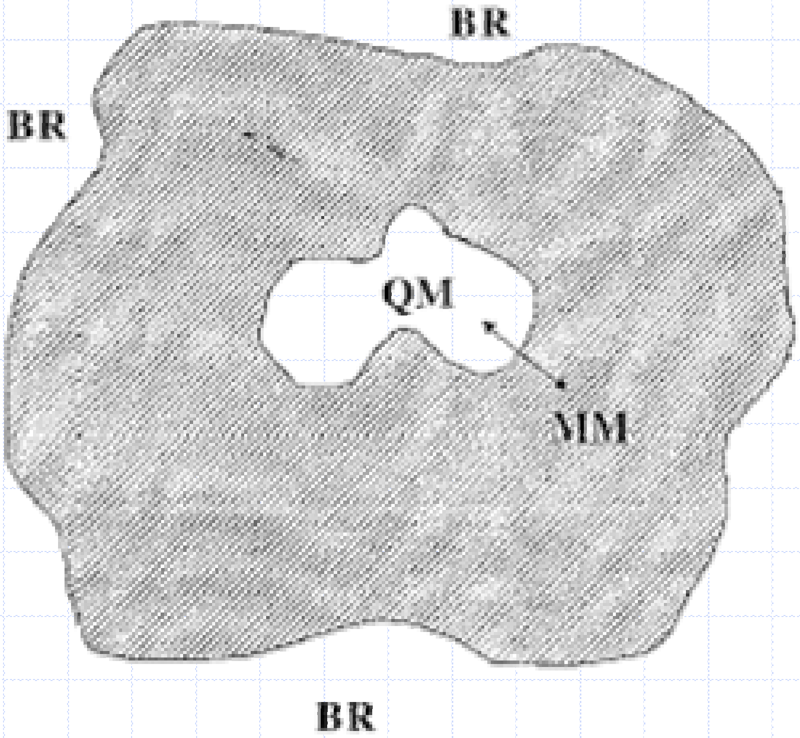
Quantum Mechanics/ Molecular Mechanics (QM/MM)

Todd J. Martinez

The QM/MM Idea

Multi-layered method



Monard, et. al, Acc. Chem. Res., **32**, 904 (1999)

QM/MM Partitioning

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

The tough part – how do QM and MM interact?

Energy of MM subsystem

$$E_{QM} = \frac{\langle \psi \hat{H} \psi \rangle}{\langle \psi \psi \rangle}$$

Warshel and Levitt, J. Mol. Biol.
Field, Bash and Karplus, J. Comp. Chem.

QM Region

- What should be used in the QM region?
  - Ab Initio
  - DFT
  - Semiempirical
- Usually, the answer to this is dictated by cost. Most QM/MM simulations to date have used semiempirical QM regions
- Why? QM/MM interaction term can be problematic – it is not good to have this boundary close to the chemistry of interest…

Pitfalls in QM/MM

$$V(\vec{R}) = \sum_{i\in bonds} k_{i,bond}\left(r_{i,bond} - r^{eq}_{i,bond}\right) + \sum_{i\in angles} k_{i,angle}\left(\theta_{i,angle} - \theta^{eq}_{i,angle}\right) + \cdots$$

$$+\tfrac{1}{2}\sum_{\substack{i\neq j\\ i,j\in atoms}} \frac{q_i q_j}{\left|r_i - r_j\right|} + \tfrac{1}{2}\sum_{\substack{i\neq j\\ i,j\in atoms}} V^{ij}_{LJ}\left(\left|r_i - r_j\right|\right)$$

Not clear which force fields to use – much experience with expected accuracy of *ab initio* methods alone and MM methods alone, but not much with QM/MM

No direct map from wavefunction to parameters

Mechanical Embedding

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

$$H_{QM/MM} = \sum_{\substack{i \in MM \\ j \in QM}} V_{ij}^{VdW}(r_i, r_j)$$

Electrostatic Embedding

- Include electrostatic interaction in $H_{QM/MM}$
- Many possible implementations – best is to evaluate integrals over continuous QM charge density and discrete MM charge density

$$H_{QM/MM} = H_{QM/MM}^{mechanical} + \sum_{i \in MM} q_i \int \frac{\rho_{QM}(r)}{|r - r_i|} dr$$

Oft-used approximation (questionable):

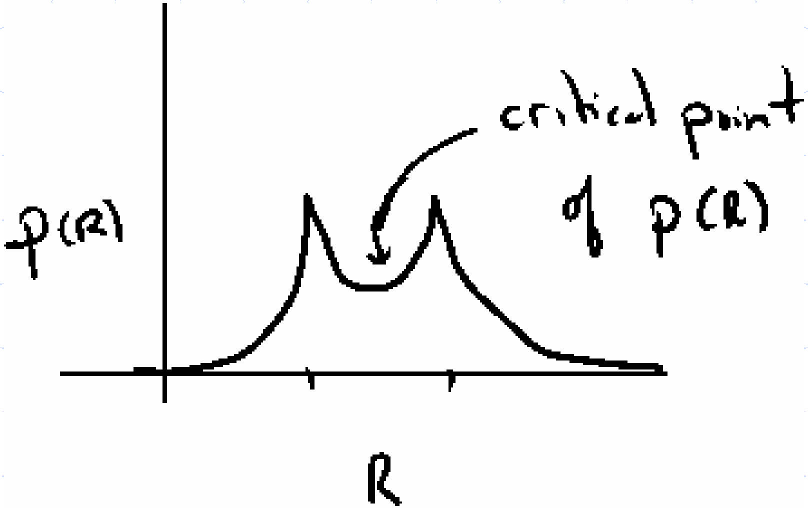
$$H_{QM/MM} = H_{QM/MM}^{mechanical} + \sum_{\substack{i \in MM \\ j \in QM}} q_i q_j (\rho_{QM})$$

Atomic Charge Schemes

- "Atoms" are not well-defined in molecules – there is no quantum mechanical operator corresponding to an atom.
- This leads to ambiguity in the definition of an atomic charge
- Population Analysis Schemes
  - Basically, sum over all electrons using the basis functions of a given atom
  - Depends on the atom-centered nature of the basis set
  - Breaks down as the basis functions become more delocalized – results do not usually converge with increasing basis set!

Charge Schemes

- Atoms-in-molecules
  - Atoms are defined by “critical points” of the charge density
  - More stable than Mulliken/Lowdin schemes with respect to basis set expansion
  - Implemented in Gaussian
  - Not clear whether stable=“correct”



Charge Schemes 2

- ESP-Fitting
  - Determine charges which reproduce the electrostatic potential generated by the molecule
  - If using charges in an MM potential, this appears to be the right way
  - But, equations have many solutions, especially when molecule has an "interior"

Charge for solvated ion will be essentially undetermined

Charge Schemes 3

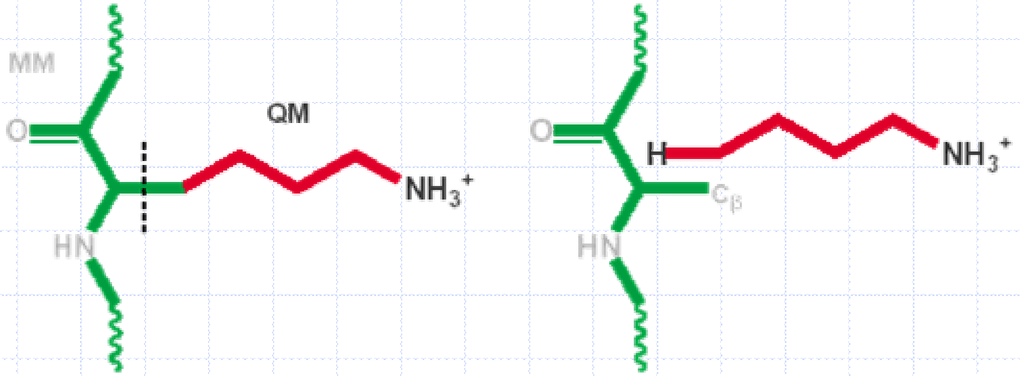
- Restricted ESP-Fitting (RESP)
  - Attempts to avoid unphysical solutions of ESP-charges
  - Requires user guidance in imposing “reasonable” values of charges

Covalent Embedding

- Most difficult embedding – cutting across covalent bonds
- Almost always required in biological context
- Many strategies; still not clear which is best or whether any of them “work”

Singh & Kollman (1986)

E_{QM}: HF E_{MM}: AMBER $E_{QM/MM}$: Link atom



Covalent Embedding 2

- Potential Problems with Link Atom Idea
  - Extra degrees of freedom which somehow need to be removed; i.e. the link atom somehow needs to be connected to the MM part of the simulation
  - Electronic structure at boundary will be very different if H and the atom it replaces do not have similar electronegativities

Covalent Embedding 3

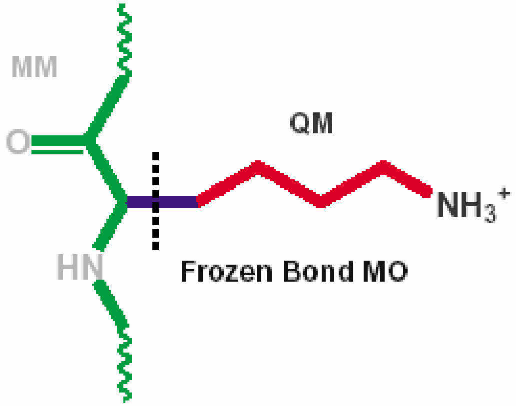
- Thiel
  - Adjust electronegativity of link atom to be equivalent to target atom. Also adjust size of atom
  - Can only do this easily with semiempirical models
  - Still can cause problems, especially with electronically excited states – the 2s-3s transition of H-like atom is much lower than the 1s-2s transition!

Covalent Embedding 4

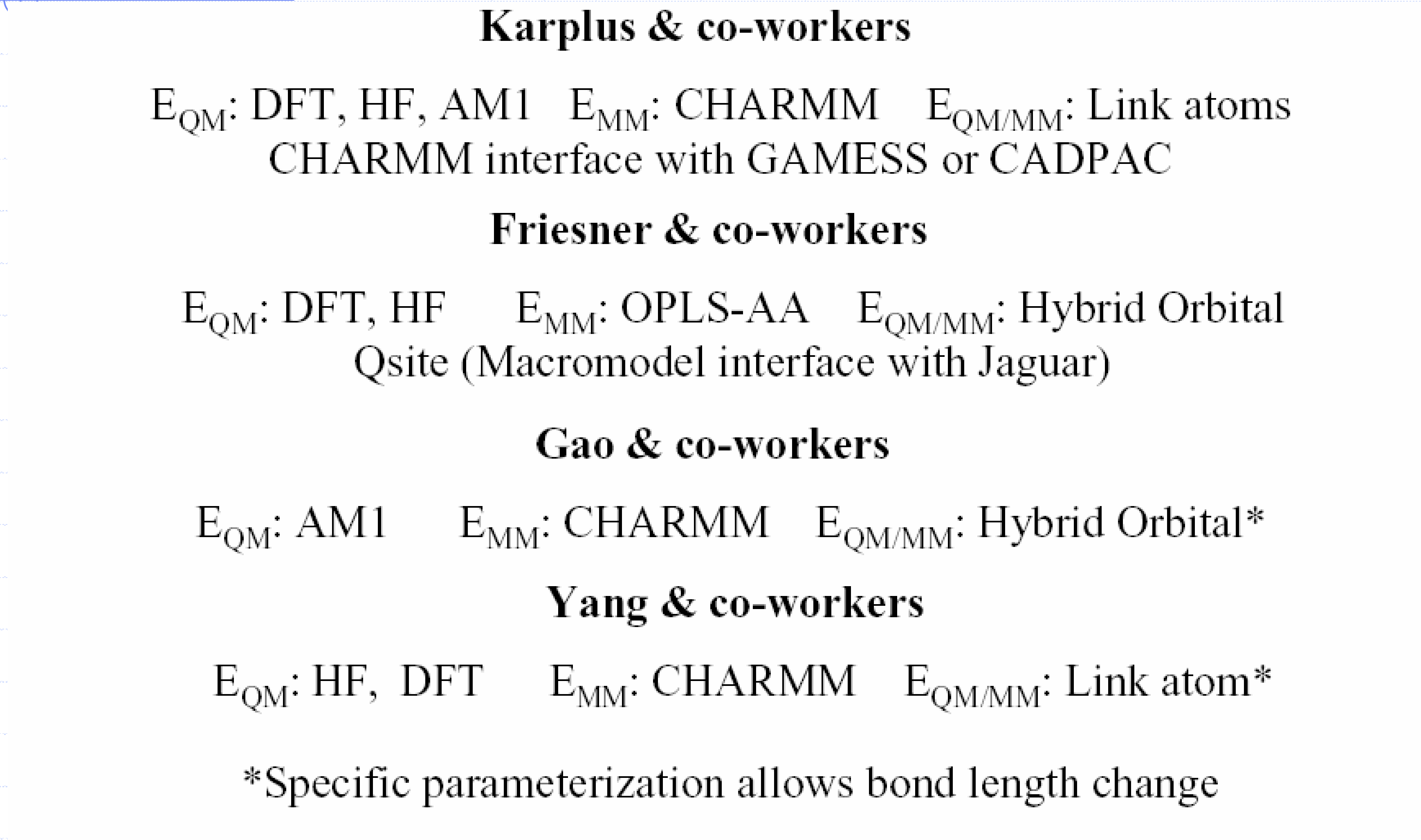
Frozen orbital ideas:

Rivail & co-workers (1994)

E_{QM}: AM1 E_{MM}: AMBER $E_{QM/MM}$: **Hybrid MO**



Summary of current approaches



Karplus & co-workers

E_{QM}: DFT, HF, AM1 E_{MM}: CHARMM $E_{QM/MM}$: Link atoms
CHARMM interface with GAMESS or CADPAC

Friesner & co-workers

E_{QM}: DFT, HF E_{MM}: OPLS-AA $E_{QM/MM}$: Hybrid Orbital
Qsite (Macromodel interface with Jaguar)

Gao & co-workers

E_{QM}: AM1 E_{MM}: CHARMM $E_{QM/MM}$: Hybrid Orbital*

Yang & co-workers

E_{QM}: HF, DFT E_{MM}: CHARMM $E_{QM/MM}$: Link atom*

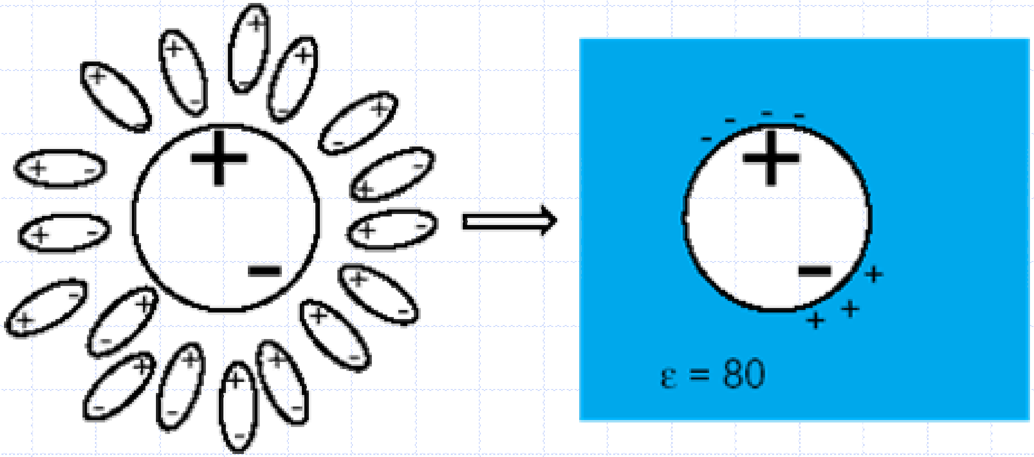
*Specific parameterization allows bond length change

Cautions

- Most force fields do not include polarizability, 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
- One needs to test carefully the dependence of the results on the QM/MM partitioning

Coarser than QM/MM?

- Continuum solvation models – treat solvent as a dielectric continuum (PCM=Polarizable Continuum Model; SCRF=Self-Consistent Reaction Field)



Continuum Solvation

- Algorithm:
  - Compute “reaction field” – polarization of dielectric continuum which generates electric field acting on solute
  - Compute electronic wavefunction in presence of new solvent-generated field
  - Loop until reaction field does not change
- Issues:
  - Shape of cavity (spherical and ellipsoidal are rarely acceptable at present)
  - Dielectric of solvent – zero vs infinite frequency?
  - H-bonding between solvent and solute will not be properly represented
  - Atomic radii used to generate cavity

Supermolecule Approach

- Explicit solvent molecules in first solvation shell
- Surround with dielectric continuum
- Expensive, but can be very accurate
- Not feasible if solute is very large

- Related approach – QM/MM/PCM