Computational Biophysics: atomistic simulations

empirical potentials, statistical mechanics

I. Dynamics of complex structures

- protein folding
- molecular motors
- protein-DNA complexes

II. Transport: water, ions, protons, …

III. Electron transfer

IV. Enzymes

- catalysis
- photochemistry

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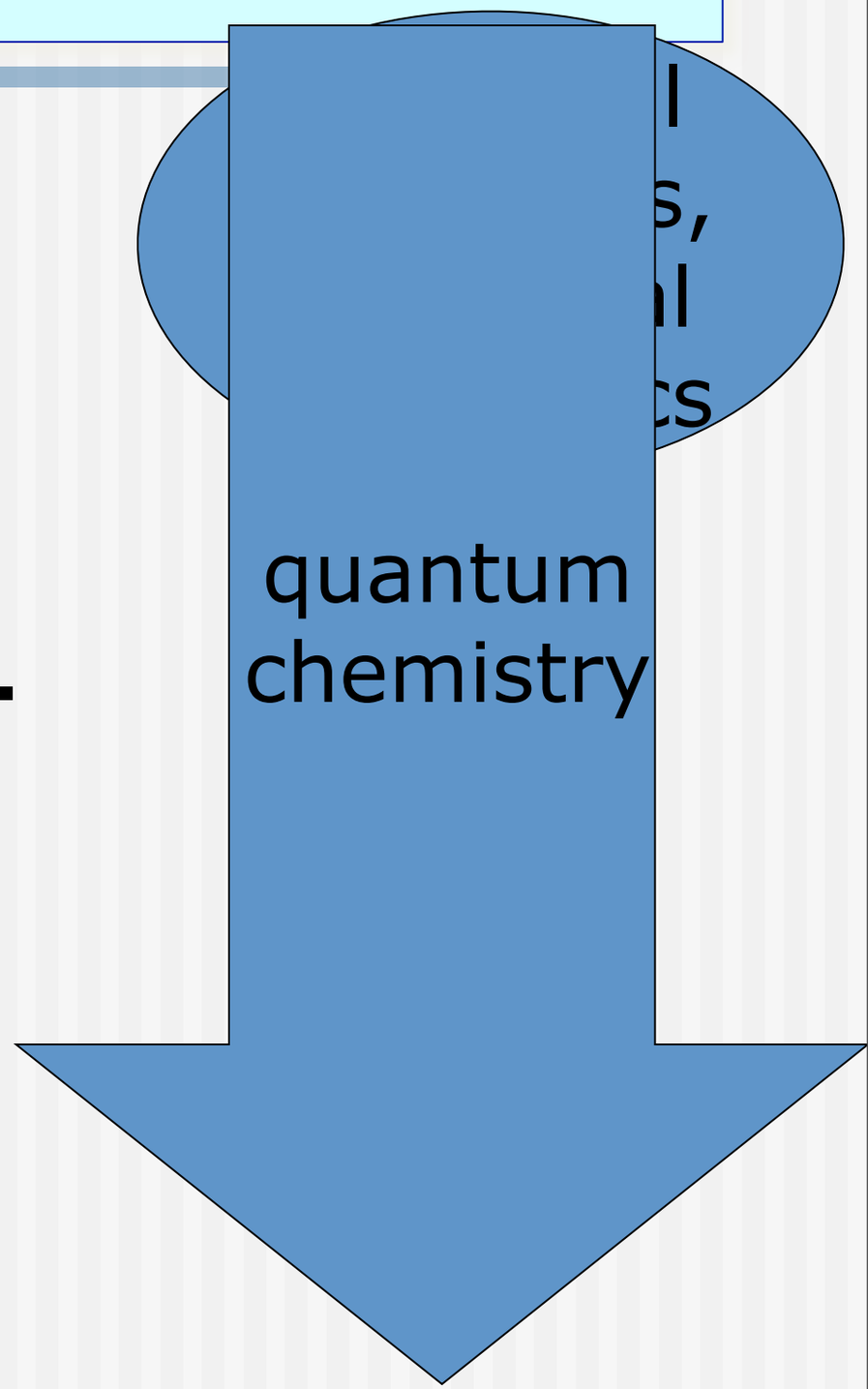

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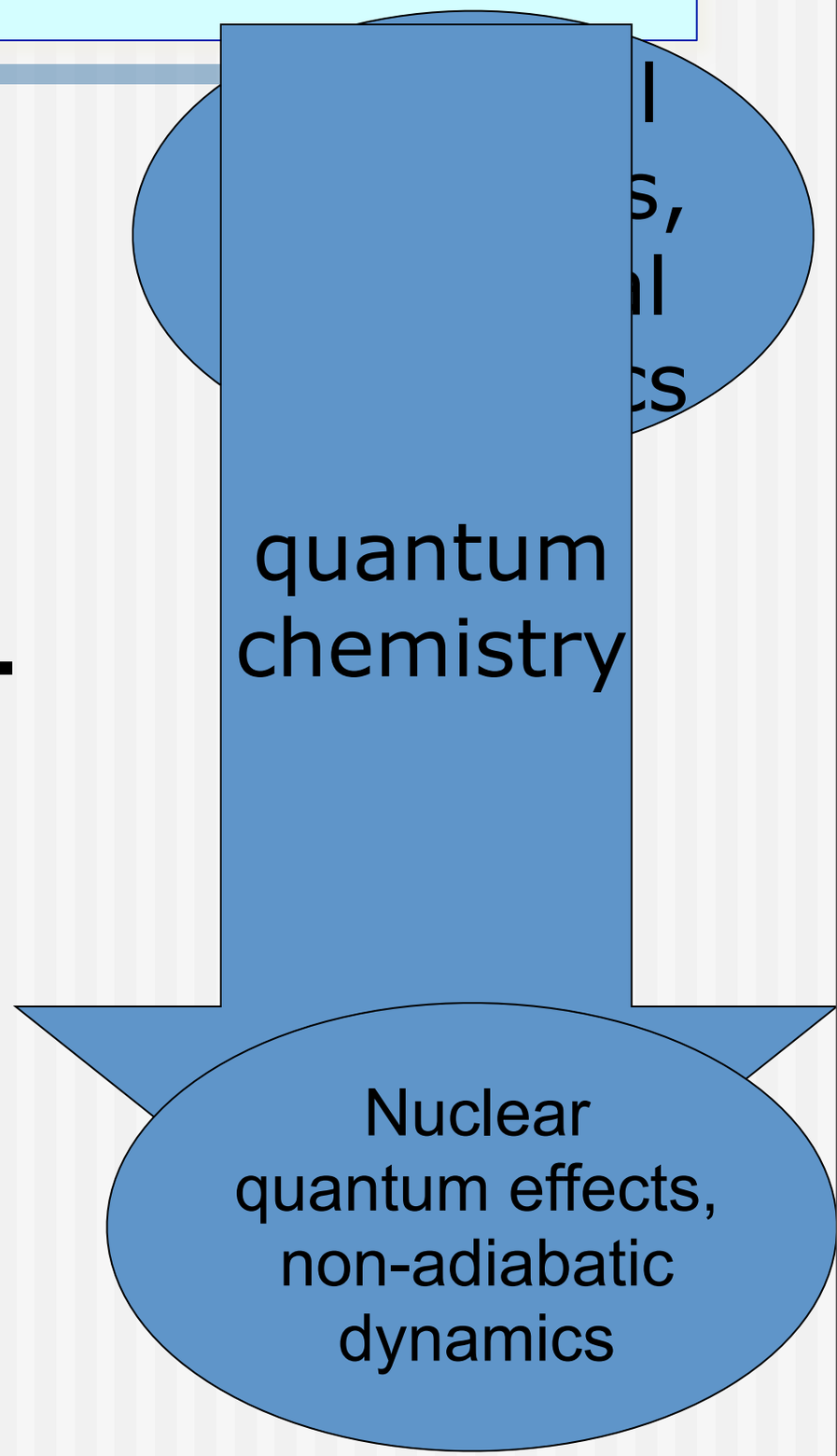
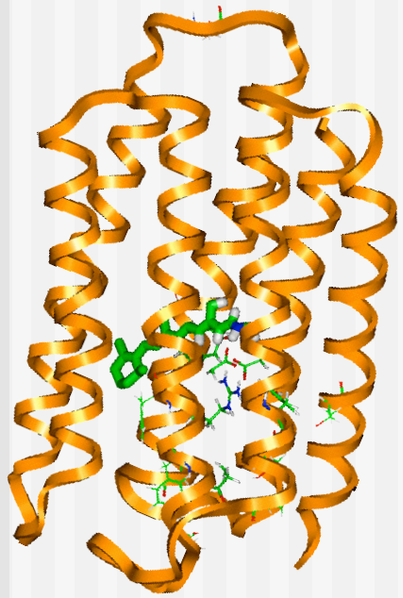
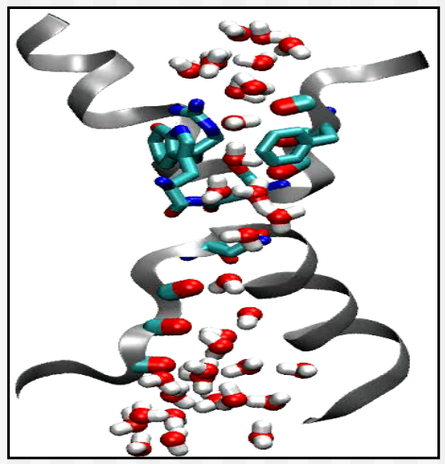


How to treat chemical reactions in proteins?

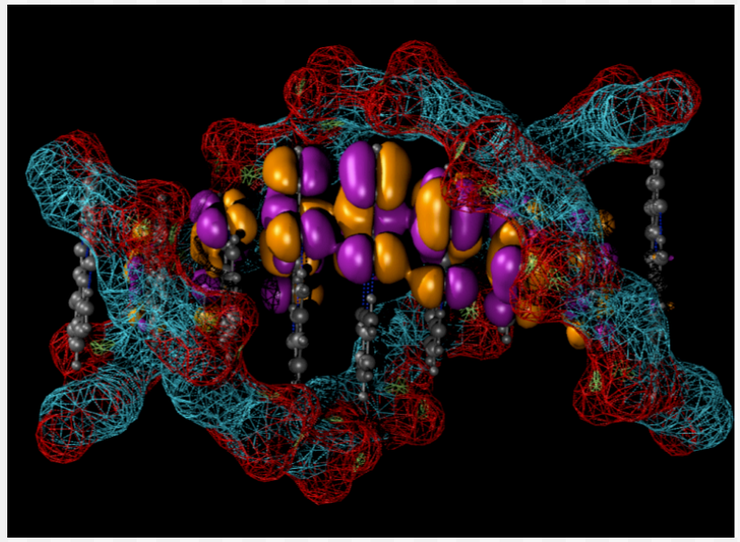
QM description needed

bioenergetics: proton transport

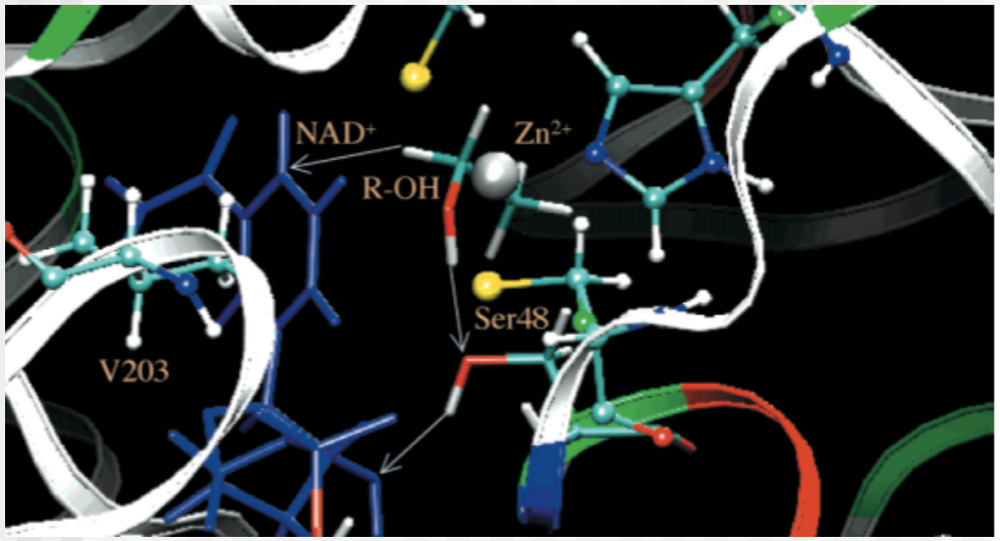




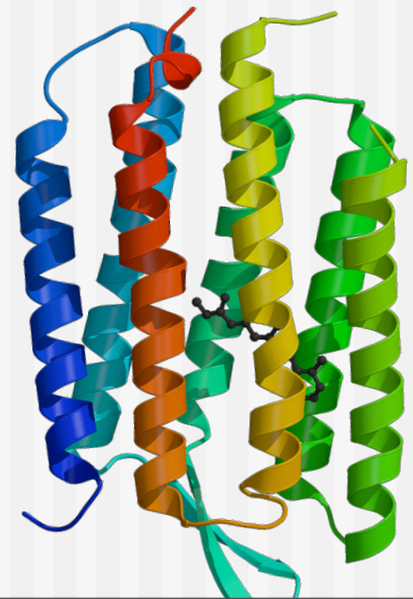
electron transport in DNA

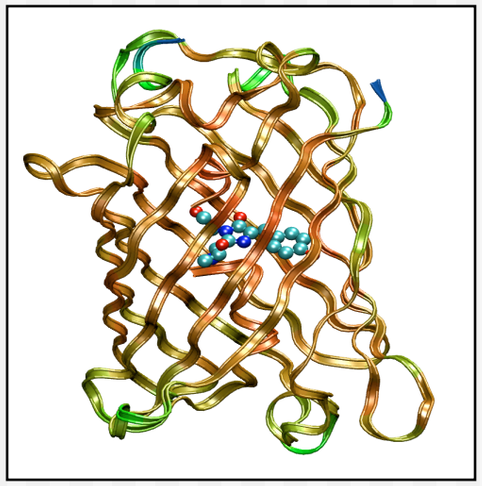


biocatalysis: alcohol dehydrogenase

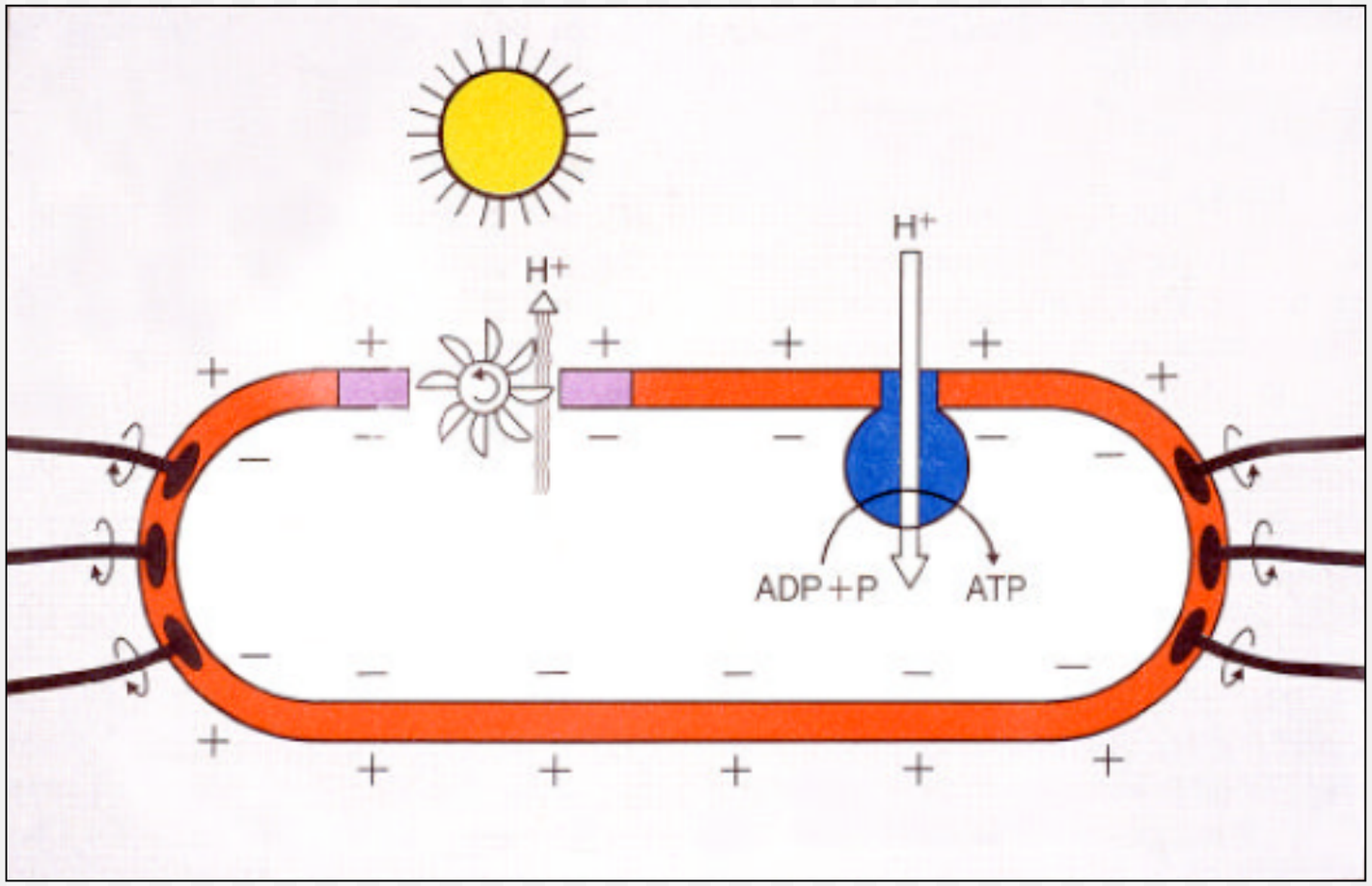


optical properties



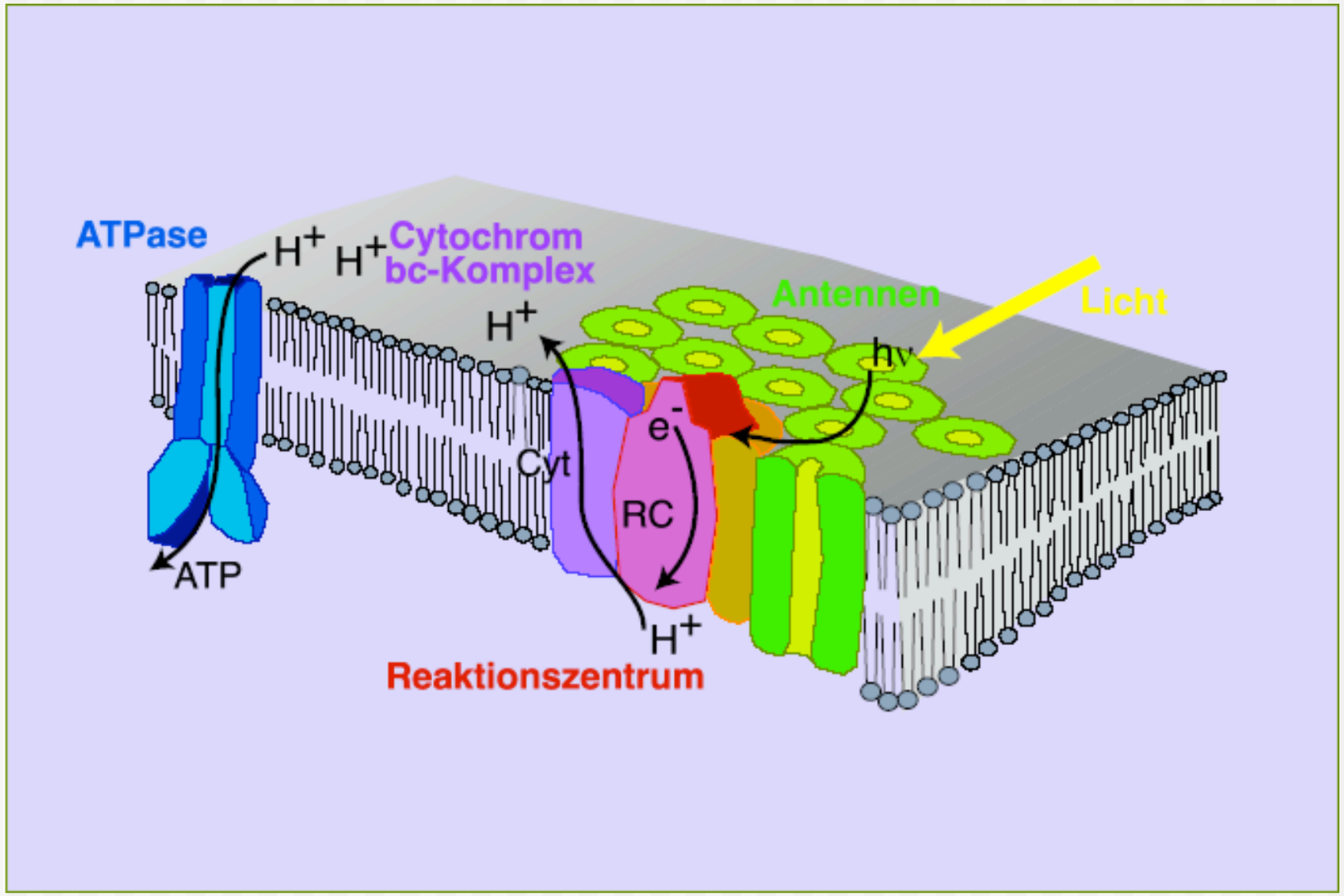


Bioenergetics: bacterial photosynthesis



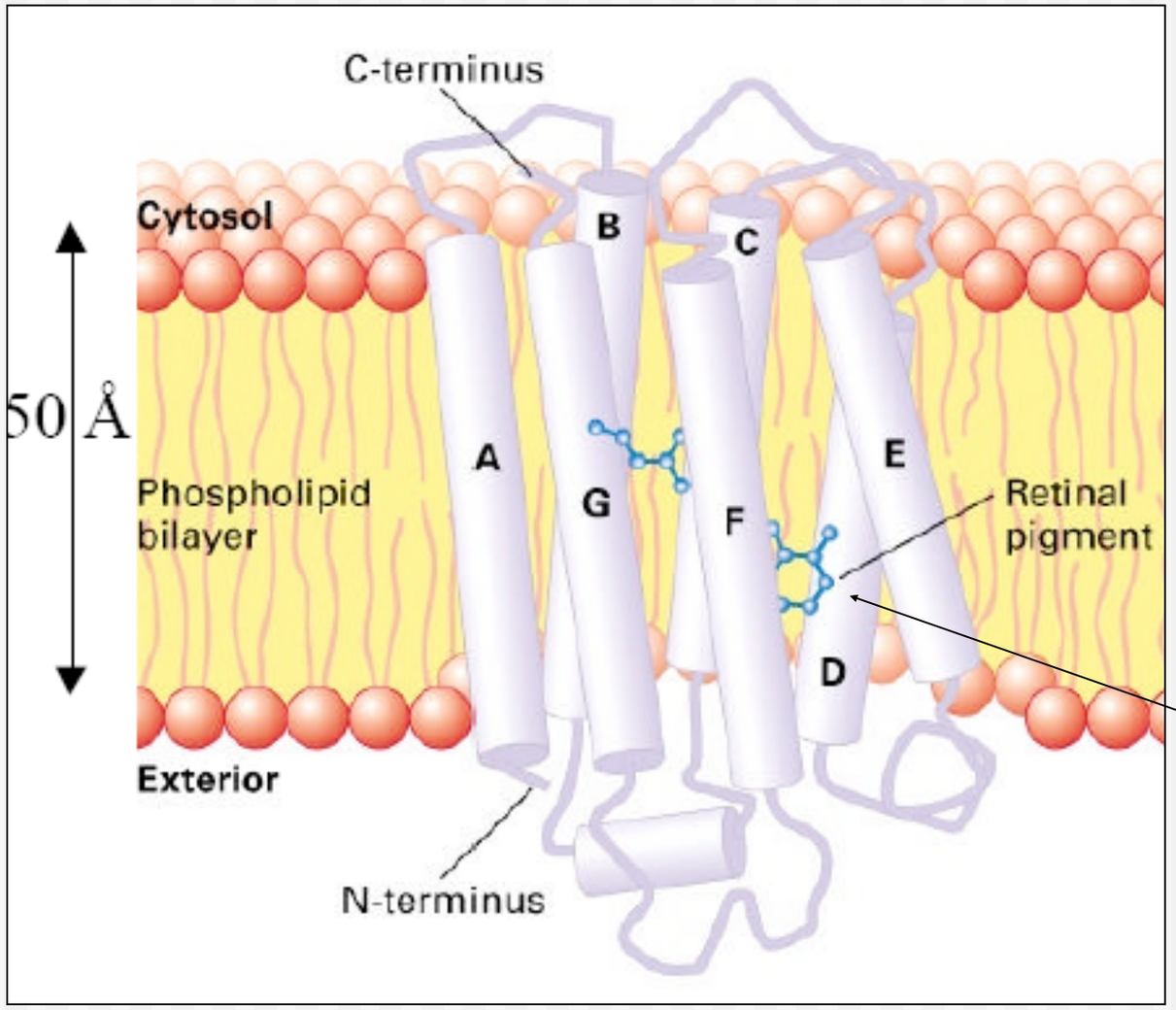
1) light absorption
2) proton transfer
3) ATP synthesis

Bacterial Reaction Center

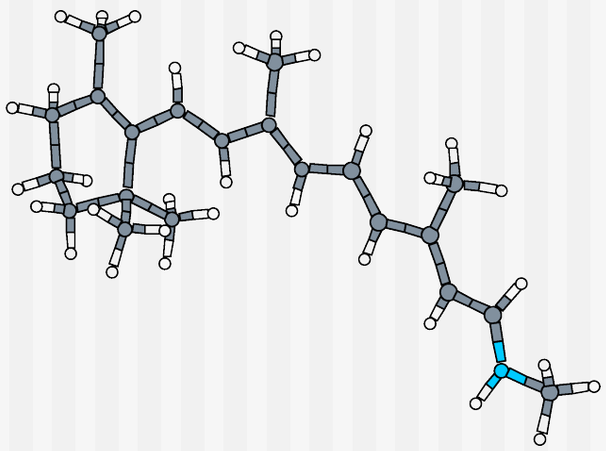


- photon absorption
- energy transfer
- electron transfer
- proton transfer
- Q_B movement:
  large structural transitions

Bacteriorhodopsin



- Transmembrane protein
- 7 α-helices
- retinal chromophor



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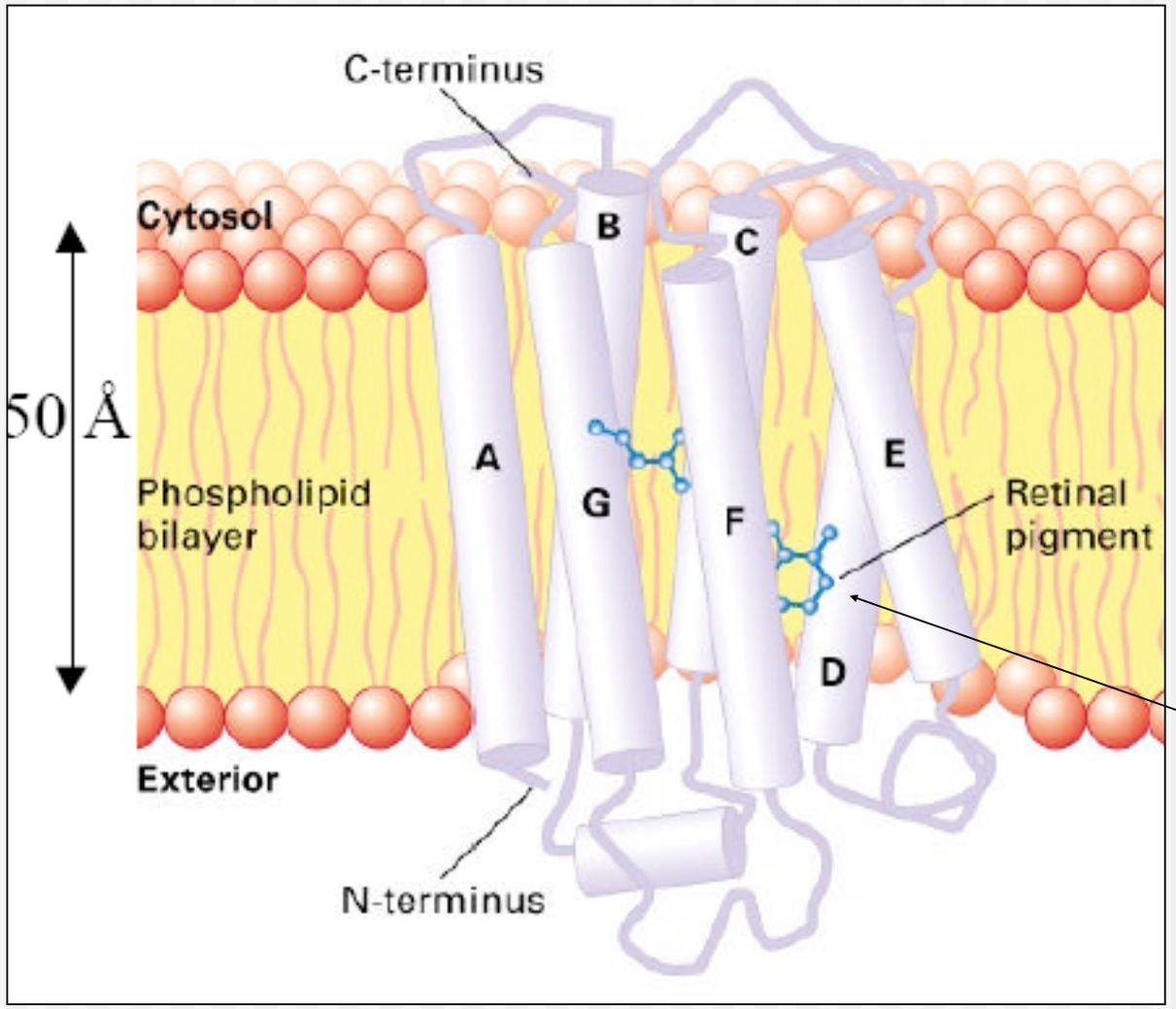

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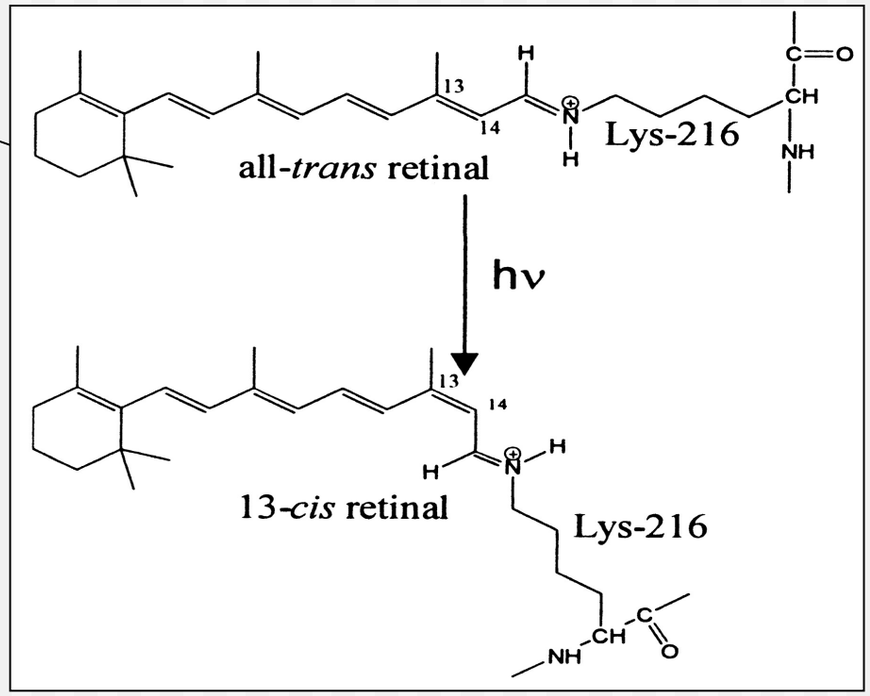

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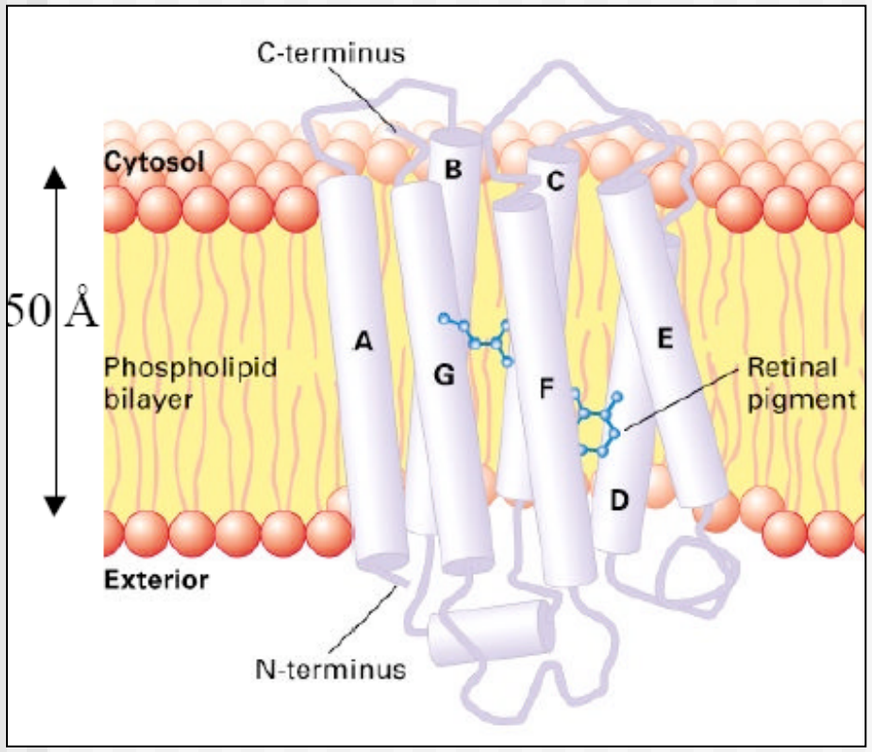
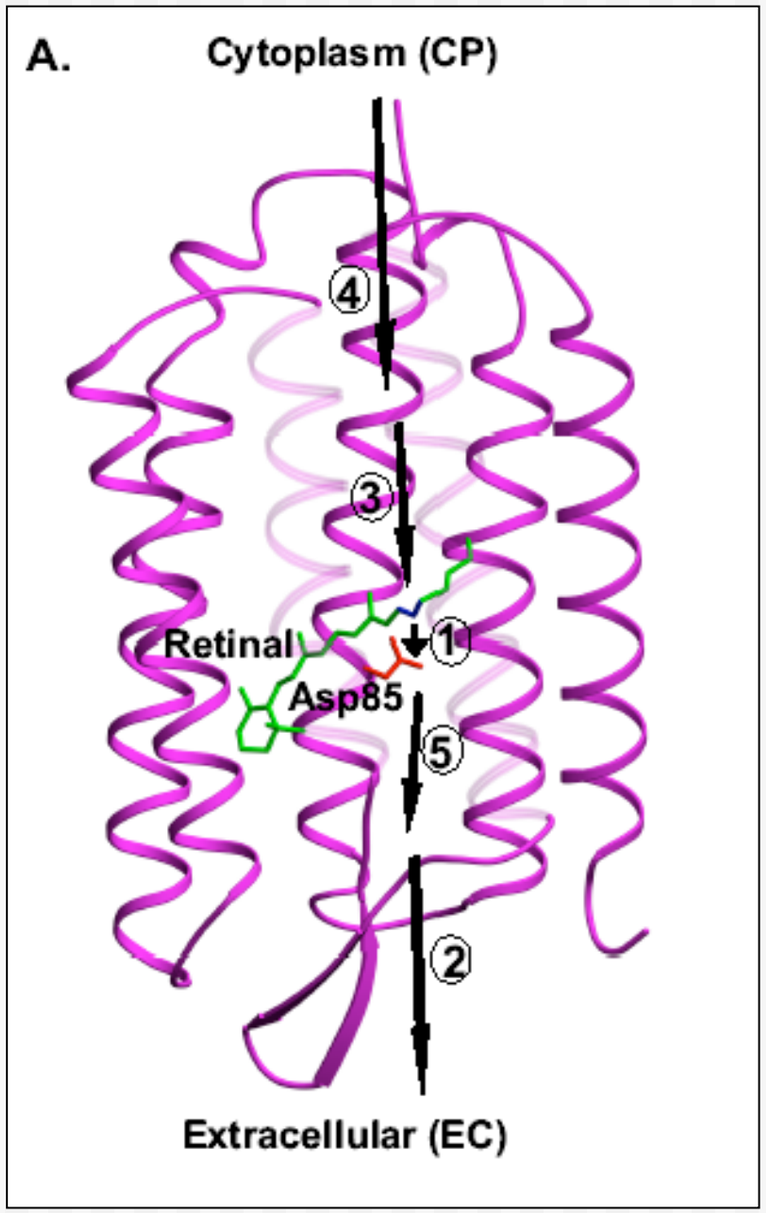


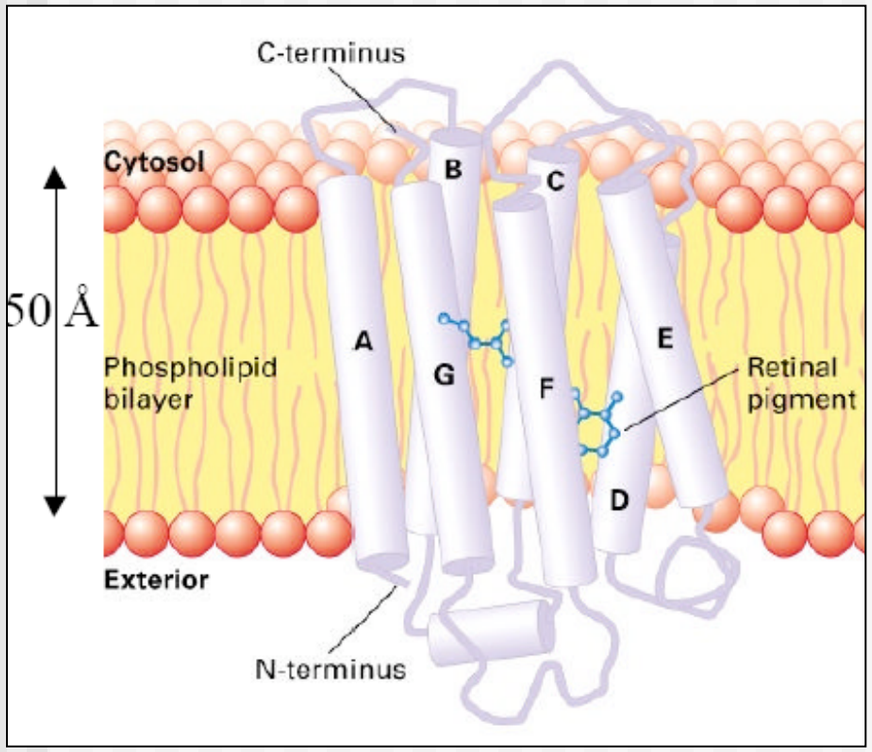


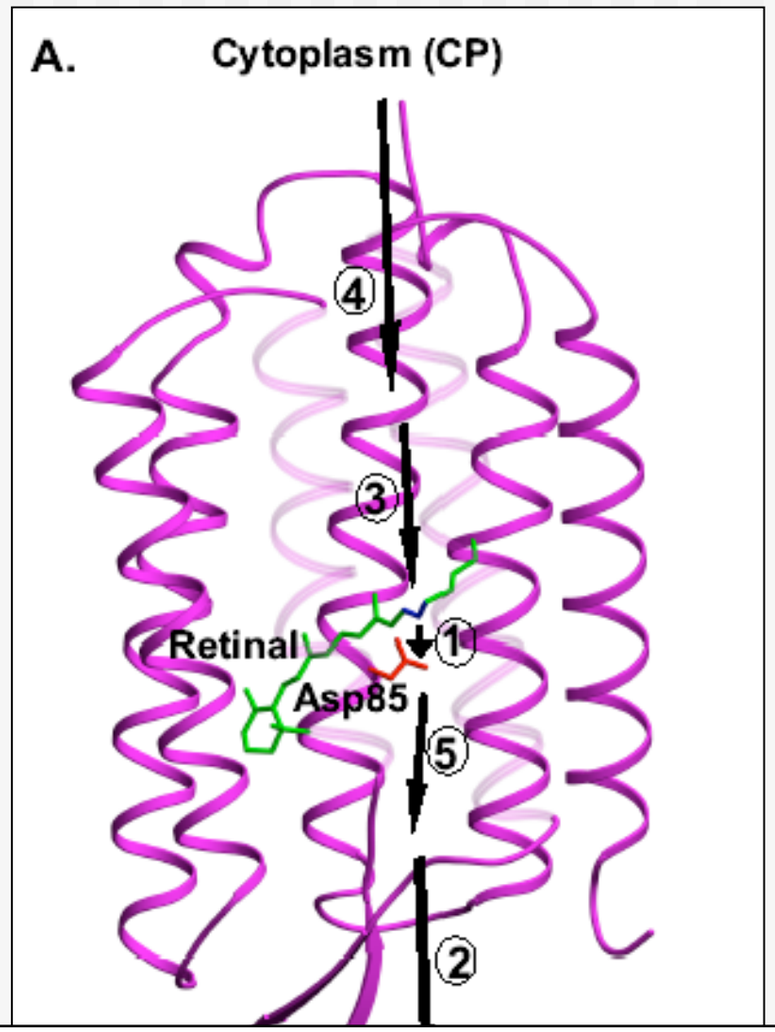
-pumps proton in 5 steps along photocycle

- structural information from x-ray
- IR/Raman/NMR spectra

However:
Complete bio-physical picture still missing

Bacteriorhodopsin





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- structural information from x-ray
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However:
Complete bio-physical picture still missing

excited states, proton transfer: need QM

Methods

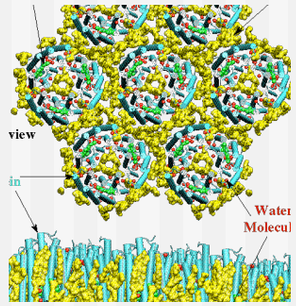
accuracy

empirical force fields

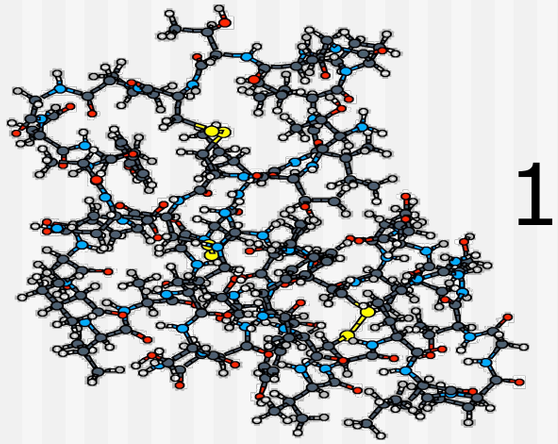
Semi-empirical methods (DFTB, MNDO etc.)

Hartree-Fock (HF), Density Functional Theory (DFT)

post-Hartree-Fock: MP2,CC, CI, MRCI ...

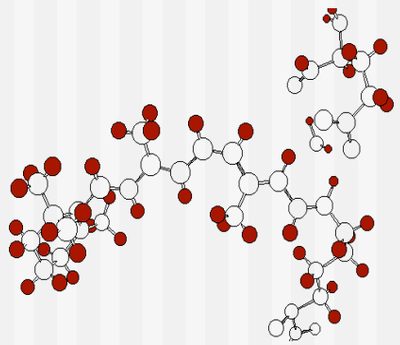


100k atoms



1000 atoms

100 atoms



10-50 atoms

speed

Methods in the QC toolbox

accuracy

Classical force fields
Molecular Mechanics (MM)

empirical potentials
fit to experiment

Semi-empirical methods

approximations
fit to exp. data

Hartree-Fock (HF), Density Functional Theory (DFT)

perturbation theory
'better wave-function'

post-Hartree-Fock:
MP2,CC, CI, MRCI ...

Semi-empirical /approximate methods

approximation, neglect and parametrization of interaction integrals from ab-initio and DFT methods

-HF-based:

CNDO, INDO, MNDO, AM1, PM3, MNDO/d, OM1,OM2

-DFT-based:

SCC-DFTB,

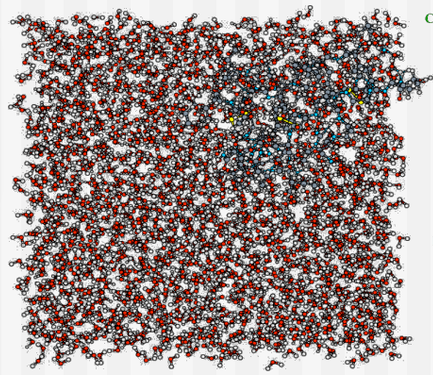
~ 1000 atoms, ~ ns MD

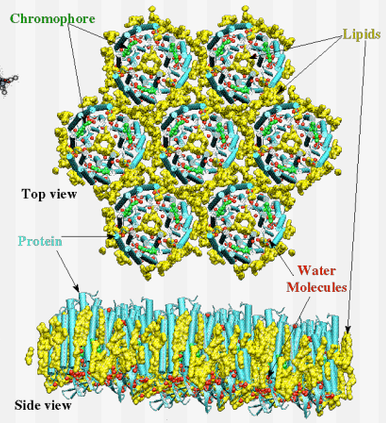
Spectrum of methods

Size and simulation time lime each other

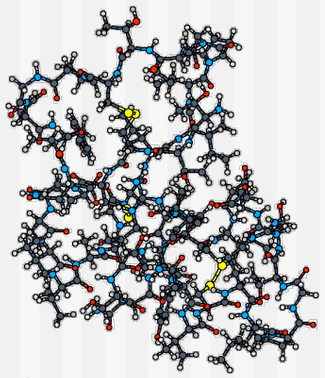
contiuum methods
"Coarse graining"

MM

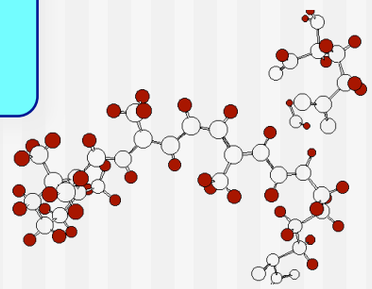




SE



HF, DFT



CI, MP
CASPT2

ns

ps

fs

time

nm

10

100

1000

10.000

atoms

Length
scale

‘speeding up QM’

Semi-empirical methods

Hartree-Fock (HF), Density Functional Theory (DFT)

integrals

solution of linear equations

post-Hartree-Fock: MP2,CC, CI, MRCI ...

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Hartree-Fock (HF), Density Functional Theory (DFT)

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integrals → **integral approximations**

solution of linear equations → **linear-scaling**

parallelization

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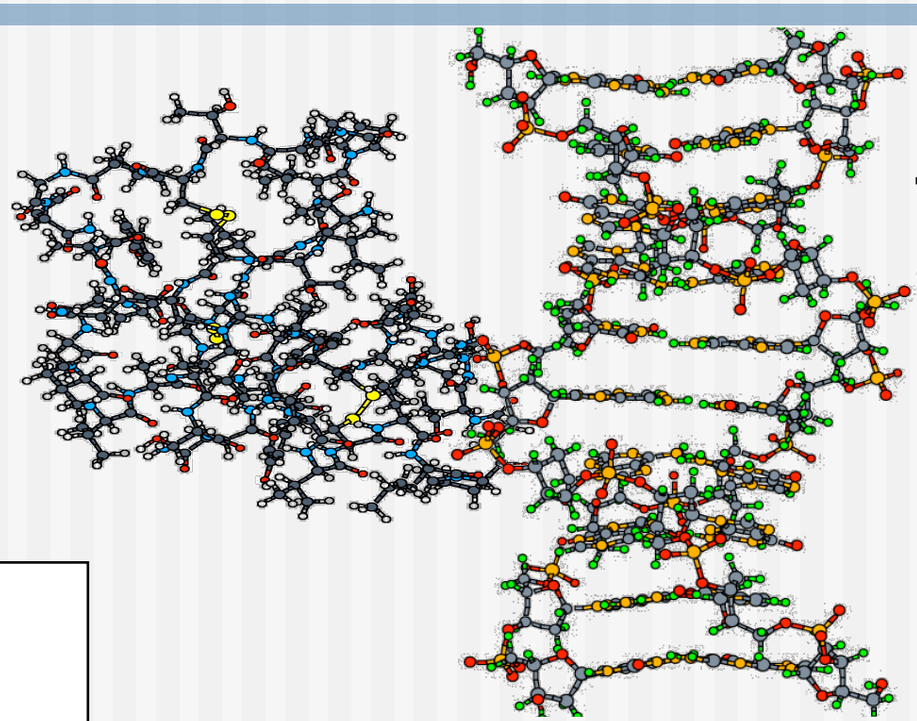

treatment of 1000 atoms with DFT/MP2 possible: e.g.

Siesta

Turbomole

…

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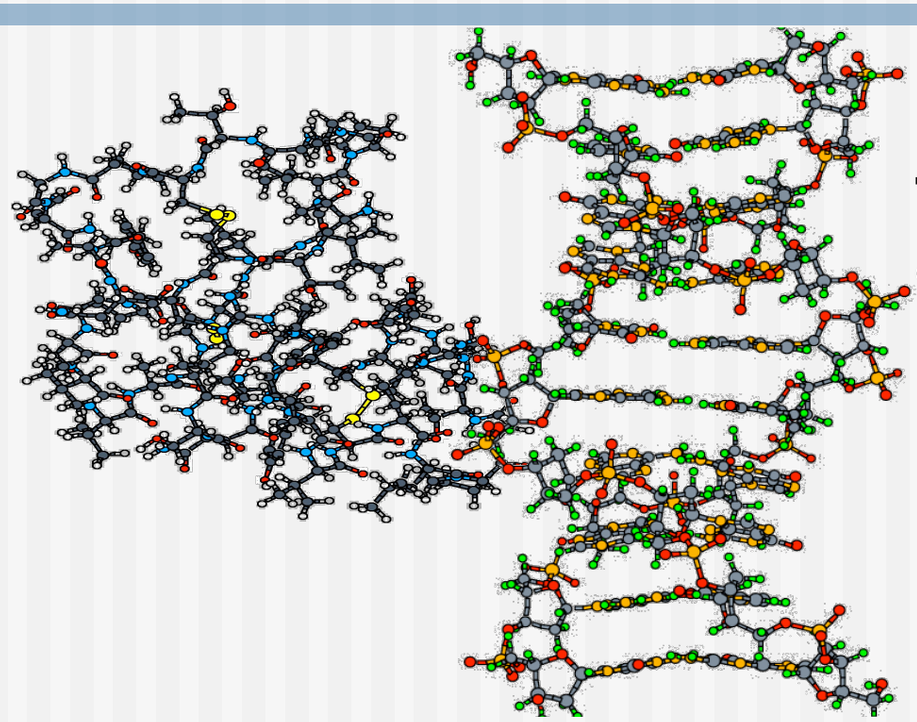

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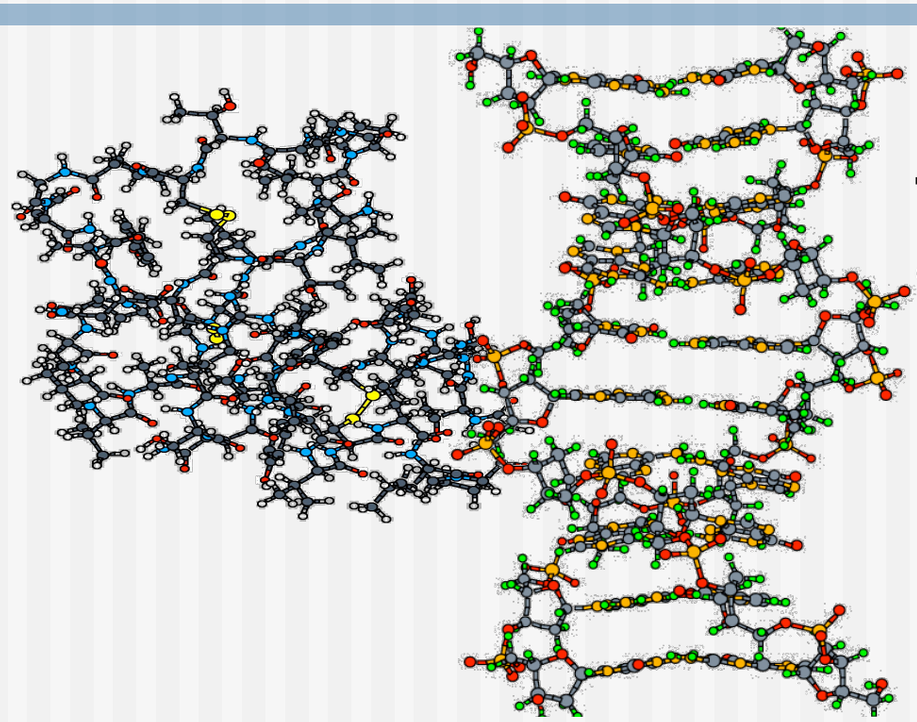

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- free energy vs potential energy

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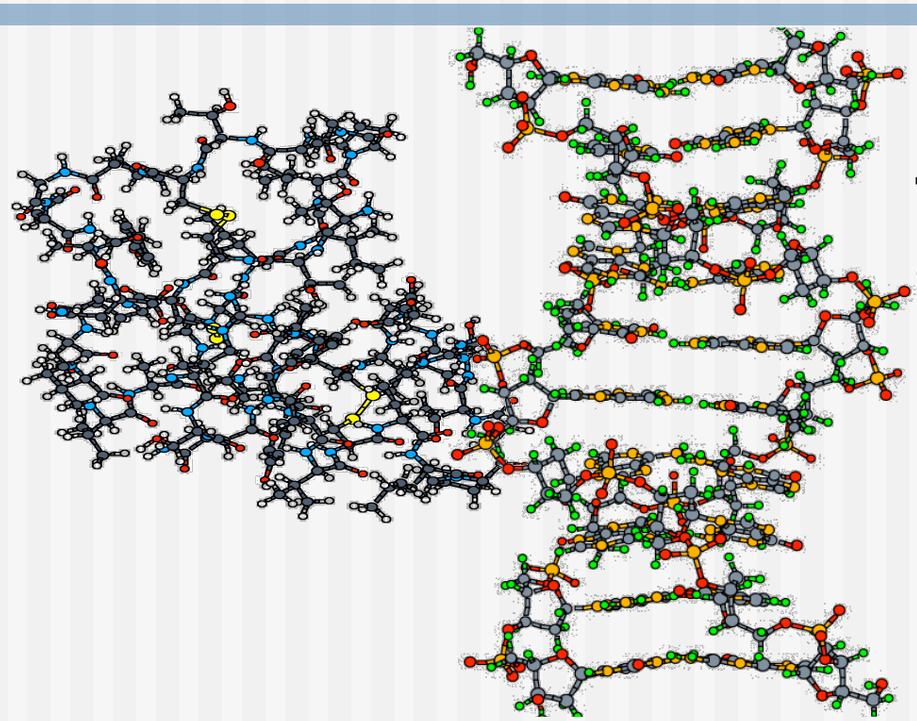

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Turbomole
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problem:

only ‘one’ (or few) structures

NEGLECTED:

- dynamics
- free energy vs potential energy

can be even more important than accurate total energy!

todays view on DFT

Still most important method and widely applied, however:

- too slow for many interesting problems:

100 atoms
10 ps

- too inaccurate for many interesting problems:

VdW interactions
electronic excited states
reaction energies (e.g. PT)
...

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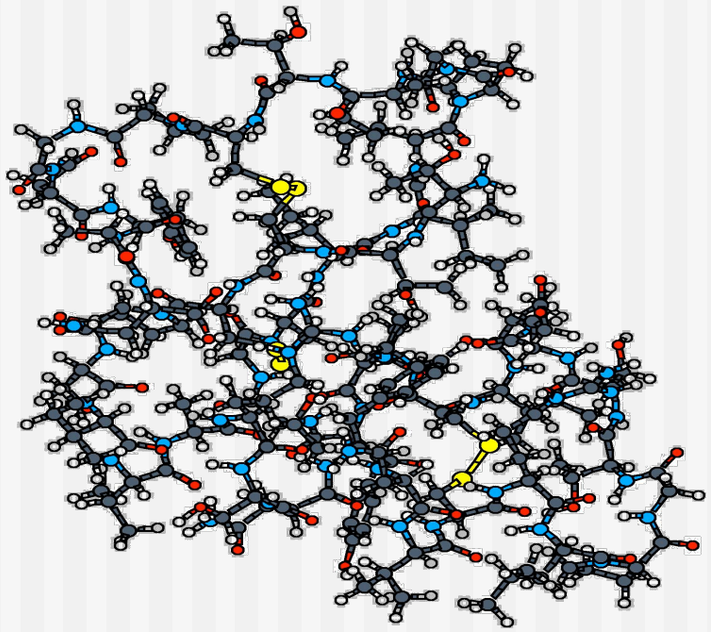
to model the variety of biological processes, one needs the WHOLE toolbox of QC, i.e.

faster AND more accurate methods

Characteristics of biological systems

1. Although looking chaotic, well ordered structure in terms of electrostatic interactions



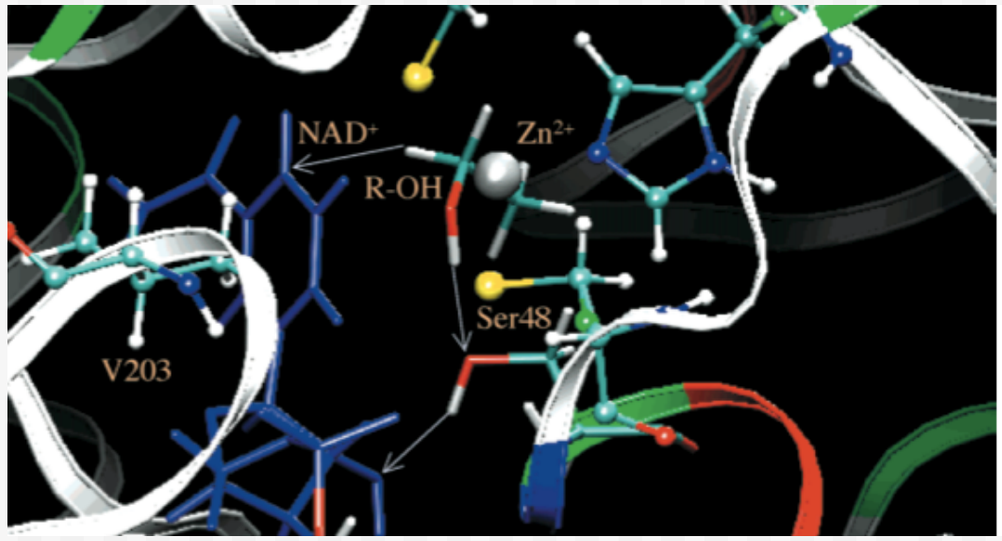
Understanding the action of enzymes

(Warshel, Annu. Rev. Biophys. Biomol. Struct. 2003. 32:425–43**)**

• in most proteins: catalytic effect due to electrostatic interaction with protein environment!

less important:

- ‚desolvation‘
- steric effects
- ‚near attac conformation‘ (NAC)
- ‚coherent dynamics‘



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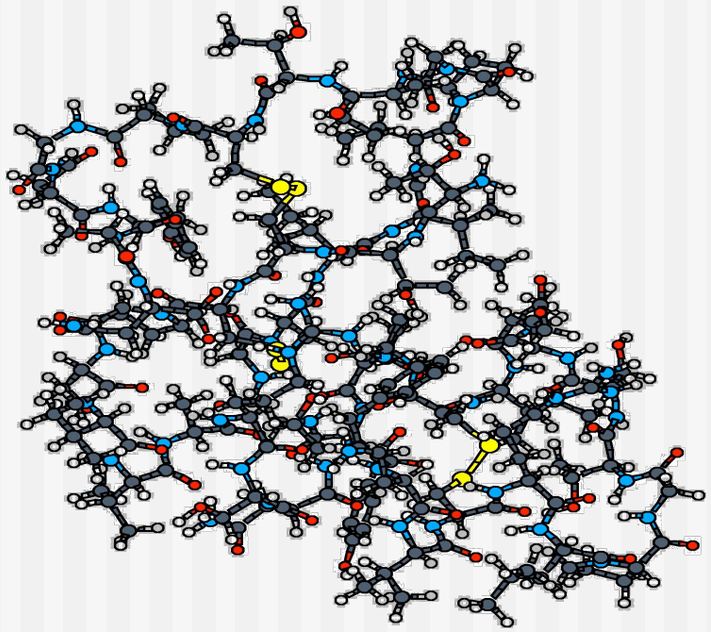

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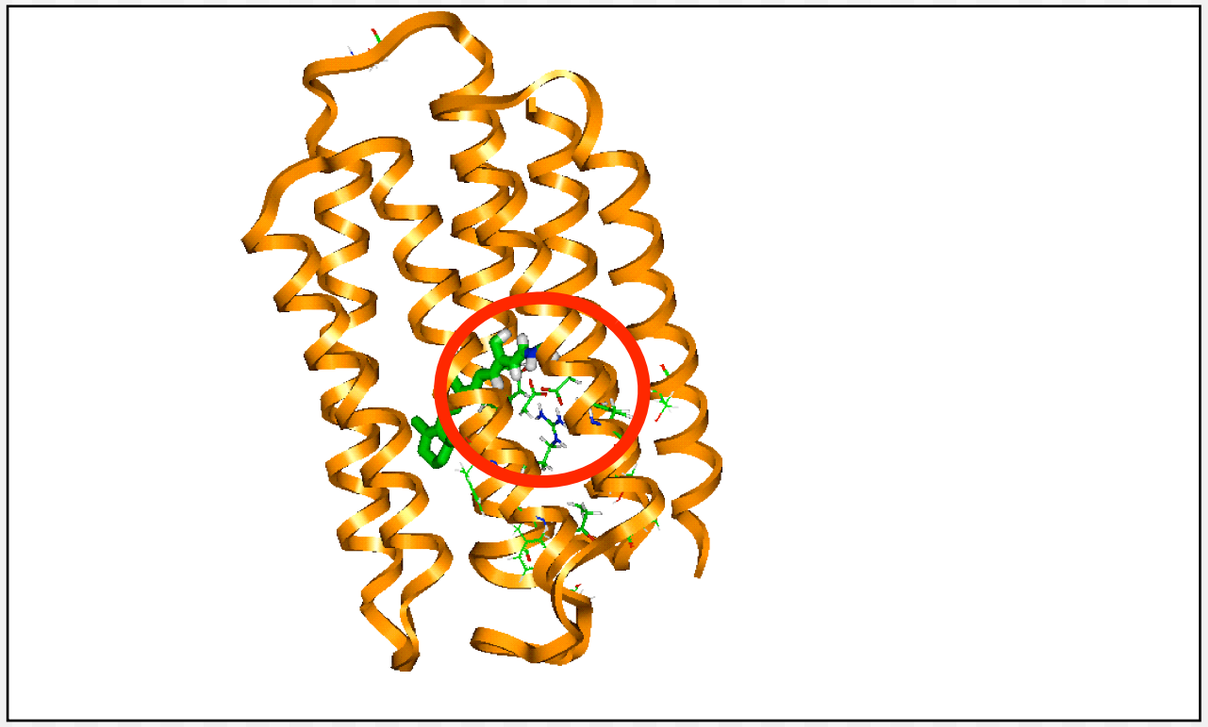

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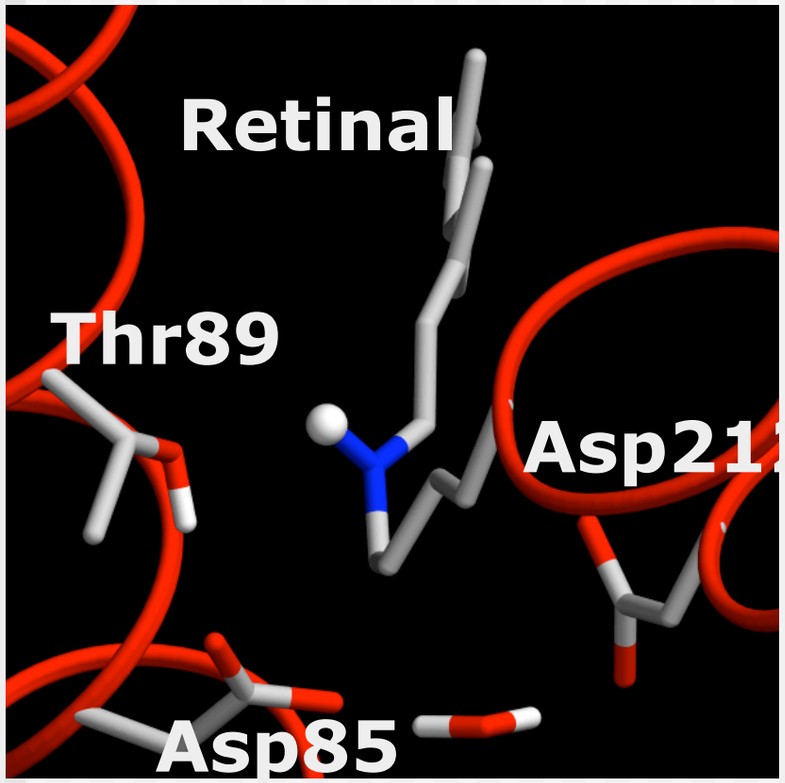

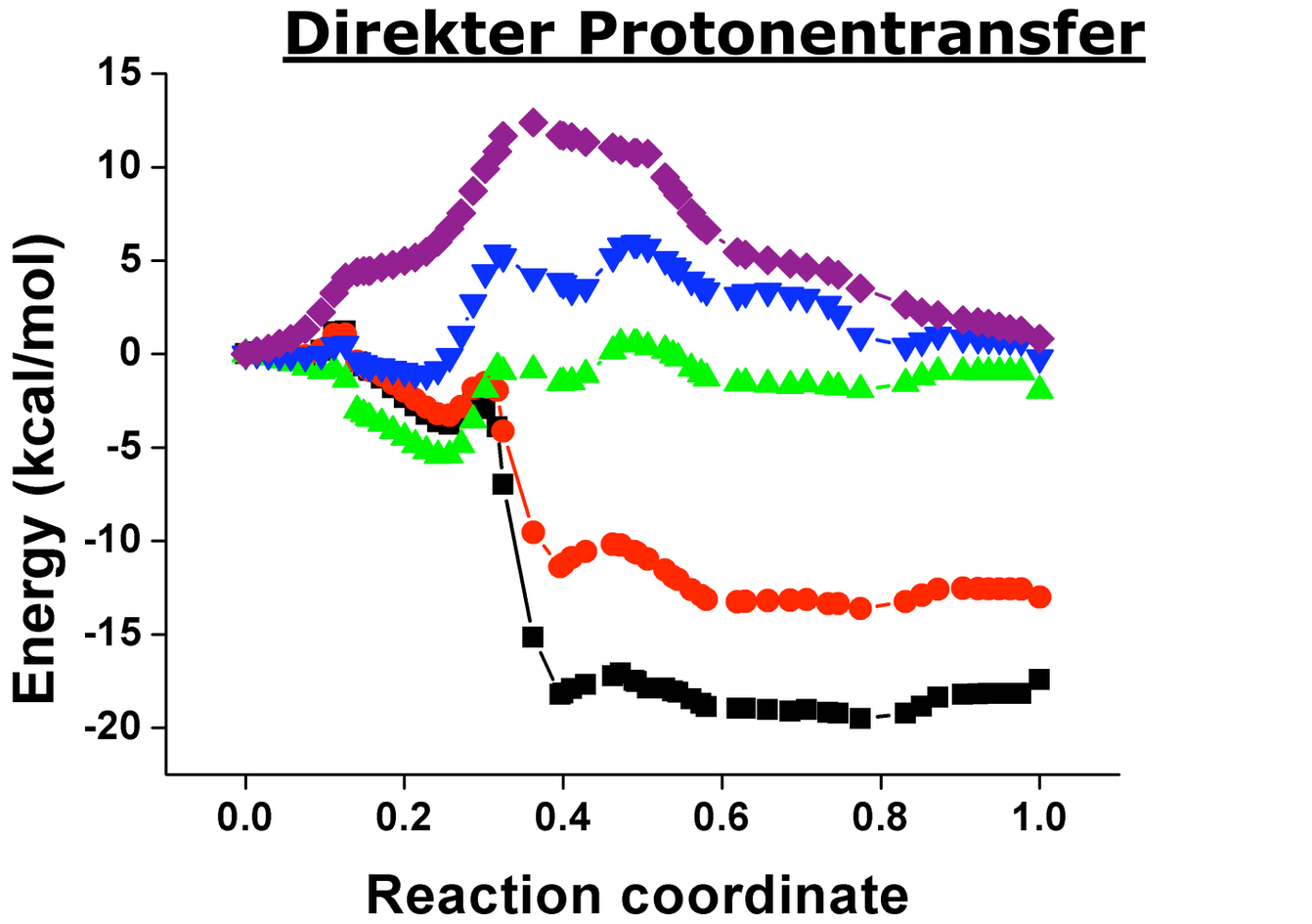

- whole protein contributes to reaction barrier
- ‘special design’ in order to provide specific function

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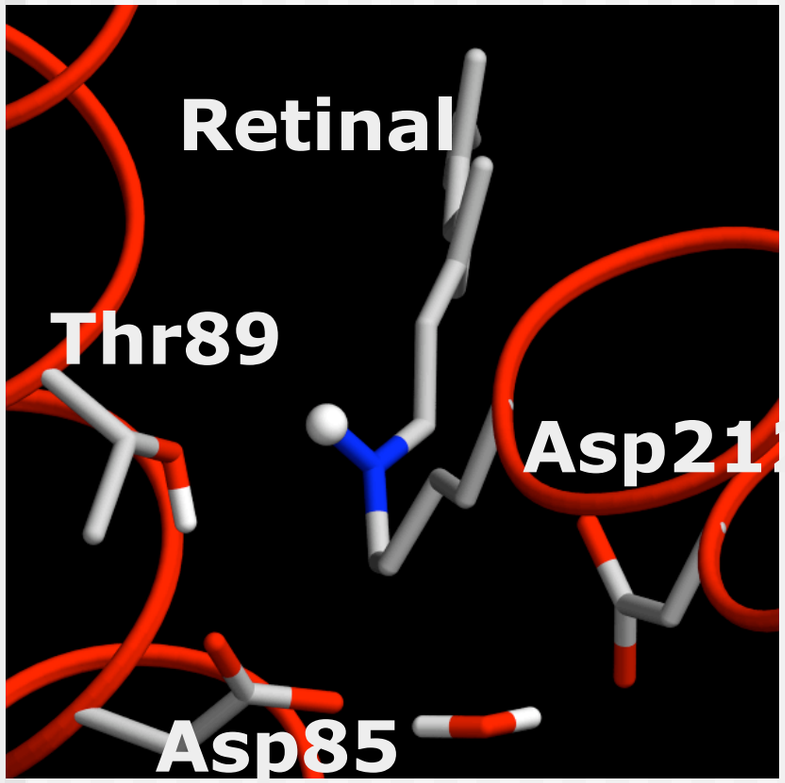

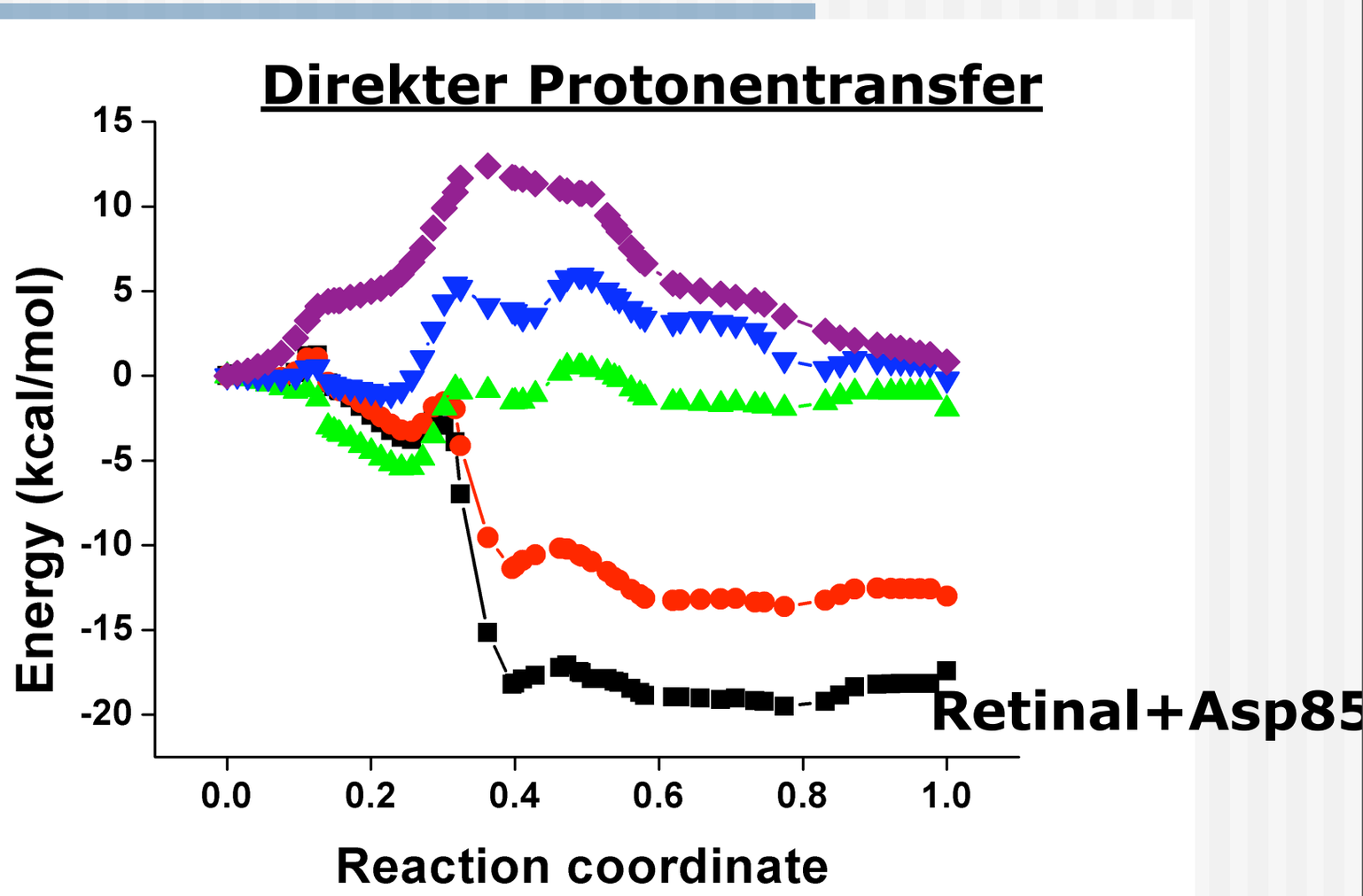

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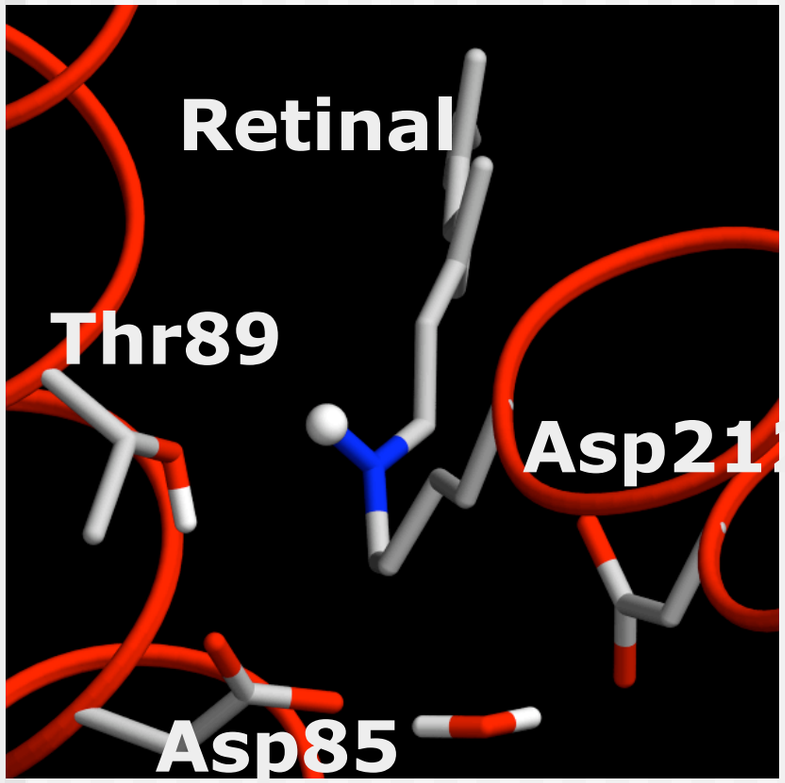

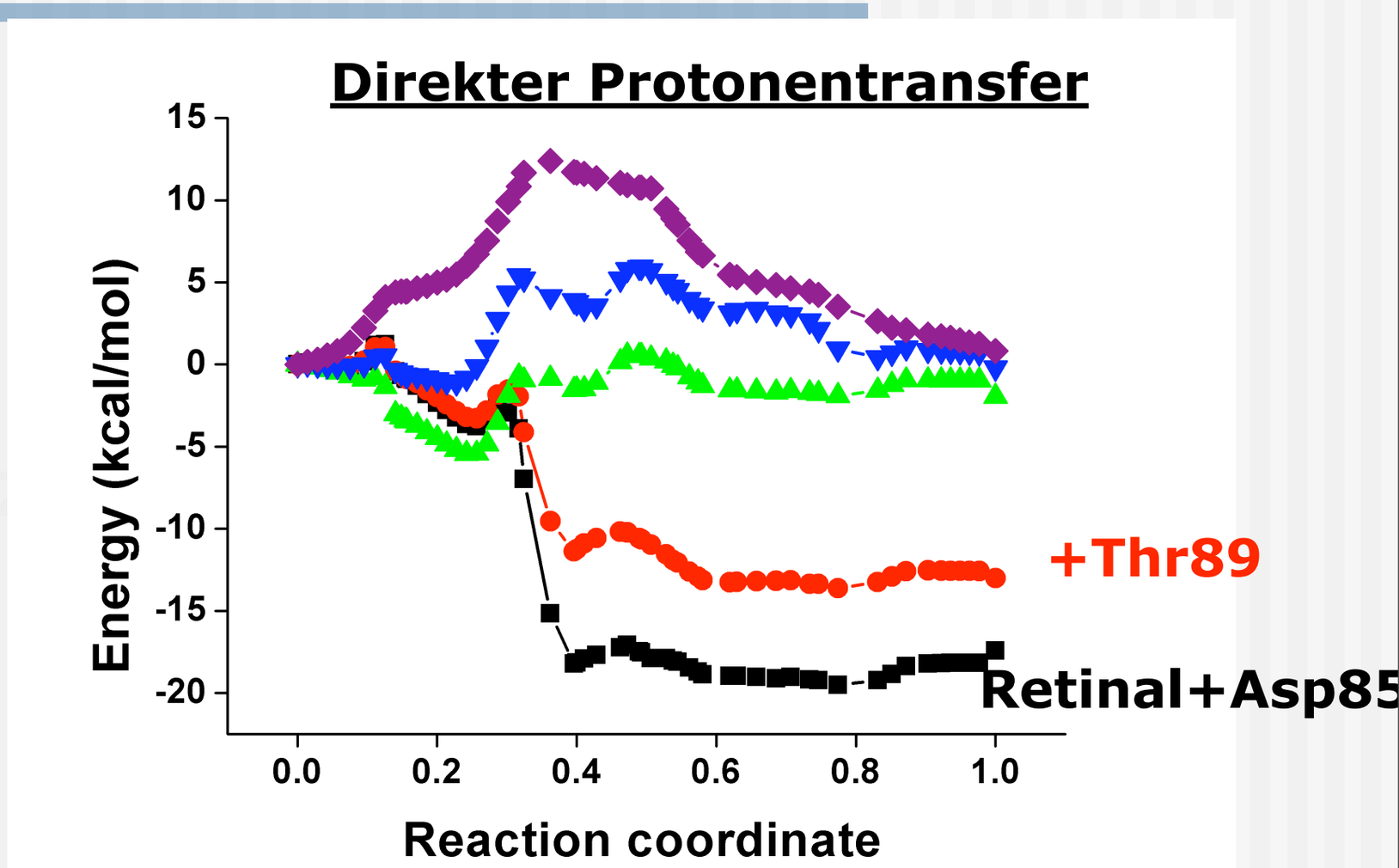

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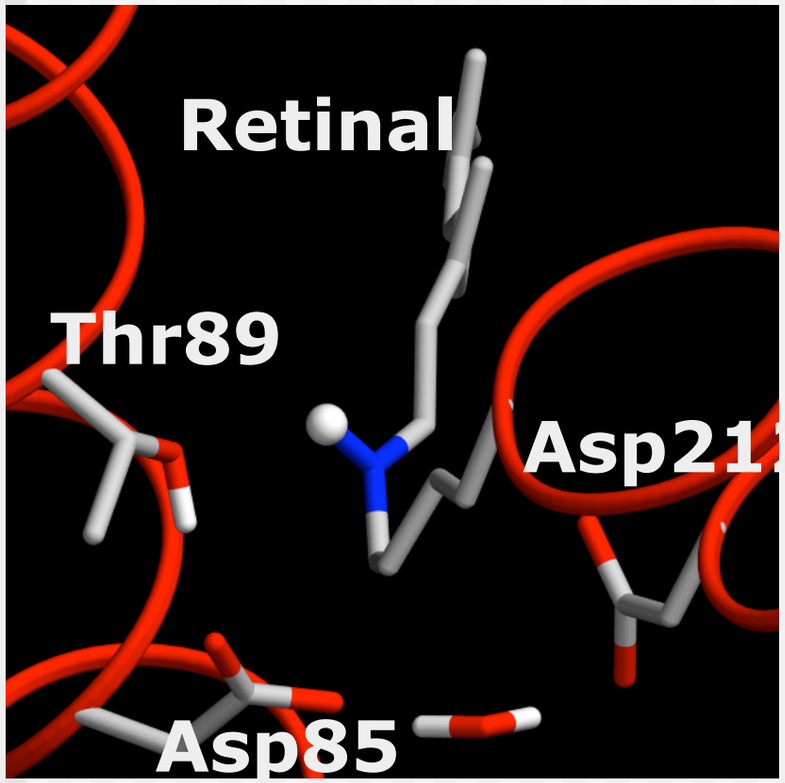

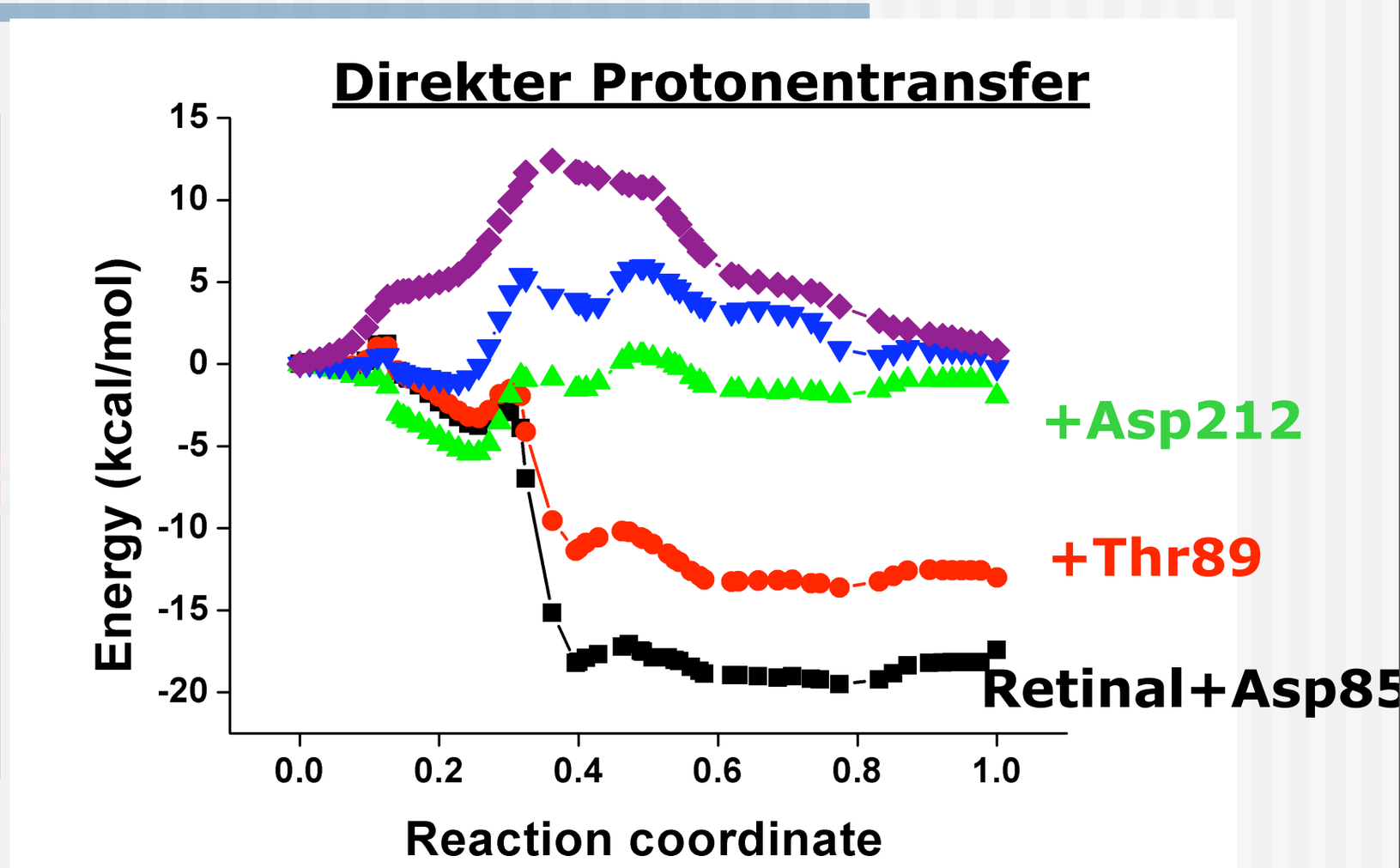

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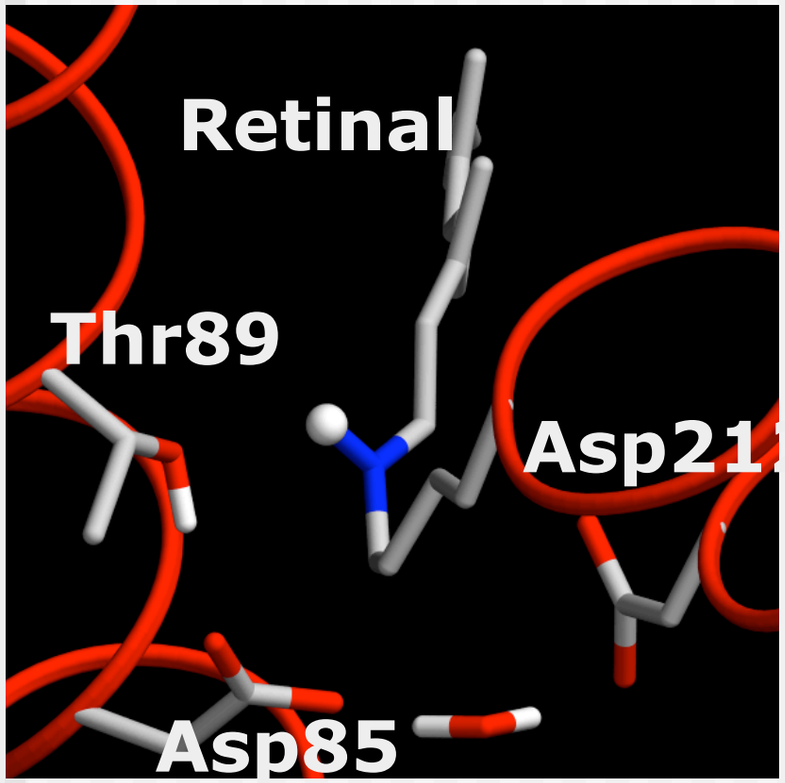

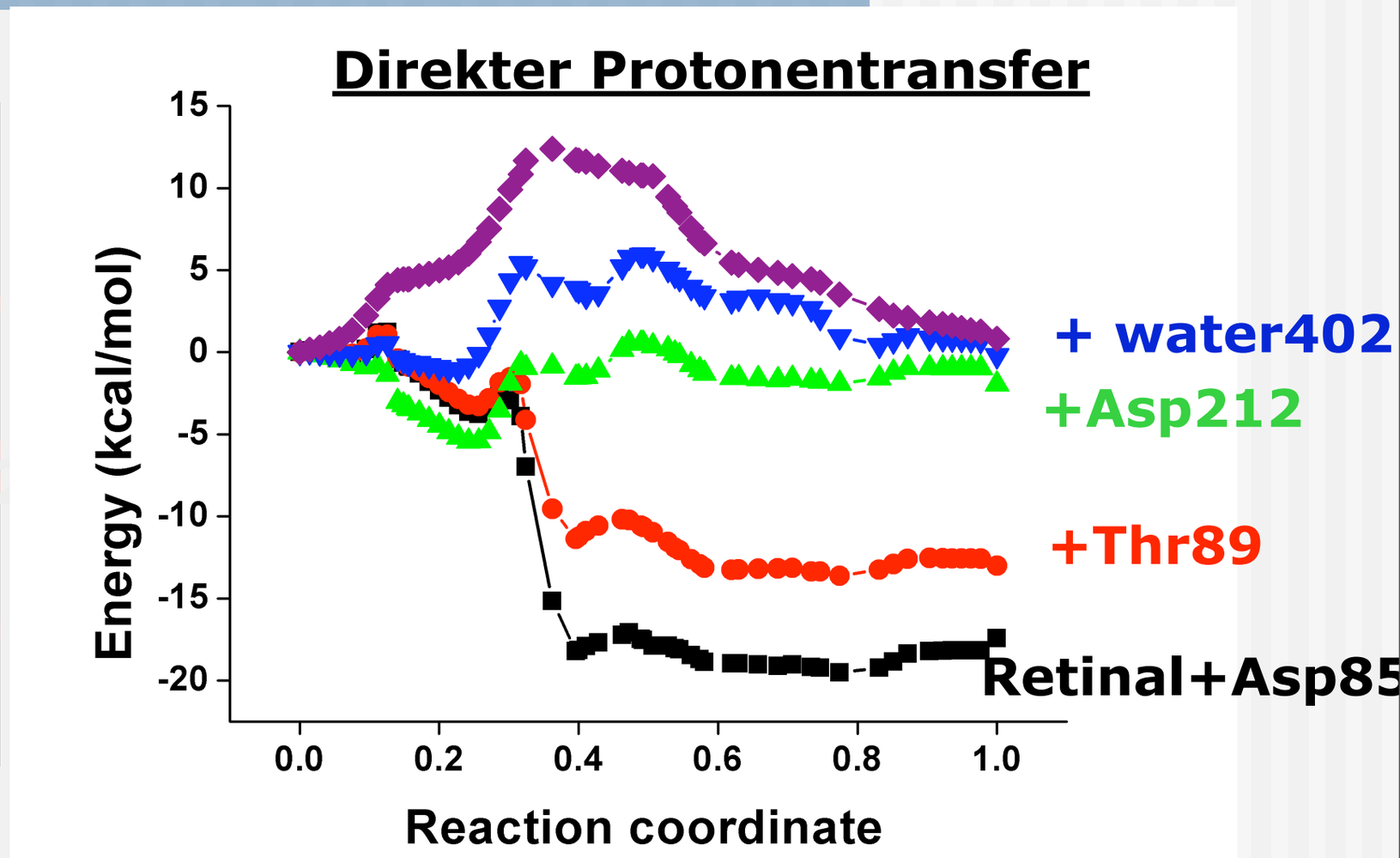

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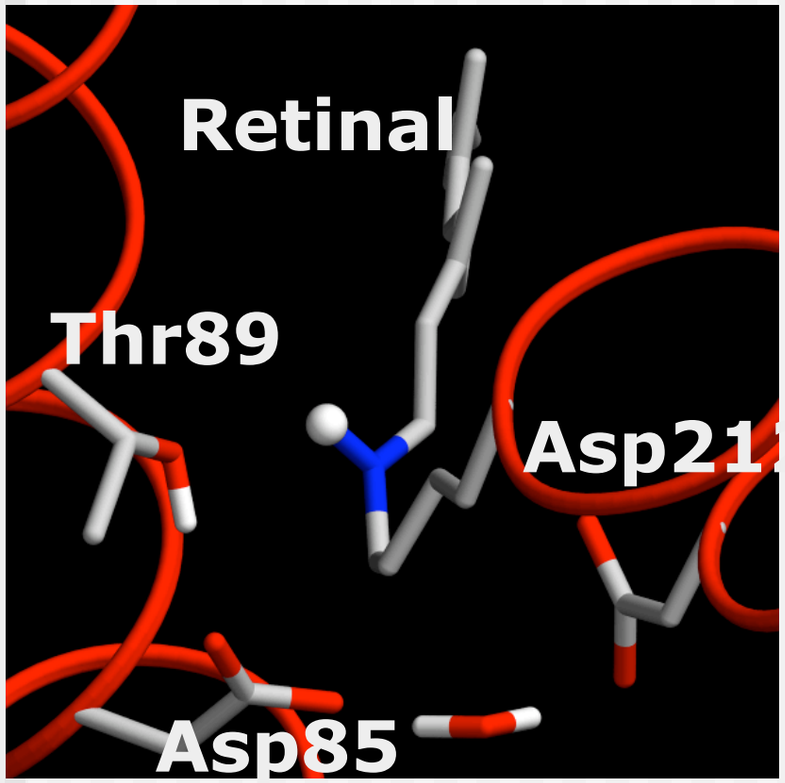

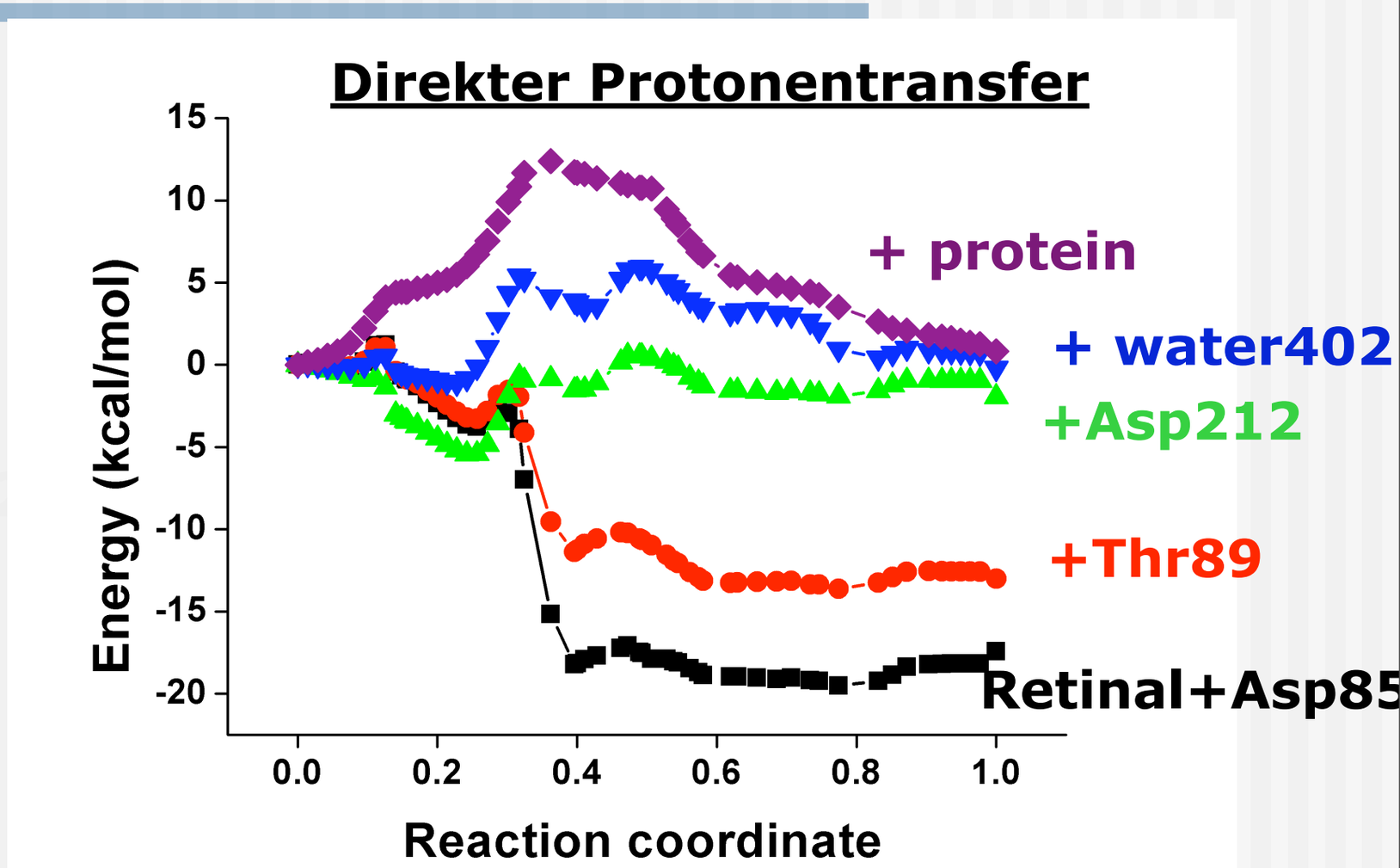

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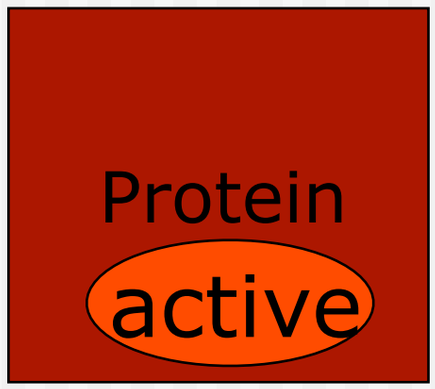
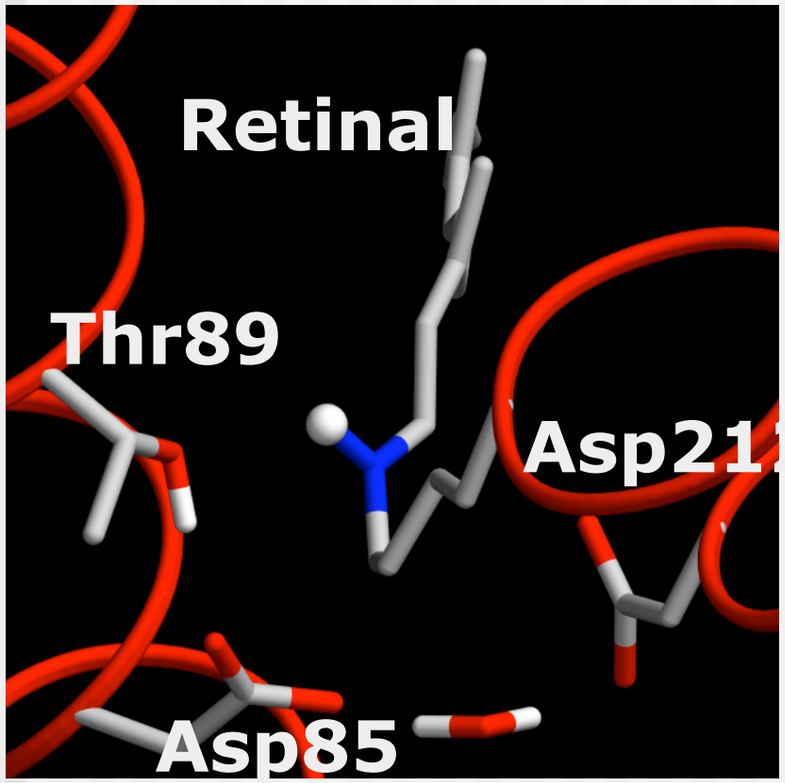
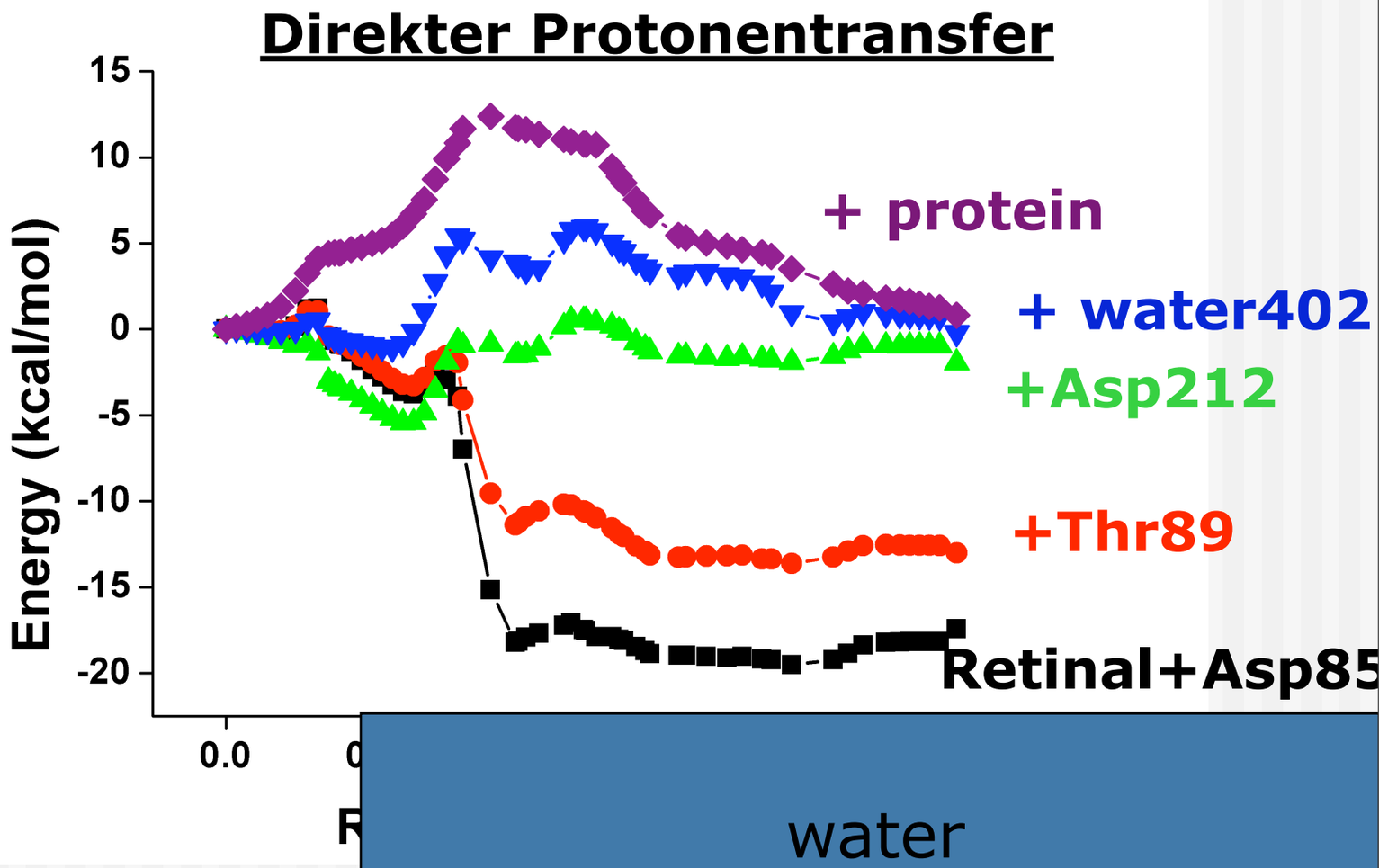


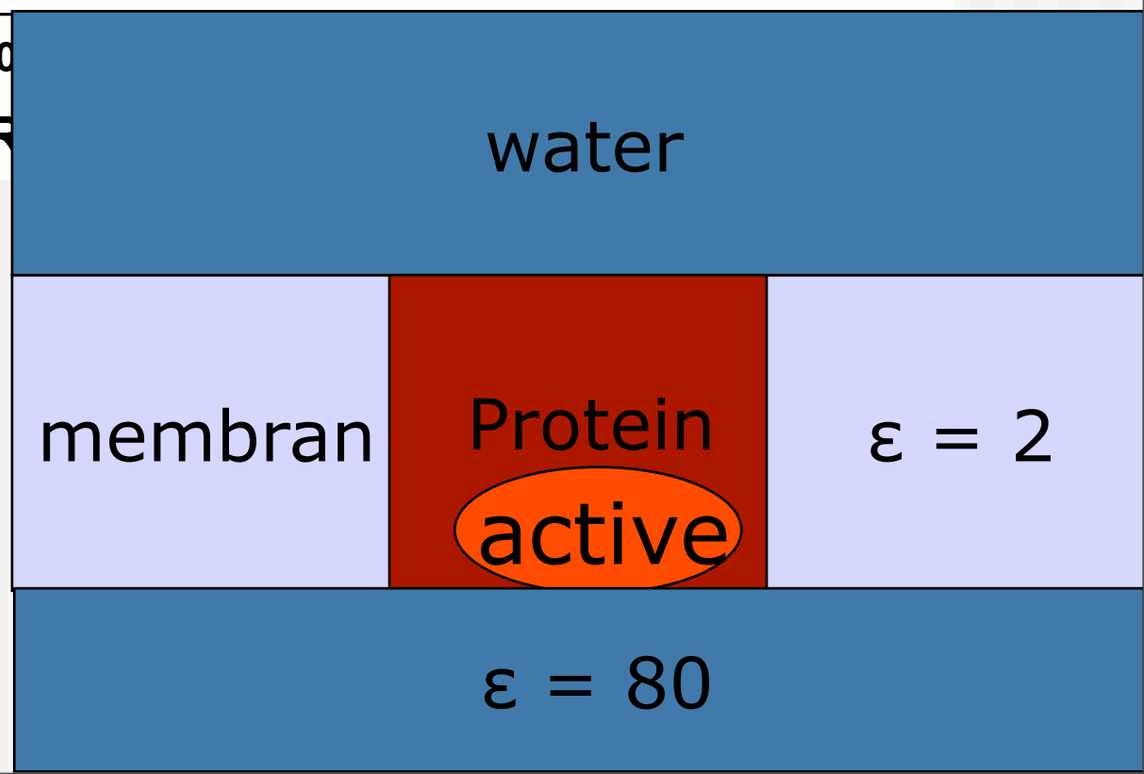
1. Although looking chaotic, well ordered structure in terms of electrostatic interactions



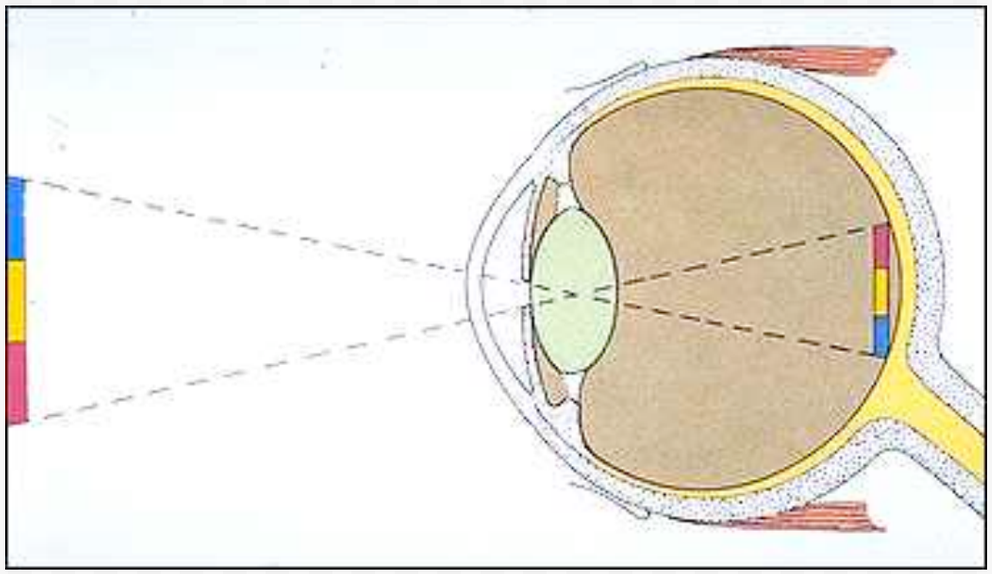


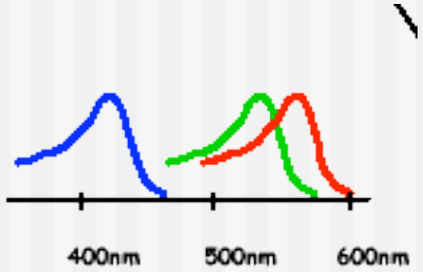
- whole protein contributes to reaction barrier
- ‘special design’ in order to provide specific function

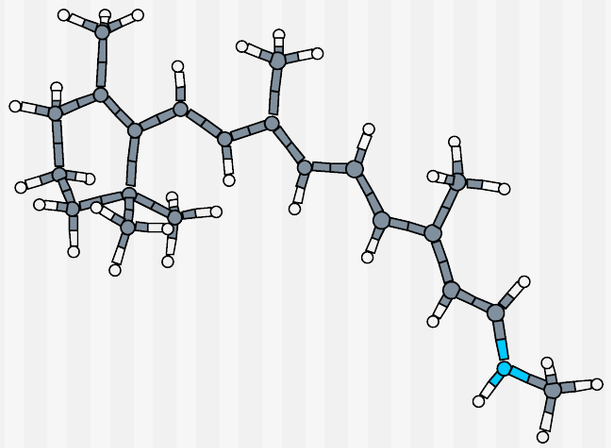
•often even water environment of importance

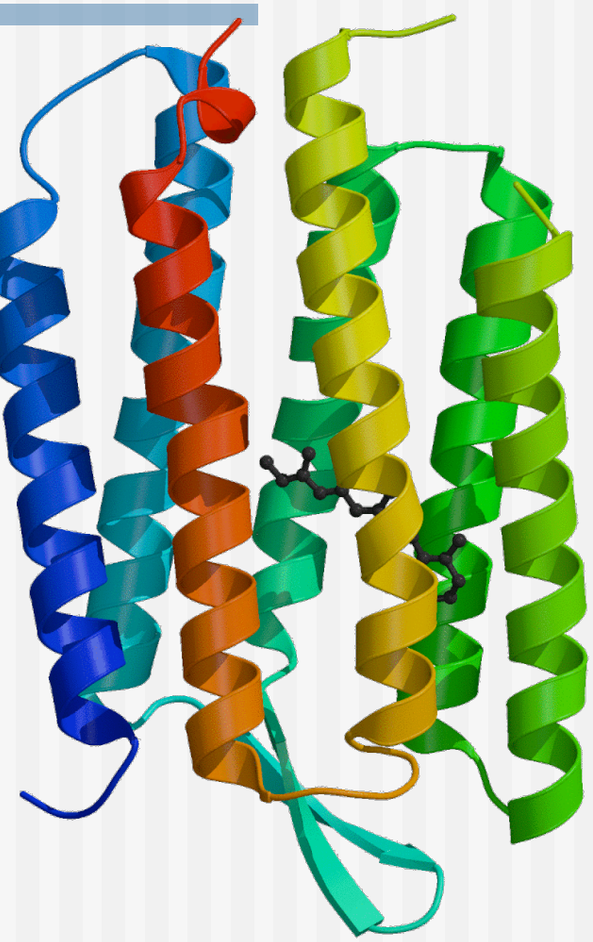


Process of vision









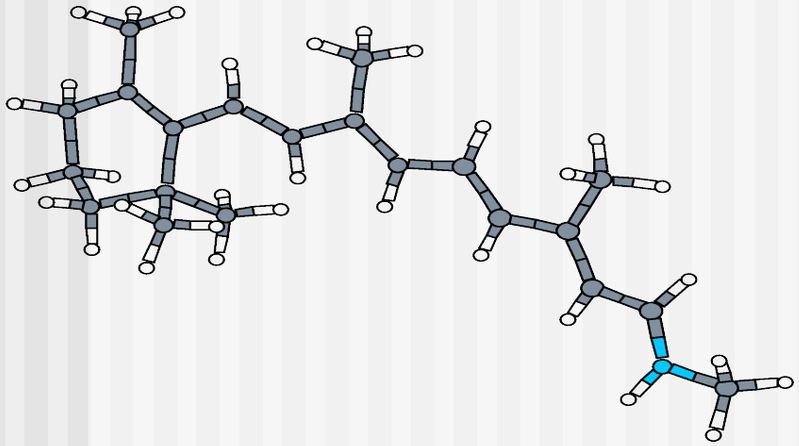
three color pigments, same chromphor:

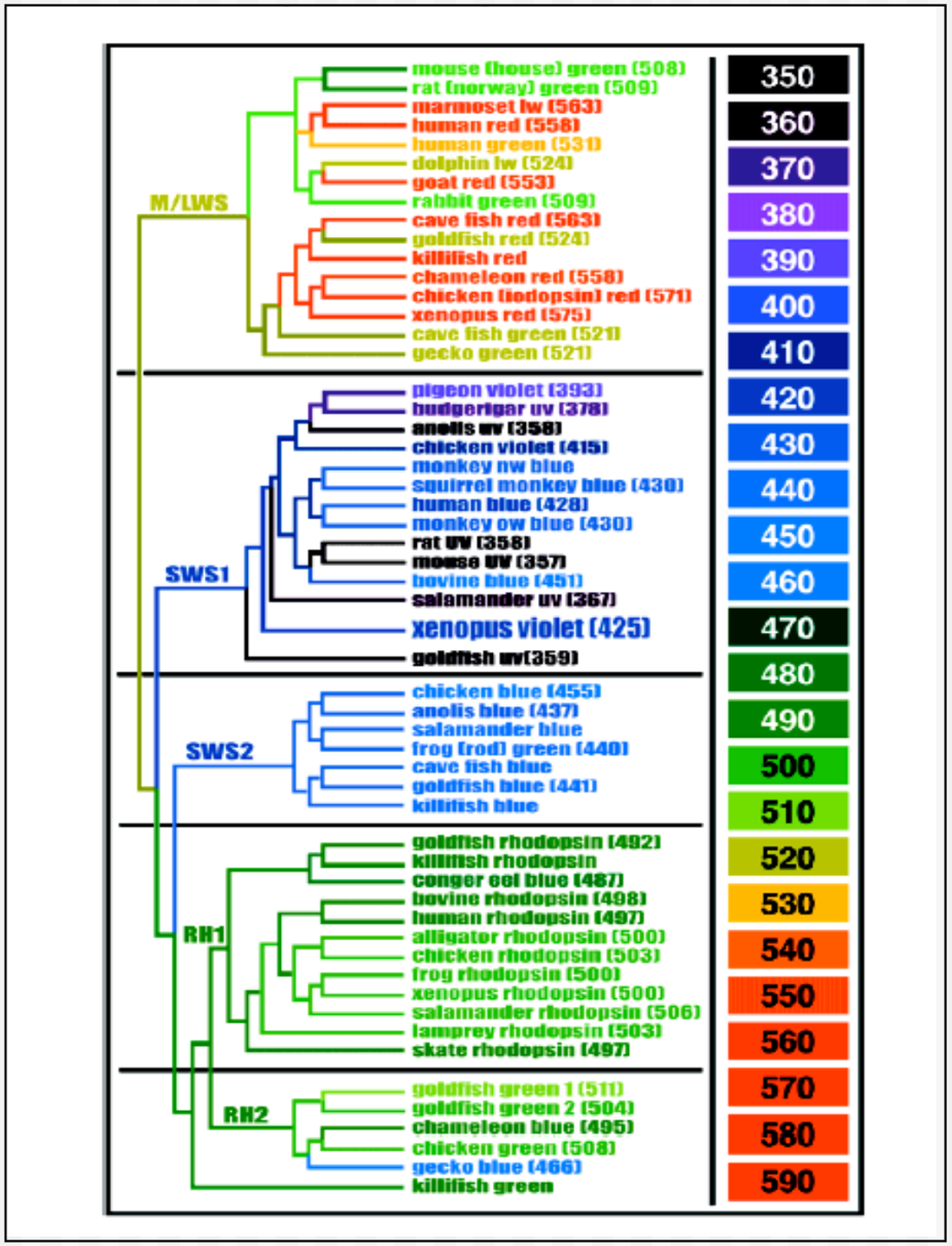
what determines the absorption maximum?

‘Spectral tuning’

Absorption over 300 nm

“Tuning” due to protein environement (opsin-shift)

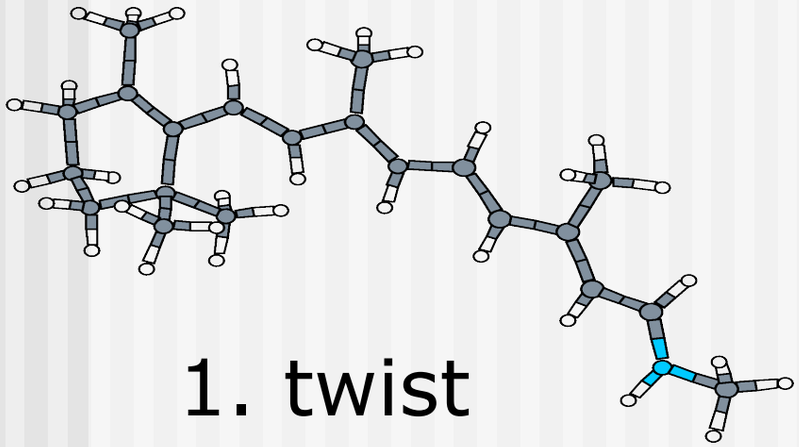




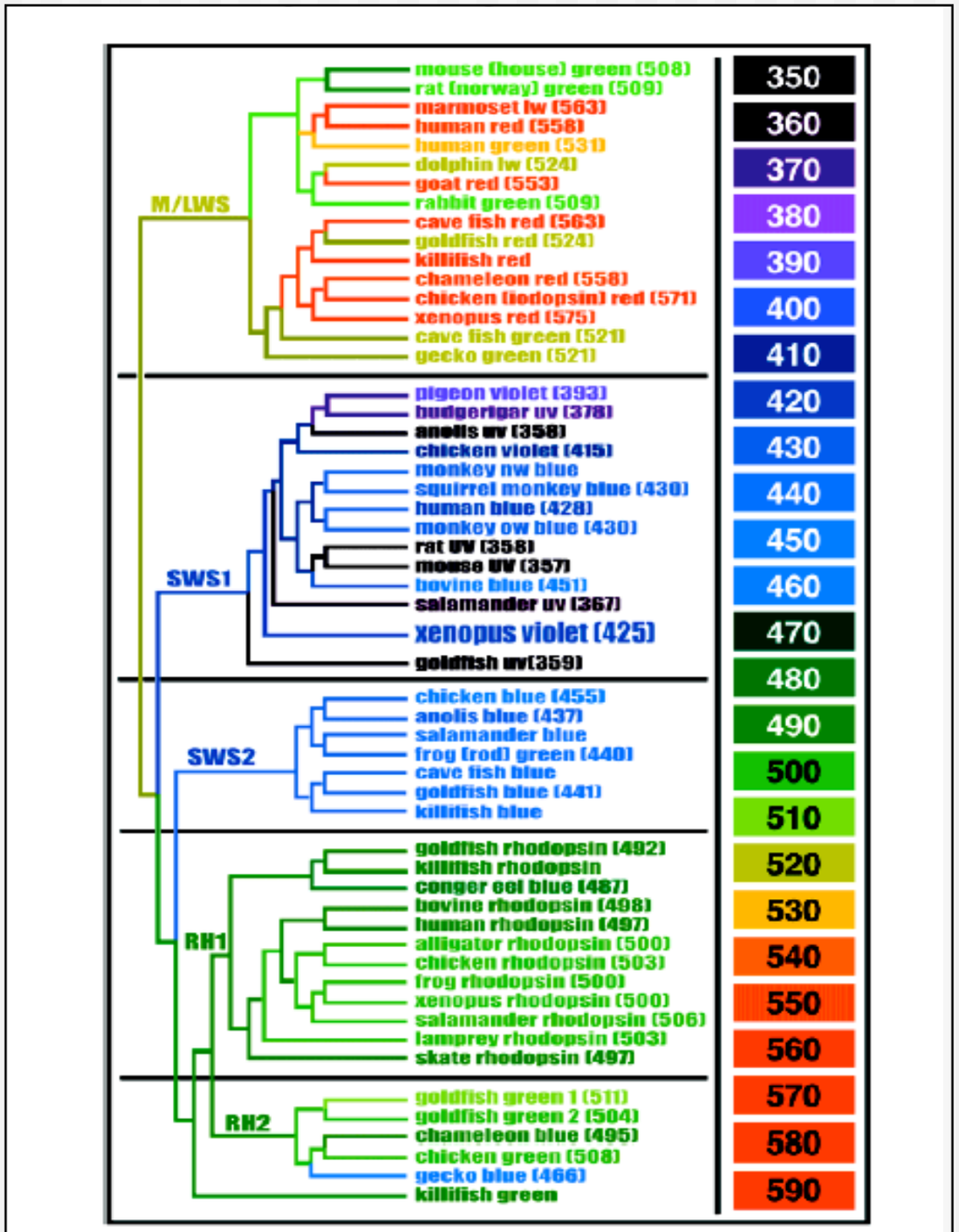
‘Spectral tuning’

Absorption over 300 nm

“Tuning” due to protein environement (opsin-shift)



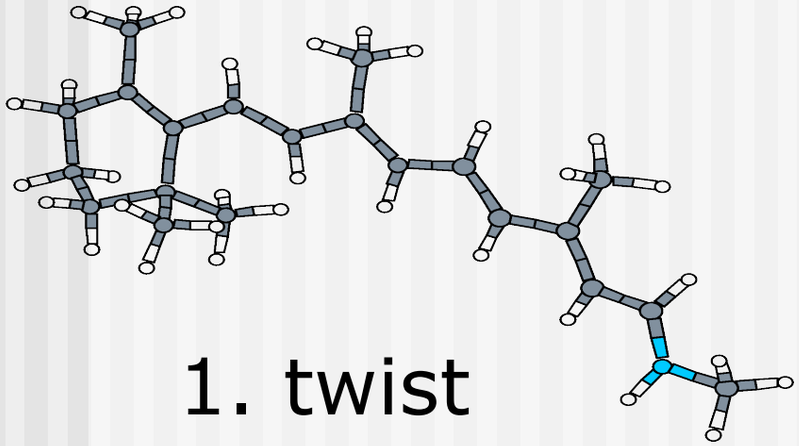
1. twist



‘Spectral tuning’

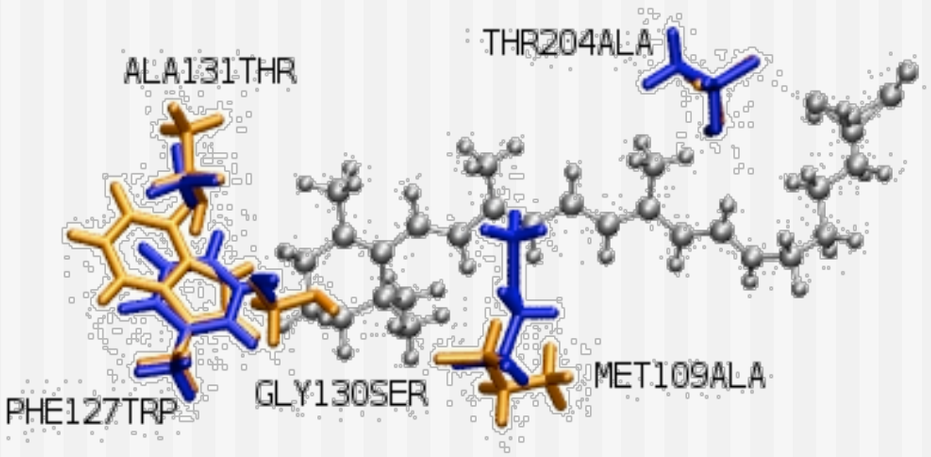
Absorption over 300 nm

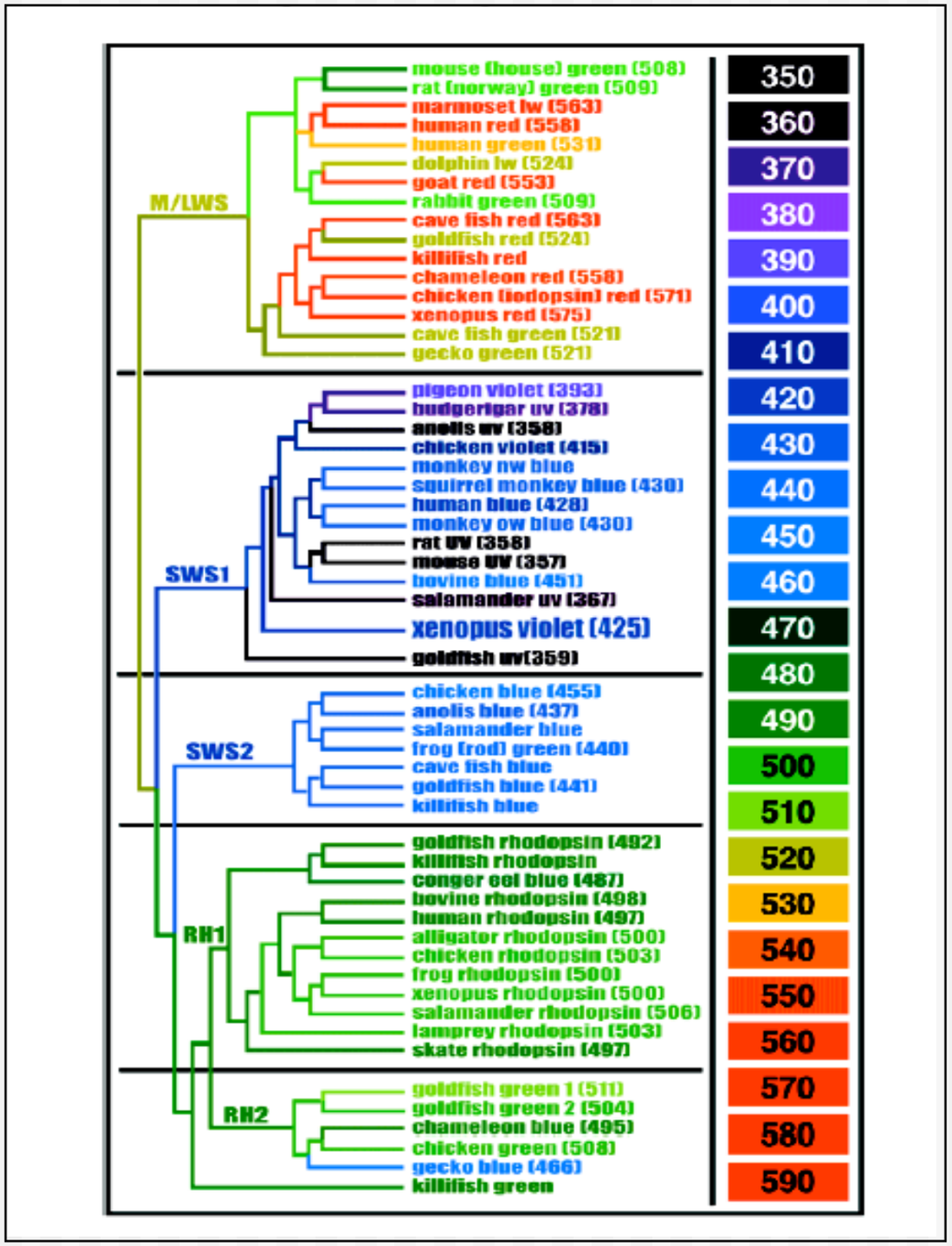
“Tuning” due to protein environement (opsin-shift)



1. twist

2. interaction with polar/ charged groups





‘Spectral tuning’

Absorption over 300 nm

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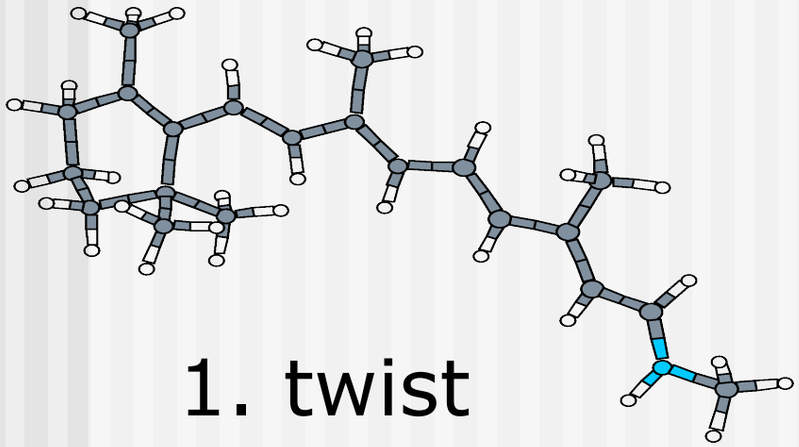
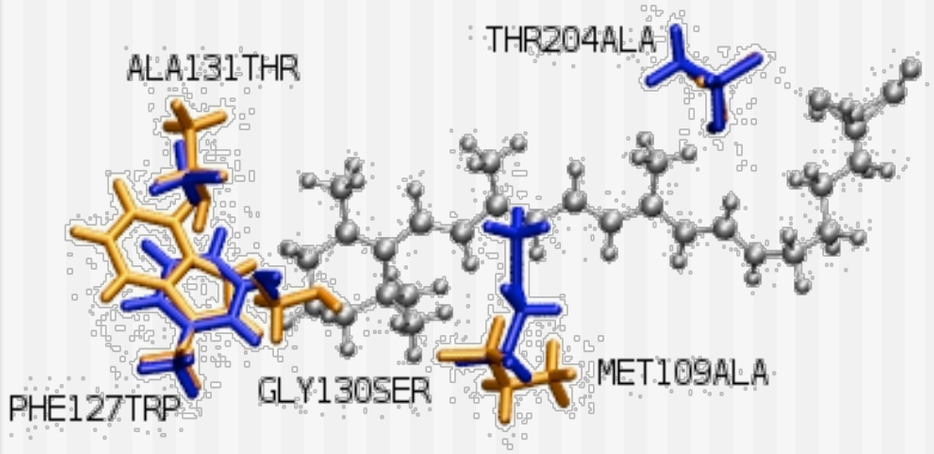
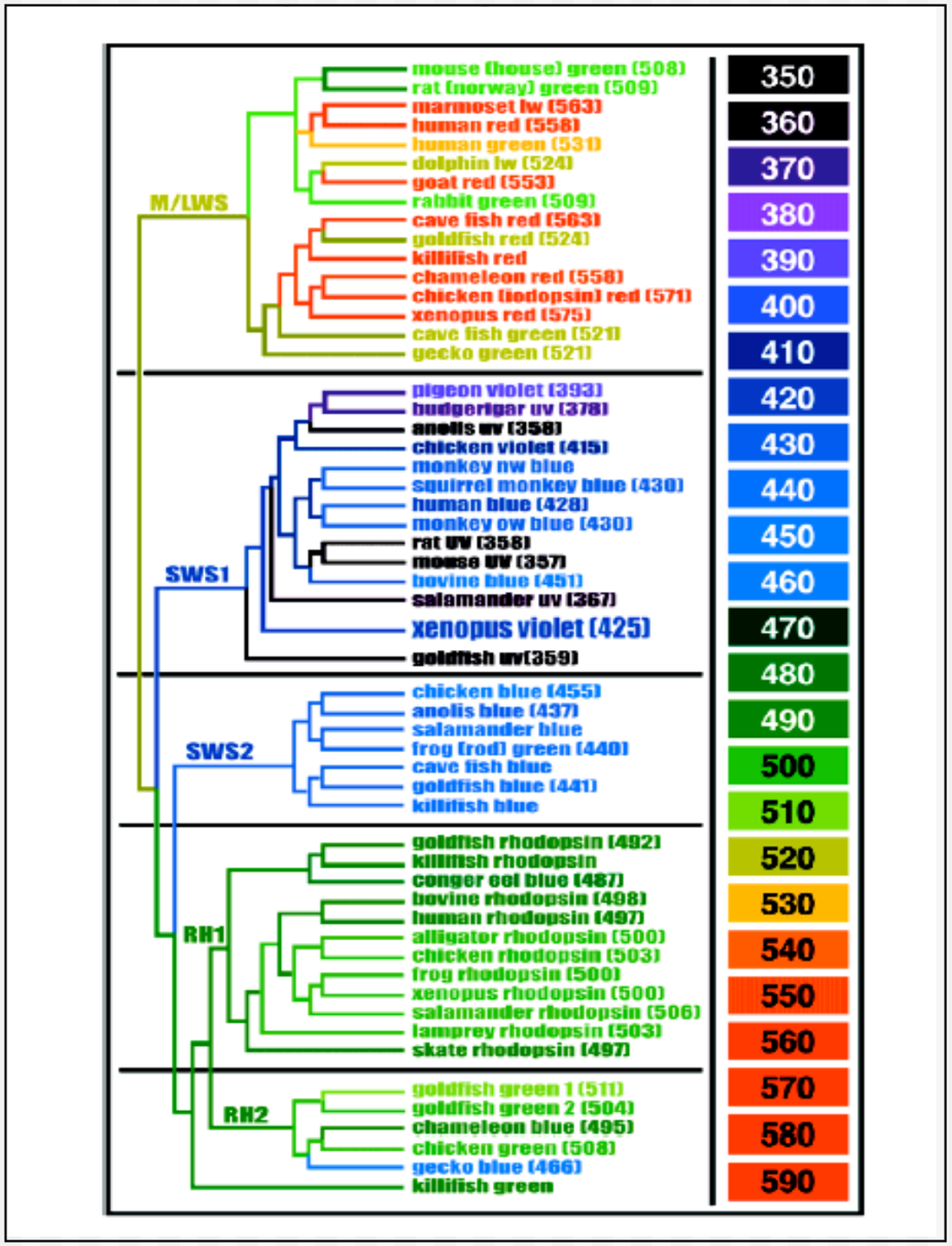


1. twist

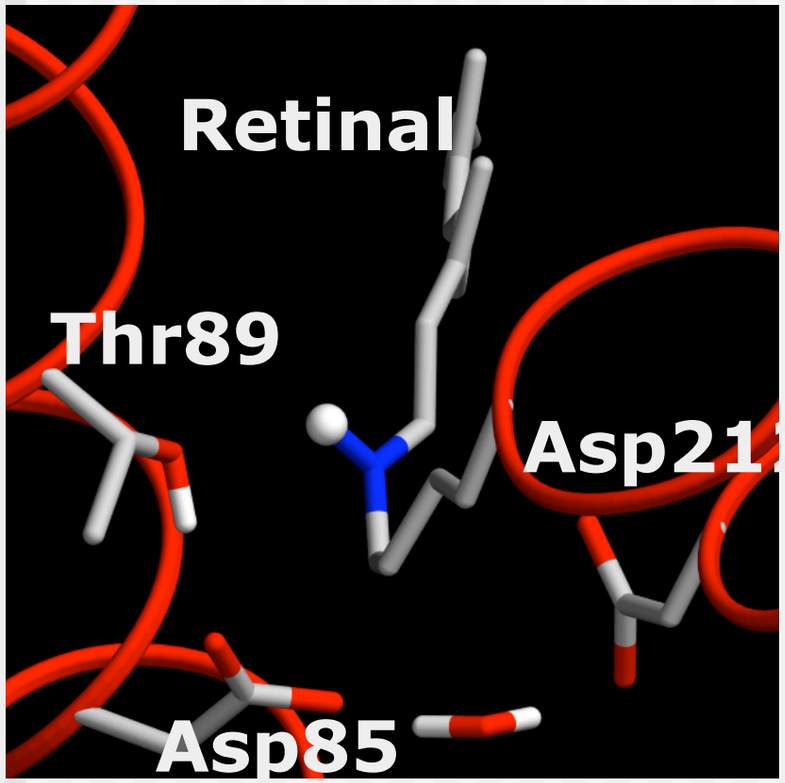
2. interaction with polar/ charged groups

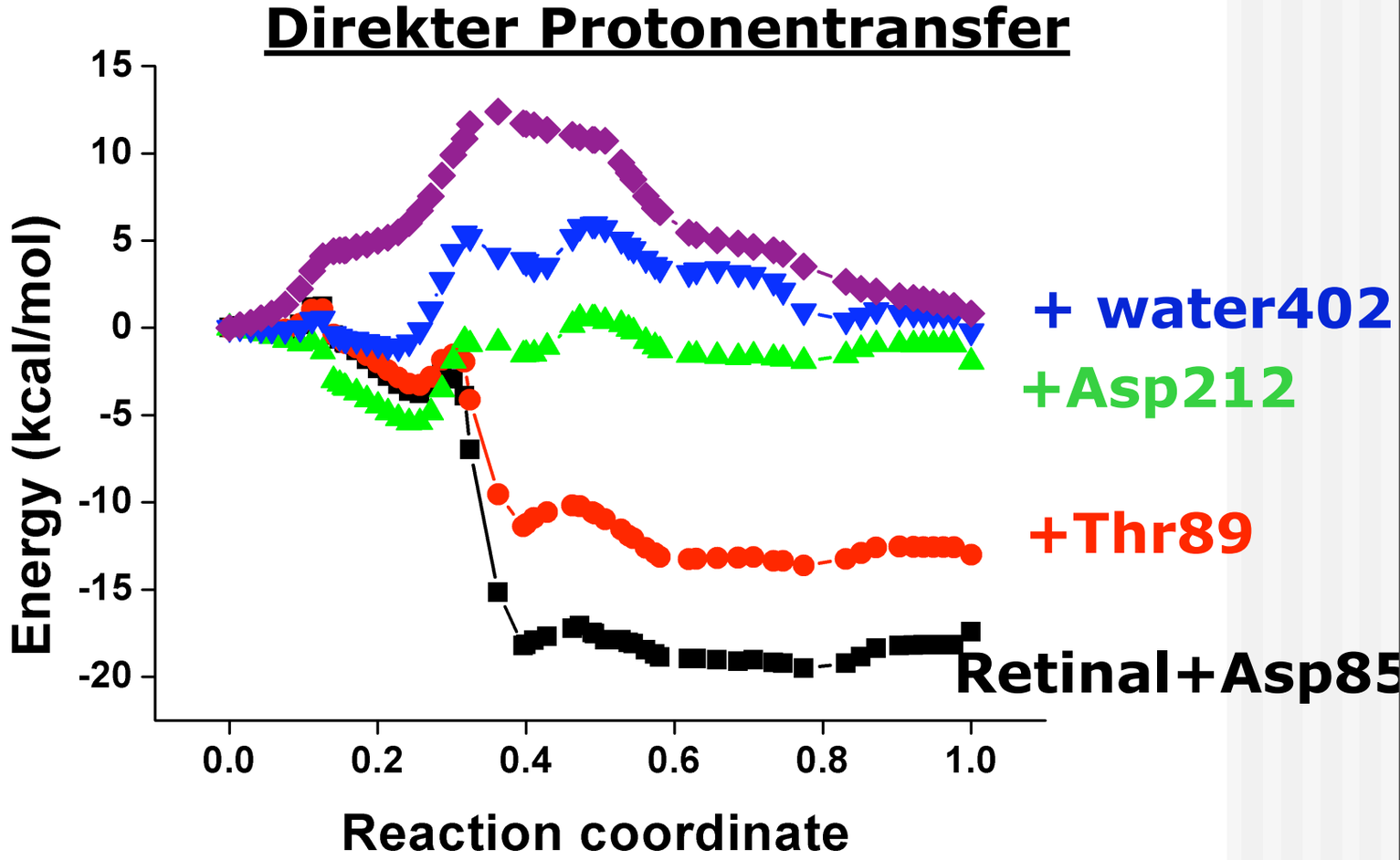


=> ‘predefined’ electrostatic interactions determine function



3. Dynamics often very important





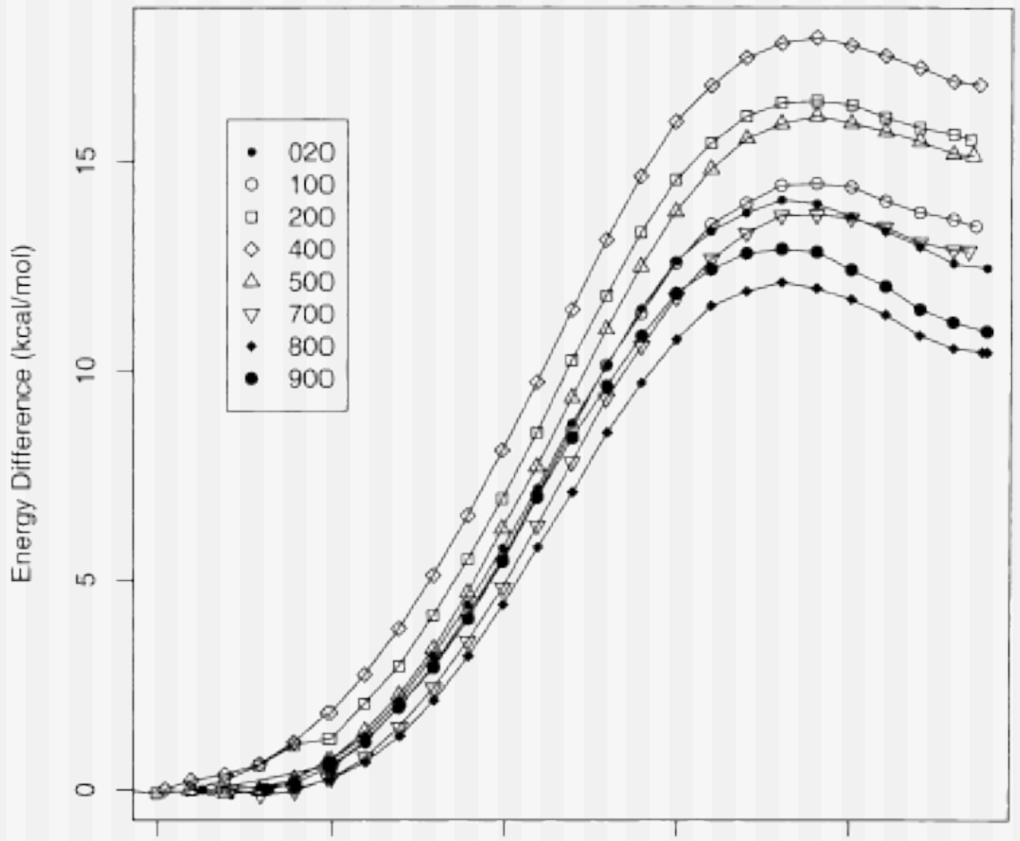
This is the total (potential) energy for one protein structure, but:

- the protein ‘moves’
- entropy

‘Problem’ of total energy

different energy-profiles

for different conformations of the surrounding protein



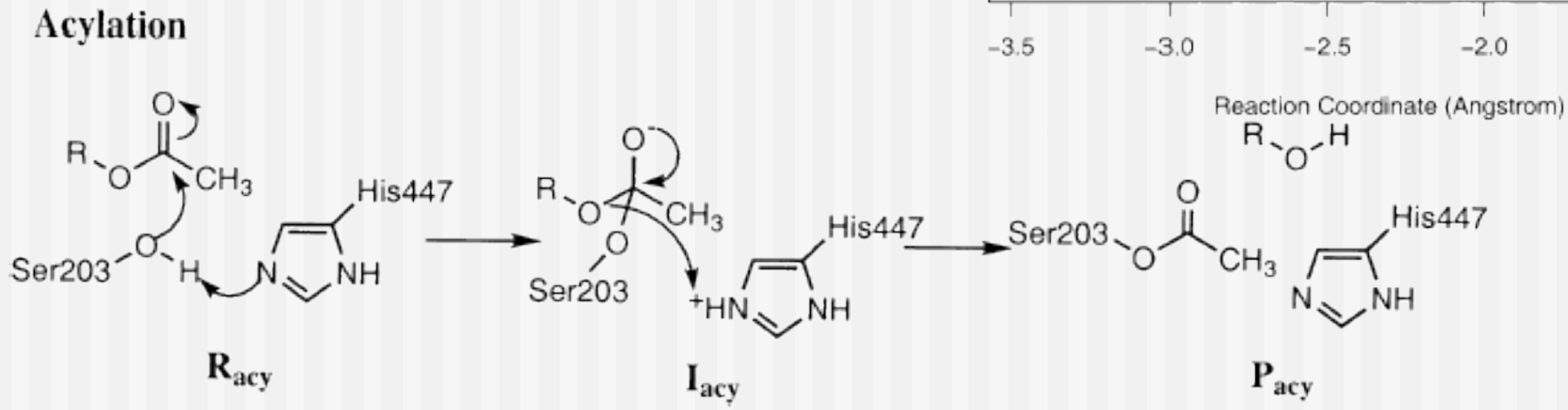


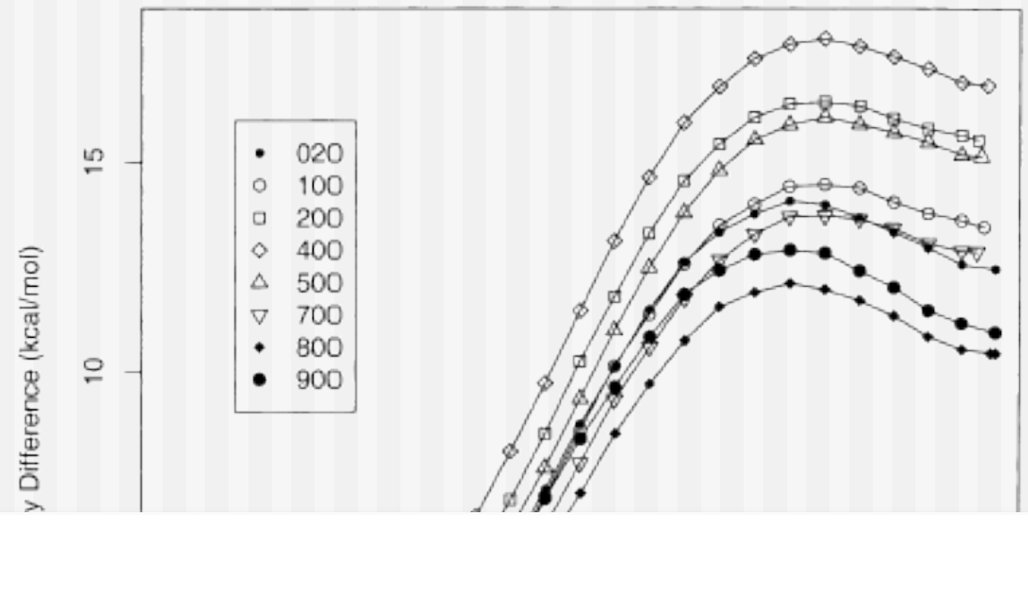
Figure 1. Acylation reaction mechanism of acetylcholine catalyzed by AChE.

Zhang et al JPCB 107 (2003) 44459

‘Problem’ of total energy

different energy-profiles

for different conformations of the surrounding protein



A) one always has to ‘average’ (sample) over acessible protein conformations :

total energy➔ inner energy

E➔ U

B) entropy is often as important as accurate total enery E:

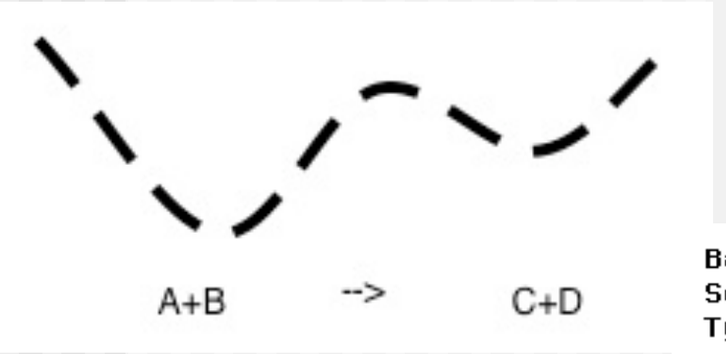
U➔ F

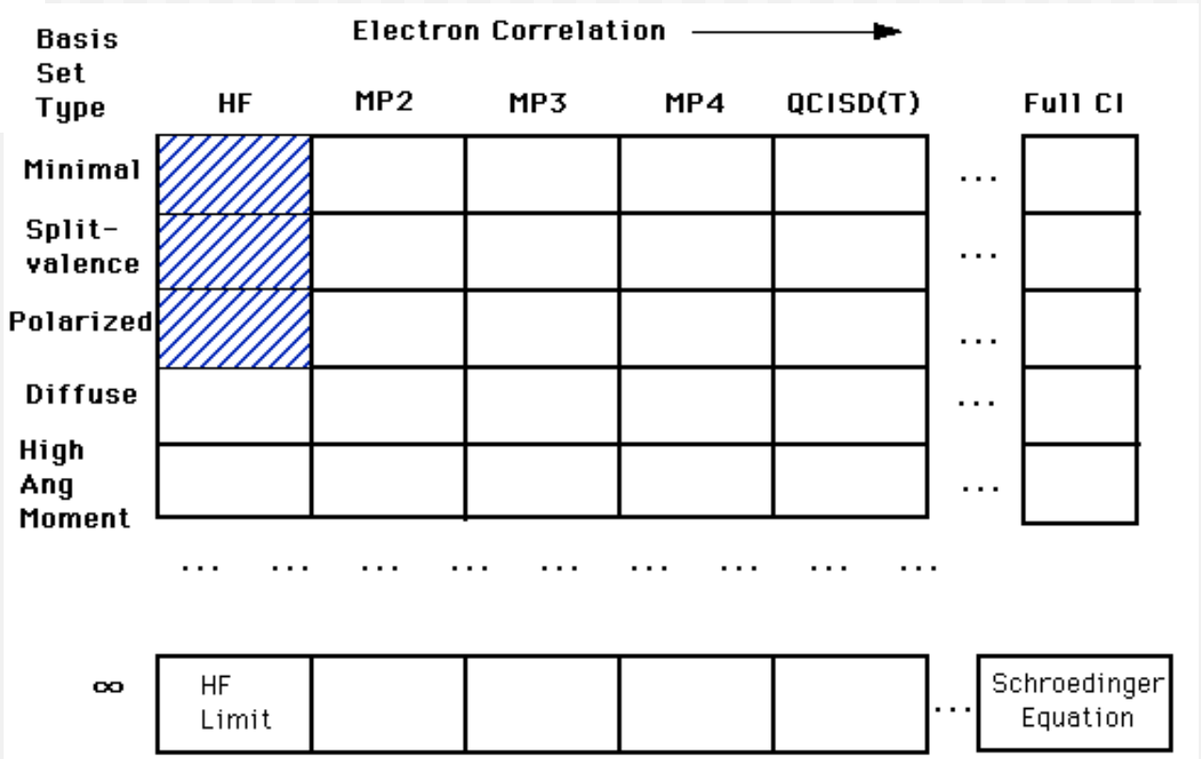
Two key problems

- include large part of system by treating some part at accurate QM level:
‘multiscale issue’
  - combine different methods
  - quantum chemistry problem: what QM level?

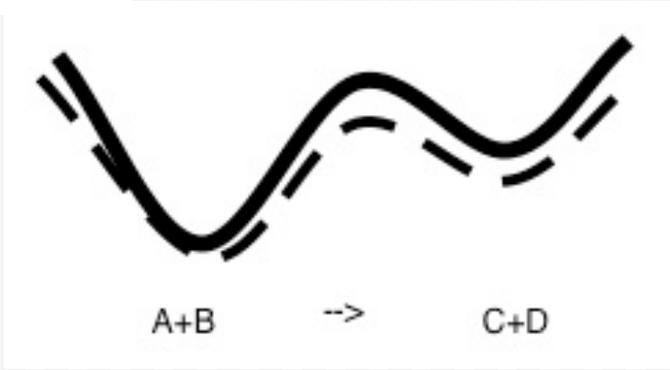
- find reaction pathway in complex environment, do the averaging and include entropic contributions
‘sampling issue’
(same as in MM MD)

Hirachy of methods in theoretical chemistry

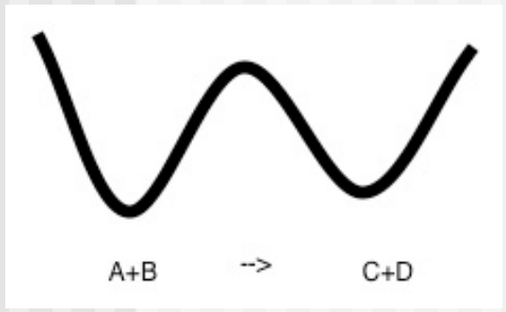




computational models and basis sets

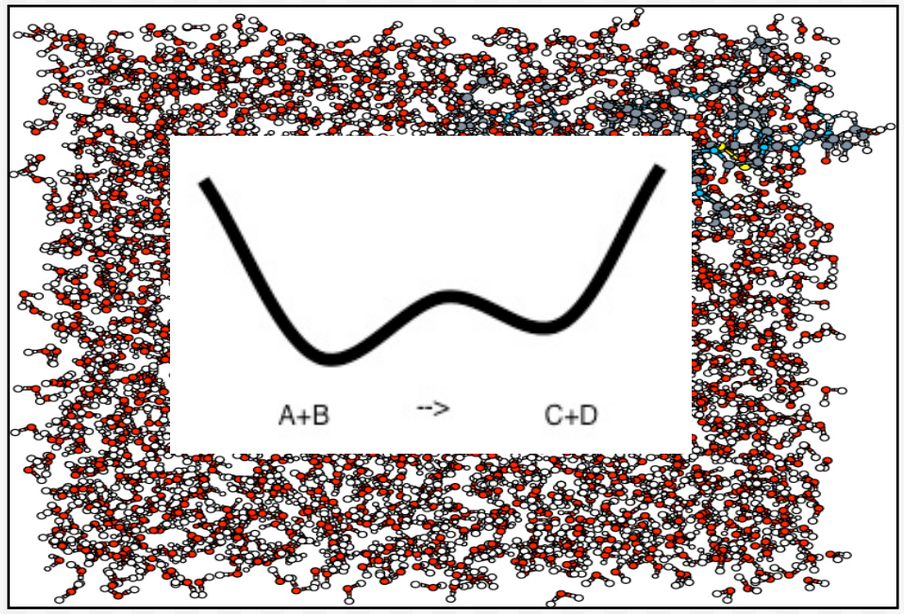


additional problems: environment and entropy

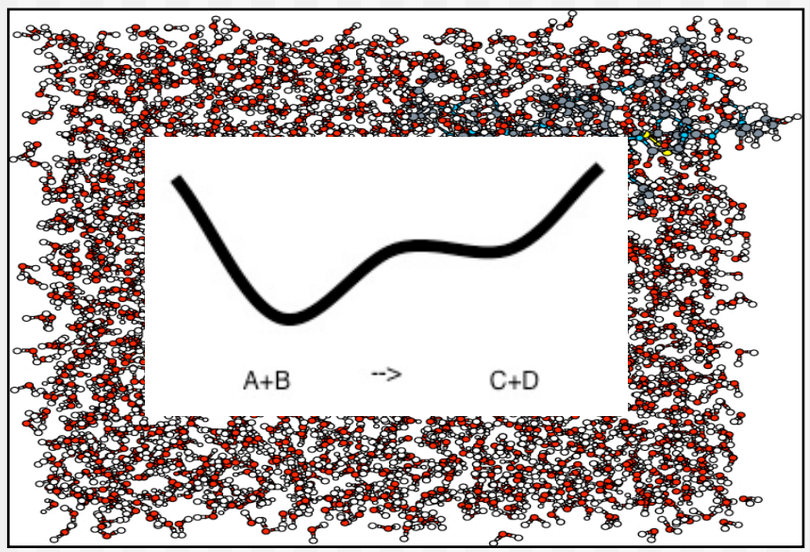


start:
QC in gas phase

environment:
multiscale methods



entropy:
'sampling'

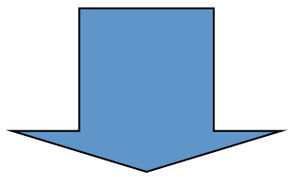


Examples of multi-scale

Understanding biological processes

Different length- and timescales are relevant

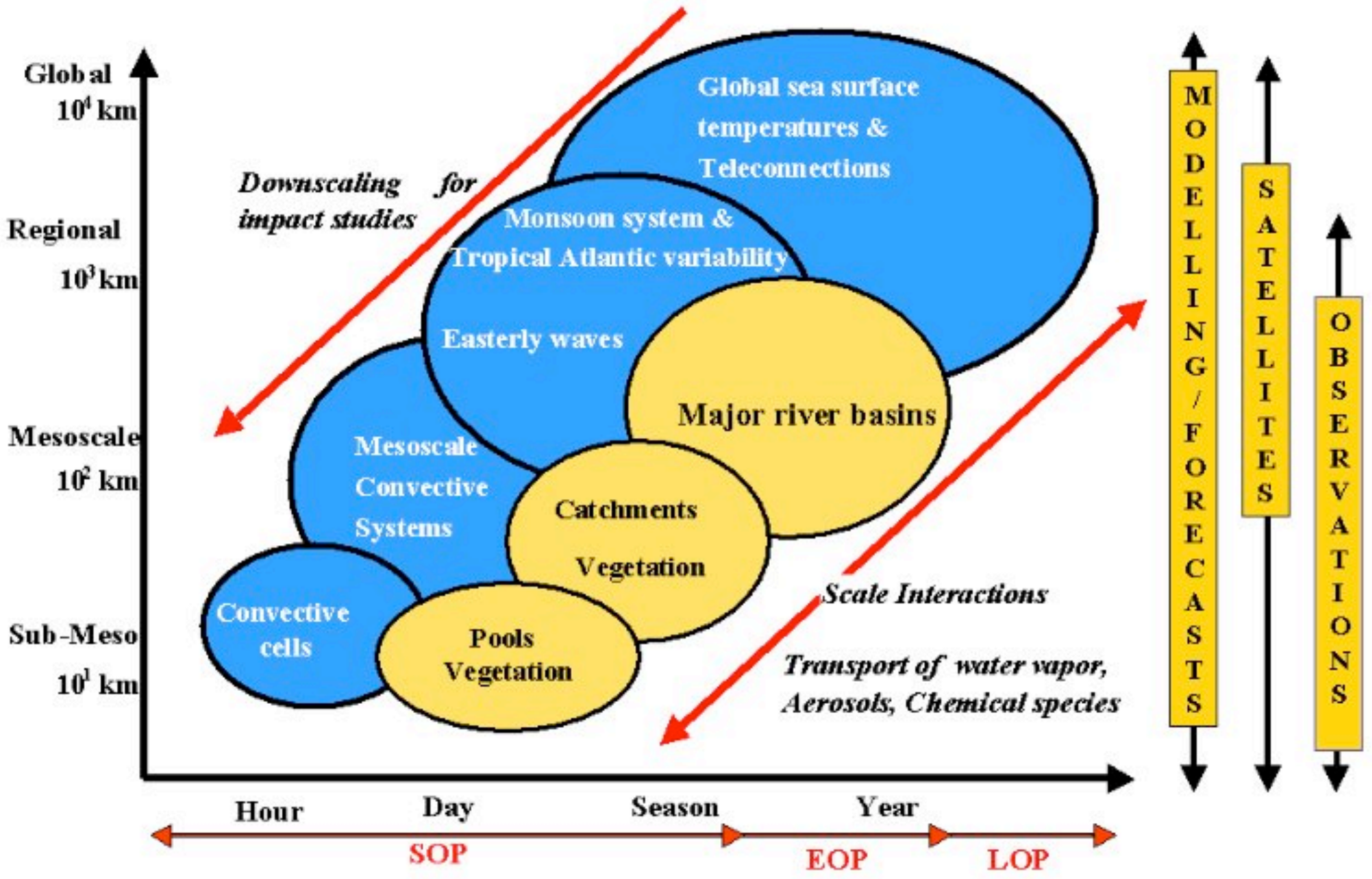
- atomistic: equations of motion for coupled N-body problem (classical/quantum mechanical)
- coarse grained simulations: include several atoms into ‘superatom’
- continuum: electrostatic and mechanical properties
- rate & transport equations, stochastic models etc.: phenomenological



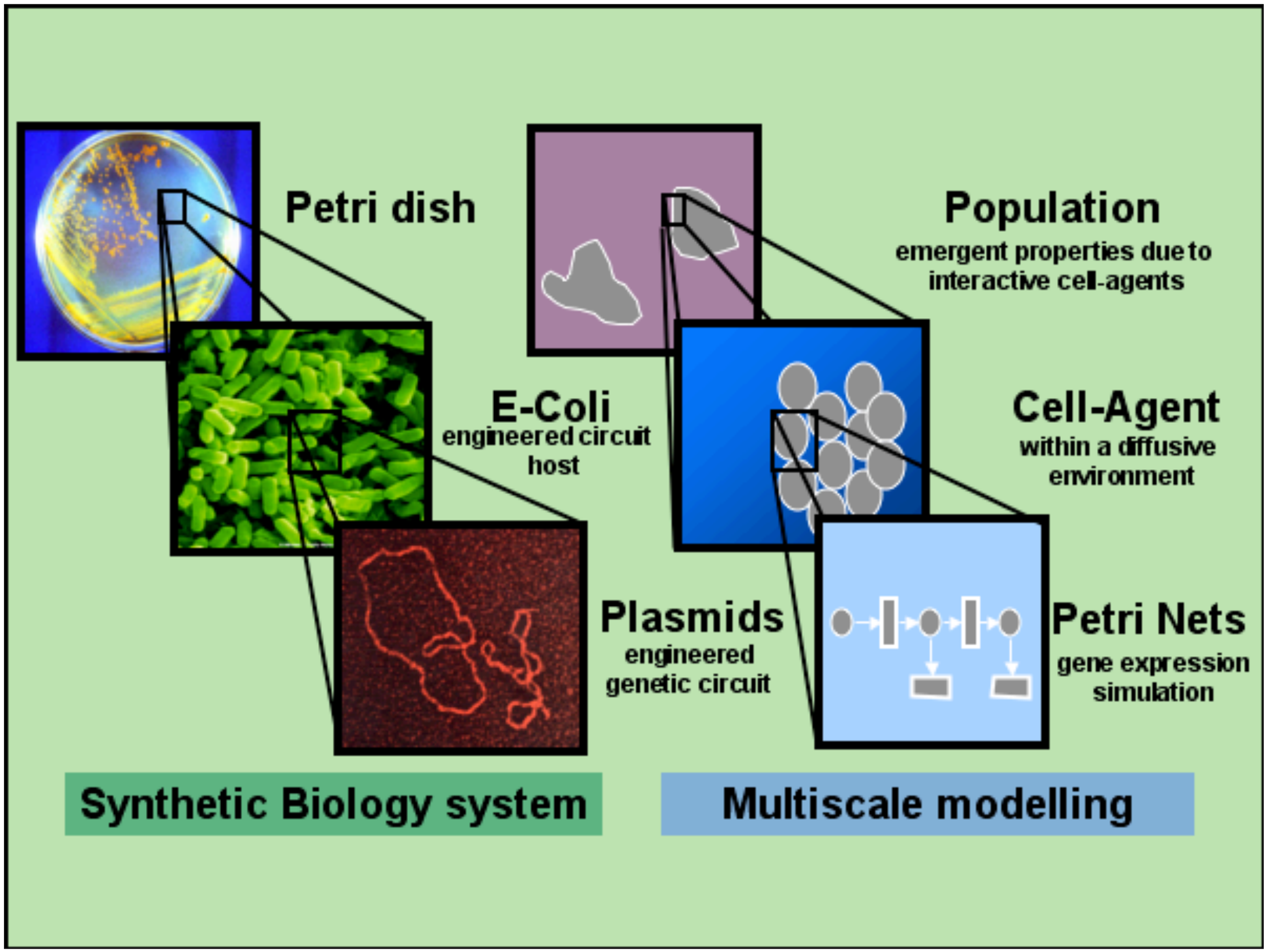
- very different theoretical models
- combination (within limits): “Multi-scale modeling”

Multi-scale methods: used in different areas

AMMA: African Monsoon Multidisciplinary Analysis

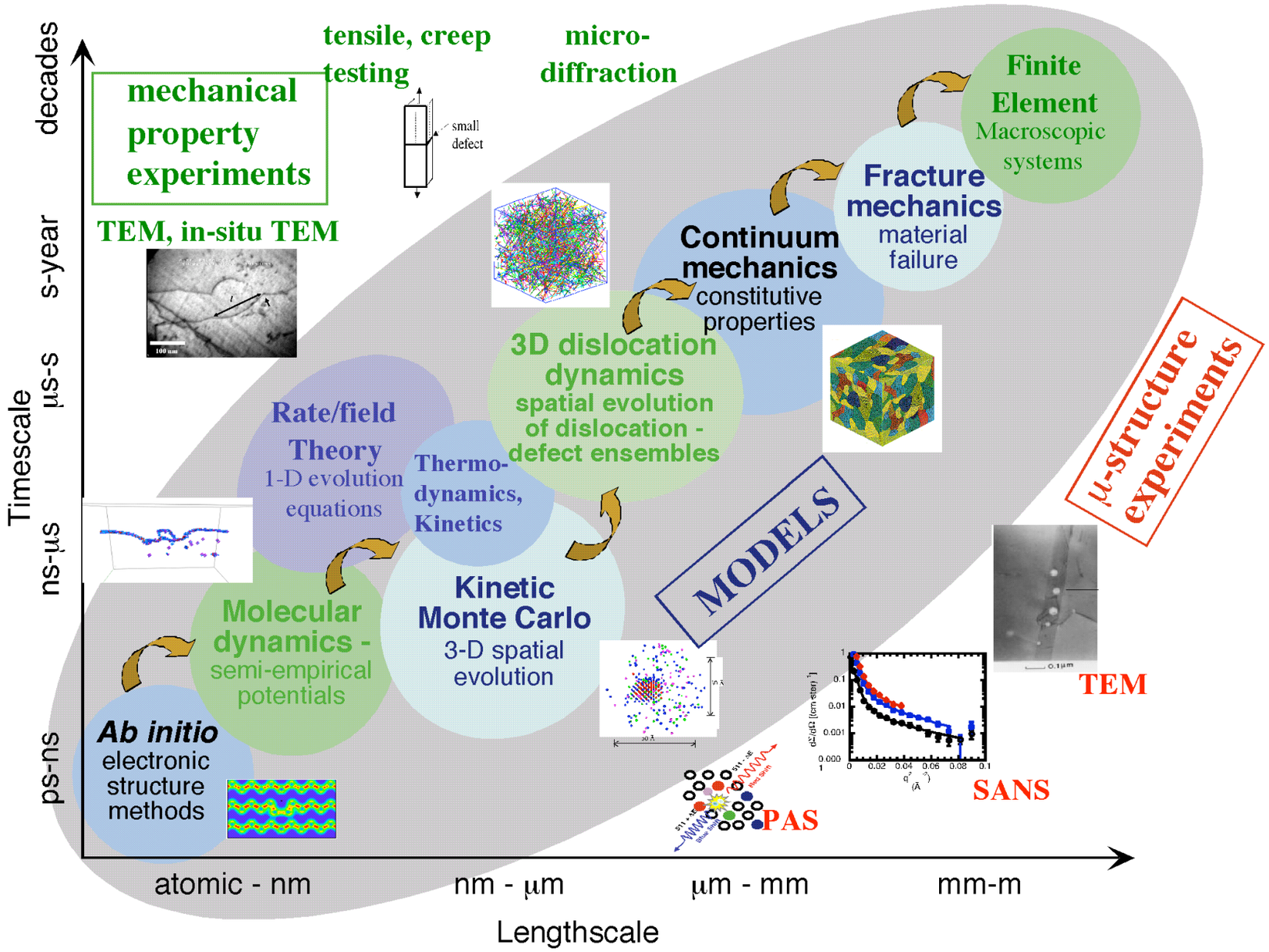


Multi-scale methods: used in different areas



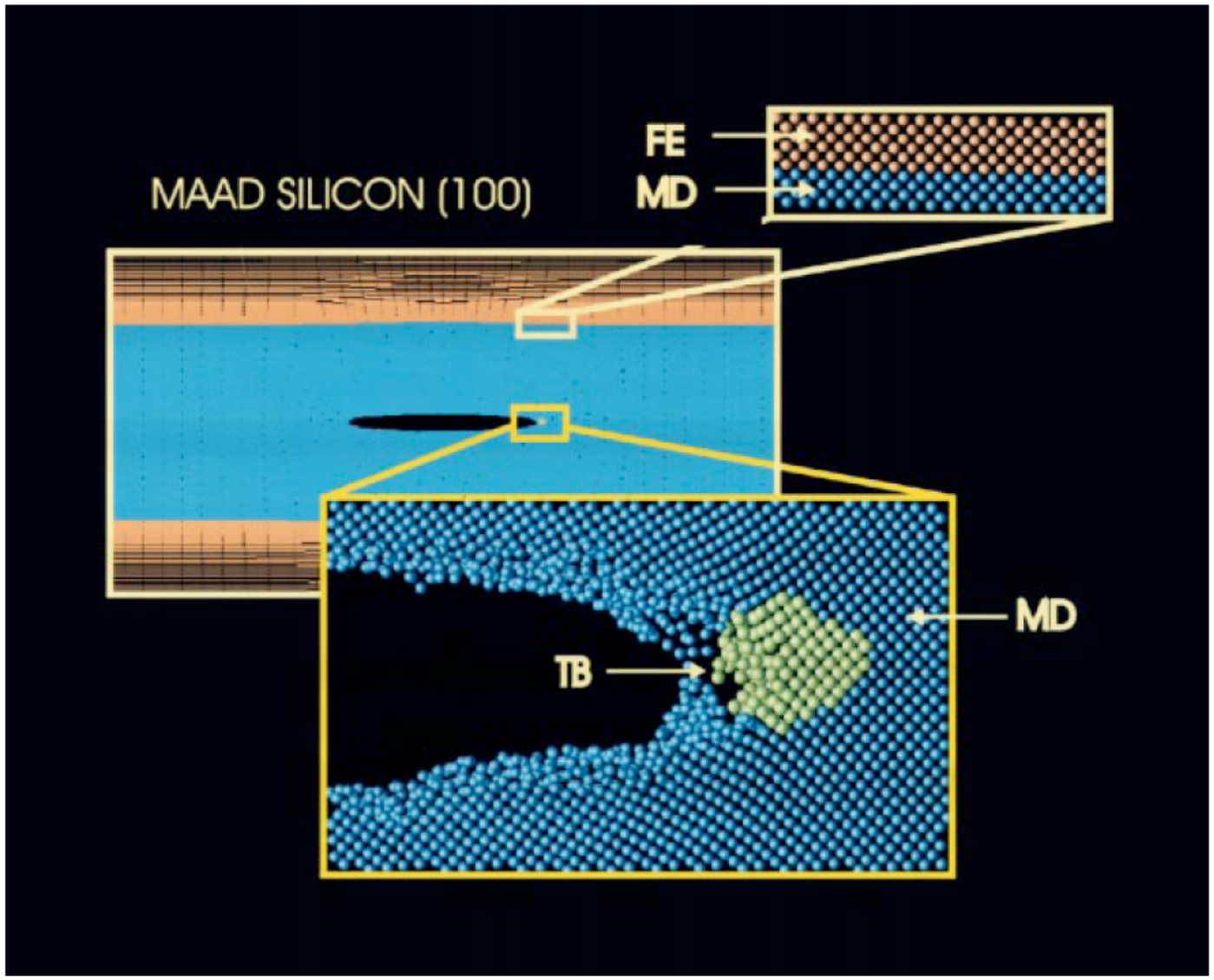
V. Rouilly. Imperial College

Multi-scale methods in computational materials science



B. Wirth, Berkeley

Crack propagation in silicon

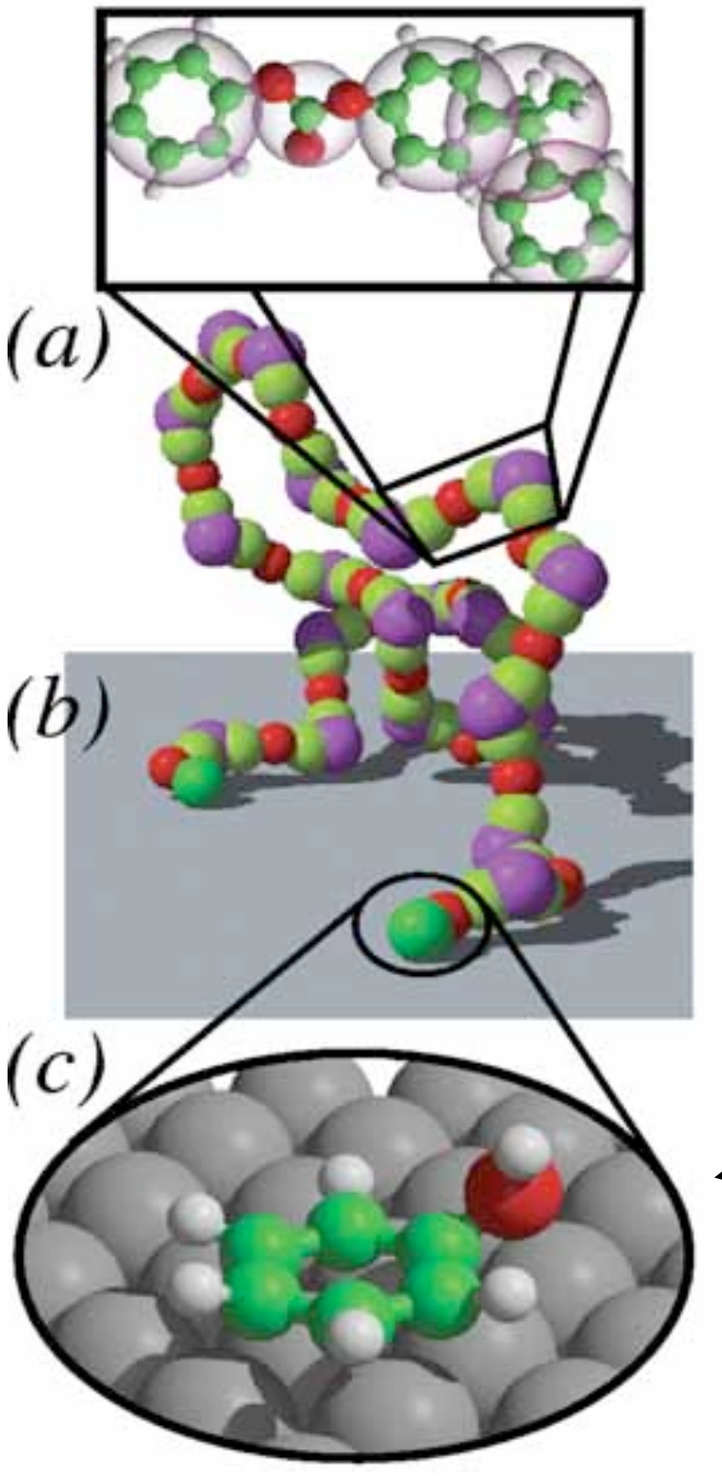


- quantum mechanics
- empirical force fields
- finite elements

Broughton et al PRB 60, 2391

‚local ' information required

Polymers on metal surfaces



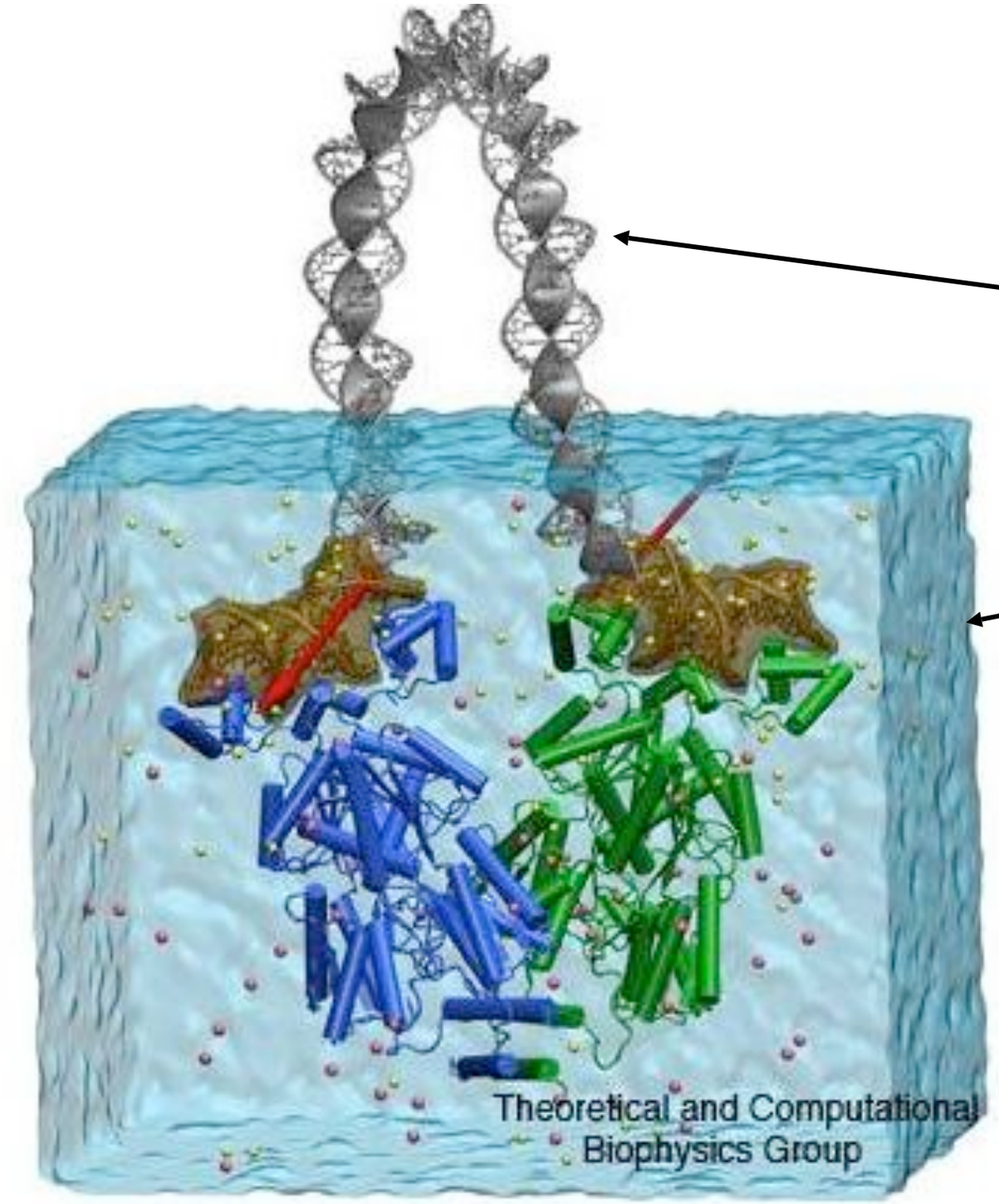
Bisphenol-A-Polykarbonat (BPA-PC) on Ni-surface.

Delle Site, Kremer, MPI Mainz

- ‚Coarse grained'
- quantum chemistry (DFT)

parametrization

Biophysics: DNA-protein interaction

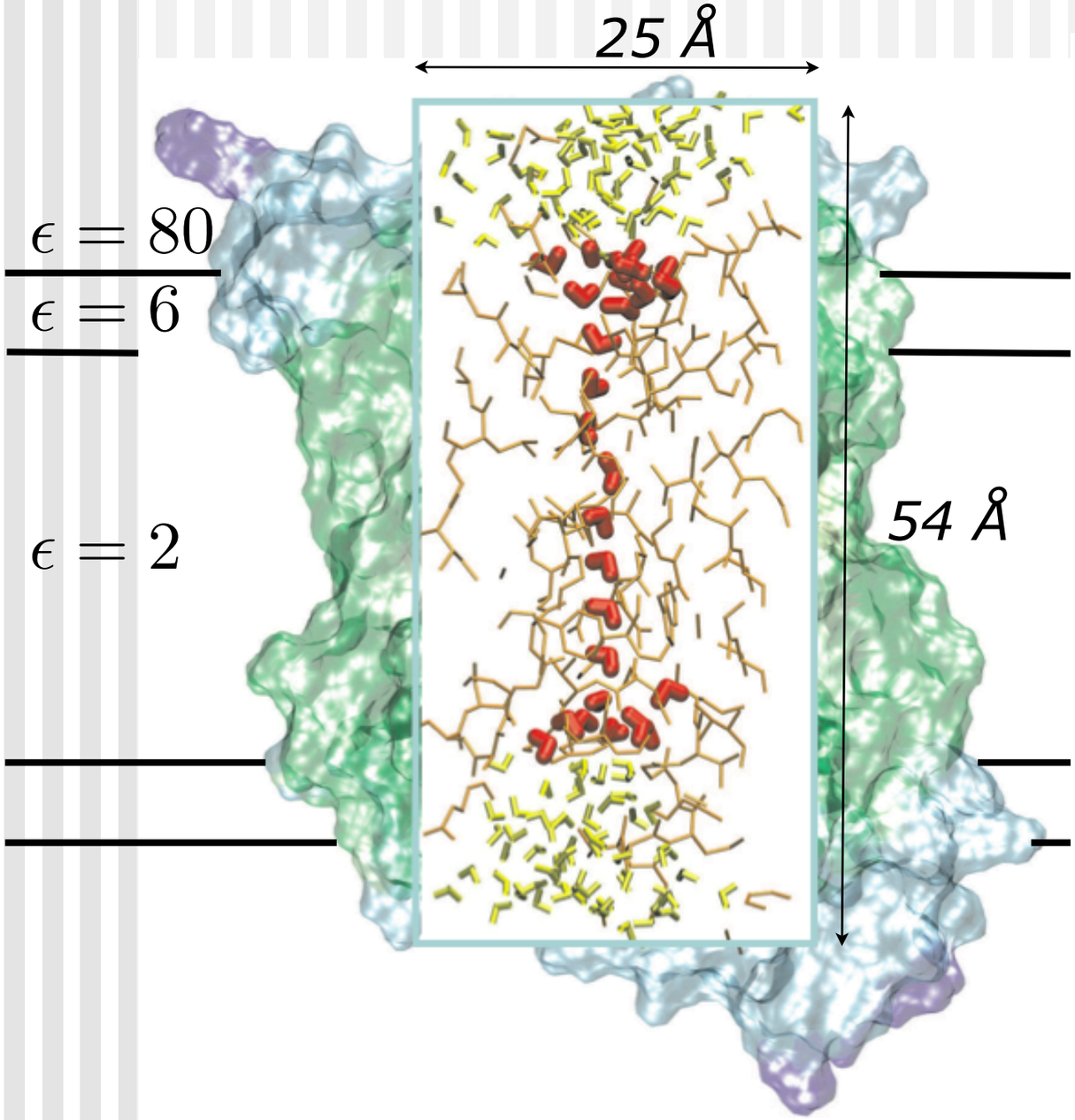


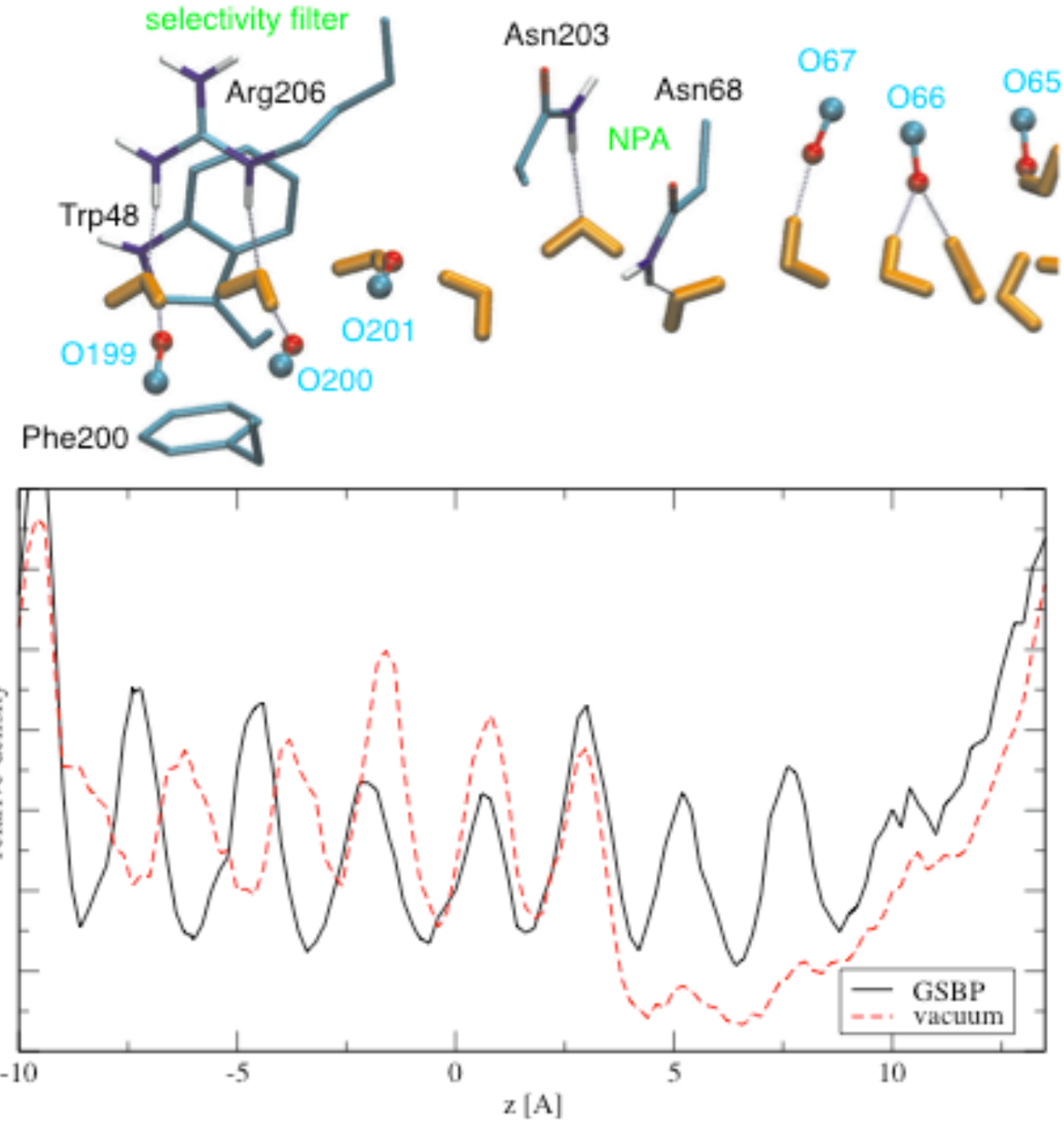
- **continuum description : elastic band for DNA**
- **empirical force field: water, protein**

Lac repressor protein

Villa et al., PNAS 102 6783

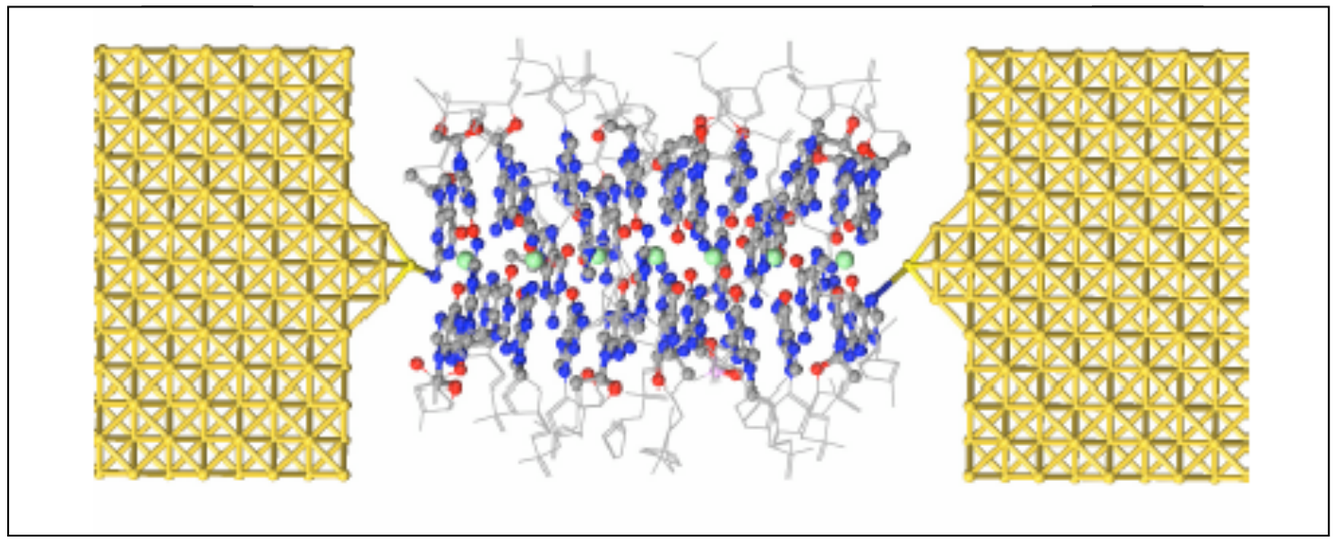
Membrane systems





P. Konig, N. Ghosh, M. Hoffman, M. Elstner, E. Tajhorshid, Th. Frauenheim, QC, *J. Phys. Chem. A* Trhular Issue, 110, 548-563 (**2006**)

Charge transfer through DNA

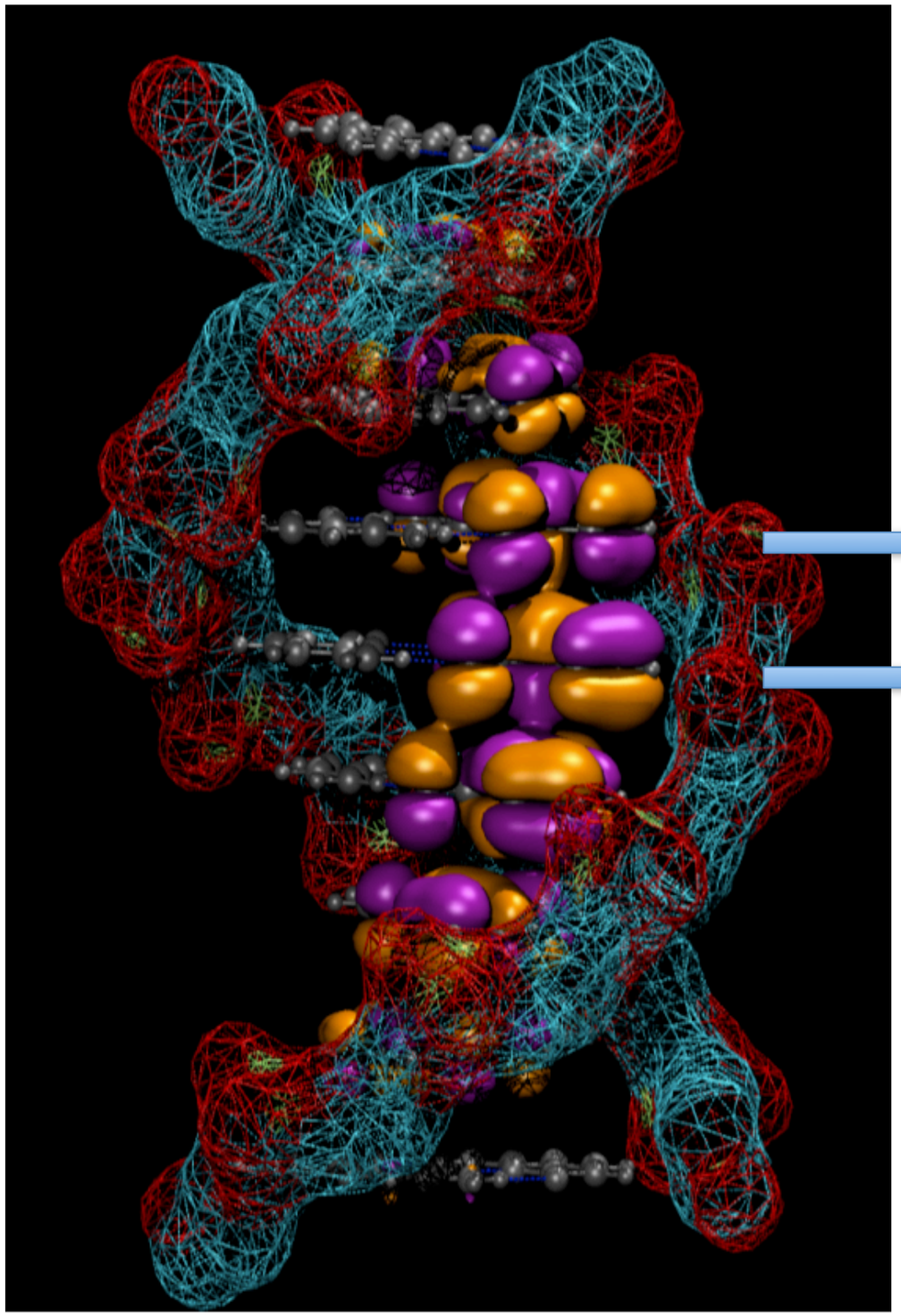


- system very large: 1000 atoms in DNA
- fluctuations important: MD for ns
- solvent explicitly required: put another 5000 atoms

Need QM description: NOT POSSIBLE

➔ Coarse graining of the electronic problem

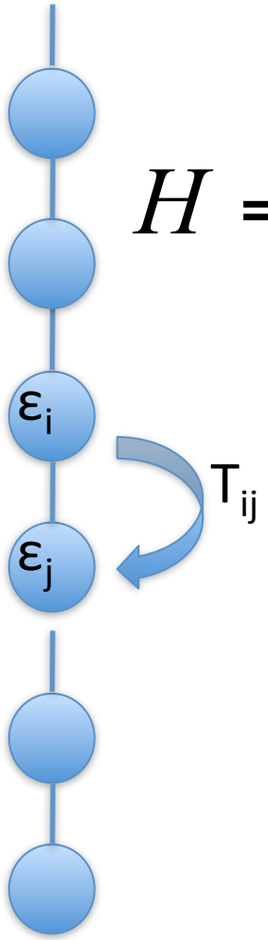
Charge transfer through DNA



site i

site j

Coarse grained Hamiltonian



$$H = \sum_i \varepsilon_i a_i^+ a_i + \sum_{ij} T_{ij} a_i^+ a_j$$

Time dependent parameters $\varepsilon_i(t)$ and $T_{ij}(t)$ contain dynamical and solvation effects

Multiscale modelling

sequential: simulation with only one method

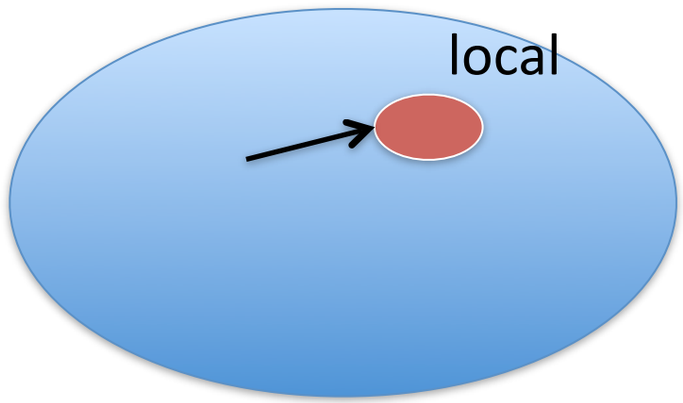
a) Get parameters : ‚bottom up' parametrization

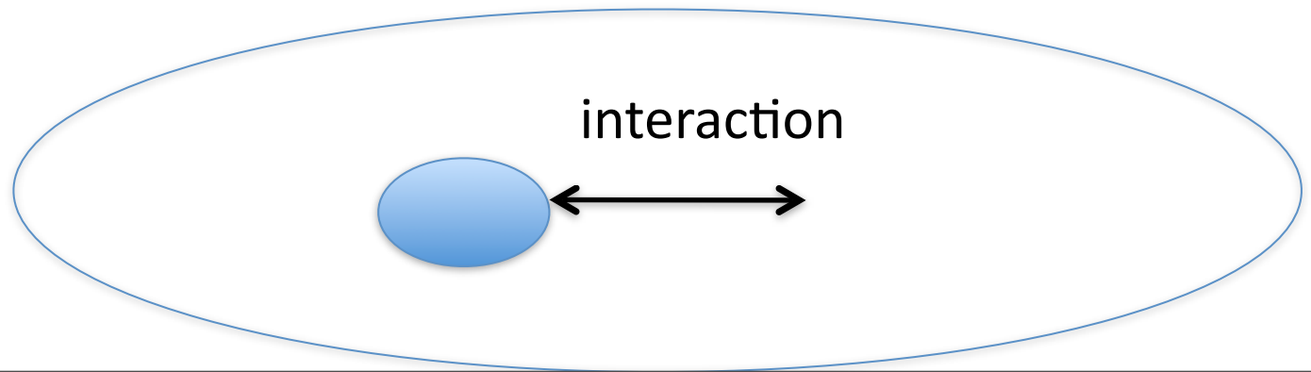
integrated : several methods combined

b) Even in a good model, often more accurate information is needed locally

e.g. crack propagation

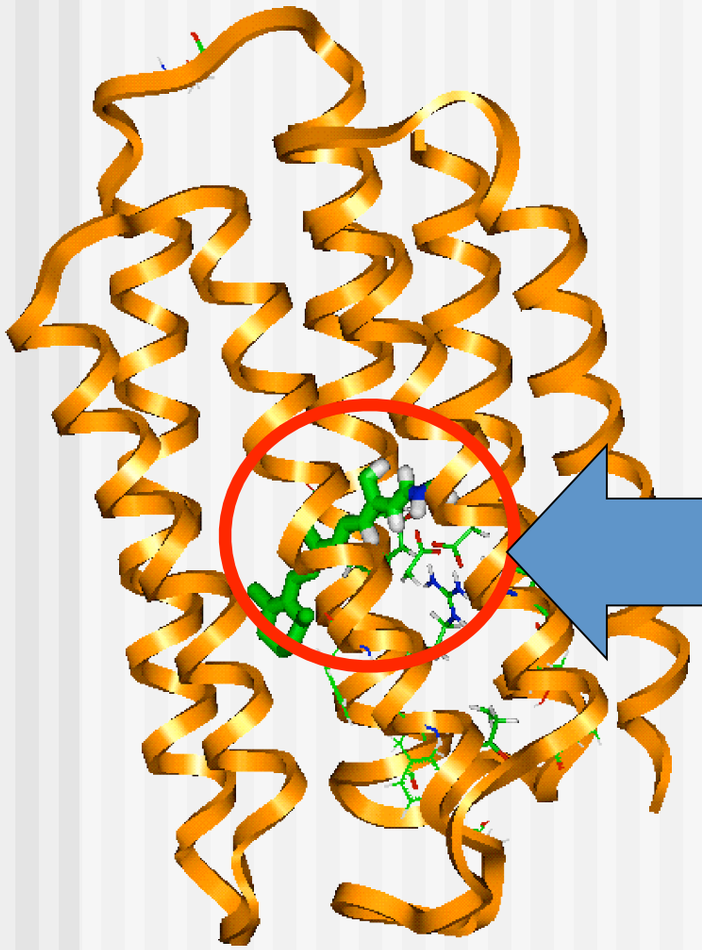
c) atomistic simulations : long-range interactions





QM/MM

Combined QM/MM methods



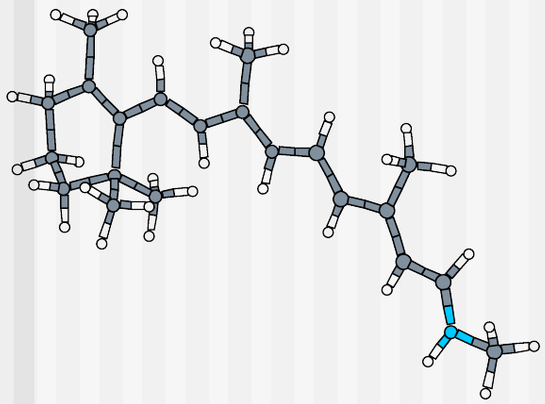
~ 1.000-100.000 atoms

~ ns MD simulations

(MD, umbrella sampling)

- chemical reactions

- excited states, spectroscopy



In many cases, the site of interest is localized

➔ apply QM locally

Recent review: Senn & Thiel, Top Curr Chem (2007) 268: 173

Combined QM/MM methods

1976 Warshel und Levitt

1986 Singh und Kollman

1990 Field, Bash und Karplus

QM

- semi-empirical methods
- quantum chemistry : DFT, HF, MP2, LMP2
- DFT ‘plane wave‘ codes: CPMD

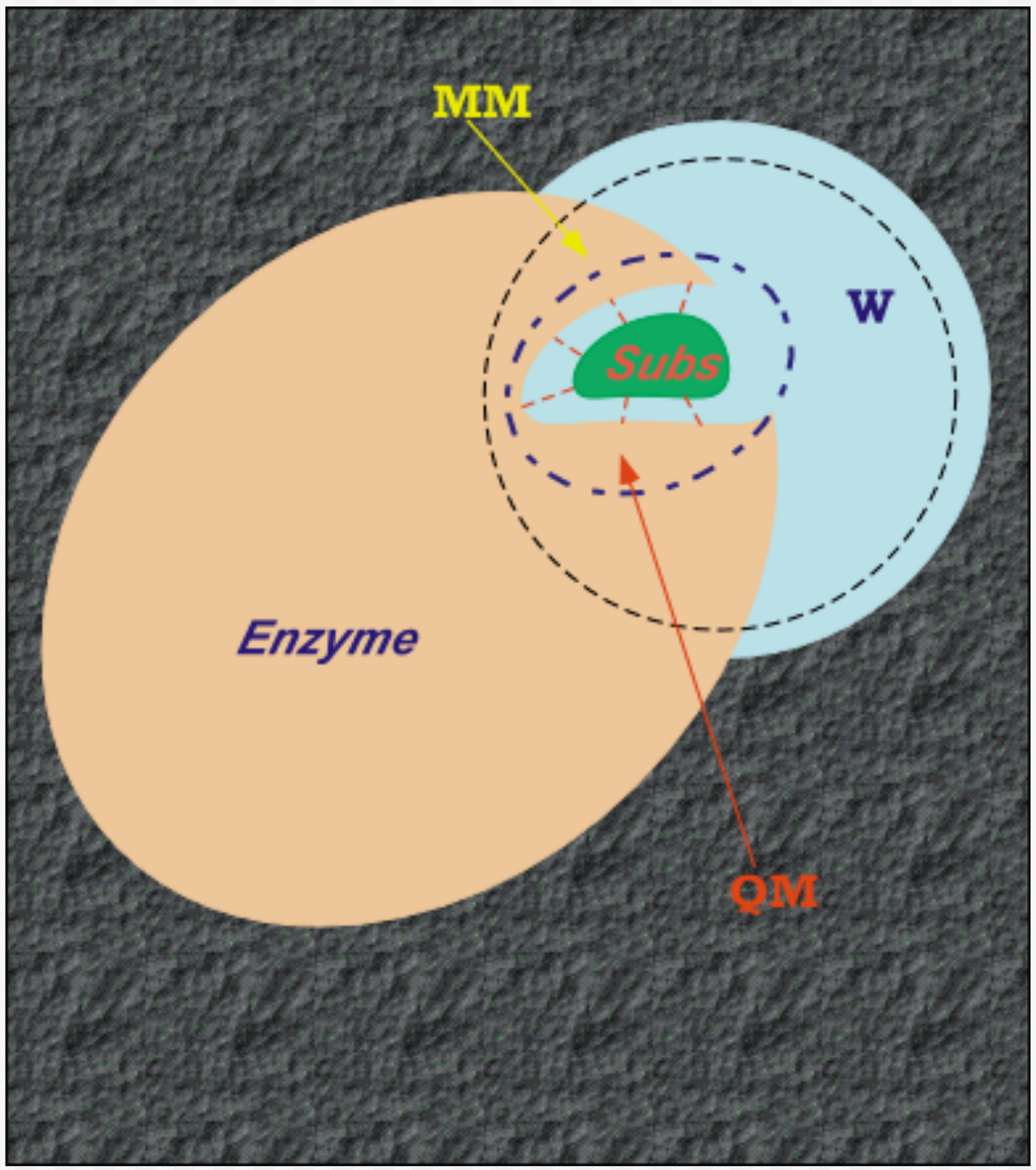
MM

- CHARMM, AMBER, GROMOS, SIGMA,TINKER, ...

Recent review: Senn & Thiel, Top Curr Chem (2007) 268: 173

Combined QM-MM methods

$\varepsilon = 80$



-QM region

- Molecular Mechanics (MM) region

Effects:

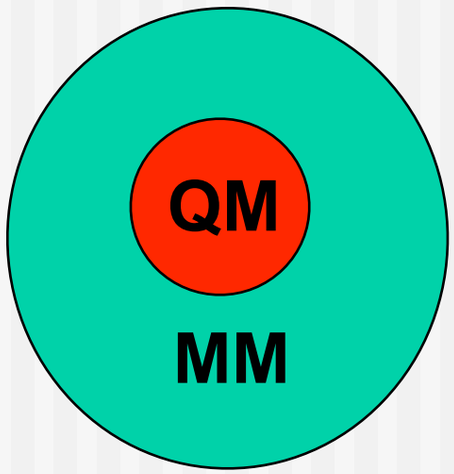
- **steric interactions**: keep the active site in place:

- **electrostatic interaction**: polarization of QM region due to MM

Recent review: Senn & Thiel, Top Curr Chem (2007) 268: 173

Main distinction between QM/MM methods

- additive vs. subtractive methods
- embedding: mechanic, electrostatic or polarizable
- treatment of the boundary:
  - link atom, pseudo atom, hybrid orbitals
  - electrostatics



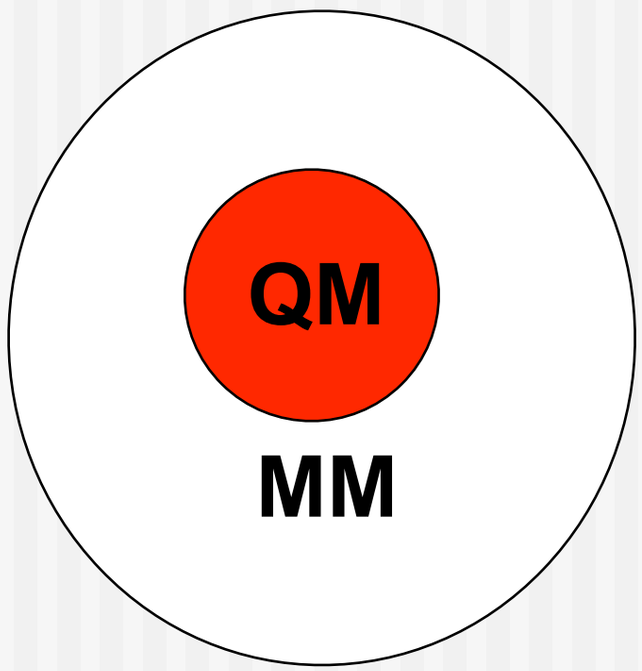
Subtractive vs. additive models

- **subtractive**: several layers: QM-MM

  double-counting of the regions is subtracted

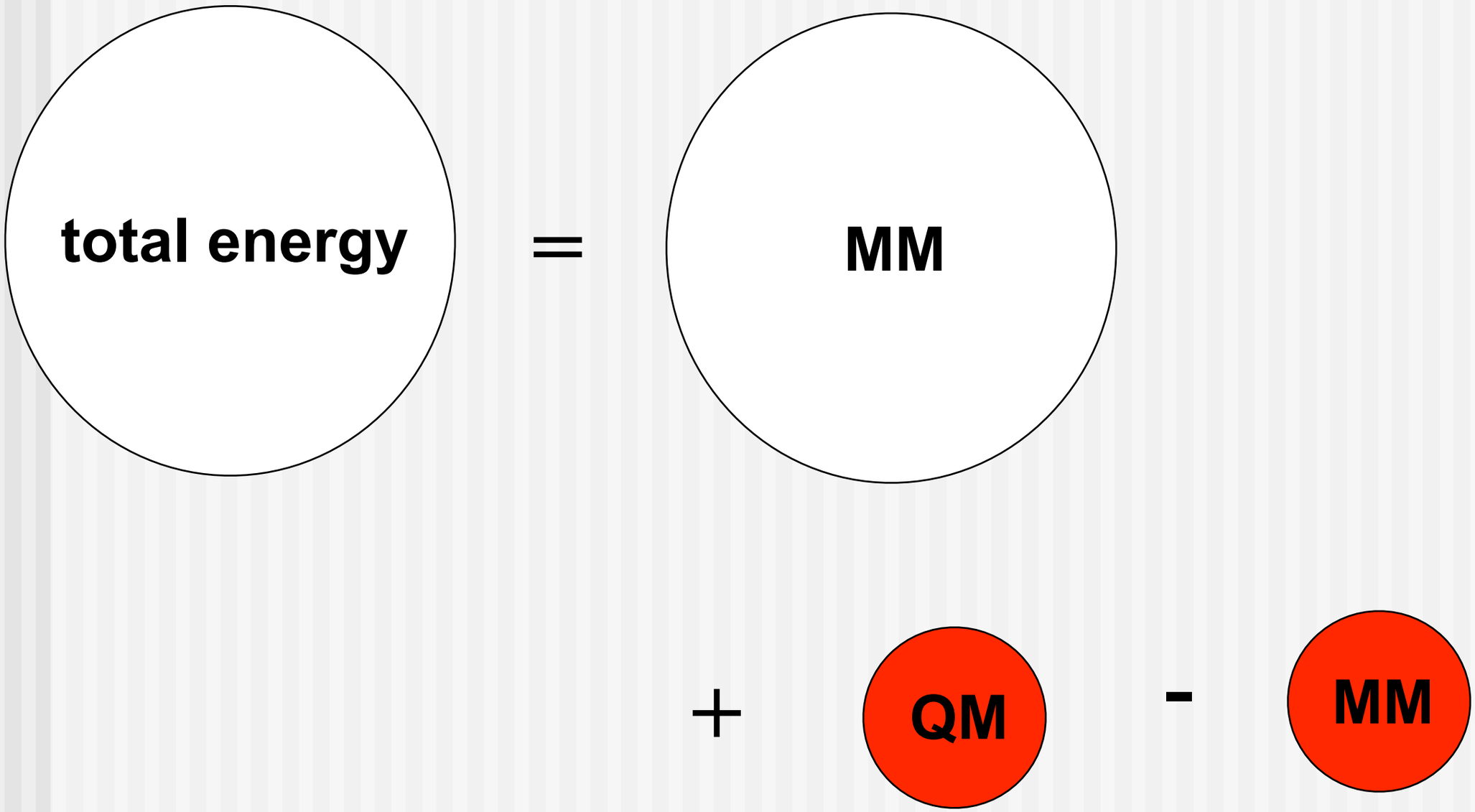
- **additive**: different methods in different regions +

  interaction between the regions

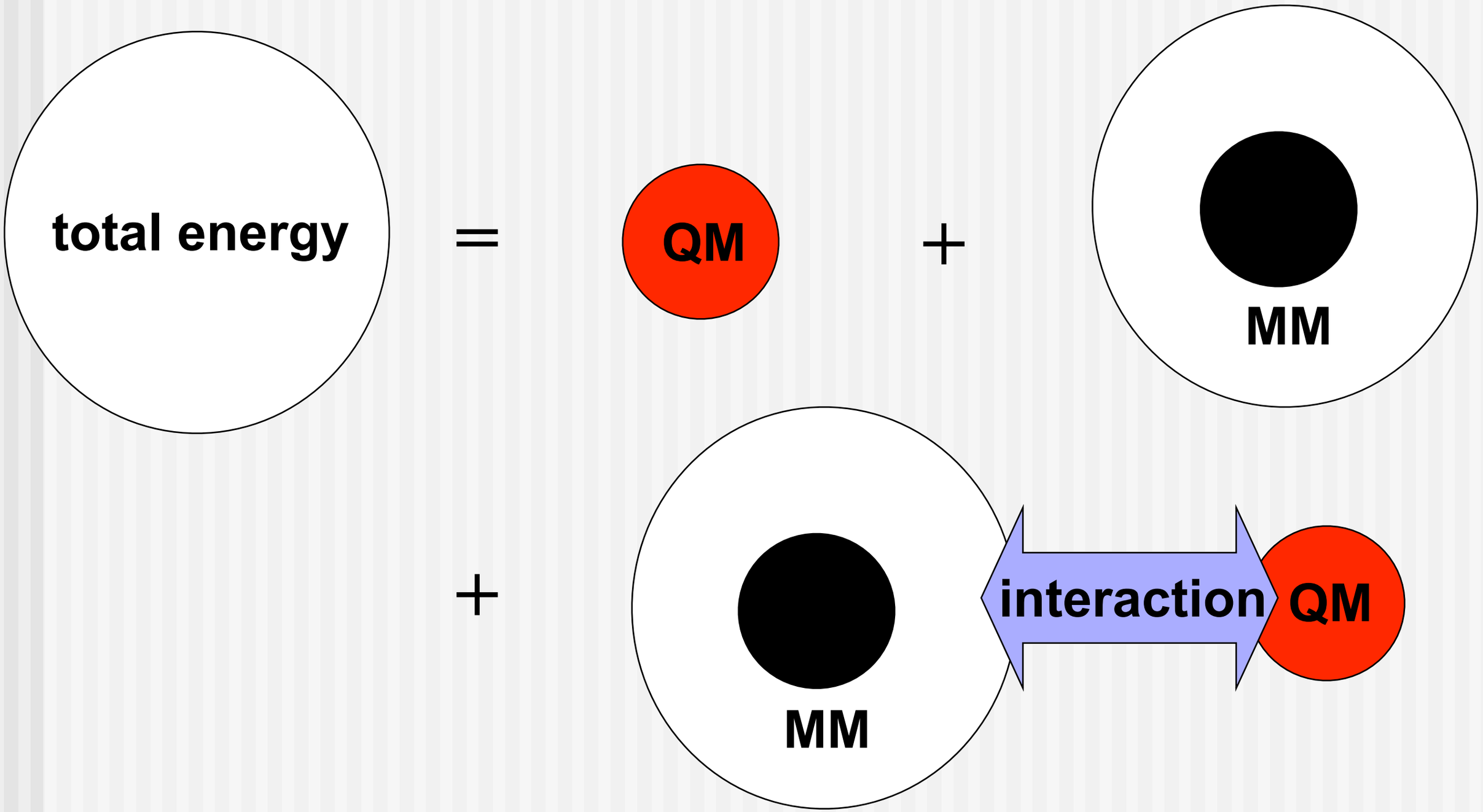


Subtractive QM/MM: ONIOM

Morokuma and co.: GAUSSIAN



Additive QM/MM



Subtractive vs. additive QM/MM

- parametrization of methods for all regions required

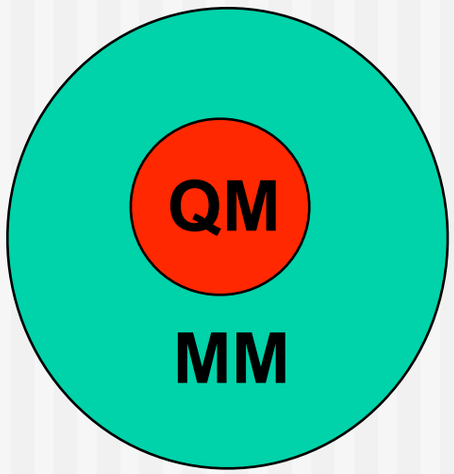
  e.g. MM for Ligands

  SE for metals

+ QM/QM/MM conceptionally simple and applicable

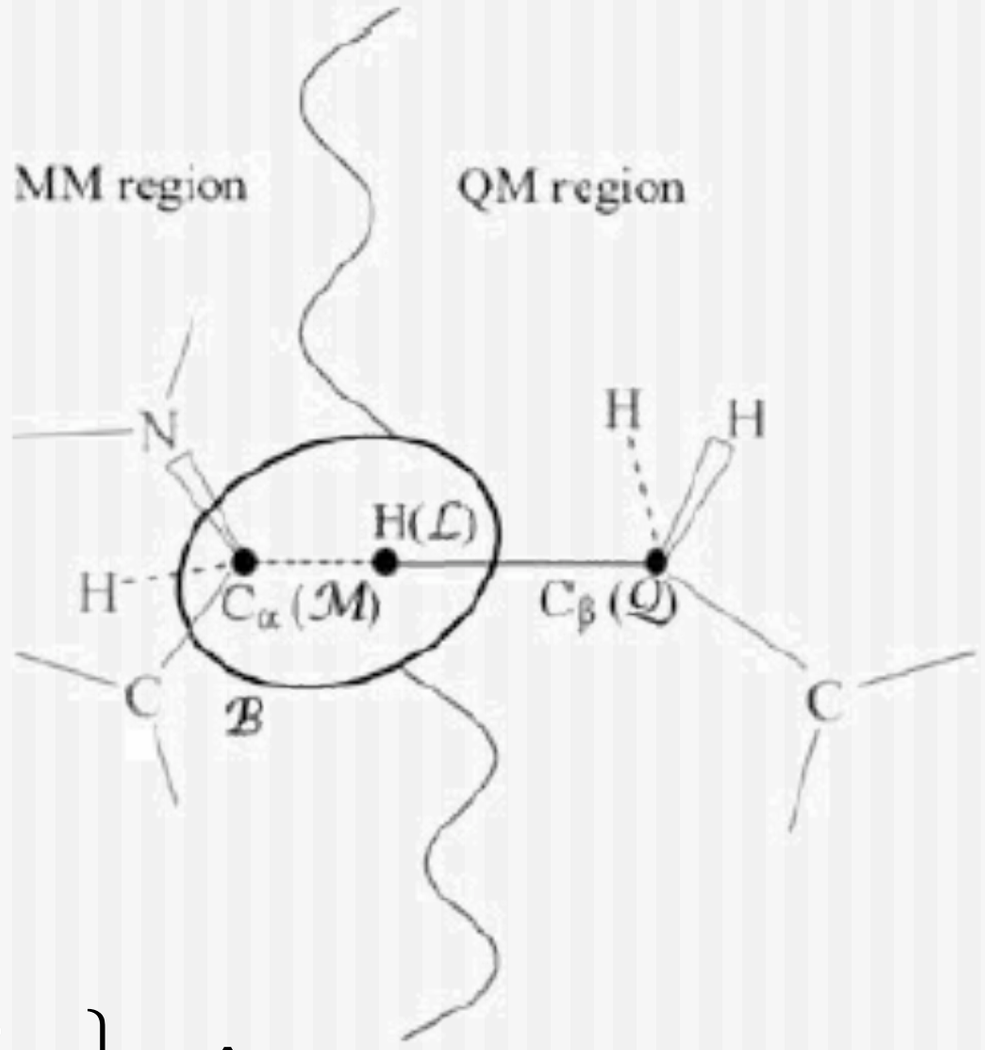
Main distinction between QM/MM methods

- additive vs. subtractive methods
- embedding: mechanic, electrostatic or polarizable
- treatment of the boundary:
  - link atom, pseudo atom, hybrid orbitals
  - electrostatics



Embedding

$$\hat{H} = \hat{H}_{QM} + \hat{H}_{MM} + \hat{H}_{QM/MM}$$



$$\hat{H}_{QM/MM} = -\sum_{i,M} \frac{q_M}{r_{iM}} + \sum_{\alpha,M} \frac{Z_\alpha q_M}{R_{\alpha M}} + \sum_{\alpha,M} \left\{ \frac{A_{\alpha M}}{R_{\alpha M}^{12}} - \frac{B_{\alpha M}}{R_{\alpha M}^{6}} \right\} + \hat{H}_{QM/MM}^{\text{int.}coor}$$

electrostatic mechanical

broken bond

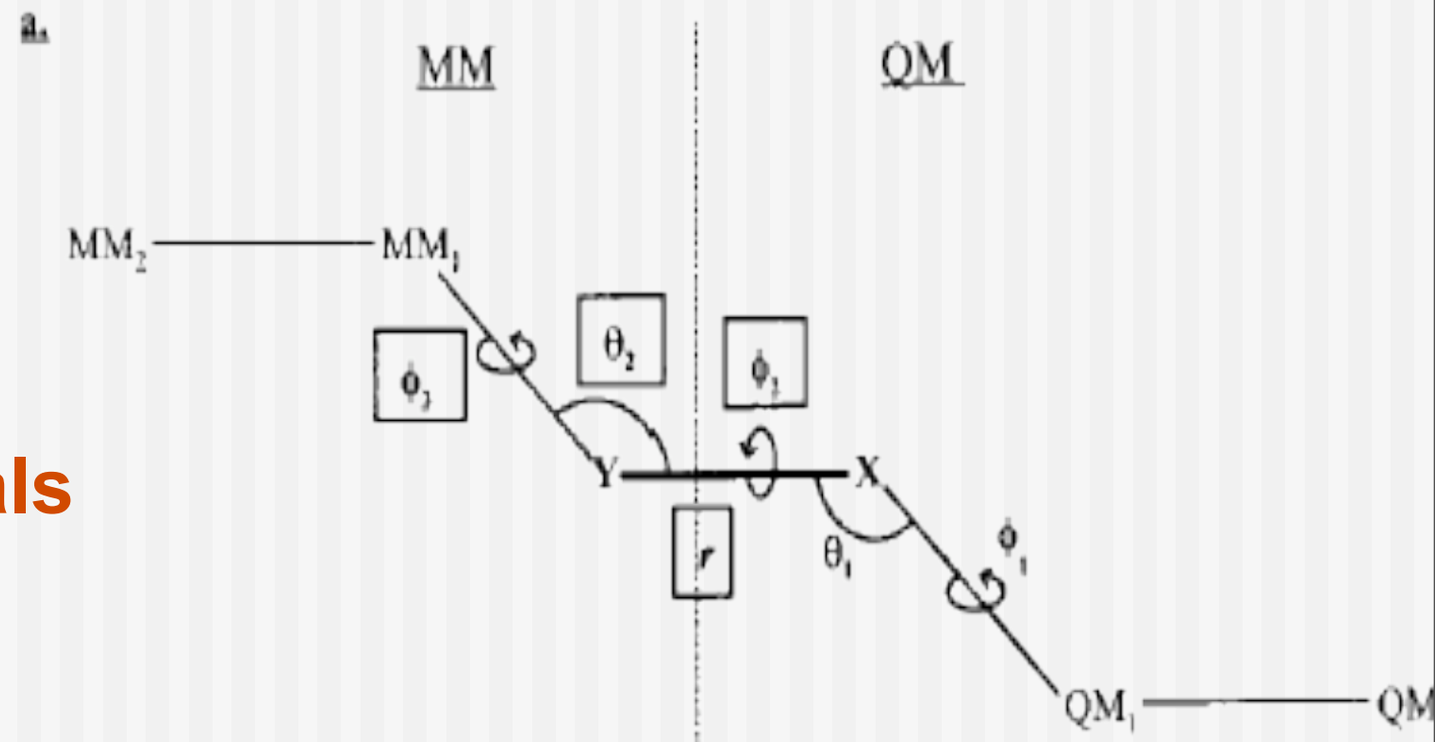
Reuter et al, JPCA 2000

the **X-Y bond**

the **X-Y-MM1, QM1-Y-X angles**

the **QM1-X-Y-MM1,**

QM2-QM1-X-Y 1 dihedrals



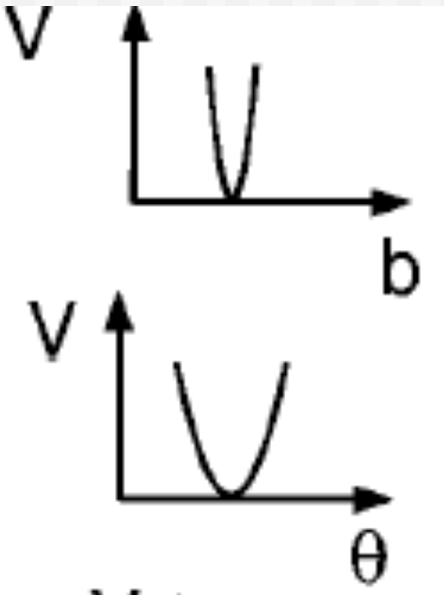
terms are taken from the

force field

$$\hat{H}_{QM/MM} = -\sum_{i,M} \frac{q_M}{r_{iM}} + \sum_{\alpha,M} \frac{Z_\alpha q_M}{R_{\alpha M}} + \sum_{\alpha,M} \left\{ \frac{A_{\alpha M}}{R_{\alpha M}^{12}} - \frac{B_{\alpha M}}{R_{\alpha M}^{6}} \right\} + \hat{H}^{\text{int.coor}}_{QM/MM}$$

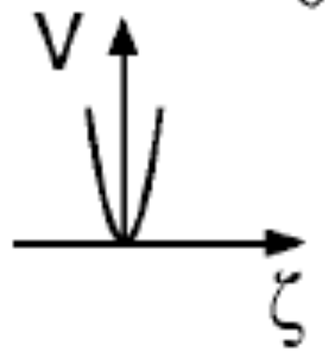
Add these terms at the boundary

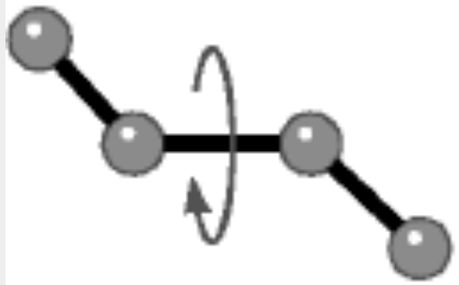
$$V_B = \sum_{\text{Bindungen}} \frac{1}{2} K_b (b - b_0)^2$$



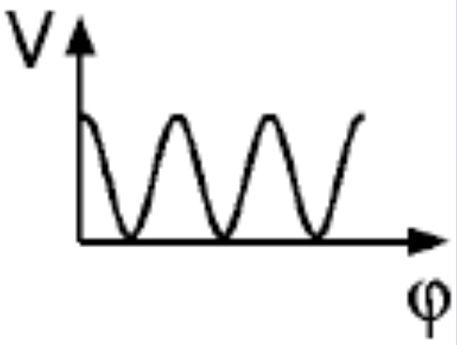
$$V_a = \sum_{\text{Winkel}} \frac{1}{2} K_\theta (\theta - \theta_0)^2$$

$$V_{imp} = \sum_{\text{Extraplanarwinkel}} \frac{1}{2} K_\zeta (\zeta - \zeta_0)^2$$





$$V_D = \sum_{\text{Dihedralwinkel}} K_\varphi [1 + \cos(n\varphi - \delta)]$$



source: Grubmüller
MPI Göttingen

VdW terms

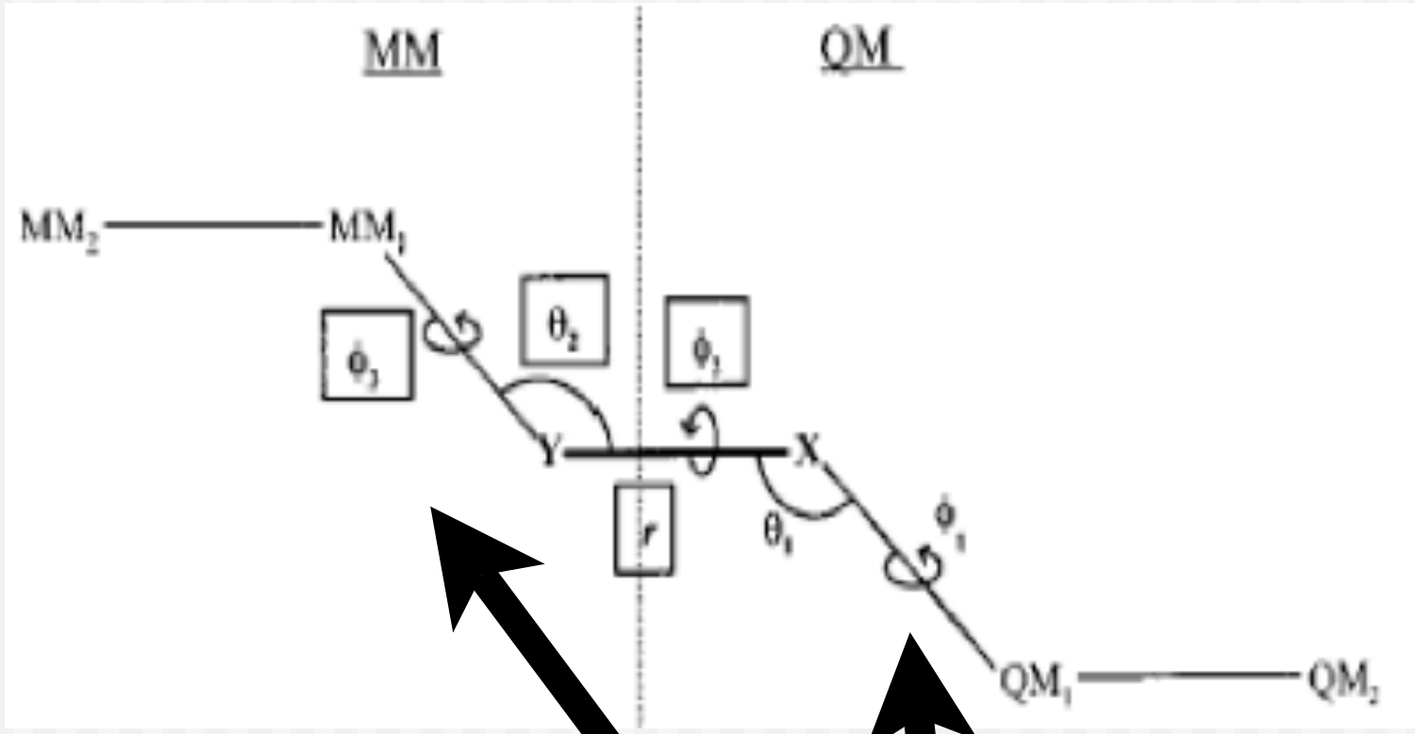
QM atom **α** interacts

with

MM atom **M**

via VdW parameters

as inherited from MM



$$\hat{H}_{QM/MM} = -\sum_{i,M} \frac{q_M}{r_{iM}} + \sum_{\alpha,M} \frac{Z_\alpha q_M}{R_{\alpha M}} + \sum_{\alpha,M} \left\{ \frac{A_{\alpha M}}{R_{\alpha M}^{12}} - \frac{B_{\alpha M}}{R_{\alpha M}^{6}} \right\} + \hat{H}^{\text{int.coor}}_{QM/MM}$$

Mechanical embedding

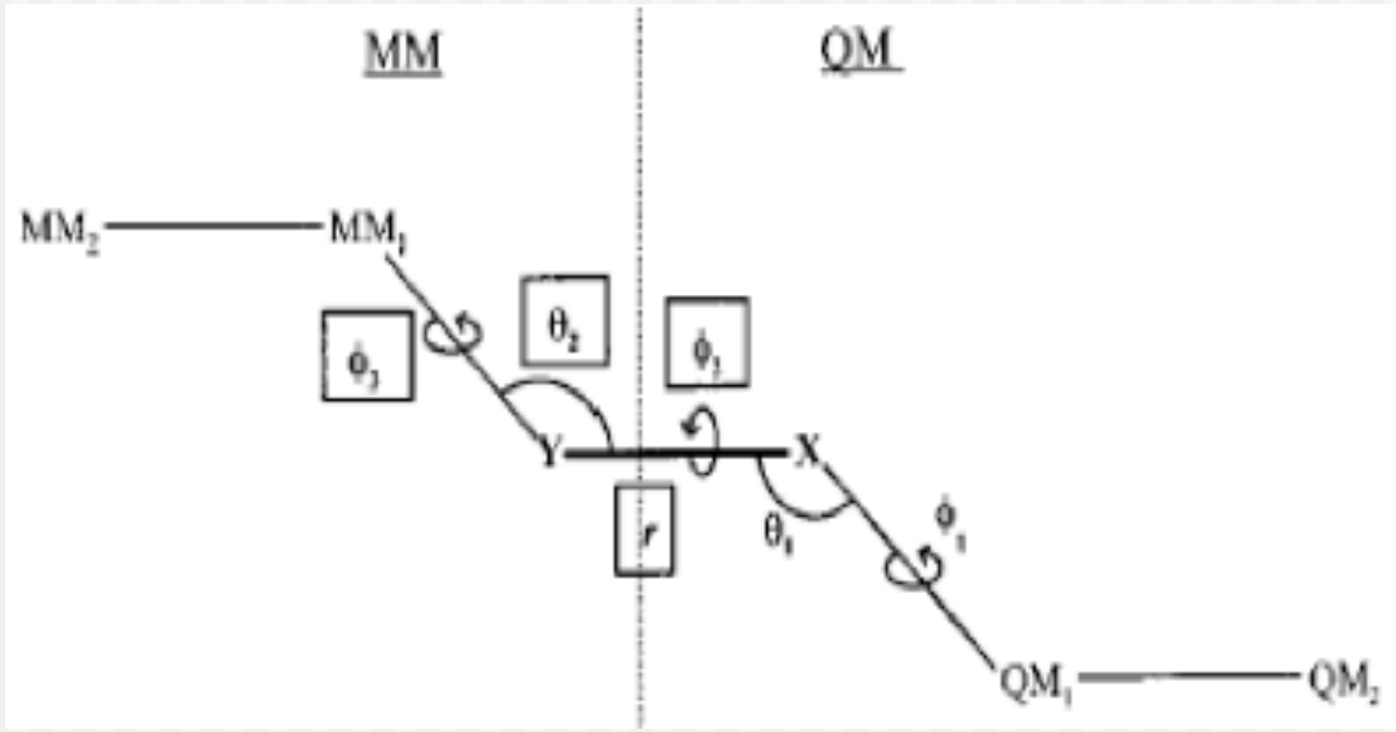
$$\hat{H}_{QM/MM} = \boxed{\phantom{\hat{H}_{QM}}} - \sum_{\alpha,M}\left\{\frac{A_{\alpha M}}{R_{\alpha M}^{12}} - \frac{B_{\alpha M}}{R_{\alpha M}^{6}}\right\} + \hat{H}_{QM/MM}^{\text{int.}coor}$$

QM-MM interaction only via

via VdW parameters and force field terms for bonds at boundary

as inherited from MM

==> active site is kept in place, but NO electrostatic interaction!!!

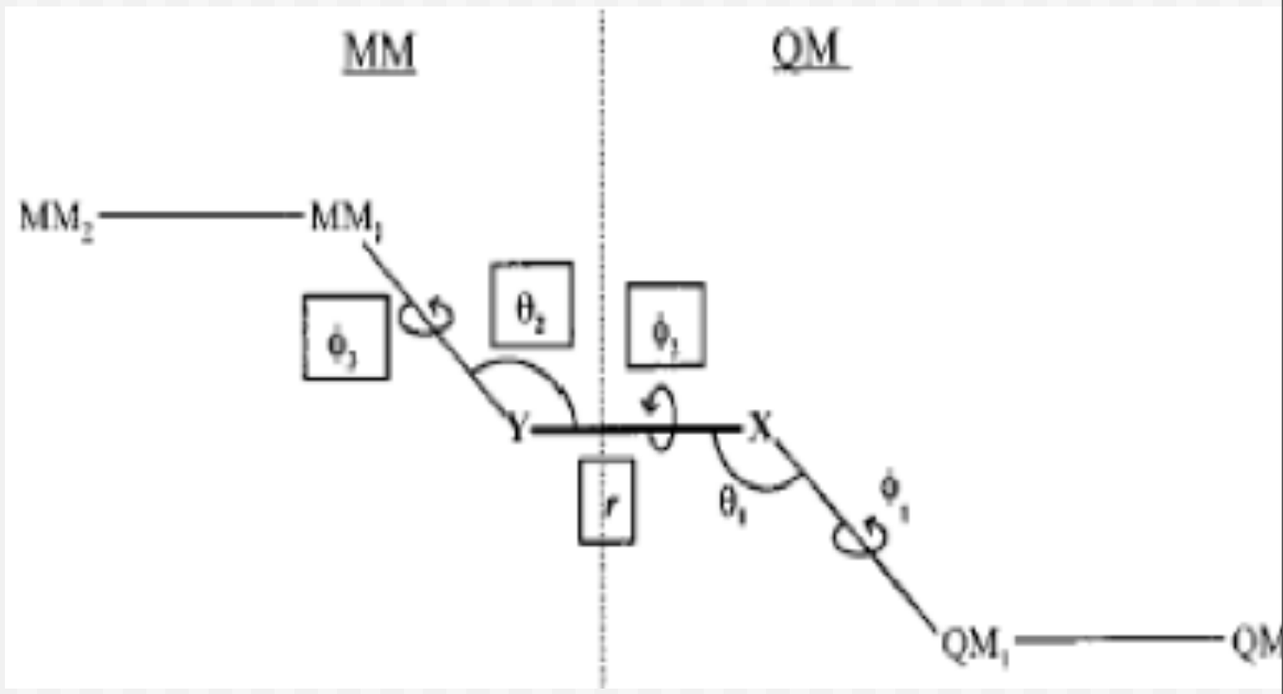


This, however, is crucial in biological systems!

Electrostatic embedding

VdW and ff as in mechanical embedding

$$\hat{H}_{QM/MM} = -\sum_{i,M} \frac{q_M}{r_{iM}} + \sum_{\alpha,M} \frac{Z_\alpha q_M}{R_{\alpha M}} + \sum_{\alpha,M} \left\{ \frac{A_{\alpha M}}{R_{\alpha M}^{12}} - \frac{B_{\alpha M}}{R_{\alpha M}^{6}} \right\} + \hat{H}_{QM/MM}^{\text{int.coor}}$$



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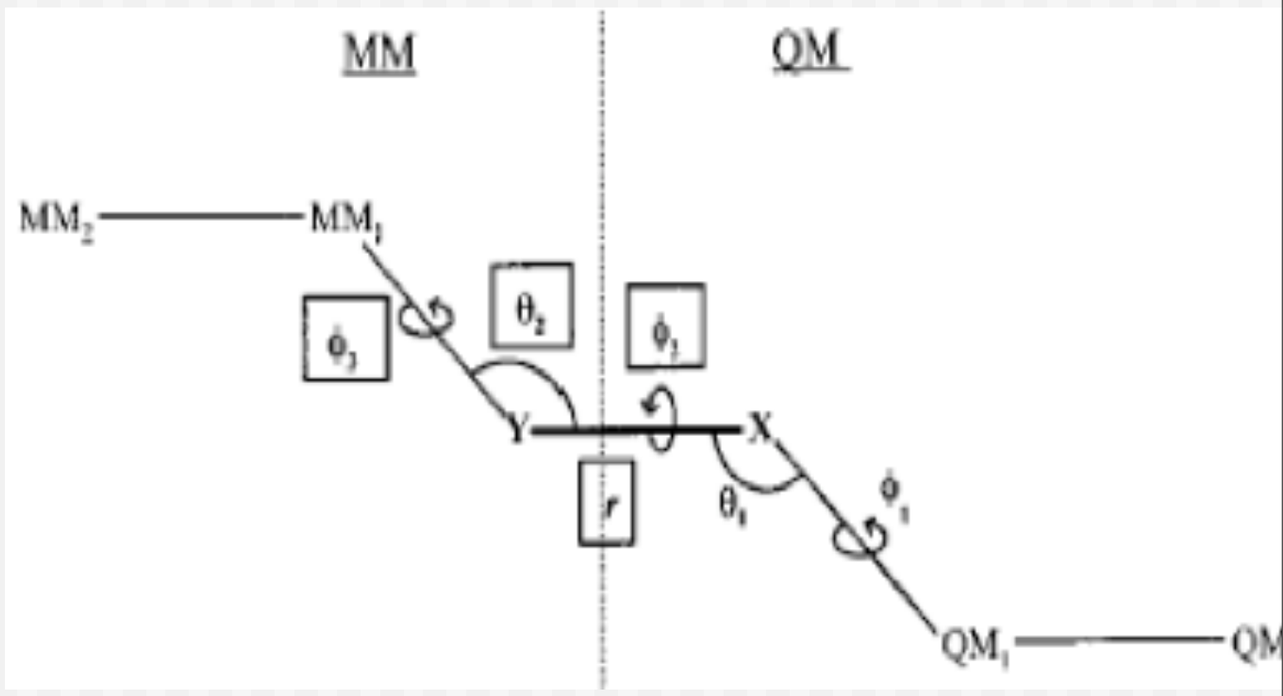
1) MM charge: q_M ⟷ Z_α: QM core charge



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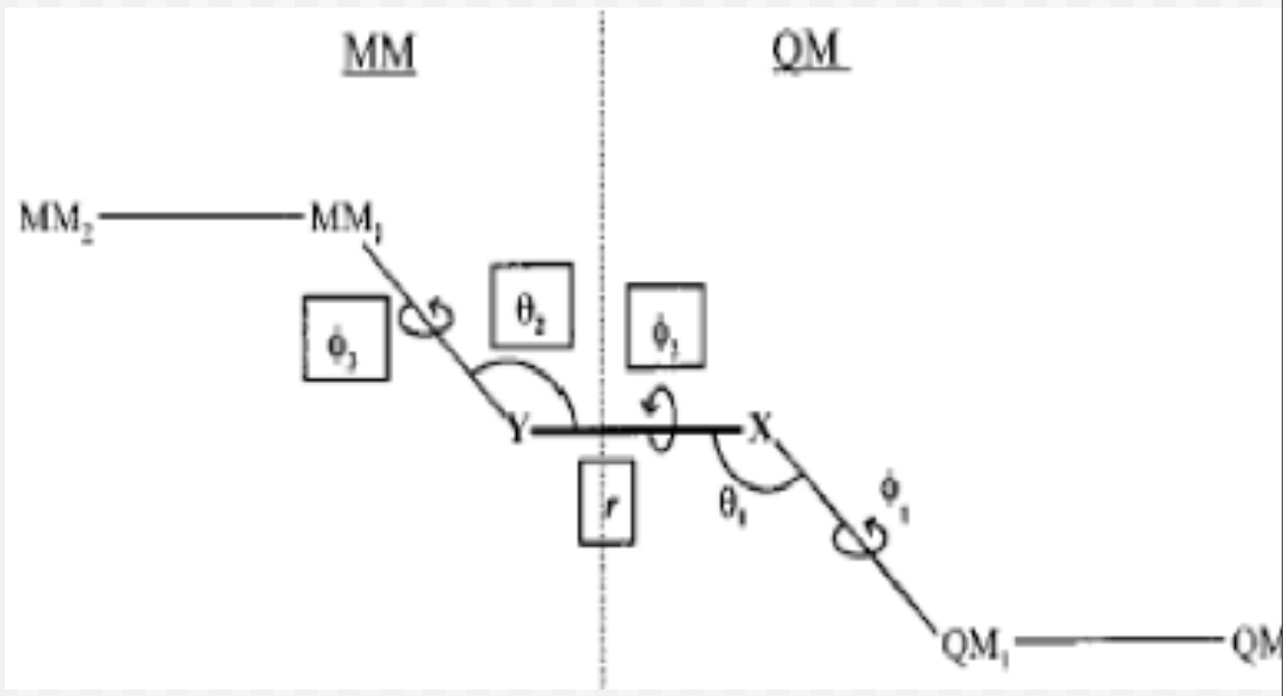


2) compute integrals:

$$< \psi | \frac{q_M}{r_{iM}} | \psi >$$

this describes the polarization of QM wavefunction ψ due to MM charges

Electrostatic embedding

$$< \psi | \frac{q_M}{r_{iM}} | \psi >$$

these are integrals like the electron-core integrals in QM methods:

==> easy to compute, however:

- they are quite **many** for several 1000 MM atoms
- **electron spill out** problem: Electron density ‘sees’ more cores,

  i.e. eventually likes to go out there when using large basis sets

  (Pauli repulsion is missing)
- **overpolarization** problem: MM atom represented as point charge. This leads to an overstimation of the electrostatic interaction.

Electrostatic embedding

$$< \psi | \frac{q_M}{r_{iM}} | \psi >$$

- **electron spill out** problem: put pseudopotenials on MM atoms

- **overpolarization** problem:

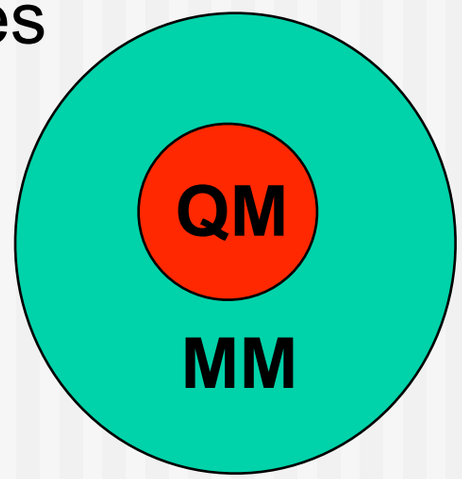
  - damp the 1/r dependence for short distances (JCP 116, 6941)

    (resembles effect of smearing out the charges)

  - gaussian broadening of the point charges at the boundary (JCP 117,10534)

polarizable embedding

standard QM/MM: MM polarizes QM, but MM charges unchanged due to changes in QM.



Large changes of QM dipole occur e.g.

- electron/proton transfer
- optical excitations

=> use **polarizable** models for MM

- mutual polarization of QM and MM

Explicit Polarization Models

- fluctuating (point) charge models (FQ)
  - QM SCF $\rightarrow$ ρ/point charges/multipoles
  - Chemical hardness models (e.g. SCC-DFTB, CHARMM-FQ)

$$E^{\mathrm{ES}}(Q) = -\sum_i \mu_i Q_i + \tfrac{1}{2}\sum_{ij} \eta_{ij}(R_{ij},\eta_i,\eta_j) Q_i Q_j$$

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- induced (atomic) dipole models
  - additive
  - interactive

$$\mu_i^{\mathrm{ind}} = \alpha_i \xi_i \left(M, \underline{\mu}^{\mathrm{ind}}\right)$$

$$E^{\mathrm{ES}}(M,\mu^{\mathrm{ind}}) = -\tfrac{1}{2}\sum_{i\neq j} M_i T_{ij} M_j - \sum_{i\neq j} \mu_i^{\mathrm{ind}} T_{ij}\left(M_j + \tfrac{1}{2}\underline{\mu_j^{\mathrm{ind}}}\right) + \tfrac{1}{2}\sum_i \frac{1}{\alpha_i}\left|\mu_i^{\mathrm{ind}}\right|^2$$

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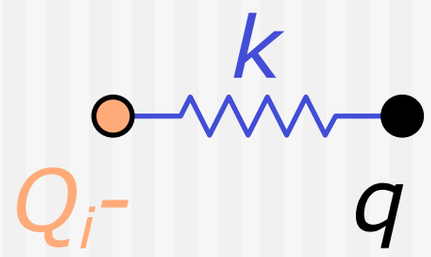
- Drude oscillator model

$$\alpha = \frac{q_{\mathrm{D}}^2}{k_{\mathrm{D}}}$$



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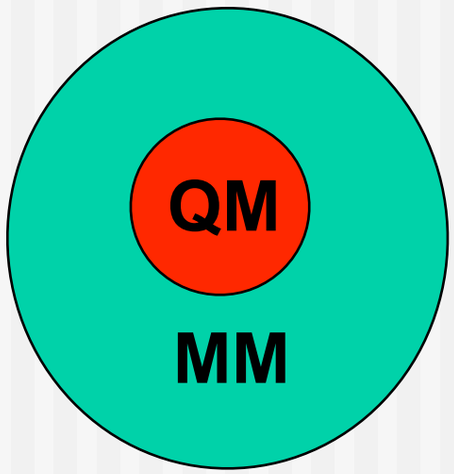
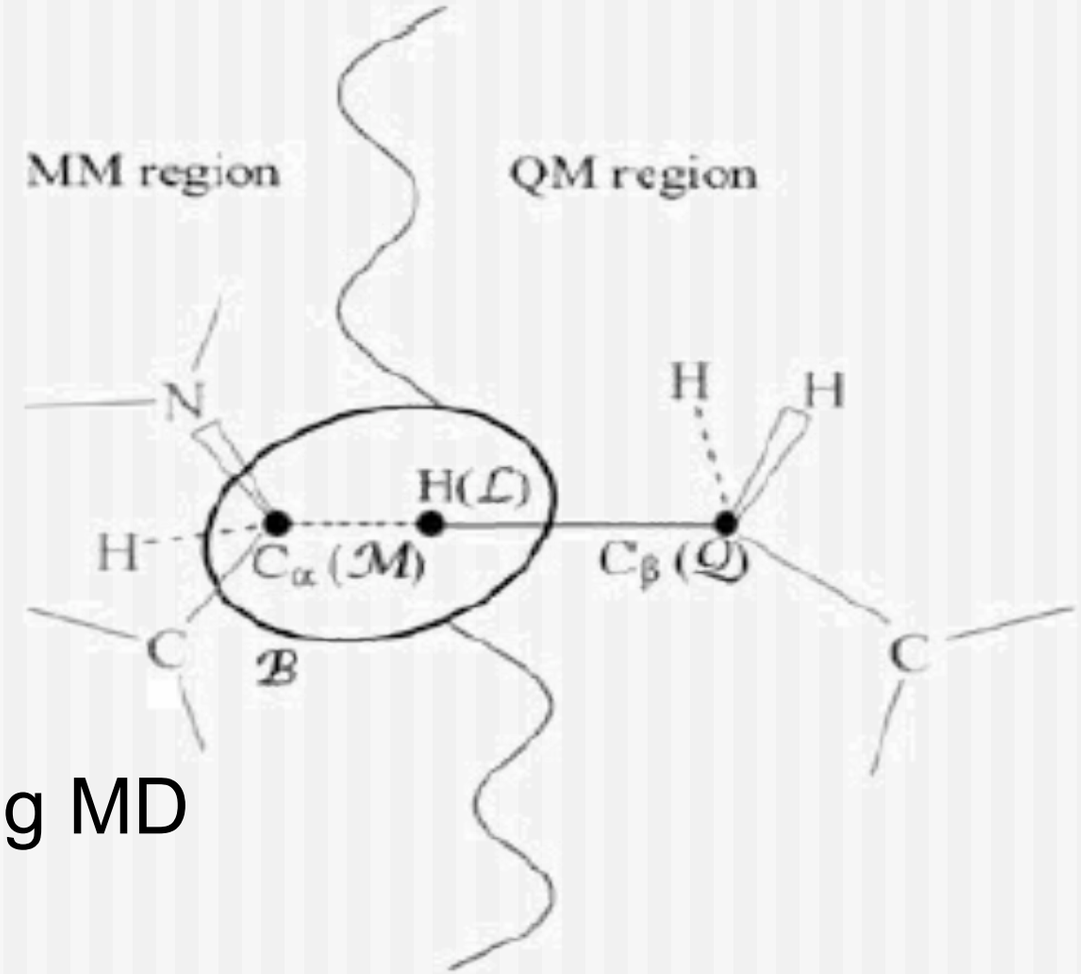


Boundary: link atom

- put a H atom between MM and QM atom
- QM description saturated



Problems:

- 3 extra degrees of freedom during MD

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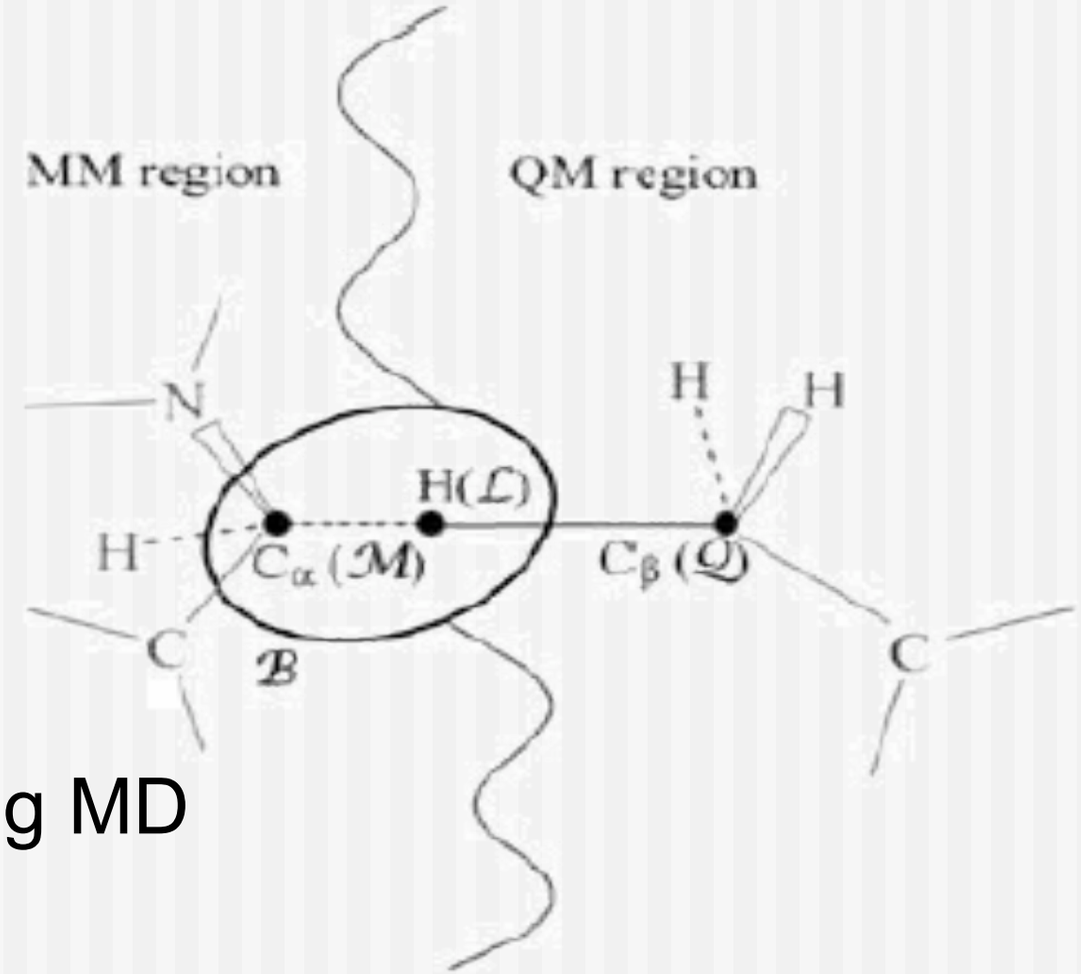

Problems:

- 3 extra degrees of freedom during MD

constrain H_{link} with respect to C_{QM} and project forces to C_{QM}

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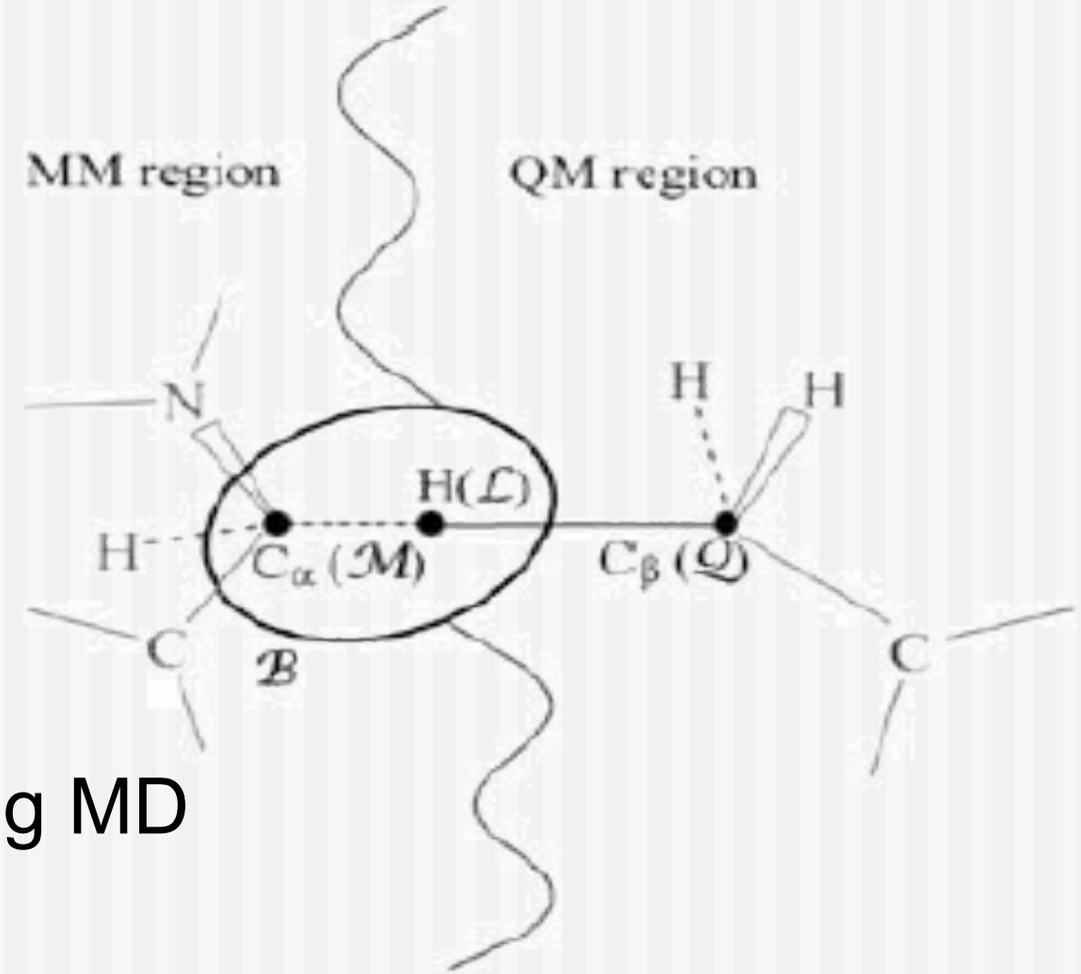

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- C_{MM} - H_{link} very short (0.4 Å): electrostatic artifacts

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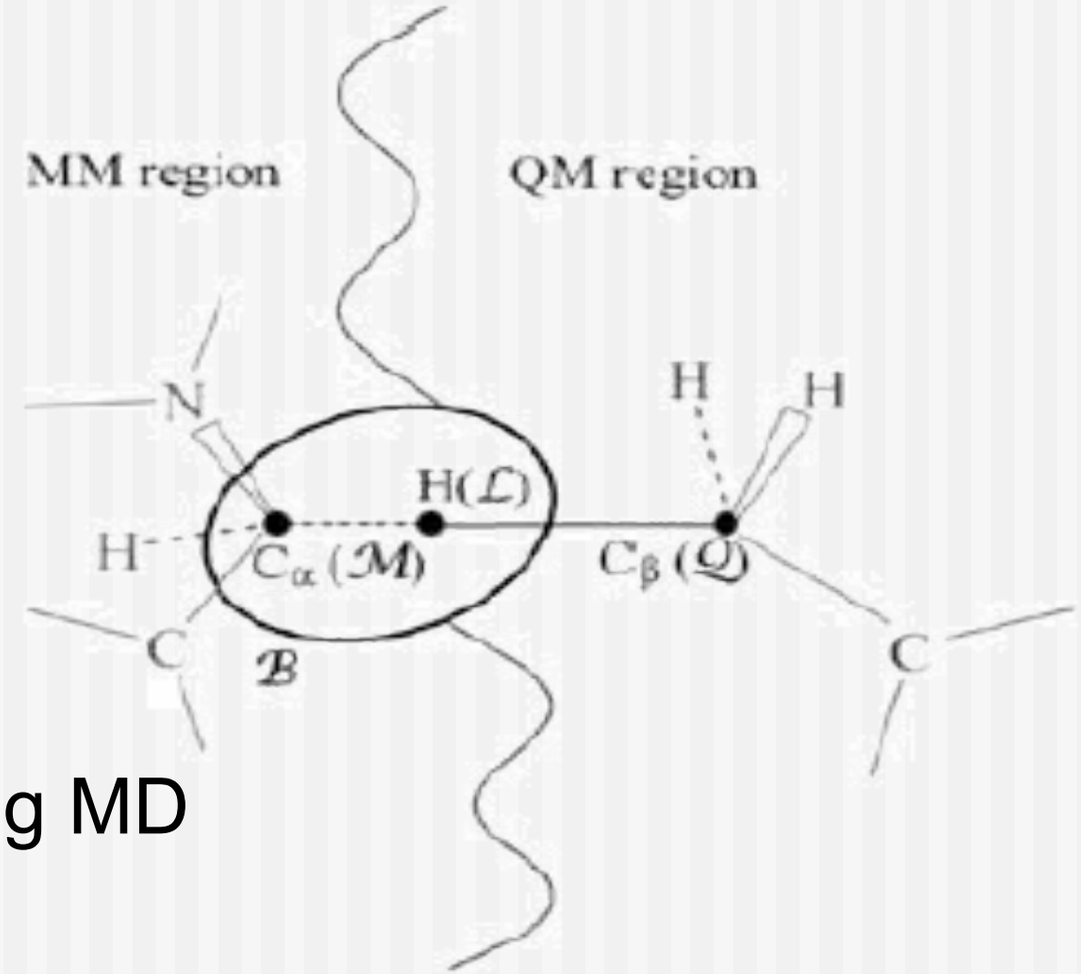

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  modify charges on MM fragment

Boundary: link atom

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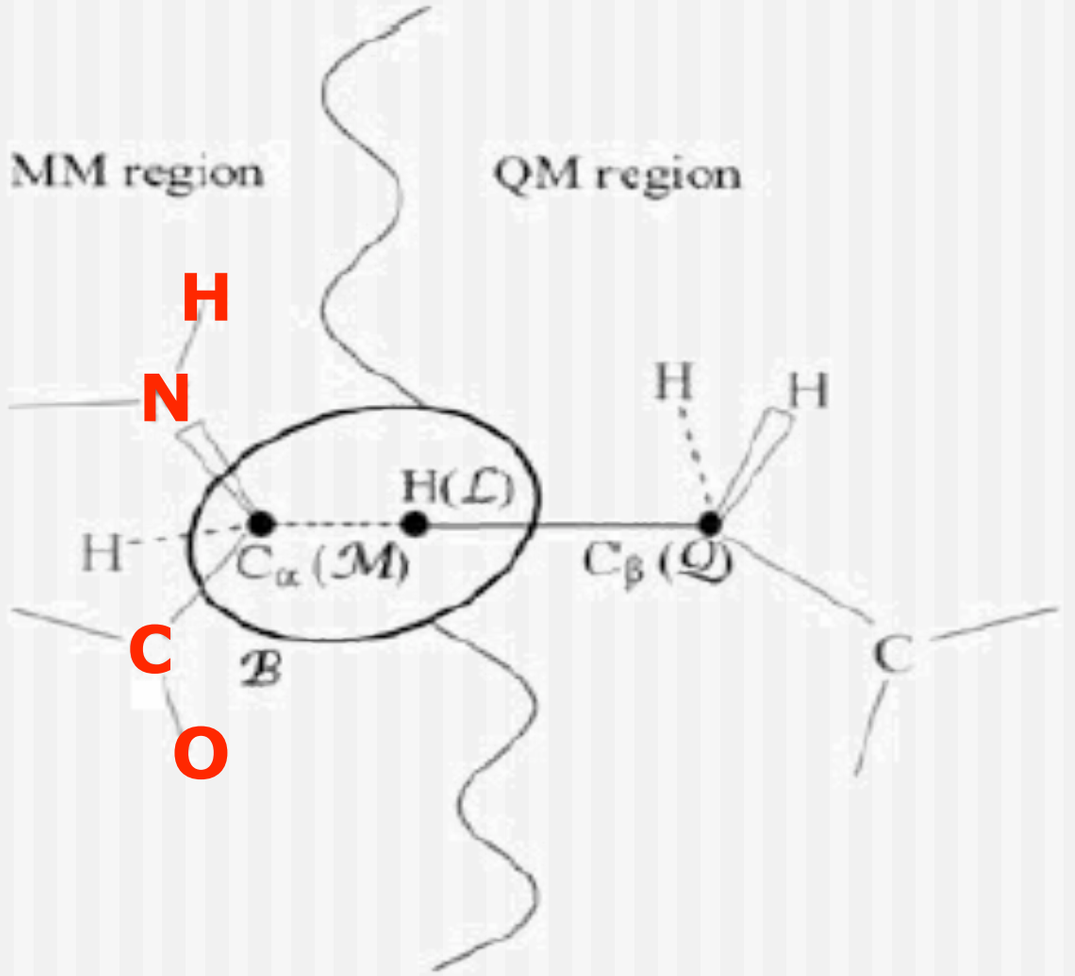
modify charges on MM fragment

a) delete charge on C_{MM}

b) delete charge on whole fragment

both options quite bad!



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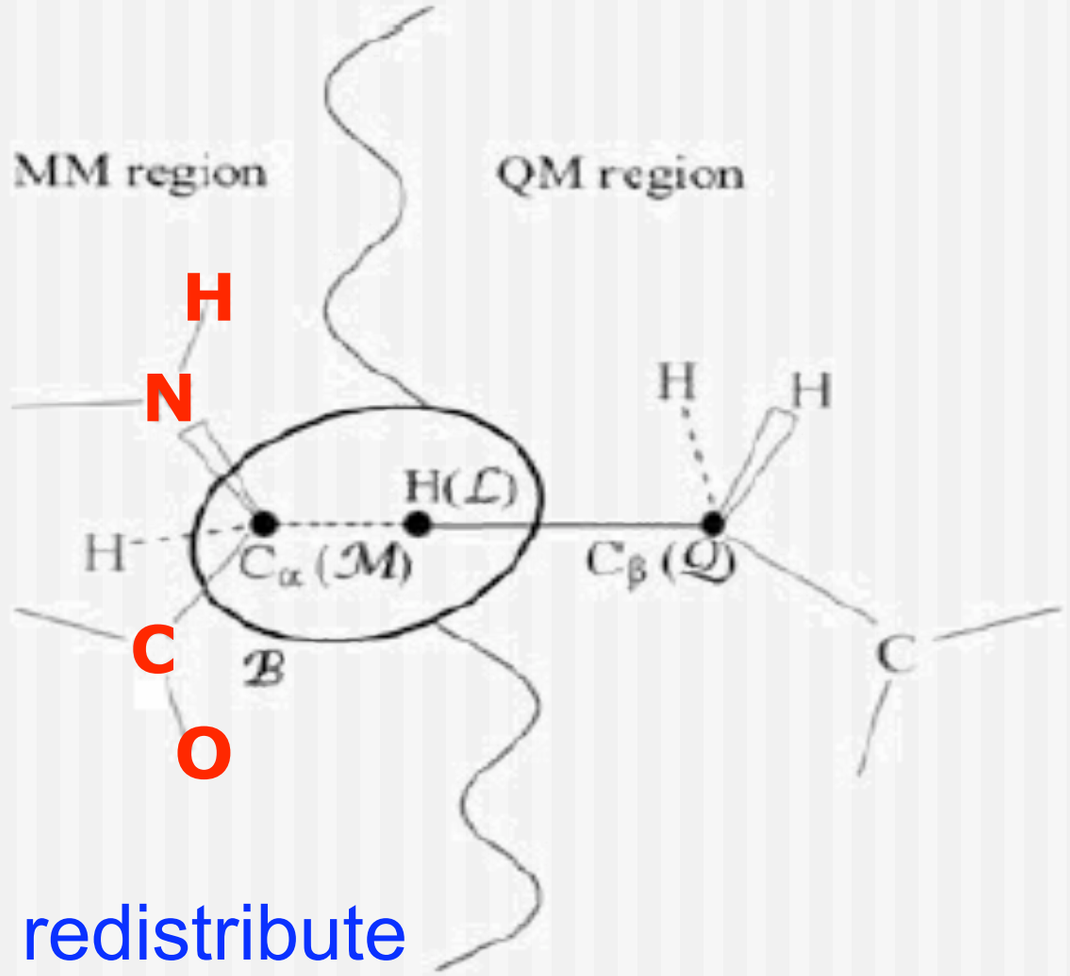


c) delete charges on C_{MM} and H and redistribute

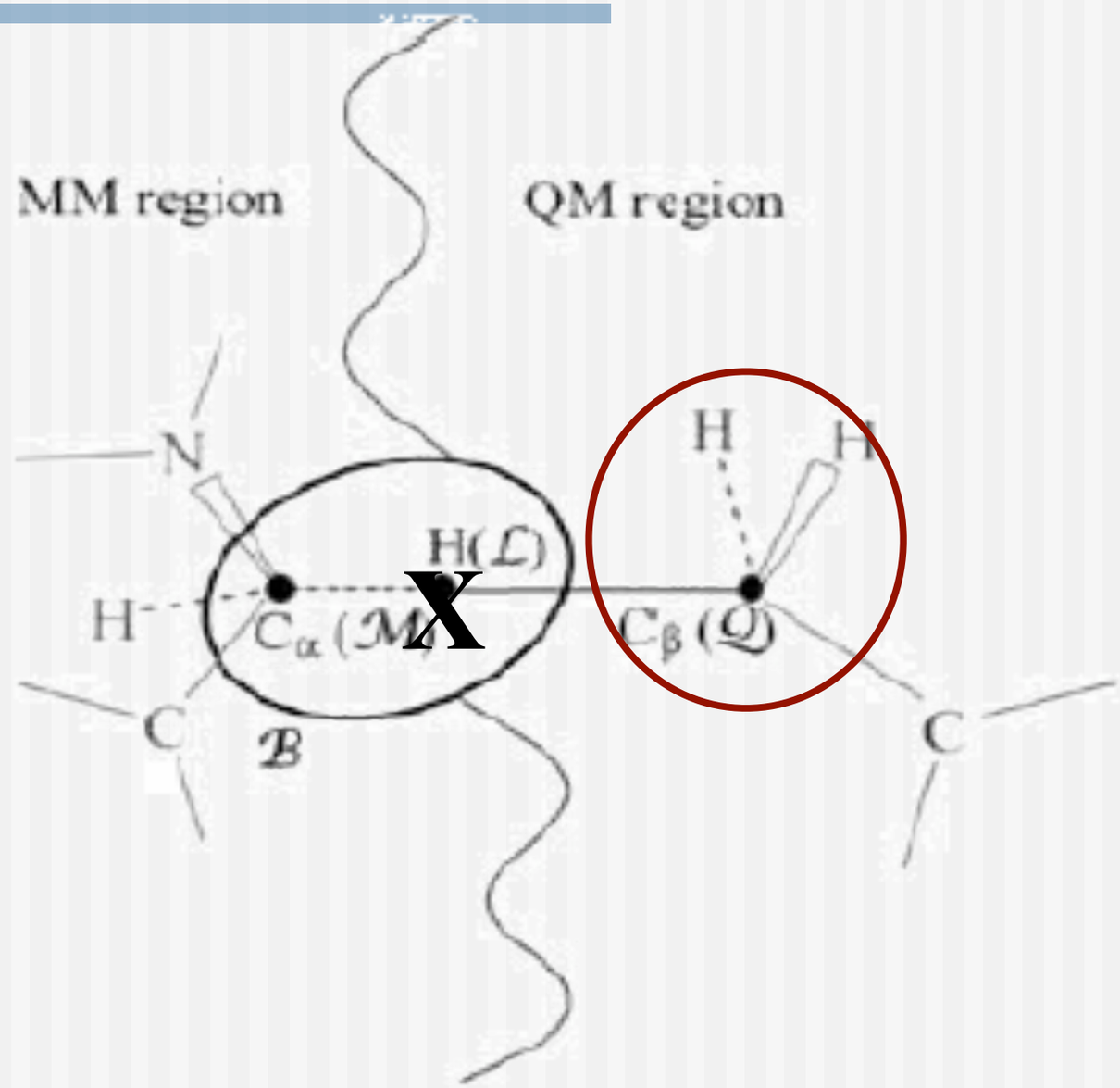
to C=O and N-H, to maintain dipole moment of MM fragment

Boundary: pseudo atom

Pseudobond- connection atom:

Zhang, Lee, Yang, JCP **110**, 46

Antes&Thiel, JPCA **103** 9290



- No link atom: parametrize $C_\beta H_2$ as pseudoatom (pseudo-F)

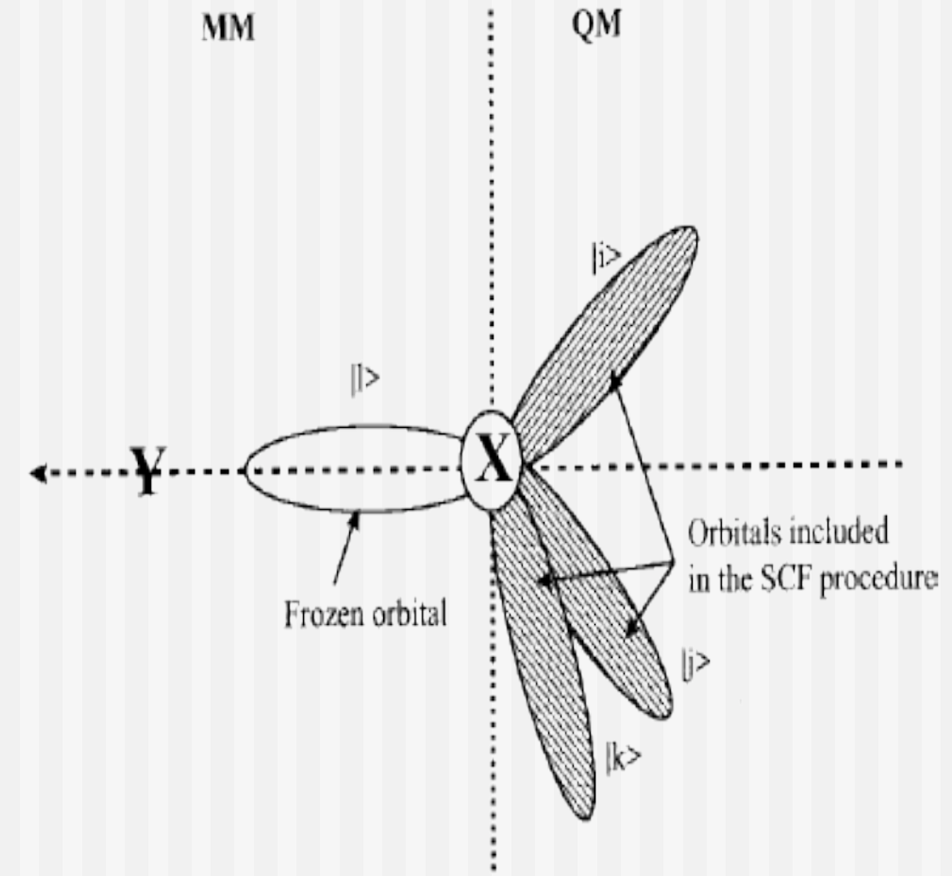
- put bonded terms at ‘pseudo’-C_β to connect with MM region

Boundary: frozen orbitals, hybride

Warshel, Levitt 1976

Rivail + co. 1996-2002

Gao et al 1998



- freeze orbital at ‘last’ QM atom
- other orbitals included in QM SCF

- put bonded terms at QM atom X
  to connect with MM region

Combined QM/MM

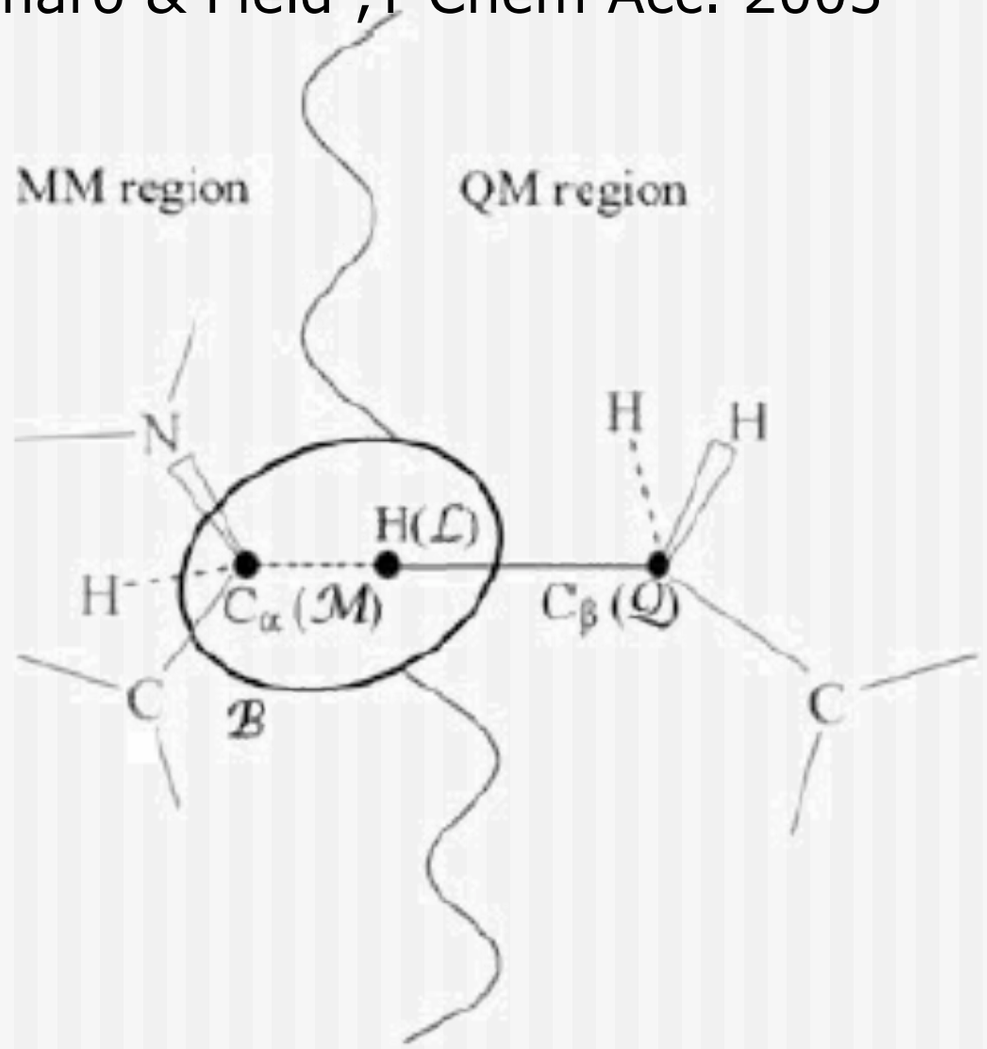
Nonbonding terms:

VdW

- take from force field

- reoptimize for QM level

Amaro & Field ,T Chem Acc. 2003



Coulomb:

which charges?

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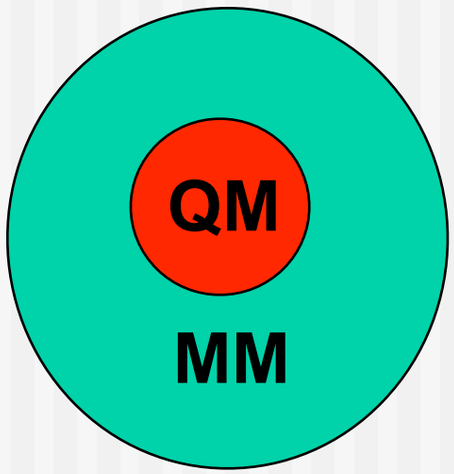

Combined QM/MM

Tests:

- C-C bond lengths, vib. frequencies
- C-C torsional barrier
- H-bonding complexes
- proton affinities, deprotonation energies

Local Orbital vs. plane wave approaches:

PW implementations

(most implementations in LCAO)

- periodic boundary conditions and large box!
lots of empty space in unit cell

- hybride functionals have better accuracy: B3LYP, PBE0 etc.

+ no BSSE

+ parallelization (e.g. DNA with ~1000 Atoms)

Problems

- QM and MM accuracy
- QM/MM coupling
- model setup: solvent, restraints
- PES vs. FES: importance of sampling

All these factors CAN introduce errors in similar magnitude