

## PREFACE

Basically all processes in a cell involve proteins and the great majority of biological functions are mediated not only by isolated proteins but also by the interaction of proteins. Powerful experimental techniques are available to systematically investigate the network of protein–protein interactions in cellular systems. However, for a full understanding of protein–protein interactions, knowledge of the three-dimensional structure of complexes formed between interacting proteins is essential. Immense progress has been achieved in recent years to elucidate protein–protein complex structures and to better understand the physical principles of complex formation. What are the driving forces for protein–protein association? What can we learn about specific recognition from studying protein–protein interfaces? How can this knowledge be used to predict protein–protein interactions and is it possible to influence protein–protein interactions by small drug molecules? These and many other questions will be tackled in the 13 chapter contributions in this volume.

Although the book covers the state-of-the-art research in the area of protein–protein complex analysis and modelling, it is not primarily directed at specialists in the field. The book is also meant to be a useful guide for students and researchers in the area of Chemistry, Biochemistry and Biophysics with an interest in proteins and protein–protein interactions. Most chapters contain significant introductory information in addition to the most recent progress in the field. Readers will gain insight into the recognition principles of proteins; how to determine, analyse and predict protein–protein interactions and complex structures, as well as learn about possibilities of interference with protein–protein interactions.

Leading researchers in the field have been selected to contribute chapters to the book. Authors were free to select the exact scope of their contribution and express their own view on the field. Possible overlapping between chapters can be profitable for the reader since key information is provided from different perspectives by leading scientists.

The first part of the volume introduces the analysis of experimentally determined structures of protein–protein complexes. Experimental protein structures contain rich information on the principles of interaction. The systematic analysis of the interface region of protein–protein complexes and the comparison with other surface regions of a protein reveal the physical characteristics of protein binding sites. A deeper understanding of the driving forces of protein–protein complex formation also requires an analysis of the thermodynamics of protein–protein association. The first part of the book includes an overview of experimental methods to investigate the thermodynamics of protein–protein binding, and also discusses theoretical methods to calculate energetic and entropic contributions. The study of the kinetics of association and dissociation of protein–protein interactions is of central importance to understanding the mechanism of protein complex formation. How the kinetics of protein–protein binding can be studied experimentally and theoretically is at the focus of a separate chapter. Proteins bind to specific sites on the surface of proteins with high affinity. The physico-chemical character of binding sites can differ from the properties of other surface regions. In addition, often the amino acids at protein binding sites are evolutionarily more conserved than the rest of the protein surface. The properties and conservation of protein functional sites and how they can be used to identify relevant amino acid residues for protein–protein recognition are discussed in the fifth chapter.

Due to the large number of putative protein–protein interactions and the transient nature of many protein–protein complexes, only a fraction of possible protein–protein complex structures can be determined experimentally. A variety of computational docking prediction methods have been developed in recent years to tackle the problem of providing at least structural models of important protein–protein complexes. A general overview of docking methods is provided, followed by chapters on how to best include experimental data or information from bioinformatics resources to high-resolution docking methodologies. Typically, modelling protein–protein complex structures is not a one-step procedure but instead distinguishes an initial exhaustive search followed by a refinement and rescoring phase. The options of refining and

identifying the most realistic predicted complex structure are also introduced.

The last five chapters of the volume shift the focus from three-dimensional modelling of protein–protein interactions towards approaches that influence or interfere with protein–protein interactions. A significant fraction of protein–protein interactions – particularly in higher organisms – are mediated by reoccurring motifs or interaction patterns. Chapter 10 gives an overview of several examples of biological and medical importance. The chapter also includes a discussion of the involvement of motif-mediated interactions in diseases. Mutations in proteins may perturb interactions with other partners. However, site-directed mutagenesis can also be used to redesign protein binding regions to create new or altered protein–protein interactions. Methods to estimate changes in protein–protein affinity, due to residue substitutions at the interface, are described and the possibility to directly and specifically interfere with protein–protein interactions is at the focus of two separate chapters. The concepts are introduced and discussed on examples that are of relevance to several human diseases. Proteins can undergo conformational changes upon association. In addition, the binding process can also influence the flexibility of binding partners which may even mediate long-range allosteric communication. The analysis of such dynamical recognition processes and the possibility to influence them by drug-like molecules is the subject of the last chapter.

It is my great pleasure to thank all authors for the time and efforts they devoted to the demanding work of contributing book chapters to this volume. I am grateful to the editors of Imperial College Press for their cooperation and also to my co-workers and family for their patience and support.

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