Multiscale modelling: hybrid quantum mechanics/molecular mechanics as an example and some recent developments

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Most of the physical phenomena are multiscale in nature and therefore, to depict it properly one requires multiscale modelling techniques, i.e. physical models that are accurate over multiple length and time scales. The seminal work by Warshel and Levitt marks the beginning of hybrid quantum mechanics/molecular mechanics (QM/MM) method as a successful strategy towards the understanding of chemistry and physics in condensed phases and especially in biological systems. Recently, these methods have been extended to problems such as light–matter interaction, where the QM sub-system is excited from the ground to the excited states. The MM environment provides a field that changes the potential energy landscape of both the ground and excited states in a distinctly different way. In this review, we discuss the general strategy of multiscale modelling with emphasis on hybrid QM/MM and the recent developments in excited state QM/MM methods.

Keywords: Biological systems, hybrid quantum mechanics/molecular mechanics, multiscale.

Multiscale modelling

MANY real-world phenomena are multiscale in nature, i.e. they show complex behaviour that spans over a large range of length and time scales. Length scales can span from few Å in case of bond lengths to a few microns in case of living cell. On the other hand, time scales can range from femtosecond (10^{-15} s) for bond vibrations to milliseconds (10^{-3} s) for protein folding. In most cases, the different scales (microscopic and macroscopic when it is the length scales) might be a continuum of varying scales. The microscopic behaviour in most cases is specific and complex, while the macroscopic behaviour can be defined by more general rules. For example, the flow of traffic or pedestrians in a crowded street. If one tracks the trajectory of individual pedestrians, they have a specific destination and, therefore, they move towards that destination while avoiding the nearest neighbour interactions or collisions. However, when one zooms out and looks at the average pattern of flow it is very similar to fluid dynamics through a constrained space.

Traditionally models have been developed that describe the physics associated with a single time and length scale. However, since the real-world phenomena requires one to span over more than one scale, simulation or modelling techniques have evolved such that they can handle multiple scales in a seamless fashion[1].

Analytical multiscale methods

Analytical multiscale approaches have been developed for quite a few decades now. In this approach, one derives the rules (or phenomenological models) of a macroscale system from that of a microscale model. Renormalization group (RG) is a classic example of such analytical multiscale method[2]. RG has been used to study phase transitions and critical phenomena. The need for renormalization arises when there are two or more different scales (time or length) and there is no clear demarcation between them. RG is a technique to reduce the degrees of freedom by integrating out less important degrees of freedom in a consistent fashion.

Numerical RG technique was developed by Wilson and co-workers to solve the Kondo problem[3]. The idea is easily understood in a 1D or 2D spin block model. Let us say we have a 2D system of atoms (Figure 1) arranged in a lattice and let us assume that only the nearest neighbours interact with each other with a strength J (coupling constant). Now, the Hamiltonian of the system can be

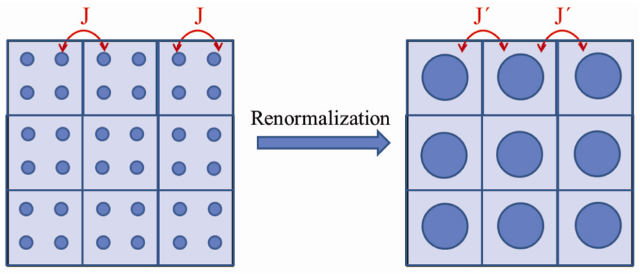

Figure 1. Renormalization group provides the tools to coarse grain interactions and have been successfully used in 2D lattice systems.

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described as a function of J. However, we can divide the system into super-blocks containing 2×2 atoms. Instead of defining the interactions in terms of atoms, we can proceed to define it in terms of these super-blocks of atoms where we have a renormalized coupling constant J'.

Similar ideas have also been used to solve the many-body quantum mechanical wave function, where renormalization is performed using information from the density matrices. The density matrices describe the importance of various electronic configurations and, therefore, can be used as a measure to eliminate less important degrees of freedom. This is called density matrix renormalization group (DMRG) and has been developed for strongly correlated electronic Hamiltonians[4–6].

Hierarchy of physical models

Physical models have been built to deal with numerical solutions in different length and time scales. As mentioned before, traditional modelling approaches focus on one or other time and length scale (Figure 2).

Continuum

Materials are made up of atoms and molecules, but from a length scales significantly larger than inter-atomic distances, it can be considered as continuous, and the dynamics can be defined by fundamental physical laws and differential equations derived from them. Continuum models disregard the atomistic or discrete nature of materials.

Polarizable continuum model (PCM) is a popular continuum model that is used to describe solvation effects[7]. Tomasi and co-workers defined the free energy of solvation as composed of electrostatics, dispersion-repulsion and cavity effects. The solvents do not have any atomistic detail but the overall dielectric constant of the medium provides the basis for electrostatics. The dispersion–repulsion and cavitation energies are derived from the overlapping van der Waals radii of the solute atoms. The various types of PCM models are dielectric PCM (D-PCM)[8], conductor like PCM (C-PCM or COSMO)[9] and other models such as SMx models[10]. The continuum models are computationally very fast but lack specific interactions since they do not have atomistic details.

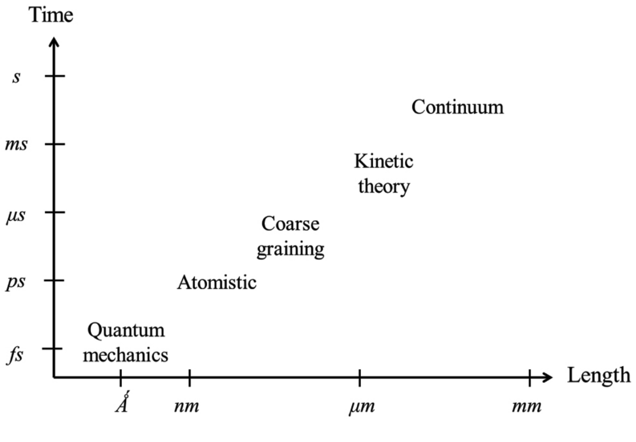

Figure 2. Different physical models that can be used for various time and length scales.

Molecular mechanics

Force field or molecular mechanics are empirical potentials for interactions between atoms in the molecules of the system. This empirical potential, once fitted with respect to either experimental data or more accurate (quantum mechanical) calculations, can be used to study the dynamics of the system. This is the basic principle of classical molecular dynamics (MD), i.e. the force on the system can be written as

$$\vec{F} = -\nabla V(\vec{r}), \qquad (1)$$

where the potential $V(\vec{r})$ is the empirically fitted potential. The motion of the atoms or molecules are derived from the forces using Newton's laws of motion

$$\vec{F} = m\vec{a}, \qquad (2)$$

where m is the mass of the molecule or atom and $\vec{a}$ is the acceleration.

The force field or the fitted potential can be divided into bonded and non-bonded interaction terms

$$V_{\mathrm{MM}} = V_{\mathrm{bonded}} + V_{\mathrm{non\text{-}bonded}}. \qquad (3)$$

Classical MD can be of two broad types depending on the level at which the force fields are computed – atomistic and coarse grain.

Coarse grain MD: The system size and time scales required for understanding some processes precludes the use of full atomistic details, but on the other hand might require more degrees of freedom than a complete continuum description. In such situations, force fields can be developed which do not depend on the position of individual atoms[11,12], but rather depend on groups of atoms. For example, in MARTINI (a popular coarse grain force field)[13], each residue on the backbone of an amino acid is described as a single bead at the centre of mass of the residue. This reduces the number of degrees of freedom significantly from the full atomistic description. These residues or beads interact with each other with bonded and non-bonded interaction energy terms.

Atomistic MD: For a more detailed (accurate) description of the system, one requires a full atomistic description, where the force field depends on the positions of all the atoms in the system. The force field is again divided into bonded and non-bonded interaction terms.

The bonded interactions can be classified into

$$\begin{aligned} V_{\text{bonded}} &= V_{\text{bond}} + V_{\text{angle}} + V_{\text{dihedral}} \\ &= \sum_{\text{bonds}} k_{\text{b}}(r-r_0)^2 + \sum_{\text{angles}} k_a(\theta-\theta_0)^2 \\ &+ \sum_{\text{torsions}} \frac{1}{2} V_n[1+\cos(n\omega-\gamma)], \end{aligned} \tag{4}$$

where the terms V_{bond}, V_{angle} and V_{dihedral} represent the interaction energies between covalently bonded atoms, between orbitals in adjacent bonds, and that due to the twisting of a bond, i.e. bond order. The bond and angle terms are most commonly parametrized as harmonic potentials and the dihedral energy term as a periodic function such as cosine. The non-bonded interactions can be classified as electrostatics and van-der Waals' interactions

$$\begin{aligned} V_{\text{non-bonded}} &= V_{\text{electrostatics}} + V_{\text{vdw}} \\ &= \sum_{i=1}^{N} \sum_{j=i+1}^{N} \left[\frac{q_i q_j}{r_{ij}} + \left(\frac{C_{12,ij}}{r_{ij}^{12}} - \frac{C_{6,ij}}{r_{ij}^{6}} \right) \right], \end{aligned} \tag{5}$$

where q_i and r_{ij} denote the charge on atom i and the distance between ith and jth atoms respectively. The C_6 and C_{12} terms depend on the van der Waals radii of atoms and the strength of van der Waals interaction energy between the non-bonded atoms. Thus, electrostatics forms the long-range interactions while the van der Waals interactions are more short range in nature. Force fields such as AMBER, CHARMM, GROMOS, OPLS, etc. follow this general form of parametrization or small changes thereof. They form the general class of non-polarizable force fields[14].

Quantum mechanics or electronic structure

While molecular dynamics in both atomistic and coarse grain scale are powerful tools for understanding large scale dynamics of systems, it is still incapable of describing chemical reactions. Chemical reactions deal with breaking and forming chemical bonds and, therefore, the motion of electrons. For understanding such phenomena one requires not only atomistic but also electronic degrees of freedom, and therefore, quantum mechanical or electronic structure methods, i.e. Schrödinger equation

$$\hat{H}\psi = E\psi, \tag{6}$$

is solved to calculate the wavefunction and energy of the system.

Semi-empirical: Semi-empirical methods are the most affordable among the quantum mechanical methods. Semi-empirical methods are based on mean field descriptions, such as Hartree-Fock, with added approximations and empirical data. Huckel's theory and extended Huckel methods are successful examples of semi-empirical methods. Such methods can deal with conjugated systems and π electronic excited states. The σ orbitals are not described explicitly in these methods and the π orbitals are described by empirical parameters, i.e. the Hamiltonian $\hat{H}$ is a reduced empirical Hamiltonian. CNDO, MNDO, INDO, etc. are other examples of semi-empirical quantum mechanical methods.

Density functional theory: Density functional theory (DFT) is one of the most successful approaches in quantum mechanics used for a wide variety of systems. In order to reduce the degrees of freedom, instead of the complex n particle wavefunction ($\psi(x_1, y_1, z_1,\ldots, x_n, y_n, z_n)$), one solves the electron density (ρ) which is a function of space (x, y, z) and time[15]. The Hohenberg-Kohn theorem states that the electron density ($\rho(x, y, z)$) determines all the properties of the ground state of the system[16,17].

Thus, by focussing on the calculation of electron density (and not the wavefunction), an effective one-electron Schrödinger equation can be derived and solved. The problem is, thus, reduced to finding the kinetic and exchange correlation energies. There are a variety of functional forms of the kinetic and exchange correlation part of the Hamiltonian that gives rise to various DFT functionals.

Many-body theory: Many-body theory requires consideration of the full electronic Hamiltonian and its solution. It is the most rigorous form of quantum mechanical calculations and is computationally expensive. One starts with the mean field approximation to get a reference wavefunction, i.e. Hartree-Fock theory. This reference wavefunction is refined most often in a perturbative approach giving rise to a variety of post Hartree Fock methods, such as MP2, CCSD, etc.

Multi-physics models

As mentioned before, there are many phenomena in nature that requires consideration of a multitude of time and length scales and, therefore, a single physical model is not adequate to describe it. Therefore, multi-physics or multiscale models have been developed. Multiscaling can be achieved in sequential and concurrent fashion.

- Sequential multiscale methods: In sequential multiscaling, one has a macroscale model, the parameters for which are pre-computed using microscale models. This is essentially parameter-passing and is conceptually simple since it does not require consideration of two physical models in the same computation.
- Concurrent multiscale methods: In concurrent multiscaling, the macro- and microscale are treated together in a hybrid framework and the interaction between them is computed on the fly. Most the multiscale methods such as hybrid quantum mechanics/molecular mechanics (QM/MM) discussed in this article are concurrent multiscale methods.

Domain decomposition methods

The idea of domain decomposition methods is often used in multiscale methods. The system of interest is divided into domains or sub-systems. The properties of subsystems are then calculated separately and at different levels of theory. Domains can either be overlapping or non-overlapping. Hybrid QM/MM belongs to the general class of domain decomposition methods[1,18,19].

Hybrid QM/MM

Proteins are typically made up of 1000 s of atoms and the system is even larger when one considers the surrounding water molecules. All these atoms and molecules contribute to the properties of the protein, in both ground and excited states. Therefore, for treatment of proteins and other biological systems, classical force fields are required.

However, chemists have always been fascinated by reactions in nature, i.e. in proteins and for that one needs to consider the electronic structure of the bio-system. Therefore, for treatment of chemical reactions in condensed phases, hybrid treatment is required. The important parts of the system, i.e. the active site, requires QM treatment. In the active sites the electronic degrees of freedom are important for phenomena such as bond breaking or formation, or electron transfer processes. The rest of the system is viewed in a more spectator-like fashion, i.e. it provides an effective field to the active site.

Thus, in such active site-driven processes in proteins, a small part of the system is treated at a higher level of theory, typically a quantum-mechanical method, while the rest of the system is treated at a lower level of theory, typically a molecular mechanical method (Figure 3 shows such a division of a enzymatic reaction where only the active site is treated quantum mechanically). Hybrid QM/MM embedding can be achieved in two ways – subtractive and additive.

1. Subtractive embedding: In subtractive embedding (shown in Figure 4), the total QM/MM Hamiltonian of a system can be written as

$$H_{\mathrm{QM/MM(sub)}} = H_{\mathrm{MM}}\ (\text{full system}) + [H_{\mathrm{QM}}\ (\text{active site}) - H_{\mathrm{MM}}\ (\text{active site})], \qquad (7)$$

where the subscript QM and MM denotes the levels of theory used in the calculation. Since QM calculation cannot be performed on the full system, that is tackled at the MM level of theory. To look at the phenomena in the active site that requires electronic degrees of freedom, QM level of theory is used. Finally to remove the double counting, MM level calculation on the active site is performed and subtracted. Thus, one needs to perform three decoupled calculations – (i) full system at the MM level of theory; (ii) active site at the QM level of theory, and (iii) active site at the MM level of theory. This sort of embedding, while reasonable for decomposition of energy, is not a good way of calculating the properties of the system since the QM wavefunction is not modified by the field due to the MM environment. An extension of the subtractive embedding, where more than 2 levels of theory are used is called ONIOM[20].

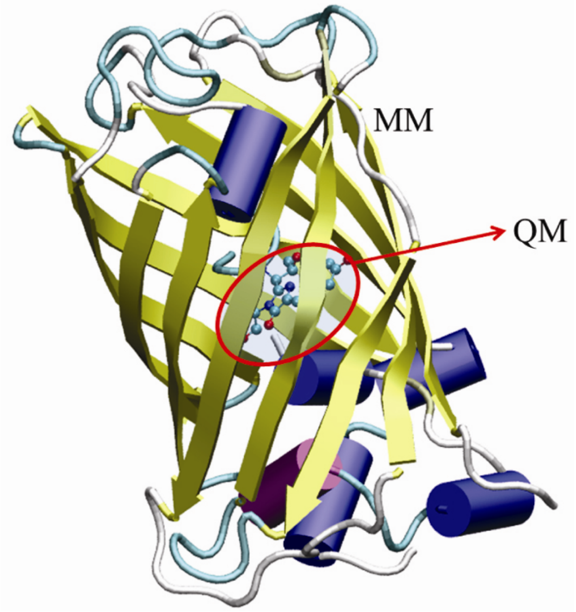

Figure 3. Hybrid QM/MM scheme shown in green fluorescent protein (GFP). The GFP chromophore lies at the centre of barrel formed by β-sheets. The chromophore (which absorbs visible and fluoresces) is treated quantum mechanically, while the rest of the system is treated at a molecular mechanical level.

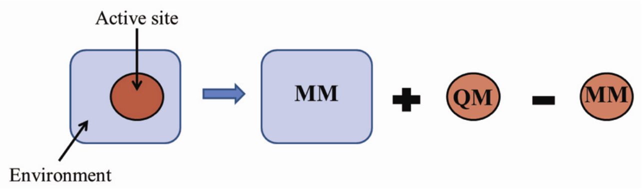

Figure 4. Subtractive scheme of QM/MM embedding.

2. Additive embedding: In the additive scheme of embedding, one writes the total Hamiltonian of the system as

$$H_{\mathrm{QM/MM(sub)}} = H_{\mathrm{QM}}\ (\text{active site}) + H_{\mathrm{MM}}\ (\text{environment}) + H_{\mathrm{QM/MM}}, \tag{8}$$

where the $H_{\mathrm{QM/MM}}$ denotes the interactions between the QM and MM sub-systems, i.e. the active site and the environment. Thus, it is the proper implementation of the QM and MM subsystem interactions that is the most crucial and complicated part. Depending on the different methods of handling the interaction terms there are three different approaches – mechanical embedding, electronic embedding and polarization embedding.

Additive scheme of hybrid QM/MM

Mechanical embedding

In case of mechanical embedding the QM and MM subsystems, i.e. H_{QM} and H_{MM} are solved separately at different levels of theory. The interaction between the QM and MM sub-systems is added as energy corrections at the end of the calculation, as Coulomb interaction energy between the charge density in the QM region and the point charges in the MM region

$$E_{\mathrm{QM/MM}} = \int \frac{\rho(r) q_i}{r_i} \mathrm{d}r, \tag{9}$$

where $\rho(r)$ denotes the charge density of the QM region at point r, q_i denotes the charge of the ith point in MM region and r_i denotes the distance from the ith MM point and position r in the QM region. The charge density $\rho(r)$ of the QM region and q_i are calculated separately and do not affect each other. This is the major drawback of this scheme.

Since this is a correction to the energy and not the Hamiltonian, this approach suffers from the same deficiencies of the subtractive scheme. Since the Hamiltonian of the QM region is not changed due to the QM/MM interactions, the wavefunction does not change due to the interactions and, therefore, properties apart from energy cannot be correctly predicted with this approach.

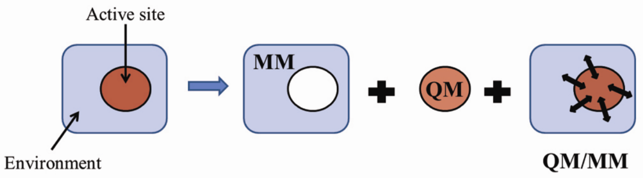

Figure 5. Additive scheme of QM/MM embedding.

Electronic embedding

To alleviate the deficiency of mechanical embedding, in electronic embedding, the effect of charges in the MM region on the QM charge density is accounted for. In other words, the effective field due to MM region on the QM region is included as a perturbation to the Hamiltonian of the QM part. Therefore, in the electronic embedding, although the QM/MM interaction energy takes a similar form as eq. (9), the charge density $\rho(r)$ is corrected due to the effect of MM environment.

Furthermore, since the Hamiltonian is changed perturbatively due to the presence of the MM region

$$\hat{H}' = \hat{H}_{\mathrm{QM}} + \hat{V}_{\mathrm{QM/MM}}. \tag{10}$$

The charge density $\rho'(r)$ obtained from solving this $\hat{H}'$ gives access to all the perturbatively corrected properties of the system.

Polarization embedding

While electronic embedding accounts for the effect of MM region on the QM region, the QM region can also affect the MM region which might self-consistently change the QM Hamiltonian. This self-consistent effect is called polarization embedding. There are various approaches of polarization embedding and this continues to be an active field of reach. Drude oscillator model, fluctuating charge model, induced dipoles, etc are some of the polarization embedding methods. Effective fragment potential (EFP)[21–23] and polarizable embedding (PE)[24] are two sophisticated polarizable force fields, which have been used for both ground and excited state properties in the hybrid QM/MM framework.

In all the embedding schemes, a crucial component for the proper functioning of the hybrid QM/MM formalism is the accurate treatment of boundary atoms, i.e. the atoms that are very near to the QM and MM boundaries. Since, in the case of MM atoms, the force field is depicted as charges and higher multipoles (permanent or induced), it can cause unphysical electric fields on the nearest neighbouring QM atoms and, therefore, charge damping schemes are often used. This situation is further complicated in a biological system, such as protein, where the QM boundary atom and MM boundary atom are bonded to each other. This requires satisfying the valency of the boundary QM atom. Methods such as link atom (LA)[25], and molecular fractionation with conjugate capping (MFCC)[26] have been developed for this purpose.

Enzyme catalysis with hybrid QM/MM

Hybrid QM/MM as a viable multiscale method was first formulated in the seminal work by Warshel and Levitt[1].

In their work, they studied the cleavage of glycosidic bond by lysozyme and the stability of the carbonium ion that is formed in the reaction. The main idea of the work is that the enzyme provides an environment that gives an effective electrostatic field, thereby preferentially stabilizing the transition state and increasing the speed of the reaction. The main reaction site is treated quantum-mechanically since it involves a bond breaking and requires electronic degrees of freedom. It was shown in this study that the effective field provided by the environment need not be described at the quantum mechanical level for understanding the mechanism of catalysis.

Since then numerous studies have been carried out on elucidating the mechanisms of various enzyme catalytic reactions in this hybrid framework.

New developments

Excited states with QM/MM

Understanding the relative changes between ground and excited states is crucial to the exploration of light–matter interactions. Light–matter interactions are important for processes such as photo-synthesis, light harvesting and so on. Excited state processes are also important for understanding biological processes, such as chemiluminiscence. Given the vast number of biological processes that involve both ground and excited states of the system, it is instrumental to develop computational methods that are capable of dealing with both ground and excited states of large systems.

While hybrid QM/MM methods have been developed quite extensively over the last three decades for chemical reactions in ground state and especially for enzyme catalysis, its use for the understanding of excited state processes and spectroscopic measurements in condensed phases is a more recent phenomena. It requires the use of not only state-of-the-art quantum mechanical methods for excited states, but also its seamless interface with MM methods. Since the charge densities of ground and excited states can be quite different, especially for charge transfer excited states, the field due to MM region can also be significantly altered in the excited state, thus, requiring a proper description of the polarizability of MM region.

Effective fragment potential (EFP) is one such polarizable and sophisticated MM method[22,23]. It is derived from an a priori *ab initio* calculation on a fragment (typically a solvent molecule) and is therefore, non-empirical. EFP was originally developed and implemented in GAMESS to study water. It was later extended to any general molecule.

The potential due to the effective fragments is divided into four terms – electrostatics (Coulomb), polarization, dispersion and exchange repulsion

$$E_{\mathrm{EFP-EFP}} = E_{\mathrm{Coul}} + E_{\mathrm{Pol}} + E_{\mathrm{Disp}} + E_{\mathrm{Ex-rep}}. \tag{11}$$

The Coulomb potential of the EFs includes charges, dipoles, quadrupoles and octupoles, and fitted using distributed multipole analysis. Apart from static multipoles, polarizability is an important factor especially for excited state properties. Polarizability is the self-consistent change in charge density of one fragment due to the presence of other fragments. In EFP, the polarizability is estimated as the self-consistently calculated induced dipole moments

$$\vec{\mu} = \alpha \vec{F}, \tag{12}$$

where α denotes the polarizability tensor and $\vec{F}$ is the field due to the rest of the multipoles. The dispersion interaction can be expanded in the London dispersion series, where only the first term is retained in EFP, i.e. it takes the C_6/R^6 form. Exchange repulsion, which has its origin in the Pauli exclusion principle, is an inherently quantum mechanical part of the interaction. It is also the most expensive part of the EFP calculation and depends on the overlap integrals of localized molecular orbitals (LMOs).

In the hybrid QM/MM framework with EFP as the MM method of choice, the Hamiltonian can be written as

$$\hat{H}_{\mathrm{QM/EFP}} = \langle \psi | \hat{H}_{\mathrm{QM}} + V_{\mathrm{Coul}} + V_{\mathrm{Pol}} | \psi \rangle + E_{\mathrm{EFP-EFP}}, \tag{13}$$

where the Hamiltonian of the QM part is perturbed by the Coulomb and polarization terms of the EFs in the environment. Since polarization is an inherently many-body property, it is solved self-consistently. The solution of this equation would give a wavefunction that is corrected for the presence of the environment. This is the ground state QM/EFP wavefunction.

The charge density of the excited state wavefunction is different from the ground state and, therefore, the many-body effect that it exerts on environment is different. Therefore, the polarization due to excited state can be drastically different from the ground state. This is especially true in case of charge transfer excited states. To account for that, an added perturbative polarization correction is included for the excited state that depends on the induced dipole moments on the environment (MM region) at the excited state.

Using this formalism, we have been able to accurately predict the ionization energies and excitation energies of biological systems such as DNA bases, GFP chromophores etc in solvation[27–29].

Redox potential with QM/MM

While excitation and ionization energies are important properties, experimentally it is easier to observe quantities such as redox potential. Therefore, it is important to estimate and predict redox potentials. Traditionally redox potentials are calculated by constructing the Hess's cycle, calculating the ionization energies in gas phase (which requires a purely quantum mechanical level of theory) and the solvation energies using continuum models. However, continuum models lack the description of specific interactions such as H-bonds which are crucial for the accurate estimation of solvation energies. Therefore, to achieve the quantitative accuracy in the redox potential calculations, one requires a hybrid QM/MM formalism with discrete atoms in the MM region and preferably polarization. Thus, we have used hybrid QM/EFP as described in the previous section. Furthermore, the total free energy change of the electron transfer process can be written as

$$\Delta G = -\frac{1}{k_{\mathrm{B}}T}\ln\left\langle \exp -\frac{\Delta E}{k_{\mathrm{B}}T}\right\rangle_i, \tag{14}$$

where $\langle\cdots\rangle_i$ denotes ensemble average over state *i*. Using linear response analysis (LRA), it can be reduced to

$$\Delta G = \frac{1}{2}(\langle \mathrm{VIE}_{\mathrm{Red}} + \mathrm{VEA}_{\mathrm{Ox}}\rangle), \tag{15}$$

where $\mathrm{VIE}_{\mathrm{Red}}$ denotes the ionization energy ensemble averaged at the reduced state and $\mathrm{VEA}_{\mathrm{Ox}}$ denotes the electron affinity ensemble averaged at the oxidized state. Both these quantities can be calculated in the hybrid QM/EFP framework described above. Using QM/EFP along with LRA we have been able to predict the redox potentials of small molecules very accurately[30]. The details of the excited state QM/EFP developments are explained by Ghosh[31].

Complex biological systems

Much of the on-going research is towards developing hybrid QM/MM formalisms for complex biological systems. Molecular tailoring approach (MTA)[32], molecular fractionation by conjugate capping (MFCC)[26], fragment molecular orbitals (FMO)[33], and molecule in molecule[34] are some examples of the divide and conquer approaches that have been extremely successful. MFCC-like approaches have also been developed for hybrid QM/EFP very recently[35]. Other fields of development are towards faster and more accurate polarizable force fields. The proper treatment of boundary between QM and MM regions, where they are covalently bonded, is another developing field. Methods such as link atom scheme[25] and frozen molecular orbitals (FMO)[33] are noteworthy among these.

Conclusion

Since the processes in nature are multiscale in nature, multi-physics methods both in analytical and numerical fields have been developed over the last few decades. With the increase in computational power these are increasingly being used to solve chemical and physical real world problems. Hybrid QM/MM is one such highly successful technique for solving chemical problems ranging from enzyme catalytic reactions to excited state phenomena in more recent times.

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