
Contents

Preface, xi

Acknowledgments, xvii

About the Author, xix

SECTION I **Building Intuition**

CHAPTER 1 ■ Variations on a Theme of Control 3

LEARNING OBJECTIVES 3

VARIATIONS 3

AUTOREGULATION 4

OUR THEME: A TYPICAL NEGATIVE AUTOREGULATORY
CIRCUIT 8

CHAPTER SUMMARY 11

RECOMMENDED READING 11

CHAPTER 2 ■ Variation: Boolean Representations 13

LEARNING OBJECTIVES 13

BOOLEAN LOGIC AND RULES 13

STATE MATRICES 17

STATE TRANSITIONS 18

DYNAMICS 19

TIMESCALES 24

ADVANTAGES AND DISADVANTAGES OF BOOLEAN
ANALYSIS 26

CHAPTER SUMMARY	26
RECOMMENDED READING	27
PROBLEMS	27
 CHAPTER 3 ■ Variation: Analytical Solutions of Ordinary Differential Equations	 35
LEARNING OBJECTIVES	35
SYNTHETIC BIOLOGICAL CIRCUITS	36
FROM COMPARTMENT MODELS TO ODES	37
SPECIFYING AND SIMPLIFYING ODES WITH ASSUMPTIONS	41
THE STEADY-STATE ASSUMPTION	43
SOLVING THE SYSTEM WITHOUT FEEDBACK: REMOVAL OF ACTIVATOR	44
KEY PROPERTIES OF THE SYSTEM DYNAMICS	46
SOLVING THE SYSTEM WITHOUT FEEDBACK: ADDITION OF ACTIVATOR	47
COMPARISON OF MODELING TO EXPERIMENTAL MEASUREMENTS	49
ADDITION OF AUTOREGULATORY FEEDBACK	50
COMPARISON OF THE REGULATED AND UNREGULATED SYSTEMS	53
CHAPTER SUMMARY	57
RECOMMENDED READING	58
PROBLEMS	59
 CHAPTER 4 ■ Variation: Graphical Analysis	 65
LEARNING OBJECTIVES	65
REVISITING THE PROTEIN SYNTHESIS ODES	66
PLOTTING X VERSUS DX/DT	67
FIXED POINTS AND VECTOR FIELDS	68
FROM VECTOR FIELDS TO TIME-COURSE PLOTS	70
NONLINEARITY	70
BIFURCATION ANALYSIS	73

ADDING FEEDBACK	75
TWO-EQUATION SYSTEMS	77
CHAPTER SUMMARY	81
RECOMMENDED READING	82
PROBLEMS	83
CHAPTER 5 ■ Variation: Numerical Integration	91
LEARNING OBJECTIVES	91
THE EULER METHOD	92
ACCURACY AND ERROR	94
THE MIDPOINT METHOD	99
THE RUNGE-KUTTA METHOD	103
CHAPTER SUMMARY	106
RECOMMENDED READING	106
PROBLEMS	107
CHAPTER 6 ■ Variation: Stochastic Simulation	111
LEARNING OBJECTIVES	111
SINGLE CELLS AND LOW MOLECULE NUMBERS	111
STOCHASTIC SIMULATIONS	113
THE PROBABILITY THAT TWO MOLECULES INTERACT AND REACT IN A GIVEN TIME INTERVAL	116
THE PROBABILITY OF A GIVEN MOLECULAR REACTION OCCURRING OVER TIME	118
THE RELATIONSHIP BETWEEN KINETIC AND STOCHASTIC CONSTANTS	119
GILLESPIE'S STOCHASTIC SIMULATION ALGORITHM	120
STOCHASTIC SIMULATION OF UNREGULATED GENE EXPRESSION	124
STOCHASTIC SIMULATIONS VERSUS OTHER MODELING APPROACHES	131
CHAPTER SUMMARY	132
RECOMMENDED READING	132
PROBLEMS	133

SECTION II From Circuits to Networks

CHAPTER 7 ■ Transcriptional Regulation	143
LEARNING OBJECTIVES	143
TRANSCRIPTIONAL REGULATION AND COMPLEXITY	144
MORE COMPLEX TRANSCRIPTIONAL CIRCUITS	145
THE TRANSCRIPTIONAL REGULATORY FEED-FORWARD MOTIF	147
BOOLEAN ANALYSIS OF THE MOST COMMON INTERNALLY CONSISTENT FEED-FORWARD MOTIF IDENTIFIED IN <i>E. COLI</i>	149
AN ODE-BASED APPROACH TO ANALYZING THE COHERENT FEED-FORWARD LOOP	152
ROBUSTNESS OF THE COHERENT FEED-FORWARD LOOP	155
EXPERIMENTAL INTERROGATION OF THE COHERENT FEED-FORWARD LOOP	155
CHANGING THE INTERACTION FROM AN AND TO AN OR RELATIONSHIP	156
THE SINGLE-INPUT MODULE	160
JUST-IN-TIME GENE EXPRESSION	162
GENERALIZATION OF THE FEED-FORWARD LOOP	164
AN EXAMPLE OF A MULTIGENE FEED-FORWARD LOOP: FLAGELLAR BIOSYNTHESIS IN <i>E. COLI</i>	166
OTHER REGULATORY MOTIFS	168
CHAPTER SUMMARY	169
RECOMMENDED READING	170
PROBLEMS	171
CHAPTER 8 ■ Signal Transduction	179
LEARNING OBJECTIVES	179
RECEPTOR-LIGAND BINDING TO FORM A COMPLEX	179
APPLICATION TO REAL RECEPTOR-LIGAND PAIRS	183
FORMATION OF LARGER COMPLEXES	187
PROTEIN LOCALIZATION	188

THE NF- κ B SIGNALING NETWORK	191
A DETAILED MODEL OF NF- κ B ACTIVITY	193
ALTERNATIVE REPRESENTATIONS FOR THE SAME PROCESS	198
SPECIFYING PARAMETER VALUES FROM DATA	200
BOUNDING PARAMETER VALUES	206
MODEL SENSITIVITY TO PARAMETER VALUES	207
REDUCING COMPLEXITY BY ELIMINATING PARAMETERS	210
PARAMETER INTERACTIONS	213
CHAPTER SUMMARY	216
RECOMMENDED READING	217
PROBLEMS	218
 CHAPTER 9 ■ Metabolism	 233
LEARNING OBJECTIVES	233
CELLULAR METABOLISM	233
METABOLIC REACTIONS	234
COMPARTMENT MODELS OF METABOLITE CONCENTRATION	237
THE MICHAELIS-MENTEN EQUATION FOR ENZYME KINETICS	237
DETERMINING KINETIC PARAMETERS FOR THE MICHAELIS-MENTEN SYSTEM	245
INCORPORATING ENZYME INHIBITORY EFFECTS	247
FLUX BALANCE ANALYSIS	252
STEADY-STATE ASSUMPTION AND EXCHANGE FLUXES	255
SOLUTION SPACES	258
THE OBJECTIVE FUNCTION	259
DEFINING THE OPTIMIZATION PROBLEM	262
SOLVING FBA PROBLEMS USING MATLAB	263
APPLICATIONS OF FBA TO LARGE-SCALE METABOLIC MODELS	271
USING FBA FOR METABOLIC ENGINEERING	274
CHAPTER SUMMARY	279

RECOMMENDED READING	281
PROBLEMS	282
CHAPTER 10 ■ Integrated Models	295
LEARNING OBJECTIVES	295
DYNAMIC FBA: EXTERNAL VERSUS INTERNAL CONCENTRATIONS	296
ENVIRONMENTAL CONSTRAINTS	298
INTEGRATION OF FBA SIMULATIONS OVER TIME	300
COMPARING DYNAMIC FBA TO EXPERIMENTAL DATA	303
FBA AND TRANSCRIPTIONAL REGULATION	304
TRANSCRIPTIONAL REGULATORY CONSTRAINTS	305
REGULATORY FBA: METHOD	306
REGULATORY FBA: APPLICATION	308
TOWARD WHOLE-CELL MODELING	310
CHAPTER SUMMARY	315
RECOMMENDED READING	316
PROBLEMS	317

GLOSSARY, 323

INDEX, 333