

# Contents

<i>Preface</i>	<i>page</i> ix
<i>Extracts</i>	xi
<b>1 Introduction to simulation of biological systems</b>	<b>1</b>
1.1 Modeling approaches	1
1.2 An introductory example: biochemistry of a home aquarium	2
1.2.1 First model: a nonmechanistic analysis	3
1.2.2 Nonmechanistic analysis with noise	6
1.2.3 Mechanistic modeling	11
1.3 Recapitulation and lessons learned	17
<b>2 Transport and reaction of solutes in biological systems</b>	<b>21</b>
2.1 Well-mixed systems: compartmental modeling	22
2.2 Passive flow of water, solutes, and electrical current across membranes	24
2.2.1 Basic equations	24
2.2.2 Example: volume changes in isolated glomeruli	28
2.3 Simulating chemical reactions	35
2.3.1 Example: synthesis of ethanol from xylose	35
2.4 Distributed transport modeling	46
2.4.1 Flowing systems: the advection equation	46
2.4.2 Reaction–diffusion systems	53
2.4.3 Advection–reaction–diffusion systems	61
2.5 Recapitulation and lessons learned	62
<b>3 Physiologically based pharmacokinetic modeling</b>	<b>66</b>
3.1 Introduction to lumped compartmental PBPK modeling	67
3.1.1 Basic equations	67
3.1.2 Comparison of distributed and lumped transport models	70
3.1.3 Quasi-steady model reduction	73

3.1.4	Lumped versus distributed transport modeling: a final word	76
3.2	Overview of the mammalian circulatory system	77
3.3	Whole-body PBPK simulation	77
3.4	Example: uptake and delivery of matrine in rat	84
3.4.1	A PBPK model for rat	84
3.4.2	Model parameters	87
3.4.3	Flow-limited transport	89
3.4.4	Model validation and discrimination	98
3.5	Recapitulation and lessons learned	101
<b>4</b>	<b>Cardiovascular systems simulation</b>	<b>105</b>
4.1	The Frank–Starling mechanism of heart	105
4.2	An analysis of the physiological factors that control cardiac output	110
4.2.1	Guyton’s model of the systemic circulation	110
4.2.2	What the model tells us about the relationship between flow and right atrial pressure	114
4.2.3	How the simple Guyton model is commonly misinterpreted	120
4.3	Pulsatile mechanics of the circulatory system	122
4.3.1	Time-varying elastance models of the heart	124
4.3.2	Simulation of the aortic pressure waveform	127
4.4	Dynamic changes in blood pressures and flows	133
4.4.1	Baroreceptor control of systemic pressure	138
4.5	Mechanisms of hypertension	141
4.6	Recapitulation and lessons learned	142
<b>5</b>	<b>Chemical reaction systems: thermodynamics and chemical equilibrium</b>	<b>145</b>
5.1	Temperature, pressure, and entropy	145
5.1.1	Microstates and macrostates	145
5.1.2	Example: a simple two-state system	146
5.1.3	Relationship between temperature and entropy	148
5.1.4	Relationship between pressure and entropy	149
5.2	Free energy under constant-temperature and constant-volume conditions	150
5.3	Free energy under constant-temperature and constant-pressure conditions	153
5.4	Thermodynamic ensembles, partition functions, and driving forces	153
5.5	Chemical reactions, stoichiometry, and equilibrium constants	154

5.6	Acids, bases, and buffers	159
5.7	Analysis of biochemical reactions	162
5.7.1	Example: equilibrium of a biochemical reaction	162
5.7.2	Example: standard enthalpy of a biochemical reaction	172
5.8	Recapitulation and lessons learned	174
<b>6</b>	<b>Chemical reaction systems: kinetics</b>	<b>178</b>
6.1	Basic principles of kinetics	178
6.1.1	Mass-action kinetics	178
6.1.2	Thermodynamic constraints on reaction kinetics	180
6.1.3	Transition state theory	181
6.1.4	Example: temperature dependence of a chemical reaction	185
6.2	Enzymes	185
6.2.1	The Michaelis–Menten rate law	186
6.2.2	Case study: mechanism and kinetics of fumarase	189
6.2.3	Systematic approaches to enzyme kinetics	197
6.3	Biochemical reaction systems	199
6.3.1	Example: feedback control of oxidative phosphorylation	199
6.4	Recapitulation and lessons learned	202
<b>7</b>	<b>Chemical reaction systems: large-scale systems simulation</b>	<b>205</b>
7.1	Biochemical systems in living cells	206
7.2	General approach to metabolic kinetics	206
7.2.1	Enzyme rate laws and biochemical networks	207
7.2.2	Simulating pH kinetics	211
7.2.3	Example: glycogenolysis in skeletal muscle	213
7.3	Reverse engineering and model discovery	219
7.3.1	Example: gene interaction in <i>Dictyostelium</i>	221
7.4	Recapitulation and lessons learned	227
<b>8</b>	<b>Cellular electrophysiology</b>	<b>230</b>
8.1	Basic concepts of cell electrophysiology	230
8.1.1	Thermodynamics of ion fluxes	231
8.2	The Hodgkin–Huxley model of the squid giant axon	233
8.2.1	The potassium conductance	235
8.2.2	The sodium conductance	239
8.2.3	Summary of model equations	245
8.2.4	Refractory period	249
8.2.5	The legacy of the Hodgkin–Huxley model	249

8.3	Models of ion channel gating	251
8.4	Stochastic simulations	255
8.5	Recapitulation and lessons learned	258
<b>9</b>	<b>Appendices: mathematical and computational techniques</b>	<b>262</b>
9.1	Finite-difference approximations for continuous processes	262
9.2	Least-squares solution to $\mathbf{Ax} = \mathbf{b}$	264
9.3	Using computers to integrate ordinary differential equations	265
9.4	Optimization for parameter estimation	268
9.5	The method of lines for the one-dimensional advection equation	271
9.6	Finite-difference approximation for simulating a FRAP experiment	274
9.6.1	Simulating two-dimensional diffusion	274
9.6.2	Simulating diffusion and reaction	277
9.7	Circuits of resistors, capacitors, and inductors	281
9.7.1	Circuit components	281
9.7.2	Circuit analysis and simulation	283
9.8	Rate laws and parameter values for glycogenolysis model	287
	<i>References</i>	299
	<i>Index</i>	304