Contents

1 Introduction **1**

2 Review of Organic Chemistry **5**
2.1 Electrovalent and Covalent Bonds 6
2.2 Some Chemical Bonds and Groups Commonly Encountered in Biological Molecules 9
2.3 Building Blocks for Common Organic Molecules 13
2.3.1 Sugars 13
2.3.2 Fatty Acids 17
2.3.3 Amino Acids 18
2.3.4 Nucleotides 20

3 Energy Considerations in Biochemical Reactions **27**
3.1 Some Common Biochemical Reactions 28
3.1.1 Photosynthesis 28
3.1.2 Cellular Respiration 29
3.1.3 Oxidation and Reduction 29
3.2 Role of Enzymes 30
3.3 Feasibility of Chemical Reactions 32
3.4 Activated Carrier Molecules and Their Role in Biosynthesis . 34

4 Proteins **37**
4.1 Protein Structure and Function 37
4.1.1 The α-helix and the β-sheet 38
4.2 Levels of Organization in Proteins 41
4.3 Protein Ligand Interactions 43
4.4 Isolating Proteins from Cells 45
4.5 Separating a Mixture of Proteins 46
4.5.1 Column Chromatography 47
4.5.2 Gel Electrophoresis 47
4.6 Protein Structure Determination 48
4.7 Proteins That Are Enzymes 49

5 DNA **53**

6 Transcription and Translation **63**
6.1 Transcription 64
6.2 Translation 69

7 Chromosomes and Gene Regulation **77**
7.1 Organization of DNA into Chromosomes 78
7.2 Gene Regulation 82

8 Genetic Variation **89**
8.1 Genetic Variation in Bacteria 89
8.1.1 Bacterial Mating 90
8.1.2 Gene Transfer by Bacteriophages 92
8.1.3 Transposons 93
8.2 Sources of Genetic Change in Eucaryotic Genomes 94
8.2.1 Gene Duplication 94
8.2.2 Transposable Elements and Viruses 96
8.2.3 Sexual Reproduction and the Reassortment of Genes . 98

9 DNA Technology **101**
9.1 Techniques for Analyzing DNA Molecules 101
9.2 Nucleic Acid Hybridization and Associated Techniques 105
9.3 Construction of Human Genomic and cDNA Libraries 107
9.4 Polymerase Chain Reaction (PCR) 109
9.5 Genetic Engineering 112
9.5.1 Engineering DNA Molecules, Proteins and RNAs . . . 112
9.5.2 Engineering Mutant Haploid Organisms 112
9.5.3 Engineering Transgenic Animals 114

10 Cell Division **117**
10.1 Mitosis and Cytokinesis 119
10.2 Meiosis 123

11 Cell Cycle Control, Cell Death and Cancer **127**
11.1 Cyclin-Dependent Kinases and Their Role 128
11.2 Control of Cell Numbers in Multicellular Organisms 131
11.3 Programmed Cell Death 132
11.4 Cancer as the Breakdown of Cell Cycle Control 133

12 Expression Microarrays **137**
12.1 cDNA Microarrays 138
12.1.1 Normalization 140
12.1.2 Ratio Analysis 142
12.2 Synthetic Oligonucleotide Arrays 145

13 Classification **147**
13.1 Classifier Design 147
13.1.1 Bayes Classifier 148
13.1.2 Classification Rules 148
13.1.3 Constrained Classifier Design 151
13.1.4 Regularization for Quadratic Discriminant Analysis . . 154
13.1.5 Regularization by Noise Injection 157
13.2 Feature Selection 158
13.3 Error Estimation 161
13.3.1 Error Estimation Using the Training Data 162
13.3.2 Performance Issues 163

14 Clustering **167**
14.1 Examples of Clustering Algorithms 168
14.1.1 k-means 168
14.1.2 Fuzzy k-means 169
14.1.3 Self-Organizing Maps 170
14.1.4 Hierarchical Clustering 171
14.2 Clustering Accuracy 173
14.2.1 Model-Based Clustering Error 173
14.2.2 Application to Real Data 174
14.3 Cluster Validation 176

15 Genetic Regulatory Networks **181**
15.1 Nonlinear Dynamical Modeling of Gene Networks 182
15.2 Boolean Networks 184
15.2.1 Boolean Model 184
15.2.2 Coefficient of Determination 187
15.3 Probabilistic Boolean Networks 188
15.4 Network Inference 192

16 Intervention **197**
16.1 PBN Notation 198
16.2 Intervention by Flipping the Status of a Single Gene 199
16.3 Intervention to Alter the Steady-State Behavior 203

17 External Intervention Based on Optimal Control Theory **207**
17.1 Finite-Horizon-Control 208
17.1.1 Solution Using Dynamic Programming 211
17.1.2 A Simple Illustrative Example 212
17.1.3 Melanoma Example 215
17.2 External Intervention in the Imperfect Information Case . . . 220
17.2.1 Melanoma Example 221
17.3 External Intervention in the Context-Sensitive Case 226
17.3.1 Melanoma Example 229

17.4 External Intervention for a Family of Boolean Networks . . . 232
17.4.1 Melanoma Example 235
17.5 External Intervention in the Infinite Horizon Case 238
17.5.1 Optimal Control Solution 240
17.5.2 Melanoma Example 244
17.6 Concluding Remarks 248

References **253**

Index **265**