Challenges and Advances
in Computational Chemistry and Physics 17
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Application of Computational Techniques in Pharmacy and Medicine

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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.

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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 epoxided *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 opprtunities and limitations are studied in the eleventh chapter. Very original QSAR methodoly named MICROCOSM is presented in chapter twelfth. The chapters 11th, 13th and 14th devoted to analysis such important properties of biologivally 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

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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 theses 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

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