

Methods in
Molecular Biology 819

Springer Protocols



Riccardo Baron *Editor*

Computational Drug Discovery and Design

 Humana Press

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Edited by

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ISSN 1064-3745 e-ISSN 1940-6029
ISBN 978-1-61779-464-3 e-ISSN 978-1-61779-465-0
DOI 10.1007/978-1-61779-465-0
Springer New York Dordrecht Heidelberg London

Library of Congress Control Number: 2011942922

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Printed on acid-free paper

Humana Press is part of Springer Science+Business Media (www.springer.com)

Preface

Assisted by the rapid and steady growth of available low-cost computer power, the use of computers for discovering and designing new drugs is becoming a central topic in modern molecular biology and medicinal chemistry. New effective methods provide access to an always-increasing level of complexity in biomolecular recognition, thus expanding the variety and the predictive power of approaches for drug development based on computational chemistry (Fig. 1).

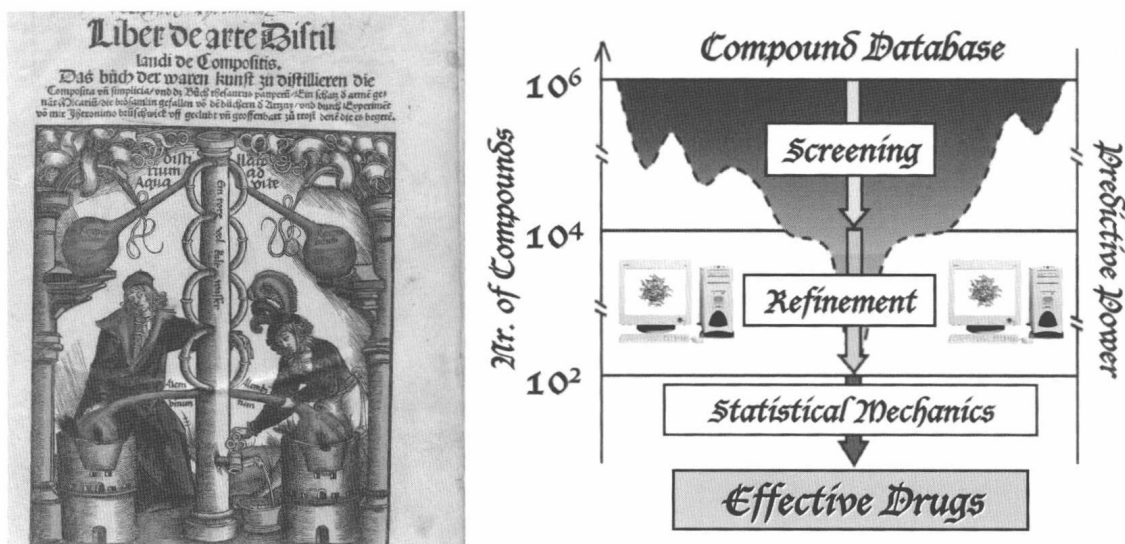


Fig. 1. From medicinal alchemy to modern medicinal chemistry. Left: the *Liber de Arte Distillandi de Compositis* by Hieronymus Brunschwig described emerging methods to extract drugs through alchemical distillation (Johann Grüninger Publisher & Printer, 1512 circa; courtesy of the National Academy of Medicine, U.S.A.). Right: five hundred years later the same long-standing problem is attacked by *in silico* distillation of large compound databases. Computers help experiments along all phases of the extraction funnel: from preliminary molecule screening, through drug discovery and refinement, to inhibitor design based on statistical mechanics

In this volume of *Methods in Molecular Biology* we present robust methods for *Computational Drug Discovery and Design*, with a particular emphasis on method development for biomedical applications. The goal is to offer an overview of highly promising themes and tools in this highly interdisciplinary research field, together with the challenges calling for new solutions in future research: from binding sites prediction to the accurate inclusion of solvent and entropic effects, from high-throughput screening of large compound databases to the expanding area of protein–protein inhibition, toward quantitative free-energy approaches in ensemble-based drug design using distributed computing. The application of physics-based methodologies—strongly coupled to molecular dynamics simulation—is leading to a novel, dynamic view of receptor–drug recognition. These concepts are progressively modifying the old dogma of single-structure-based drug design into the concept of ensemble-based drug design, where conformational diversity and selection play key roles. In this scenario, the current scientific literature is

often highlighting success stories and happy-end examples. However, the basis of this success is often the back-stage, everyday research filled with ingenious and creative strategies to bypass critical obstacles. Thus, this volume has the goal of presenting as well such obstacles and practical guidance for the use of computational resources for researchers new to these topics. Finally, this volume includes recent, successful examples of applications in the description of receptor-drug interactions and computer-based discovery of new drugs against human-lethal diseases, opening to future computer-based drug patents.

The reader will hopefully use this volume as an introductory manual for state-of-the-art concepts and methodologies, as well as an advanced, specialized tool to design novel and original research for public health.

Salt Lake City, UT, USA

Riccardo Baron

Acknowledgments

I would like to warmly thank Andy McCammon for his support during the whole course of this work; Sara Nichols for preparing the cover illustration; Nadeem Vellore for a critical reading of the final proofs. Startup funding from The University of Utah is also greatly acknowledged for the last part of their publication process.

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Part I

Drug Binding Site Prediction, Design, and Descriptors

A Molecular Dynamics Ensemble-Based Approach for the Mapping of Druggable Binding Sites

Anthony Ivetac and J. Andrew McCammon

Abstract

An expanding repertoire of “allosteric” drugs is revealing that structure-based drug design (SBDD) is not restricted to the “active site” of the target protein. Such compounds have been shown to bind distant regions of the protein topography, potentially providing higher levels of target specificity, reduced toxicity and access to new regions of chemical space. Unfortunately, the location of such allosteric pockets is not obvious in the absence of a bound crystal structure and the ability to predict their presence would be useful in the discovery of novel therapies. Here, we describe a method for the prediction of “druggable” binding sites that takes protein flexibility into account through the use of molecular dynamics (MD) simulation. By using a dynamic representation of the target, we are able to sample multiple protein conformations that may expose new drug-binding surfaces. We perform a fragment-based mapping analysis of individual structures in the MD ensemble using the FTMAP algorithm and then rank the most prolific probe-binding protein residues to determine potential “hot-spots” for further examination. This approach has recently been applied to a pair of human G-protein-coupled receptors (GPCRs), resulting in the detection of five potential allosteric sites.

Key words: Allosteric, Molecular dynamics simulation, Docking, Binding site, Drug design

1. Introduction

Structure-based drug design (SBDD) efforts are typically initiated when a high-resolution crystal structure of the target protein complexed with a small molecule is available. The co-crystallized ligand is usually some form of the endogenous substrate/agonist or a synthetic drug compound with affinity for the same binding site. This region of the protein surface is referred to as the “active” or “orthosteric” site and is highly conserved among closely related proteins. Relatively recently however, it has emerged that there are other “druggable” sites on the protein surface, which may be bound by therapeutic small molecules and which are spatially distinct from known active sites (1, 2). Such pockets are known