The role of quantum mechanics in structure-based drug design

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INTRODUCTION

The routine use of quantum mechanics (QM) in all phases of in silico drug design is the logical next step in the evolution of this field. The first principles nature of QM allows it to systematically improve the accuracy of the description of the nature of the interactions between molecules. Moreover, the systematic way in which one can approach the use of QM methods to solve chemical and biological problems is quite appealing, but the practical use of many of the appealing features of QM in in silico drug design applications is still to be realized in large part because of computational limitations. In recent years it has become clear that classical potential functions are being pushed to their limits and as many pitfalls of using them are coming to light, one is tempted to explore the use of QM procedures. This is a somewhat naïve view, however, because one of the main observations of a large body of computational work has shown that sampling of relevant conformational states can be as important as providing an accurate representation of an inter-or intramolecular interaction. Hence, even as QM becomes a routine tool used to calculate the energy of individual states of a biological system, one still faces the daunting task of sampling relevant conformational space, which, in our view, will for the near term be largely confined to classical models.

Since the mid-2000s there have been significant advances with respect to use of QM in all aspects of drug design.[1,2] This has in part been fueled by the extraordinary increase in computational power and the plummeting cost of CPU time and storage space, which has in turn sped up development and validation of more sophisticated algorithms for calculating wave functions of macromolecular systems. Moreover, there have been equally impressive improvements in algorithms and software that allow researchers to address large-scale biological questions using QM models. The following sections highlight the evolving role played by QM in all aspects of in silico drug design and describe what, in our view, are significant recent advances. The focus of this review is on the use of QM in drug design, but QM has found broad application, for example, in the study of enzyme catalysis. The latter is not discussed here, but the interested reader is directed to many of the recent reviews on QM studies of enzyme catalysis.[3,4]

The use of QM in in silico drug design can be divided into two broad categories: receptor- or structure-based and ligand-based methods (see Figure 8.1). Structure-based drug design (SBDD) methods involve the explicit treatment of the receptor as well as its associated ligands and include scoring protein/ligand poses using QM or quantum mechanics/molecular mechanics (QM/MM) methods, homology modeling of the receptor (prior to docking studies, for example), and energy decomposition methods like COMBINE that is based on a quantitative structure/activity relationship (QSAR) of pairwise interaction energies between a receptor and a series of ligand. SBDD requires either an x-ray or nuclear magnetic resonance (NMR) structure of the ligand in complex with the receptor and this information is shown as inputs in Figure 8.1. An important aspect of the structure determination process is the refinement process, which we show below can be impacted by QM-based methods as well. Although ligand-based drug design (LBDD) methods include various QSAR methods, they rely only on the knowledge of the ligand structure. QSAR can be carried out using 2D, 2.5D (structures generated from 2D), or 3D structures and ligand structures can come from NMR or x-ray studies, but they are generally obtained from purely computational means. However, one has to use 3D structures when using QM because of the need to have an all-atom description of the nuclei and associated electrons.

QUANTUM MECHANICS IN X-RAY AND NMR REFINEMENT

X-ray refinement of protein/ligand complexes

Three-dimensional structural information about therapeutic targets and their bound substrates and inhibitors is vitally important to structure-based drug design. To date the majority of this information has been supplied by x-ray crystallography, which captures static snapshots of the protein/inhibitor complexes and can be used to make hypotheses about the interactions that are relevant to the observed binding affinity. Spurred by recent advances in protein