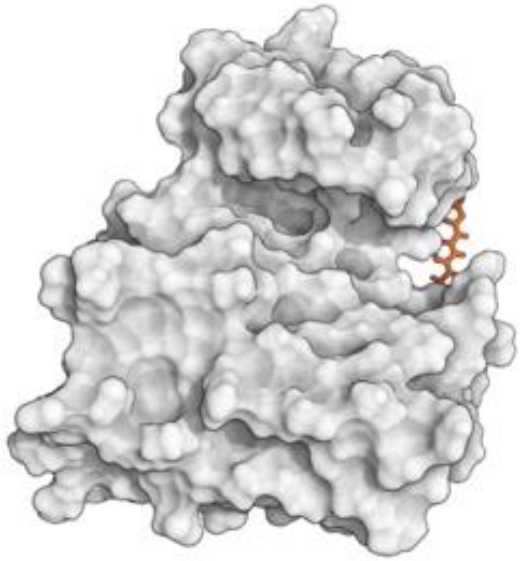
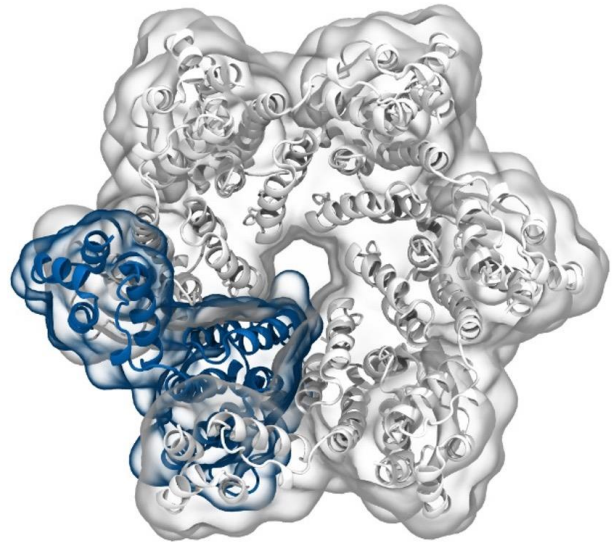
Simulation of Biomolecules



Basic Simulation Analysis



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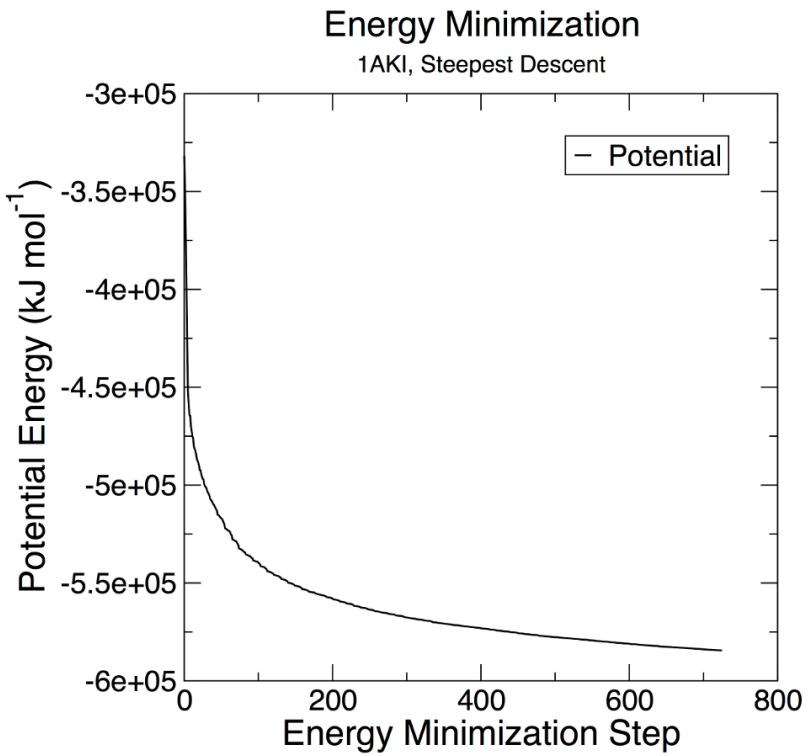
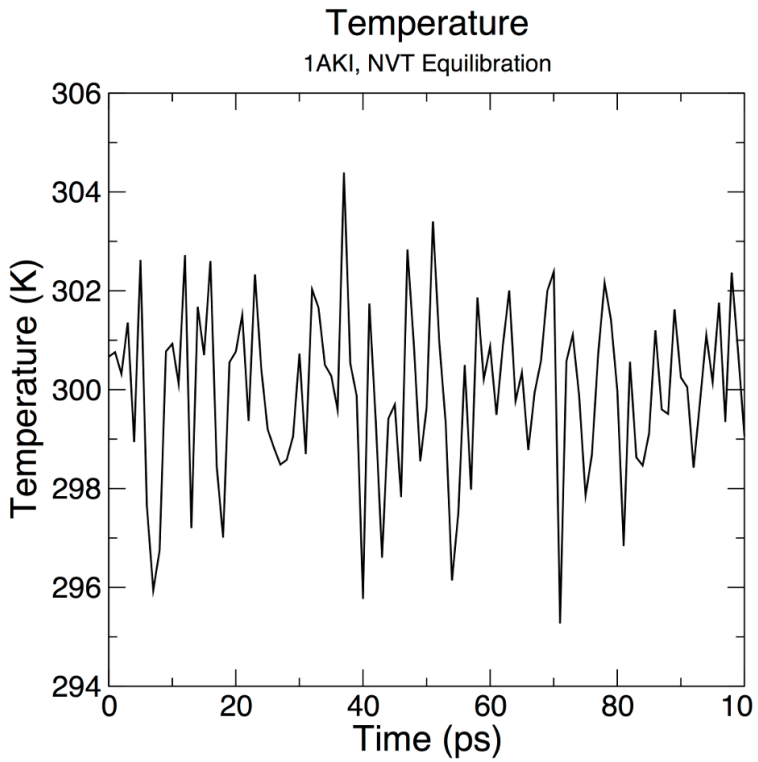
Volume and pressure equilibration

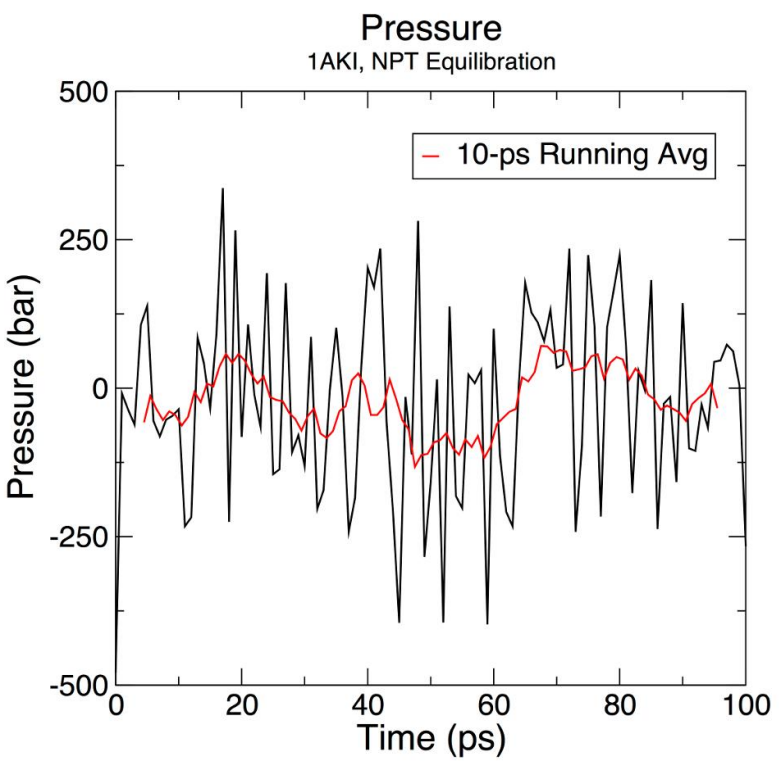
Steps until production:

Production ensemble

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

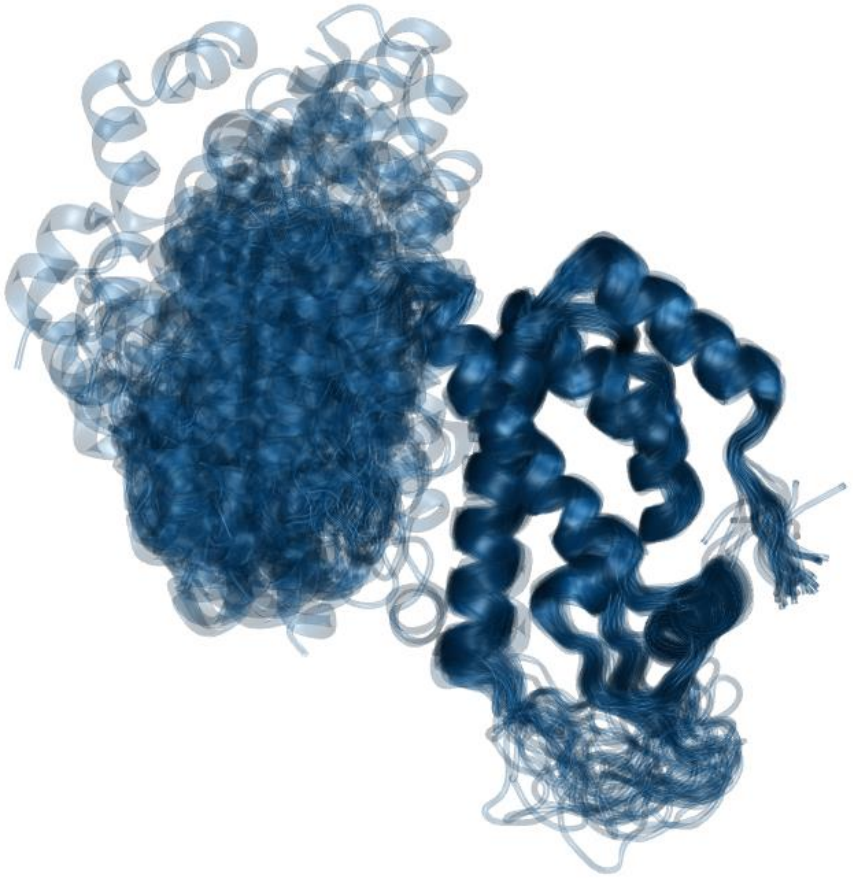


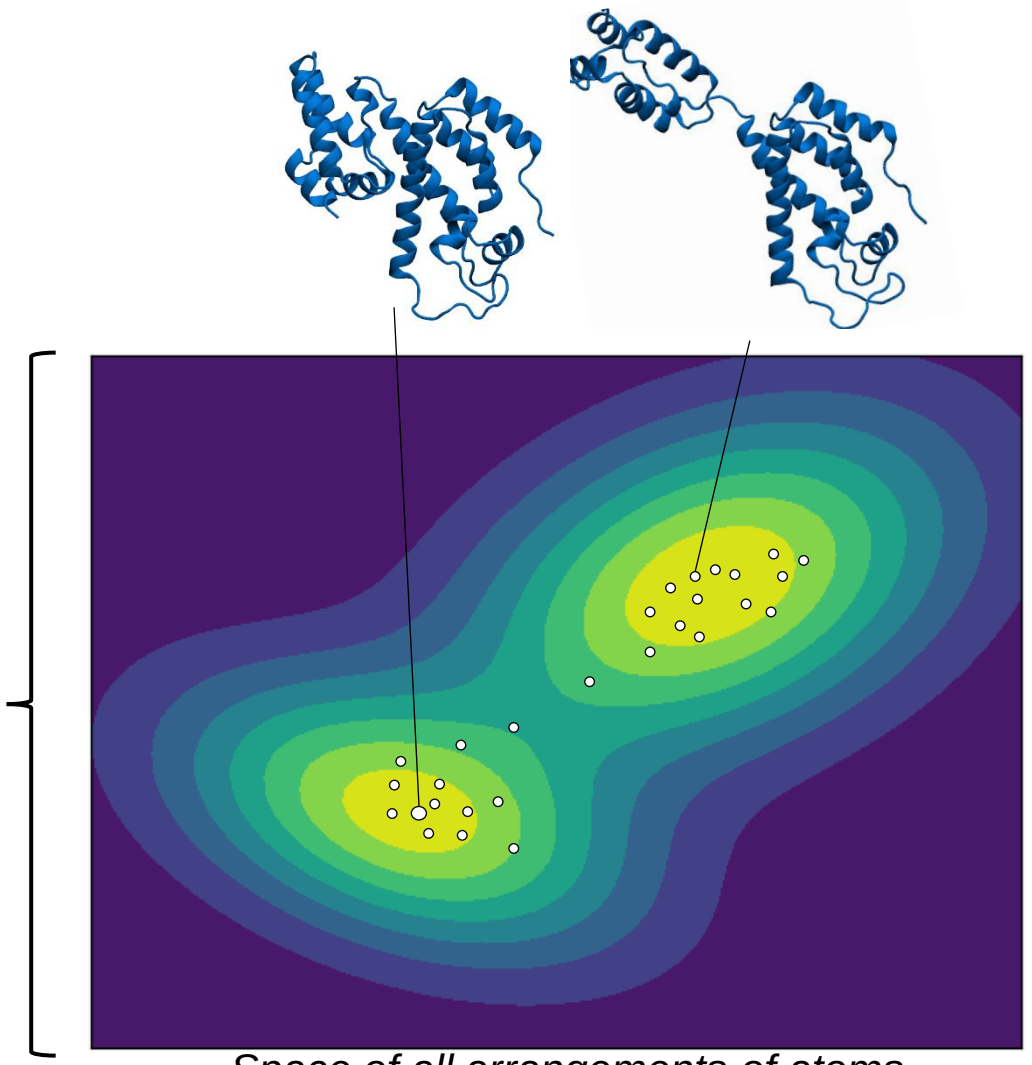




*Living J.Comp.Mol.Sci. 2019,**1**,5957*

Sampling the conformational space





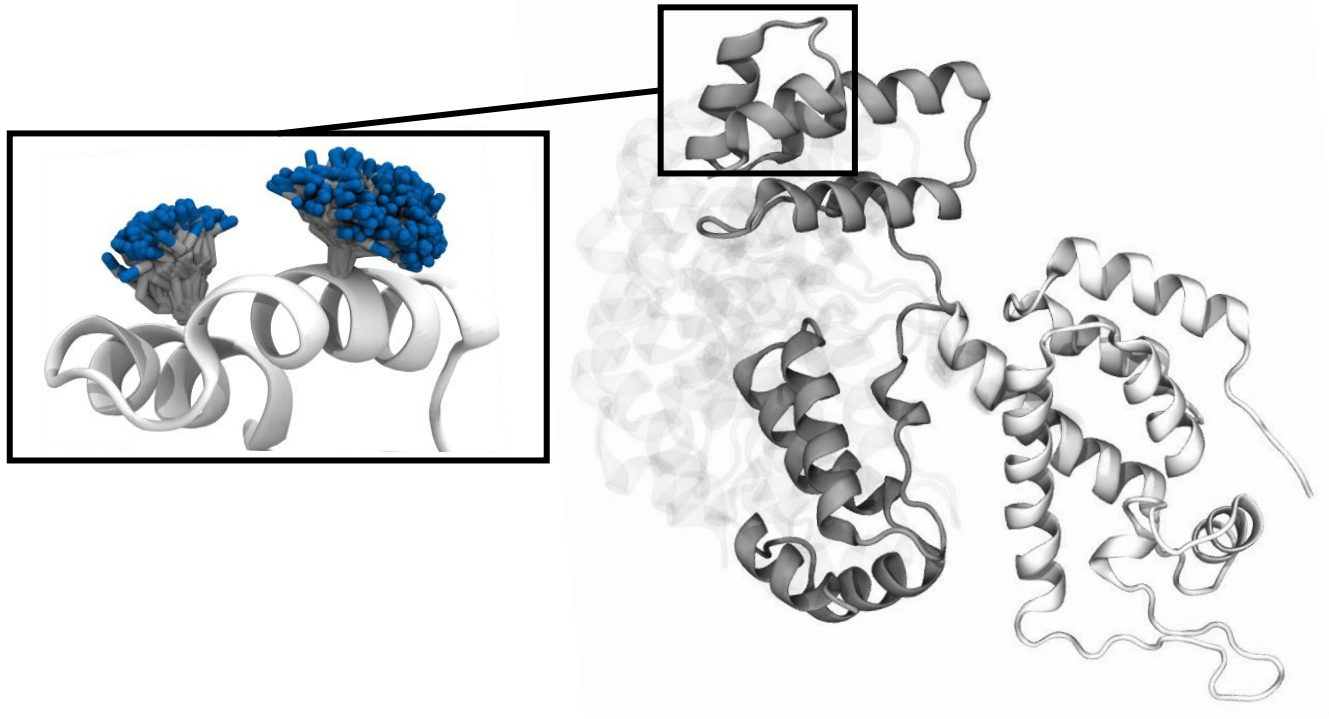
Space of all arrangements of atoms

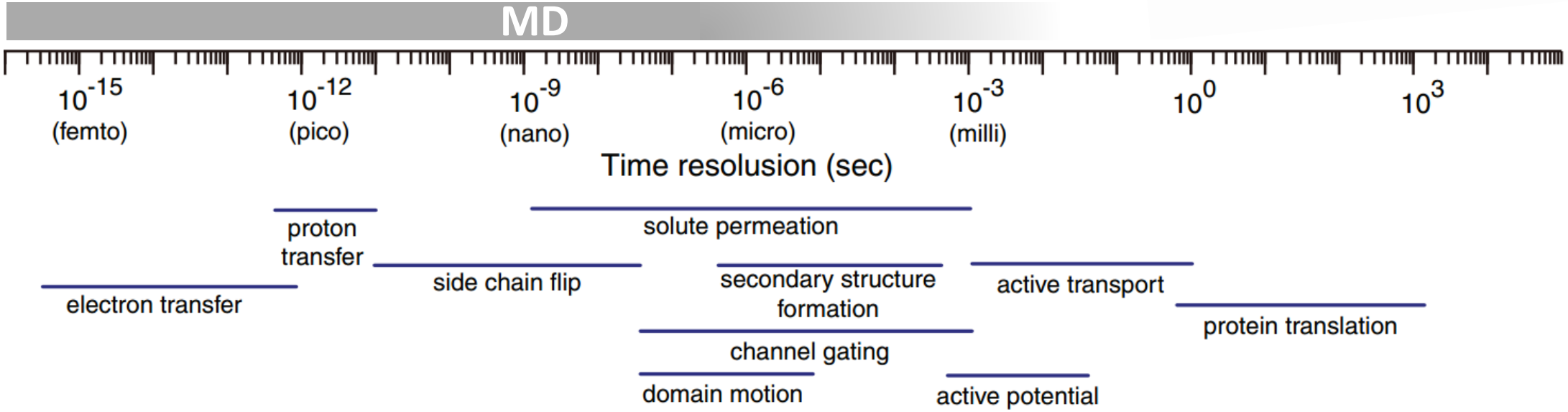
Probability of sampling a conformation is inversely proportional to its energy: $p_i \propto e^{-\varepsilon_i / kT}$

Timescales in biology

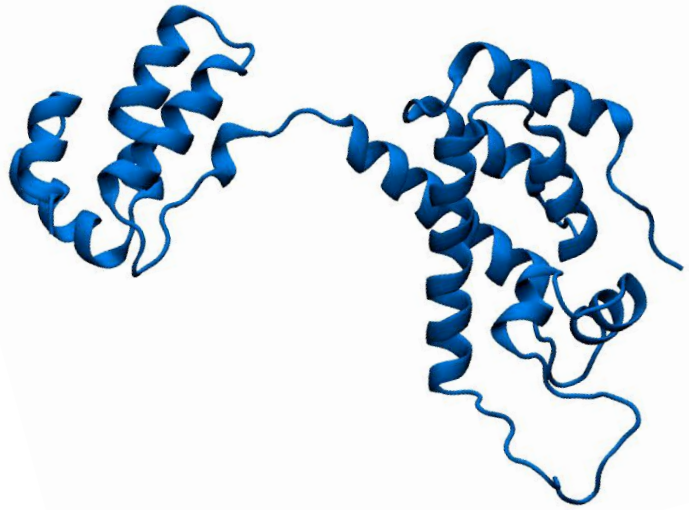
Different regions, different timescales:

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





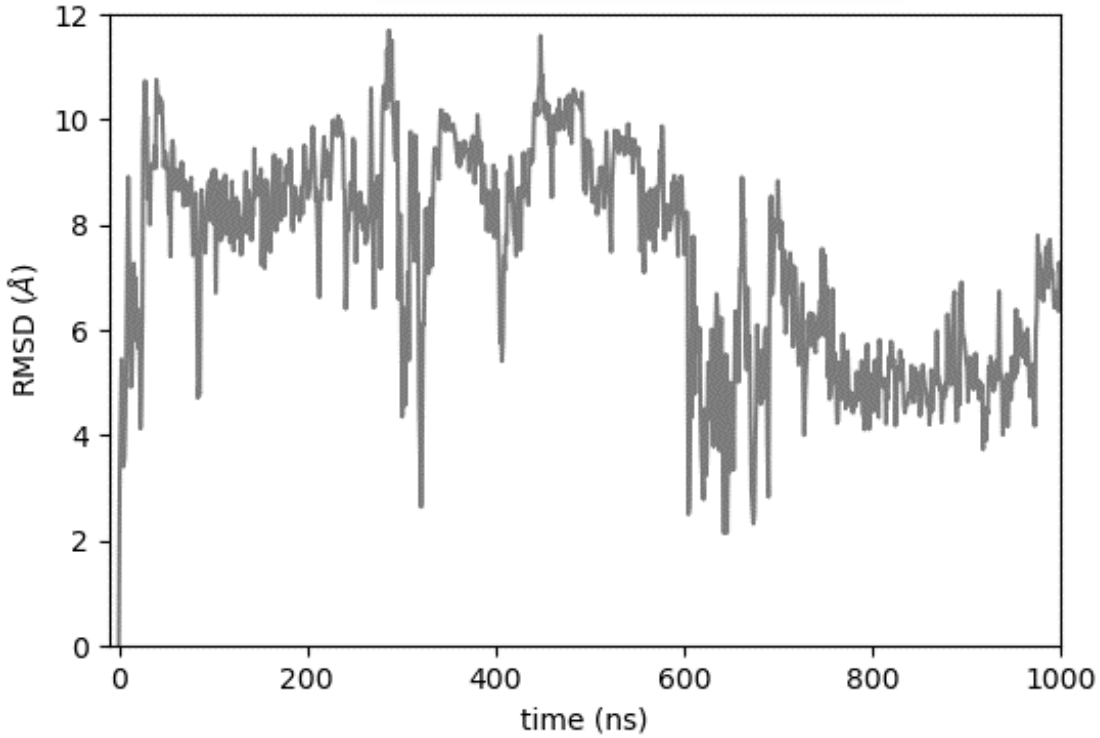
Root Mean Square Deviation (RMSD)



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

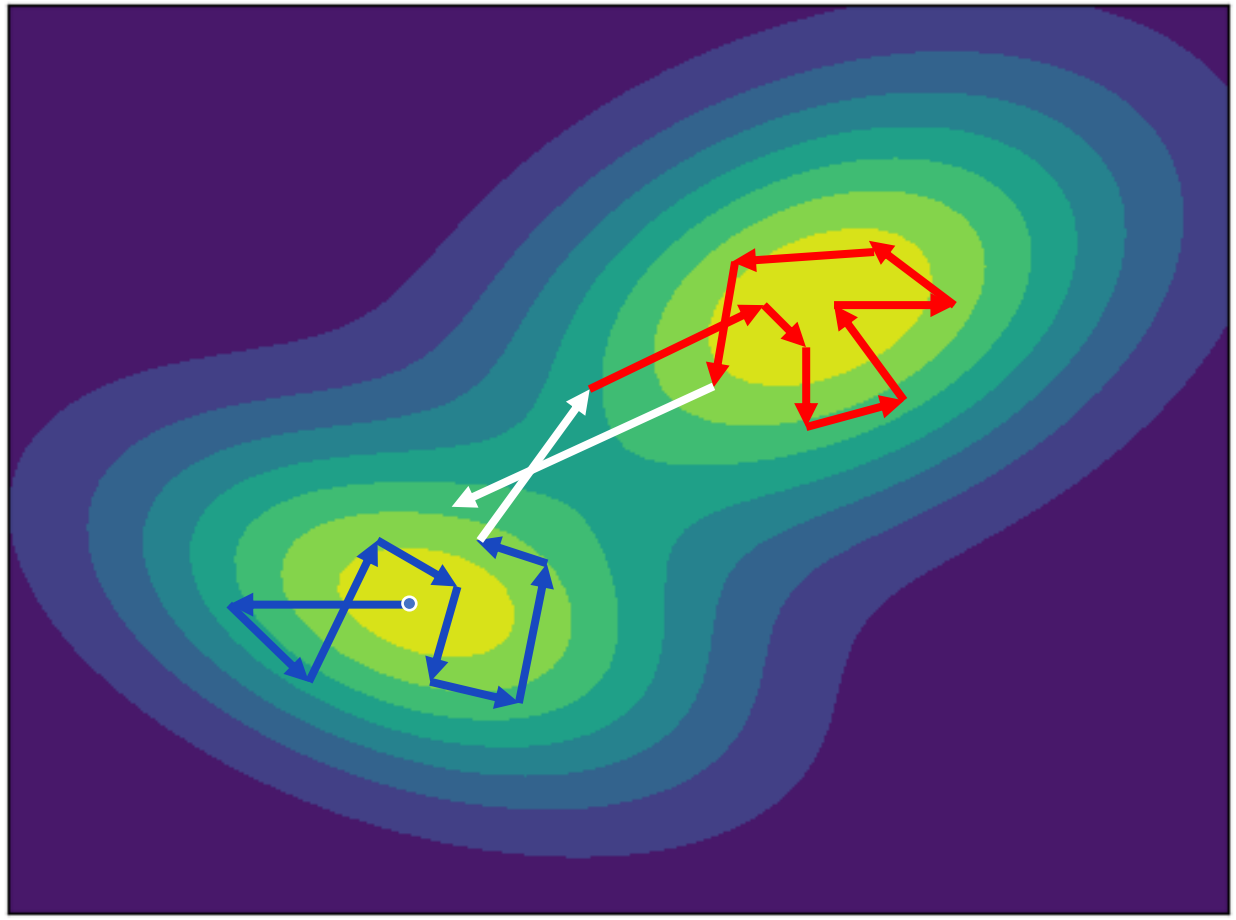
$$RMSD = \sqrt{\frac{1}{N}\sum_{i=0}^{N}(X_i - x_0)^2}$$

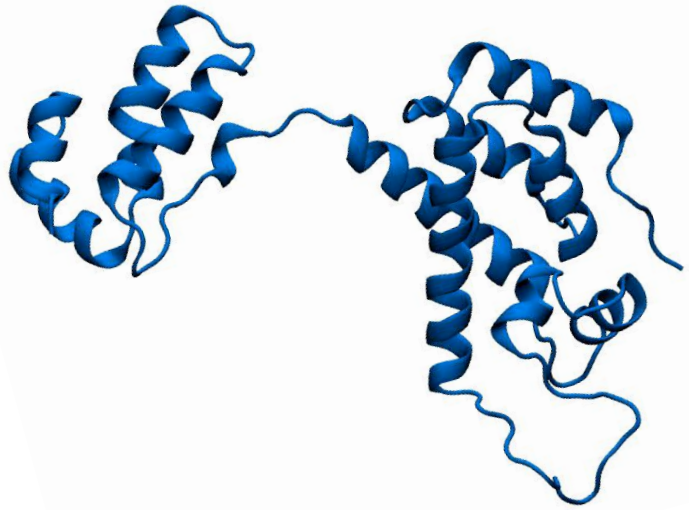
In MD, x_0 is often the first conformation in the simulation.

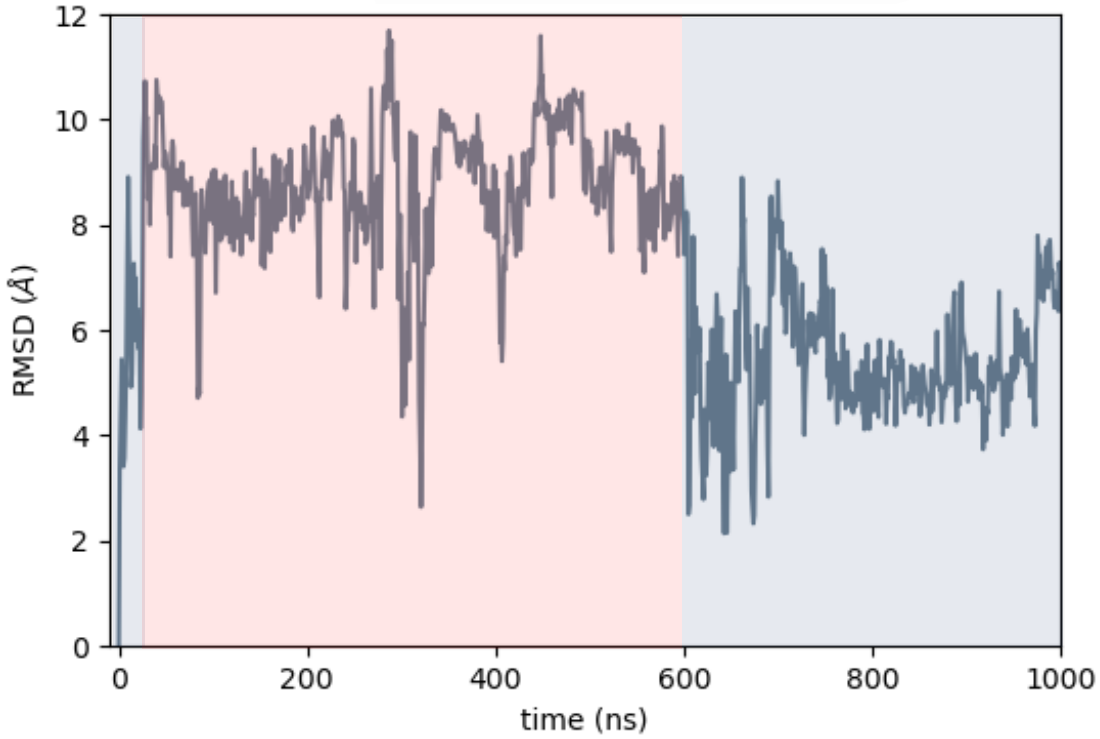


HIV-1 capsomer simulation from: *Degiacomi & Dal Peraro,* ***Structure****, 2013*

Convergence?



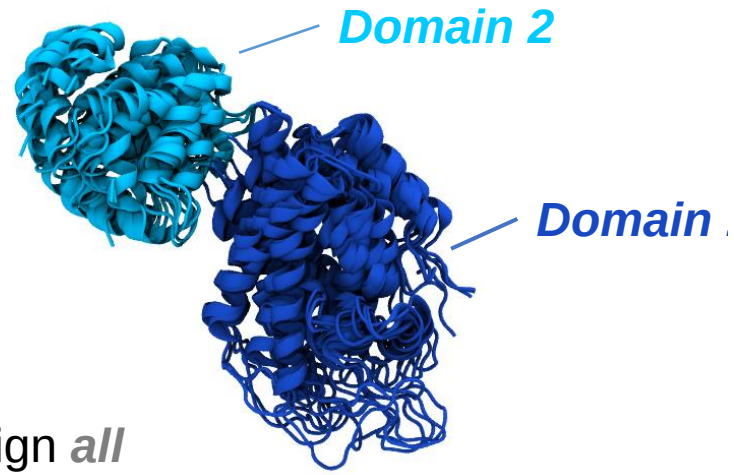




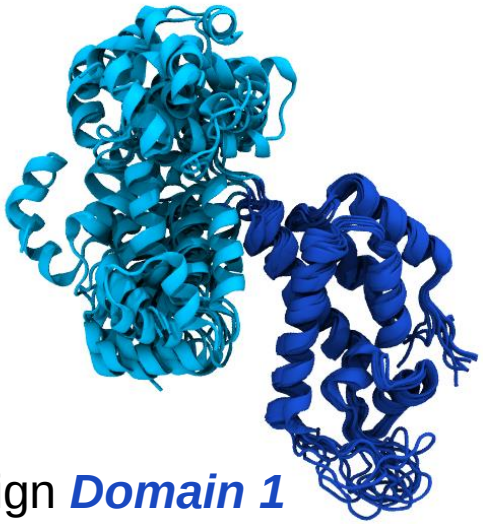
Refrain from using RMSD as a single indicator of simulation convergence.

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

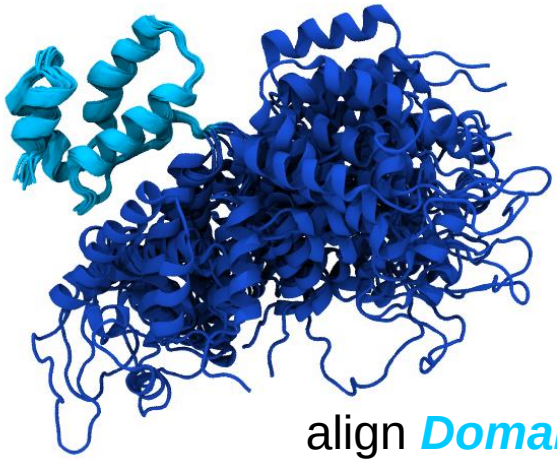
RMSD is alignment- and selection-dependent



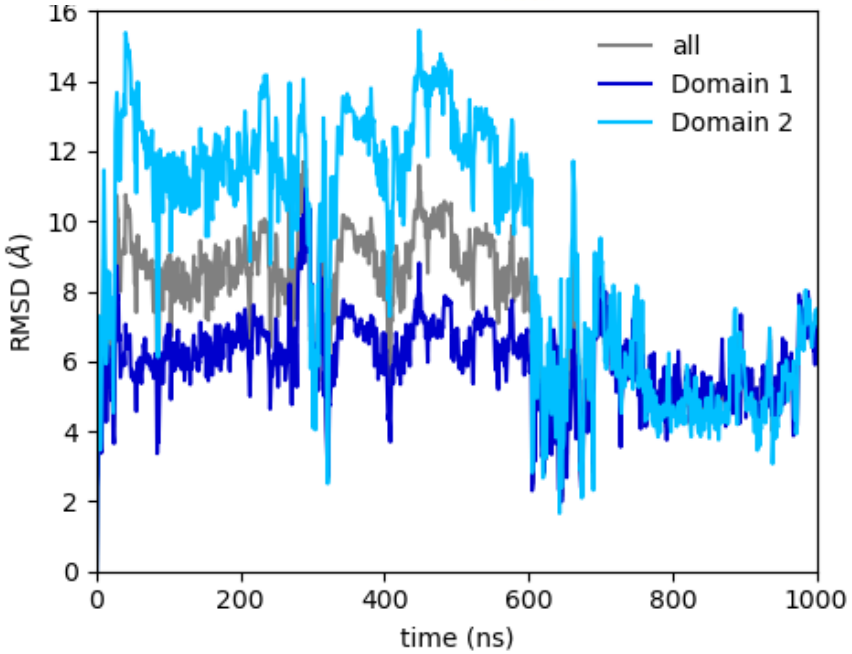
align *all*



align ***Domain 1***

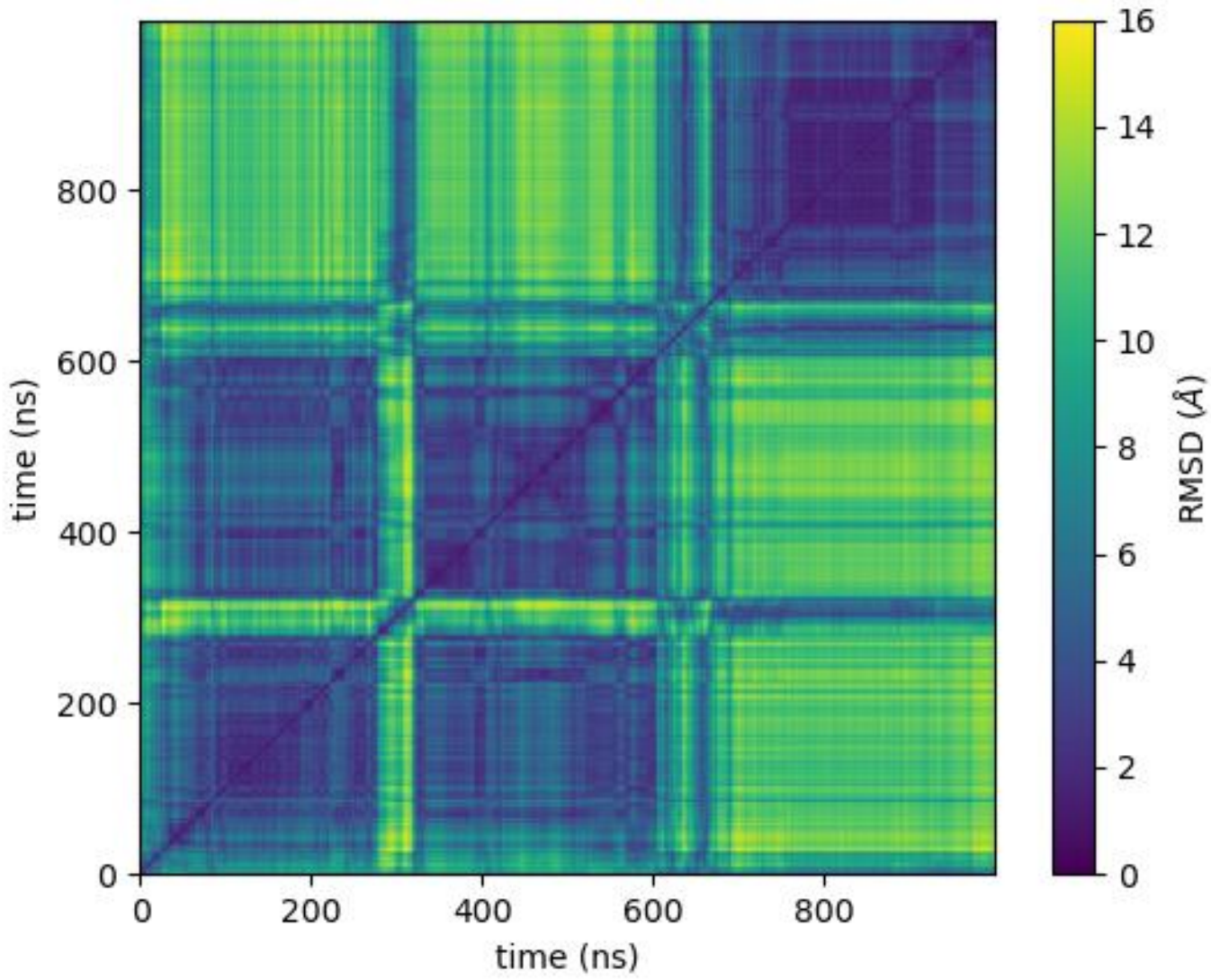


align ***Domain 2***



Pairwise RMSD

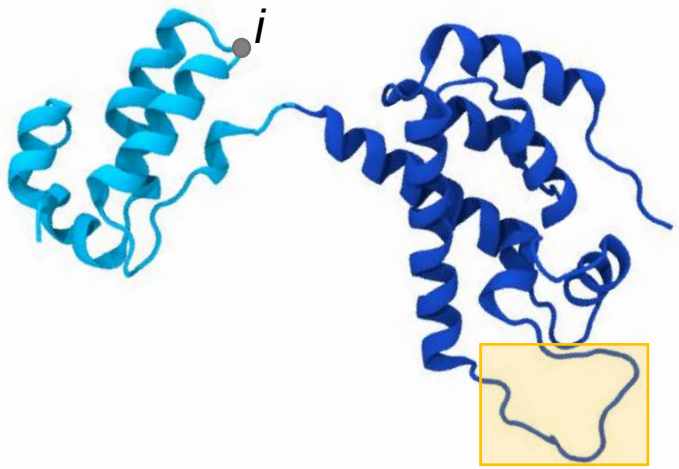
- Two structures with same RMSD from a reference are not forcefully similar to each other.
- Pairwise RMSD helps seeing if protein re-visits conformations throughout the simulation.

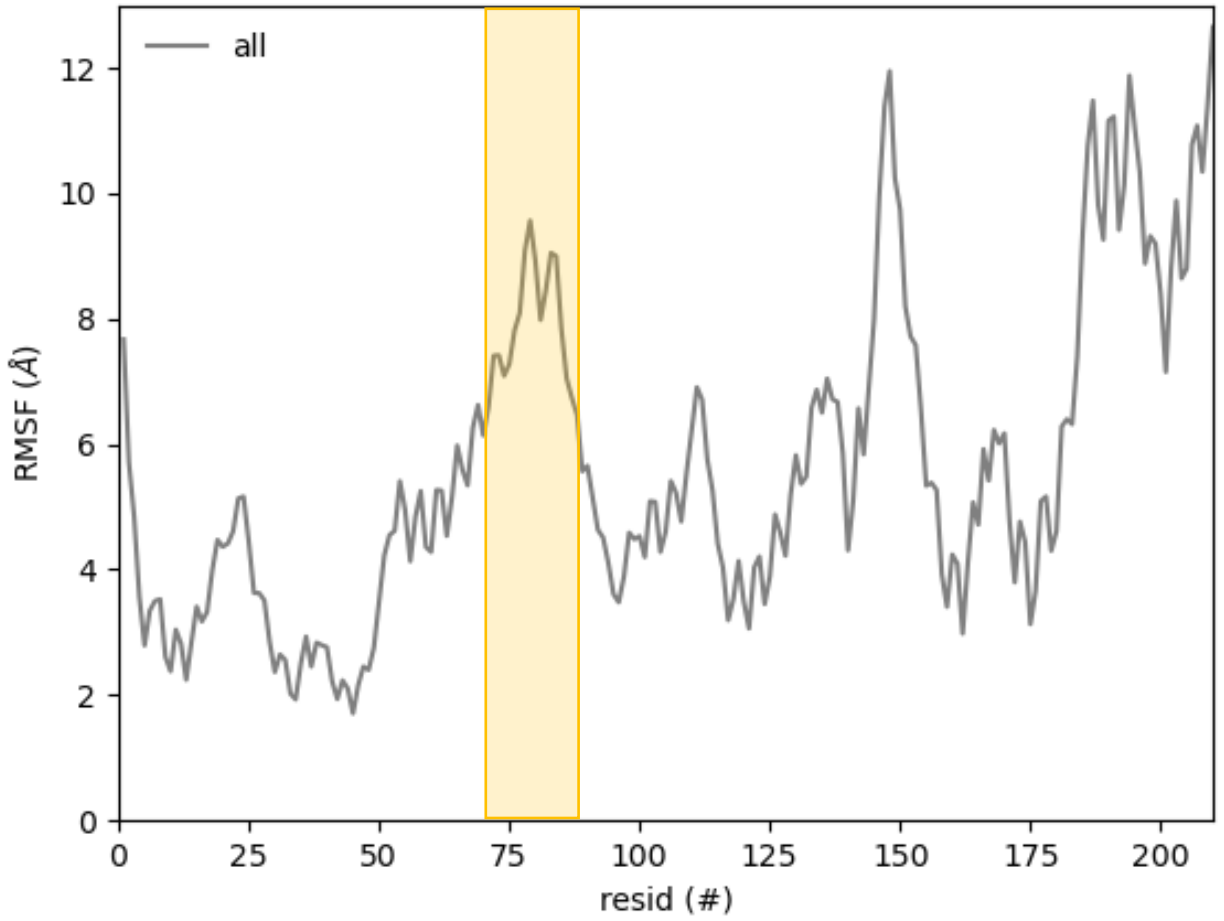


Root Mean Square Fluctuation (RMSF)

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

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



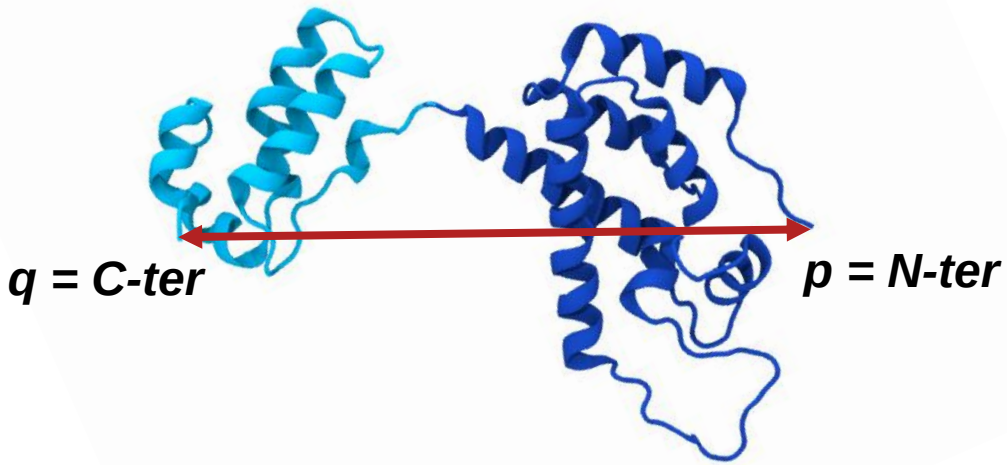


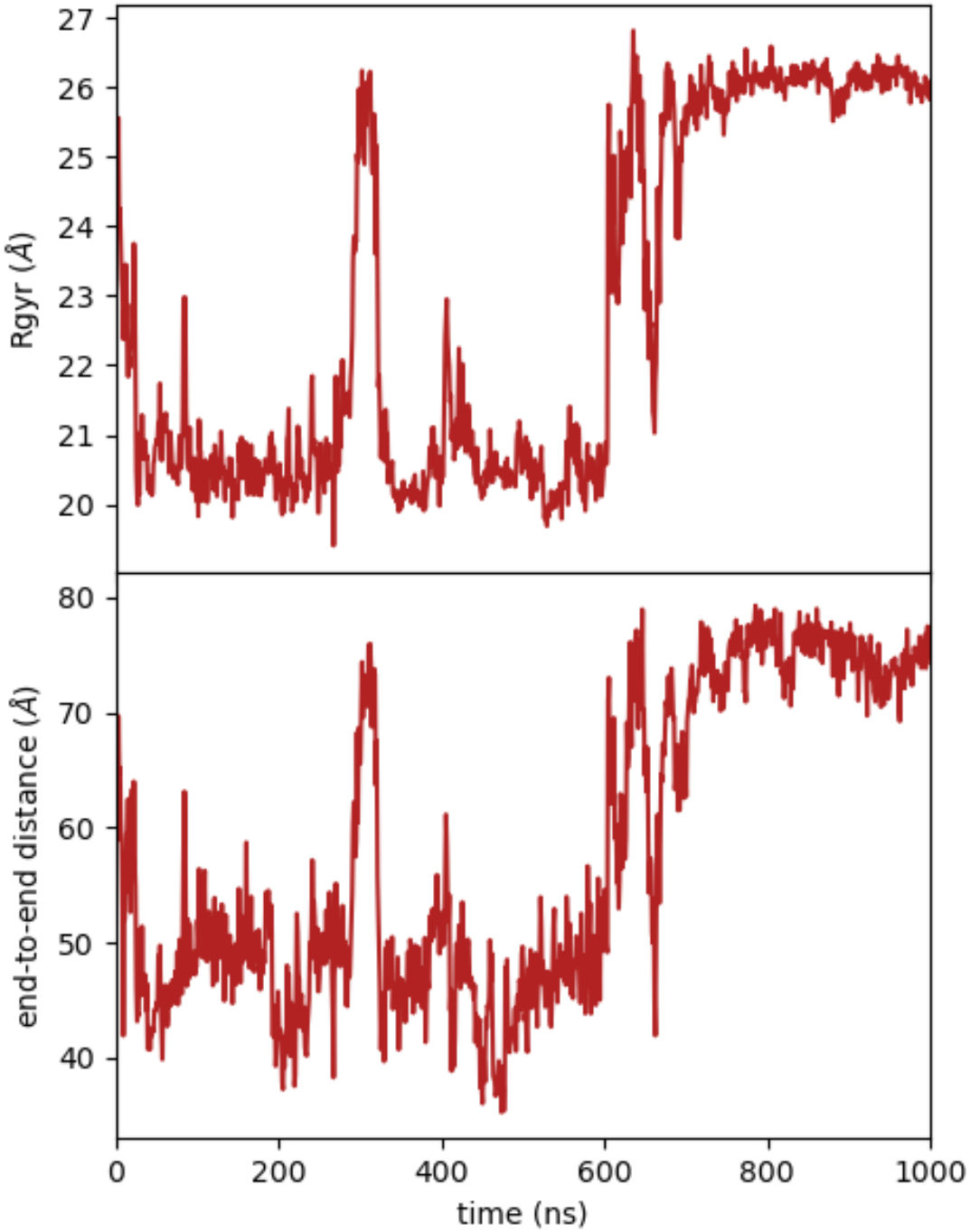
Typically done on C_α atoms.
Result depends on alignment!

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

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

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



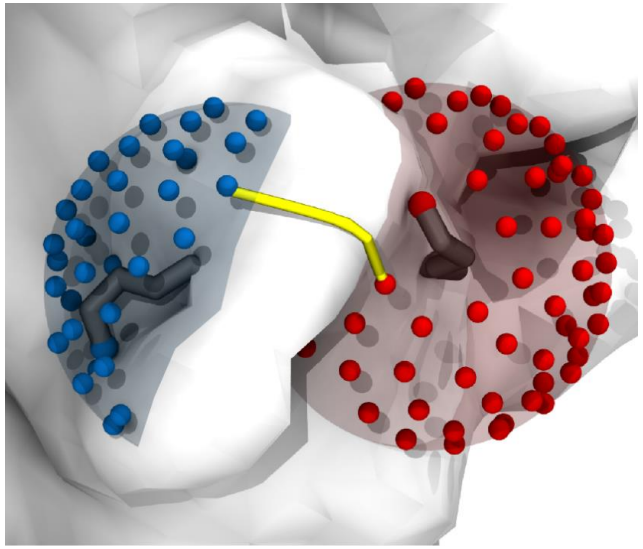


Internal properties do *not* depend on alignment

Some quantities are not *directly* measurable

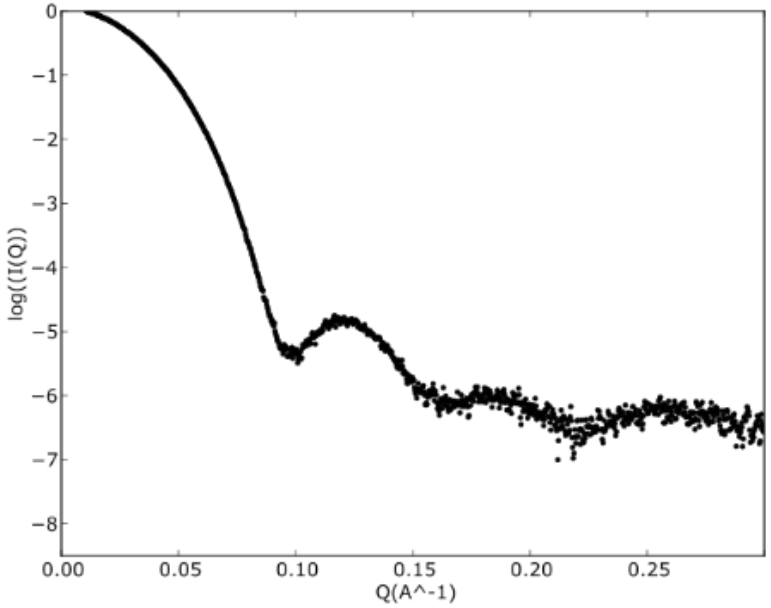
Submit MD conformers to external software simulating experimental data, e.g.:

Chemical cross-linking



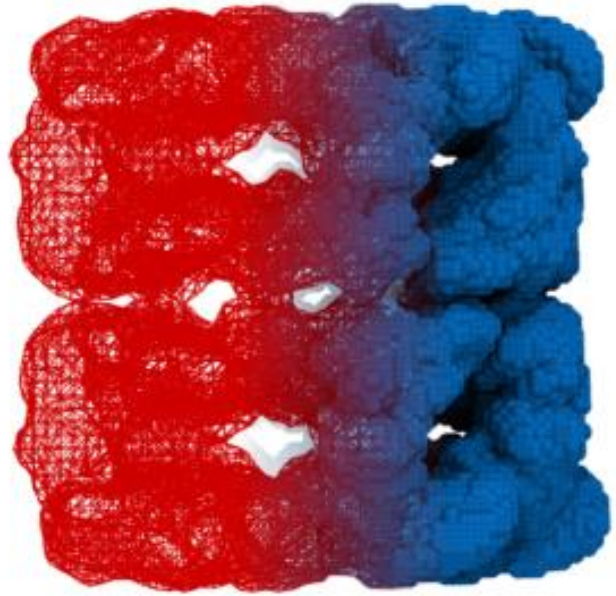
DynamXL, Xwalk, …

SAXS



CRYSOL, FoXS, …

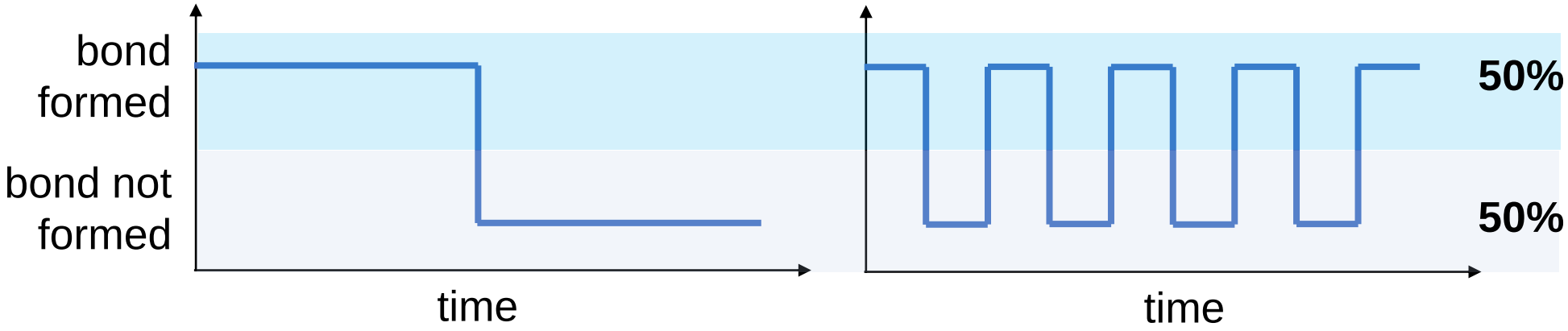
Collision cross-section



IMPACT, MobCal, CollisionCode, …

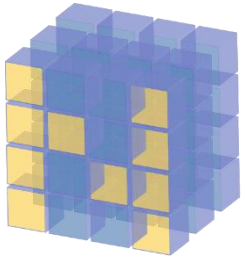
Warning: time averaging may hide processes

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!

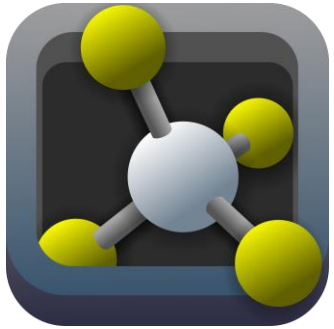
Large ecosystem of software and packages for data analysis



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