# Preface

Proteins exert a variety of fascinating functions to participate in virtually all cellular processes. Underlying these highly controlled activities are the ordered conformational changes, which lead to molecular events that drive efficient and precise regulation and control of these processes. Although it has been widely acknowledged that the conformational dynamics of proteins contributes enormously in these molecular events and their biological function, it remains a major challenge to unambiguously discern their working mechanism both experimentally and computationally. The difficulties primarily arise from the complexity and heterogeneity of protein assemblies, the ruggedness of free energy landscapes, and the largely varied scales of temporal and spatial changes in different events.

Complementary to experimental studies, computational simulation has become a powerful and unique tool to dissect the working mechanism of proteins and provide information otherwise inaccessible to other methods. In recent years, the persistent progress in methodologies (super-computational resources, multi-scale modeling, enhanced sampling methods, etc.) has demonstrated a number of important applications in biological processes, e.g. molecular recognition, enzyme catalysis, molecular transport, protein folding and aggregation, and signal transduction. In this book, we present an extensive review of the recent theoretical and computational advances as well as their applications to key biological questions.

In Chaps, 1, 2, and 3, different methods are described to generate the conformational ensembles during the folding and function of proteins. Chapter 1 describes the generalized-ensemble algorithms and their applications to the protein folding problem. Chapter 2 introduces another powerful tool in conformational sampling, the Markov State Models (MSMs), which can increase the simulation length to microseconds or even milliseconds. This chapter explains the general concepts of MSMs, the model construct procedure, and its application to the long time-scale molecular dynamics simulation of biological macromolecules. As the conformational dynamics can now be characterized by advanced experimental methods, Chap. 3 shows how these information can be combined with computational simulation to build the conformational ensembles.

The conformational ensembles in biological macromolecules contain useful information that describes the important features of the system. Methods to extract this information will be summarized in Chaps. 4, 5, 6, and 7. Chapter 4 reviews methods that produce generative models of conformational dynamics to manifest the hidden thermodynamic and kinetic properties from the ensembles generated during simulations. To study the large-scale motions of proteins, Chap. 5 describes various coarse-grain elastic network models (ENMs) that predict the magnitudes and directions of protein motion, focusing on the recently developed generalized spring tensor model. When the size of biological systems increase, high-resolution structure can only be obtained in fragments and the structural information of the system is often of low-resolution. Several flexible fitting methods are presented in Chap. 6 to extract deeper understanding from the combination of these experimental data. Along this line, various coarse-grained models are discussed in Chap. 7 to study the functional change of the polypeptide backbones around their native states.

Protein folding is a critical biological process in which proteins acquire their defined three-dimensional structures from linear polypeptides. Chapters 8 and 9 focus on this topic and review methods that unveil this dynamic process. Because the cellular environment plays a major role in regulating the dynamics of protein folding, Chap. 8 describes novel coarse-grained methods that go beyond traditional aqueous solvent conditions and study *in vivo* protein folding dynamics. Since various optical spectroscopic techniques have been used to probe protein folding/unfolding events, Chap. 9 addresses progress on modeling the unfolding dynamics of several model proteins using the combined theoretical spectroscopic and MSMs approaches.

Conformational dynamics plays a major role in dictating function of proteins. Chapters 10 and 11 explore the conformational flexibility in enzyme catalysis and drug designs. Chapter 12 addresses how the nuclear magnetic resonance spectroscopy and computational methods are combined to understand the receptor-ligand interaction. The structural dynamics of membrane proteins stands as a major challenge and Chap. 13 presents a survey of the current methods and technique issues for simulations of membrane proteins. Besides the well-structured proteins, the intrinsically disordered proteins (IDPs) play important roles in a range of biological processes through the distinct coupled folding and binding mechanism. Chapter 14 presents the free energy analysis of the IDPs with the enhanced sampling methods.

Chapters 15, 16, 17, and 18 summarize recent computational studies on several biological processes. In Chap. 15, two machineries that transform chemical energy to mechanical work are studied using atomistic molecular dynamics simulations, coarse-grained analyses, and stochastic modeling techniques. In Chap. 16, recent theoretical and experimental progresses are reviewed on the universally conserved signal recognition particle machinery that mediates co-translational protein targeting reaction. Chapter 17 discusses the detailed analyses of the ATP-driven rotary motor enzyme that can perform ATP synthesis/hydrolysis using reversible motor rotation. Among different membrane proteins, the G protein coupled receptor (GPCR) is one of the most important families, which constitutes the target of about

one third drugs in the market. Chapter 18 summarizes recent computational studies on the chemo-sensorial GPCRs that are responsible to detect odorant and tasting molecules.

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