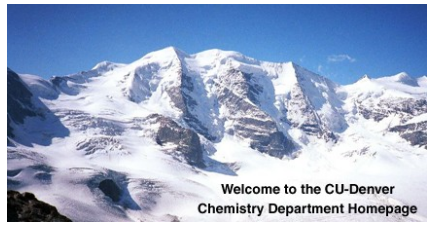


Toward More Realistic Simulations of Large-Size Reactive Systems by Combining Quantum Mechanics and Molecular Mechanics in New Ways

(NWChem 2007 Meeting, Jan. 25-26, 2007)

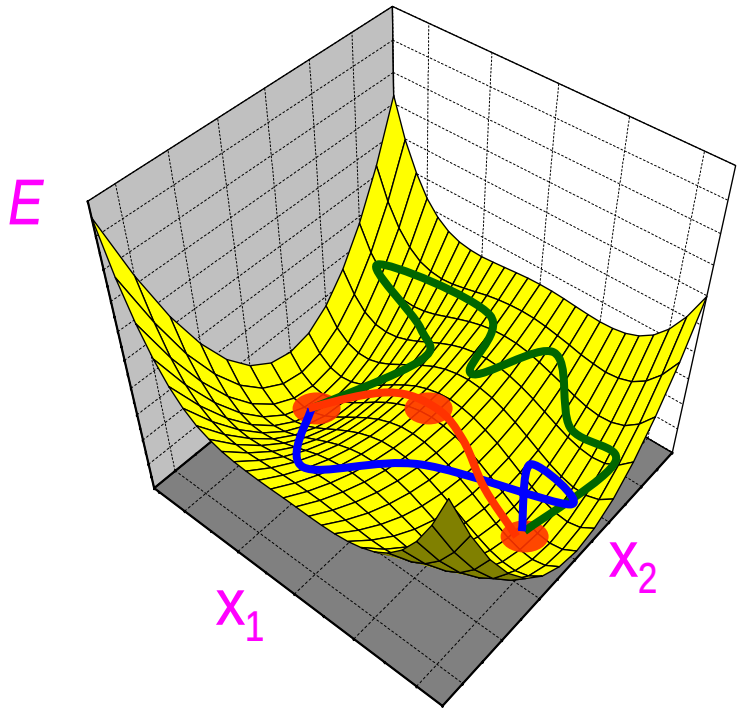
Hai Lin[a] and Donald G. Truhlar[b]

[a]*Chemistry Department, University of Colorado at Denver and Health Sciences Center*
[b]*Chemistry Department and Supercomputing Institute, University of Minnesota*

What do we need?

- Potential Energy Surfaces
  - ✓ Accuracy (kcal/mol):

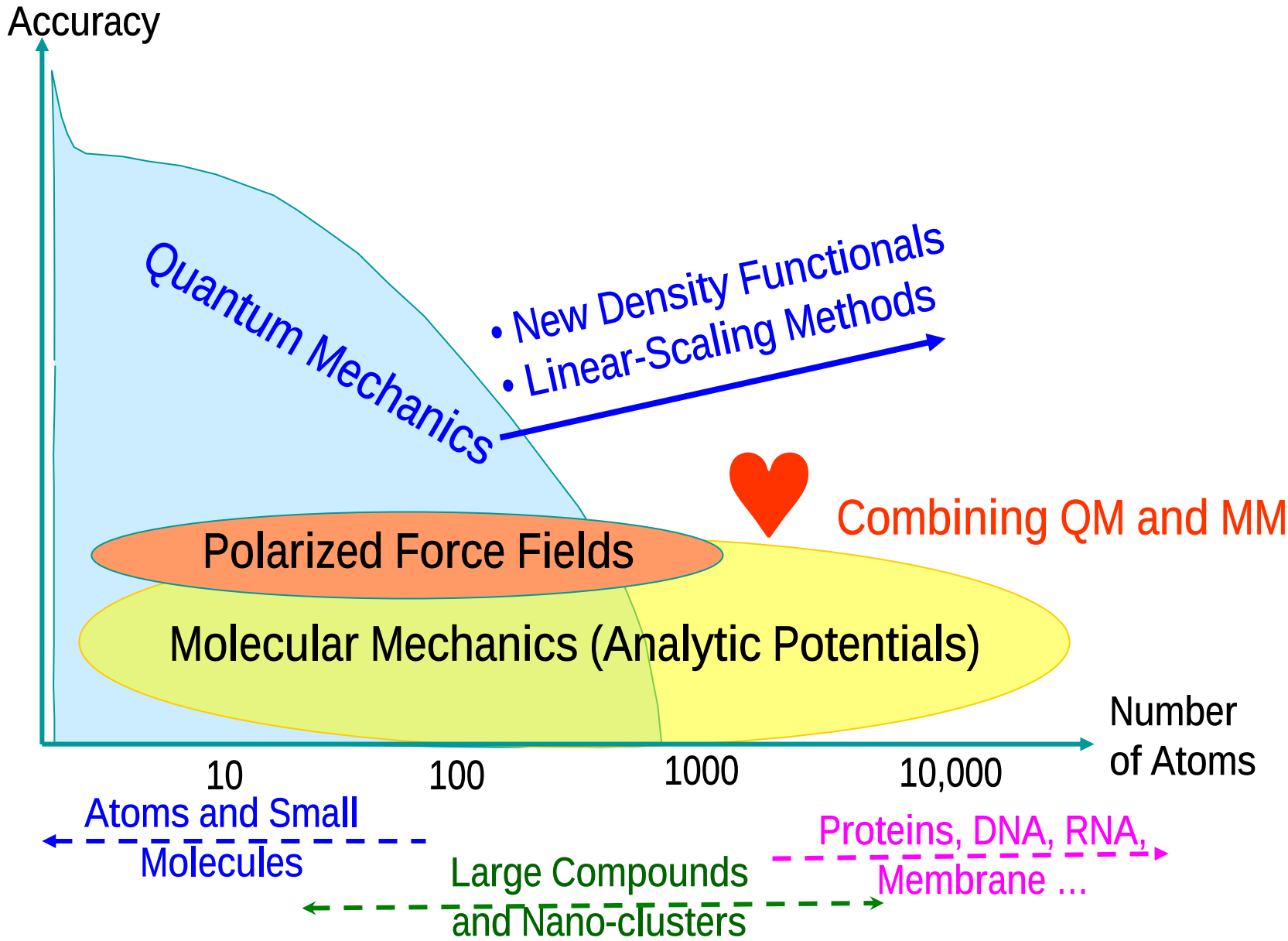
    ☹ 10 → 😐 1 → ☺ 0.1 → …
  - ✓ Scaling w/r the Size of the System: Linear or Even Better?



- Dynamics Theory
  - ✓ Molecular Dynamics (MD) and Monte Carlo (MC)
  - ✓ Variational Transition State Theory (VTST)
  - ✓ Combined with Efficient Sampling

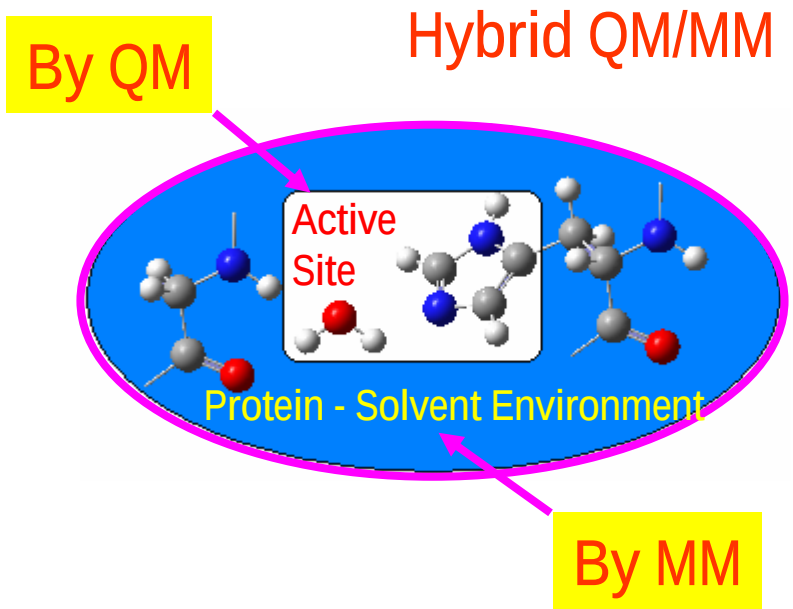
    E.g., Temperature-Accelerated Dynamics (Voter)

Potential Energy Surfaces



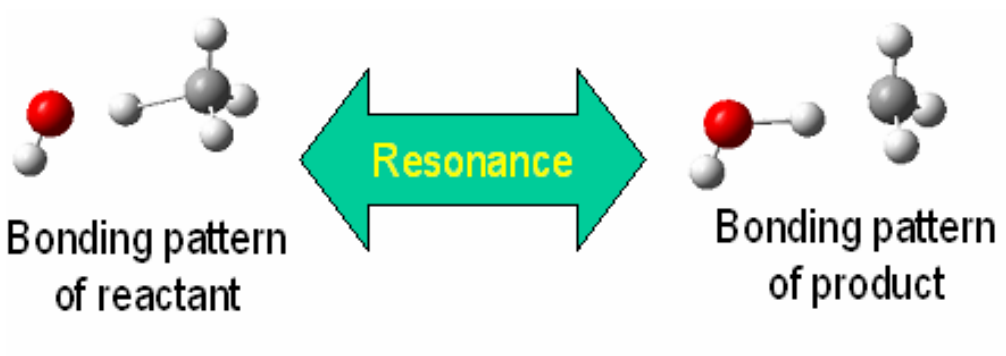
Combining QM and MM (1): Extending the Size

- Often only a small number of atoms change their electronic structure in a reaction.
- Combine an accurate QM treatment of the active site with an inexpensive MM treatment of the environment.



- Provides a realistic description of the active site in the presence of
  - protein–solvent environment
  - solid-state oxide environment
  - ...
- Very Popular Now (Chemistry, Biochemistry, Material Sciences…)

Combining QM and MM (2): Building in QM Vertically



Diabatic Representation

$$V = \begin{pmatrix} V_{11} & V_{12} \\ V_{21} & V_{22} \end{pmatrix}$$

Adiabatic Representation

$$\begin{pmatrix} V+ & 0 \\ 0 & V- \end{pmatrix}$$

An Idea that has been Extensively Used:

- ✓ Resonance Theory (Pauling, Organic Chemistry)
- ✓ Empirical Valence-bond Theory (London, Eyring, Polanyi, Sato, Raff, Warshel, Shurki, ...)
- ✓ Multi-Configuration Self-consistent Field Theory (Quantum Chemistry)
- ✓ Multi-Configuration Molecular Mechanics (Truhlar and Coworkers)

Our Recent Progress and Future Developments

❖ Potential Energy Surface

- New DFT Models[1] (Please see the poster by Dr. Yan Zhao.)

  High Accuracy and Broadly Applicable

  (*main-group thermochemistry, kinetics, noncovalent interactions, transition metals, charge transfer excited states* …)

- Hybrid QM/MM methods[2]
- Multi-Configuration Molecular Mechanics (MCMM)[3]

❖ Dynamics Theory

- Quantum Effects in Enzymatic Reactions[4]

  Ensemble-Averaged Variational Transition State Theory with Multi-dimensional Tunneling Contributions

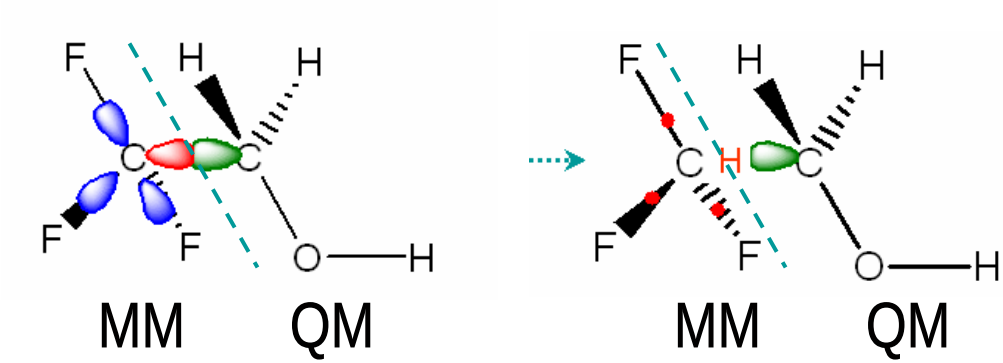
- Adaptive Partitioning Scheme for MD Simulations Based on Hybrid QM/MM Descriptions[5]

[1] Zhao, Y.; Schultz, N. E.; Truhlar, D. G. *J. Chem. Phys*. 2005, *123*, 161103.
[2] Lin, H.; Truhlar, D. G. *Theoret. Chem. Acc.* In press.
[3] Lin, H.; Zhao, Y., Tishchenko, O.; Truhlar, D. G. *J. Chem. Theory Comput.* 2006, *2*, 1237.
[4] Gao, J.; Truhlar, D. G. *Annu. Rev. Phys. Chem*. 2002, *53*, 467.
[5] Heyden, A.; Lin, H.; Truhlar, D. G. *J. Phys. Chem. B.* In press.

Flexible-Boundary QM/MM

- Step 1: Polarization of the QM Subsystem

  Redistributed Charge and Dipole Schemes[1]



✓Active Hybrid Orbital → Hydrogen Link Atom

✓Auxiliary Hybrid Orbitals →Redistributed Point Charges

✓Preservation of Charge and Bond Dipoles

☺ No New Parameters

☺ No Modifications to QM or MM Programs

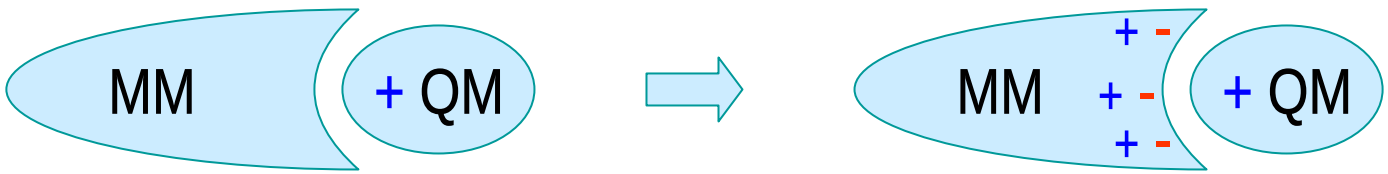
☺ Good Accuracy in Energies

[1] Lin, H.; Truhlar, D. G. *J. Phys. Chem. A* **2005**, *109*, 391.

Flexible-Boundary QM/MM (cont.)

- Step 2: Mutual Polarization between the QM and MM Subsystems

  Polarized-Boundary Redistributed Charge and Dipole Schemes[1]

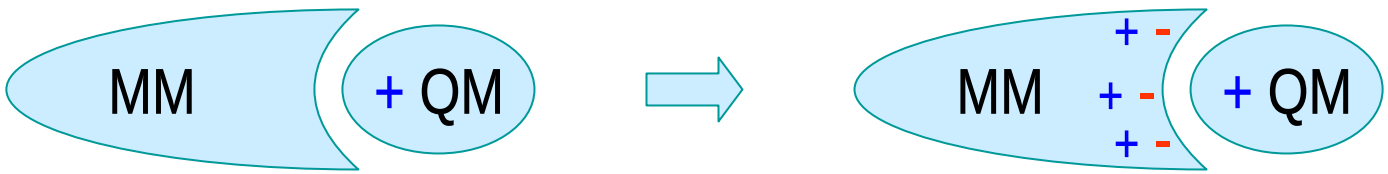


[1] Zhang, Y.; Lin, H.; Truhlar, D. G. *J. Chem. Theory Comput.* Submitted.

Flexible-Boundary QM/MM (cont.)

- Step 2: Mutual Polarization between the QM and MM Subsystems

  Polarized-Boundary Redistributed Charge and Dipole Schemes[1]



✓ Adjust the charges on the MM atoms near the boundary in response to the QM charge distribution.

- Electronegativity Equalization
- Charge Conservation

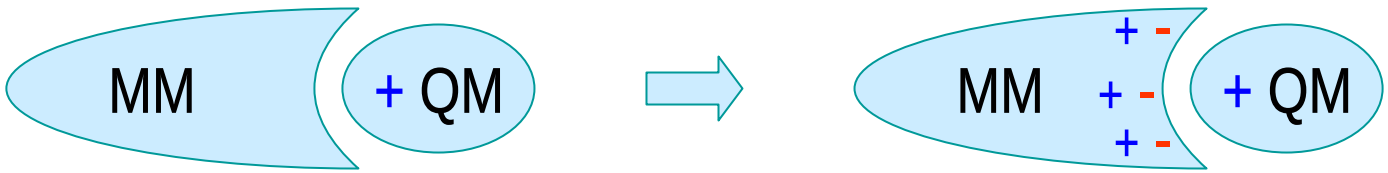
✓ Achieve improved accuracy in energies.

[1] Zhang, Y.; Lin, H.; Truhlar, D. G. *J. Chem. Theory Comput.* Submitted.

Flexible-Boundary QM/MM (cont.)

- Step 3: Both Mutual Polarization and Charge Transfer between the QM and MM Subsystems

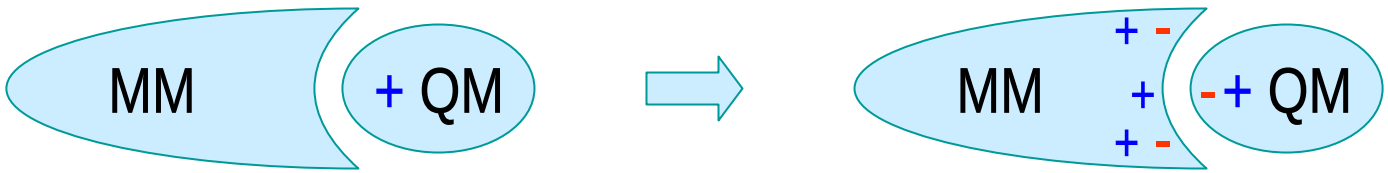
  Flexible-Boundary Redistributed Charge and Dipole Schemes (Work in Progress)



Flexible-Boundary QM/MM (cont.)

- Step 3: Both Mutual Polarization and Charge Transfer between the QM and MM Subsystems

  Flexible-Boundary Redistributed Charge and Dipole Schemes (Work in Progress)



✓QM with Fractional Electrons
✓MM Charge Redistribution
✓QM/MM Energy Minimization

QM/MM-MCMM

- Unique Features in MCMM[1,2]

Diabatic Representation

$$V=\begin{pmatrix} V_{11} & V_{12} \\ V_{21} & V_{22} \end{pmatrix}$$

The key is V_{12}!

Adiabatic Representation

$$\begin{pmatrix} V+ & 0 \\ 0 & V- \end{pmatrix}$$

How to express V_{12}?

- ✓Taylor Expansion of V_{12} at Selected Geometries
- ✓Shepard Interpolation[3,4] of V_{12} (Smoother than V)
- ✓Parameters Determined from Electronic-structure Calculations

☺ Full-dimensional Potential Energy Surface

☺ Low Computational Cost (Similar to Standard MM)

☺ Systematically Improvable Accuracy

[1] Kim et al, *J. Chem. Phys.* 112, 2718 (2000). [2] Albu et al., *J. Phys. Chem. A* 105, 8465 (2001).
[3] Ischtwan et al., *J. Chem. Phys.* 100, 8080 (1994). [4] Nguyen et al., *J. Chem. Phys.* 103, 5522 (1995).

QM/MM-MCMM (cont.)

- Building in the QM Contributions both Laterally and Vertically[1]

  ✓ View QM/MM as a generalized electronic-structure method.

  - Should do a good job as long as QM/MM does a good job.
  - Efficiently construct reactive potential energy surfaces for large-size systems.

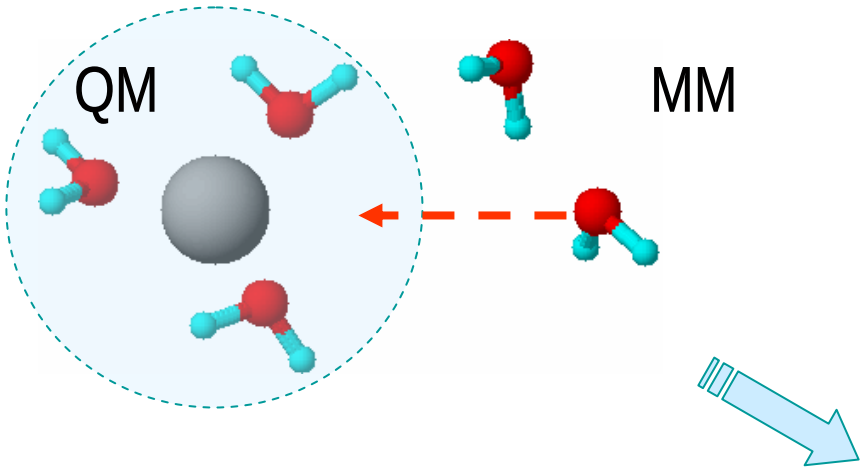
  ✓ Tests showed good accuracy in dynamics calculations at the level of variational transition state theory with multi-dimensional tunnelling contributions.

  ✓ May be applied to trajectory simulations (future work).

[1] Lin, H.; Zhao, Y., Tishchenko, O.; Truhlar, D. G. *J. Chem. Theory Comput.* **2006**, *2*, 1237.

Adaptive-Partitioning Schemes

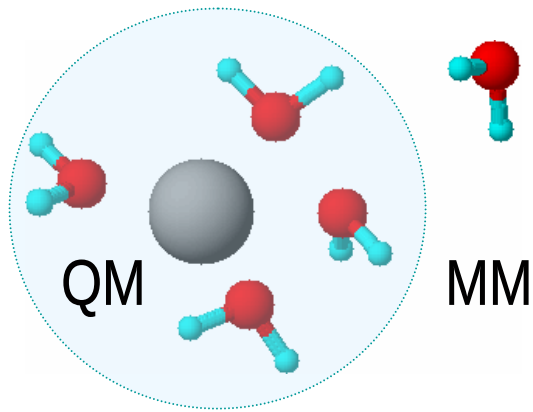
- Why?



✓A reactive moiety diffuses through a liquid.

✓A dislocation propagates through a material.

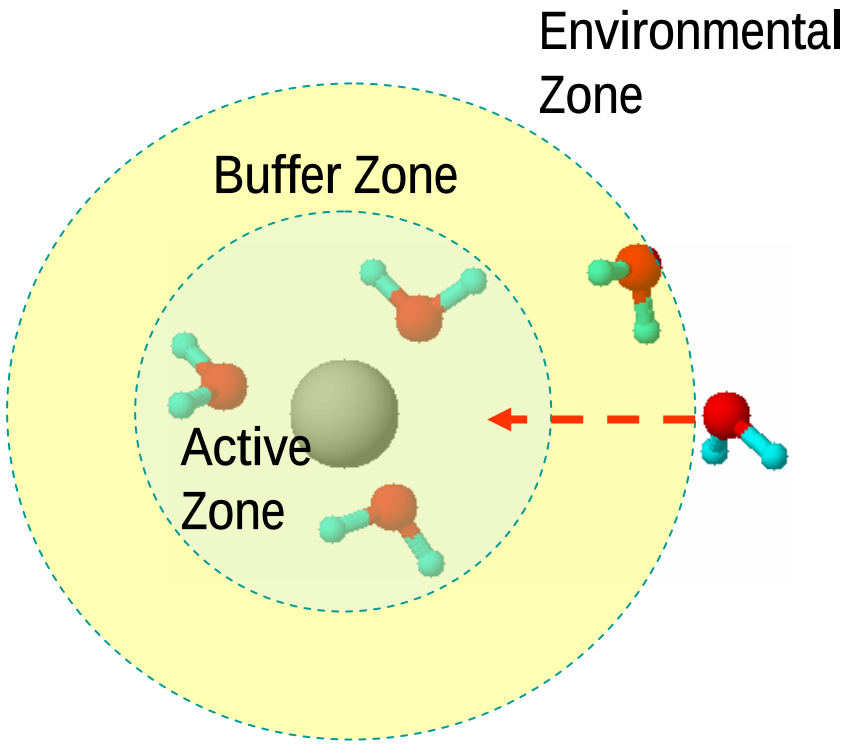
✓The 1st and 2nd coordination shells exchange solvent molecules.



The atoms enter and leave the QM region dynamically,
and they change their QM or MM characteristics as they do so.

Adaptive-Partitioning Schemes (cont.)

- Strategy
  - ✓Buffer Zone
  - ✓Smoothing Function on Energy and/or Forces



- Must conserve the energy and momentum; if not …
  - ✓May cause numerical instability.
  - ✓Risk sampling of configuration space from an unknown ensemble.

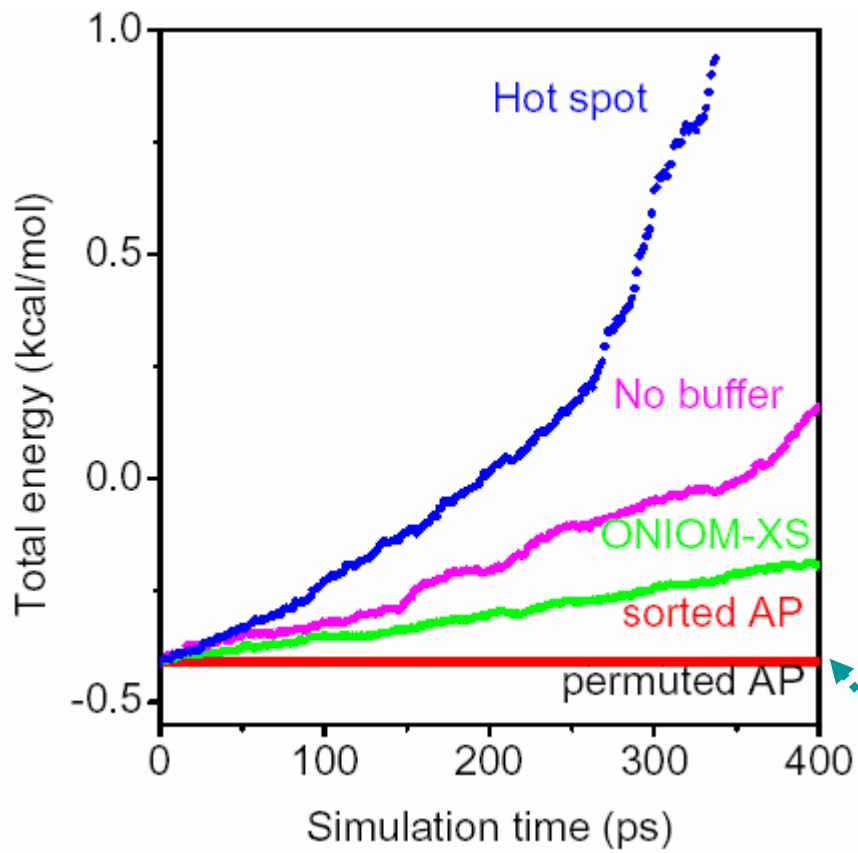
Adaptive-Partitioning Schemes (cont.)

- Comparisons of Schemes

Schemes	Conserve energy?	Conserve momentum?
Hot Spot [1]	No	No
ONIOM-XS [2]	No	Yes
Permuted Adaptive-Partitioning [3]	Yes	Yes
Sorted Adaptive-Partitioning [3]	Yes	Yes

[1] Kerdcharoen, T.; Leidel, K. R.; Rode, B. M. *Chem. Phys.* **1996**, *211*, 313.
[2] Kerdcharoen, T.; Morokuma, K. *Chem. Phys. Lett.* **2002**, *355*, 257.
[3] Heyden, A.; Lin, H.; Truhlar, D. G. *J. Phys. Chem. B,* in press.

Adaptive-Partitioning Schemes (cont.)



NVE Simulations[1]

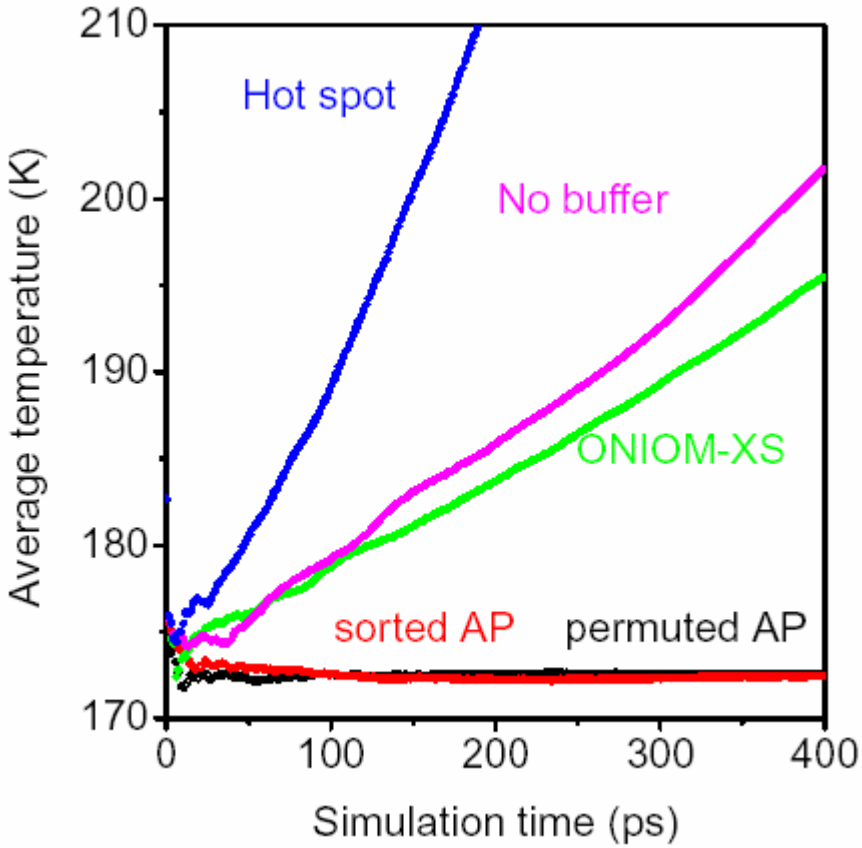
- ✓ 171 Ar Atoms
- ✓ 1st Atom as the Active Zone Center
- ✓ Periodic Box (L = 20 Å)
- ✓ 5 Å < Buffer Zone < 5.5 Å

Only the AP methods conserve energy.

The permuted AP curve is right underneath the sorted AP curve.

[1] Heyden, A.; Lin, H.; Truhlar, D. G. *J. Phys. Chem. B,* in press.

Adaptive-Partitioning Schemes (cont.)



NVE Simulations[1]

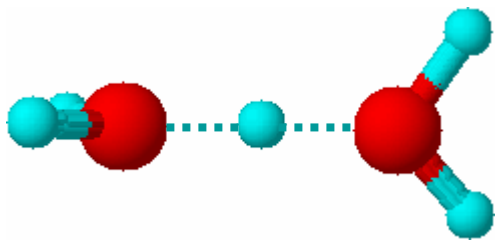
Hot Spot and ONIOM-XS heat up the system.
(A convective flow of atoms is superimposed on the diffusive movement of the atoms.)

AP: Free of this Artifact.

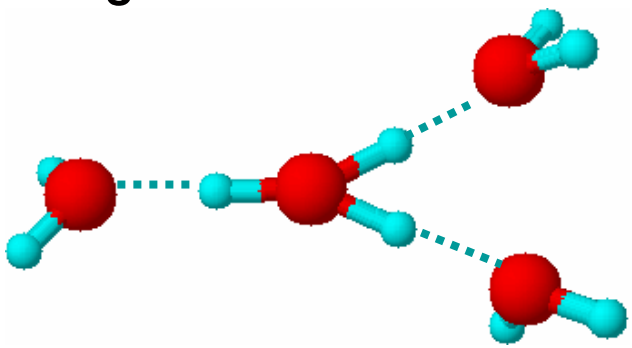
[1] Heyden, A.; Lin, H.; Truhlar, D. G. *J. Phys. Chem. B,* in press.

Adaptive-Partitioning Schemes (cont.)

Zundel



Eigen



Energy: Fuel Cells

Work in Progress

Proton Transport in Solution and in Ion Channel

The Transfer of the Structural Feature rather than a Given Proton

Summary

- Seamless Connections between the QM and MM Subsystems
  - ✓ Polarization of the QM Subsystem
  - ✓ Self-Consistent Mutual Polarization of the QM and MM Subsystems
  - ✓ Flexible-Boundary = Mutual Polarization + Charge Transfer

- QM/MM–MCMM
  - ✓ Building in the QM Contributions both Laterally and Vertically.

- Dynamics Based on Combined QM and MM Descriptions
  - ✓ Adaptive Partitioning Schemes

The Future ...

- Computers: Faster (Peta!) and Larger Storages; Fast Turnaround

- Methods: More Accurate, More Efficient, and More Realistic

- Programs:

  (1) More Capacity, Better Parallelization, and Hopefully Less Bugs

  (2) User Friendly

  (3) **Integrated**: Multi-capability Codes for Multi-scale Modeling

- Answer lots of questions, and raise even more questions to be answered ...

Acknowledgements

Andreas Heyden, Oksana Tishchenko, Yan Zhang, Yan Zhao

Department of Energy
National Science Foundation
Office of Naval Research
Research Corporation
Minnesota Supercomputing Institute

Organizer for the Invitation

Abstract

We will present our recent progress in methodology and computer programs for the modeling of large-size reactive systems by combining quantum mechanics (QM) and molecular mechanics (MM). These methods can be applied for multiscale modeling or whenever one needs to treat a portion of a large system at a higher level than the whole system. Two kinds of advances will be discussed, and some future developments will be outlined. The first set of advances to be discussed includes polarized-boundary[1] and flexible-boundary QM/MM schemes, which account for self-consistent mutual polarization and charge transfer between the QM and MM moieties to build more seamless connections between them. These methods are especially powerful when combined with the redistributed charge algorithm[2] for treating the QM-MM boundary. The second kind of advance involves new techniques for dynamics simulations, including (1) adaptive partitioning schemes,[3] which allow atoms to switch between the QM and MM subsystems or to change their QM or MM characteristics during the trajectory propagation or any molecular dynamics simulation. and (2) QM/MM-based multi-configuration molecular mechanics,[4,5] which is highly efficient in generating potential energy surfaces for dynamics calculations at the level of variational transition state theory with multi-dimensional tunneling contributions or at other levels of dynamical simulation. These advancements will contribute to more accurate, more efficient, and more realistic molecular modeling and simulations in the areas of chemistry, biology, and material sciences.

[1] Zhang, Y.; Lin, H.; Truhlar, D. G., *J. Chem. Theory Comput.*, submitted.
[2] Lin, H.; Truhlar, D. G., *J. Phys. Chem. A* **2005,** *109*, 3991.
[3] Heyden, A.; Lin, H.; Truhlar, D. G., *J. Phys. Chem. B*, **2007 in press.**
[4] Lin, H.; Zhao, Y.; Tishchenko, O.; Truhlar, D. G., *J. Chem. Theory Comput.* **2006,** *2*, 1237.
[5] Lin, H.; Truhlar, D. G., *Theor. Chem. Acc.* **2007,** in press [available in On-line First at DOI 10.1007/s00214-006-0143-z]

Our Recent Progress and Future Developments

- Potential Energy Surface
  - ✓ New DFT models[1] (Please see the poster by Dr. Yan Zhao.)

    High Accuracy and Broadly Applicable

    (*main-group thermochemistry, kinetics, noncovalent interactions, transition metals, charge transfer excited states* …)
  - ✓ Hybrid QM/MM methods[2]

    More Accurate Descriptions of the Interactions between the QM and MM Subsystems
  - ✓ Multi-Configuration Molecular Mechanics (MCMM)[3]

    Based on Hybrid QM/MM Descriptions, Incorporating the QM Contributions both Laterally and Vertically — QM/MM-MCMM

[1] Zhao, Y.; Schultz, N. E.; Truhlar, D. G. *J. Chem. Phys*. **2005**, *123*, 161103.
[2] Lin, H.; Truhlar, D. G. *Theoret. Chem. Acc.* In press.
[3] Lin, H.; Zhao, Y., Tishchenko, O.; Truhlar, D. G. *J. Chem. Theory Comput.* **2006**, *2*, 1237.

Our Recent Progress and Future Developments (cont.)

- Dynamics Theory
  - ✓ Quantum Effects in Enzymatic Reactions[1]

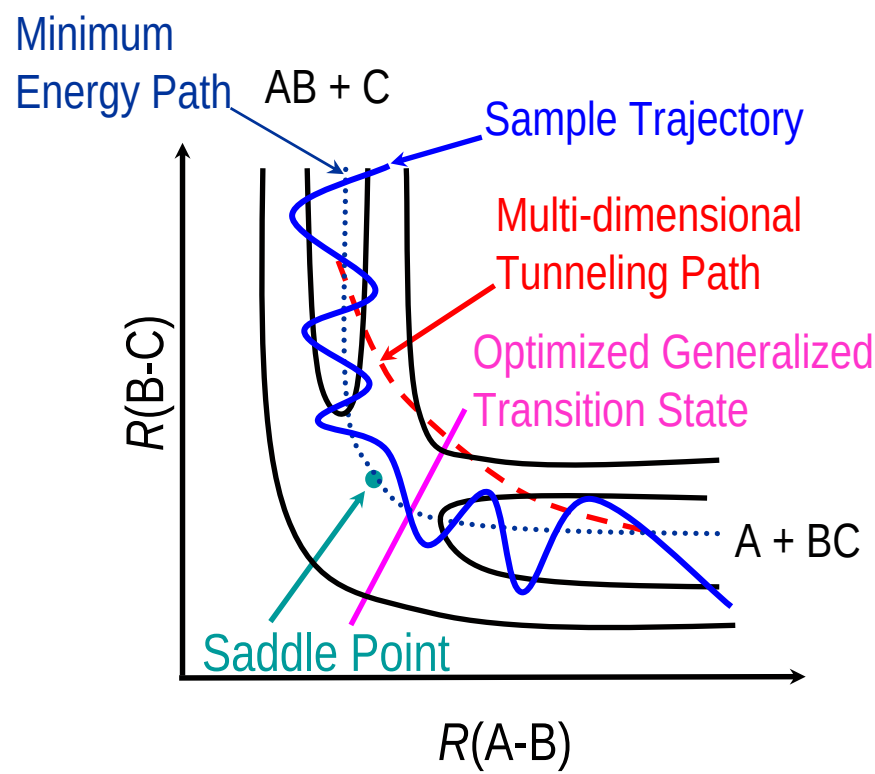
    Ensemble-Averaged Variational Transition State Theory with Multi-dimensional Tunneling Contributions

    Umbrella Sampling, Variational and Recrossing Effects, Zero-Point Energy, and Tunneling Contributions
  - ✓ Adaptive Partitioning Scheme for MD Simulations Based on Hybrid QM/MM Descriptions[2]

    A Dynamically Defined QM and MM Partitioning Scheme that Allows Atoms to Switch between the QM and MM Subsystems (and Change Their QM or MM Characteristics) on the Fly

[1] Gao, J.; Truhlar, D. G. *Annu. Rev. Phys. Chem.* **2002**, *53*, 467.
[2] Heyden, A.; Lin, H.; Truhlar, D. G. *J. Phys. Chem. B.* In press.

Dynamics Theory

- Dynamical or Equilibrium Simulation
  - ✓"Smart" MD and MC Algorithms that Sample the Phase Space Efficiently
  - ✓Efficient Coupling with Methods that Compute the Potentials (e.g., the Car-Parrinello or other Efficient Direct Dynamics Schemes)

- Transition State Theory
  - ✓Variational Effect and Tunneling Contributions in Complex Environments