Outline
Fully atomistic QM/MM approaches
Embedding in continuum environment
An example of QM/MM calculations

Density Functional Theory: from theory to Applications

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January 17, 2011

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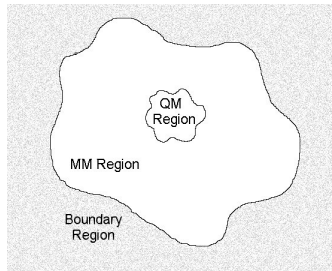Fully atomistic QM/MM approaches
    CP-PAW Interface
    CPMD/ GROMOS Interface
    Real space multi-grid approach

Embedding in continuum environment
    CP-PAW/COSMO Interface

An example of QM/MM calculations

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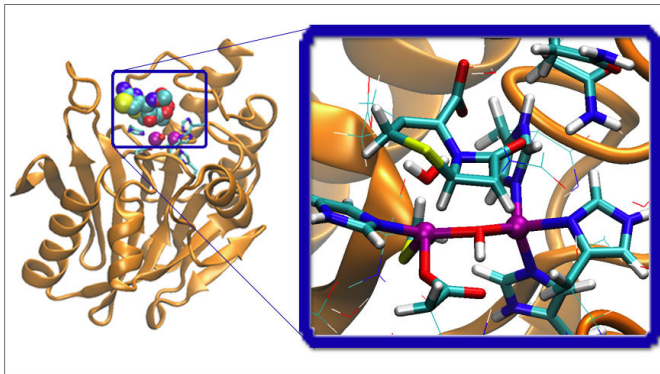Fully atomistic QM/MM approaches
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Mixed quantum/ classical molecular dynamics (QM/MM)

- ▶ Quantum mechanics is computationally expensive
- ▶ Idea: subdivide a complex system in a small, relevant part (QM) and the environment which is not neglected but treated at lower level of accuracy (MM). [1]

[1] See pioneering work of Warshel and Levitt, JMB 1976, 103, 227.

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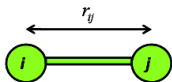An example of QM/MM calculations

Metallo-beta-lactamase enzyme. Two zinc ions (purple spheres) are in the enzyme's active site (with amino acids coordinating the metals represented as sticks).

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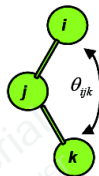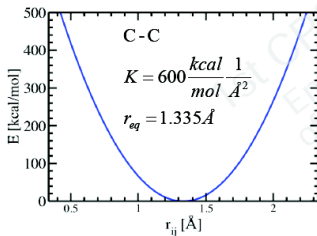Fully atomistic QM/MM approaches: both QM and MM are based on particle representation. The full Hamiltonian is:

$$E^{QM/MM} = E^{QM}(\{\mathbf{R}_\alpha\}) + E^{MM}(\{\mathbf{R}_I\}) + E^{QM-MM}(\{\mathbf{R}_\alpha\}, \{\mathbf{R}_I\}) \tag{1}$$

- ► $E^{QM}(\{\mathbf{R}_\alpha\})$ is the Kohn-Sham Hamiltonian H_e^{KS}, e.g. in a plane wave / pseudopotential representation.
- ► $E^{MM}(\{\mathbf{R}_I\})$ are force field energy expressions: short-range bonded interaction with fixed topology + non-bonded interaction (electrostic and van der Waals)

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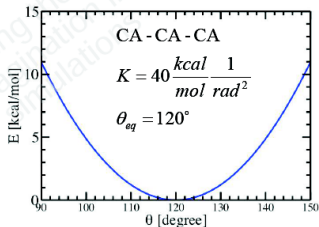CPMD/ GROMOS Interface
Real space multi-grid approach

MM: Bonds and bends

$$V(r_{ij}) = K(r_{ij} - r_{eq})^2$$

$$V(\theta_{ijk}) = K(\theta_{ijk} - \theta_{eq})^2$$

C - C

$$K = 600 \frac{kcal}{mol} \frac{1}{\AA^2}$$

$$r_{eq} = 1.335 \AA$$

CA - CA - CA

$$K = 40 \frac{kcal}{mol} \frac{1}{rad^2}$$

$$\theta_{eq} = 120°$$

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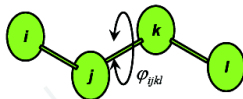
MM: Urey-Bradley and Dihedral
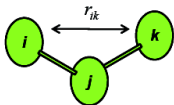
$$V_{UB}(r_{ik}) = K_{UB}(r_{ik} - r_{eq})^2$$
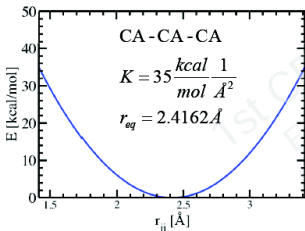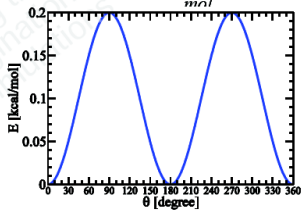
$$V(\theta) = K[1 + \cos(n\varphi - \gamma)]$$

CTL2 - CTL2 - CTL2 - CLT2

$$n = 2, K = 0.10 \frac{kcal}{mol}, \gamma = 180°$$

CA - CA - CA

$$K = 35 \frac{kcal}{mol} \frac{1}{\mathring{A}^2}$$

$$r_{eq} = 2.4162 \mathring{A}$$

Seen in CHARMM.

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MM: Improper (Out of plane motion)

$$V(\theta_{ijkl}) = K(\varphi_{ijkl} - \varphi_{eq})^2$$

$$CPB - CPA - NPH - CPA$$

$$K = 20.8 \frac{kcal}{mol} \frac{1}{rad^2}$$
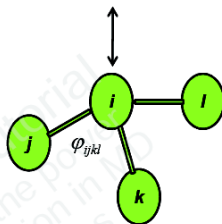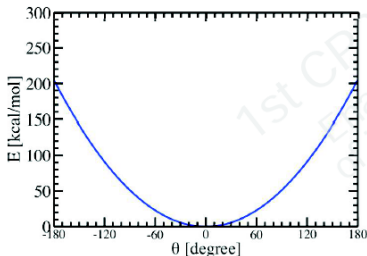
By definition, from the force field parameter and documentation, the first atom listed is the central atom. Therefore just like a normal torsion, the angle of interest is between the plane defined of particle *ijk* to that of the plane defined by particle *jkl*. This is only used for special situations.

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MM: Non-bonded

▶ Steric interactions are usually described by standard Lenard-Jones interaction, but different functional forms are also possible

$$V(r_{ij}) = \varepsilon_{ij} \left(\left(\frac{R_{min}}{r_{ij}} \right)^{12} - 2 \left(\frac{R_{min}}{r_{ij}} \right)^{6} \right)$$
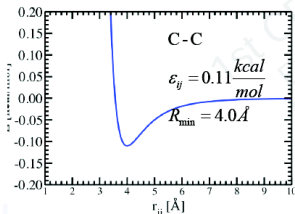
▶ Electrostatics:

$$V(r_{ij}) = \frac{q_i q_j}{\epsilon r_{ij}} \tag{2}$$

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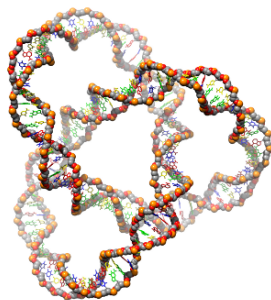Embedding in continuum environment
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Biomolecular simulations: AMBER

$$V_{total} = \sum_{bonds} K_b \left(b - b_{eq} \right)^2 +$$

$$\sum_{angle} K_\theta \left(\theta - \theta_{eq} \right)^2 +$$

$$\sum_{dihedrals} \frac{V_n}{2} \left[1 + \cos(n\phi - \gamma) \right] +$$

$$\sum_{i<j} \left[\frac{A_{ij}}{R_{ij}^{12}} - \frac{B_{ij}}{R_{ij}^6} - \frac{q_i q_j}{\varepsilon R_{ij}} \right]$$

http://ambermd.org/

D.A. Case, T.E. Cheatham, III, T. Darden, H. Gohlke, R. Luo, K.M. Merz, Jr., A. Onufriev, C. Simmerling, B. Wang and R. Woods. The Amber biomolecular simulation programs. J. Computat. Chem. 26, 1668-1688 (2005).

J.W. Ponder and D.A. Case. Force fields for protein simulations. Adv. Prot. Chem. 66, 27-85 (2003).

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Biomolecular simulations: CHARMM

$$V_{total} = \sum_{bonds} K_b \left(b - b_{eq}\right)^2 +$$

$$\sum_{UB} K_{UB} \left(S - S_{eq}\right)^2 +$$

$$\sum_{angle} K_\theta \left(\theta - \theta_{eq}\right)^2 +$$

$$\sum_{dihedrals} K_\phi \left[1 + \cos\left(n\phi - \gamma\right)\right] +$$

$$\sum_{impropers} K_{imp} \left(\varphi - \varphi_{eq}\right)^2 +$$

$$\sum_{i<j} \varepsilon \left[\left(\frac{R_{min_{ij}}}{r_{ij}}\right)^{12} - \left(\frac{R_{min_{ij}}}{r_{ij}}\right)^6\right] + \frac{q_i q_j}{r_{ij}}$$

$$\varepsilon_{ij} = \sqrt{\varepsilon_{ii} \varepsilon_{jj}} \qquad R_{min_{ij}} = \tfrac{1}{2}\left(R_{min_i} + R_{min_j}\right)$$

http://www.charmm.org

CHARMM: A Program for Macromolecular Energy, Minimization, and Dynamics Calculations, J. Comp. Chem. 4, 187-217 (1983), by B. R. Brooks, R. E. Bruccoleri, B. D. Olafson, D. J. States, S. Swaminathan, and M. Karplus.
CHARMM: The Energy Function and Its Parameterization with an Overview of the Program, in The Encyclopedia of Computational Chemistry, 1, 271-277, P. v. R. Schleyer et al., editors (John Wiley & Sons: Chichester, 1998), by A. D. MacKerell, Jr., B. Brooks, C. L. Brooks, III, L. Nilsson, B. Roux, Y. Won, and M. Karplus.

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OPLS (Optimized Potentials for Liquid Simulations)

$$V_{total} = \sum_{bonds} K_r \left(r - r_{eq} \right)^2 +$$
$$\sum_{angle} K_\theta \left(\theta - \theta_{eq} \right)^2 +$$
$$\sum_{dihedrals} \frac{V_1}{2} \left[1 + \cos(\phi - \gamma_1) \right] +$$
$$\frac{V_2}{2} \left[1 + \cos(2\phi - \gamma_2) \right] +$$
$$\frac{V_3}{2} \left[1 + \cos(3\phi - \gamma_3) \right] +$$
$$\sum_{i<j} \left[4\varepsilon_{ij} \left(\frac{\sigma_{ij}^{12}}{r_{ij}^{12}} - \frac{\sigma_{ij}^6}{r_{ij}^6} \right) - \frac{q_i q_j e^2}{r_{ij}} \right] f_{ij}$$

Jorgensen WL, Tirado-Rives J (1988). "The OPLS Force Field for Proteins. Energy Minimizations for Crystals of Cyclic Peptides and Crambin". J. Am. Chem. Soc. 110: 16571666.
Jorgensen WL, Maxwell DS, Tirado-Rives J (1996). "Development and Testing of the OPLS All-Atom Force Field on Conformational Energetics and Properties of Organic Liquids". J. Am. Chem. Soc. 118 (45): 1122511236.

$\gamma_1 = \gamma_2 = \gamma_3 = 0°$ $\sigma_{ij} = \sqrt{\sigma_{ii}\sigma_{jj}}$ $f_{ij} = 0.5$ for 1-4 interactions

$\varepsilon_{ij} = \sqrt{\varepsilon_{ii}\varepsilon_{jj}}$ $f_{ij} = 1.0$ for everything else

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Class II force fields

▶ Greater transferability: Application of empirical force field parameters to molecules not explicitly included during the parameter optimization.

▶ Example: Merck Molecular Force Field (MMFF), a Class II force field designed to be a transferable force field for pharmaceutical compounds that accurately treats conformational energetics and non-bonded interactions. This would, ideally, produce a force field that was adequate for both gas phase and condensed phase calculations.

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Class II force fields: MMFF

$$V_{total} = \sum_{bonds} K_{bond} \left(r - r_{eq}\right)^2 \left(1 + cs\left(r - r_{eq}\right) + \tfrac{7}{12}\left(cs^2\left(r - r_{eq}\right)^2\right)\right) +$$

$$\sum_{angle} K_\theta \left(\theta - \theta_{eq}\right)^2 \left(1 + cb\left(\theta - \theta_{eq}\right)\right) +$$

$$\sum_{angle,linear} K_{al}\left(1 + \cos(\theta)\right) +$$

$$\sum_{stretch,bend} \left(K_{ijk}\left(r_{ij} - r_{eq}\right) + K_{kji}\left(r_{kj} - r_{eq}\right)\right)\left(\theta - \theta_{eq}\right) +$$

$$\sum_{outofplane} K_{OOP}\left(\chi\right)^2 +$$

$$\sum_{dihedrals} \frac{V_1}{2}\left[1 + \cos(\phi)\right] + \frac{V_2}{2}\left[1 + \cos(2\phi)\right] + \frac{V_3}{2}\left[1 + \cos(3\phi)\right] +$$

$$\sum_{i<j} \left[\varepsilon_{ij}\left(\frac{1.07\sigma}{r_{ij} + 0.07\sigma}\right)^7\left(\frac{1.12\sigma^7}{r_{ij}^7 + 0.07\sigma^7} - 2\right) - \frac{q_i q_j}{D\left(r_{ij} + \delta\right)}\right]$$

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$E^{QM-MM}(\{\mathbf{R}_\alpha\}, \{\mathbf{R}_I\})$

$$E^{QM-MM} = E_b^{QM-MM} + E_{nb}^{QM-MM} \tag{3}$$

$$E_{nb}^{QM-MM} = E_{es}^{QM-MM} + E_{steric}^{QM-MM} \tag{4}$$

▶ E_{steric}^{QM-MM} generally follows the model used in E^{MM} (Lenard-Jones-type potentials).

▶ For the E_{es}^{QM-MM} there different coupling schemes:
  ▶ mechanical embedding: no influence of MM charges on the QM system
  ▶ electrostatic embedding: electrostatic interaction between mm charges and charge density of the QM system
  ▶ polarized embedding: MM polarization due to the QM system is also included

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Technical issues connected with the electrostic coupling

- Straightforward numerical evaluation of the electrostatic coupling term:

$$E_{es}^{QM-MM} = \sum_{I \in MM} q_I \int \frac{n(r)}{|\mathbf{r} - \mathbf{R}_I|} d\mathbf{r} \qquad (5)$$

is prohibitive. Indeed it would involve a number of operations which scales as N_g (number of grid points) times N_{MM} (number of MM atoms).

- Electron spill out or charge leakage

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CP-PAW Interface

Pioneering qm/mm work by Bloch and coworkers[2].
Motivation: studying chemical reaction of complex system and computing free energy profile using thermodynamics integration.
The instaneous electronic density of the QM system is mapped onto a set of Gaussian smearing functions tied to the QM sites. The corresponding Lagrangian is:

$$
\begin{aligned}
\mathcal{L}^{QM/MM} &= \mathcal{L}^{QM}_{CP} + \mathcal{L}^{MM} + \mathcal{L}^{QM-MM} &(6) \\
&= \sum_{\alpha} \frac{1}{2} M_{\alpha} \dot{\mathbf{R}}^2_{\alpha} + \sum_i \mu \left\langle \dot{\phi_i} | \dot{\phi_i} \right\rangle - \left\langle \Psi_0 | \tilde{H}^{KS}_e(\{\mathbf{R}_{\alpha}\}) | \Psi_0 \right\rangle &(7) \\
&+ \sum_{i,j} \Lambda_{i,j} (\langle \phi_i | \phi_j \rangle - \delta_{ij}) &(8) \\
&+ \sum_I \frac{1}{2} M_I \dot{\mathbf{R}}^2_I + E^{MM}(\{\mathbf{R}_I\}) + E^{QM-MM}(\{\mathbf{R}_I\}, \{\mathbf{R}_{\alpha}\}) &(9)
\end{aligned}
$$

[2]J. Chem. Phys. 103, 7422

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CP-PAW Interface

- ▶ Separate Nose'-Hoover thermostats for the QM/MM regions
- ▶ Decoupling scheme between periodic images
- ▶ The continuous charge density is compressed to a linear superposition of of atom-centered spherical Gaussian functions:

$$n^G(\mathbf{r}) = \sum_\alpha q_\alpha G(\mathbf{r} - \mathbf{R}_\alpha) \tag{10}$$

Gaussian parameters are determined imposing that $n^G(\mathbf{r})$ reproduce the multiple moments of $n(\mathbf{r})$.
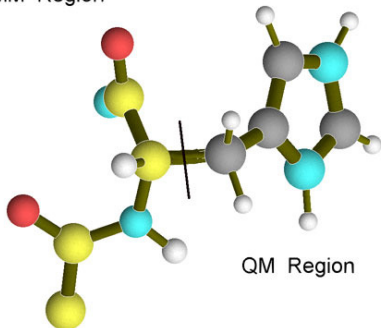
In the limit of infinitesimally small width the Gaussian density becomes:

$$n^{pc}(\mathbf{r}) = \sum_\alpha q_\alpha \delta(\mathbf{r} - \mathbf{R}_\alpha) \tag{11}$$

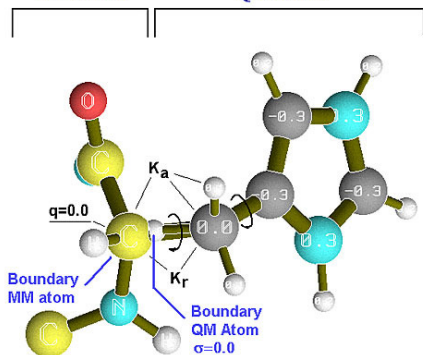The electrostatic coupling is obtained between these effective QM charges and the MM charges.

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Handling bond cuts: the hydrogen capping

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A multiple timestep scheme

Relevant dynamical changes in the QM and MM systems typically occur on quite disparate time scales.
Accessible time-scale for QM dynamics is the ps time scale, whereas large amplitude conformational changes in large biomolecules occurs on the ns timescale.

▶ Multiple time step scheme
▶ oversampling artificially decreasing the MM masses, in this case the generated dynamics is fictious.

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The CPMD/ GROMOS Interface

Full Hamiltonian QM/MM coupling. The QM/MM interface[3] is tailored to study dynamics of complex biomolecular systems and chemical reactions. The non-bonded part of the total energy is written as:

$$E_{nb}^{QM-MM} = E_{es}^{QM-MM} + E_{steric}^{QM-MM} \tag{12}$$

$$= \sum_{I \in MM} q_I \int \frac{n(\mathbf{r})}{|\mathbf{r} - \mathbf{R}_I|} d\mathbf{r} + \sum_{I \in MM} \sum_{\alpha \in QM} v_{vdW}(|\mathbf{R}_\alpha - \mathbf{R}_I|) \tag{13}$$

Short range electrostatic: the spill out problem.

$$E_{es}^{QM-MM} = \sum_{I \in MM} q_I \int n(\mathbf{r}) v_I^{eff}(|\mathbf{r} - \mathbf{R}_I|) d\mathbf{r} \tag{14}$$

$$v_I^{eff}(r_I) = \frac{r_{cI}^m - r_I^m}{r_{cI}^{m+1} - r_I^{m+1}} \to \frac{1}{r_I} (r_I \to \infty) \tag{15}$$

where $m- = 4$ and $R_{c,I}$ covalent radius for the Ith atom is a reasonable choice.

[3]Laio, VandeVondele, Rothlisberger, J. Chem. Phys. 116, 6941 (2002).

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Long Range Electrostatic

The Coulombic electrostatic field is included exactly only for a set of MM atoms in the vicinity of the QM system.

The electrostatic field on the MM atoms that do not belong to the NN set is calculated by a multi-polar expansion

$$\int dr \frac{\rho(r)}{|r - r_j|} = C \frac{1}{|r_j - \bar{r}|} + \sum_\alpha D^\alpha \frac{(r_j^\alpha - \bar{r}^\alpha)}{|r_j - \bar{r}|^3}$$

$$+ \frac{1}{2} \sum_{\alpha\beta} Q^{\alpha\beta} \frac{(r_j^\alpha - \bar{r}^\alpha)(r_j^\beta - \bar{r}^\beta)}{|r_j - \bar{r}|^5}$$

$$+ \mathcal{O}\left(\frac{R_q}{|r_j - \bar{r}|}\right)^4,$$

$$C = \int dr \rho(r),$$
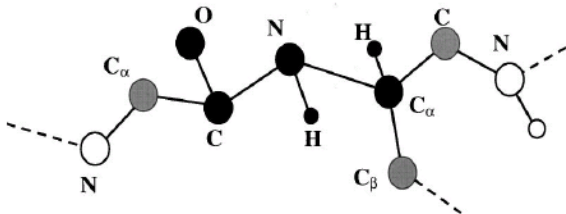
$$D^\alpha = \int dr \rho(r)(r^\alpha - \bar{r}^\alpha),$$

$$Q^{\alpha\beta} = \int dr \rho(r)[3(r^\alpha - \bar{r}^\alpha)(r^\beta - \bar{r}^\beta)$$

$$- \delta^{\alpha\beta}|r - \bar{r}|^2],$$

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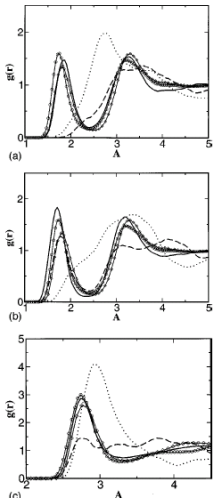**Fully atomistic QM/MM approaches**
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Bonded Interactions

Two option have been employed:

- ▶ Hydrogen capping
- ▶ Carbon monovalent pseudopotentials

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CPMD/GROMS: validation

QM water in MM (SPC) water

Pair correlation functions for qm/mm compared with continuous line with circles (SPC water) continuous line with diamonds (full QM)
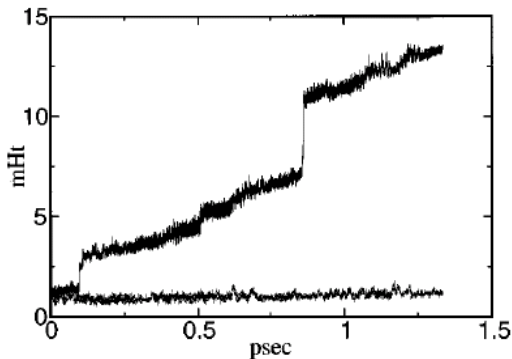Continuous line: r_c for oxygen and hydrogen are 0.8 and 0.4 Å, respectively;
dashed line: r_c for oxygen and hydrogen are 0.8 and 0.8 Å;
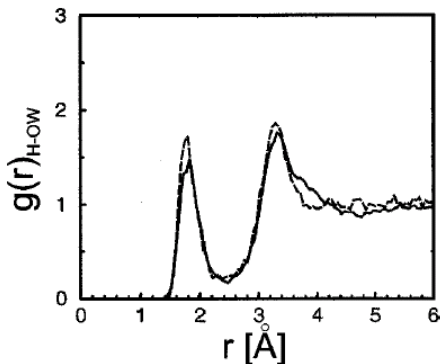dotted line: r_c for oxygen and hydrogen are 1.4 and 0.8 Å.
1) QM oxygen-MM hydrogen.
2) QM hydrogen-MM oxygen.
3) QM oxygen-MM oxygen.

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CPMD/GROMS: validation

Fictitious electronic kinetic energy for a QM water in a box of classical SPC water at 300 K and normal density. The time step is 6 a.u. Continuous line: no modification of the Coulomb potential . Dotted line: modified Coulomb

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Hydrogen-water oxygen pair correlation function for a ammonium ion in a box of water. Continuous line: full quantum result Dashed line: QM/MM result. The quantum ammonium ion is solvated in a box of SPC water.

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Real space multi-grid approach

This approach[4] is implemented in CP2K[5]. Which is a GPWs code, suing a mixed Gaussian and plane wave basis set for the expansion of the wavefunction and of the charge density.

▶ This approach is based on the use of a multi-grid technique in conjunction with a Gaussian expansion of the electrostatic potential (GEEP)

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[4] JCTC 2005, 1, 1176.
[5] www.cp2k.berlios.de

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The exact Coulomb potential is replaced by

$$v_a(\mathbf{r},\mathbf{r}_a) = \frac{\mathrm{Erf}\left(\frac{|\mathbf{r} - \mathbf{r}_a|}{r_{c,a}}\right)}{|\mathbf{r} - \mathbf{r}_a|}$$
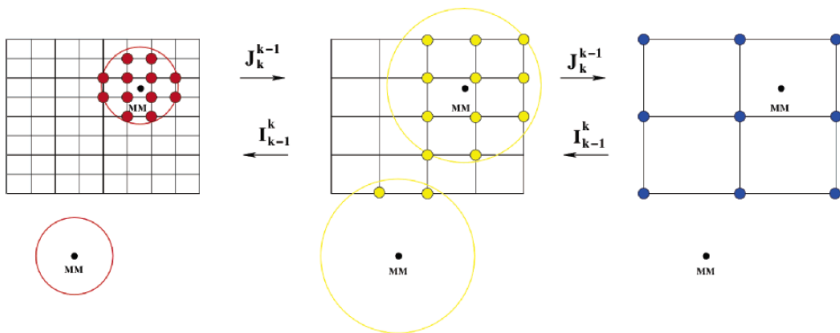
which is the exact potential energy function originated by a Gaussian charge distribution and has the desired property of tending to $1/r$ at large distances and going smoothly to a constant for small r. This potential can be written as sum of Gaussian functions with different cutoffs according to

$$v_a(\mathbf{r},\mathbf{r}_a) = \frac{\mathrm{Erf}\left(\frac{|\mathbf{r} - \mathbf{r}_a|}{r_{c,a}}\right)}{|\mathbf{r} - \mathbf{r}_a|} = \sum_{N_g} A_g \exp\left(-\left(\frac{|\mathbf{r} - \mathbf{r}_a|}{G_g}\right)^2\right) + R_{\mathrm{low}}(|\mathbf{r} - \mathbf{r}_a|)$$

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CP-PAW Interface
CPMD/ GROMOS Interface
Real space multi-grid approach

The advantage of this decomposition scheme is that grids of different spacing can be used to represent the different contributions to $v_a(r, r_a)$.

T. Laino, F. Mohamed, A. Laio and M. Parrinello, *J. Chem. Th. Comp.*, 1, **2005**, pp. 1176-1184
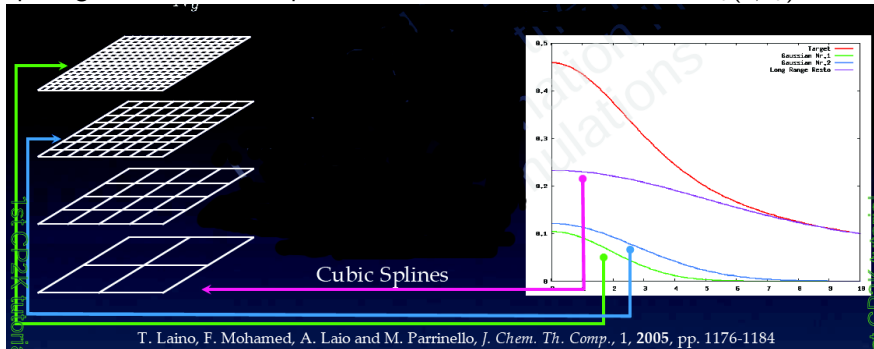
Sharp Gaussians require fine grids, while coarser grids are necessary for the smoothest components. Gaussians can be truncated beyond a certain threshold value, which makes the collocation of the Gaussians on the grid very efficient.

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Gaussian will be represented on the same number of grid points irrespective of its width. (e.g. a mesh of 25 X 25 × 25 suffices for an optimal Gaussian representation). The Gaussian can be considered a compact domain function, i.e., it is zero beyond a certain distance. Thus only MM atoms embedded into the QM box, or close to it, will contribute to the finest grid levels.

The speed up is abut 2 order of magnitude

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CP-PAW/COSMO Interface

Embedding in continuum environment

CP-PAW/COSMO: the environment is treated with a conductor-like screening model

- ▶ homogeneous and inert solvent treated as dielectric continuum: suitable if environment is not involved in the ongoing chemistry

- ▶ the essential aspect of this approach is to treat the surface charges at the cavity boundaries as fictious dynamical variables:

$$
\begin{aligned}
\mathcal{L}^{QM/MM} &= \mathcal{L}_{CP}^{QM} + \mathcal{L}^{MM} + \mathcal{L}^{COSMO} \quad (16) \\
\mathcal{L}^{COSMO} &= \sum_I \frac{1}{2} M_I \dot{Q}_I^2 + G_{es}^{COSMO}(\{Q_I\}, \{\mathbf{R}_\alpha\}) \\
&\quad - G_{steric}(\{\mathbf{R}_\alpha\}) - \sum_I k(1 - \Theta_I)Q_I^2 \quad (17)
\end{aligned}
$$

where the

$$
G_{steric} = \sigma_0 + \sigma_1 A \quad (18)
$$

with A surface area of the cavity and σ_i empirical fixed parameters

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CP-PAW/COSMO Interface
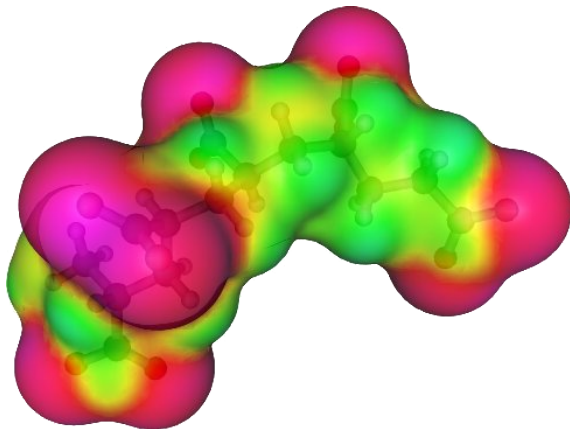
COSMO surface of a pentaacrylate molecule (red = negative, green = positive equilibrium layer).

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CP-PAW/COSMO Interface

▶ A bonded term between the QM and MM parts, E_b^{QM-MM} does not exists in this approach.

▶ The fictious variables Q_I, with associated inertia parameters M_I^Q, are discretized, scaled surface charges, located at the center of segments $\mathbf{s_I}$.

▶ Switching functions are introduced to switch off the charges of the segments which are not exposed to the solvent.

▶ Last term in eq:17 is a penalty function introduced to keep the instantaneous switched off charges from blowing-up during the dynamics

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CP-PAW/COSMO Interface

The COSMO free energy can be written down in terms of of electrostatic solute-solvent, solvent-solvent, and self energy contributions:

$$G_{es}^{COSMO} = \sum_I Q_I \Theta_I \int_V \frac{n(\mathbf{r})}{|\mathbf{r} - \mathbf{s}_I|} d\mathbf{r} + \frac{1}{f} \sum_{I<J} \frac{Q_I \Theta_I Q_J \Theta_J}{|\mathbf{s}_I - \mathbf{s}_J|} \quad (19)$$

$$+ \frac{c}{f} \sum_I \frac{Q_I^2 \Theta_I^2}{\sqrt{a_I}} \quad (20)$$

$$G_{steric} = \sigma_0 + \sigma_1 \sum_I a_I \Theta_I \quad (21)$$

f is a constant screening factor, c is a geometry-dependent constant and V is the cavity volume.
Spill-out is prevented using the Gaussian model density as described for the CP-PAW/AMBER.

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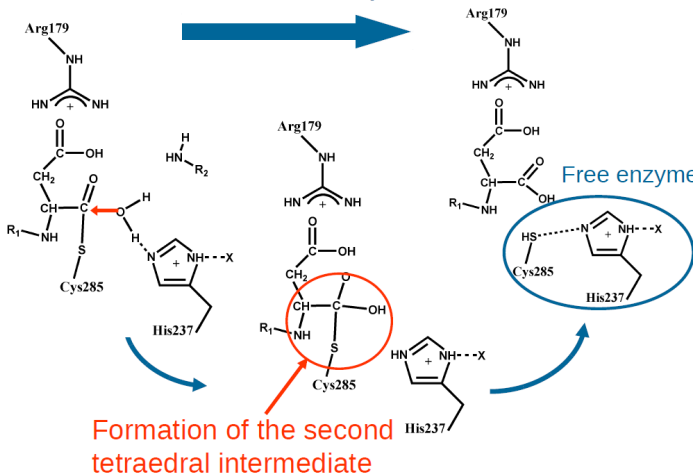# A QM/MM application: reaction mechanism of caspase

Caspase-3 is a cysteine protease involved in the programmed cell-death (apoptosis). Idea: study the enzymatic reaction in the protein environment. Calculate free energy barrier associated with the proposed mechanism[6].
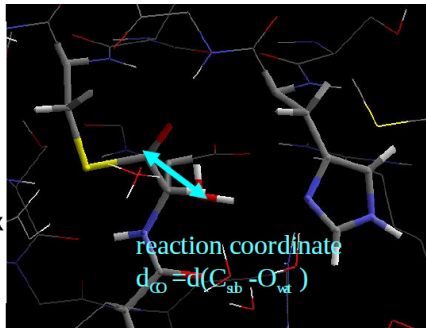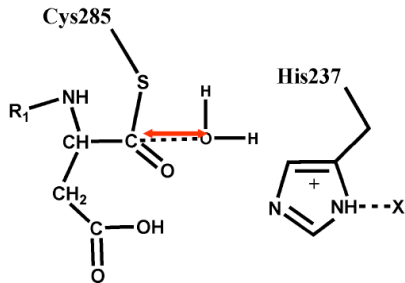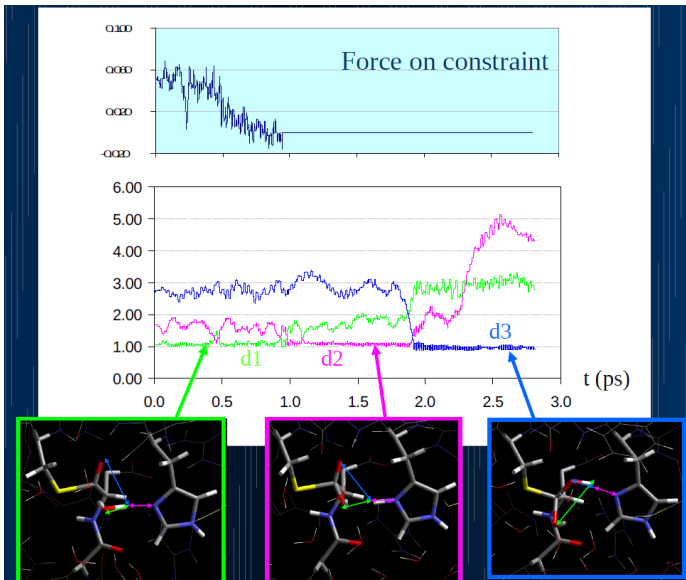

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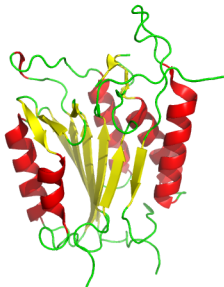
[6]Sulpizi *et al*, Proteins, 52(2): 212 (2003).

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Fully atomistic QM/MM approaches
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Reaction step 1

Formation of first
tetraedral intermediate

acylenzyme

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Fully atomistic QM/MM approaches
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Reaction step 2

Formation of the second
tetraedral intermediate

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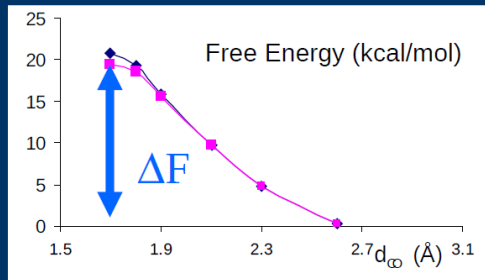Embedding in continuum environment
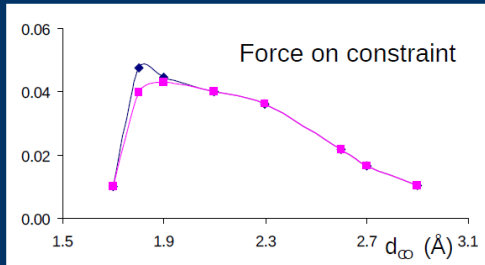**An example of QM/MM calculations**

Force on constraint

Ciccotti *et al*.
Chem. Phys. 129, 241(1989)
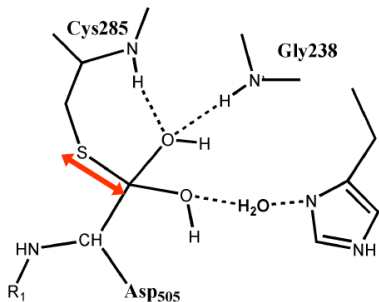
Free energy

$$\Delta\mathrm{F}=\int dQ\, f_s(Q)$$

Force on constraint

Reaction coordinate

Free Energy (kcal/mol)

$\Delta\mathrm{F}$

For our calculation a ΔF 20 kcal/mol is compatible with the

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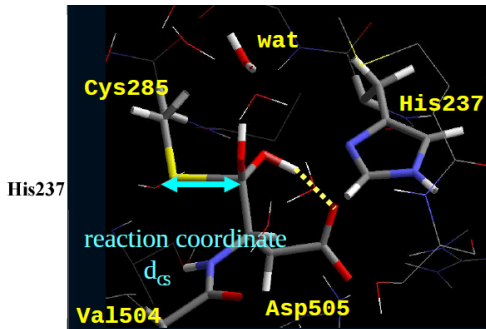
The free energy barrier associated with this step is only 5 kcal/mol, so the previous step results to be the rate determing one.

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Importance of the environment

- ▶ No secondary structure elements which are relevant to active site electric field (as i.e. in papain and cathepsins)

- ▶ Protein structure seems to act as geometrical constraint which reduces entropy of reaction provides proper conformation to catalytic dyad