAKING PATTERNS	
	Implement Negative Control Activators Are the Proteins That Implement Positive Control	808 809	20.1 20.1.1	INTRODUCTION: MAKING PATTERNS	893
	Implement Negative Control Activators Are the Proteins That Implement Positive Control Genes Can Be Regulated During Processes Other	809	20.1 20.1.1 20.1.2	INTRODUCTION: MAKING PATTERNS Patterns in Space and Time Rules for Pattern-Making	893 894 895
19.2.2	Implement Negative Control Activators Are the Proteins That Implement Positive Control Genes Can Be Regulated During Processes Other Than Transcription	809 809	20.1 20.1.1 20.1.2 20.2	INTRODUCTION: MAKING PATTERNS Patterns in Space and Time Rules for Pattern-Making MORPHOGEN GRADIENTS	893 894 895 896
19.2.2	Implement Negative Control Activators Are the Proteins That Implement Positive Control Genes Can Be Regulated During Processes Other	809	20.1 20.1.1 20.1.2 20.2 20.2.1	INTRODUCTION: MAKING PATTERNS Patterns in Space and Time Rules for Pattern-Making MORPHOGEN GRADIENTS The French Flag Model	893 894 895 896 896
19.2.2	Implement Negative Control Activators Are the Proteins That Implement Positive Control Genes Can Be Regulated During Processes Other Than Transcription The Mathematics of Recruitment and Rejection Recruitment of Proteins Reflects Cooperativity Between Different DNA-Binding Proteins	809 809	20.1 20.1.1 20.1.2 20.2 20.2.1	INTRODUCTION: MAKING PATTERNS Patterns in Space and Time Rules for Pattern-Making MORPHOGEN GRADIENTS The French Flag Model How the Fly Got His Stripes	893 894 895 896
19.2.2	Implement Negative Control Activators Are the Proteins That Implement Positive Control Genes Can Be Regulated During Processes Other Than Transcription The Mathematics of Recruitment and Rejection Recruitment of Proteins Reflects Cooperativity Between Different DNA-Binding Proteins The Regulation Factor Dictates How the Bare RNA	809 809 810	20.1 20.1.1 20.1.2 20.2 20.2.1	INTRODUCTION: MAKING PATTERNS Patterns in Space and Time Rules for Pattern-Making MORPHOGEN GRADIENTS The French Flag Model How the Fly Got His Stripes Bicoid Exhibits an Exponential Concentration Gradient Along the Anterior-Posterior Axis of Fly	893 894 895 896 896 898
19.2.2	Implement Negative Control Activators Are the Proteins That Implement Positive Control Genes Can Be Regulated During Processes Other Than Transcription The Mathematics of Recruitment and Rejection Recruitment of Proteins Reflects Cooperativity Between Different DNA-Binding Proteins The Regulation Factor Dictates How the Bare RNA Polymerase Binding Probability Is Altered by	809 809 810 810	20.1 20.1.1 20.1.2 20.2 20.2.1	INTRODUCTION: MAKING PATTERNS Patterns in Space and Time Rules for Pattern-Making MORPHOGEN GRADIENTS The French Flag Model How the Fly Got His Stripes Bicoid Exhibits an Exponential Concentration Gradient Along the Anterior-Posterior Axis of Fly Embryos	893 894 895 896 896
19.2.2	Implement Negative Control Activators Are the Proteins That Implement Positive Control Genes Can Be Regulated During Processes Other Than Transcription The Mathematics of Recruitment and Rejection Recruitment of Proteins Reflects Cooperativity Between Different DNA-Binding Proteins The Regulation Factor Dictates How the Bare RNA Polymerase Binding Probability Is Altered by Transcription Factors	809 809 810	20.1 20.1.1 20.1.2 20.2 20.2.1	INTRODUCTION: MAKING PATTERNS Patterns in Space and Time Rules for Pattern-Making MORPHOGEN GRADIENTS The French Flag Model How the Fly Got His Stripes Bicoid Exhibits an Exponential Concentration Gradient Along the Anterior-Posterior Axis of Fly Embryos A Reaction-Diffusion Mechanism Can Give Rise to	893 894 895 896 898
19.2.2	Implement Negative Control Activators Are the Proteins That Implement Positive Control Genes Can Be Regulated During Processes Other Than Transcription The Mathematics of Recruitment and Rejection Recruitment of Proteins Reflects Cooperativity Between Different DNA-Binding Proteins The Regulation Factor Dictates How the Bare RNA Polymerase Binding Probability Is Altered by Transcription Factors Activator Bypass Experiments Show That Activators	809 809 810 810	20.1 20.1.1 20.1.2 20.2 20.2.1 20.2.2	INTRODUCTION: MAKING PATTERNS Patterns in Space and Time Rules for Pattern-Making MORPHOGEN GRADIENTS The French Flag Model How the Fly Got His Stripes Bicoid Exhibits an Exponential Concentration Gradient Along the Anterior-Posterior Axis of Fly Embryos A Reaction-Diffusion Mechanism Can Give Rise to an Exponential Concentration Gradient	893 894 895 896 898 898
19.2.2	Implement Negative Control Activators Are the Proteins That Implement Positive Control Genes Can Be Regulated During Processes Other Than Transcription The Mathematics of Recruitment and Rejection Recruitment of Proteins Reflects Cooperativity Between Different DNA-Binding Proteins The Regulation Factor Dictates How the Bare RNA Polymerase Binding Probability Is Altered by Transcription Factors Activator Bypass Experiments Show That Activators Work by Recruitment	809 809 810 810	20.1 20.1.1 20.1.2 20.2 20.2.1 20.2.2	INTRODUCTION: MAKING PATTERNS Patterns in Space and Time Rules for Pattern-Making MORPHOGEN GRADIENTS The French Flag Model How the Fly Got His Stripes Bicoid Exhibits an Exponential Concentration Gradient Along the Anterior-Posterior Axis of Fly Embryos A Reaction-Diffusion Mechanism Can Give Rise to an Exponential Concentration Gradient Precision and Scaling	893 894 895 896 898 898 899 905
19.2.2	Implement Negative Control Activators Are the Proteins That Implement Positive Control Genes Can Be Regulated During Processes Other Than Transcription The Mathematics of Recruitment and Rejection Recruitment of Proteins Reflects Cooperativity Between Different DNA-Binding Proteins The Regulation Factor Dictates How the Bare RNA Polymerase Binding Probability Is Altered by Transcription Factors Activator Bypass Experiments Show That Activators Work by Recruitment Repressor Molecules Reduce the Probability	809 809 810 810	20.1 20.1.1 20.1.2 20.2 20.2.1 20.2.2	INTRODUCTION: MAKING PATTERNS Patterns in Space and Time Rules for Pattern-Making MORPHOGEN GRADIENTS The French Flag Model How the Fly Got His Stripes Bicoid Exhibits an Exponential Concentration Gradient Along the Anterior-Posterior Axis of Fly Embryos A Reaction-Diffusion Mechanism Can Give Rise to an Exponential Concentration Gradient Precision and Scaling	893 894 895 896 898 898
19.2.2	Implement Negative Control Activators Are the Proteins That Implement Positive Control Genes Can Be Regulated During Processes Other Than Transcription The Mathematics of Recruitment and Rejection Recruitment of Proteins Reflects Cooperativity Between Different DNA-Binding Proteins The Regulation Factor Dictates How the Bare RNA Polymerase Binding Probability Is Altered by Transcription Factors Activator Bypass Experiments Show That Activators Work by Recruitment	809 809 810 810 812 813	20.1 20.1.1 20.1.2 20.2 20.2.1 20.2.2	INTRODUCTION: MAKING PATTERNS Patterns in Space and Time Rules for Pattern-Making MORPHOGEN GRADIENTS The French Flag Model How the Fly Got His Stripes Bicoid Exhibits an Exponential Concentration Gradient Along the Anterior-Posterior Axis of Fly Embryos A Reaction-Diffusion Mechanism Can Give Rise to an Exponential Concentration Gradient Precision and Scaling	893 894 895 896 898 898 899 905
	Implement Negative Control Activators Are the Proteins That Implement Positive Control Genes Can Be Regulated During Processes Other Than Transcription The Mathematics of Recruitment and Rejection Recruitment of Proteins Reflects Cooperativity Between Different DNA-Binding Proteins The Regulation Factor Dictates How the Bare RNA Polymerase Binding Probability Is Altered by Transcription Factors Activator Bypass Experiments Show That Activators Work by Recruitment Repressor Molecules Reduce the Probability Polymerase Will Bind to the Promoter Transcriptional Regulation by the Numbers: Binding Energies and Equilibrium Constants	809 809 810 810 812 813	20.1 20.1.1 20.1.2 20.2 20.2.1 20.2.2	INTRODUCTION: MAKING PATTERNS Patterns in Space and Time Rules for Pattern-Making MORPHOGEN GRADIENTS The French Flag Model How the Fly Got His Stripes Bicoid Exhibits an Exponential Concentration Gradient Along the Anterior-Posterior Axis of Fly Embryos A Reaction-Diffusion Mechanism Can Give Rise to an Exponential Concentration Gradient Precision and Scaling Morphogen Patterning with Growth in Anabaena	893 894 895 896 898 898 898 905 912
	Implement Negative Control Activators Are the Proteins That Implement Positive Control Genes Can Be Regulated During Processes Other Than Transcription The Mathematics of Recruitment and Rejection Recruitment of Proteins Reflects Cooperativity Between Different DNA-Binding Proteins The Regulation Factor Dictates How the Bare RNA Polymerase Binding Probability Is Altered by Transcription Factors Activator Bypass Experiments Show That Activators Work by Recruitment Repressor Molecules Reduce the Probability Polymerase Will Bind to the Promoter Transcriptional Regulation by the Numbers: Binding Energies and Equilibrium Constants Equilibrium Constants Can Be Used To Determine	809 809 810 810 812 813 814 819	20.1 20.1.1 20.1.2 20.2 20.2.1 20.2.2 20.2.3 20.2.4 20.3 20.3.1	INTRODUCTION: MAKING PATTERNS Patterns in Space and Time Rules for Pattern-Making MORPHOGEN GRADIENTS The French Flag Model How the Fly Got His Stripes Bicoid Exhibits an Exponential Concentration Gradient Along the Anterior-Posterior Axis of Fly Embryos A Reaction-Diffusion Mechanism Can Give Rise to an Exponential Concentration Gradient Precision and Scaling Morphogen Patterning with Growth in Anabaena REACTION-DIFFUSION AND SPATIAL PATTERNS Putting Chemistry and Diffusion Together: Turing Patterns	893 894 895 896 898 898 899 905 912 914
19.2.3	Implement Negative Control Activators Are the Proteins That Implement Positive Control Genes Can Be Regulated During Processes Other Than Transcription The Mathematics of Recruitment and Rejection Recruitment of Proteins Reflects Cooperativity Between Different DNA-Binding Proteins The Regulation Factor Dictates How the Bare RNA Polymerase Binding Probability Is Altered by Transcription Factors Activator Bypass Experiments Show That Activators Work by Recruitment Repressor Molecules Reduce the Probability Polymerase Will Bind to the Promoter Transcriptional Regulation by the Numbers: Binding Energies and Equilibrium Constants Equilibrium Constants Can Be Used To Determine Regulation Factors	809 809 810 810 812 813 814	20.1 20.1.1 20.1.2 20.2 20.2.1 20.2.2 20.2.3 20.2.4 20.3 20.3.1 20.3.2	INTRODUCTION: MAKING PATTERNS Patterns in Space and Time Rules for Pattern-Making MORPHOGEN GRADIENTS The French Flag Model How the Fly Got His Stripes Bicoid Exhibits an Exponential Concentration Gradient Along the Anterior-Posterior Axis of Fly Embryos A Reaction-Diffusion Mechanism Can Give Rise to an Exponential Concentration Gradient Precision and Scaling Morphogen Patterning with Growth in Anabaena REACTION-DIFFUSION AND SPATIAL PATTERNS Putting Chemistry and Diffusion Together: Turing Patterns How Bacteria Lay Down a Coordinate System	893 894 895 896 898 898 899 905 912 914 914 920
	Implement Negative Control Activators Are the Proteins That Implement Positive Control Genes Can Be Regulated During Processes Other Than Transcription The Mathematics of Recruitment and Rejection Recruitment of Proteins Reflects Cooperativity Between Different DNA-Binding Proteins The Regulation Factor Dictates How the Bare RNA Polymerase Binding Probability Is Altered by Transcription Factors Activator Bypass Experiments Show That Activators Work by Recruitment Repressor Molecules Reduce the Probability Polymerase Will Bind to the Promoter Transcriptional Regulation by the Numbers: Binding Energies and Equilibrium Constants Equilibrium Constants Can Be Used To Determine Regulation Factors A Simple Statistical Mechanical Model of Positive	809 809 810 810 812 813 814 819	20.1 20.1.1 20.1.2 20.2 20.2.1 20.2.2 20.2.3 20.2.4 20.3 20.3.1	INTRODUCTION: MAKING PATTERNS Patterns in Space and Time Rules for Pattern-Making MORPHOGEN GRADIENTS The French Flag Model How the Fly Got His Stripes Bicoid Exhibits an Exponential Concentration Gradient Along the Anterior-Posterior Axis of Fly Embryos A Reaction-Diffusion Mechanism Can Give Rise to an Exponential Concentration Gradient Precision and Scaling Morphogen Patterning with Growth in Anabaena REACTION-DIFFUSION AND SPATIAL PATTERNS Putting Chemistry and Diffusion Together: Turing Patterns How Bacteria Lay Down a Coordinate System	893 894 895 896 898 898 899 905 912 914
19.2.3	Implement Negative Control Activators Are the Proteins That Implement Positive Control Genes Can Be Regulated During Processes Other Than Transcription The Mathematics of Recruitment and Rejection Recruitment of Proteins Reflects Cooperativity Between Different DNA-Binding Proteins The Regulation Factor Dictates How the Bare RNA Polymerase Binding Probability Is Altered by Transcription Factors Activator Bypass Experiments Show That Activators Work by Recruitment Repressor Molecules Reduce the Probability Polymerase Will Bind to the Promoter Transcriptional Regulation by the Numbers: Binding Energies and Equilibrium Constants Equilibrium Constants Can Be Used To Determine Regulation Factors A Simple Statistical Mechanical Model of Positive and Negative Regulation	809 809 810 810 812 813 814 819 819	20.1 20.1.1 20.1.2 20.2 20.2.1 20.2.2 20.2.3 20.2.4 20.3 20.3.1 20.3.2	INTRODUCTION: MAKING PATTERNS Patterns in Space and Time Rules for Pattern-Making MORPHOGEN GRADIENTS The French Flag Model How the Fly Got His Stripes Bicoid Exhibits an Exponential Concentration Gradient Along the Anterior-Posterior Axis of Fly Embryos A Reaction-Diffusion Mechanism Can Give Rise to an Exponential Concentration Gradient Precision and Scaling Morphogen Patterning with Growth in Anabaena REACTION-DIFFUSION AND SPATIAL PATTERNS Putting Chemistry and Diffusion Together: Turing Patterns How Bacteria Lay Down a Coordinate System Phyllotaxis: The Art of Flower Arrangement	893 894 895 896 898 898 899 905 912 914 914 920
19.2.3	Implement Negative Control Activators Are the Proteins That Implement Positive Control Genes Can Be Regulated During Processes Other Than Transcription The Mathematics of Recruitment and Rejection Recruitment of Proteins Reflects Cooperativity Between Different DNA-Binding Proteins The Regulation Factor Dictates How the Bare RNA Polymerase Binding Probability Is Altered by Transcription Factors Activator Bypass Experiments Show That Activators Work by Recruitment Repressor Molecules Reduce the Probability Polymerase Will Bind to the Promoter Transcriptional Regulation by the Numbers: Binding Energies and Equilibrium Constants Equilibrium Constants Can Be Used To Determine Regulation Factors A Simple Statistical Mechanical Model of Positive and Negative Regulation The <i>lac</i> Operon	809 809 810 810 812 813 814 819	20.1 20.1.1 20.1.2 20.2 20.2.1 20.2.2 20.2.3 20.2.4 20.3 20.3.1 20.3.2 20.3.3	INTRODUCTION: MAKING PATTERNS Patterns in Space and Time Rules for Pattern-Making MORPHOGEN GRADIENTS The French Flag Model How the Fly Got His Stripes Bicoid Exhibits an Exponential Concentration Gradient Along the Anterior-Posterior Axis of Fly Embryos A Reaction-Diffusion Mechanism Can Give Rise to an Exponential Concentration Gradient Precision and Scaling Morphogen Patterning with Growth in Anabaena REACTION-DIFFUSION AND SPATIAL PATTERNS Putting Chemistry and Diffusion Together: Turing Patterns How Bacteria Lay Down a Coordinate System	893 894 895 896 898 898 899 905 912 914 914 920
19.2.3	Implement Negative Control Activators Are the Proteins That Implement Positive Control Genes Can Be Regulated During Processes Other Than Transcription The Mathematics of Recruitment and Rejection Recruitment of Proteins Reflects Cooperativity Between Different DNA-Binding Proteins The Regulation Factor Dictates How the Bare RNA Polymerase Binding Probability Is Altered by Transcription Factors Activator Bypass Experiments Show That Activators Work by Recruitment Repressor Molecules Reduce the Probability Polymerase Will Bind to the Promoter Transcriptional Regulation by the Numbers: Binding Energies and Equilibrium Constants Equilibrium Constants Can Be Used To Determine Regulation Factors A Simple Statistical Mechanical Model of Positive and Negative Regulation	809 809 810 810 812 813 814 819 819	20.1 20.1.1 20.1.2 20.2 20.2.1 20.2.2 20.2.3 20.2.4 20.3 20.3.1 20.3.2 20.3.3 20.4 20.4.1	INTRODUCTION: MAKING PATTERNS Patterns in Space and Time Rules for Pattern-Making MORPHOGEN GRADIENTS The French Flag Model How the Fly Got His Stripes Bicoid Exhibits an Exponential Concentration Gradient Along the Anterior-Posterior Axis of Fly Embryos A Reaction-Diffusion Mechanism Can Give Rise to an Exponential Concentration Gradient Precision and Scaling Morphogen Patterning with Growth in Anabaena REACTION-DIFFUSION AND SPATIAL PATTERNS Putting Chemistry and Diffusion Together: Turing Patterns How Bacteria Lay Down a Coordinate System Phyllotaxis: The Art of Flower Arrangement TURNING TIME INTO SPACE: TEMPORAL OSCILLATIONS IN CELL FATE SPECIFICATION Somitogenesis	893 894 895 896 896 898 898 899 905 912 914 914 926
19.2.3	Implement Negative Control Activators Are the Proteins That Implement Positive Control Genes Can Be Regulated During Processes Other Than Transcription The Mathematics of Recruitment and Rejection Recruitment of Proteins Reflects Cooperativity Between Different DNA-Binding Proteins The Regulation Factor Dictates How the Bare RNA Polymerase Binding Probability Is Altered by Transcription Factors Activator Bypass Experiments Show That Activators Work by Recruitment Repressor Molecules Reduce the Probability Polymerase Will Bind to the Promoter Transcriptional Regulation by the Numbers: Binding Energies and Equilibrium Constants Equilibrium Constants Can Be Used To Determine Regulation Factors A Simple Statistical Mechanical Model of Positive and Negative Regulation The Iac Operon The Iac Operon Has Features of Both Negative and Positive Regulation The Free Energy of DNA Looping Affects the	809 809 810 810 812 813 814 819 819 820 822	20.1 20.1.1 20.1.2 20.2 20.2.1 20.2.2 20.2.3 20.2.4 20.3 20.3.1 20.3.2 20.3.3	INTRODUCTION: MAKING PATTERNS Patterns in Space and Time Rules for Pattern-Making MORPHOGEN GRADIENTS The French Flag Model How the Fly Got His Stripes Bicoid Exhibits an Exponential Concentration Gradient Along the Anterior-Posterior Axis of Fly Embryos A Reaction-Diffusion Mechanism Can Give Rise to an Exponential Concentration Gradient Precision and Scaling Morphogen Patterning with Growth in Anabaena REACTION-DIFFUSION AND SPATIAL PATTERNS Putting Chemistry and Diffusion Together: Turing Patterns How Bacteria Lay Down a Coordinate System Phyllotaxis: The Art of Flower Arrangement TURNING TIME INTO SPACE: TEMPORAL OSCILLATIONS IN CELL FATE SPECIFICATION Somitogenesis	893 894 895 896 896 898 898 899 905 912 914 914 926
19.2.3	Implement Negative Control Activators Are the Proteins That Implement Positive Control Genes Can Be Regulated During Processes Other Than Transcription The Mathematics of Recruitment and Rejection Recruitment of Proteins Reflects Cooperativity Between Different DNA-Binding Proteins The Regulation Factor Dictates How the Bare RNA Polymerase Binding Probability Is Altered by Transcription Factors Activator Bypass Experiments Show That Activators Work by Recruitment Repressor Molecules Reduce the Probability Polymerase Will Bind to the Promoter Transcriptional Regulation by the Numbers: Binding Energies and Equilibrium Constants Equilibrium Constants Can Be Used To Determine Regulation Factors A Simple Statistical Mechanical Model of Positive and Negative Regulation The Iac Operon The Iac Operon Has Features of Both Negative and Positive Regulation The Free Energy of DNA Looping Affects the Repression of the Iac Operon	809 809 810 810 812 813 814 819 819 820 822 822	20.1 20.1.1 20.1.2 20.2 20.2.1 20.2.2 20.2.3 20.2.4 20.3 20.3.1 20.3.2 20.3.3 20.4 20.4.1 20.4.2	INTRODUCTION: MAKING PATTERNS Patterns in Space and Time Rules for Pattern-Making MORPHOGEN GRADIENTS The French Flag Model How the Fly Got His Stripes Bicoid Exhibits an Exponential Concentration Gradient Along the Anterior-Posterior Axis of Fly Embryos A Reaction-Diffusion Mechanism Can Give Rise to an Exponential Concentration Gradient Precision and Scaling Morphogen Patterning with Growth in Anabaena REACTION-DIFFUSION AND SPATIAL PATTERNS Putting Chemistry and Diffusion Together: Turing Patterns How Bacteria Lay Down a Coordinate System Phyllotaxis: The Art of Flower Arrangement TURNING TIME INTO SPACE: TEMPORAL OSCILLATIONS IN CELL FATE SPECIFICATION Somitogenesis Seashells Forming Patterns in Space and Time	893 894 895 896 898 898 899 905 912 914 920 926
19.2.3 19.2.4 19.2.5	Implement Negative Control Activators Are the Proteins That Implement Positive Control Genes Can Be Regulated During Processes Other Than Transcription The Mathematics of Recruitment and Rejection Recruitment of Proteins Reflects Cooperativity Between Different DNA-Binding Proteins The Regulation Factor Dictates How the Bare RNA Polymerase Binding Probability Is Altered by Transcription Factors Activator Bypass Experiments Show That Activators Work by Recruitment Repressor Molecules Reduce the Probability Polymerase Will Bind to the Promoter Transcriptional Regulation by the Numbers: Binding Energies and Equilibrium Constants Equilibrium Constants Can Be Used To Determine Regulation Factors A Simple Statistical Mechanical Model of Positive and Negative Regulation The Iac Operon The Iac Operon Has Features of Both Negative and Positive Regulation The Free Energy of DNA Looping Affects the Repression of the Iac Operon Inducers Tune the Level of Regulatory Response	809 809 810 810 812 813 814 819 819 820 822 822 824 829	20.1 20.1.1 20.1.2 20.2 20.2.1 20.2.2 20.2.3 20.2.4 20.3 20.3.1 20.3.2 20.3.3 20.4 20.4.1	INTRODUCTION: MAKING PATTERNS Patterns in Space and Time Rules for Pattern-Making MORPHOGEN GRADIENTS The French Flag Model How the Fly Got His Stripes Bicoid Exhibits an Exponential Concentration Gradient Along the Anterior-Posterior Axis of Fly Embryos A Reaction-Diffusion Mechanism Can Give Rise to an Exponential Concentration Gradient Precision and Scaling Morphogen Patterning with Growth in Anabaena REACTION-DIFFUSION AND SPATIAL PATTERNS Putting Chemistry and Diffusion Together: Turing Patterns How Bacteria Lay Down a Coordinate System Phyllotaxis: The Art of Flower Arrangement TURNING TIME INTO SPACE: TEMPORAL OSCILLATIONS IN CELL FATE SPECIFICATION Somitogenesis Seashells Forming Patterns in Space and Time	893 894 895 896 898 898 899 905 912 914 914 920 926 931 932 935
19.2.3	Implement Negative Control Activators Are the Proteins That Implement Positive Control Genes Can Be Regulated During Processes Other Than Transcription The Mathematics of Recruitment and Rejection Recruitment of Proteins Reflects Cooperativity Between Different DNA-Binding Proteins The Regulation Factor Dictates How the Bare RNA Polymerase Binding Probability Is Altered by Transcription Factors Activator Bypass Experiments Show That Activators Work by Recruitment Repressor Molecules Reduce the Probability Polymerase Will Bind to the Promoter Transcriptional Regulation by the Numbers: Binding Energies and Equilibrium Constants Equilibrium Constants Can Be Used To Determine Regulation Factors A Simple Statistical Mechanical Model of Positive and Negative Regulation The Iac Operon The Iac Operon Has Features of Both Negative and Positive Regulation The Free Energy of DNA Looping Affects the Repression of the Iac Operon Inducers Tune the Level of Regulatory Response Other Regulatory Architectures	809 809 810 810 812 813 814 819 819 820 822 822	20.1.1 20.1.2 20.2 20.2.1 20.2.2 20.2.3 20.2.4 20.3 20.3.1 20.3.2 20.3.3 20.4 20.4.1 20.4.2	INTRODUCTION: MAKING PATTERNS Patterns in Space and Time Rules for Pattern-Making MORPHOGEN GRADIENTS The French Flag Model How the Fly Got His Stripes Bicoid Exhibits an Exponential Concentration Gradient Along the Anterior-Posterior Axis of Fly Embryos A Reaction-Diffusion Mechanism Can Give Rise to an Exponential Concentration Gradient Precision and Scaling Morphogen Patterning with Growth in Anabaena REACTION-DIFFUSION AND SPATIAL PATTERNS Putting Chemistry and Diffusion Together: Turing Patterns How Bacteria Lay Down a Coordinate System Phyllotaxis: The Art of Flower Arrangement TURNING TIME INTO SPACE: TEMPORAL OSCILLATIONS IN CELL FATE SPECIFICATION Somitogenesis Seashells Forming Patterns in Space and Time PATTERN FORMATION AS A CONTACT SPORT The Notch-Delta Concept	893 894 895 896 898 898 899 905 912 914 920 926
19.2.3 19.2.4 19.2.5	Implement Negative Control Activators Are the Proteins That Implement Positive Control Genes Can Be Regulated During Processes Other Than Transcription The Mathematics of Recruitment and Rejection Recruitment of Proteins Reflects Cooperativity Between Different DNA-Binding Proteins The Regulation Factor Dictates How the Bare RNA Polymerase Binding Probability Is Altered by Transcription Factors Activator Bypass Experiments Show That Activators Work by Recruitment Repressor Molecules Reduce the Probability Polymerase Will Bind to the Promoter Transcriptional Regulation by the Numbers: Binding Energies and Equilibrium Constants Equilibrium Constants Can Be Used To Determine Regulation Factors A Simple Statistical Mechanical Model of Positive and Negative Regulation The <i>lac</i> Operon The <i>lac</i> Operon Has Features of Both Negative and Positive Regulation The Free Energy of DNA Looping Affects the Repression of the <i>lac</i> Operon Inducers Tune the Level of Regulatory Response Other Regulatory Architectures The Fold-Change for Different Regulatory Motifs	809 809 810 810 812 813 814 819 819 820 822 822 824 829	20.1 20.1.1 20.1.2 20.2 20.2.1 20.2.2 20.2.3 20.2.4 20.3 20.3.1 20.3.2 20.3.3 20.4 20.4.1 20.4.2 20.5 20.5.1 20.5.2	INTRODUCTION: MAKING PATTERNS Patterns in Space and Time Rules for Pattern-Making MORPHOGEN GRADIENTS The French Flag Model How the Fly Got His Stripes Bicoid Exhibits an Exponential Concentration Gradient Along the Anterior-Posterior Axis of Fly Embryos A Reaction-Diffusion Mechanism Can Give Rise to an Exponential Concentration Gradient Precision and Scaling Morphogen Patterning with Growth in Anabaena REACTION-DIFFUSION AND SPATIAL PATTERNS Putting Chemistry and Diffusion Together: Turing Patterns How Bacteria Lay Down a Coordinate System Phyllotaxis: The Art of Flower Arrangement TURNING TIME INTO SPACE: TEMPORAL OSCILLATIONS IN CELL FATE SPECIFICATION Somitogenesis Seashells Forming Patterns in Space and Time PATTERN FORMATION AS A CONTACT SPORT The Notch-Delta Concept Drosophila Eyes	893 894 895 896 898 898 899 905 912 914 920 926 931 932 935 939 944
19.2.3 19.2.4 19.2.5	Implement Negative Control Activators Are the Proteins That Implement Positive Control Genes Can Be Regulated During Processes Other Than Transcription The Mathematics of Recruitment and Rejection Recruitment of Proteins Reflects Cooperativity Between Different DNA-Binding Proteins The Regulation Factor Dictates How the Bare RNA Polymerase Binding Probability Is Altered by Transcription Factors Activator Bypass Experiments Show That Activators Work by Recruitment Repressor Molecules Reduce the Probability Polymerase Will Bind to the Promoter Transcriptional Regulation by the Numbers: Binding Energies and Equilibrium Constants Equilibrium Constants Can Be Used To Determine Regulation Factors A Simple Statistical Mechanical Model of Positive and Negative Regulation The Iac Operon The Iac Operon Has Features of Both Negative and Positive Regulation The Free Energy of DNA Looping Affects the Repression of the Iac Operon Inducers Tune the Level of Regulatory Response Other Regulatory Architectures	809 809 810 810 812 813 814 819 819 820 822 822 824 829	20.1 20.1.1 20.1.2 20.2 20.2.1 20.2.2 20.2.3 20.2.4 20.3 20.3.1 20.3.2 20.3.3 20.4 20.4.1 20.4.2 20.5 20.5.1 20.5.2	INTRODUCTION: MAKING PATTERNS Patterns in Space and Time Rules for Pattern-Making MORPHOGEN GRADIENTS The French Flag Model How the Fly Got His Stripes Bicoid Exhibits an Exponential Concentration Gradient Along the Anterior-Posterior Axis of Fly Embryos A Reaction-Diffusion Mechanism Can Give Rise to an Exponential Concentration Gradient Precision and Scaling Morphogen Patterning with Growth in Anabaena REACTION-DIFFUSION AND SPATIAL PATTERNS Putting Chemistry and Diffusion Together: Turing Patterns How Bacteria Lay Down a Coordinate System Phyllotaxis: The Art of Flower Arrangement TURNING TIME INTO SPACE: TEMPORAL OSCILLATIONS IN CELL FATE SPECIFICATION Somitogenesis Seashells Forming Patterns in Space and Time PATTERN FORMATION AS A CONTACT SPORT The Notch-Delta Concept Drosophila Eyes SUMMARY AND CONCLUSIONS	893 894 895 896 898 898 899 905 912 914 920 926 931 932 935 939 944 947
19.2.3 19.2.4 19.2.5	Implement Negative Control Activators Are the Proteins That Implement Positive Control Genes Can Be Regulated During Processes Other Than Transcription The Mathematics of Recruitment and Rejection Recruitment of Proteins Reflects Cooperativity Between Different DNA-Binding Proteins The Regulation Factor Dictates How the Bare RNA Polymerase Binding Probability Is Altered by Transcription Factors Activator Bypass Experiments Show That Activators Work by Recruitment Repressor Molecules Reduce the Probability Polymerase Will Bind to the Promoter Transcriptional Regulation by the Numbers: Binding Energies and Equilibrium Constants Equilibrium Constants Can Be Used To Determine Regulation Factors A Simple Statistical Mechanical Model of Positive and Negative Regulation The Iac Operon The Iac Operon Has Features of Both Negative and Positive Regulation The Free Energy of DNA Looping Affects the Repression of the Iac Operon Inducers Tune the Level of Regulatory Response Other Regulatory Architectures The Fold-Change for Different Regulatory Motifs Depends Upon Experimentally Accessible Control	809 809 810 810 812 813 814 819 820 822 822 824 829 829	20.1 20.1.1 20.1.2 20.2 20.2.1 20.2.2 20.2.3 20.2.4 20.3 20.3.1 20.3.2 20.3.3 20.4 20.4.1 20.4.2 20.5 20.5.1 20.5.2 20.6 20.7	INTRODUCTION: MAKING PATTERNS Patterns in Space and Time Rules for Pattern-Making MORPHOGEN GRADIENTS The French Flag Model How the Fly Got His Stripes Bicoid Exhibits an Exponential Concentration Gradient Along the Anterior-Posterior Axis of Fly Embryos A Reaction-Diffusion Mechanism Can Give Rise to an Exponential Concentration Gradient Precision and Scaling Morphogen Patterning with Growth in Anabaena REACTION-DIFFUSION AND SPATIAL PATTERNS Putting Chemistry and Diffusion Together: Turing Patterns How Bacteria Lay Down a Coordinate System Phyllotaxis: The Art of Flower Arrangement TURNING TIME INTO SPACE: TEMPORAL OSCILLATIONS IN CELL FATE SPECIFICATION Somitogenesis Seashells Forming Patterns in Space and Time PATTERN FORMATION AS A CONTACT SPORT The Notch-Delta Concept Drosophila Eyes SUMMARY AND CONCLUSIONS PROBLEMS	893 894 895 896 898 898 898 899 905 912 914 920 926 931 932 935 939 944 947 948
19.2.3 19.2.4 19.2.5	Implement Negative Control Activators Are the Proteins That Implement Positive Control Genes Can Be Regulated During Processes Other Than Transcription The Mathematics of Recruitment and Rejection Recruitment of Proteins Reflects Cooperativity Between Different DNA-Binding Proteins The Regulation Factor Dictates How the Bare RNA Polymerase Binding Probability Is Altered by Transcription Factors Activator Bypass Experiments Show That Activators Work by Recruitment Repressor Molecules Reduce the Probability Polymerase Will Bind to the Promoter Transcriptional Regulation by the Numbers: Binding Energies and Equilibrium Constants Equilibrium Constants Can Be Used To Determine Regulation Factors A Simple Statistical Mechanical Model of Positive and Negative Regulation The <i>lac</i> Operon The <i>lac</i> Operon Has Features of Both Negative and Positive Regulation The Free Energy of DNA Looping Affects the Repression of the <i>lac</i> Operon Inducers Tune the Level of Regulatory Response Other Regulatory Architectures The Fold-Change for Different Regulatory Motifs Depends Upon Experimentally Accessible Control Parameters	809 809 810 810 812 813 814 819 820 822 822 824 829 829	20.1 20.1.1 20.1.2 20.2 20.2.1 20.2.2 20.2.3 20.2.4 20.3 20.3.1 20.3.2 20.3.3 20.4 20.4.1 20.4.2 20.5 20.5.1 20.5.2	INTRODUCTION: MAKING PATTERNS Patterns in Space and Time Rules for Pattern-Making MORPHOGEN GRADIENTS The French Flag Model How the Fly Got His Stripes Bicoid Exhibits an Exponential Concentration Gradient Along the Anterior-Posterior Axis of Fly Embryos A Reaction-Diffusion Mechanism Can Give Rise to an Exponential Concentration Gradient Precision and Scaling Morphogen Patterning with Growth in Anabaena REACTION-DIFFUSION AND SPATIAL PATTERNS Putting Chemistry and Diffusion Together: Turing Patterns How Bacteria Lay Down a Coordinate System Phyllotaxis: The Art of Flower Arrangement TURNING TIME INTO SPACE: TEMPORAL OSCILLATIONS IN CELL FATE SPECIFICATION Somitogenesis Seashells Forming Patterns in Space and Time PATTERN FORMATION AS A CONTACT SPORT The Notch-Delta Concept Drosophila Eyes SUMMARY AND CONCLUSIONS	893 894 895 896 898 898 899 905 912 914 920 926 931 932 935 939 944 947

	er 21 Sequences, Specificity, volution	951		Evolution and Drug Resistance Viruses and Evolution The Court of Court of Advance it Rescribes to Trace	998 1000
21.1 21.1.1	BIOLOGICAL INFORMATION Why Sequences?	952 953		The Study of Sequence Makes It Possible to Trace the Evolutionary History of HIV The Luria-Delbrück Experiment Reveals the	1001
21.1.2	Genomes and Sequences by the Numbers	957		Mathematics of Resistance	1002
21.2	SEQUENCE ALIGNMENT AND HOMOLOGY	960	21.4.4	Phylogenetic Trees	1008
	Sequence Comparison Can Sometimes Reveal Deep Functional and Evolutionary Relationships Between	961	21.5 21.5.1	THE MOLECULAR BASIS OF FIDELITY Keeping It Specific: Beating Thermodynamic	1010
21.2.1	Genes, Proteins, and Organisms The HP Model as a Coarse-Grained Model for Bioinformatics	964		Specificity The Specificity of Biological Recognition Often Far	1011
21.2.2	Scoring Success	966		Exceeds the Limit Dictated by Free-Energy Differences	1011
,,,,	A Score Can Be Assigned to Different Alignments Between Sequences	966		High Specificity Costs Energy	1015
	Comparison of Full Amino Acid Sequences Requires		21.6	SUMMARY AND CONCLUSIONS	1016
	a 20-by-20 Scoring Matrix	968	21.7	PROBLEMS	1017
	Even Random Sequences Have a Nonzero Score	970	21.8	FURTHER READING	1020
	The Extreme Value Distribution Determines the Probability That a Given Alignment Score Would Be Found by Chance	971	21.9	REFERENCES	1021
	False Positives Increase as the Threshold for		61		1023
	Acceptable Expect Values (also Called E-Values) Is Made Less Stringent	973	_	ter 22 Whither Physical Biology?	
	Structural and Functional Similarity Do Not Always	9/3	22.1	DRAWING THE MAP TO SCALE	1023
	Guarantee Sequence Similarity	976	22.2	NAVIGATING WHEN THE MAP IS WRONG	1027
21.3 21.3.1	THE POWER OF SEQUENCE GAZING Binding Probabilities and Sequence	976 977	22.3	INCREASING THE MAP RESOLUTION	1028
21.5.1	Position Weight Matrices Provide a Map Between	3//	22.4	"DIFFICULTIES ON THEORY"	1030
	Sequence and Binding Affinity	978		Modeler's Fantasy	1031
	Frequencies of Nucleotides at Sites Within a			Is It Biologically Interesting?	1031
	Sequence Can Be Used to Construct Position Weight			Uses and Abuses of Statistical Mechanics	1032
	Matrices	979		Out-of-Equilibrium and Dynamic	1032
	Using Sequence to Find Binding Sites	983		Uses and Abuses of Continuum Mechanics	1032
21.3.3	Do Nucleosomes Care About Their Positions on Genomes?	000		Too Many Parameters	1033
	DNA Sequencing Reveals Patterns of Nucleosome	988		Missing Facts	1033
	Occupancy on Genomes	989		Too Much Stuff	1033
	A Simple Model Based Upon Self-Avoidance Leads to			Too Little Stuff	1034
	a Prediction for Nucleosome Positioning	990		The Myth of "THE" Cell	1034
	-	330		Not Enough Thinking	1035
21.4	SEQUENCES AND EVOLUTION	993			
21.4.1	Evolution by the Numbers: Hemoglobin and		22.5	THE RHYME AND REASON OF IT ALL	1035
	Rhodopsin as Case Studies in Sequence Alignment	994	22.6	FURTHER READING	1036
	Sequence Similarity Is Used as a Temporal Yardstick to Determine Evolutionary Distances Modern-Day Sequences Can Be Used to Reconstruct	994	22.7	REFERENCES	1037
	the Past	996	Index		1039