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Computer-aided drug design, quantum-mechanical methods for biological problems

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Abstract

Quantum chemistry enables to study systems with chemical accuracy (<1 kcal/mol from experiment) but is restricted to a handful of atoms due to its computational expense. This has led to ongoing interest to optimize and simplify these methods while retaining accuracy. Implementing quantum mechanical (QM) methods on modern hardware such as multiple-GPUs is one example of how the field is optimizing performance. Multiscale approaches like the so-called QM/molecular mechanical method are gaining popularity in drug discovery because they focus the application of QM methods on the region of choice (*e.g.*, the binding site), while using efficient MM models to represent less relevant areas. The creation of simplified QM methods is another example, including the use of machine learning to create ultra-fast and accurate QM models. Herein, we summarize recent advancements in the development of optimized QM methods that enhance our ability to use these methods in computer aided drug discovery.

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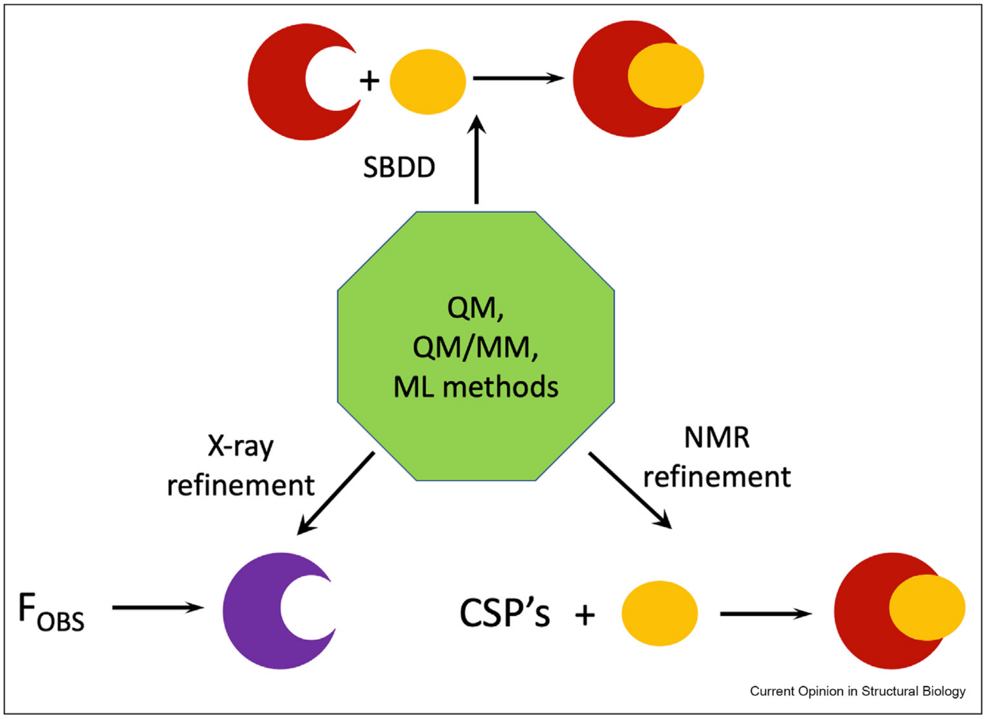
Introduction

The use of QM in computer aided drug design [1] (CADD) has been evolving over the past several decades [2,3]. The early focus in quantum mechanics (QM) was on small molecules due to the computational expense, but with a range of algorithmic and computer hardware innovations the ability to realistically use QM in CADD has emerged. In what follows we will summarize relevant advances in the past couple of years, but for those interested in digging deeper into the field they could do no worse than consulting a recent book on QM in Drug Discovery, which provides a good overview of the field with contributed chapters covering QM methods, protocols, and applications [4]. Here, we will review recent developments in QM methods, hybrid quantum mechanical/molecular mechanical (QM/MM) methods, and newly emerging quantum machine learning (QML) methods of relevance to CADD (Scheme 1).

Advances in QM methods for structure-based drug design

QM methods have had a long tradition in CADD campaigns and continue to have impact in the form of tools/workflows based on QM methods and novel computational implementations of traditional quantum chemical (QC) methods. Among the recent QC method developments, extended tight binding methods developed by Grimme et al. [5] are particularly interesting. Their most recent method, GFN2-xTB, which is based on a revised version of tight binding and on the D4 dispersion correction, has become popular due to its applicability across the periodic table in combination with good accuracy and low-computational cost. Several workflows centered around GFN2-xTB and GFNFF (a partially polarizable forcefield) have appeared recently [6–9]. Meanwhile, traditional semi-empirical methods, Hartree-Fock (HF), and density functional theory (DFT) methods with improved exchange correlation functionals continue to be useful in various branches of CADD, while approaches using highly accurate correlated wave function methods also start to appear. Useful benchmark datasets consisting of 547 protein fragment interaction energies (PLF547) and 15 active site-ligand models (PLA15) were established and used to assess the accuracy of several semi-empirical QM methods, demonstrating that PM6 and DFTB3 can achieve results nearly on par with dispersion corrected DFT when

Scheme 1



Diverse use of QM, QM/MM and ML methods in CADD applications, including structure-based drug design (SBDD), X-ray refinement based on differences between computed and observed structure factors (F_{OBS}), and NMR refinement using differences in chemical shifts of free and bound ligands (chemical shift perturbations, CSP's).

combined with noncovalent dispersion and hydrogen bonding corrections [10]. An example for state-of-the-art *ab initio* methods is the linear scaling domain-based local pair natural orbital coupled cluster method, DLPNO-CCSD(T), which was recently applied to quantify ligand—residue interactions in nicotinic acetylcholine receptor agonist binding through a local energy decomposition analysis [11]. While computationally tractable, DLPNO-CCSD(T) is still computationally demanding, and such highly accurate calculations thus remain limited to single point energy calculations of moderately sized cluster models for the foreseeable future.

In the area of conformer generation, Udvarhely et al. [12] reported the ReSCoSS workflow for generating conformers of druglike molecules in solution. In this semiautomated workflow, the initial conformer generation is performed using traditional methods, but the subsequent ranking of conformers based on the relative free energies uses geometry optimizations using the DFT-D method with the COSMO-RS solvent model. Meanwhile, Grimme's group has reported on the CREST tool [6], where the sampling in conformational space is performed using an iterative procedure and the subsequent energy calculation is performed using the GFN2-xTB method. This tool has been shown to provide reasonable conformers with a sufficient accuracy at a lower computational cost [13]. A related software tool has been reported that is aimed at generating torsional conformers of small acyclic molecules [14]. In this approach, the torsional space is explored based on chemical knowledge and a random search and geometry optimizations and Hessian calculations are carried out at a low (usually HF/3-21G) and high level of theory (M08HX/MG3S).

High-throughput docking is one of the most widely used tools in drug lead discovery, holding the potential for triaging potential drug candidates much faster and cheaper than experimentally. In this context, Cavasotto and Aucar have introduced a PM7 based scoring function [15]. Using enrichment factors computed for a set of 10 proteins representing different families and binding site characteristics, the authors reported that their function outperforms a traditional docking method. More recently, full DFT calculations were employed to successfully rank order a scaffold-diverse set of ligands to a SARS-CoV-2 main protease (Mpro) model with nearly 3000 atoms based on absolute ligand binding energies [16]. DFT calculations for such large models are significantly more expensive than semi-empirical scoring functions, however, this work demonstrates the practical possibility to employ more rigorous and large-scale QM approaches with reasonable turnaround times where required in the drug discovery pipeline.

In the area of pKa prediction, new QM based workflows have been reported by Haslak et al. and the Grimme group [7,17]. The former, which exclusively focuses on carboxylic acids, is based on a linear relationship between computed atomic charges of the anionic carboxylic fragment and experimental pKa values. In contrast, Grimme's is a widely applicable protocol based on a new cubic free energy relationship equation. In the area of C13 and proton NMR spectra prediction, MOSS-DFT for organic molecules in solution, and the MIM2-NMR workflow for large biomolecules have been reported [18,19]. Das and co-workers have reported a QM based NMR [20] and collisional cross section (CCS) workflow [21] for metabolites. A new hybrid density functional aimed at C13 chemical shift prediction has also been introduced [22]. This functional called xOPBE, was constructed by mixing HF exchange into the previously reported OPBE functional. The authors report that the predicted C13 chemical shifts using this functional are more accurate than its parent functional. Among other new tools/workflows, Grimme's group incorporated collision-induced dissociation spectra calculations into their QCEIMS software tool [8]. Another significant development from the same group is a new workflow to compute the optical rotation of organic molecules in solution [9].

Among the recent work related to dipole moment calculation, Zapata and McKemmish studied the accuracy and performance of different basis sets using different quantum chemical methods and documented a few useful recommendations [23]. The authors used a dataset consisting of over a hundred small molecules containing second and third row elements. They reported that DFT calculations with a hybrid functional such as ωB97X−V or SOGGA11-X and augmented double zeta basis sets from Jensen (aug-pc-1 or augpcseg-1) and Dunning (aug-cc-pvDZ) families can provide accurate dipole moments at an affordable computational cost. Furthermore, the authors concluded that single zeta quality and Pople style basis sets are unsuitable for dipole moment calculation.

There has been a number of recent efforts to increase the performance of traditional quantum chemistry methods. This mainly includes implementing algorithms to harness the power of new computer architectures, particularly GPUs. Among these, SCF implementation by Gordon group [24], XC quadrature scheme reported by NWChemX group [25] and work related to the QUICK code in the AMBERtools package are notable [26,27]. Finally, it is important to highlight that semi-empirical methods, particularly xTB methods, are becoming increasingly popular. Given the fast evolution of computer hardware and the pace of method development, it is likely that these methods and QML potentials will either replace classical force fields (FFs) in drug development workflows or will be used interoperably with *ab inito* QM calculation, QML potentials and FFs.

Multiscale QM/MM models

Multiscale simulation methods divide a large molecular system into different regions that are modeled at appropriate levels of theory to focus the computational effort on regions where it is required. Of particular interest are QM/MM approaches that embed a QM region into a molecular mechanics (MM) description of the environment, opening the door for simulations of entire proteins in their native environment without making gross approximations. A fairly recent editorial and collection of articles discuss developments and applications of QM/MM approaches with a focus on biomolecular systems [28] and a recent perspective highlights current developments and challenges in the field [29]. QM/MM approaches are often employed to investigate enzymatic reaction mechanisms and the interested reader is pointed to recent reviews [30,31]. In the context of CADD, an understanding of enzymatic reaction mechanisms enables the design of scaffolds based on transition state analogs for the development of enzyme inhibitors with improved affinity and specificity if enzymes are known as therapeutic targets. QM/MM methods are also successfully employed in X-ray crystal structure refinement. Recent work employed a PM6 semi-empirical Hamiltonian in combination with the AMBER force field for the protein environment to the set of structures from the Community Structure Activity Resource data set and demonstrated improved protein-ligand geometries in comparison to conventional refinement methods [32].

Due to the computational cost of *ab initio* and DFT methods, QM/MM studies of reaction mechanism are often restricted to geometry optimizations of reactant, product, and transition states or reaction paths while QM/MM molecular dynamics (MD) simulations often employ semi-empirical QM methods. However, even full scale DFT based MD simulations of entire small proteins have become feasible exploiting the latest GPU accelerators, although these are still limited to small basis sets and short time scales on the order of 10 ps [33]. A recent publication on the other hand computed the potential of mean force (PMF) along predetermined reaction paths of enzymatic reactions from biased QM/MM MD simulations with the dispersion corrected hybrid exchange-correlation functional B3LYP-D3 and a relatively large aug-cc-pVDZ basis set [34]. The development of widely available and open-source implementations such as the efficient GPU accelerated QUICK code in AmberTools [27] mentioned above hold the promise to make such investigations routine.

A challenge that any practitioner of QM/MM approaches faces is the appropriate selection of the QM region. A promising approach that aims to alleviate this burden by automating the construction of QM/MM models has recently presented [35]. In this approach the size and composition of the QM region are evaluated in an automated manner such that the hybrid model describes the atomic forces in the center of the QM region accurately. Furthermore, a good FF potential to describe the MM region must be chosen. For biomolecular simulations there are a range of well-established and highly successful pairwise additive force fields with fixed point charges that are readily available. In some cases, however, it may be important to explicitly account for electronic polarization in the MM region. Progress has been made in developing QM/MM methods and software implementations towards this end using different methods to represent polarization, for example polarizable point dipoles [36−38]. Whether these methods will become useful for CADD applications will depend on further improvements of the underlying polarizable FFs and wider availability in user-friendly software packages.

Another aspect that is of critical importance for QM/MM simulations in condensed phase under periodic boundary conditions (PBC), is the treatment of long-range electrostatic interactions between the QM and MM regions. It is common practice to truncate electrostatics beyond a cutoff distance in *ab initio* and DFT based QM/MM simulations, thus introducing uncontrolled errors into the simulation. A notable method that properly accounts for long-range electrostatics is the ambient potential composite Ewald method that performs a direct interaction of the QM charge density both with the real space and reciprocal space electrostatic potential, which was shown to remedy numerical instabilities and artifacts in DFT based QM/MM simulations [39]. An alternative approach that was recently developed projects the long-range electrostatic potential in form of augmentary charges onto MM atoms within the cutoff region and is applicable both to large finite clusters and PBC simulations [40]. With these approaches rigorous QM/MM simulations with bounded errors are now possible.

Finally, it is worth to mention recent developments in QM “bookending” methods, which are commonly known as reference potential methods which were originally pioneered 30 years ago [41,42]. These methods enable highly efficient QM/MM free energy simulations via an indirect route using free energy perturbation, thermodynamic integration, or employing Bennett’s acceptance ratio (BAR). The trick of bookending is to invoke a thermodynamic cycle in which the bulk of the free energy simulation, for instance an alchemical transformation, is performed using a series of computationally cheap reference potentials, while only the end points (bookends so to say) need to be sampled with the expensive QM/MM potential [43]. This opens the door to compute solvation free energies and ligand binding free energies with accurate QM/MM methods that otherwise would be computationally too demanding. In a similar vein, mapping to reference potentials has been developed for the targeted free energy perturbation approach (TFEP) using neural networks, resulting in an approach that requires only a small number of single point calculations with the expensive target potential, thus improving the accuracy and convergence of absolute and relative free energies and free energy surfaces [44].

Emergence of quantum machine learning models

The use of ML and NN models to develop potential energy functions of relevance to chemistry have been undergoing rapid development. Reflecting the interest in this field several reviews have appeared in 2021 for those interested in further details of the advances of the last decade [45,46]. An exciting area for CADD is to take large databases of QM derived information and then create a QML model that reproduces this data set with the expectation that the resultant model would be extensible to molecules not represented by the training data set [45]. In CADD applications these *ab* initio ML potential energy functions should be superior to MM potentials, but have a similar computational cost. However, while many of the potentials described aim at reproducing *ab initio* or DFT data for small molecules the use of these models in condensed phase simulation are just emerging. In particular, interoperability or the ability to mix and match ML force field, *ab initio*, *etc*. potentials is an area ripe for exploitation and validation. Combined together these models can be used to mitigate deficiencies in each other: for example, force fields aren’t great at conformational energies, but QM based ML models can improve this situation. Overall, the use of QML potentials in drug design has the potential to greatly improve computed binding or relative free energies using modern free energy methods [47]. Many advances along these lines will be seen in the coming years and could speed up free energy calculations while improving their accuracy.

The evolution of QML potentials is readily described by a series of generations [48]. In the first generation rudimentary potentials that can be used to model simple systems were described [49]. To overcome this deficiency and to generate models that can be used in 3-dimensional space second generation potentials were developed. Examples of these so-called second generation models like ANI [50−55] or AP-net [56] among many others [45] are based off of high-dimensional neural network potentials (HDNNPs) described by Behler and Parrinello [57], which while effective to study large systems lack long-range electrostatics and dispersion interactions thereby reducing their effectiveness to model intermolecular interactions in particular in inhomogeneous systems [48,56,58]. A major drawback of many of these models is the lack of atomic charges and the use of fixed charges in the third generation addressed these issues [59–61]. Finally, fourth generation (4G) models have begun to appear combining many of the earlier generation models with atomic charges determined on the fly using, for example, charge equilibration (Ceq) [62] models [48,60,63]. In these 4G models the intramolecular degrees of freedom are modeled using accurate 2G-HDNNP coupled with a charge equilibration model that updates the charges on the fly allowing the model to respond to the local environment and effectively deal with multiple charge states and long-range charge transfer. Ko et al. [48] reported an initial attempt at a 4G model and showed that it had the proper behavior on a series of test systems. These 4G models have the potential to have an impact on CADD because they have all the required features: an accurate intermolecular potential combined with an accounting for polarization and charge transfer. Combining 4G models with classical force fields incorporating long-range electrostatic interactions could usher in a new generation of accurate relative free energy calculations. While the field is not quite there yet it is a very exciting avenue to pursue that will challenge standard paradigms where many potentials can be layered on top of one another to create hybrid models to solve problems in CADD.

Applications of QML potentials, in the context of chemical reactivity, have been reported in the past year and we highlight just a few here. Böselt et al. [64], Zeng et al. [65], Gastegger et al. [66] and Pan and coworkers [67], building on earlier work of the Yang lab [68–70], have reported the use of QML potentials in combination with QM/MM methods. The studies of Böselt et al. and Pan and co-workers use Δ-machine learning (Δ-ML) approaches [71] where the differences between a lower level of QM theory *versus* that of a higher level of theory is learned for a specific reaction and then applied to correct the cheaper QM models to achieve high quality results. The work of Zeng et al. [65] introduces range-corrections to the ML potentials to also improve short-range QM/MM interactions affecting the MM atoms within a relevant cutoff of the QM region. These application studies are interesting and point to the need for improvements in the treatment of long-range interactions and in building standalone 4G potentials that can deliver high-quality results without resorting to Δ-ML approaches. That said these latter models may ultimately prove to be the best way forward. While these studies are of interest in studying chemical reactivity how these methods can be applied to drug discovery applications will need to be more fully fleshed out in the coming years.

Conclusions and outlook

QM has been a key field in theoretical and computational chemistry for decades and will continue to be of importance going forward since it is the only method available in the computational armamentarium that guarantees to asymptotically reach the correct answer via the variational principle. That said, improvement in the performance of traditional QM methods by exploiting modern hardware and novel algorithms continues to be an area worth pursuing. The development of new QM/MM methods that take advantage of the advancements has already begun to appear in CADD applications. The ML/AI field is advancing rapidly to provide the CADD field with fast and accurate potentials that directly mimic QM models that can be applied to a myriad of problems in CADD. The most exciting aspect of the use of QM in CADD has been the emergence of many new directions that all promise to deliver chemical accuracy to several aspects of CADD in the coming years.

CRediT author statement

Madushanka Manathunga: Writing - Original Draft, Writing - Review & Editing, **Andreas W. Götz**: Writing - Original Draft, Writing - Review & Editing, Funding acquisition, **Kenneth M. Merz, Jr.**: Conceptualization, Writing - Original Draft, Writing - Review & Editing, Funding acquisition.

Conflict of interest statement

Nothing to declare

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