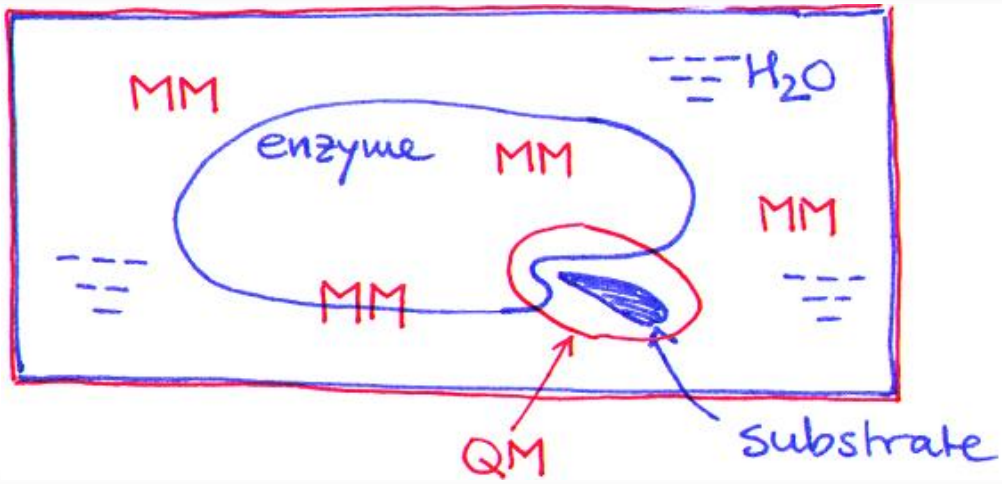
Karlsruhe Institute of Technology

QM/MM simulations with PLUMED and GROMACS

Tomáš Kubař

Institute of Physical Chemistry & Center for Functional Nanostructures



DFTB3

- “semi-empirical density-functional theory (DFT)”
- Taylor expansion of total energy in density up to the 3rd order

$$E^{\mathrm{DFTB3}} = \sum_{i,a,b} \sum_{\mu \in a} \sum_{\nu \in b} n_i \, c_{\mu i} \, c_{\nu i} \, H^0_{\mu\nu}$$

$$+ \frac{1}{2} \sum_{a,b} \gamma_{ab} \, \Delta q_a \, \Delta q_b + \frac{1}{3} \sum_{a,b} (\Delta q_a)^2 \Delta q_b \, \Gamma_{ab}$$

$$+ E^{\mathrm{rep}} + E^{\mathrm{disp}}$$

- optimized minimal basis set
- charge-independent Hamiltonian pre-calculated and tabulated
  – no calculation of integrals at run time needed
- electron density represented by atom-centered spherical contributions
- not charge dependent: “repulsive” energy, dispersive energy (D3)

DFTB3

- Self-consistent solution of charge-dependent Hamiltonian

$$H_{\mu\nu} = H^0_{\mu\nu} + \frac{1}{2} S_{\mu\nu} \sum_c^{\mathrm{QM}} \Delta q_c \Bigg[\frac{1}{2} \left(\gamma_{ac} + \gamma_{bc}\right) + \frac{1}{3} \left(\Delta q_a \, \Gamma_{ac} + \Delta q_b \, \Gamma_{bc}\right) + \frac{1}{6} \Delta q_c \left(\Gamma_{ca} + \Gamma_{cb}\right) \Bigg]$$

- QM/MM:

$$\hat{H} = \hat{H}^{\mathrm{QM}} + \hat{H}^{\mathrm{MM}} + \hat{H}^{\mathrm{QM/MM}}$$

$$H^{\mathrm{QM/MM}}_{\mu\nu} = S_{\mu\nu} \cdot \frac{1}{2} \left(\Phi_a \, \Delta q_a + \Phi_b \, \Delta q_b\right)$$

$$\Phi_a = \sum_{A \in \mathrm{MM}} \frac{Q_A}{|\vec{r}_A - \vec{r}_a|}$$

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QM/MM in GROMACS

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

- DFTB – newly implemented and fully integrated within Gromacs
- No file-based communication
- Gromacs PME routines used for Φ – efficiency
  (PME used also for QM–QM interaction, and not full Ewald)

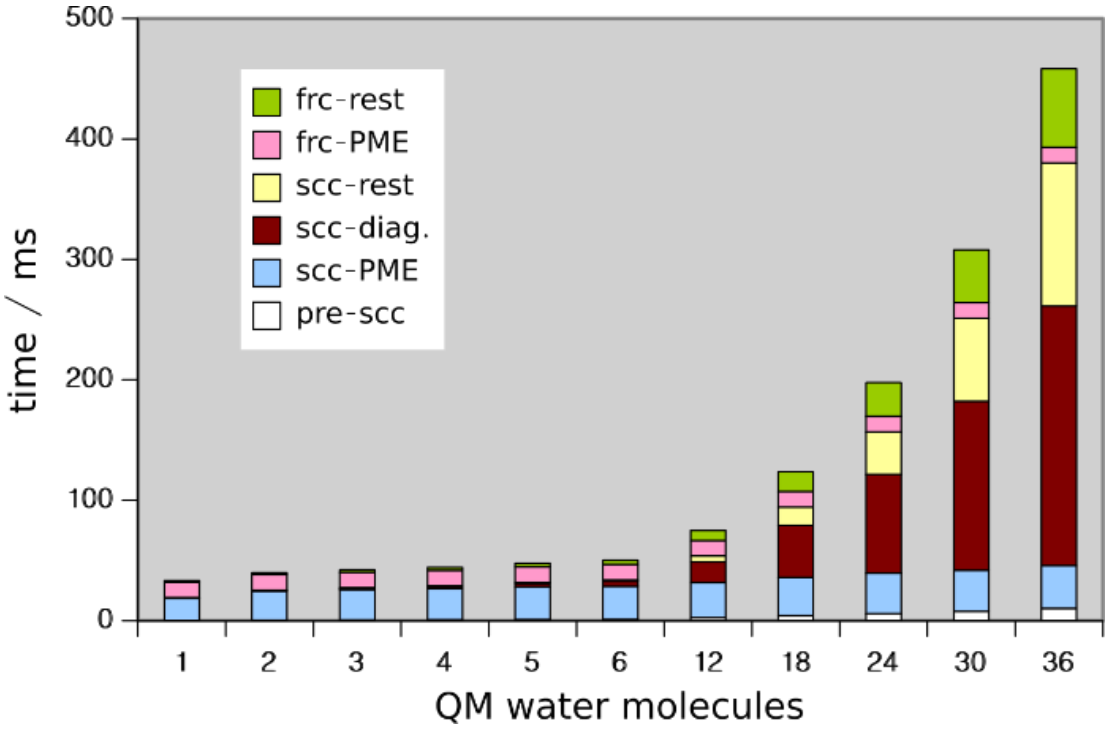
- Free energies – internal Gromacs functionality
  or available external tools (PLUMED)

```
; 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
```

Computational efficiency

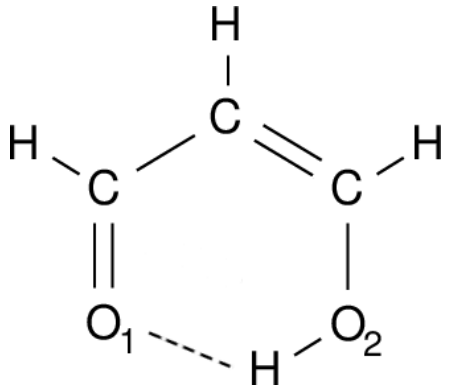
- One DFTB calculation of forces



- Multi-nanosecond simulations possible

Application 1 – PT in malonaldehyde

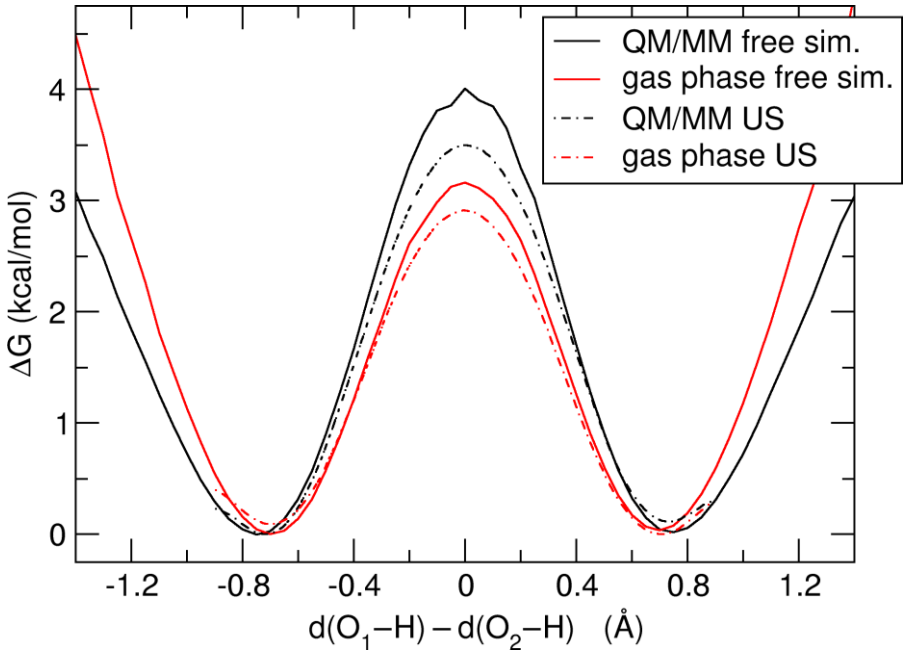
- Malonaldehyde – ultra-fast intramolecular proton transfer



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

Application 1 – PT in malonaldehyde

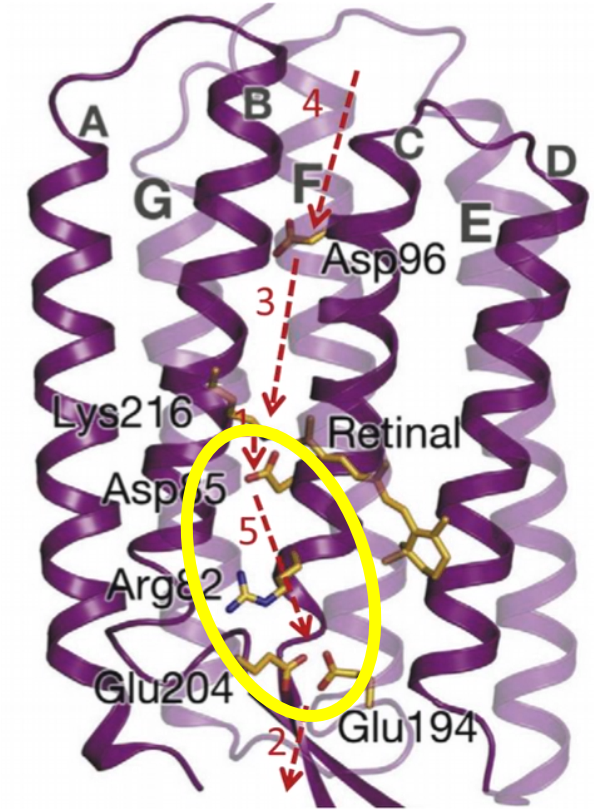
- With QM/MM and in the gas phase
  reaction coordinate: difference of O–H distances

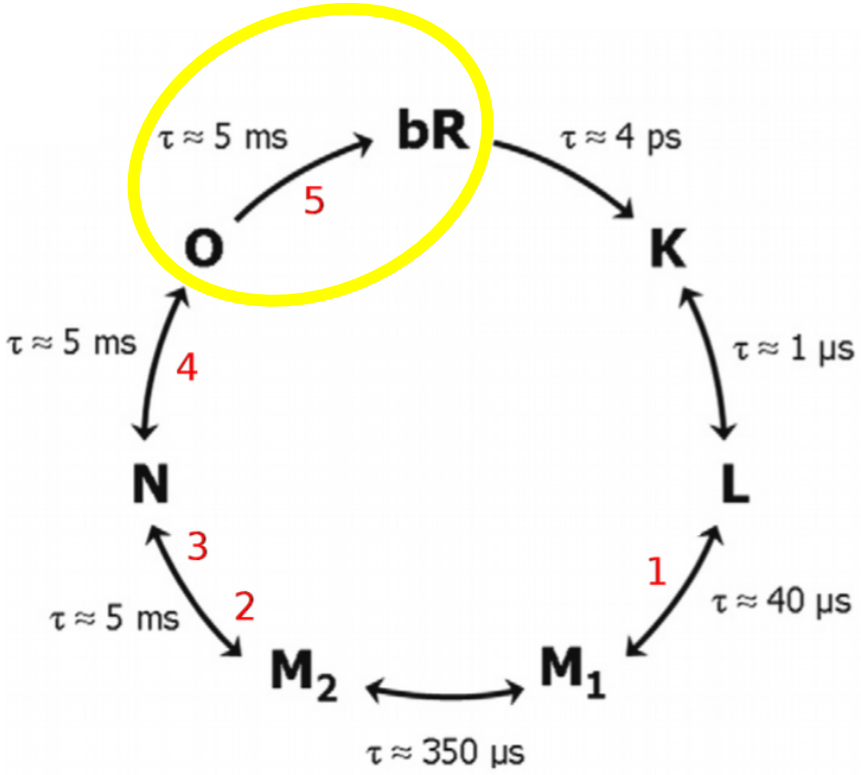


- NB: classical simulation → no quantum effects (ZPE) considered
  → barrier possibly overestimated

Application 2 – PT in bacteriorhodopsin

- Proton pump – long-range proton transport
- Photocycle – sequence of individual PT steps





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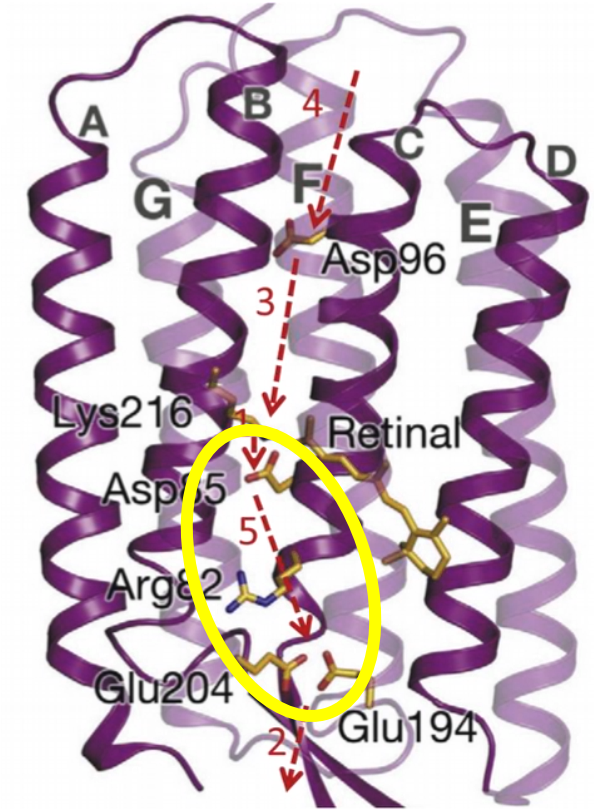
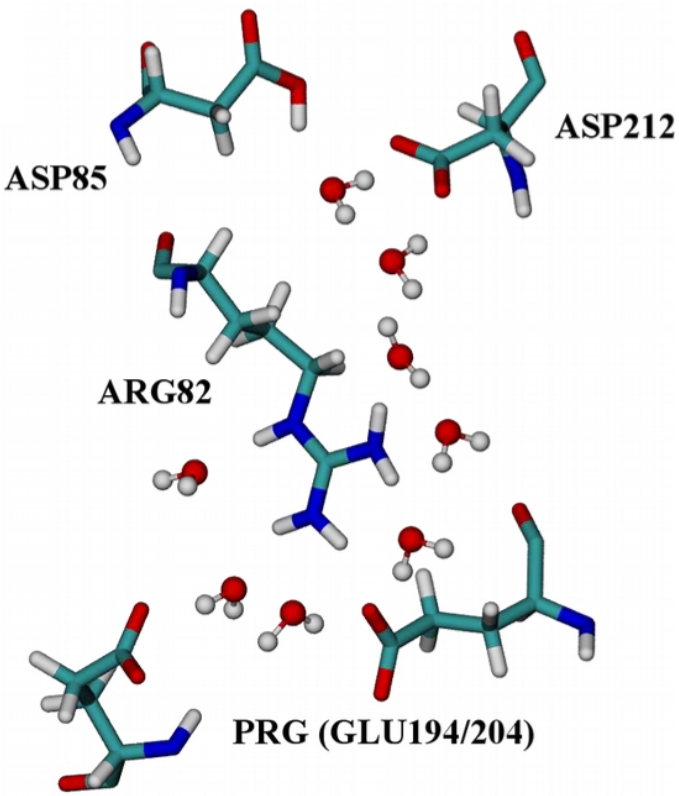
Application 2 – PT in bacteriorhodopsin

- Proton pump – long-range proton transport
- Photocycle – sequence of individual PT steps





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Application 2 – PT in bacteriorhodopsin

- Reaction coordinate: “modified center of excess charge” (mCEC)

548 *J. Phys. Chem. A* **2006,** *110,* 548−563

Toward Theoretical Analyis of Long-Range Proton Transfer Kinetics in Biomolecular Pumps†

P. H. König,⊥ N. Ghosh,‡ M. Hoffmann,⊥ M. Elstner,⊥ E. Tajkhorshid,§ Th. Frauenheim,*,⊥ and Q. Cui*,‡

10.1021/jp052328q CCC: $33.50

$$\vec{\xi} = \sum_{i=1}^{N_H} \vec{r}^{H_i} - \sum_{j=1}^{N_X} w^{X_j} \vec{r}^{X_j} - \sum_{i=1}^{N_H} \sum_{j=1}^{N_X} f_{sw}(d_{X_j,H_i})(\vec{r}^{H_i} - \vec{r}^{X_j})$$

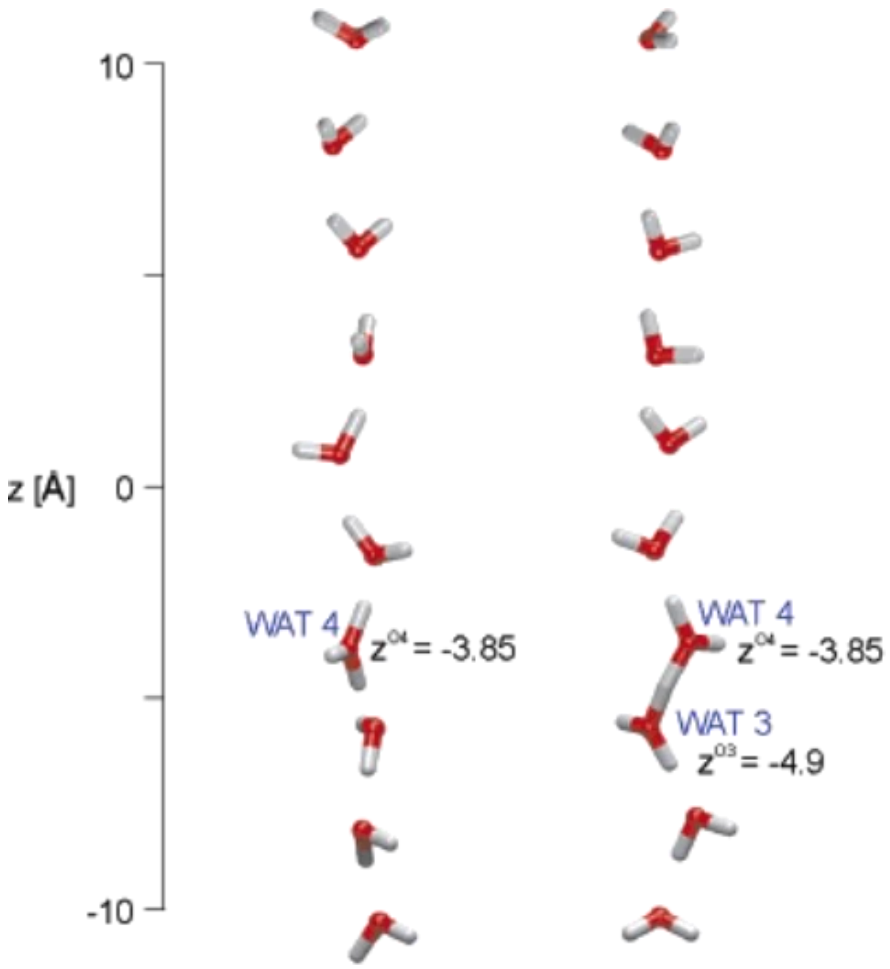
$$f_{sw}(d) = \frac{1}{1 + \exp[(d - r_{sw})/d_{sw}]}$$

$$\zeta_R = \frac{d_{\xi,D}}{d_{\xi,D} + d_{\xi,A}}$$

– takes values between 0 (donor) and 1 (acceptor)

Application 2 – PT in bacteriorhodopsin

- Reaction coordinate: mCEC
- Not one, but many protons, which are indistinguishable
- mCEC is on the heavy atom rather than on the proton itself
- Special cases like Zundel ion



Application 2 – PT in bacteriorhodopsin

```
###     Atoms of the PT members     ###
OD1:     POSITION ATOM=3273 NOPBC
OD2:     POSITION ATOM=3274 NOPBC
HD:      POSITION ATOM=3275 NOPBC
O1:      POSITION ATOM=3625 NOPBC
H11:     POSITION ATOM=3626 NOPBC
...

###     Definition of switching function components     ###
cx: COORDINATION_X GROUPA=3273,3274,3137,3138,3625,3628,3631,3634,3637,3640,3643,3646,3
                   GROUPB=3275,3626,3627,3629,3630,3632,3633,3635,3636,3638,3639,3641,3
                   R_SW=0.115
                   D_SW=0.0045
cy: COORDINATION_Y ...
cz: COORDINATION_Z ...

###     XI-x-DIM     ###
COMBINE ...
  LABEL=x
  ARG=HD.x,O1.x,H11.x,H12.x,O2.x,H21.x,H22.x,O3.x,H31.x,H32.x,O4.x,H41.x,H42.x,O5.x,H51
  COEFFICIENTS=1,-2,1,1,-2,1,1,-2,1,1,-2,1,1,-2,1,1,-2,1,1,-2,1,1,-2,1,1,-2,1,1,-2,1,1,
  PERIODIC=NO
... COMBINE

###     XI-y-DIM     ###
...

###     XI-z-DIM     ###
...

###     Definition of zeta     ###
MATHEVAL ...
  LABEL=zeta
  ARG=x,y,z,OD1.x,OD1.y,OD1.z,OD2.x,OD2.y,OD2.z,OA1.x,OA1.y,OA1.z,OA2.x,OA2.y,OA2.z
  VAR=x,y,z,d1x,d1y,d1z,d2x,d2y,d2z,a1x,a1y,a1z,a2x,a2y,a2z
  FUNC=(sqrt((x-d1x)*(x-d1x)+(y-d1y)*(y-d1y)+(z-d1z)*(z-d1z))*sqrt((x-d2x)*(x-d2x)+(y-d
  PERIODIC=NO
... MATHEVAL
```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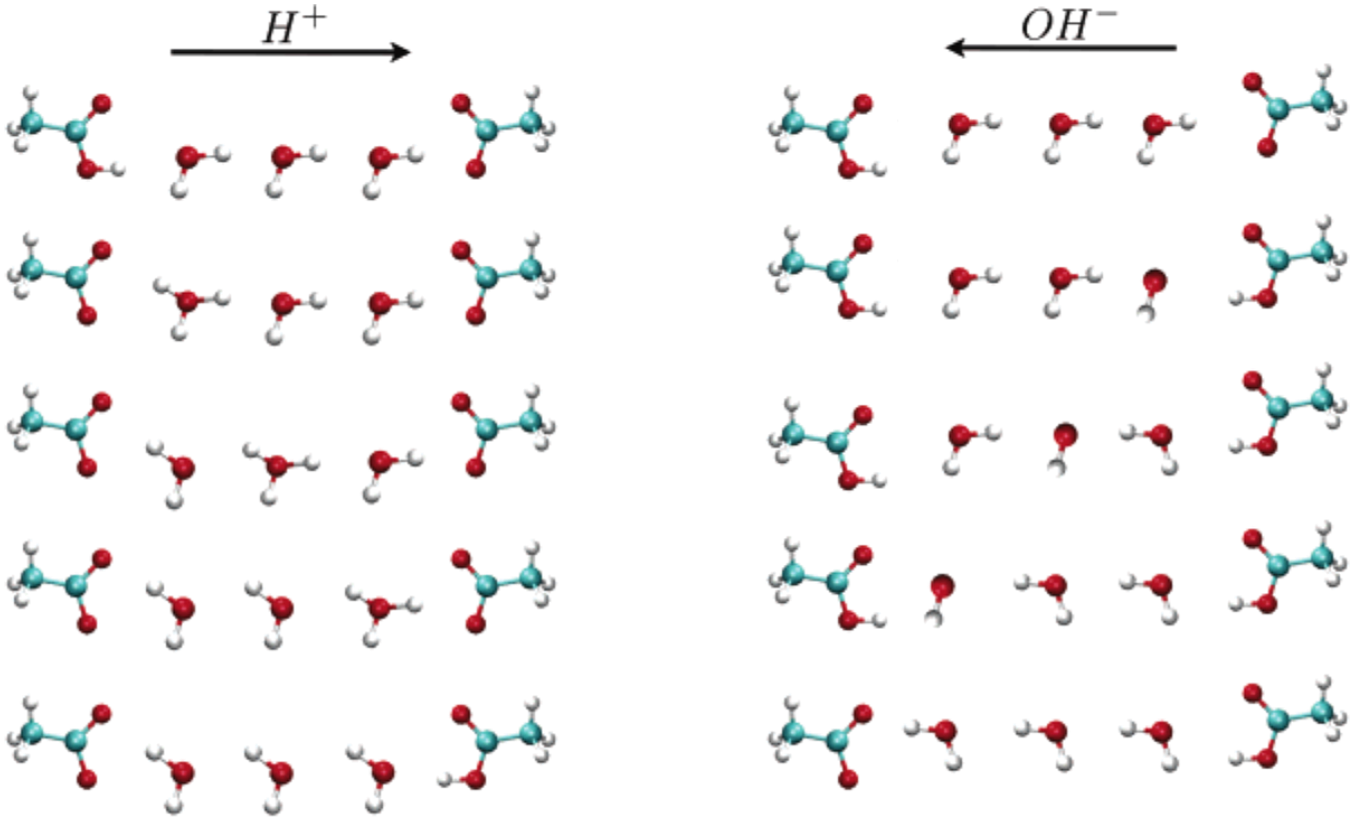
Application 2 – PT in bacteriorhodopsin

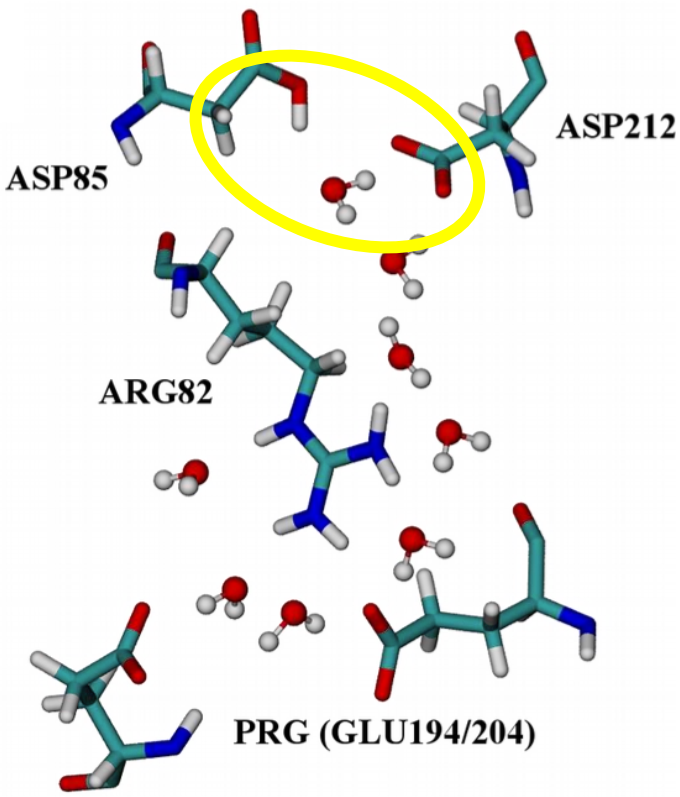
- Mechanism – an excess proton or a proton hole?



- Description – averaged coordination number

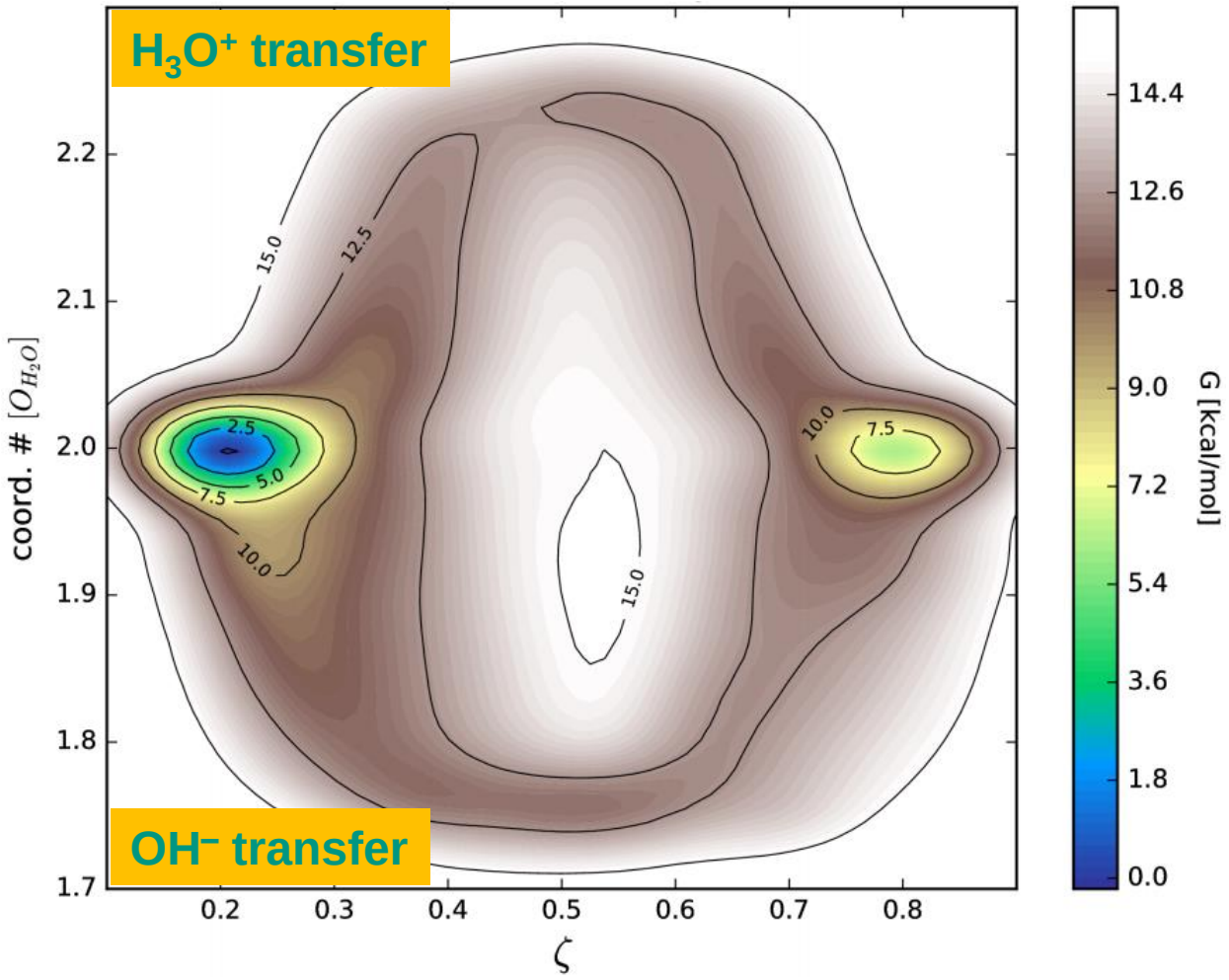
Application 2 – PT in bacteriorhodopsin

- First sub-step



Application 2 – PT in bacteriorhodopsin

- First sub-step – 2D projection of 3D MW metadynamics



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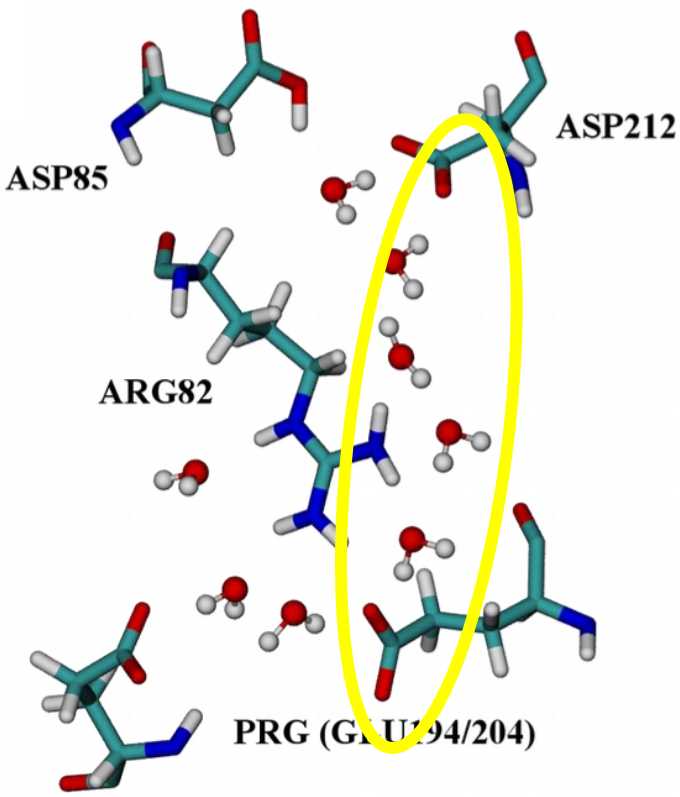
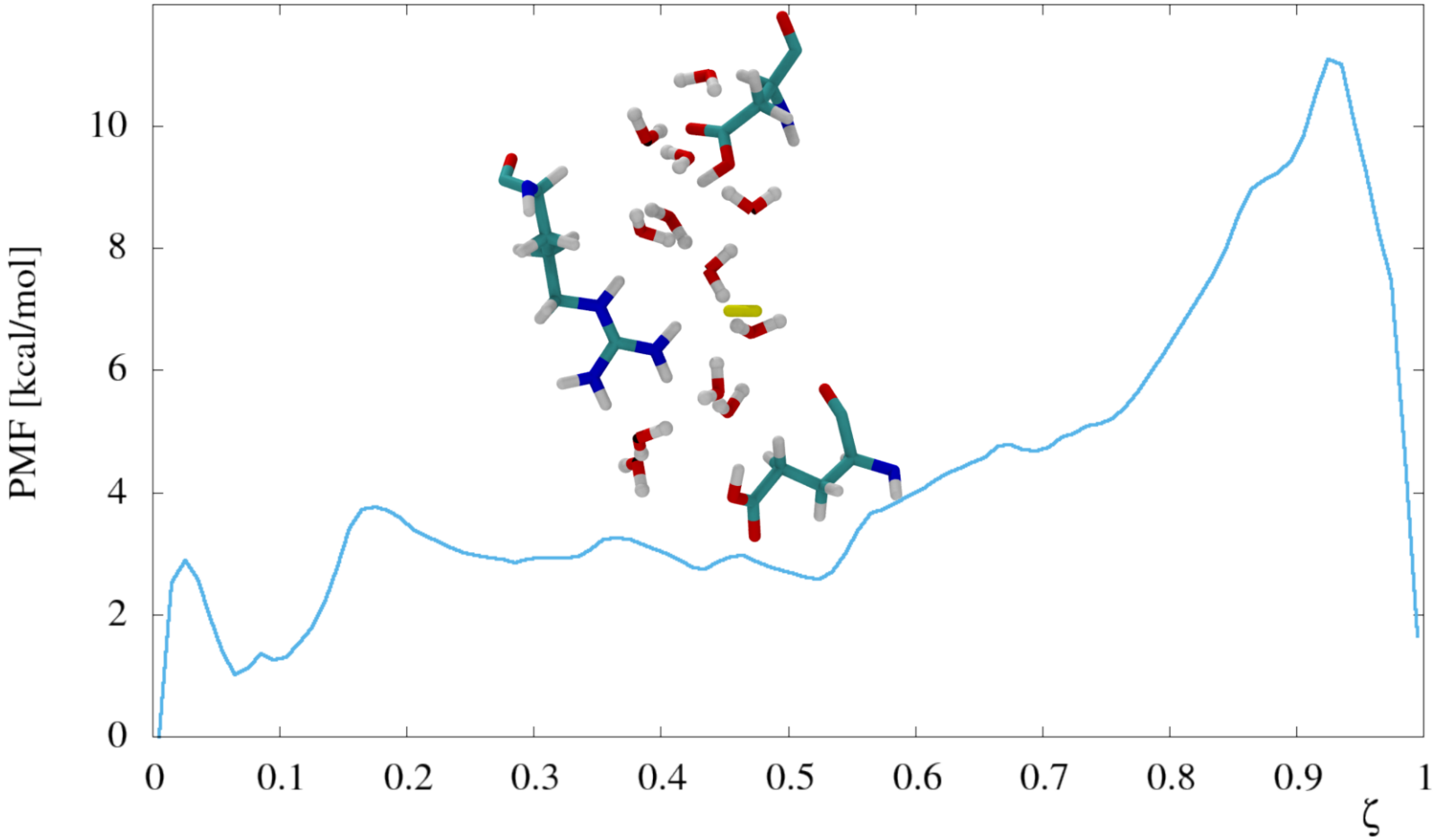
Application 2 – PT in bacteriorhodopsin

- Second sub-step
- Problem of the Arg82 side chain



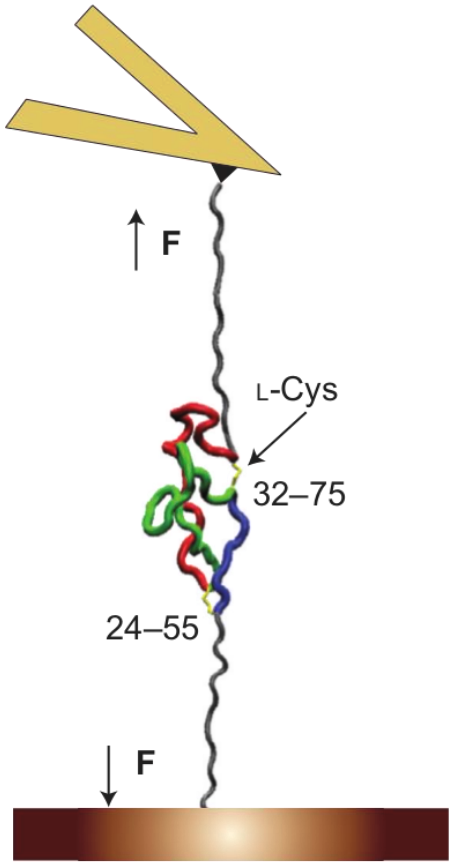
Application 2 – PT in bacteriorhodopsin

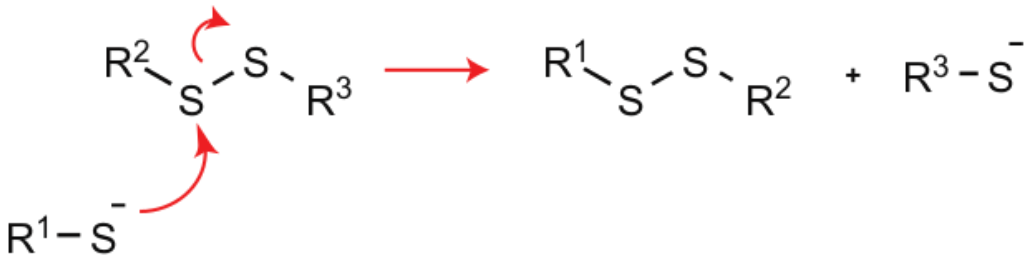
- Second sub-step – (preliminary) umbrella sampling



Application 3 – disulfide shuffling

- Force induced exchange reaction in a protein





ARTICLES
PUBLISHED ONLINE: 9 OCTOBER 2011 | DOI: 10.1038/NCHEM.1155
nature chemistry

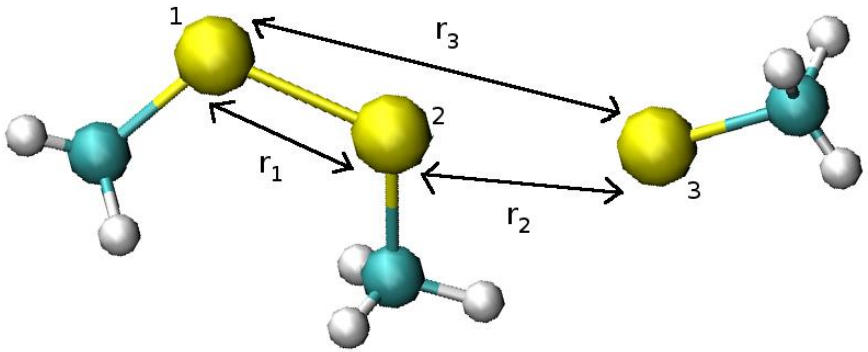
Direct observation of disulfide isomerization in a single protein

Jorge Alegre-Cebollada[1]*, Pallav Kosuri[2], Jaime Andrés Rivas-Pardo[1,3] and Julio M. Fernández[1]*

882 NATURE CHEMISTRY | VOL 3 | NOVEMBER 2011 | www.nature.com/naturechemistry

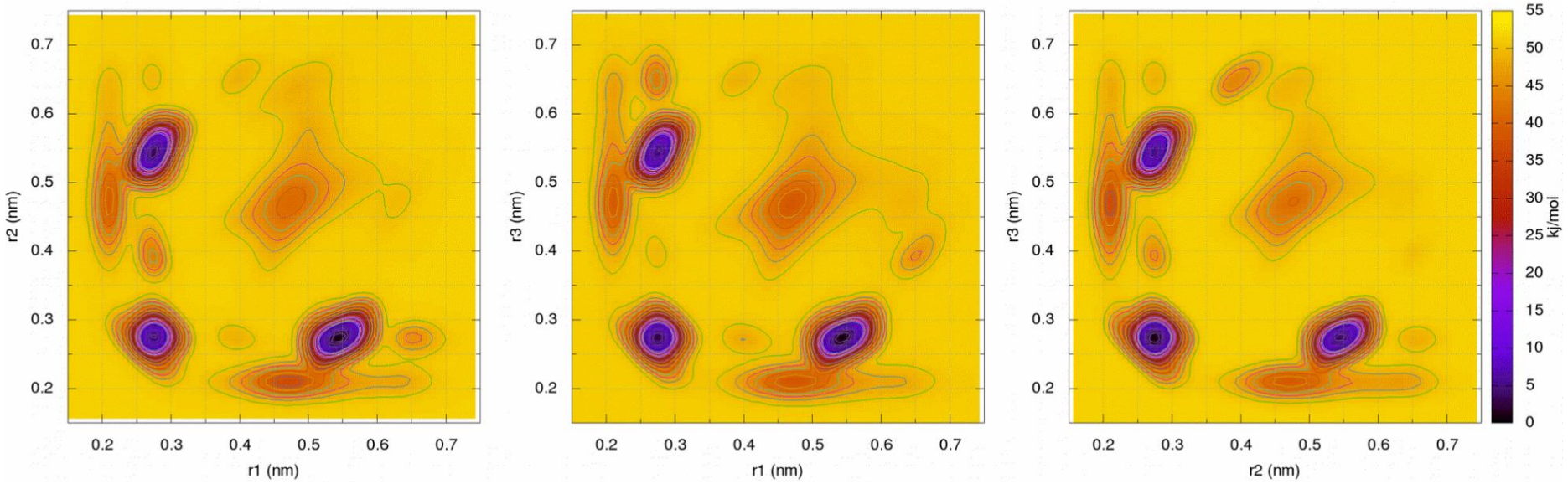
Application 3 – disulfide shuffling

- Test A: in vacuo
- Energetics & mechanism of the elementary exchange reaction
- 3D metadynamics with all S–S distances



Application 3 – disulfide shuffling

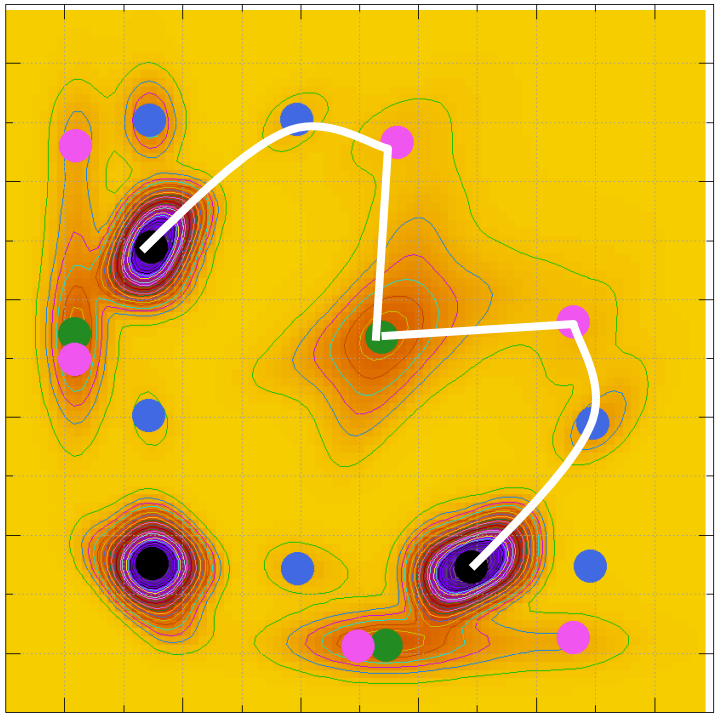
- Vacuo – 3D metadynamics



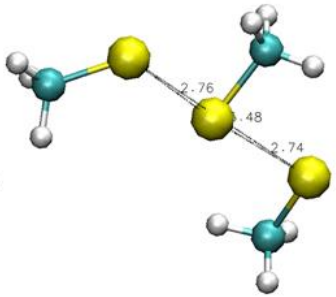
- Global minimum: S–S–S

Application 3 – disulfide shuffling

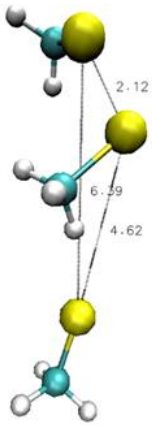
- Test A: in vacuo
- The minima identified:



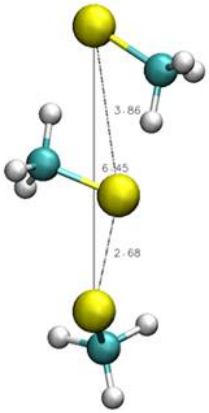
MIN 1



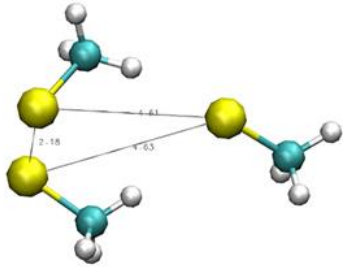
MIN 4



MIN 3
~ 45 kJ/mol



MIN 2
~ 40 kJ/mol



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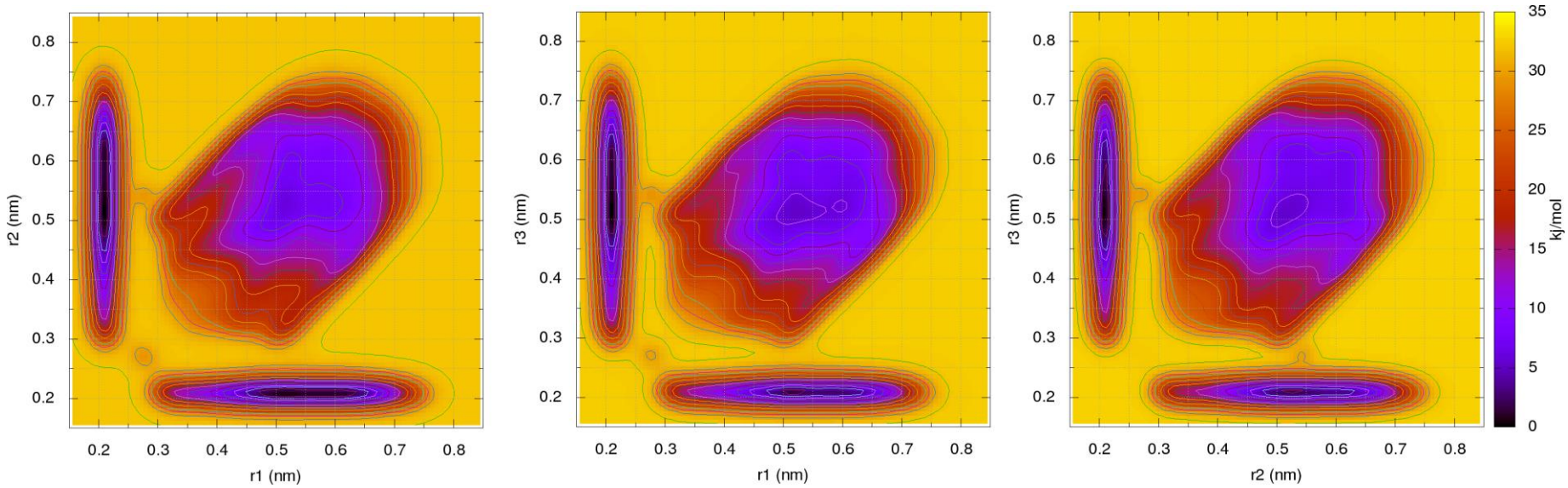
Application 3 – disulfide shuffling

- Test B: in an environment of MM-only water
- Position restraints on QM region
- 3D metadynamics



- Global minimum: S–S…S

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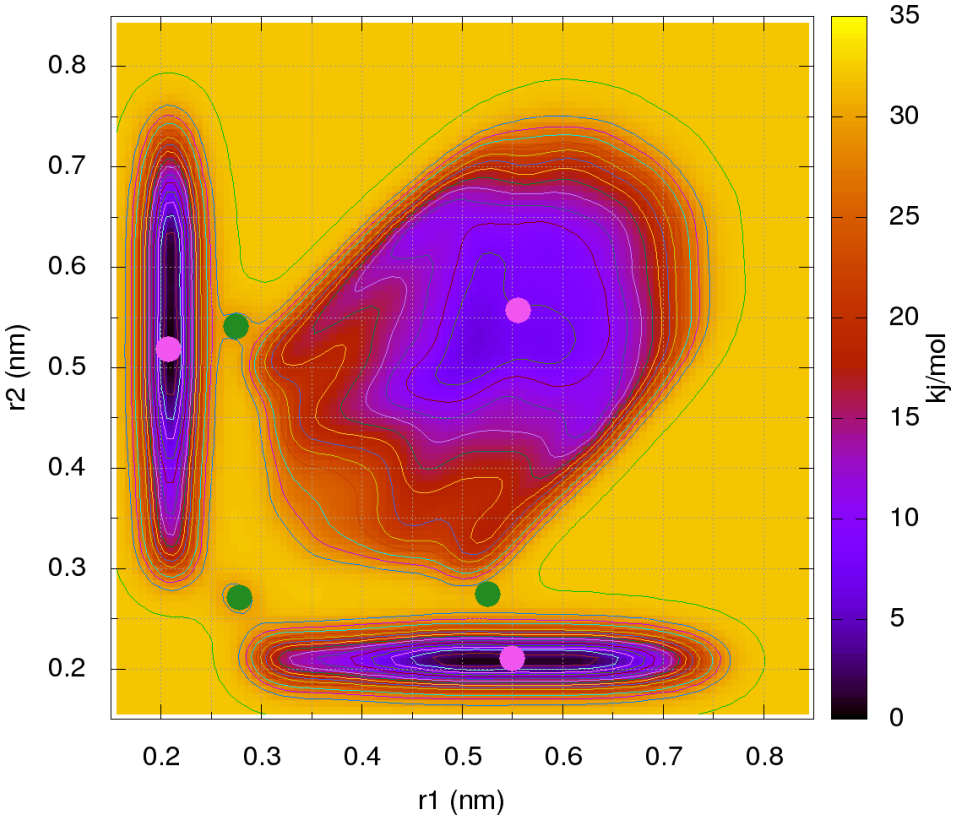
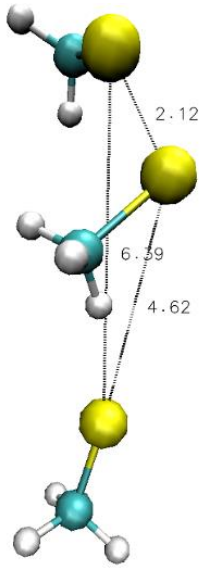
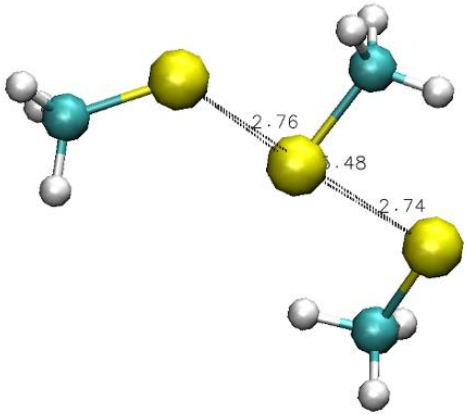
Application 3 – disulfide shuffling

- Test B: in an environment of MM-only water



MIN 1





MIN 2

~ 25 kJ/mol

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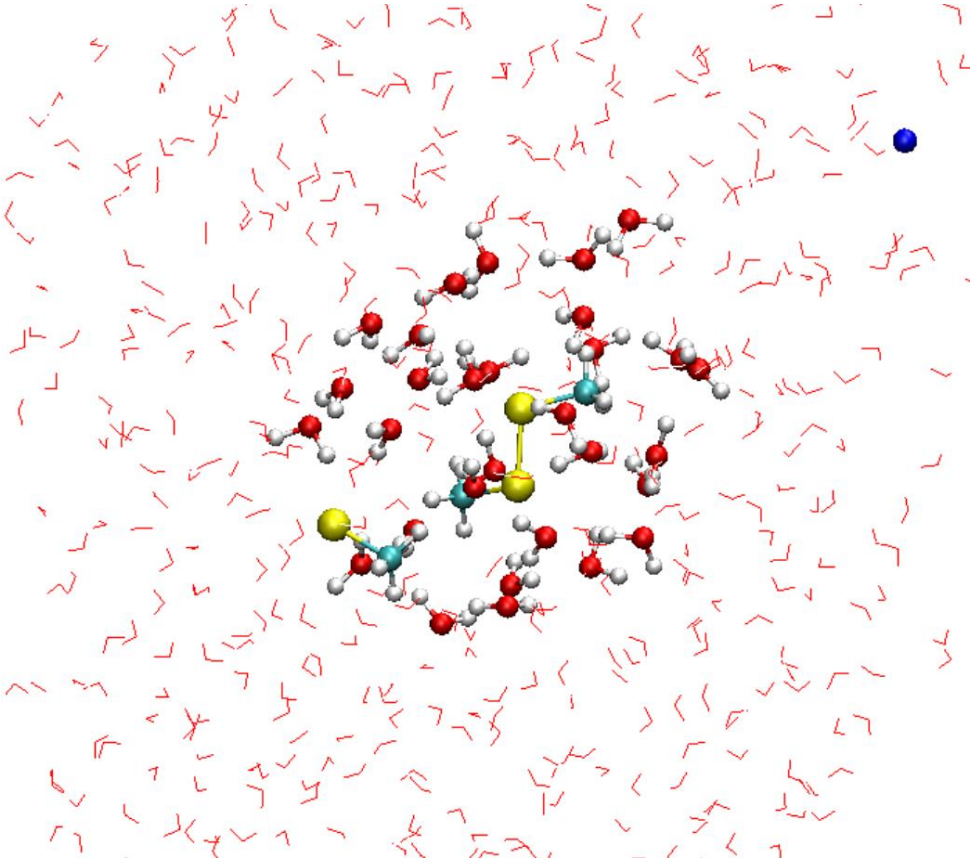
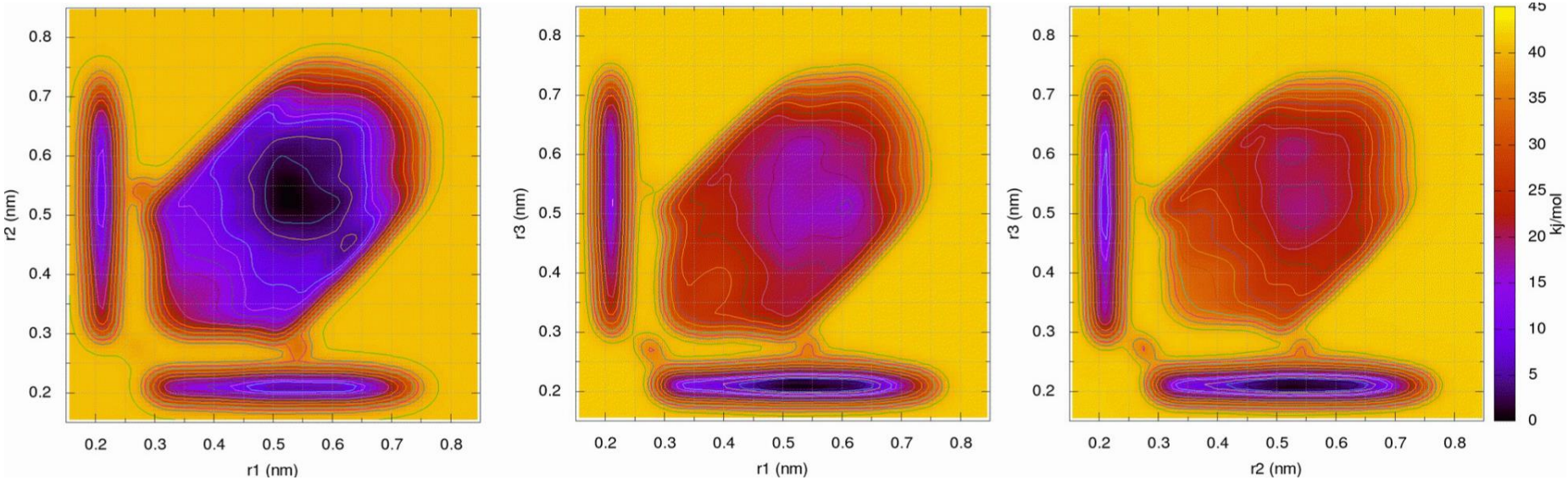
Application 3 – disulfide shuffling

- Test C: in a spherical shell, 30 QM water molecules,
  flat-bottomed position restraints to keep geometry reasonable



Application 3 – disulfide shuffling

- Hydration shell – 3D metadynamics



- Convergence issues (simulation is slooower…)
- Global minimum: S–S…S
- Very similar results to test B (MM-only water)

Thanks

- Marina Putzu, Thilo Mast, **Daniel Holub**, Gesa Lüdemann, Sabine Reißer
- Marcus Elstner
- Gerrit Groenhof (Göttingen → Jyväskylä)
- Kai Welke (KIT → Nagoya)
- Hiroshi C. Watanabe (KIT → Tokyo)
- Qiang Cui (WI–Madison)
- Carsten Kutzner (Göttingen)

- future users – start at `http://cbp.cfn.kit.edu/joomla`


SOFTWARE NEWS AND UPDATES WWW.C-CHEM.ORG Journal of COMPUTATIONAL CHEMISTRY

New QM/MM Implementation of the DFTB3 Method in the Gromacs Package

Tomáš Kubař,*[a] Kai Welke,[b] and Gerrit Groenhof[c]

Journal of Computational Chemistry **2015**, *36*, 1978–1989 WWW.CHEMISTRYVIEWS.COM ChemistryViews