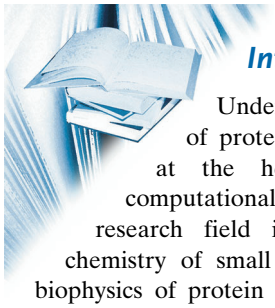


Protein–Ligand Interactions

Understanding the principles of protein–ligand interactions is at the heart of rational and computational drug design. This research field involves the medicinal chemistry of small organic molecules, the biophysics of protein structure and dynamics, and the physical chemistry of the surrounding solvent medium. It has therefore become a beautiful interdisciplinary forum for researchers from different experimental and theoretical backgrounds. Even if one focuses exclusively on computational research in this field, this involves researchers with backgrounds in several different disciplines, ranging from computational chemistry to theoretical biophysics and to structural bioinformatics. Many textbooks and more advanced texts have already addressed various facets of this field. An important new contribution is the book *Protein–Ligand Interactions*, edited by Holger Gohlke of the University of Düsseldorf, which recently appeared as Volume 53 in the Wiley-VCH series *Methods and Principles in Medicinal Chemistry*.

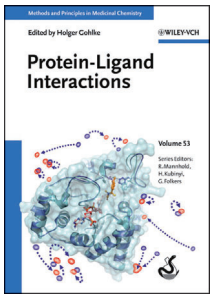
The book starts by reviewing the basic thermodynamics of the protein–ligand binding process, and then takes the reader to the absolute forefront of current research in several modern application areas. Without saying this explicitly, the foundations of this book are partly rooted in the classic review entitled "The Statistical-Thermodynamic Basis for Computation of Binding Affinities: a Critical Review".[1] For this book Gohlke has assembled 15 chapters contributed by prominent leaders in their fields. Most authors have provided well-balanced discussions and reviews of the important basics and concepts of the respective topics, from their own personal viewpoints, of course. The reader will soon notice that there is some overlapping between the contents of the chapters (e.g., about free energy perturbation theory, or on the LIE technique). However, this can also be seen as a plus, because individual chapters can be studied independently without having to consult other chapters.

The chapters are grouped in four parts entitled "Binding Thermodynamics", "Learning from Biophysical Experiments", "Modeling Protein–Ligand Interactions", and "Challenges in Molecular Recognition".

Part I begins with a didactic chapter by Kim Sharp on the statistical thermodynamics of binding. The author is an authority on this subject and manages to present this challenging topic in a crystal-clear way in only a few pages of text. He introduces and explains all necessary mathematical equations, but keeps them at a level that is accessible to everybody with a basic knowledge of statistical mechanics. This chapter is followed by a more design-orientated chapter by Ernesto Freire, who explains how thermodynamic concepts can be exploited when evaluating drug candidates. Lastly, Athel Cornish-Bowden reviews the phenomenon of enthalpy–entropy compensation that is often observed in protein–ligand systems. This chapter ends with some sharp comments on how modern textbooks (mis)treat this topic.

Part II contains two contributions on experimental techniques that are often used in studying protein–ligand interactions. First, U. Helena Danielson introduces the surface plasmon resonance technique and discusses its applications. Secondly, Dieter Willbold and co-workers discuss aspects of protein–ligand interactions that can be investigated by NMR spectroscopy, such as mapping the binding site. These five introductory chapters lay the ground for Parts III and IV, which deal with the computational modeling of protein–ligand interactions.

Part III consists of seven chapters, and is the central part of the book. It describes several methodological challenges faced by researchers in the field, and discusses how they might be overcome. It is assumed that the reader has a solid basic knowledge of atomic force fields, and of sampling methods such as molecular dynamics simulations. Some chapters also require a basic familiarity with the terminology of machine learning methods. The part begins with a chapter on the modern theory of polarizable force fields, in particular the AMOEBA force field model. It is quite understandable that the authors of this chapter focus on their own work in this area, which is based on AMOEBA. However, explicit polarizability is also a subject of intensive current research in connection with some of the other important force field models (e.g., AMBER and CHARMM). I found this chapter a bit too narrow. It is followed by a chapter by Ulf Ryde and co-workers on the use of quantum mechanics in structure-based ligand design. This is an important contribution, since quantum mechanics is, in principle, able to overcome many of the shortcomings of classical force field models in dealing with induced polarization through ligand binding. It remains to be seen whether quantum mechanics or explicit polarizability, or both, will take protein–ligand modeling to the next higher level of accuracy. Baron, Setny, and McCammon then discuss the challenges of computational modeling of hydrophobic interactions with a proper treatment of the role of the solvent. Based on explicit solvent simulations, the authors have recently made important breakthroughs that will probably also lead to the development of new



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implicit solvent models that deal properly with phenomena such as de-wetting. Luchko and Case then discuss various implicit solvent models. David Case is one of the pioneers of this field. This chapter nicely contrasts the GB/SA models with other models that are being used. Part III ends with three well-rounded chapters by Lazaridis, Steinbrecher, and Sotriffer on different aspects of computing protein–ligand binding energies. Lazaridis focuses on conformational energies, Steinbrecher on the theory of free energy perturbation, and Sotriffer on scoring methods.

The last part introduces the reader to four challenging topics that are currently subjects of active research. All of these are close to the heart of the editor, Holger Gohlke. First, Barril and co-workers discuss the prediction of druggability. This concerns the question of which of the pockets formed on protein surfaces are "druggable", in other words suitable for binding small-molecule ligands. This topic is of eminent importance to the field of rational drug design. The chapter takes a ligand-design-orientated view that is shaped by the senior author's previous career in the pharmaceutical industry. Then, Rueda and Abagyan discuss the question of the plasticity of a protein surface, whereby multiple protein conformations may reveal different geometries of the binding site(s). Abagyan has pioneered the PDB-wide characterization of the "pocketeome". His research combines the rigor of basic science with mission-orientated research. The chapter ends with a brief discussion of the GPCR Dock 2010 contest, which is a key example of the challenge of designing correctly shaped pockets during homology modeling. As in the case of the AMOEBA chapter, this one also is a bit too much centered around the ICM program developed in the Abagyan group. In the last chapter, MacKerell and co-workers discuss the challenges of designing small-molecule ligands that target protein–protein binding interfaces. They spend several pages on reviewing the principles of virtual screening, and then discuss several recent examples involving important protein–protein interactions (ERK kinase, BCL6, S100B, SH2).

In summary, this book contains a superb collection of 15 chapters describing the latest state of research in the field of computational analysis and design of protein–ligand interactions. Some of the content is similar to the book *Free Energy Calculations in Rational Drug Design* which appeared 12 years ago.[2] However, as indicated by the title, that book had a stronger focus on free-energy calculations, and its applications chapters focused rather on enzyme mechanisms than on druggability prediction and protein–protein inhibitors. Also, the field has certainly seen major advances, so that a fresh look is perfectly justified. I expect that Gohlke's book will be of great value to beginning post-graduate students who are entering into any of the research fields that are discussed, as well as to experienced researchers in academia and industry who want to fresh up on some of the latest results. In his preface, Gohlke emphasizes his opinion that "*rigorous approaches … will be more successful in the long term than ad hoc ones*". Indeed, rigorous approaches tend to become part of the methods portfolio of molecular modeling and to continue being used. From that aspect, I expect that this book will become a valuable addition to the bookshelves of many researchers working in this field, and it will continue to be a useful compendium for many years.

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[1] M. K. Gilson, J. A. Given, B. L. Bush, J. A. McCammon, *Biophys. J.* **1997**, *72*, 1047 – 1069.
[2] *Free Energy Calculations in Rational Drug Design* (Eds.: M. R. Reddy, M. D. Erion), Springer, New York, **2001**.

