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Advancing Frontiers of Condensed Matter Physics:**

"Fundamental Interactions and Excitations in Confined Systems"

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Bridging the time scale and length gap: from QM/MM to history-dependent metadynamics

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Bridging the time scale and length gap: from QM/MM to history dependent metadynamics

Alessandro Laio

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The time scale problem

Direct simulation allows only very short runs:
~ 10 ps for ab-initio MD, ~10 ns for classical MD

Many relevant phenomena take place on a larger time scale: chemical reactions, conformational changes, protein folding, etc.

The size problem

How to describe a chemical reaction in an heterogeneous complex medium, like o protein?

The time-scale problem: Accelerating Car-Parrinello Simulations

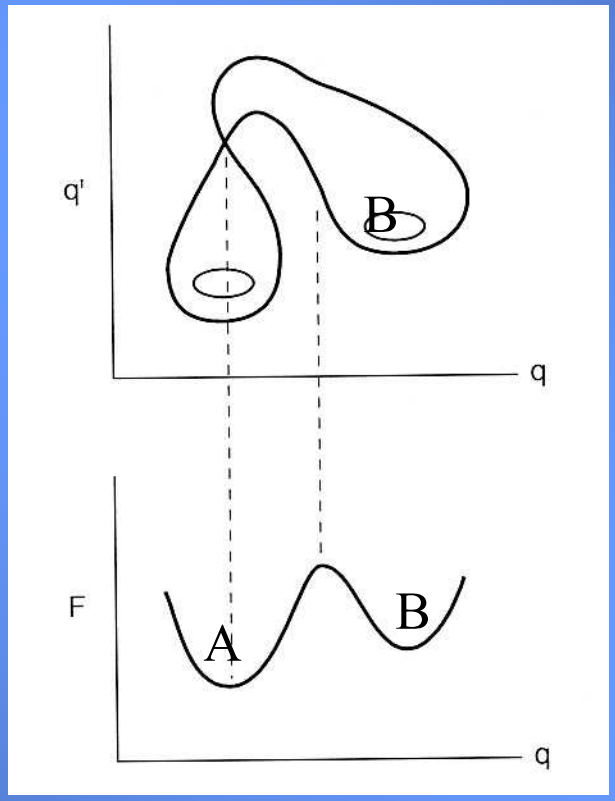
With Michele Parrinello,
Marcella Iannuzzi,
Roman Martonak,

Centro Svizzero di Calcolo Scientifico, Lugano

MANY DIFFERENT SOLUTIONS PROPOSED

- Thermodynamic integration.
- "flattening" the surface (hyperdynamics, puddle-skimming, umbrella sampling …).
- Trajectory-based schemes (reaction path sampling, Lagrangean action minimization, nudged elastic band…).
- Finding the saddle points (eigenvalue following, dimer method, hessian based methods,…).
- Temperature enhanced sampling (histogram reweighting, parallel tempering, …)
- …

The right reaction path?



- Activated events are often intrinsically multidimensional!!!

How to explore a multidimensional free energy surface?

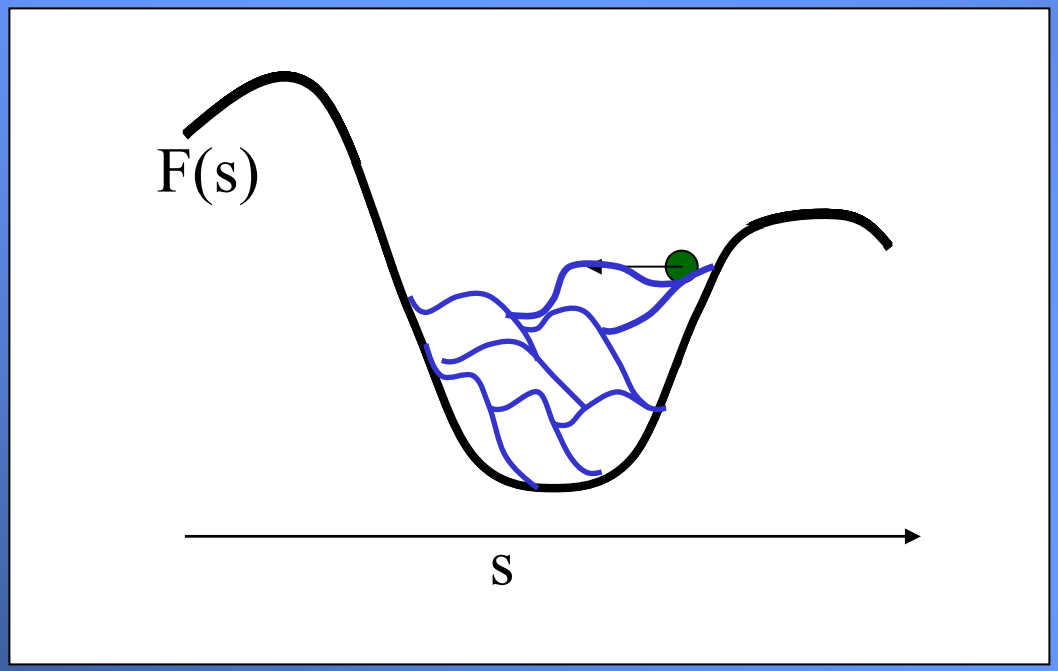
Need to be able to escape from intrinsically multidimensional free energy minima

Our solution:
Non-Markovian coarse-grained dynamics

A. Laio, M. Parrinello, PNAS 99, p. 12562 (2002)

The algorithm:

- Wherever you go put a “small” Gaussian
- Always move in the direction of the direction that minimizes the sum of F(s) and all the Gaussians



Collective variables

Choose a set of **relevant** collective variables:

$$s_\alpha = s_\alpha(\{r_i\}) \quad \alpha = 1, n$$

We want to study the free energy as a function of these variables:

$$F(s) = k_b T \ln(P(s))$$

Calculating the forces:

- Molecular Dynamics with restraint on the collective variables:

$$\text{Normal Hamiltonian} + \sum_{\alpha} \frac{k_\alpha}{2} \left(s_\alpha(r_i) - s_\alpha \right)^2$$

The derivative of the Free Energy with respect to the collective variable s_α is

$$\varphi_\alpha^{\text{FES}} = \left\langle k_\alpha \left(s_\alpha(r_i) - s_\alpha \right) \right\rangle$$

Average over time

Introduce a metadynamics in the space of the scaled collective variables:

$$s_\alpha^{t+1} = s_\alpha^t + ds \frac{\varphi_\alpha^t}{\left|\varphi^t\right|}$$

Steepest descent in the direction of the force

I. G. Kevrikidis, C. Theodoropoulos and C. W. Gear

Filling the wells: We change the forces with a time-dependent term

Forces from Gaussians localized on configurations already explored

$$\varphi_\alpha^t = \varphi_\alpha^{FES} - \frac{\partial}{\partial s_\alpha} \sum_{t'<t} w \exp\left(- \frac{\| s - s^{t'} \|^2}{2 \delta s^2} \right)$$

Forces from the Free Energy

T. Huber, T. Torda, and W. F. van Gunsteren, J. Comput. A. Des. **8**, 695 (1994)

Drawing the free energy surface

- The sum of gaussians tends to the free energy!!!

For large t,

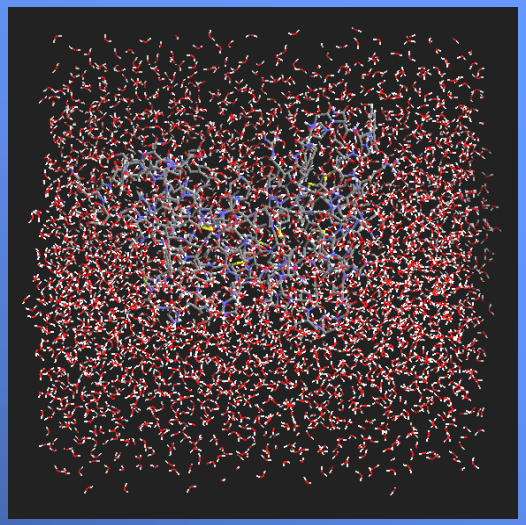
$$\sum_{t'<t} w \exp\left(-\frac{\left\|s - s^{t'}\right\|^2}{2\delta s^2}\right) \longrightarrow F(s)$$

Mixed Quantum-Classical QM/MM- Car-Parrinello Simulations

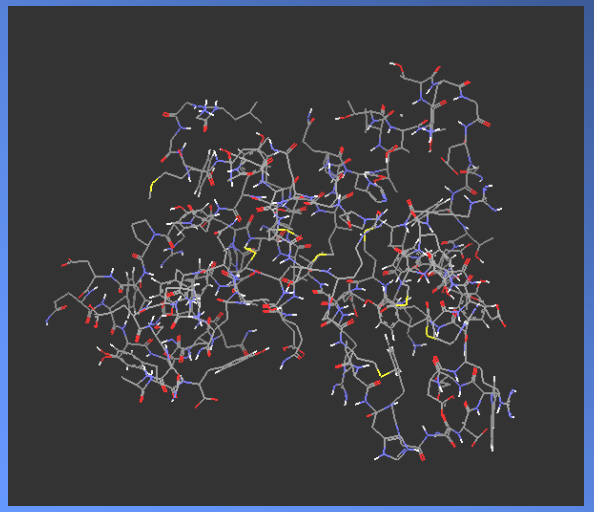
With Joost VandeVondele and Ursula Rothlisberger

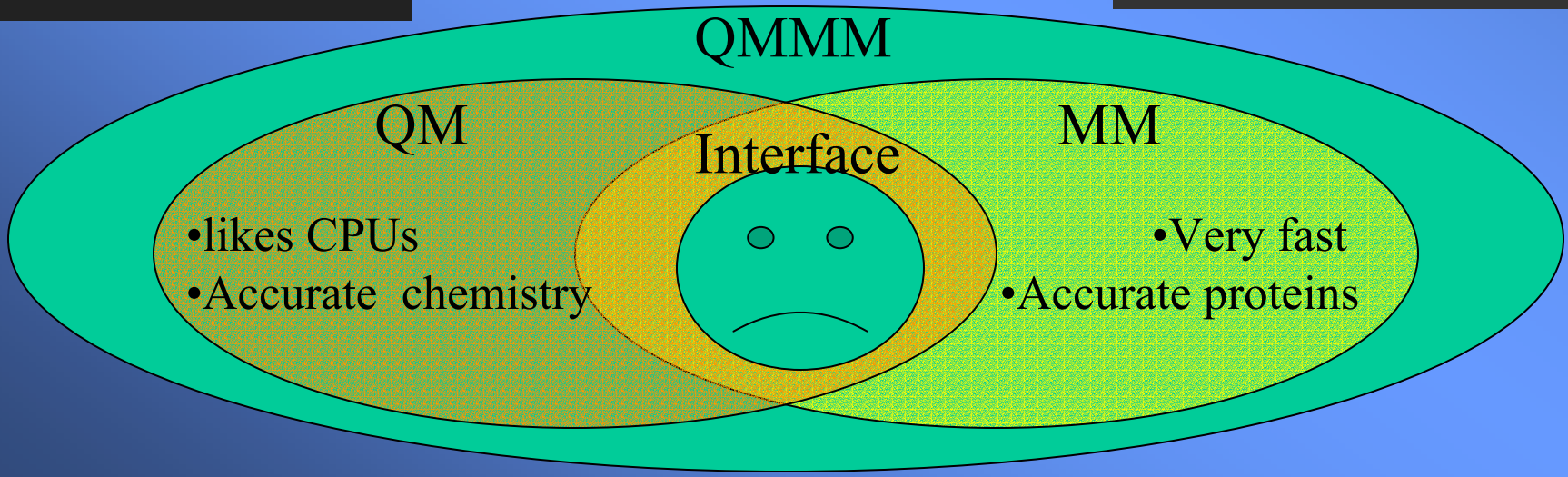
Why combining QM and MM ?

Bio-systems are typically very large and catalyse complicated reactions



- Proteins >1000 atoms
- Solvent >10000 atoms
- The active site ~ 100 atoms

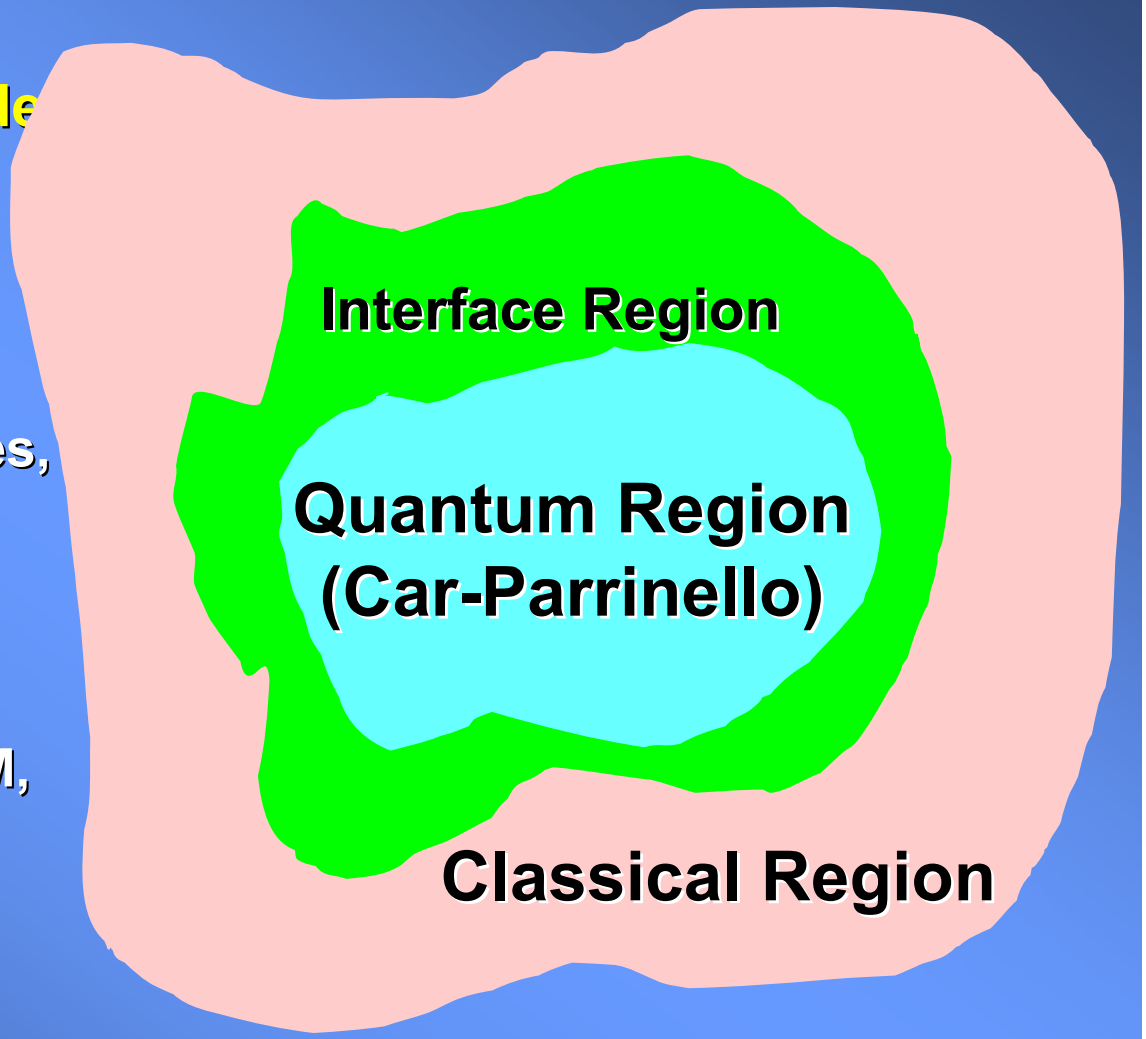




- highly parallel QM/MM Car-Parrinello hybrid code
- Fully Hamiltonian
- MD driver: CPMD

QM-Part: CPMD 3.3
(pbcs (2 boxes), plane waves, pseudo potentials, GGAs: BP86, BLYP, PW91, PBE...)
n-1 nodes

MM-Part: GROMOS96 + P3M, AMBER)
1 node



Mixed Quantum-Classical QM/MM- Car-Parrinello Simulations

- **Development of improved QM/MM interfaces:**

  - pseudo potentials for boundary atoms
  - efficient treatment of long-range electrostatics
  - short range electrostatic: the hydrogen bond
  - consistent treatment of ‘exclusions’

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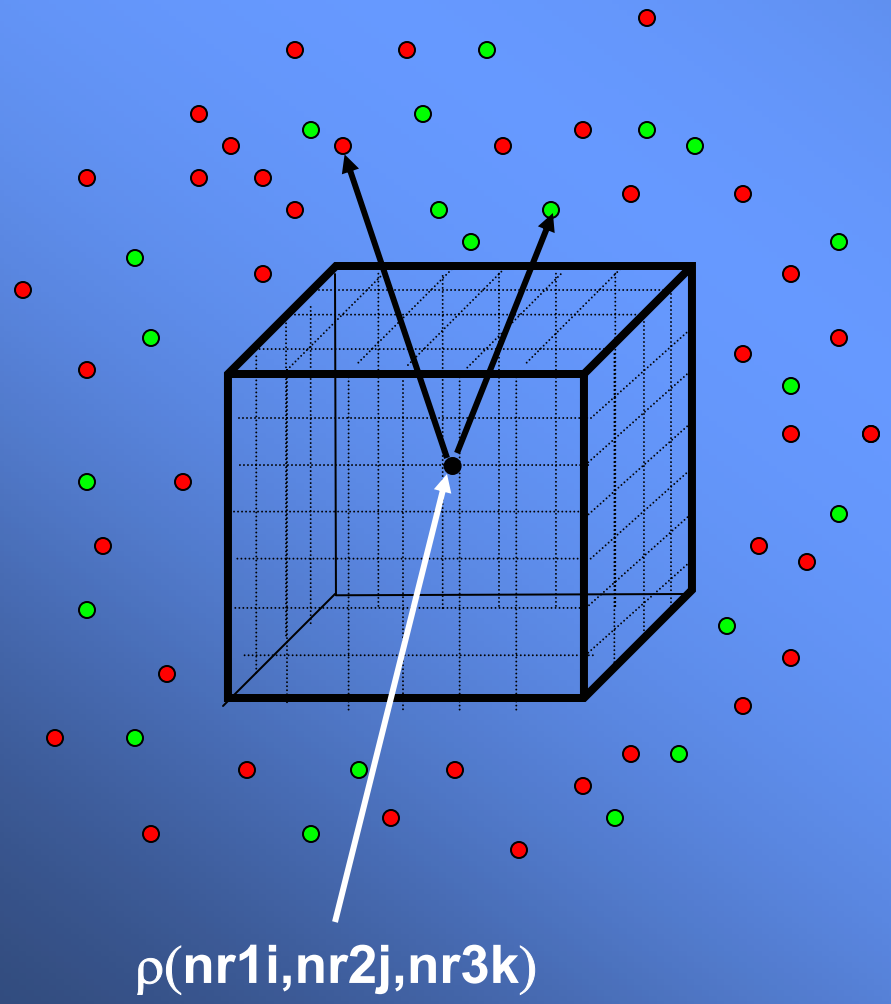

Coulomb interaction:

$$H_{el} = \sum_{i \in MM} q_i \int dr \frac{\rho(r)}{|r - r_i|}$$

3D-grid: (NR1,NR2,NR3) NR~100

MM atoms ~10000-100000

NR1*NR2*NR3*MM DISTANCE CALCULATIONS!!!

Hierarchical computation of electrostatic interaction

Region 1:
(within R_q of any quantum atom)
R_q ~ 8-12 au (250-300 atoms)
ordinary coulomb interaction
20-50% overhead
(parallelized over real space grid)

$$H_{sr} = \sum_{i \in NN} q_i \int dr \frac{\rho(r)}{|r - r_i|}$$

Region 2:

Multipole expansion of quantum charge distribution coupled with the classical charges by a Hamiltonian term

negligible computational cost

$$H_{lr} = \sum_{i \notin NN} q_i \frac{D^{\alpha} r_i^{\alpha}}{r_i^3} + \sum_{i \notin NN} q_i \frac{Q^{\alpha\beta} r_i^{\alpha} r_i^{\beta}}{r_i^3}$$

$$D^{\alpha} = \int \rho(r) r^{\alpha} dr$$

Convergence to Exact Result

(test on a QM system of ~ 20 atoms in the Prion protein)

R_c[au]	E_{ele} [mH]	E_{mec} [mH]
5	0.339	17.476
10	2.700	23.762
14	0.101	15.961
20	0.478	-10.730
25	0.259	3.477

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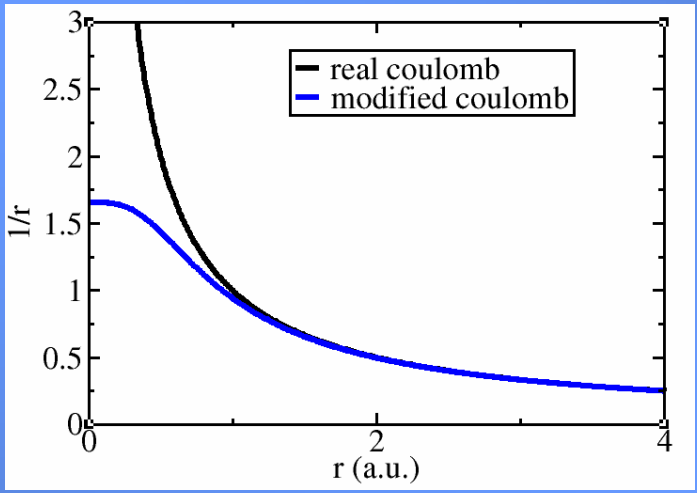
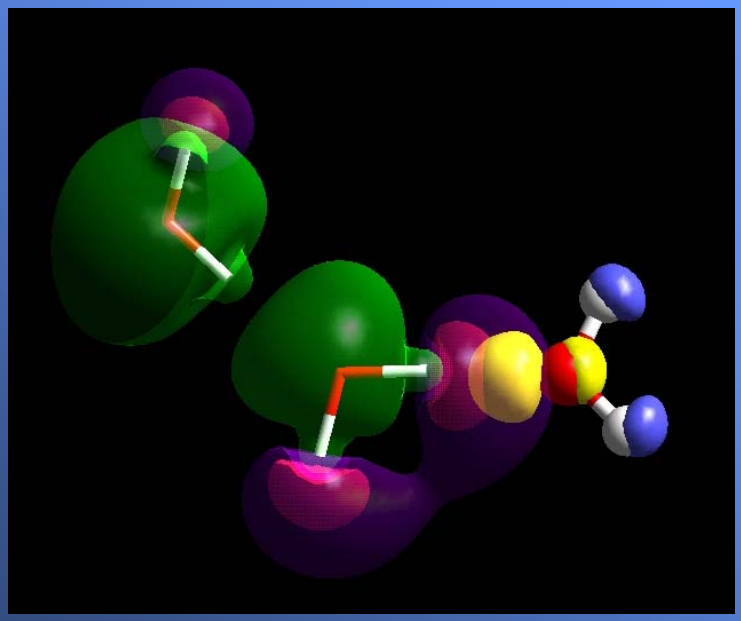
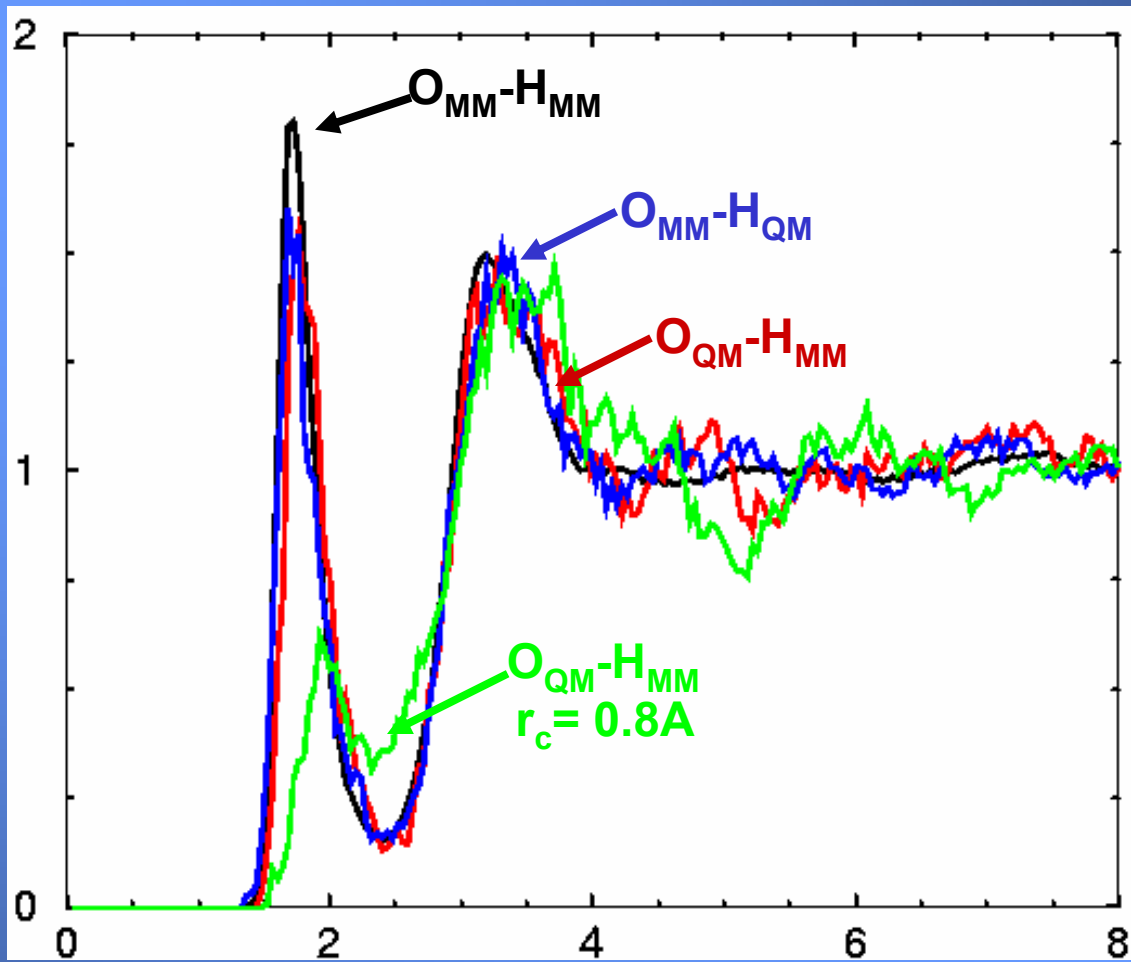


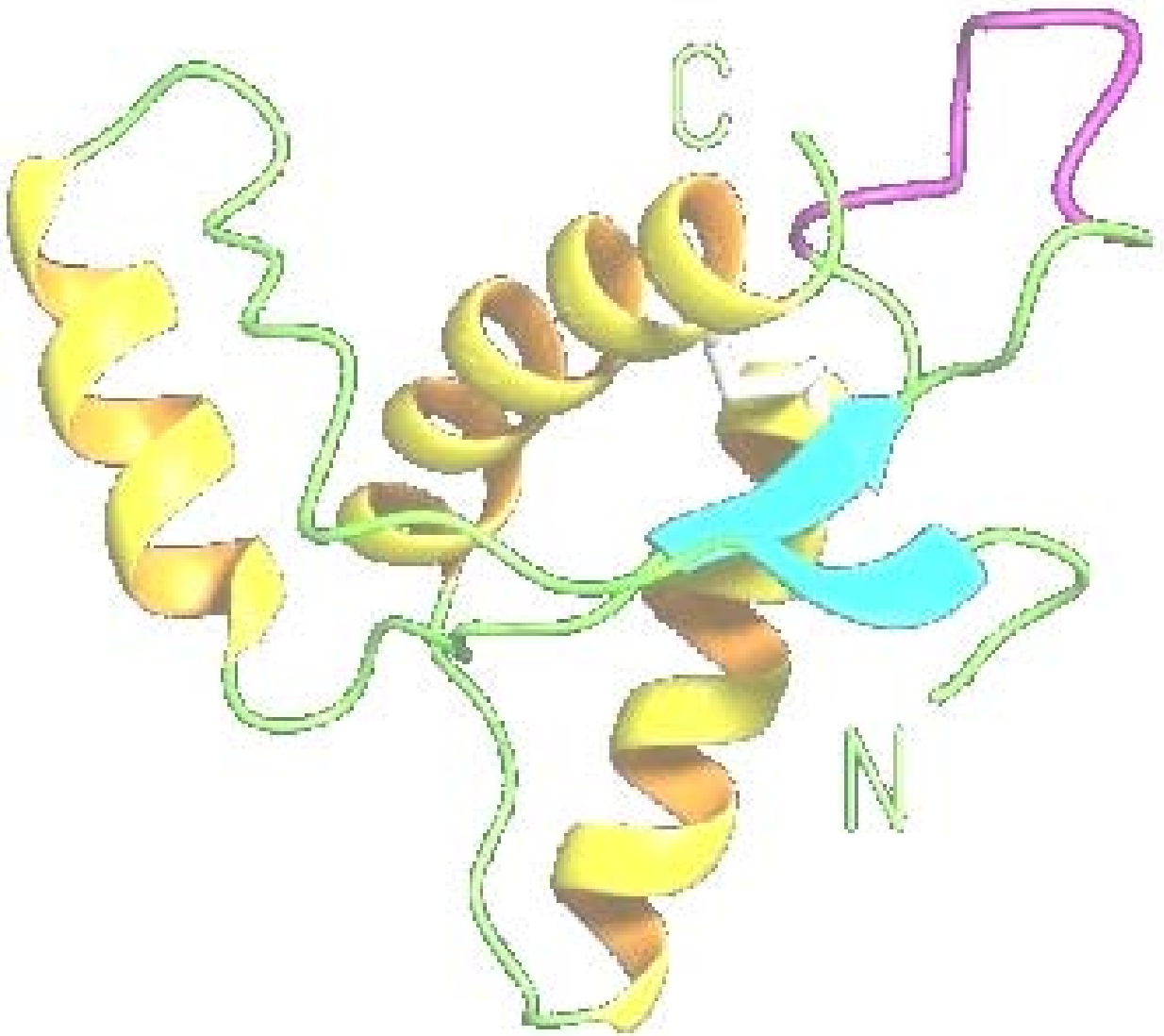
Modified coulomb potential for MM charges

Water: 255 MM + 1 QM H_2O



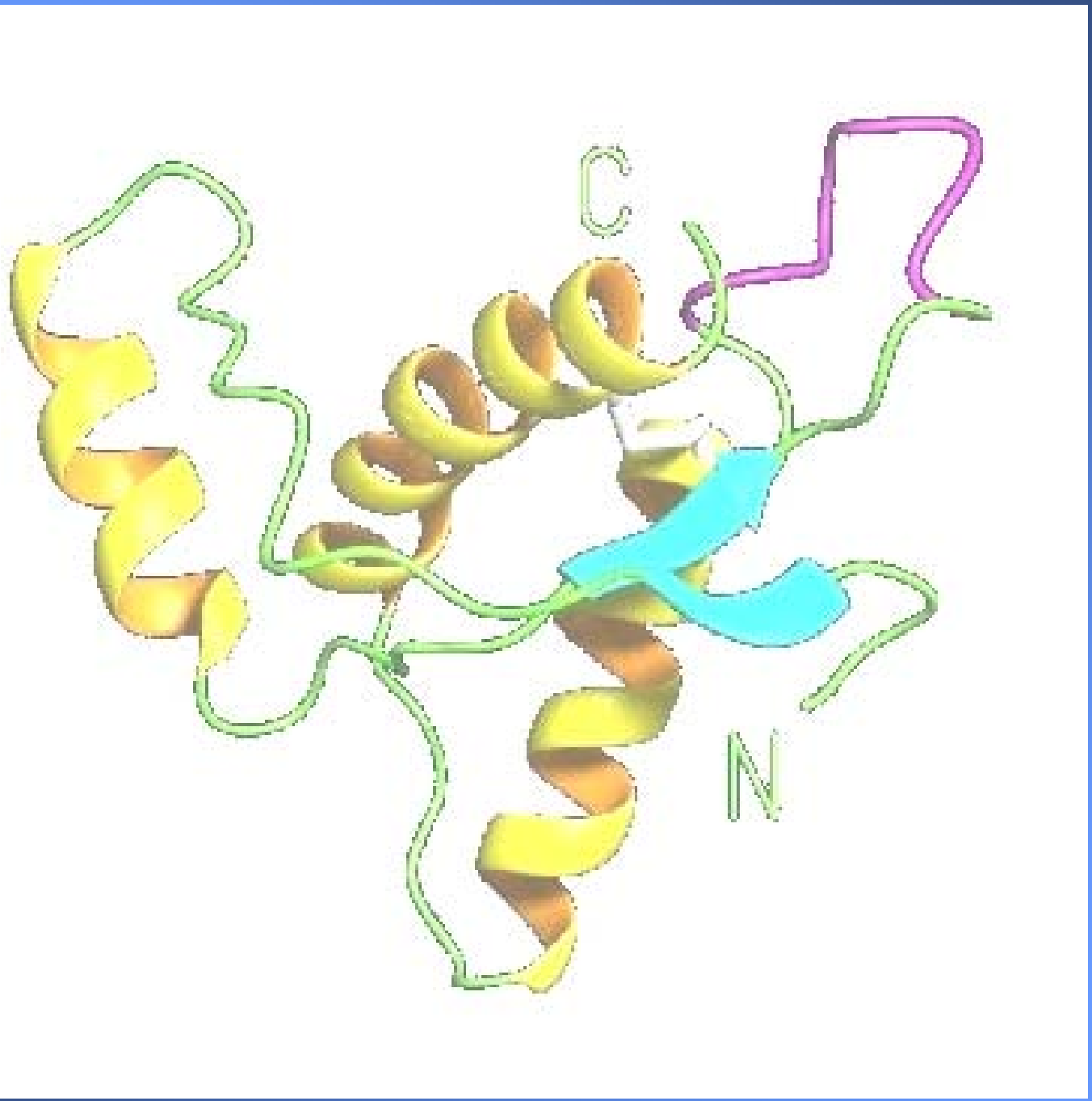
Polarization Density




C
N

Features of our QMMM model

- **Boundary atoms**
- **Extended electrostatic coupling**
- **Exclusion scheme**
- **P3M classical**
- **Hamiltonian**
- **Energy conserving MD**
- **Well parallelised**
- **Efficient code for the coupling**
- **User friendly**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Applications

- **Copper binding sites in the Prion protein** (M.C. Colombo)
- **Cis-Trans photoisomerization in rhodopsine chromophore** (U. Roehrig)
- **Photoactive Yellow protein** (C. Molteni)
- **NO-Binding to Myoglobine** (C. Rovida)
- **Excitation energies of acetone in solution** (U. Roehrig)
- **Reaction mechanism of Caspases** (M.L. Sulpizi)
- **Lindskog mechanism for the CO2 conversion in Human Carbonic Anhydrase** (U. Roethisberger)
- **HIV-1 Protease** (S. Piana)