The frontiers and challenges of biodynamics research

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1 Background

As scientists unravel the secrets of the organization of life, an understanding of the temporal and spatiotemporal *dynamics* of biological processes is deemed crucial for creating a coherent, fully integrative picture of living organisms. In this endeavour, the basic challenge is to reveal how the coordinated, dynamical behavior of cells and tissues at the *macroscopic* level, emerges from the vast number of random molecular interactions at the *microscopic* level. This is the central task of modern biology and, traditionally, it has been tackled by focusing on the participating molecules and their microscopic properties, ultimately at the quantum level. Biologists often tacitly assume that once all the molecules have been identified, the complete functioning of the whole biological system can finally be derived from the sum of the individual molecular actions. This reductionistic approach has proven spectacularly successful in many areas of biological and medical research. As an example, the advances in molecular biology, which have led to the ability to manipulate DNA at the level of specific genes, will have a profound effect on the future course of medicine through the introduction of gene-based therapies. Despite this progress, however, the consensus is growing that the reductionist paradigm, by itself, may be too limiting for successfully dealing with fundamental questions such as (1) how living systems function *as a whole*, (2) how they transduce and process *dynamical information*, and (3) how they respond to *external perturbations*.[1]

2 Self-organization

The difficulties of addressing these questions by purely reductionistic approaches become immediately apparent when considering – from the

[1] For recent perspectives see Hess and Mikhailov (1994), Glanz (1997), Spitzer and Sejnowski (1997), Williams (1997), Coffey (1998) and Gallagher and Appenzeller (1999).

standpoint of physics – the following two defining features. (1) Living organisms are thermodynamically open systems; that is, they are in a state of permanent flux, continuously exchanging energy and matter with their environment. (2) They are characterized by a complex organization, which results from a vast network of molecular interactions involving a high degree of nonlinearity. Under appropriate conditions, the combination of these two features, *openness* and *nonlinearity*, enables complex systems to exhibit properties that are *emergent* or *self-organizing*. In physical and biological systems alike, such properties may express themselves through the spontaneous formation, from random molecular interactions, of long-range correlated, macroscopic dynamical patterns in space and time – the process of *self-organization*. The dynamical states that result from self-organizing processes may have features such as excitability, bistability, periodicity, chaos or spatiotemporal pattern formation, and all of these can be observed in biological systems.

Emergent or self-organizing properties can be defined as properties that are possessed by a dynamical system as a whole but not by its constituent parts. In this sense, the whole is *more* than the sum of its parts. Put in different terms, emergent phenomena are phenomena that are expressed at higher levels of organization in the system but not at the lower levels. One attempt to help to visualize the concept of self-organization is the sketch in Figure 1, which shows the dynamical interdependence between the molecular interactions at the microscopic level and the emerging global structure at the macroscopic level. The upward arrows indicate that, under nonequilibrium constraints, molecular interactions tend to spontaneously synchronize their behavior, which initiates the beginnings of a collective, macroscopically ordered state. At the same time, as indicated by the downward arrows, the newly forming macroscopic state acts upon the microscopic interactions to force further synchronizations. Through the continuing, *energy-driven* interplay between microscopic and macroscopic processes, the emergent, self-organizing structure is then stabilized and actively maintained.

Amongst the earliest examples for this behavior in a simple physical system is the spontaneous organization of long-range correlated macroscopic structures; that is, of convection cells (Bénard instability) in a horizontal water layer with a thermal gradient (e.g., Chandrasekhar, 1961). In this well-known case of hydrodynamic self-organization, the size of the emergent, global structures – that is, of spatiotemporal hexagonal patterns of the order of millimeters – is greater by many orders of magnitude than the size of the interacting water molecules. This implies that, when the thermal gradient has reached a critical value, the initially uncorrelated, random motions of billions of billions of

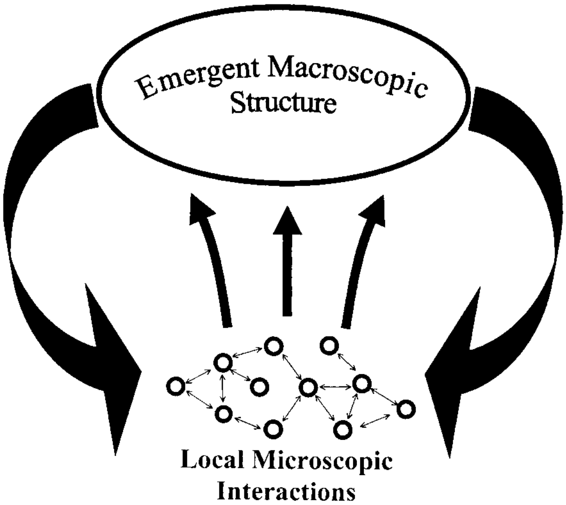

Figure 1. Sketch illustrating the dynamical interdependence between microscopic molecular interactions and the emerging global structure at the macroscopic level. The system under consideration is open to the flow of matter or energy. The upward arrows indicate that, under nonequilibrium constraints, molecular interactions tend to spontaneously synchronize their behavior, which initiates the beginnings of a macroscopic, ordered state. As indicated by the downward arrows, this newly forming state acts upon the microscopic interactions to force further synchronizations. Through the continuing, energy-driven interplay between microscopic and macroscopic processes, the emergent, self-organizing structure is stabilized and actively maintained.

molecules have synchronized spontaneously *without* any external instructions, hence, the term ‘self-organization’.

3 Theoretical foundations and computer simulations

The above arguments reveal that the origins and dynamics of emergent, macroscopic patterns, including in biological systems, cannot be simply deduced from the sum of the individual actions of the system’s microscopic elements. What is needed is an analysis of the system’s collective, macroscopic dynamics, which results from the complex web of nonlinear interactions between the elements. During the early 1970s, general theoretical frameworks for this type of analysis, which are based on a branch of mathematics called *nonlinear dynamics*, became more widely available and recognized. In 1977, I. Prigogine was awarded a Nobel prize for the discovery that, in *apparent* contradiction to the second law of thermodynamics, physico-chemical systems far from thermodynamic equilibrium tend to self-organize by exporting entropy and form, what he termed, *dissipative structures* (Glansdorff and

Prigogine, 1971; Prigogine and Nicolis, 1971; Nicolis and Prigogine, 1977). Other pioneers in the physical or biological sciences, for example, include H. Haken and M. Eigen. Haken presented a theory of nonequilibrium phase transitions and self-organization as an outgrowth of his work on the theory of lasers (Haken, 1975, 1978), and Eigen developed a theoretical framework for a role of molecular self-organization in the origin of life (Eigen, 1971). There are, of course, many other scientists who are directly responsible for developing this field. Only a few names can be mentioned here, however, and the reader may consult Chapter 1 by Kaiser for a brief introduction to the history of this science.

Armed with the tools of nonlinear dynamics, scientists are now able to describe and simulate highly nonlinear biological behaviors such as biochemical and cellular rhythms or oscillations. The availability of the appropriate mathematical tools is an important prerequisite for making progress in the rapidly growing area of biological dynamics or 'biodynamics'. One specific reason stems from the fact that mechanistic explanations of self-organizing, biodynamical processes frequently defy intuition. This is due to the complexity of the dynamical interactions that underlie such processes, whose emergent properties cannot be readily grasped by the human observer (compare Figure 1). Thus, as is reflected in many of the contributions to this volume, scientists must rely heavily on computer simulations to explore complex biological dynamics and to make predictions about experimental outcomes. Common to all these approaches is the treatment of a biological system as an open system of nonlinearly interacting elements. Consequently, the field of *biodynamics* might be defined as *the study of the complex web of nonlinear dynamical interactions between and among molecules, cells and tissues, which give rise to the emergent functions of a biological system as a whole.*

4 Nonlinear dynamics moves into cell and molecular biology: cellular oscillators, biological signaling and biochemical reaction networks

Although the self-organization of macroscopic patterns, including temporal oscillations and spatiotemporal wave patterns, was first studied and theoretically understood in physical and chemical systems, numerous examples are now known at all levels of biological organization (for recent overviews, see Goldbeter, 1996; Hess, 1997). The most conspicuous examples of self-organizing biological activity are *biological rhythms* and *oscillations*. The formation of oscillatory dynamical states of different periodicities plays a fundamental role in living organisms. In humans, the observed oscillation periods cover a wide range from the subsecond time domain of neuronal oscillations to the 28-day period of the ovarian cycle. For instance, the perception of visual stimuli is associated with oscillatory synchronizations of neuronal assemblies at frequencies of 10s of hertz. At the cellular level, oscillatory signaling and metabolic processes such as oscillations in the intracellular concentration of calcium (Ca^{2+}), adenosine triphosphate (ATP) or nicotinamide adenine dinucleotide phosphate (NADPH) have periods of the order of seconds to minutes. For example, the activity of human neutrophils, a key component of cellular immune defense, involves oscillatory cell biochemical processes with periods on the order of 10 to 20 s. Finally, the cell cycle itself is a prime example of a biological oscillator: cell cycle progression is controlled by the mitotic oscillator whose oscillation periods may range from about 10 min to 24 h. Many more examples are known and several of them are covered in detail in this book.

The processes that underlie cellular oscillators are organized in complexly coupled *biochemical reaction networks*, wherein feedforward and feedback information flows provide the links between the different levels in the hierarchy of cell biochemical network organization. Such networks are also central components of the cellular machinery that controls biological signaling. Computer modeling has recently enabled scientists to investigate the properties of *biological signaling networks* such as their capacity to detect, transduce, process and store information. In these efforts, it was found that cellular signaling pathways may also exhibit properties of emergent complexity (for a recent example, see Bhalla and Iyengar, 1999). Such findings serve to demonstrate the difficulties that scientists face when they attempt to predict the dynamics of cellular signal transduction processes only on the basis of isolated signaling molecules and their individual microscopic actions. In order to develop an integrative, dynamical picture of biological signaling processes, therefore, it will be necessary to characterize the nonlinear relationships among the different molecular species making up the biochemical reaction networks, which control all aspects of cellular regulation as, for example, from RNA transcriptional control to cellular division. Theoretical models of biochemical reaction networks have been proposed that simulate, for example, cellular dynamics of Ca^{2+} oscillations (e.g., Goldbeter *et al*., 1990), interactions between different cell signaling pathways (e.g., Weng *et al*., 1999), genetic regulatory circuits (e.g., McAdams and Arkin, 1998), cellular control networks for DNA replication (Novak and Tyson, 1997) and cellular division (Borisuk and Tyson, 1998). Such theoretical work is not limited, however, to the analysis of normal cell function. Nonlinear modeling has been applied, for example, to pathological cell signaling involved in cancer formation (Schwab and Pienta, 1997).

From this and related work the perspective is developing that biological cells can be viewed as highly sophisticated information-processing devices that can discern complex patterns of extracellular stimuli (Bray, 1995). In line with this view is the finding that, in analogy to electrical circuits, biochemical reaction networks can perform computational functions such as switching, amplification, hysteresis, or band-pass filtering of frequency information (e.g., Arkin and Ross, 1994). The development of the theoretical and computational tools for deducing the function of complex biochemical reaction and nonlinear signaling networks will become even more important for biologists now that many genome projects are nearing completion. The ambitious goal of these projects is to provide researchers with a complete list of all cellular proteins and genetic regulatory systems. The daunting task that biologists face is to functionally integrate the massive amount of data from these projects. Clearly, this will require an approach that can account for the emergent, collective properties of the vast network of nonlinear biochemical reactions that underlie the biocomplexity of cells, tissues and of the whole organism.

5 Biological interactions with external stimuli and nonlinear control

The nonlinear dynamical nature of living processes turns out to be crucial for understanding how biological systems interact with the external environment. Specifically, the intrinsic nonlinearity of living systems is of great significance to scientists who study the response of cells, tissues and whole organisms to natural or artificial stimuli. The reason is that the response behavior of a nonlinear system may differ drastically from that of a linear system. In a linearly behaving system, the response magnitude to an applied stimulus is proportional to the strength of the stimulus. In contrast, disproportionately large changes may result in a nonlinear system. The inherent *amplification properties* of nonlinear systems thus represent one critical aspect that defines the system's sensitivity and the magnitude of its response to external perturbations.

Another aspect concerns the capacity of complex, nonlinear systems to detect and process information contained in incoming signals. For instance, the response of nonlinear systems can depend, in a highly nonlinear fashion, on the frequency information contained in an oscillating external perturbation. For these and other reasons discussed further below, the response of nonlinear processes such as may occur in biological systems may lead to unexpected sensitivities and complex response patterns. Knowledge about this behavior is not only of significance for revealing the mechanistic basis of stimulus–response effects but, importantly, can be exploited for the *nonlinear control* of dynamical biological processes for practical purposes.

Within the context of this volume, nonlinear control refers to mechanisms or methods that control chemical, biochemical or biological processes by exploiting the nonlinear dynamical features that underlie these processes. For example, the goals of nonlinear control may be to cause excitation or suppression of oscillations, entrainment and synchronization, or transitions from chaotic to periodic oscillations and vice versa. Specifically, the term ‘control’ refers to the modification of the behavior of a nonlinear system by variation of one or more of the *control parameters* that govern the system’s macroscopic dynamics. This may be achieved by variations that are caused either by processes within the system or by appropriately designed external perturbations. In this approach, global macroscopic dynamics, rather than microscopic kinetics, thus provides the critical information for system control.

6 Purpose and contents

This volume provides an introduction to the application of a broad range of concepts from nonlinear dynamics such as self-organization, emergent phenomena, stochastic resonance, coherence, criticality, fractals and chaos to biology and medicine. The selected contributions cover nonlinear self-organized dynamics at all major levels of biological organization, ranging from studies on enzyme dynamics to psychophysical experiments with humans. The emphasis is on work from (1) experimentalists who study the response of nonlinear dynamical states in biological and other excitable systems to external stimuli and (2) theorists who create predictive models of nonlinear stimulus–response interactions. The investigated stimuli cover a variety of different influences, including chemical perturbations, electromagnetic signals, mechanical vibrations, light stimuli or combinations thereof. The interaction targets include cyclical, excitable and oscillatory behavior in biological and related systems. They include membrane ion channels and pumps, biochemical reaction networks, oscillatory chemical or enzyme activity, oscillations in cellular metabolites, Ca^{2+} oscillations, genetic regulatory networks, excitable states in neurons and sensory cells, and chaotic or periodic heart and brain tissue dynamics. This volume’s two main purposes are: (1) to introduce the reader to the present state of theoretical and experimental knowledge in this rapidly expanding field of interdisciplinary research, and (2) to outline the future research needs and opportunities from the perspective of the different disciplines, from theoretical physics to biomedical engineering.

The individual contributions summarize a wide range of experimental and theoretical investigations by biologists, neuroscientists, chemists, physicists, bioengineers and medical researchers. This selection emphasizes (1) the need for cross-disciplinary dialogue and (2) the importance of the interplay between theoretical modeling and laboratory experiments. It also reflects the responsibility of the recent focus on collaborations between theorists and experimentalists for the increasing progress in understanding complex stimulus–response interactions in biosystems. This volume covers both the basic research aspects as well as the emerging technological dimensions. Basic research includes the interplay between theory development, laboratory experimentation and computer simulations. The promise of future technologies comes from the development of techniques that exploit the self-organized dynamics intrinsic to living systems for diagnostic, prognostic and therapeutic purposes. Special attention is given to three interconnected components of the stimulus–response paradigm:

(1) The often surprising sensitivity of biological and related excitable systems to weak external influences, whether they are chemical, mechanical or electromagnetic in nature, is illustrated by many examples. The stimuli are either time-varying or constant. Time-dependent stimuli include periodic oscillations and random fluctuations. These are applied to systems that generate deterministic temporal or spatiotemporal behavior by methods that in some cases involve feedback control. A major focus is the application of electromagnetic stimuli as a specific, minimally invasive tool for influencing biodynamical systems, which is the subject of the research area known as *bioelectromagnetics*. This volume includes important information regarding (a) the theoretical limits of the interaction of electromagnetic field signals with chemical, biochemical and biological systems and (b) the laboratory evidence for electric or magnetic field interactions with isolated enzymes, cells and tissues. The targets of electromagnetic fields may be any physicochemical processes that are sensitive to these fields and that play a role in the generation or maintenance of self-organizing dynamics. The fundamental physical constraints that govern these interactions are explained for both the initial energy transduction step in the presence of thermodynamic noise and for the responsiveness of the dynamical state to a weak perturbation.

(2) The recognition of deterministic macroscopic dynamics in biological systems also opens up unanticipated opportunities for probing biological systems. For example, information regarding the intrinsic dynamics of a biological system can be obtained by analyzing its response to an applied stimulus. Computer simulations have long shown that the imposition of weak stimuli on systems with complex dynamics, including living systems, may induce responses that depend not only on the intensity of the stimulus but, importantly, on its temporal pattern as well as the initial state of the system. State dependence and sensitivity to the temporal characteristics of the applied stimulus is a fundamental feature of self-organized biological activity. There now exists experimental evidence that is in excellent agreement with the predictions from theoretical modeling: an increasing number of laboratories report that excitable systems, including chemical, biochemical and biological systems, display complex responses with nonlinear dependence on imposed tem-

poral patterns. For example, resonance-like responses to coherently oscillating stimuli that depend strictly on the frequency of the imposed stimulus have been observed in many experiments in recent years. They include excitable chemical reactions, isolated enzymes and membrane ion transporters, biochemical reaction networks, Ca^{2+}-dependent gene expression, and neuronal or heart muscle cell activity in single cells and tissue preparations.

(3) The identification of self-organized dynamical states in living systems and the knowledge about their sensitivity has also paved the way for developing new strategies for influencing or controlling biological dynamics. Importantly, it was found that the sensitivity of biodynamical systems to appropriately designed stimuli could be exploited for practical purposes, like the ability to shift the dynamics of biological activity from an unwanted state to a desired one. The discovery of deterministic biological chaos, for example, offers novel strategies for therapeutic interventions. Here, chaos does not refer to disordered, random processes, but rather characterizes hidden dynamical order within apparent disorder. As this book illustrates, methods initially developed to control chaos in physical systems have also been found to be effective in controlling chaotic dynamics in chemical and biological systems. Dramatic demonstrations of this possibility are experiments in which chaos control techniques were applied to heart and brain tissue preparations and, most recently, to human heart patients. This book discusses implications of these possibilities for treating so-called 'dynamical diseases' such as heart arrhythmias and epileptic seizures.

A new research area that is critical to each of the three components of the stimulus–response paradigm is the exploration of the constructive role that intrinsic or external random fluctuations may play in physiological functions. Consequently, one part of the volume is devoted to theory and experimentation on the previously unsuspected, beneficial role of stochastic noise in controlling or influencing nonlinear dynamic and transport phenomena in living systems. At first glance this notion seems counterintuitive, but established physical concepts, including the ones known as *stochastic resonance* and *fluctuation-driven transport*, make such phenomena theoretically plausible (see, e.g., Astumian and Moss, 1998). This volume covers both the applied and basic research dimensions of noise-assisted biochemical and biological processes. It summarizes theoretical and experimental evidence demonstrating a beneficial or even necessary role for noise in biological signaling, including neuronal information processing. The developing technological applications, which are based on the principle of stochastic resonance, are also addressed. This work includes the modulation of biological signal transmission through the controlled addition of noise to diagnose or to improve human sensory perception.

7 Frontiers and outlook

What is the physical basis of biological self-organization? How do the basic elements of biological activity interact to give rise to the function of a living organism as a whole? How do biodynamical systems respond to weak biochemical or electromagnetic perturbations? How can the nonlinear features of biodynamical processes be put to practical use, for example, in clinical diagnosis and therapy? These are among the questions that are explored in the 18 chapters that follow. The presented ideas and experimental observations demonstrate that many important features of the dynamics of living processes can be understood on a theoretical basis. Importantly, the validity of this knowledge is confirmed by the success of the emerging biomedical applications that have already resulted from this work, for example by employing fractal time series analysis and nonlinear control methods.

In summary, the perspective of a living system as a self-organizing, complex, far-from-equilibrium biochemical state allows physics to enter the study of dynamical biological functions in a quantitative, predictive manner. While the nonlinear dynamical systems approach does not yet, however, represent a physical theory for the organization of life, its broad scope and power suggests that it will be a crucial building block in the construction of any such theory in the future. At a minimum, biodynamics research is revealing how complex, sophisticated and remarkably sensitive living processes really are. Finally, this work suggests that any integrated understanding of the functional complexity observed in dynamical biology is probably beyond the scope of standard reductionistic approaches. It is our hope that the reader can share the excitement of discovery conveyed in the following chapters and thus will be motivated to view and explore biological processes from a new perspective.

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