Biological Physics
Energy, Information, Life
Updated First Edition

Philip Nelson
University of Pennsylvania
with the assistance of Marko Radosavljević and Sarina Bromberg

W. H. Freeman and Company
New York
Front cover: Purkinje neuron from rat brain, visualized by two-photon laser scanning microscopy. The scale bar represents 15 μm. The neuron shown is alive and surrounded by a dense network of other neurons; a fluorescent dye has been injected into the cell from the micropipette at lower left, to reveal only the one cell of interest. The dendritic tree of this neuron (top) receives over 100,000 synaptic inputs. Dendritic spines are visible as tiny bumps on the dendrites. A single axon (lower left) sends output signals on to other neurons. [Digital image kindly supplied by K. Svoboda; see also Svoboda et al., 1996.] The inset shows a detail from Albert Einstein’s original article on Brownian motion.

Title page: DNA from a bacterium that has been lysed (burst) by osmotic shock. The bacterial genome that once occupied a small region in the center of the figure now extends in a series of loops from the core structure. Top to bottom, about 10 μm. [Electron micrograph by Ruth Kavenoff.]
# Contents

To the Student  
To the Instructor  
Acknowledgments  

## Part I  Mysteries, Metaphors, Models

### Chapter 1  What the Ancients Knew  

<table>
<thead>
<tr>
<th>Section</th>
<th>Title</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.1</td>
<td>Heat is a form of energy</td>
</tr>
<tr>
<td>1.1.1</td>
<td>Just a little history</td>
</tr>
<tr>
<td>1.1.3</td>
<td>Preview: The concept of free energy</td>
</tr>
<tr>
<td>1.2</td>
<td>How life generates order</td>
</tr>
<tr>
<td>1.2.1</td>
<td>The puzzle of biological order</td>
</tr>
<tr>
<td>1.2.2</td>
<td>Osmotic flow as a paradigm for free energy transduction</td>
</tr>
<tr>
<td>1.2.3</td>
<td>Preview: Disorder as information</td>
</tr>
<tr>
<td>1.3</td>
<td>Excursion: Commercials, philosophy, pragmatics</td>
</tr>
<tr>
<td>1.4</td>
<td>How to do better on exams (and discover new physical laws)</td>
</tr>
<tr>
<td>1.4.1</td>
<td>Most physical quantities carry dimensions</td>
</tr>
<tr>
<td>1.4.2</td>
<td>Dimensional analysis can help you catch errors and recall definitions</td>
</tr>
<tr>
<td>1.4.3</td>
<td>Dimensional analysis can also help you formulate hypotheses</td>
</tr>
<tr>
<td>1.4.4</td>
<td>Some notational conventions involving flux and density</td>
</tr>
<tr>
<td>1.5</td>
<td>Other key ideas from physics and chemistry</td>
</tr>
<tr>
<td>1.5.1</td>
<td>Molecules are small</td>
</tr>
<tr>
<td>1.5.2</td>
<td>Molecules are particular spatial arrangements of atoms</td>
</tr>
<tr>
<td>1.5.3</td>
<td>Molecules have well-defined internal energies</td>
</tr>
<tr>
<td>1.5.4</td>
<td>Low-density gases obey a universal law</td>
</tr>
<tr>
<td></td>
<td>The big picture</td>
</tr>
</tbody>
</table>

Track 2  
Problems
Chapter 4

Random Walks, Friction, and Diffusion

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 1  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 and inertia 166
  5.2.3 The time-reversal properties of a dynamical law signal its dissipative character 169
Chapter 6

Entropy, Temperature, and Free Energy

6.1 How to measure disorder 196
6.2 Entropy 199
   6.2.1 The Statistical Postulate 199
   6.2.2 Entropy is a constant times the maximal value of disorder 200
6.3 Temperature 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 Second Law 206
   6.4.1 Entropy increases spontaneously when a constraint is removed 206
   6.4.2 Three remarks 209
6.5 Open 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 Microscopic 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-state systems 225
Chapter 7

Entropic Forces at Work

7.1 Microscopic view of entropic forces 246
  7.1.1 Fixed-volume approach 246
  7.1.2 Fixed-pressure approach 247

7.2 Osmotic 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 Beyond 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 259

7.4 A repulsive interlude 260
  7.4.1 Electrostatic interactions are crucial for proper cell functioning 261
  7.4.2 The Gauss Law 263
  7.4.3 Charged surfaces are surrounded by neutralizing ion clouds 264
  7.4.4 The repulsion of like-charged surfaces arises from compression of their ion clouds 269
  7.4.5 Oppositely charged surfaces attract by counterion release 272

7.5 Special properties of water 273
  7.5.1 Liquid water contains a loose network of hydrogen bonds 273
  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 big picture 281

Track 2 283
Problems 290

Chapter 8

Chemical Forces and Self-Assembly

8.1 Chemical potential 294
  8.1.1 \( \mu \) measures the availability of a particle species 295
  8.1.2 The Boltzmann distribution has a simple generalization accounting for particle exchange 298
8.2 Chemical 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 Dissociation 308
  8.3.1 Ionic and partially ionic bonds dissociate readily in water 308
  8.3.2 The strengths of acids and bases reflect their dissociation equilibrium constants 309
  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-assembly 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 Excursion: On fitting models to data 321

8.6 Self-assembly 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 big picture 332

Track 2 335
Problems 337

Part III  Molecules, Machines, Mechanisms

Chapter 9

Cooperative Transitions in Macromolecules 341

  9.1 Elasticity models of polymers 342
    9.1.1 Why physics works (when it does work) 342
    9.1.2 Four phenomenological parameters characterize the elasticity of a long, thin rod 344
    9.1.3 Polymers resist stretching with an entropic force 347

  9.2 Stretching single macromolecules 350
    9.2.1 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
Chapter 10  Enzymes and Molecular Machines

10.1 Survey of molecular devices found in cells  402
   10.1.1 Terminology  402
   10.1.2 Enzymes display saturation kinetics  403
   10.1.3 All eukaryotic cells contain cyclic motors  404
   10.1.4 One-shot machines assist in cell locomotion and spatial organization  407

10.2 Purely 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
10.3 Molecular implementation of mechanical principles 422
   10.3.1 Three ideas 423
   10.3.2 The reaction coordinate gives a useful reduced description of a chemical event 423
   10.3.3 An enzyme catalyzes a reaction by binding to the transition state 425
   10.3.4 Mechanoochemical motors move by random-walking on a two-dimensional landscape 431
10.4 Kinetics of real enzymes and machines 432
   10.4.1 The Michaelis–Menten rule describes the kinetics of simple enzymes 433
   10.4.2 Modulation of enzyme activity 436
   10.4.3 Two-headed kinesin as a tightly coupled, perfect ratchet 437
   10.4.4 Molecular motors can move even without tight coupling or a power stroke 446
10.5 Vista: Other molecular motors 451
   The big picture 451

Track 2 455
Problems 464

Chapter 11

Machines in Membranes 469
11.1 Electroosmotic effects 469
   11.1.1 Before the ancients 469
   11.1.2 Ion concentration differences create Nernst potentials 470
   11.1.3 Donnan equilibrium can create a resting membrane potential 474
11.2 Ion pumping 476
   11.2.1 Observed eukaryotic membrane potentials imply that these cells are far from Donnan equilibrium 476
   11.2.2 The Ohmic conductance hypothesis 478
   11.2.3 Active pumping maintains steady-state membrane potentials while avoiding large osmotic pressures 481
11.3 Mitochondria as factories 486
   11.3.1 Busbars and driveshafts distribute energy in factories 487
   11.3.2 The biochemical backdrop to respiration 487
   11.3.3 The chemiosmotic mechanism identifies the mitochondrial inner membrane as a busbar 491
   11.3.4 Evidence for the chemiosmotic mechanism 492
   11.3.5 Vista: Cells use chemiosmotic coupling in many other contexts 496
Chapter 12  Nerve Impulses

12.1 The problem of nerve impulses 506
  12.1.1 Phenomenology of the action potential 506
  12.1.2 The cell membrane can be viewed as an electrical network 509
  12.1.3 Membranes with Ohmic conductance lead to a linear cable equation with no traveling wave solutions 514

12.2 Simplified mechanism of the action potential 518
  12.2.1 The puzzle 518
  12.2.2 A mechanical analogy 519
  12.2.3 Just a little more history 521
  12.2.4 The time course of an action potential suggests the hypothesis of voltage gating 524
  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 underpinnings 532
  12.3.1 Each ion conductance follows a characteristic time course when the membrane potential changes 532
  12.3.2 The patch clamp technique allows the study of single ion channel behavior 536

12.4 Nerve, muscle, synapse 545
  12.4.1 Nerve cells are separated by narrow synapses 545
  12.4.2 The neuromuscular junction 546
  12.4.3 Vista: Neural computation 548

The big picture 549

Epilogue

Appendix A  Global List of Symbols and Units

Notation 559
Named quantities 560
Dimensions 565
Units 565