Methods in Molecular Biology 2053

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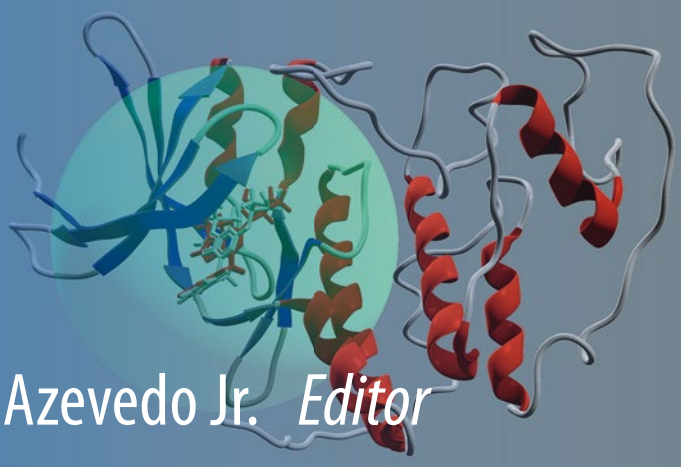

Walter Filgueira de Azevedo Jr. *Editor*

Docking Screens for Drug Discovery

Humana Press

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Docking Screens for Drug Discovery

Edited by

Walter Filgueira de Azevedo Jr.

Escola de Ciências da Saúde, Pontifícia Universidade Católica do Rio Grande do Sul—PUCRS, Porto Alegre, Ria Grande do Sul, Brazil

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Editor
Walter Filgueira de Azevedo Jr.
Escola de Ciências da Saúde
Pontifícia Universidade Católica do Rio Grande do Sul—PUCRS
Porto Alegre, Ria Grande do Sul, Brazil

ISSN 1064-3745 ISSN 1940-6029 (electronic)
Methods in Molecular Biology
ISBN 978-1-4939-9751-0 ISBN 978-1-4939-9752-7 (eBook)
https://doi.org/10.1007/978-1-4939-9752-7

Dedication

This book is dedicated to my beloved mother Marion de Fátima Pereira de Azevedo and my darling wife Maria do Carmo Dantas de Santana Azevedo.

Preface

The data explosion in the number of biological macromolecules deposited in the Protein Data Bank (PDB) [1–3] opened the possibility to investigate the correlation of these experimentally determined structures with biological information, which is a favorable scenario for the application of computational systems biology approaches to develop a mathematical model to predict ligand-binding affinity for this target protein. It is also possible to use these three-dimensional structures to study target proteins employed in the development and design of drugs [4–10]. The use of structural information for a target protein makes it possible to apply virtual screening methodology to identify new hits and guide the future development of new medicines. The primary approach to investigate potential new hits for a target protein is the methodology of protein-ligand docking simulation [11].

Docking is a simulation method that predicts the structure of a receptor-ligand complex, in which the receptor is a protein and the ligand is a small molecule [12–16]. This simulation is equivalent to the key-lock theory of enzyme specificity [17, 18], in which the lock is the receptor and the key is the ligand. The goal in any protein-ligand docking simulation is to adjust the position of the key (ligand) in the lock (ligand-binding pocket in a protein). From the computational view, we see the protein-ligand docking as an optimization problem, where our goal is to find the best solution (right position for the ligand) from a set of possible locations. Protein-ligand docking often makes use of one or more of the following computational methodologies: genetic algorithm, differential evolution, Lamarckian genetic algorithm, fast shape matching, incremental construction, distance geometry, simulated annealing, and others [19]. Protein-ligand docking methodology can produce several positions for the key in the lock. Therefore, we need a scoring function that will allow evaluations of all possible positions of the key, and then a selection can be carried out for the best location. For general reviews of the principles underlying molecular docking programs, see references [12–16].

Also, to evaluate the ligand-binding affinity for a specific target protein, we can employ a scoring function to compute scores that resemble ligand-binding energy functions. For both approaches, experimental information is vital to validate protein-ligand docking simulations and the ability of scoring functions to estimate ligand-binding affinity [20].

For protein-ligand docking simulations, it is common to start investigating if the computational approach is capable of reproducing an experimental 3D structure for a complex involving a protein and at least one ligand. If such structure is available, we employ it to check whether a specific molecular docking protocol is capable of predicting the crystallographic position for the ligand in the protein structure, a procedure called redocking. The most used criteria to evaluate redocking success are the root-mean-square deviation (RMSD) between the crystallographic position for the ligand and the pose (generated by the computer simulation). In docking simulations, we expect that the best results generate RMSD values less than 2.0 Å compared with crystallographic structures [12–16].

Furthermore, if we have more than one structure complexed with a ligand, we can take the validation process further, applying the molecular docking protocol to an ensemble of complexes structures. In this ensemble, we could have the same protein structure in complex with different ligands. For instance, a search in the PDB for structures containing the name

cyclin-dependent kinases (CDKs) and for which there is inhibition constant (K_i) information returned 31 structures. These structures have water molecules close to the active ligand and without repeated ligands (search carried out on March 20, 2019). This data set is an ensemble of CDK structures, where each entry is a structure complexed with a different ligand. This ensemble of structures can be employed to validate a docking strategy for a specific protein target. Moreover, it could also be used to test scoring functions.

For validation of scoring functions, it is common to investigate the correlation between the experimental binding affinity with scoring functions. Here we evaluated the predictive performance using squared Pearson's (R^2) or Spearman's (ρ) correlation coefficients [21]. Application of machine learning methods can improve the predictive performance of scoring functions trained against data sets composed of experimentally determined structures for which ligand-binding data is available [22–32].

The focus of the present book is on recent developments in docking simulations for target proteins. We have chapters dealing with specific techniques or applications for docking simulations. For instance, we describe the major docking programs. Also, we explain the scoring functions developed for the analysis of docking results and to predict ligand-binding affinity. Due to the importance of docking simulations for the initial stages of drug discovery, we believe that the present volume will appeal to those interested in molecular docking simulation and also in the application of these methodologies for drug discovery.

Finally, I would like to express my gratitude to all authors who accepted the challenge of bringing to a book their scientific knowledge. I want to thank Prof. John M. Walker (series editor for the *Methods in Molecular Biology* series) for his patience and assistance during the editorial process. This book wouldn't be possible without the aid of Anna Rakovsky (Assistant Editor at Springer Science + Business Media, LLC). Many others contributed directly or indirectly to this book. I want to thank all my students who tested the tutorials and protocols described here. They did a great job of helping to improve the quality of the material described in this work. This book is a dream coming true, and it wouldn't be possible without the comprehension and love of my wife Carminha (Maria do Carmo Dantas de Santana Azevedo) who understood my absence and helped me during the months of preparation of this book. To her: "Obrigado minha linda. Este livro é para você. Te amo muito."

Porto Alegre, RS, Brazil *Walter Filgueira de Azevedo Jr.*

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Acknowledgments

This work was supported by grants from CNPq (Brazil) (308883/2014-4). This study was financed in part by the Coordenação de Aperfeiçoamento de Pessoal de Nivel Superior—Brasil (CAPES)—Finance Code 001. WFA is a researcher for CNPq (Brazil) (Process Numbers: 308883/2014-4 and 309029/2018-0).

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Contributors

Pedro J. Ballester • *Cancer Research Center of Marseille, INSERM U1068, Marseille, France; Institut Paoli-Calmettes, Marseille, France; Aix-Marseille Université, Marseille, France; CNRS UMR7258, Marseille, France*

Gabriela Bitencourt-Ferreira • *Escola de Ciências da Saúde, Pontifícia Universidade Católica do Rio Grande do Sul—PUCRS, Porto Alegre, RS, Brazil*

Ernesto R. Caffarena • *Programa de Computação Científica, Fundação Oswaldo Cruz, Rio de Janeiro, RJ, Brazil*

Nelson J. F. da Silveira • *Laboratory of Molecular Modeling and Computer Simulation/MolMod-CS, Institut of Exact Science/ICEx, Federal University of Alfenas/UNIFAL-MG, Alfenas, MG, Brazil*

Walter Filgueira de Azevedo Jr. • *Escola de Ciências da Saúde, Pontifícia Universidade Católica do Rio Grande do Sul—PUCRS, Porto Alegre, RS, Brazil*

Thiago C. Elias • *Laboratory of Molecular Modeling and Computer Simulation/MolMod-CS, Institut of Exact Science/ICEx, Federal University of Alfenas/UNIFAL-MG, Alfenas, MG, Brazil*

Rafaela S. Ferreira • *Laboratório de Modelagem Molecular e Planejamento de Fármacos, Departamento de Bioquímica e Imunologia, Universidade Federal de Minas Gerais, Belo Horizonte, MG, Brazil*

Tiago Henrique • *Departament of Molecular Biology, Medical School of São José do Rio Preto/FAMERP, São José do Rio Preto, SP, Brazil*

Felipe Siconha S. Pereira • *Laboratory of Computacional Modeling, National Laboratory of Scientific Computing (LNCC), Petrópolis, RJ, Brazil*

Val Oliveira Pintro • *Escola de Ciências da Saúde, Pontifícia Universidade Católica do Rio Grande do Sul—PUCRS, Porto Alegre, RS, Brazil*

Lucianna H. S. Santos • *Laboratório de Modelagem Molecular e Planejamento de Fármacos, Departamento de Bioquímica e Imunologia, Universidade Federal de Minas Gerais, Belo Horizonte, MG, Brazil*

Pawel Siedlecki • *Institute of Biochemistry and Biophysics PAS, Warsaw, Poland; Department of Systems Biology, Institute of Experimental Plant Biology and Biotechnology, University of Warsaw, Warsaw, Poland*

Martina Veit-Acosta • *Escola de Ciências da Saúde, Pontifícia Universidade Católica do Rio Grande do Sul—PUCRS, Porto Alegre, RS, Brazil*

Maciej Wójcikowski • *Institute of Biochemistry and Biophysics PAS, Warsaw, Poland*

About the Editor

Walter Filgueira de Azevedo Jr. is Frontiers Section Editor (Bioinformatics and Biophysics) for the *Current Drug Targets*, member of the editorial board of *Current Bioinformatics*, and section editor (Bioinformatics in Drug Design and Discovery) for the *Current Medicinal Chemistry*. Prof. Azevedo graduated in physics (BSc in physics) from the University of São Paulo (USP) in 1990. He completed a Master's Degree in Applied Physics also from the USP (1992), working under the supervision of Prof. Yvonne P. Mascarenhas, the founder of crystallography in Brazil. His dissertation was about X-ray crystallography applied to organometallic compounds. During his Ph.D., he worked under the supervision of Prof. Sung-Hou Kim (University of California, Berkeley), on a split Ph.D. program with a fellowship from Brazilian Research Council (CNPq) (1993–1996). His Ph.D. was about the crystallographic structure of CDK2. At present, he is the coordinator of the Structural Biochemistry Laboratory at Pontifical Catholic University of Rio Grande do Sul (PUCRS). His research interests are interdisciplinary with two major emphases: molecular simulations and protein-ligand interactions. He published over 160 scientific papers about protein structures and computer simulation methods applied to the study of biological systems (H-index: 40, RG Index > 41.0). These publications have over 5000 citations.