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QM/MM: What have we learned, where are we, and where do we go from here?

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Abstract. This paper briefly reviews the current status of the most popular methods for combined quantum mechanical/molecular mechanical (QM/MM) calculations, including their advantages and disadvantages. There is a special emphasis on very general link atom methods and various ways to treat the charge near the boundary. Mechanical and electric embedding are contrasted. We consider methods applicable to gas-phase organic chemistry, liquid-phase organic and organometallic chemistry, biochemistry, and solid-state chemistry. Then we review some recent tests of QM/MM methods and summarize what we learn about QM/MM from these studies. We also discuss some available software. Finally, we present a few comments about future directions of research in this exciting area, where we focus on more intimate bleeds of QM with MM.

I. Introduction

Despite of the increasing computational capability now available, molecular modeling and simulation of large, complex systems at the atomic level remains a challenge to computational chemists. At the same time, there is increasing interest in nanostructured materials, condensed-phase reactions, and catalytic systems, including designer zeolites and enzymes, and in modeling systems over longer time scales that reveal new mechanistic details. The central problem is: can we efficiently accomplish accurate calculations for large reactive systems over long time scales? As usual, we require advances in modeling potential energy surfaces, in statistical mechanical sampling, and in dynamics. The present article is concerned with the potentials.

Models based on classical mechanical constructs such as molecular mechanical (MM) force fields that are based on empirical potentials describing small-amplitude vibrations, torsions, van der Waals interactions, and electrostatic interactions have been widely used in molecular dynamics (MD) simulations of large and complex organic and biological systems[1-25] as well as inorganic and solid-state systems.[26-31] However, the MM force fields are unable to describe the changes in the electronic structure of a system undergoing a chemical reaction. Such changes in electronic structure in processes that involve bond-breaking and bond-forming, charge transfer, and/or electronic excitation, require quantum mechanics (QM) for a proper treatment. However, due to the very demanding computational cost, the application of QM is still limited to relatively small systems consisting of up to tens or several hundreds of atoms, or even smaller systems when the highest levels of theory are employed.

Algorithms that combine quantum mechanics and molecular mechanics provide a solution to this problem. These algorithms in principle combine the accuracy of a quantum mechanical description with the low computational cost of molecular mechanics, and they have become popular in the past decades. The incorporation of quantum mechanics into molecular mechanics can be accomplished in various ways, and one of them is the so-called combined quantum mechanical and molecular mechanical (QM/MM) methodology.[32-151]

A QM/MM method (see Fig. 1) treats a localized region, e.g., the active site and its neighbors in an enzyme (called the primary subsystem, PS), with QM methods and includes the influence of the surroundings (e.g., the protein environment, called secondary subsystem, or SS) at the MM level. The QM/MM energy for the entire system (ES) can be formally defined by

Fig. 1. Illustration for the QM/MM method in the enzyme system. The active center is treated at the QM level and the surroundings is treated at the MM level.

$$E(\text{QM/MM;ES}) = E(\text{QM;PS}) + E(\text{MM;SS}) + E(\text{QM/MM;PS|SS}), \quad (1)$$

i.e., as a summation of the energy of the PS, the energy for the SS, and the interaction energy between them. The relation between ES, PS, and SS is given by

$$\text{ES} = \text{SS} + \text{PS}. \quad (2)$$

The PS is also called the QM subsystem (or — sometimes — the MO subsystem), and the SS is often called the MM subsystem. The inclusion of the interactions between the active center and its environment allows a more realistic description of the system, in comparison with isolated QM calculations on subsystems, which are often called model systems. Such a PS-SS coupling is the heart of a QM/MM method.

Recently, there has been much exciting progress on QM/MM algorithm development, implementation in programs, and applications. In this contribution, we will briefly review the current status of the most popular methods for QM/MM calculations, including their advantages and disadvantages. There are many reviews of QM/MM methods available in literature.[49,58,59,65,66,74,75,81,95,113,119] The present study will put a special emphasis on very general link atom methods and various ways to treat the charge near the boundary. Mechanical and electrostatic embedding will be contrasted. We will review some recent tests and applications from our work and that of other groups and summarize what we learn about QM/MM from these studies. We will also discuss some available software. Finally, we will present a few comments about future directions of
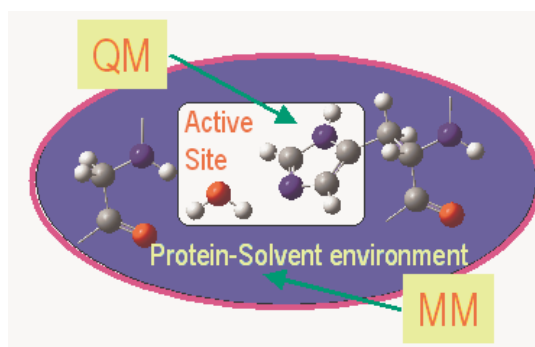
research in this exciting area. The *applications* of QM/MM methods are very interesting and very important, but they are not emphasized in this review.

II. Interactions between the Primary and Secondary Subsystems

The coupling between the primary system (PS) and the secondary subsystem (SS) is the heart of a QM/MM method. The coupling, in general, must be capable of treating both bonded interactions (bond stretching, bond bending, and internal rotation, sometimes called valence forces) and non-bonded interactions (electrostatic interaction and van der Waals interactions). Various QM/MM schemes have been developed to treat the interactions between the PS and SS.

As might be expected from its general importance in a myriad of contexts,[152] the electrostatic interaction is the key element of the coupling. Depending on the treatment of the electrostatic interaction between the PS and SS, the QM/MM schemes can be divided into two groups, the group of mechanical embedding and the group of electric embedding.[44] A mechanical embedding (ME) scheme performs QM computations for the PS in the absence of the SS, and treats the interactions between the PS and SS at the MM level. These interactions usually include both bonded (stretching, bending, and torsional) interactions and non-bonded (electrostatic and van der Waals) interactions. The original integrated molecular-orbital molecular-mechanics (IMOMM) scheme[39,52,62] by Morokuma and coworkers, which is also known as the two-layer ONIOM(MO:MM) method, is an ME scheme.

In an electrostatic embedding (EE) scheme, also called electric embedding, the QM computation for the PS is carried out in the presence of the SS by including terms that describe the electrostatic interaction between the PS and SS as one-electron operators that enter the QM Hamiltonian. Because most popular MM force fields, like CHARMM[18] or OPLS-AA,[17,19,20,22,24,25] have developed extensive sets of atomic-centered partial point charges for calculating electrostatic interactions at the MM level, it is usually convenient to represent the SS atoms by atomic-centered partial point charges in the effective QM Hamiltonian. However, more complicated representations involving distributed multipoles have also been attempted.[46,89] The bonded (stretching, bending, and torsional)

interactions and non-bonded van der Waals interactions between the PS and SS are retained at the MM level.

A comparison for between the ME and EE schemes are presented in Table 1, which will be discussed in detail in Subsections II.A and II.B.

Table 1. A Comparison between the Mechanical Embedding (ME) and Electrostatic Embedding (EE) Schemes

	ME	EE
Electrostatic interaction between the primary system (PS) and the secondary system (SS)	Handled in the standard MM way	Treated by including certain one-electron terms in the QM Hamiltonian
Advantage	Simple	1. Do not need electrostatic MM parameters for PS atoms, which may change their character during the simulation 2. The electronic structure of the PS adjusts to the charge distribution in the SS
Disadvantage	1. An accurate set of electrostatic MM parameters is often not available for PS atoms 2. Ignores the potential perturbation of the electronic structure of the PS by the charge distribution of the SS	1. More computational effort 2. Need to construct an appropriate representation for the charge distribution in the SS

II.A. Mechanical Embedding?

The key difference between an ME scheme and an EE scheme is how they treat the electrostatic interaction between PS and SS. An ME scheme handles the interaction at the MM level, which is simpler. However, such a treatment has drawbacks. First, the treatment requires an accurate set of MM parameters such as atom-centered point charges for both the PS and SS. It is relatively easier to get such parameters for the SS, and the problem with getting such parameters for the PS, where reactions are taking place, was the central reason for moving from MM to QM in the first place. Since the charge distribution in the PS usually changes as reaction progresses, the error in using a single set of MM parameters could be very serious. The second drawback of an ME scheme is that it ignores the potential perturbation of the electronic structure of the PS due to the electrostatic interaction between the PS and SS. The atom-centered charges in the SS polarize the PS and alter its charge distribution. This is especially a problem if the reaction in the PS is accompanied by charge transfer. Another problematic situation would be a system (e.g., an open-shell system containing transition metals) having several electronic states close in energy, for which the polarization could change the energetic order of these states, e.g., predicting a different ground state with a different charge and/or spin distribution.

To deal with the lack of accurate MM electrostatic parameters for the PS atoms during a reaction, one might consider obtaining these parameters dynamically as the reaction progresses, e.g., deriving atom-centered point charges for the PS atoms when the system evolutes along the reaction path. This idea works in principle, but in practice, it requires a large PS to achieve the desired accuracy due to the second drawback of ME schemes, which was just discussed above. That is, the PS system must be large enough to assure that its calculated charge distribution is converged with respect to the location of the QM/MM boundary. Moreover, an accurate and fast algorithm is necessary to derive the MM electrostatic parameters on the fly (with no or only a little calibration by experimental data or validation by doing pure MM simulation). These requirements will apparently increase the computational effort considerably.

This problem motivates consideration of the mechanically embedded three-layer ONIOM(MO:MO:MM) method.[52] This method attempts to overcome the drawbacks of a

mechanically embedded two-layer ONIOM(MO:MM)[39] by introducing a buffer (middle) layer, which is treated by an appropriate lower-level QM theory (e.g., semi-empirical molecular orbital theory), which is computationally less expensive than the method used for the innermost primary subsystem. One can label such a treatment as QM1:QM2:MM or QM1/QM2/MM. The second QM layer is designed to allow a consistent treatment of the polarization of the active center by the environment. The new treatment does improve the description, but, with mechanical embedding, it does not solve the problem completely, since the QM calculation for the first layer is still performed in the absence of the rest of the atoms.

II.B. Electrostatic Embedding?

In contrast to an ME scheme, an EE scheme does not require the MM electrostatic parameters for the PS atoms, because the electrostatic interaction between PS and SS is now treated at a more advanced level by including certain one-electron terms in the QM Hamiltonian. The polarization of the PS by the charge distribution of the SS is also taken into account automatically. The recent progress in the development of electrostatic embedded ONIOM method[137,138] reflects the trend of moving from ME to EE in QM/MM methodology. The price to pay for this improvement is more complicated implementation and increased computational cost.

The unsolved issue for EE schemes is how to construct the one-electron terms in the effective QM Hamiltonian. As mentioned earlier, the simplest way is to represent the charge distribution of the SS as a background of atom-centered partial charges. This is further facilitated by the availability of a set of pre-parameterized MM point charges in many MM force fields; these MM point charges have in principle been parameterized consistently with the other MM parameters to give accurate MM energies, and they have been validated by extensive test calculations. The use of these MM atom-centered partial charges is very efficient, and it is the most popular way in constructing the effective QM Hamiltonian. Nevertheless, the question is raised: are charge parameterized for a particular MM context also appropriate for use in a QM Hamiltonian? In an extreme case, for example, a zeolite-substrate system, the formal atomic charges used in aluminosilicate force field are chosen to reproduce the structural rather than electrostatic data; such

charges may not be appropriate for the construction of the one-electron terms in the effective QM Hamiltonian.[56]

The MM point charges actually include the contributions due to higher-order multipoles implicitly, i.e., the higher-order contributions are folded into the zero-order parameters. By considering higher-order multipole contributions explicitly, one might increase the accuracy of calculated electrostatic interactions, but this makes the implementation more difficult, and the computational costs grow. The development of distributed multipole parameters is also a difficult and time-consuming task, but the biggest obstacle is that the higher-order terms are generally sensitive to the geometry or conformation changes.[153-155] The high conformation-dependence of the multipole expansion limits the transferability.[156] For example, only about 20 amino acids are commonly encountered in proteins. It would be ideal to have one set of parameters for these 20 amino acids, which could be used to simulate any proteins, and it would be very inconvenient if one had to develop a new set of parameters whenever another protein is studied or whenever the conformation of a given protein changes considerably.

Another unsolved issue in ascertaining the best EE strategy is the question of the polarization of the SS. In principle, the PS and SS will polarize each other until their charge distributions are self-consistent; properly account for this in a computation is usually accomplished by an iterative scheme[157] (or matrix inversion) or by an extended Lagrangian scheme.[158] Ideally, an EE scheme should include this self-consistency; but usually the charge distribution of the SS is considered frozen for a given set of SS nuclear coordinates. Schemes that relax this constraint can be called self-consistent embedding schemes (or polarized embedding schemes). However, self-consistency is difficult to achieve, because it requires a polarizable MM force field,[157-169] which has the flexibility to respond to perturbation by an external electric field. Such flexibility is not available in today's most popular MM force fields, although research to develop a polarizable force field has received much attention.[164,166] Moreover, the use of a self-consistent embedding scheme also brings additional complication to the treatment of the boundary between the PS and SS, which we will discuss later in next section. Finally, it increases the computational effort, since iterations are required to achieve self-consistent polarization of the PS and SS. Thus, in most EE implementations, the PS is polarized by the SS, but

the SS is not polarized by the PS. Early examinations on the self-consistent embedding scheme was carried out by Thompson and Schenter[42] and Bakowies and Thiel.[44] Their treatments are based on models that describe the mutual polarization of QM and MM fragments in the sprit of reaction field[170-173] theory, with the difference that the response is generated by a discrete reaction field (atomic polarizabilities) rather than a continuum. Their results suggests that the polarization of the SS by the PS can be crucial in applications involving a charged PS that generates large electric fields.

II.C. *Interactions Other than Electrostatic*

Although, as discussed above, the key difference between the ME and EE schemes is the treatment of the electrostatic interaction between the PS and the SS, there are also important issues involving in the treatments of the other interactions between the PS and the SS. These interactions include the bonded (stretching, bending, and torsional) interactions and the non-bonded van der Waals interactions, which are handled at the MM level.

A similar question arises here, as in the case of electrostatic interactions for the ME scheme, but now even for the EE schemes, i.e., all the interactions calculated at the MM level rely on the availability of MM parameters for the PS atoms. These parameters are not necessarily the same for the PS atoms in the reactant and product because the atom types are changed for some atoms, e.g., a carbon atom may change from C=O type to C–O–H type. Which set of MM parameters should we use? Should one switch between two sets of MM parameters during a dynamics calculation following the reaction path? Switching between these two sets of parameters during a dynamics calculation or along the reaction path is not convenient, and, again, avoiding this was the one of the reasons for moving up from MM to QM. Moreover, even if the switching between parameters could be done, one does not know at which point along the reaction path it should be done and how suddenly if the change is gradual. There is no unambiguous answer.

One key difference between the need for non-bonded electrostatic parameters and the need for bonded parameters is that the latter requirement can always be obviated by making the PS bigger, i.e., moving the QM-MM boundary out. The change of atom types might change the force constants for associated bonded-interactions. Usually force

constants for stretches are much bigger than force constants for bends, and force constants for torsions are the smallest. The changes of force constants due to the change of atom types are often in this order, too. This provides us with gauge for monitoring the error due to using a single set of MM parameters. The bonded interactions between PS and SS are localized at the boundary. In principle, the use of a larger PS pushes the boundary away from the reaction center and helps to alleviate the uncertainty due to parameter choices, but at a price of increasing computational effort. In many cases, though, enlarging the PS is not a practical solution. What then? Our suggestion is to keep using one set of MM parameters, and examine whether the errors introduced by using one set of parameters exceeds the errors produced by other approximations that are introduced by the QM/MM framework. Although our treatment is not a perfect solution, it is very practical, and it appears to be reasonable.

For the van der Waals interactions, any PS atoms that change atom types are intrinsically ambiguous; this problem cannot be avoided even if a larger QM subsystem is adopted. Fortunately, in practice, it does not appear to be a serious problem in most cases, since the van der Waals interactions are significant only at short distances (as compared to longer range forces associated charged species and permanent dipoles), and the use of only one set of van der Waals parameters is often adequate.

II.D. Treating Solid-State Systems

So far we have been talking about QM/MM methodology in a very general sense. In this subsection, we more specifically address some question about how to treat periodic systems and other solid-state materials such as metals, metal oxides, and surface-adsorbate systems. Excellent discussions[47,56,74,85,96,97,101-103,108,115,133,140,145] are available for many aspects, and we focus here especially on studies of zeolites.

As we mentioned above, the most important interaction between the PS and the SS is the electrostatic interaction. Thus, the central problem in treating periodic systems like the zeolite-substrate systems is how to incorporate the long-range electrostatic interactions between the SS and PS into a cluster model. The basis idea[174] is to develop a representation of charge distribution with a finite number of multipoles (usually point charges) to mimic the infinite and periodic charge distribution of the environment in

which the cluster model is embedded. This effective charge-distribution can be obtained by minimizing the difference between the electrostatic potentials that are generated by the effective charge distribution and by the original infinite and periodic charge distribution at a set of sampling points at the active site. Additional effective core potentials can be associated with selected point charges if needed. For example, parameterized effective core potentials can be use to replace point charges that are close to anions in the PS in order to reduce the overpolarization of these anions.[175] By doing so, one truncates the infinite and periodic system to a finite embedded cluster model, which is now much easier to handle.

A simple example is the Surface Charge Representation of the Electrostatic Embedding Potential (SCREEP) method, in which the electrostatic potential from the infinite crystal lattice is modeled by a finite number (usually several hundred) of point charges located on a surface enclosing the cluster.[176] More sophisticated models[97,101,103] also include polarization effects on the SS by using the shell-model.[159] The shell model[159] represents an ion, e.g., an O^{2-} ion in silica, by a pair of charges, namely, a positive core and a negative shell. The pair of charges are connected by a harmonic potential. The positions of all charge are optimized to get the lowest energy, i.e., the polarization effect is modeled as charge redistribution.

It is a concern that, in QM/MM calculations, as a consequence of the finite size of the cluster, the calculated HOMO-LUMO gap for solid is still typically larger than that for the corresponding extended solid, despite corrections to the energy to take into account the electrostatic contribution of the MM region. One might expect this to cause some errors in the calculation of absorption (of ions, electrons, or molecules) into the QM center. One important question that seems to be involved is whether the neglect of orbital interactions between the QM and MM subsystems underestimates the bandwidth of the QM system. This would be a serious problem if the QM-MM boundary passed through a conjugated system or a metallic region. But what if the boundary passes through a covalent bond? First, it is important to keep in mind that the HOMO-LUMO gap is not a physical observable, and the LUMO itself is somewhat arbitrary as long as it remains unoccupied. (For example, the LUMO of Hartree-Fock theory is unphysical, and the

meaning of orbital energies in DFT is still a subject of debate.) It is most profitable to cast the problem in terms of observables.

An example of a physical observable of concern would be the absorption energy of an electron into the QM region, i.e., the electron affinity of a molecule in the QM region. This is a difficult question to address because one of the main failings of QM/MM methods is that they neglect charge transfer between the QM and MM subsystems, although in reality there is almost always some charge transfer between non-identical systems in close proximity, and it is not expected to an integer. Nevertheless we can imagine the case of transferring an integer charge into the QM region and ask whether the electron affinity might be systematically in error, due to a systematic error in the HOMO-LUMO gap caused by neglecting the overlap of QM orbitals with the (missing) MM orbitals. This would be hard to answer because the electron affinity of a subsystem is not well defined. Therefore, one might ask a related practical question such as whether one systematically underestimates the energy of anionic QM subsystems, such as carboxylates. In practice, we have not seen such an effect. The errors due to the inexact treatment of the electrostatic effects of the MM system are large enough that the error in energies of reaction can be in either direction.

Another practical example might be the calculation of electronic excitation energies. Is there a way, other than increasing the size of the QM region, to stabilize the excitation energy? Or: can one calculate accurate electronic excitation energies of a non-isolated QM system without converging the calculation with respect to enlarging the size of subsystem that is treated quantum mechanically. We think that it is reasonable to hope that one can do this, if one makes the QM/MM treatment sophisticated enough. For example, one can obtain reasonable values for solvatochromic shifts from continuum solvation models in which the solvent is not treated quantum mechanically.[177]

II.E. Adaptive QM/MM

An important issue that arises in simulating liquid-state phenomena and diffusion through solids is the adaptive movement of the quantum mechanical region, which is called the "hot spot".[50,77,116,178] Algorithms have been reported for liquid-phase simulation that allow water molecules to enter and leave the QM region dynamically. The

basic idea is to identify a narrow "buffer-region" or "switching shell" between the QM and MM regions. The cut-off is group-based, i.e., a solvent molecule like water is considered to be in the buffer region when its center of mass is in the buffer region. In order to avoid a discontinuity in the force as a solvent molecule enters or leaves the hot spot, Rode and coworkers[50] proposed to use a smooth function for the forces experienced by the atoms in the buffer region to ensure a smooth transition between QM and MM force. The smooth function takes the same form as the one[179] used in the CHARMM program to handle the discontinuity in energy and force due to the use of cut-offs for non-bonded (especially electrostatic) interactions. Despite its success, this treatment lacks a unique definition for the energy, which is obtained by integration of the force. Later, Kerdcharoen and Morokuma[116] described another scheme to cope with the discontinuity. In their scheme, two QM/MM calculations are performed for a given configuration of the whole system. The first calculation is done with the atoms in the buffer region and the atoms in the MM region treated at the MM level, and the second calculation is carried out with the atoms in the buffer region and the atoms in the QM region treated at the QM level. The total QM/MM energy is a weighted average of the QM/MM energies obtained in these two calculations; the weight function is determined by the position of the atoms in the buffer region. This treatment can be viewed as making a smooth connection of two potential energy surfaces.

III. QM/MM Boundary Treatment

In this section, we examine the problem with a stronger microscope, and we consider details, especially for the troublesome implementation of the EE scheme. In some cases, the boundary between PS and SS does not go through a covalent bound, e.g., a molecule being solvated in water, where the solute is the PS and the solvent (water) molecules is the SS.[36,69] The effective fragment potential method[46] can also be considered as a special case of MM in this catalog. In many cases, however, one cannot avoid passing the boundary between the PS and SS through covalent bonds (e.g., in enzymes or reactive polymers) or through ionic bonds (in solid-state catalysts). This is called cutting a bond. In such cases, special care is required to treat the boundary, and this section (Section III) is mainly concerned with this problem.

III.A. Link Atom or Local Orbital?

Treatments of the boundary between PS and SS regions can be largely grouped into two classes. The first is the so-called link atom approach, where a link-atom is used to saturate the dangling bond at the "frontier atom" of the PS. This link atom is usually taken to be a hydrogen atom,[34,39,52,72,106,116,119] or a parameterized atom, e.g., a one-free-valence atom in the "connection atom",[70] "pseudobond",[82] and "quantum capping potential"[111] schemes, which involve a parameterized semi-empirical Hamiltonian[70] or a parameterized effective core potential (ECP)[82,111] adjusted to mimic the properties of the original bond being cut. The second class of QM/MM methods consists of methods that use localized orbitals at the boundary between the PS and SS. An example is the so-called local self-consistent field (LSCF) algorithm,[35,38,43,51,112] where the bonds connecting the PS and SS are represented by a set of strictly localized bond orbitals (SLBOs) that are determined by calculations on small model compounds and assumed to be transferable. The SLBOs are excluded from the self-consistent field (SCF) optimization of the large molecule to prevent their admixture with other QM basis functions. Another approach in the spirit of the LSCF method is the generalized hybrid orbital (GHO) method.[63,83,113,123,125,142,144,149] In this approach, a set of four sp^3 hybrid orbitals is assigned to each MM boundary atom. The hybridization scheme is determined by the local geometry of the three MM atoms to which the boundary atom is bonded, and the parametrization is assumed to be transferable. The hybrid orbital that is directed toward the frontier QM atom is called the active orbital, and the other three hybrid orbitals are called auxiliary orbitals. All four hybrid orbitals are included in the QM calculations, but the active hybrid orbital participates in the SCF optimizations, while the auxiliary orbitals do not.

Each kind of boundary treatment has its strength and weakness. The link atom method is straightforward and is widely used. However, it introduces the artificial link atoms that are not present in the original molecular system, and this makes the definition of the QM/MM energy more complicated. It also presents complications in optimizations of geometries. In addition, it is found, at least in the original versions of the link atom method, that polarization of the bond between the QM frontier atom and the link atom is unphysical due to the nearby point charge on the MM "boundary atom" (an MM

boundary atom is the atom whose bond to a frontier QM atom is cut). The distance between the link atom and the MM boundary atom is about 0.5 Å in the case of cutting a C–C bond (the bond distance is about 1.1 Å for a C-H bond and about 1.5 Å and for a C-C bond). Similar problem is found in the case of cutting a Si–O bond (the bond distance is about 1.4 Å for a Si–H bond and about 1.6 Å and for a Si–O bond). At such a short distance, the validity of using a point charge to represent the distribution of electron density is questionable. Special treatments are applied to the MM charges near the boundary so as to avoid this unphysical polarization.[33,44,70,71,82,93,110,124] We will discuss this problem in more detail later Subsection III.B.

The methods using local orbitals are theoretically more fundamental than the methods using link atoms, since they provide a quantum mechanical description of the charge distribution around the QM/MM boundary. The delocalized representation of charges in these orbitals helps to prevent or reduce the over-polarization that, as mentioned above, is sometimes found in the link-atom methods. However, the local-orbital methods are much more complicated than the link-atom methods. The local-orbital method can be regarded as a mixture of molecular-orbital and valence-bond calculations; a major issue in these studies is the implementation of orthogonality constraints of MOs.[142] Moreover, additional work is required to obtain an accurate representation of the local orbitals before the actual start of a QM/MM calculation. For example, in the LSCF method, the SLBOs are pre-determined by calculations on small model compounds, and specific force field parameters are needed to be developed to work with the SLBOs. In the GHO method, extensive parameterization for integral scaling factors in the QM calculations is needed.[63,125,142,144,149] Such parameters usually require reconsideration if one switches MM scheme (e.g., from CHARMM to OPLS-AA), QM scheme (e.g., from semi-empirical molecular orbital methods to density functional theory or post-Hartree-Fock *ab initio* methods), or QM basis set. The low transferability limits the wide application of the local orbital methods.

The performance of both the link-atom and local-orbital approaches has been examined by extensive test calculations. The conclusion is that reasonably good accuracy can be achieved by both approaches if they are used with special care. It is expected that

development and application of both the link-atom and local-orbital methods will continue in the future.

III.B. Using Link-Atom Methods

A central objective in the development of a universal QM/MM algorithm is to make the algorithm as general as possible and to avoid or to minimize the requirement of introducing any new parameters. Thus, for example, one way to define a universally applicable method would be that, when one makes an application to a new system, no MM parameters need to be changed, no QM integral scaling factors needed to be determined, no effective core potentials (ECP) needed to be developed. From this point of view, the link-atom method seems very attractive. Furthermore the method will be more easily built into a standard QM code if the link atom is an ordinary hydrogen atom with a standard basis set. Methods having these features will be examined in more detail in this section.

To facilitate our further discussion, we will label the atoms according to "tiers". The MM boundary atom will be denoted as M1. Those MM atoms directly bonded to M1 will be called second-tier molecular mechanics atoms or M2; similarly, one defines M3 atoms as those MM atoms bonded to M2 atoms … The QM boundary atom that is directly connected to M1 is labeled Q1. Similarly, one defines Q2 and Q3 atoms in the QM subsystem. We will denote the link-atom as HL, which stands for "hydrogen-link", emphasizing that an ordinary hydrogen atom is used/preferred.

III.B.1. Location of the Link-Atom

As we mentioned in the previous section, the link-atom method has its problems. The first problem is the introduction of the coordinates of the link atom, which are extra degrees of freedom. By definition, a link atom is neither a QM nor an MM atom, because it is not present in the original PS or SS. This causes ambiguity to the definition of QM/MM energy for the ES. One way to avoid this problem is to make the coordinates of a link atom depend on the coordinates of the PS frontier atom and the SS boundary atom, i.e., the Q1 and M1 atoms. Such a constraint removes the extra degrees of freedom due to the link atom. Usually the link-atom is put on the line that connects the corresponding Q1 and M1 atoms. Morokuma and coworkers[72,180] proposed to scaled the Q1−HL distance R(Q1−HL) with respect to the Q1−M1 distance R(Q1−M1) by a scaling factor C_{HL}:

$$R(\text{Q1}-\text{HL}) = C_{HL}\, R(\text{Q1}-\text{M1}) \tag{3}$$

During a QM/MM geometry optimization or a molecular dynamics of reaction path calculation, the equilibrium Q1−HL and Q1−M1 distances are constrained to satisfy equation (3). The scaling factor, C_{HL}, depends on the nature of the bonds being cut and constructed. It has been suggested[72] that it should be the ratio of standard bond lengths between Q1−HL and Q1−M1 bonds, which is close to 0.71 for replacement of a C−C single bond by a C−H bond. This treatment is reasonable, and its simplicity facilitates implementation of analytic energy derivatives (gradient and Hessians). However, the meaning of "standard bond length" is ambiguous. Our treatment is to set the scaling factor by

$$C_{HL} = R_0(\text{Q1}-\text{H}) / R_0(\text{Q1}-\text{M1}), \tag{4}$$

where R_0(Q1−H) and R_0(Q1−M1) are the MM bond distance parameters for the Q1−H and Q1−M1 stretches in the employed MM force field, respectively.

It is worthwhile to mention that Eichinge *et al.*[73] also proposed a scaled-bond-distance scheme that is similar to the above scheme by Morokuma and coworkers. However, the scheme by Eichinge *et al.* makes the scaling factor depend on the force constants of the C−C stretch and C−H stretch instead of the bond distances, and it introduces some additional terms to correct the energy.

III.B.2. MM Charges near the Boundary

Another problem (in fact, the problem that has caused the most concern) for the link atom method, as we mention in the previous section, is the over-polarization of the Q1–HL bond due to the nearby M1 point charge. The main reason for this problem is that at such a short distance (usually about 0.5 Å in the case of cutting a C–C bond and about 0.2 Å in the case of cutting a Si–O bond), a point charge assigned to the M1 nucleus does not provide a good approximation for the smeared distribution of charge density. For nearby charge distributions, one must considers screening and charge penetration, and dipole or higher order multipole moments can also become important. Various approaches have been attempted to avoid or minimize this over-polarization effect, and they are outlined below.

If a scheme does nothing to modify the MM charges, we label the scheme as straight-electrostatic-embedding (SEE). The SEE scheme causes the over-polarization problem.

The simplest way to avoid over-polarization is to ignore the M1 charge by setting it to zero;[181] we call this method the Z1 scheme. One can also zero out both M1 and M2 charges; the method can be called Z2. If all M1, M2, and M3 charges are omitted,[33] the scheme is called Z3. The Z3 scheme is the default option for electrostatic embedding in ONIOM calculations carried out by the *Gaussian03* package;[182] but *Gaussian03* also allows one to use scaling factors other than zero for M2, M3, and M4 charges (the M1 charge is always set to zero). The scaled-charge schemes are generalizations of the eliminated-charge scheme. Schemes that eliminate or scale MM charges often result in changing the net charge of the SS, e.g., a neutral SS might become partially charged, and generate artifacts in the calculation of energies or spurious long-range forces.

In many force fields such as CHARMM, the neutrality of certain groups is enforced during the parameterization by imposing a constraint that the sum of charges for several neighboring atoms is zero. An improved eliminated-group-charge scheme[58] takes advantage of this feature by deleting the atomic charges for the whole group that contains the M1 atom. This ensures that the net charge of the SS does not change. It has been found that this scheme is more robust than the Z1, Z2, and Z3 schemes because it preserves the charge for SS.

A shifted-charge scheme[67] has been developed to work with force fields where the neutral-groups feature is not available. (Of course, the scheme can also be used for force fields having the neutral-groups feature). In this scheme, called the Shift scheme, the M1 charge is shifted evenly onto the M2 atoms that are connected to M1, and an additional pair of point charges is placed in vicinity of the M2 atom in order to compensate for the modification of the M1−M2 dipole by the initial shift.

As pointed out above, the over-polarization effect is largely due to the poor approximation for the distribution of charge density around the M1 atom by a point charge. Therefore, one might think of using a more realistic description for the charge distribution. Recently, it has been proposed[110,124] to use Gaussian charge distributions instead of point charges for selected atoms.
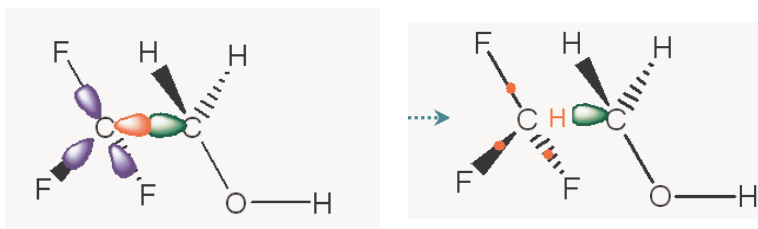

Fig. 2. The redistributed charge scheme (right) is a molecular mechanical analog to the quantal description by the generalized hybrid orbital (GHO) theory (left). The MM boundary atom and the active hybrid orbital (shown in red) in the GHO theory are now modeled by an H atom, and the auxiliary orbitals (shown in blue) are modeled by three point charges.

Recently, we[147] developed two new schemes: a redistributed-charge (RC) scheme and a redistributed-charge-and-dipole (RCD) scheme, which are based on combining the link-atom treatment and the local-orbital treatment.

As indicated in Fig. 2, both schemes use redistributed charges as molecular mechanical mimics of the auxiliary orbitals associated with the MM boundary atom in the GHO theory. In the RC scheme, the M1 charge is distributed evenly onto mid-points of the M1−M2 bonds, i.e., at the nominal centers of the bond charge distributions. The redistributed charge and M2 charges are further modified in the RCD scheme to restore the original M1−M2 bond dipole. The RC and RCD schemes handle the charges in ways that are justified as molecular mechanical analogs to the quantal description of the charge distribution offered by GHO theory.

IV. Validation of a QM/MM Algorithm

Validating QM/MM methods by comparing to high-level calculations or experiment is essential, since the use of unvalidated methods is unacceptable. Although the motivation for developing QM/MM methods is to apply them to large systems (e.g., reactions in the condensed phase, including liquids, enzymes, nanoparticles, and solid-state materials), most of the validation studies have been based on small gas-phase model systems, where a "model system" is a small- or medium-sized molecule. It is important, in interpreting such validation tests, to keep two important issues in mind.

First, the molecular mechanics parameters, especially partial charges, are usually designed for treating condensed-phase systems where partial charges are systematically larger due to polarization effects in the presence of dielectric screening; thus electrostatic effects of the MM subsystem may be overemphasized in the gas phase. Special attention is given to alkyl groups that are frequently involved in these test examples, because a non-polar C–C bond is often considered to be the most suitable place for putting the QM/MM boundary. An alkyl group in the gas phase appears to be very unpolar, and the C and H atoms are often assign atom-center point charges of small values. For example, in a recent study,[147] charges for the C and H atoms in a C_2H_6 molecule are –0.05 e and 0.02 e, respectively, as derived by the Merz-Singh-Kollmann[33,183] electrostatic potential (ESP) fitting procedure. An alkyl group becomes more polar in water or in other polar solvents, and the point charges on the atoms in the alkyl group increase significantly. The OPLS-AA force field assigns a charge of –0.18 e for each C atom and 0.06 e for each H atom in the C_2H_6 molecule, and in the CHARMM force field, the values are even larger (–0.27 e for each C atom and 0.09 e for each H atom). Our calculations[147] on the proton affinity of several gas-phase molecules having alkyl groups found much bigger errors when using the charges developed for simulations in water than when using the ESP-fitted charges. We believe that our conclusion is general since we tested several QM/MM schemes that treat the MM charges near the boundary differently, and observed a similar trend. We learned from this that it is very hard to test schemes designed for complex processes in the condensed phase by carrying calculations on small molecules in the gas phase.

It is probably more important to focus on the fact that the QM/MM interface can introduce artifacts. Thus, the main goal of validation tests should usually be to ensure that no unacceptably large energetic or structural artifacts are introduced, rather than to achieve high quantitative accuracy for MM substituent effects. In this regard, a QM/MM method is often tested by examples that are more difficult in one or another sense than those in a normal application because one wants to know where the performance envelope lies. Thus, calculations on examples having large proton affinities are very suitable for testing. Proton or hydride transfer involves significant charge transfer and is thus a crucial test for the treatment of electrostatic interactions (especially the procedure for handling MM charges near the QM/MM boundary) in a QM/MM method. A large value of the energy difference between the reactant and product also helps us to draw conclusions that are not compromised by the intrinsic uncertainty of the QM/MM approach.

The proton affinity of $CF_3CH_2O^-$, where CF_3 is the SS and CH_2O^- is the PS, is one of these difficult examples, due to both the close location of the reaction center to the boundary and the presence of significant point charges on the atoms in the CF_3 group near the boundary. A recent study[147] on this difficult example by making comparisons between full QM computations and various QM/MM schemes with the ESP-fitted MM charges for the CF_3 group. The QM/MM schemes include the capped PS, the SEE scheme, three eliminated-charge (Z1, Z2, and Z3) schemes, the Shift scheme, the RC scheme, and the RCD scheme. It is found that the Shift and RCD schemes, both of which preserve both the charge of the SS and the M1−M2 bond dipoles, are superior to the other schemes in comparison. For example, when, the errors for the RC and Shift schemes are 1 and 2 kcal/mol, respectively. It is also found that the largest error is caused by the Z1 scheme (75 kcal/mol), where neither the charge nor the dipole is preserved. The results suggest that it is critical to retain the feature of charge distribution near the QM/MM boundary. By this criterion, the SEE scheme does not seem to be too bad with an error of 9 kcal/mol; actually it is even better than the RC scheme (error of 12 kcal/mol) and the best charge-elimination schemes Z2 and Z3 (errors of 25 kcal/mol). However, the error in the optimized Q1−M1 (C−C) distance is 3 to 4 times larger for the SEE scheme than for

any of the other schemes to which comparison was made, and this makes the SEE scheme a poor choice in practical applications.

V. Implementation and Software

As summarized in a recent review article, there are basically three kinds of programming architecture for implementing QM/MM methods.

1. Extension of a "traditional" QM package by incorporating the MM environment as a perturbation. Many QM packages are have added or are adding the QM/MM options. A well-known example is the ONIOM method implemented in *Gaussian03* (http://www.gaussian.com/). Other examples include the ADF (http://www.scm.com/), CHIMISTE/MM (http://www.lctn.uhp-nancy.fr/logiciels.html), GAMES-UK (http://www.cse.clrc.ac.uk/qcg/gamess-uk/), MCQUB (http://www.chem.umn.edu/groups/gao/software.htm), MOLCAS (http://www.teokem.lu.se/molcas/), MOZYME (http://www.chem.ac.ru/Chemistry/Soft/MOZYME.en.html), and QSite (http://www.schrodinger.com/Products/qsite.html) packages.

2. Extension of a "traditional" MM package by incorporating a QM code as a force-field extension. Examples include AMBER (http://amber.scripps.edu/), CHARMM (http://www.charmm.org/), and CGPLUS (http://comp.chem.umn.edu/cgplus/).

3. A central control program interfacing QM and MM packages, where users can select between several QM and/or MM packages. For example, CHEMSHELL (http://www.cse.clrc.ac.uk/qcg/chemshell/) and QMMM (http://comp.chem.umn.edu/qmmm/) belong to this catalog.

Each kind of program architecture has its own merits and disadvantages. The options based on extension of traditional QM and/or MM packages can make use of the many features of the original program, for example, the ability of the MM program to manipulate large, complex biological systems. The disadvantage is that both options need modification of the codes.

The third option is based on module construction and is more flexible. It often needs no or little modification on the original QM and MM programs. The program is automatically updated when the QM or MM packages that it interfaces are updated. The

drawback is that it requires a considerable amount of effort to transfer the data between the QM and MM packages, which is usually done by reading data from files, rearranging the data, and writing the data to files. Such additional manipulations can lower the efficiency.

Our recently developed program QMMM adopts the third programming architecture. The QMMM program currently interfaces *Gaussian03* for doing QM computations and TINKER for doing MM calculations. Geometry optimization and transition-state searching can be done by using the algorithm built into the QMMM program or by using an optimizer in the *Gaussian03* program via the external option of *Gaussian03*. In addition to the RC and RCD schemes, the QMMM program also implements several other schemes such as the SEE, scaled-charge, and shifted-charge schemes for handling the MM point charges near the QM/MM boundary. Currently we are working on combination of the QMMM program with the molecular dynamics program POLYRATE (http://comp.chem.umn.edu/polyrate/) for doing QM/MM direct dynamics calculations.[184]

VI. What do We Learn from a QM/MM Calculation?

As discussed in the introduction, one benefit that QM/MM calculations bring to us is the inclusion of the effect of a chemical environment (secondary subsystem, SS) on the reaction center (primary subsystem, PS). The interactions between a PS and an SS are of two kinds: (1) interactions that are significant even at long range (electrostatic interaction), and (2) interactions that are local (bonded interactions) or are only significant at short range (van der Waals interactions). The electrostatic interactions are usually dominant, as they perturb the electronic structure of the PS, and they often have great effects on energetic quantities such as the reaction energy. The bonded and van der Waals interaction act in other ways; for example in enzyme reactions or solid-state reactions, they impose geometry constraints by providing a rigid frame in the active site or lattice site to hold the PS. (In fact, the electrostatic interaction will also affect the equilibrium geometry of the PS.)

A practical way to examine the effect of the environment is to compare quantities such as reaction energies or barrier heights as calculated from an isolated QM model and from a QM/MM model. Usually such quantities show significant differences for

processes that involve significant changes in the charge distribution. The calculations for proton transfer reactions are good examples (see the discussion on the proton affinity in Section IV).

However, one sometimes finds the same or very similar reaction energies and barrier heights from isolated QM model systems and QM/MM model calculations. This is likely to be observed for a reaction without much change transfer, e.g., a radical abstraction reaction. This does not mean that the SS does not affect the PS. In such a case, it is likely that the effect due to the SS is roughly the same for the reactant, transition state, and product, and the cancellation leads to small net effects. An approximate analysis of the effects due to SS can be obtained by an energy-decomposition as follows (see also Fig. 3).

The energy difference between the QM energy for the PS (or CPS, i.e., a PS capped by link atoms) in the gas phase and the QM energy for the PS in an interacting MM environment is defined by

$$E_{PS/MM} = E(QM;PS^{**}) - E(QM;PS), \quad (5)$$

where $E(QM;PS^{**})$ is the QM energy for the PS embedded in the background point charges of SS, and $E(QM;PS)$ is the QM energy for the PS in the gas phase. In either case, the geometry is fully optimized at the corresponding level of theory, i.e., at the QM/MM level for $E(QM;PS^{**})$ and at the QM level for $E(QM;PS)$. Equation (5) provides a measure of the magnitude of the perturbation on the QM subsystem
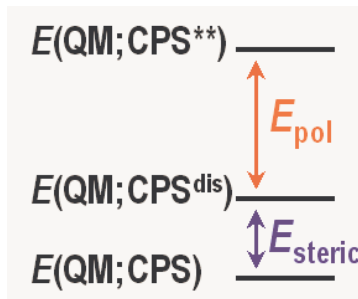
Figure 3. Decomposition of energy due to MM environment into two contributions: the energy due to the polarization by the background point charges (E_{pol}) and the energy due to the geometry distortion (E_{steric}). See Equations (5) to (8).

due to the MM subsystem. Generally speaking, the two geometries in Equation (5) are different. We further decompose $E_{PS/MM}$ into two contributions: the energy due to the polarization of the background point charges (E_{pol}) and the energy due to the geometry distortion from the PS in the gas phase (E_{steric}), which are defined as

$$E_{pol} = E(QM;PS^{**}) - E(QM;PS^{dis}), \quad (6)$$

$$E_{steric} = E(QM;PS^{dis}) - E(QM;PS), \quad (7)$$

$$E_{PS/MM} = E_{pol} + E_{steric}, \tag{8}$$

where $E(QM;PS^{dis})$ is the gas-phase single-point PS energy for the QM/MM optimized geometry, i.e., one takes the PS geometry that resulted from QM/MM optimization and removes the MM point charges. Although such an energy-decomposition is approximate, it is informative and provides us deeper understanding of the QM/MM calculations.

The energy decomposition is applied to a reaction that we studied recently[147] (Fig. 4).

$$CH_3 + CH_3CH_2CH_2OH \rightarrow CH_4 + CH_2CH_2CH_2OH \tag{R-1}$$

The PS is $CH_3 + CH_3CH_2$, giving rise to a CPS as $CH_3 + CH_3CH_3$. The SS is CH_2OH. For each of the reactant, saddle point, and product of this reaction, we found a small steric effect (0.1 kcal/mol) and a dominant polarization effect (9 kcal/mol). It is not surprising to see such a small setic effect, since the distortion of geometry for the CPS from the fully relaxed geometry in the gas phase can be rather small. The critical point is that the energies due to geometry distortion and polarization are so similar along the reaction path that they almost cancel out, giving rise to negligibly small net contributions to the reaction energy and barrier height.

Although the MM environment does not have a large net effect on the relative energies of the H atom transfer reaction (R1), it does have effects on the electronic structure of the CPS through polarization and perturbs the charge distribution. The ESP-fitted charges in Fig. 4 clearly show a trend of stepwise change from the unperturbed CPS (denoted as CPS), to the CPS with distorted geometry (CPS^{dis}), then to the CPS embedded in the background
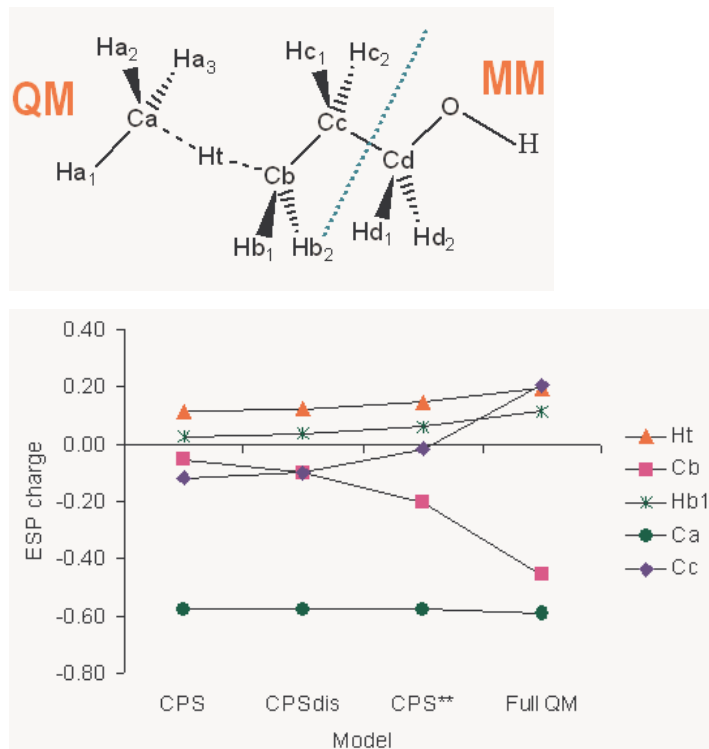

Fig. 4. ESP-fitted charges for selected atoms in reaction CH_3 + $CH_3CH_2CH_2OH \rightarrow CH_4 + CH_2CH_2CH_2OH$.

point charge distribution (CPS**), and finally to the ES, as modeled by full QM calculations. It is interesting to note that the Cb–Cc bond seems to be very unpolar according to the CPS calculations, with a small bond dipole pointing from the Cb to the Cc atom. The CPS** calculations predict that the Cb–Cc bond is more polar, with a larger and *inverse* bond dipole pointing from the Cc to the Cb atom, in qualitative agreement with full QM calculations. The CPS** result is generally closer to the full QM results, suggesting that QM/MM calculations provide a more realistic description for the QM subsystem than the isolated gas-phase QM model calculations.

The conclusion that for a reaction that does not involve much charge transfer, the inclusion of the electrostatic field of the SS will yield small effects in relative energies but large affects in the electronic structure of the PS also gain supports from studies of zeolite-substrate systems.[56] In Ref. [56], it has been found that the inclusion of the electrostatic field of the SS slightly alters the barrier (by ca. 2 kcal/mol) of a methyl shift reaction over a zeolite acid site, but has considerably large effects on the charge

distribution and vibrational frequencies. For example, the charge on the O atoms is changed by 0.16 e.

Comparing the results of QM/MM calculations with experimental results is the ultimate test of a QM/MM scheme. However, such a comparison is not trivial, and we mention here several points that need attention in general.

First, one should consider what kinds of experimental results, including their temperature and pressure, are most informative to be compared, and how reliable these results are, i.e., what is the error bar associated with the observed quantity. It is also important to understand, in the case of the experimental data were derived from fitting to a simplified model, what kinds of assumptions and simplifications have been invoked. In addition, it is important to understand the parameters characterizing the QM/MM calculations. For example, are the results converged with respect to increasing the size of the PS, increasing the QM level of theory and/or basis sets, tightening of the optimization convergence threshold, and increasing the cutoff distance or cutoff threshold if any, in the calculation of MM nonbonded interactions? If we are treating a complex system like an enzyme solvated in water, is the phase space sampled adequately? If we cannot afford an extensive phase-space sampling, can we examine several representative conformations? Do we need to consider potential anharmonicity in vibrational analysis?

Of particular importance is to separate, at least approximately, the errors due to the insufficient QM treatment of the PS and the errors due to the insufficient consideration of the SS effect. As we showed previously, the barrier height and reaction energy are often not sensitive to the electrostatic interaction between the PS and SS for a reaction that does not involve significant charge transfer. In such a case, it may be more desirable to increase the QM level of theory to improve the results than to improve the MM level or the QM/MM interface. On the other hand, for reactions that are sensitive to the electrostatic interaction between the PS and the SS, simply increasing the QM level of theory does not necessarily improve the reliability.

V. Where Do We Go from Here?

Combining QM and MM by applying them to separate subsystems with a boundary in physical space is very natural, and it is safe to say that it is now a permanent part of the theoretical toolbox. However, there are other ways to combine QM and MM, and future work may see greater use of methods that blend QM and MM more intimately.

A venerable example of such an approach is the use of quantum mechanics to suggest new functional forms for molecular mechanics. The oldest example would be the Morse curve, which was originally derived by a QM treatment of H_2^+.[185] Replacing a harmonic bond stretching potential by a Morse curve allows MM to treat bond breaking. It is much harder to treat synchronous bond breaking and bond forming, but this was also accomplished in the early days of quantum mechanics, resulting in the London equation.[186-188] Raff[189] was apparently the first to combine the valence-bond-derived QM London equation with molecular mechanics terms to make a QM/MM reactive potential, and in recent years many other workers,[190,191] especially Espinosa-Garcia and coworkers,[192-197] have made fruitful use of this technique. Various workers, of whom we single out Brenner[198-200] and Goddard and coworkers[201-204] for noteworthy systematic efforts, have made generalizations to more complex reactive systems. However, these methods are neither universal nor systematically improvable like the methods discussed in Sections III and IV.

One way to make the combination of valence bond theory and molecular mechanics more universal and systematic is multi-configuration molecular mechanics[205-209] (MCMM). MCMM combines QM and MM in a different way than QM/MM; in MCMM the whole system is treated by QM, and simultaneously the whole system is treated by MM. In fact, every atom is treated by two different MM schemes, one corresponding to a reactant and the other to a product, and the two MM energy expansions interact by a 2×2 configuration interaction matrix highly reminiscent of London's 2×2 matrix matrices or the similar 2×2 matrices used by Raff,[189] Warshel and Weiss,[210] and others. However, in MCMM the off-diagonal elements of the Hamiltonian are not empirical MM parameters as in previous work, but rather are determined by systematically improvable QM methods. The method is very young but very promising.

In the future, we can expect further progress in MCMM. One straightforward improvement is to use QM/MM to replace QM in determination of the off-diagonal element of the Hamiltonian matrices, and this scheme can be called QM/MM-based-MCMM, or QM/MM-MCMM for short. Another even more promising scheme is to combine MCMM with MM in the "same way" that QM is combined with MM in combined QM/MM methods. That is, use MCMM to replace the QM in QM/MM; this scheme can be called MCMM-based-QM/MM, or MCMM-QM/MM. Both schemes make MCMM suitable for handling very large systems. Work in this direction is in progress, and encouraging preliminary results have been obtained.[211]

Another area of future improvement is use of improved MM formalisms in QM/MM methods. We have already mentioned polarizable MM force fields (see Section II.B).[166] Even without allowing polarization, the charges in MM force fields can be improved in various ways. In particular, various charge models have been developed or are in refinement. Examples include the restrained electrostatic potential[212] (RESP) fitting procedure and its latest improved version "dynamically generated restrained electrostatic potential" (DRESP)[213] for QM/MM calculations, the family of CMx (x = 1,[214] 2,[215,216] 3[217-219], and 4[220]) charge models, the charge equilibration[221,222] (CEq) method, and the consistent charge equilibration (CQEq)[223-225] method.

An interesting and important future development is the adaptive QM/MM scheme, which was discussed in Section II E. If we allow atoms to be exchanged between the QM and MM regions, can we take one more step forward, allowing fractional (or whole) charges to be transferred between the QM and MM regions? Of course, to accomplish this goal, we need to work out how to describe the electronic structure of a system with fractional electrons.[226,227]

Another important trend we can expect to see in the near future is the incorporation in MM of methods for modeling metallic systems that were developed in the physics community. For example, just as simplified valence bond theory can be used to obtain functional forms for extending MM to reacting systems, the second-moment approximation to the tight-binding approximation (also known as extended Hückel theory) can be used to obtain new forms for modeling metals.[228] An example of this kind

of approach is the use of the embedded-atom functional form to develop MM potentials for Al nanoparticles.[229]

A theme that emerges from several of the approaches discussed in this section is the difficulty of classifying the potential energy function as QM or MM. For example, is the embedded-atom method an approximate version of density functional theory or is it MM? Is MCMM an automatic fitting method for QM energies or is it an extension of MM to reactive systems? We prefer to think of these methods as new kinds of QM-MM hybrids where the QM-MM combination is more intimate than in the first generation of combined QM/MM methods.

Acknowledgments

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