Introduction to Numerical Simulations and High Performance Computing: From Materials Science to Biochemistry

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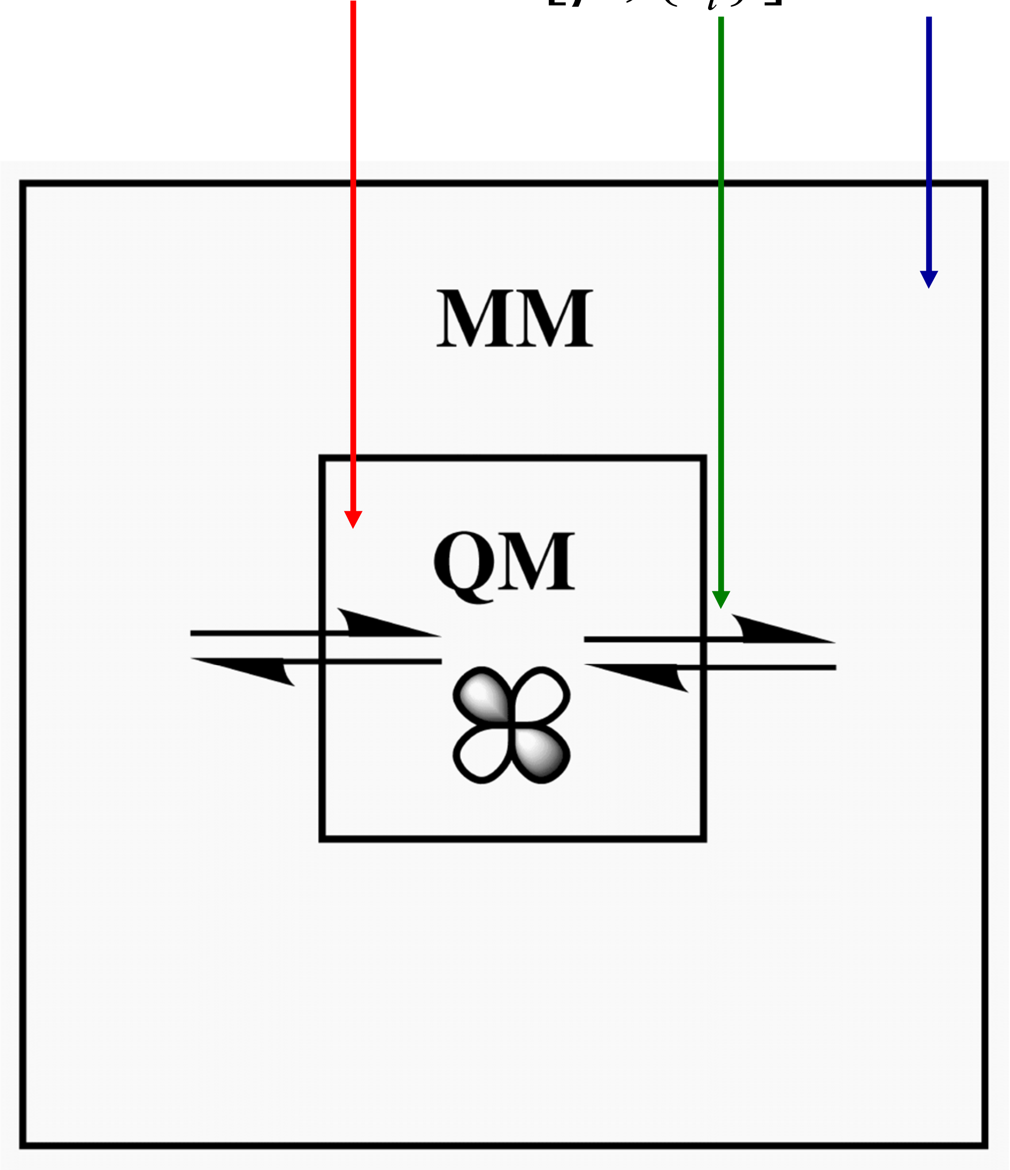
Part 3:
Quantum/Classical
Hybrid Schemes

Joining two worlds: Classical MD + First Principles MD = QM/MM

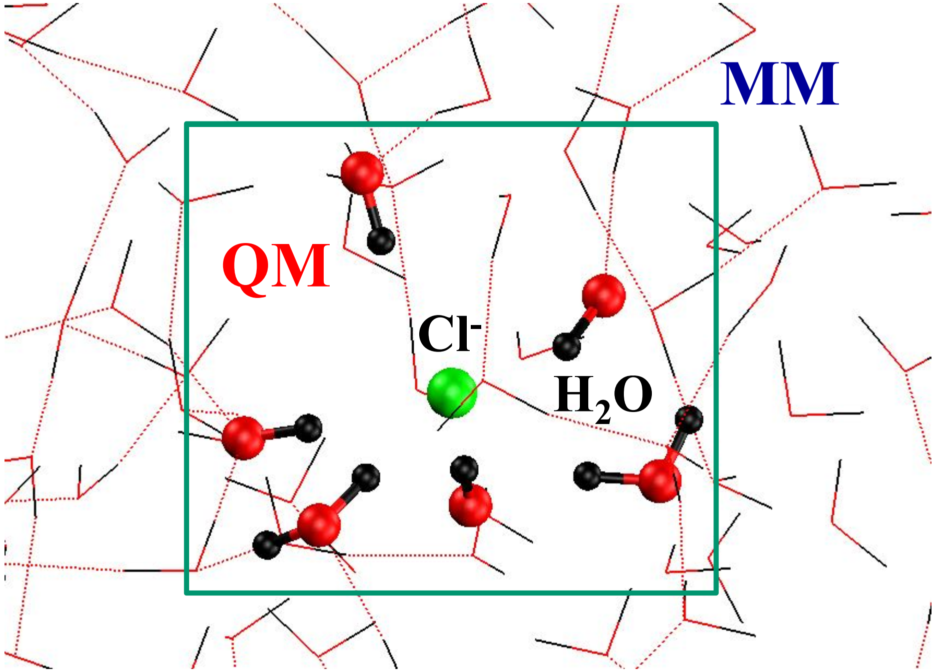
How to handle very big systems ?… Well, let’s think before computing

- Not every atom in a large system generally needs a QM treatment, anyhow they are there in real life
- Let’s try to Identify a small portion of the large system that is ***interesting*** (***localized***) and that is ***tractable*** by QM/DFT
- Classical-Quantum interface: be careful about the interaction between the two *worlds*
- Define classical-like point charges suitable to couple with the nearby QM system and an electrostatic potential (ESP) a variational *hamiltonian* formulation
- Dynamics of the QM and MM ensembles must preserve the constants of motion

$$H^{tot} = H^{QM} + E^{\text{int}}[\rho, \{\mathbf{r}_i\}] + H^{MM}$$



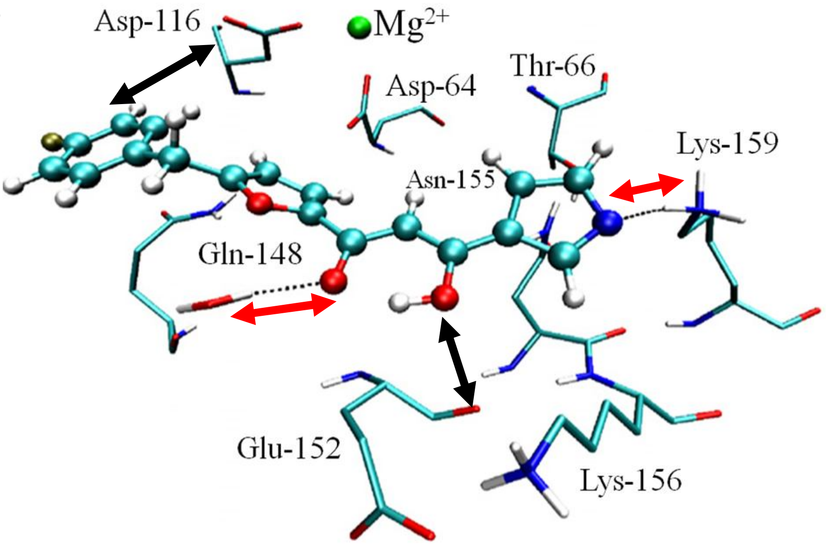
- In the easiest (lucky) case, QM atoms interact with the MM atoms via:
  - H-bonds
  - Non-bonding interactions (e.g. Coulomb or van der Waals)



QM and MM atoms are **not** chemically bonded.

- In the case of QM atoms and MM atoms not chemically bonded, selection of the QM/MM frontier does not pose particular difficulties. ***But*** due to the weak interaction QM atoms ***can escape*** from the QM box upon long dynamics (watch out !)

Examples: (*i*) QM solute surrounded by MM water molecules, or ligand-protein interacting via non-bonding forces, e.g. complex HIV-1 integrase and its inhibitor S-13



(see C. N. Alves et al. *Bioorg. Med. Chem*. **15**, 3818 (2007))

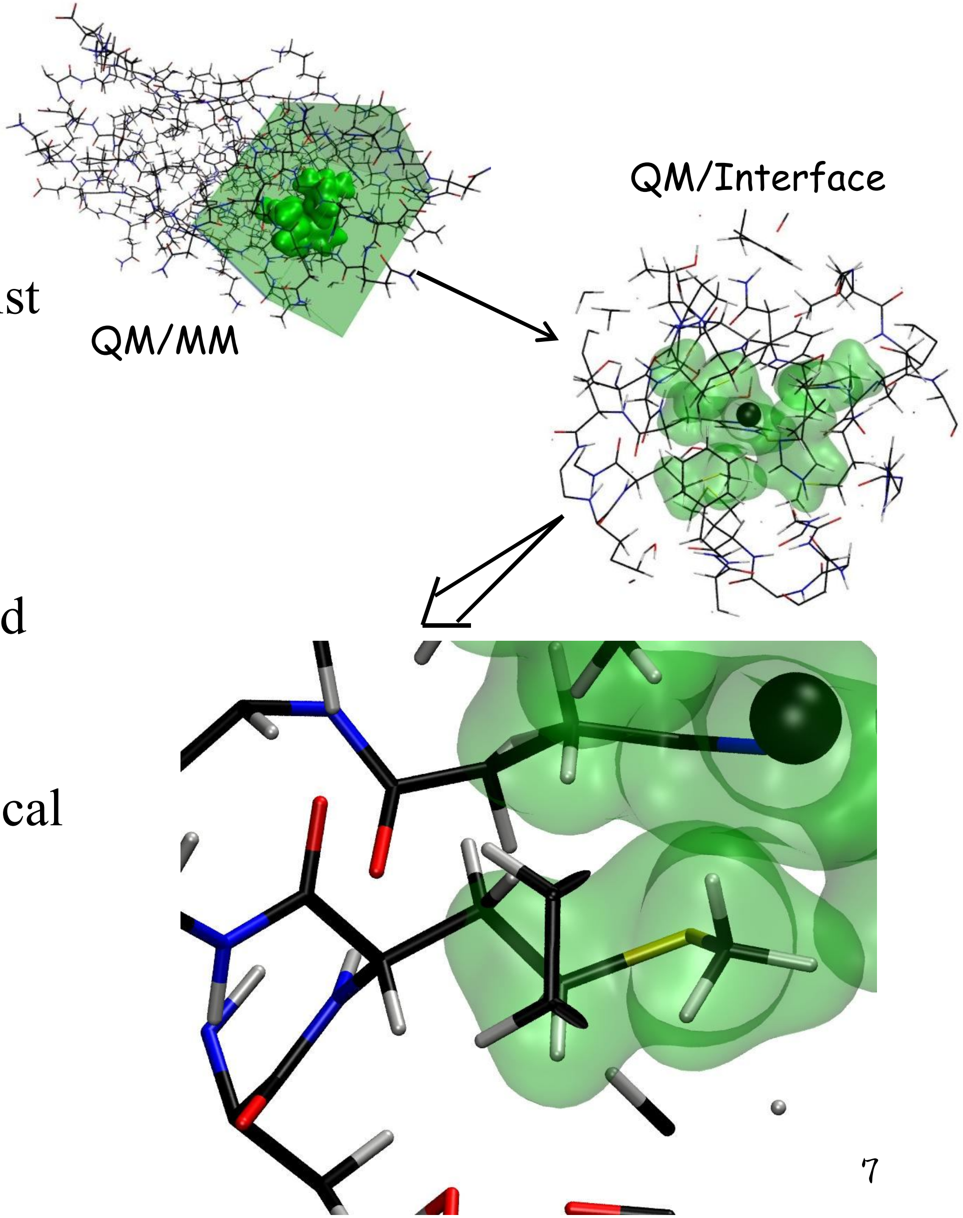
QM/MM system with chemical bonds at the border

Partitioning the system: shopping list

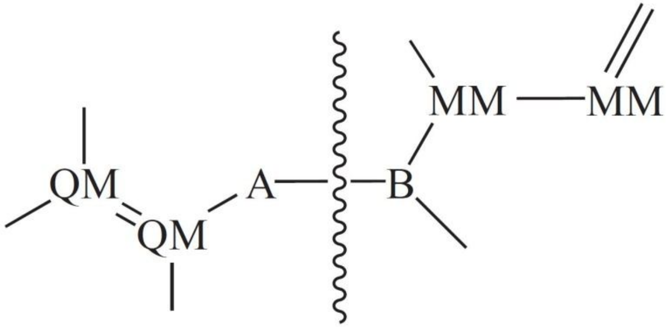
1. chemical active part treated by QM methods

2. large environment that is modeled by a classical force field (MM)

3. Interface between QM and classical parts



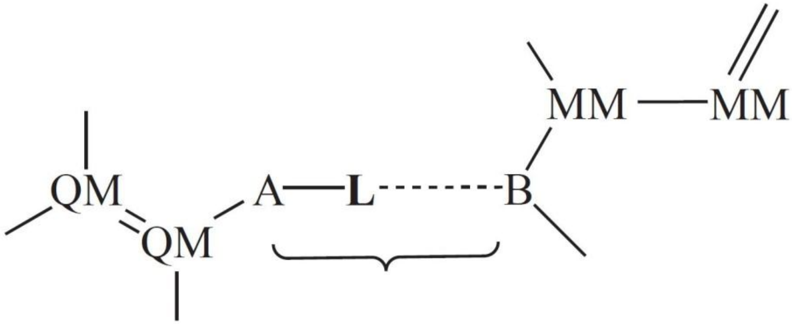
- In most of the cases, the QM/MM frontier passes across a (covalent) chemical



- Suitable termination of the boundary is required in order not to create artificial *dangling bonds*.
- To this aim, the methods proposed in the literature can be classified into three groups:

1. Link atoms,
2. Frontier orbitals
3. Optimized effective pseudopotentials

1. Link atoms (L)



Link (L) atoms are additional monovalent hydrogen-like atoms added to the QM subsystem to saturate the cut covalent bonds.

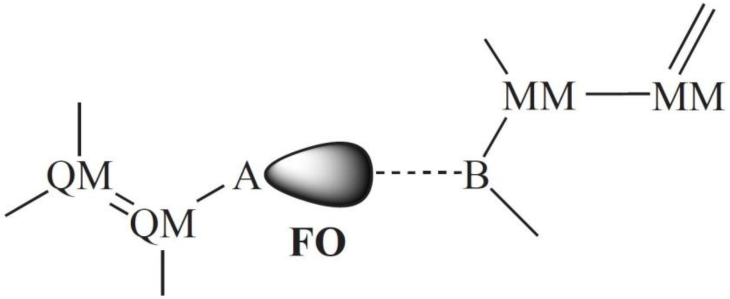
- L atoms are generally invisible to the MM atoms
- L atom should reproduce the local chemical environment (e.g. *sp*^{3}, *sp*^{2}, etc.)
- They are preferentially placed far from each other to avoid spurious interactions

(Singh and Kollman, J. Comp. Chem. **7**, 718 (1986); Field *et al.* J. Comp. Chem. **11**, 700 (1990))

1. Link atoms (L) – continue

- Beside monovalent H-like L-atoms, F or CH_3 (Adjusted Connection Atom) can be used. Anes & Thiel, *J. Phys. Chem. A* **103**, 9290 (1999)
- L-atoms, generally invisible to the MM atoms, interact via the force field directly with the border QM atoms to ensure that the QM-MM covalent bond are not affected by the frontier passing across these chemical bonds.
- There are cases in which L-atoms must be kept into account also from the MM side, e.g for C species in which non-negligible polarization effects occur.
- Polarization of L-atom – C bonds could bias the results if L atoms are neglected in the calculation of the MM interactions. N. Reuter et al. *J. Phys. Chem. A* **104**, 1720 (2000)

2. Frontier Orbitals (FO)



The unsaturated covalent bond of a border QM atom is compensated by an additional localized orbital $\psi_{FO}(\mathbf{x}\text{-}\mathbf{R}_A)$ treated as frozen during the calculation.

Note: the freezing of FOs can give problems in variational approaches in which wavefunctions or the charge density are used as dynamical variables.

(Assfel and Rivail, Chem. Phys. Lett. **263**, 100 (1996); Gao *et al.* J. Phys. Chem. A **102**, 4714 (1990))

2. Frontier Orbitals (FO) - continue

- Frozen FOs work well in self-consistent field optimization
- However, contributions to the forces can result in spurious components that can bias the dynamics

One of the most recent (and remarkable) applications is the study of H transfer by tunneling to the active site catalyzed by coenzyme B_{12}-dependent methylmalonyl-CoA mutase. QM subsystem = 45 atoms, including the ligand and a portion of the methylmalonyl-CH_2- substrate.

FO = at the carbon atoms C_2 of the b-mercaptoethylamine part of the CoA.

Dybala-Defratyka, et al. *Proc. Nat. Acad. Sci. USA* **104**, 10774(2007)

General Warning about Link Atoms / Capping Atoms (and not only)

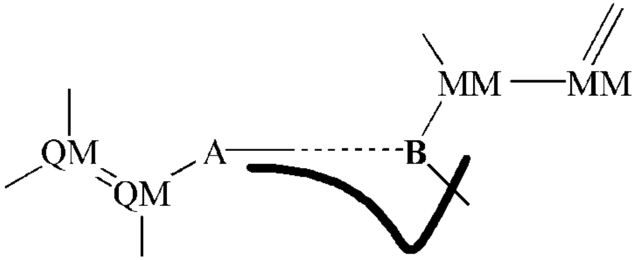
- L-atoms must not be too close to each other to avoid spurious ***link atom-link atom*** interactions. Remember that they carry a wavefunction $\psi_{link}(\mathbf{x})$ that in a DFT-like scheme enters in the total electron density $\rho(\mathbf{x})$ as

$$\rho(\mathbf{x}) = \sum_{i=1}^{QM} f_i \left|\psi_i(\mathbf{x})\right|^2 + \sum_{link=1}^{LINK} f_{link} \left|\psi_{link}(\mathbf{x})\right|^2$$

with all the related consequences on the Kohn-Sham Hamiltonian and potential. For instance the Coulomb interaction

$$\frac{\left|\psi_{link}(\mathbf{x})\right|^2 \left|\psi_{link'}(\mathbf{y})\right|^2}{\left|\mathbf{x} - \mathbf{y}\right|} \xrightarrow[\left|\mathbf{x}-\mathbf{y}\right|\to\infty]{} 0$$

3. Optimized Effective Core Pseudopotentials (OECP)



Border PP written as a sum of a local and a non-Local part

$$V_I^{\text{OECP}}(\mathbf{r},\mathbf{r}') = V^{loc}(\mathbf{r})\,\delta(\mathbf{r}-\mathbf{r}') + \sum_l V_l^{NL}(\mathbf{r},\mathbf{r}')$$

$\mathbf{r} = \mathbf{x} - \mathbf{R}_I$, being $\mathbf{R}_I$ the a capping atom at the QM/MM interface. All the PP parameters are optimized by minimizing iteratively the differences in electron density between the QM subsystem and a full QM reference configuration including atoms beyond the QM/MM boundary

(DiLabio *et al*. J. Chem. Phys. **116**, 9578 (2002), von Lilienfeld *et al*. J. Chem. Phys. **122**, 014133 (2005))

3. Optimized Effective Core Pseudopotentials (OECP)
- continue

- Local part:

$$V^{loc}(\mathbf{r}) = -\frac{Z_I}{r}\,\mathrm{erf}\left(\frac{r}{r_0\sqrt{2}}\right) + e^{-(r/r_o)^2/2}\left[c_1 + c_2\left(\frac{r}{r_0}\right)^2 + c_3\left(\frac{r}{r_0}\right)^4 + c_4\left(\frac{r}{r_0}\right)^6\right]$$

- Non-local part:

$$V_l^{NL}(\mathbf{r},\mathbf{r}') = \sum_{m=-l}^{l} Y_{lm}^{*}(\hat{\mathbf{r}})Y_{lm}(\hat{\mathbf{r}})\sum_{i,j=1}^{3} p_{lj}(r)h_{lji}\,p_{li}(r')$$

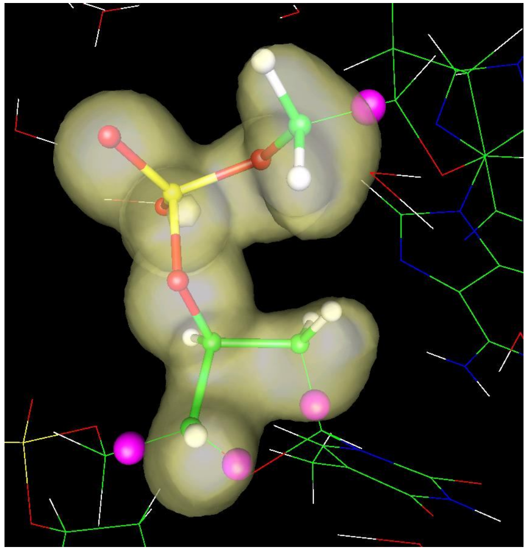
where $p_{ij}(r)$ = const $r^{l+2(h\text{-}1)}$ exp(-0.5 r^2/r_l^2) and Y_{lm} are the spherical harmonics.

- All the parameters $\{r_0, c_1, c_2, c_3, c_4, h_{lji}, r_l\}$ are optimized by minimizing iteratively the differences in electron density between the QM subsystem and a full quantum reference configuration including atoms beyond the QM/MM boundary.

3. Optimized Effective Core Pseudopotentials (OECP) – continue

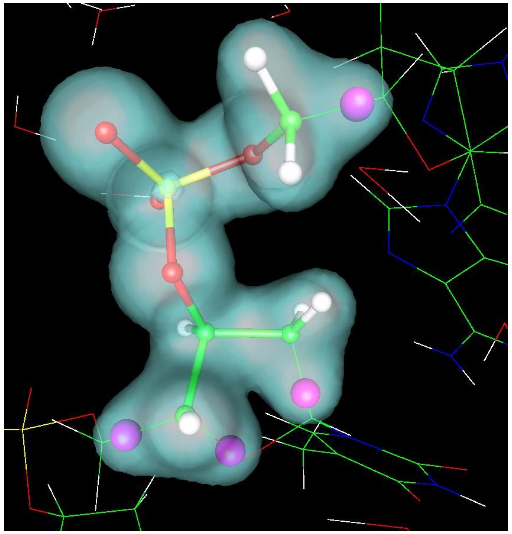
- We remark that the dimensionality of the parameter space is determined by the maximum angular momentum in the non-local part of the OECP.
- In practical applications (von Lilienfeld et al. 2005) it has been shown that a maximum value l = s or, rarely, l = p is enough to achieve a good optimization for oxygen in water or carbon in acetic acid.
- OECPs are particularly suitable in the cases in which the QM subsystem embedded in the MM environment is characterized by the presence of highly ionic species.

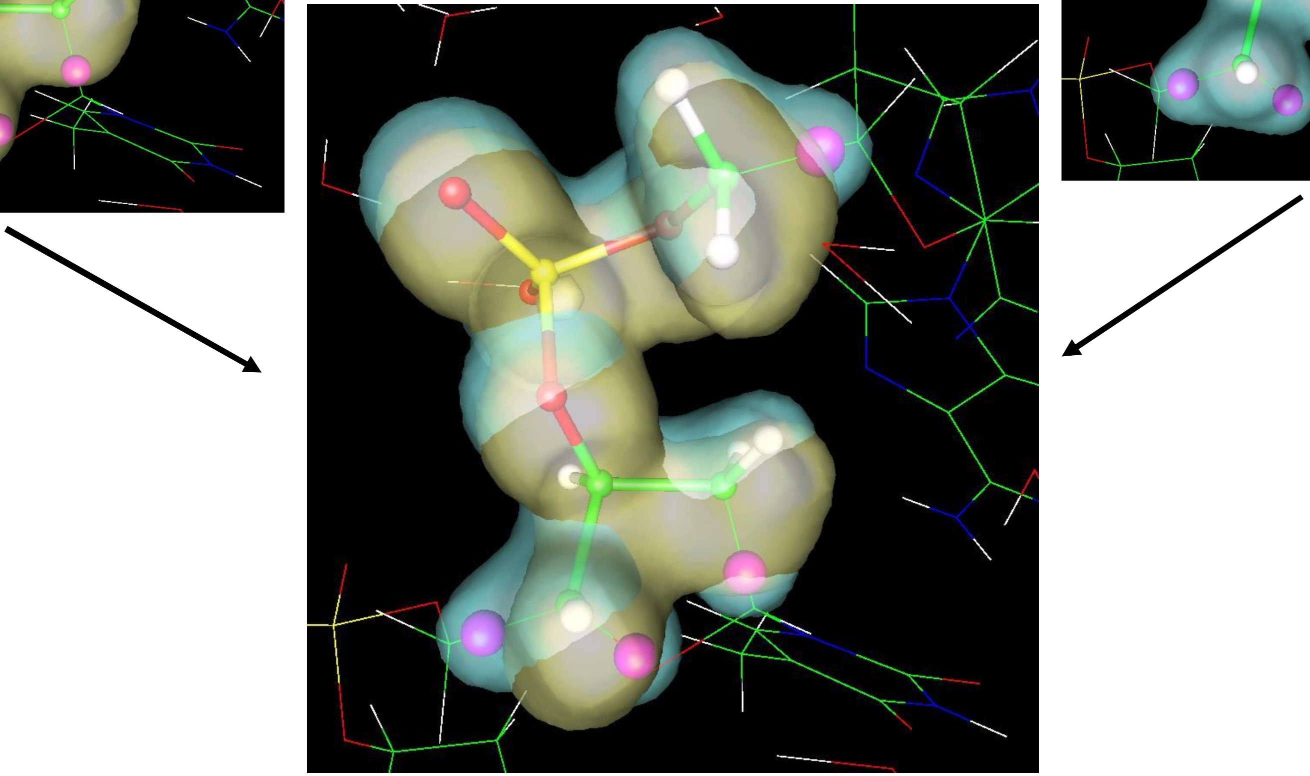
QM/MM Dangling bonds: influence on the local electronic structure (isosurface at $4 \times 10^{-2}\ e/\text{A}^3$)



No H-capping

H-Capping





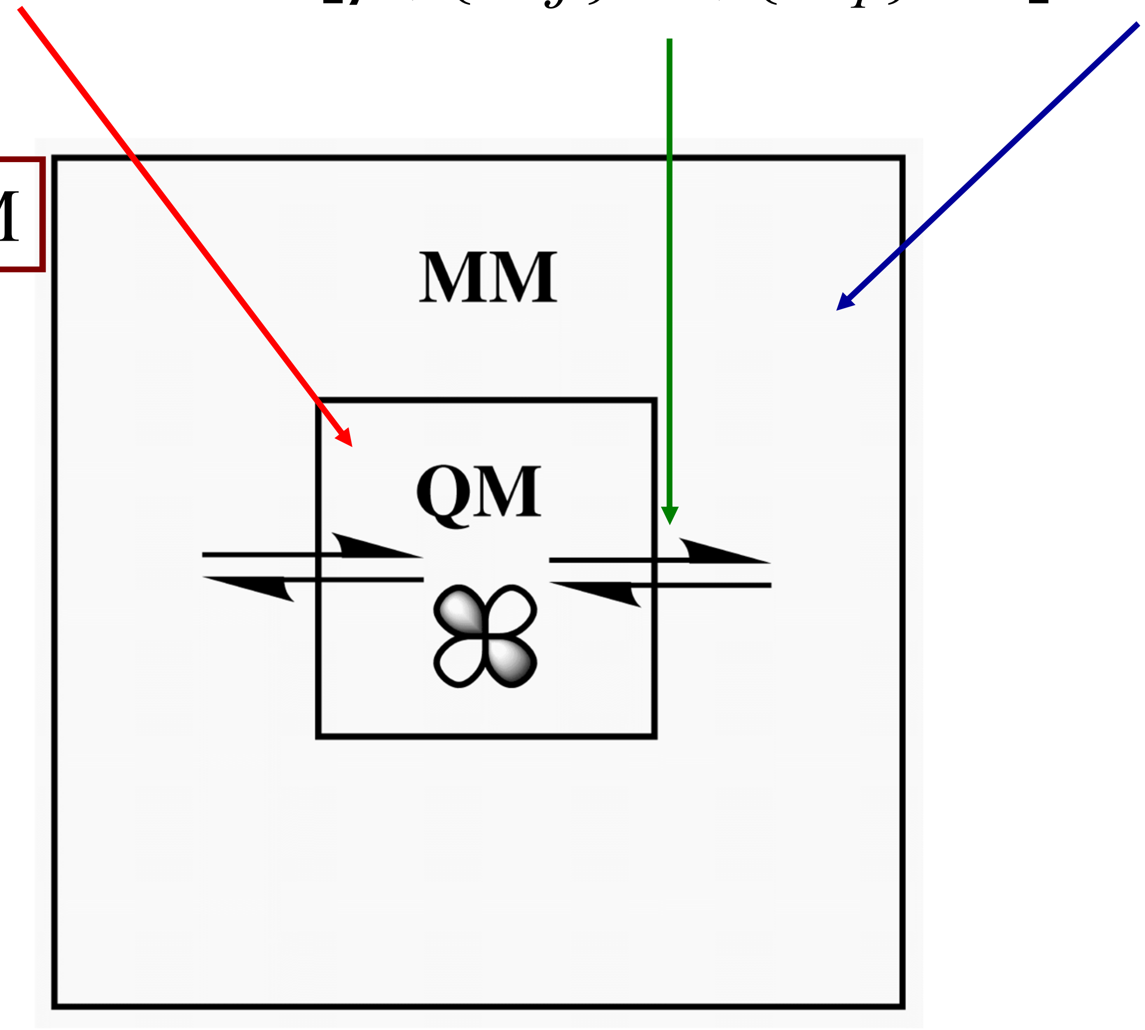
Splitting of the system into a QM inner region and an outer MM region

- The two subsystems are in strong interaction with each other
- Hence the total energy (Hamiltonian) is **not** the simple (linear) sum of the energies of the two sub-parts
- Coupling interaction must be accounted for
- Particular care must be taken at the boundary especially ***if the border cuts through chemical bonds*** (more later)

Additive scheme: Total Hamiltonian

$$H^{\text{tot}}(\Sigma) = H^{\text{QM}} + H^{\text{int}}[\rho, \{\mathbf{R}_J\}^{\text{QM}}, \{\mathbf{R}_I\}^{\text{MM}}] + H^{\text{MM}}$$

$\Sigma = \text{QM+MM}$



Subtractive scheme (e.g. IMOMM/ONIOM)

(K. Morokuma et al. *J. Comp. Chem.* **16**, 1170 (1995))

1. Compute $H^{MM}(\Sigma)$
2. Compute $H^{QM}(QM)$ of the QM subsystem
3. Compute $H^{MM}(QM)$, i.e. MM calculation of the QM subsystem
4. Sum up terms 1 and 2 and subtract term 3 to get rid of the double counting

$$H^{tot}(\Sigma) = H^{MM}(\Sigma) + H^{QM}(QM) - H^{MM}(QM)$$

Warning: The coupling between QM and MM is driven by MM and this can give problems in Coulomb interactions between QM and MM, especially if moving (MD).

Typical form of the MM Hamiltonian:

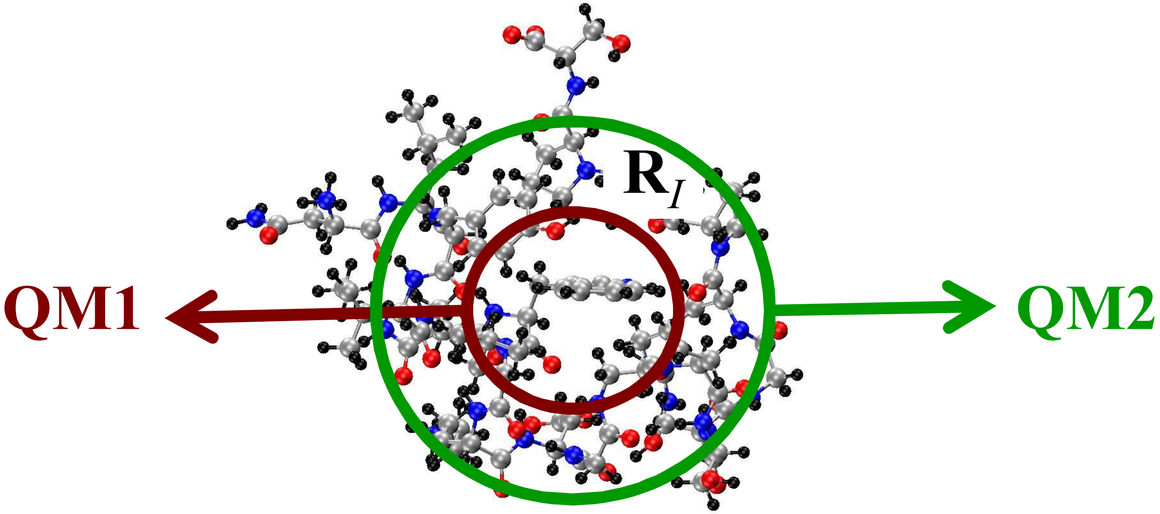
$$H^{\mathrm{MM}} = \frac{1}{2}\sum_{I}^{\mathrm{MM}} M_I^{\mathrm{MM}} \left(\dot{\mathbf{R}}_I^{\mathrm{MM}}\right)^2 + V^{\mathrm{MM}}\left(\mathbf{R}_I^{\mathrm{MM}}\right)$$

Classical kinetic term

Parameterized form of the electrostatic interactions, i.e. an analytical function of the positions only (***not of the velocities***) keeping into account many-body effects up to the third (bending modes) or fourth (torsion modes) order.

QM/MM selection and protocol

- The choice of the QM subsystem is always somehow arbitrary, hence it must be carefully checked.



e.g. by extending the QM region from QM1 to QM2 (or by reducing from QM2 to QM1) do forces on the atoms change ?

$$\text{QM1} \longleftarrow \mathbf{F}^{\mathrm{MM}}(\mathbf{R}_I) \approx \mathbf{F}^{\mathrm{QM}}(\mathbf{R}_I) \longrightarrow \text{QM2} \quad ??????$$

Typical form of the MM potential (force field):

$$V^{\mathrm{MM}}(\mathbf{R}_I^{\mathbf{MM}}) = \sum_{I<J} k_{IJ}\left[(\mathbf{R}_I - \mathbf{R}_J) - d_{IJ}^0\right]^2$$ Bond stretching

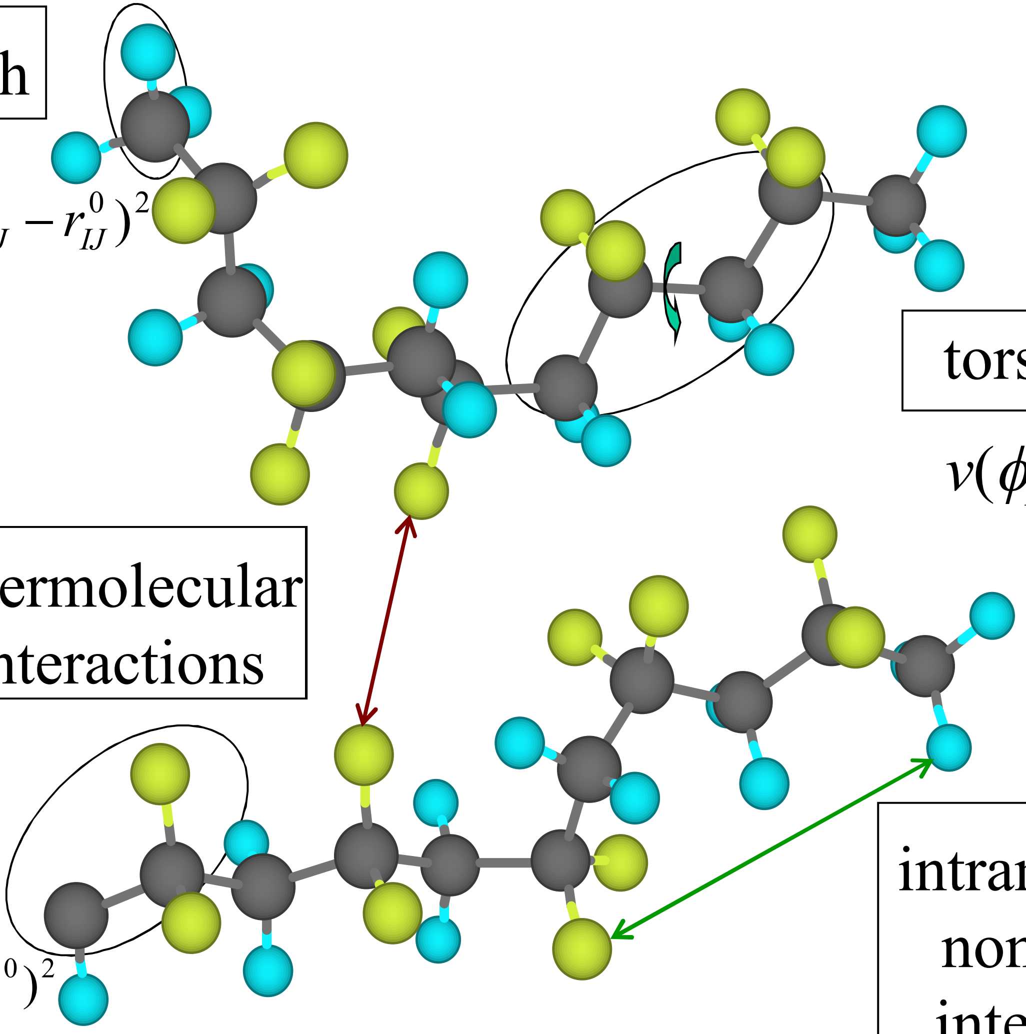
$$+\sum_{I<J} k_\theta\left[\theta(\mathbf{R}_I) - \theta^0\right]^2$$ Bond bending

$$+\sum_{I<J} k_\phi\left[1 + \cos(n\phi(\mathbf{R}_I) + \delta)\right]$$ Torsion angles

$$+\frac{1}{4\pi\varepsilon_0}\sum_{non-bond\ IJ}\frac{q_I q_J}{|\mathbf{R}_I - \mathbf{R}_J|}$$ Coulomb interaction

$$+\sum_{non-bond\ IJ}\varepsilon_{IJ}\left[-\left(\frac{\sigma_{IJ}}{|\mathbf{R}_I - \mathbf{R}_J|}\right)^6 + \left(\frac{\sigma_{IJ}}{|\mathbf{R}_I - \mathbf{R}_J|}\right)^{12}\right]$$ Van der Waals

MM: what is a Force Field ? Which interactions ?



bond stretch

$$v(r_{IJ}, k_{IJ}) = \tfrac{1}{2} k_{IJ} (r_{IJ} - r_{IJ}^{0})^{2}$$

torsion

$$v(\phi_{IJKL})$$

intermolecular interactions

bending

$$v(\theta_{IJK}) = \tfrac{1}{2} k_{\theta} (\theta_{IJK} - \theta^{0})^{2}$$

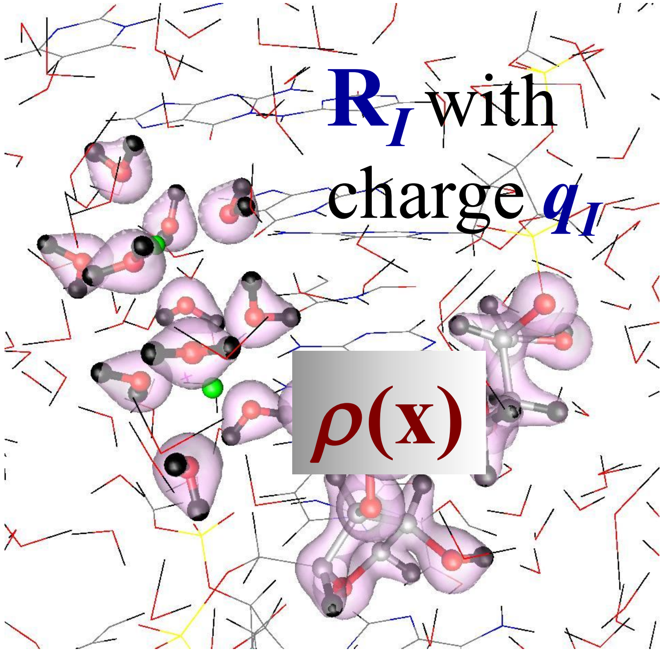
intramolecular nonbonded interactions

Typical form of the QM-MM Hamiltonian:

Basically just the electrostatic interaction between the two subsystems, i.e.

$$H^{\text{int}}[\rho(\mathbf{x}),\{\mathbf{R}_J\}\{q_I,\mathbf{R}_I\}] = \sum_{I=1}^{MM} q_I \int_{\text{QM}} \frac{\rho(\mathbf{x})}{|\mathbf{x}-\mathbf{R}_I|}\, d^3x + \sum_{I=1}^{\text{MM}}\sum_{J=1}^{\text{QM}} \frac{q_I Z_J}{|\mathbf{R}_I-\mathbf{R}_J|}$$

QM atom-MM atom



QM electron-MM atom

<u>Particle-mesh interaction</u>:

We need good charge models for the MM part and a lot of computation

Total hamiltonian: scaling in a plane wave basis set

$$H^{\text{tot}}(\Sigma) = H^{\text{QM}} + H^{\text{int}}[\rho, \{\mathbf{R}_J\}^{\text{QM}}, \{\mathbf{R}_I\}^{\text{MM}}] + H^{\text{MM}}$$

Pure QM interaction

$N_{\mathbf{el}} \times N_{\mathbf{G}} \times N_{\mathbf{G}}$

with

$\psi_j(\mathbf{x}) = \Sigma_{\mathbf{G}}\, c_j(\mathbf{G})\, e^{i\mathbf{G}\mathbf{x}}$

QM/MM interface

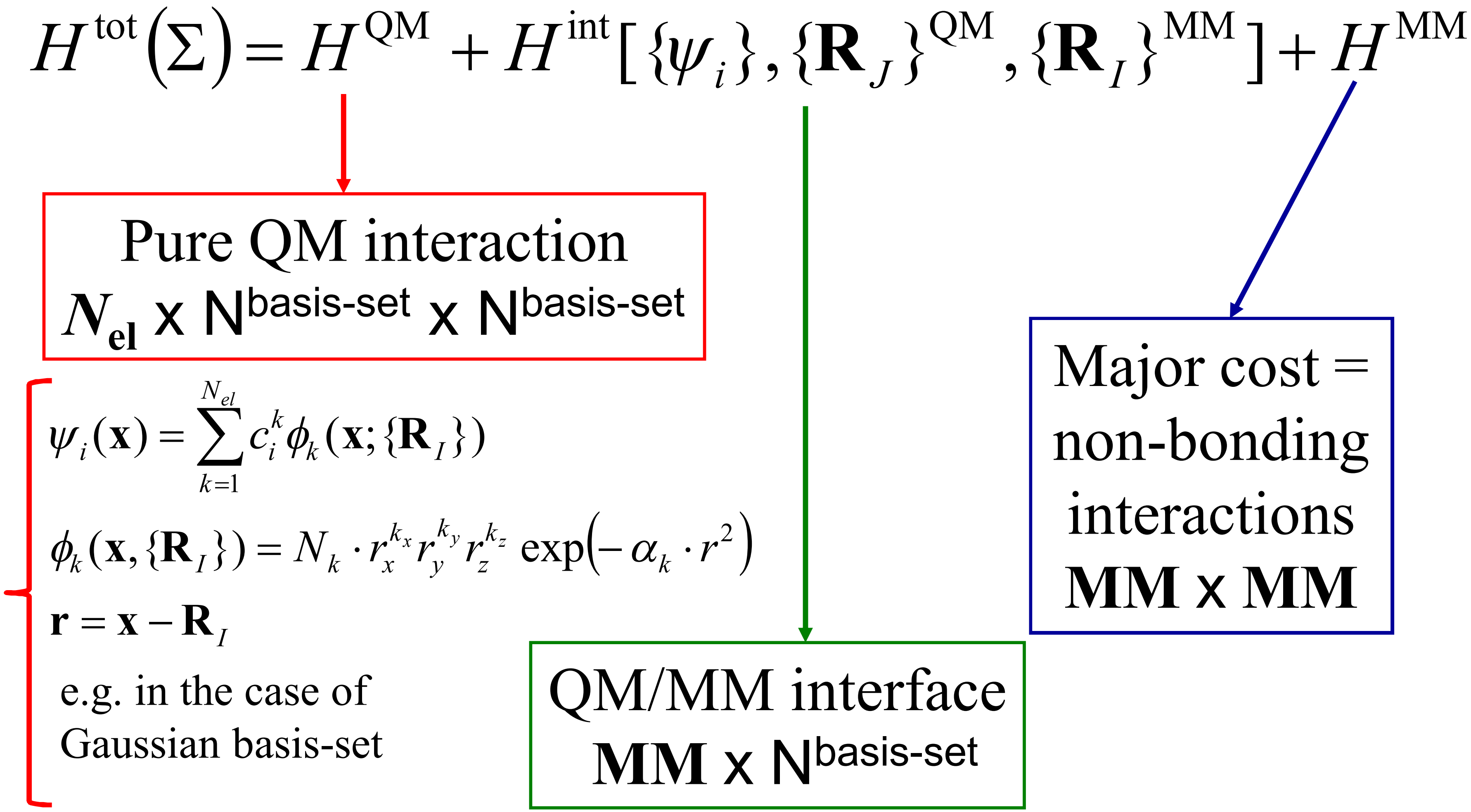
$MM \times N_{\mathbf{G}}$

Major cost =
non-bonding
interactions*

$MM \times MM$

*Ewald summations ($O(MM \log MM)$) or spherical cut-off techniques ($O(MM)$) can reduce the MM computational cost.

Total Hamiltonian: scaling in a localized basis set



$$H^{\text{tot}}(\Sigma) = H^{\text{QM}} + H^{\text{int}}[\{\psi_i\},\{\mathbf{R}_J\}^{\text{QM}},\{\mathbf{R}_I\}^{\text{MM}}] + H^{\text{MM}}$$

Pure QM interaction

$N_{\mathbf{el}}$ x $N^{\text{basis-set}}$ x $N^{\text{basis-set}}$

$$\left\{\begin{array}{l} \psi_i(\mathbf{x}) = \sum_{k=1}^{N_{el}} c_i^k \phi_k(\mathbf{x};\{\mathbf{R}_I\}) \\ \phi_k(\mathbf{x},\{\mathbf{R}_I\}) = N_k \cdot r_x^{k_x} r_y^{k_y} r_z^{k_z} \exp\left(-\alpha_k \cdot r^2\right) \\ \mathbf{r} = \mathbf{x} - \mathbf{R}_I \\ \text{e.g. in the case of} \\ \text{Gaussian basis-set} \end{array}\right.$$

QM/MM interface

MM x $N^{\text{basis-set}}$

Major cost = non-bonding interactions

MM x MM

…and now the forces: CPMD as the QM driver
- the inner part -

- Euler-Lagrange EOM for electrons, ions & Co. inside the QM region + interaction with MM region

$$\mu\ddot{\psi}_i = -\frac{\delta E^{DFT}}{\delta\psi_i^*} + \sum_j \Lambda_{ij}\psi_j + ????$$

$$M_I\ddot{\mathbf{R}}_I = -\nabla_{\mathbf{R}_I}E^{DFT} + ????$$

$$\mu_q\ddot{\alpha}_q = -\frac{\partial E^{DFT}}{\partial\alpha_q}$$

New force components ?

- QM atoms interact in the usual DFT-based way inside the QM box and also with the outer MM atoms (warning: No periodic boundary conditions here !)
- Electrons interact in the usual DFT-based way (Kohn-Sham potential) but also with the outer MM electrostatic charges (again, no PBC allowed here)

MM interaction: forces on atoms

Forces acting on the MM atoms:

$$H^{MM}\left[\{\mathbf{R}_I\},\{q_I\}\right]=\nabla_{\mathbf{R}_I}V^{MM}\left(\mathbf{R}_I\right)+????$$

Remember that computing this gradient means evaluating the derivatives with respect to each atom position $\mathbf{R}_I$ of all the five components of V^{MM} (TOPOLOGY)

- stretching
- bending
- torsion
- Coulomb electrostatics
- van der Waals – Lennard-Jones
- + contribution from the QM atoms !

TOPOLOGY ?

Any force field (of course) does not do any electronic strucrure calculations. So giving the coordinates (x,y,z) as in standard CPMD is insufficient. We must tell the code also which chemical species and which type of bond we want.

Suppose that we have an atom at (x,y,z). The numbers x,y,z are listed in COORDINATES. Now we want this atom to be C and we want it in sp^3 configuration. Evidently a force field for sp^3 is an analytical function different from the one for sp^2.

$$V^{sp^3}\left(r,\theta,\phi\right) \neq V^{sp^2}\left(r,\varphi,z\right)$$

This information is given in the file called TOPOLOGY.

QM/MM electrostatic interaction (1): atoms

$$H^{\text{int}}_{\textbf{QM-MM}}\left[\{\mathbf{R}_I, q_I\}^{\text{MM}}, \{\mathbf{R}_J, Z_J\}^{\text{QM}}\right] = \sum_{I=1}^{\text{MM}} \sum_{J}^{\text{QM}} \frac{q_I Z_J}{\left|\mathbf{R}_I - \mathbf{R}_J\right|}$$

where MM = number of classical atoms, QM = number of quantum atoms, q_I = MM charge, Z_J = QM charge. We have then two forces components:

$$-\frac{\partial H^{\text{int}}_{\text{QM}-\text{MM}}}{\partial \mathbf{R}_J} = Z_J \sum_{I=1}^{\text{MM}} \frac{q_I}{\left|\mathbf{R}_I - \mathbf{R}_J\right|^3} \left(\mathbf{R}_I - \mathbf{R}_J\right) = \mathbf{F}^{\text{int}}_J (1)$$ From MM to QM

$$-\frac{\partial H^{\text{int}}_{\text{QM}-\text{MM}}}{\partial \mathbf{R}_I} = q_I \sum_{J=1}^{\text{QM}} \frac{Z_J}{\left|\mathbf{R}_I - \mathbf{R}_J\right|^3} \left(\mathbf{R}_I - \mathbf{R}_J\right) = \mathbf{F}^{\text{int}}_I (2)$$ From QM to MM

QM/MM electrostatic interaction (2): electrons

Functional form (MM = number of classical atoms):

$$H^{\text{int}}_{e-\mathbf{MM}}\left[\rho(\mathbf{x}),\{\mathbf{R}_I,q_I\}\right]=\sum_{I=1}^{\text{MM}} q_I\int_{\text{QM}} d^3x\,\frac{\rho(\mathbf{x})}{|\mathbf{x}-\mathbf{R}_I|}$$

Expensive if MM is large and/or QM is too accurate !

Potential acting on the QM wave functions $\psi_i(\mathbf{x})$:

$$\frac{\delta H^{\text{int}}_{e-\mathbf{MM}}}{\delta\rho(\mathbf{x})}=\sum_{I=1}^{\text{MM}}\frac{q_I}{|\mathbf{x}-\mathbf{R}_I|}=V^{\text{int}}(\mathbf{x})$$

Forces acting on the MM charged atoms:

$$-\frac{\partial H^{\text{int}}_{e-\mathbf{MM}}}{\partial\mathbf{R}_I}=-q_I\int_{\text{QM}} d^3x\,\frac{\rho(\mathbf{x})}{|\mathbf{x}-\mathbf{R}_I|^3}(\mathbf{x}-\mathbf{R}_I)=\mathbf{F}^{\text{int}}_I(3)$$

Equations of motion: what we have in the code(s)

$$M_I \ddot{\mathbf{R}}_I = -\nabla_{\mathbf{R}_I} V^{MM}\left(\mathbf{R}_I\right) + \mathbf{F}_I^{\text{int}}(2) + \mathbf{F}_I^{\text{int}}(3)$$

MM

$$\mu \ddot{\psi}_i = -\frac{\delta E^{DFT}}{\delta \psi_i^*} + \sum_j \Lambda_{ij} \psi_j + V^{\text{int}}(\mathbf{x}) \psi_i\left(\mathbf{x}\right)$$

$$M_J \ddot{\mathbf{R}}_J = -\nabla_{\mathbf{R}_J} E^{DFT} + \mathbf{F}_J^{\text{int}}(1)$$

$$\mu_q \ddot{\alpha}_q = -\frac{\partial E^{DFT}}{\partial \alpha_q}$$

QM

A possible way to reduce the QMxMM computational cost:

Divide the world in 3 domains

1) Close to the QM region ($r < r_1$)
2) Not too far, i.e. ESP region ($r_1 < r < r_2$)
3) Far MM world ($r > \mathbf{r}_2$)

Generally we test

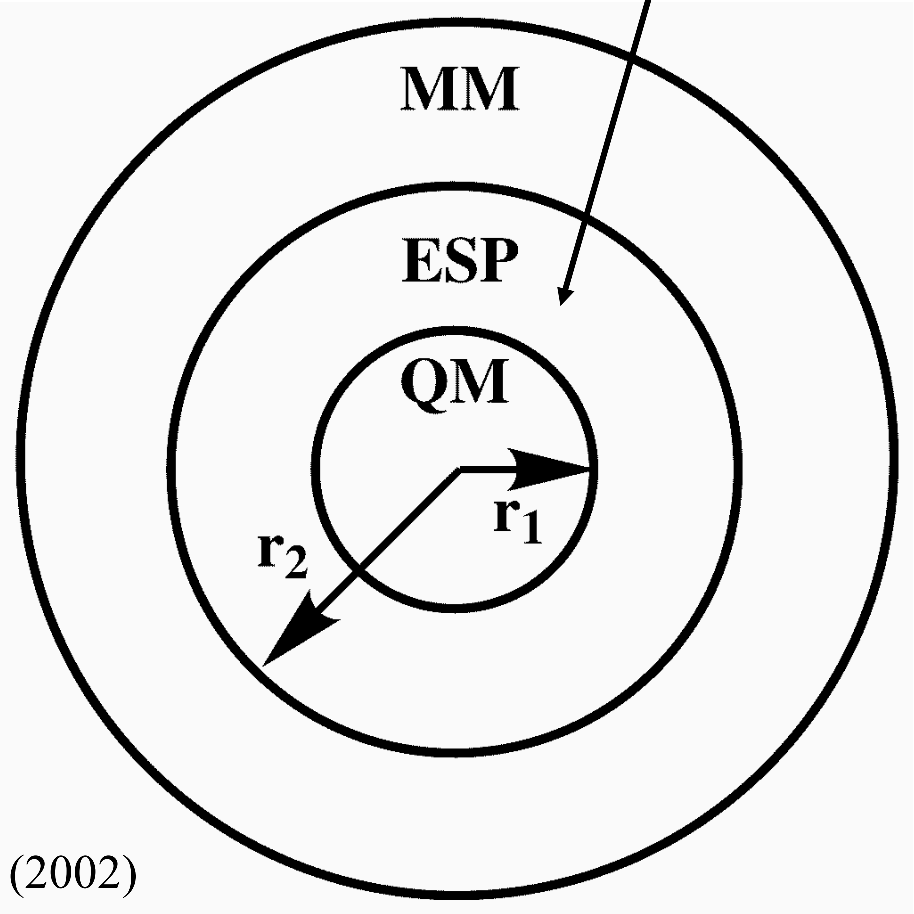
$$r_1 = r_2 = \infty$$

as a check, however in all the known cases it is

$r_1 \sim$ 10-12 a.u.

$r_2 \sim$ 20-25 a.u.

Only *NN* < MM atoms in this shell



A. Laio et al. *J. Chem. Phys.* **116**, 6941 (2002)

The 3-regions scheme

Region 1: NN = subset of classical MM atoms inside this region

$$\sum_{I=1}^{NN} q_I \int d^3x \frac{\rho(\mathbf{x})}{|\mathbf{x}-\mathbf{R}_I|} \qquad r = |\mathbf{x}| < r_1$$

Region 2: Classical-RESP charges interaction:

$$\sum_{I \in NN} q_I \sum_{J \in \mathbf{QM}} \frac{q_J^{RESP}(\rho, \mathbf{R}_I)}{|\mathbf{R}_I - \mathbf{R}_J|} \qquad r_1 < r < r_2$$

Region 3: Multipolar expansion on MM charges:

$$\sum_{I \in NN} q_I \sum_{\alpha} \frac{\wp^{\alpha}(\rho)(\mathbf{x}-\mathbf{R}_I)^{\alpha}}{|\mathbf{x}-\mathbf{R}_I|^3} + quadrupole \quad r > r_2$$

D-RESP: Dynamical – Restrained ElectroStatic Potential derived charges

- Define atomic point charges by fitting their value to the electrostatic potential (ESP) due to the QM charge density seen by the close MM atoms
- A restrain penalty function (RESP) is included, since unphysical charge fluctuations have been observed in unrestrained ESP charges during dynamics. Namely, we minimize the norm

$$\chi = \sum_{I \in NN} \left(\sum_{J \in \mathrm{QM}} \frac{q_J^D}{\left| \mathbf{R}_I - \mathbf{R}_J \right|} - V_I \right)^2 + w_q \sum_{J \in \mathrm{QM}} \left(q_J^D - q_J^H \right)^2$$

ESP $\quad \boxed{q_I^D = q_I^{RESP}} \quad$ Restrain

D-RESP:

q_I^D are the dynamical RESP charges

$$\chi = \sum_{I \in NN} \left(\sum_{J \in \mathrm{QM}} \frac{q_J^D}{\left| \mathbf{R}_I - \mathbf{R}_J \right|} - V_I \right)^2 + w_q \sum_{J \in \mathrm{QM}} \left(q_J^D - q_J^H \right)^2$$

is minimized *on the fly* during the dynamics.

w_q = weight parameter to reduce charge fluctuations

$w_q \approx 0.10 - 0.25$

$$V_J = \int d^3x \, \rho(\mathbf{x}) \, u\left(\left| \mathbf{x} - \mathbf{r}_J \right| \right)$$

Where $u(|\mathbf{r} - \mathbf{r}_J|)$ is a Coulomb potential modified at short range to avoid spurious over-polarization effects

D-RESP: the Hirshfeld charges

In the restrain term $w_q \sum_{J \in QM} \left(q_J^D - q_J^H \right)$

q_I^H are the so-called Hirshfeld charges defined as

$$q_J^H = \int d^3x \, \rho(\mathbf{x}) \frac{\rho^{at}\left(\left|\mathbf{x} - \mathbf{R}_J\right|\right)}{\sum_K \rho^{at}\left(\left|\mathbf{x} - \mathbf{R}_K\right|\right)} - Z_J$$

where ρ^{at} is the atomic (pseudo) valence charge density and

$$Z_J = \int d^3x \, \rho^{at}\left(\mathbf{x} - \mathbf{R}_J\right)$$

is the bare valence charge of the *I*-th atom

D-RESP: the minimization of χ is a least-square procedure

$$\chi = \sum_J \left(\sum_I A_I^J q_I^D - T^J \right)^2$$

$$A_I^J = \begin{cases} 1/\left|\mathbf{R}_I - \mathbf{R}_J\right| & J \in NN \\ w_q \delta_{IJ} & J \in \mathrm{QM} \end{cases} \qquad T^J = \begin{cases} V_J & J \in NN \\ w_q q_J^H & J \in \mathrm{QM} \end{cases}$$

Note that a short-hand notation is used in which

$$A_I^J \quad J = \text{high index running on } NN \cup QM, \quad I = \text{low index running on } QM$$

D-RESP: the least-square minimization with respect to q_I^D reads

$$\frac{\partial \chi}{\partial q_I^D} = 0 \quad \Rightarrow \quad \sum_J \left(\sum_K A_K^J q_K^D - T^J \right) \cdot A_I^J = 0$$

and the (analytical) solution is trivially

$$q_I^D = \sum_K H_{IK}^{-1} t_K$$

where

$$H_{IK} = \sum_J A_I^J A_K^J$$

$$t_K = \sum_J A_K^J T^J$$

The RESP coupling potential

$$V^{RESP}\left(\rho,\{q_J\}\right)=\sum_{I\in NN}\sum_{J\in QM}\frac{q_I q_J^D}{\left|\mathbf{R}_I-\mathbf{R}_J\right|}$$

This replaces the more expensive $\sum_{I\in \mathrm{MM}} q_I \int d^3x\, \rho(\mathbf{x})\, u\left(\left|\mathbf{x}-\mathbf{R}_I\right|\right)$

and the dependence on the QM $\rho\,(\mathbf{x})$ is given by q_J^D.

The additional coupling potential on the electrons is then

$$v(\mathbf{x})=\frac{\delta V^{RESP}}{\delta\rho(\mathbf{x})}=\sum_{J\in \mathrm{QM}}\frac{\partial V^{RESP}}{\partial q_J^D}\frac{\delta q_I^D}{\delta\rho(\mathbf{x})}$$

while the (extra) forces on the atoms are

$$\mathbf{F}_I=-\nabla_{\mathbf{R}_I}V^{RESP}=-\frac{\partial V^{RESP}}{\partial\mathbf{R}_I}-\sum_{J\in \mathrm{QM}}\frac{\partial V^{RESP}}{\partial q_J^D}\frac{\partial q_J^D}{\partial\mathbf{R}_I}$$

An example of hybrid QM/MM-MD:
RNA enzymes =Ribozymes

1) Biological function

Contribution to transfer of genetic information
from DNA to protein

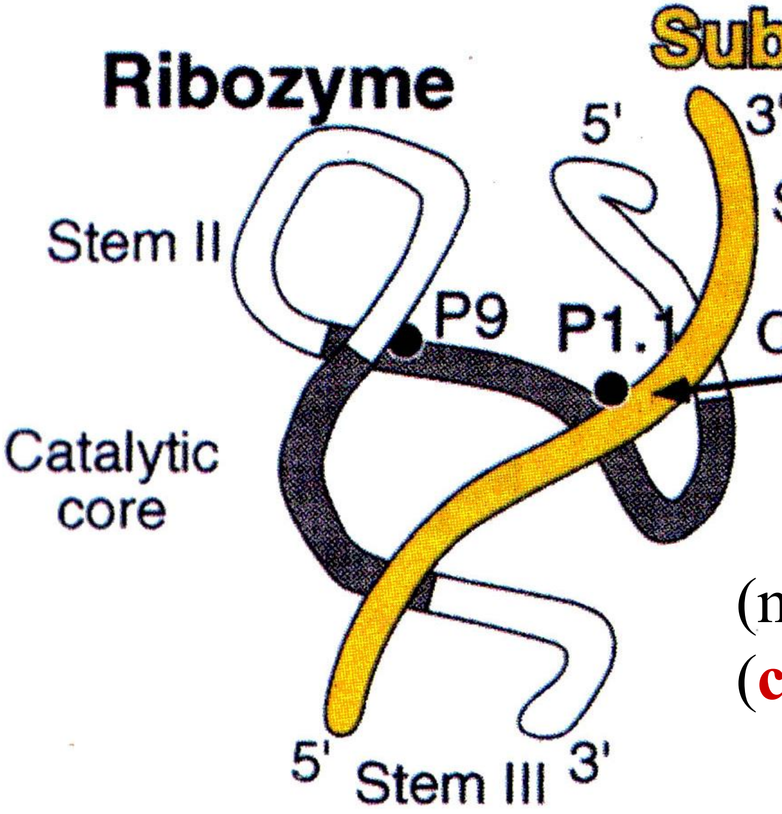
2) Evolution of organisms

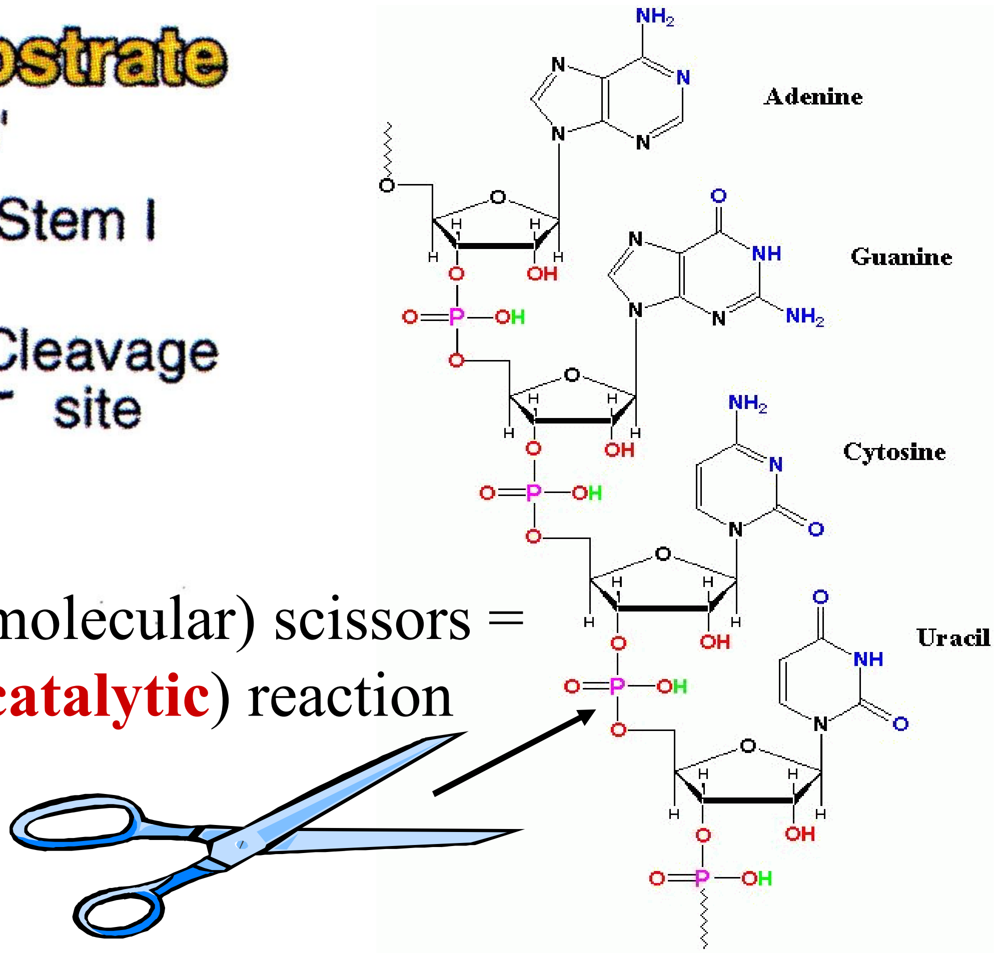
	primordial organism (in the RNA world)	present organism (in the RNP world)
gene	RNA	DNA
enzyme	RNA	protein

3) Medical application

Inhibition of expression of genes, such as oncogene
(cancer gene therapy)

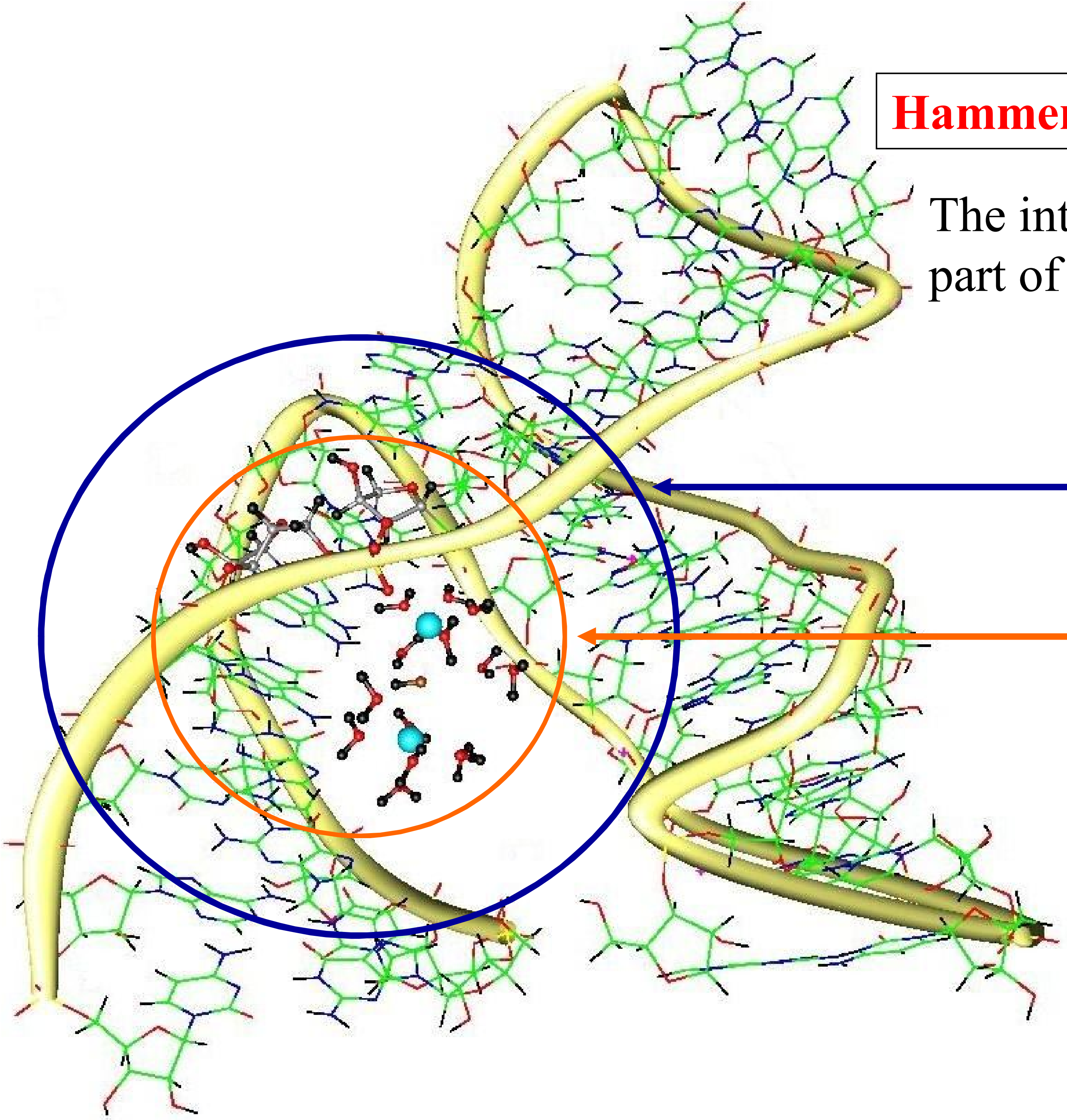
An example of 3D structure of riboyzme: hammerhead ribozyme





(molecular) scissors =
(**catalytic**) reaction

Hammerhead ribozyme



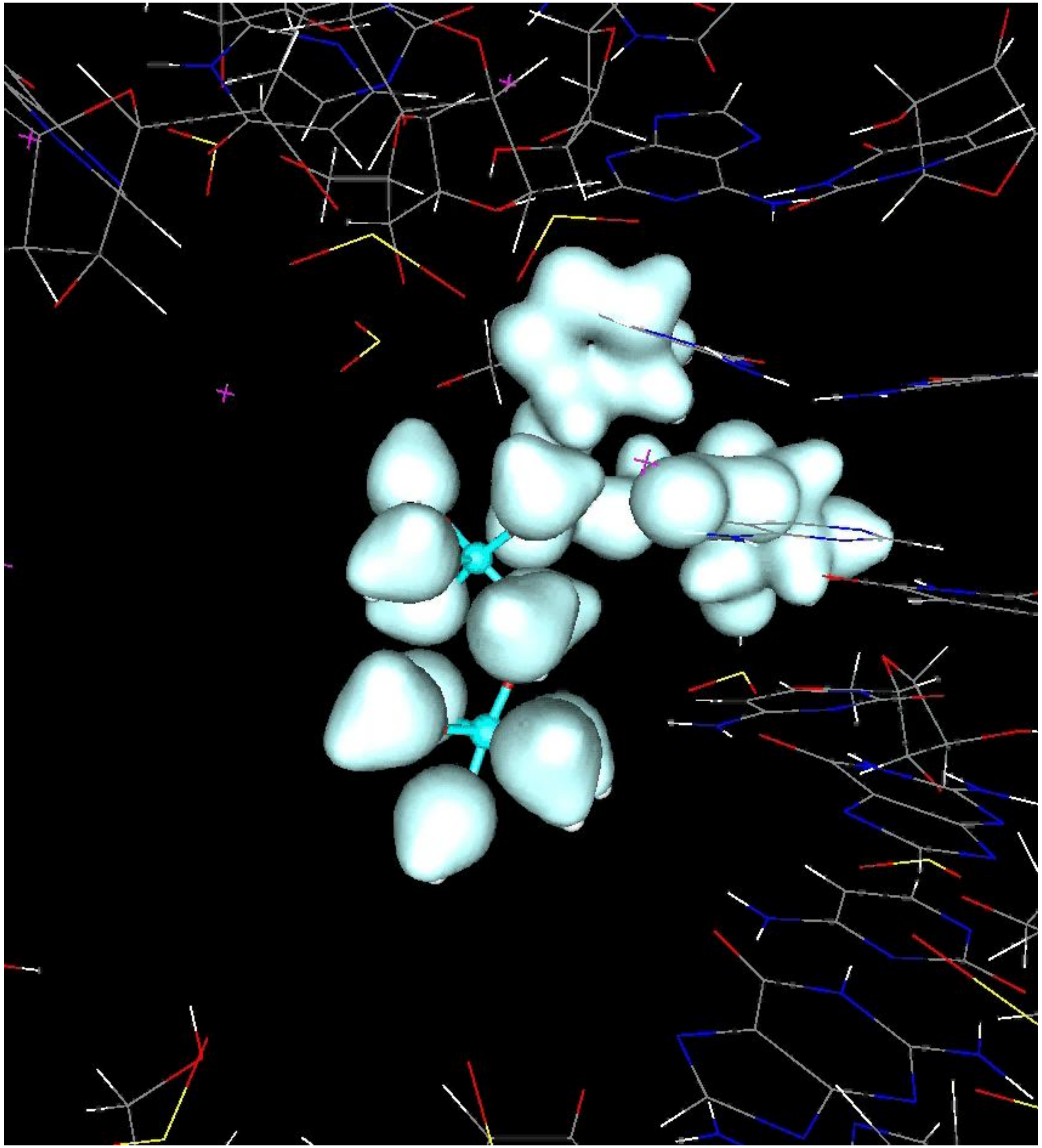
The interacting QM/MM part of the system

D-RESP

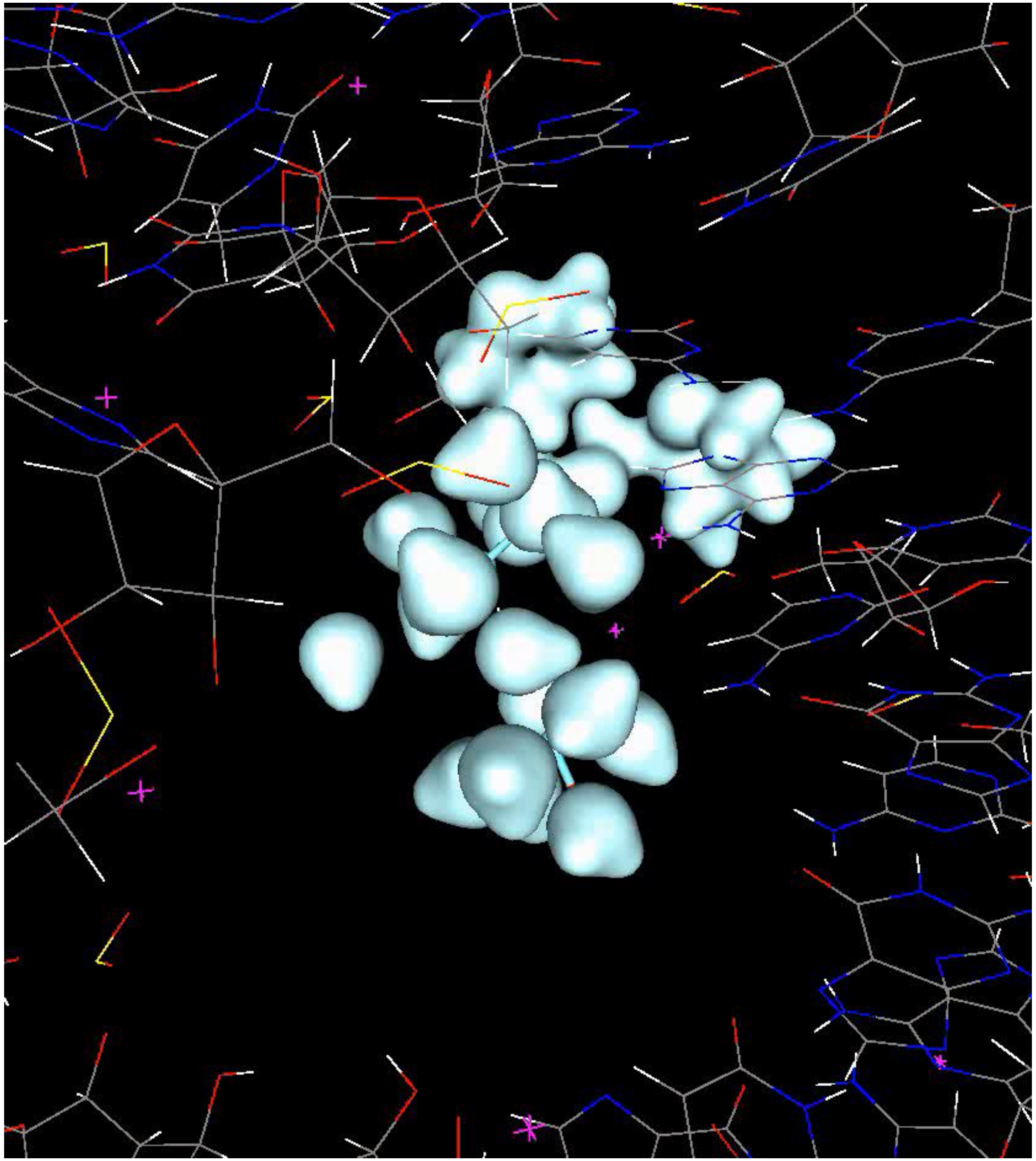
$r_1 < r < r_2$

QM

$r < r_1$



QMMM dynamical simulation in the absence of OH^-



QMMM dynamical simulation in the presence of OH^-

$Mg^{2+}{}_1$-$Mg^{2+}{}_2$ distance during the simulation