Preface

When I was invited to edit this volume, I wanted to take the opportunity to assemble reviews of different biophysical methodologies for protein interactions at a level sufficiently detailed to understand how complex systems can be studied. There are several excellent introductory texts for biophysical methodologies, many with hands-on descriptions or embedded in general introductions to physical biochemistry. The goal of the present volume was to present state-of-the-art reviews that do not necessarily enable the reader to carry out these techniques, but to gain a deep understanding of the biophysical observables, to stimulate creative thought on how the techniques may be applied to study a particular biological system, and to foster collaboration and multidisciplinary work.

Reversible protein interactions involve noncovalent chemical bonds, producing protein complexes with free energies not far from the order of magnitude of the thermal energy kT. As a consequence, they can be highly dynamic and may be controlled, for example, by protein expression levels and changes in the intracellular or microenvironment. Reversible protein complexes may have sufficient stability to be purified for study, but frequently their short lifetime essentially limits their existence to solutions of mixtures of the binding partners in which they remain populated through dissociation and reassociation processes. To understand the function of such protein complexes, it is important to study their structure and dynamics. Even when these studies take place *in vitro*, they elucidate the principles of the interactions imposed by the protein structures, principles which may be quantitatively modulated but have to be followed *in vivo*.

Maps of protein interaction networks display the interdependence of protein interactions and highlight the importance of interactions of more than two proteins. It is probably safe to assume that we currently know only a small fraction of the protein interactome, in particular, triple or higher-order complexes. Proteins that are able to interact with multiple protein binding partners or other ligands can exhibit higher functionality. This can include, for example, logical switches, with cooperativity steepening the isotherms of binding, resulting in highly sensitive and

discriminate response to a cellular stimulus. In many systems, this involves interplay of multiprotein complexes, binding of small ligands, covalent protein modifications, and conformational changes in proteins.

Techniques to elucidate such linked protein interactions and/or multiprotein complexes, with regard to thermodynamics, kinetics, conformation, and flexibility, and the possible role of spatial confinements to surfaces define the scope of the present volume. The side-by-side presentation of different approaches highlights aspects they have in common and orthogonal viewpoints that may provide opportunities for a synergistic combination. For example, an important recurring theme is the role of protein solvation, which is addressed in many chapters from different perspectives. To illustrate the use of the techniques, some applications are described, which, at the same time, are also aimed at providing a kaleidoscopic view of different biological systems and principles of protein interactions.

The list of biophysical methods reviewed in the present volume is far from complete. The selection of topics should not be understood in the sense of merit or importance of the different methods, but rather is a reflection of practical limitations in the scope and assembly of this work.

I want to thank the authors for their contributions. I also want to thank the series editor Dr. Zou Atassi, the publisher, and the National Institutes of Health for making this work possible. Finally, I want to thank my beloved wife Teresa for her patience and support.

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