

---

# Contents

---

Introduction, xv

## PART 1 Network Motifs

CHAPTER 1 ■ Transcription Networks: Basic Concepts	3
1.1 Introduction	3
1.2 The Cognitive Problem of the Cell	3
1.3 Elements of Transcription Networks	5
1.3.1 Separation of Timescales	7
1.3.2 The Signs on the Arrows: Activators and Repressors	8
1.3.3 The Numbers on the Arrows: Input Functions	9
1.3.4 Logic Input Functions: A Simple Framework for Understanding Network Dynamics	10
1.3.5 Multi-Dimensional Input Functions Govern Genes with Several Inputs	11
1.4 Dynamics and Response Time of Simple Regulation	13
1.4.1 The Response Time of Stable Proteins Is One Cell Generation	15
Further Reading	15
Exercises	16
Bibliography	18
CHAPTER 2 ■ Autoregulation: A Network Motif	21
2.1 Introduction	21
2.2 Patterns, Randomized Networks and Network Motifs	21
2.2.1 Detecting Network Motifs by Comparison to Randomized Networks	23
2.3 Autoregulation Is a Network Motif	23

2.4	Negative Autoregulation Speeds the Response Time of Gene Circuits	24
2.4.1	Rate Analysis Shows Speedup for Any Repressive Input Function $f(X)$	28
2.5	Negative Autoregulation Promotes Robustness to Fluctuations in Production Rate	29
2.6	Summary: Evolution as an Engineer	30
	Further Reading	31
	Exercises	31
	Bibliography	36
<b>CHAPTER 3 ■ The Feedforward Loop Network Motif</b>		37
3.1	Introduction	37
3.2	The Feedforward Loop Is a Network Motif	37
3.3	The Structure of the Feedforward Loop Gene Circuit	39
3.4	Dynamics of the Coherent Type-1 FFL with AND Logic	41
3.5	The C1-FFL Is a Sign-Sensitive Delay Element	42
3.5.1	Delay Following an ON Step of $S_x$	43
3.5.2	No Delay Following an OFF Step of $S_x$	44
3.5.3	The C1-FFL Is a Sign-Sensitive Delay Element	44
3.5.4	Sign-Sensitive Delay Can Protect against Brief Input Fluctuations	44
3.5.5	Sign-Sensitive Delay in the Arabinose System of <i>E. coli</i>	45
3.6	OR-Gate C1-FFL Is a Sign-Sensitive Delay for OFF Steps	46
3.7	The Incoherent Type-1 FFL Generates Pulses of Output	47
3.7.1	The Incoherent FFL Can Speed Response Times	48
3.7.2	Interim Summary: Three Ways to Speed Your Response Time	49
3.7.3	The I1-FFL Can Provide Biphasic Steady-State Response Curves	50
3.8	The Other Six FFL Types Can Also Act as Filters and Pulse Generators	51
3.9	Convergent Evolution of FFLs	51
3.10	Summary	52
	Further Reading	52
	Exercises	53
	Bibliography	59
<b>CHAPTER 4 ■ Temporal Programs and the Global Structure of Transcription Networks</b>		61
4.1	Introduction	61
4.2	The Single-Input Module (SIM) Network Motif	61

4.3	The SIM Can Generate Temporal Gene Expression Programs	62
4.4	The Multi-Output Feedforward Loop	64
4.5	The Multi-Output FFL Can Generate FIFO Temporal Programs	66
4.5.1	The Multi-Output FFL Also Acts as a Persistence Detector for Each Output	68
4.6	Signal Integration by Bi-Fans and Dense-Overlapping Regulons	68
4.7	Network Motifs and the Global Structure of Sensory Transcription Networks	70
4.8	Interlocked Feedforward Loops in the <i>B. subtilis</i> Sporulation Network	70
	Further Reading	73
	Exercises	73
	Bibliography	75
<hr/> <b>CHAPTER 5 ■ Positive Feedback, Bistability and Memory</b>		77
5.1	Network Motifs in Developmental Transcription Networks	77
5.1.1	Positive Autoregulation Slows Responses and Can Lead to Bistability	78
5.1.2	Two-Node Positive Feedback Loops for Decision-Making	80
5.1.3	Regulating Feedback and Regulated Feedback	83
5.1.4	Long Transcription Cascades and Developmental Timing	84
5.2	Network Motifs in Protein–Protein Interaction Networks	85
5.2.1	Hybrid Network Motifs Include a Two-Node Negative Feedback Loop	85
5.2.2	Hybrid FFL Motifs Can Provide Transient Memory	87
5.2.3	Feedforward Loops Show a Milder Version of the Functions of Feedback Loops	87
5.3	Network Motifs in Neuronal Networks	88
5.3.1	Multi-Input FFLs in Neuronal Networks	89
5.4	Reflection	91
	Further Reading	91
	Exercises	92
	Bibliography	94
<hr/> <b>CHAPTER 6 ■ How to Build a Biological Oscillator</b>		97
6.1	Oscillations Require Negative Feedback and Delay	97
6.1.1	In Order to Oscillate, You Need to Add a Sizable Delay to the Negative Feedback Loop	97

6.2	Noise Can Induce Oscillations in Systems That Have Only Damped Oscillations on Paper	101
6.3	Delay Oscillators	102
6.4	Many Biological Oscillators Have a Coupled Positive and Negative Feedback Loop Motif	103
6.5	Robust Bistability Using Two Positive Feedback Loops	107
	Further Reading	110
	Exercises	110
	Bibliography	112

## PART 2 Robustness

CHAPTER 7 ■	Kinetic Proofreading and Conformational Proofreading	117
7.1	Introduction	117
7.2	Kinetic Proofreading of the Genetic Code Can Reduce Error Rates	118
7.2.1	Equilibrium Binding Cannot Explain the Precision of Translation	119
7.2.2	Kinetic Proofreading Can Dramatically Reduce the Error Rate	121
7.3	Recognition of Self and Non-Self by the Immune System	123
7.3.1	Equilibrium Binding Cannot Explain the Low Error Rate of Immune Recognition	124
7.3.2	Kinetic Proofreading Increases Fidelity of T-Cell Recognition	125
7.4	Kinetic Proofreading Occurs in Diverse Processes in the Cell	127
7.5	Conformational Proofreading Provides Specificity without Consuming Energy	128
7.6	Demand Rules for Gene Regulation Can Minimize Errors	129
	Further Reading	130
	Exercises	131
	Bibliography	136

CHAPTER 8 ■	Robust Signaling by Bifunctional Components	137
8.1	Robust Input–Output Curves	137
8.2	Simple Signaling Circuits Are Not Robust	138
8.3	Bacterial Two-Component Systems Can Achieve Robustness	140
8.3.1	Limits of Robustness	143
8.3.2	Remarks on the Black-Box Approach	143

8.3.3 Bifunctional Components Provide Robustness in Diverse Circuits	144
Further Reading	144
Exercises	145
Bibliography	150
<b>CHAPTER 9 ■ Robustness in Bacterial Chemotaxis</b>	<b>153</b>
9.1 Introduction	153
9.2 Bacterial Chemotaxis, or How Bacteria Think	153
9.2.1 Chemotaxis Behavior	153
9.2.2 Response and Exact Adaptation	155
9.3 The Chemotaxis Protein Circuit	156
9.3.1 Attractants Lower the Activity of $X$	157
9.3.2 Adaptation Is Due to Slow Modification of $X$ That Increases Its Activity	158
9.4 The Barkai–Leibler Model of Exact Adaptation	159
9.4.1 Robust Adaptation and Integral Feedback	162
9.4.2 Experiments Show That Exact Adaptation Is Robust, Whereas Steady-State Activity and Adaptation Times Are Fine-Tuned	164
9.5 Individuality and Robustness in Bacterial Chemotaxis	165
Further Reading	166
Exercises	166
Bibliography	172
<b>CHAPTER 10 ■ Fold-Change Detection</b>	<b>175</b>
10.1 Universal Features of Sensory Systems	175
10.2 Fold-Change Detection in Bacterial Chemotaxis	176
10.2.1 Definition of Fold-Change Detection (FCD)	177
10.2.2 The Chemotaxis Circuit Provides FCD by Means of a Nonlinear Integral-Feedback Loop	178
10.3 FCD and Exact Adaptation	180
10.4 The Incoherent Feedforward Loop Can Show FCD	180
10.5 A General Condition for FCD	182
10.6 Identifying FCD Circuits from Dynamic Measurements	183
10.7 FCD Provides Robustness to Input Noise and Allows Scale-Invariant Searches	184

Further Reading	186
Exercises	186
References	188
<b>CHAPTER 11 ■ Dynamical Compensation and Mutant Resistance in Tissues</b>	<b>191</b>
11.1 The Insulin-Glucose Feedback Loop	191
11.2 The Minimal Model Is Not Robust to Changes in Insulin Sensitivity	193
11.3 A Slow Feedback Loop on Beta-Cell Numbers Provides Compensation	194
11.4 Dynamical Compensation Allows the Circuit to Buffer Parameter Variations	197
11.5 Type 2 Diabetes Is Linked with Instability Due to a U-Shaped Death Curve	200
11.6 Tissue-Level Feedback Loops Are Fragile to Invasion by Mutants That Misread the Signal	201
11.7 Biphasic (U-Shaped) Response Curves Can Protect against Mutant Takeover	202
11.8 Summary	203
Further Reading	204
Exercises	204
Bibliography	207
<b>CHAPTER 12 ■ Robust Spatial Patterning in Development</b>	<b>209</b>
12.1 The French Flag Model Is Not Robust	210
12.2 Increased Robustness by Self-Enhanced Morphogen Degradation	212
12.3 Network Motifs That Provide Degradation Feedback for Robust Patterning	214
12.4 The Robustness Principle Can Distinguish between Mechanisms of Fruit Fly Patterning	215
Further Reading	220
Exercises	220
Bibliography	223
<b>PART 3 Optimality</b>	
<b>CHAPTER 13 ■ Optimal Gene Circuit Design</b>	<b>227</b>
13.1 Introduction	227
13.2 Optimal Expression Level of a Protein under Constant Conditions	228

13.2.1 Cost of the LacZ Protein	229
13.2.2 The Benefit of the LacZ Protein	230
13.2.3 Fitness Function and the Optimal Expression Level	231
13.2.4 Cells Reach Optimal LacZ Levels in a Few Hundred Generations in Laboratory Evolution Experiments	232
13.3 To Regulate or Not to Regulate? Optimal Regulation in Changing Environments	234
13.4 Environmental Selection of the Feedforward Loop Network Motif	236
13.5 Inverse Ecology	238
Further Reading	239
Exercises	239
Bibliography	247
<b>CHAPTER 14 ■ Multi-Objective Optimality in Biology</b>	<b>249</b>
14.1 Introduction	249
14.2 The Fitness Landscape Picture for a Single Task	249
14.3 Multiple Tasks Are Characterized by Performance Functions	250
14.4 Pareto Optimality in Performance Space	251
14.5 Pareto Optimality in Trait Space Leads to Simple Patterns	252
14.6 Two Tasks Lead to a Line Segment, Three Tasks to a Triangle, Four to a Tetrahedron	253
14.7 Trade-Offs in Morphology	254
14.8 Archetypes Can Last over Geological Timescales	256
14.9 Trade-Offs for Proteins	257
14.10 Trade-Offs in Gene Expression	258
14.11 Division of Labor in the Individual Cells That Make Up an Organ	259
14.12 Variation within a Species Lies on the Pareto Front	260
Further Reading	263
Exercises	263
Bibliography	271
<b>CHAPTER 15 ■ Modularity</b>	<b>273</b>
15.1 The Astounding Speed of Evolution	273
15.2 Modularity Is a Common Feature of Engineered and Evolved Systems	273
15.3 Modularity Is Found at All Levels of Biological Organization	274
15.4 Modularity Is Not Found in Simple Computer Simulations of Evolution	275

15.5 Simulated Evolution of Circuits Made of Logic Gates	275
15.6 Randomly Varying Goals Cause Confusion	278
15.7 Modularly Varying Goals Lead to Spontaneous Evolution of Modularity	278
15.8 The More Complex the Goal, the More MVG Speeds Up Evolution	280
15.9 Modular Goals and Biological Evolution	281
Further Reading	283
Exercises	283
Bibliography	284
<b>APPENDIX A ■ The Input Functions of Genes: Michaelis–Menten and Hill Equations</b>	<b>287</b>
A.1 Binding of a Repressor to a Promoter	287
A.2 Binding of an Inducer to a Repressor Protein: The Michaelis–Menten Equation	289
A.3 Cooperativity of Inducer Binding and the Hill Equation	291
A.4 The Monod–Changeux–Wyman Model	292
A.5 The Input Function of a Gene Regulated by a Repressor	293
A.6 Binding of an Activator to Its DNA Site	294
A.6.1 Comparison of Dynamics with Logic and Hill Input Functions	295
A.7 Michaelis–Menten Enzyme Kinetics	295
Further Reading	297
Exercises	297
Bibliography	298
<b>APPENDIX B ■ Multi-Dimensional Input Functions</b>	<b>299</b>
B.1 Input Function That Integrates an Activator and a Repressor	299
Exercise	301
Bibliography	301
<b>APPENDIX C ■ Graph Properties of Transcription Networks</b>	<b>303</b>
C.1 Transcription Networks Are Sparse	303
C.2 Transcription Networks Have Long-Tailed Out-Degree Sequences and Compact In-Degree Sequences	303
C.3 Clustering Coefficients	305
C.4 Quantitative Measure of Network Modularity	305
Bibliography	306

---

<b>APPENDIX D ■ Noise in Gene Expression</b>	<b>307</b>
D.1 Introduction	307
D.2 Extrinsic and Intrinsic Noise	307
D.3 Distribution of Protein Levels	308
D.4 Network Motifs Affect Noise	309
D.5 Position of Noisiest Step	310
Further Reading	311
Bibliography	311
<b>WORDS OF THANKS</b>	<b>313</b>
<b>INDEX</b>	<b>315</b>

---