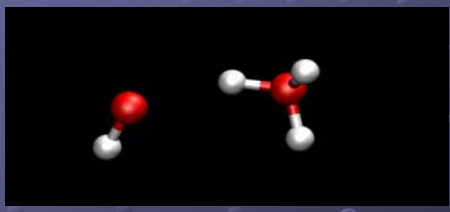


## QM/MM Theory and Practice



By  
Ross Walker

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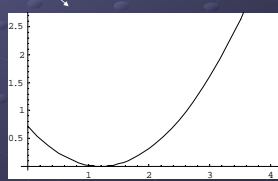
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## Classical Force Field Limitations

$$E_{total} = \sum_{bonds} K_r (r - r_{eq})^2 + \sum_{angles} K_\theta (\theta - \theta_{eq})^2 + \sum_{dihedrals} \frac{V_n}{2} (1 + \cos(n\phi - \gamma)) + \sum_{i < j} \left[ \frac{A_{ij}}{R_{ij}^{12}} - \frac{B_{ij}}{R_{ij}^6} + \frac{q_i q_j}{\epsilon R_{ij}} \right]$$

- 1) Need parameters for each atom type and with the types of it's 1-2, 1-3 and 1-4 interactions.
- 2) We cannot break bonds during a simulation.



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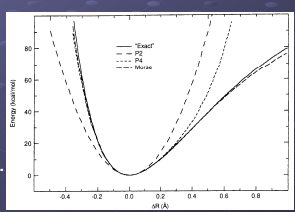
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## Quantum Mechanics

Offers a solution to these limitations.

Need only parameters for each element.  
Bond breaking and formation is possible.  
Also allows for polarisation as electrons are explicitly dealt with.



But pure QM calculations are too expensive to use with proteins.

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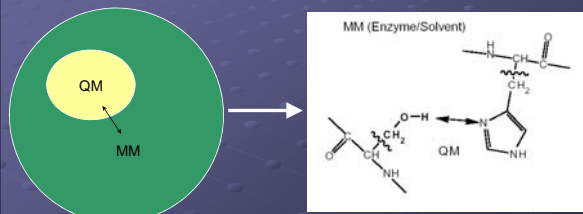
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## The QM/MM Idea

### Multi-layered method



- First proposed by Warshel and Levitt in 1976 (Lysozyme).

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## The Hybrid QM/MM Potential

Effective Hamiltonian for the system.

$$\hat{H}_{eff} \Psi(x_e, x_{QM}, x_{MM}) = E(x_e, x_{QM}, x_{MM}) \Psi(x_e, x_{QM}, x_{MM})$$

$$\hat{H}_{eff} = \hat{H}_{QM} + \hat{H}_{MM} + \hat{H}_{QM/MM}$$

$$E_{eff} = E_{QM} + E_{MM} + E_{QM/MM}$$

If we write  $E_{eff}$  as expectation value of  $H_{eff}$  then we can remove  $E_{MM}$  from the integral since it is independent of the positions of the electrons.

$$E_{eff} = \langle \Psi | \hat{H}_{QM} + \hat{H}_{QM/MM} | \Psi \rangle + E_{MM}$$

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## The Hybrid QM/MM Potential

- $E_{MM}$  can be evaluated classically.  
(i.e. Amber force field equation)
- $E_{QM}$  can be evaluated using a standard QM method.  
(i.e. Semi-empirical (PM3, AM1...), *Ab initio* (HF, MP2) or DFT)
- $E_{QM/MM}$  is the tricky bit.

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## QM Region

- What should be used in the QM region?
  - Ab initio* (HF, MP2...)
  - DFT (B3LYP, B3P86...)
  - Semiempirical (PM3, AM1...)
- Usually answer is dictated by cost. Most QM/MM MD simulations to date have used semiempirical QM regions.
- Why? Need as big a QM region as we can afford. Not good to have QM/MM boundary close to the chemistry of interest.

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## Pitfalls in QM/MM

- Not clear which force fields to use.
  - Much experience with expected accuracy of *ab initio* methods alone.
  - Much experience with MM methods alone.
  - Not much experience with QM/MM
- No direct map from wavefunction to parameters.
- How do we treat QM/MM VDW interaction?
  - Normally done classically
  - But do we need to scale the interaction? Why?

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## Dealing with $E_{QM/MM}$

- Mechanical Embedding
  - Crudest level of QM/MM
  - Include only classical Van der Waals in  $E_{QM/MM}$
  - Useful to impose only steric constraints
  - Can take advantage of this to isolate MM and QM effects.

$$\hat{H}_{QM/MM} = \sum_{\substack{i \in MM \\ j \in QM}} V_{ij}^{VDW}(\vec{r}_i, \vec{r}_j)$$

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## Electrostatic Embedding

- Also include interaction of MM point charges with:
  - Electron Cloud of QM Region
  - QM atomic cores
- Many possible implementations – best? is to evaluate integrals over continuous QM charge density and discrete MM charge density

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## Electrostatic Embedding

$$\hat{H}_{QM/MM} = -\sum_e \sum_m q_m \hat{h}_{electron}(\vec{r}_e, \vec{r}_m) + \sum_q \sum_m z_q q_m \hat{h}_{core}(\vec{r}_q, \vec{r}_m) + \sum_q \sum_m \left( \frac{A_{qm}}{r_{qm}^{12}} - \frac{B_{qm}}{r_{qm}^6} \right)$$

Electrostatic interaction between MM charge and QM electron cloud

Electrostatic interaction between MM charge and QM core charge

VdW interaction between MM and QM atoms

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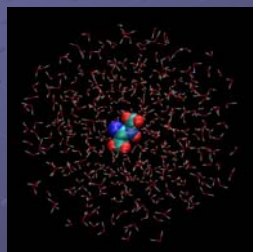
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## Some Examples

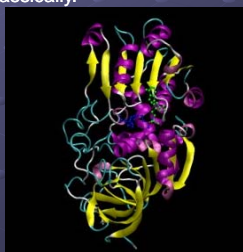
### In solution

Reactants treated by QM are surrounded by MM waters:



### Co-enzyme

Non-covalently bound co-enzyme treated quantum mechanically. Protein and solvent treated classically.




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## Covalent Embedding

- More difficult embedding – cutting across covalent bonds.
- Almost always required for systems of biological interest. (Active Site QM, remainder MM)
- Many Strategies; still not clear which is best or how well they “work”.
- Probably the most debated subject in hybrid QM/MM simulations.

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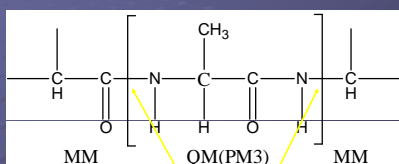
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## Covalent Embedding



How do we deal with these MM-QM bonds?

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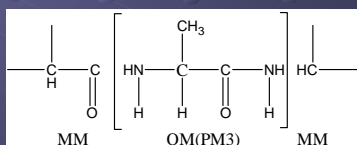
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## Link atom approach

- First introduced by Singh and Kollman (1986)
- Method implemented in AMBER.
- Include extra atoms (typically H) in the QM region to fill valence.




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## Link atom approach

- Maintain QM to MM covalent terms.
  - Calculate all bonds angles and dihedrals that include at least one MM atom using classical force field.
- MM atoms not bound directly to the QM region see all QM atoms (including link atom) and vice versa.
- Link atom sees all but MM atoms bonded to link atoms.
- Some debate over whether omitting the  $Q_{link}$ -MM atom interaction causes problems. (Reuter *et al.*, 2000)
- Do you include 1-2 and 1-3 MM-QM atoms in QM-Interaction? Singh and Kollman did not include. Amber 9 and Dynamo do include...

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## Link atom approach

- Amber 8 and Amber 9/10 link atom approaches differ.
- In Amber 8 link atom undergoes dynamics.
  - Details are appended to end of force and parameter arrays
  - Extra bookkeeping can lead to mistakes
  - Short time step required for stability (0.5fs)
  - Link atom only influences forces on QM region (unbalanced?)

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## Link atom approach

- Amber 10 uses a constrained link atom. (same as Dynamo)
- Link atom is *always* placed at a fixed distance along the bond vector that is broken using:

$$\bar{r}_L = \bar{r}_{QM} + d_{L-QM} \frac{\bar{r}_{MM} - \bar{r}_{QM}}{|\bar{r}_{MM} - \bar{r}_{QM}|}$$

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## Link Atom – Amber 10 Implementation

- Once QM link atom gradient is known the force on the link atom is re-distributed between QM and MM link pair using:

$$F'_{x_{QM}} = -\frac{\partial V(\bar{r}_L)}{\partial x_{QM}} = -\nabla_L V \cdot \frac{\partial \bar{r}_L}{\partial x_{QM}} = \bar{F}_L \cdot \frac{\partial \bar{r}_L}{\partial x_{QM}}$$

$$F'_{x_{MM}} = \bar{F}_L \cdot \frac{\partial \bar{r}_L}{\partial x_{MM}}$$

And corresponding y and z component forms.

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## Link Atom – Amber 9 Implementation

- Partial Derivatives can be expressed as:

$$\frac{\partial \bar{r}_L}{\partial x_{QM}} = \left(1 - \frac{d_{L-QM}}{d_{MM-QM}}\right) \bar{i} + \frac{d_{L-QM}(x_{MM} - x_{QM})}{d_{MM-QM}^3} (\bar{r}_{MM} - \bar{r}_{QM})$$

$$\frac{\partial \bar{r}_L}{\partial x_{MM}} = \frac{d_{L-QM}}{d_{MM-QM}} \bar{i} - \frac{d_{L-QM}(x_{MM} - x_{QM})}{d_{MM-QM}^3} (\bar{r}_{MM} - \bar{r}_{QM})$$

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## Link Atom – Amber 10 Implementation

- Has several advantages over AMBER 8 approach.
  - Removes issue of “extra” degrees of freedom introduced by Amber 8 method.
  - Completely transparent to the user.
  - No extra bookkeeping required to keep track of link atom position. Restart and MDCRD file compatibility is maintained.
  - Always know exactly where the link atom is.
  - Seems to be much more stable – 2 fs time step with Shake is stable for QM/MM simulation.

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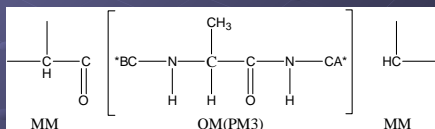
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## Alternative Approaches

### ● Capping Potential Methods

- Also known as pseudo bond methods.
- Use element of fictitious type to 'cap' each bond between QM and MM region.
- E.g. if MM atom in QM-MM pair is an  $sp^3$  carbon then MM atom is replaced by *univalent* QM atom that is parameterised to behave like an  $sp^3$  carbon.




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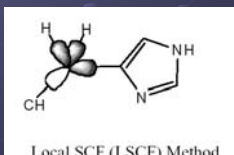
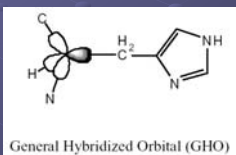
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## Alternative Approaches

### ● Hybrid-orbital approach

- Method used by Warshel and Levitt in their seminal QM/MM work.
- Either place hybrid or localised orbitals on the QM atom which point towards MM atom.
- These orbitals are kept frozen during the QM calculation.




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## Covalent Embedding

- All methods for dealing with covalent bonds have their advantages and disadvantages.
- Link Atom approach is arguably the easiest to implement and requires the fewest parameters.
- Experience has shown that if used carefully the link atom method can give satisfactory results.

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## QM/MM Cautions

- Most force fields do not include polarisability, but QM region will.
- This can lead to imbalance and amplification of errors.
- All covalent embedding schemes should be treated with caution – it is surely possible to break almost every implemented scheme.
- Dependence of results on QM/MM partitioning must be carefully tested.

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## QM/MM Cautions

- Newton's equations are typically used to propagate MD. No tunnelling contributions.
- SCF convergence must be very stringent to obtain forces accurate enough to conserve energy.

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## History of QM/MM in AMBER

- 1) Singh and Kollman used modified version of Gaussian 80 linked to an early version of AMBER.
- 2) A fork of AMBER v4.0 was used as the basis of ROAR which provided semi-empirical QM/MM support via modified version of MOPAC. Part of AMBER suite up to AMBER v7.
- 3) AMBER v8 - ROAR removed and QM/MM support, on a functionally limited basis, provided by special version of sander linked against a library provided by DIVCON.

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## QM/MM support in AMBER 10

- AMBER 10 has QM/MM support as part of regular sander.
- Support for semi-empirical QM including: PM3, AM1, MNDO, PDDG-PM3, PDDG-MNDO, PM3CARB1, SCC-DFTB
- Support for Gas Phase, Stochastic Boundary and PME based periodic boundary QM/MM calculations.

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## QM/MM support in AMBER 10

- Support for Generalised Born implicit solvent QM/MM simulations.
- Simulation of low energy reaction pathways involving bond breaking and formation using a QM/MM implementation of the Nudged Elastic Band Method.
- Full dynamic memory allocation.
- Support for running simulations in parallel using MPI.

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## Amber 10 QM/MM Speed

Malachite Green QM MD – Gas Phase

Program	Time (s)	PS/Day	Notes
SANDER v9	132.9	650.1	
SANDER v8	493.3	175.1	
ROAR v2.0	464.4	186.0	
DYNAMO v2.0	393.1	217.0	
CHARMM v31b2	548.7	157.5	Runs longer than 1073 steps end with a segmentation fault.

<sup>a</sup> Simulation Details: Malachite Green (50 Atoms), pure QM simulation in gas phase. No cutoff, PM3. Time step = 1fs. Total steps = 1,000. No Shake, no coordinate file was written.

<sup>b</sup> Compiler: Intel ifort v8.1.023 was used to compile all codes.

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## Amber 10 Example Input File

```
Example QMMM MD Script for Sander 10
&cntrl
  imin=0, nstlim=10000, dt=0.002,
  ntt=1, tempi=0.0, temp0=300.0,
  ntb=1, ntf=2, ntc=2, cut=12.0,
  ifqnt=1,
/
&qmmm
  qmmask=':753',
  qmcharge=-2,
  qm_theory='PM3',
/
```

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## Amber QM/MM Tutorials

An Amber v10 QM/MM tutorial is the next hands on session.

We will try out some QM/MM simulations as part of the next hands on session.

If you want to try out some QM/MM simulations on your own systems feel free to ask me for help.

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