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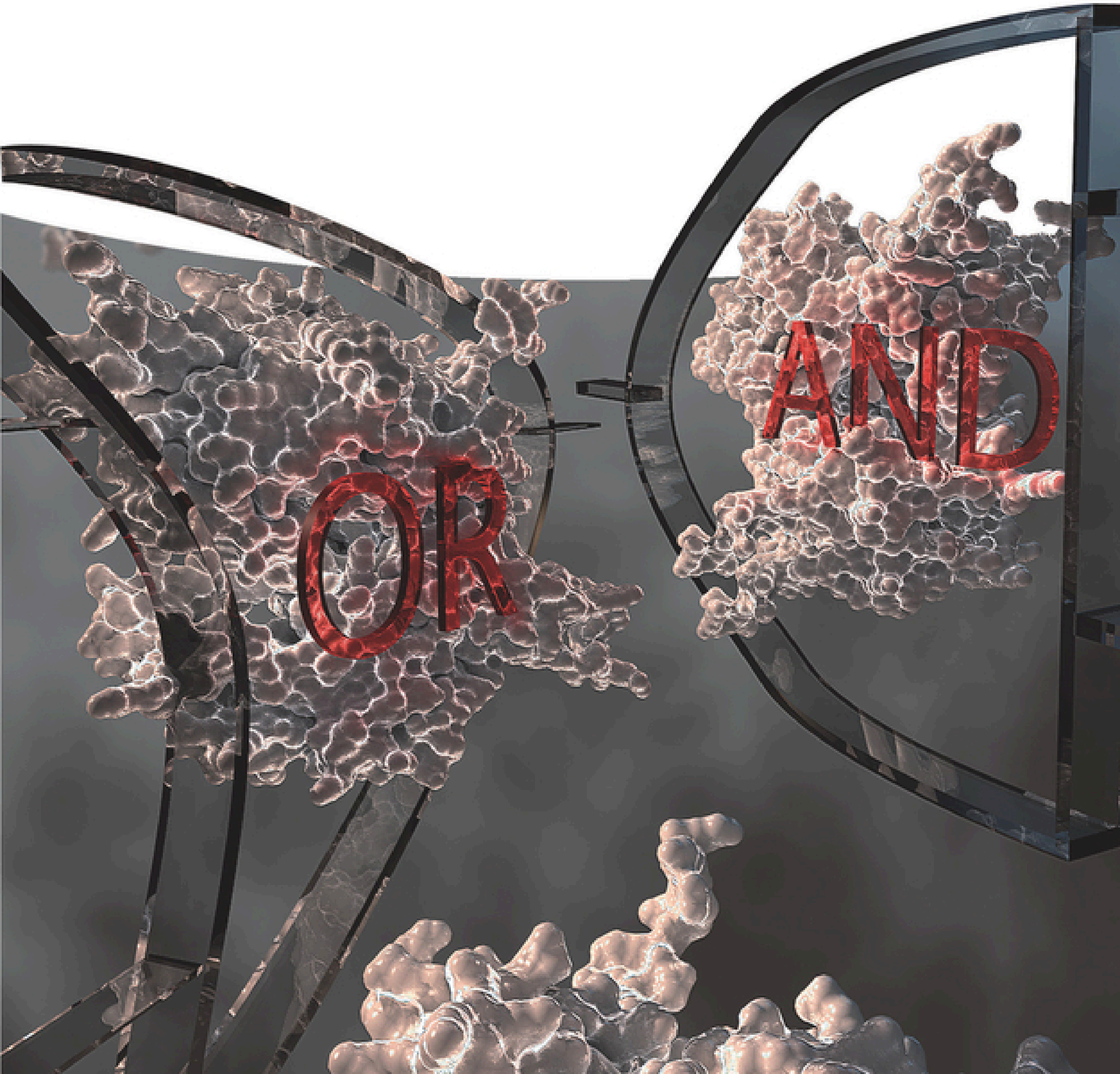

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In the memory of Professor Vladimir Privman, my good friend and collaborator.

Contents

Preface

The use of biomolecular systems for processing information, performing logic operations, computational operations, and even automata performance is a rapidly developing research area. The entire field was named with the general buzzwords, "biomolecular computing" or "biocomputing." Exciting advances in the area include the use of various biomolecular systems including proteins/enzymes, DNA, RNA, DNAzymes, antigens/antibodies, and even whole biological (usually microbial) cells operating as "hardware" for unconventional computing. The present book concentrates on enzymatic systems, which involve biocatalytic reactions utilized for information processing (biocomputing). Extensive ongoing research in the enzyme-based biocomputing, mimicking Boolean logic gates, has been motivated by potential applications in biotechnology and medicine. Furthermore, novel biosensor concepts have been contemplated with multiple inputs processed biochemically before the final output is coupled to transducing electronic or optical systems. These applications have warranted recent emphasis on networking of enzyme logic gates. First few gate networks have been experimentally realized, including coupling, for instance, to signal-responsive electrodes for signal readout. In order to achieve scalable, stable network design and functioning, considerations of noise propagation and control have been initiated as a new research direction. Optimization of single enzyme-based gates for avoiding analog noise amplification has been explored, as were certain network optimization concepts. The book reviews and exemplifies these developments, as well as offers an outlook for possible future research foci. The latter include design and uses of non-Boolean network elements, e.g., filters, as well as other developments motivated by potential novel biosensor and biotechnology applications. The most important feature of the enzyme biocomputing systems is their operation in biochemical and even biological environment. Many different applications of these systems, in addition to unconventional computation, are feasible, while their biosensor/biomedical use is obviously one of the most important applications. Interfacing of biological systems with biosensors, "smart" signal-responsive materials, and bioelectronic devices is of highest importance for future developments in the area of biomolecular computing.

The various topics covered highlight key aspects and the future perspectives of the enzyme-based computing. The different topics addressed in this book will be of high interest to the interdisciplinary community active in the area of unconventional biocomputing. The readers can find additional complementary material on molecular [1] and biomolecular [2] computing published recently by Wiley-VCH. It is hoped that the book will be important and beneficial for researchers and students working in various areas related to biochemical computing, including biochemistry, materials science, computer science, and so on. Furthermore, the book is aimed to attract young scientists and introduce them to the field while providing newcomers with an enormous collection of literature references. I, indeed, hope that the book will spark the imagination of scientists to further develop the topic.

The text was carefully proofread, and the figures were meticulously redrawn and checked to eliminate possible typos, mistakes, and unclear meaning. Still because of the large volume and big number (230) figures, some problems may appear. If this happens, the readers are advised to go to the original publications following the references provided.

A significant amount of the discussed material has originated from the studies to which I have personally contributed. I am very grateful to all scientists, researchers, and students who have participated in this research and have made the achieved results possible.

I would like to conclude this preface by thanking my wife Nina for her support in every respect in the past 47 years. Without her help and support, it would not have been possible to complete this work.

Evgeny Katz

Potsdam, NY, USA
January 2019

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2 Katz, E. (ed.) (2012). *Biomolecular Information Processing – From Logic Systems to Smart Sensors and Actuators*. Weinheim: Wiley-VCH.

Acknowledgment

Professor Vladimir Privman (1955–2018), Director of the Center for Quantum Device Technology and Robert A. Plane Professor of Physics with joint appointments in the Department of Chemistry and Biomolecular Science and Department of Electrical and Computer Engineering (Clarkson University, NY, USA), was a great contributor to the research area of enzyme computing, and this book would not be possible without his work. The majority of the material presented in this book includes contributions by Professor Privman.

His research interests spanned broad areas of advanced technology, including bio-inspired information processing, synthesis of colloids and nanoparticles, kinetics of surface processes at the nanoscale, physics of semiconductor devices, spintronics, quantum computing, statistical mechanics, chemical kinetics, and surface and polymer science.

Professor Privman began earning recognition early in his career, receiving the Petroleum Research Fund Young Investigator Award and the Clarkson University Graham Award for Young Faculty Excellence. He contributed to a wide range of scientific fields and was a lecturer or moderator at national and international conferences every year. He authored/coauthored over 280 research papers, major reviews, and books. He served on numerous boards of scientific journals, and national funding agencies, and received an American Physical Society Outstanding Referee Award. In 2005 he was named a fellow of the American Physical Society, which recognized his fundamental contributions and professional leadership in statistical physics; surface, colloid, and polymer science; and quantum information science. In 2010 he was named an International Academy, Research, and Industry Association (IARIA) fellow.

Over the past 10 years, Professor Privman has been among the key players in the unconventional computing field. Particularly noteworthy are his contributions to the integration of biomolecular computing and actuation, implementation of biochemical logical gates, biomolecular signal processing, networked enzymatic gates with filtering, associative memory based on enzymatic cascades, biochemical logic for drug release, biomolecular filters for signal separation, enzymatic systems for information processing, and digital biosensors. Professor Privman's contributions to quantum computing were in the evaluation of decoherence for quantum computing architectures, modeling of semiconductor spintronics, quantum control, nuclear spin-based memory and

logic in quantum hall semiconductors, Hamiltonians for quantum computing, and three-spin XOR gate.

In 2005 Professor Privman edited the Special Issue containing papers from the 2004 IEEE Nanotechnology Council (NTC) Quantum Device Technology Workshop, which was held on 17–21 May 2004, in Clarkson University, Potsdam, NY. The contents of the issue demonstrated breakthroughs in several fields of novel materials and devices, including biochemical logical gates, styrene butadiene rubber nanocomposites, swarms of microscale nanorobots, robots for target therapies, biomolecular motors, magnetoresistive detection of nanoparticles, and self-assembly of quantum dots. In 2017 the *International Journal of Parallel, Emergent and Distributed Systems* (vol. 32, issue 1) published a special issue *Signal processing, biosensing, and computing with bio-inspired and biochemical systems* compiled and edited by Professor Privman. He presented the field of unconventional computing with diverse contributions such as reaction–diffusion chemistry implementation of neural networks, fluidic infrastructure for enzyme-based Boolean logic circuits, architectures of nano-biointerfaces, modeling of enzymatic signal processing, wireless sensor networks with biological cultures, biosensors and memristors in networks of plants, oscillator dynamics of slime mold, insulin biosensor, and biocomputing in forensic analysis.

Professor Privman was highly regarded by his peers and students. He was proud of his trainee's success and advancement and took an active role in mentoring undergraduate, graduate, postdoc, and senior researchers in several departments at Clarkson University. He enjoyed training and collaborating with scientists throughout the United States and internationally. His passing is a great loss to the scientific community.

Professor Vladimir Privman's Works on Biomolecular and Enzymatic Computing

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Vladimir Privman

List of Abbreviations

αAmy	α-amylase (enzyme)
βAmy	β-amylase (enzyme)
α-KTG	α-ketoglutaric acid
Δf	oscillation frequency change measured by QCM
λ	wavelength
λ_{max}	wavelength of maximum absorbance in optical spectra
Θ	angle of incident light beam (in SPR measurements)
2-OG	2-oxoglutarate
2-PGA	2-phosphoglyceric acid (or salt form)
3-oxo-C12-HSL	3-oxododecanoyl homoserine lactone (QS signaling molecule)
AA	African American (ethnic origin)
Abs	optical absorbance
ABT	abdominal trauma
ABTS	2,2′-azino-*bis*(3-ethylbenzothiazoline-6-sulfonic acid) (chromogenic substrate used to follow peroxidase activity)
$ABTS_{ox}$	oxidized ABTS (colored product)
Ac	acetic acid
AChE	acetylcholinesterase (enzyme)
AcP	acetyl phosphate
AcidP	acid phosphatase (enzyme)
ADH	alcohol dehydrogenase (enzyme)
ADP	adenosine 5′-diphosphate
AFM	atomic force microscope (microscopy)
Ala	alanine (amino acid)
Ald	acetaldehyde
ALT	alanine transaminase (enzyme)
AMG	amyloglucosidase (enzyme)
AND	AND Boolean logic gate
anti-DNP	anti-dinitrophenyl IgG polyclonal antibody
anti-NT	anti-nitrotyrosine IgG polyclonal antibody
AOx	alcohol oxidase (enzyme)
AP	alkaline phosphatase (enzyme)
APTES	(3-aminopropyl)triethoxysilane (silanizing agent for modification of electrodes and nanoparticles)

ArNHOH	oxidizable hydroxylamine (product of TNT biocatalytic reduction)
ArNO	nitroso compound (product of ArNHOH biocatalytic oxidation)
Asc	ascorbate
ASCII	American Standard Code for Information Interchange
ATM	automated teller machine (as an example of an electronic device with a keypad lock system)
ATP	adenosine 5′-triphosphate
BHQ2	Black Hole Quencher® (fluorescence quencher)
Bo	borrow digit (output signal in a half-subtractor)
BSA	bovine serum albumin
Bu	butyric acid
Bu-O-Et	ethyl butyrate ester
Bu-O-Me	methyl butyrate ester
C	carry digit (output signal in a half-adder)
C4-HSL	*N*-butanoyl-l-homoserine lactone (QS signaling molecule)
CA	Caucasian (ethnic origin)
CA	chronoamperometry
CaM	calmodulin
cAMP	cyclic adenosine monophosphate (a second messenger important in biological processes)
ChOx	choline oxidase (enzyme)
CK	creatine kinase (enzyme)
CoA	coenzyme A
CN	4-chloro-1-naphthol
CNOT	Controlled NOT (reversible logic gate)
CN-ox	CN insoluble oxidized product
CNT(s)	carbon nanotube(s)
Crt	creatine
CrtP	creatine phosphate
CSWAP	Controlled-Swap (logic gate)
D	delay (flip-flop memory)
D	difference digit (output signal in a half-subtractor)
DC	direct current
DCPIP	dichlorophenolindophenol ($DCPIP_{red}$ and $DCPIP_{ox}$ are reduced and oxidized forms of DCPIP, respectively; DCPIP also corresponds to the oxidized form)
DDC	diethyldithiocarbamate (product of DS reduction)
DFG	double Feynman gate (reversible logic gate)
DHA	dehydroascorbate (product of Asc oxidation)
Diaph	diaphorase (enzyme)
dmo-bpy	4,4′-dimethoxy-2,2′-bipyridine (ligand in the redox active complex: $Os(dmo\text{-}bpy)_2Cl$)
DNA	deoxyribonucleic acid
DNAzyme	deoxyribozyme (catalytically active DNA)
DNP	2,4-dinitrophenyl (used as an antigen for anti-DNP)

DNT	2,4-dinitrotoluene
DS	disulfiram
DTT	dithiothreitol
Dz	another abbreviation for DNAzyme
E	potential applied or measured in electrochemical experiments
$E°$	standard redox potential (derived from electrochemically reversible cyclic voltammogram)
EDC	1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (carbodiimide coupling reagent)
EIS	electrolyte–insulator–semiconductor
ELISA	enzyme-linked immunosorbent assay
EN	enolase (enzyme)
Est	esterase (enzyme)
Et-O-Ac	ethyl acetate ester
EtOH	ethanol
f	oscillation frequency measured with QCM
FAM	fluorescein derivative used for labeling biomolecules
FET	field-effect transistor
FITC	fluorescein isothiocyanate (fluorescent label)
Frc	fructose
G6PDH	glucose 6-phosphate dehydrogenase (enzyme)
GDH	glucose dehydrogenase (enzyme)
Glc	glucose
Glc1P	glucose-1-phosphate
Glc6P	glucose-6-phosphate
Glc6PA	gluconate-6-phosphate acid (product of Glc6P oxidation)
GlcA	gluconic acid (product of glucose oxidation)
Glu	glutamate (amino acid, salt form)
GluOx	glutamate oxidase (enzyme)
GlutOx	glutathione oxidase (enzyme)
GOx	glucose oxidase (enzyme)
GR	glutathione reductase (enzyme)
GSH	glutathione (reduced form)
GSSG	glutathione (dimeric oxidized form)
HEPES	(4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid) (buffer)
HK	hexokinase (enzyme)
HPLC	high-performance liquid chromatography
HRP	horseradish peroxidase (enzyme)
HRP-Ab	antibody labeled with HRP enzyme
HS	hemorrhagic shock
HAS	human serum albumin
i	current density produced by a biofuel cell on an external ohmic resistance
ID	Identity (YES) gate
INHIB	Inhibited Boolean logic gate

Inv	invertase (enzyme)
INV	Inverter (logic element)
I_p	peak current (measured with cyclic voltammetry)
IPTG	isopropyl β-D-thiogalactoside (artificial inducer in cellular regulating processes).
IR	infrared (light)
i_{sc}	short circuit current density produced by a biofuel cell on an external ohmic resistance
ITO	indium tin oxide (electrode)
JK	Jack Kilby (flip-flop memory)
Lac	lactate
LDH	lactate dehydrogenase (enzyme)
LI	liver injury
LOx	lactate oxidase (enzyme)
LSPR	localized surface plasmon resonance
Luc	luciferase (enzyme)
Lucif	luciferin
M13	calmodulin-binding peptide
Maj	majority logic gate
Mal	malate
Malt	maltose
MB	methylene blue (electron transfer mediator operating with GOx); MB_{ox} and MB_{red} are oxidized and reduced forms of MB, respectively
MDH	malate dehydrogenase (enzyme)
MHC I	MHC class I molecules are one of two primary classes of major histocompatibility complex molecules and are found on the cell surface of all nucleated cells in the bodies of jawed vertebrates
Min	minority logic gate
MMP2 and MMP7	matrix metalloproteinases (cancer biomarkers)
MNP(s)	magnetic nanoparticle(s)
MP-11	microperoxidase-11
MPh	maltose phosphorylase (enzyme)
MPAX	methyl paraoxon (acetylcholinesterase inhibitor; model nerve agent)
MWCNT(s)	multiwalled carbon nanotube(s)
NAD^+	nicotinamide adenine dinucleotide (oxidized form)
NADH	nicotinamide adenine dinucleotide (reduced form)
NADH-POx	NADH peroxidase (enzyme)
$NADP^+$	β-nicotinamide adenine dinucleotide phosphate oxidized
NADPH	β-nicotinamide adenine dinucleotide phosphate reduced
NAD(P)H	represent either NADH or NADPH
NAND	NOT–AND Boolean logic gate
NE	norepinephrine (catecholamine hormone neurotransmitter)
NHS	*N*-hydroxysuccinimide

NOR	NOT–OR Boolean logic gate
NOT	Inverted Identity Boolean logic gate
NP(s)	nanoparticle(s)
NRd	nitroreductase (enzyme)
NT	3-nitro-L-tyrosine (used as an antigen for anti-NT)
NXOR	NOT-Exclusive-OR Boolean logic gate
O.D.	optical density (in optical absorbance measurements)
QCM	quartz crystal microbalance
Q-F	oligonucleotide labeled with a fluorescent dye at one end and with a quencher at another end; F is a fluorescent dye; Q is a quencher
QS	quorum sensing
OPH	organophosphorous hydrolase (enzyme)
OR	OR Boolean logic gate
OS	oxidative stress
Q_t	initial (present) state of a flip-flop device
Q_{t+1}	next state of a flip-flop device
Q_{t+2}	next, next state of a flip-flop device
OxAc	oxaloacetate
O/W	oil-in-water Pickering emulsion
Qz6	Quasar 670 (fluorescent dye)
P2VP	poly(2-vinyl pyridine)
P4VP	poly(4-vinyl pyridine)
PAX	paraoxon (acetylcholinesterase inhibitor; model nerve agent)
PB	Prussian blue
PBSE	1-pyrenebutanoic acid succinimidyl ester (heterobifunctional reagent)
P.D.	power density produced by a biofuel cell on an external ohmic resistance
$P.D._{max}$	maximum power density produced by a biofuel cell on an external optimized ohmic resistance
PDH	pyruvate dehydrogenase (enzyme)
PDI	protein disulfide-isomerase (enzyme)
PEI	polyethyleneimine
PEO	poly(ethylene oxide)
PEP	phospho(enol)pyruvic acid (or phosphoenol pyruvate in the form of salt)
Pi	inorganic phosphate
PK	pyruvate kinase (enzyme)
pK_a	acid dissociation constant
PNP	*p*-nitrophenol
PNPP	*p*-nitrophenyl phosphate
POx	pyruvate oxidase (enzyme)
Ppy	polypyrrole
Ppy-ox	polypyrrole oxidized state
Ppy-red	polypyrrole reduced state

PQQ	pyrroloquinoline quinone
PQQ-GDH	PQQ-dependent glucose dehydrogenase (enzyme)
PS	polystyrene
Pyr	pyruvate
R	reset signal
R	reflectance measured by SPR
R	external load resistance connected to a biofuel cell
R_{cell}	ohmic resistance measured in a bulk solution in an electrochemical cell
RE	reference electrode
R_{et}	electron transfer resistance (measured by Faradaic impedance spectroscopy)
RI	radiation injury
RNA	ribonucleic acid
RNS	reactive nitrogen species
ROC	receiver operating characteristic
ROS	reactive oxygen species
S	set signal
S	sum digit (output signal in a half-adder)
SAND	single inversion AND (logic gate equivalent to NOT–AND operation, where inversion NOT is applied to one of the inputs)
SEM	scanning electron microscopy
SPE	screen-printed electrode
SPR	surface plasmon resonance
SR	set/reset (flip-flop memory)
STI	soft tissue injury
SWV	square wave voltammetry
T	toggle (flip-flop memory)
TBI	traumatic brain injury
t_g	gate time (time of reaction after which the gate response is measured)
TMB	3,3′,5,5′-tetramethylbenzidine (chromogenic substrate used to follow peroxidase activity)
TMB_{dox}	TMB double-oxidized product
TMB_{ox}	oxidized colored form of TMB
TMB_{red}	TMB reduced original state (the same as TMB)
TMB_{sox}	TMB single-oxidized product (the same as TMB_{ox})
TNT	trinitrotoluene (explosive)
Tris	2-amino-2-(hydroxymethyl)propane-1,3-diol (buffer)
UV	ultraviolet (light)
Ure	urease (enzyme)
V	voltage produced by a biofuel cell on an external ohmic resistance
V_a	alternative voltage applied between the conducting support and reference electrode of the EIS devise