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## Preface

The field of molecular simulations has evolved, during the past 40 years, from picosecond studies of isolated macromolecules in vacuum to studies of complex, chemically heterogeneous biomolecular systems consisting of millions of atoms, with the simulation time scales spanning up to milliseconds. Much of the impressive progress in biomolecular simulations has been simply due to more powerful computers. However, tackling the sheer complexity of macromolecular systems of biological interest has never relied on Moore's law alone. Among the most important factors contributing to such enormous progress are the development of faster simulation algorithms and entirely novel approaches to molecular modelling, such as multiscale methods employing different levels of theory for different regions of the system studied. As the number of researchers in the field has increased, limitations inherent in each methodology have also been described, creating awareness of the pros and cons of different techniques, and contributing significantly to the progress in the field. Quantum mechanical (QM) calculations, while in principle providing a rigorous description of the molecules of interest, necessitate the use of some approximations in the underlying theory. Practical methodological solutions within these frameworks (for example, computationally efficient basis sets) have been crucial in QM calculations becoming a powerful tool in biomolecular modelling. Classical simulations employing empirical force fields have steadily become more versatile and accurate, thanks to more sophisticated potential energy functions even including explicit functions for hydrogen bonding and electronic polarization, and to more accurate parameterizations. The general level of accuracy of the classical simulations, combined with their speed, has made them perhaps the most widely used method in molecular modelling of biological systems. Coarse-graining the atomistic description of the molecules of interest has simplified the computations immensely while still retaining some of the key physicochemical properties of the system studied.

One major challenge in modelling biological systems is the very large span of length and time scales involved. Depending on the problem at hand, researchers look at motions occurring on time scales from femtoseconds ( $10^{-15}$  s) to hours, and covering distances from sub-atomic scale to cell size. Another challenge is the great chemical complexity and heterogeneity of biological systems. Even the smallest biological sample contains a wide variety of molecules. Computational studies – just as simple *in vitro* experiments – require much simplification. It is assumed that by understanding the properties and behaviour of simple model systems one can learn about the properties and behaviour of real, much more complex systems. When such assumption and other simplifications are justified, simulations can make a significant contribution to understanding biological systems' structure and functioning.

Excellent books are available to students and researchers who venture into the field of molecular modelling, covering both the basic foundations as well as more specialized aspects. With the present volume, we aim to present the foundations of well-established simulation techniques together with some of the recent developments in methods and practices. The latter rarely find ample coverage in traditional textbooks, but are being used more and more by researchers in the biological field. We also aim at giving

some practical examples on how to carry out simulations of some particular systems of great biological interest, and particularly systems including biological macromolecules.

The book consists of three sections, with the division based on the predominant classes of methods used in modelling at various length and time scales. The covered methodologies include electronic structure calculations, classical molecular dynamics simulations and coarse-grained techniques. Each section comprises a methodological and an application part. The former provides an introduction to the basic physics and chemistry underlying the computational models, and focuses particularly on recent developments. The application part illustrates examples on the four main classes of biological macromolecules, namely proteins, nucleic acids, lipids, and carbohydrates. This subdivision is in line with the traditions of the *Methods in Molecular Biology* series, with an introductory overview, theoretical foundations, and good practices of the methodologies used, followed by chapters illustrating their practical application in studies of biological macromolecules.

The target audience of the book includes both graduate students and researchers interested in computational modelling of biomolecular systems in physics, chemistry, and biology. The structuring of the different sections has been made so that after reading the first methodological chapters in the section in question, a non-expert reader can understand and appreciate the following application-oriented chapters. An expert on a given methodology can, in turn, jump directly to the chapters on state-of-the-art applications of the methodology covered. We hope that the readers will find this structure of the book useful and easy to approach.

The general structure of the book is as follows. The QM section contains reviews covering the most central contemporary methodologies of biomolecular modelling. The section begins with an overview of different electronic structure calculation methods with an emphasis on methodological issues related to the investigation of biological systems. The so-called *ab initio* molecular dynamics methodology for dynamic electronic structure calculations is then introduced. The remaining three chapters in the section address a more practical side of QM calculations of biological systems, that is, the hybrid QM and molecular mechanics methodology (QM/MM). These chapters feature a particular emphasis on studies of proteins, reflecting the most common domain of application of QM/MM methods.

In the section on atomistic simulations we cover the basic ideas and the most common techniques (molecular dynamics and classical force fields), and we also give space to a few recent developments that gained more and more importance in recent years: enhanced sampling algorithms, allowing for crossing energetic barriers and speed up the sampling; free energy calculations, that were rarely found in the literature only a decade ago due to the high computational cost, but are now accessible to a wide audience; polarizable force fields, which aim to increase the accuracy of classical empirical simulations with a tolerable computational overhead, and have become increasingly popular during recent years.

Coarse-graining has been perhaps the fastest evolving area in biomolecular modelling over the past few years, with new techniques and new force fields published monthly. Coarse-graining rarely finds any space in traditional textbooks, but it is becoming attractive for a very wide public. The diversity in the techniques developed is such that a thorough review would require an entire volume. The book covers some of the most exciting recent developments in the area, with applications to lipid membranes and membrane proteins in particular.

The increasing speed of molecular simulations hardware and software, and the development of force fields and methodologies make it possible to describe increasingly

complex biological systems and processes. Progress in several directions can be foreseen in the near future, with the development of faster and more accurate methodologies for electronic structure calculations, more refined classical force fields, and improved coarse-graining techniques. Multiscale modelling, that currently is one of the most challenging problems in molecular simulations, will require substantial theoretical and methodological development. Yet, the great interest in combining descriptions at different length scales bears expectations of a significant growth in this area.

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