Contents

Preface *XIII*
List of Contributors *XV*

1 **Biomolecular Computing: From Unconventional Computing to "Smart" Biosensors and Actuators – Editorial Introduction** *1*
Evgeny Katz
References *5*

2 **Peptide-Based Computation: Switches, Gates, and Simple Arithmetic** *9*
Zehavit Dadon, Manickasundaram Samiappan, Nathaniel Wagner, Nurit Ashkenasy, and Gonen Ashkenasy
2.1 Introduction *9*
2.2 Peptide-Based Replication Networks *10*
2.2.1 Template-Assisted Replication *10*
2.2.2 Theoretical Prediction of the Network Connectivity *11*
2.2.3 *De novo* Designed Synthetic Networks *12*
2.3 Logic Gates within Ternary Networks *13*
2.3.1 Uniform Design Principles of All Two-Input Gates *13*
2.3.2 OR Logic *14*
2.3.3 AND Logic *15*
2.3.4 NAND Logic *15*
2.3.5 XOR Logic *15*
2.4 Symmetry and Order Requirements for Constructing the Logic Gates *16*
2.4.1 Symmetry and Order in Peptide-Based Catalytic Networks *16*
2.4.2 How Symmetry and Order Affect the Replication of RNA Quasispecies *17*
2.5 Taking the Steps toward More Complex Arithmetic *19*
2.5.1 Arithmetic Units *19*
2.5.2 Network Motifs *20*

2.6 Experimental Logic Gates *21*
2.6.1 OR Logic *21*
2.6.2 NOT, NOR, and NOTIF Logic *21*
2.6.3 Additional Logic Operations *23*
2.7 Adaptive Networks *24*
2.7.1 Chemical Triggering *24*
2.7.2 Light Triggering *24*
2.7.3 Light-Induced Logic Operations *25*
2.8 Peptide-Based Switches and Gates for Molecular Electronics *28*
2.9 Summary and Conclusion *29*
Acknowledgments *30*
References *30*

3 Biomolecular Electronics and Protein-Based Optical Computing *33*
Jordan A. Greco, Nicole L. Wagner, Matthew J. Ranaghan, Sanguthevar Rajasekaran, and Robert R. Birge
3.1 Introduction *33*
3.2 Biomolecular and Semiconductor Electronics *34*
3.2.1 Size and Speed *34*
3.2.2 Architecture *36*
3.2.3 Nanoscale Engineering *37*
3.2.4 Stability *38*
3.2.5 Reliability *38*
3.3 Bacteriorhodopsin as a Photonic and Holographic Material for Bioelectronics *40*
3.3.1 The Light-Induced Photocycle *40*
3.3.2 The Branched Photocycle *42*
3.4 Fourier Transform Holographic Associative Processors *42*
3.5 Three-Dimensional Optical Memories *45*
3.5.1 Write, Read, and Erase Operations *46*
3.5.2 Efficient Algorithms for Data Processing *48*
3.5.3 Multiplexing and Error Analysis *50*
3.6 Genetic Engineering of Bacteriorhodopsin for Device Applications *51*
3.7 Future Directions *53*
Acknowledgments *54*
References *54*

4 Bioelectronic Devices Controlled by Enzyme-Based Information Processing Systems *61*
Evgeny Katz
4.1 Introduction *61*
4.2 Enzyme-Based Logic Systems Producing pH Changes as Output Signals *62*

4.3 Interfacing of the Enzyme Logic Systems with Electrodes Modified with Signal-Responsive Polymers *64*
4.4 Switchable Biofuel Cells Controlled by the Enzyme Logic Systems *68*
4.5 Biomolecular Logic Systems Composed of Biocatalytic and Biorecognition Units and Their Integration with Biofuel Cells *70*
4.6 Processing of Injury Biomarkers by Enzyme Logic Systems Associated with Switchable Electrodes *74*
4.7 Summary and Outlook *77*
Acknowledgments *78*
References *78*

5 Enzyme Logic Digital Biosensors for Biomedical Applications *81*
Evgeny Katz and Joseph Wang
5.1 Introduction *81*
5.2 Enzyme-Based Logic Systems for Identification of Injury Conditions *82*
5.3 Multiplexing of Injury Codes for the Parallel Operation of Enzyme Logic Gates *85*
5.4 Scaling Up the Complexity of the Biocomputing Systems for Biomedical Applications – Mimicking Biochemical Pathways *89*
5.5 Application of Filter Systems for Improving Digitalization of the Output Signals Generated by Enzyme Logic Systems for Injury Analysis *94*
5.6 Conclusions and Perspectives *96*
Acknowledgments *98*
Appendix *98*
References *99*

6 Information Security Applications Based on Biomolecular Systems *103*
Guinevere Strack, Heather R. Luckarift, Glenn R. Johnson, and Evgeny Katz
6.1 Introduction *103*
6.2 Molecular and Bio-molecular Keypad Locks *104*
6.3 Antibody Encryption and Steganography *108*
6.4 Bio-barcode *113*
6.5 Conclusion *114*
Acknowledgments *114*
References *114*

7 Biocomputing: Explore Its Realization and Intelligent Logic Detection *117*
Ming Zhou and Shaojun Dong
7.1 Introduction *117*
7.2 DNA Biocomputing *119*

7.3 Aptamer Biocomputing *121*
7.4 Enzyme Biocomputing *124*
7.5 Conclusions and Perspectives *128*
References *129*

8 Some Experiments and Models in Molecular Computing and Robotics *133*
Milan N. Stojanovic and Darko Stefanovic
8.1 Introduction *133*
8.2 From Gates to Programmable Automata *133*
8.3 From Random Walker to Molecular Robotics *139*
8.4 Conclusions *142*
Acknowledgments *143*
References *143*

9 Biomolecular Finite Automata *145*
Tamar Ratner, Sivan Shoshani, Ron Piran, and Ehud Keinan
9.1 Introduction *145*
9.2 Biomolecular Finite Automata *146*
9.2.1 Theoretical Models of a Molecular Turing Machine *146*
9.2.2 The First Realization of an Autonomous DNA-Based Finite Automaton *150*
9.2.3 Three-Symbol-Three-State DNA-Based Automata *155*
9.2.4 Molecular Cryptosystem for Images by DNA Computing *157*
9.2.5 Molecular Computing Device for Medical Diagnosis and Treatment *In Vitro* *159*
9.2.6 DNA-Based Automaton with Bacterial Phenotype Output *161*
9.2.7 Molecular Computing with Plant Cell Phenotype *163*
9.3 Biomolecular Finite Transducer *167*
9.4 Applications in Developmental Biology *172*
9.5 Outlook *176*
References *178*

10 *In Vivo* Information Processing Using RNA Interference *181*
Yaakov Benenson
10.1 Introduction *181*
10.1.1 Regulatory Pathways as Computations *181*
10.1.2 A Computation Versus a Computer *182*
10.1.3 Prior Work on Synthetic Biomolecular Computing Circuits *182*
10.2 RNA Interference-Based Logic *183*
10.2.1 General Considerations *183*
10.2.2 Logic Circuit Blueprint *184*
10.2.3 Experimental Confirmation of the Computational Core *188*
10.3 Building the Sensory Module *189*
10.3.1 Direct Control of siRNA by mRNA Inputs *191*

10.3.2 Complex Transcriptional Regulation Using RNAi-Based Circuits *194*
10.4 Outlook *195*
References *197*

11 Biomolecular Computing Systems *199*
Harish Chandran, Sudhanshu Garg, Nikhil Gopalkrishnan, and John H. Reif
11.1 Introduction *199*
11.1.1 Organization of the Chapter *199*
11.2 DNA as a Tool for Molecular Programming *200*
11.2.1 DNA Structure *200*
11.2.2 Review of DNA Reactions *200*
11.3 Birth of DNA Computing: Adleman's Experiment and Extensions *203*
11.3.1 NP-Complete Problems *203*
11.3.2 Hamiltonian Path Problem via DNA Computing *204*
11.3.3 Other Models of DNA Computing *204*
11.3.4 Shortcomings and Nonscalability of Schemes Using DNA Computation to Solve NP-Complete Problems *204*
11.4 Computation Using DNA Tiles *205*
11.4.1 TAM: an Abstract Model of Self-Assembly *205*
11.4.2 Algorithmic Assembly via DNA Tiling Lattices *206*
11.4.2.1 Source of Errors *206*
11.4.3 Algorithmic Error Correction Schemes for Tilings *207*
11.5 Experimental Advances in Purely Hybridization-Based Computation *209*
11.6 Experimental Advances in Enzyme-Based DNA Computing *212*
11.7 Biochemical DNA Reaction Networks *217*
11.8 Conclusion: Challenges in DNA-Based Biomolecular Computation *218*
11.8.1 Scalability of Biomolecular Computations *218*
11.8.2 Ease of Design and Programmability of Biomolecular Computations *220*
11.8.3 *In Vivo* Biomolecular Computations *220*
11.8.4 Conclusions *220*
Acknowledgments *221*
References *221*

12 Enumeration Approach to the Analysis of Interacting Nucleic Acid Strands *225*
Satoshi Kobayashi and Takaya Kawakami
12.1 Introduction *225*
12.2 Definitions and Notations for Set and Multiset *226*
12.3 Chemical Equilibrium and Hybridization Reaction System *227*
12.4 Symmetric Enumeration Method *230*

12.4.1 Enumeration Graph *230*
12.4.2 Path Mappings *231*
12.4.3 Enumeration Scheme *232*
12.4.4 An Example of Enumeration Scheme – Folding of an RNA Molecule *233*
12.4.5 Convex Programming Problem for Computing Equilibrium *235*
12.5 Applying SEM to Nucleic Acid Strands Interaction *236*
12.5.1 Target Secondary Structures *237*
12.5.2 Introducing Basic Notations *237*
12.5.3 Definition of Enumeration Graph Structure *239*
12.5.4 Associated Weight Functions *241*
12.5.5 Symmetric Properties *242*
12.5.6 Complexity Issues *242*
12.6 Conclusions *243*
References *244*

13 Restriction Enzymes in Language Generation and Plasmid Computing *245*
Tom Head
13.1 Introduction *245*
13.2 Wet Splicing Systems *246*
13.3 Dry Splicing Systems *249*
13.4 Splicing Theory: Its Original Motivation and Its Extensive Unforeseen Developments *252*
13.5 Computing with Plasmids *253*
13.6 Fluid Memory *254*
13.7 Examples of Aqueous Computations *255*
13.8 Final Comments about Computing with Biomolecules *260*
References *261*

14 Development of Bacteria-Based Cellular Computing Circuits for Sensing and Control in Biological Systems *265*
Michaela A. TerAvest, Zhongjian Li, and Largus T. Angenent
14.1 Introduction *265*
14.2 Cellular Computing Circuits *267*
14.2.1 Genetic Toolbox *267*
14.2.1.1 Engineered Gene Regulation *267*
14.2.1.2 Quorum Sensing *269*
14.2.2 Implementations *269*
14.2.2.1 Oscillators *269*
14.2.2.2 Switches *270*
14.2.2.3 AND Logic Gates *270*
14.2.2.4 Edge Detector *271*
14.2.2.5 Complex Logic Functions with Multiple Strains *272*
14.2.3 Transition to *In Silico* Rational Design *273*

14.2.4 Transition from Enzyme Computing to Bacteria-Based Biocomputing *274*
14.3 Conclusion *276*
Acknowledgments *277*
References *277*

15 The Logic of Decision Making in Environmental Bacteria *279*
Rafael Silva-Rocha, Javier Tamames, and Víctor de Lorenzo
15.1 Introduction *279*
15.2 Building Models for Biological Networks *281*
15.3 Formulation and Simulation of Regulatory Networks *283*
15.3.1 Stochastic Versus Deterministic Models *284*
15.3.2 Graphical Models *285*
15.4 Boolean Analysis of Regulatory Networks *285*
15.4.1 Translating Biological Networks into Logic Circuits *286*
15.4.2 Integration of Regulatory and Metabolic Logic in the Same Boolean Circuit *287*
15.4.3 From Digital Networks to Workable Models *288*
15.5 Boolean Description of m-xylene Biodegradation by *P. putida* mt-2: the TOL logicome *289*
15.5.1 Narrative Description of the TOL Regulatory Circuit *291*
15.5.2 Deconstruction of the Ps–Pr Regulatory Node into Three Autonomous Logic Units *292*
15.5.3 Formalization of Regulatory Events at the Upper and Lower TOL Operons *294*
15.5.4 3MB Is the Endogenous Signal Carrier through the Domains of the TOL Network *296*
15.5.5 The TOL Logicome *296*
15.6 Conclusion and Outlook *298*
Acknowledgments *299*
References *299*

16 Qualitative and Quantitative Aspects of a Model for Processes Inspired by the Functioning of the Living Cell *303*
Andrzej Ehrenfeucht, Jetty Kleijn, Maciej Koutny, and Grzegorz Rozenberg
16.1 Introduction *303*
16.2 Reactions *304*
16.3 Reaction Systems *305*
16.4 Examples *307*
16.5 Reaction Systems with Measurements *310*
16.6 Generalized Reactions *312*
16.7 A Generic Quantitative Model *315*
16.8 Approximations of Gene Expression Systems *316*

16.9 Simulating Approximations by Reaction Systems *318*
16.10 Discussion *319*
Acknowledgments *321*
References *321*

17 Computational Methods for Quantitative Submodel Comparison *323*
Andrzej Mizera, Elena Czeizler, and Ion Petre
17.1 Introduction *323*
17.2 Methods for Model Decomposition *324*
17.2.1 Knockdown Mutants *324*
17.2.2 Elementary Flux Modes *325*
17.2.3 Control-Based Decomposition *325*
17.3 Methods for Submodel Comparison *327*
17.3.1 Mathematically Controlled Model Comparison *327*
17.3.2 An Extension of the Mathematically Controlled Comparison *328*
17.3.3 Local Submodel Comparison *329*
17.3.4 A Quantitative Measure for the Goodness of Model Fit Against Experimental Data *329*
17.3.5 Quantitative Refinement *330*
17.3.6 Parameter-Independent Submodel Comparison *331*
17.3.7 Model Comparison for Pathway Identification *332*
17.4 Case Study *332*
17.4.1 A Biochemical Model for the Heat Shock Response *332*
17.4.2 Control-Based Decomposition *334*
17.4.3 The Knockdown Mutants *335*
17.4.4 Local Comparison of the Knockdown Mutants *336*
17.4.5 Parameter-Independent Comparison of the Mutant Behavior *337*
17.4.6 Pathway Identification for the Phosphorylation-Driven Control of the Heat Shock Response *341*
17.5 Discussion *342*
Acknowledgments *343*
References *343*

18 Conclusions and Perspectives *347*
Evgeny Katz
References *349*

Index *351*