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

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> “ . . . 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.

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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].

~4–100 μm, axon (diameter) ~0.5–20 μm, axon length ~1 mm–1 m, neural circuits ~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 ~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 accuracy and consistency between the macroscales observed and the underlying microscale models assumed. Among the various applications benefiting from homogenization, electric impedance tomography (EIT) images the electrical conductivity of a body by measuring electrical potentials consequential to electric currents applied to the exterior of the body. EIT is routinely used in breast cancer detection and cardiopulmonary imaging, where current flow in fine-scale tissues underlies the resulting coarse-scale images. The authors introduce a geometric procedure for the homogenization (simulation) and inverse homogenization (imaging) of divergence-form elliptic operators with coefficients in dimension two. They also consider inverse homogenization, which is known to be both nonlinear and severely ill-posed. The method enables them to decompose this problem into a linear ill-posed one and a well-posed nonlinear problem. The chapter ends by demonstrating an application of this novel geometric technique to EIT. This approach is closely related to the so-called geometric multiscale analysis, an active area of research, with applications in a wide variety of fields, including high-dimensional signal processing, data analysis/visualization, fluid mechanics, and so on (see, for example, http://www.geometry.caltech.edu/).

1.1.3
Model Interpretation and Verification: Experimental/Simulation Data

The third stage of modeling is model verification. The results from experiments or simulations often require the analysis of nonstationary time series with multiscale variations of frequency and amplitude. The locations of these variations in time cannot be grasped by the Fourier transform. To comprehend the multiscale nature of such time series, the so-called wavelet-based multiresolution approach to signal processing was developed ([57], and references there). To fully appreciate how surprisingly strong the connection between multiscale analysis of signals/images and neuroscience is, one needs only to recollect that it was the attempt to understand the ability of the mammalian visual system to perform encoding at various scales that stimulated the early development of mathematical MRA based on wavelets [58]. Wavelets eventually evolved into a highly interdisciplinary field of research with a variety of methods and applications providing a general unifying framework for dealing with various aspects of information processing (see also Section 1.2).

In this book, Conor Houghton and Thomas Kreuz, in their chapter called "Measures of Spike Train Synchrony: From Single Neurons to Populations," address the subtle issues of analyzing and comparing time-series recordings from multiple neurons. This chapter gives an overview of different approaches designed to quantify multiple neuron synchrony. It addresses measures of synchrony within a group of neurons as well as measures that estimate the degree of synchronization between populations of neurons. The authors show that the various existing measures have different advantages and disadvantages that depend on the properties of the spike trains. This analysis deals only with two different scales: that of individual neurons and of small populations. However, the types of measures the authors discuss are likely to be good models for a broader quantification of similarity and synchrony and should be useful across multiple scales.

Besides time-frequency analysis of the one-dimensional time series discussed above, more complicated multiresolution analysis of high-dimensional information is required for data-intensive sciences such as Systems Biology and Systems Neuroscience. This is the subject of the next section.

1.2
Multiresolution Analysis and Processing of High-Dimensional Information/Data

Modern scientific instruments generate large amounts of new data types, such as data defined on graphs and manifolds, vector and tensor data. In fact, the problem of multiscale representation/analysis of data defined on manifolds is ubiquitous in neuroscience, biology, medical diagnostics, etc. One important example comes from fMRI data, where the functional time series can be described as sampled vector-valued functions on the sphere S^2 in R^3, while various statistics derived from the data can be described as functionals on the sphere. In general, brain activity is highly dimensional and this, combined with the coming era of recording from multiple neurons will lead to extremely complex, large data sets (for multineuronal recordings of visual signaling in populations of ganglion cells, see Refs [42,59]; for simultaneous recordings of neural activity from multiple areas in lateral prefrontal and posterior parietal cortical regions, see Ref. [35]; for applying multivariate pattern analysis to fMRI, see Ref. [60]). A Neuroscience information framework (NIF) that would encompass all of neuroscience and facilitate the integration of existing knowledge and databases of many types is advocated by Akil *et al.* [61]. These complex data sets cannot be adequately understood without detecting various scales that might be present in the data. However, traditional MRA tools based on wavelets are restricted mostly to one-dimensional or two-dimensional signals. Thus, the development of multiscale analysis applicable to functions defined on graphs or manifolds is of great importance to Systems Biology and Systems Neuroscience. This will enable bio- and neuro-informatics to deal with the processing and visualization of complex information, pattern analysis, statistical modeling, etc.

Extending multiresolution analysis from Euclidean to curved spaces and networks presents a significant challenge to applied mathematics. Spectral methods and diffusion maps have recently emerged as effective approaches to capturing the degrees of freedom, scales, and structures (clusters, patterns) within high-dimensional data [62,63]. Diffusion maps applied to complex neural data allowed Coifman *et al.* [64] to integrate essential features at all scales in a coherent multiscale structure. Diffusion maps have also been applied to stochastic chemical reaction network simulations to recover the dynamically meaningful slowly varying coordinates [65]. Such a procedure is important for modeling multiscale chemical reactions, and in this sense, diffusion maps are relevant to the problems discussed in Section 1.1.

Compressed sensing and sparse representations offer promising new approaches to modern data processing. Traditionally it has been considered unavoidable that any signal must be sampled at a rate of at least twice its highest frequency in order to be represented without errors. However, compressed sensing permits sampling at a lower rate, and it has been the subject of much recent research [66]. Many fundamental problems of applied mathematics and engineering, including statistical data analysis, can be formulated as sparse approximation problems, making algorithms for solving such problems versatile and relevant to multiple applications [67]. In Neuroscience, the multidimensional nature of odors and sparse representations in the olfactory networks were discussed by Laurent [68]; sparse coding in neural circuits was also addressed in Ref. [69].

Wavelets or frames consisting of nearly exponentially localized band-limited functions are imperative for computational harmonic analysis and its applications in statistics, approximation theory, and so on. Wavelet-type bases and frames encapsulate smoothness of functions and provide sparse representation of natural function spaces. In this book, Isaac Pesenson, in his chapter called "Multiresolution Analysis on Compact Riemannian Manifolds," describes multiscale analysis, sampling, and approximation of functions defined on general compact Riemannian manifolds. The author constructs band-limited and space-localized frames, and variational splines on manifolds. These frames have Parseval property and, together with the constructed splines, enable multiscale analysis on arbitrary compact manifolds. For such manifolds as the two-dimensional sphere and group of its rotations, these approaches have already found a number of important applications in statistics, analysis of the cosmic microwave background, and crystallography. The results of this chapter may also be useful in the neurophysics of electroencephalography (EEG) (see Chapter 8 of Ref. [70]).

Overall, MRA is a powerful tool for efficient representation/analysis of complex information (signals, images, etc.) at multiple levels of detail with many inherent advantages, including compression, visualization, and denoising. In Systems/Synthetic Biology and Systems Neuroscience, large integrated data are often connected with complex nonlinear dynamical processes on hierarchical networks. This is the subject of the section that follows.

1.3
Multiscale Analysis, Networks, and Nonlinear Dynamics

The human brain and gene circuits/networks, which are the main topics of this book, demonstrate nontrivial organization and nonlinear dynamics across multiple spatial and temporal scales, which ultimately result in complex, adaptive behavior and emergence. The human brain has about 10^{11} neurons with $\sim 10^{14}$ contacts between them. The approach based on network or graph theory is especially well suited for describing multiscale systems and nonlinear dynamics on them ([4–13, 21,23–25,51,52,71–90]. In Systems Biology a graph can be utilized, for example, to describe the cellular differentiation hierarchy. Overall, network theory enables one to analyze the effect of multiscale structure (spatial scales) on multiscale evolutionary dynamics (and vice versa), and as such provides a general framework for the integration of multiscaling and collective dynamics. This perspective is illuminated by a few contributions, which are described below.

Paul Nunez, Ramesh Srinivasan, and Lester Ingber, in their contribution "Theoretical and Experimental Electrophysiology in Human Neocortex: Multiscale Dynamic Correlates of Conscious Experience," treat human brains as the preeminent complex system with consciousness assumed to emerge from dynamic interactions within and between brain subsystems. Given this basic premise, they first look for general brain features underlying such complexity and, by implication, the emergence of consciousness. They then propose general dynamic behaviors to be expected in such systems and outline several tentative connections between theoretical predictions and experimental observations, particularly the large-scale ($\sim$cm) extracranial electric field recorded with electroencephalographic technology (EEG).

Danielle Bassett and Felix Siebenhühner, in their chapter called "Multiscale Network Organization in the Human Brain," examine the multiscale organization evident in brain network models. Structural brain networks, derived from estimated anatomical pathways, display similar organizational features over different topological and spatial scales. In fact, these networks are hierarchically organized into large, highly connected modules that are in turn composed of smaller and smaller modules. Together, these properties suggest that the cortex is cost-efficiently, but not cost-minimally, embedded into the 3D space of the brain. Functional brain networks, derived from indirect relationships in regional activity, are similarly organized into hierarchical modules that are altered in disease states and adaptively reconfigure during cognitive efforts such as learning. In general, it is the multiscale structure of complex systems that is responsible for their major functional properties. Thus, multiscale organization might have important implications for cortical functions in the human brain in particular. A better understanding of this structure could potentially help elucidate healthy cognitive functions such as learning and memory, and provide quantitative biomarkers for psychiatric diagnosis and the monitoring of treatment and rehabilitation.

Michel Le Van Quyen, Vicente Botella-Soler, and Mario Valderrama, in their contribution "Neuronal Oscillations Scale Up and Scale Down Brain Dynamics," approach brain dynamics from the perspective of their recent work on simultaneous recording from micro- and macroelectrodes in the human brain. They propose a physiological description of these multilevel interactions that is based on phase–amplitude coupling of neuronal oscillations that operate at multiple frequencies and on different spatial scales. Specifically, the amplitude of the oscillations at a particular spatial scale is modulated by variations of phases in neuronal excitability induced by lower frequency oscillations that emerge on a larger spatial scale. Following this general principle, it is possible to scale up or scale down multiscale brain dynamics. It is expected that large-scale network oscillations in the low-frequency range, mediating downward effects, may play an important role in attention and consciousness.

Michael Cohen and Bradley Voytek, in their chapter called "Linking Nonlinear Neural Dynamics to Single-Trial Human Behavior," emphasize that human neural dynamics are complex and high dimensional. There seem to be limitless possibilities for developing novel data-driven analyses to examine patterns of activity that unfold over time, frequency, and space, and interactions within and among these dimensions. A better understanding of the neurophysiological mechanisms that support cognition, however, requires linking these complex neural dynamics to ongoing behavioral performance. Performance on cognitive tasks (measured, e.g., via response accuracy and reaction time) typically varies across trials, thus providing a means to determine which neural dynamical processes are related to which cognitive processes. They review and present several methods for linking nonlinear neural dynamics, based on oscillatory phase, phase-based synchronization, and phase–amplitude cross-frequency coupling. There are two major advantages of linking nonlinear neural phase dynamics with trial-varying task performance. First, if the goal of the research is to identify the neural dynamics that underlie cognition, linking phase dynamics to task performance helps identify task-related features of the EEG, and dissociate those from background (and nontask-related) neural dynamics. Second, because the oscillation phase has been linked to a variety of synaptic, cellular, and systems-level phenomena implicated in learning, information processing, and network formation, linking trial-varying performance to EEG phase provides a neurophysiologically grounded framework within which results are interpreted. That is, not only can the features in EEG data be linked to cognition, but they also bridge cognition and neurophysiological properties.

Etienne Hugues, Juan Vidal, Jean-Philippe Lachaux, and Gustavo Deco, in their contribution called "Brain Dynamics at Rest: How Structure Shapes Dynamics," study neural activity present at rest. By using EEG and magnetoencephalography (MEG) techniques it has been well established that neural resting-state activity exhibits prominent alpha oscillations. More recently, data obtained in humans by using blood oxygen level-dependent functional magnetic resonance imaging (BOLD fMRI) revealed the existence of spatial structures across the brain called functional connectivity (FC) patterns, and the so-called resting-state networks (RSNs). FC patterns have also been found in EEG and MEG studies. Lately, the RSNs detected by BOLD fMRI have also been observed in the alpha and beta bands by using MEG technique. Although the alpha oscillations and the RSNs are now well characterized experimentally, their neural origin remains a matter of debate. To study this issue, they introduce a model of the spontaneous neural activity of the brain, comprising local excitatory and inhibitory neural networks connected via white matter fibers. Theoretical analysis and numerical simulations of this model reveal that neural activity exhibits various modes. Many of these modes are found to be oscillatory and the most dominant ones can be identified with the different alpha oscillations. They show that these modes are responsible for correlated activity in the alpha band as well as in the BOLD signal. Comparison with intracranial EEG in humans validates the dynamical scenario proposed by the model.

Misha Pesenson, in his contribution "Adaptive Multiscale Encoding – A Computational Function of Neuronal Synchronization," addresses the problem of multiscale encoding of information by human perception systems. A nonlinear mechanism based on neural synchronization that achieves the desired multiscale encoding is proposed. Entrainment of different neurons produces larger receptive fields than that of a single cell alone, leading to a multiresolution representation. Such receptive fields can be called entrainment receptive fields (ERF), or synchronization receptive fields. The size of ERF is determined by external stimulus (bottom-up activation along the sensory pathways), as well as by attention (top-down activation), which selects or forms the underlying network structure. In other words, the receptive field size is controlled by this bidirectional signaling and the proposed mechanism does not rely solely on a fixed structure of the receptive fields (or a bank of fixed, predetermined filters), but instead attains multiscale representation adaptively and dynamically. In this way the model goes beyond the classically defined receptive fields. This entrainment-based mechanism may underlie multiscale computations in various sensory modalities, as well as experimentally observed correlations between multiple sensory channels. From the information processing perspective, the importance of the model lies in the fact that it allows one to generalize the scale concept to functions defined on manifolds and graphs. The model also leads to what can be called a synchronization pyramid. In addition, it enables gradient-preserving smoothing of images, dimension reduction, and scale-invariant recognition.

1.4
Conclusions

The examples discussed demonstrate the crucial role of multiscaling in modeling various natural phenomena and in exploring (the associated) complex data sets. Taken together, the chapters in this book deal with diverse multiscale processes in Systems Biology and Systems Neuroscience, as well as describe some general mathematical constructs to parse essential multiscale features. Collective dynamics together with mechanisms operating simultaneously on multiple scales often trigger adaptive, emergent behavior, so the unified point of view based on iMCD gives insights into these processes by emphasizing the conceptual and mathematical principles that are common to them. In summary, this book focuses on parallels between different fields and approaches and it is hoped that this perspective will contribute to taking the task of exploring analogies to the next level – building "analogies between analogies."

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