Multiscale Materials Modeling

Lecture 09

Quantum Mechanics/Molecular Mechanics (QM/MM) Techniques

STAIR
Sustainable Technology through
Advanced Interdisciplinary Research

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Outline

This QM/MM lecture is based upon the review article

"QM/MM: what have we learned, where are we, and where do we go from here?" by Hai Lin and Donald G. Truhlar in *Theoretical Chemistry Accounts* **117**(2) 2007 pp. 185-199.

I. Introduction
II. Types of QM/MM Techniques
III. Example Applications
IV. Conclusions

Motivation

Molecular Mechanics (MM):
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 as well as inorganic and solid-state systems.

However, the MM force fields are unable to describe the changes in the electronic structure of a system undergoing a chemical reaction.

Quantum Mechanics (QM):
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.

Lin & Truhlar,*Theoretical Chemistry Accounts* **117**(2) 2007.

QM/MM Definition

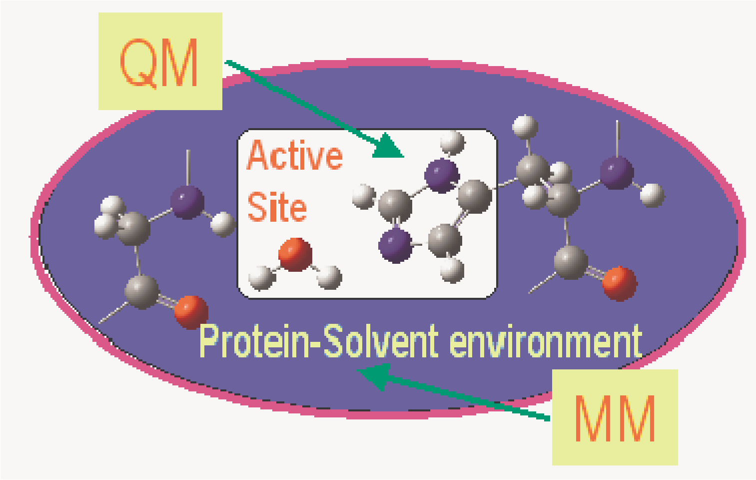

Fig. 1. Illustration for the QM/MM method in the enzyme system. The active center is treated at the QM level and the surroundings is treated at the MM level.

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, active center is treated at the QM level and the surroundings is treated at the MM level called secondary subsystem, or SS) at the MM level.

Lin & Truhlar,*Theoretical Chemistry Accounts* **117**(2) 2007.

QM/MM Definition

The QM/MM energy for the entire system (ES) can be formally defined by

$$E(QM/MM;ES) = E(QM;PS) + E(MM;SS) + E(QM/MM;PS|SS)$$

i.e., as a summation of the energy of the primary subsystem (PS), the energy for the secondary subsystem (SS), and the interaction energy between them.

The relation between ES, PS, and SS is given by

$$ES = SS + PS$$

The PS is also called the QM subsystem and the SS is often called the MM subsystem.

Interactions between within the PS are treated by standard QM techniques. Interactions between atoms within the Ss are treated by standard classical MM techniques.

It is the interactions between one atom in the PS and one atom in the SS that require special consideration and are the heart of QM/MM techniques.

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QM/MM Potentials

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).

Bonded Interactions appear when treating only part of a large molecule with QM techniques. Thus the molecule straddles the PS and SS. A chemical bond connects atoms in the PS and SS.

Nonbonded interactions appear when examining a hydrated system in which the solute is treated with QM and some or all of the solvent is treated with MM.

Lin & Truhlar, *Theoretical Chemistry Accounts* **117**(2) 2007.

QM/MM Types: Static vs Adaptive

Static

In a static QM/MM simulation, atoms do not switch from the PS to the SS (or vice versa) during the simulation. An atom that begins in the PS remains in the PS for the entirety of the simulation. Similarly an atom that begins in the SS remains in the SS for the entirety of the simulation.

Adaptive

In an adaptive QM/MM simulation, atoms can switch from the PS to the SS (or vice versa) during the simulation.

For example in a hydrated protein, a water molecule near the active site (in the PS) can exchange with a water molecule in the surrounding solvent (in the SS).

A discussion of adaptive techniques (for QM/MM and for MM/Mesoscale simulations) is the subject of a subsequent lecture.

Lin & Truhlar, *Theoretical Chemistry Accounts* **117**(2) 2007.

QM/MM: Mechanical vs Electrostatic Embedding

Of the non-bonded interactions, frequently the electrostatic interaction is the most important. Based on how the electrostatics is handled, we can divide QM/MM techniques into two groups.

Mechanical Embedding (ME):
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.

Electrostatic Embedding (EE):
In an electrostatic embedding (EE) scheme, 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 or OPLS-AA 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. 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.

Lin & Truhlar, *Theoretical Chemistry Accounts* **117**(2) 2007.

QM/MM: Mechanical vs Electrostatic Embedding

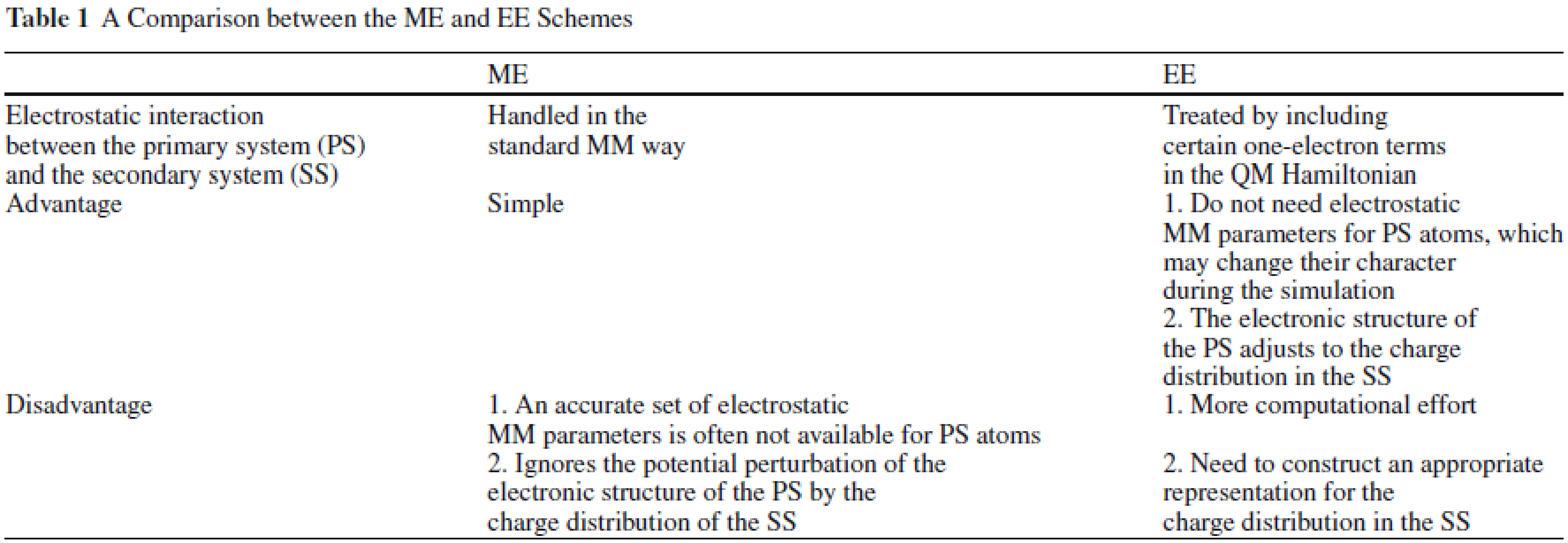

Table 1 A Comparison between the ME and EE Schemes

	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

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QM/MM: Mechanical vs Electrostatic Embedding

Mechanical Embedding Disadvantages:

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.

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QM/MM: Mechanical vs Electrostatic Embedding

Electrostatic Embedding Disadvantages:

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? Such charges may not be appropriate for the construction of the one-electron terms in the effective QM Hamiltonian.

Also, in most EE implementations, the PS is polarized by the SS, but the SS is not polarized by the PS.

Lin & Truhlar,*Theoretical Chemistry Accounts* **117**(2) 2007.

QM/MM: Boundary Treatment

Boundary Treatment
When molecules straddle the PS and SS domains, chemical bonds connect atoms in the PS and SS domains. One needs special treatment for the dangling bonds in the QM description. There are two categories of boundary treatments.

Link Atom Approach:
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 or a parameterized atom, which involve a parameterized semi-empirical Hamiltonian or a parameterized effective core potential (ECP) adjusted to mimic the properties of the original bond being cut.

Localized Orbital Approach:
The second class o f methods use localized orbitals at the boundary between the PS and SS. An example is the so-called local self-consistent field (LSCF) algorithm, 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.

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QM/MM: Link Atom Approach

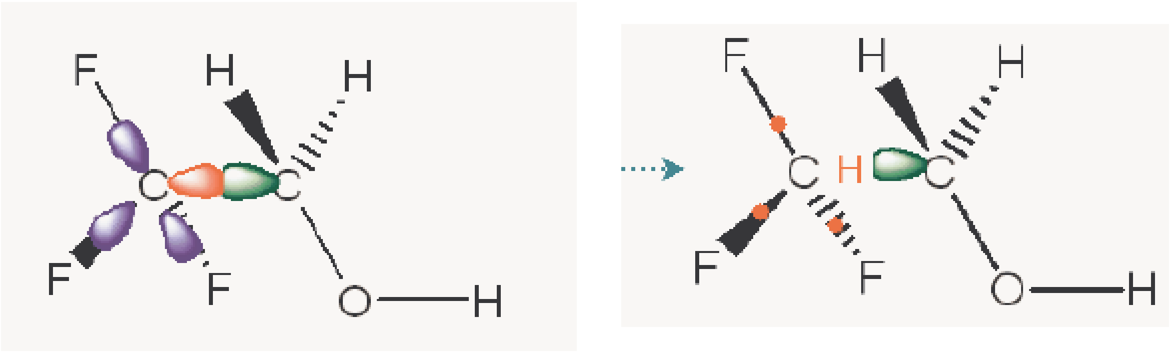

Fig. 2. The redistributed charge scheme (right) is a molecular mechanical analog to the quantal description by the generalized hybrid orbital (GHO) theory (left). The MM boundary atom and the active hybrid orbital (shown in red) in the GHO theory are now modeled by an H atom, and the auxiliary orbitals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

In this sample example, the CF_3 is the SS and the CH_2OH is the PS. (Of course this molecule is small enough to be treated fully QM, but it is used to illustrate a point.) A H atom is added to cap the PS system. This H atom is too close to the C in the SS. Charge must be redistributed to account for this artificially imposed atom.

Lin & Truhlar,*Theoretical Chemistry Accounts* **117**(2) 2007.

QM/MM: Validation

The way that QM/MM approaches are validated is typically by comparing full QM treatments with QM/MM treatments on smaller systems.

Difficult because gas-phase systems have different charge distributions that solvated systems.

It is found that the schemes that preserve both the net charge of the SS and the M1−M2 bond dipoles, are superior to the other schemes in comparison with fully QM treatment.

Lin & Truhlar,*Theoretical Chemistry Accounts* **117**(2) 2007.

QM/MM: Implementation

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*
.

2. Extension of a “traditional” MM package by incorporating a QM code as a forcefield extension. Examples include AMBER.

3. A central control program interfacing QM and MM packages, where users can select between several QM and/or MM packages. For example, CHEMSHELL and QMMM belong to this catalog.

Lin & Truhlar,*Theoretical Chemistry Accounts* **117**(2) 2007.

QM/MM: **What do We Learn from QM/MM?**

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).

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.

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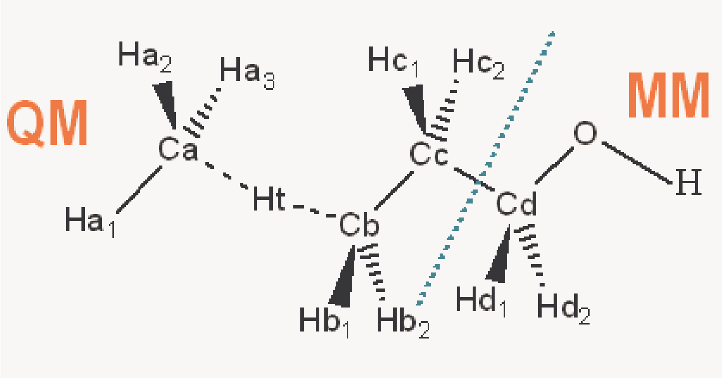
QM/MM: **Example**



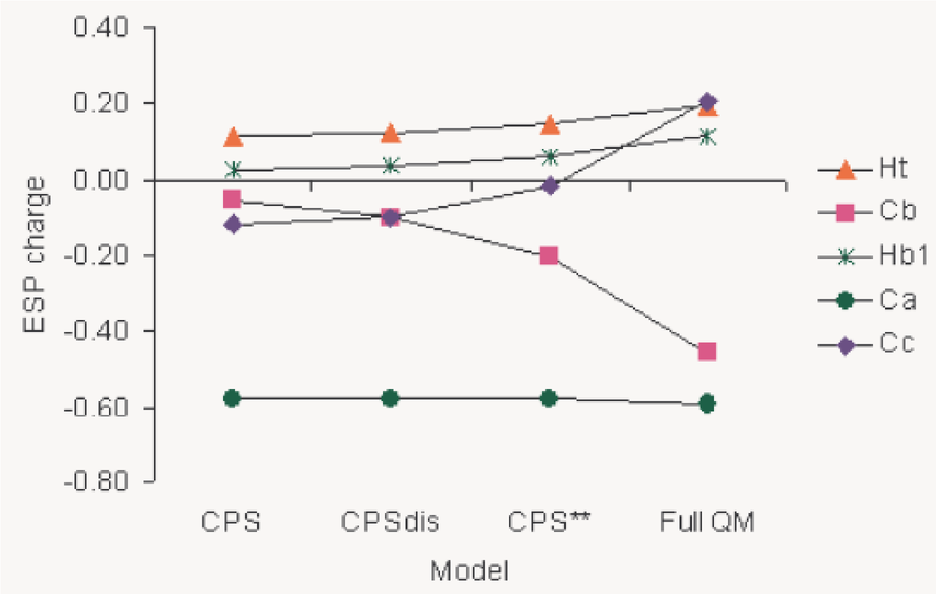


Fig. 4. ESP-fitted charges for selected atoms in reaction CH_3 + $CH_3CH_2CH_2OH$ → CH_4 + $CH_2CH_2CH_2OH$.

Evaluate partial charges for several cases

CPS = capped PS only, no MM

CPSdis = capped PS in geometry distorted by MM, no charges

CPS** = full QM/MM

Full QM

QM/MM is “closest” to full QM and thus best.

Lin & Truhlar, *Theoretical Chemistry Accounts* **117**(2) 2007.

QM/MM: **Conclusions**

QM/MM calculations allow the inclusion of the effect of a chemical environment (secondary subsystem, SS) on the reaction center (primary subsystem, PS) with computational efficiency.

As with any coarse-graining technique, the approaches are approximate and must be validated.

QM/MM is sufficiently established that commercial programs like Gaussian allow one to include the effects of the SS on the QM calculation.

QM/MM is still an active area of research for improved techniques.

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