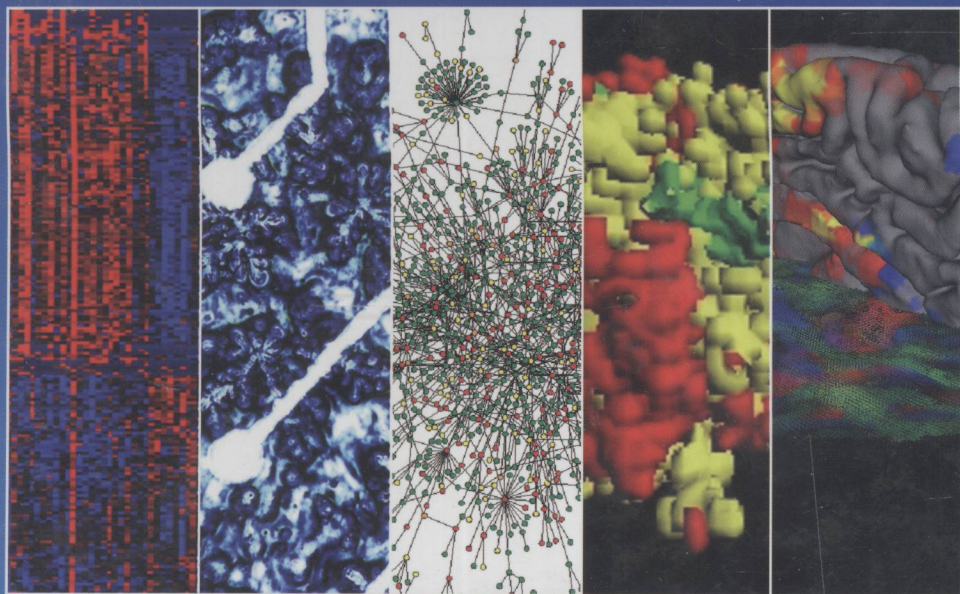


Topics in
Biomedical Engineering
International Book Series
Series Editor: Evangelia Micheli-Tzanakou

Complex Systems Science in Biomedicine



Edited by
Thomas S. Deisboeck
J. Yasha Kresh

R318
C-11.2

Complex Systems Science in Biomedicine

Edited by

Thomas S. Deisboeck

*Department of Radiology
Massachusetts General Hospital, and
Harvard Medical School
Boston, Massachusetts*

and

J. Yasha Kresh

*Department of Cardiothoracic Surgery and Medicine
Drexel University College of Medicine
Philadelphia, Pennsylvania*



E200603335



Springer

Thomas S. Deisboeck, M.D.
Assistant Professor of Radiology (HMS,
MGH, HST)
Director, Complex Biosystems Modeling
Laboratory
Harvard–MIT (HST) Athinoula A.
Martinos Center for Biomedical
Imaging
Massachusetts General Hospital–East
Bldg. 149, 13th Street, Charlestown,
MA 02129
deisboec@helix.mgh.harvard.edu

J. Yasha Kresh, Ph.D., F.A.C.C.
Professor and Research Director
Dept. of Cardiothoracic Surgery
and
Professor of Medicine
Director, Cardiovascular Biophysics
Drexel Univ. College of Medicine
215 N. 15th Street, MS# 111
Philadelphia, PA 19102-1192
jkresh@drexelmed.edu

Front cover: The first figure appears courtesy of Gustavo Stolovitzky (IBM T. J. Watson Research Center). The second appears courtesy of J. Yasha Kresh (Drexel University College of Medicine). The third appears with permission from the publisher *Nature* <http://www.nature.com/> and originally appeared in print as Figure 1 in *Nature* **411**:41–42, 2001 “Lethality and centrality in protein networks,” by H. Jeong, S. P. Mason, A.-L. Barabási, and Z. N. Oltvai. The fourth appears courtesy of Ricard V. Solé (ICREA Complex Systems Lab, Universitat Pompeu Fabra). The right-hand figure appears courtesy of Josh Snyder, David Tuch, Nouchine Hadjikhani, and Bruce Fischl (Athinoula A. Martinos Center for Biomedical Imaging, Harvard Medical School).

Library of Congress Control Number: 2005934914

ISBN-10: 0-387-30241-7

ISBN-13: 978-0387-30241-6

©2006 Springer Inc.

All rights reserved. This work may not be translated or copied in whole or in part without the written permission of the publisher (Springer Inc., 233 Spring Street, New York, NY 10013, USA), except for brief excerpts in connection with reviews or scholarly analysis. Use in connection with any form of information storage and retrieval, electronic adaptation, computer software, or by similar or dissimilar methodology now known or hereafter developed is forbidden.

The use in this publication of trade names, trademarks, service marks and similar terms, even if they are not identified as such, is not to be taken as an expression of opinion as to whether or not they are subject to proprietary rights.

Printed in Singapore

9 8 7 6 5 4 3 2 1

springer.com

*Complex Systems Science
in Biomedicine*

TOPICS IN BIOMEDICAL ENGINEERING INTERNATIONAL BOOK SERIES

Series Editor: Evangelia Micheli-Tzanakou
Rutgers University
Piscataway, New Jersey

Signals and Systems in Biomedical Engineering:
Signal Processing and Physiological Systems Modeling
Suresh R. Devasahayam

Models of the Visual System
Edited by George K. Hung and Kenneth J. Ciuffreda

PDE and Level Sets: Algorithmic Approaches to Static and Motion Imagery
Edited by Jasjit S. Suri and Swamy Laxminarayan

Frontiers in Biomedical Engineering:
Edited by Ned H.C. Hwang and Savio L-Y. Woo

Handbook of Biomedical Image Analysis:
Volume I: Segmentation Models Part A
Edited by Jasjit S. Suri, David L. Wilson, and Swamy Laxminarayan

Handbook of Biomedical Image Analysis:
Volume II: Segmentation Models Part B
Edited by Jasjit S. Suri, David L. Wilson, and Swamy Laxminarayan

Handbook of Biomedical Image Analysis:
Volume III: Registration Models
Edited by Jasjit S. Suri, David L. Wilson, and Swamy Laxminarayan

Complex Systems Science in Biomedicine
Edited by Thomas S. Deisboeck and J. Yasha Kresh



A Continuation Order Plan is available for this series. A continuation order will bring delivery of each new volume immediately upon publication. Volumes are billed only upon actual shipment. For further information please contact the publisher.

ACKNOWLEDGMENTS

We gratefully acknowledge the participation of everyone involved in the making of this textbook. Our special thanks go to the contributing authors, whose expertise and enthusiastic commitments made this volume a reality. We also thank our colleagues, whose insights helped shape this book, in particular Tom Kepler, Stuart Kauffman, Ary Goldberger, and Bernard Blickman, as well as Yuri Mansury, Chaitanya Athale, Brian Gregor, Meg Etherington, and Pam Fried. We especially appreciate the energy and excitement of the Springer publishing team (Aaron Johnson, Tim Oliver, Jasmine Benzvi, Shoshana Sternlicht, and Krista Zimmer), whose unwavering patience and tenacity ensured that the project go the distance. Finally, our deepest thanks to our families, who encouraged us with their love and support through the years of continuous intensity and concentration that this effort required. We could not have done it without you: Lizette M. Pérez-Deisboeck and Myrna P. Kresh.

Thomas S. Deisboeck, MD
Boston, Massachusetts

J. Yasha Kresh, PhD
Philadelphia, Pennsylvania

PREFACE

Work on Deisboeck and Kresh's *Complex Systems Science in BioMedicine* started years ago. In fact, thoughts and ideas leading up to this textbook date back to our first conversation, sometime in the fall of 1996. We quickly found common ground, and talked about emergence and self-organization and their relevance for medicine. We were both fascinated by the idea of complexity and marveled about its tremendous possibilities for cancer research, which was then and still is Tom's main scientific interest. Much has happened in science and technology since we first discussed our vision. For instance, in a remarkable international effort the human genome has been deciphered, nanotechnology has become a household name, and computing infrastructure, a critical enabler, is as powerful and affordable as ever before.

It is exactly *because* of this unprecedented progress that *Complex Systems Science in BioMedicine* is now making a case for a new approach in the life sciences. So let us start then with the obvious question first: why do we need a new fresh approach to ensure continued progress in the biomedical sciences? Did decades of methodically thorough research not yield great accomplishments and trigger an unparalleled productivity, with each year seeing thousands of scientific papers published in peer-reviewed journals? Certainly. *Reductionism* has led to ever-growing knowledge about isolated molecular pathways and selected portions of disease processes. We concede, dissecting biological mechanisms into bits and pieces has been utterly successful—if the number of fragmented discoveries is to be the decisive parameter. However, if we take understanding connectivity across scales, or better yet, *function* as the yardstick for measuring scientific achievements, much less progress can be claimed. Neither the vision nor the technical tools necessary to achieve these goals are "mainstream" yet. But there are signs in the biomedical sciences that things are changing—clear signs.

Indeed, most of the field involved in mapping the human genome in the 1990s is now engaged in *functional* genomics. Beginning to realize that the sum of its genes and proteins will not be able to explain a single cell's behavior, much less cell–cell interaction dynamics, let alone entire organ systems, we remember Aristotle, who had already argued that "*The whole is more than the sum of its parts.*" For biomedicine it means that, no matter how many more

details we enthusiastically discover on ever smaller scales, we fail in deducing the complexity of a cell or multicellular tissue on the basis of this fragmented knowledge alone. In other words, piecing it together afterwards will not work. We need a new scientific approach, one that takes the nonlinearity of the majority of biological processes as much into account as their multi-scaled character. We believe that we are at a crucial bifurcation, where we need to integrate knowledge rather than dissect it, where we need to collaborate intensely across disciplines, theoretically and experimentally, in order to move forward. Complex systems science can match this challenge. Intrinsically multidisciplinary, it comprises concepts and quantitative tools that enable us to investigate how multiple biological elements interact and how molecular networks guide cell behavior and ultimately determine tissue function.

You might wonder how this is any different from, say physiology, a cornerstone of classic biomedical training. Indeed, physiology, the science of how living organisms function, may well be regarded as a predecessor of what many in the computational biology community now call "systems biology" and which clearly overlaps with complexity science in its goals. Where they differ, however, is in the *approach* to get there. Complex systems science applies a set of concepts and quantitative tools that are based on analogy and commonality, if not universality, between distinctively different systems, biologically or otherwise. Let us give you an example. The reason my, i.e., Tom's, laboratory developed an agent-based model to study cancer cell migration was an admittedly rather tired look out of a window while approaching London's Heathrow Airport by night several years back. What caught my attention was that, from above, the busy suburbs and streets resembled the cellular clusters and path patterns of a growing biosystem where single cells rather than people represent the system's individual "agents." Could one possibly investigate the metabolism-driven interaction of a rapidly evolving multicellular system, internally and with its microenvironment, in a way similar to how social scientists analyze the adaptive, economically driven behavior seen in expanding human societies? If so, then why not try an urban-planning approach for cancer research in an effort to better understand the dynamics of growth, migration and aggregation in tumor cell populations? Chapter 6.3 (Part III) summarizes some of the intriguing results arising from this line of work. This example illustrates how complex systems science approaches the problem at hand with tools adapted from nonlinear dynamics, applying sometimes rather abstract modeling and simulation techniques ranging from network theory to agent-based frameworks. It follows a "top-down" concept based on the claim that abstraction, not simplification, is the key to understanding the complexity of interaction between multiple parts on and across various scales of interest. That, however, is distinctively different from classic physiology, which uses biophysics and engineering concepts to describe the biological entity of interest in as much detail as available and, thus, "bottom-up." Let us emphasize that tackling the very same scientific problem from two seemingly opposing sides should not be seen as much as a case of competing approaches but as an exciting opportunity to exploit their mutual strengths in going forward.

Complex Systems Science in BioMedicine presents some of the fundamental theoretical basics of this rapidly emerging field and exemplifies the potential of the new approach by studying such diverse areas as molecular networks and developmental processes, the immune and nervous systems, the heart, cancer, and multi-organ failure. In this effort, the book itself follows a *multi-scaled* approach from molecular to macroscopic, thereby discussing both the normal and diseased states in selected topics. The invited contributions intentionally represent the dynamic state of the field in that biophysics, bioengineering, and computational biology modeling works are put side by side with complex systems-driven approaches. We believe that such juxtaposition not only anchors the new approach properly in established terrain but also helps showcase the differences.

A section on *emergent* technologies, no matter how long, can hardly ever be complete and, since the book was started years back, must run the risk of being outdated by the time of publication. By taking this risk we show by example that this novel approach has already led to and will continue to inspire design and development of cutting edge technology, ranging from micro-fluidics and innovative database management to multi-scale bioengineering, neuromorphic systems, functional MR imaging, and even operating room design. Undoubtedly, these and other techniques will feedback vital data and thus help complex systems science achieve its goals.

Finally, is there something like complex systems *science* at all or is it merely a powerful tool kit? As stated earlier and as reviewed in the book, there are certain techniques that are ubiquitous for the study of complex systems in economics, population dynamics, and biology. The title of the book reveals that we advocate the application of these techniques *also* to relevant areas in biomedicine where reductionism may have reached its limits. Nothing more, nothing less. As such, this book presents visionary ideas and their potential impact on future directions in biomedical research. It is not and cannot be definitive. Rather, we let the reader judge how far this, our field, has come, and if the presented work at this stage represents merely a promising, fresh approach or if it already signals the dawn of a new and yet to be fully defined science.

As described in detail in Yasha Kresh's introductory chapter, the origins of applying systems ideas in one form or another to the life sciences date back at least several decades. And while initial efforts to move complex systems further into the center of mainstream medicine were undertaken by a few pioneers, this has certainly changed. Over the last years, many colleagues have embraced the necessity of moving in this new direction, also documented by the enthusiastic feedback we received when we asked for participation in this multi-authored book. The newly established multidisciplinary graduate and postgraduate training curricula, sprouting complex systems-related academic centers as well as novel crosscutting grant funding programs, are testimony that these ideas are starting to catch on. What counts now are the steps we take in order to further foster this nascent development. As such, if *Complex Systems Science in BioMedicine* can help draw more attention to the application of complexity techniques to important questions in biomedicine and thus help support ongoing

and upcoming scientific, teaching, and training efforts, we will consider it successful.

The quest for novel ways of thinking was what brought us together back in 1996, first as colleagues, now also as friends. It is the immense potential of complex systems science that provided a source of relentless energy for this textbook and that continues to fuel our scientific work.

Thomas S. Deisboeck, MD
Boston, Massachusetts

Stuart A. Kauffman, MD
Santa Fe, New Mexico

CONTENTS

Part I: Introduction

INTEGRATIVE SYSTEMS VIEW OF LIFE: PERSPECTIVES FROM GENERAL SYSTEMS THINKING.....	3
<i>J. Yasha Kresh</i>	
1. Introduction	4
2. General System Theory: The Laws of Integrated Wholes	5
3. Systemic Principles of Cybernetics.....	6
4. Biological Systematics: Understanding Whole Systems.....	9
5. Systems Biology and Mathematical Modeling	17
6. Emergence: Complex Adaptive Systems	21
7. The Complex Systems in Systems Biology	26

Part II: Complex Systems Science: The Basics

Chapter 1	
METHODS AND TECHNIQUES OF COMPLEX SYSTEMS SCIENCE: AN OVERVIEW	33
<i>Cosma Rohilla Shalizi</i>	
1. Introduction	33
2. Statistical Learning and Data-Mining	37
3. Time-Series Analysis.....	46
4. Cellular Automata.....	63
5. Agent-Based Models	65
6. Evaluating Models of Complex Systems	70
7. Information Theory.....	76
8. Complexity Measures	81
9. Guide to Further Reading	95
Chapter 2	
NONLINEAR DYNAMICAL SYSTEMS	115
<i>Joshua E. S. Socolar</i>	
1. Introduction	115
2. Dynamical Systems in General.....	118

3. Linear Systems and Some Basic Vocabulary.....	119
4. Nonlinear Effects in Simple Systems.....	121
5. Two Types of Complexity: Spatial Structure and Network Structure.....	130
6. Discussion and Conclusions	136

Chapter 3

BIOLOGICAL SCALING AND PHYSIOLOGICAL TIME:

BIOMEDICAL APPLICATIONS	141
-------------------------------	-----

*Van M. Savage and Geoffrey B. West, in collaboration with A.P. Allen,
J.H. Brown, B.J. Enquist, J.F. Gillooly, A.B. Herman, and W.H. Woodruff*

1. Introduction	142
2. Model Description: Theory for the Origin of Scaling Relationships	146
3. Biomedical Applications.....	153
4. Discussion and Conclusions	158

Chapter 4

THE ARCHITECTURE OF BIOLOGICAL NETWORKS	165
---	-----

Stefan Wuchty, Erszébet Ravasz, and Albert-László Barabási

1. Introduction	165
2. Basic Network Features	166
3. Networks Models.....	169
4. Biological Networks	172
5. Conclusions	176

Chapter 5

ROBUSTNESS IN BIOLOGICAL SYSTEMS:

A PROVISIONAL TAXONOMY	183
------------------------------	-----

David C. Krakauer

1. A Fundamental Biological Dichotomy: Robustness and Evolvability	183
2. Genotypic versus Environmental versus Functional Robustness	185
3. Principles and Parameters of Robust Organization	185
4. Case Studies of Robust Principles	190
5. Awaiting a Synthesis of Robustness in Biological Systems	201

Part III: Complex Adaptive Biosystems: A Multi-Scaled Approach

Section III.1: Complexity in Molecular Networks

Chapter 1.1

NOISE IN GENE REGULATORY NETWORKS	211
---	-----

Juan M. Pedraza and Alexander van Oudenaarden

1. Introduction	211
2. The Master Equation Approach.....	212
3. The Langevin Approach	220
4. Discussion and Conclusions	224

Chapter 1.2	
MODELING RNA FOLDING.....	227
<i>Ivo L. Hofacker and Peter F. Stadler</i>	
1. Introduction	227
2. RNA Secondary Structures and Their Prediction	230
3. Neutral Networks in the Sequence Space	232
4. Conserved RNA Structures.....	235
5. Discussion.....	236
Chapter 1.3	
PROTEIN NETWORKS.....	247
<i>Andreas Wagner</i>	
1. Introduction	247
2. Large-Scale Approaches to Identify Protein Expression.....	248
3. Identifying Protein Interactions	253
4. Medical Applications.....	259
Chapter 1.4	
ELECTRONIC CELL ENVIRONMENTS: COMBINING GENE, PROTEIN, AND METABOLIC NETWORKS	265
<i>Pawan Dhar and Masaru Tomita</i>	
1. Introduction	265
2. Biomedical Background	266
3. Modeling and Simulation.....	268
4. Future Work and Its Relevance to Biomedicine	277

Section III.2: The Cell as a Complex System

Chapter 2.1	
TENSEGRITY, DYNAMIC NETWORKS, AND COMPLEX SYSTEMS BIOLOGY: EMERGENCE IN STRUCTURAL AND INFORMATION NETWORKS WITHIN LIVING CELLS.....	283
<i>Sui Huang, Cornel Sultan, and Donald E. Ingber</i>	
1. Introduction: Molecular Biology and Complex System Sciences.....	284
2. Complexity in Living Systems.....	287
3. Model: Networks as the General Conceptual Framework	288
4. Results	290
5. Conclusion.....	306
Chapter 2.2	
SPATIOTEMPORAL DYNAMICS OF EUKARYOTIC GRADIENT SENSING	311
<i>K.K. Subramanian and Atul Narang</i>	
1. Introduction	312
2. Model and Simulation.....	317
3. Future Work.....	327

Chapter 2.3	
PATTERNING BY EGF RECEPTOR: MODELS FROM <i>DROSOPHILA</i> DEVELOPMENT	333
<i>Lea A. Goentoro and Stanislav Y. Shvartsman</i>	
1. Introduction	333
2. Two Examples of EGFR Signaling in Fruit Fly Development	335
3. Modeling and Computational Analysis of Autocrine and Paracrine Networks.....	341
4. Conclusions and Outlook.....	349

Section III.3: Developmental Biology and the Cardiac System

Chapter 3.1	
DEVELOPMENTAL BIOLOGY: BRANCHING MORPHOGENESIS	357
<i>Sharon R. Lubkin</i>	
1. Introduction	357
2. Previous Work	360
3. Model.....	361
4. Discussion and Conclusions	368
Chapter 3.2	
MODELING CARDIAC FUNCTION	375
<i>Raimond L. Winslow</i>	
1. Introduction	375
2. Cellular Models	376
3. Models of the Cardiac Ventricles	392
4. Discussion and Conclusions	402
Chapter 3.3	
CARDIAC OSCILLATIONS AND ARRHYTHMIA ANALYSIS	409
<i>Leon Glass</i>	
1. Introduction	409
2. Two Arrhythmias with a Simple Mathematical Analysis	412
3. Reentrant Arrhythmias.....	414
4. Future Prospects	416

Section III.4: The Immune System

Chapter 4.1	
HOW DISTRIBUTED FEEDBACKS FROM MULTIPLE SENSORS CAN IMPROVE SYSTEM PERFORMANCE: IMMUNOLOGY AND MULTIPLE-ORGAN REGULATION	425
<i>Lee A. Segel</i>	
1. Introduction	425
2. Therapy as an Information-Yielding Perturbation	426
3. Employing Information on Progress toward Multiple Goals to Regulate the Immune Response.....	427

4. Cytokines 431
 5. Contending with Multiple Independent Goals 432
 6. Relevance to Biomedicine 433
 Appendix: Equations for the Mathematical model 435

Chapter 4.2

MICROSIMULATION OF INDUCIBLE REORGANIZATION

IN IMMUNITY 437
Thomas B. Kepler

1. Introduction 437
 2. Model 440
 3. Results 444
 4. Discussion and Conclusion 447

Chapter 4.3

THE COMPLEXITY OF THE IMMUNE SYSTEM: SCALING LAWS 451

Alan S. Perelson, Jason G. Bragg, and Frederik W. Wiegel

1. Introduction 451
 2. Scaling Laws in Immunology 453
 3. Conclusions 457

Section III.5: The Nervous System

Chapter 5.1

NEUROBIOLOGY AND COMPLEX BIOSYSTEM MODELING 463

George N. Reeke Jr.

1. Neuronal Systems Dynamics 464
 2. Future Work and Relevance to Biomedicine 473
 3. Conclusions 477

Chapter 5.2

MODELING SPONTANEOUS EPISODIC ACTIVITY IN DEVELOPING

NEURONAL NETWORKS 483

Joël Tabak and John Rinzel

1. Introduction 484
 2. Spontaneous Activity in Developing Networks 484
 3. Model of Spontaneous Activity in the Embryonic Chick Spinal Cord 487
 4. Properties and Applications of the Model 490
 5. Discussion and Future Work 500

Chapter 5.3

CLINICAL NEURO-CYBERNETICS: MOTOR LEARNING

IN NEURONAL SYSTEMS 507

Florian P. Kolb and Dagmar Timmann

1. Introduction 507
 2. Experimental Approaches and Behavioral Data 512
 3. Theoretical Approaches 522
 4. Relevance for Patients and Therapy 529

Section III.6: Cancer: A Systems Approach

Chapter 6.1	
MODELING CANCER AS A COMPLEX ADAPTIVE SYSTEM: GENETIC INSTABILITY AND EVOLUTION	537
<i>Kenneth J. Pienta</i>	
1. Introduction	537
2. Cancer Risk in the Context of an Evolutionary Paradigm	538
3. Cancer Evolution in the Context of Recent Human Evolution	540
4. Modeling Cancer as a Complex Adaptive System at the Level of the Cell	544
5. Conclusion: Applying Complexity Theory toward a Cure for Cancer.....	551
Chapter 6.2	
SPATIAL DYNAMICS IN CANCER.....	557
<i>Ricard V. Solé, Isabel González García, and José Costa</i>	
1. Introduction	557
2. Population Dynamics.....	559
3. Competition in Tumor Cell Populations	560
4. Competition with Spatial Dynamics	563
5. Metapopulation Dynamics and Cancer Heterogeneity.....	565
6. Discussion.....	569
Chapter 6.3	
MODELING TUMORS AS COMPLEX BIOSYSTEMS: AN AGENT-BASED APPROACH.....	573
<i>Yuri Mansury and Thomas S. Deisboeck</i>	
1. Introduction	573
2. Previous Works.....	576
3. Mathematical Model.....	579
4. Specifications of the Model	586
5. Basic Model Setup.....	589
6. Results	592
7. Discussion, Conclusions, and Future Work	597

Section III.7: The Interaction of Complex Biosystems

Chapter 7.1	
THE COMPLEXITY OF DYNAMIC HOST NETWORKS	605
<i>Steve W. Cole</i>	
1. Introduction	605
2. Model.....	606
3. Results	607
4. Discussion and Conclusions	621
Appendix	622

Chapter 7.2	
PHYSIOLOGIC FAILURE: MULTIPLE ORGAN DYSFUNCTION SYNDROME	631
<i>Timothy G. Buchman</i>	
1. Introduction	631
2. Previous Work	633
3. Model.....	635
4. Results	636
5. Implications for Treatment	637
6. Summary and Perspective.....	638
 Chapter 7.3	
AGING AS A PROCESS OF COMPLEXITY LOSS	641
<i>Lewis A. Lipsitz</i>	
1. Introduction	641
2. Measures of Complexity Loss	643
3. Examples of Complexity Loss with Aging.....	646
4. Mechanisms of Physiologic Complexity	648
5. Loss of Complexity as a Pathway to Frailty in Old Age.....	649
6. Interventions to Restore Complexity in Physiologic Systems	650
7. Conclusion.....	652

Part IV: Enabling Technologies

Chapter 1	
BIOMEDICAL MICROFLUIDICS AND ELECTROKINETICS	657
<i>Steve Wereley and Carl Meinhart</i>	
1. Introduction	658
2. DC Electrokinetics.....	659
3. AC Electrokinetics.....	663
4. Experimental Measurements of Electrokinetics.....	671
5. Conclusions	675
 Chapter 2	
GENE SELECTION STRATEGIES IN MICROARRAY EXPRESSION DATA: APPLICATIONS TO CASE-CONTROL STUDIES.....	679
<i>Gustavo A. Stolovitzky</i>	
1. Introduction	679
2. Previous Work: Gene Selection Methods in Microarray Data.....	681
3. Combining Selection Methods Produces a Richer Set of Differentially Expressed Genes	685
4. Gene Expression Arrays Can Be Used for Diagnostics: A Case Study	690
5. Discussion and Conclusions	695