

- **Chapter 1 Introduction** (p. 1)
- **Chapter 2 Transcription Networks: Basic Concepts** (p. 5)
  - **2.1 Introduction** (p. 5)
  - **2.2 The Cognitive Problem of the Cell** (p. 5)
  - **2.3 Elements of Transcription Networks** (p. 7)
    - **2.3.1 Separation of Timescales** (p. 9)
    - **2.3.2 The Signs on the Edges: Activators and Repressors** (p. 12)
    - **2.3.3 The Numbers on the Edges: The Input Function** (p. 13)
    - **2.3.4 Logic Input Functions: A Simple Framework for Understanding Network Dynamics** (p. 15)
    - **2.3.5 Multi-Dimensional Input Functions Govern Genes with Several Inputs** (p. 16)
    - **2.3.6 Interim Summary** (p. 18)
  - **2.4 Dynamics and Response Time of Simple Gene Regulation** (p. 18)
    - **2.4.1 The Response Time of Stable Proteins Is One Cell Generation** (p. 21)
  - **Further Reading** (p. 22)
  - **Exercises** (p. 22)
- **Chapter 3 Autoregulation: A Network Motif** (p. 27)
  - **3.1 Introduction** (p. 27)
  - **3.2 Patterns, Randomized Networks, and Network Motifs** (p. 27)
    - **3.2.1 Detecting Network Motifs by Comparison to Randomized Networks** (p. 29)
  - **3.3 Autoregulation: A Network Motif** (p. 30)
  - **3.4 Negative Autoregulation Speeds the Response Time of Gene Circuits** (p. 31)
  - **3.5 Negative Autoregulation Promotes Robustness to Fluctuations in Production Rate** (p. 34)
    - **3.5.1 Positive Autoregulation Slows Responses and Can Lead to Bi-Stability** (p. 37)
  - **3.6 Summary** (p. 37)
  - **Further Reading** (p. 37)
  - **Exercises** (p. 38)
- **Chapter 4 The Feed-Forward Loop Network Motif** (p. 41)
  - **4.1 Introduction** (p. 41)
  - **4.2 The Number of Appearances of a Subgraph in Random Networks** (p. 42)
  - **4.3 The Feed-Forward Loop Is a Network Motif** (p. 45)
  - **4.4 The Structure of the Feed-Forward Loop Gene Circuit** (p. 46)
  - **4.5 Dynamics of the Coherent Type-1 FFL with AND Logic** (p. 49)
  - **4.6 The C1-FFL Is a Sign-Sensitive Delay Element** (p. 50)
    - **4.6.1 Delay Following an ON Step of  $S_x$**  (p. 51)
    - **4.6.2 No Delay Following an OFF Step of  $S_x$**  (p. 52)
    - **4.6.3 The C1-FFL Is a Sign-Sensitive Delay Element** (p. 52)
    - **4.6.4 Sign-Sensitive Delay Can Protect against Brief Input Fluctuations** (p. 52)
    - **4.6.5 sign-Sensitive Delay in the Arabinose System of E. coli** (p. 54)
    - **4.6.6 The OR Gate C1-FFL Is a Sign-Sensitive Delay for OFF Steps of  $S_x$**  (p. 56)
    - **4.6.7 Interim Summary** (p. 56)
  - **4.7 The Incoherent Type-1 FFL** (p. 57)
    - **4.7.1 The Structure of the Incoherent FFL** (p. 57)
    - **4.7.2 Dynamics of the I1-FFL: A Pulse Generator** (p. 58)

- **4.7.3 The I1-FFL Speeds the Response Time** (p. 62)
- **4.7.4 Response Acceleration Is Sign Sensitive** (p. 63)
- **4.7.5 Experimental Study of the Dynamics of an I1-FFL** (p. 63)
- **4.7.6 Three Ways to Speed Your Responses (An Interim Summary)** (p. 64)
- **4.8 Why Are Some FFL Types Rare?** (p. 65)
- **4.8.1 Steady-State Logic of the I1-FFL:  $S_{[y]}$  Can Turn on High Expression** (p. 65)
- **4.8.2 I4-FFL, a Rarely Selected Circuit, Has Reduced Functionality** (p. 65)
- **4.9 Convergent Evolution of FFLs** (p. 68)
- **4.10 Summary** (p. 69)
- **Further Reading** (p. 70)
- **Exercises** (p. 71)
- **Chapter 5 Temporal Programs and the Global Structure of Transcription Networks** (p. 75)
- **5.1 Introduction** (p. 75)
- **5.5 The Multi-Output FFL Can Generate FIFO Temporal Order** (p. 83)
- **5.2 The Single-Input Module (SIM) Network Motif** (p. 76)
- **5.3 SIMs Can Generate Temporal Expression Programs** (p. 77)
- **5.4 Topological Generalizations of Network Motifs** (p. 81)
- **5.5.1 The Multi-Output FFL Can Also Act as a Persistence Detector for Each Output** (p. 87)
- **5.6 Signal Integration and Combinatorial Control: Bi-Fans and Dense Overlapping Regulons** (p. 88)
- **5.7 Network Motifs and the Global Structure of Sensory Transcription Networks** (p. 89)
- **Further Reading** (p. 92)
- **Exercises** (p. 93)
- **Chapter 6 Network Motifs in Developmental, Signal Transduction, and Neuronal Networks** (p. 97)
- **6.1 Introduction** (p. 97)
- **6.2 Network Motifs in Developmental Transcription Networks** (p. 98)
- **6.2.1 Two-Node Positive Feedback Loops for Decision Making** (p. 99)
- **6.2.2 Regulating Feedback and Regulated Feedback** (p. 101)
- **6.2.3 Long Transcription Cascades and Developmental Timing** (p. 102)
- **6.2.4 Interlocked Feed-Forward Loops in the *B. subtilis* Sporulation Network** (p. 102)
- **6.3 Network Motifs in Signal Transduction Networks** (p. 104)
- **6.4 Information Processing Using Multi-Layer Perceptrons** (p. 106)
- **6.4.1 Toy Model for Protein Kinase Perceptrons** (p. 106)
- **6.4.2 Multi-Layer Perceptrons Can Perform Detailed Computations** (p. 111)
- **6.5 Composite Network Motifs: Negative Feedback and Oscillator Motifs** (p. 115)
- **6.6 Network Motifs in the Neuronal Network of *C. elegans*** (p. 118)
- **6.6.1 The Multi-Input FFL in Neuronal Networks** (p. 122)
- **6.6.2 Multi-Layer Perceptrons in the *C. elegans* Neuronal Network** (p. 125)
- **6.7 Summary** (p. 127)
- **Further Reading** (p. 128)

- Exercises (p. 129)
- **Chapter 7 Robustness of Protein Circuits: The Example of Bacterial Chemotaxis** (p. 135)
  - **7.1 The Robustness Principle** (p. 135)
  - **7.2 Bacterial Chemotaxis, or How Bacteria Think** (p. 136)
    - **7.2.1 Chemotaxis Behavior** (p. 136)
    - **7.2.2 Response and Exact Adaptation** (p. 137)
  - **7.3 The Chemotaxis Protein Circuit of E. coli** (p. 140)
    - **7.3.1 Attractants Lower the Activity of X** (p. 141)
    - **7.3.2 Adaptation Is Due to Slow Modification of X That Increases Its Activity** (p. 142)
  - **7.4 Two Models Can Explain Exact Adaptation: Robust and Fine-Tuned** (p. 142)
    - **7.4.1 Fine-Tuned Model** (p. 143)
    - **7.4.2 The Barkai-Leibler Robust Mechanism for Exact Adaptation** (p. 146)
    - **7.4.3 Robust Adaptation and Integral Feedback** (p. 148)
    - **7.4.4 Experiments Show That Exact Adaptation Is Robust, Whereas Steady-State Activity and Adaptation Times Are Fine-Tuned** (p. 149)
  - **7.5 Individuality and Robustness in Bacterial Chemotaxis** (p. 149)
  - **Further Reading** (p. 151)
  - **Exercises** (p. 152)
- **Chapter 8 Robust Patterning in Development** (p. 159)
  - **8.1 Introduction** (p. 159)
  - **8.2 Exponential Morphogen Profiles Are Not Robust** (p. 161)
  - **8.3 Increased Robustness by Self-Enhanced Morphogen Degradation** (p. 163)
  - **8.4 Network Motifs That Provide Degradation Feedback for Robust Patterning** (p. 165)
  - **8.5 The Robustness Principle Can Distinguish between Mechanisms of Fruit Fly Patterning** (p. 166)
  - **9.1 Introduction** (p. 175)
  - **Further Reading** (p. 172)
  - **Exercises** (p. 172)
- **Chapter 9 Kinetic Proofreading** (p. 175)
  - **9.2 Kinetic Proofreading of the Genetic Code Can Reduce Error Rates of Molecular Recognition** (p. 176)
    - **9.2.1 Equilibrium Binding Cannot Explain the Precision of Translation** (p. 177)
    - **9.2.2 Kinetic Proofreading Can Dramatically Reduce the Error Rate** (p. 180)
  - **9.3 Recognizing Self and Non-Self by the Immune System** (p. 182)
    - **9.3.1 Equilibrium Binding Cannot Explain the Low Error Rate of Immune Recognition** (p. 183)
    - **9.3.2 Kinetic Proofreading Increases Fidelity of T-Cell Recognition** (p. 185)
  - **9.4 Kinetic Proofreading May Occur in Diverse Recognition Processes in the Cell** (p. 187)
  - **Further Reading** (p. 188)
  - **Exercises** (p. 188)
- **Chapter 10 Optimal Gene Circuit Design** (p. 193)
  - **10.1 Introduction** (p. 193)

- **10.2 Optimal Expression Level of a Protein under Constant Conditions** (p. 194)
- **10.2.1 The Benefit of the LacZ Protein** (p. 195)
- **10.2.2 The Cost of the LacZ Protein** (p. 196)
- **10.2.3 The Fitness Function and the Optimal Expression Level** (p. 197)
- **10.2.4 Laboratory Evolution Experiment Shows That Cells Reach Optimal LacZ Levels in a Few Hundred Generations** (p. 199)
- **10.3 To Regulate or Not to Regulate: Optimal Regulation in Variable Environments** (p. 201)
- **10.4 Environmental Selection of the Feed-Forward Loop Network Motif** (p. 203)
- **10.5 Summary** (p. 207)
- **Further Reading** (p. 207)
- **Exercises** (p. 208)
- **Chapter 11 Demand Rules for Gene Regulation** (p. 215)
- **11.1 Introduction** (p. 215)
- **11.2 The Savageau Demand Rule** (p. 217)
- **11.2.1 Evidence for the Demand Rule in E. coli** (p. 217)
- **11.2.2 Mutational Explanation of the Demand Rule** (p. 219)
- **11.2.3 The Problem with Mutant-Selection Arguments** (p. 220)
- **11.3 Rules for Gene Regulation Based on Minimal Error Load** (p. 220)
- **11.4 The Selection Pressure for Optimal Regulation** (p. 222)
- **11.5 Demand Rules for Multi-Regulator Systems** (p. 223)
- **11.6 Summary** (p. 228)
- **Further Reading** (p. 230)
- **Exercises** (p. 230)
- **Chapter 12 Epilogue: Simplicity in Biology** (p. 233)
- **Appendix A The Input Function of a Gene: Michaelis-Menten and Hill Equations** (p. 241)
- **A.1 Binding of a Repressor to a Promoter** (p. 241)
- **A.2 Binding of a Repressor Protein to an Inducer: Michaelis-Menten Equation** (p. 244)
- **A.3 Cooperativity of Inducer Binding and the Hill Equation** (p. 245)
- **A.4 The Monod, Changeux, and Wymann Model** (p. 247)
- **A.5 The Input Function of a Gene Regulated by a Repressor** (p. 247)
- **A.6 Binding of an Activator to Its DNA Site** (p. 248)
- **A.6.1 Comparison of Dynamics with Logic and Hill Input Functions** (p. 250)
- **A.7 Michaelis-Menten Enzyme Kinetics** (p. 250)
- **Further Reading** (p. 251)
- **Exercises** (p. 251)
- **Appendix B Multi-Dimensional Input Functions** (p. 253)
- **B.1 Input Function That Integrates an Activator and a Repressor** (p. 253)
- **Exercises** (p. 255)
- **Appendix C Graph Properties of Transcription Networks** (p. 257)
- **C.1 Transcription Networks Are Sparse** (p. 257)
- **C.2 Transcription Networks Have Long-Tailed Output Degree Sequences and Compact Input Degree Sequences** (p. 257)
- **C.3 Clustering Coefficients of Transcription Networks** (p. 259)

- **C.4 Quantitative Measures of Network Modularity** (p. 259)
- **Appendix D Cell-Cell Variability in Gene Expression** (p. 261)
- **Further Reading** (p. 264)
- **Glossary** (p. 265)
- **Bibliography** (p. 271)
- **Index** (p. 295)