Methods in Molecular Biology 819

Springer Protocols

Riccardo Baron *Editor*

Computational Drug Discovery and Design

Humana Press

Computational Drug Discovery and Design

Edited by

Riccardo Baron

Department of Medicinal Chemistry, College of Pharmacy, The Henry Eyring Center for Theoretical Chemistry, University of Utah, Salt Lake City, UT, USA

Humana Press

Editor
Riccardo Baron
Department of Medicinal Chemistry
College of Pharmacy
The Henry Eyring Center for Theoretical Chemistry
University of Utah
Salt Lake City, UT, USA
r.baron@utah.edu

ISSN 1064-3745 e-ISSN 1940-6029
ISBN 978-1-61779-464-3 e-ISBN 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

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).

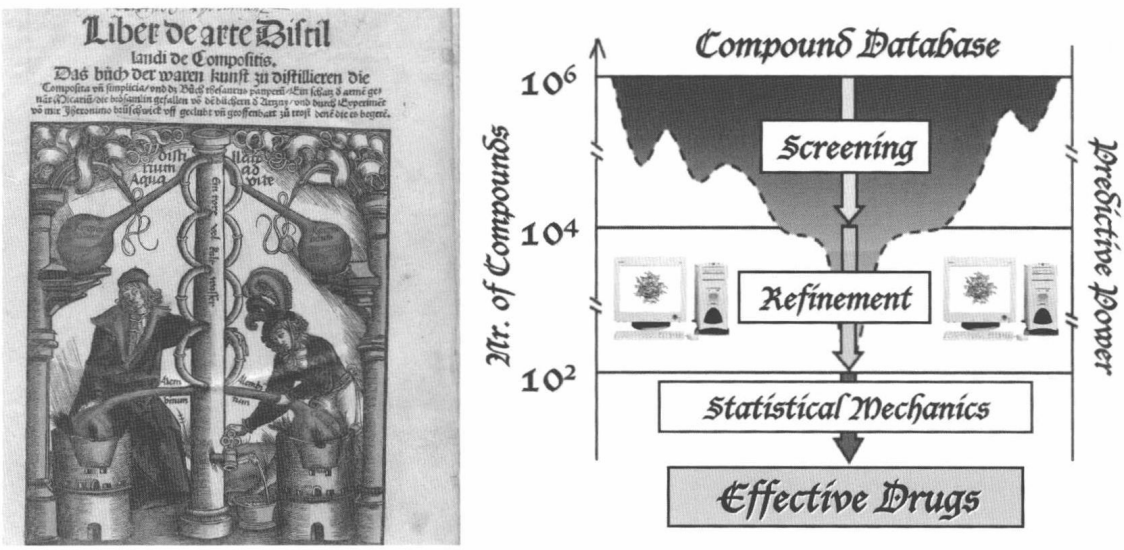

Fig. 1. From medicinal alchemy to modern medicinal chemistry. *Left*: the *Liber de Arte Distillandi de Compositis* by Hieronymus Brunschwig described emerging methods to extract drugs through alchemical distillation (Johann Grüninger Publisher & Printer, 1512 circa; courtesy of the National Academy 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, trough 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.

Contributors

Rizi Ai • *Department of Chemistry, University of California, Riverside, CA, USA*

Rommie E. Amaro • *Departments of Pharmaceutical Sciences, Computer Science, and Chemistry, University of California, Irvine, CA, USA*

Johan Åqvist • *Department of Cell and Molecular Biology, Uppsala University, Uppsala, Sweden*

Flavia Autore • *Randall Division for Cellular and Molecular Biophysics, King's College London, London, UK*

Jürgen Bajorath • *Departments of Chemical Biology and Medicinal Chemistry, University of Bonn, Bonn, Germany*

Riccardo Baron • *Department of Medicinal Chemistry, College of Pharmacy, The Henry Eyring Center for Theoretical Chemistry, University of Utah, Salt Lake City, UT, USA*

Neva Bešker • *Spanish National Cancer Research Centre, Madrid, Spain*

Alexandre M.J.J. Bonvin • *Bijvoet Center for Biomolecular Research, Utrecht University, Utrecht, The Netherlands*

Giovanni Bottegoni • *Department of Drug Discovery and Development, Istituto Italiano di Tecnologia, Genova, Italy*

Yufeng Cai • *Department of Biochemistry and Molecular Pharmacology, University of Massachusetts Medical School, Worcester, MA, USA*

Virginia Castillo • *Department de Bioquímica i Biologia Molecular and Institut de Biotecnologia i de Biomedicina, Universitat Autónoma de Barcelona, Barcelona, Spain*

Andrea Cavalli • *Department of Drug Discovery and Development, Istituto Italiano di Tecnologia, Genova, Italy; Department of Pharmaceutical Sciences, University of Bologna, Bologna, Italy*

Claudio N. Cavasotto • *School of Biomedical Informatics, The University of Texas Health Center, Houston, TX, USA*

Nesrine Chakroun • *Randall Division for Cellular and Molecular Biophysics, King's College London, London, UK*

Chia-en Chang • *Department of Chemistry, University of California, Riverside, CA, USA*

Andrew J. Christofferson • *National Institute of Biological Sciences, Beijing, People Republic of China*

Natalia S. de Groot • *Department de Bioquímica i Biologia Molecular and Institut de Biotecnologia i de Biomedicina, Universitat Autónoma de Barcelona, Barcelona, Spain*

César A.F. de Oliveira • *Department of Chemistry and Biochemistry, Center for Theoretical Biological Physics, Howard Hughes Medical Institute, University of California, La Jolla, CA, USA*

Roland Dunbrack • *Institute for Cancer Research, Fox Chase Cancer Center, Philadelphia, PA, USA*

SERKAN ERDIN • *Department of Molecular and Human Genetics, Baylor College of Medicine, Houston, TX, USA; W. M. Keck Center for Interdisciplinary Bioscience Training, Houston, TX, USA*
HAO FAN • *Departments of Bioengineering & Therapeutic Sciences and Pharmaceutical Chemistry and California Institute for Quantitative Biosciences, University of California, San Francisco, CA, USA*
SEBASTIEN FIORUCCI • *UMR-CNRS, Université de Nice-Sophia Antipolis, Nice Cedex 2, France*
ARIANNA FORNILI • *Randall Division for Cellular and Molecular Biophysics, King's College London, London, UK*
VEDRAN FRANKE • *Department of Molecular Biology, University of Zagreb, Zagreb, Croatia*
FRANCA FRATERNALI • *Randall Division for Cellular and Molecular Biophysics, King's College London, London, UK*
SIMONE FULLE • *Institute of Pharmaceutical and Medicinal Chemistry, Department of Mathematics and Natural Sciences, Heinrich-Heine-University, Düsseldorf, Germany*
FRANCESCO L. GERVASIO • *Spanish National Cancer Research Centre, Madrid, Spain*
HOLGER GOHLKE • *Institute of Pharmaceutical and Medicinal Chemistry, Department of Mathematics and Natural Sciences, Heinrich-Heine-University, Düsseldorf, Germany*
RICARDO GRAÑA-MONTES • *Department de Bioquímica i Biologia Molecular and Institut de Biotecnologia i de Biomedicina, Universitat Autónoma de Barcelona, Barcelona, Spain*
CRISTIANO R.W. GUIMARÃES • *Worldwide Medicinal Chemistry Department, Pfizer Inc., Groton, CT, USA*
HUGO GUITIÉRREZ-DE-TERÁN • *Fundación Pública Galega de Medicina Xenómica, Santiago University Hospital, Santiago de Compostela, Spain*
ATTILA GURSOY • *Center for Computational Biology and Bioinformatics and College of Engineering, Koc University Rumelifeneri Yolu, Istanbul, Turkey*
MICHAEL GUTIERREZ • *Department of Chemistry, University of California, Riverside, CA, USA*
DAVID R. HALL • *Departments of Biomedical Engineering and Chemistry, Biomolecular Engineering Research Center, Boston University, Boston, MA, USA*
ROB HOOFT • *Center for Molecular and Biomolecular Informatics, Radboud University Nijmegen Medical Centre, Nijmegen, The Netherlands*
DANZHI HUANG • *Department of Biochemistry, University of Zurich, Zurich, Switzerland*
NIU HUANG • *National Institute of Biological Sciences, Beijing, People Republic of China*
ZUNNAN HUANG • *Department of Chemistry and Biochemistry, University of Missouri-St. Louis, St. Louis, MO, USA*
JOHN J. IRWIN • *Department of Pharmaceutical Chemistry, California Institute for Quantitative Biosciences, University of California, San Francisco, CA, USA*
ANTHONY IVETAC • *Department of Chemistry and Biochemistry, Center for Theoretical Biological Physics, University of California, San Diego, La Jolla, CA, USA*

Panagotis L. Kastritis • *Bijvoet Center for Biomolecular Research, Utrecht University, Utrecht, The Netherlands*
Ozlem Keskin • *Center for Computational Biology and Bioinformatics and College of Engineering, Koc University Rumelifeneri Yolu, Istanbul, Turkey*
Dima Kozakov • *Departments of Biomedical Engineering and Chemistry, Biomolecular Engineering Research Center, Boston University, Boston, MA, USA*
Barbara Krieger • *YASARA Biosciences GmbH, Vienna, Austria*
Elmar Krieger • *Center for Molecular and Biomolecular Informatics, Radboud University Nijmegen Medical Centre, Nijmegen, The Netherlands*
Guray Kuzu • *Center for Computational Biology and Bioinformatics and College of Engineering, Koc University Rumelifeneri Yolu, Istanbul, Turkey*
David Lagorce • *Molécules Thérapeutiques in Silico, Université Paris Diderot, Paris, France*
Morgan Lawrenz • *Department of Chemistry and Biochemistry, Center for Theoretical Biological Physics, University of California, San Diego, La Jolla, CA, USA*
Themis Lazaridis • *Department of Chemistry, City College of New York, New York, NY, USA*
Gordon Lemmon • *Department of Chemistry, Vanderbilt University, Nashville, TN, USA*
Wilfred W. Li • *National Biomedical Computation Resource, University of California, San Diego, La Jolla, CA, USA*
Zheng Li • *Department of Chemistry, City College of New York, New York, NY, USA*
Olivier Lichtarge • *Department of Molecular and Human Genetics, Verna and Marrs Mclean Department of Biochemistry and Molecular Biology, Baylor College of Medicine, Houston, TX, USA; W. M. Keck Center for Interdisciplinary Bioscience Training, Houston, TX, USA*
Rhonald Lua • *Department of Molecular and Human Genetics, Baylor College of Medicine, Houston, TX, USA*
Michael J. Marsella • *Department of Chemistry, University of California at Riverside, Riverside, CA, USA*
Pierre Martinez • *Randall Division for Cellular and Molecular Biophysics, King's College London, London, UK*
J. Andrew McCammon • *Howard Hughes Medical Institute, Departments of Chemistry and Biochemistry and Pharmacology, Center for Theoretical Biological Physics, University of California, San Diego, La Jolla, CA, USA*
Jens Meiler • *Department of Chemistry, Vanderbilt University, Nashville, TN, USA*
Maria A. Miteva • *Molécules Thérapeutiques in Silico, Université Paris Diderot, Paris, France*
Sara E. Nichols • *Department of Chemistry and Biochemistry, Center for Theoretical Biological Physics, University of California, San Diego, La Jolla, CA, USA*
Britta Nisius • *Departments of Chemical Biology and Medicinal Chemistry, University of Bonn, Bonn, Germany*
Ruth Nussinov • *Center for Cancer Research Nanobiology Program, National Cancer Institute, Frederick, MD, USA; Department of Human Genetics and Molecular Medicine, Sackler School of Medicine, Tel Aviv University, Tel Aviv, Israel*

CHRIS OOSTENBRINK • *Institute of Molecular Modeling and Simulation, University of Natural Resources and Life Sciences, Vienna, Austria*
ILZA PAJEVA • *Institute of Biophysics and Biomedical Engineering, Bulgarian Academy of Sciences, Sofia, Bulgaria*
TANIA PENCHEVA • *Institute of Biophysics and Biomedical Engineering, Bulgarian Academy of Sciences, Sofia, Bulgaria*
ANTON POLYANSKY • *Laboratory of Computational Biophysics, Department of Structural and Computational Biology, Max Perutz Laboratories, Vienna, Austria*
CHANTAL PRÉVOST • *CNRS UPR, Université Paris Diderot, Paris, France*
ENRICO PURISIMA • *Biotechnology Research Institute, National Research Council, Ottawa, ON, Canada*
WALTER ROCCHIA • *Department of Drug Discovery and Development, Istituto Italiano di Tecnologia, Genova, Italy*
ADRIEN SALADIN • *Molécules Thérapeutiques in Silico, Université Paris Diderot, Paris, France*
ANDREJ SALI • *Departments of Bioengineering & Therapeutic Sciences and Pharmaceutical Chemistry and California Institute for Quantitative Biosciences, University of California, San Francisco, San Francisco, CA, USA*
CELIA SCHIFFER • *Department of Biochemistry and Molecular Pharmacology, University of Massachusetts Medical School, Worcester, MA, USA*
SEBASTIAN SCHNEIDER • *Physik-Department, Technische Universität München, Garching, Germany*
YI SHANG • *Department of Chemistry, State University of New York, Stony Brook, NY, USA*
MICHAEL R. SHIRTS • *Department of Chemical Engineering, University of Virginia, Charlottesville, VA, USA*
EMMA SIERECKI • *Department of Pharmacology, University of California, San Diego, La Jolla, CA, USA*
MILE ŠIKIĆ • *Department of Electronic Systems and Information Processing, University of Zagreb, Zagreb, Croatia*
CARLOS SIMMERLING • *Department of Chemistry, State University of New York, Stony Brook, NY, USA*
WILLIAM SINKO • *Department of Chemistry and Biochemistry, Center for Theoretical Biological Physics, University of California, San Diego, La Jolla, CA, USA*
TRAIAN SULEA • *Biotechnology Research Institute, National Research Council, Ottawa, ON, Canada*
SANDOR VAJDA • *Departments of Biomedical Engineering and Chemistry, Biomolecular Engineering Research Center, Boston University, Boston, MA, USA*
AALT D. J. VAN DIJK • *Wageningen UR, Plant Research International, Wageningen, The Netherlands*
SALVADOR VENTURA ZAMORA • *Department de Bioquímica i Biologia Molecular and Institut de Biotecnologia i de Biomedicina, Universitat Autónoma de Barcelona, Barcelona, Spain*
BRUNO O. VILLOUTREIX • *Molécules Thérapeutiques in Silico, Université Paris Diderot, Paris, France*

KRISTIAN VLAHOVIČEK • *Department of Molecular Biology, Division of Biology, Bioinformatics Group, University of Zagreb, Zagreb, Croatia*
MARTIN VOGT • *Departments of Chemical Biology and Medicinal Chemistry, University of Bonn, Bonn, Germany*
YI WANG • *Department of Chemistry and Biochemistry, Center for Theoretical Biological Physics, University of California, San Diego, La Jolla, CA, USA*
ANNE MAI WASSERMANN • *Departments of Chemical Biology and Medicinal Chemistry, University of Bonn, Bonn, Germany*
JEFF WERESZCZYNSKI • *Department of Chemistry and Biochemistry, Center for Theoretical Biological Physics, University of California, San Diego, La Jolla, CA, USA*
ANGELA WILKINS • *Department of Molecular and Human Genetics, Baylor College of Medicine, Houston, TX, USA; W. M. Keck Center for Interdisciplinary Bioscience Training, Houston, TX, USA*
CHUNG F. WONG • *Department of Chemistry and Biochemistry, University of Missouri-St. Louis, St. Louis, MO, USA*
MARTIN ZACHARIAS • *Physik-Department, Technische Universität München, Garching, Germany*
BOJAN ZAGROVIC • *Laboratory of Computational Biophysics, Department of Structural and Computational Biology, Max Perutz Laboratories, Vienna, Austria*
RUBEN ZUBAC • *Laboratory of Computational Biophysics, Department of Structural and Computational Biology, Max Perutz Laboratories, Vienna, Austria*

Contents

Part I

Drug Binding Site Prediction, Design, and Descriptors

Chapter 1

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

Riccardo Baron (ed.), *Computational Drug Discovery and Design*, Methods in Molecular Biology, vol. 819,
DOI 10.1007/978-1-61779-465-0_1,