

Contents

Preface	xvii
Acknowledgments	xxi
Authors	xxiii

PART I Introduction, Approach, and Tools

1	Introduction to a New World	3
1.1	Biophysics and Genetic Engineering	3
1.2	Biological and Nonliving Worlds Contrasted	4
1.3	Hierarchical Structure and Function	9
1.4	Some Important Quantities to Get Started	12
1.5	Biophysics and Biochemistry Operate in Water (Water 1)	14
1.6	Important or "Hot" Issues in Biophysics, or How to Be Out-of-Date Quickly	16
1.7	Read Appendix A	17
1.8	Problem-Solving	18
	References	21
2	How (Most) Physicists Approach Biophysics	23
2.1	Dealing with Nonspherical Cows: Drive for Simplicity	23
2.2	Two Approaches to Biosystems	24
2.2.1	Approach 1: Use Principles to Explain and Predict the Phenomena	24
2.2.2	Approach 2: Describe the System as Completely as Possible and Infer the Organizing Principles	24
2.3	Comparison of "Physics" and "Biology" Approaches to Organism 1.2e	25
2.3.1	Approach 1	25
2.3.2	Approach 2	26
2.4	Memorization: Its Advantages and Dangers	26
2.5	Problem-Solving	27
	References	31
3	Math Tools: First Pass	33
3.1	What Math Do We Need?	33
3.2	Notation: Mathematics versus Physics Notations	33
3.2.1	Derivatives and Differentials	33
3.3	Approximations	33
3.3.1	Complexity: Approximations That Eliminate the "Butterfly Effect"	33
3.3.2	Experimental: Ignoring Chemical Components in the Biosystem	34
3.3.3	Mathematical: Approximations to Biological Structure and Dynamics	35
3.3.3.1	Expansions: Taylor Series	35
3.3.3.2	Example 1: Oscillation in an Asymmetric Potential Well	35
3.3.3.3	Example 2: Small Angles	38
3.3.3.4	Example 3: Exponentials	38

3.3.4	Approximations in Differential Equations	39
3.3.4.1	Small and Large: Compared to What?	39
3.3.4.2	Short Time	40
3.3.4.3	Long Time	40
3.4	Vectors	41
3.5	Two- and Three-Dimensional Geometry	41
3.5.1	Rectangular Coordinates: $\vec{r}$, or (x, y, z)	42
3.5.2	Cylindrical Coordinates	42
3.5.3	Spherical Coordinates	43
3.6	Calculus	43
3.6.1	Drawing Diagrams That Help You Do the Math	44
3.6.2	Differentials in Two and Three Dimensions	45
3.6.3	Derivatives and Partial Derivatives	46
3.6.4	Change of Variables and Jacobians	47
3.7	Differential Equations	48
3.7.1	First Order, Linear	48
3.7.2	First Order, Nonlinear (but Not the Most General Nonlinear)	49
3.7.3	Second Order, Linear	50
3.7.4	Boundary (Spatial) and Initial (Time) Conditions	51
3.7.5	Sketching and Guessing Solutions	51
3.7.6	Steady State and Equilibrium	52
3.8	Distributions	53
3.8.1	Large Populations and Single Particles	53
3.8.2	Intrinsic versus Measured Probabilities	54
3.8.3	Discrete Distributions: Averages and Deviations	54
3.8.4	Continuous Distributions	55
3.8.5	Distribution Functions	56
3.8.5.1	Uniform	56
3.8.5.2	Binomial	56
3.8.5.3	Gaussian	57
3.8.5.4	Poisson	58
3.8.5.5	Maxwell-Boltzmann Velocity Distribution	59
3.8.5.6	From Velocity, to Speed, to Momentum, to Kinetic Energy Distributions	59
3.9	Problem-Solving	59
	References	63

PART II Structure and Function

4	Water	67
4.1	Introduction	67
4.2	Structure	67
4.2.1	Molecular Structure	68
4.2.2	Water: Liquid and Solid	68
4.2.2.1	Solid Water (Ice)	69
4.2.2.2	Liquid Water Experiments	69
4.2.2.3	Fluctuating Structure	71

4.3	Unusual Physical Properties	71
4.3.1	Macroscopic Flow Properties: Viscosity	71
4.3.2	Heat Storage: Specific Heat c	72
4.3.3	Heat Conduction: Thermal Conductivity	72
4.3.4	Phase Changes of Water	74
4.3.5	Water Has a High Surface Tension	75
4.3.6	Surface Tension: Viscosity Ratio	76
4.3.7	Dielectric Properties	76
4.4	Summary of Important Physical Properties	78
4.5	Bulk versus Local Structures	78
4.5.1	Cytoskeleton Fills and Organizes the Interior of Eukaryotic Cells	79
4.5.2	"Bound" Water Molecules	80
4.6	Diffusion and Chemical Reactions in Water	82
4.7	Solutes and the Solvent Power of Water	82
4.7.1	Solubility in Water	83
4.7.2	Water Ionization	83
4.8	Points to Remember	84
4.9	Problem-Solving	84
	References	88
5	Structures: From 0.1 to 10 nm and Larger	91
5.1	Software to Display and Analyze Biological Structures	92
5.2	Solvents	94
5.3	Small Molecules	95
5.3.1	Important Ions	95
5.3.1.1	Counterions	95
5.3.1.2	Ionic Equilibrium	97
5.3.2	Carriers of Energy and Genetic Information: Nucleotides	97
5.3.3	Carriers of Energy and Electron-Donating Capability: NADH and NADPH	98
5.4	Medium-Sized Molecules: Components of Large Biomolecules	100
5.4.1	Ringlike Structures and Delocalized Electrons: Prosthetic Groups and Catalysis	100
5.4.1.1	Heme	100
5.4.1.2	Characteristics Common to Heme and Chlorophyll	101
5.4.1.3	Chlorophyll	102
5.4.2	Multipurpose Molecules: Building Blocks, Energy Carriers, Control/Signaling Molecules	102
5.4.2.1	Amino Acids	102
5.4.2.2	Nucleotides	104
5.4.2.3	Sugars	105
5.5	Forces and Free Energies	106
5.6	Biopolymers	108
5.6.1	Proteins	108
5.6.1.1	Polypeptides	110
5.6.1.2	Structural Rules and Protein Folding	111
5.6.1.3	Alpha and Other Helices	115
5.6.1.4	Interactions that Govern Protein Structure	116
5.6.1.5	β Sheet	122

5.6.2	Hints of Function: Structural vs. Catalytic Proteins	123
5.6.2.1	Fibrous Proteins	123
5.6.2.2	Globular Proteins and Active Sites	125
5.6.3	Polynucleotides	129
5.6.3.1	DNA: Deoxyribonucleic Acids	130
5.6.3.2	RNA: Ribonucleic Acids and Folding	135
5.6.3.3	What Is a "Random Coil"?	139
5.6.4	Carbohydrates and Saccharides	140
5.6.5	Membranes	141
5.7	Macromolecules: When Does a Molecule Become a Macroscopic Object?	141
5.7.1	Visible to the Naked Eye?	141
5.7.2	Optical Resolution	142
5.7.3	Quantum versus Classical Behavior	142
5.7.4	Surface Atoms/Bulk Atoms	143
5.7.5	Energies Compared to $k_B T$	143
5.7.6	Gravitational Energy	144
5.7.7	Statistical Measures of "Large" Numbers of Particles	144
5.8	Points to Remember	145
5.9	Problem-Solving	145
	References	152
6	First Pass at Supramolecular Structures: Assemblies of Biomolecules	157
6.1	Measuring Properties of Three-Dimensional Aggregates	157
6.1.1	Sedimentation Coefficient	158
6.1.2	Separating Subunits of Small Aggregates: Chromatography	158
6.1.2.1	Affinity Chromatography	160
6.1.2.2	Competitive Binding	163
6.2	Small Aggregates	164
6.2.1	Protein Aggregates	164
6.2.2	Hemoglobin and Light Absorption	165
6.2.3	Aggregated Membrane Channel Protein	166
6.3	Large Aggregates	168
6.3.1	Large Protein Aggregates: Vaults	168
6.3.2	Ribosome	168
6.3.3	Saccharide Aggregates	169
6.3.3.1	Oligosaccharides	169
6.3.3.2	Polysaccharides	170
6.3.3.3	Structural Polysaccharides	170
6.3.4	Composite Materials	170
6.4	Two-Dimensional Aggregates: Membranes	173
6.4.1	Two-Dimensional Membranes Result from One-Dimensional Properties of Lipid Molecules	174
6.4.2	Lipid Vesicles, Liposomes, and Flat Bilayers	174
6.4.2.1	Energy and Membrane Change of Area	175
6.4.2.2	Energy and Membrane Curvature	175
6.4.3	Multilamellar Membrane Structures	176
6.4.3.1	Energetics of Membrane Stacking	177
6.4.3.2	Exclusion Zones and Entropy	178
6.4.4	Bilayers Are Dynamic	179
6.4.4.1	Lateral Motion in Membranes	179

6.4.4.2	Vertical Motion of Lipids	179
6.4.4.3	Lipid Flip-Flop Rates in Membranes	181
6.4.5	Membrane Fluidity	181
6.4.6	Membranes Must Have Controllable Holes in Them	182
6.4.7	Charge Movement Across Membranes	183
6.5	Points to Remember	187
6.6	Problem-Solving	187
	References	192
7	Putting a Cell Together: Physical Sketch	195
7.1	Minimal, Prokaryotic, and Eukaryotic Cells	195
7.1.1	Minimal Cell	196
7.1.2	Prokaryotes and Eukaryotes: Differences	198
7.1.3	Prokaryotes: Parts	200
7.1.3.1	Prokaryotic Cell Structure	201
7.1.3.2	Cyanobacteria (Blue-Green Algae) and Other Photosynthetic Bacteria	202
7.1.3.3	Halobacteria	204
7.1.4	Eukaryotes: Parts	205
7.2	Physiology: Selective Overview	206
7.2.1	Energy Transduction: Mitochondrion	206
7.2.2	Energy Generation: Eukaryotic Photosynthetic Cells and the Chloroplast	207
7.2.3	Endoplasmic Reticula and the Golgi Apparatus	208
7.3	Reproduction, DNA, and the Cell Nucleus	209
7.3.1	Nuclear Envelope and the Nuclear Pore Complex	209
7.3.2	Nucleolus	210
7.3.3	Cell Division: Some Major Structural Changes Are Needed	210
7.4	Sensors and Recognition: Responding to the Outside World without Eyes	210
7.4.1	Sensing through Diffusion	211
7.4.2	Purposeful and Random Movement: Preliminary Comments	211
7.4.3	Cell-Cell Recognition: Example	212
7.4.4	The Bacterial "Brain" Has No Neurons	213
7.5	Points to Remember	214
7.6	Problem-Solving	215
	References	220

PART III Biological Activity: Quantum Microworld

8	Quantum Primer	225
8.1	Quantum Glossary	226
8.1.1	Quantum, Quantum Behavior, Quantum Mechanics, and Wave Mechanics	226
8.2	Schrödinger Equation and Other Tools of Quantum Mechanics	227
8.2.1	Time-Dependence: Plane Waves	227
8.2.2	Uncertainty Principle and Sketched Wave Functions	231
8.2.2.1	Confined Particles Want to Expand	231
8.2.2.2	Sketched Wave Functions and de Broglie Wavelength	231
8.2.2.3	Quantum Mechanics Limits Exactness	233
8.2.3	Stationary States: Time-Independent Wave Functions	233
8.2.4	Energy-Level Diagrams	235

8.2.5	Normalization Constants	235
8.2.6	Average Values	236
8.3	Pauli Exclusion Principle	238
8.4	From Atoms to Molecules	240
8.5	Collisions of Atoms and Molecules	241
8.6	Classical vs. Quantum: Is a 1-mm-Long Molecule of DNA a Quantum Object?	242
8.7	Points to Remember	242
8.8	Problem-Solving	243
	References	245
9	Light, Life, and Measurement	247
9.1	Light: Our Energy Source	247
9.2	Crucial Differences between One 5-eV and Two 2.5-eV Photons	249
9.3	Measuring the Properties of Photons	249
9.3.1	Waves versus Particles: How Many Photons Are in a Wave?	250
9.3.2	Photon Momentum	252
9.3.3	Photon Angular Momentum	252
9.4	Scattering and Refraction	253
9.4.1	Rayleigh and Mie Scattering	253
9.4.2	Refraction: Interfaces and Whispering-Gallery Modes	255
9.4.3	Optical Forces: Laser Tweezers	255
9.4.3.1	Trapping of Cells	258
9.4.3.2	Measurement of Single-Molecule Interactions	259
9.5	Absorption Spectra	259
9.5.1	Energy-Level Diagram	260
9.5.2	Biomolecular Absorption Spectra Are Broad	260
9.5.3	Spectrum as a Digital Distribution Function	261
9.5.4	Absorbance and Absorption (Extinction) Coefficient	261
9.5.5	Proteins That Unexpectedly Absorb Light	263
9.6	Emission Spectra	264
9.6.1	Stokes Shift	265
9.6.2	Time Scales and Excited-State Kinetics	265
9.6.3	Non- or Multiexponential Decay and Solvent Relaxation	266
9.6.4	Fluorescence Quantum Yield	266
9.6.5	Nanoparticles: New Fluorescence Labels for Biological Applications	267
9.7	Einstein Relations between Absorption and Emission of Atoms (Graduate Section)	271
9.8	Intersystem Crossing: Singlets ($S = 0$) To Triplets ($S = 1$)	272
9.9	Energy Transfer (FRET)	272
9.10	Points to Remember	274
9.11	Problem-Solving	275
	References	280
10	Photosynthesis	283
10.1	Global Numbers	283
10.2	Overall Process	284
10.2.1	Finding Cellular and Subcellular Structures	285
10.2.2	Light and Dark Reactions: Products and Yields	286
10.2.3	Time Sequence of Photosynthesis	287

10.2.4	"Z Scheme"	288
10.2.5	Absorption Spectra of Photosynthetic Pigments	288
10.3	Structural Organization of Photosynthetic Units	292
10.4	Light-Harvesting (Antenna) Proteins: Arrays of Absorbers	295
10.4.1	Green Plant Light-Harvesting Complexes	296
10.4.2	From Green Plant to Cyanobacterial to Purple-Bacterial Light-Harvesting Systems	296
10.4.3	Quantum Efficiency of Electron Transfer	297
10.4.4	Phycocyanin Antennae	297
10.4.5	Purple Bacterial Photosystem	297
10.4.6	Exciton States	300
10.4.7	Hierarchy and Timing of Energy Transfer	302
10.5	Reaction Centers and Charge Separation: Purple Bacteria and Cyanobacteria	303
10.6	Artificial Models and Nonpolluting Energy Production	306
10.7	Points to Remember	307
10.8	Problem-Solving	307
	References	312
11	Direct Ultraviolet Effects on Biological Systems	317
11.1	Types and Sources of UV Light	318
11.1.1	Extreme or Vacuum UV: 4–200 nm	318
11.1.2	Far UV: 200–300 nm	320
11.1.3	Near UV: 300–400 nm	320
11.2	Divisions of the UV for Health Purposes: UV-A, UV-B, and UV-C	320
11.3	UV Damage to Organisms: "Action Spectra"	321
11.4	Wavelength-Dependent Photochemical Yields and Protein Damage	323
11.5	UV Damage to DNA	325
11.5.1	Molecular Orbitals of DNA Bases	327
11.5.2	UV Excitations and Spin	328
11.5.3	DNA Damage Products	328
11.5.4	Mutagenesis and Carcinogenesis (Brief!)	328
11.5.5	Photon Damage and Photon-Assisted DNA Repair	329
11.5.6	Photolyases: Thymine Dimer Repair via Collaboration of an Enzyme and a Photon	331
11.6	Optical Properties of the Skin	332
11.6.1	Structure of the Skin	332
11.6.2	Light Penetration into Skin	333
11.6.2.1	Wavelength Dependence	333
11.6.2.2	Random Walk of Light in Tissue	335
11.7	Sunscreens	337
11.7.1	Absorption Spectra	338
11.7.2	Sun Protection Factor	338
11.7.3	Excited States of Sunscreens	339
11.7.3.1	Getting Rid of Absorbed UV Energy	339
11.7.3.2	High Absorption without a High Radiative Rate	339
11.7.3.3	$^1\text{O}_2$ and Other Radicals Produced from Sunscreen Excited States	340
11.7.3.4	Padimate O Case	340
11.7.4	Beneficial Effects of UV	341
11.8	Points to Remember	341
11.9	Problem-Solving	341
	References	345

PART IV Biological Activity: (Classical) Microworld

12	Classical Biodynamics and Biomechanics	351
12.1	Conservation Laws, Newton's Laws, Forces, and Torques	351
12.2	Friction: Familiar and Less Familiar Examples of Motion	353
12.2.1	Surface Friction	353
12.2.2	Air Friction (High Reynolds Number)	354
12.2.3	Liquid Friction (Stokes, Low Reynolds Number)	355
12.3	Gravitational Forces	356
12.4	Volume Changes and Compressibility	357
12.5	Stress and Strain	358
12.5.1	Shear Stress	358
12.6	Force of Friction, Dissipation, Inertia, and Disorder	360
12.6.1	Viscosity, Scaling Exponent, and Friction	361
12.6.2	Scaling Exponent	361
12.6.3	Object Shape and Frictional Loss	362
12.6.4	Asymmetry of Frictional Force	363
12.6.5	Note on Cilia and Flagella	363
12.7	Fluids and Turbulence	364
12.7.1	Critical Force	364
12.7.2	Viscous Flow through Tubes	365
12.7.3	Motor Design and the Reynolds Number	366
12.7.4	Viscosity Variations: Temperature and Dissolved Materials	367
12.7.5	Dissolved Solutes Change the Viscosity	367
12.7.6	Bacterial Foraging: Escaping Low- R and the Peclet Number	367
12.7.7	Concluding Thoughts	368
12.8	Points to Remember	369
12.9	Problem-Solving	369
	References	373
13	Random Walks, Diffusion, and Polymer Conformation	375
13.1	Review of Kinetic Theory of Gases: Implications for Biomolecular Averaging	375
13.2	One-Dimensional Random Walk: Probabilities and Distributions	377
13.2.1	Gaussian Distribution	381
13.2.2	Attempt Frequencies and Probabilities	383
13.3	Spreadsheet Model for a One-Dimensional Random Walk	383
13.3.1	Stepper Motion with More Possible Steps	386
13.3.2	First-Transit Time	387
13.3.3	Average Movement of N Steppers	387
13.3.4	Casino of Real Life	388
13.4	Three-Dimensional Random Walk	388
13.5	Diffusion in the Bulk	390
13.5.1	Diffusion Equation	390
13.5.2	Diffusion from an Abrupt Front (Graduate Section)	392
13.5.3	Three-Dimensional Diffusion from a Point	393
13.5.4	Radially Symmetric, Steady-State Solutions	395
13.5.5	Diffusion Constant: Stokes and Einstein	396
13.5.6	Reminder: Cell Interiors Are Usually Not "Bulk"	397
13.6	Reprise of Photosynthetic Light Harvesting	398

13.7	Biopolymers—Random Reprise	400
13.7.1	Average End-to-End Distance	400
13.7.2	Persistence Length, Bending, and Dynamics	401
13.7.2.1	Dynamics of Movement	402
13.7.2.2	Elastic Forces	402
13.8	Points to Remember	403
13.9	Problem-Solving	403
	References	408
14	Statistical Physics and Thermodynamics Primer	411
14.1	Important Quantities: Temperature, Pressure, Density, and Number	412
14.2	Statistical Mechanical View and Distributions	413
14.2.1	Boltzmann Distribution: Discrete Energies	415
14.2.2	Boltzmann Distribution: Continuous Energies	417
14.2.3	Boltzmann, Fermi–Dirac, and Bose–Einstein Statistics	417
14.3	Equipartition of Energy	418
14.4	“Internal” Energy: Kinetic (K) and Potential (U)	418
14.5	Heat, Internal Energy, Work, and Enthalpy	420
14.6	Conservative and Nonconservative Forces: DNA Example	421
14.6.1	Cooperativity	423
14.7	Ideal Gas Law	423
14.8	Entropy: Gases and Polymers	426
14.8.1	Persistence Length and Entropy	429
14.8.2	Variable Persistence Length of DNA	429
14.8.3	Entropy, Knots, and Chain Stiffness	432
14.8.4	Topoisomerases I, II, Equilibrium, and Free Energy	434
14.8.5	Knots, Topology, and Equilibrium	436
14.9	Free Energy (Gibbs)	436
14.9.1	Free Energy Differences Govern Reactions	436
14.9.2	Standard Free Energies: Chemical Potentials, ΔG° and $\Delta G^\circ'$	438
14.9.3	ATP: Enthalpy and Free Energy of Hydrolysis	439
14.9.4	Coupling of ATP Hydrolysis to Other Reactions	439
14.10	Energy Diagrams	440
14.11	Boltzmann Distribution If Numbers Vary: Gibbs Distribution	441
14.12	Equilibrium Constants in Ideal, Uniform Solutions	442
14.13	Free Energy: Enthalpy, Entropy, Mixing, Gradients, Potential, and ATP	443
14.13.1	Mixing Entropy	443
14.13.2	Membrane Gradients	444
14.13.3	Separation of Charge	444
14.13.4	Membrane Potentials and Work	445
14.13.5	ATP Free Energy (Again)	446
14.14	Points to Remember	446
14.15	Problem-Solving	447
	References	451
15	Reactions: Physical View	455
15.1	Energy, Entropy, and Free Energy Diagrams	455
15.1.1	Equilibrium	455
15.1.1.1	Macromolecule Conformational Changes: Denaturation	458

	15.1.1.2	Missing Structural Detail in Early Biochemical Reaction Data	460
	15.1.1.3	Rate-Determining Step	460
	15.1.2	Kinetics	461
	15.1.2.1	Enzymes and Reaction Kinetics: First Pass	462
15.2		Rate Theory I: Activation-Energy Model	463
15.3		Diffusion-Controlled Rates (Bimolecular)	465
	15.3.1	Diffusion-Limited Reaction Rate Theory	465
15.4		Effects of Temperature on Rate Constants	468
	15.4.1	Temperature Dependence of Classical "Over-the-Barrier" Rates	468
	15.4.2	Measurement Biases	469
	15.4.3	Compensation Effect	470
15.5		Quantum Tunneling	470
	15.5.1	O ₂ and CO Binding to Myoglobin: Activated Tunneling and Structural and Energy Distributions	472
	15.5.2	Reminder: Mathematical Form of a Straight Line on a Log-Log Plot	474
	15.5.3	Proton Tunneling	475
15.6		A $\rightleftharpoons$ B: Unimolecular Reactions	478
15.7		A + B $\rightarrow$ C Binding Reactions: Free-Solution Reactions	479
15.8		Complex Reactions: Rate-Determining Steps and Michaelis-Menten Analysis	481
	15.8.1	Michaelis-Menten Models of Enzyme-Catalyzed Reactions	482
	15.8.2	Michaelis-Menten Summary	484
	15.8.3	Control of Enzymatic Reactions: Feedback and Inhibition	484
15.9		Driving Forces	485
15.10		Reversibility and Detailed Balance	485
15.11		Single-Molecule Behavior	487
	15.11.1	"Strange Kinetics": Biomolecular Movement in Living Cells Is Sometimes Slower	488
	15.11.2	Fluorescence Spectroscopy of Single Molecules	490
15.12		Points to Remember	493
15.13		Problem-Solving	493
		References	498
16		Molecular Machines: Introduction	501
16.1		Basic Considerations for Motors	502
	16.1.1	Random Walk	502
	16.1.1.1	Asymmetric Steppers	503
	16.1.1.2	Thermal Ratchets	503
	16.1.1.3	Coupling	505
	16.1.1.4	Directionality	506
	16.1.1.5	Flagella and Direction	507
	16.1.1.6	Step Size, Step Time, and Rate of Motion	508
	16.1.1.7	Detachment and Processivity	509
	16.1.2	Friction and Dissipation	509
	16.1.2.1	Reynolds Number and Microscopic Motion	510
	16.1.2.2	Story of the Eggshell	510
	16.1.2.3	Catching a Runaway	510
	16.1.3	Michaelis-Menten Enzyme Analysis and Molecular Motors	511
16.2		DNA-Manipulating Motors	513
	16.2.1	Manipulating DNA	513
	16.2.1.1	EcoRI Endonuclease and DNA Cleavage	515
	16.2.1.2	"Free" Energy Machines?	516

16.2.1.3	Biomolecular Search	516
16.2.1.4	Entropic Force of DNA Stretching	516
16.2.1.5	DNA Bending	518
16.2.1.6	Lac Repressor Search for Its DNA Binding Site	518
16.2.1.7	CAP and the DNA Bend	518
16.2.2	Rotary Motor That Bends DNA: Bacteriophage ϕ 29 Portal Motor	519
16.2.3	Direct Measurement of DNA Twist, Writhe, and Torque	521
16.3	Points to Remember	522
16.4	Problem-Solving	524
	References	528
17	Assembly	531
17.1	Overview of Assembly Issues	532
17.1.1	Protein Folding	533
17.1.2	Chaperonins: Eukaryotic Chaperonin TRiC	533
17.2	Kinetics and Equilibrium	534
17.3	Restricted Space for Assembly	536
17.4	Entropic Drive: Ordered Structures Can Be Driven by Random Processes	537
17.4.1	Energy Landscape and Local Minima	537
17.4.2	Correlations (Cooperativity)	538
17.4.3	Fractal Structures	539
17.4.4	Assembly by Osmotic Pressure	540
17.4.5	Commercial Application: Entropic Forces for DNA Purification	541
17.4.6	Size Distributions	542
17.4.7	Summary of "Random" Assembly (Aggregation, No Chaperonins or Assembly Apparatus)	543
17.5	Nucleosomes and Nucleosome-Like Structures	543
17.5.1	Nucleosomes Are Not Static	545
17.5.1.1	Charge Switching	545
17.5.1.2	Nucleosome Sliding	545
17.5.2	Artificial Nucleosome-Like Structures	545
17.6	Imaging the Assembly of Nanoparticles	548
17.7	Points to Remember	551
17.8	Problem-Solving	551
	References	555
18	Preparation for Experimental Biophysics	559
18.1	What Do You Want to Find Out, What Tools Might You Need, and Where Might You Find These Tools?	561
18.1.1	Searching Scientific Meeting Web Sites for Experimental Methods	561
18.1.1.1	Explore the Meeting	562
18.1.2	Imaging: Searching a Biological Institute Website	564
18.2	Tools Already Described in the Book	569
18.3	The Role(s) of a Computer in Experimental Biophysics	570
18.4	The Centrality of Structure, Motion, and Imaging	572
18.5	Points to Remember	573
18.6	Problem-Solving	574
	References	577

19	Atomic Force Microscopy	579
19.1	A Brief History of Scanning Probe Microscopy	579
19.2	Working Principles of AFM	580
19.2.1	The Feedback Loop	580
19.2.2	The Cantilever	581
19.2.3	The Deflection Measurement System	583
19.3	Measurement Techniques	584
19.3.1	Mechanics of AFM Measurements	584
19.3.2	Imaging Modes	586
19.3.3	Imaging Channels	586
19.3.4	Force-Distance Measurements	587
19.3.4.1	Types of Force-Distance Experiments	588
19.3.4.2	Indentation Measurements and Contact Mechanics	588
19.3.4.3	Adhesion Measurements	591
19.4	Types of Forces	591
19.4.1	Chemical Bonding	591
19.4.2	Van der Waals Forces	592
19.4.3	Electrostatic Forces	592
19.4.4	Double-Layer Forces	593
19.4.5	Steric Forces	593
19.4.6	Capillary Forces	593
19.4.7	Hydrophobic Forces	593
19.4.8	Hydration or Solvation Forces	594
19.5	Biological Applications	594
19.5.1	Cell Biology	594
19.5.1.1	Cell Imaging	594
19.5.1.2	Bacteria and Viruses	595
19.5.1.3	Cell Mechanics and Mechanobiology	596
19.5.1.4	Mechanical Manipulation	597
19.5.2	Biomolecular Biology	597
19.5.2.1	Imaging of Biomolecules	597
19.5.2.2	Single-Molecule Force Measurements	598
19.5.2.3	Recognition and Localization Microscopy	598
19.5.3	Tissues	599
19.5.4	Ultrafast AFM	599
19.5.5	Other Related Techniques and Future Developments	600
19.6	Problem-Solving	600
	References	602
	Index	603