

# Hybrid Quantum – Classical Simulations:

## Lecture 3

### QM/MM: Basic Methodology

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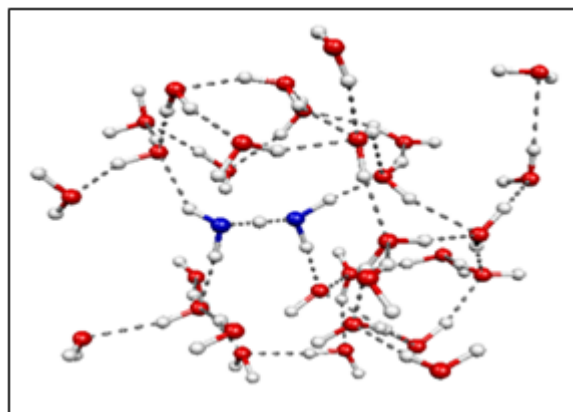
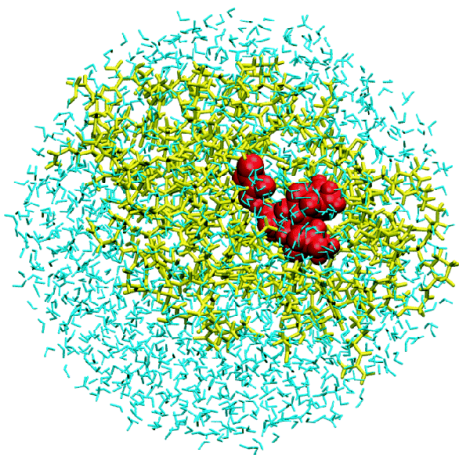
# Content

- Hybrid QM/MM scheme to treat quantum and classical parts of a system in a combined simulation.
- QM/MM energy schemes, additive and subtractive methods, different embedding schemes, treatment of boundaries etc.
- Results of some simple QM/MM systems
- Brief description of second hands-on session

Case studies of biological systems will be discussed by Prof. Elstner.

# Quantum Mechanics (QM)

- Required for describing chemical reactions and other electronic processes such as charge transfer or electronic excitations.
  - QM methods are restricted to systems up to a few tens (or a few hundred) atoms.
- **Chemical processes in condensed phases**
  - Reactants and products
  - Environment (Steric, electrostatic, polarization effects)
  - Bio-molecules (1000~10000 atoms)  
Total no. of atoms → 1000 – 100000 or more  
⇒ Computational Challenge

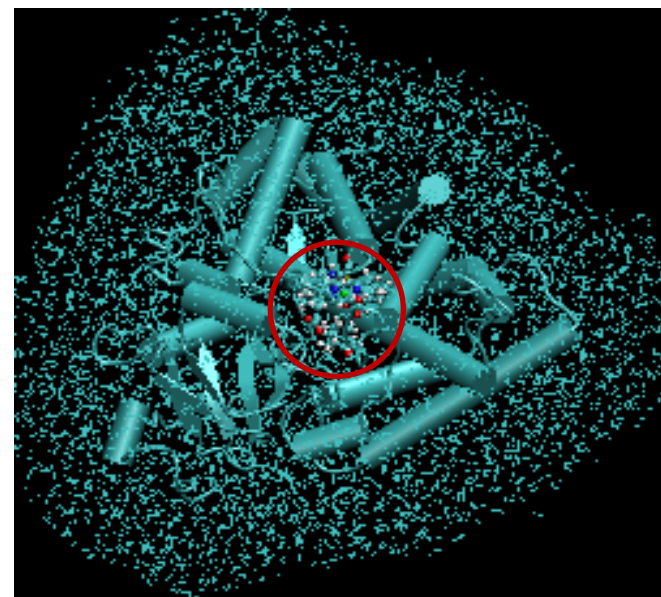


# Molecular Mechanics : Empirical Force Fields

- Many of the problems that we would like to deal with are unfortunately too large to be considered by quantum mechanical methods.

Number of atoms – 1000 or 100,000 or more.

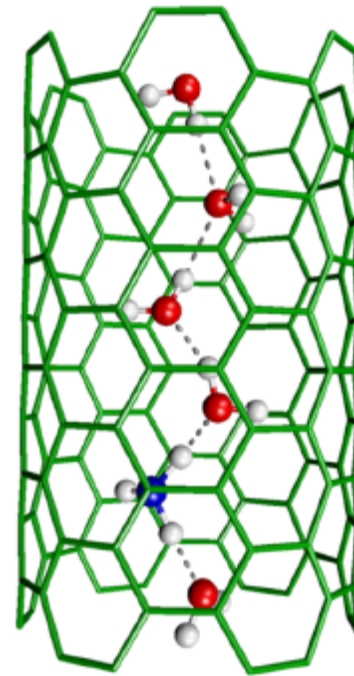
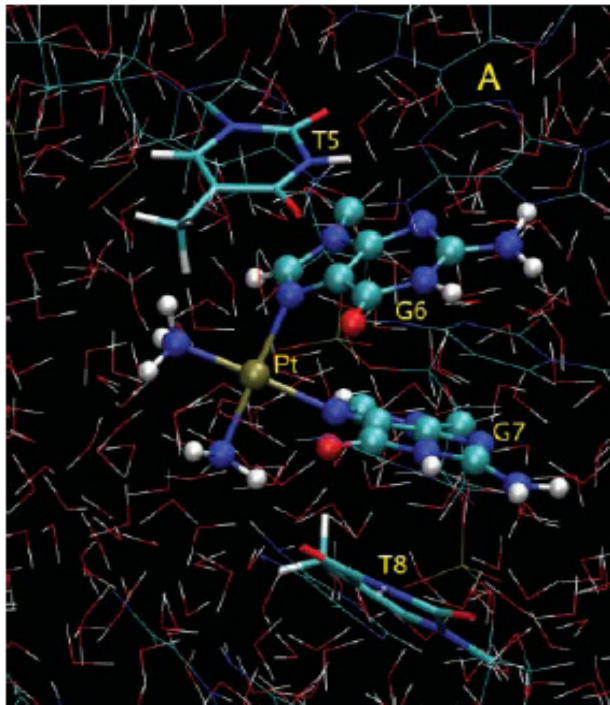
- Force field methods (MM) ignore the electronic motions and calculate the energy of a system as a function of the nuclear coordinates only.
- MM is suitable for performing calculations on systems with large number of molecules. Models contain parameters which can be tuned to improve accuracy.
- MM, of course, cannot provide properties that depend upon the electronic distributions (chemical reactions, electronic excitations, charge transfers etc.)





# Optimal Setup

- Take best of both sides – Quantum mechanics (QM) / Molecular mechanics (MM)
- QM / MM is the method of choice for studying chemical reactions in large chemical/biological systems.

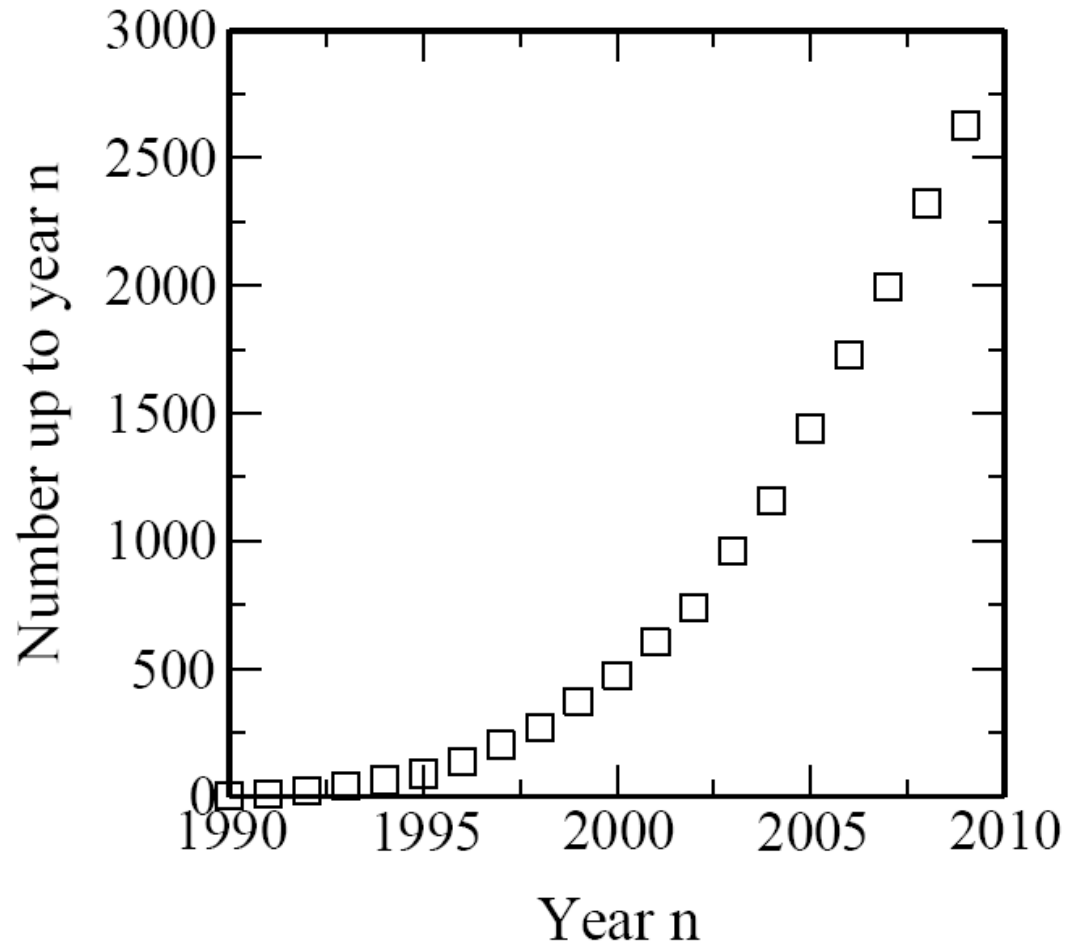


(cispt-d(CCTCTG\*G\*TCTCC)-d(GGAGACCAGAGG))

# QM/MM has been used for cases where

- Reorganization of the electronic structure
- Formation and breaking of chemical bonds
- Studies of Enzymatic Reactions
  - Structure
  - Energetics etc.
- Spectroscopic properties
- Excited-States properties
- Study of Transition metal complexes

# Publications Employing QM/MM Method



Hybrid QM/MM approach is a molecular simulation method that combines the strength of both QM (accuracy) and MM (speed) calculation.

...Methodology was introduced by Warshel and Levitt in 1976.

A. Walshel and M. Levitt, J. Mol. Biol. **103**, 227(1976)

- H. M. Senn and W. Thiel, Top Curr. Chem. **268**, 173(2007); Angew Chemie **48**, 1198 (2009)
- P. Carloni, U. Rothlisberger and M. Parrinello, Acc. Chem. Res. **35**, 455 (2002)
- J. Aquist and A. Warshel, Chem. Rev. **93**, 2523 (1993).

## QM calculations:

$$\hat{H}\psi = E\psi$$

$$\hat{H} = -\sum_I \frac{\hbar^2}{2M_I} \nabla_I^2 - \sum_i \frac{\hbar^2}{2m_e} \nabla_i^2 + \frac{1}{4\pi\epsilon_0} \sum_{i<j} \frac{e^2}{|r_i - r_j|}$$
$$- \frac{1}{4\pi\epsilon_0} \sum_{I,i} \frac{e^2 Z_I}{|R_I - r_i|} + \frac{1}{4\pi\epsilon_0} \sum_{I<J} \frac{e^2 Z_I Z_J}{|R_I - R_J|}$$

## (QM) Dynamical Simulation Methods:

- Born-Oppenheimer molecular dynamics:

$$M_I \ddot{R}_I(t) = -\nabla_I \min_{\{\Psi_i\}} \{ \langle \Psi_0 | H_e | \Psi_0 \rangle \}$$

$$0 = -H_e \phi_i + \sum_j \Lambda_{ij} \phi_j ; \Psi_0 = \det \{ \phi_i \}$$

- Ehrenfest Molecular Dynamics :

$$M_I \ddot{R}_I(t) = -\nabla_I \langle \Psi | H_e | \Psi \rangle$$

$$i\hbar \dot{\Psi}(t) = H_e \Psi$$

- Car- Parrinello Molecular Dynamics

$$M_I \ddot{R}_I(t) = -\nabla_I \langle \Psi_0 | H_e | \Psi_0 \rangle$$

$$\mu_i \ddot{\phi}_i(t) = -H_e \phi_i + \sum_j \Lambda_{ij} \phi_j ; \Psi_0 = \det \{ \phi_i \}$$

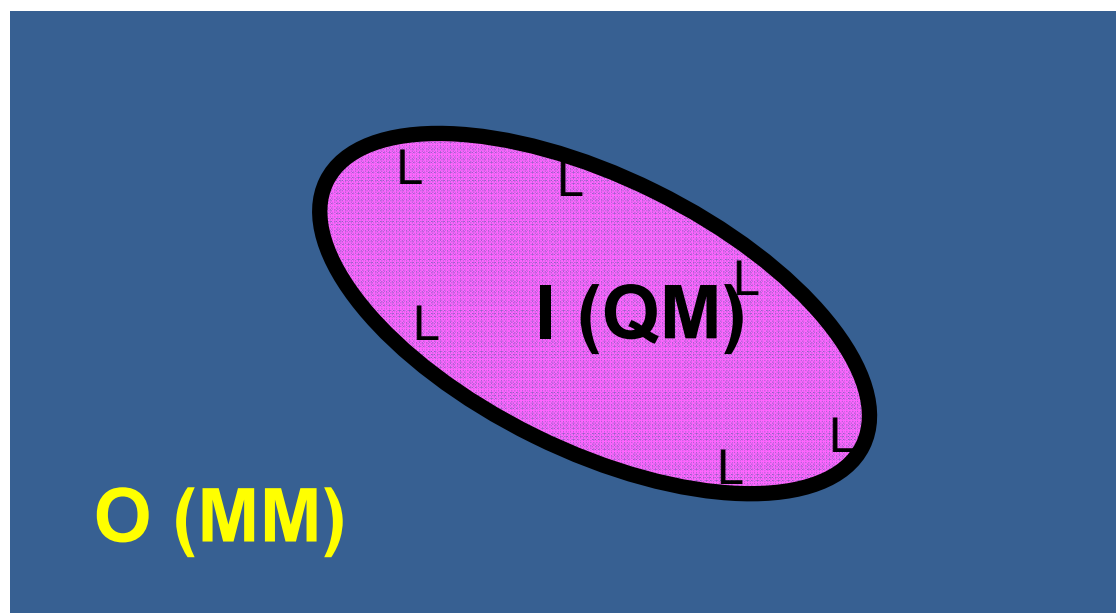
## MM method (Force field method)

- Ignores the electronic degrees of freedom
- Calculates energy as a function of the nuclear positions only
- Can treat more than 100,000 or more atoms

$$E_{MM} = \sum_{bonds} k_d (d - d_0)^2 + \sum_{angles} k_\theta (\theta - \theta_0)^2 + \sum_{dihedrals} k_\phi [1 + \cos(n\phi + \delta)]$$
$$+ \sum_{\substack{non-bonded \\ pairs AB}} \left\{ 4 \epsilon_{AB} \left[ \left( \frac{\sigma_{AB}}{r_{AB}} \right)^{12} - \left( \frac{\sigma_{AB}}{r_{AB}} \right)^6 \right] + \frac{1}{4\pi\epsilon_0} \frac{q_A q_B}{r_{AB}} \right\}$$

# Methodology

S



S-whole system, I-Inner subsystem, O-Outer subsystem, L-Link atoms

H. M. Senn and W. Thiel, Top Curr. Chem. **268**, 173(2007);



# The QM/MM Energy Schemes

- Subtractive QM/MM scheme

$$E_{QM/MM}^{sub}(S) = E_{MM}(S) + E_{QM}(I + L) - E_{MM}(I + L)$$



- Additive QM/MM scheme

$$E_{QM/MM}^{add} = E_{MM}(O) + E_{QM}(I + L) + E_{QM-MM}(I, O)$$

- $E_{QM-MM}(I, O)$  term defines a particular QM/MM method

$$E_{QM-MM}(I, O) = E_{QM-MM}^b + E_{QM-MM}^{vdW} + E_{QM-MM}^{el}$$

Bonding  
Interaction

Van der Waals  
Interaction

Electrostatic  
Interaction

H. M. Senn and W. Thiel, Top Curr. Chem. **268**, 173(2007);

# QM-MM Bonded Interactions

- MM parameters are used to describe for Bond stretching, angle bending , torsional interactions.

# QM-MM Van der Waals Interactions

- Described by Lennard-Jones potentials

$$E_{QM-MM}^{vdW} = \sum_{\substack{\text{non-bonded} \\ \text{pairs } AB}} \left\{ 4 \epsilon_{AB} \left[ \left( \frac{\sigma_{AB}}{r_{AB}} \right)^{12} - \left( \frac{\sigma_{AB}}{r_{AB}} \right)^6 \right] \right\}$$

# The Electrostatic QM-MM Interaction

## Model A - Mechanical embedding

- Electrostatic interaction is treated at the MM level
- Charge model of MM methods are used – rigid atomic point charge
- But other approaches also possible – e.g. bond dipoles

# The Electrostatic QM-MM Interaction

## Model B - Electrostatic embedding

- QM calculation in presence of MM charge model
- Electronic structure of the inner region can adapt to changes in the charge distribution of the environment
- $E^{\text{el}}_{\text{QM-MM}}$  is treated as at QM level

$$H^{\text{el}}_{\text{QM-MM}} = - \sum_i^N \sum_{j \in O}^L \frac{q_J}{|r_i - R_J|} + \sum_{\alpha \in I+L}^M \sum_{J \in O}^L \frac{q_J Q_\alpha}{|R_\alpha - R_J|}$$

# The Electrostatic QM-MM Interaction

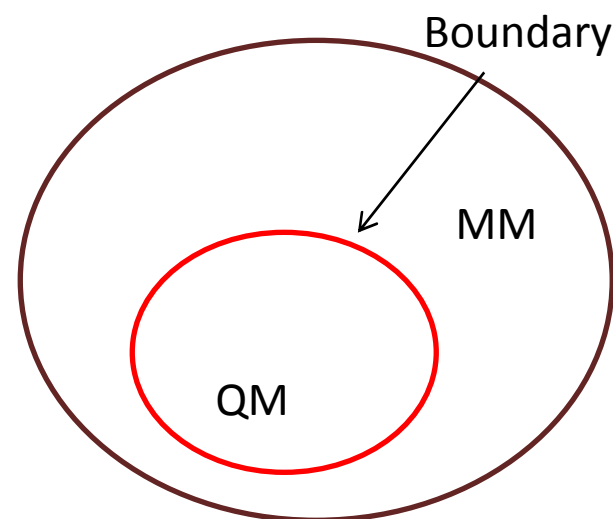
## Polarized embedding

- Model C – Polarizable charge model in the MM region is polarized by QM region

# Overview of Boundary

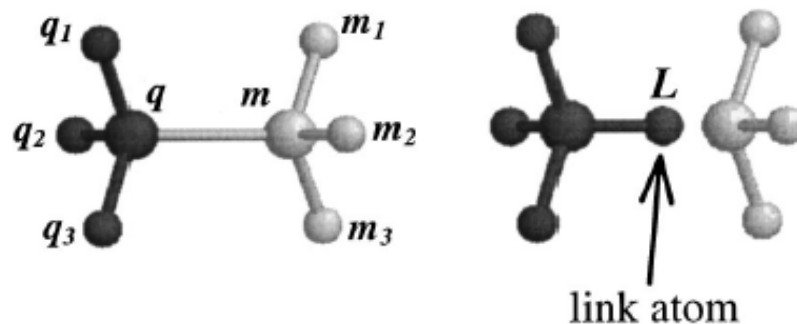
## a) No covalent bond is cut through the boundary

- e.g. Solvation Studies
- QM part– Solute or (Solute + First solvation shell)
- MM part– surrounded solvent molecules



## b) Covalent bonds cut through boundary

- Link Atom Schemes
- Localized-orbital schemes



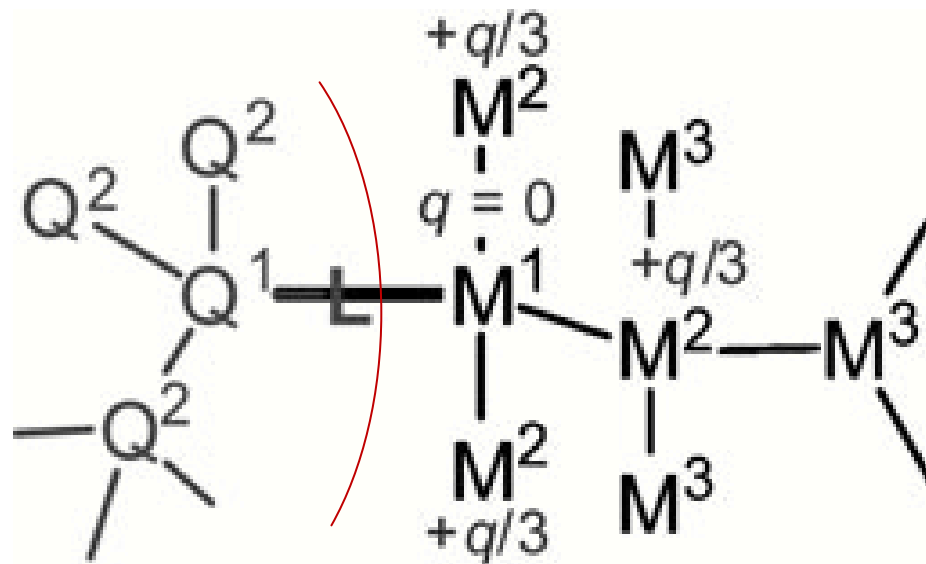
# Covalent bonds across QM-MM boundary

## Where to cut?

- The bond being cut should be non-polar
- Bond should not be involved in any conjugate interaction
- Cutting through a charge group is to be avoided
- A good place to cut is an aliphatic C – C bond

# Link Atom Scheme

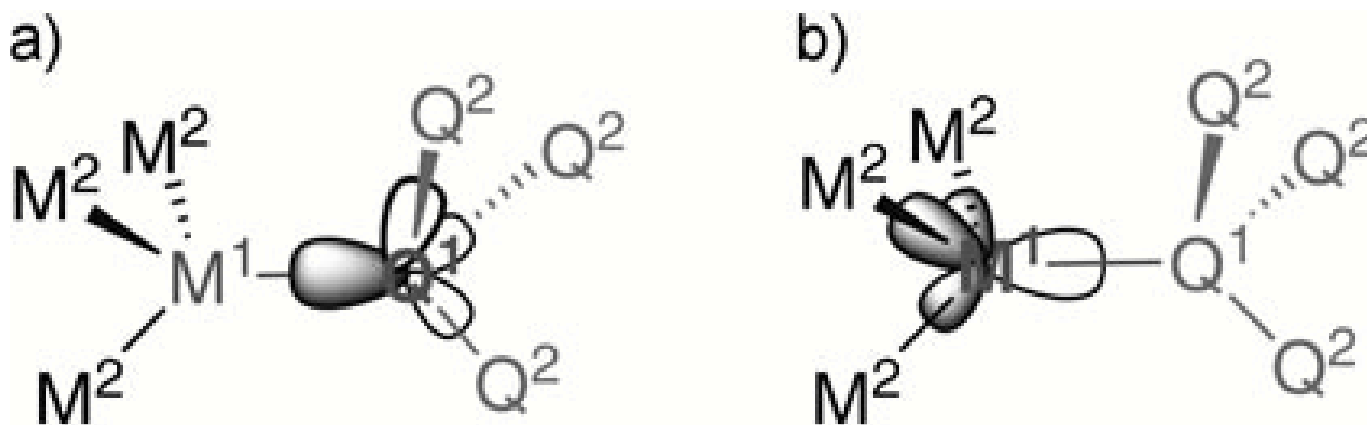
- Link atom schemes introduce an additional atomic centre **L** (usually H)
- It is covalently bound to  $Q^1$  and saturates its free valency





# Localized Orbital Scheme

Approach of using Frozen Hybrid Orbital to saturate the bond at QM-MM boundary



# Choice of QM/MM Method

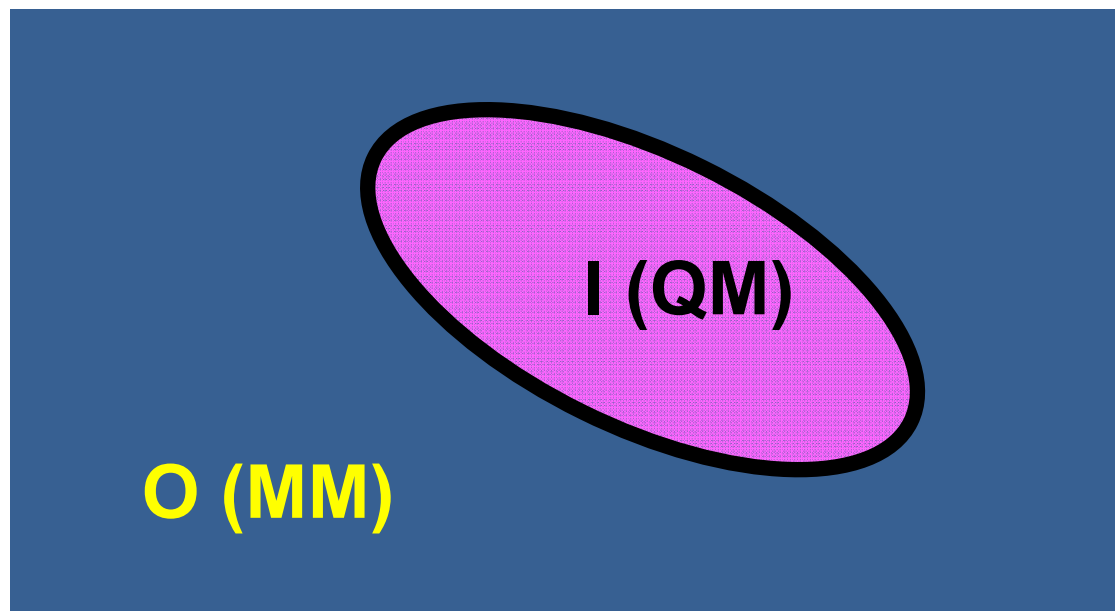
## Choice of QM Method

- QM code must be able to perform the SCF treatment in the presence of the external point-charge field
- Semi-empirical, HF, DFT etc

## Choice of MM Method

- MM force fields: GROMOS, AMBER, CHARMM, OPLS-AA

## Coupling between QM and MM regions



$$H_{nonbonded} = \sum_{i \in MM} q_i \int dr \frac{\rho(r)}{|r - r_i|} + \sum_{\substack{i \in MM \\ j \in QM}} v_{vdw}(r_{ij})$$

Problems: Electron spilling effects

Coulomb interactions with charges at each grid

## MODIFICATION OF ELECTROSTATIC INTERACTIONS

$$H_{el} = \sum_{j \in MM} q_j \int dr \rho(r) v_j(|r - r_j|)$$

$$v_j(r) = \frac{r_{cj}^n - r^n}{r_{cj}^{n+1} - r^{n+1}}, \quad n=4$$

A. Laio et al. JCP, 116, 6941 (2002)

**For large distance:**

$$\int dr \frac{\rho(r)}{|r - r_j|} = C \frac{1}{|r_j - \bar{r}|} + \sum_{\alpha} D^{\alpha} \frac{\left(r_j^{\alpha} - \bar{r}^{\alpha}\right)}{|r_j - \bar{r}|^3} + \frac{1}{2} \sum_{\alpha\beta} Q^{\alpha\beta} \frac{\left(r_j^{\alpha} - \bar{r}^{\alpha}\right)\left(r_j^{\beta} - \bar{r}^{\beta}\right)}{|r_j - \bar{r}|^5} + O\left(\frac{R_q}{|r_j - \bar{r}|}\right)^4$$

$$C = \int dr \rho(r)$$

$$D^\alpha = \int dr \rho(r) \left( r^\alpha - \overline{r^\alpha} \right)$$

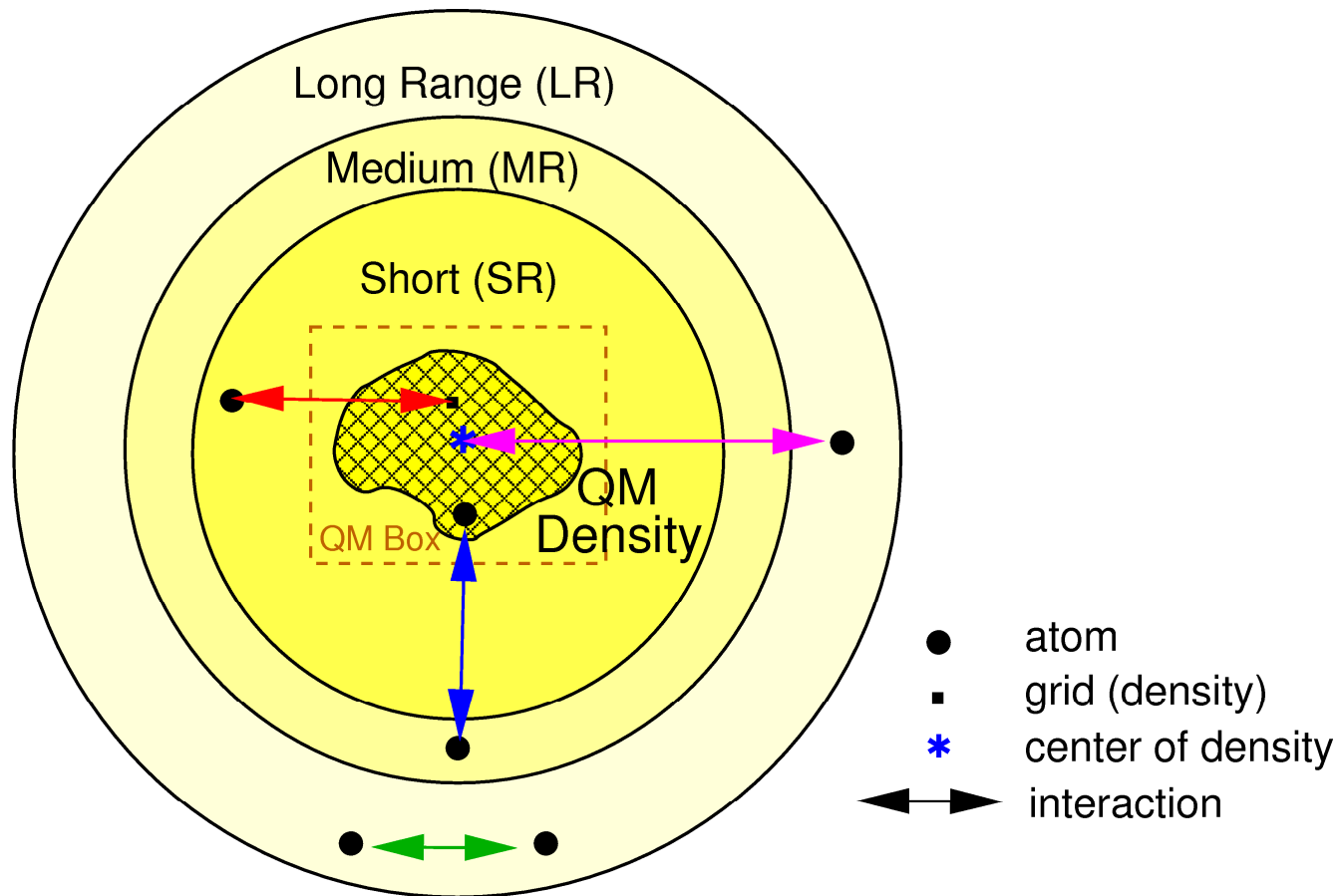
$$Q^{\alpha\beta} = \int dr \rho(r) \left[ 3 \left( r^\alpha - \overline{r^\alpha} \right) \left( r^\beta - \overline{r^\beta} \right) - \delta^{\alpha\beta} \left| r - \overline{r} \right|^2 \right]$$

$$H_{el} = \sum_{j \in NN} q_j \int dr \rho_e(r) v_j (|r - r_j|) + H_{Ir}$$

$$H_{Ir} = C \sum_{j \notin NN} \frac{q_j}{\tau_j} + \sum_{\alpha} D^{\alpha} \sum_{j \notin NN} \frac{q_j}{\tau_j^3} \tau_j^{\alpha} + \frac{1}{2} \sum_{\alpha\beta} Q^{\alpha\beta} \sum_{j \notin NN} \frac{q_j}{\tau_j^5} \tau_j^{\alpha} \tau_j^{\beta}$$

$$\tau_j^{\alpha} = \tau_j^{\alpha} - \overline{\tau^{\alpha}}$$

Note: In the RHS of above equation, tau should be r.



Thanks to N. Nair 28



# Some case studies

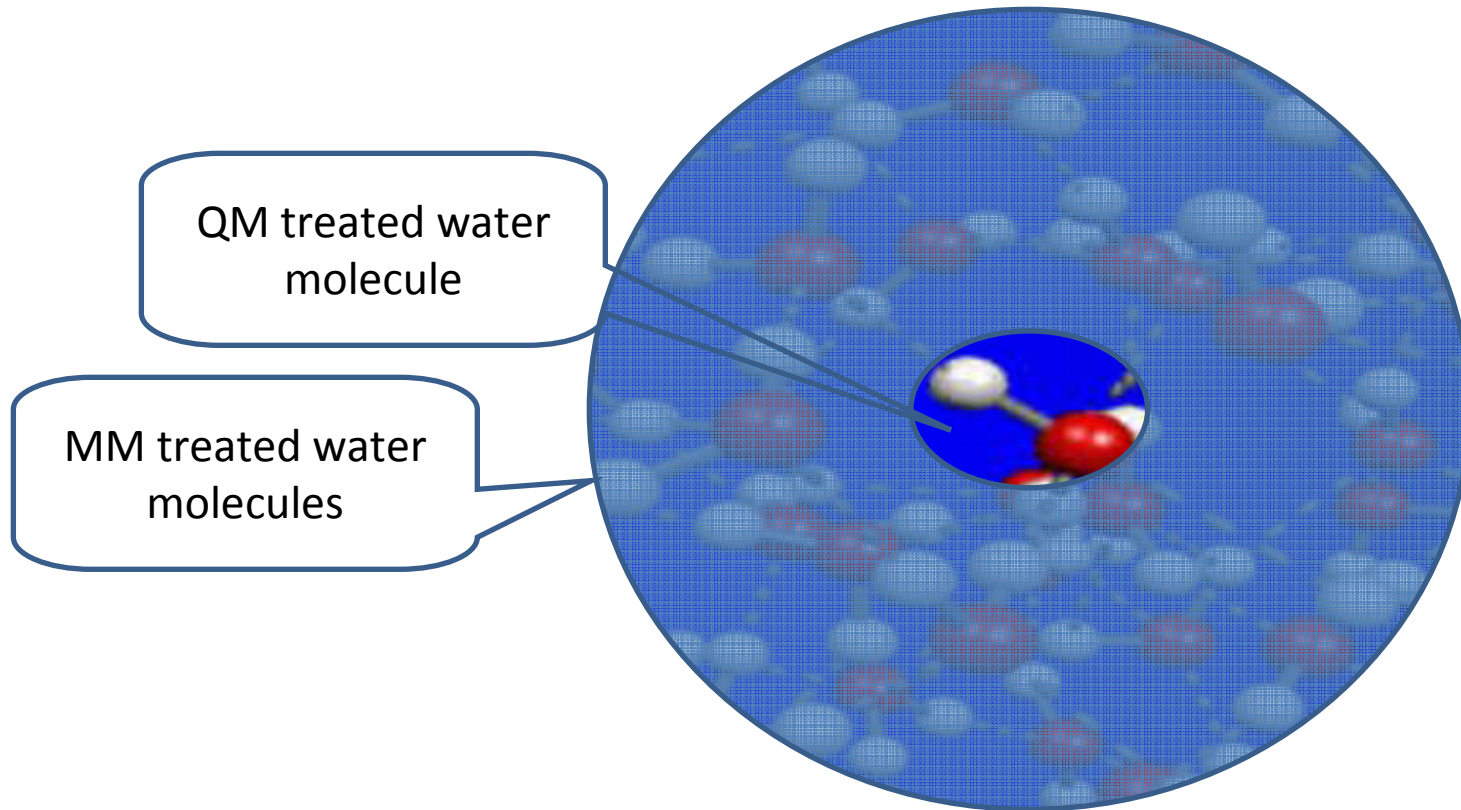
## Non-bonded Interactions

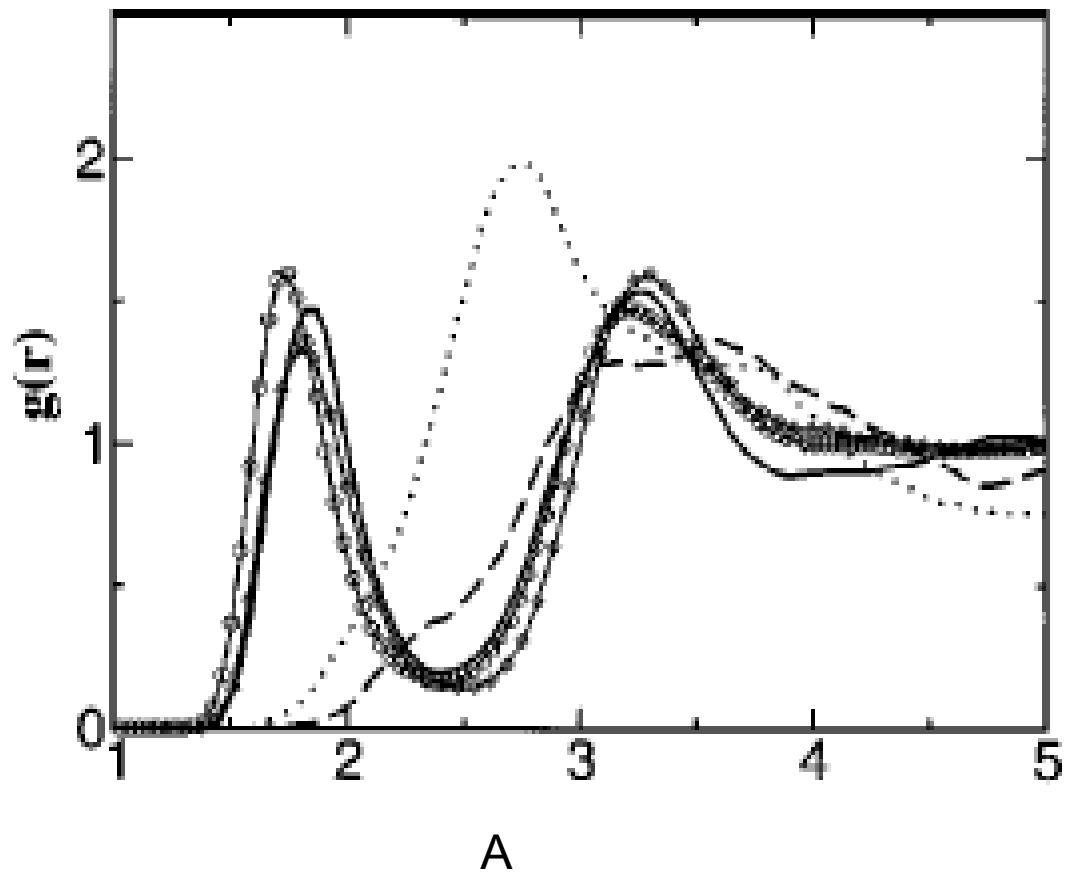
- A Water Molecule in Aqueous Solution

## Bonded Interactions

- Biomolecular System (Bovine Cytochrome c oxydase)

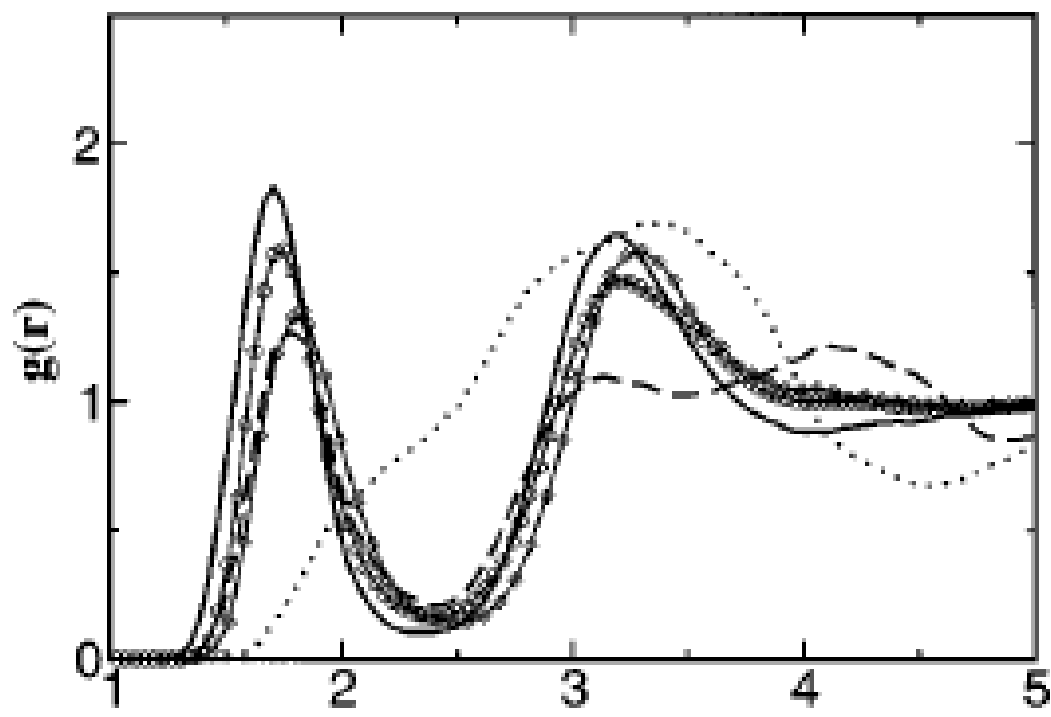
# A Water Molecule in Aqueous Solution





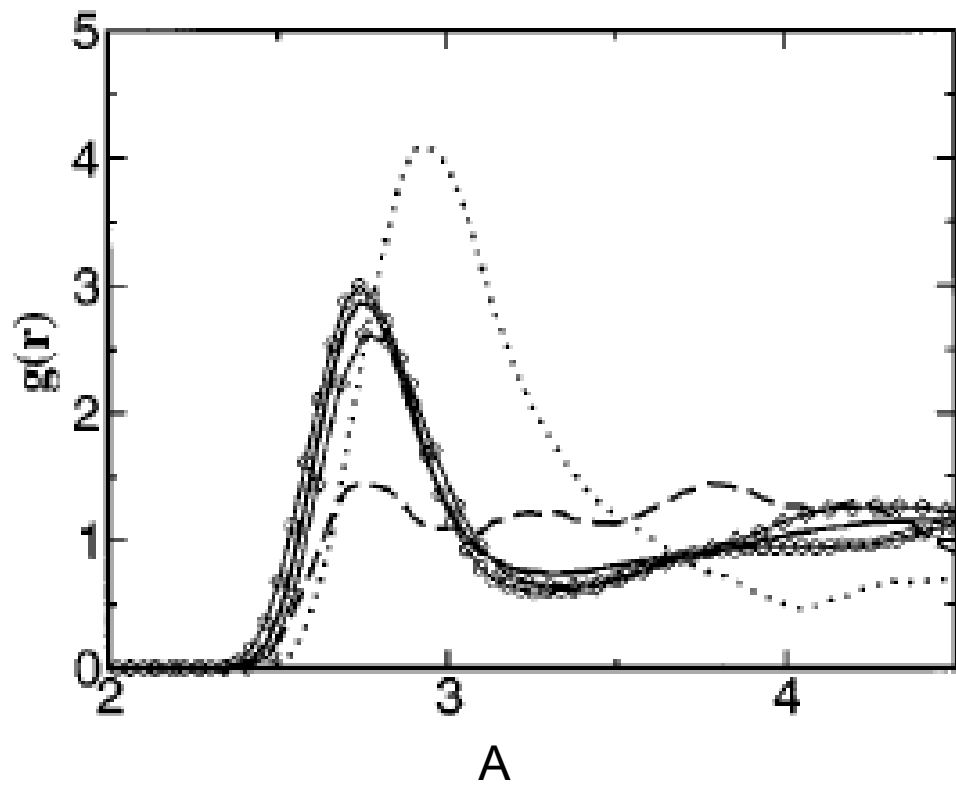
Quantum oxygen-classical hydrogen pair correlation function

A. Laio et al. JCP, 116, 6941 (2002)



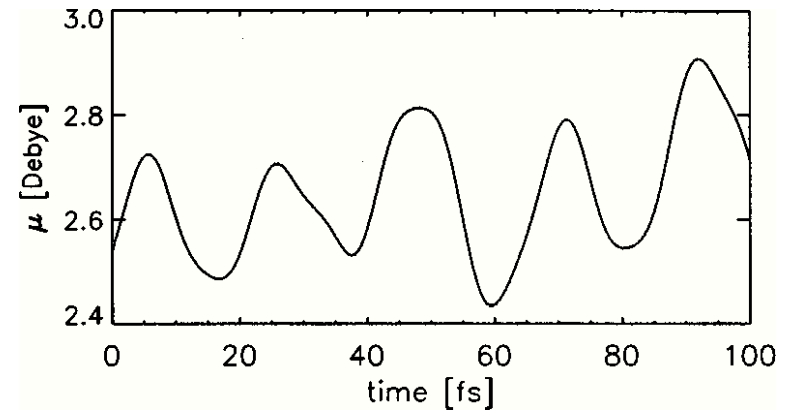
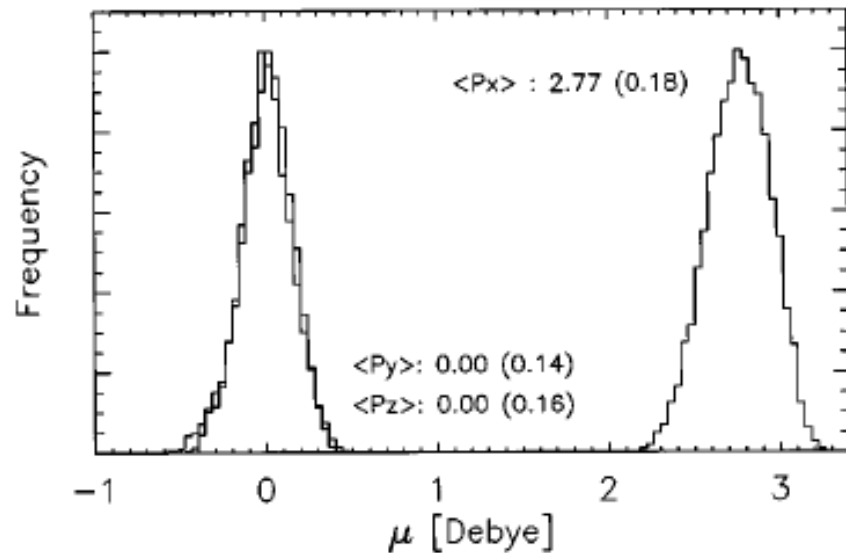
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Quantum hydrogen-classical oxygen pair correlation function



Quantum oxygen-classical oxygen pair correlation function

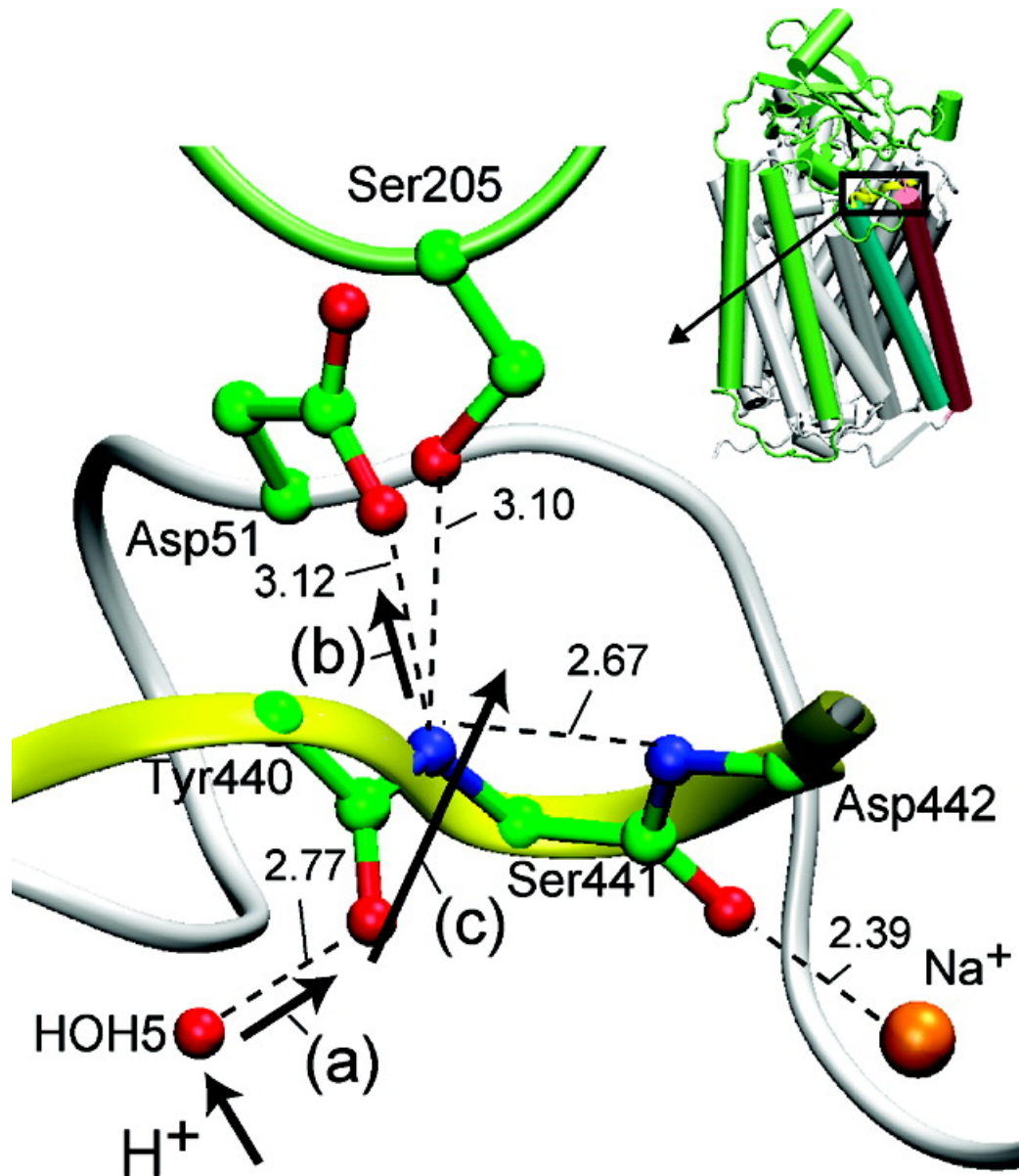
# Dipole Moment



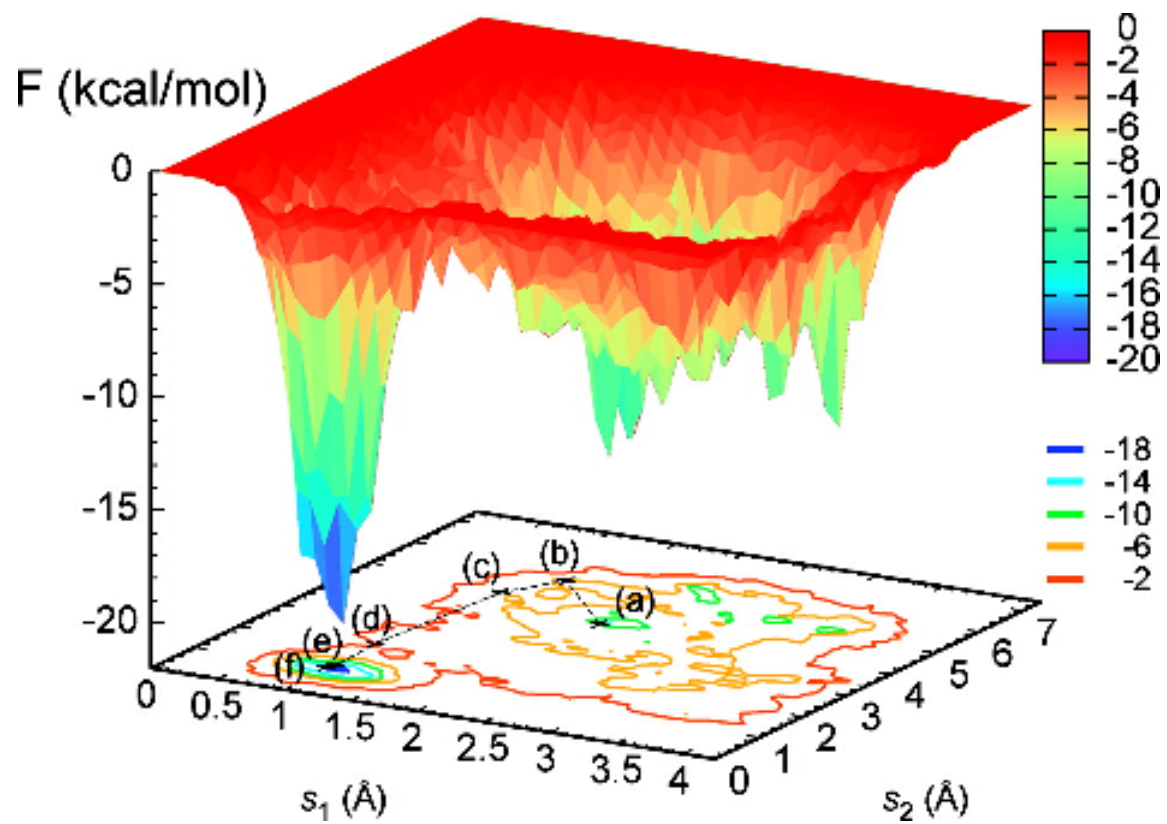
Dipole moment of QM water molecule solvated in the TIP3P water

Fully QM – CPMD simulation gives dipole moment of water molecule is 2.66D.

M. Eichinger ,P. Tavan, J. Hutter and M. Parrinello, J. Chem. Phys.**110**,10452 (1999)



K. Kamiya et al. JACS, 129, 9663 (2007)



K. Kamiya et al. JACS, 129, 9663 (2007)



# Conclusions

- Hybrid QM/MM simulation method based on mutual interaction of the quantum mechanical and molecular mechanical subsystems of the whole system in addition to QM and MM interaction of quantum and classical subsystems respectively.
- QM/MM methods are now established as computational techniques to treat reactive and other electronic phenomena in chemical and biological processes.
- QM and hybrid QM/MM descriptions can be made nearly equivalent as far as the intramolecular properties of the QM fragments are concerned.
- QM/MM methods appear to be good enough for modeling of real world chemical processes in large systems.