APPLICATIONS OF QUANTUM MECHANICS IN DRUG DESIGN-

- A Brief Review

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ABSTRACT
The pharmaceutical industry is progressively operating in an era where development costs are constantly under pressure, higher percentages of drugs are demanded, and drug discovery process is a trial-and-error run. The application of quantum mechanical (QM) methods in drug discovery is becoming increasingly popular. This is a consequence of improvements in computing hardware, which have led to advances in QM-algorithm development and new applications of QM methods. The first-principles nature of quantum mechanics requires no implicit parameterization, and therefore should allow for the calculation of highly accurate molecular geometries and properties. However, in reality this level of accuracy needs to be balanced with the high computational expense of precise calculations as well as the rigorous pace of drug-discovery research. As a result, a number of approximations are required, resulting in numerous methodological developments in QM. This has spurred the development of QM methods for many computer-aided drug-discovery problems, such as describing molecular interactions, providing estimates of binding affinities, determining ligand energies, refining molecular geometries, scoring of docked protein–ligand poses, describing molecular similarity, and deriving descriptors for quantitative structure–activity relationships. This article shows importance of concept and applications of quantum mechanics in drug design and pharmaceutical field.
Key word: Quantum Mechanics (QM), Computer Aided Drug Design (CADD), QSAR.

Introduction:

Drug discovery plays an important role in the growth of any pharmaceutical company and society, as newer and safer drugs are launched in the market with the sole objective of improving the therapeutic value and safety of drugs. The pharmaceutical industry has consistently shown that it can discover and develop innovative medicines for a wide range of diseases.

Quantum mechanics is the branch of mechanics that deals with the mathematical description of motion and interaction of subatomic particles, incorporating the concepts of quantization of energy, wave particle duality, and correspondence principle.

Quantum mechanics is a technique, developed by Erwin Schrodinger (of the university of Zurich) in 1926. It is an important technique for "Drug design". Erwin Schrodinger worked out mathematical expressions to describe the motion of an electron in terms of its energy.Those mathematical expressions are called wave equations, since they are based upon the concept that electrons show properties not only of particles but also of waves.

A wave equation has a series of solutions, called wave functions, each corresponding to a different energy level for the electron. For all but the simplest of systems, doing the mathematics is so time consuming that at present and super high-speed computers will someday change these only solutions can be obtained.

The QM method treats molecules as collections of nuclei and electrons without any reference to "chemical bonds". QM is important in understanding the behaviour of systems at the atomic level. QM methods apply the laws of QM to approximate the wave function and to solve the Schrödinger equation. However, the Schrödinger equation cannot actually be solved for any but a one-electron system (the hydrogen atom), and approximations need to be made. According to QM, an electron bound to an atom cannot possess any arbitrary energy or occupy any position in space.

QM models are the most accurate, but also the most expensive methods in terms of time and computational resources, and are thus applied on small systems. CADD is aimed at improving the development and efficacy of drugs using modern computational tools that are fast and cost-effective compared to conventional methods. A biomolecular system can be simulated using molecular mechanics (MM), QM, or a hybrid method (QM/MM), depending on the research problem to be answered.

Objectives

The application of QM-based approaches in guiding SBDD is not new. QM has featured in some medicinally relevant chemistry calculations in providing informative descriptors for QSAR and 3-D conformation for ligands. QM methods offer the ability to provide an accurate representation of ligands and proteins where MM parameterization struggles. QM approaches hold promise in addressing pharmacological problems on the time scale demanded by drug-discovery research. After ups and downs in the perception of CADD and perhaps some overhyping of its promises in drug development, it could be said that CADD is becoming a routinely used component of drug discovery.

The use of QM and QM-MM approaches in computation of protein–ligand binding affinities has met with mixed success. However, the QM-MM approach appears to be of most benefit for low-resolution X-ray structures, where an incorrectly assigned ligand structure due to its MM force field is more likely. Studies demonstrate that the use of accurate charges, in many cases, leads to improvement in docking accuracy in a wide range of Protein Data Bank complexes.

QM should be applied to "lead" compounds to provide insight into the free-energy landscape. Most importantly, before embarking on CADD, it is appropriate to evaluate the diversity and demand of accuracy of molecules to be designed in the project.

Finally, QM methods have proved valuable in quantitative analysis of the energetics of ligand deformation on binding.

Methodology:

QM-MM MD

The hybrid QM-MM method is a molecular simulation approach that combines the accuracy of QM to treat the region of the system where the chemical process takes place and the speed of MM to the rest of the system, thus allowing for the study of chemical processes in large systems. This approach has been applied to target proteins, such as human acetylcholinesterase, heme peroxidases, metallo-β-lactamases, α-synuclein, ligase ribozymes, and trypsin.

QM-MM DOCKING

The accuracy of electric charges plays an important role in protein–ligand docking, which is why QM-MM calculations are incorporated into docking procedures. Fixed charges of ligands obtained from force-field parameterization are replaced by QM-MM calculations in the protein–ligand complex, treating only the ligand as the quantum region. This approach has been applied to target proteins, including F-actin, protein kinases, and metalloproteins.

QM-QSAR

QSAR models combined with QM-MM allow the prediction of drug ADMET and give reliable information on how the modification of a compound affects or improves pharmacokinetic/ pharmacological profiles. QM-QSAR has been applied to such targets as ACE and cytochrome P450.

QM-VS

The QM-VS approach provides unprecedented accuracy in structure-based binding-energy calculations that enable application of QM methodologies to noncovalent interactions in systems as large as protein–ligand complexes and conformational ensembles. This method bridges the gap between the high accuracy of QM and high-volume computations (VS) in drug research and has been applied to such targets as HIV1 integrase and butyrylcholinesterase.

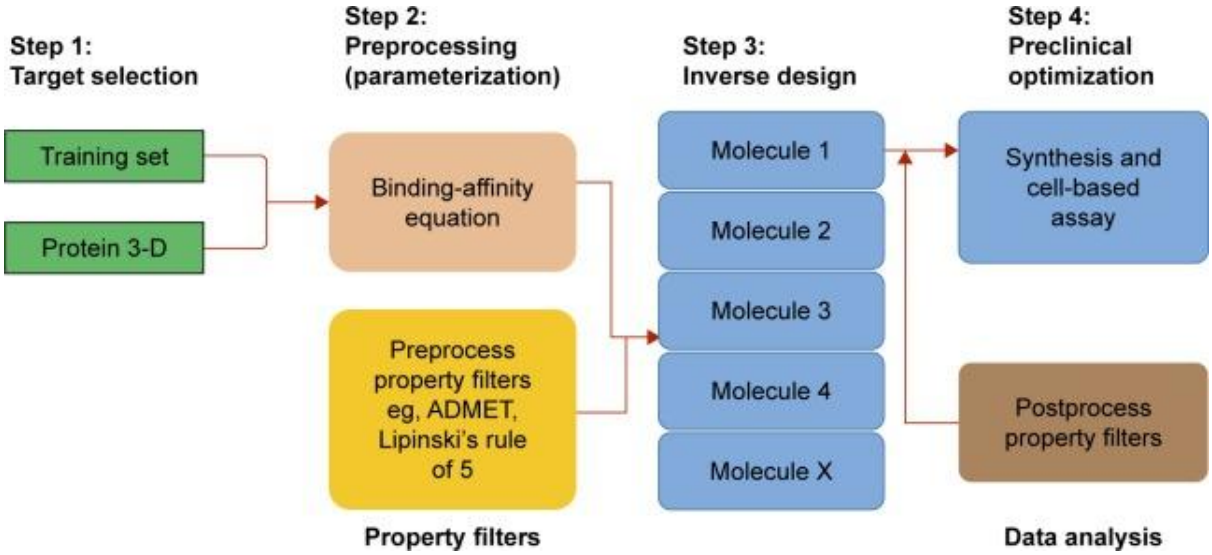

Fig.1 Implementation of QM in Pharmaceutical Companies Drug Design workflow

Recent QM developments in drug discovery:

Tangible advances in the use of QM to solve relevant pharmaceutical problems have been seen in the last decade, eg, the use of the hybrid QM-MM approach to determine the free-energy landscape of the enzymatic reaction mechanism.

The next step in the evolution of drug discovery is the routine use of QM in all levels of in silico Drug Design. Silico Based Drug Design is an important factor in the drug-discovery process, and designs more potent molecules with few alterations made, ie, derivatives of "lead" molecules.

In silico tools can be used to design molecules to investigate existing protein–ligand interactions, as well as explore the active site for any supplementary hydrophilic or hydrophobic interactions that can increase binding affinity. The use of in silico tools allows the testing of a theory in a short time frame, using high-throughput empirical methods.
The in-silico approach is fast and environmentally friendly, but it does not replace experimentation. Regardless, failures encountered in the pharmaceutical industry at the drug-discovery stage can be attributed to a number of factors that are not limited to wrong force-field parameters, especially for metals, disregard for protein flexibility or domain of applicability, or nonrigorous validation of the QSAR model.
QM, a method used to replicate an experimental work accurately, proffers a potential solution to the failures mentioned. Increasingly, QM-MM methods are being applied to enzymes that are drug targets, often with the aim of providing information for DD. Examples include the HIV1-replication enzymes: reverse transcriptase, protease, and integrase. The reaction mechanisms of these enzymes have been studied using the QM-MM approach. Other examples are G-protein-coupled receptors,
5-HT_4 receptors, design and evaluation of a novel class of FKBP12 ligands, and novel inhibitors of human DHFR.
Another development in DD research is the hybrid QM-MM method, developed to improve the accuracy of biomolecular simulations, QM docking, QM virtual screening, and QM-QSAR

Significance:
The application of QM-based approaches in guiding SBDD is not new. QM has featured in some medicinally relevant chemistry calculations in providing informative descriptors for QSAR and 3-D conformation for ligands. QM methods offer the ability to provide an accurate representation of ligands and proteins where MM parameterization struggles. QM approaches hold promise in addressing pharmacological problems on the time scale demanded by drug-discovery research. After ups and downs in the perception of CADD and perhaps some overhyping of its promises in drug development, it could be said that CADD is becoming a routinely used component of drug discovery.
Currently, sophisticated CADD tools are typically applied by modeling experts, but are increasingly spreading to the desktops of medicinal chemists as well. Ligand poses predicted from docking to receptors, such as metalloproteins, have been shown to resemble experiments more closely when partial charges are derived from QM or QM-MM calculations. The use of QM and QM-MM approaches in computation of protein–ligand binding affinities has met with mixed success. However, the QM-MM approach appears to be of most benefit for low-resolution X-ray structures, where an incorrectly assigned ligand structure due to its MM force field is more likely. Studies demonstrate that the use of accurate charges, in many cases, leads to improvement in docking accuracy in a wide range of Protein Data Bank complexes. The principal uncertainty at this point is whether this improved performance in docking can be noticed in other in silico methods.

Conclusion:
In this review, we have discussed how the implementation of QM-based methods could help the drug-discovery and DD process in the pharmaceutical industry. This review outlines the major roles played by QM in the DD workflow and its importance in the drug-discovery process to avoid “dead-end” lead compounds. This method could have strong impact in future drug development, because of the endless demand for new drugs and the short time frame pharmaceutical companies have in developing them. Pharmaceutical companies have to reach a compromise between accuracy and productivity by applying QM in their research. The selection of the most appropriate method (MM, QM, or QM-MM) during drug development is of extreme importance. QM should be applied to “lead” compounds to provide insight into the free-energy landscape. Most importantly, before embarking on CADD, it is appropriate to evaluate the diversity and demand of accuracy of molecules to be designed in the project, which in turn dictates the most appropriate approach to select. It is also possible to reparameterize approximate methods in order to improve the accuracy of results in specific reactions that require numerous energy evaluations. A number of studies have sought to incorporate QM and QM-MM into their approaches for calculating ligand–receptor binding affinities. These approaches show promising results, but require further development to be broadly applicable. Finally, QM methods have proved valuable in quantitative analysis of the energetics of ligand deformation on binding. Although computation of binding energies remain a challenging and evolving area, current QM approaches could offer detailed information on the nature and relative strengths of complex active-site interaction, which is valuable in molecular design. It is likely that QM will become a more prominent tool in the repertoire of the computational medicinal chemist. Therefore, modern QM approaches will play a more direct role in informing and streamlining the drug-discovery process. The insight gained from this review could serve as a cornerstone for medicinal chemists, industry R&D and clinicians. This could provide better understanding of the in silico tools in drug design and development with improved ADMET, pharmacokinetics and the timely assessment of property profiles.

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