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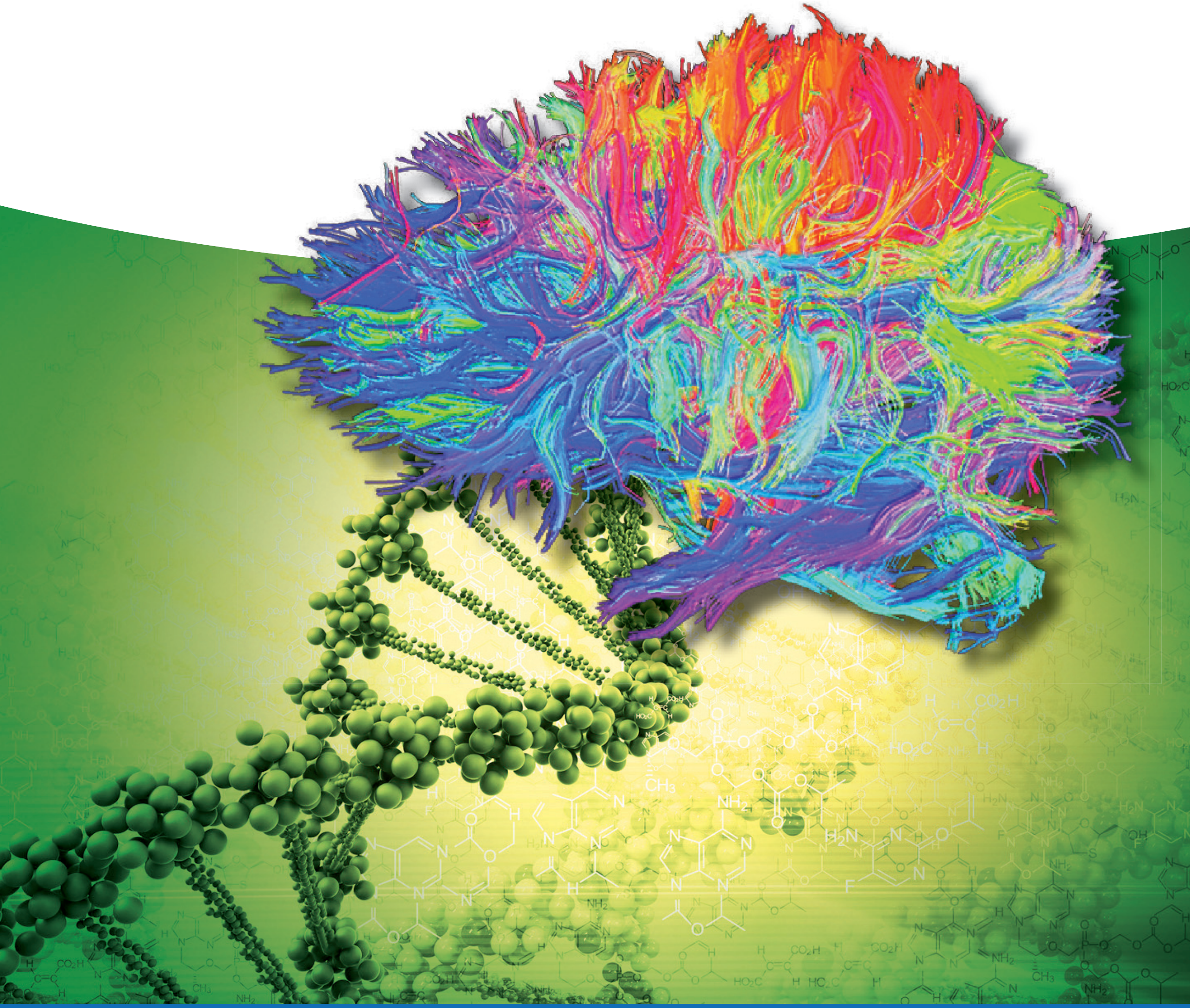
Misha (Meyer) Z. Pesenson

Multiscale Analysis and Nonlinear Dynamics

From Genes to the Brain



Reviews of Nonlinear Dynamics and Complexity

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Multiscale Analysis and Nonlinear Dynamics

From Genes to the Brain

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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[1]

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

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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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Pasadena, 2013 *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.

Multiscale Analysis and Nonlinear Dynamics: From Genes to the Brain,
First Edition. Edited by Misha (Meyer) Z. Pesenson.

This book concentrates on the investigation of multiscale problems in Systems Biology and Systems Neuroscience, and on mathematical approaches to multiresolution 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[1] 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

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[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 ω interacting with the transmitting media whose electrons have the intrinsic frequency ω_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.[2] 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.

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[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 multiscaling 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.[3] Some spatial characteristic magnitudes are as follows: molecules $\sim$1 Å, synaptic cleft in chemical synapse (width) $\sim$20–40 nm, neurons

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[3] For “directly” interacting with a brain, as opposed to modeling, the interested reader is referred to Musil’s amusing, surrealistic 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$4–100 μm, axon (diameter) $\sim$0.5–20 μm, axon length $\sim$1 mm–1 m, neural circuits $\sim$1 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$0.025–0.066 Hz to slow-one, and then to delta = 1.5–4 Hz → theta = 4–10 Hz → beta = 10–30 Hz → gamma = 30–80 Hz → high frequency = 80–200 Hz → the ultrahigh frequency = 200–600 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