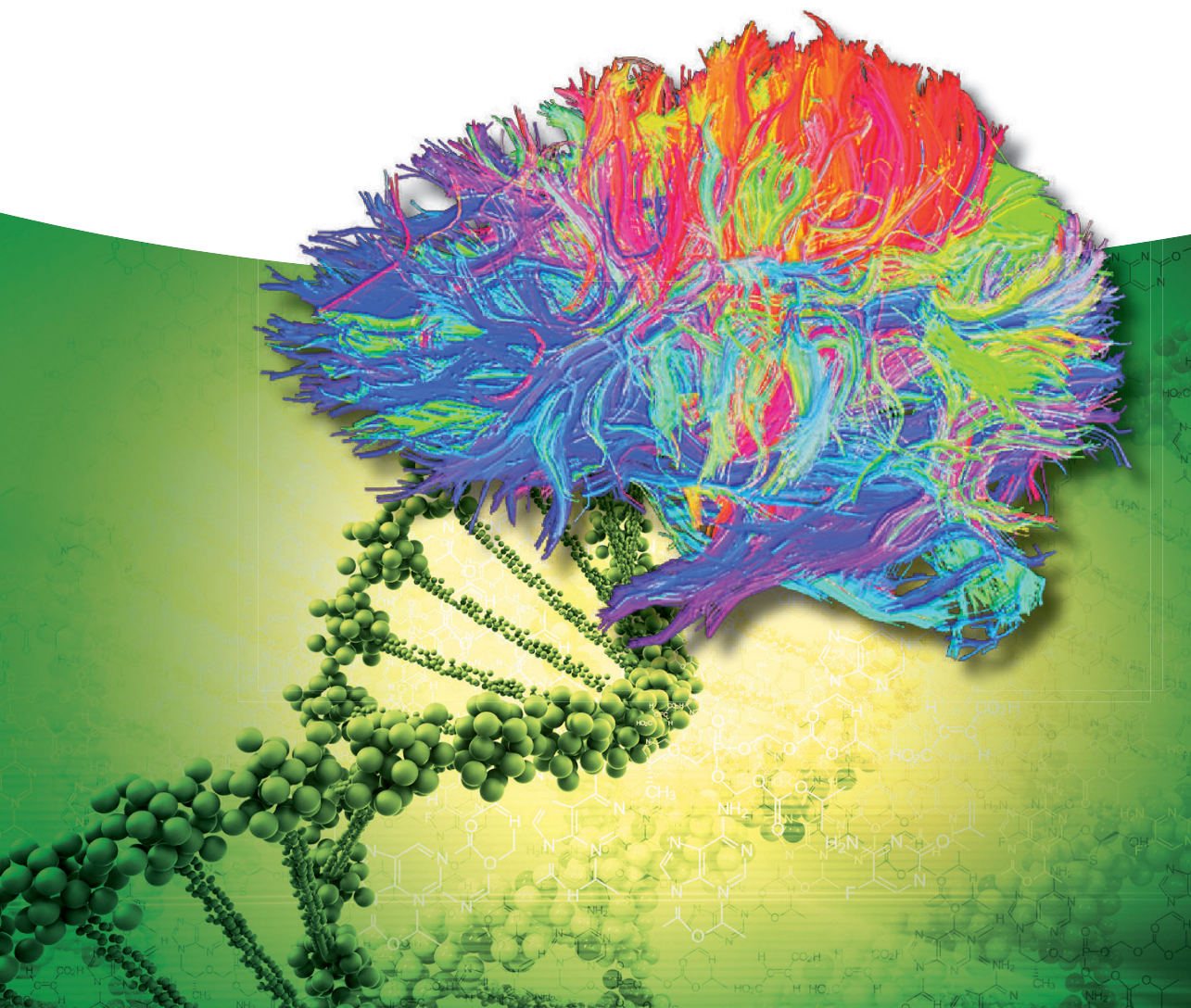


Edited by  
Misha (Meyer) Z. Pesenson

# Multiscale Analysis and Nonlinear Dynamics

From Genes to the Brain





*Edited by*  
*Misha (Meyer) Z. Pesenson*

**Multiscale Analysis and  
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## **Multiscale Analysis and Nonlinear Dynamics**

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#### The Editor

Dr. Misha (Meyer) Z. Pesenson  
California Institute of Technology  
Dept. of Computing & Mathemat. Sciences.  
Pasadena, CA, USA  
[mzp@cms.caltech.edu](mailto:mzp@cms.caltech.edu)

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## Contents

**List of Contributors** XIII

**Preface** XVII

<b>1</b>	<b>Introduction: Multiscale Analysis – Modeling, Data, Networks, and Nonlinear Dynamics</b>	<b>1</b>
	<i>Misha (Meyer) Z. Pesenson</i>	
1.1	Multiscale Modeling	5
1.1.1	Domain-Specific Modeling	6
1.1.2	Analysis	7
1.1.3	Model Interpretation and Verification: Experimental/Simulation Data	9
1.2	Multiresolution Analysis and Processing of High-Dimensional Information/Data	10
1.3	Multiscale Analysis, Networks, and Nonlinear Dynamics	11
1.4	Conclusions	14
	References	14

### **Part One Multiscale Analysis** 19

<b>2</b>	<b>Modeling Across Scales: Discrete Geometric Structures in Homogenization and Inverse Homogenization</b>	<b>21</b>
	<i>Mathieu Desbrun, Roger D. Donaldson, and Houman Owhadi</i>	
2.1	Introduction	21
2.2	Homogenization of Conductivity Space	23
2.2.1	Homogenization as a Nonlinear Operator	24
2.2.2	Parameterization of the Conductivity Space	26
2.3	Discrete Geometric Homogenization	31
2.3.1	Homogenization by Volume Averaging	32
2.3.2	Homogenization by Linear Interpolation	33
2.3.3	Semigroup Properties in Geometric Homogenization	37
2.4	Optimal Weighted Delaunay Triangulations	39
2.4.1	Construction of Positive Dirichlet Weights	40

2.4.2	Weighted Delaunay and $Q$ -Adapted Triangulations	43
2.4.3	Computing Optimal Weighted Delaunay Meshes	44
2.5	Relationship to Inverse Homogenization	47
2.6	Electrical Impedance Tomography	49
2.6.1	Numerical Tests	52
2.6.1.1	Harmonic Coordinate Iteration	53
2.6.1.2	Divergence-Free Parameterization Recovery	55
	References	61
<b>3</b>	<b>Multiresolution Analysis on Compact Riemannian Manifolds</b>	<b>65</b>
	<i>Isaac Z. Pesenson</i>	
3.1	Introduction	65
3.2	Compact Manifolds and Operators	66
3.2.1	Manifolds without Boundary	66
3.2.2	Compact Homogeneous Manifolds	67
3.2.3	Bounded Domains with Smooth Boundaries	68
3.3	Hilbert Frames	69
3.4	Multiresolution and Sampling	70
3.5	Shannon Sampling of Band-Limited Functions on Manifolds	72
3.6	Localized Frames on Compact Manifolds	73
3.7	Parseval Frames on Homogeneous Manifolds	76
3.8	Variational Splines on Manifolds	79
3.9	Conclusions	81
	References	81
<b>Part Two</b>	<b>Nonlinear Dynamics: Genelets and Synthetic Biochemical Circuits</b>	<b>83</b>
<b>4</b>	<b>Transcriptional Oscillators</b>	<b>85</b>
	<i>Elisa Franco, Jongmin Kim, and Friedrich C. Simmel</i>	
4.1	Introduction	85
4.2	Synthetic Transcriptional Modules	86
4.2.1	Elementary Activation and Inhibition Pathways, and Simple Loops	87
4.2.2	Experimental Implementation	88
4.3	Molecular Clocks	89
4.3.1	A Two-Node Molecular Oscillator	90
4.3.2	Analysis of the Oscillatory Regime	91
4.3.3	Experimental Implementation and Data	95
4.4	Scaling Up Molecular Circuits: Synchronization of Molecular Processes	96
4.4.1	Analysis of the Load Dynamics	97
4.4.1.1	Quasisteady State Approximation of the Load Dynamics	99
4.4.1.2	Efficiency of Signal Transmission	99
4.4.2	Perturbation of the Oscillator Caused by the Load	100
4.4.2.1	Consumptive Coupling	100

4.4.2.2	Nonconsumptive Coupling and Retroactivity	100
4.4.3	Insulation	102
4.4.3.1	Reduction of Perturbations on the Oscillator Dynamics	103
4.4.3.2	Signal Transmission to the Insulated Load	104
4.5	Oscillator Driving a Load: Experimental Implementation and Data	105
4.6	Deterministic Predictive Models for Complex Reaction Networks	105
4.7	Stochastic Effects	107
4.8	Conclusions	110
	References	110
<b>5</b>	<b>Synthetic Biochemical Dynamic Circuits</b>	<b>113</b>
	<i>Raphaël Plasson and Yannick Rondelez</i>	
5.1	Introduction	113
5.2	Out-of-Equilibrium Chemical Systems	114
5.2.1	A Short Historical Overview	114
5.2.1.1	Discovery of Nonlinear Chemical Systems	114
5.2.1.2	Unexpected Oscillating Chemical Systems	115
5.2.2	Building Nonequilibrium Systems	116
5.2.2.1	Energetic Requirements	116
5.2.2.2	System Closure	116
5.2.2.3	Instabilities and Dynamic Stability	118
5.2.3	Design Principles	119
5.2.3.1	Dynamism	119
5.2.3.2	Interacting Feedbacks Processes	121
5.2.3.3	Modularity	122
5.3	Biological Circuits	123
5.3.1	Biological Networks Modeled by Chemistry	123
5.3.2	Biosystems: A Multilevel Complexity	124
5.3.3	A First Example of a Biological Reaction Circuit	124
5.3.4	Biological Networking Strategy	125
5.3.4.1	GRNs Are Templated Networks	125
5.3.4.2	Regulation and Feedback Loops	125
5.3.4.3	Nonlinearities in Genetic Regulation	127
5.3.4.4	Delays	128
5.3.4.5	Titration Effects	129
5.3.5	Higher Level Motifs and Modularity of Biochemical Networks	129
5.4	Programmable <i>In Vitro</i> Dynamics	130
5.4.1	Enzymatic Systems	130
5.4.1.1	DNA–RNA Sequence Amplification	131
5.4.1.2	The Genelet System	131
5.4.1.3	The PEN Toolbox	132
5.4.2	Nonenzymatic Networks: Strand Displacement Systems	134
5.4.3	Numerical Modeling	135
5.4.3.1	Mathematical Descriptions	135
5.4.3.2	LSA and Bifurcation Analysis for Design	137

- 5.4.3.3 Time Evolutions 138
- 5.4.3.4 Robustness Analysis and *In Silico* Evolutions 138
- 5.5 Perspectives 139
- 5.5.1 DNA Computing 140
- 5.5.2 Self Organizing Spatial Patterns 140
- 5.5.3 Models of Biological Networks 141
- 5.5.4 Origin of Life 141
- References 142

### Part Three Nonlinear Dynamics: the Brain and the Heart 147

- 6 Theoretical and Experimental Electrophysiology in Human Neocortex: Multiscale Dynamic Correlates of Conscious Experience 149**  
*Paul L. Nunez, Ramesh Srinivasan, and Lester Ingber*
- 6.1 Introduction to Brain Complexity 149
- 6.1.1 Human Brains and Other Complex Adaptive Systems 149
- 6.1.2 Is “Consciousness” a Four-Letter Word? 150
- 6.1.3 Motivations and Target Audiences for this Chapter 151
- 6.1.4 Brain Imaging at Multiple Spatial and Temporal Scales 151
- 6.1.5 Multiple Scales of Brain Dynamics in Consciousness 153
- 6.2 Brief Overview of Neocortical Anatomy and Physiology 154
- 6.2.1 The Human Brain at Large Scales 154
- 6.2.2 Chemical Control of Brain and Behavior 155
- 6.2.3 Electrical Transmission 156
- 6.2.4 Neocortex 156
- 6.2.5 The Nested Hierarchy of Neocortex: Multiple Scales of Brain Tissue 158
- 6.2.6 Corticocortical Connections Are Nonlocal and “Small World” 159
- 6.3 Multiscale Theory in Electrophysiology 160
- 6.3.1 Characteristic EEG and Physiological Time Scales 160
- 6.3.2 Local versus Global Brain Models and Spatial Scale 161
- 6.3.3 A Large-Scale Model of EEG Standing Waves 162
- 6.3.4 Relationships between Small, Intermediate, and Large Scales: A Simple Mechanical Analog 164
- 6.4 Statistical Mechanics of Neocortical Interactions 166
- 6.4.1 SMNI on Short-Term Memory and EEG 166
- 6.4.1.1 SMNI STM 167
- 6.4.1.2 SMNI EEG 168
- 6.4.2 Euler–Lagrange Equations 168
- 6.4.2.1 Columnar EL 169
- 6.4.2.2 Strings EL 170
- 6.4.2.3 Springs EL 171
- 6.4.3 Smoking Gun 171

6.4.3.1	Neocortical Magnetic Fields	172
6.4.3.2	SMNI Vector Potential	172
6.5	Concluding Remarks	173
	References	174
<b>7</b>	<b>Multiscale Network Organization in the Human Brain</b>	<b>179</b>
	<i>Danielle S. Bassett and Felix Siebenhüner</i>	
7.1	Introduction	179
7.2	Mathematical Concepts	181
7.3	Structural Multiscale Organization	182
7.4	Functional Multiscale Organization	187
7.5	Discussion	191
7.5.1	Structure and Function	191
7.5.2	Hierarchical Modularity	193
7.5.3	Power-Law Scaling	194
7.5.4	Network Models of Multiscale Structure	194
	References	195
<b>8</b>	<b>Neuronal Oscillations Scale Up and Scale Down</b>	
	<b>Brain Dynamics</b>	<b>205</b>
	<i>Michel Le Van Quyen, Vicente Botella-Soler, and Mario Valderrama</i>	
8.1	Introduction	205
8.2	The Brain Web of Cross-Scale Interactions	206
8.3	Multiscale Recordings of the Human Brain	208
8.4	Physiological Correlates of Cross-Level Interactions	210
8.5	Level Entanglement and Cross-Scale Coupling of Neuronal Oscillations	212
8.6	Conclusions	213
	References	214
<b>9</b>	<b>Linking Nonlinear Neural Dynamics to Single-Trial Human Behavior</b>	<b>217</b>
	<i>Michael X Cohen and Bradley Voytek</i>	
9.1	Neural Dynamics Are Complex	217
9.2	Data Analysis Techniques and Possibilities Are Expanding Rapidly	218
9.3	The Importance of Linking Neural Dynamics to Behavior Dynamics	219
9.4	Linear Approaches of Linking Neural and Behavior Dynamics	220
9.5	Nonlinear Dynamics and Behavior: Phase Modulations	221
9.6	Cross-Frequency Coupling	224
9.7	Linking Cross-Frequency Coupling to Behavior	226



9.8	Testing for Causal Involvement of Nonlinear Dynamics in Cognition and Behavior	228
9.9	Conclusions	229
	References	229
<b>10</b>	<b>Brain Dynamics at Rest: How Structure Shapes Dynamics</b>	<b>233</b>
	<i>Etienne Hugues, Juan R. Vidal, Jean-Philippe Lachaux, and Gustavo Deco</i>	
10.1	Introduction	233
10.2	Model	234
10.3	Results	236
10.3.1	Neural Dynamics	236
10.3.1.1	Case of Infinite Conduction Velocity	236
10.3.1.2	Case of Finite Conduction Velocity	238
10.3.2	BOLD Dynamics	238
10.4	Comparison with Experimental Data	239
10.5	Discussion	240
	References	242
<b>11</b>	<b>Adaptive Multiscale Encoding: A Computational Function of Neuronal Synchronization</b>	<b>245</b>
	<i>Misha (Meyer) Z. Pesenson</i>	
11.1	Introduction	245
11.2	Some Basic Mathematical Concepts	247
11.3	Neural Synchronization	247
11.3.1	Connections with Some Existing Approaches to MRA	253
11.4	Concluding Remarks	253
	References	254
<b>12</b>	<b>Multiscale Nonlinear Dynamics in Cardiac Electrophysiology: From Sparks to Sudden Death</b>	<b>257</b>
	<i>Zhilin Qu and Michael Nivala</i>	
12.1	Introduction	257
12.2	Subcellular Scale: Criticality in the Transition from Ca Sparks to Ca Waves	258
12.3	Cellular Scale: Action Potential and Ca Cycling Dynamics	260
12.3.1	Intracellular Ca Alternans	260
12.3.2	Fast Pacing-Induced Complex APD Dynamics	262
12.3.3	EAD-Mediated Nonlinear Dynamics at Slow Heart Rates	264
12.4	Excitation Dynamics on the Tissue and Organ Scales	266
12.4.1	Spatially Discordant APD Alternans	266
12.4.2	Spiral and Scroll Wave Dynamics	267
12.4.3	Chaos Synchronization	269
12.5	Conclusions	271
	References	271

<b>13</b>	<b>Measures of Spike Train Synchrony: From Single Neurons to Populations</b>	<b>277</b>
	<i>Conor Houghton and Thomas Kreuz</i>	
13.1	Introduction	277
13.2	Measures of Spike Train Distance	278
13.2.1	Notation	278
13.2.2	The Victor–Purpura Metric	279
13.2.3	The van Rossum Metric	280
13.2.4	The ISI- and the SPIKE-Distance	282
13.2.4.1	The ISI-Distance	284
13.2.4.2	The SPIKE-Distance	285
13.2.5	Entropy-Based Measure	286
13.3	Comparisons	286
13.3.1	The ISI- and the SPIKE-Distance	286
13.3.2	The ISI-Distance and the van Rossum Metric	287
13.3.3	The SPIKE-Distance and the Victor–Purpura Metric	288
13.3.4	Comparison of All Distances on Birdsong Data	289
13.4	Measuring the Dissimilarity within a Population	290
13.5	Measuring the Dissimilarity between Populations	292
13.5.1	The Population Extension of the Victor–Purpura Metric	292
13.5.2	The Population Extension of the van Rossum Metric	293
13.6	Discussion	294
	References	296
	<b>Index</b>	<b>299</b>



## List of Contributors

**Danielle S. Bassett**

University of California,  
Santa Barbara  
Department of Physics  
6213 Broida Hall  
Santa Barbara, CA 93106  
USA

**Vicente Botella-Soler**

Institute of Science and Technology  
(IST) Austria  
Am Campus 1  
A-3400 Klosterneuburg  
Austria

**Michael X Cohen**

University of Amsterdam  
Department of Psychology  
Weesperplein 4  
1018 XA Amsterdam  
The Netherlands

**Gustavo Deco**

University Pompeu Fabra  
Center of Brain and Cognition  
Theoretical and Computational  
Neuroscience Group  
Roc Boronat, 138  
08018 Barcelona  
Spain

**Mathieu Desbrun**

California Institute of Technology  
Department of Computing &  
Mathematical Sciences  
MC 305-16  
1200 E. California Blvd.  
Pasadena, CA 91125  
USA

**Roger D. Donaldson**

California Institute of Technology  
Department of Computing &  
Mathematical Sciences  
MC 305-16  
1200 E. California Blvd.  
Pasadena, CA 91125  
USA

**Elisa Franco**

University of California, Riverside  
Department of Mechanical  
Engineering  
900 University Avenue  
Bourns Hall A311  
Riverside, CA 92521  
USA

**Conor Houghton**

University of Bristol  
Department of Computer Science  
Merchant Venturers Building  
Woodland Road  
Bristol BS8 1UB  
UK

***Etienne Hugues***

University Pompeu Fabra  
Center of Brain and Cognition  
Theoretical and Computational  
Neuroscience Group  
Roc Boronat, 138  
08018 Barcelona  
Spain

***Lester Ingber***

Lester Ingber Research  
545 Ashland Creek Drive  
Ashland, OR 97520  
USA

***Jongmin Kim***

California Institute of Technology  
Department of Bioengineering  
MC 107-81  
1200 E. California Blvd.  
Pasadena, CA 91125  
USA

***Thomas Kreuz***

Consiglio Nazionale delle Ricerche  
(CNR)  
Istituto dei Sistemi Complessi (ISC)  
Via Madonna del Piano 10  
50119 Sesto Fiorentino  
Italy

***Jean-Philippe Lachaux***

Lyon Neuroscience Research Center  
Brain Dynamics and Cognition Team  
INSERM U1028 – CNRS UMR5292  
F-69500 Lyon-Bron  
France

***Michel Le Van Quyen***

University Pierre et Marie Curie  
Research Center of the Brain and  
Spinal Cord Institute (ICM)  
INSERM UMRS 975 – CNRS  
UMR 7225  
Hôpital de la Pitié-Salpêtrière  
47 Bd de l'Hôpital  
75651 Paris Cedex 13  
France

***Michael Nivala***

University of California, Los Angeles  
David Geffen School of Medicine,  
Department of Medicine (Cardiology)  
650 Charles E. Young Drive South  
A2-237 CHS  
Los Angeles, CA 90095  
USA

***Paul L. Nunez***

Cognitive Dissonance, LLC  
1726 Sienna Canyon Dr  
Encinitas, CA 92024  
USA

***Houman Owhadi***

California Institute of Technology  
Department of Computing &  
Mathematical Sciences  
MC 9-94  
1200 E. California Blvd.  
Pasadena, CA 91125  
USA

***Isaac Z. Pesenson***

Temple University  
Department of Mathematics  
1805 N. Broad St.  
Philadelphia, PA 19122  
USA

**Misha (Meyer) Z. Pesenson**

California Institute of Technology  
 Department of Computing &  
 Mathematical Sciences  
 MC 305-16  
 1200 E. California Blvd.  
 Pasadena, CA 91125  
 USA

**Raphaël Plasson**

Harvard University  
 Department of Earth & Planetary  
 Sciences  
 100 Edwin H. Land Blvd.  
 Cambridge, MA 02142-1204  
 USA

**Zhilin Qu**

University of California, Los Angeles  
 David Geffen School of Medicine,  
 Department of Medicine (Cardiology)  
 650 Charles E. Young Drive South  
 A2-237 CHS  
 Los Angeles, CA 90095  
 USA

**Yannick Rondelez**

LIMMS/CNRS-IIS (UMI 2820)  
 The University of Tokyo  
 Institute of Industrial Science  
 4-6-1 Komaba, Meguro-ku  
 Tokyo 153-8505  
 Japan

**Felix Siebenhühner**

University of Helsinki  
 Neuroscience Center  
 Viikinkaari 4  
 00014 Helsinki  
 Finland

**Friedrich C. Simmel**

Technische Universität München  
 Physics Department and ZNN/WSI  
 Systems Biophysics and  
 Bionanotechnology  
 Am Coulombwall 4a  
 85748 Garching  
 Germany

**Ramesh Srinivasan**

University of California, Irvine  
 Department of Cognitive Sciences  
 2201 Social & Behavioral Sciences  
 Gateway Building (SBSG)  
 Irvine, CA 92697-5100  
 USA

**Mario Valderrama**

Universidad de Los Andes  
 Department of Biomedical  
 Engineering  
 Cra 1 N° 18A- 12, Bogotá  
 Colombia

**Juan R. Vidal**

Lyon Neuroscience Research Center  
 Brain Dynamics and Cognition Team  
 INSERM U1028 – CNRS UMR5292  
 69500 Lyon-Bron  
 France

**Bradley Voytek**

University of California,  
 San Francisco  
 Department of Neurology  
 1550 4th Street  
 San Francisco, CA 94143-2922  
 USA





## Preface

“Those who study complex adaptive systems are beginning to find some general principles that underlie all such systems, and seeking out those principles requires discussions and collaboration among specialists in a great many fields.”

*M. Gell-Mann*<sup>1)</sup>

Modern science and engineering deal with problems that involve wide ranges of spatial and temporal scales. Moreover, data-intensive sciences such as Systems Biology and Systems Neuroscience, besides dealing with complex physical, chemical, and biological phenomena, need to handle enormous amounts of high-dimensional data produced by modern high-throughput experimental technologies. All this creates a critical need for modeling sophisticated, natural/artificial systems and analyzing modern high-dimensional data across multiple scales ranging from molecules to macroscales. However, traditional mathematical approaches to modeling/analyzing complex phenomena/data are often limited because of the multiscale nature of the problems. At the same time, it is well known that biological systems solve computationally demanding problems with many scales and process multiscale information deftly. Indeed, in order to resolve a broad range of spatial/temporal scales present in input signals, perception systems perform sophisticated multiscale encoding, analysis, and decoding in real time. A second example is related to data dimension reduction (which is intimately connected with feature extraction, recognition and learning). In fact, the input signals to all mammalian perception systems, despite their coming from low-dimensional Euclidian space, are transformed internally into extremely high-dimensional representations. This counterintuitive drastic increase in complexity is followed by a concealed, effortless and perpetual nonlinear dimension reduction, that is, converting the complex representations back into low-dimensional signals to be, ultimately, executed by the motor system. Another example comes from Systems Biology where embryonic development is, in fact, an immense information processing task in which DNA sequence data generate and direct the system level spatial deployment of specific cellular functions [2]. These examples indicate that the theoretical understanding of biological computational mechanisms and their experimental implementation can

1) Cited in Ref. [1].

greatly enhance our ability to develop efficient artificial information processing systems. An important advance in the engineering of biological computing systems has recently been achieved and the first network of artificial neurons made from DNA was created, suggesting that DNA strand displacement cascades could endow biochemical systems with the capability of recognizing patterns [3]. Pattern recognition and multiresolution are quintessential for information processing, which, in turn, is closely connected with learning and adaptivity.

Complex biological systems capable of adaptive behavior and effective information processing are often governed by mechanisms operating simultaneously on multiple spatial and temporal scales. Thus, in order to analyze the machinery that underlies biological information processing and computations in general, this book focuses on modeling multiscale phenomena in Synthetic/Systems Biology and Systems Neuroscience, as well as on mathematical approaches to multiresolution analysis. Because of the inherently interdisciplinary nature of this task, the editor of this book invited experts (theoreticians and experimentalists) in bioengineering, chemistry, cardiology, neuroscience, computer science, and applied mathematics, to provide their perspectives (“seeking out those principles requires . . . collaboration among specialists in a great many fields.”). The contributions to this book may broadly be categorized as belonging to mathematical methods, Systems Biology, and Systems Neuroscience. Multiscale analysis is the major integrating theme of this book, as indicated by its title. The subtitle does not call for bridging the scales all the way from genes to behavior, but rather stresses the unifying perspective provided by the concepts referred to in the title. The contributions emphasize the importance of taking into account the *interplay* between *multiscale structure* and *multiscale dynamics*. One of our goals is to attract the attention of scientists working in Systems Biology and Systems Neuroscience by demonstrating that some of the seemingly unrelated problems from these disciplines may be modeled using virtually identical powerful mathematical methods from the inclusive paradigms emphasized here. Each chapter provides a window into the current state of the art in the areas of research discussed. This book is thus intended for advanced researchers interested in recent developments in these areas. It is believed that the interdisciplinary perspective adopted here will be beneficial for all the above-mentioned disciplines. The roads between different sciences, “while often the quickest shortcut to another part of our own science, are not visible from the viewpoint of one science alone” [4].

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Misha Z. Pesenson

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## 1

**Introduction: Multiscale Analysis – Modeling, Data, Networks,  
and Nonlinear Dynamics**

Misha (Meyer) Z. Pesenson

“ . . . the twin difficulties of scale and complexity.”

*P. Anderson [1]*

“ . . . I spelled out a moral for the general structure of scientific knowledge: that scale changes in a wide variety of instances can lead to qualitative change in the nature of phenomenon.”

*P. Anderson [2]*

“ . . . to find a really appropriate name for that stratification or layering of the structures involved which we are all tempted to describe as ‘hierarchies’. . . . We need a conception of tiers of networks with the highest tier as complex as the lower ones.”

*F. Hayek [3]*

The human brain is the archetype of a natural complex adaptive system. It is composed of impenetrable “jungles” of neurons, which interact both within and across multiple spatial and temporal scales (see, for example, recent books: [4–13]). In Systems Biology the situation is similarly complicated and biological systems, besides being characterized by a large number of components and their interactions, demonstrate a very complex organization at multiple spatial scales [14,15]. As a result, the fields of Systems Neuroscience and Systems Biology deal with phenomena of intricate complexity that are governed by various mechanisms integrated across many levels of detail. In addition, high-throughput experimental technologies and powerful simulation/analysis tools generate new types of heterogeneous data with a density and depth previously unimaginable. All this creates a critical need for modeling sophisticated, natural/artificial systems and analyzing modern high-dimensional data from multiple levels ranging from molecules → synapses → neurons → networks (and ideally, all the way to behavior). The attempts to model/analyze such complex phenomena/data are hindered by the fact that traditional mathematical approaches are often limited because of the multiscale nature of the problems.

This book concentrates on the investigation of multiscale problems in Systems Biology and Systems Neuroscience, and on mathematical approaches to multi-resolution analysis (MRA). Systems Biology analyzes how hierarchical, multiscale molecular structures control the dynamic linkages between different genes and their products and give rise to the emergent properties and functions of a unified organism [14,15]. Similarly, the goal of Systems Neuroscience is to unravel how neurons and the intricate structure of neural networks shape information flow, perceptual grouping, multiscale processing, the emergent functions of neural circuits, and ultimately – cognition and behavior [13]. Despite these obvious parallels between Systems Biology and Systems Neuroscience, there is, surprisingly little interaction among the corresponding research communities [16]. It is unfortunate, since these two fields can learn quite a bit from each other regarding the use of physical, mathematical/computational modeling, data processing, and so on. In addition, identifying methods common to both, Systems Biology and Systems Neuroscience, may, in turn, drive the development of systematic mathematical approaches to modeling complex phenomena/data. To promote stronger interaction between these fields and to aid their “coming together,” as Kandel<sup>1)</sup> phrased it, the editor of this book invited contributions from experts representing a highly interdisciplinary group of scientists in computer science, applied mathematics, bioengineering, chemistry, cardiology, and neuroscience. The chapters in this book may broadly be categorized as belonging to mathematical methods, Systems Biology, and Systems Neuroscience. One of the goals of this book is to attract the attention of scientists working in these supposedly distinct fields, by demonstrating that some of the seemingly unrelated problems in Systems Biology and Systems Neuroscience may be modeled using virtually identical powerful methods from the inclusive paradigms articulated here. There are three main paradigms, which are the unifying threads of this book – multiscale analysis, networks, and nonlinear dynamics. Multiscale analysis is the major integrating theme of the book, as indicated by its title. The subtitle does not call for bridging the scales all the way from genes to behavior, but rather stresses the unifying perspective provided by the concepts referred to in the title, and especially by multiscaling. Multiscaling, in essence the consideration of problems on many spatial and temporal scales, is one of the major recent developments in solid-state physics, fluid mechanics, and applied mathematics (some examples are briefly discussed later in this introduction). This book emphasizes the importance of taking into account the *interplay* between *multiscale structure* and *multiscale dynamics*. It is network theory that provides a general framework for the integration of multiscaling and collective dynamics.

In neuroscience, multiscale network interactions may account for much of the brain’s complex behavior. The importance of multiple time/space scales and their interaction was emphasized by Hebb, Hayek, and Luria [18–20], and has been stressed by a number of authors over the past few years [5–12,21–25]. Nunez focuses on the importance of nested modular hierarchy in brain tissue and quotes

1) I think that the history of science is the history of unification of knowledge, disciplines coming together [17].

V. Mountcastle: “the brain is a complex of widely and reciprocally interconnected systems and the dynamic interplay of neural activity within and between these systems is the very essence of brain function.” [8]. Mountcastle also explicitly referred to the emergent behavior of the brain: “The properties of microcircuit operations are emergent, for they cannot be predicted from what is known of the action of single neurons.” [26]. The hierarchy of neural networks figures in the global neuronal workspace model of consciousness that is based on dynamic links between specialized processing modules (dynamically formed networks) [27–31]. This model includes long-range cortico-cortical axons (densely distributed in prefrontal, parieto-temporal, and cingulate cortices) that integrate sub networks into a single large system, and suggests that highly distributed synchronized activity provides neural correlates of conscious states of the brain. Another model of memory and consciousness, the multiregional retroactivation framework, also rejects a single anatomical site for the integration of memory and motor processes, and involves time-locked neuronal ensembles located in multiple and separate regions [32,33]. Based on simultaneous electrophysiological and fMRI measurements in non-human primates, Logothetis [34] states that “the concurrent study of components and networks” is needed and “simultaneous studies of microcircuits, of local and long-range interconnectivity between small assemblies, and of the synergistic activity of larger neuronal populations are essential.” Another experimental illustration of the significance of dynamics and multiple scales comes from a work of Salazar *et al.* [35], who, by using simultaneous recordings of neural activity from various areas, demonstrated that short-term memories are represented by patterns of synchronization, widely distributed throughout the frontoparietal network (I’d like to thank Lester Ingber for bringing this work to my attention). Overall, there is mounting experimental evidence that sensory neurons change their responses, as well as the structure of neuronal correlations, adaptively. In Systems Biology it is also being increasingly recognized that various bionetworks are interrelated and influence each other dynamically. To sum up, modeling in Systems Neuroscience and Systems/Synthetic Biology must take into account a large number of components, their nonlinear dynamic interactions, and multiscale, dynamically changing hierarchical interconnections.

These factors may lead to an emergent, self-organized (in contrast to centrally controlled), adaptive behavior that is often encountered in Systems Neuroscience and Systems Biology. Indeed, in the context of neural networks, it was shown some 30 years ago that new properties may *emerge* as a result of the collective dynamic interaction of a large number of components [36]. Hopfield’s network consisted of simple equivalent components, and *the network had little structure*. Nonetheless, new collective properties spontaneously emerged. This had been anticipated by Anderson: “We expect to encounter fascinating and, I believe, very fundamental questions at each stage in fitting together less complicated pieces into the more complicated system and understanding the basically new types of behavior which can result” [1]. As Aristotle put it, “In the case of all things which have several parts and in which the whole is not, as it were, a mere heap, but the totality is something besides the parts, there is a cause of unity.” [37]. Interactions among multiple scales also may give rise to new phenomena. Let us consider just a few classical examples. The first one dates back to 1869, when



Maxwell solved the problem of anomalous dispersion of a monochromatic electromagnetic wave of the frequency  $\omega$  interacting with the transmitting media whose electrons have the intrinsic frequency  $\omega_0$  [38–40]. In essence, this theory links the macroscopically observed refraction and absorption to the microscopic oscillations of electrons. Another example concerns spatial scales and comes from nonlinear waves in elastic media with microstructure [41]. Microstructure induces the spatial dispersion that, together with nonlinearity, gives rise to a striking new type of nonlinear waves – solitons, described by the macroscopic Korteweg–de Vries (KdV) equation. These examples indicate that both collective behavior and the effect of multiple scales may separately lead to changes in the nature of a system. Therefore, the integration of multiscaling and collective dynamics (iMCD), the paradigm advocated here, takes into account the convoluted interplay between these two factors, thus providing a broad, inclusive way of describing *emergence* and *adaptivity* of complex systems.

Besides furnishing a theoretical perspective, modeling based on iMCD will also be important for how Systems Biology and Systems Neuroscience collect experimental data. In neuroscience, for example, it will soon be possible to record from thousands of neurons, but for studies of a particular phenomenon, it is important to know from which (and from how many) neurons the spikes should be recorded (see, for example, Refs [35,42,43]).

Moreover, the iMCD paradigm, being comprehensive, will help to grasp and interpret this flood of experimental/ simulated data. Indeed, one primarily detects what he/she is looking for (“The decisive point is not observation but expectation” as Popper put it [44]), and even when there is something unforeseen and a model proves to be inadequate, it is the comprehensiveness of the modeling that helps one to spot the unanticipated.<sup>2)</sup> In addition to providing useful technical tools, multiscaling is in fact a way of thinking. For example, let us take a look at the so-called model equations. The KdV equation mentioned above is just one example of such equations which describe a large number of physical, chemical, technical, and biological phenomena. These equations include the nonlinear Schrödinger equation, the sine–Gordon equation, the Ginzburg–Landau equation, and so on [39,45,46]. Their derivation, which utilizes multiple space/time scales essential to a phenomenon, has led to advances in the understanding of diverse phenomena and also to the establishment of new, rich branches of research in physics and applied mathematics. In other words, multiscaling is not only a mathematical language common to various disciplines, but, more importantly, a way of thinking.

Even though multiscale analysis is probably the oldest among the above-mentioned unifying concepts of the book, it is less universally recognized as a powerful, indispensable framework for describing complex natural phenomena (“ . . . linking models at different scales . . . is as old as modern science itself” – see examples in Ref. [40]). The main manifestations of multiscaling pertinent to this book are multiscale modeling (physical, chemical, biological, etc.), multiresolution analysis of high-dimensional information/data, and multiscale nonlinear dynamics on networks.

2) “In preparing for a battle, I have always found that plans are useless, but planning is indispensable.” D. D. Eisenhower.

In what follows, I briefly discuss them and how they are exemplified in this book. Since these embodiments of multiscale modeling are interconnected, the discussion inevitably goes back and forth between them. Each section starts with a short account of the section's main topic and ends with a description of pertinent chapters of the book.

## 1.1

### Multiscale Modeling

Multiscale modeling/analysis has become a large part of modern applied mathematics. But what is multiscale analysis to begin with? It is, in fact, an overarching concept of treating problems on multiple scales. It has developed into a large spectrum of techniques that have different meanings and flavors depending on whether they belong to physical modeling, asymptotic methods, numerical simulations, information theory, or applied harmonic analysis. Under various disguises, multiscale analysis enters virtually every scientific/engineering endeavor. Indeed, in analyzing a phenomenon, practically all fields rely on mathematical modeling in order to characterize the mechanisms involved, to make predictions, to guide new experiments, and to aid the design in technology. The iterative model building process consists of the following three major stages, each of which depends greatly on a particular incarnation of multiscale analysis:

- 1) Domain(s)-specific modeling (physical, chemical, biological, and so on, or a combination of these)
  - data collecting and analyzing,
  - mathematical formulation, equations (not always possible).
- 2) Analysis
  - asymptotic study, computational simulations,
  - quantifying uncertainty.
- 3) Model verification
  - data generating and analyzing.

These stages are not completely independent of each other. Moreover, they are not strictly sequential and the pursuit of the comprehensive model may require their simultaneous combined efforts. It is interesting to note that such a non-sequential modeling procedure, in fact, provides a paradigmatic account of knowledge generation in general and parallels the cognition process where the knowledge-dependent brain does not follow the traditional information processing input–output scheme, but rather continuously generates internal variations, anticipating and testing the outside world with reference to its own representation of the world [19,29,31–33].

The first thing one notices from the stages 1–3 above is that modeling starts and ends with data analysis. In fact, the intermediate stages also implicitly depend on data processing. Nowadays, there is usually more data available than can be processed by using traditional data analysis tools (this situation is briefly discussed in Section 1.2), and even fields with well-established data archives, such as genomics, are facing new and mounting challenges in data management and exploration.

Let us start by considering in a nutshell how multiscale analysis manifests itself in the various stages of modeling.

### 1.1.1

#### Domain-Specific Modeling

Any model is an idealization of a phenomenon, and as such, it inevitably neglects some details and generates an abstraction that captures what is most important for a particular analysis. How does one know what is essential? This crucial process of prioritizing begins by building a hierarchy of scales that underlie the phenomenon. Indeed, it is obvious that any parameter whose magnitude depends on measurement units could hardly be useful for modeling. At the same time, the significance of various parameters is determined by their magnitudes. Thus, one of the first steps should be to find scales that are intrinsic to the problem and to normalize the parameters accordingly. In addition, this process of prioritizing scales is instrumental in quantifying the uncertainty of the chosen representation. It is important to note, however, that basic dimensional analysis is not always sufficient for obtaining the so-called scaling laws [47,48].

To consider some effects of multiple scales, let us start with a simple example of a harmonic oscillator. In this case, there is only one intrinsic time scale – the inverse frequency of the pendulum. As we move to a more realistic model with damping, an additional time scale – the characteristic damping scale – appears [49,50]. The appearance of *just one additional scale* makes the phenomenon and its computational/mathematical treatment much more complicated. A straightforward solution is not uniformly valid (in time) anymore, and a singularity near  $t=0$  complicates the analysis. In fact, singular behavior can often be inferred by analyzing dimensionless characteristic magnitudes. If one considers, for example, a limiting case when a parameter of a problem is small, a general rule states: “A perturbation solution is uniformly valid in the space and time coordinates unless the perturbation quantity is the ratio of two lengths or two times” [50]. This is, in general, a very formidable complication that was caused by having just two scales instead of one. The theory of singular perturbations was developed in fluid mechanics (the boundary layer theory), but a similar situation occurs in modeling biochemical reactions, where the Michaelis–Menten kinetics results from a reduction of a singularly perturbed model. As the simple example of an oscillator with damping demonstrates, the initial choice of the intrinsic scales is of the utmost importance to modeling. Such a selection requires a deep physical, chemical, and biological understanding of the collected data and the phenomena being investigated.

The contributions to this book by Elisa Franco *et al.*, Raphaël Plasson *et al.*, and Zhilin Qu *et al.* belong to this category of modeling complex, multiscale phenomena with applications to transcriptional networks, biochemical oscillators, and nonlinear dynamics of the heart. Elisa Franco, Jongmin Kim, and Friedrich Simmel, in their chapter “Transcriptional Oscillators,” study a class of cell-free synthetic biological systems – “genelet circuits” – that are entirely based on *in vitro* gene transcription. In these systems a reduced number of biological components – DNA and RNA strands and a few enzymes – are used to construct artificial gene regulatory circuits that are

roughly analogous to biologically occurring counterparts, for example, bistable molecular switches or oscillators. Among the most attractive features of *in vitro* transcription circuits is that, in principle, all of their molecular components are known. This not only makes these systems amenable to a thorough quantitative treatment, but also enables one to comparatively easily feedback to the experimental realization of the systems insights gained from computational modeling.

Raphaël Plasson and Yannick Rondelez, in their contribution, trace the historical developments of the concept of out-of-equilibrium networks of chemical reactions, from small molecules systems to biology, to generalized experimental chemistries. They focus on the building of out-of-equilibrium chemical systems and review the discoveries and theoretical advances that eventually allowed the dynamical description of molecular assemblies. They also describe the world of biological reaction networks and provide examples of natural implementation of such chemical circuits. Their survey highlights some of the most recent schemes for the rational molecular programming of complex out-of-equilibrium behaviors, and also gives a further incentive for the study of complex chemical systems as models of their biological counterparts. Some examples of realizations based on these experimental schemes are described.

Zhilin Qu and Michael Nivala, in their chapter “Multiscale Nonlinear Dynamics in Cardiac Electrophysiology: From Sparks to Sudden Death,” analyze the nonlinear dynamics of the heart, which are regulated by nonlinear dynamics occurring on multiple scales, ranging from random molecular motions to more regular cellular and tissue-level behaviors. They review experimental observations and mechanistic insights gained from the mathematical modeling of biological functions across subcellular, tissue, and organ scales in the heart. They also discuss the role of nonlinear dynamics in the genesis of lethal cardiac events.

In the next subsection, we briefly discuss motivations for and approaches to linking various scales.

### 1.1.2

#### Analysis

Bridging various scales is a very challenging problem of applied mathematics. To get a better feel for the issues analyzed in this book, let us take a quick look at the spectrum of characteristic spatial/time values in Systems Neuroscience. The brain is a complex system with a huge range of structural and functional scales [4–13,51,52]. In order to understand the function of the brain, modeling and simulation techniques are applied at many different levels from subcellular to systems: cell → circuit → network → cognition.<sup>3)</sup> Some spatial characteristic magnitudes are as follows: molecules  $\sim 1 \text{ \AA}$ , synaptic cleft in chemical synapse (width)  $\sim 20\text{--}40 \text{ nm}$ , neurons

3) For “directly” interacting with a brain, as opposed to modeling, the interested reader is referred to Musil’s amusing, surrealist visit to his brain in 1913: “This writer’s brain: I hastily slid down the fifth turn in the vicinity of the third mound. . . . The mass of the cerebral cortex arched over

me . . . unfathomable, like strange mountains at dusk. Night was already falling over the region of the medulla; . . . hummingbird colors [like the colors of modern neuroimages (MP)], . . . , disconnected sounds [neuron spikes (MP)] . . .” [53].

$\sim 4\text{--}100\ \mu\text{m}$ , axon (diameter)  $\sim 0.5\text{--}20\ \mu\text{m}$ , axon length  $\sim 1\ \text{mm}\text{--}1\ \text{m}$ , neural circuits  $\sim 1\ \text{mm}$ , and from here to the whole brain and cognition. The characteristic time scales in neuroscience correspond to frequencies spanning four orders of magnitude, from the so-called slow-four  $\sim 0.025\text{--}0.066\ \text{Hz}$  to slow-one, and then to delta =  $1.5\text{--}4\ \text{Hz}$   $\rightarrow$  theta =  $4\text{--}10\ \text{Hz}$   $\rightarrow$  beta =  $10\text{--}30\ \text{Hz}$   $\rightarrow$  gamma =  $30\text{--}80\ \text{Hz}$   $\rightarrow$  high frequency =  $80\text{--}200\ \text{Hz}$   $\rightarrow$  the ultrahigh frequency =  $200\text{--}600\ \text{Hz}$  [7]. Moreover, realistic models of a single neuron contain two distinct time scales – slow and fast. These ranges of the spatial and temporal scales are bewildering. However, since the scales are so disparate, why not analyze each of them independently? Indeed, traditionally, this is exactly how problems with multiple scales are approached – different scales are separated and their interaction with each other only takes place through some “passive,” phenomenological parameters. For highly informative, inspiring discussions of modeling and bridging multiple scales see Phillips [40], especially Chapter 12; it is the subtitle of the book – Modeling Across Scales – not the title that articulates its relevance to our discussion. For an extensive, far-reaching account of the physical perspective on biological modeling, see Phillips *et al.* [15]. The traditional way of separating scales has been successful in dealing with many problems. However, as we have discussed, there are numerous important situations where different scales cannot be considered independently, and it is precisely the interactions between disparate scales that give rise to phenomena otherwise absent. In Neuroscience, for example, the interactions between theta and gamma oscillations may represent a cellular basis of long-term memory formation in humans (see review [54] and references therein). When dealing with a complex system that is characterized by multiple scales (“ . . . the twin difficulties of scale and complexity.”), it is often desirable to reduce the complexity by constructing an effective model that is a coarsened version of the original one. Homogenization is one possible principled way to perform multiscale analysis and to “bridge the scales” (for other powerful multiscale methods, see Ref. [55] and references there). Homogenization is used to properly average out, or homogenize, the fast scales in systems of ordinary or partial differential equations (these fast scales reflect high-frequency variations, in time or space, of some characteristic physical parameters). Doing so leads to effective equations that do not contain a small parameter and are hence more amenable to numerical solution or analysis. In neuroscience homogenization was applied, for example, to the propagation of traveling wave fronts in an inhomogeneous, excitable neural medium [56].

Homogenization (or multiscale analysis) in the presence of a large number of nonseparated (spatial or temporal) scales has been recognized as very important for applications and is far from being well understood mathematically. This book opens with a chapter by Mathieu Desbrun, Roger Donaldson, and Houman Owhadi “Modeling Across Scales: Discrete Geometric Structures in Homogenization and Inverse Homogenization” that addresses a situation with *nonseparated* spatial scales. Imaging and simulation methods are typically constrained to resolutions much coarser than the scale of physical microstructures present in body tissues. Both mathematical homogenization and numerical homogenization address this practical issue by identifying and computing appropriate spatial averages that result in