Overview of hybrid QM/MM methods

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Quantum mechanics

- In theory, a very accurate treatment of the system
- Largely *ab initio*, i.e. parameter-free
- Very expensive — typically scales as $\mathcal{O}(N^4)$ or worse
- Limited to very small systems at high accuracy (e.g. DFT)
- Can be used for larger systems at lower accuracy (e.g. semi-empirical)
- Entire proteins cannot be simulated without enormous supercomputer power

Molecular mechanics

- Treats the electrons implicitly — no handling of polarization or electron transfer
- Bonds, angles, and dihedrals are held by a parameterized force field

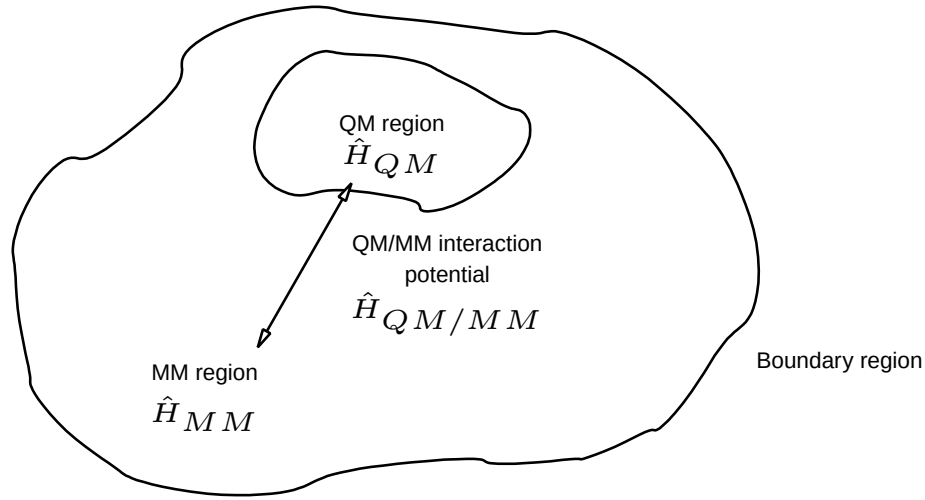
$$V_{total} = \sum_{\text{bonds}} V_{bond} + \sum_{\text{angles}} V_{angle} + \sum_{\text{dihed.}} V_{dihed}$$
$$+ \sum_{\text{impr.}} V_{impr} + \sum_{i \neq j} (V_{vdW} + V_{elec})$$

- Can be used to simulate very large systems — e.g. transmembrane proteins
- Cannot handle bond breaking or formation, so cannot be used to simulate chemical reactions

Hybrid QM/MM

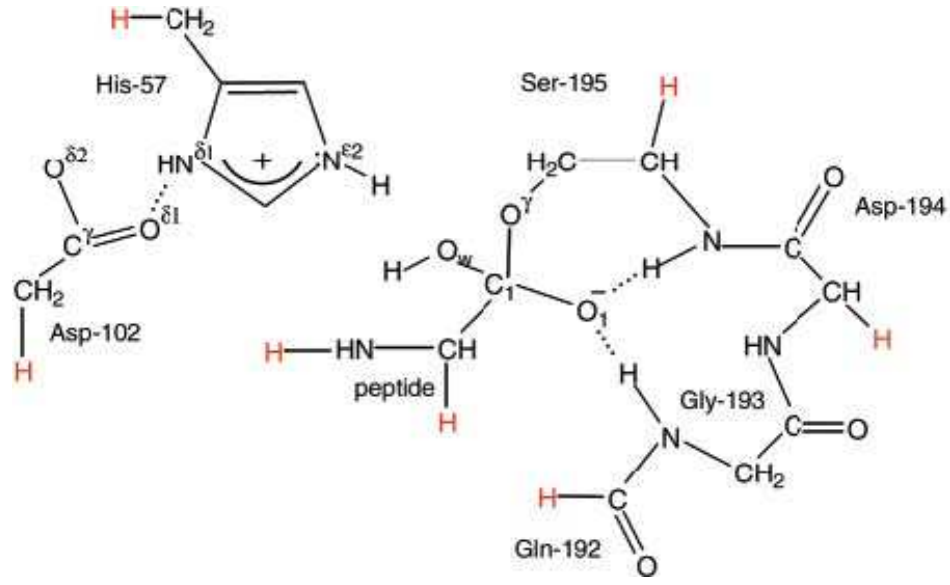
- Combines quantum mechanical and molecular mechanical methods
- Treats just the reacting part of the system quantum mechanically, and uses MM for the surroundings
- Uses a combined Hamiltonian for the system:

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



Example systems

- Study of serine protease deacylation reaction [a]



- Catalyzed isomerization of methylmalonyl-CoA [b]

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[a] Topf, M., Várnai, P. and Richards, W. G. *J. Am. Chem. Soc.* **2002**, *124*, 14780

[b] Loferer, M., Webb, B., Grant, G, and Liedl, K. *J. Am. Chem. Soc.* **2003**, *125*, 1072

Boundary treatment

- The boundary term $\hat{H}_{QM/MM}$ is given by

$$\hat{H}_{QM/MM} = -\sum_{e,i} \frac{Q_i}{r_{e,i}} + \sum_{m,i} \frac{Z_m Q_i}{r_{m,i}} + \hat{H}_{vdW}$$

  where i is summed over all MM partial charges, m over all QM nuclei, and e over all QM electrons

- First term: 1-electron interaction between QM electron density and MM partial charges
- Second term: standard Coulomb interaction between QM nuclei and MM charges

Boundary treatment (2)

- The final term is required because electron density (and hence dispersion) is explicitly treated in the QM region, but not in the MM region
- The HF energy of interaction between the QM system and a single MM partial charge Q_i is then given by

$$E^i_{QM/MM} = \left\langle \Psi \middle| \hat{H}^i_{QM/MM} \middle| \Psi \right\rangle$$
$$= \sum_\mu \sum_\nu P_{\mu\nu} I^i_{\mu\nu} + \sum_m \frac{Z_m Q_i}{r_{m,i}} + E^i_{vdW}$$

  where $I^i_{\mu\nu}$ is a one-electron integral, and $P_{\mu\nu}$ a density matrix element
- Note that only one-electron terms are required

Boundary treatment (3)

- How do we deal with bonds between the QM and MM regions?
  - The valence of the QM region must be satisfied
  - MM bond, angle, dihedral terms need a partner atom to act on, in order to maintain the geometry of the system
- QM/MM is often used to simulate a solute quantum mechanically, with explicit solvent treated with MM — in this instance, the problem of QM-MM bonds is avoided

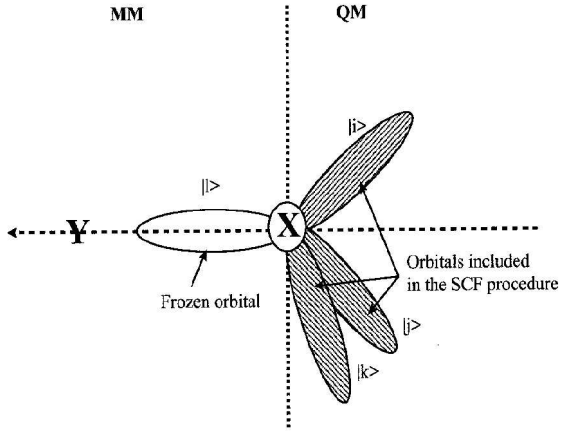
Link atoms

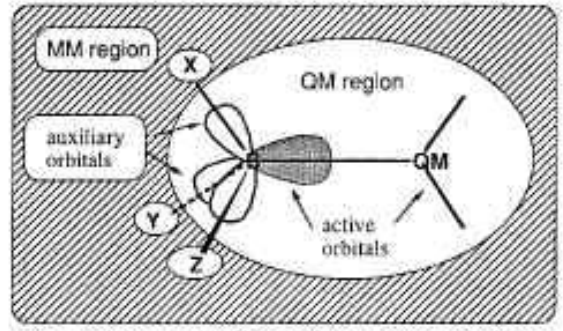
- Conventional solution: ‘link atoms’ (usually hydrogen atoms, but sometimes halogens or even methyl groups) are added along the bond [a]
  - The link atom satisfies the valence of the QM region
  - The QM atom is used for calculation of all MM bond terms
  - For nonbond (electrostatic terms), originally the link atom did not interact with any MM atom (termed a ‘QQ’ link in CHARMM parlance)
  - Better properties are usually obtained if the link atom interacts with the entire MM region (‘HQ’ link)
  - Poor handling of electron density

[a] Singh, U. and Kollman, P. *J. Comput. Chem.* **1986**, *7*, 718

Improved bond treatments

- Local Self-Consistent Field (LSCF) [a] uses a parameterized frozen orbital along the QM-MM bond, which is not optimized in the SCF
- Generalized Hybrid Orbital (GHO) [b] includes the QM-MM orbitals in the SCF





[a] Warshel, A. and Levitt, M. *J. Mol. Biol.* **1976**, *103*, 227

[b] Gao, J. *et. al. J. Phys. Chem. A* **1998**, *102*, 4714

Dynamics

- Chemical reactions are often simulated by molecular dynamics, e.g. with umbrella sampling
- Dynamics of a QM/MM system are almost identical to those of an MM system:
  - Forces are calculated from first derivatives on each atom
  - The QM nuclei are treated identically to the MM partial charges
  - The system is propagated by standard Newtonian dynamics

Monte Carlo

- QM/MM can also be used in conjunction with Monte Carlo methods
- A complication: the MM atoms affect the QM electron density, so an SCF is required for every Monte Carlo move
- Workaround: approximate the energy change of the QM region by first-order perturbation theory ('Perturbative QM/MC') as long as moves are far enough away from the QM region [a]

[a] Truong, T. and Stefanovich, E. *Chem. Phys. Lett.* **1996**, *256*, 348

Drawbacks of QM/MM

- Some parameterization is still required for the boundary treatment
- The choice of the size of the QM region is still something of an art
- Although the QM region polarizes in response to the MM partial charges, the reverse is not also true (although fully polarizable QM/MM methods are being developed)
- The free energy of a QM system can be determined via frequency calculation; however, this is rather inaccurate when applied to QM/MM systems (second derivatives are poorly determined, e.g. due to the harmonic approximation)

Other approaches

- ONIOM [a] divides the system into the 'real' (full) system and the 'model' (subset) and treats the model at high level, and the real at low level, giving the total energy as

$$E(high, real) \simeq E(low, real) + E(high, model) - E(low, model)$$

  which relies on the approximation

$$E(high, model) - E(low, model) \simeq E(high, real) - E(low, real)$$

- The 'model' system still has to be properly terminated
- Extension to three level systems is relatively straightforward (e.g. *ab initio* core, semi-empirical boundary, MM surroundings)

[a] Svensson, M. *et. al. J. Phys. Chem.* **1996**, *100*, 19357

Other approaches(2)

- Empirical Valence Bond method [a] treats any point on a reaction surface as a combination of two or more valence bond structures
  - Parameterization is made from QM or experimental data
  - An effective method, but must be carefully set up for each system
- Effective Fragment Potential [b] adds 'fragments' to a standard QM treatment, which are fully polarizable and are 'parameterized' from separate *ab initio* calculations
  - Treatment of bonds between the 'true' QM region and the fragments is still problematic

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[a] Warshel, A. and Weiss, M. *J. Am. Chem. Soc.* **1980**, *102*, 6218

[b] Webb, P. and Gordon, M. *J. Phys. Chem.* **1999**, *103*, 1265

Available codes

- CHARMM has been interfaced with MOPAC, GAMESS-US, GAMESS-UK, CADPAC, DeFT
- AMBER works with ROAR and with Gaussian (unreleased)
- DYNAMO implements semi-empirical QM/MM
- QSite is a commercial package from Schrödinger, Inc.