Karlsruhe Institute of Technology

QM/MM

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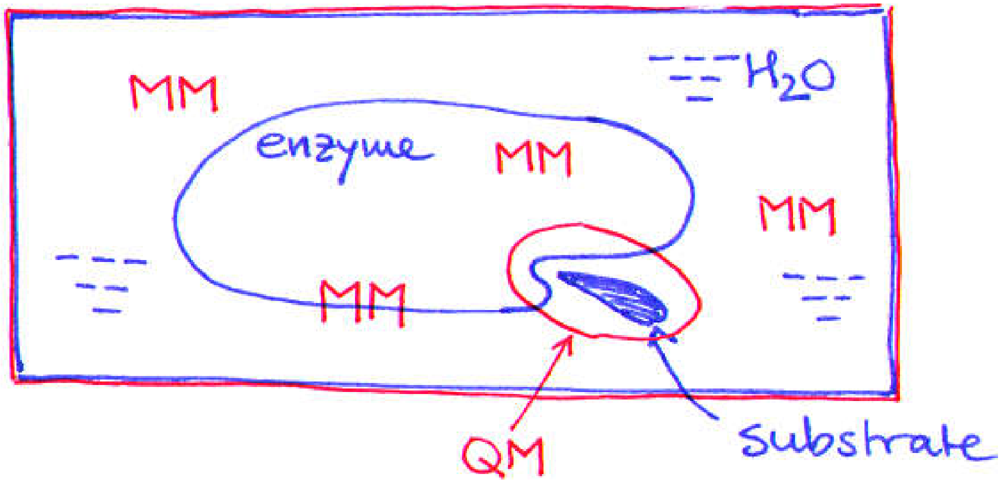
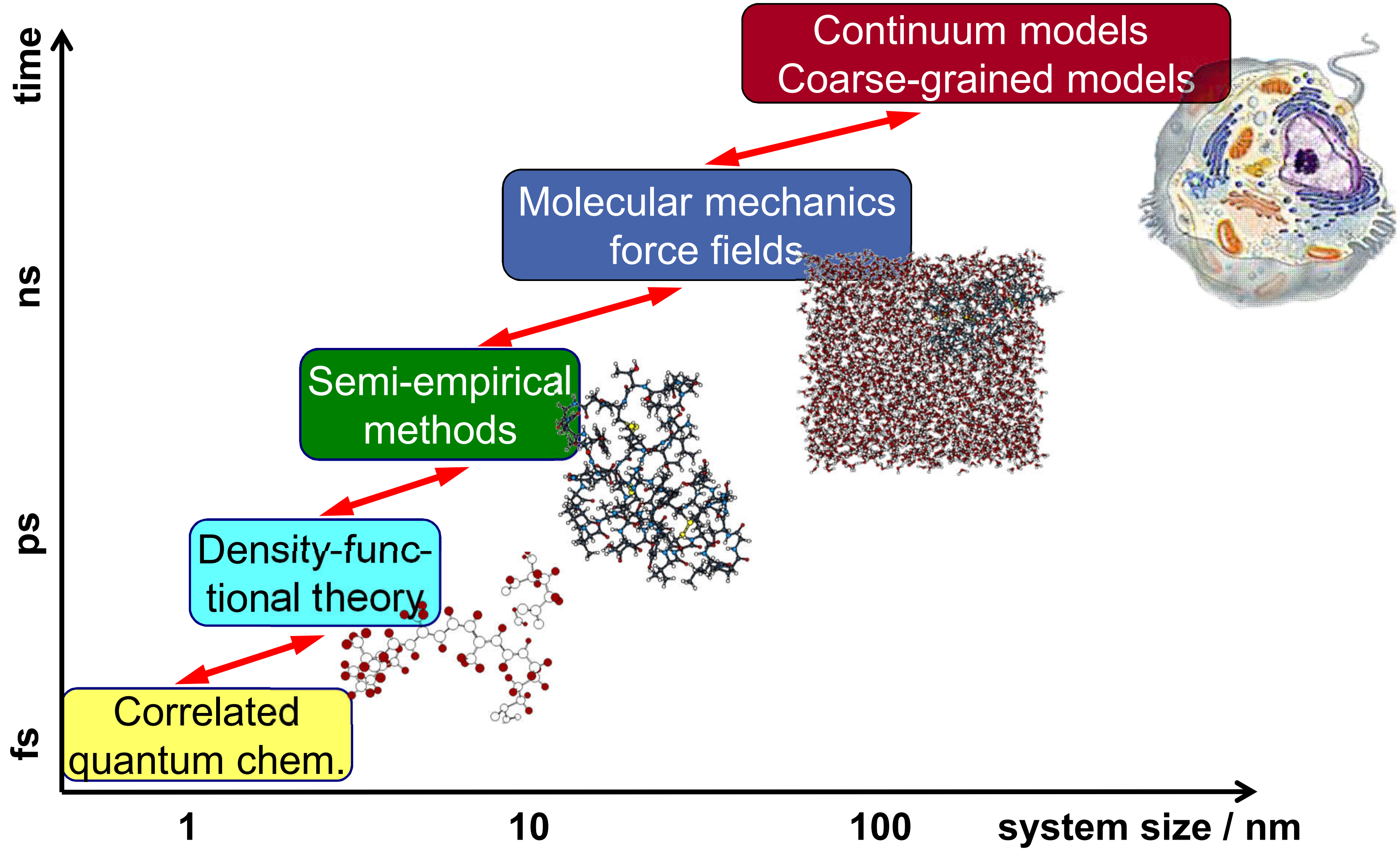
Institute of Physical Chemistry & Center for Functional Nanostructures



Computational chemistry



time

ns

ps

fs

Continuum models
Coarse-grained models

Molecular mechanics
force fields

Semi-empirical
methods

Density-func-
tional theory

Correlated
quantum chem.

1

10

100

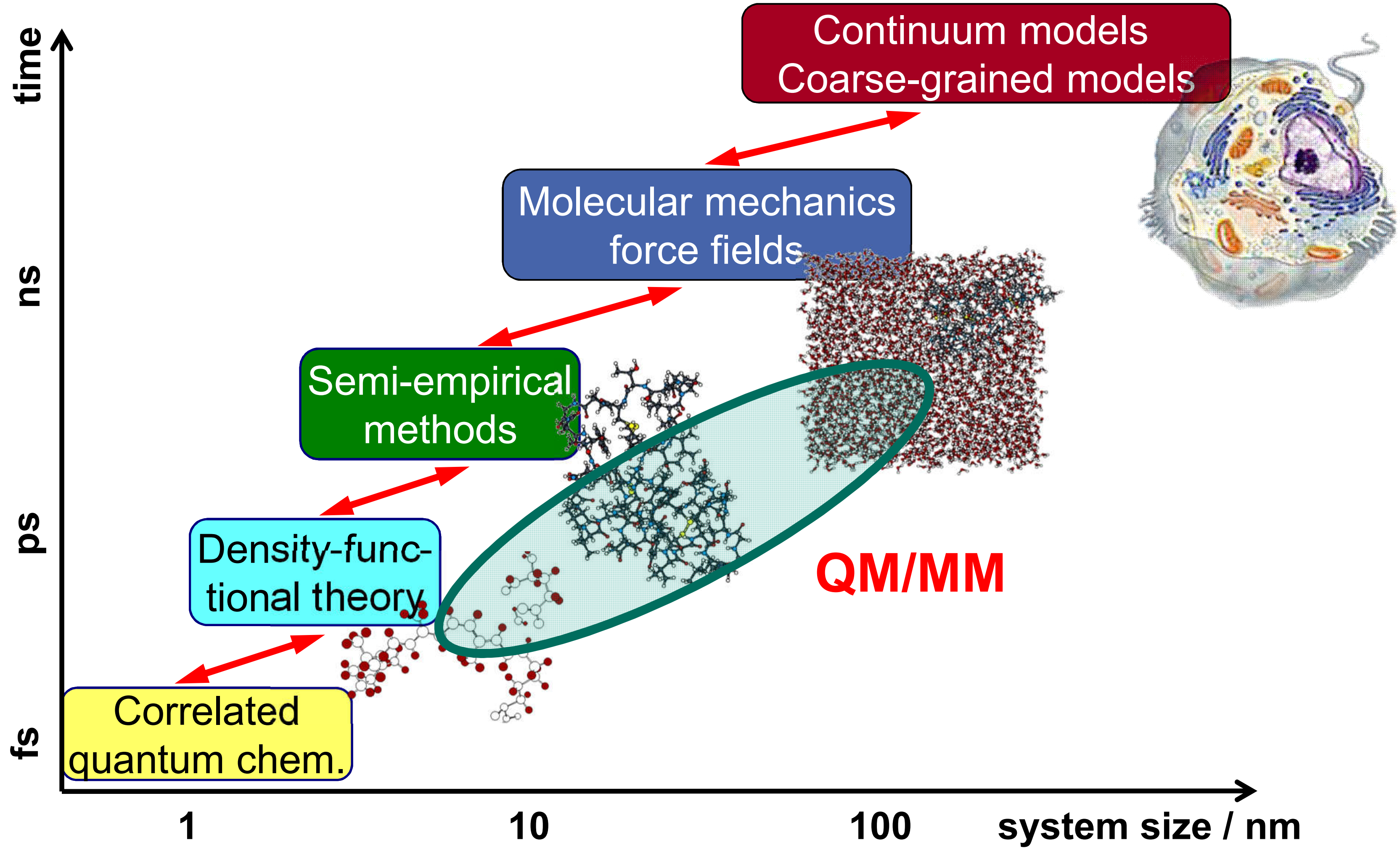
system size / nm

Computational chemistry

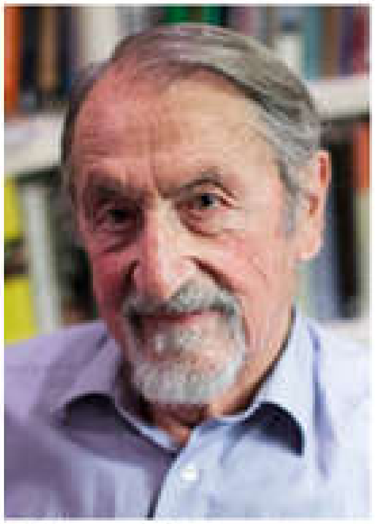
- Molecular mechanics (force fields)
  - Large efficiency
  - Crude approximations necessary
  - Constant electron density → covalent bonds cannot be created / broken
  - Chemical reactions cannot be described
  - Problems also if electron density differs for different conformations

- Quantum chemistry
  - No or little assumptions → large transferability
  - Description of chemical reactions possible
  - Larger computational cost
  - Semi-empirical methods – involve parameters, compromise (decreased transferability, increased efficiency)

Computational chemistry



The Nobel Prize in Chemistry 2013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Martin Karplus


Photo: © S. Fisch

Michael Levitt


Photo: Wikimedia Commons

Arieh Warshel

The Nobel Prize in Chemistry 2013 was awarded
jointly to Martin Karplus, Michael Levitt and Arieh Warshel
"for the development of multiscale models for complex chemical systems".

Empirical approaches to chemical reactions

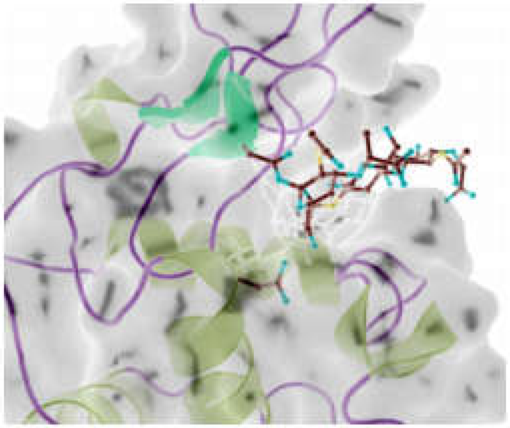
- Description of a reaction with a force field possible (but difficult)
- Using approximations that are appropriate for the specific case

- Re-parametrization of the bonds being created / broken (e.g. with Morse potential)
- Ad hoc model of the molecule, considerable parametrization effort
- Still, constant atomic charges – perhaps very problematic
- Limited or no transferability; hardly ever used (rather – QM/MM)

- Note: many chemical processes involve changes of electron density
  - Reactions involving charge transfer
  - Photochemistry

Hybrid QM/MM methods

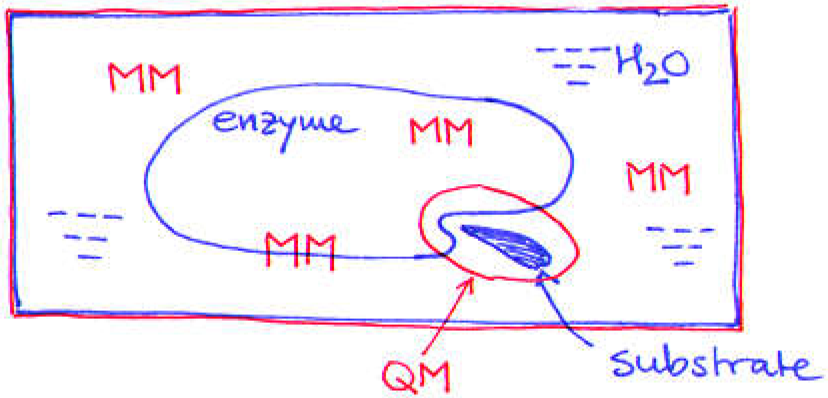
- Assumption – changing electron density localized
  in a small part of the molecular system
  – e.g. the binding site of a ligand in an enzyme



- Only a small number of atoms are involved in a chemical reaction
- The large remainder of the system stays outside of the process,
  but still may interact by way of non-covalent interactions

Hybrid QM/MM methods

- Assumption – changing electron density localized
  in a small part of the molecular system
  – e.g. the binding site of a ligand in an enzyme



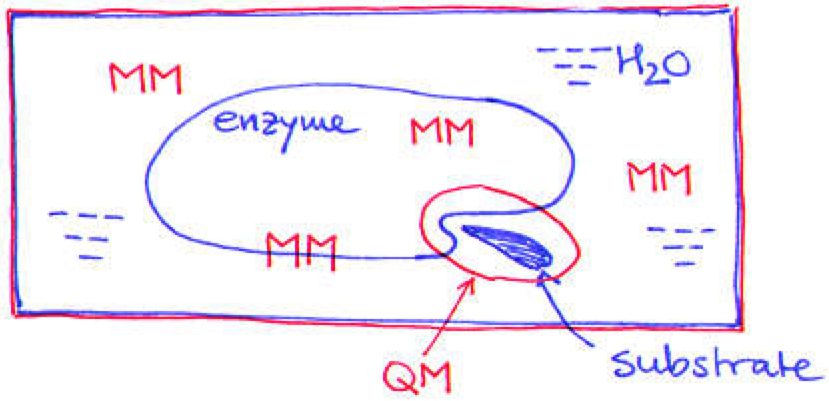
- Region where chemical reaction occurs – quantum chemistry (QM)
- The large remainder – MM force field
- Interaction of both regions must be accounted for – QM/MM / embedding

$$E_{\mathrm{total}} = E_{\mathrm{QM}} + E_{\mathrm{MM}} + E_{\mathrm{QM/MM}}$$

Hybrid QM/MM methods

- Interaction of both regions must be accounted for – QM/MM / embedding

$$E_{\text{total}} = E_{\text{QM}} + E_{\text{MM}} + E_{\text{QM/MM}}$$



- The QM and MM calculations – performed in the usual way
- Key issue – how to couple the QM and MM regions?
  Goal – to obtain $E_{\text{QM/MM}}$

Embedding schemes

- Many various schemes proposed
- Differences – how much of the QM–MM interaction is neglected

In the order of increasing complexity / completeness:

- Mechanical embedding
- Electronic embedding
- Polarized embedding

Mechanical embedding

- Unpolarized interactions

- Entirely independent QM and MM calculations
- Interaction between the QM and MM regions – with a force field

$$E_{\mathrm{QM/MM}} = \sum_{i}^{\text{QM atoms}} \sum_{m}^{\text{MM atoms}} \left(\frac{q_i^{\mathrm{Mull}} \cdot q_m}{r_{im}} + 4\varepsilon_{im} \left(\frac{\sigma_{im}^{12}}{r_{im}^{12}} - \frac{\sigma_{im}^{6}}{r_{im}^{6}} \right) \right)$$

- QM atoms have to be assigned Lennard-Jones parameters and their quantum-chemical charges are used (e.g. Mulliken charges)

- Specific combinations of force fields and quantum-chemical methods lead to very good results for specific classes of molecules / reactions
- Generally, care must be taken

Mechanical embedding

- Problem – the electron density in the QM region
  is unaffected by (‘does not feel’) the MM region
  – therefore ‘unpolarized’ scheme
- As if the QM region was calculated ‘in vacuum’
  – this may deviate from reality considerably
  – imagine that the reaction center of the enzyme is surrounded
  by charged amino acid side chains – affects the reaction strongly

Electronic embedding

- Polarized QM / unpolarized MM

- Electrostatic interaction with the MM atomic charges
  is included in the QM Hamiltonian
- Works with any electronic structure method
  – HF, DFT, correlated wave-function, semi-empirical…

Electronic embedding

Interaction of QM electrons with MM point charges

- moves from the QM/MM term (described with a force field) to the quantum chemical contribution
- the charge density interacts with a set of point charges
- *little* increase of the computational cost

$$\hat{H}'_{\mathrm{QM}} = \hat{H}_{\mathrm{QM}} - \sum_{j}^{\text{QM electrons}} \sum_{m}^{\text{MM atoms}} \frac{q_m}{r_{jm}}$$

Interaction of QM nuclei with MM point charges may remain in QM/MM

$$E'_{\mathrm{QM/MM}} = \sum_{i}^{\text{QM atoms}} \sum_{m}^{\text{MM atoms}} \left(\frac{Z_i \cdot q_m}{r_{im}} + 4\varepsilon_{im} \left(\frac{\sigma_{im}^{12}}{r_{im}^{12}} - \frac{\sigma_{im}^{6}}{r_{im}^{6}} \right) \right)$$

Electronic embedding

- A good approach with chances for acceptable accuracy
- Possible imbalance
  - QM region is polarized by MM
  - MM region cannot be polarized
    because of the constant atomic charges

Polarized embedding

- Fully polarized interactions

- Involves a polarizable MM force field
  - Every MM atom is assigned a polarizability α
  - Induced point dipole on the atom obtained from the field intensity $\vec{E}$:

$$\vec{\mu}^{\mathrm{ind}} = \alpha \cdot \vec{E}$$

  - To be calculated iteratively until self-consistence
  - Possible problems – computational cost, difficult convergence of dipoles

- The induced dipoles interact with MM point charges as well as with the QM electron density and nuclei
- Both QM and MM calculations are iterative → convergence of both is required!

Polarized embedding

- Formally the most complete approach
- Dramatically increased computational cost

- Question: Does the improvement of the quality of results justify the extreme cost of calculation?
- Electronic embedding may be sufficient in many cases

QM/MM study – work plan

1. Define the QM region
   - shall involve all of the interactions for which MM is insufficient
2. Choose the QM (and MM) methods
   - QM is the crucial and by far most consuming part of calculation
   - accuracy as well as efficiency shall be judged
3. Determine the type of embedding (perhaps electronic)
   - also introduce LJ parameters for QM atoms (usual MM, or special)
4. Simulate
   - each MD step involves 1 QM calculation (and 1 MM, 1 QM/MM)
5. Analyze

Covalent bond crossing the QM/MM boundary

- What shall be done if a QM atom and an MM atom are bound covalently?
- Usually inevitable in studies of proteins…

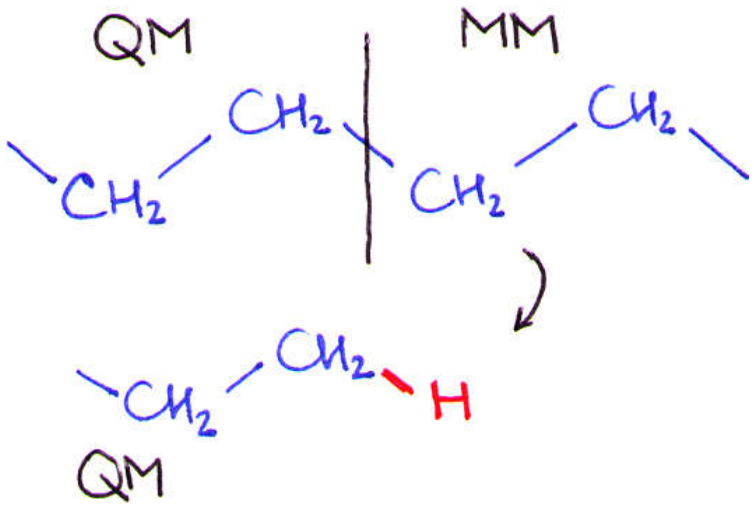
- Special treatment of the boundary is necessary
  (because the QM region is no real 'molecule' etc.)

- Linear combination of molecular fragments
- Link atoms (additive or subtractive coupling)
- Frozen orbitals
- other, further, current development…

Link atom approach

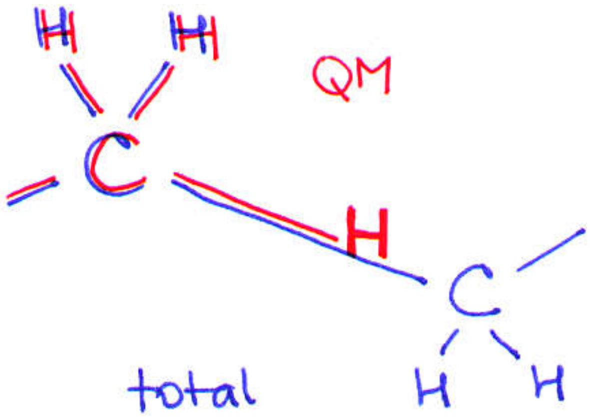
- More difficult – if there is electrostatic QM–MM interaction
- Typically in proteins – polar and charged amino acids in the MM region
  a – polarization of the electron density of the QM region
- Missing in the electronic embedding
  – description of covalent bonds crossing the QM–MM boundary

- Link atom – replaces the covalently bonded MM system at the boundary



Link atom approach

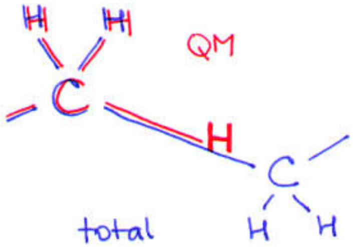
- Usually:
  - bonds between two sp^3-carbon atoms chosen to be cut
  - hydrogens used as link atoms (similar electronegativity of C and H)
    – also methyl 'atoms' may be used with some quantum chem. Methods
- Desirable – define the QM region such that
  the bonds to be cut are as unpolar as possible (to minimize errors)
- Link atom – placed on the original C–C bond in a typical C–H distance



Link atom approach

Additive coupling

- Bonded interactions crossing the QM–MM boundary calculated with the MM force field
- Sometimes omitted – angles involving 2 QM atoms and 1 MM atom, dihedrals with 3 QM atoms and 1 MM atom



- MM atoms situated close to the QM system
  - almost overlap with the link atom
  - unphysically large influence on the electronic structure of the QM system
  - their charges may be scaled down or even removed
  - good alternative 1: replace point charges by gaussian charge distributions
  - good alternative 2: divide the charge among not-so-close MM atoms (motivation: the total charge should remain, and should not move far)

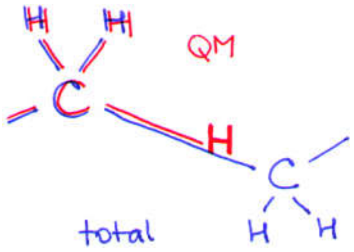
Link atom approach

Subtractive coupling

- Two MM calculations: one for the entire system, and
  one for the QM region including the link atom(s)
  – the same as for the QM calculation

$$E_{\text{total}} = E_{\text{MM}}^{\text{large}} + \left(E_{\text{QM}}^{\text{small+L}} - E_{\text{MM}}^{\text{small+L}}\right)$$

(large = entire system, small+L = QM region)

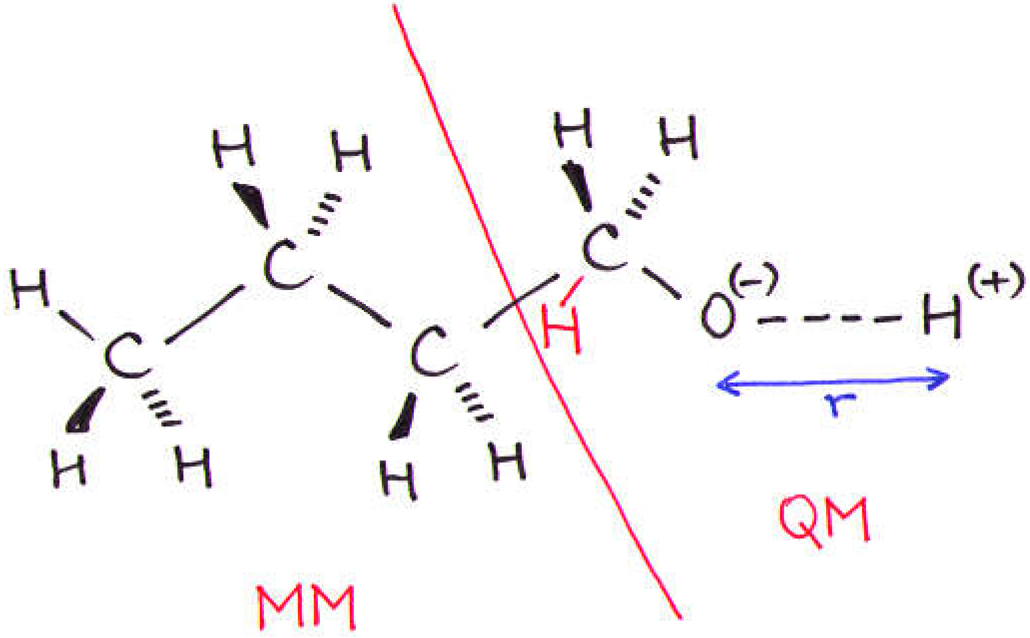


- May be deficient in some applications…

Link atom approach

Deficiency of subtractive coupling – example

- Reaction $$\mathrm{CH_3CH_2CH_2CH_2OH \rightarrow CH_3CH_2CH_2CH_2O^- + H^+}$$
- QM region – methanol fragment, MM region – remainder
- Goal – evaluate the energy as a function of the O–H distance *r*



Link atom approach

Deficiency of subtractive coupling – example

- Reaction $\mathrm{CH_3CH_2CH_2CH_2OH \rightarrow CH_3CH_2CH_2CH_2O^- + H^+}$
- Assume – parameters for methanol and butanol differ only in the force constant *k* for the O–H bond; all remaining terms give a constant independent of *r*

$$E^{\mathrm{QM/MM}}_{\mathrm{butanol}}(r) = E^{\mathrm{QM}}_{\mathrm{methanol}}(r) + \left(\frac{1}{2}k^{\mathrm{OH}}_{\mathrm{butanol}} \cdot (r-r_0)^2 - \frac{1}{2}k^{\mathrm{OH}}_{\mathrm{methanol}} \cdot (r-r_0)^2\right) + \mathrm{const.}$$

$$= E^{\mathrm{QM}}_{\mathrm{methanol}}(r) + \frac{1}{2}\left(k^{\mathrm{OH}}_{\mathrm{butanol}} - k^{\mathrm{OH}}_{\mathrm{methanol}}\right) \cdot (r-r_0)^2 + \mathrm{const.}$$

- MM energy – retains the form of r^2
- QM energy – for large *r*, proportional to 1/*r* due to Coulomb's law

Link atom approach

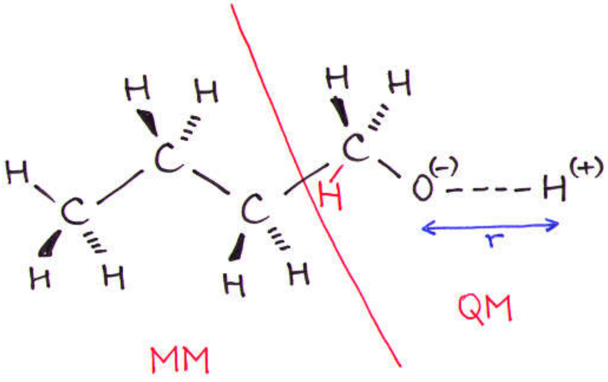
Deficiency of subtractive coupling – example

- Reaction $$\mathrm{CH_3CH_2CH_2CH_2OH} \rightarrow \mathrm{CH_3CH_2CH_2CH_2O^-} + \mathrm{H^+}$$
- Asymptotic behavior of total energy:

$$\lim_{r\to\infty} E^{\mathrm{QM/MM}}_{\mathrm{butanol}}(r) = \lim \left(-\frac{1}{r} + \frac{1}{2}k\cdot r^2\right) = \lim r^2 = \infty$$

- Slightly different parameter values (really possible)
  → total energy grows over all limits
  – absolutely useless calculation

- Additive coupling – no such problem
  - methanol would be calculated with QM
  - propyl would be calculated with MM
    – MM parameters for the O–H bond not required!



Link atom approach

- Example – QM is an amino-acid side chain (starting from CB)

```
RESI SER          0.00
GROUP
ATOM N    NH1    -0.47  !     |
ATOM HN   H       0.31  !  HN-N
ATOM CA   CT1     0.07  !     |   HB1
ATOM HA   HB      0.09  !     |   |
GROUP                   !  HA-CAH-CB--OG
ATOM CB   CT2     0.05  !     |   |     \
ATOM HB1  HA      0.09  !     |   HB2    HG1
ATOM HB2  HA      0.09  !   O=C
ATOM OG   OH1    -0.66  !     |
ATOM HG1  H       0.43
GROUP
ATOM C    C       0.51
ATOM O    O      -0.51
```

- CA is very close to the link atom (which is between CA and CB)
- The point charge on CA would disturb the QM region drastically
- Simply removing CA would break electroneutrality

Link atom approach

Possible solutions to the problem:

- ‘exgroup’ – remove all charges of the charge group close to QM region
  - Here – CA, HA, N, H
  - Drastic – many important electrostatic interactions lost (hydrogen bonds…)

- ‘div’ – divide the charge of CA among the remaining atoms in the group
  - Here – q: CA = 0.07
  - After re-distribution: CA=0, HA=0.11, N= 0.44, HN=0.33
  - Strictly possible only if QM–MM boundary lies between two charge groups
  - The idea may be adapted to each specific case

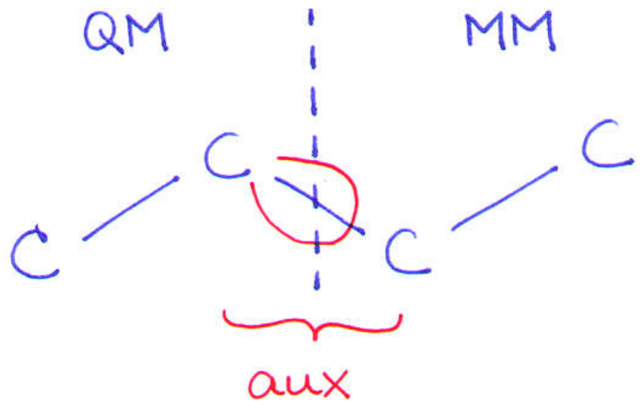
Link atoms or something else?

- Link atoms – may cause problems with non-bonded interactions
  - possibly extremely close to nearby MM atoms
  - representation of charge densities by MM point charges may lead to inaccuracy / computational instability

- Alternative – introduce no new *atoms*, rather treat the *orbitals* on the QM/MM boundary in a special way
- Shape of these orbitals can be held constant during the simulation → ‘frozen orbitals’

Frozen orbital approach

- 3 regions: QM, MM, and auxiliary region on the boundary



- Atoms in the auxiliary region
  - possibly a small number
  - normal nuclei
  - electron density with atomic-orbital basis
  - possess quantum character
  - their interaction with itself and with MM region can be calculated classically (interaction of frozen density with itself, of frozen density with point charges)

- Interaction of the QM region with the auxiliary
  - another term in the Hamiltonian: interaction of a wave function with a frozen charge density
  - only slightly more complex than the interaction with point charges

Frozen orbital approach

- Localized SCF method (LSCF)
  - every covalent bond crossing the boundary – a single frozen orbital:
  - the (hybrid) atomic orbital localized on the boundary-QM atom
  - calculated once at the start of the simulation, does not change afterwards
  - careful with the occupation of frozen orbitals (to handle density correctly) – accurate accounting required

- Generalized hybrid orbital approach (GHO)
  - the QM/MM boundary passes through an atom (instead of cutting a bond)
  - the (hybrid) atomic orbitals on this atom are considered to be frozen
  - populations of the GHO: resulting density equiv. to MM charge of this atom
  - the remaining orbital on the atom – points inwards the QM region – frozen in shape; its occupation is free to vary

- Considerable attention, ongoing development

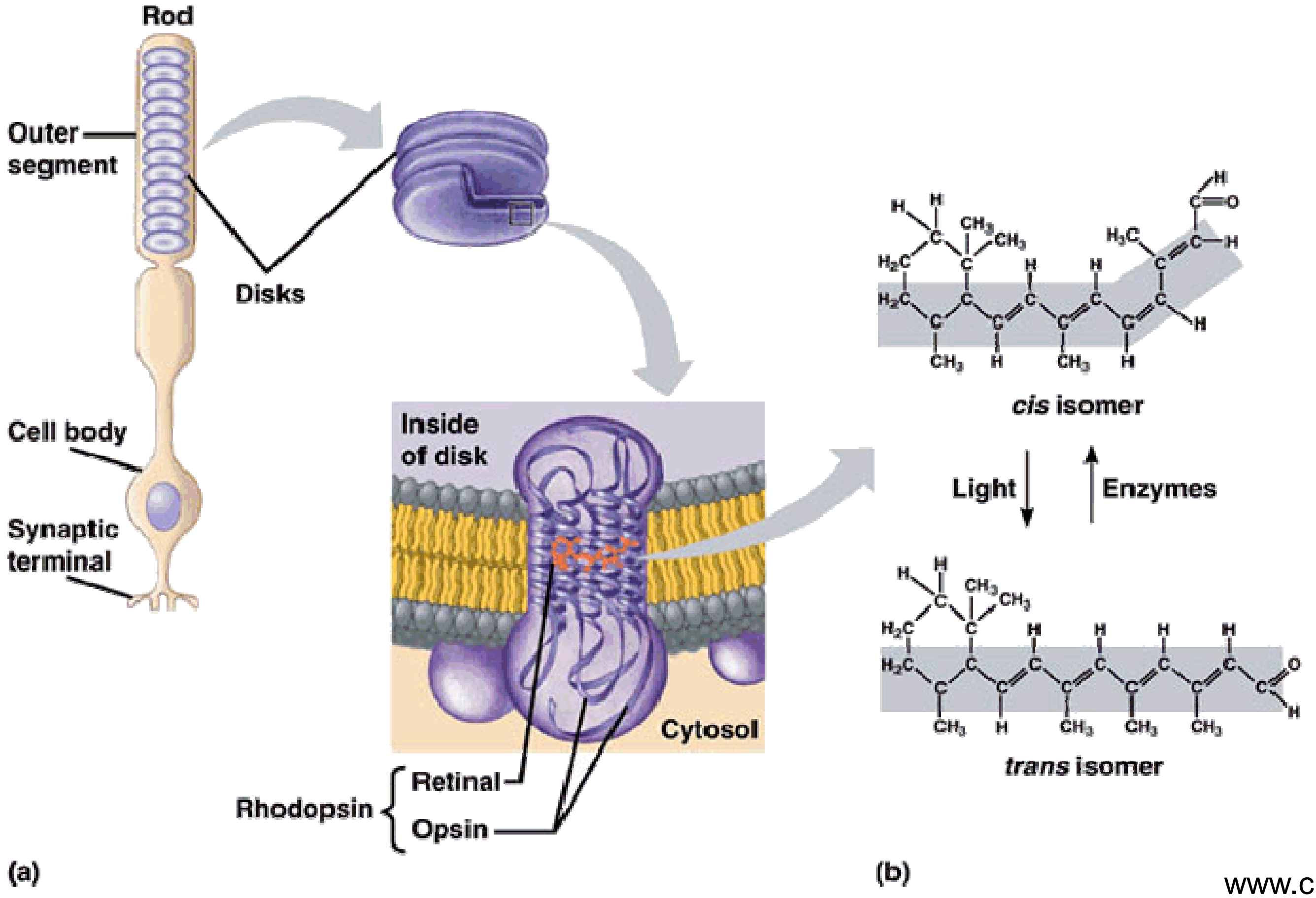
Beyond QM/MM

- Divide the system even more – 3 disjunctive regions, QM1/QM2/MM
- QM1 – advanced, expensive electronic structure method
  (highly correlated like CC, CAS…)
- QM2 – more approximative and efficient electronic structure method
  (DFT or even semi-empirical)
- MM

- Example – ONIOM in the Gaussian package

Choice of the QM region – illustration

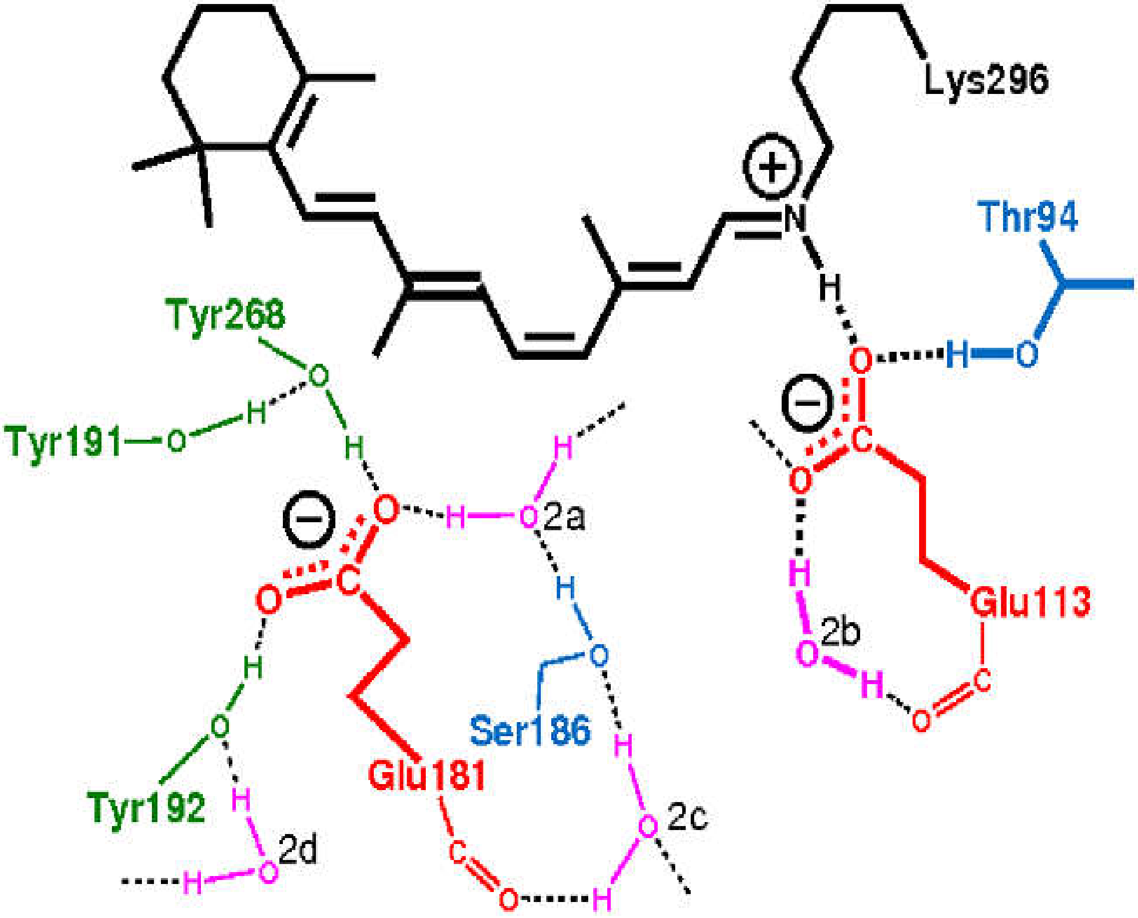
- Retinal – polyene bound covalently via a protonated Schiff base to a lysine side chain in a protein from the rhodopsin family



www.chm.bris.ac.uk

Choice of the QM region – illustration

- Many different choices possible



- polyene (ring to NH): **bad**, boundary cuts a polar bond
- retinal + CH2 **bad**, link atom too close to the important region
- retinal + sidechain to CB **fair, but** no charge transfer to Glu113 possible
- + counterion Glu113 **better, but** no charge transfer to Wat possible
- + Wat2b+Thr94 **good, but** no polarization at Glu181
- + Glu181 **very good, but**…

Adaptive QM/MM

- Problematic situation – molecules entering and leaving QM zone
- Exchange of QM and MM characters desirable
- Naïve exchange impossible due to discontinuities:
- Spatial – structure changes abruptly at the QM–MM boundary
- Temporal – forces change abruptly upon an exchange of characters

- 1st gen. – alleviates spatial discontinuity, temporal discontinuity persists
- 2nd gen. – several partitionings, they however contain different numbers of QM molecules (QM core region, and transition region), and there is a certain required number of partitionings

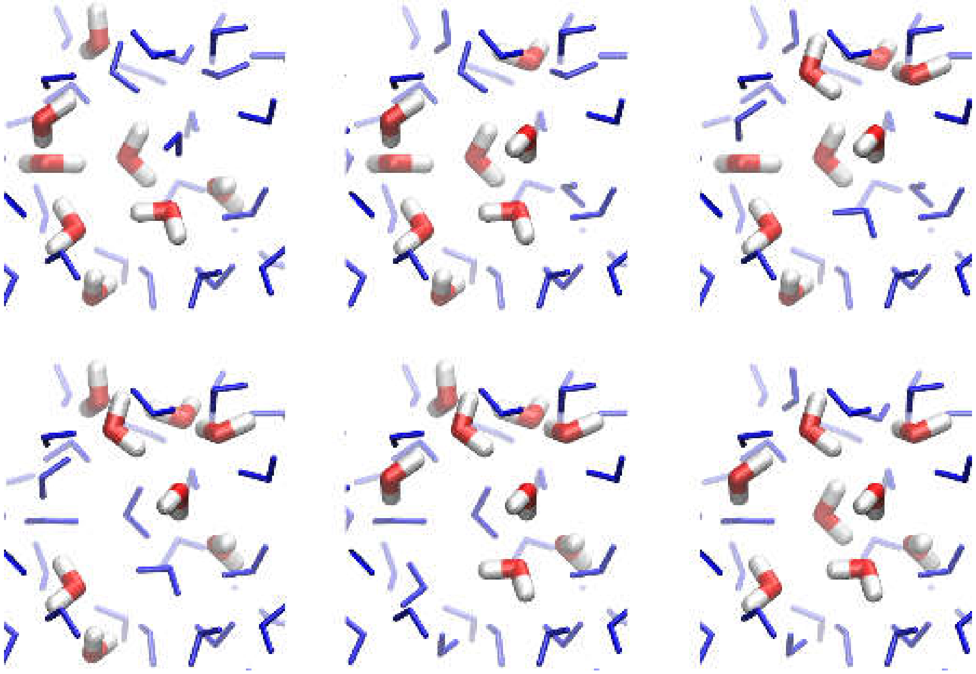
- Size-consistent multi-partitioning adaptive QM/MM
  – removes discontinuities, avoids artificial forces
  author: Hiroshi C. Watanabe (JCTC 10, 4242 (2014))

Adaptive QM/MM – SCMP

- Forces obtained by averaging from several QM/MM calculations

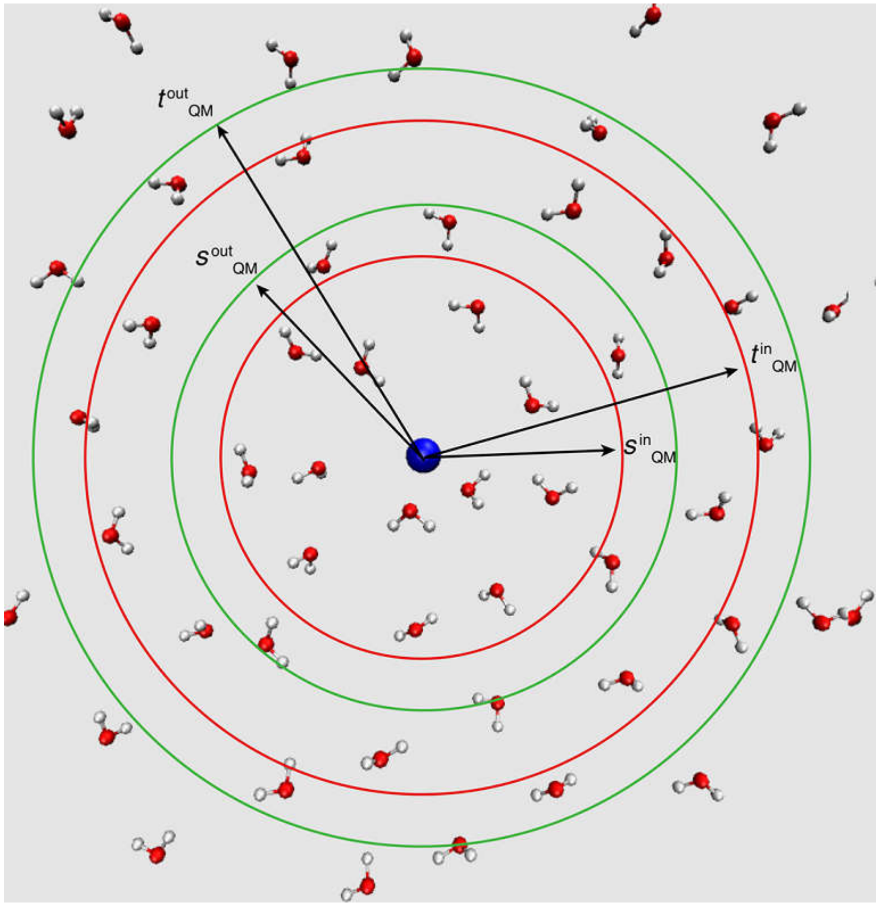
$$\mathbf{F}_j^{\text{eff}}(\mathbf{r}) = \sum_n^N \sigma^{(n)}(\mathbf{r}) \cdot \mathbf{f}_j^{(n)}(\mathbf{r})$$

- Partitionings with identical sizes of the QM region are considered



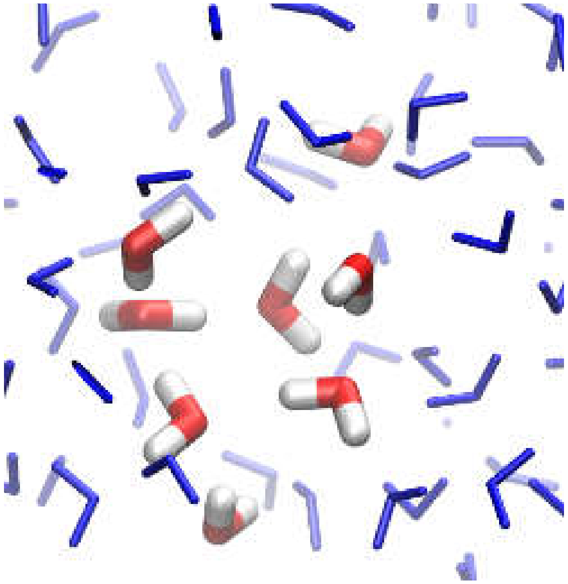
Adaptive QM/MM – SCMP

- Weight function σ
  – depends on distances of QM and MM molecules from the center



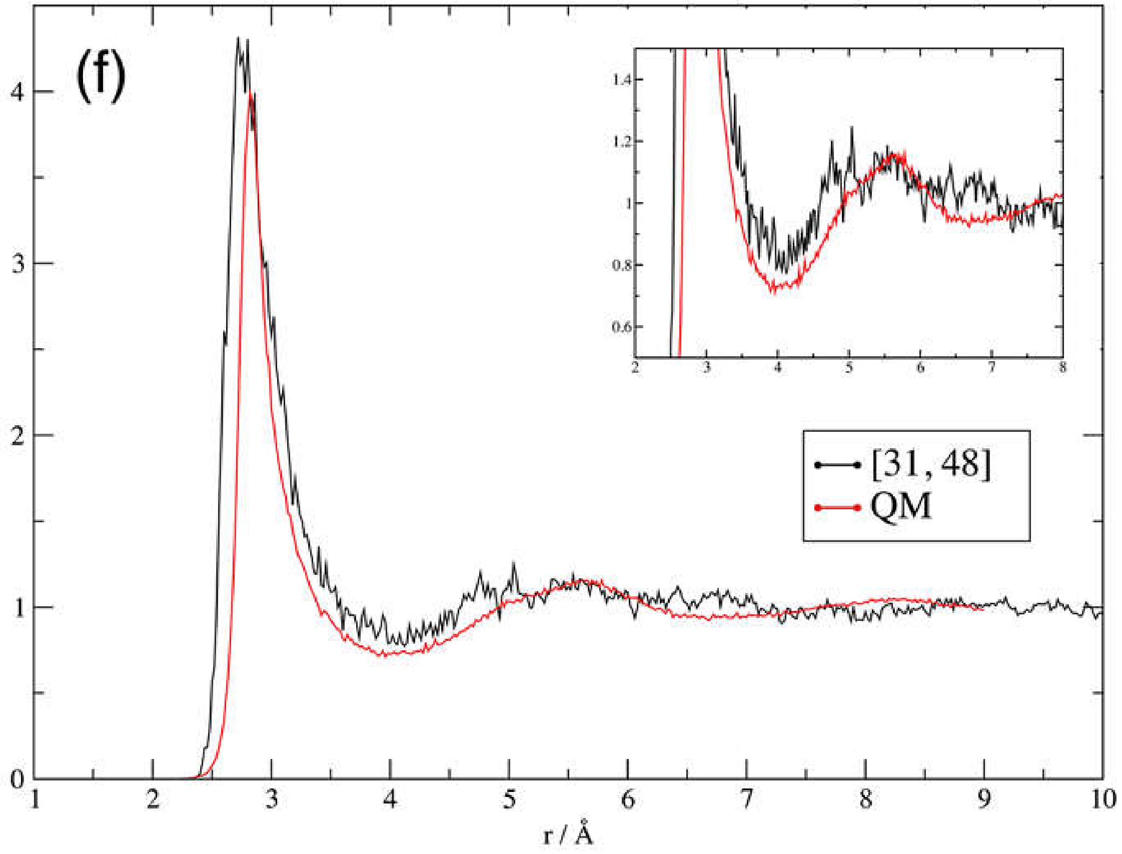
Adaptive QM/MM – SCMP

- Weight function σ
  – vanishes for a partitioning with fragmented QM zone
  – also vanishes for the most compact partitioning,
- Is σ of a partitioning lower than threshold?
  replace by the most compact, so-far not considered partitioning
  – zero weight of both – discontinuities avoided



Adaptive QM/MM – SCMP

- Example: RDF of “QM water in MM water”
  – 31 QM water molecules, 48 partitionings considered



Adaptive QM/MM – SCMP

- Continuous forces (no artificial forces on the QM–MM boundary)
- Continuous switching of properties at the boundary
- Improvement upon many previous multi-partitioning methods
  – applicability for large QM core regions
  (no required number of partitionings)
  – conserved energy independent of the number of partitionings
- Efficient parallel implementation
  – identical sizes of QM regions – similar computational cost

QM/MM in GROMACS FAST. FLEXIBLE. FREE.

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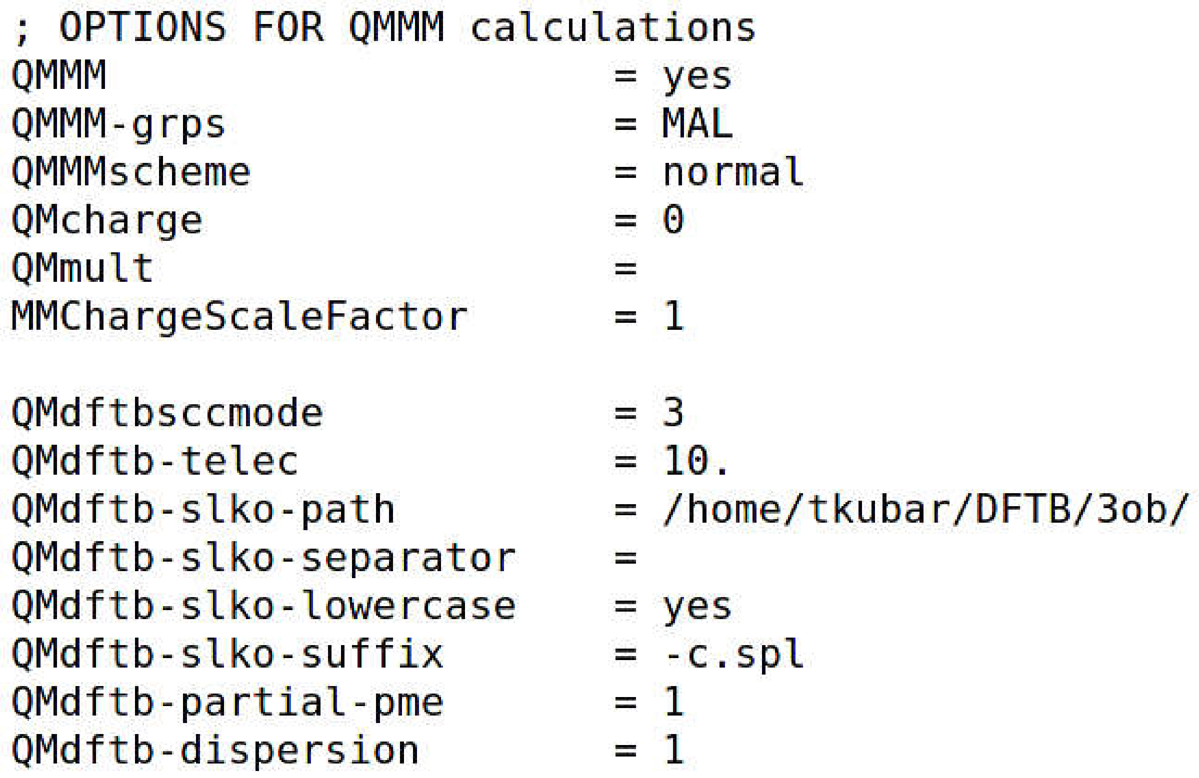
- Interface by G. Groenhof
- Communicates with external QM software
  (Gaussian, Mopac, Orca, Gamess UK)
- Additive scheme, electrostatic embedding

- DFTB3 – ‘semi-empirical density-functional theory’
  – newly implemented and fully integrated within Gromacs
- No file-based communication
- Gromacs PME routines used for electric potential – efficiency
  (PME used also for QM–QM interaction, and not full Ewald)

- Free energies – internal Gromacs functionality
  or available external tools (PLUMED)

QM/MM in GROMACS

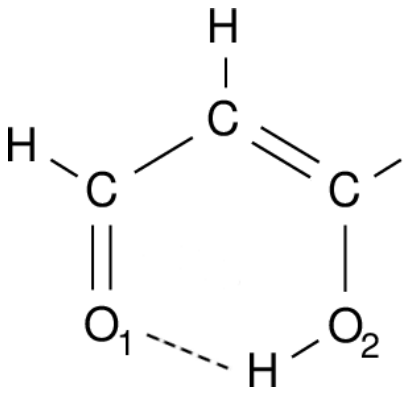


```
; OPTIONS FOR QMMM calculations
QMMM                        = yes
QMMM-grps                   = MAL
QMMMscheme                  = normal
QMcharge                    = 0
QMmult                      =
MMChargeScaleFactor         = 1

QMdftbsccmode               = 3
QMdftb-telec                = 10.
QMdftb-slko-path            = /home/tkubar/DFTB/3ob/
QMdftb-slko-separator       =
QMdftb-slko-lowercase       = yes
QMdftb-slko-suffix          = -c.spl
QMdftb-partial-pme          = 1
QMdftb-dispersion           = 1
```

Application 1 – Proton Transfer

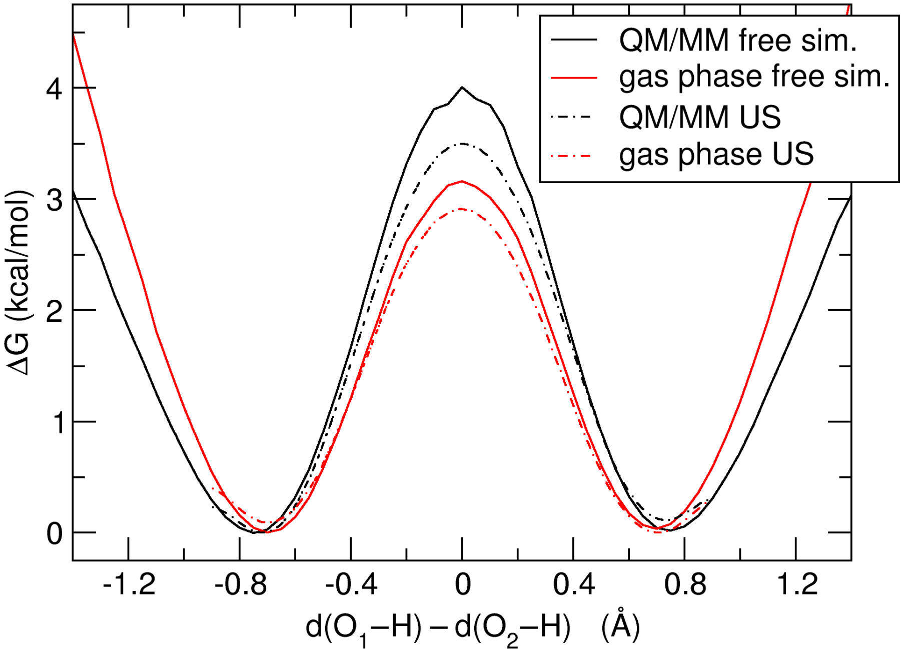
- Malonaldehyde – ultra-fast intramolecular PT



- Free energy barrier of few kcal/mol – rate of several times per ns
- Popular test case for QM/MM

Application 1 – Proton Transfer

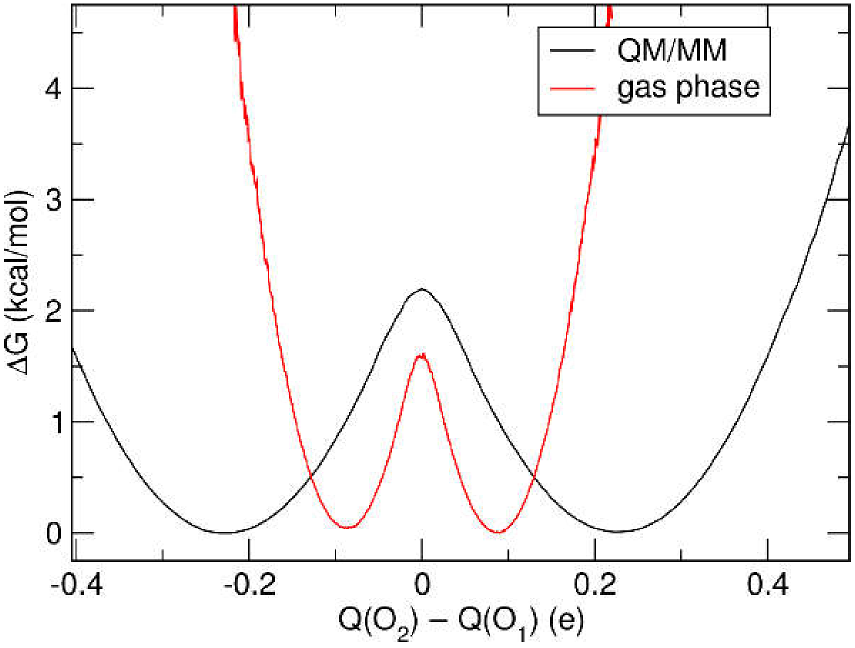
- With QM/MM and in the gas phase
  reaction coordinate: difference of O–H distances



- Barrier from free simulation slightly higher than from umbrella sampling
  (possibly undersampled?)

Application 1 – Proton Transfer

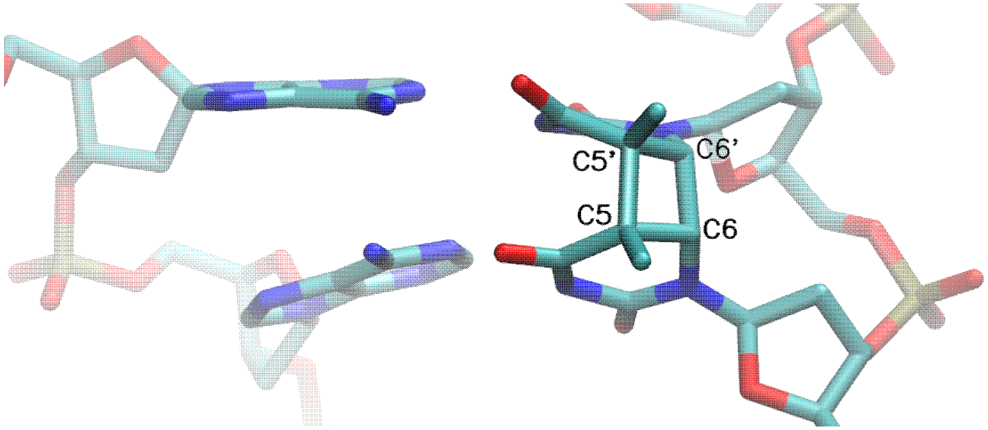
- How to choose the reaction coordinate?
  (generally non-trivial for PT with intermediate molecules)



- Perhaps non-geometrical RC – difference of Mulliken charges
- Disadvantage: biased sampling not easily possible

Application 2 – DNA Lesion

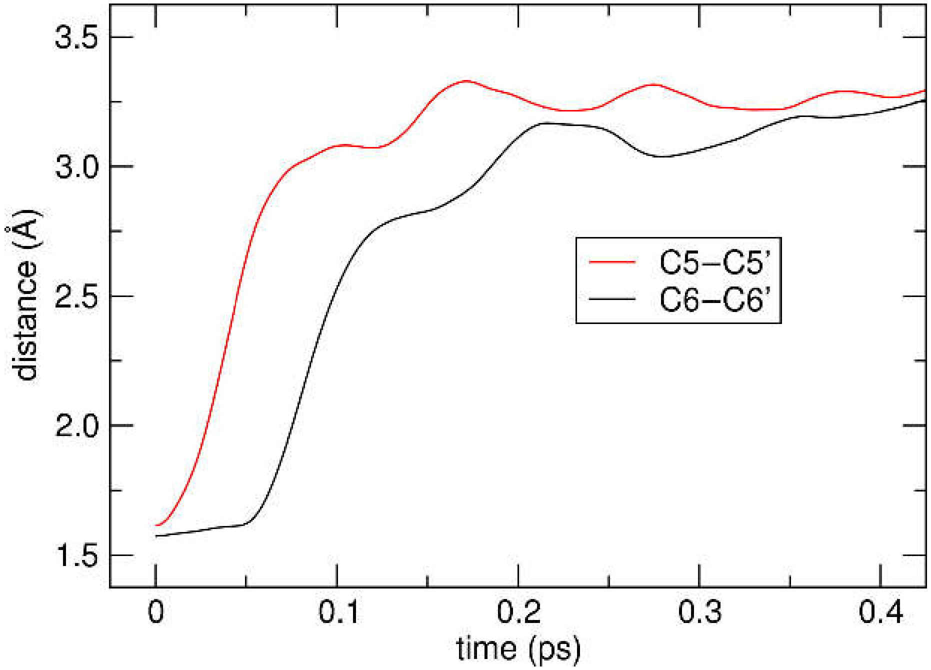
- Cyclobutane pyrimidine dimer



- Stable in the electro-neutral state
- Uptake of excess electron leads to disintegration
- Mechanism debated (experimental and QM/MM studies)

Application 2 – DNA Lesion

- Free simulation of the lesion
  after the electron uptake – radical anion

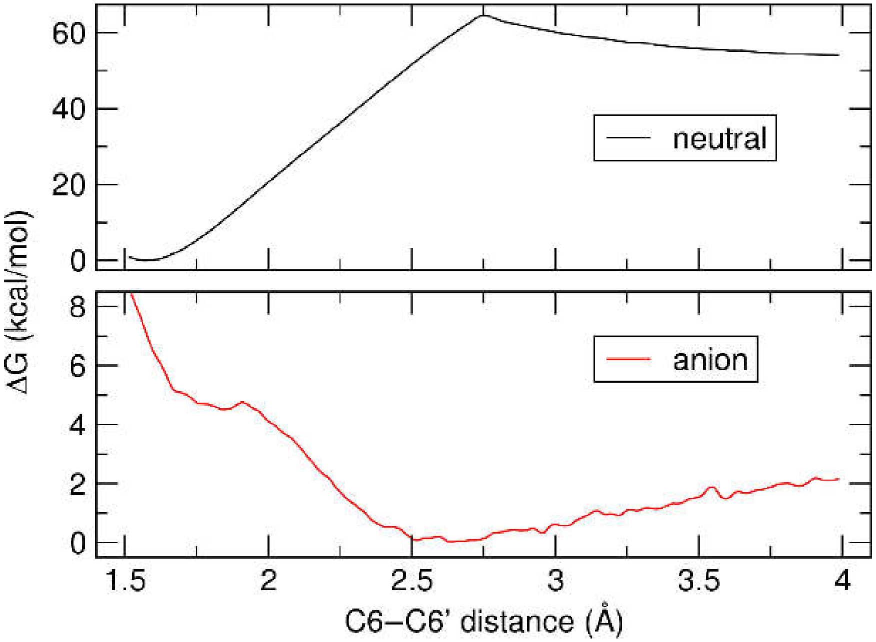


- The C5 – C5' bond breaks first, immediately
- The C6 – C6' bond follows

(averages from 100 simulations)

Application 2 – DNA Lesion

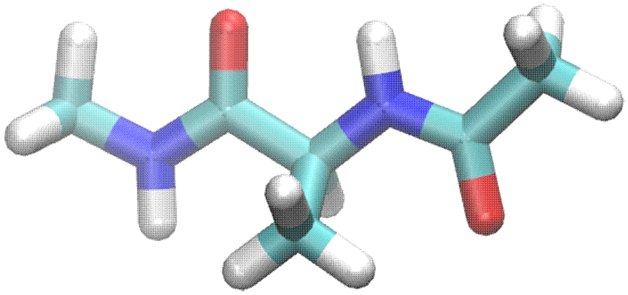
- Umbrella sampling – stretching of the C6–C6' bond
  – CPD electro-neutral or after the electron uptake (radical anion)



- Meta-stable state with C5–C5' broken and C6–C6' intact?
- Tiny barrier for complete disintegration
  (NB: improved sampling and DFTB benchmark necessary)

Application 3 – Peptide Conformation

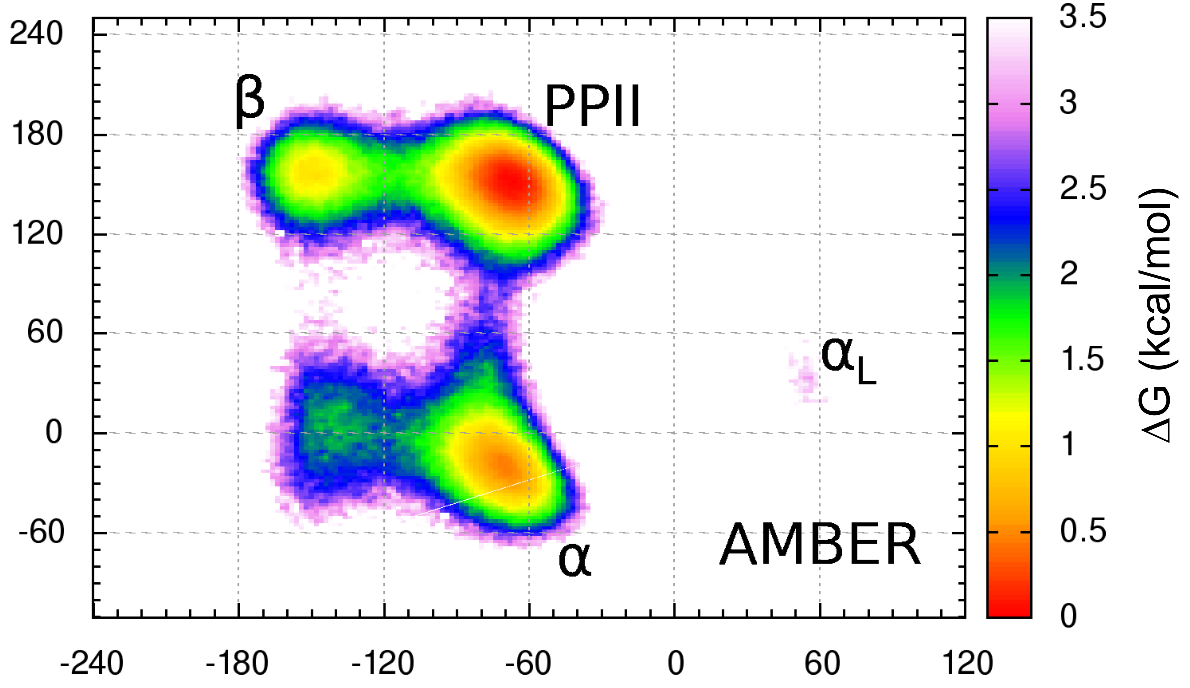
- Alanine “dipeptide” – 2 peptide bonds, 1 pair φ–ψ



- Also frequent subject of QM/MM studies,
  comparison with highly optimized force fields
- 2D free energy maps for φ–ψ

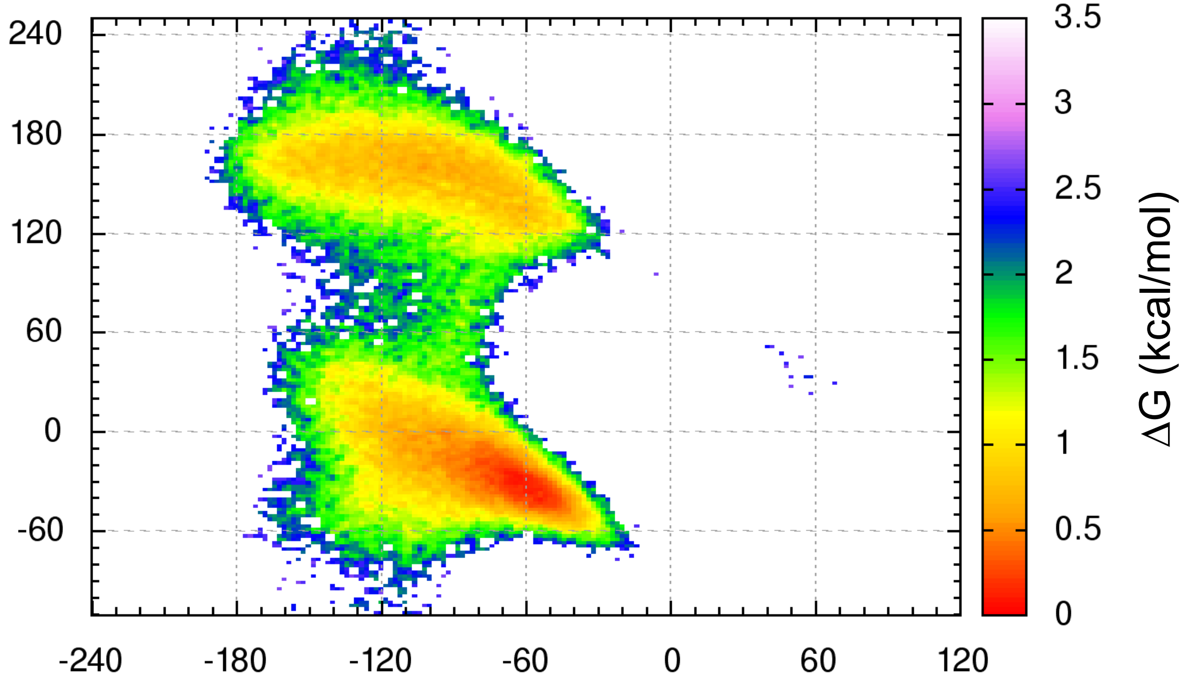
Application 3 – Peptide Conformation

- Amber14SB force field



Application 3 – Peptide Conformation

- QM/MM with DFTB – free simulation



- PPII and β not distinguished (single basin)
- Rather than PPII, α is the global minimum
- Barrier between α and PPII much lower – which one is correct?

Application 3 – Peptide Conformation

- QM/MM with DFTB – well-tempered metadynamics