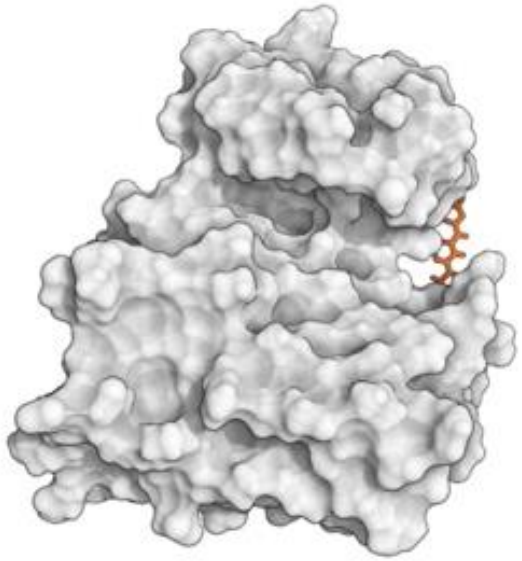
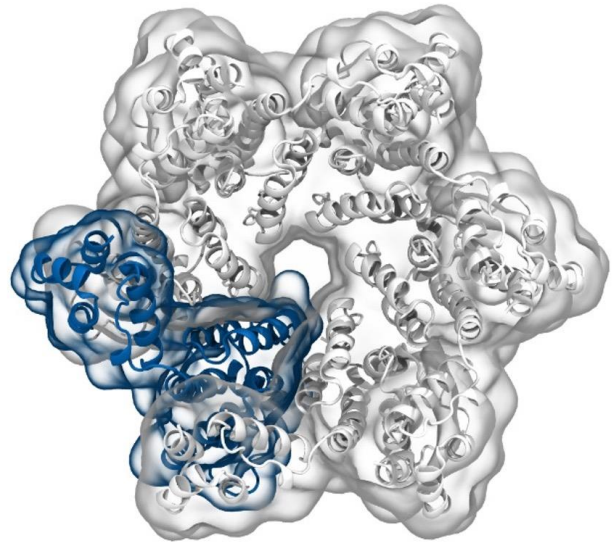
Simulation of Biomolecules



Basic Simulation Analysis



2024 CCP5 Summer School

Dr Matteo Degiacomi
Durham University
matteo.t.degiacomi@durham.ac.uk

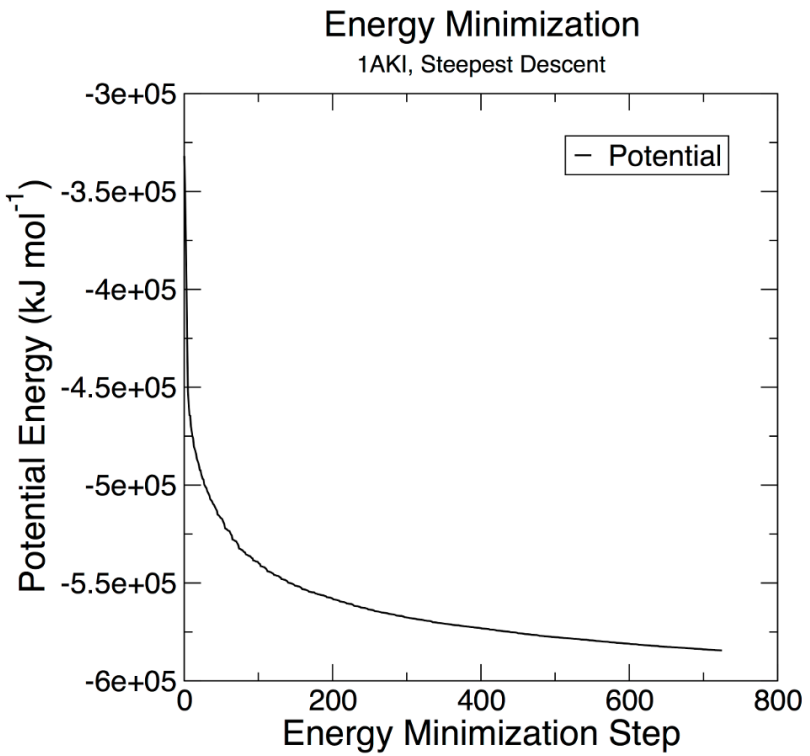
Dr Antonia Mey
University of Edinburgh
antonia.mey@ed.ac.uk

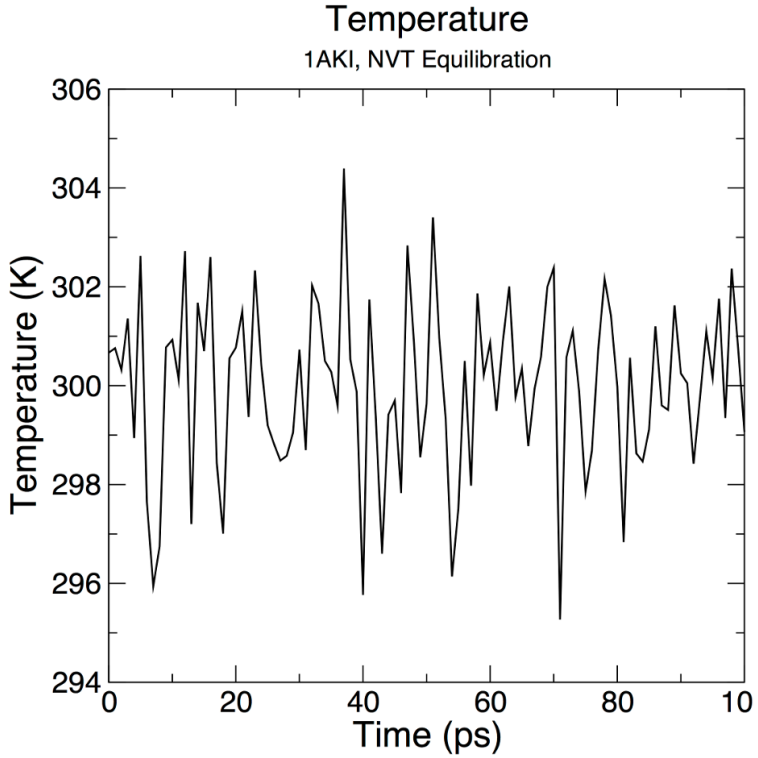
Volume and pressure equilibration

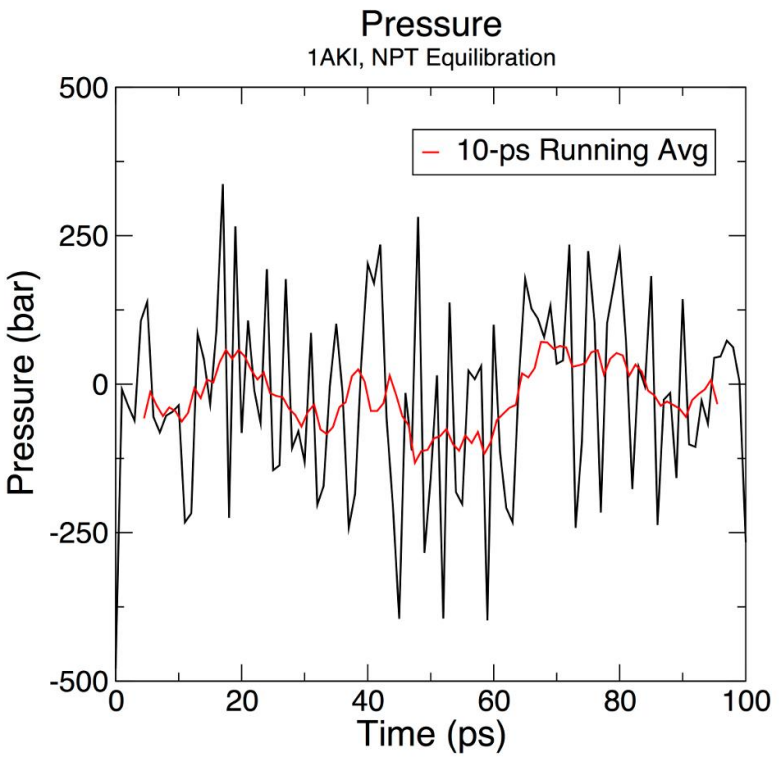
Steps until production:

Production ensemble

Minimisation → NVT (short simulation to relax to temperature of interest) → NPT (short simulation to relax to density of interest) → NPT

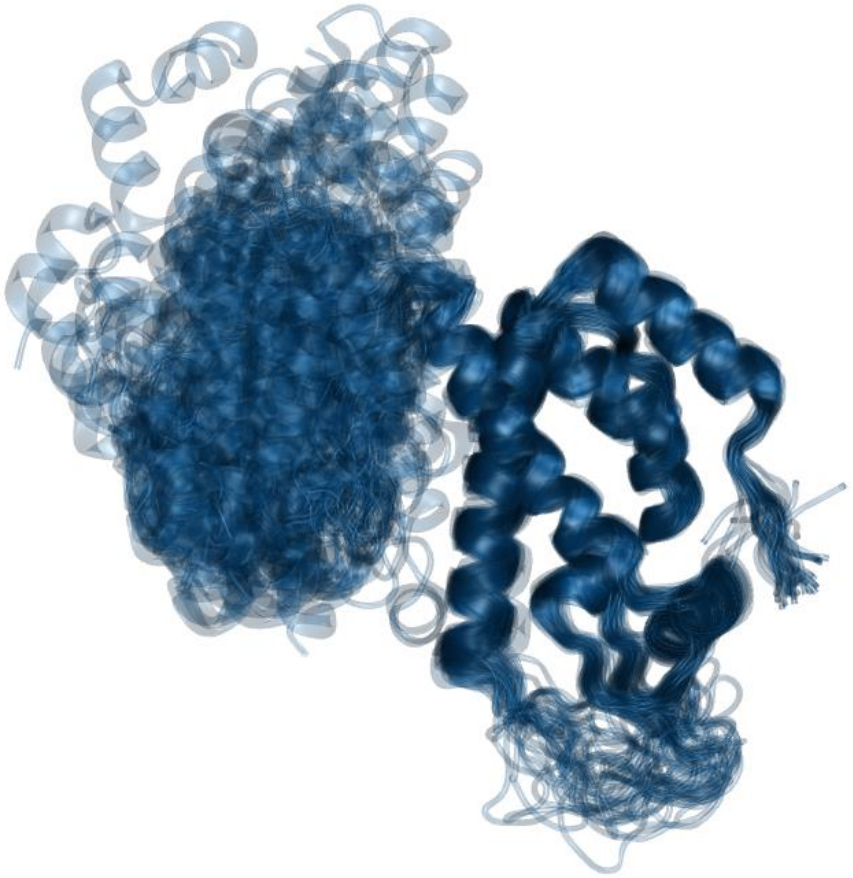


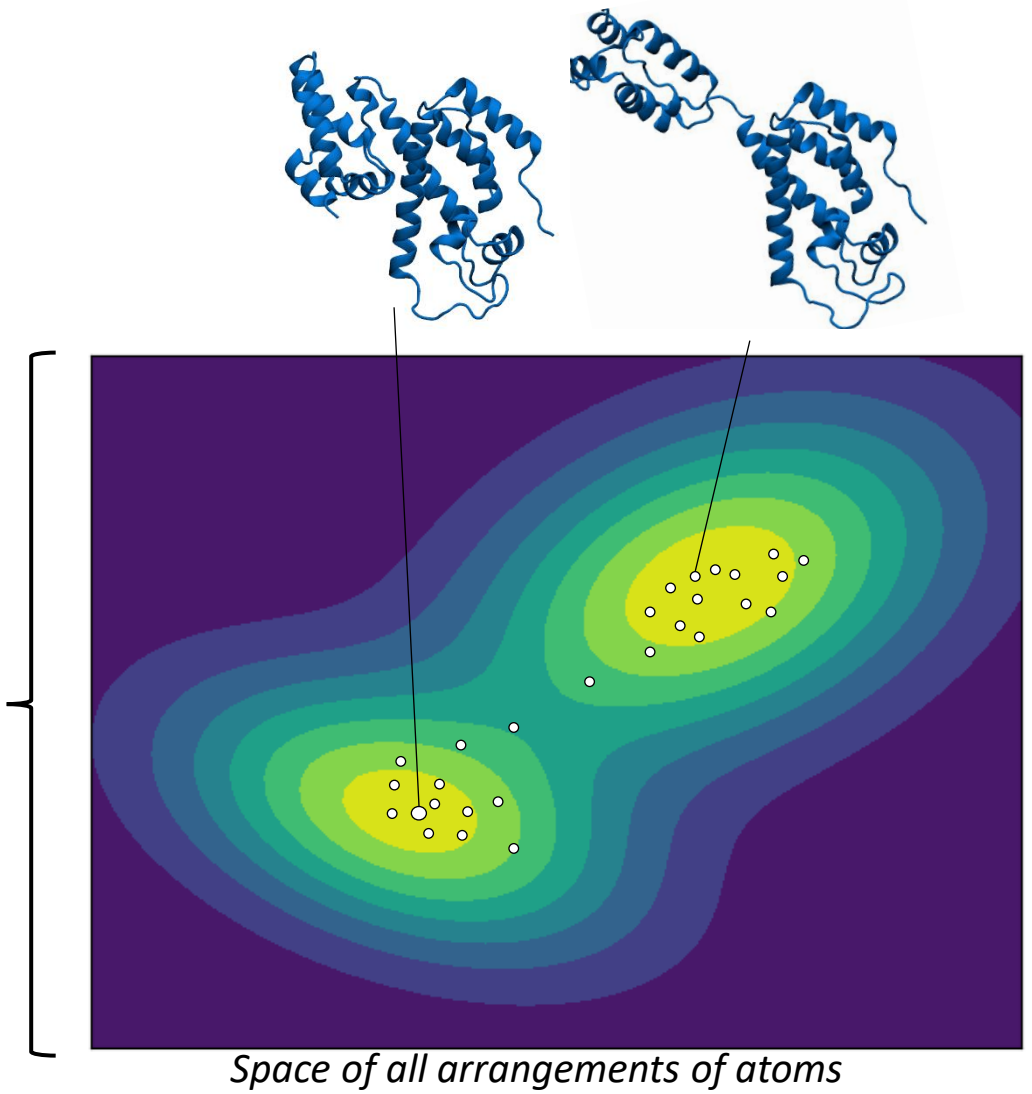




Living J.Comp.Mol.Sci. 2019,1,5957

Sampling the conformational space





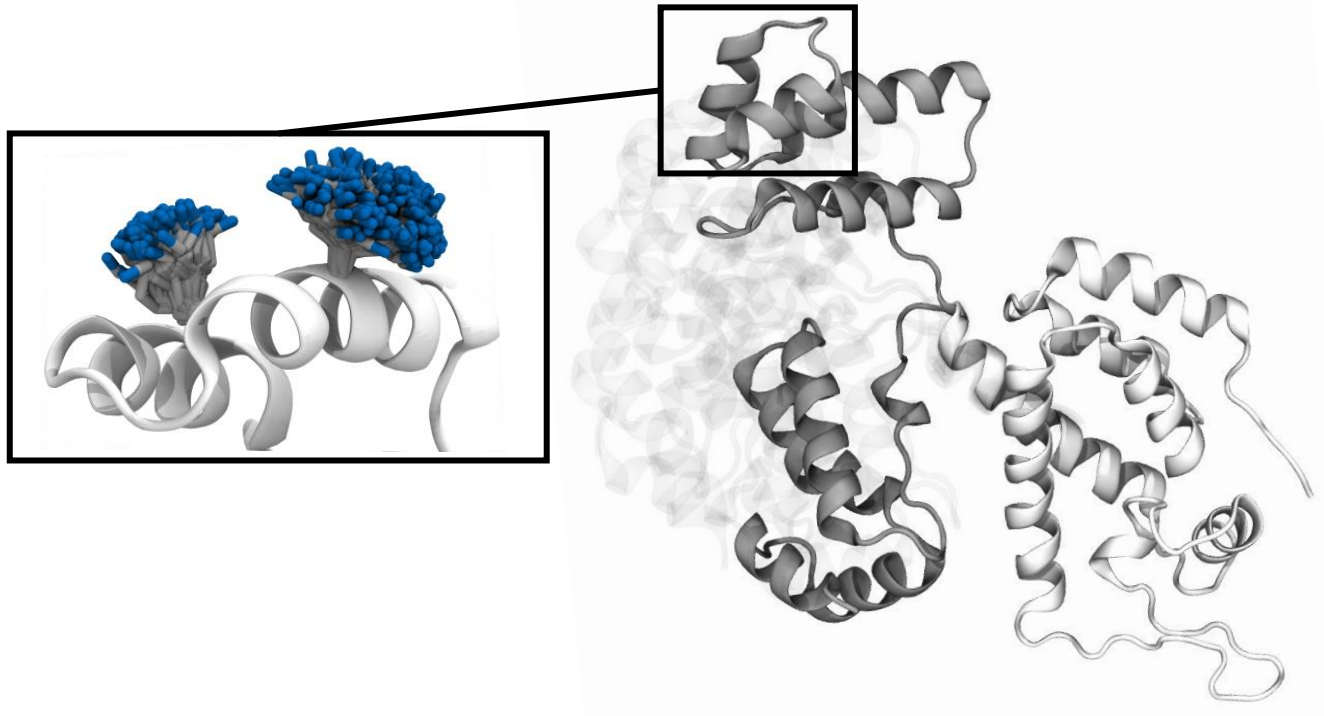
Space of all arrangements of atoms

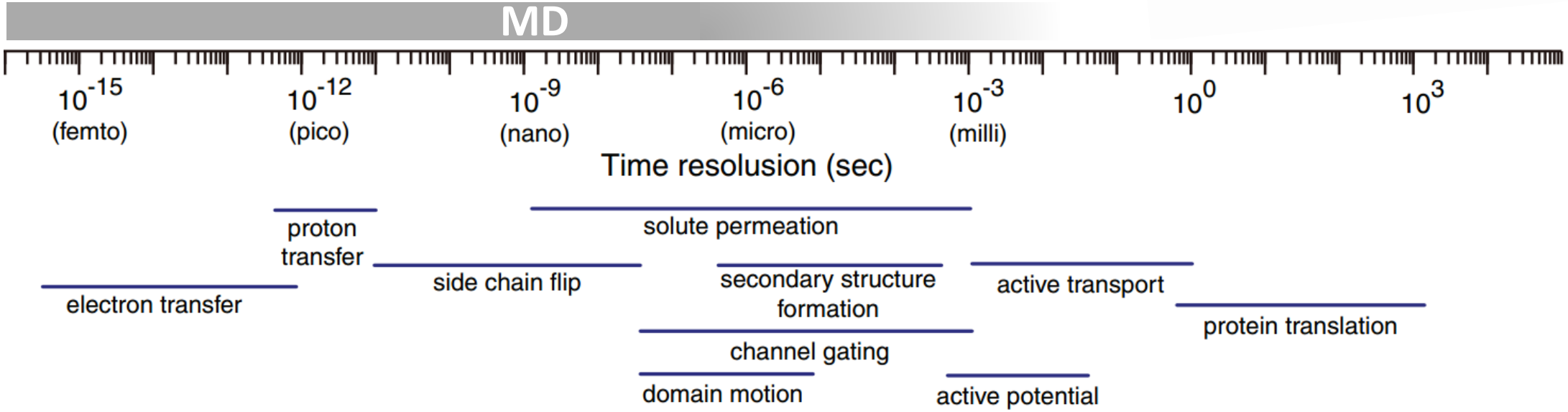
Probability of sampling a conformation is inversely proportional to its energy: $p_i \propto e^{-\varepsilon_i / kT}$

Timescales in biology

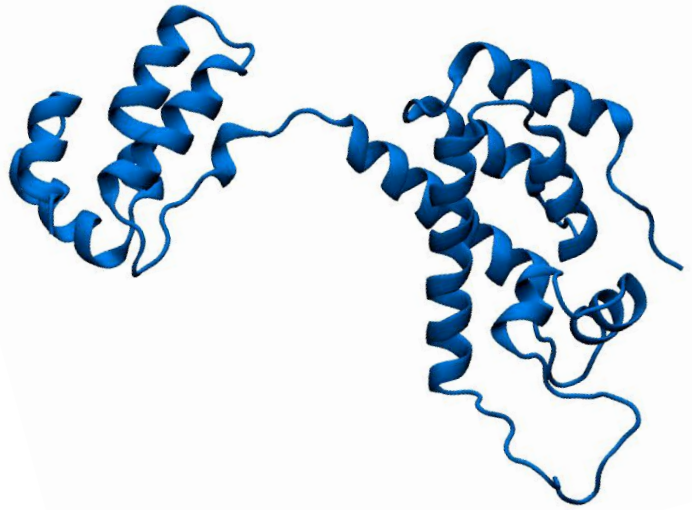
Different regions, different timescales:

- Side chains faster than backbone
- Loops faster than helices and sheets
- backbone faster than side chains
- Protein surface faster than core





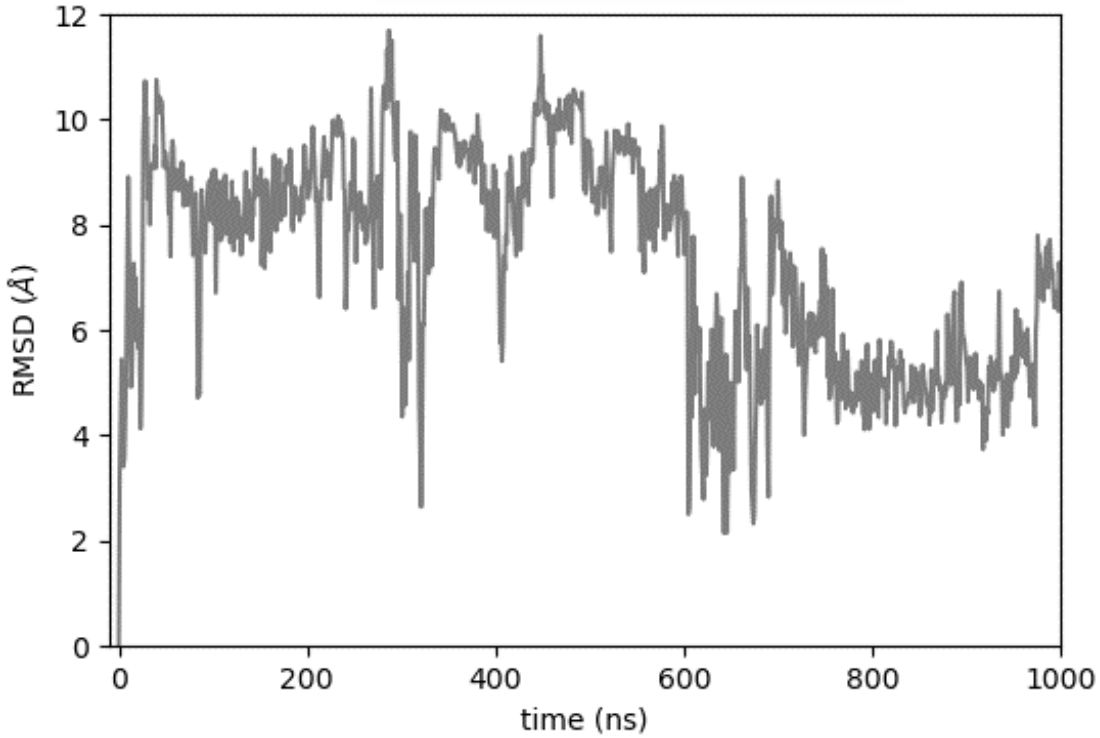
Root Mean Square Deviation (RMSD)



Given a system with *N* atoms, and a reference arrangement x_0:

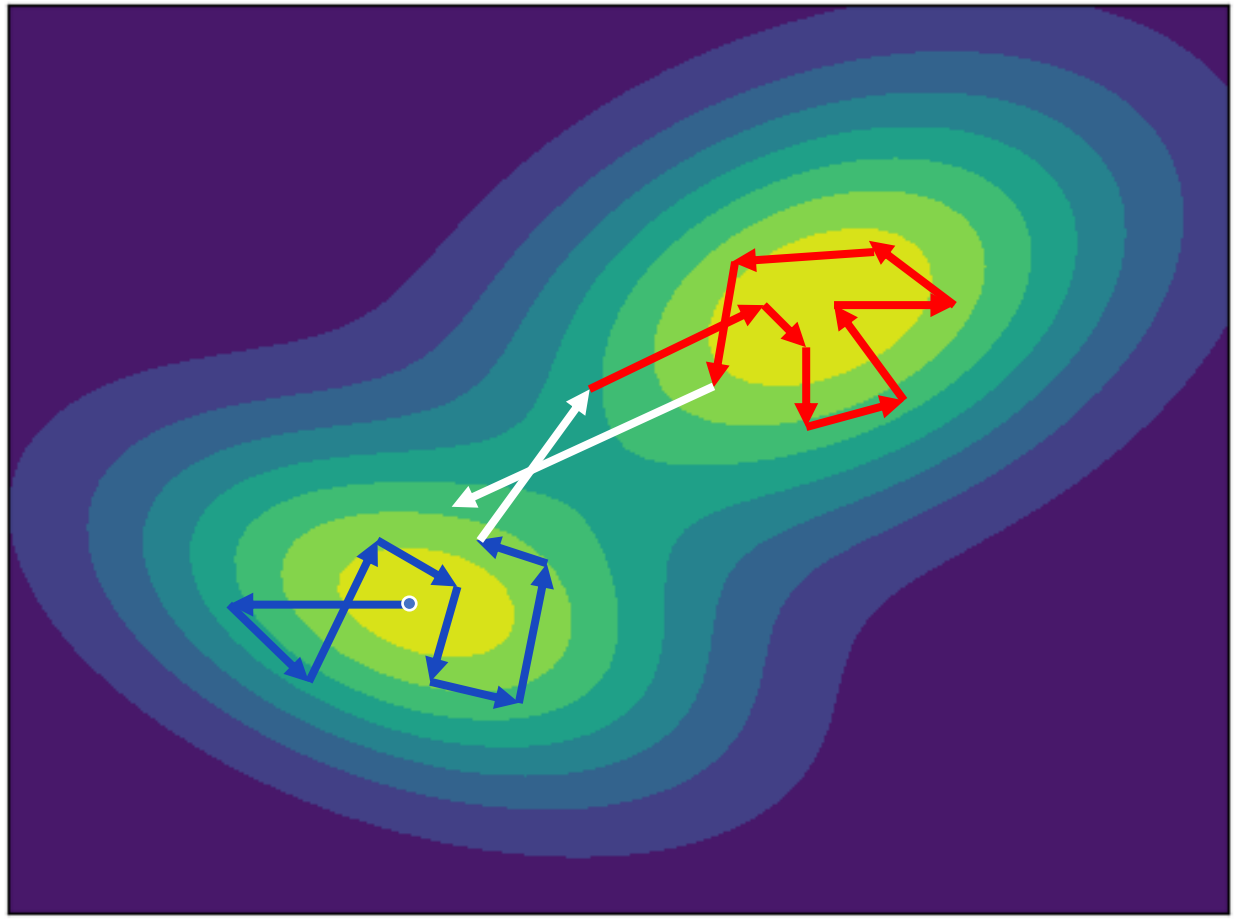
$$RMSD = \sqrt{\frac{1}{N}\sum_{i=0}^{N}(X_i - x_0)^2}$$

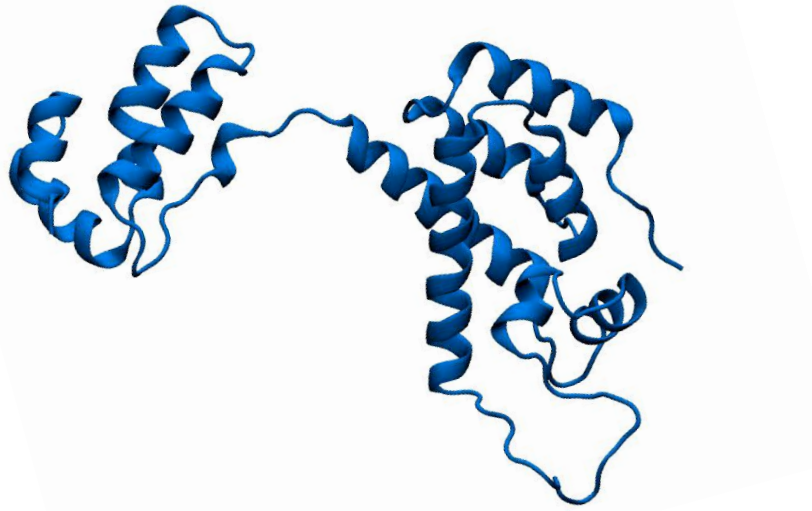
In MD, x_0 is often the first conformation in the simulation.

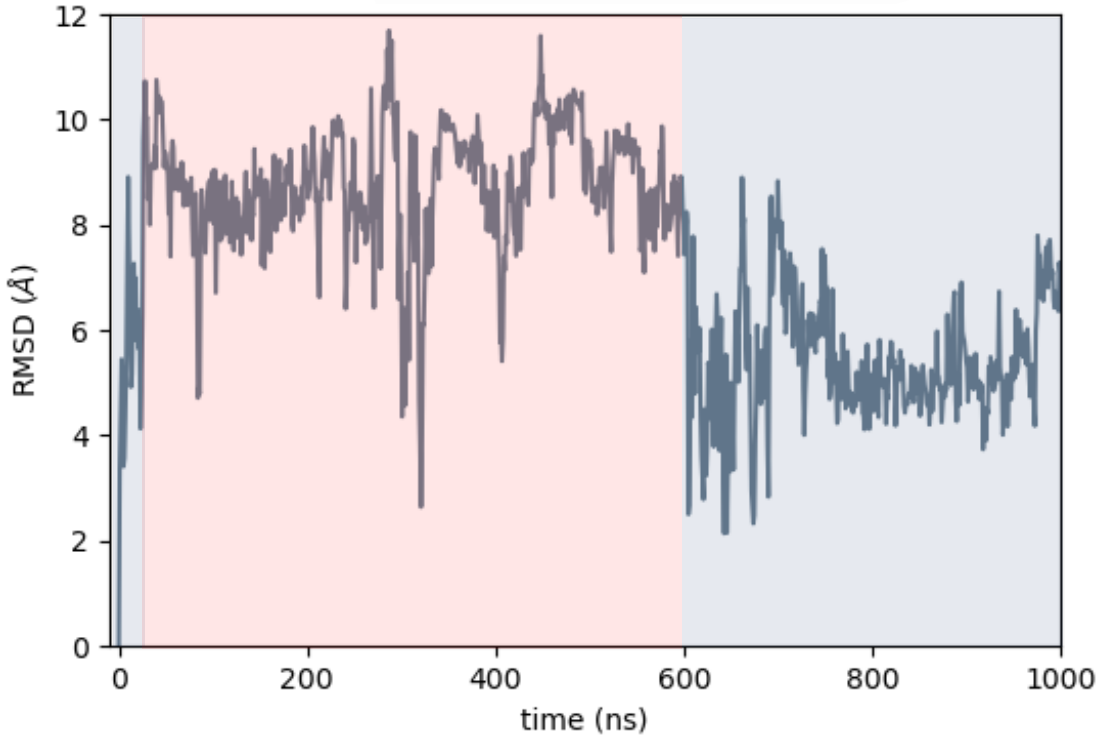


HIV-1 capsomer simulation from: *Degiacomi & Dal Peraro, Structure, 2013*

Convergence?



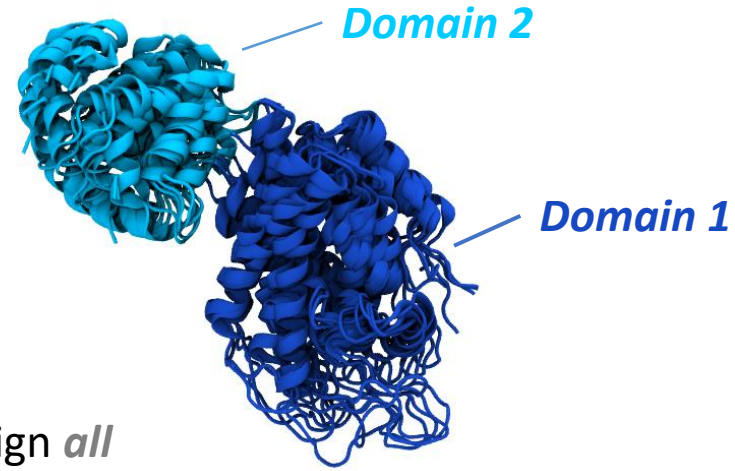


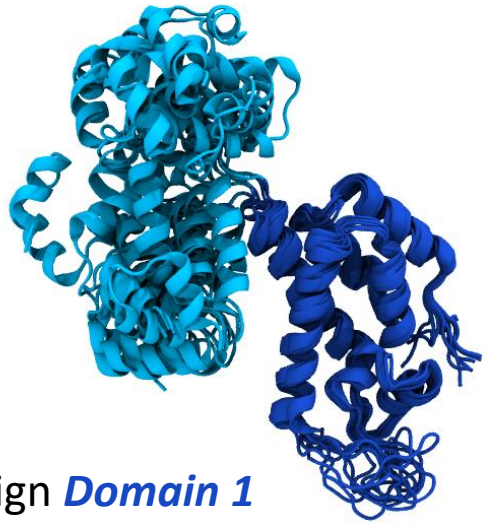


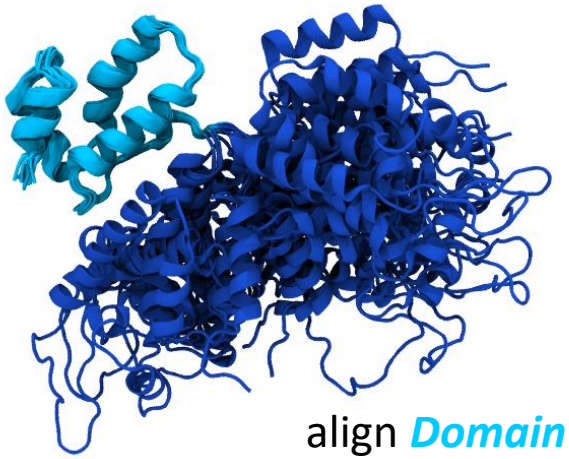
Refrain from using RMSD as a single indicator of simulation convergence.

HIV-1 capsomer simulation from: *Degiacomi & Dal Peraro, Structure, 2013*

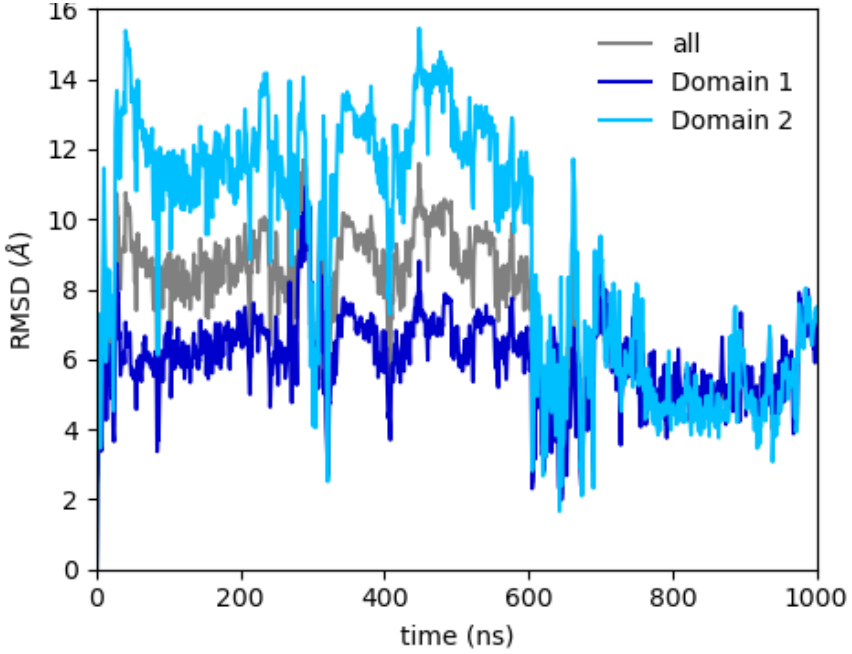
RMSD is alignment- and selection-dependent



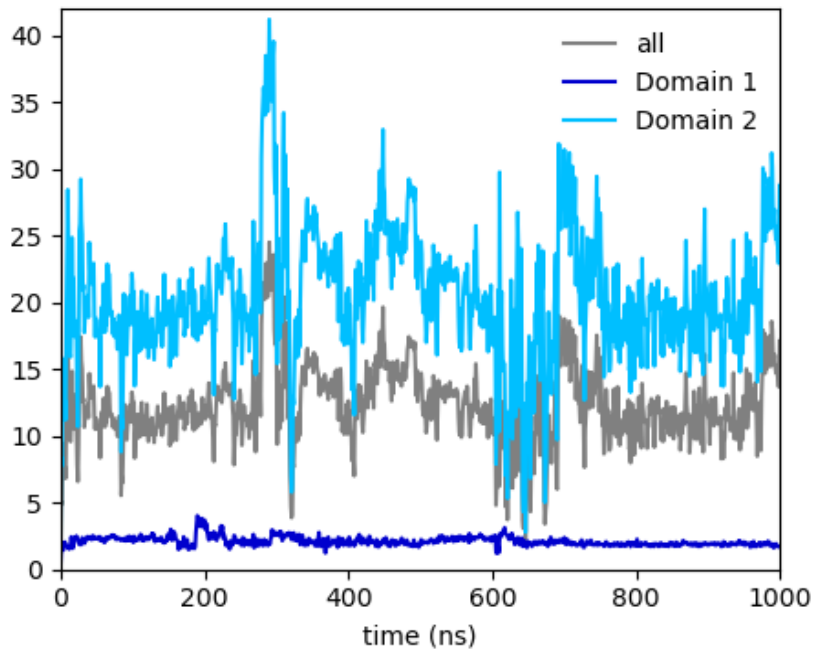




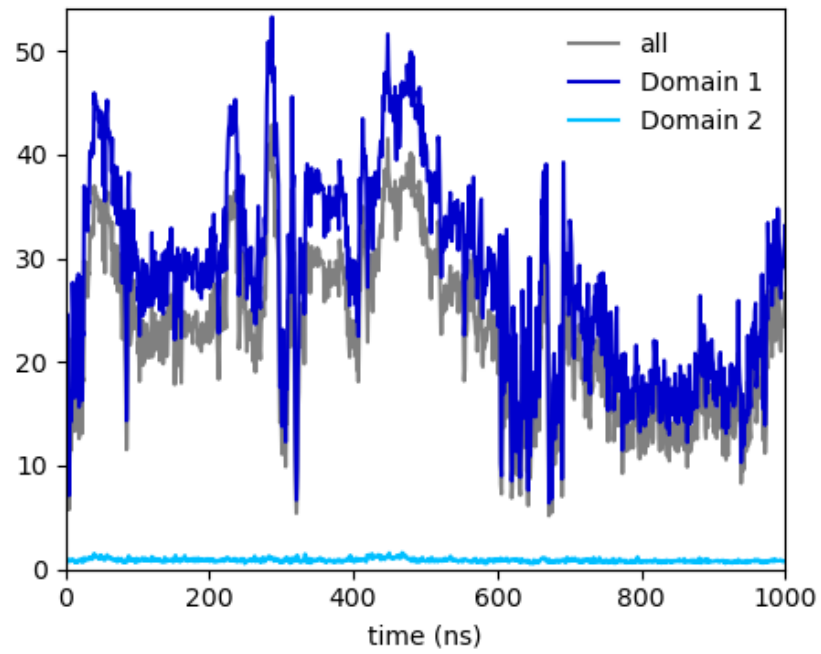
align *all*



align ***Domain 1***

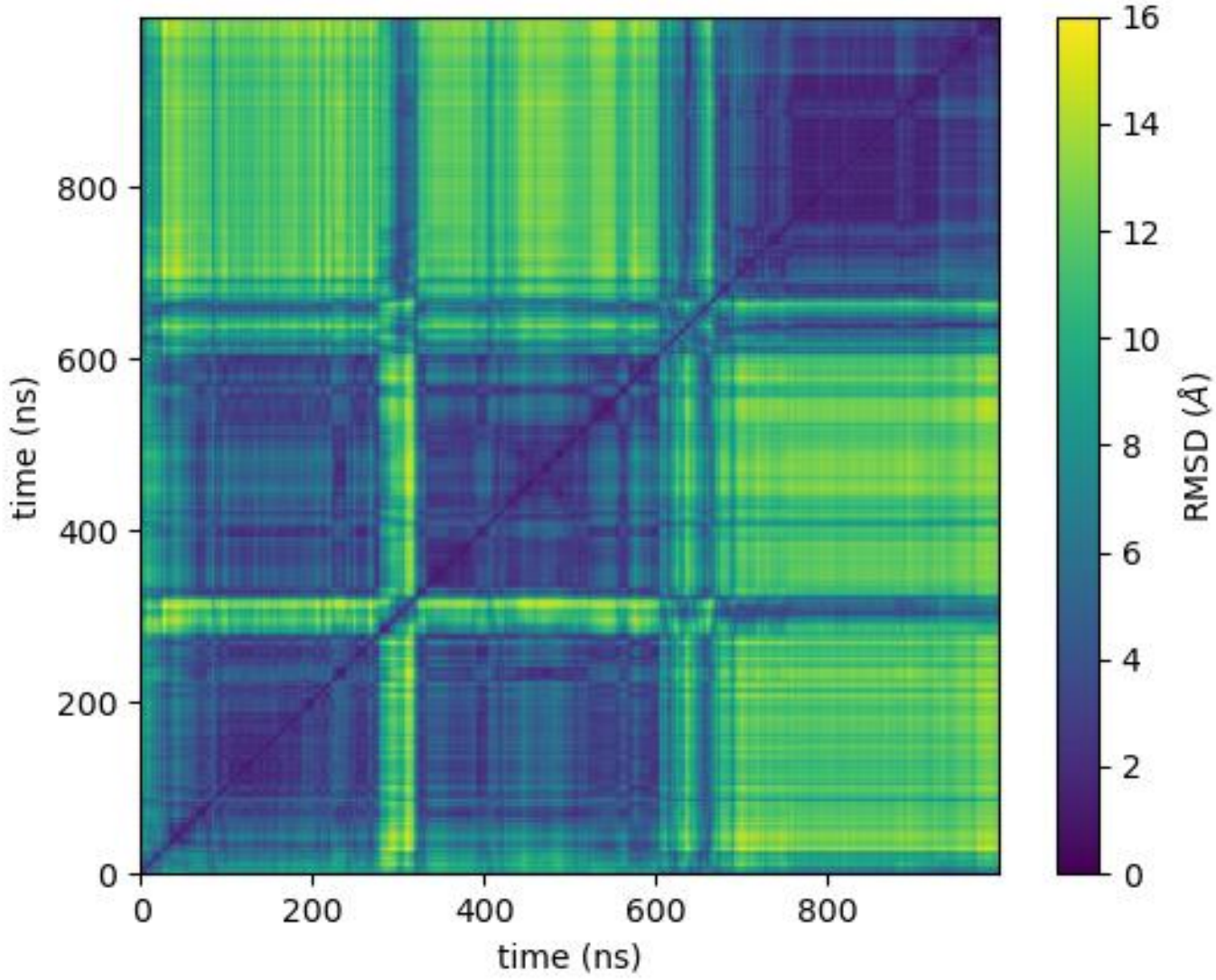


align ***Domain 2***



Pairwise RMSD

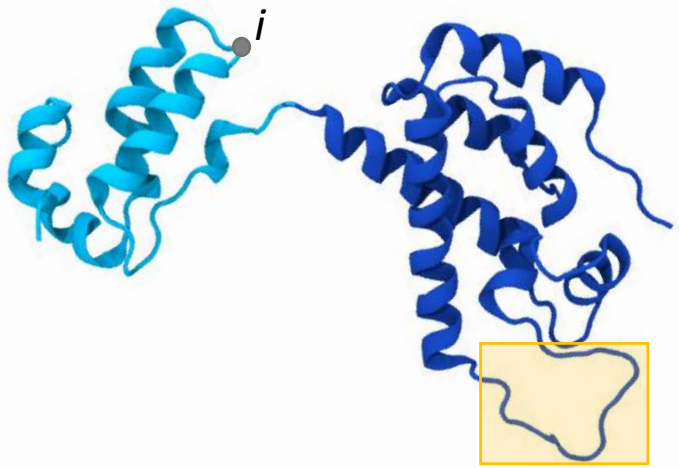
- Two structures with same RMSD from a reference are not forcefully similar to each other.
- Pairwise RMSD helps seeing if protein re-visits conformations throughout the simulation.

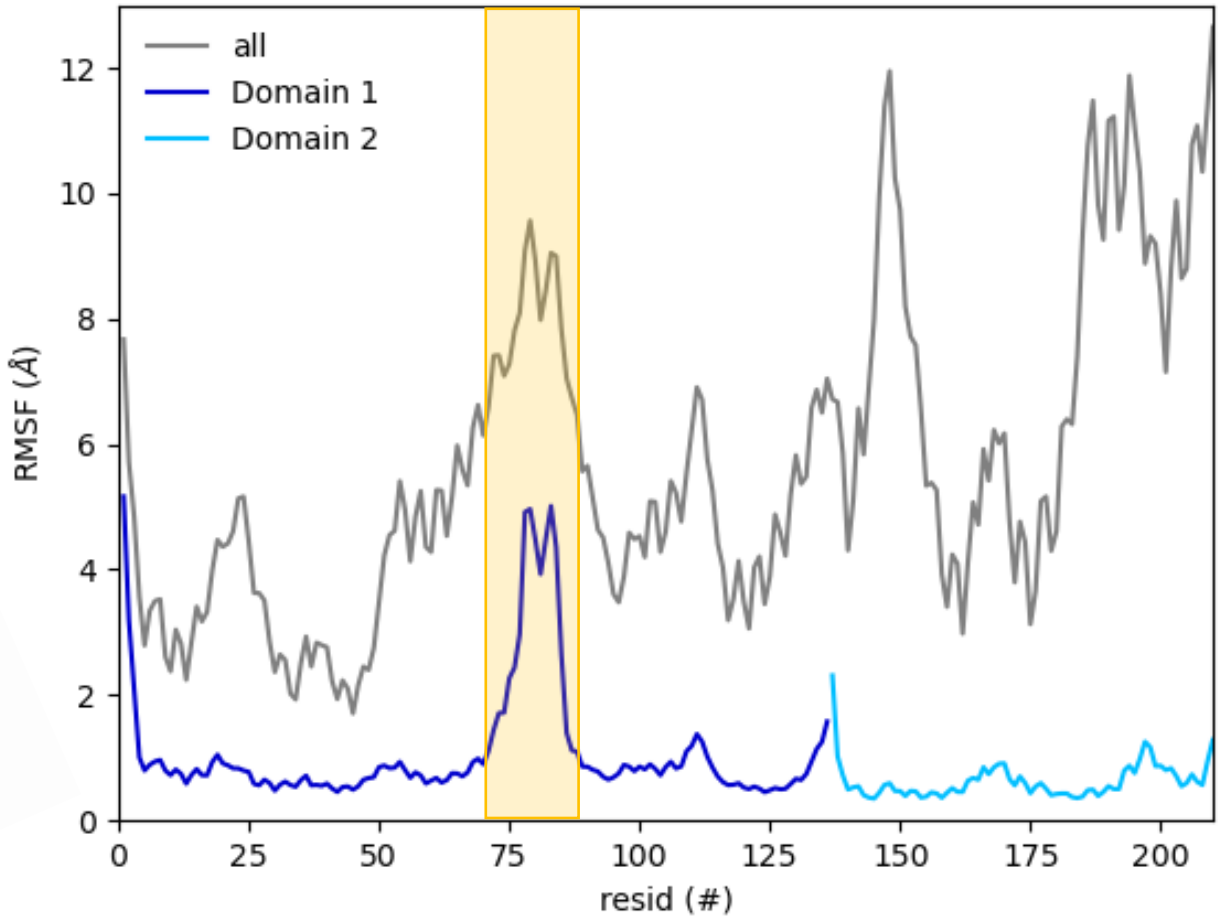


Root Mean Square Fluctuation (RMSF)

The RMSF σ_i of atom *i* calculates how much it fluctuates around its mean position $\langle X_i \rangle$.

$$\sigma_i = \sqrt{\langle (X_i - \langle X_i \rangle)^2 \rangle}$$



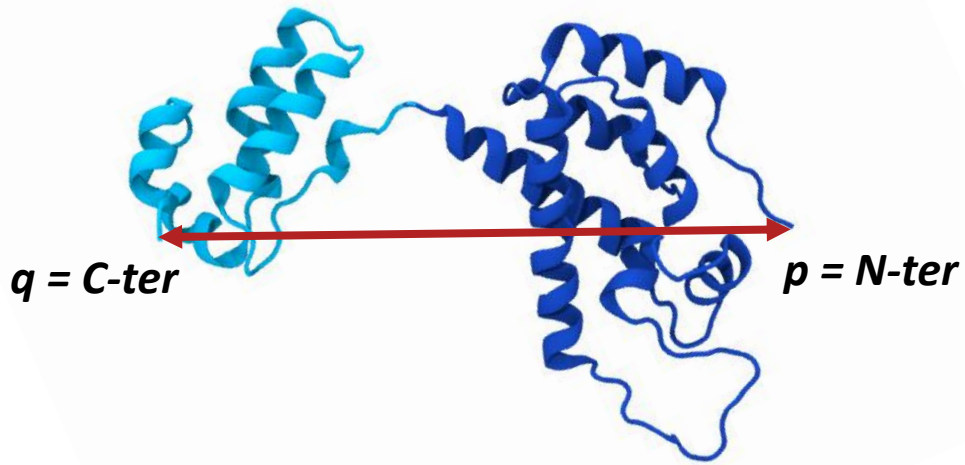


Typically done on C_α atoms.
Result depends on alignment!

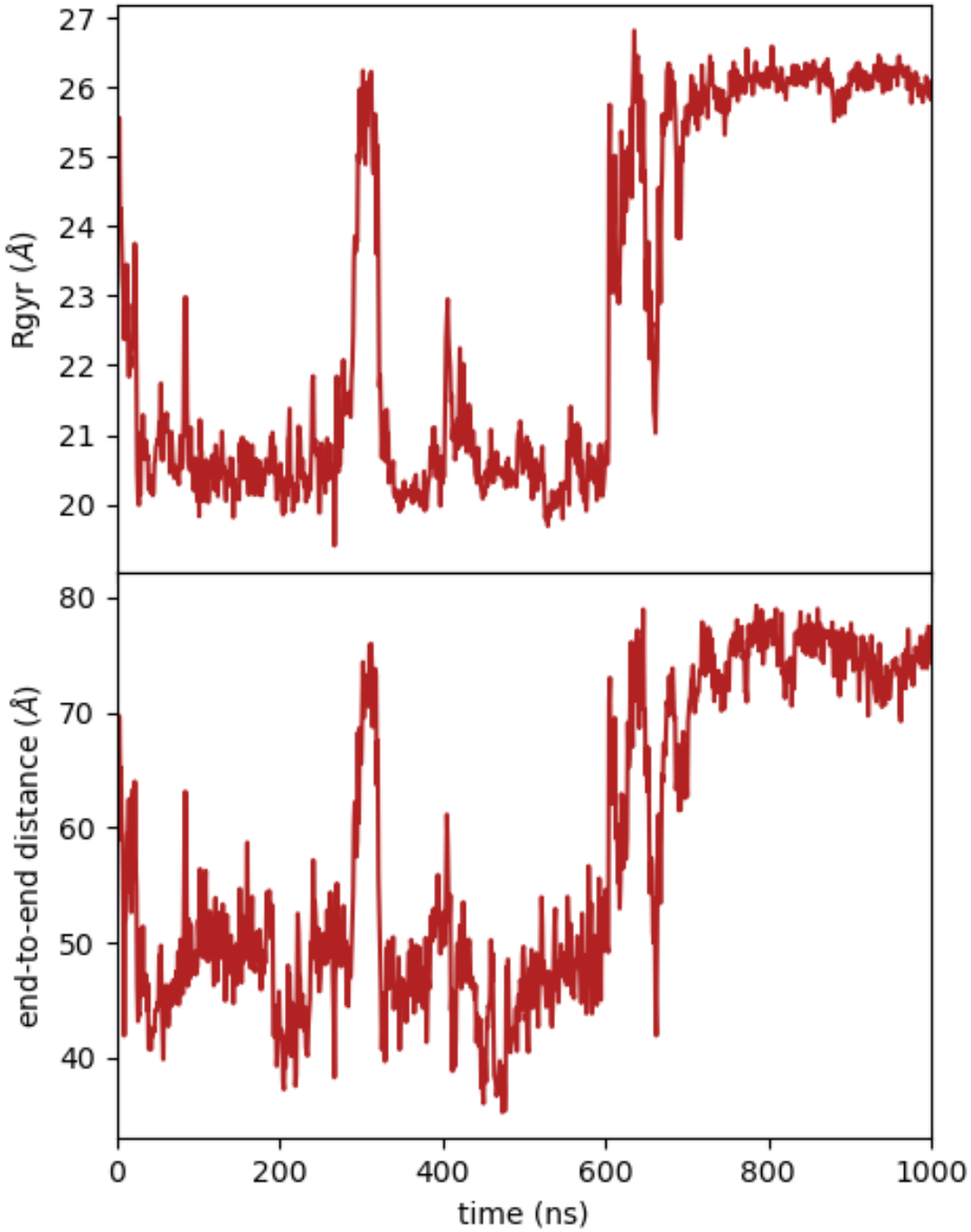
end-to-end distance and Radius of Gyration (Rg)

$$d(p,q) = \|p - q\|$$

$$R_g = \sqrt{\frac{1}{N}|r_k - r_{mean}|^2}$$



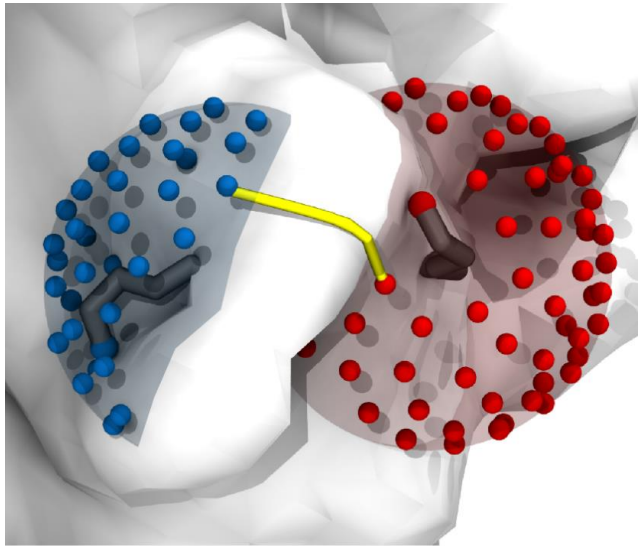
Internal properties do *not* depend on alignment



Some quantities are not *directly* measurable

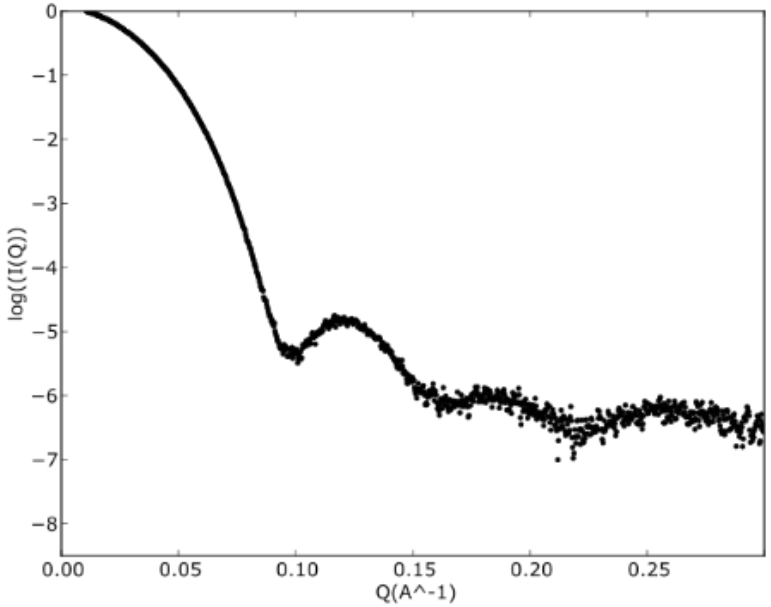
Submit MD conformers to external software simulating experimental data, e.g.:

Chemical cross-linking



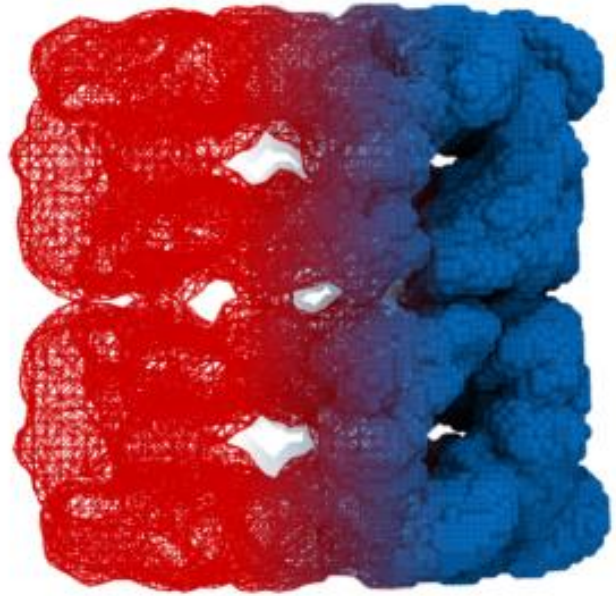
DynamXL, Xwalk, …

SAXS



CRYSOL, FoXS, …

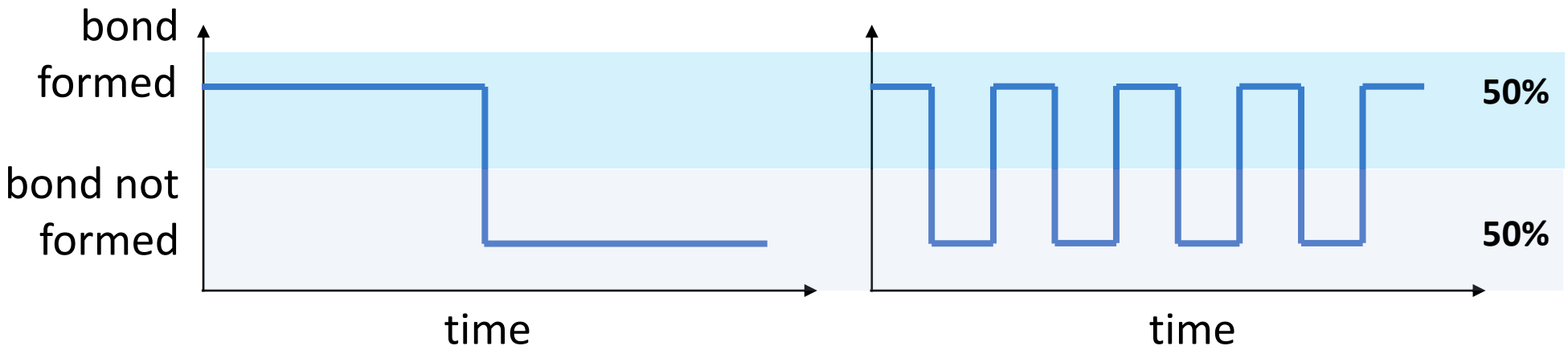
Collision cross-section



IMPACT, MobCal, CollisionCode, …

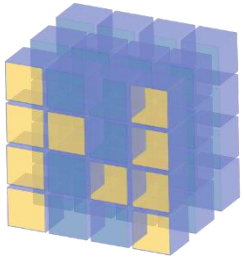
Warning: time averaging may hide processes

Thought experiment: typically hydrogen bond is considered established if donor-acceptor distance <2.5 Å, and donor-acceptor-hydrogen angle <20°.



Reporting % time a bond is established in simulation can be misleading!

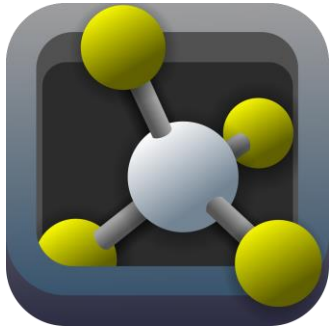
Large ecosystem of software and packages for data analysis



NumPy

SciPy

MD ANALYSIS



scikit learn

RDKit

Open-Source Cheminformatics and Machine Learning

PyEMMA

VMD Visual Molecular Dynamics

MDTRAJ

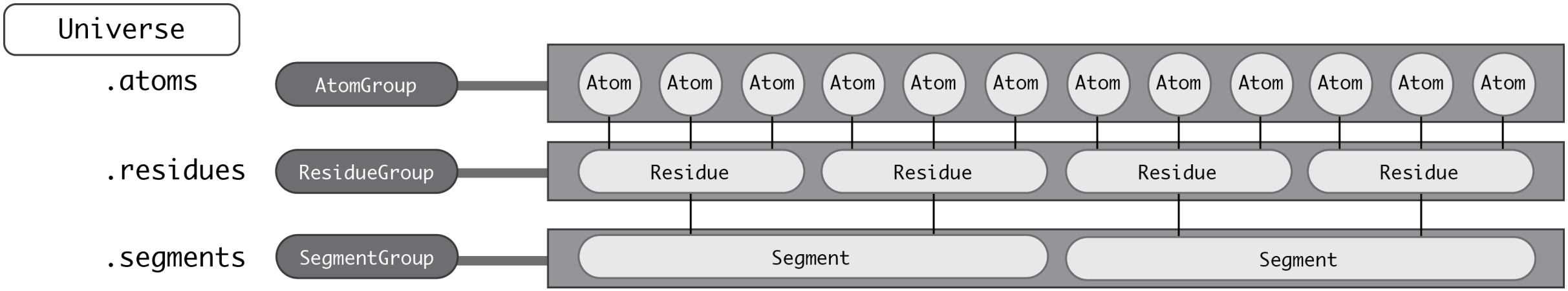
And many more…

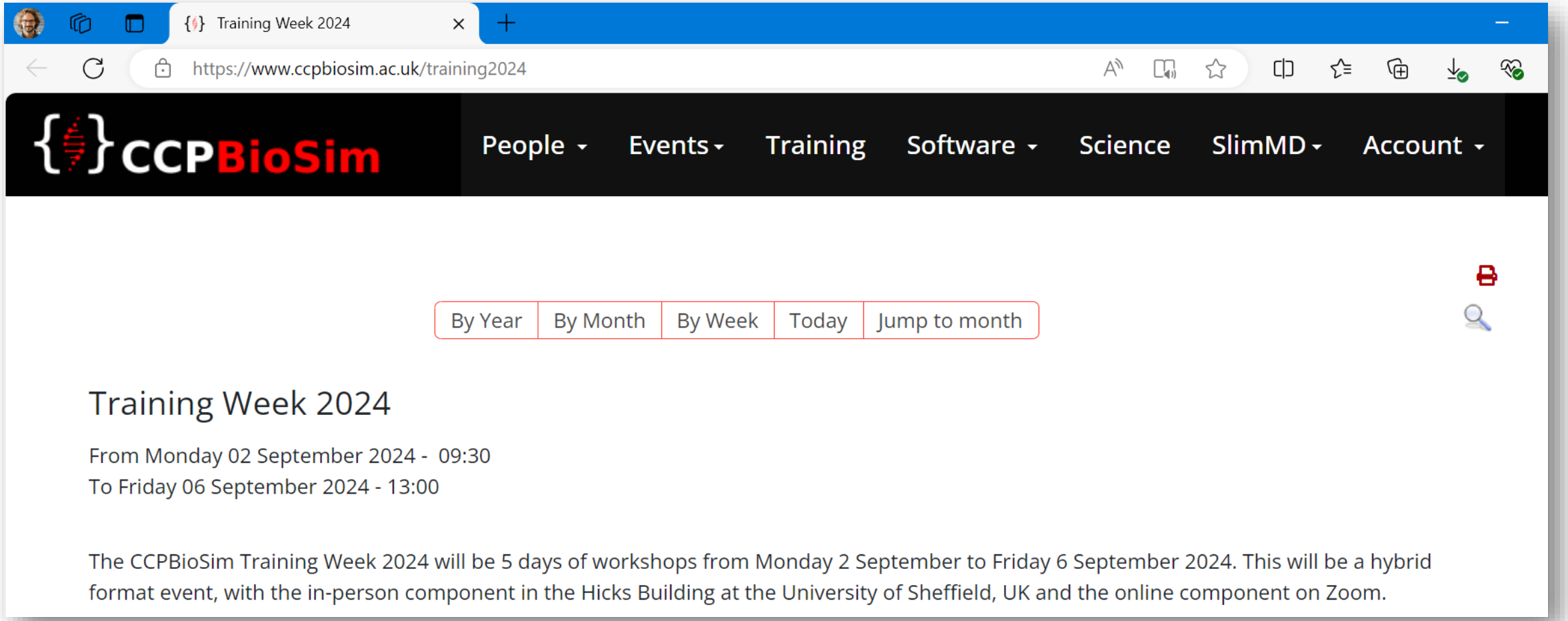
MDAnalysis

The **Universe** contains everything about a MD system

- *Static information*: atoms and their connectivities
- *Dynamic information*: The trajectory

Data accessible via a hierarchy of containers





Thursday 03 September 2024, 9:30am – 5pm : **Intermediate and Advanced MDAnalysis**

This workshop will build on basic MDAnalysis skills to learn about building more complex analysis scripts. Please feel free to bring your own systems and problems to get help from the experts.