DRUG DESIGN: STRUCTURE- AND LIGAND-BASED APPROACHES

Structure-based drug design (SBDD) and ligand-based drug design (LBDD) are active areas of research in both the academic and commercial realms. This book provides a current snapshot of the field of computer-aided drug design and associated experimental approaches. Topics covered include x-ray crystallography, nuclear magnetic resonance, fragment-based drug design, free-energy methods, docking and scoring, linear-scaling quantum calculations, quantitative structure/activity relationship, pharmacophore methods, computational absorption/distribution/metabolism/excretion-toxicity, and drug discovery case studies. Authors from academic and commercial institutions all over the world have contributed to this book, which is illustrated with more than 200 images. This book covers SBDD and LBDD, and it provides the most up-to-date information on a wide range of topics for the practicing computational chemist, medicinal chemist, or structural biologist.

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Drug Design

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Contents

Contributors *page* vii
Preface ix

1 Progress and issues for computationally guided lead discovery and optimization 1
William L. Jorgensen

PART I. STRUCTURAL BIOLOGY

2 X-ray crystallography in the service of structure-based drug design 17
Gregory A. Petsko and Dagmar Ringe

3 Fragment-based structure-guided drug discovery: strategy, process, and lessons from human protein kinases 30
Stephen K. Burley, Gavin Hirst, Paul Sprengeler, and Siegfried Reich

4 NMR in fragment-based drug discovery 41
Christopher A. Lepre, Peter J. Connolly, and Jonathan M. Moore

PART II. COMPUTATIONAL CHEMISTRY METHODOLOGY

5 Free-energy calculations in structure-based drug design 61
Michael R. Shirts, David L. Mobley, and Scott P. Brown

6 Studies of drug resistance and the dynamic behavior of HIV-1 protease through molecular dynamics simulations 87
Fangyu Ding and Carlos Simmerling

7 Docking: a domesday report 98
Martha S. Head

8 The role of quantum mechanics in structure-based drug design 120
Kenneth M. Merz, Jr.

9 Pharmacophore methods 137
Steven L. Dixon

10 QSAR in drug discovery 151
Alexander Tropsha

11 Predicting ADME properties in drug discovery 165
William J. Egan

PART III: APPLICATIONS TO DRUG DISCOVERY

12 Computer-aided drug design: a practical guide to protein-structure-based modeling 181
Charles H. Reynolds

13 Structure-based drug design case study: p38 197
Arthur M. Doweyko

14 Structure-based design of novel P2-P4 macrocyclic inhibitors of hepatitis C NS3/4A protease 209
M. Katharine Holloway and Nigel J. Liverton

15 Purine nucleoside phosphorylases as targets for transition-state analog design 215
Andrew S. Murkin and Vern L. Schramm

16 GPCR 3D modeling 248
Frank U. Axe

17 Structure-based design of potent glycogen phosphorylase inhibitors 257
Qiaolin Deng

Index 265

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Preface

Our goal in producing this book is to provide a broad overview of the most important approaches used in protein- and ligand-structure-based drug design. Beyond this we aim to illustrate how these approaches are currently being applied in drug discovery efforts. We hope this book will be a useful resource to practitioners in the field, as well as a good introduction for researchers or students who are new to the field. We believe it provides a snapshot of the most important trends and capabilities in the application of modeling and structural data in drug discovery.

Since the 1990s the role of structure and modeling in drug discovery has grown enormously. There have been remarkable scientific advances in both the experimental and computational fields that are the underpinnings of modern drug design. For example, x-ray capabilities have improved to the point that protein structures are now routinely available for a wide range of protein targets. One only need look at the exponential growth of the Protein Databank (RCSB) for evidence. Tremendous strides have been made in all aspects of protein structure determination, including crystallization, data acquisition, and structure refinement. Modeling has made similar gains. Recent years have brought more realistic force fields, new and more robust free-energy methods, computational models for absorption/distribution/metabolism/excretion (ADME)-toxicity, faster and better docking algorithms, automated 3D pharmacophore detection and searching, and very-large-scale quantum calculations. When coupled with the inexorable increase in computer power, new and improved computational methods allow us to incorporate modeling into the drug discovery process in ways that were not possible just a short time ago.

In addition to improvements in methods, academic and industrial groups have gained significant experience in the application of these approaches to drug discovery problems. Protein structures, docking, pharmacophore searches, and the like have all become a staple of drug discovery and are almost universally applied by large and small pharma companies. A recent example of a new approach that is gaining wider acceptance is fragment-based drug design. The goal of fragment-based design is to build up drug candidates from small low-affinity, but high-information-content, hit structures. As such, fragment-based design relies critically on structural, computational, and biophysical methods to identify, characterize, and elaborate small low-affinity ligands.

The book is divided into three broad categories: structural biology, computational chemistry, and drug discovery applications. Each section contains chapters authored by acknowledged experts in the field. Although no book of reasonable size can be completely comprehensive, we have attempted to address the most significant topics in each category, as well as some areas we see as emergent. We are fortunate to have an introductory chapter from Professor William Jorgensen that sets the tone for the book.

The structural biology section begins with a comprehensive review of the strengths and weaknesses of x-ray crystallography. This is the logical starting point for most protein-structure-based design programs, as crystallography is certainly the most common approach for obtaining the three-dimensional structures of therapeutically important proteins. This section also includes two chapters on fragment-based drug design, including one devoted to the important role nuclear magnetic resonance has played in this new approach.

The computational chemistry section covers a range of modeling techniques, including free-energy methods, dynamics, docking and scoring, pharmacophore modeling, quantitative structure/activity relationships, computational ADME, and quantum methods. Each topic was selected either because it is a commonly employed tool in drug discovery (e.g., docking and scoring) or because it is seen as an emerging technology that may have an increasing role in the future (e.g., linear-scaling quantum calculations). Taken together, these chapters provide a fairly comprehensive overview of the computational approaches being used in drug discovery today.

The final section on applications in drug discovery provides a few concrete examples of using the methods outlined in the first two sections for specific drug discovery programs. This is the ultimate validation of any experimental or computational approach, at least with regard to drug discovery. These examples from six diverse protein targets are useful to the expert as examples of best practices and to the novice as examples of what can be done. An overview of G-protein-coupled receptor (GPCR) modeling and

structure is of keen current interest given that this class has historically been a rich source of drugs, and it has recently seen a major advance in access to experimental structures. This bodes well for the future application of structure-based design to GPCR targets.

Finally, we must thank all the authors who generously agreed to participate in this project for their efforts and patience. Without them, of course, there would be no book. We have been particularly fortunate to enlist such a talented group of authors.

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