Contents

Chapter 1

To the Student	XV
To the Instructor	XX
Acknowledgments	xxiv
Part I Mysteries, Metaphors, Models	
What the Ancients Knew	3
1 Heat 3	
1.1.1 Heat is a form of energy 4	
1.1.2 Just a little history 6	
1.1.3 Preview: The concept of free energy 8	
.2 How life generates order 9	
1.2.1 The puzzle of biological order 9	
1.2.2 Osmotic flow as a paradigm for free energy transduction 1	2
1.2.3 Preview: Disorder as information 14	
3 Excursion: Commercials, philosophy, pragmatics 15	
.4 How to do better on exams (and discover new physical laws) 18	
1.4.1 Most physical quantities carry dimensions 18	
1.4.2 Dimensional analysis can help you catch errors and recall definitions 20	
1.4.3 Dimensional analysis can also help you formulate hypothese	s 22
1.4.4 Some notational conventions involving flux and density 22	1
.5 Other key ideas from physics and chemistry 23	
1.5.1 Molecules are small 23	
1.5.2 Molecules are particular spatial arrangements of atoms 25	
1.5.3 Molecules have well-defined internal energies 26	
1.5.4 Low-density gases obey a universal law 27	
The big picture 28	
Track 2 30	
Problems 31	

Chapter

	Contents VII
Chapter 4	Random Walks, Friction, and Diffusion 108
-	4.1 Brownian motion 109
	4.1.1 Just a little more history 109
•	4.1.2 Random walks lead to diffusive behavior 110
	4.1.3 The diffusion law is model independent 117
	4.1.4 Friction is quantitatively related to diffusion 118
	4.2 Excursion: Einstein's role 121
	4.3 Other random walks 122
	4.3.1 The conformation of polymers 122
	4.3.2 Vista: Random walks on Wall Street 126
	4.4 More about diffusion 127
	4.4.1 Diffusion rules the subcellular world 127
	4.4.2 Diffusion obeys a simple equation 128
	4.4.3 Precise statistical prediction of random processes 131
	4.5 Functions, derivatives, and snakes under the rug 132
	4.5.1 Functions describe the details of quantitative relationships 132
	4.5.2 A function of two variables can be visualized as a landscape 134
	4.6 Biological applications of diffusion 135
	4.6.1 The permeability of artificial membranes is diffusive 135
	4.6.2 Diffusion sets a fundamental limit on bacterial metabolism 138
	4.6.3 The Nernst relation sets the scale of membrane potentials 139
	4.6.4 The electrical resistance of a solution reflects frictional dissipation 142
	4.6.5 Diffusion from a point gives a spreading, Gaussian profile 142
	The big picture 144
	Track 2 147
	Problems 153
Chapter 5	Life in the Slow Lane: The Low Reynolds-Number World 158
	5.1 Friction in fluids 158
	5.1.1 Sufficiently small particles can remain in suspension indefinitely 158
	5.1.2 The rate of sedimentation depends on solvent viscosity 160
	5.1.3 It's hard to mix a viscous liquid 161
	5.2 Low Reynolds number 163
	5.2.1 A critical force demarcates the physical regime dominated by friction 164

5.2.2 The Reynolds number quantifies the relative importance of friction

5.2.3 The time-reversal properties of a dynamical law signal its

and inertia 166

dissipative character 169

2.	1.1	Internal gross anatomy	40
2.	1.2	External gross anatomy	43

What's Inside Cells

2.1 Cell physiology 37

2.2 The molecular parts list 45

2.2.1 Small molecules 46

2.2.2 Medium-sized molecules 48

2.2.3 Big molecules 50

2.2.4 Macromolecular assemblies 54

2.3 Bridging the gap: Molecular devices 54

2.3.1 The plasma membrane 55

2.3.2 Molecular motors 58

2.3.3 Enzymes and regulatory proteins 58

2.3.4 The overall flow of information in cells 59

The big picture 62

Track 2 63

Problems 64

Part II Diffusion, Dissipation, Drive

3	The	Mol	lecu	ar	Dance	9

69

35

3.1 The probabilistic facts of life 69

3.1.1 Discrete distributions 70

3.1.2 Continuous distributions 71

3.1.3 Mean and variance 73

3.1.4 Addition and multiplication rules 75

3.2 Decoding the ideal gas law 78

3.2.1 Temperature reflects the average kinetic energy of thermal motion 78

3.2.2 The complete distribution of molecular velocities is experimentally measurable 82

3.2.3 The Boltzmann distribution 83

3.2.4 Activation barriers control reaction rates 86

3.2.5 Relaxation to equilibrium 87

3.3 Excursion: A lesson from heredity 89

3.3.1 Aristotle weighs in 89

3.3.2 Identifying the physical carrier of genetic information 90

3.3.3 Schrödinger's summary: Genetic information is structural 96 The big picture 101

Track 2 104

Problems 105

5.3	Biologie	cal applications 172	C.
	5.3.1	Swimming and pumping 172	
	5.3.2	To stir or not to stir? 177	
	5.3.3	Foraging, attack, and escape 178	
	5.3.4	Vascular networks 179	
	5.3.5	Viscous drag at the DNA replication fork 182	
5.4	Excursi	on: The character of physical Laws 184	
	The big	picture 185	
Trac	k 2 187	7	•
Prob	olems 1	90	
Ent	ropy, 7	Temperature, and Free Energy	195
6.1	How to	measure disorder 196	
6.2	Entrop	у 199	
	6.2.1	The Statistical Postulate 199	
	6.2.2	Entropy is a constant times the maximal value of disorder 200	
6.3	Temper	rature 202	
	6.3.1	Heat flows to maximize disorder 202	
	6.3.2	Temperature is a statistical property of a system in equilibrium 203	
6.4	The Sec	cond Law 206	
	6.4.1	Entropy increases spontaneously when a constraint is removed 206	
	6.4.2	Three remarks 209	
6.5	Open s	systems 210	
	6.5.1	The free energy of a subsystem reflects the competition between entropy and energy 210	
	6.5.2	Entropic forces can be expressed as derivatives of the free energy 213	
	6.5.3	Free energy transduction is most efficient when it proceeds in small, controlled steps 214	
	6.5.4	The biosphere as a thermal engine 216	
6.6	Micros	scopic systems 217	
-	6.6.1	The Boltzmann distribution follows from the Statistical Postulate 218	
	6.6.2	Kinetic interpretation of the Boltzmann distribution 220	
	6.6.3	The minimum free energy principle also applies to microscopic subsystems 223	
	6.6.4	The free energy determines the populations of complex two-statesystems 225	e

	Prol	olems	239	
	Ent	ropic	Forces at Work	245
_	7.1	Micro	oscopic view of entropic forces 246	
		7.1.1	•	
		7.1.2	Fixed-pressure approach 247	
	7.2	Osmo	otic pressure 248	
		7.2.1	Equilibrium osmotic pressure follows the ideal gas law 248	
		7.2.2	Osmotic pressure creates a depletion force between large molecules 251	
	7.3	Beyon	nd equilibrium: Osmotic flow 254	
		7.3.1	Osmotic forces arise from the rectification of Brownian motion 255	
		7.3.2	Osmotic flow is quantitatively related to forced permeation 25	9
	7.4	A rep	oulsive interlude 260	
		7.4.1	Electrostatic interactions are crucial for proper cell functioning 261	
		7.4.2	The Gauss Law 263	
		7.4.3	20 Indicate the surface of indicate and in clouds 20	
		7.4.4	The repulsion of like-charged surfaces arises from compression of their ion clouds 269	of
		7.4.5	Oppositely charged surfaces attract by counterion release 272	
	7.5	Specia	al properties of water 273	
		7.5.1	1	
		7.5.2	The hydrogen-bond network affects the solubility of small molecules in water 276	
		7.5.3	Water generates an entropic attraction between nonpolar objects 280	
		The b	ig picture 281	
	Trac	k 2 28	83	
	Prob	lems	290	
	Che	emica	al Forces and Self-Assembly	294
-	8.1	Chem	nical potential 294	
		8.1.1	μ measures the availability of a particle species 295	

8.1.2 The Boltzmann distribution has a simple generalization

accounting for particle exchange 298

6.7 Excursion: "RNA folding as a two-state system" by J. Liphardt, I. Tinoco, Jr., and C. Bustamante 226

The big picture 229

Track 2 232

Chapter 7

Chapter 8

401

8.2	Chem	ical reactions 299
	8.2.1	Chemical equilibrium occurs when chemical forces balance 299
	8.2.2	ΔG gives a universal criterion for the direction of a chemical reaction 301
	8.2.3	Kinetic interpretation of complex equilibria 306
	8.2.4	The primordial soup was not in chemical equilibrium 307
8.3	Disso	ciation 308
	8.3.1	Ionic and partially ionic bonds dissociate readily in water 308
	8.3.2	Chemical equilibrium occurs when chemical forces balance 299 \$\Delta G\$ gives a universal criterion for the direction of a chemical reaction 301 Kinetic interpretation of complex equilibria 306 The primordial soup was not in chemical equilibrium 307 ciation 308 Ionic and partially ionic bonds dissociate readily in water 308 The strengths of acids and bases reflect their dissociation equilibrium constants 309 The charge on a protein varies with its environment 311
	8.3.3	The charge on a protein varies with its environment 311
	8.3.4	Electrophoresis can give a sensitive measure of protein composition 312
8.4	Self-as	ssembly of amphiphiles 315
	8.4.1	Emulsions form when amphiphilic molecules reduce the oil–water interface tension 315
	8.4.2	Micelles self-assemble suddenly at a critical concentration 317
8.5	Excur	sion: On fitting models to data 321
8.6	Self-as	ssembly in cells 322
	8.6.1	Bilayers self-assemble from two-tailed amphiphiles 322
	8.6.2	Vista: Macromolecular folding and aggregation 327
	8.6.3	Another trip to the kitchen 330
	The b	ig picture 332
Trac	k 2 33	35
Prob	olems	337
D	.1 111	Mologulos Mashinos Moshanisms
Pai	rt III	Another trip to the kitchen 330 ig picture 332 Molecules, Machines, Mechanisms tive Transitions in Macromolecules Stity models of polymers 342 Why physics works (when it does work) 342
Cod	opera	tive Transitions in Macromolecules 341
9.1	Elastic	city models of polymers 342
	9.1.1	Why physics works (when it does work) 342
	9.1.2	
	9.1.3	Polymers resist stretching with an entropic force 347
9.2	Stretc	hing single macromolecules 350
	9.2.1	Four phenomenological parameters characterize the elasticity of a long, thin rod 344 Polymers resist stretching with an entropic force 347 hing single macromolecules 350 The force–extension curve can be measured for single DNA molecules 350
	9.2.2	A two-state system qualitatively explains DNA stretching at low force 352

9.3	Eigenv	values for the impatient 354
	9.3.1	Matrices and eigenvalues 354
	9.3.2	Matrix multiplication 357
9.4	Coope	erativity 358
	9.4.1	The transfer matrix technique allows a more accurate treatment of
		bend cooperativity 358
	9.4.2	DNA also exhibits linear stretching elasticity at moderate applied force 361
	9.4.3	Cooperativity in higher-dimensional systems gives rise to infinitely sharp phase transitions 363
9.5	Therm	nal, chemical, and mechanical switching 363
	9.5.1	The helix–coil transition can be observed by using polarized light 364
	9.5.2	Three phenomenological parameters describe a given helix–coil transition 366
	9.5.3	Calculation of the helix-coil transition 369
	9.5.4	DNA also displays a cooperative "melting" transition 373
	9.5.5	Applied mechanical force can induce cooperative structural transitions in macromolecules 375
9.6	Alloste	ery 376
	9.6.1	Hemoglobin binds four oxygen molecules cooperatively 376
	9.6.2	Allostery often involves relative motion of molecular subunits 379
	9.6.3	Vista: Protein substates 380
	The bi	g picture 382
Trac	k 2 38	4
Prob	olems :	396
	-	and Molecular Machines 4
10.1	-	of molecular devices found in cells 402
		Terminology 402
		Enzymes display saturation kinetics 403
		All eukaryotic cells contain cyclic motors 404
	10.1.4	One-shot machines assist in cell locomotion and spatial organization 407
10.2		mechanical machines 409
	10.2.1	Macroscopic machines can be described by an energy landscape 409

10.2.2 Microscopic machines can step past energy barriers 413 10.2.3 The Smoluchowski equation gives the rate of a microscopic

machine 415

Chapter 10

10.3 Molecular implementation of mechanical principles 422

10.3.1 Three ideas 423

505

557

559

11.4 Excursion: "Powering up the flagellar motor" by H. C. Berg and D. Fung 497

The big picture 499

10.3.2 The reaction coordinate gives a useful reduced description of a chemical event 423	The big picture 499 Track 2 501
10.3.3 An enzyme catalyzes a reaction by binding to the transition	Problems 503
state 425 10.3.4 Mechanochemical motors move by random-walking on a	Chapter 12 Nerve Impulses 5
two-dimensional landscape 431	12.1 The problem of nerve impulses 506
10.4 Kinetics of real enzymes and machines 432	12.1.1 Phenomenology of the action potential 506
10.4.1 The Michaelis-Menten rule describes the kinetics of simple	12.1.2 The cell membrane can be viewed as an electrical network 509
enzymes 433	12.1.3 Membranes with Ohmic conductance lead to a linear cable
10.4.2 Modulation of enzyme activity 436	equation with no traveling wave solutions 514
10.4.3 Two-headed kinesin as a tightly coupled, perfect ratchet 437	12.2 Simplified mechanism of the action potential 518
10.4.4 Molecular motors can move even without tight coupling or a	12.2.1 The puzzle 518
power stroke 446	12.2.2 A mechanical analogy 519
10.5 Vista: Other molecular motors 451	12.2.3 Just a little more history 521
The big picture 451	12.2.4 The time course of an action potential suggests the hypothesis of voltage gating 524
Track 2 455 Problems 464	12.2.5 Voltage gating leads to a nonlinear cable equation with traveling wave solutions 527
	12.3 The full Hodgkin–Huxley mechanism and its molecular
Machines in Membranes 469	underpinnings 532
11.1 Electroosmotic effects 469	12.3.1 Each ion conductance follows a characteristic time course when the membrane potential changes 532
11.1.1 Before the ancients 469	12.3.2 The patch clamp technique allows the study of single ion channel
11.1.2 Ion concentration differences create Nernst potentials 470	behavior 536
11.1.3 Donnan equilibrium can create a resting membrane potential 474	12.4 Nerve, muscle, synapse 545
11.2 Ion pumping 476	12.4.1 Nerve cells are separated by narrow synapses 545
11.2.1 Observed eukaryotic membrane potentials imply that these cells	12.4.2 The neuromuscular junction 546
are far from Donnan equilibrium 476	12.4.3 Vista: Neural computation 548
11.2.2 The Ohmic conductance hypothesis 478	The big picture 549
11.2.3 Active pumping maintains steady-state membrane potentials while	Track 2 552
avoiding large osmotic pressures 481	Problems 553
11.3 Mitochondria as factories 486	
11.3.1 Busbars and driveshafts distribute energy in factories 487	Epilogue 5
11.3.2 The biochemical backdrop to respiration 487	
11.3.3 The chemiosmotic mechanism identifies the mitochondrial inner membrane as a busbar 491	Appendix A Global List of Symbols and Units Notation 559 55
11.3.4 Evidence for the chemiosmotic mechanism 492	Named quantities 560
11.3.5 Vista: Cells use chemiosmotic coupling in many other	Dimensions 565
contexts 496	Units 565

Appendix B	Numerical Values		569
		569	
	Magnitudes 569		
	Specialized values 571		
Appendix C	Additional Problem	IS	575
	Problems for Chapter 1	575	
	Problems for Chapter 2	577	•
	Problems for Chapter 3	578	
	Problems for Chapter 4	579	
	Problems for Chapter 5	584	
	Problems for Chapter 6	586	
	Problems for Chapter 7	588	
	Problems for Chapter 8	592	
	Problems for Chapter 9	594	
	Problems for Chapter 10	596	
	Problems for Chapter 11	602	
	Problems for Chapter 12	604	
	Credits		607
	Bibliography		609
	Index		623