GROMACS-CP2K Interface

Multiscale QM/MM simulations for exploring reactions in biological systems

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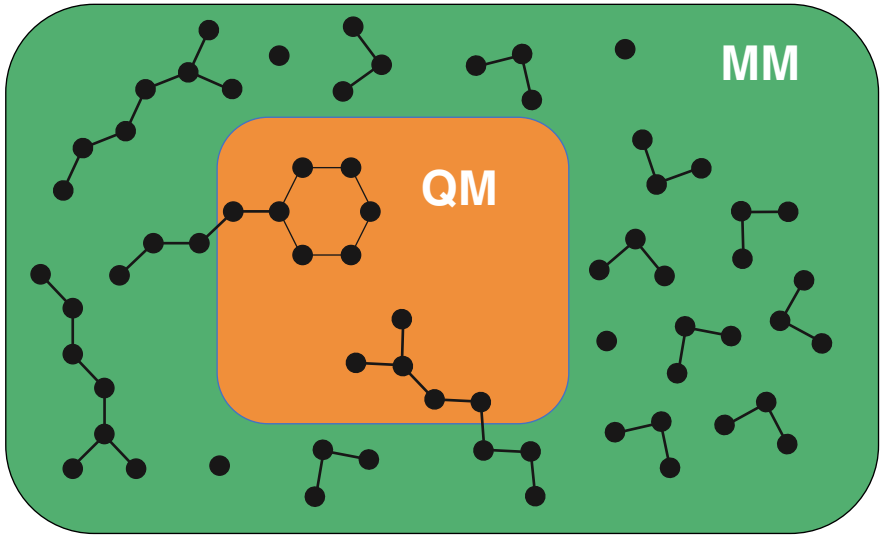
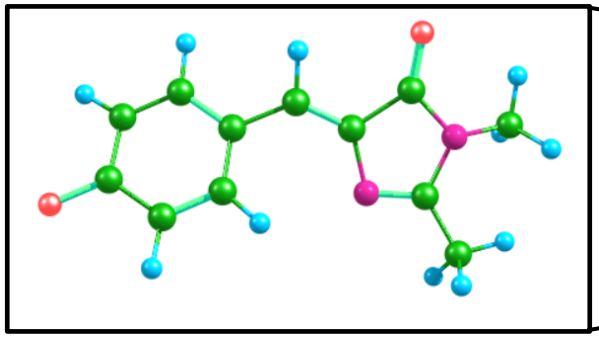
What is QM/MM and why we want to do it?



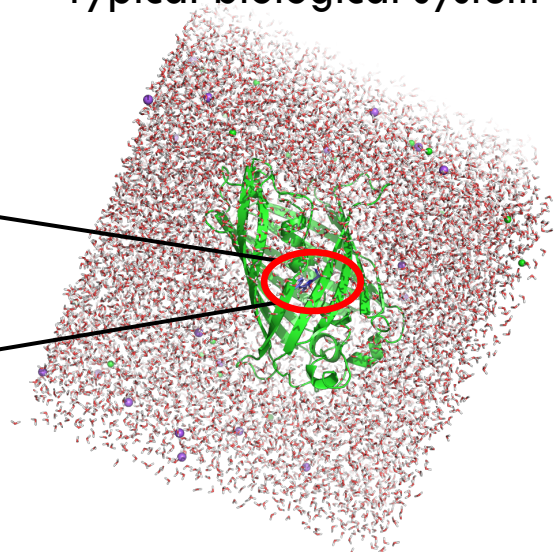
Modeling of biological systems

Typical system for QM simulations



Small number of atoms
(max of 100-200)

Typical biological system



≫10,000 atoms

Multiscale approach: QM/MM

Combining different levels of theory and resolutions

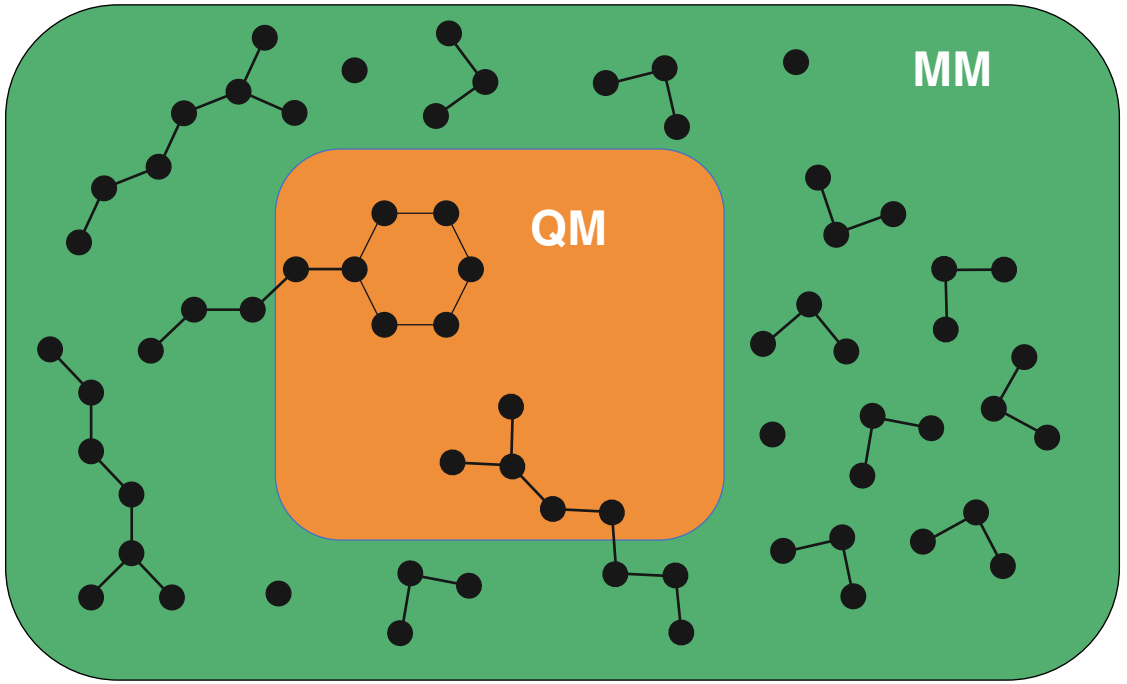
Hybrid multiscale description

A small **QM part** comprises the **chemically/photophysically active region** treated by computationally demanding electronic structure methods.

QM/MM Interface

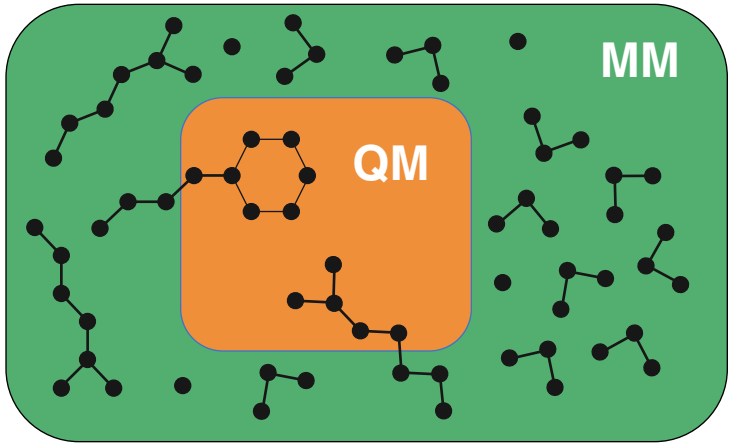
The remainder **MM part** is **described efficiently** at a lower level of theory by classical force fields.

The system is separated into two parts:



Nobel Prize Chemistry 2013: Karplus, Levitt, Warshel

Interactions in QM/MM



Hybrid QM/MM scheme:

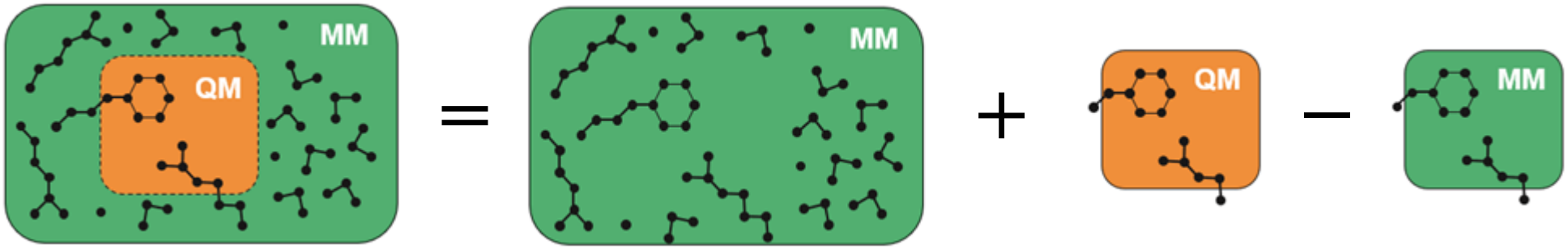
- Small part of the system at quantum (QM) level
- Rest of the system at forcefield (MM) level

The hybrid QM/MM **potential energy** contains three types of interactions:

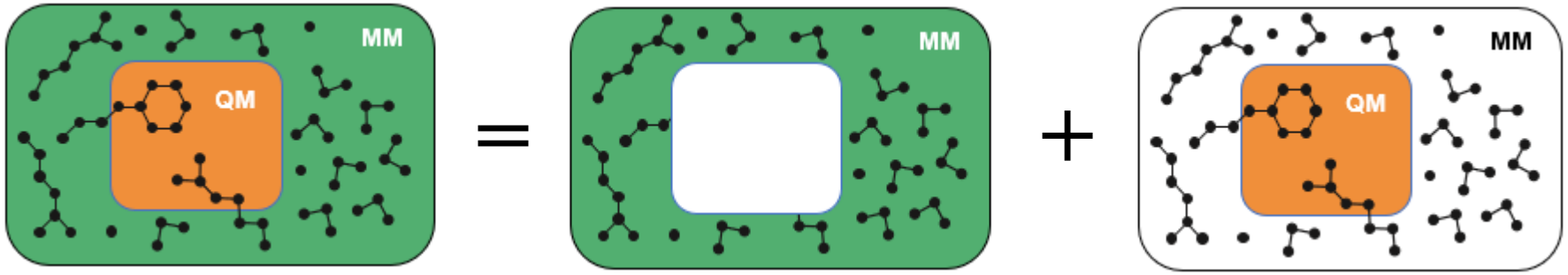
- Interactions between particles in the QM region (straightforward description)
- Interactions between atoms in the MM region (straightforward description)
- Interactions between QM and MM particles

QM and MM Coupling Approaches

- **Mechanical embedding: no influence of MM charges on the QM part,** i.e QM calculation is gas-phase-like without additional potential due to the MM atoms.



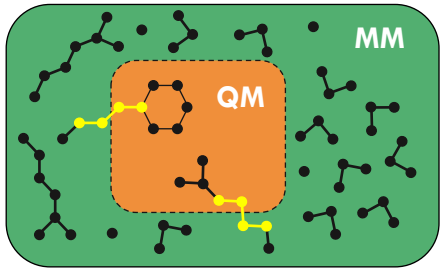
- **Electrostatic embedding: QM polarization due to the MM part included.**



- **Polarized embedding: MM polarization due to the QM part included as well** (non-self consistently or fully self-consistently).

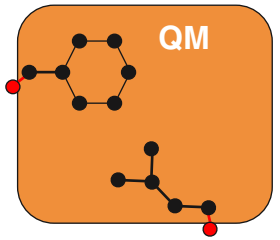
Bonded interactions

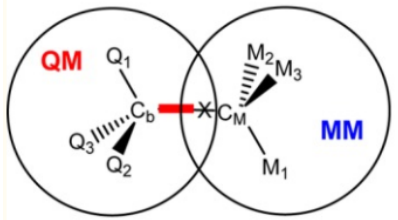
Introduced when covalent bonds connecting the QM and the MM regions are cut:



In addition, in this case care has to be taken when evaluating the QM wave function. Some methods to deal with dangling valences:

- **Monovalent capping Link-atoms:** usually hydrogen atoms at an appropriate position along the bond vector
- **Capping pseudopotentials:** linking atom with scaled down pseudopotential and the required valence charge, which requires to constrain the bond distance appropriately.
- **Generalized hybrid orbitals:** hybrid orbitals are placed on the boundary atom and one of them participates in the SCF calculation for the WF of the QM region.





GROMACS-CP2K Interface

Quickstep: Mixed Gaussian and Plane wave basis implementation of Density Functional Theory

+

GEEP: **Gaussian Expansion of Electrostatic Potential (GEEP) to compute the QM/MM coupling**

GROMACS FAST. FLEXIBLE. FREE.

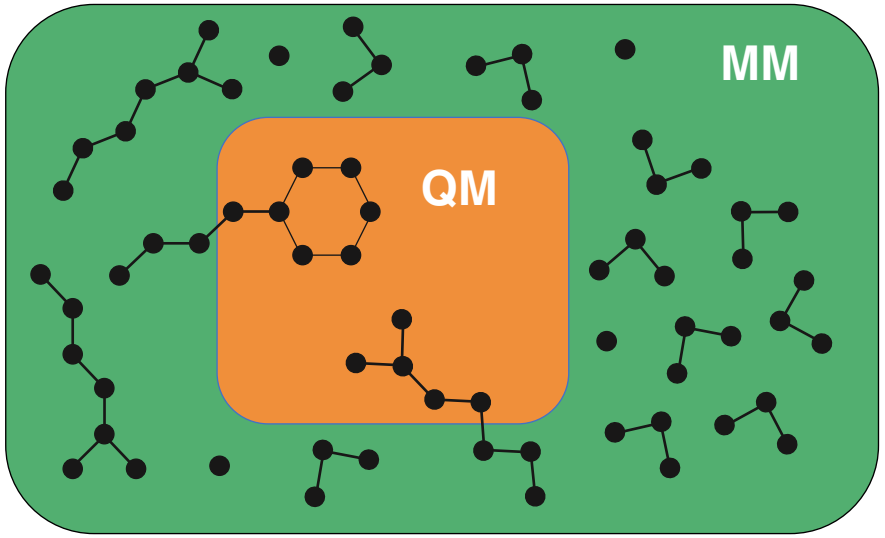
Forcefield: Classical MM-MM interactions both bonded and non-bonded (PME)

+

Integration: Classical MD using fully periodic QM/MM forces

$$H = H_{MM} + H_{QM} + H_{QM/MM}$$

Forcefield Quickstep GEEP



Forcefield (MM) - GROMACS

- Force field description of MM region

$$H = H_{MM} + H_{QM} + H_{QM/MM}$$

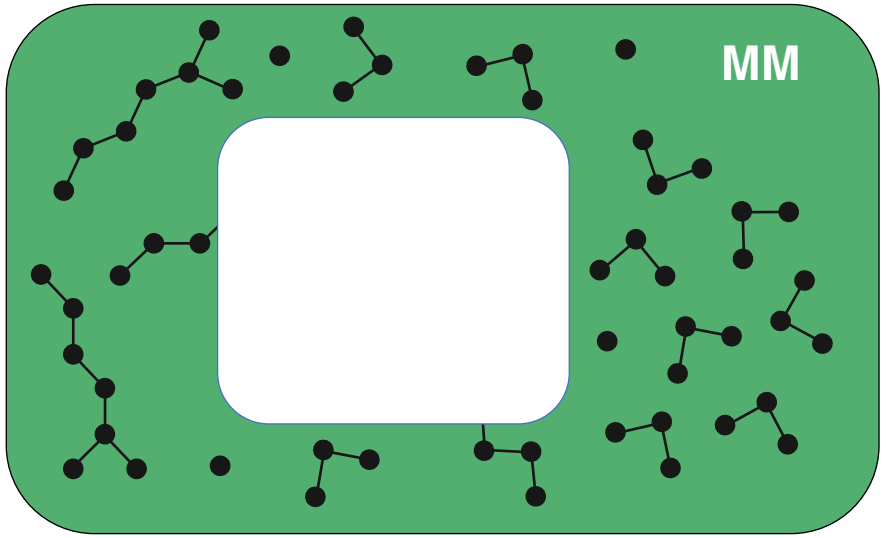
Forcefield Quickstep GEEP

$$V(r_1, r_2, \ldots r_N) = V_{bonded}(r_1, r_2, \ldots r_N) + V_{non-bonded}(r_1, r_2, \ldots r_N)$$

$$V_{bonded} = \sum_{bonds} \frac{1}{2} k_b (r - r_0)^2 + \sum_{angles} \frac{1}{2} k_\theta (\theta - \theta_0)^2 + \sum_{torsions} k_\xi (\xi - \xi_0)^2$$

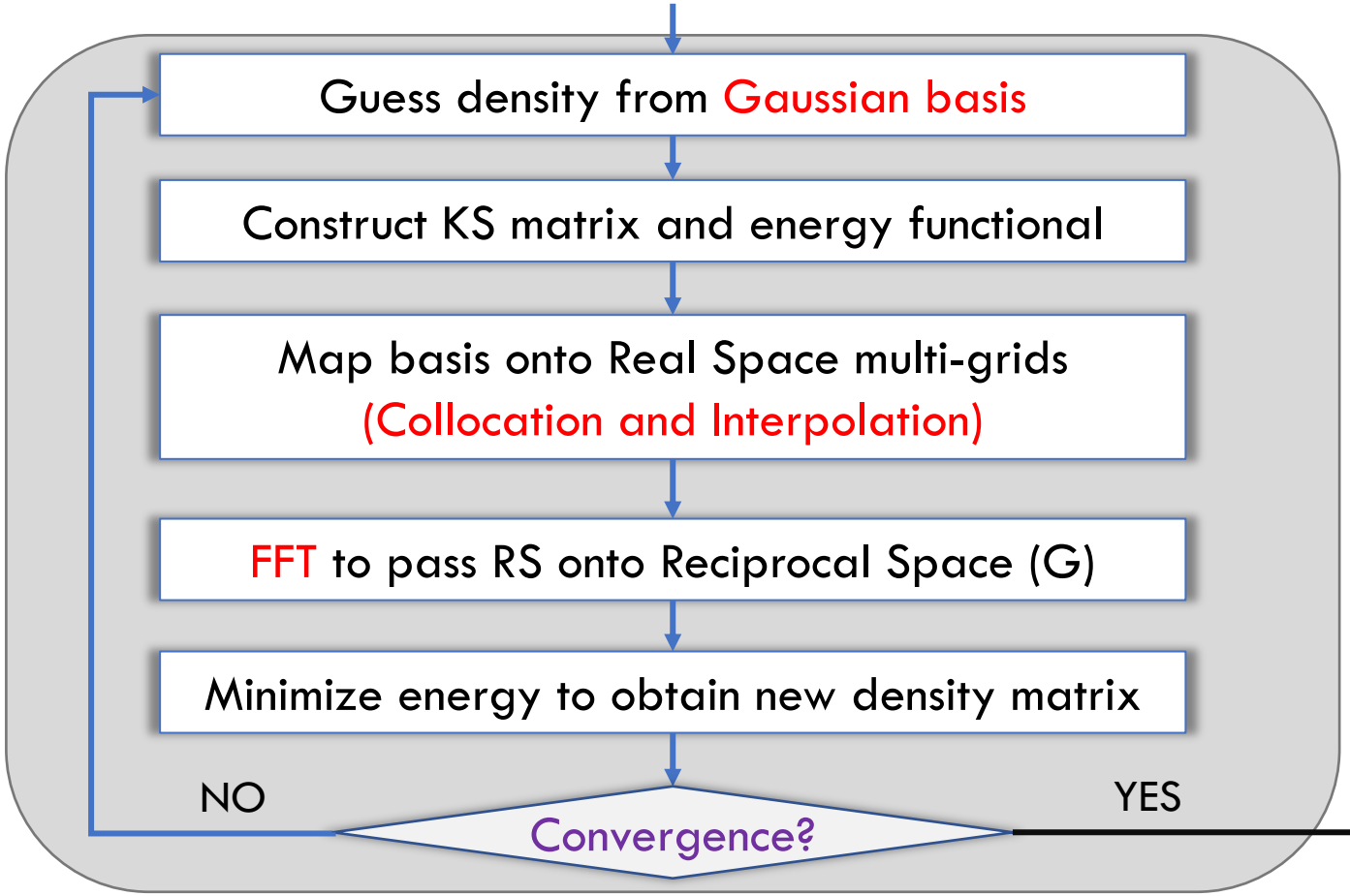
$$+ \sum_{torsions} \frac{1}{2} k_\phi [1 + \cos(n\phi - \phi_0)]$$

$$V_{non-bonded} = \sum_{LJ} 4\epsilon_{ij} \left(\frac{C_{ij}^{(12)}}{r_{ij}^{12}} - \frac{C_{ij}^{(6)}}{r_{ij}^{6}} \right) + \sum_{Coul.} \frac{q_i q_j}{r_{ij}}$$



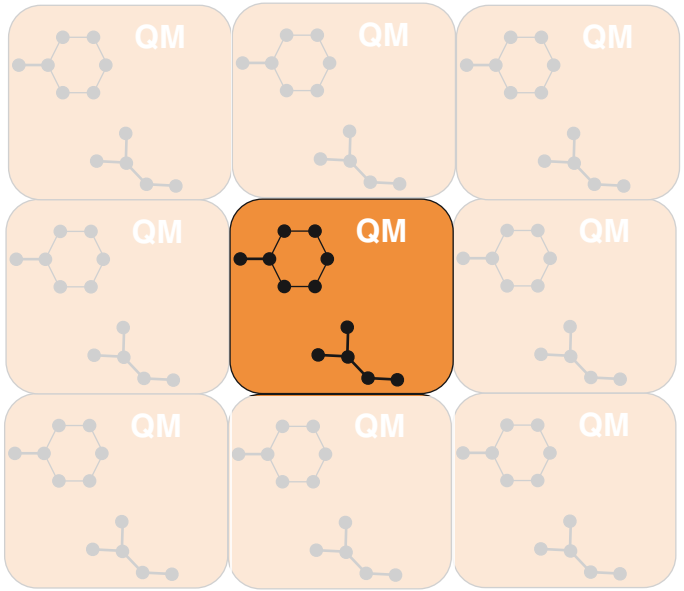
Quickstep (QM) - CP2K

QM region as CP2K input



$$H = H_{MM} + H_{QM} + H_{QM/MM}$$

Forcefield Quickstep GEEP



Energy, Forces and other properties

GEEP for QM/MM Coupling - CP2K

- **QM polarization due to the MM part included.**

$$H = H_{MM} + H_{QM} + H_{QM/MM}$$

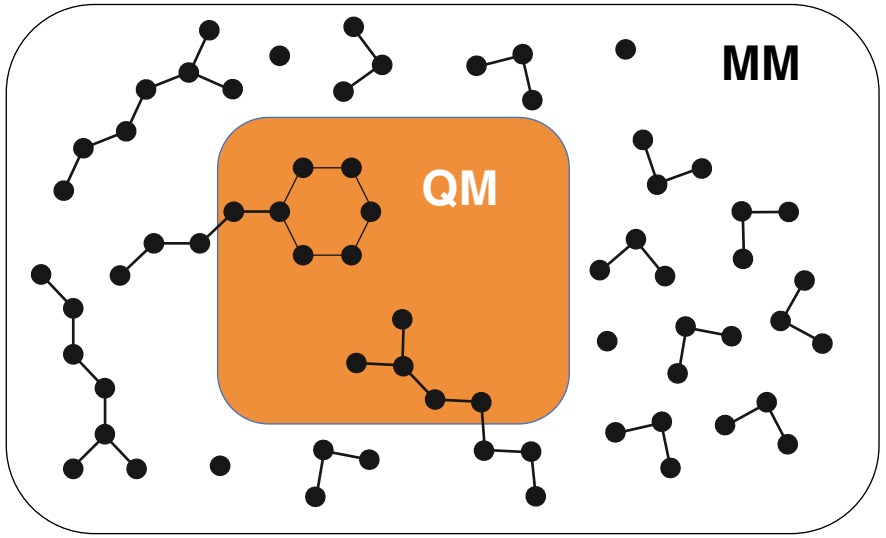
Forcefield Quickstep GEEP

$$E^{QM-MM}_{electrostatic} = \sum_{I \in MM} q_I \int \rho(\mathbf{r})\, v_I^{smear}(|\mathbf{r} - \mathbf{R}_I|) d\mathbf{r}$$

$$v_I^{smear}(|\mathbf{r} - \mathbf{R}_I|) = \frac{\mathrm{Erf}\left(\frac{|\mathbf{r} - \mathbf{R}_I|}{\mathbf{r}_{c,I}}\right)}{|\mathbf{r} - \mathbf{R}_I|} = \sum_{N_g} A_g e^{-\left(|\mathbf{r} - \mathbf{R}_I|/G_g\right)^2} + R_{low}(|\mathbf{r} - \mathbf{R}_I|)$$

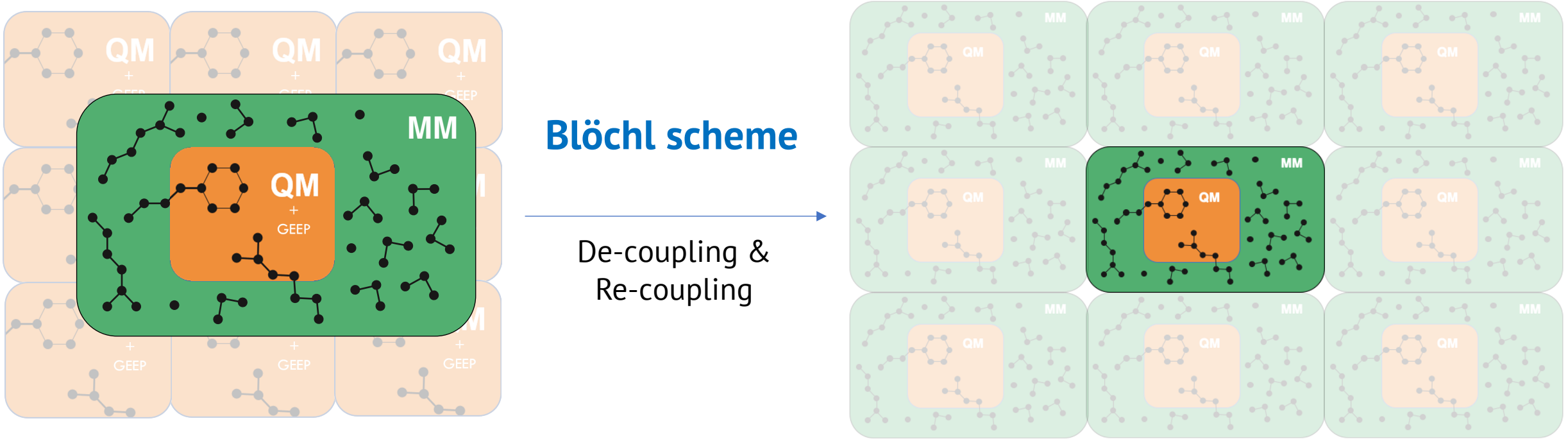
+

Real Space multi-grid approach

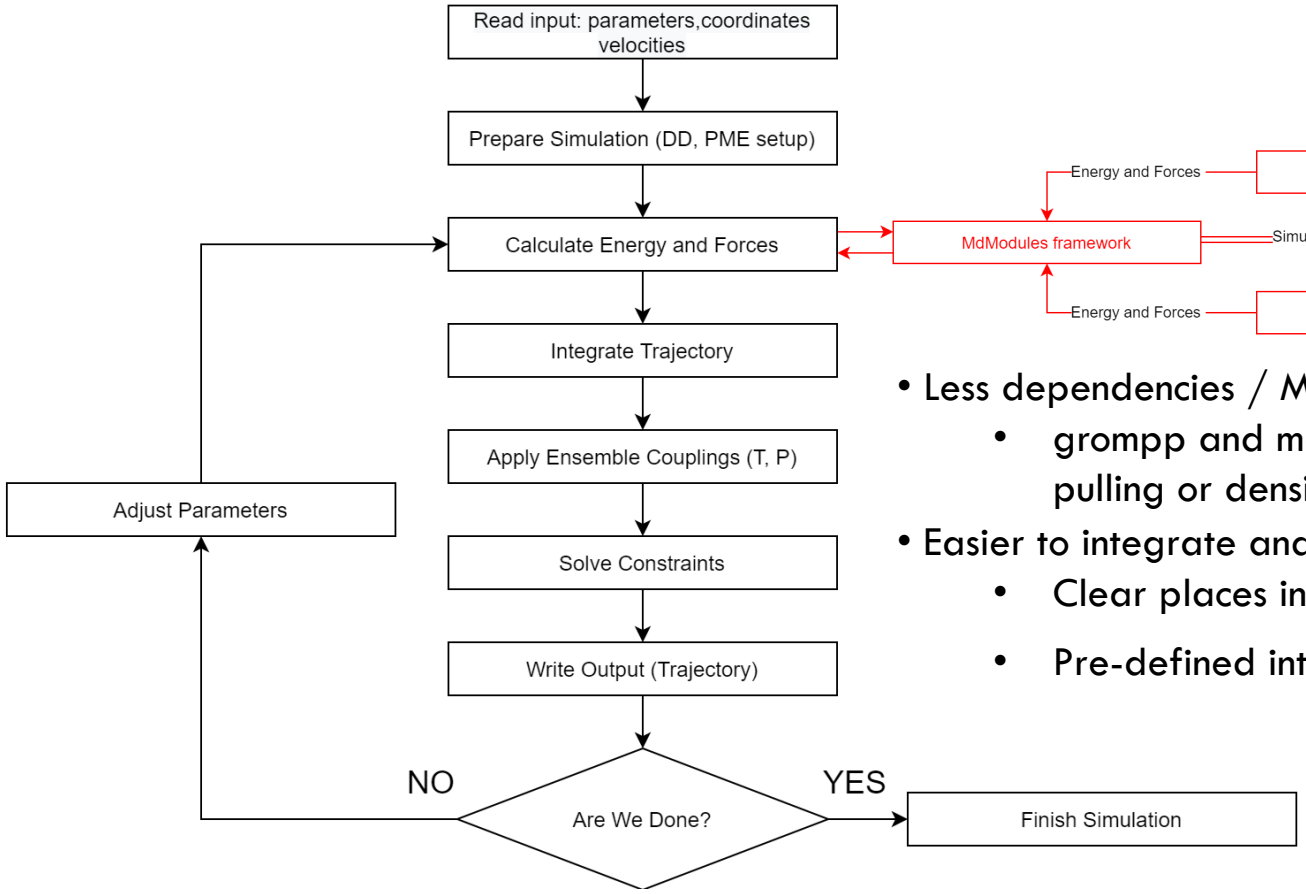


Fully periodic QM/MM

- GEEP projects electrostatic potential from point charges onto the multi-grid of QM box
- QM-QM periodic interactions are threated efficiently with Quickstep
- Unless the QM and MM box have same dimensions the QM images over PBC will have incorrect periodicity
- Blöchl scheme is used in CP2K to restore full system box periodicity



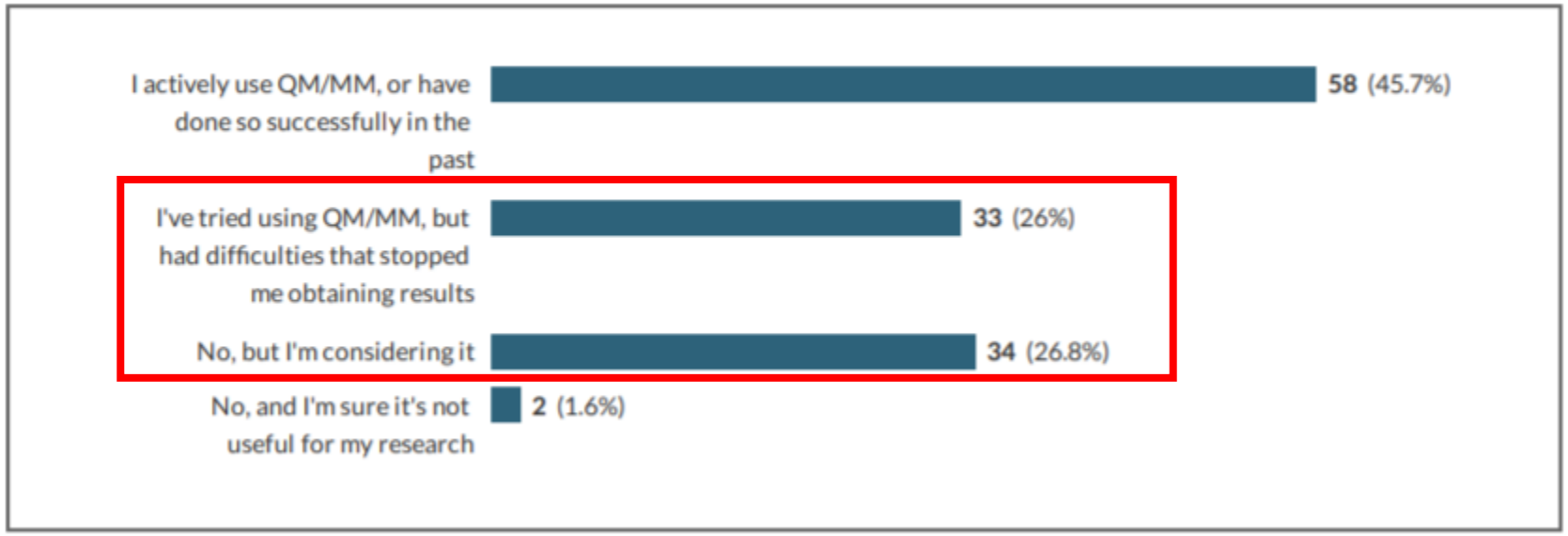
Simulation flow – Gromacs (MdModules)



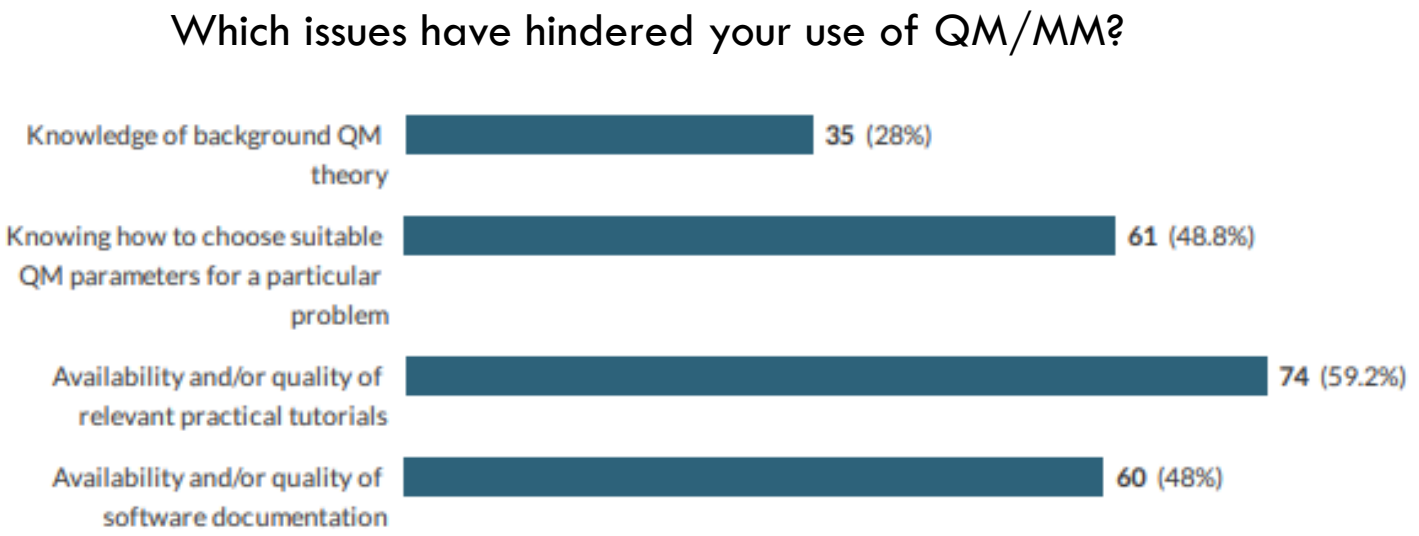
- Less dependencies / More encapsulation
  - grompp and mdrun does not need to know about QM/MM, pulling or density-guided simulations
- Easier to integrate and maintain
  - Clear places interaction of new code with GROMACS
  - Pre-defined interaction pattern with rest of code

Why QM/MM is difficult to use?

Do you use QM/MM simulations in your research?



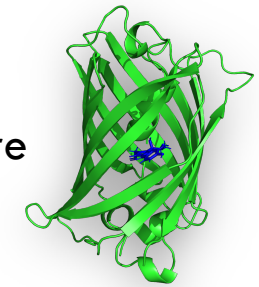
Why QM/MM is difficult to use?

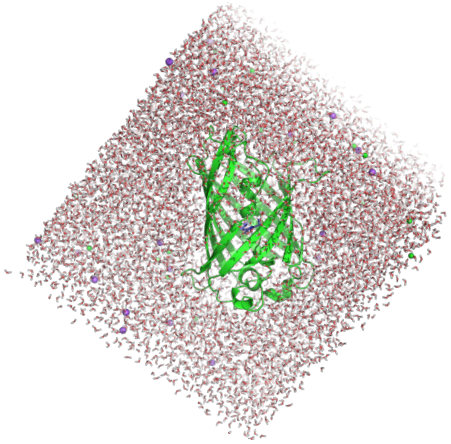


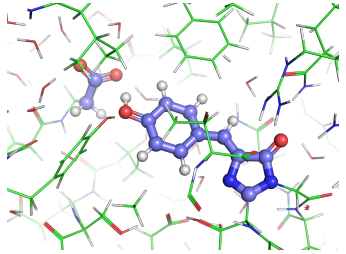
Make it simpler to use!

Typical workflow for biochemical QM/MM modelling

Input structure







SYSTEM SETUP

- Missing residues
- Residue protonation
- pdb2gmx
- Define box
- Add solvent and ions
- ….

MD SIMULATIONS

- Prepare .mdp files
- Energy minimization
- Pressure & temperature equilibration
- Production run
- …

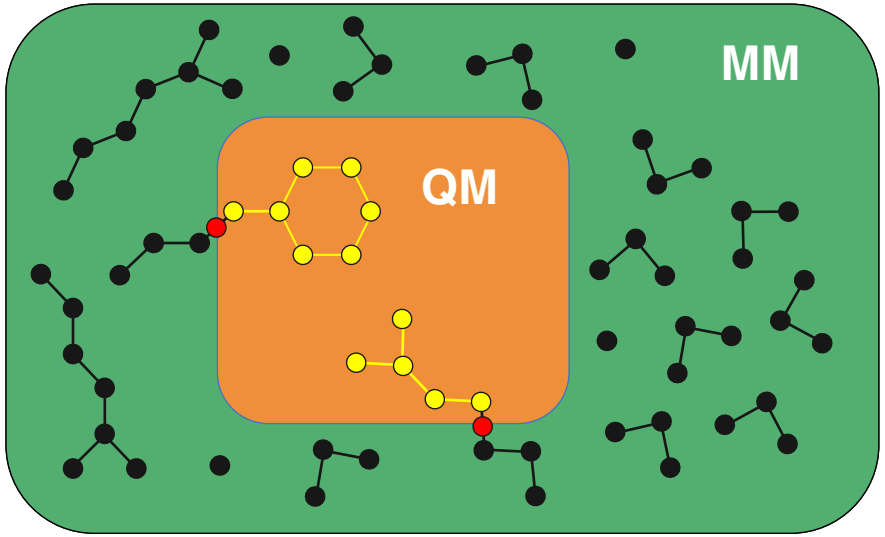
- Index file
- .mdp parameters for QM/MM

- Keep it flexible for advanced users

QM/MM Calculations

- Geometry optimization
- Atomic charges
- QM/MM MD
- Absorption spectra
- Umbrella Sampling
- ….

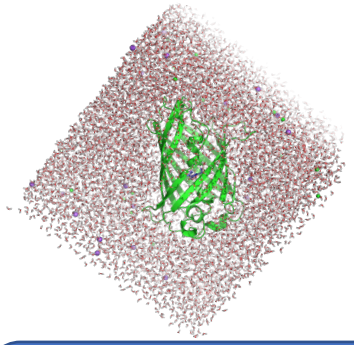
Topology processing and features

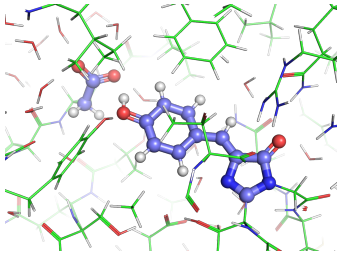


1. Remove partial charges from QM atoms
2. Remove LJ interactions between QM-QM atoms (keep with QM-MM)
3. Remove Bonds (which connects 2 QM atoms)
4. Remove Angles, which contains 2 or more QM atoms
5. Remove Dihedrals, which contains 3 or more QM atoms
6. Cleanup water constraints (SETTLE) from QM waters
7. Generate CP2K Input (including Link atoms)

- Sample CP2K QM parameters setup for the biological systems
- Compatibility with the most simulation techniques available in Gromacs
- Compatibility with Gromacs tools and third-party software for analysis
- Supports highly parallelizable simulation methods, like umbrella sampling

Easy to use: simple QM/MM setup

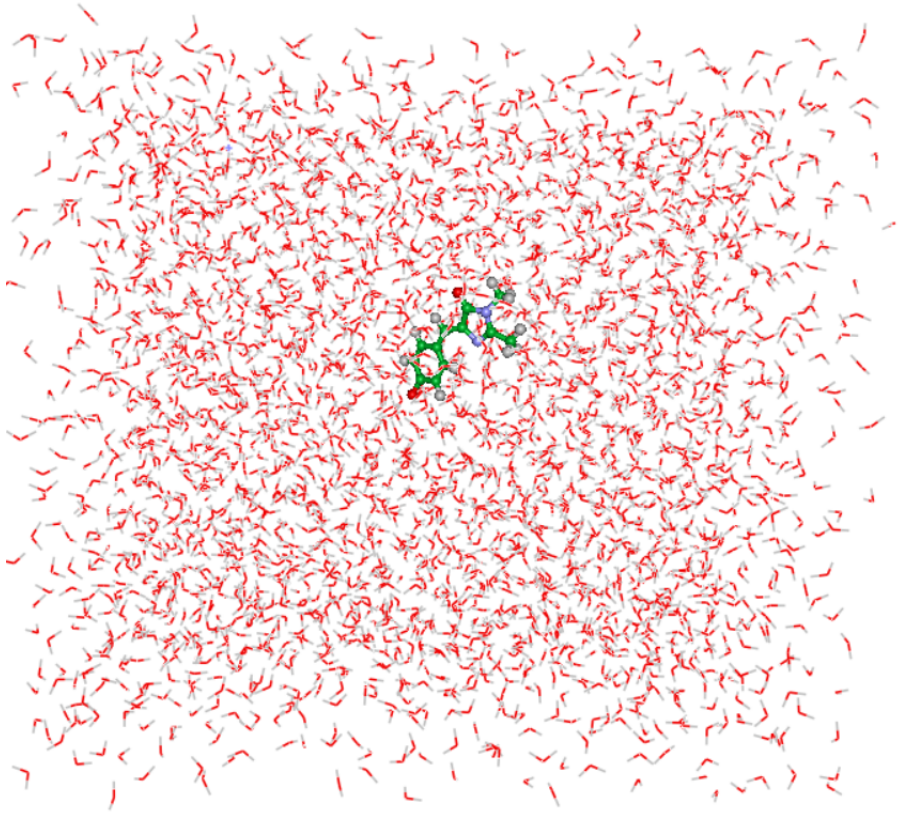




Classical MD Simulations → - Index file - .mdp parameters for QM/MM → - topol.tpr - topol.inp (CP2K Input) - topol.pdb (QM-MM split and point charges) → **QM/MM Calculations**

```
qmmm-active          = true      ; Activates QMMM MdModule
qmmm-qmgroup         = QMatoms   ; Index group with QM atoms
qmmm-qmmethod        = PBE       ; Pre-set parameters for DFT (PBE/DZVP)
qmmm-qmcharge        = 0         ; Total Charge of QM system
qmmm-qmmultiplicity  = 1         ; Spin-state of QM system
```

Example system



QM subsystem : HBDI (GFP Chromophore)

MM subsystem : 3237 TIP3P waters and Na^+ Ion

QM charge: -1

QM multiplicity: 1

Functional: PBE

Basis: DZVP-MOLOPT

```
qmmm-active          = true
qmmm-qmgroup         = HBDI
qmmm-qmmethod        = PBE
qmmm-qmcharge        = -1
qmmm-qmmultiplicity  = 1
```

CP2K: Generated Input File

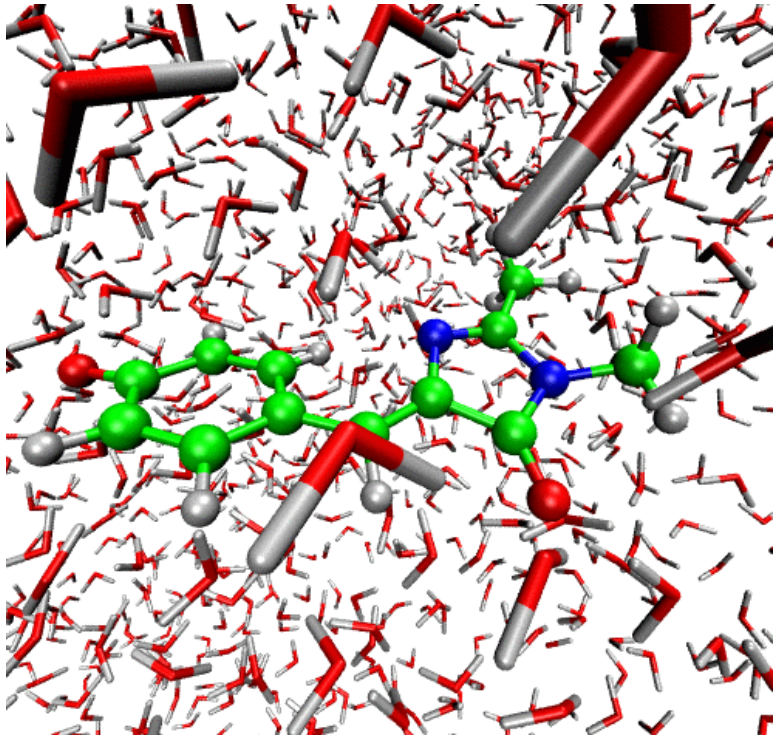
```
&GLOBAL
   PRINT_LEVEL LOW
   PROJECT GROMACS
   RUN_TYPE ENERGY_FORCE
&END GLOBAL
&FORCE_EVAL                    ! parameters for force evaluation
  METHOD QMMM                  ! method employed e.g. QMMM (Quickstep + GEEP)
  &DFT                         ! Grids setup, SCF and Functional parameters
    .... contents of DFT section
  &END DFT
  &QMMM                        ! Set up for QM box, GEEP, Blöchl scheme, Link atoms
    .... contents of QMMM section
  &END QMMM
  &MM                          ! Needed to switch off MM-MM interactions
    .... contents of MM section
  &END MM
  &SUBSYS                      ! Coordinates, atom kinds (Gaussian basis sets)
    .... contents of SUBSYS section
  &SUBSYS
&END FORCE_EVAL
```

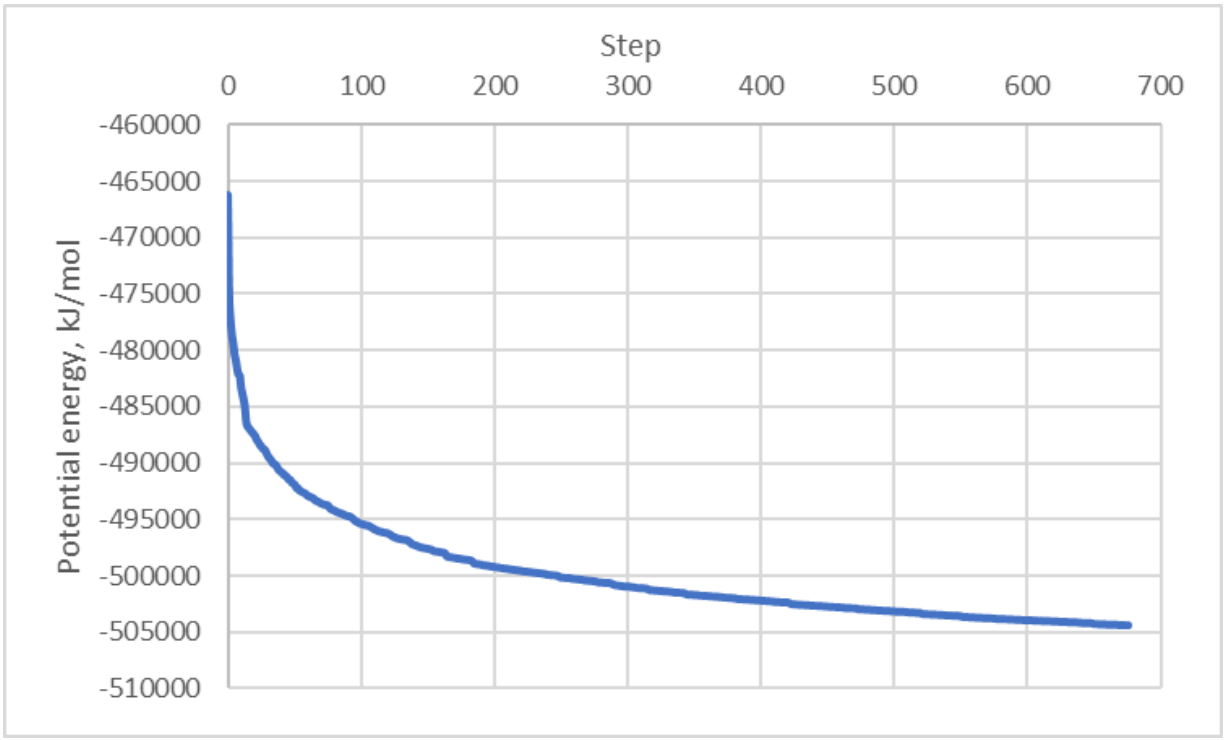
CP2K: Point Charges

```
....
ATOM     24  H   QM     1      22.990  26.200  25.510  1.00  0.00        H   0.000000
ATOM     25  C   QM     1      24.150  24.930  26.660  1.00  0.00        C   0.000000
ATOM     26  O   QM     1      23.620  23.820  26.190  1.00  0.00        O   0.000000
ATOM     27  O   MM     2      23.740  30.770  14.650  1.00  0.00        O  -0.820000
ATOM     28  H   MM     2      24.150  29.860  14.630  1.00  0.00        H   0.410000
ATOM     29  H   MM     2      24.070  31.260  15.460  1.00  0.00        H   0.410000
ATOM     30  O   MM     2      16.410  39.470  20.500  1.00  0.00        O  -0.820000
ATOM     31  H   MM     2      17.320  39.650  20.870  1.00  0.00        H   0.410000
ATOM     32  H   MM     2      16.140  40.230  19.900  1.00  0.00        H   0.410000
ATOM     33  O   MM     2      16.020  28.300  22.750  1.00  0.00        O  -0.820000
ATOM     34  H   MM     2      16.010  28.580  23.700  1.00  0.00        H   0.410000
ATOM     35  H   MM     2      15.130  27.920  22.490  1.00  0.00        H   0.410000
....
```

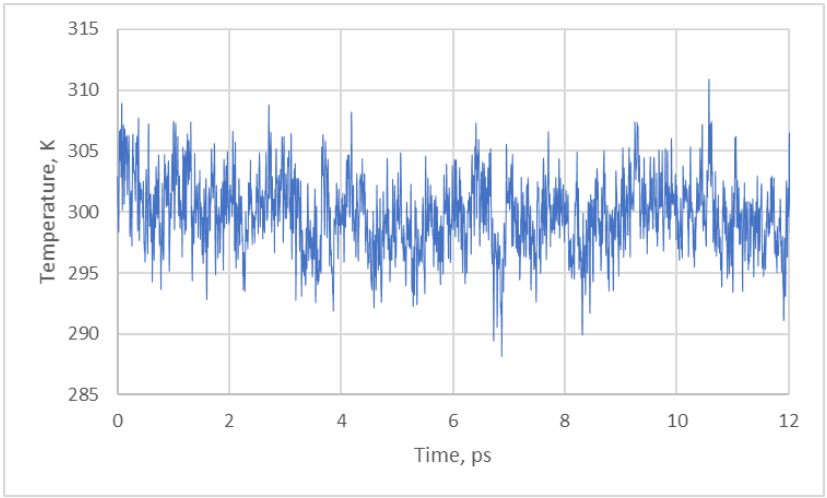
TIP3P water

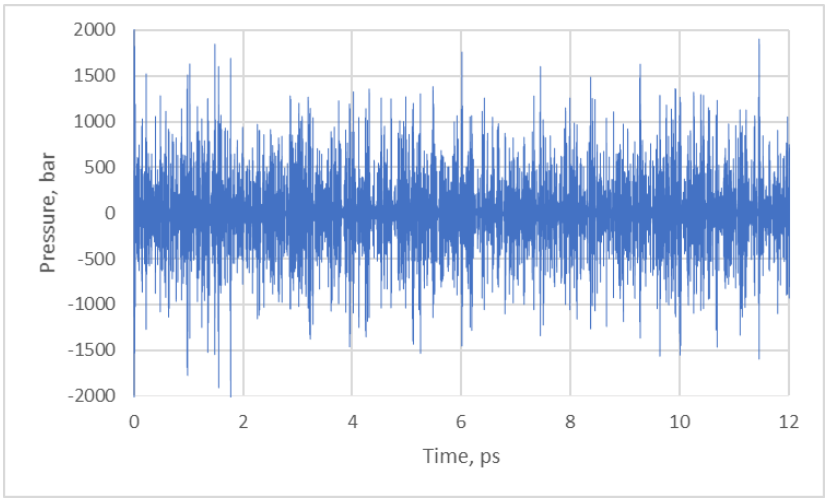
Energy minimization





Dynamics with Pressure and Temperature coupling (NPT)

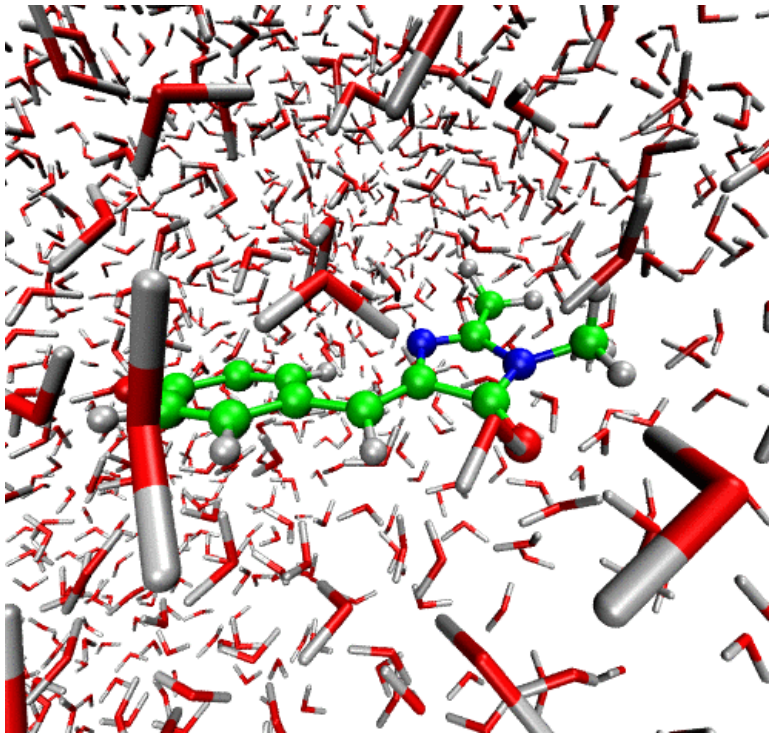




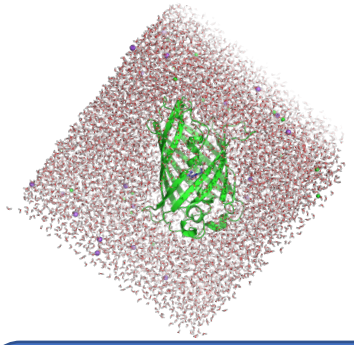
Thermostat: V-rescale 300K, 0.1 ps

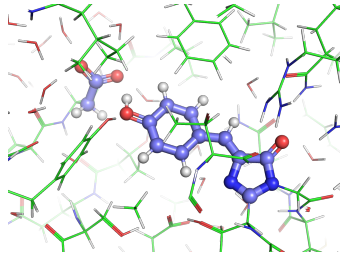
Barostat: Berendsen 1 bar, 0.1 ps

Dynamics: 1 fs time-step, approximately 10 ps/day



Flexible input: advanced QM/MM setup





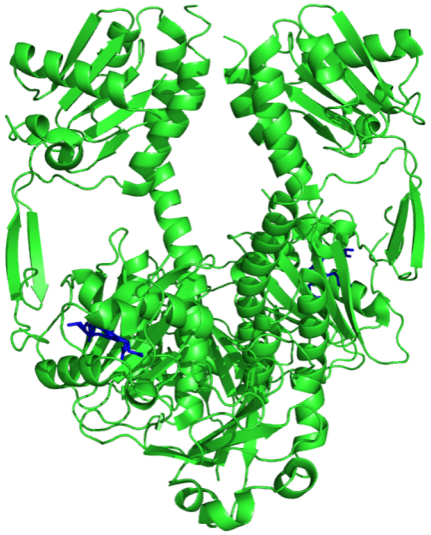
Classical MD Simulations

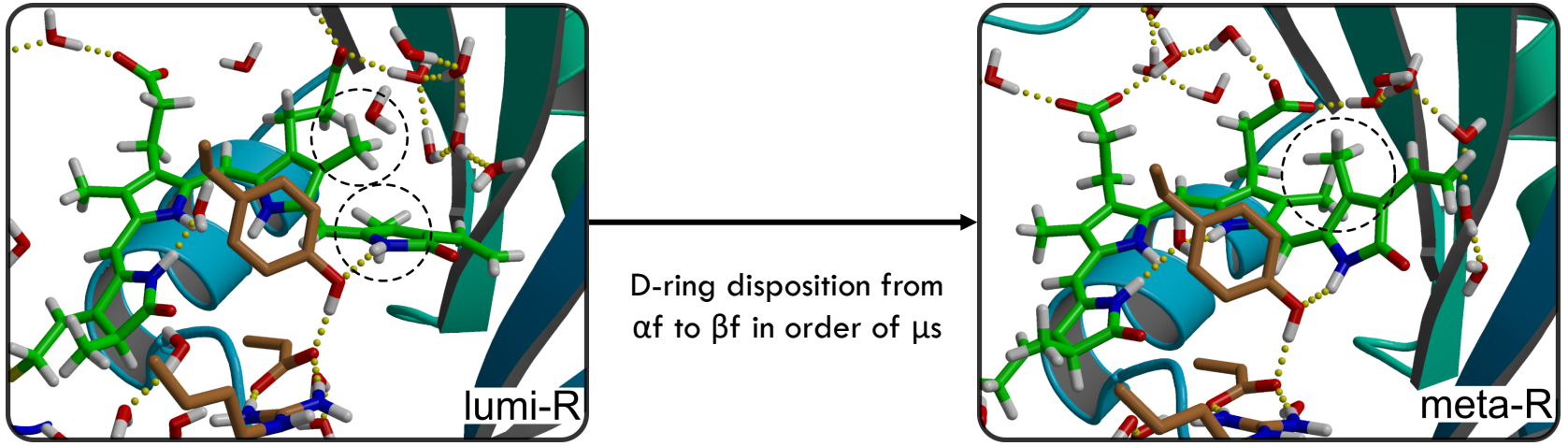
- Index file
- .mdp parameters for QM/MM
- Your own CP2K input

QM/MM Calculations

```
qmmm-active          = true      ; Activates QMMM MdModule
qmmm-qmgroup         = QMatoms   ; Index group with QM atoms
qmmm-qmmethod        = INPUT     ; Provide your own input for CP2K
qmmm-qminputfile     = cp2k.inp  ; Input file to be used
```

Protein simulations: Phytochrome





Objective:

D-ring disposition energy barrier (α_f —> β_f)

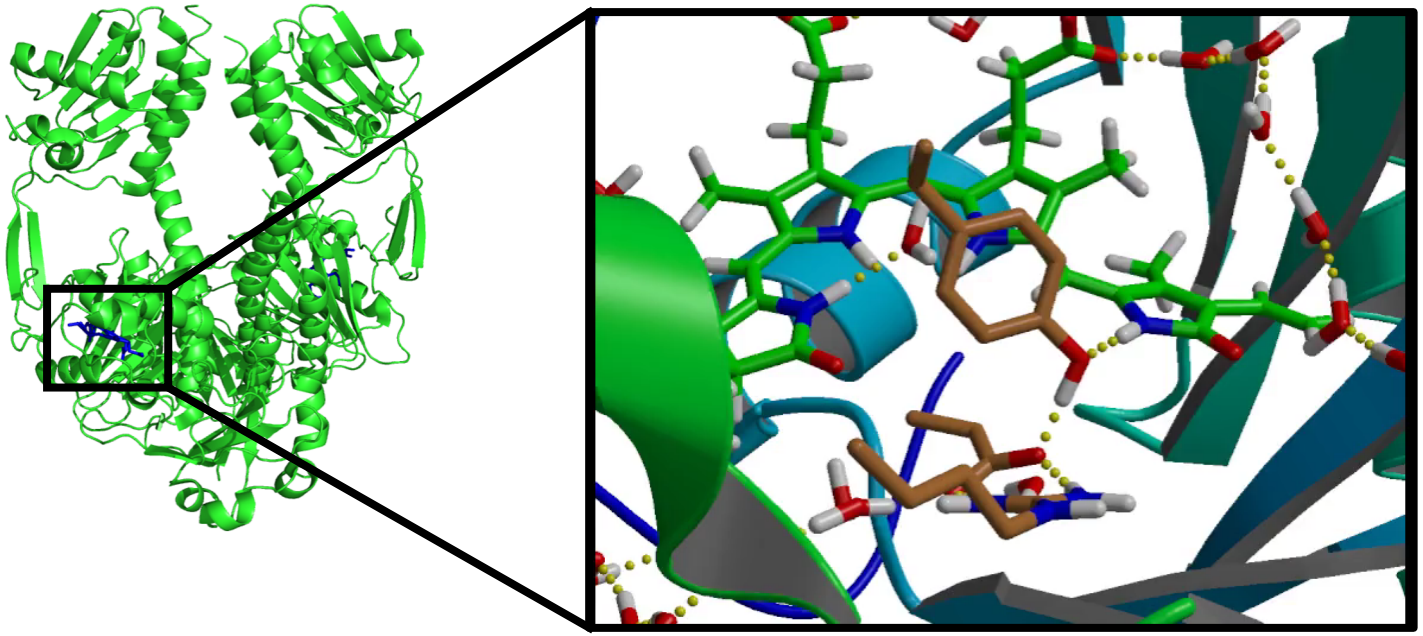
Free energy with Umbrella sampling simulations

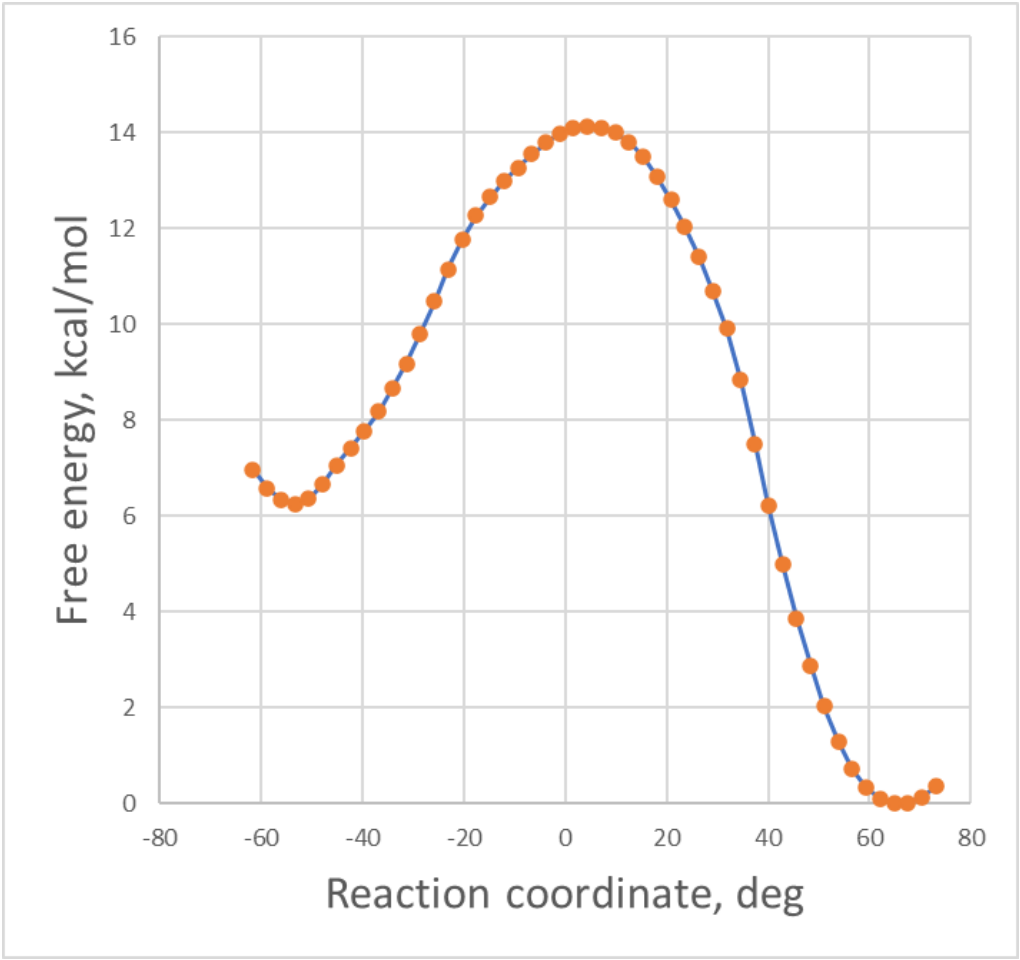
QM part - Chromophore

QM method - PBE/DZVP-MOLOPT-GTH

MM Forcefield - Amber03

Protein simulations: umbrella sampling





CP2K: Advanced Input Parameters

For further information:

https://docs.bioexcel.eu/qmmm_bpg/en/main/

1) Best practice guides
2) Explanations on parameters and combinations
3) Simulations of biological systems with CP2K
4) Understanding of CP2K output
5) Troubleshooting

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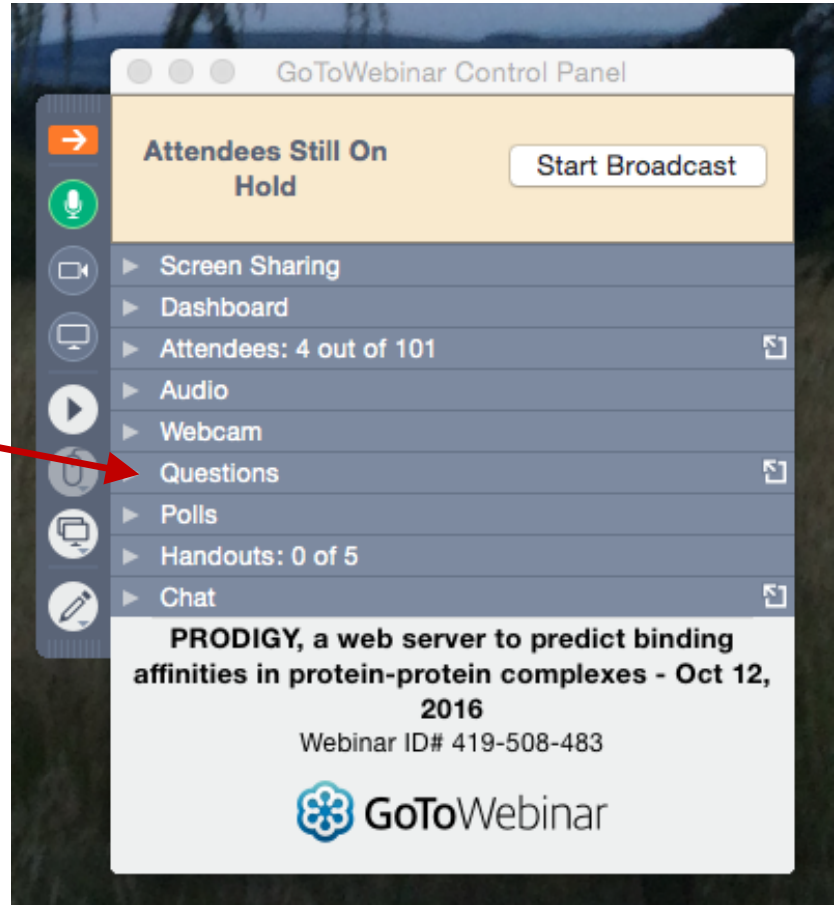
Audience Q&A session

- Please use the Questions function in GoToWebinar application
  - If you *don't have audio*, please mention that in the question.

- Any other questions or points to discuss after the live webinar? Join the discussions at http://ask.bioexcel.eu.



Next webinar occasions

See https://bioexcel.eu/

18 January 2021

Student Webinar: Winter School 2020 Edition

Starting with February 2021

Spring BioExcel Webinars

- Paul Bauer/Berk Hess – Feature of GROMACS 2021
- Magnus Lundborg/Berk Hess -Solvation free energy and Advance Weight Histogram
- Joe Jordan - NB-library

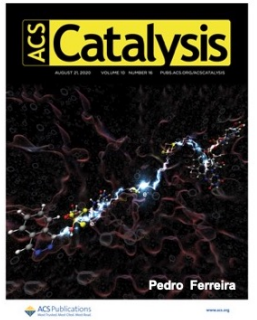
QM/MM Best Practice workshop webinar: Studies on enzyme-catalysed reactions

Prof. Maria João Ramos

University of Porto

10/12/2020

https://bioexcel.eu/qmmm-best-practice-workshop-4



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