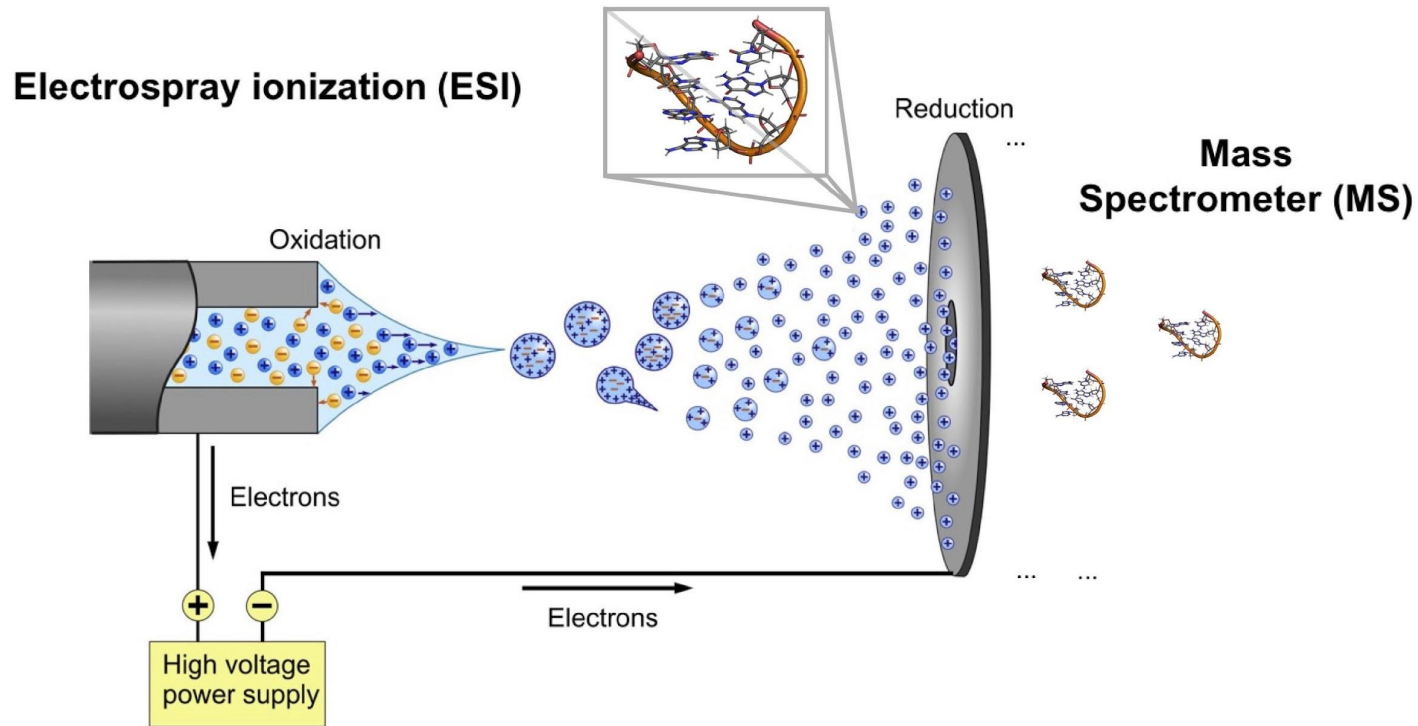# Proton Dynamics in Mass Spectrometry

BioExcel Webinar– 10th of May 2022

Mirko Paulikat

m.paulikat@fz-juelich.de
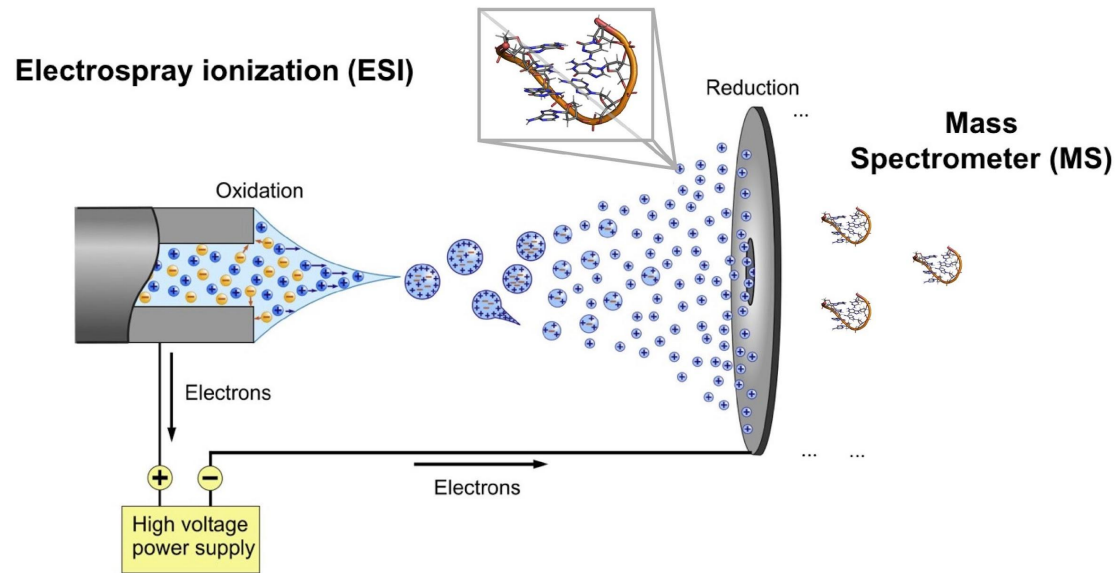
Electrospray Ionization Mass Spectrometry

Electrospray ionization (ESI)

Oxidation

Electrons

Electrons

High voltage
power supply

Reduction

...

**Mass
Spectrometer (MS)**

... ...

Ionization process in ESI-MS

- Analytes in low concentrations are sprayed directly from solution into the gas phase through a capillary applied to an electric field

- Droplets are formed and shrinked by solvent evaporation to provide single analytes

- Fully desolvated ions result from a complete evaporation of the analytes

Native ESI/IM Mass Spectrometry

Electrospray ionization (ESI)

Oxidation

Electrons

+ −

High voltage power supply

Electrons

Reduction

...

Mass Spectrometer (MS)

... ...

Ion Mobility Mass Spectrometry

Electric Field

Ions

Drift Gas

Drift Tube
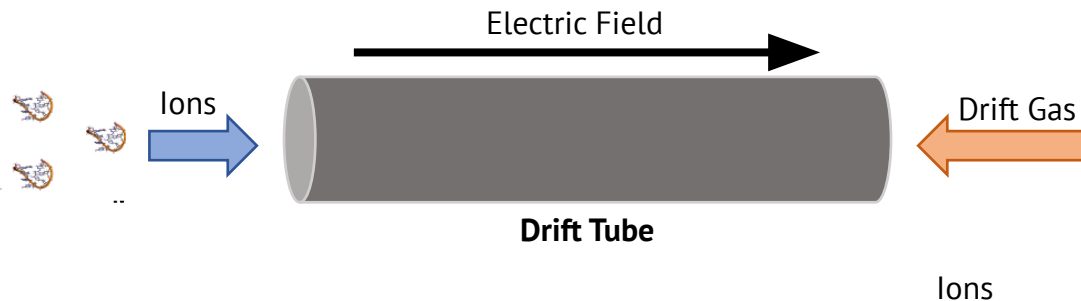
Ions

Mass Spectrometry of Biomolecular Systems

- "native" MS: solution conditions compatible with ESI process, but the biomolecular system hast to be in the same state as und physiological conditions
  ☐ typically 150 mM NH_4OAc aqueous solution

- Coupling to ion mobility mass spectrometry: determination of the shape of biomolecules based on the electrophoretic mobility of ions in a buffer gas

Experimental Observables

- *m/z*, charge state distribution, collisional cross section
  ☐ conformations of biomolecules, topology of biomelecular complexes and conformational changes upon ligand binding at **low** resolution

⇒ *Atomisitic simulations as important complementary tool*

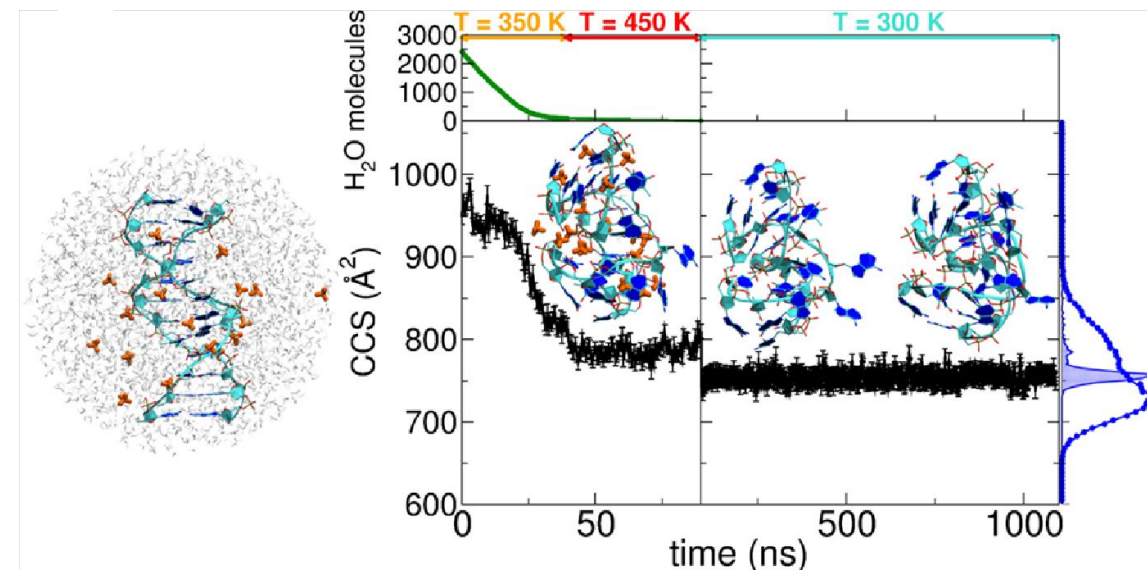# DNA – MD Simulation in the Gas Phase

Computational Protocol

1. Run classical molecular dynamics simulations in aqueous solution
2. Select (randomly) snapshots and remove solvent molecules
3. Localize charges (protons)
4. Run extended gas phase MD simulations
5. Derive ESI/IM-MS properties and compare with experimental data
6. Identify atomistic details for (non-)matching biomolecular conformations and complexes

Compaction of duplex nucleic acids in gas phase

Porrini et al., *ACS Cent. Sci.* **2017**

- Gas phase MD simulations, even in the μs-time scale starting from solution structures do not reproduce the observed experimental compaction
- Gradual evaporation starting from water droplets to obtain progressive structural rearrangements (point 2)


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Proton Dynamics in the Gas Phase

- Biomolecular simulations applying classical force fields do not allow to study the transfer of protons and their induced structural rearrangements ☐ QM/MM methodology to study such reactive processes

- Protonation pattern may vary between solution and the gas phase

Proton dynamics in oligonucleotides in the gas phase
Arcella et al., *Angew. Chem. Int. Ed.* **2015**

- Heptanucleotide with sequence d(GpCpGpApApGpC)

- Total charge state increased by protonation of phosphate groups

- Change in hydrogen bonding pattern by proton transfer between phosphate groups

short B-DNA fragment

d(GAA) triloop
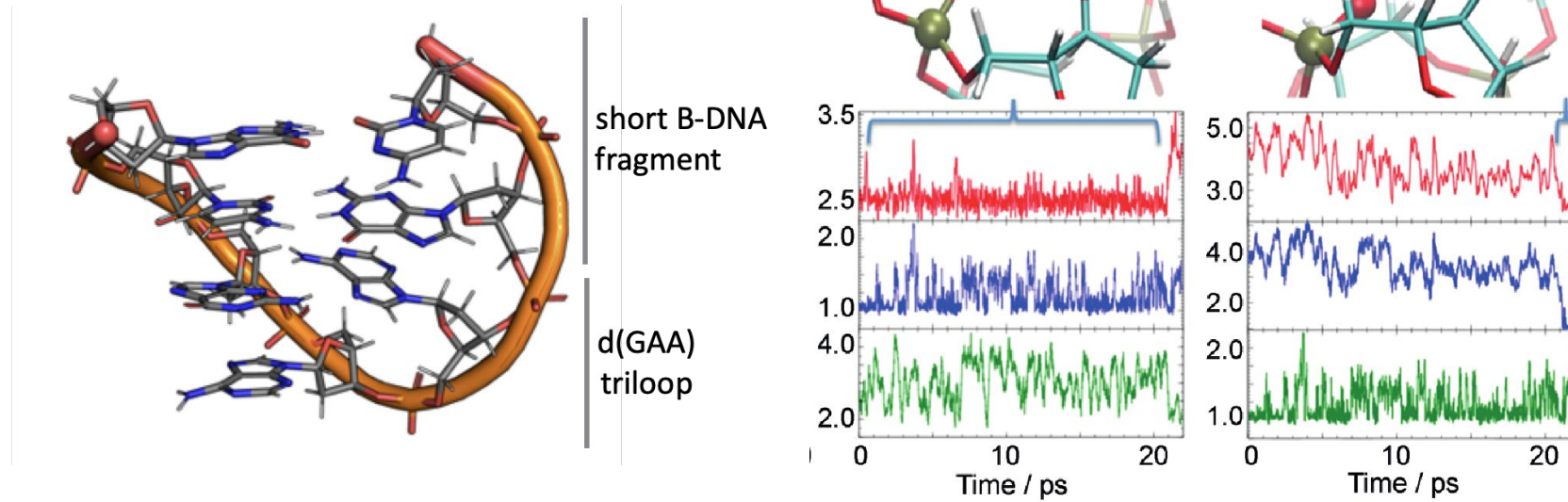
Problem – Protonation of DNA/counterion complexes

- Polyanionic DNA under physiolocical conditions ☐ negativley charged phosphate backbone

- The energetics dramatically differ in the gas phase: significant portion of phosphate groups are protonated using NH_4OAC solutions ☐ proton transfer from NH_4^+ ions to the DNA backbone + dissociation of NH_3

Illustration – Model System $NH_4^+ – PO_4Me_2^-$
- Aqueous solution $pK_a(NH_4^+)$ = 9.25 and $pK_a(PO_4Me_2H)$ = 1.29
  ☐ fully solvated ions under solution conditions

- Energetics and simulation in the gas phase:
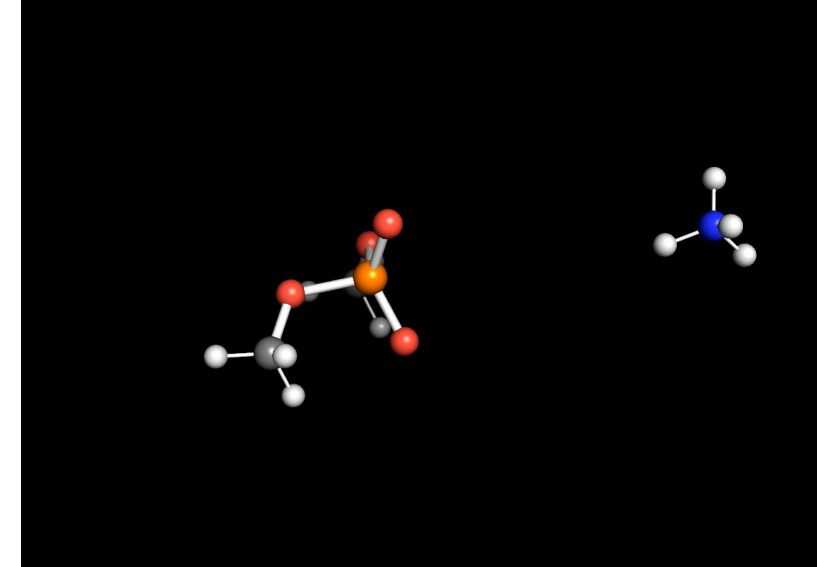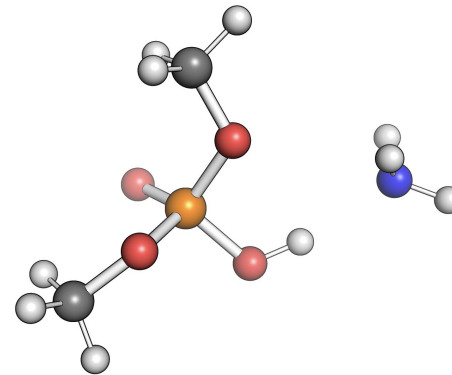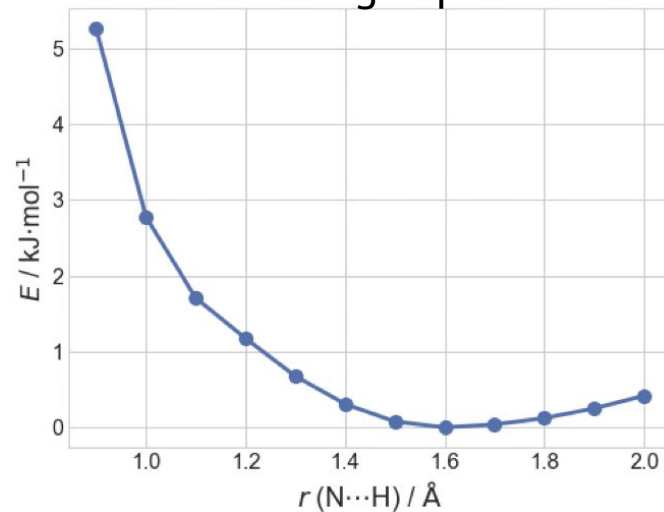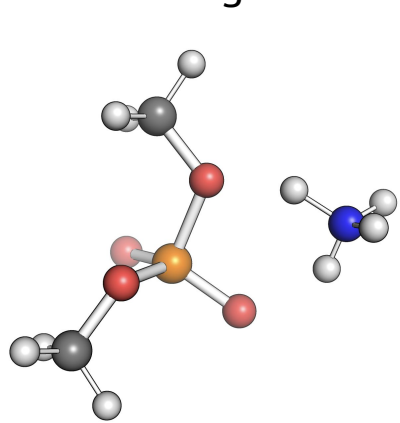
Preparatory Work – MD in Aqueous Solution

- Reexamination of the aqueous solution structure of the heptanucleotide *(Q = −6)* with sequence d(GpCpGpApApGpC) with six NH_4^+ counter ions

- 500 ns of classical molecular dynamics simulations in the *NPT* ensemble (T = 300 K, p = 1 bar) using the GROMACS software package (collaboration with Modesto Orozco's group)

- Preservation of its hairpin structure

short B-DNA fragment

d(GAA) triloop

NH_4^+ – Phosphate pairs
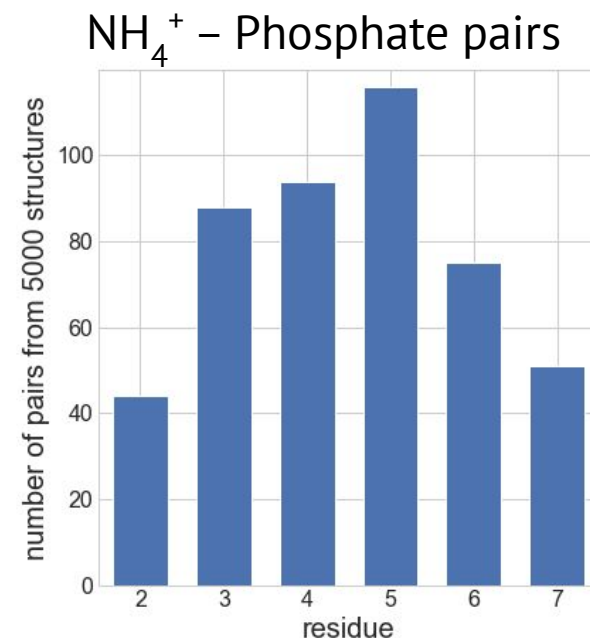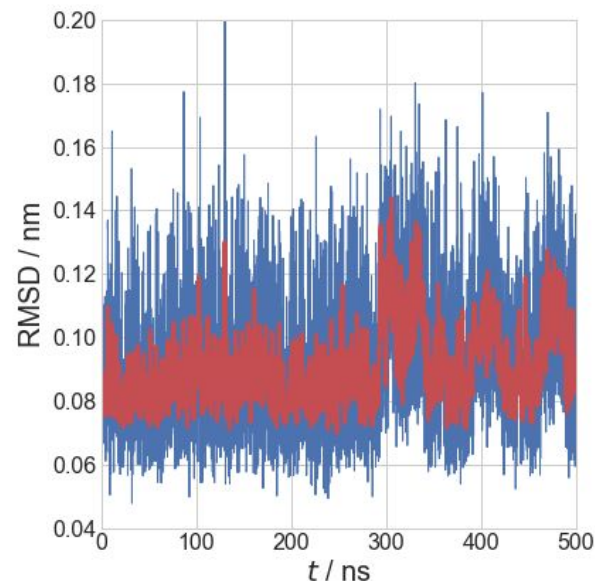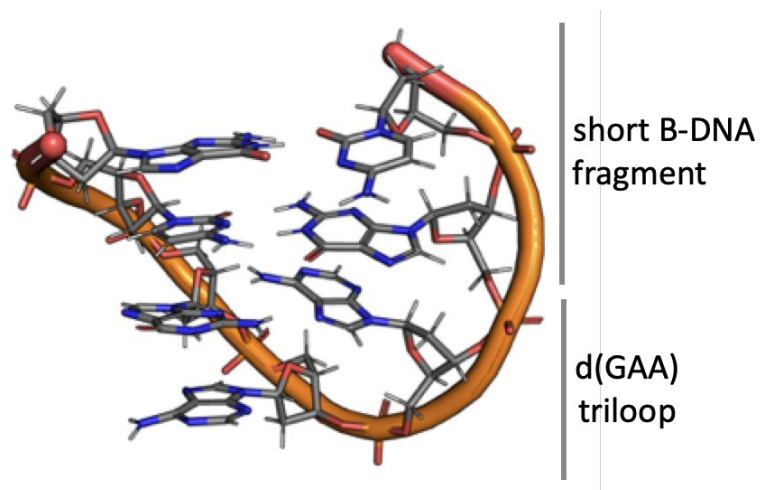
Simulation of the Evaporation Process

- 30 Å water droplet around the COM of the DNA oligo

- 500 ps chunks of gas phase MD simulations

- Large simulation box and direct Coulomb summation to evaluate the electrostatics

- Strip out evaporated water molecules
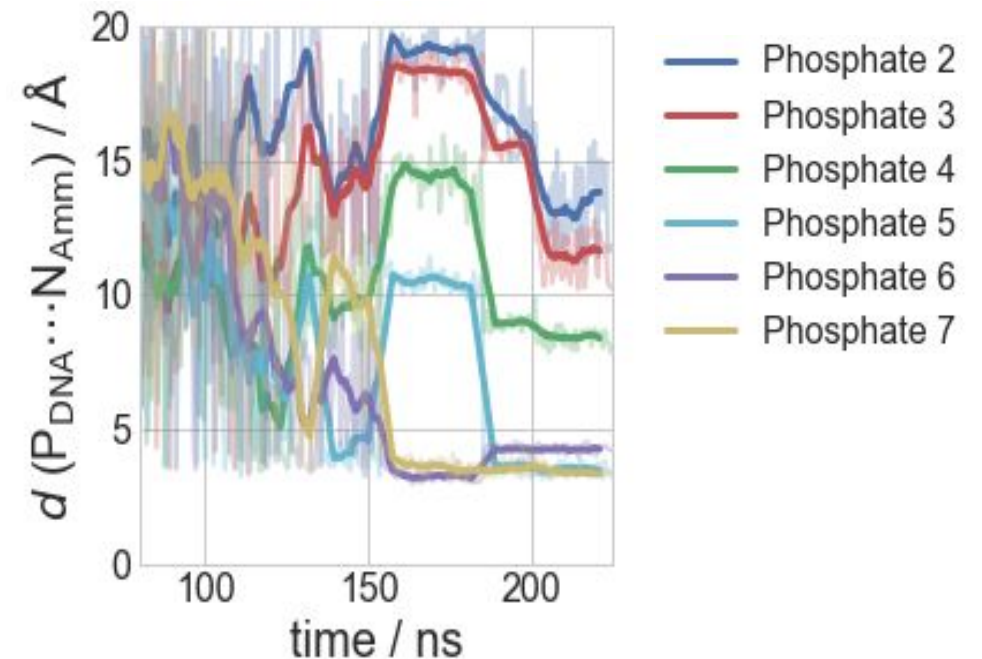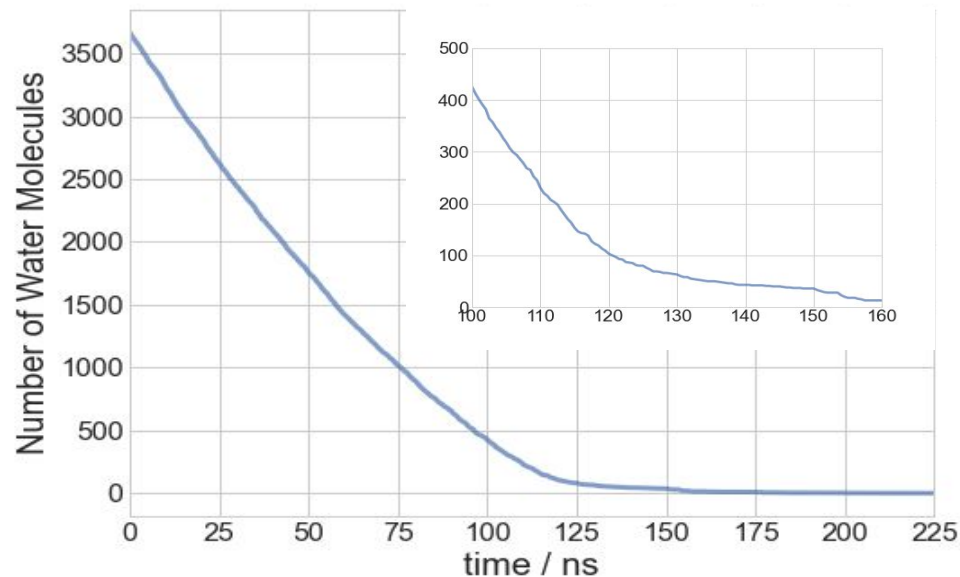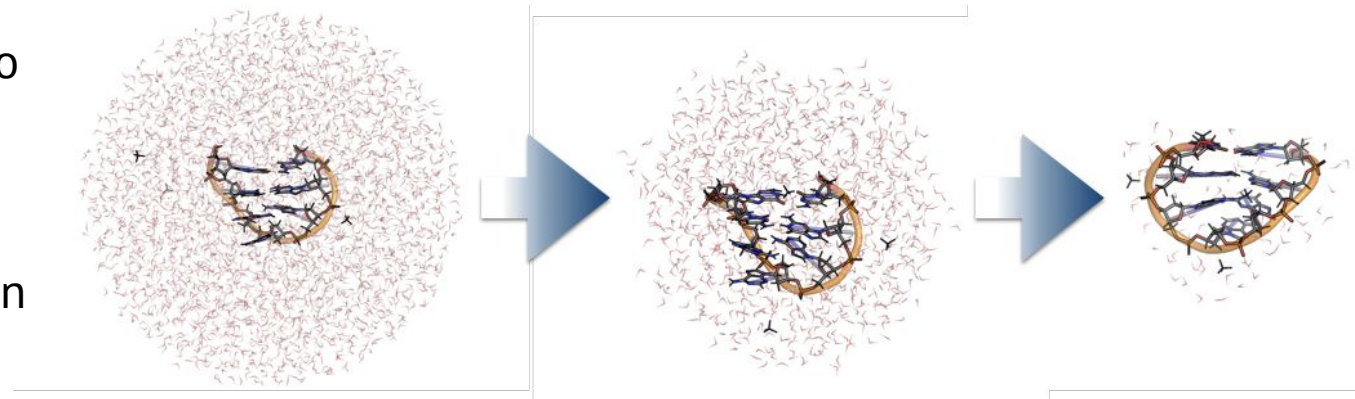
QM/MM Setup

Descriptors for the identification of snapshots for proton transfer

1. Total number of water molecules ⇔ time span of the evaporation

2. Distance between NH_4^+ ions and DNA phosphate groups

3. Local coordination number of NH_4^+ ions

$$\mathrm{CN}(i) = \sum_j \frac{1 - \left(\frac{r_{ij} - d_0}{r_0}\right)^6}{1 - \left(\frac{r_{ij} - d_0}{r_0}\right)^{12}}$$

HPC QM/MM software developed in BioExcel

- MiMiC – interface coupling CPMD and GROMACS
  - DFT with a plane wave – pseudopotential approach

- GROMACS/CP2K interface
  - DFT with a mixed Gaussian and plane wave (and pseudopotentials) approach
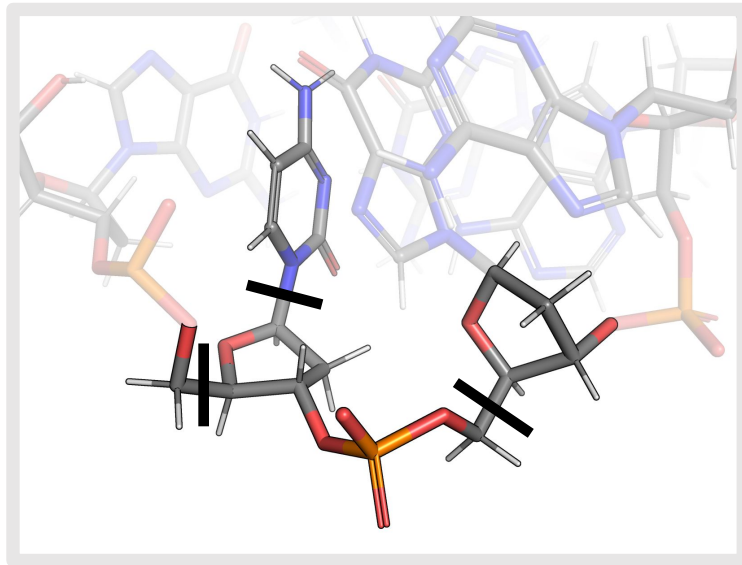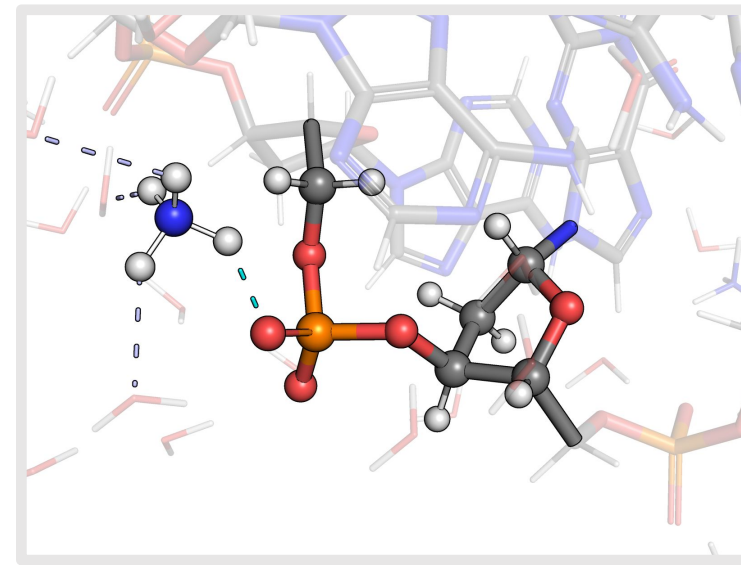 - Multi-grid implementation
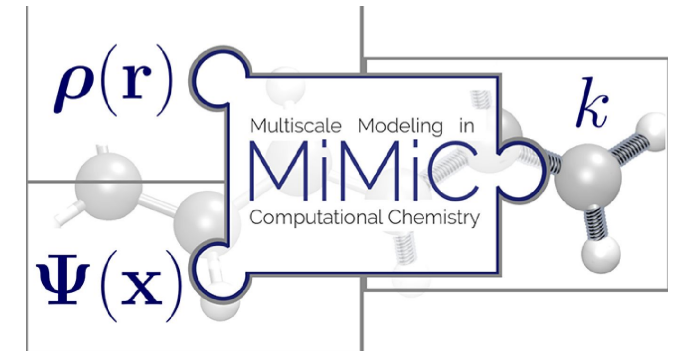
QM/MM Setup

QM/MM Methodology

- OM region
  - NH_4^+ ion and phosphate group with adjacent desoxyribose moiety
 - cut C4'–C5' and C1'–N^{base} covalent bonds (▬)
  - H-link atoms

- GPW approach with DFT using PBE-D3/DZVP and GTH-PPs

- Benchmark OM settings
  - PW cutoff (500 Ry)
  - Relative cutoff for multi-grid approach (80 Ry)
 - Number of grids (4)

QM/MM Simulations

QM/MM Performance

- Hybrid MPI/OpenMP parallization ☐ 2 nodes (48 cores/node) with 12 tasks/node and 4CPUs/task on Intel Skylake Xeon Platinum 8174 machines

- ~3.5–6.0 ps/day (dependent on the QM size)
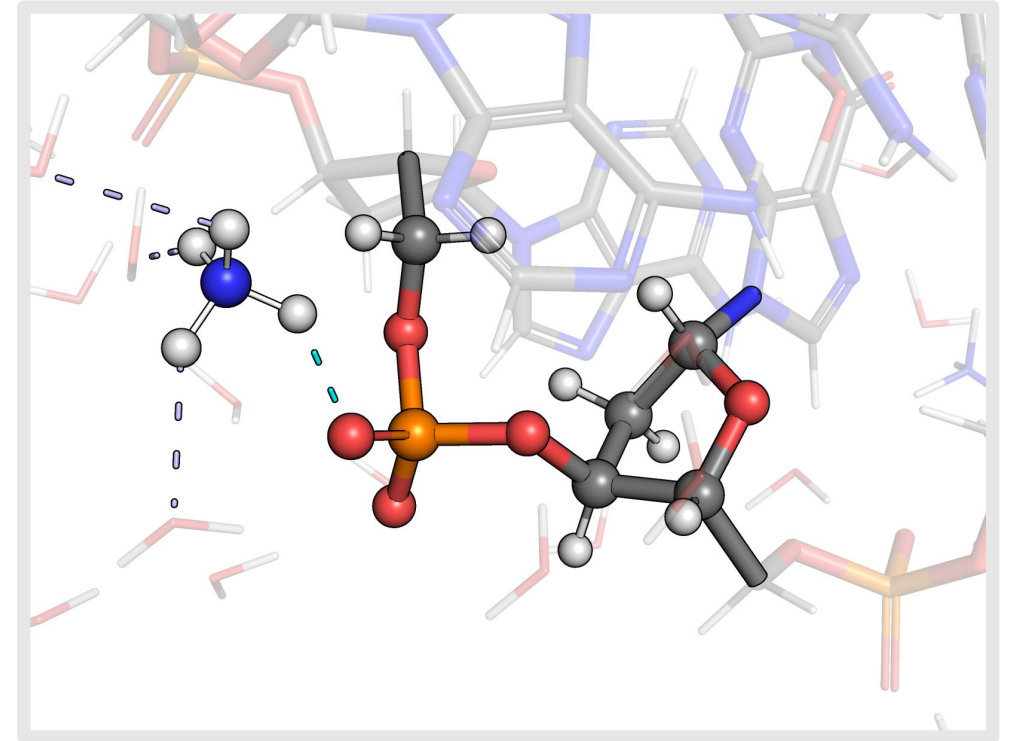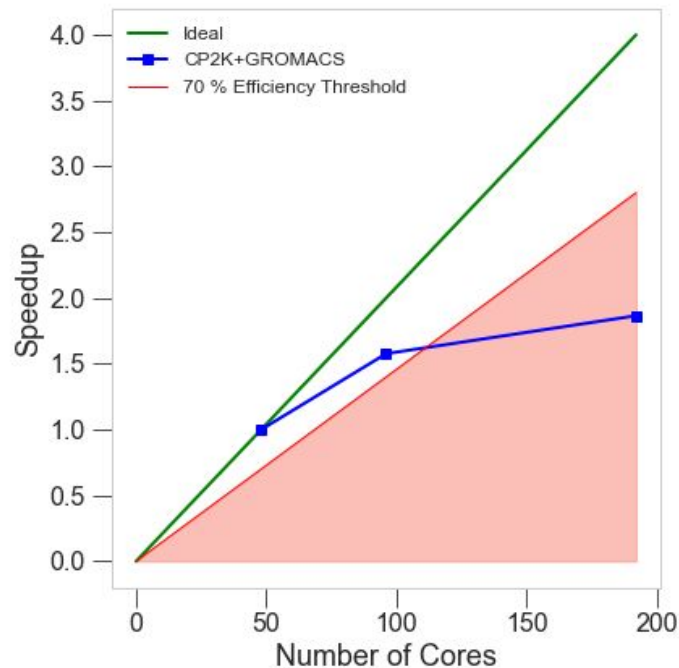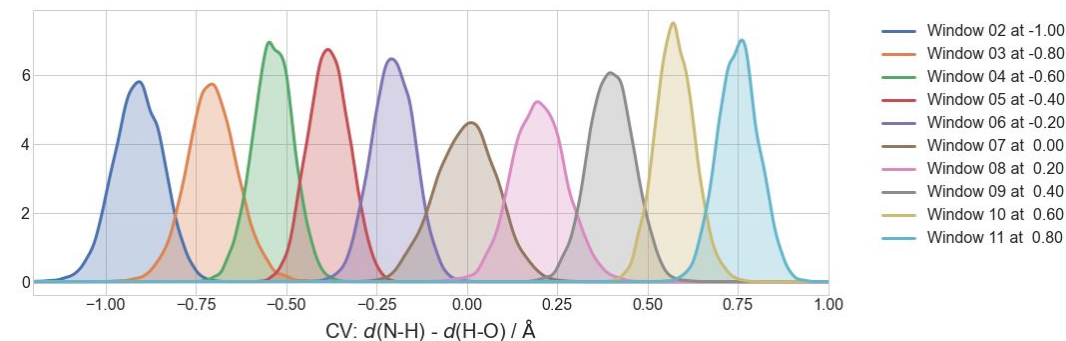
QM/MM Simulations

1. Minimization: 2000 steps steepest descent

2. Heating: re-heat the system from 0 to 300 K in 2.5 ps (5000 steps) QM/MM simulations

3. Equilibration: 2.5 ps QM/MM simulations at 300 K

4. Scan of the proton transfer (PT):

   - GROMACS/CP2K patched with Plumed

   - PT coordinate $CV_{\mathrm{PT}} = d_{\mathrm{N-O}} - d_{\mathrm{H-O}}$

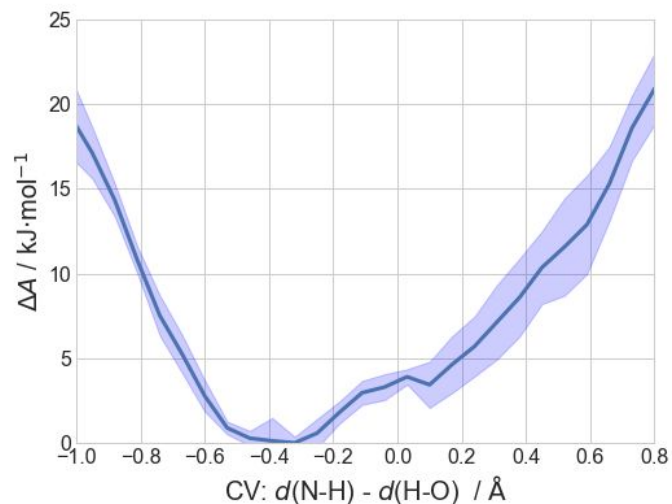   - move the proton to ionic configuration (0.25 ps) and scan the PT coordinate (2.5 ps)
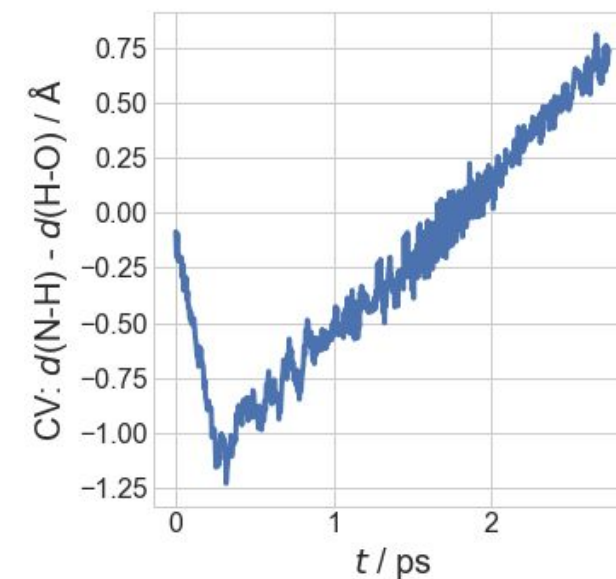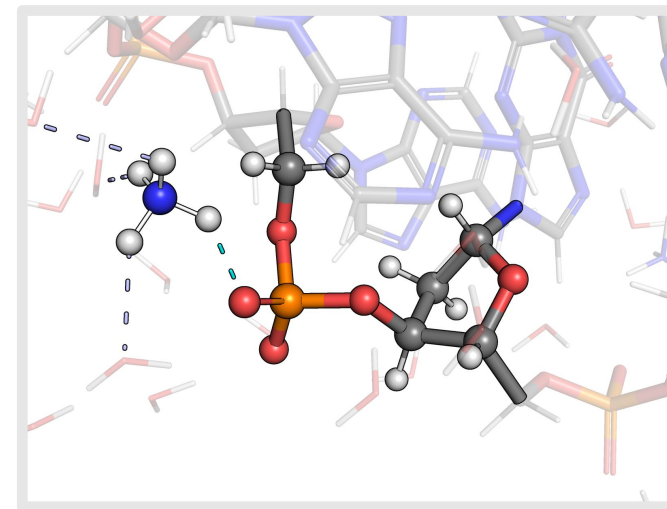
QM/MM Simulations

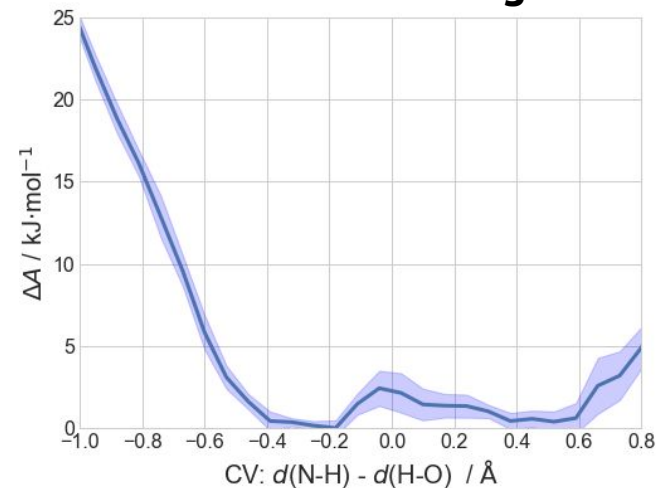## Umbrella sampling for local proton transfer profiles

- Extract starting configurations from scan along the PT coordinate $CV_{\mathrm{PT}} = d_{\mathrm{N-O}} - d_{\mathrm{H-O}}$

- 10 equidistant windows in the range of $CV = [-1.0; 0.8]$ Å

- 25 ps QM/MM simulations per window

Legend:
- Window 02 at -1.00
- Window 03 at -0.80
- Window 04 at -0.60
- Window 05 at -0.40
- Window 06 at -0.20
- Window 07 at 0.00
- Window 08 at 0.20
- Window 09 at 0.40
- Window 10 at 0.60
- Window 11 at 0.80

CV: d(N-H) - d(H-O) / Å

Ionic Configurations

Proton Transfer Configurations

BioExcel Partners

Audience Q&A session

- Please use the Q&A function at the bottom of **Zoom** application
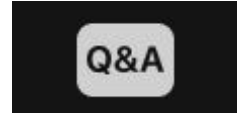
- Any other questions or points to discuss after the webinar?
  Join the discussions at http://ask.bioexcel.eu