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Computational Modeling of Solvent Effects on Protein-Ligand Interactions Using Fully Polarizable Continuum Model and Rational Drug Design

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Abstract. This is a brief review of the computational modeling of protein-ligand interactions using a recently developed fully polarizable continuum model (FPCM) and rational drug design. Computational modeling has become a powerful tool in understanding detailed protein-ligand interactions at molecular level and in rational drug design. To study the binding of a protein with multiple molecular species of a ligand, one must accurately determine both the relative free energies of all of the molecular species in solution and the corresponding microscopic binding free energies for all of the molecular species binding with the protein. In this paper, we aim to provide a brief overview of the recent development in computational modeling of the solvent effects on the detailed protein-ligand interactions involving multiple molecular species of a ligand related to rational drug design. In particular, we first briefly discuss the main challenges in computational modeling of the detailed protein-ligand interactions involving the multiple molecular species and then focus on the FPCM model and its applications. The FPCM method allows accurate determination of the solvent effects in the first-principles quantum mechanism (QM) calculations on molecules in solution. The combined use of the FPCM-based QM calculations and other computational modeling and simulations enables us to accurately account for a protein binding with multiple molecular species of a ligand in solution. Based on the computational modeling of the detailed protein-ligand interactions, possible new drugs may be designed rationally as either small-molecule ligands of the protein or engineered proteins that bind/metabolize the ligand. The computational drug design has successfully led to discovery and development of promising drugs.

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1 Introduction

Structures and functions of biomolecular systems (such as protein, DNA, RNA, and their complexes with small-molecule ligands) are essential issues for understanding life processes at molecular level. Specially, when the biomolecule under consideration is a drug target, understanding the detailed structure and functions of the drug target at molecular level will provide a solid base for computational drug design. Information from experiments is always necessary, but often insufficient to achieve a complete understanding of the detailed structure and functions. Modern computational techniques of molecular modeling have been recognized to be a valuable complement to experiments, because an appropriate use of the state-of-the-art molecular modeling techniques can provide more detailed structural and mechanistic information that cannot be obtained from experiments alone, as demonstrated in many reports such as [1–8].

On the other hand, development of high-accuracy computational approaches to studying the structures and functions of biomolecules is particularly challenging. This is because many biomolecules is usually large in size and surrounded by a very complex chemical environment. The chemical environment surrounding a molecule in living system always includes a large number of solvent water molecules. Intermolecular interactions between a molecule under consideration (as the solute) and its solvent environment could dramatically change the structure and functions of the solute molecule. The experimental response of chemical, physical, and biochemical phenomena depends critically on the solvent effects. Thus, a reliable computational approach must appropriately account for the solvent effects in the practical computations.

A theoretically ideal computational approach would be to perform electronic structure calculations on the entire solvated biomolecular system, *i.e.* the entire biomolecule with its explicit chemical environment, at a sufficiently high-level ab initio quantum mechanical (QM) theory. This is a first-principles approach, which has been proven reliable in predicting the structures, properties, and chemical reactions of isolated small molecules (in vacuum, or in the gas phase). The reliability of the results calculated with this approach would not rely on any adjustable empirical parameters. Unfortunately, a high-level *ab initio* QM calculation on a biomolecule with its adequate chemical environment is impractical from a computational point of view [9], because the computing time required for a QM calculation will dramatically increase by adding additional atoms to the QM-treated system. For this reason, empirical molecular mechanics (MM) and related methods are currently very popular computational methodologies used in modeling and simulation of biomolecules.

A MM method simply considers all atoms to be classical particles with atomic forces determined by a set of parameterized interaction functions (force field), including bonded interactions (bonds, angles, and dihedral angles), non-bonded van der Waals interactions, and electrostatic interactions based on net atomic charges. By use of an empirical force field, a classical molecular dynamics (MD) simulation enables the study of time evolution of a large biomolecular system by taking many small successive time steps under