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Quantum mechanical-based strategies in drug discovery: Finding the pace to new challenges in drug design

Tiziana Ginex[1], Javier Vázquez[1,2,3], Carolina Estarellas[2,4] and F. Javier Luque[2,3,4]

Abstract

The expansion of the chemical space to tangible libraries containing billions of synthesizable molecules opens exciting opportunities for drug discovery, but also challenges the power of computer-aided drug design to prioritize the best candidates. This directly hits quantum mechanics (QM) methods, which provide chemically accurate properties, but subject to small-sized systems. Preserving accuracy while optimizing the computational cost is at the heart of many efforts to develop high-quality, efficient QM-based strategies, reflected in refined algorithms and computational approaches. The design of QM-tailored physics-based force fields and the coupling of QM with machine learning, in conjunction with the computing performance of supercomputing resources, will enhance the ability to use these methods in drug discovery. The challenge is formidable, but we will undoubtedly see impressive advances that will define a new era.

Addresses

[1] Pharmacelera, Parc Científic de Barcelona (PCB), Baldiri Reixac 4-8, 08028 Barcelona, Spain
[2] Departament de Nutrició, Ciències de l'Alimentació i Gastronomia, Universitat de Barcelona, Institut de Biomedicina (IBUB), 08921 Santa Coloma de Gramenet, Spain
[3] Institut de Biomedicina (IBUB), 08921 Santa Coloma de Gramenet, Spain
[4] Institut de Química Teòrica i Computacional (IQTCUB), 08921 Santa Coloma de Gramenet, Spain

Corresponding author: Luque, F. Javier (fjluque@ub.edu)

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Introduction

Electronic structure methods provide a robust, versatile framework to explore chemical reactivity in biomolecular systems. The quantum mechanical (QM) cluster and the multiscale quantum mechanics/molecular mechanics (QM/MM) approaches have disclosed the factors that underlie the catalytic efficiency of enzymes [1–4]. Beyond the reaction mechanisms, applications involve a variety of problems, such as the design of covalent inhibitors, the enzymatic and light-induced activation of prodrugs, and the engineering of enzymes [5,6].

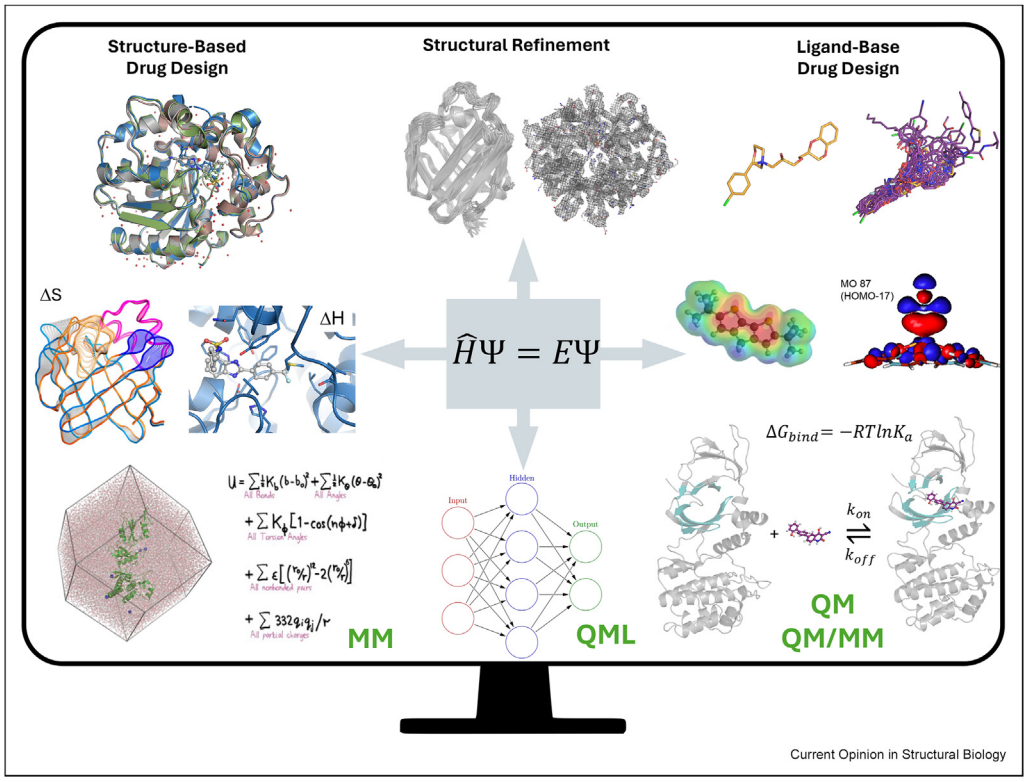
QM methods have also permeated drug discovery over the past decades. While the computational cost limited the early application to small molecules, the development of novel algorithms, including the combination with machine learning (ML), and the advances in computer performance enabled the blooming of QM-based strategies in structure-based drug design. The reader is addressed to the review by Manathunga et al. [7] for a description of methodological refinements in optimized QM/MM methods and the emergence of quantum machine learning (QML). Similarly, a critical analysis of the merits of QM/MM techniques relative to traditional computer-aided drug design methods has been recently reported [8].

Our aim here is to summarize relevant advances in the past couple of years in the application of QM-based methods in areas related to the characterization of the bioactive species, the structure-guided *hit*-to-*lead* optimization, and the identification of molecular features of bioactivity (Figure 1).

Conformational sampling of ligands

Assessment of torsional preferences of small molecules and identification of low-energy rotamers are valuable to characterize the physicochemical properties of drug-like compounds and rationalize their activities [9]. Likewise, generation of accessible conformer ensembles permits to identify the bioactive species, to define pharmacophore models and assist the choice of templates in 3D ligand-based screenings [10,11]. Furthermore, the analysis of conformer populations in distinct solvent environments is relevant to predict the solubility and permeability of 'chameleonic' compounds categorized beyond the rule-of-5 [12].

Figure 1



Schematic representation of the permeation of QM-based strategies in computer-aided drug design promoted by the development of QM semiempirical and multiscale QM/MM methods, QM-tailored physics-based force fields, and the integration between QM and ML techniques.

Despite the efforts in force field refinements, the accuracy of MM methods is still challenged by the functional form of the torsional energy and incomplete parameterization [13]. This limits the suitability of MM methods to explore the conformational space of compounds, especially with novel chemical motifs [14,15]. Nevertheless, the development of high-quality force fields with a broad coverage of chemical motifs is an active area of research, as noted in the development of the XFF force field, which was trained with a large set of functional fragments and QM energies [16]. In this context, QM methods emerge as a suitable strategy to predict the conformational preferences of (bio)organic molecules. This is illustrated by the systematic conformational analysis performed by Rulisek et al. for di- and tripeptides by combining DFT and implicit solvation calculations to discern the propensities to adopt secondary structural elements in proteins [17,18]. Furthermore, an additional example is the characterization by means of QM/MM calculations of the atropisomerism of PI3Kδ inhibitors [19].

A key achievement has been the development of dedicated software with greater computational efficiency to explore the conformational sampling of ligands. This is exemplified with the open-source conformer-rotamer ensemble sampling (CREST) program, which enables the automated conformer exploration of drug-like molecules at the extended tight-binding (xTB) level, including calculation of configurational entropy and solvation effects [20,21]. Boz and Stein used this approach to examine the impact of conformational flexibility in the binding of ligands to macrocyclic synthetic receptors [22]. The binding-free energy calculated using the automated QM sampling with CREST led to a mean error of ∼3 kcal/mol relative to the experimental data. The efficacy is supported by the comparison with the results obtained from meta-GGA PW6B95 calculations with the COSMO-RS solvation model at TPSS-D3(COSMO) optimized geometries, which showed a deviation of ∼2 kcal/mol.

Endeavors have also been conducted to implement ML tools trained with accurate QM data. In this regard, Liu et al. [23] developed the Python-based Auto3D package for generating the stereoisomeric conformational space of small compounds. Auto3D is based on the ANI-2xt neural network model, which was trained to mimic the energy and force output from DFT calculations using a tautomer-rich dataset. Likewise, TorsionNet illustrates the efforts to develop a fast and accurate ML-based assessment of small-molecule dihedral energetics [24].

It is a deep neural network model designed to predict torsion energy profiles with QM-level accuracy. To this end, a dataset of 1.2 million DFT energies were compiled for torsional scans of chemical fragments. They were used in the training of the model, leading to a root-mean square deviation of 1.3 kcal/mol relative to the DFT energies. TorsionNet is expected to capture efficiently the high-dimensional potential energy surface of flexible molecules, although the performance may degrade for molecules containing novel chemistries that are not adequately represented in the training set. On the other hand, a distinct strategy to estimate the internal energy of molecules is the QDπ model [25]. This method combines a QM description that exploits a fast third-order self-consistent density-functional tight-binding (DFTB3/3OB) with a deep-learning potential trained against reference data computed at the ωB97X/6-31G* level. Besides providing a reasonable description of the conformational potential energy landscape, this method model is also suitable for describing changes in the charge, protonation, and spin states in a size-consistent manner.

Finally, Das et al. [26] have reported an *ab initio* workflow for the prediction of collisional cross section (CCS) data obtained from ion mobility-mass spectrometry studies of small molecules. The workflow incrementally refines generated structures by combining MM, deep learning potentials, conformational clustering and QM calculations. Recently, Das et al. [27] have compared the conformational space generated by Auto3D, CREST and force field-based approaches (Ballon and ETKDG). While Auto3D was found to exhibit a better performance in global minima identification, CREST showed higher accuracy in predicting the CCS data.

Refinement of the experimental binding pose

The definition of the ligand pose in the binding pocket is crucial for the success of medicinal chemistry studies. In this regard, QM and QM/MM are well suited to assist the ligand's geometry refinement under the electrostatic field created from the protein environment, improving the description of internal parameters and intermolecular distances. For the sake of brevity, we limit ourselves to cite as illustrative examples the identification of the productive orientation of the *O*-arylcarbamate URB524 inhibitor of fatty acid amide hydrolase, as QM/MM computations enabled the discrimination between two putative binding poses [28], and the elucidation of the mechanism leading to the formation of the covalent adduct of dipeptidyl nitriles with cruzain [29].

The usage of QM and QM/MM methods as a powerful strategy to assist the structure refinement through the comparison of experimental and calculated properties, thus enabling the distinction between native poses from decoys, has been recently exploited in distinct studies.

Conventional crystallographic refinement of protein–ligand complexes uses stereochemistry restraints coupled with energy functional to ensure the correct geometry of the ligand within the experimental X-ray density. Borbulevych et al. [30] adopted a QM/MM scheme to assist the refinement protocol of the curated set of structures included in the community structure activity resource, paying attention to the correct assignment of tautomer/protomer states. More recently, the Quantum Mechanical Restraints (QMR) procedure has been proposed to optimize the ligand geometry *in situ* during the macromolecular crystallographic structure refinement [31]. Accordingly, the ligand geometry is determined in the binding pocket considering the effect of neighboring protein residues and waters on the local energy minima of the ligand. The refinement of more than 1700 protein–ligand models showed that the QMR-restrained parameters lead to geometries that fit better to the protein environment compared to the use of conventionally generated restraints, providing accurate torsion restraints for flexible ligands.

The automated fragmentation QM/MM (AF-QM/MM) method has been shown to be an efficient platform for protein–ligand binding structure prediction based on NMR data [32]. In this approach the ligand and/or the protein binding pocket are automatically divided into capped fragments for DFT calculations of NMR chemical shifts, including the electrostatic polarization effect from the solvent. The perturbation of the ^{1}H chemical shifts triggered upon ligand binding is then used to complement the docking score. The AF-QM/MM has also been used to develop the empirical HECSP method, which provides a fast, accurate tool to predict the chemical shift perturbation of protein protons induced by ligand binding [33]. Finally, the extension to ligands bound to membrane proteins has recently been studied by Zhang et al. [34], considering the effect of the local environment (cross-protomer interactions, phospholipid composition, and solvent) on the ^{15}N and ^{13}C chemical shifts of retinal bound to the light-driven sodium pump rhodopsin 2.

On the other hand, comparison of the experimental chemical shifts with those computed from the X-ray structure using QM/MM has been valuable to highlight disagreements for parts of the ligand between the two experimental techniques. The discrepancies observed for protons involved in hydrogen bonding interactions support the inadequacy of considering a single structure to represent the solution state of the protein-ligand complex. In this regard, Platzer et al. have shown that QM/MM molecular dynamics ensembles can be used to refine the initial X-ray co-crystal structure, resulting in a

better agreement with experimental ligand chemical shift values [35].

Prediction of binding affinity

One of the largest challenges in drug discovery is the accurate calculation of the binding free energy between ligand and target. Since the binding affinity is a cornerstone in structure-guided drug design, there is continued interest in developing robust, accurate physics-based models for application in drug discovery. Different QM methods have been employed, ranging from semiempirical QM calculations, *via* DFT, to strict coupled-cluster calculations [36].

Cavasotto and Aucar [37] showed that the choice of a QM-based scoring function that combines PM7 calculations for ligand-protein interactions with changes in the solvation and entropy components led to much higher enrichment than a traditional docking method in the high-throughput docking against 10 distinct targets. Recently, Pecina et al. have reported SQM2.20 [38], which is a semiempirical QM-based scoring function that extents the previous SQM/COSMO tool [39]. The SQM2.20 score combines the gas-phase interaction energy determined at the PM6-D3H4X level, the change of solvation free energy upon complex formation, the conformational contribution of the ligand to the binding, the free energy of proton transfer between ligand and buffer, and the loss of ligand conformational entropy upon binding. The score is evaluated on a model of $\sim$2000 atoms, comprising residues within 10 Å around all the overlaid ligands in each target protein, with an average time of $\sim$20 min per protein−ligand complex.

Several alternative strategies have been proposed within the framework of the linear response approximation. By exploiting the '"divide-and-conquer' fragment molecular orbital (FMO) method, SophosQM [40] computes the interaction between ligand and target from the addition of the pairwise interaction energy between ligand and fragments, whereas nonenthalpic components are captured through the octanol/water partition coefficient (logP). Thus, the binding affinity is expressed as a multilinear regression based on the interaction energy and logP, where the coefficients are derived from the fitting to known binding affinities of ligands. The method assumes the preservation of the binding mode for ligands interacting at the same target, excluding the occurrence of large conformational rearrangements in the pocket. The linear fitting of the FMO-determined interaction energy, deformation energy of the ligand, and solvation free energy also underlies the development of FMOScore, which was applied to the lead optimization against Src homology-2-containing protein tyrosine phosphatase 2 [41]. Finally, the QMH-L approach exploits a single target−ligand complex structure pre-optimized at the MM level, taking into account the interfacial water molecules between ligand and target [42]. Then, the binding free energy is estimated combining i) the QM interaction energy between the fragments of the target, ligand and interfacial waters, and ii) a descriptor of the normalized molecular size of the ligand, which was introduced as a measure of the entropic term. The results determined for protein complexes bound to small molecules and peptides support the balance between accuracy, applicability, and computational cost.

QM/MM calculations can also be used to correct the binding free energy determined from classical simulations using the 'so-called' "indirect" approach, in which a QM/MM "correction" is introduced at the classical endpoints of interest. This strategy reduces the computational expensiveness that would require a complete QM/MM free energy simulation and corrects deficiencies of the classical description, provided that there is sufficient configurational overlap between the MM and QM/MM levels of theory. In this regard, a recent study has examined the suitability of force-matching procedures to predict the binding free energy of several narcotics within the SAMPL blind challenge [43].

The expensiveness of QM and QM/MM calculations has stimulated the search of alternative strategies that exploit the development of i) tailored force fields and ii) ML-based methods for predicting the binding affinity of ligands.

The former category is illustrated by the ARROW force field [44], which was conceived to mitigate the deficiencies of standard force fields to provide an accurate description of electrostatic and exchange interactions, non-additivity effects of atomic interactions, and low transferability of parameters. ARROW is an advanced physics-based model that includes multipolar electrostatics and anisotropic polarization, with parameters fitted exclusively to high-level QM data. Indeed, MP2/aug-cc-pVQZ calculations were performed for monomeric model compounds, and MP2/complete basis set were used for dimers with amino acid fragments and water. Furthermore, nonbonded interactions include electrostatic and exchange-repulsion, which are treated via multipolar expansion, dispersion terms, which are described via spherical (C6 and C8) expressions, and many-body effects described with anisotropic-induced dipoles. A refined version of ARROW includes a short-range neural network correction to the intermolecular interaction energy has been recently reported [45].

A distinct strategy to improve the quality of the force field is represented by the work of González et al. [46] and Macaya et al. [47] regarding the implementation of the Minimal Basis Iterative Stockholder method. In this approach the aim is to derive atomic charges and Lennard-Jones parameters from the polarized electron

density of the ligand in conjunction using various configurations of the bound and unbound state.

Rizzi et al. [48] have reported the implementation of the targeted free energy perturbation to calculate the binding free energy at a target high level (QM) of theory from a cheap reference potential (MM). To this end, a neural network is used to train a mapping function that enhances the overlap between target and reference distributions in conjunction with a limited number of QM calculations of energy and gradients. The application to binding free energy of 22 ligands led to close agreement with the benchmark results.

Another example of the QM-guided efforts to develop ML-based methods is the work by Isert et al. [49], where the critical points (CPs) of the electron density are used as a fundamental representation of the intermolecular interactions formed between ligand and protein. Thus, the ML model was trained using the CPs determined at the GFN2-xTB level in conjunction with a linearized Poisson–Boltzmann water model. The results showed a modest predictive performance relative to benchmark methods, which may reflect limitations due to the QM method, the CP-centered representations, and the inability to account for other contributions, such as ligand strain and entropy.

Beyond the binding affinity, it is also worth emphasizing the efforts in predicting the dissociation rate constant (k_{off}) of the ligand, since the residence time of the ligand-target complex is a key parameter to analyze the drug activity [50]. A review of recent progresses in molecular simulation methodologies for the prediction of k_{off} has been reported by Ahmad et al. [51], paying attention to the use of massively parallel DFT-QM/MM calculations, often complemented by ML techniques, to account for electronic polarizability and charge transfer effects in the unbinding kinetics constant. For our purposes here, we limit ourselves to the work by Ojha et al. [52], who implemented QMrebind in the framework of the Simulation Enabled Estimation of Kinetic Rates v.2 (SEEKR2) method, which exploits MD simulations to predict the unbinding kinetics. QMrebind incorporates QM methods into generating system-specific force fields through re-parameterizing ligand partial charges in the bound state. The results obtained for host–guest complexes and Hsp90-inhibitor complexes highlight the potential of the improved force field parameters to enhance the simulation accuracy.

Molecular determinants of bioactivity

Understanding the structural and chemical features that determine the bioactivity profile of a ligand, including both pharmacodynamics and pharmacokinetics, is fundamental to assist the rational design of drug-like candidates.

QM permits to examine the contribution of specific interactions that cannot be properly assessed by MM force fields, such as halogen-bonds [53,54], polarized CH/n, CH/π, and XH/π interactions [55], and peptide amide-π or alkene-π stacking contacts [56,57]. The limitations of MM methods are also reflected in the binding to metal centers [58]. Similarly, QM-derived properties, such as reactivity indexes of covalent inhibitors, have been used in structure-activity relationships studies [59].

Efforts have also been devoted to address the inaccuracies of molecular descriptors, thus complementing classical approaches in similarity-guided, pharmacophore-based and docking screenings [60]. In this context, using similarity-based approaches, COSMO-RS σ-profiles derived from the QM(B3LYP/DNP)/MM-optimized conformation of remdesivir were used in the screening of analogues targeting the SARS-CoV2 RNA-dependent RNA polymerase [61]. Recently, a virtual screening campaign targeting the soluble epoxide hydrolase enzyme showed how 3D-hydrophobic atomic descriptors derived from QM continuum solvation calculations played a major role in the prioritization of the top-ranked compounds in docking screenings [62,63]. On the other hand, QM FMO calculations have been used to identify hotspots at the interface between two interacting proteins, thus disclosing clues for the design of protein-protein modulators [64].

QM cluster GFN2-xTB calculations have also been used to examine the suitability of bioisosteric replacements, which can be used to tune properties related to activity, bioavailability, and metabolism of ligands [65]. Finally, QM-based descriptors derived from COSMO-RS have been used to explore bioisosteric replacements on the passive permeability for a series of protein arginine methyl transferase 5 inhibitors [66]. Interestingly, the results highlighted the hydrogen-bond acceptor propensity as a key parameter to optimize the transport properties of these compounds.

Although ML may be instrumental in many areas of drug design, the current challenge lies in the absence of curated comprehensive collections of data. To alleviate this limitation, the open-access -mechanical properties of drug-like molecules (Q-Mugs) dataset [67] has been developed to include QM (GFN2-xTB) properties of more than 665,000 molecules extracted from the ChEMBL database. In parallel, Merck & Co. proposed QM9-extended [68], a dataset comprising 153,716 compounds commonly found in drug discovery focusing on QM (B3LYP/6-31G(2df,p)) properties for ADME predictions. Similarly, Isert et al. [69] established an *in-house* training set to develop a ML QM-based protocol for predicting the octanol/water partition coefficient. Among the algorithms tested, message passing neural

network model Chemprop [70] emerged as the best model with mean absolute errors of 0.34 log units.

Conclusions

High-throughput screening is the dominant strategy to identify novel small molecules that modulate the biological activity of selected targets [71]. The explosive growth of the available chemical space, which reaches billions of molecules, opens opportunities for finding hits with novel chemical scaffolds, less biased toward *bio-like* molecules, and better fitting to the target binding site [72]. However, this also challenges the capability of computational approaches for prioritizing the best hits, avoiding the occurrence of biasing artifacts in the screening of chemical libraries [73].

In this scenario, the success of QM-based strategies in drug design will be determined by the development in both algorithms and hardware. Current efforts reflect three major tendencies, which involve (i) the development of accurate, but computationally effective semi-empirical methods as well as the calibration of multiscale QM/MM methods, (ii) the redefinition of QM-tailored physics-based force-fields suitably refined to provide an accurate description of the complex network of intermolecular interactions, and (iii) the generation of QM-assisted ML models. Regarding hardware, the advent of novel supercomputing architectures [74,75] and especially quantum computing [76,77], although requiring the implementation of current codes, will pave the way for a significant leap in quantum chemistry simulations. Overall, the flourishing of algorithmic progresses in the past years in conjunction with the enhanced resources provided by novel hardware platforms suggests that we will witness an exciting evolution of quantum chemistry in drug discovery.

Author contributions

All authors contributed to conceptualization, writing - original draft, and writing - review and editing of the final manuscript.

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Declaration of competing interest

TG and JV are employees of Pharmacelera S.L. The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this article.

Data availability

No data was used for the research described in the article.

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