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9.1 Introduction to Volume 9 – Theoretical Biophysics: A Cornerstone of Understanding in Modern Biology and Biomedicine

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To cover key topics in the rapidly growing field of theoretical and computational biophysics, the contributions to this volume by leading researchers concentrate on three major aspects: (i) In silico approaches to learning the relation between structure and function of cell components and their aggregates; (ii) computational simulations of molecular machines that enable cell signaling and function; and (iii) mathematical modeling of complex biological systems and interactions in the cell. Each of the chapters introduces, explains and illustrates exciting new findings achieved with both well established and novel methodology in each of these aspects that are central to current research in biophysics.

A common perspective in this volume is the theoretical and computational treatment of fundamental processes in biological systems, anchored in rigorous physics and mathematics and relating directly to experimentally determined knowledge. Thus, each contributed chapter offers a powerful demonstration that the increasingly high resolution of the experimentally-gained information about structure (e.g., from x-ray crystallography, and advanced microscopy), about dynamics and energetics (e.g., from a variety of single molecule approaches), and about complex physiological systems (e.g., from advanced molecular biology and imaging methods) is enabling a tight and rigorously accurate interplay between experiment and theory. Most often leading to quantitative modeling and simulation, this strong relation between theoretical and experimental biophysics yields unprecedented insight and a deep level of mechanistic understanding of fundamental biological processes that carry as well powerful practical implications.

The impact of this synergistic interplay, made possible by rapid new developments in both experimental and theoretical biophysics, is clearly illustrated in the chapters addressing mechanisms of macromolecular cellular components. Thus, even when the structures of enzymes, G protein coupled receptors and membrane-embedded transporters became known in atomistic detail, and detailed biochemical and electrophysiology enabled the proposal of molecular mechanisms, the understanding of the processes remained incomplete, because inferences from analogy to other systems and from reasoning in mechanical terms involving rigid body motions were unsatisfactory. In contrast, chapters devoted to the various aspects of molecular biophysics in this volume show how a detailed, quantitative and predictive mechanistic understanding can be achieved with powerful new theoretical developments in molecular biophysics, and computational simulation methods that take advantage of rigorous physics embedded in novel computational algorithms. This is taken up in this volume by introducing the most compelling technological advances in simulation, outlining powerful methodology including electrostatics, the use of quantum mechanical (and combined quantum and molecular mechanics) methods in the study of biological processes, and the development and application of advances in computational biophysics for atomistic and coarse grained simulation of protein and membrane systems. From the quantitative evaluation of structural details and dynamic processes of the cell’s membrane and its interaction with integral proteins, to the atomistic details of the functional mechanisms of the molecular machines it contains, the chapters in this volume demonstrate how the synergy established between the advanced experimental and computational approaches produces an understanding about complex biomolecular systems as large as the ribosome and as fast as the channels and light processing molecules, at a level that is unprecedented in structural and dynamic detail, quantitative information, and predictive power.

Even as the elucidation of detailed molecular mechanisms is achieved from the close quantitative relation and complementarity between theoretical and experimental molecular biophysics described in this volume, the challenge presented by the complexity of the cells and organs in which these biomolecules function, remains formidable. Yet is appears absolutely necessary to be able to address in a rigorous manner the formal and quantitative biophysical underpinnings of the integrated biological systems in order to make sense of their behaviors, because these are most often the result of nonlinear emergent properties characteristic of interrelated systems that contain large numbers of complex components, such as the cell. The theory and mathematical methods needed to address the complexity of interactions among cell components that determine its system-level behavior is illustrated in one of the four chapters of this volume covering the third aspect of theoretical biophysics mentioned above. Moreover, that biophysical theory and new combinations of mathematical modeling and systems level simulations present exciting promises to enable mechanistic and predictive understanding of integrated biological systems, is illustrated by contributions that describe new discoveries in organized physiological systems – from the heart and kidney to the immune system – made possible by such theory and novel approaches. Together, these examples lead to the compelling conclusion that theoretical approaches, empowered by mathematical formulations that enable systems level thinking while co-opting the formal biophysical description of the component biomolecular systems, constitute a cornerstone of understanding in modern biology and biomedicine.