

Challenges and Advances
in Computational Chemistry and Physics 17
Series Editor: J. Leszczynski

Leonid Gorb
Victor Kuz'min
Eugene Muratov *Editors*

Application of Computational Techniques in Pharmacy and Medicine

Challenges and Advances
in Computational Chemistry and Physics 17
Series Editor: J. Leszczynski

Leonid Gorb
Victor Kuz'min
Eugene Muratov *Editors*

Application of Computational Techniques in Pharmacy and Medicine

Challenges and Advances in Computational Chemistry and Physics

Volume 17

Series Editor

Jerzy Leszczynski
Jackson State University, Jackson, Mississippi, USA

This book series provides reviews on the most recent developments in computational chemistry and physics. It covers both the method developments and their applications. Each volume consists of chapters devoted to the one research area. The series highlights the most notable advances in applications of the computational methods. The volumes include nanotechnology, material sciences, molecular biology, structures and bonding in molecular complexes, and atmospheric chemistry. The authors are recruited from among the most prominent researchers in their research areas. As computational chemistry and physics is one of the most rapidly advancing scientific areas such timely overviews are desired by chemists, physicists, molecular biologists and material scientists. The books are intended for graduate students and researchers.

More information about this series at <http://www.springer.com/series/6918>

Leonid Gorb • Victor Kuz'min • Eugene Muratov
Editors

Application of Computational Techniques in Pharmacy and Medicine

 Springer

Editors

Leonid Gorb
Department of Molecular Biophysics
Laboratory of Computational
Structural Biology
Kiev
Ukraine

Victor Kuz'min
Department of Molecular Structure
and Chemoinformatics
A.V. Bogatsky Physical-Chemical Institute,
National Academy of Sciences
of Ukraine
Odessa
Ukraine

Eugene Muratov
Department of Chemical Biology
and Medicinal Chemistry
University of North Carolina, Laboratory
for Molecular Modeling
Chapel Hill
North Carolina
USA

ISBN 978-94-017-9256-1

ISBN 978-94-017-9257-8 (eBook)

DOI 10.1007/978-94-017-9257-8

Springer Dordrecht Heidelberg New York London

Library of Congress Control Number: 2014952367

© Springer Science+Business Media Dordrecht 2014

This work is subject to copyright. All rights are reserved by the Publisher, whether the whole or part of the material is concerned, specifically the rights of translation, reprinting, reuse of illustrations, recitation, broadcasting, reproduction on microfilms or in any other physical way, and transmission or information storage and retrieval, electronic adaptation, computer software, or by similar or dissimilar methodology now known or hereafter developed. Exempted from this legal reservation are brief excerpts in connection with reviews or scholarly analysis or material supplied specifically for the purpose of being entered and executed on a computer system, for exclusive use by the purchaser of the work. Duplication of this publication or parts thereof is permitted only under the provisions of the Copyright Law of the Publisher's location, in its current version, and permission for use must always be obtained from Springer. Permissions for use may be obtained through RightsLink at the Copyright Clearance Center. Violations are liable to prosecution under the respective Copyright Law.

The use of general descriptive names, registered names, trademarks, service marks, etc. in this publication does not imply, even in the absence of a specific statement, that such names are exempt from the relevant protective laws and regulations and therefore free for general use.

While the advice and information in this book are believed to be true and accurate at the date of publication, neither the authors nor the editors nor the publisher can accept any legal responsibility for any errors or omissions that may be made. The publisher makes no warranty, express or implied, with respect to the material contained herein.

Printed on acid-free paper

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

Preface

Advances in computer hardware parallel by recent enormous progress in developing computer algorithms that utilize hundreds and even thousand of computer nodes made applications of computational techniques to be indispensable in scientific research and fundamental science applications. Such research areas as computational biology, molecular pharmacy and molecular medicine are certainly among those where these computational applications are actively introduced. As the result, modern multiprocessor computers are able to treat real-life biological systems consisting of millions of atoms (ribosoms, nucleosoms, or even viruses) in a time frame of hundred nanoseconds. This tendency manifests itself even more clearly in the area of bioinformatics. Nowadays, combinatorial and high-throughput screening (HTS) technologies are widely used in both academia and industry. The pharmaceutical companies run the HTS platforms, incorporating libraries of several millions of compounds. Also, there are more and more academic centers that conduct HTS and integrate their platform with industrial drug discovery centers. Therefore, one can safely say that the computational chemist has become a respectable member of a drug design community, playing the same role as the synthetic or pharmacologists chemists. More and more often such projects have interdisciplinary character presenting an interplay between the theory and the experiment. They are intended to provide basic information as well as the data which could be used in practical pharmacological and medical applications.

The proposed volume provides basic information as well as the details of computational and computational-experimental studies improving our knowledge on functioning of alive, different properties of drugs, and predictions of new medicines. Whenever it is possible the interplay between the theory and the experiment is provided. The unique feature of the book is the fact that such different in principles computational techniques as quantum-chemical and molecular dynamic approaches on one hand and quantitative structure–activity relationships on another hand are considered inside one volume. The reviews presented in the volume cover main tendencies and priorities in application of computational methods of quantum chemistry, molecular dynamics and chemoinformatics to solve the tasks of pharmacy and medicine.

The present book is aimed at a relatively broad readership that includes advanced undergraduate and graduate students of chemistry, physics and engineering, post-doctoral associates and specialists from both academia and industry who carry out research in the fields that require molecular and QSA(P)R modeling. This book could also be useful to students in biochemistry, structural biology, bioengineering, bioinformatics, pharmaceutical chemistry, as well as other related areas, who have an interest in molecular-level computational techniques.

The book starts from the reviews that describe the studies of biological systems which are performed by the methods of quantum chemistry and classical molecular dynamics. The two initial chapters describe the theory and application of such methods as hybrid quantum-mechanical/molecular mechanical approximation, Monte-Carlo, molecular docking and molecular dynamics, in conjunction with the application of experimental techniques as Infra-Red, Raman, UV-VIS spectroscopies, and microcalorimetry. Next four chapters continue to describe the current status of the investigations in such vital area as functioning of DNA. It covers formation of DNA lesions, computational rational design of DNA polymerase inhibitors, modeling the structure of DNA quadruplexes, and the study on the structure, relative stability, and proton affinities of such building blocks as nucleotides. The seventh, eighth, ninth and tenth chapters are devoted to the application of computational and experimental techniques in such areas of medical and pharmaceutical chemistry as enzyme-inhibitor interactions, interaction of enzymes with biological membranes and a probe of polyphenol glycosides as potential remedies in kidney stones therapy and transformations of epoxidized *in vivo* and *in vitro*. The following six reviews describe the advantages in the area of chemoinformatics. Most of them are devoted to developing and applications of the QSAR methodology to predict an activity and design of novel biologically active compounds. In particular, the criteria for correct QSAR models, their opportunities and limitations are studied in the eleventh chapter. Very original QSAR methodology named MICROCOSM is presented in chapter twelfth. The chapters 11th, 13th and 14th devoted to analysis such important properties of biologically active compounds (possible drugs) as toxicity and farmokinetics. Very interesting methodology which combines molecular dynamics and docking approaches is described in the 15th chapter. The book is closing up by the 16th chapter which describes modern state of chemoinformatics, new problems and perspectives of treatment of avalanche-like amount of experimental chemical and biological information.

The editors of this book gratefully thank all the authors for their time and contribution. We hope that this volume may give the reader (both in academia and in an industrial pharmaceutical community) a useful overview of the computational and experimental techniques that are currently in use in the areas of computational pharmacy and medicine.

May, 2014

Leonid Gorb
Victor Kuz'min
Eugene Muratov

Contents

1 Hybrid QM/MM Methods: Treating Electronic Phenomena in Very Large Molecular Systems.....	1
Antonio Monari and Xavier Assfeld	
2 Structure, Thermodynamics and Energetics of Drug-DNA Interactions: Computer Modeling and Experiment	21
Maxim P. Evstigneev and Anna V. Shestopalova	
3 Formation of DNA Lesions, its Prevention and Repair	59
Nihar R. Jena, Neha Agnihotri and Phool C. Mishra	
4 DNA Dependent DNA Polymerases as Targets for Low-Weight Molecular Inhibitors: State of Art and Prospects of Rational Design	95
Alexey Yu. Nyporko	
5 Molecular Structures, Relative Stability, and Proton Affinities of Nucleotides: Broad View and Novel Findings	137
Tetiana A. Zubatiuk, Gennady V. Palamarchuk, Oleg V. Shishkin, Leonid Gorb and Jerzy Leszczynski	
6 Quantum Chemical Approaches in Modeling the Structure of DNA Quadruplexes and Their Interaction with Metal Ions and Small Molecules	181
Mykola Ilchenko and Igor Dubey	
7 Density Functional Theory Calculations of Enzyme-Inhibitor Interactions in Medicinal Chemistry and Drug Design.....	207
Alexander B. Rozhenko	

8 Molecular Dynamics Simulations of Lipid Bilayers with Incorporated Peptides	241
Milan Melicherčík, Tibor Hianik and Ján Urban	
9 Polyphenol Glycosides as Potential Remedies in Kidney Stones Therapy. Experimental Research Supported by Computational Studies	271
D. Toczek, E. Klepacz, S. Roszak and R. Gancarz	
10 Quantum-Chemical Investigation of Epoxidic Compounds Transformation. Application for <i>In Vitro</i> and <i>In Vivo</i> Processes Modeling	295
Sergiy Okovytyy	
11 Computational Toxicology in Drug Discovery: Opportunities and Limitations	325
Alexey Zakharov and Alexey Lagunin	
12 Consensus Drug Design Using It Microcosm	369
Pavel M. Vassiliev, Alexander A. Spasov, Vadim A. Kosolapov, Aida F. Kucheryavenko, Nataliya A. Gurova and Vera A. Anisimova	
13 Continuous Molecular Fields Approach Applied to Structure-Activity Modeling	433
Igor I. Baskin and Nelly I. Zhokhova	
14 Quantitative Structure-Property Relationship Analysis of Drugs' Pharmacokinetics Within the Framework of Biopharmaceutics Classification System Using Simplex Representation of Molecular Structure	461
N. Ya. Golovenko, I. Yu. Borisyuk, M. A. Kulinskiy, P. G. Polishchuk, E. N. Muratov and V. E. Kuz'min	
15 (How to) Profit from Molecular Dynamics-based Ensemble Docking	501
Susanne von Grafenstein, Julian E. Fuchs and Klaus R. Liedl	
16 Cheminformatics: At the Crossroad of Eras	539
Denis Fourches	
Index	547

Contributors

Neha Agnihotri Department of Chemistry, University of Saskatchewan, Saskatoon, Canada

Vera A. Anisimova Institute of Physical and Organic Chemistry at Southern Federal University (IPOC SFU), Rostov-on-Don, Russian Federation

Xavier Assfeld Université de Lorraine, Nancy, France

Igor I. Baskin Faculty of Physics, M. V. Lomonosov Moscow State University, Moscow, Russia

I. Yu. Borisjuk A.V. Bogatsky Physico-Chemical Institute NAS of Ukraine, Odessa, Ukraine

Igor Dubey Institute of Molecular Biology and Genetics, National Academy of Sciences of Ukraine, Kyiv, Ukraine

Maxim P. Evstigneev Sevastopol National Technical University (SevNTU), Sevastopol, Ukraine

Belgorod State University (BGU), Belgorod, Russia

Denis Fourches Laboratory for Molecular Modeling, University of North Carolina, Chapel Hill, NC, USA

Julian E. Fuchs Institute of General, Inorganic and Theoretical Chemistry, University of Innsbruck, Innsbruck, Austria

R. Gancarz Organic and Pharmaceutical Technology Group, Chemistry Department, Wrocław University of Technology (WUT), Wrocław, Poland

Susanne von Grafenstein Institute of General, Inorganic and Theoretical Chemistry, University of Innsbruck, Innsbruck, Austria

N. Ya. Golovenko A.V. Bogatsky Physico-Chemical Institute NAS of Ukraine, Odessa, Ukraine

Leonid Gorb Laboratory of Computational Structural Biology, Department of Molecular Biophysics, Institute of Molecular Biology and Genetics, National Academy of Sciences of Ukraine, Kyiv, Ukraine

Nataliya A. Gurova Volgograd State Medical University (VSMU), Volgograd, Russian Federation

Tibor Hianik Department of Nuclear Physics and Biophysics, Faculty of Mathematics, Physics and Informatics, Comenius University, Bratislava, Slovak Republic, Europe

Mykola Ilchenko Institute of Molecular Biology and Genetics, National Academy of Sciences of Ukraine, Kyiv, Ukraine

Nihar R. Jena Discipline of Natural Sciences, Indian Institute of Information Technology, Design and Manufacturing, Jabalpur, India

School of Chemistry and Molecular Biosciences, University of Queensland, Brisbane, Australia

E. Klepacz Organic and Pharmaceutical Technology Group, Chemistry Department, Wrocław University of Technology (WUT), Wrocław, Poland

Vadim A. Kosolapov Volgograd State Medical University (VSMU), Volgograd, Russian Federation

Aida F. Kucheryavenko Volgograd State Medical University (VSMU), Volgograd, Russian Federation

M. A. Kulinskiy A.V. Bogatsky Physico-Chemical Institute NAS of Ukraine, Odessa, Ukraine

V. E. Kuz'min A.V. Bogatsky Physico-Chemical Institute NAS of Ukraine, Odessa, Ukraine

Alexey Lagunin Orechovich Institute of Biomedical Chemistry of Russian Academy of Medical Sciences, Laboratory of Structure-Function Based Drug Design, Moscow, Russia

Jerzy Leszczynski Interdisciplinary Center for Nanotoxicity, Department of Chemistry and Biochemistry, Jackson State University, Jackson, MS, USA

Klaus R. Liedl Institute of General, Inorganic and Theoretical Chemistry, University of Innsbruck, Innsbruck, Austria

Milan Melicherčík Department of Nuclear Physics and Biophysics, Faculty of Mathematics, Physics and Informatics, Comenius University, Bratislava, Slovak Republic, Europe

Institute of Nanobiology and Structural Biology of GCRC, Academy of Sciences of the Czech Republic, Nové Hradky, Zámek 136, Czech Republic

Phool C. Mishra Department of Physics, Banaras Hindu University, Varanasi, India

Antonio Monari Université de Lorraine, Nancy, France

E. N. Muratov A.V. Bogatsky Physico-Chemical Institute NAS of Ukraine, Odessa, Ukraine

University of North Carolina, Chapel Hill, NC, USA

Alexey Yu. Nyporko High Technology Institute, Taras Shevchenko National University of Kyiv, Kyiv, Ukraine

Sergiy Okovytyy Department of Organic Chemistry, Oles Honchar Dnipropetrovsk National University, Dnipropetrovsk, Ukraine

Gennady V. Palamarchuk SSI “Institute for Single Crystals” of National Academy of Science of Ukraine, Kharkiv, Ukraine

P. G. Polishchuk A.V. Bogatsky Physico-Chemical Institute NAS of Ukraine, Odessa, Ukraine

S. Roszak Institute of Physical and Theoretical Chemistry, Wrocław University of Technology (WUT), Wrocław, Poland

Alexander B. Rozhenko Institute of Organic Chemistry, National Academy of Sciences of Ukraine, Kyiv, Ukraine

Anna V. Shestopalova A.Usikov Institute for Radiophysics and Electronics National Academy of Sciences of Ukraine (IRE NASU), Kharkov, Ukraine

Oleg V. Shishkin SSI “Institute for Single Crystals” of National Academy of Science of Ukraine, Kharkiv, Ukraine

Alexander A. Spasov Volgograd State Medical University (VSMU), Volgograd, Russian Federation

D. Toczek Organic and Pharmaceutical Technology Group, Chemistry Department, Wrocław University of Technology (WUT), Wrocław, Poland

Ján Urban Department of Nuclear Physics and Biophysics, Faculty of Mathematics, Physics and Informatics, Comenius University, Bratislava, Slovak Republic, Europe

Pavel M. Vassiliev Volgograd State Medical University (VSMU), Volgograd, Russian Federation

Alexey Zakharov National Institutes of Health, National Cancer Institute, Chemical Biology Laboratory, Frederick, MD, USA

Nelly I. Zhokhova Faculty of Physics, M. V. Lomonosov Moscow State University, Moscow, Russia

Tetiana A. Zubatiuk SSI “Institute for Single Crystals” of National Academy of Science of Ukraine, Kharkiv, Ukraine

About the Editors

Leonid Gorb Laboratory of Computational Structural Biology, Department of Molecular Biophysics, Institute of Molecular Biology and Genetics, National Academy of Sciences of Ukraine, Zabolotnogo Str., 150, Kyiv, 03143, Ukraine

Victor Kuz'min Department of Molecular Structure and Chemoinformatics, A.V. Bogatsky Physical-Chemical Institute, National Academy of Sciences of Ukraine, 86 Lustdorfskaya Doroga, Odessa, 65080, Ukraine

Eugene Muratov Laboratory for Molecular Modeling, Department of Chemical Biology and Medicinal Chemistry, Eshelman School of Pharmacy, University of North Carolina, Chapel Hill, NC, 27599, USA

Chapter 1

Hybrid QM/MM Methods: Treating Electronic Phenomena in Very Large Molecular Systems

Antonio Monari and Xavier Assfeld

Abstract Hybrid methods, combining the accuracy of Quantum Mechanics and the potency of Molecular Mechanics, the so-called QM/MM methods, arise from the desire of theoretician chemists to study electronic phenomena in large molecular systems. In this contribution, a focus, on the Physics and Chemistry on which these methods are based on, is given. The advantages, flaws, and limitations of each type of methods are exposed. A special emphasis is put on the Local Self-Consistent Field method, developed in our group. The latest developments are detailed and illustrated by chosen examples.

1.1 Introduction

Except some very specific experiments dealing with gas phase with very low pressure, or some particular media (interstellar space, high atmosphere, ...), chemists encounter molecules in interaction with their surroundings. In fact, most of chemical or biochemical reactions take place in solution or involve macromolecules. The role of the surroundings is crucial. For example, some chemical reactions, like ethylene bromination, are quasi unfeasible in gas phase, very slow in apolar solvents, but instantaneous in water [1]. In the same vein, most biochemical reactions wouldn't be possible if not catalyzed by enzymes [2]. In addition to the role played in enzymatic catalysis, the environment is also crucial to modify, to precisely tune or to induce the response to light in photo-active systems. A paradigmatic example being for instance the role played by opsin protein in assuring an ultra-fast highly efficient photo isomerization of retinal chromophore in vision process [3, 4]. The precise understanding and tuning of light-induced responses in complex biosystems

X. Assfeld (✉) · A. Monari
Université de Lorraine, Théorie-Modélisation-Simulation, SRS MC UMR 7565,
Vandœuvre-lès-Nancy, 54506 France
e-mail: xavier.assfeld@univ-lorraine.fr

A. Monari
e-mail: antonio.monari@univ-lorraine.fr