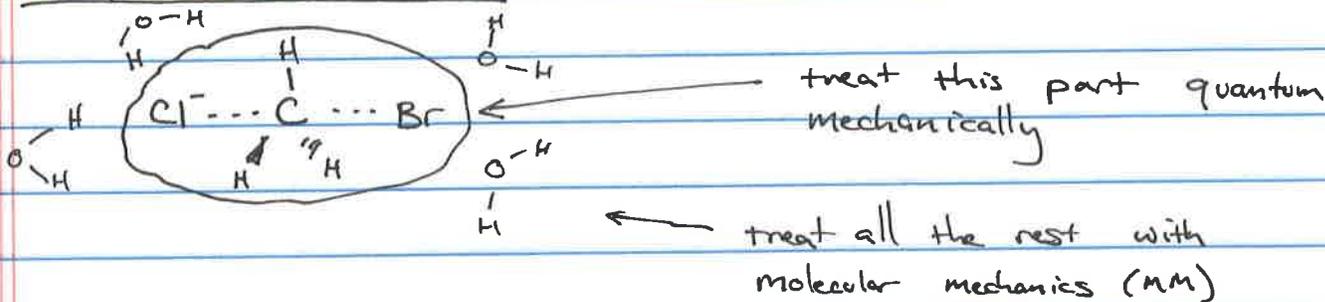


# QM/MM & Reactions



Reacting subsystem: QM

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

← due entirely to non-bonded interactions between regions

Because this is QM, we need to write down the Hamiltonian operator:

$$H = -\frac{1}{2} \sum_{\text{electrons}} \nabla_i^2 - \sum_i \sum_{\text{nuclei } A} \frac{Z_A}{R_{iA}} + \sum_i \sum_{j>i} \frac{e^- e^-}{r_{ij}} + \sum_A \sum_{B>A} \frac{Z_A Z_B}{R_{AB}}$$

With external charges there would be 2 additional terms:

$$- \sum_i \sum_k \frac{Q_k}{R_{ik}} + \sum_A \sum_k \frac{Z_A Q_k}{R_{Ak}}$$

(k is summed over partial charges  $Q_k$  in MM region)

## Drawbacks of this approach to $E_{QM/MM}$

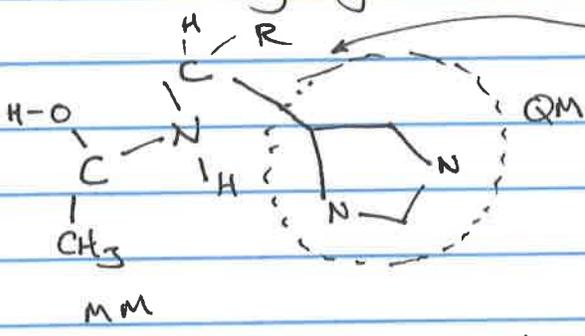
- lowest energy state has QM nuclei collapsing onto negative external point charges
- Some MM atoms (eg.  $CH_2$  beads) have no charge!
- vdw terms are sole distinguishing feature of some MM ions:  $Cl^-$ ,  $Br^-$ ,  $I^-$

Adding vdW terms to QM/MM

A. Warshel & M. Levitt J. Mol. Bio. 103, pp. 227-49 (1976)

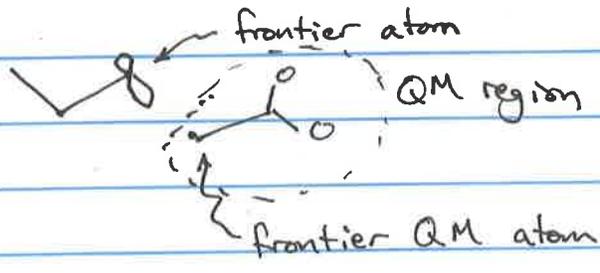
$$\hat{H}_{QM/MM} = -\sum_C \sum_K \frac{Q_K}{r_{iK}} + \sum_A \sum_k \frac{Z_A Q_k}{R_{AK}} + \sum_A \sum_k \left\{ \frac{A_{AK}}{R_{AK}^6} + \frac{B_{AK}}{R_{AK}^{12}} \right\}$$

Suppose our reacting region is covalently bound to our MM region

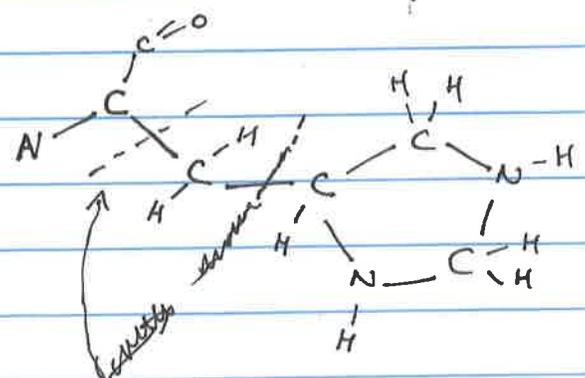


what do we do at this boundary?

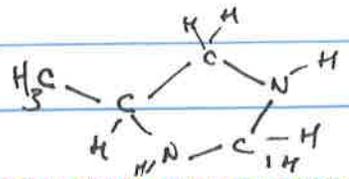
1) Hybrid orbital on "frontier" MM atom



2) "Link" atoms (hydrogens & halogens)



Breaking this bond places H atom fragment on QM side:



Link atoms require special treatment on MM side:

- 1) partial charge on link MM atom = 0
- 2) All vdw interactions for 1-2, and 1-3 bonded sets to the QM region are ignored
- 3)  $\sigma$  &  $\epsilon$  on capping Hydrogens are both 0. The only interactions with the MM region are charges.

Another subtlety:

Only  $\frac{1}{r}$  terms enter the QM treatment  
Using one-electron integrals as an example

$$\langle \mu | H_{QM/MM} | \nu \rangle = \sum_i \sum_k \frac{Q_k}{4\pi\epsilon_0} \int \phi_\mu^*(i) \frac{1}{r_{ik}} \phi_\nu(i) d\vec{r}_i$$

The other terms are purely additive!

To go any further, we're going to need a very brief review of Hartree-Fock. Remember:  $\vec{r}_i$  = electrons  
 $\vec{R}$  = nuclei

$$\hat{H} \Psi(\vec{r}; \vec{R}) = E_{el}(\vec{R}) \Psi(\vec{r}; \vec{R})$$

$$\left[ -\frac{1}{2} \sum_i \nabla_i^2 - \sum_{A,i} \frac{Z_A}{r_{iA}} + \sum_{A>B} \frac{Z_A Z_B}{R_{AB}} + \sum_{i>j} \frac{1}{r_{ij}} \right] \Psi(\vec{r}; \vec{R}) = E_{el}(\vec{R}) \Psi(\vec{r}; \vec{R})$$

$$\left[ \hat{T}_e(\vec{r}) + \hat{V}_{eN}(\vec{r}; \vec{R}) + \hat{V}_{NN}(\vec{R}) + \hat{V}_{ee}(\vec{r}) \right] \Psi(\vec{r}; \vec{R}) = E_{el}(\vec{R}) \Psi(\vec{r}; \vec{R})$$

The Born-Oppenheimer approximation means  $E_{el} + V_{NN}$  gives nuclear Potential Energy Surface

## More on Hartree-Fock

(4)

Assume:

$$\Psi_{\text{HP}}(\vec{r}_1, \vec{r}_2) = \phi_1(\vec{r}_1)\phi_2(\vec{r}_2) \quad \leftarrow \text{separable electronic wave functions}$$

$\Rightarrow$  Hartree product

$\phi_i(\vec{r}_i)$  = a spatial orbital

This violates anti-symmetry or the Pauli exclusion principle, so we must include spin coordinates:

$$\vec{x}_i = \{ \vec{r}_i, \omega_i \} \quad \leftarrow \text{spin coordinate } (\alpha \text{ or } \beta) \text{ for electron } i$$

$\Rightarrow$  space-spin coordinate for electron  $i$

$$\chi_i(\vec{x}_i) = \begin{cases} \phi_i(\vec{r}_i)\alpha \\ \phi_i(\vec{r}_i)\beta \end{cases} \quad \leftarrow \text{spin-orbitals}$$

$$\Psi_{\text{HP}}(\vec{x}_1, \dots, \vec{x}_N) = \chi_1(\vec{x}_1)\chi_2(\vec{x}_2)\dots\chi_N(\vec{x}_N)$$

$\Rightarrow$  this is still in violation of anti-symmetry as exchange of 2 electrons doesn't reverse the sign of  $\Psi$

We need Slater Determinants:

$$\Psi(\vec{x}_1, \vec{x}_2) = \frac{1}{\sqrt{2}} \left[ \chi_1(\vec{x}_1)\chi_2(\vec{x}_2) - \chi_1(\vec{x}_2)\chi_2(\vec{x}_1) \right]$$

$\Rightarrow$  this does satisfy anti-symmetry also equal to:

$$\Psi(\vec{x}_1, \vec{x}_2) = \frac{1}{\sqrt{2}} \begin{vmatrix} \chi_1(\vec{x}_1) & \chi_2(\vec{x}_1) \\ \chi_1(\vec{x}_2) & \chi_2(\vec{x}_2) \end{vmatrix} \quad \leftarrow \text{electrons}$$

$\leftarrow$  spin-orbitals

Slater Determinants automatically satisfy antisymmetry:

(5)

$$\Psi = \frac{1}{\sqrt{N!}} \begin{vmatrix} \chi_1(x_1) & \chi_2(x_1) & \dots & \chi_N(x_1) \\ \chi_1(x_2) & \chi_2(x_2) & \dots & \chi_N(x_2) \\ \vdots & \vdots & \ddots & \vdots \\ \chi_1(x_N) & \chi_2(x_N) & \dots & \chi_N(x_N) \end{vmatrix}$$



unwieldy to write this out each time, so:

$|\chi_i \chi_j \dots \chi_k\rangle$  = shorthand for normalized Slater determinant wavefunction!  
 $\begin{matrix} \uparrow \\ \text{position} \end{matrix}$  gives electron  
 $i, j, k$  denote spinorbital

Notation:

$$h(i) = -\frac{1}{2} \nabla_i^2 - \sum_A \frac{Z_A}{r_{iA}} \quad \text{one electron operator}$$

$$v(i,j) = \frac{1}{r_{ij}} \quad \text{two electron operator}$$

$$\hat{H}_{el} = \sum_i h(i) + \sum_{i < j} v(i,j) + V_{NN}$$

$\uparrow$  constant for fixed  $\{\vec{R}\}$

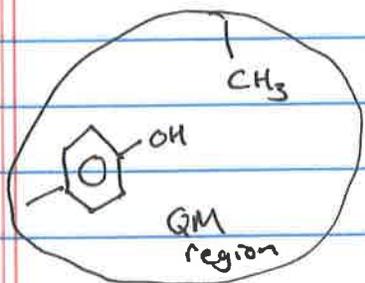
$$E_{el} = \langle \Psi | \hat{H}_{el} | \Psi \rangle$$

$$= \sum_i \langle i | h | i \rangle + \frac{1}{2} \sum_{ij} [ii | jj] - [ij | ji]$$

$$\langle i | h | j \rangle = \int d\vec{x} \chi_i^*(\vec{x}) h(\vec{r}) \chi_j(\vec{x})$$

$$[ij | kl] = \int d\vec{x}_1 \int d\vec{x}_2 \chi_i^*(\vec{x}_1) \chi_j(\vec{x}_1) \frac{1}{r_{12}} \chi_k^*(\vec{x}_2) \chi_l(\vec{x}_2)$$

6



$\Psi$  = Slater determinant wavefunction  
of one electron spin orbitals

$\vec{r}$  = electrons

$\vec{R}_q$  = nuclei in QM region

$\vec{R}_c$  = nuclei in CM region

$$\hat{H}_{\text{eff}} \Psi(\vec{r}; \vec{R}_q; \vec{R}_c) = E(\vec{R}_q; \vec{R}_c) \Psi(\vec{r}; \vec{R}_q; \vec{R}_c)$$

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

If we left-multiply by  $\Psi^*$  eg, close:  $\langle \Psi | \hat{H}_{\text{eff}} | \Psi \rangle$   
we get

$$E(\vec{R}_q, \vec{R}_c) = \frac{\langle \Psi | \hat{H}_{\text{QM}} | \Psi \rangle + \langle \Psi | \hat{H}_{\text{QM/MM}} | \Psi \rangle}{\langle \Psi | \Psi \rangle} + E_{\text{MM}}$$

Variational treatments tell us how to get <sup>better</sup> estimates of  
the ground state energy:

If  $|\Psi\rangle$  is not the exact ground state wavefunction

$$\frac{\langle \Psi | \hat{H} | \Psi \rangle}{\langle \Psi | \Psi \rangle} \geq E_0 \leftarrow \text{true ground state energy}$$

This means that if there are parameters ( $c$ ) that  
are in the wavefunction, we can minimize to  
find the best choices:

$$\frac{\partial}{\partial c} \left( \frac{\langle \Psi | \hat{H} | \Psi \rangle}{\langle \Psi | \Psi \rangle} \right) = 0 \leftarrow \text{minimize with respect to parameter } c$$

(7)

Now individual electrons are handled in a basis set:

$$|\psi_i\rangle = \sum_k C_k^i |\chi_k\rangle$$

$\swarrow$  orbital for electron  $i$ 
 $\longleftarrow$  coefficients
 $\longleftarrow$  basis functions (the set of spin orbitals we're using)

The optimization step using all coefficients can be recast as a matrix equation where we treat row & column positions as basis functions:

Overlap matrix:  $S_{\mu\nu} = \int d\vec{x}_1 \chi_\mu^*(\vec{x}_1) \chi_\nu(\vec{x}_1) = \langle \chi_\mu | \chi_\nu \rangle$

Coulomb integral:  $J_{\mu\nu}(\vec{x}_1) = \int d\vec{x}_2 \chi_\mu^*(\vec{x}_2) \frac{1}{|\vec{x}_2 - \vec{x}_1|} \chi_\nu(\vec{x}_2) = \langle \chi_\mu | \frac{1}{r_{12}} | \chi_\nu \rangle$

Exchange integrals:  $K_{\mu\nu}(\vec{x}_1) \chi_\mu(\vec{x}_1) = \left[ \int d\vec{x}_2 \chi_\mu^*(\vec{x}_2) \frac{1}{|\vec{x}_2 - \vec{x}_1|} \chi_\nu(\vec{x}_2) \right] \chi_\nu(\vec{x}_1)$

Fock operator:  $f(\vec{x}_1) = h(\vec{x}_1) + \sum_{\nu} [2J_{\nu}(\vec{x}_1) - K_{\nu}(\vec{x}_1)]$

Fock Matrix:  $F_{\mu\nu} = \int d\vec{x}_1 \chi_\mu^*(\vec{x}_1) f(\vec{x}_1) \chi_\nu(\vec{x}_1) = \langle \chi_\mu | \hat{f} | \chi_\nu \rangle$

The variational treatment condenses down to:

$$\sum_{\nu} F_{\mu\nu} C_{\nu}^i = \epsilon_i \sum_{\nu} S_{\mu\nu} C_{\nu}^i$$

or

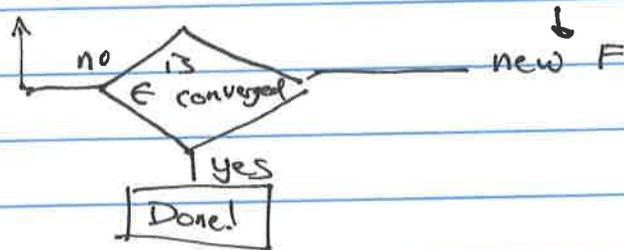
$$\underline{F} \cdot \underline{C} = \underline{S} \cdot \underline{C} \cdot \underline{\epsilon}$$

$\swarrow$  Fock Matrix
  $\swarrow$  overlap matrix
 $\swarrow$  diagonal matrix of orbital energies
  
 $\uparrow$  coefficient matrix

Hartree-Fock-Roothan looks like an eigenvalue equation (solved by diagonalizing  $\underline{F}$ ) and it is (sort of)

$\underline{F}$  depends on its own solution

Solve  $FC = SCe$  for  $C \rightarrow$  new orbitals



Once we converge the energies, the coefficients are known:

$C_k^i \leftarrow$  best coefficients for a particular geometry of all the nuclei

If we move the nuclei a little bit, one hypothesis is that these coefficients shouldn't be too perturbed by that motion.

Perhaps we could treat them as dynamic variables: and find equations of motion...

$$\dot{C}_k^i = ?$$

Then we can do dynamics where we move the nuclei & the wave function at the same time!

# Approaching CPMD by way of Electronegativity Equalization (9)

Suppose atomic sites have a default charge of 0 and there's an energetic cost to perturb that charge:

$$E(Q) = E(0) + \chi^0 Q + \frac{1}{2} J^0 Q^2$$

$\chi^0$  Mulliken electronegativity /  $e^-$

$J^0$  electronic "hardness"

Each type of atom might have different values of these parameters

$$E(Q_A) = E_A(0) + \chi_A^0 Q_A + \frac{1}{2} J_{AA}^0 Q_A^2$$

The total long range potential is now a function of partial charge values  $\{Q_\alpha\}$  as well as atomic positions  $\{\vec{R}_\alpha\}$ :

$$U(\vec{R}, \vec{Q}) = \sum_{\alpha=1}^N E_\alpha(0) + \chi_\alpha^0 Q_\alpha + \frac{1}{2} J_{\alpha\alpha}^0 Q_\alpha^2 \quad \leftarrow \text{self energy}$$

$$+ \sum_{\alpha < \beta} J_{\alpha\beta}(r_{\alpha\beta}) Q_\alpha Q_\beta \quad \leftarrow \text{Coulomb term}$$

$$+ \sum_{\alpha < \beta} V(r_{\alpha\beta}) \quad \leftarrow \text{all non-Coulomb terms}$$

Dynamically, these charge variables have forces:

$$F_{Q_\alpha} = -\frac{\partial U}{\partial Q_\alpha} = -\chi_\alpha^0 - J_{\alpha\alpha}^0 Q_\alpha - \sum_{\beta} J_{\alpha\beta}(r_{\alpha\beta}) Q_\beta$$

$$= -\tilde{\chi}_\alpha \quad \leftarrow \text{"instantaneous electronegativity"}$$

(10)

The forces can't take on any value they want because the total charge is constrained:

$$\sum_{\alpha} Q_{\alpha} = 0 \quad \text{for a neutral system}$$

So we set up "extended" Lagrangian methods with extra degrees of freedom for charges (just like we did with thermostats & barostats):

$$L = \sum_i^{\text{atoms}} \frac{1}{2} m_i \dot{R}_i^2 + \sum_{\alpha}^{\text{charges}} \frac{1}{2} m_{\alpha} \dot{Q}_{\alpha}^2 - U(\vec{R}, \vec{Q}) - \lambda \underbrace{\sum_{\alpha} Q_{\alpha}}_{\text{constraint}}$$

↑ mass of atom  $i$ 
↑ charge mass (time<sup>2</sup>/charge<sup>2</sup>)

Newton's equations: come out of the Lagrangian:

$$m_i \ddot{R}_i = - \frac{\partial U(\vec{R}, \vec{Q})}{\partial R_i}$$

$$m_{\alpha} \ddot{Q}_{\alpha} = - \frac{\partial U(\vec{R}, \vec{Q})}{\partial Q_{\alpha}} - \lambda$$

We can solve for the constraint using:

$$\sum_{\alpha} Q_{\alpha} = 0 \Rightarrow \sum_{\alpha} \dot{Q}_{\alpha} = 0 \Rightarrow \sum_{\alpha} \ddot{Q}_{\alpha} = 0$$

(the total charge is a constant of the motion)

This makes  $\lambda$ :

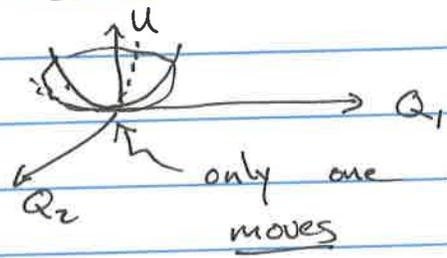
$$\lambda = - \frac{1}{N_{\text{charge}}} \sum_{\alpha} \tilde{X}_{\alpha}$$

$\therefore$

$$M_{\alpha} \ddot{Q}_{\alpha} = - \frac{1}{N_{\text{charges}}} \sum_{\beta} (\tilde{X}_{\alpha} - \tilde{X}_{\beta})$$

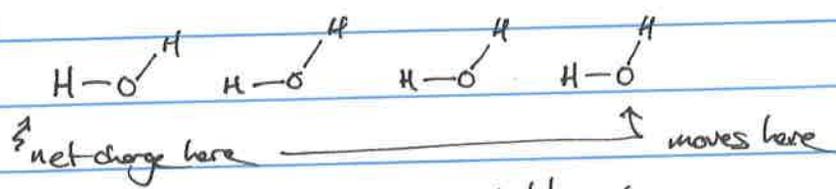
We can then model the system on the fluctuating charge surface with velocity-Verlet dynamics:

- 1) time step depends on  $M_Q \approx 6 \times 10^{-5} \left(\frac{ps}{e}\right)^2$   
 $\Delta t \approx 1 fs$
- 2) If electronegativity equalization is correct, the electrons would go infinitely quickly to lowest energy state
- 3) Charges live on a big harmonic bowl that moves in response to atomic motion



As atoms rearrange the charges should always be at the bottom of the bowl.

- 4) T leaks from atoms  $\rightarrow$  charges, so sometimes  $\vec{Q}$  is thermostatted separately from  $\vec{R}$
- 5) Charge moves across molecular & spatial boundaries



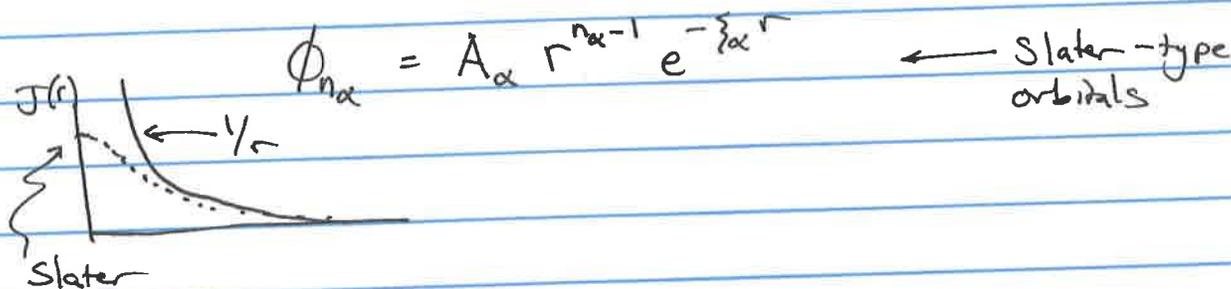
to fix this, we can constrain total charge on each molecule

- 6) Other variants: bond charges  
 bond polarization (QTPIE)  
 charge positions on springs (Drude)  
 point polarizabilities (AMOEBA)

How does this connect to CPMD?

$$J_{\alpha\beta}(\vec{r}) = \int d\vec{r}_1 d\vec{r}_2 |\phi_{n\alpha}(\vec{r}_1)|^2 \frac{1}{|\vec{r}_1 - \vec{r}_2 - \vec{r}|} |\phi_{n\beta}(\vec{r}_2)|^2$$

↗ orbitals on atom 1
↗ vector between nuclei
↗ orbitals on atom 2



In CPMD, as we move nuclei around, the Kohn-Sham orbitals don't change much. If we think of the wavefunction as expanded in the basis sets:

$$\Psi_i = \sum_k \overset{\text{basis}}{C_k^i} \overset{\text{coefficients evolve in time}}{\chi_k}$$

$$= \sum_k C_k^i(t) \chi_k$$

In density terms:

$$\rho(\vec{r}) = \sum_i f_i |\Psi_i(\vec{r})|^2$$

↗ occupation # of KS orbital
↗ coefficients are squared

We'll also have constraints:

$$\sum_k C_k^{i*} C_k^j = \delta_{ij}$$

one-e electron functions are orthonormal

So:

$$M_k \ddot{C}_k^i = - \frac{\partial E}{\partial C_k^i} - \sum_j \lambda_{ij} C_k^j$$

↗ fictitious mass
↗ "force" on coefficients
↗ orthonormality constraint

The force on the constraints:

$$-\frac{\partial E}{\partial c_k^i} = -\sum_l n_l \langle \chi_k | \hat{H}_{KS} | \chi_l \rangle c_l^i$$