
Preface

Protein Folding Protocols presents protocols for studying and characterizing steps and conformational ensembles populating pathways in protein folding from the unfolded to the folded state. It further presents a sample of approaches toward the prediction of protein structure starting from the amino acid sequence, in the absence of overall homologous sequences. Protein folding is a crucial step in the transfer of genetic information from the DNA to the protein. The Genome Project has led to a huge number of available DNA sequences and, therefore, protein sequences. The Structural Genomics initiative largely aims to obtain “new” folds not currently present in the Protein Data Bank. Yet, the number of available structures inevitably lags behind the number of sequences. At the same time, an equally important problem is to find out the types and scope of dissimilar (nonhomologous) protein sequences that adopt a similar fold. Assembling data and comprehension of the sequence space of protein folds should be very useful in computational protein structure prediction. This would enhance the scope of homology modeling, which currently is the method of choice. Thus, experimental and theoretical studies on the relationship between sequence and structure are critical. Figuring out the relationship between sequence and structure would further assist in the prediction of fibril structures observed in protein misfolding diseases, and in figuring out the conformational changes and dynamics resulting from mutations. Protein folding is one of the most important and challenging problems in current molecular and chemical biology. This book reviews some of the recently developed methods for studying protein folding.

The starting point of a folding process is the unfolded state. Eliezer describes how some of the local structural properties of the unfolded state may be characterized using multidimensional nuclear magnetic resonance (NMR). Gebel and Shortle review how the global structures of the unfolded state may be characterized by measuring the residual dipolar couplings, again with NMR. Another state that generally occurs in the process of protein folding is the rate-limiting transition state. Pandit and coworkers describe how it can be characterized by using the psi value analysis. Rao and coworkers employ molecular dynamics simulation to characterize the transition state of small proteins. They propose a technique to estimate the folding probability of those structures that are sampled along near-equilibrium, constant temperature molecular dynamics simulations. Bai and coworkers describe how the native-state hydrogen exchange method could be combined with protein engineering to populate the intermediate

state for high-resolution structure determination by multidimensional NMR. Lassalle and Akasaka describe how the high-pressure NMR technique can be used to denature proteins and populate partially unfolded intermediates. Thirumalai and Klimov describe the use of computer simulations and simple models to investigate the formation of the intermediates. They show that the equilibrium intermediates occur “on pathway” and that there is a substantial probability that they be revisited after the native state is reached, in contrast to kinetic intermediates. Haspel and coworkers described how a building block-based protein folding model may be used toward a reduction of the computational complexity of protein folding. The model is based on the cutting of the target protein sequences into building block fragments that are relatively stable and whose conformations in solution are similar to those observed when the fragments are chain connected in the protein molecule from which they were derived.

One of the cutting-edge methods for studying protein folding is the single molecule technique. Ng and coworkers show that atomic force microscopy may be used to study the process of protein folding and unfolding. Schuler describes how the single molecule technique coupled with fluorescence resonance transfer may be used to study the population of proteins under equilibrium conditions and the process of kinetic folding. The study of very fast folding process, in the time-scale of microseconds or less, constitutes another important area in current protein folding studies. Gai and coworkers describe the use of T-jump coupled with infrared spectroscopy to characterize such a fast folding process. Fierz and coworkers outline a new method that uses triplet–triplet energy transfer to measure conformational dynamics in polypeptide chains in the unfolded ensembles, which can set the uplimit of folding times. Streicher and Makhatadze describe recent advances in the analysis of conformational transition in peptides using differential scanning calorimetry. Zhou describes the replica exchange molecular dynamics (REMD) method for enhanced sampling of the conformational space. REMD couples molecular dynamics trajectories with a temperature exchange Monte Carlo process. Replicas are run in parallel at different temperatures. This procedure allows surmounting local barriers encountered in the simulation. REMD has proven to be a very powerful tool, and it is increasingly used in MD simulations for small proteins/peptides. Jernigan and Kloczowski describe a computational result that relates the packing regularities of biological structures to their dynamics. Prediction of protein structures is the central issue of protein folding studies. Casadio and coworkers describe how protein structures might be predicted with and without the existence of homologs. This feat has been achieved with the aid of machine learning-based methods specifically suited for predicting structural features. For protein–protein interaction, a

knowledge-based strategy may provide predictions of putative interaction patches on the protein surface.

It behooves us to note that not all proteins fold into stable conformations. Recently, there has been an increasing amount of data that a large percentage of the proteins exist in what is commonly called the natively disordered state. This state describes a spectrum of conformations with variable stabilities. Although on its own the stability of the native state is low (hence the term *disordered*), binding to its partner enhances its stability. Thus, here too, the native state is the functional state. Folding, misfolding, and protein disorder are all related to each other. Progress in the understanding of one assists in comprehension of the other. Above all, all relate to protein function and malfunction.

Altogether, *Protein Folding Protocols* is a comprehensive collection of chapters describing a broad range of techniques to study, predict, and analyze the protein folding process. It covers experiment and theory, bioinformatics approaches, and state-of-the-art simulation protocols for better sampling of the conformational space. Protein folding remains one of the most challenging problems in the biological/natural sciences. Making progress in this area will have tremendous implications, ranging from drug design, functional assignment, comprehension of the nature of regulation, figuring out molecular machines, viral entry into cells, and putting together cellular pathways and their dynamics. The challenge still remains; however, experiment and theory have been making steps toward an eventual practical solution.

Yawen Bai
Ruth Nussinov

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