

# Contents

<b>List of Figures</b>		<b>ix</b>
<b>List of Tables</b>		<b>xv</b>
<b>Acknowledgments</b>		<b>xvii</b>
<b>Preface</b>		<b>xix</b>
<b>1 Introduction</b>		<b>1</b>
1.1	When to model . . . . .	2
1.2	What is a model . . . . .	2
1.3	Formulation of a mathematical model . . . . .	3
1.4	Solving the model equations . . . . .	5
1.5	Drawing qualitative conclusions . . . . .	6
1.6	Choosing parameters . . . . .	7
1.7	Robustness . . . . .	7
1.8	Analysis of results . . . . .	9
1.9	Successes and failures of modeling . . . . .	9
1.10	Final remarks . . . . .	11
1.11	Other sources of information on mathematical modeling in biology . . . . .	12
<b>2 Introduction to biochemical kinetics</b>		<b>13</b>
2.1	Transitions between states at the molecular level . . . . .	13
2.2	Transitions between states at the population level . . . . .	16
2.3	The law of mass action . . . . .	23
2.4	Enzyme kinetics: Saturating and cooperative reactions . . . . .	24
2.5	Simple models for polymer growth dynamics . . . . .	27
2.6	Discussion . . . . .	36
	Exercises . . . . .	37
<b>3 Review of linear differential equations</b>		<b>43</b>
3.1	First-order differential equations . . . . .	44
3.2	Linear second-order equations . . . . .	50
3.3	Linear second-order equations with constant coefficients . . . . .	52
3.4	A system of two linear equations . . . . .	55

3.5	Summary of solutions to differential equations in this chapter . . . . .	61
	Exercises . . . . .	61
<b>4</b>	<b>Introduction to nondimensionalization and scaling</b>	<b>67</b>
4.1	Simple examples . . . . .	67
4.2	Rescaling the dimerization model . . . . .	72
4.3	Other examples . . . . .	76
	Exercises . . . . .	79
<b>5</b>	<b>Qualitative behavior of simple differential equation models</b>	<b>83</b>
5.1	Revisiting the simple linear ODEs . . . . .	83
5.2	Stability of steady states . . . . .	86
5.3	Qualitative analysis of models with bifurcations . . . . .	88
	Exercises . . . . .	99
<b>6</b>	<b>Developing a model from the ground up: Case study of the spread of an infection</b>	<b>103</b>
6.1	Deriving a model for the spread of an infection . . . . .	103
6.2	Dimensional analysis applied to the model . . . . .	105
6.3	Analysis . . . . .	107
6.4	Interpretation of the results . . . . .	111
	Exercises . . . . .	111
<b>7</b>	<b>Phase plane analysis</b>	<b>115</b>
7.1	Phase plane trajectories . . . . .	115
7.2	Nullclines . . . . .	117
7.3	Steady states . . . . .	118
7.4	Stability of steady states . . . . .	120
7.5	Classification of steady state behavior . . . . .	122
7.6	Qualitative behavior and phase plane analysis . . . . .	124
7.7	Limit cycles, attractors, and domains of attraction . . . . .	132
7.8	Bifurcations continued . . . . .	135
	Exercises . . . . .	138
<b>8</b>	<b>Quasi steady state and enzyme-mediated biochemical kinetics</b>	<b>145</b>
8.1	Warm-up example: Transitions between three states . . . . .	145
8.2	Enzyme-substrate complex and the quasi steady state approximation . . . . .	152
8.3	Conditions for validity of the QSS . . . . .	158
8.4	Overview and discussion of the QSS . . . . .	165
8.5	Related applications . . . . .	167
	Exercises . . . . .	168
<b>9</b>	<b>Multiple subunit enzymes and proteins: Cooperativity</b>	<b>173</b>
9.1	Preliminary model for rapid dimerization . . . . .	173
9.2	Dimer binding that induces conformational change: Model formulation . . . . .	176
9.3	Consequences of a QSS assumption . . . . .	178
9.4	Ligand binding to dimer . . . . .	179

9.5	Results for binding and their interpretation: Cooperativity . . . . .	183
9.6	Cooperativity in enzyme action . . . . .	184
9.7	Monod–Wyman–Changeaux (MWC) cooperativity . . . . .	185
9.8	Discussion . . . . .	190
	Exercises . . . . .	190
<b>10</b>	<b>Dynamic behavior of neuronal membranes</b>	<b>195</b>
10.1	Introduction . . . . .	195
10.2	An informal preview of the Hodgkin–Huxley model . . . . .	198
10.3	Working towards the Hodgkin–Huxley model . . . . .	202
10.4	The full Hodgkin–Huxley model . . . . .	214
10.5	Comparison between theory and experiment . . . . .	216
10.6	Bifurcations in the Hodgkin–Huxley model . . . . .	219
10.7	Discussion . . . . .	222
	Exercises . . . . .	222
<b>11</b>	<b>Excitable systems and the FitzHugh–Nagumo equations</b>	<b>227</b>
11.1	A simple excitable system . . . . .	227
11.2	Phase plane analysis of the model . . . . .	229
11.3	Piecing together the qualitative behavior . . . . .	234
11.4	Simulations of the FitzHugh–Nagumo model . . . . .	236
11.5	Connection to neuronal excitation . . . . .	241
11.6	Other systems with excitable behavior . . . . .	246
	Exercises . . . . .	247
<b>12</b>	<b>Biochemical modules</b>	<b>251</b>
12.1	Simple biochemical circuits with useful functions . . . . .	251
12.2	Genetic switches . . . . .	257
12.3	Models for the cell division cycle . . . . .	262
	Exercises . . . . .	277
<b>13</b>	<b>Discrete networks of genes and cells</b>	<b>283</b>
13.1	Some simple automata networks . . . . .	284
13.2	Boolean algebra . . . . .	294
13.3	Lysis-lysogeny in bacteriophage $\lambda$ . . . . .	299
13.4	Cell cycle, revisited . . . . .	304
13.5	Discussion . . . . .	306
	Exercises . . . . .	308
<b>14</b>	<b>For further study</b>	<b>311</b>
14.1	Nondimensionalizing a functional relationship . . . . .	311
14.2	Scaled dimensionless variables . . . . .	312
14.3	Mathematical development of the Michaelis–Menten QSS via scaled variables . . . . .	316
14.4	Cooperativity in the Monod–Wyman–Changeaux theory for binding . . . . .	318
14.5	Ultrasensitivity in covalent protein modification . . . . .	320
14.6	Fraction of open channels, Hodgkin–Huxley Model . . . . .	324

14.7	Asynchronous Boolean networks (kinetic logic)	327
	Exercises	333
<b>15</b>	<b>Extended exercises and projects</b>	<b>337</b>
	Exercises	337
<b>A</b>	<b>The Taylor approximation and Taylor series</b>	<b>355</b>
	Exercises	361
<b>B</b>	<b>Complex numbers</b>	<b>363</b>
	Exercises	365
<b>C</b>	<b>A review of basic theory of electricity</b>	<b>367</b>
	C.1 Amps, coulombs, and volts	367
	C.2 Ohm's law	370
	C.3 Capacitance	371
	C.4 Circuits	373
	C.5 The Nernst equation	375
	Exercises	377
<b>D</b>	<b>Proofs of Boolean algebra rules</b>	<b>379</b>
	Exercises	381
<b>E</b>	<b>Appendix: XPP files for models in this book</b>	<b>385</b>
	E.1 Biochemical reactions	385
	E.2 Linear differential equations	386
	E.3 Simple differential equations and bifurcations	387
	E.4 Disease dynamics models	389
	E.5 Phase plane analysis	389
	E.6 Chemical reactions and the QSS	391
	E.7 Neuronal excitation and excitable systems	392
	E.8 Biochemical modules	394
	E.9 Cell division cycle models	396
	E.10 Boolean network models	401
	E.11 Odell–Oster model of Exercise 15.7	403
	<b>Bibliography</b>	<b>405</b>
	<b>Index</b>	<b>417</b>