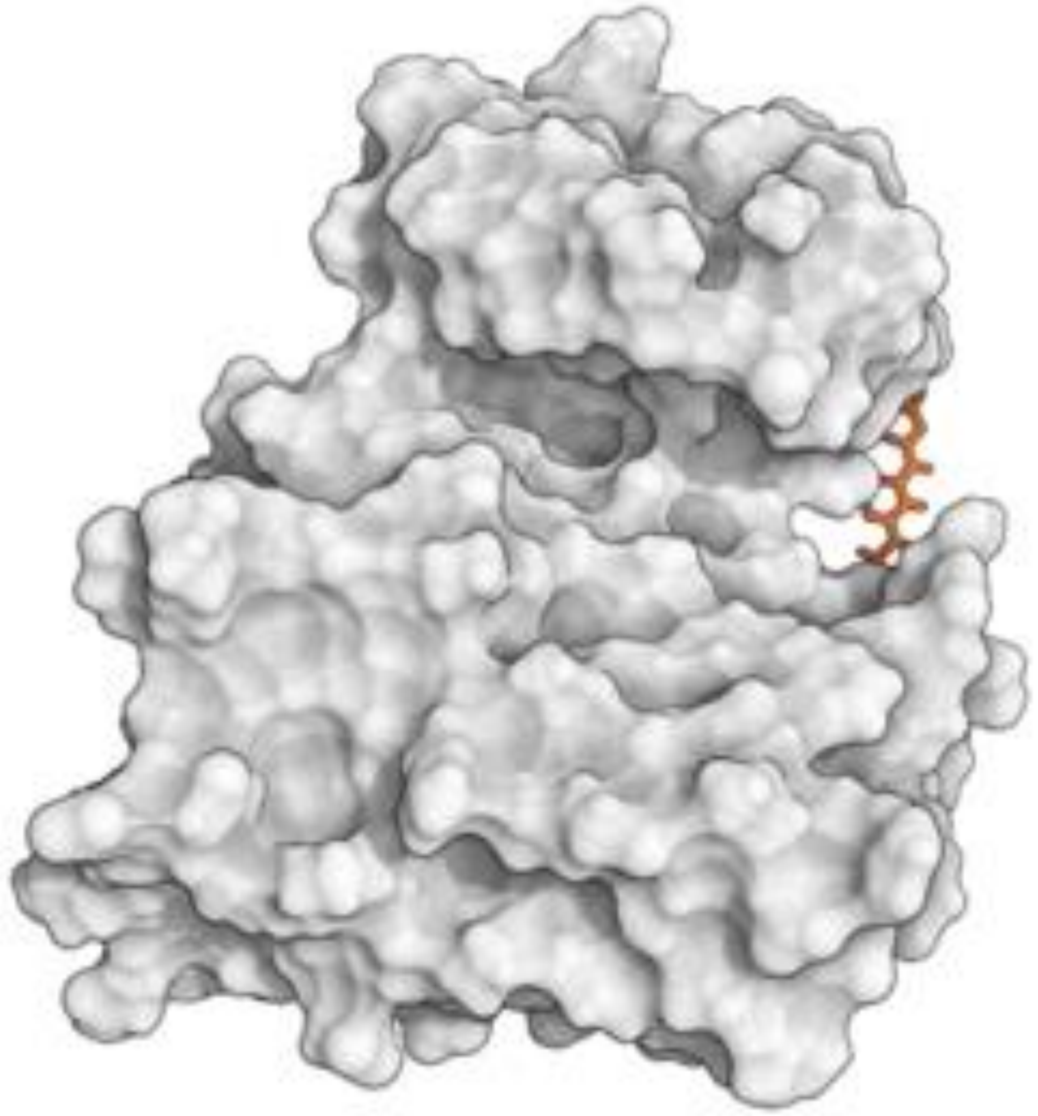
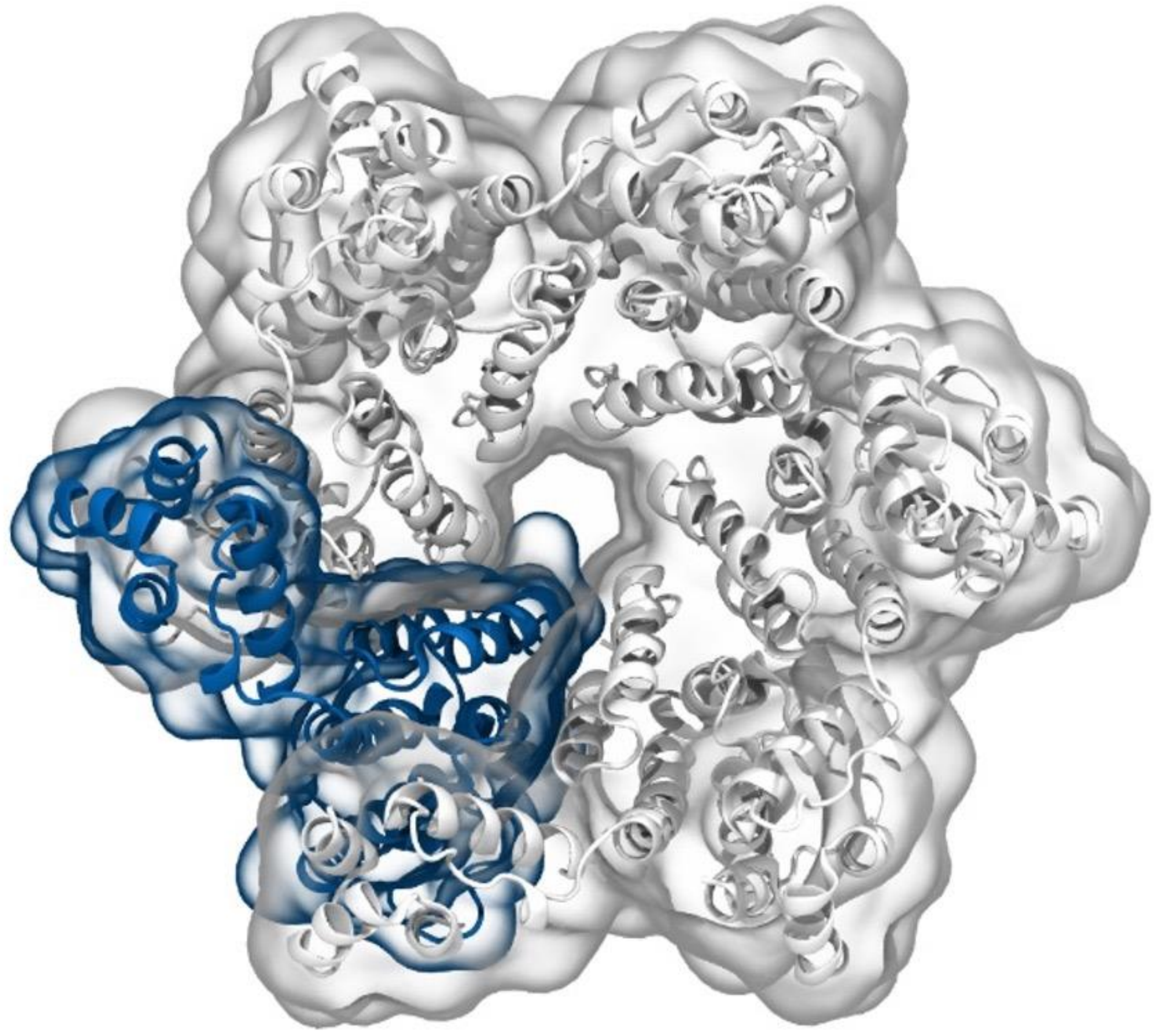
Simulation of Biomolecules



Setting up a protein simulation

2024 CCP5 Summer School



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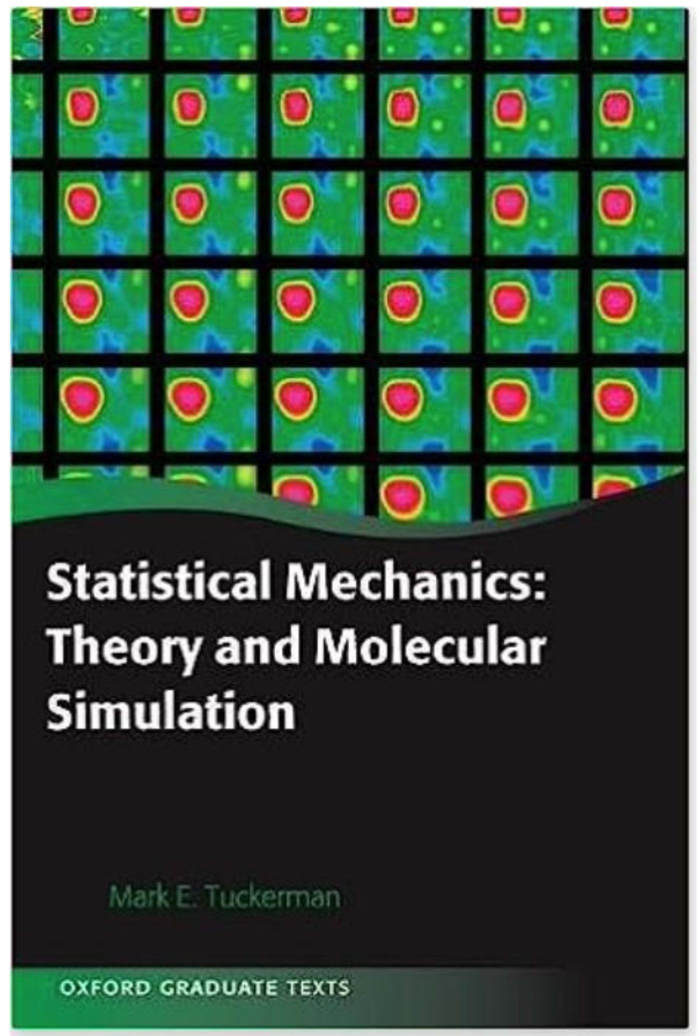
Useful resources to learn running simulations

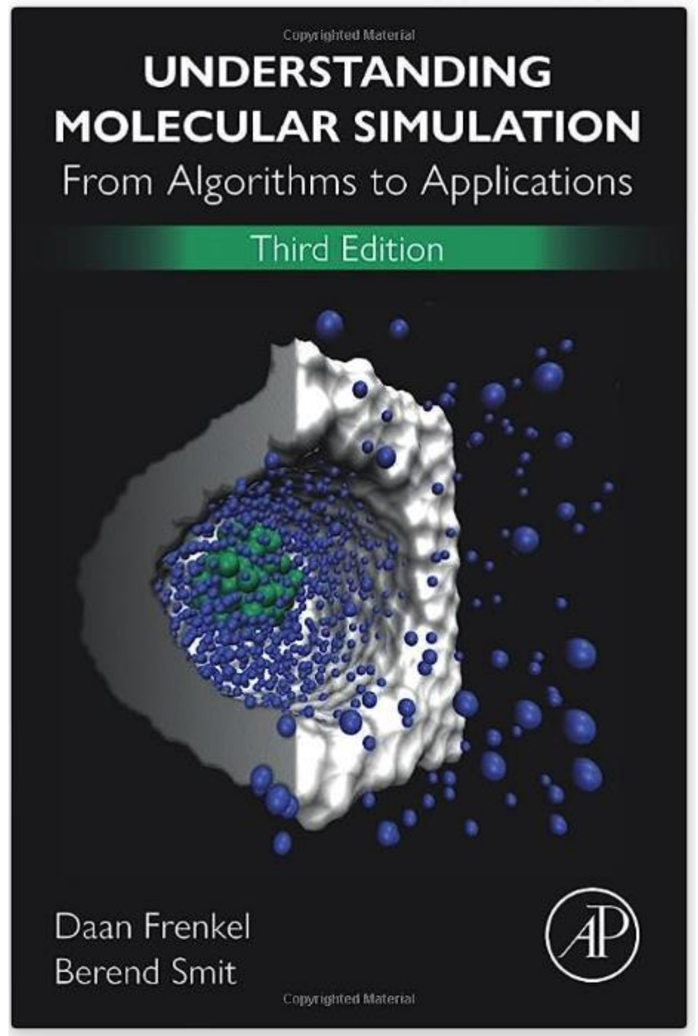
Best Practices for Foundations in Molecular Simulations [Article v1.0]

Efrem Braun[1], Justin Gilmer[2], Heather B. Mayes[3], David L. Mobley[4], Jacob I. Monroe[5], Samarjeet Prasad[6], Daniel M. Zuckerman[7]

A suite of tutorials for the BioSimSpace framework for interoperable biomolecular simulation [Article v1.0]

Lester O. Hedges[1,2*], Sofia Bariami[3†], Matthew Burman[2], Finlay Clark[3], Benjamin P. Cossins[4], Adele Hardie[3], Anna M. Herz[3], Dominykas Lukauskis[5], Antonia S.J.S. Mey[3], Julien Michel[2,3*], Jenke Scheen[3‡], Miroslav Suruzhon[4], Christopher J. Woods[1], Zhiyi Wu[4]





From Proteins to Perturbed Hamiltonians: A Suite of Tutorials for the GROMACS-2018 Molecular Simulation Package [Article v1.0]

Justin A. Lemkul
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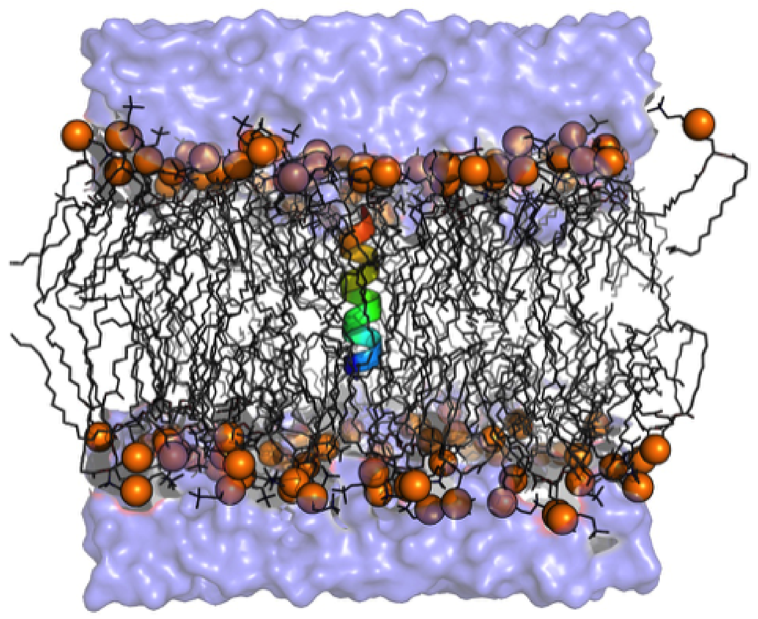


DOI: https://doi.org/10.33011/livecoms.1.1.5068

Keywords: tutorials, gromacs, molecular dynamics simulation, computational chemistry

PDF

ARTICLE CODE REPOSITORY

GROMACS: tutorials.gromacs.org

Amber: ambermd.org/tutorials

OpenMM: docs.openmm.org/latest/userguide/library/03_tutorials.html

A typical workflow for molecular dynamics

Get protein structure

↓

Prep for simulation

↓

Simulation setup

↓

Run Simulation Protocol

↓

Simulation Analysis

Getting your protein structure

AlphaFold Protein Structure Database

RCSB PDB PROTEIN DATA BANK

Getting ligands/co-factors

ZINC20

RCSB PDB PROTEIN DATA BANK

A typical workflow for molecular dynamics

Get protein structure

Prep for simulation

Simulation setup

Run Simulation Protocol

Simulation Analysis

Prepping your protein and/or ligand(s)

SCHRÖDINGER
Maestro

SeeSAR
The drug design dashboard

[...]

A typical workflow for molecular dynamics

Get protein structure

Prep for simulation

Simulation setup

Run Simulation Protocol

Simulation Analysis

Setup and run on your favourite MD engine

Gromacs

OpenMM

Amber

NAMD

BioSimSpace

SOMD

Charmm

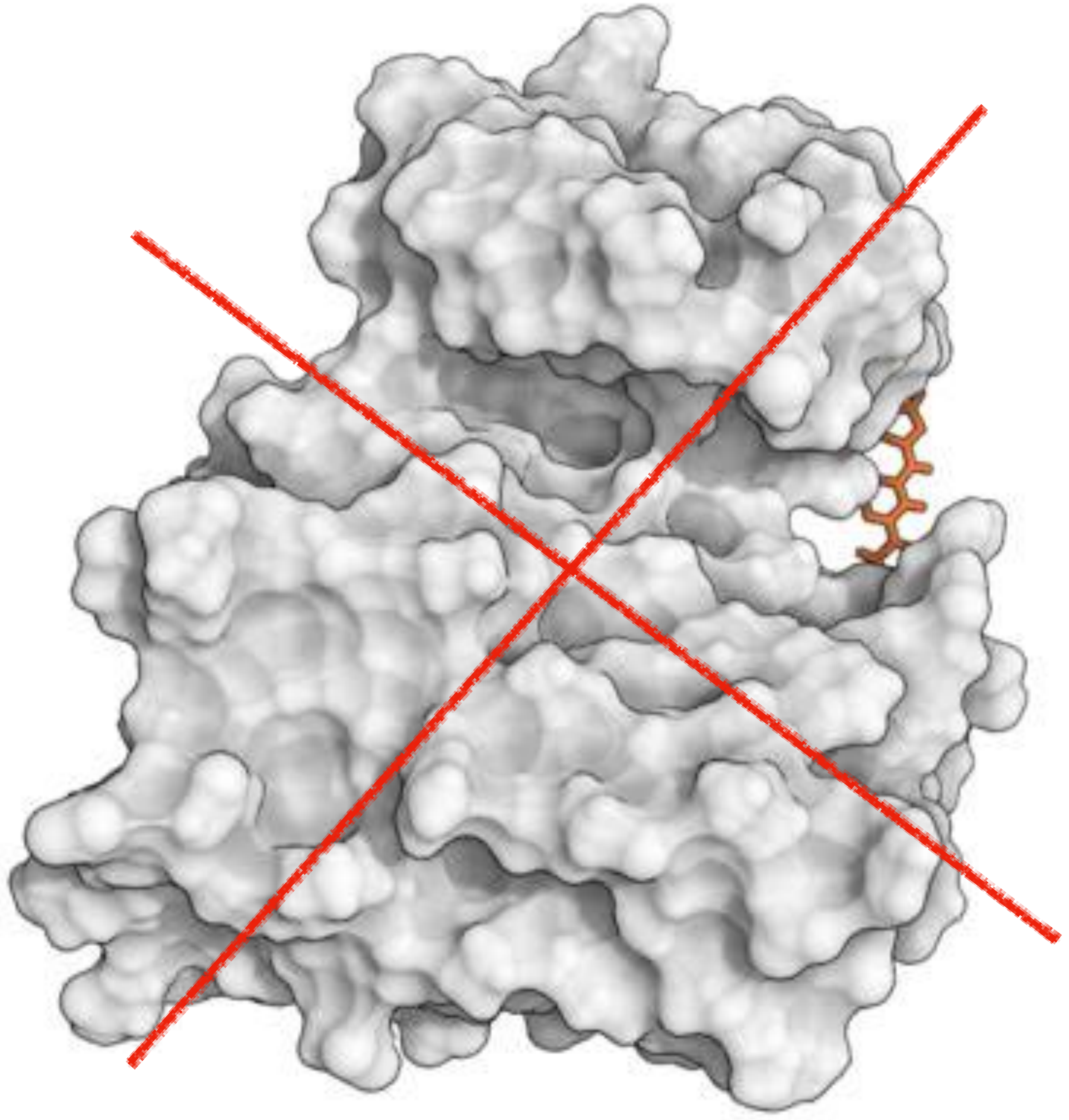
DLPoly

LAMMPS

mostly C++ command line

Python API

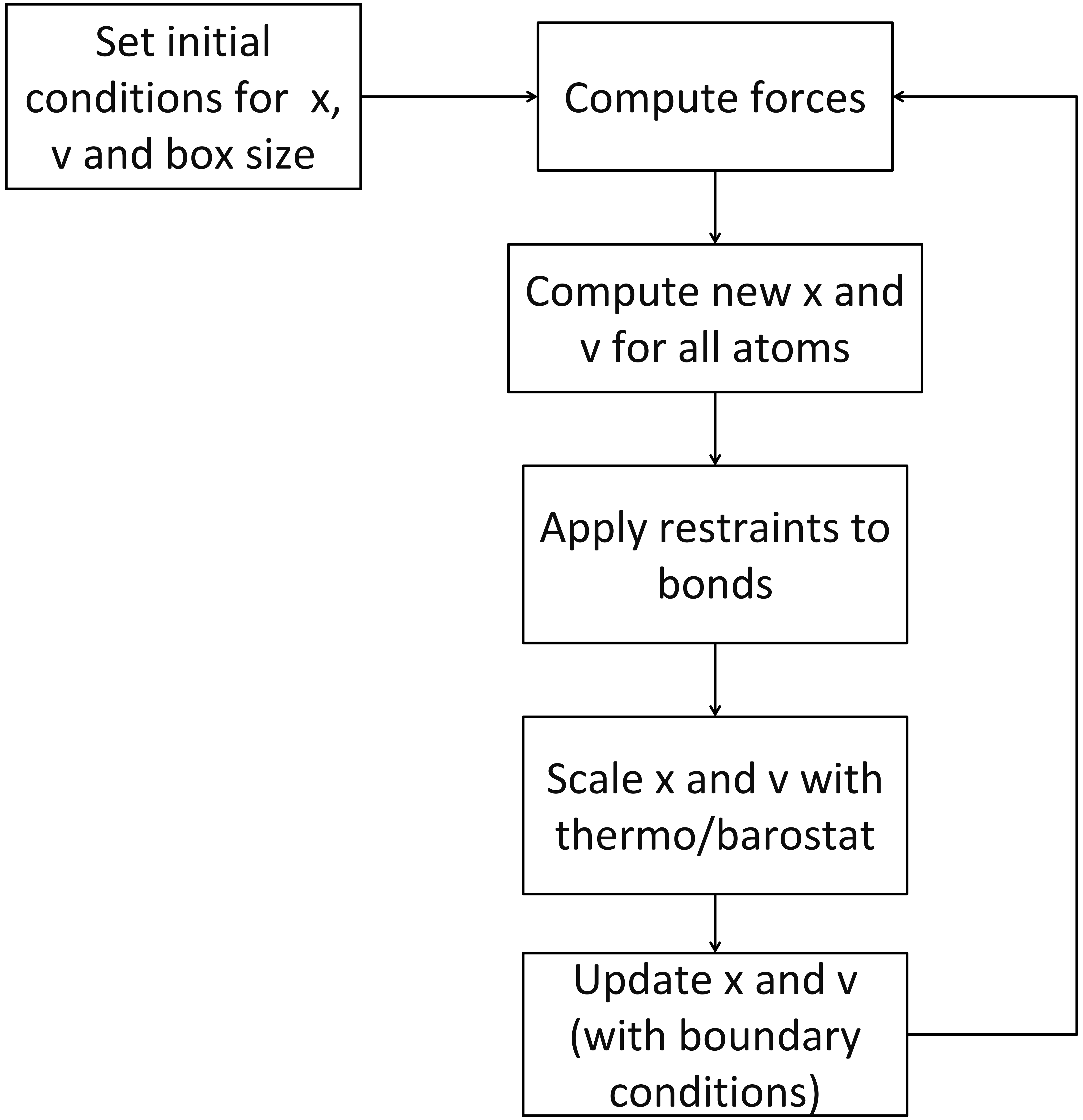
Disclaimer!



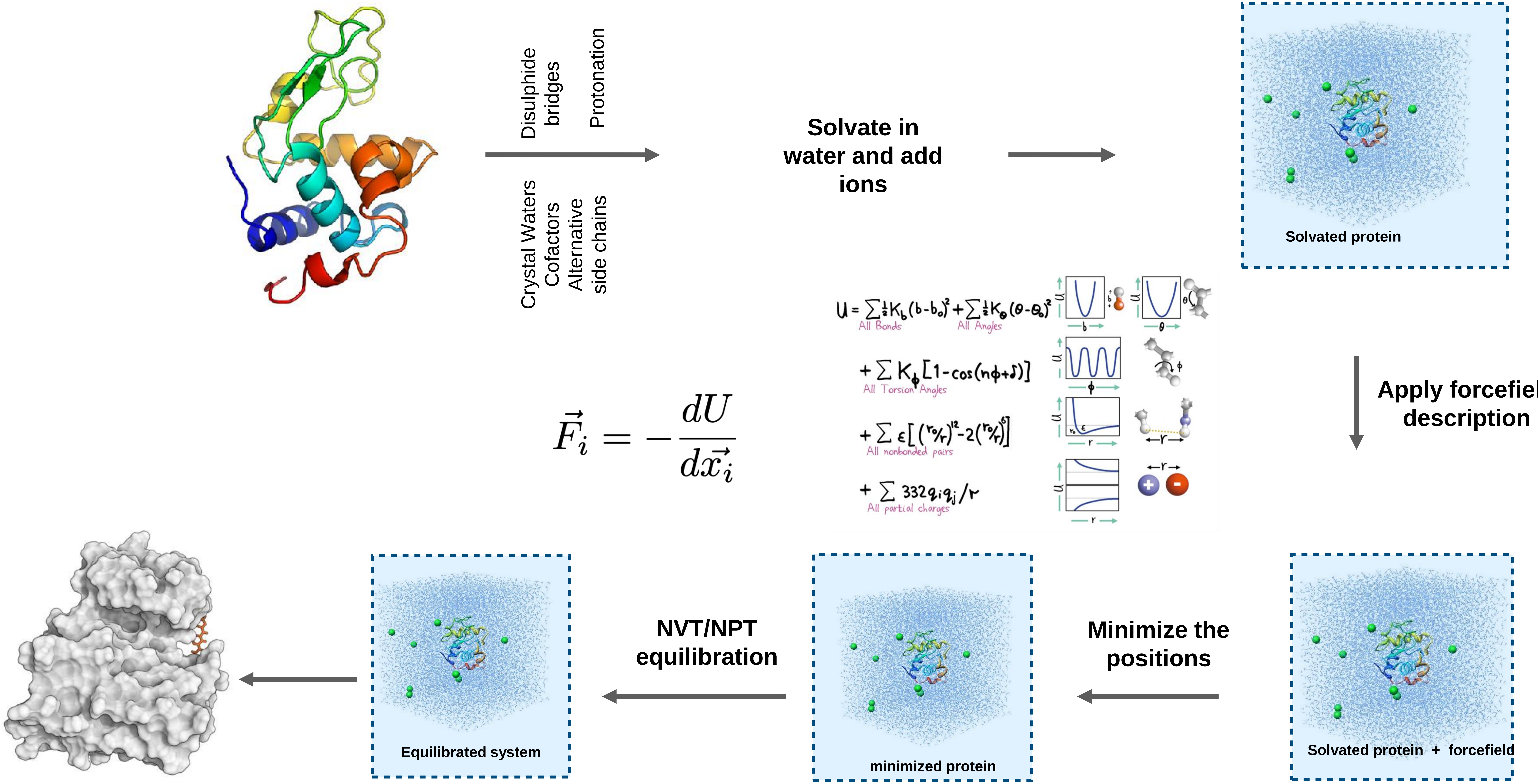
Running biomolecular MD can take days on specialised hardware.

Today we will *not* run any of them, and instead will focus on fundamental principles.

A Molecular Dynamics timestep



Molecular dynamics require multiple steps for the setup of simulations



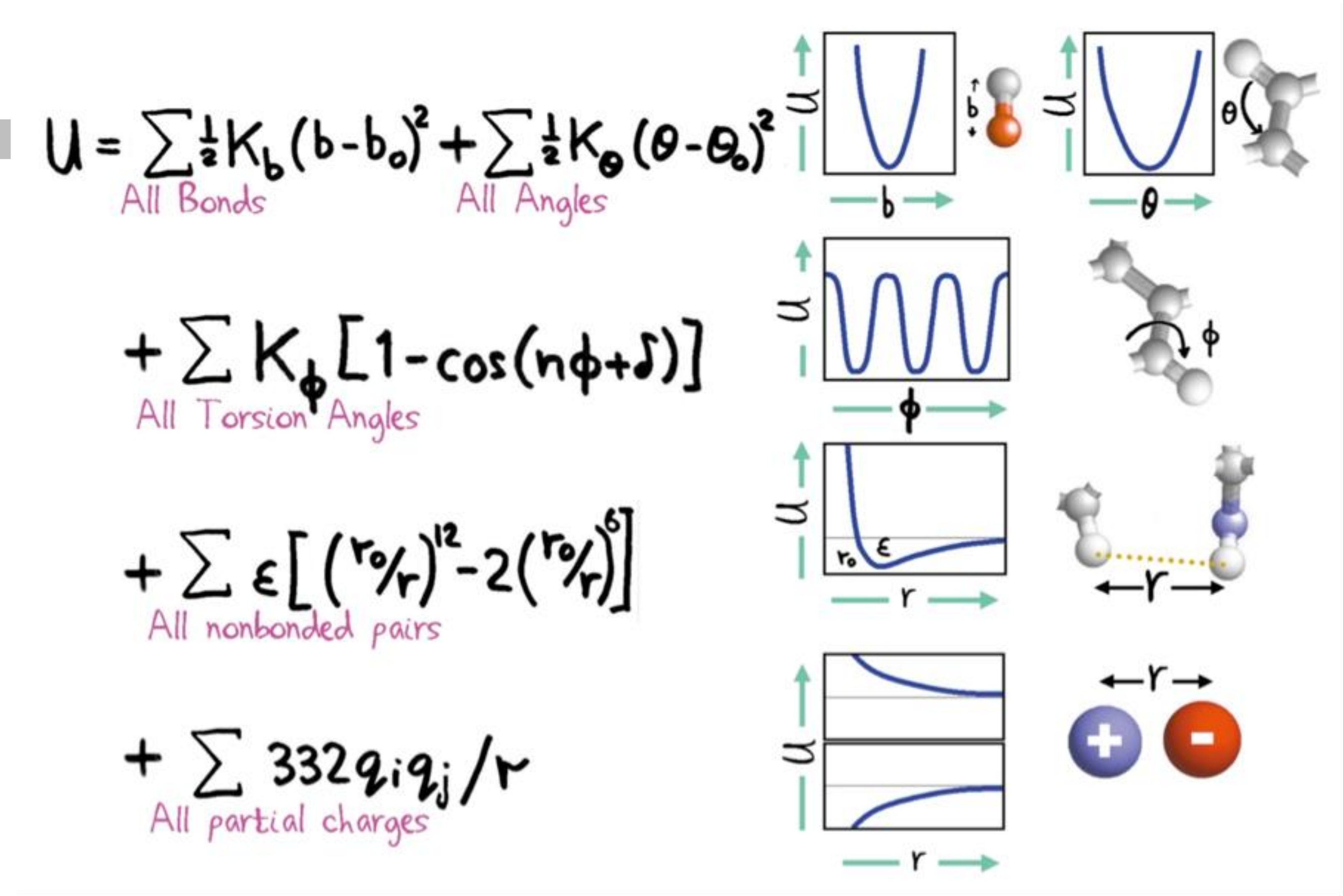
Production simulation

http://www.bevanlab.biochem.vt.edu/Pages/Personal/justin/gmx-tutorials/lysozyme/01_pdb2gmx.html

Levitt, *Nature Structural Biology*, ***8,*** 392–393(2001)

There are many different choices for force fields to be made

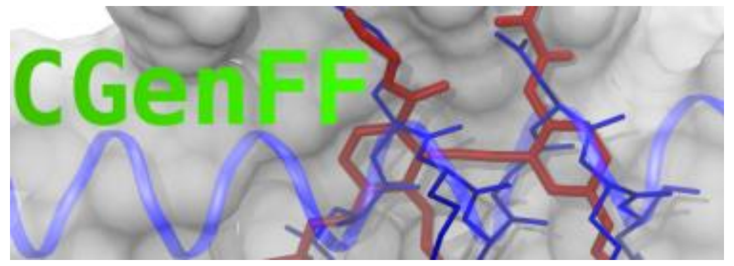
$$\vec{F}_i = -\frac{dU}{d\vec{x}_i}$$



- **Amber** (Peter Kollmann, UCSF)
  –Glycam parameters cover most sugars
  (Robert J. Woods, University of Georgia)
- **CHARMM** (Martin Karplus, Harvard)
  –POPC, POPE, DPPC lipids
- **OPLS** (William Jorgensen, Yale)
- **GROMOS** (Wilfried van Gunsteren, ETHZ)

There is no “best force field”!

Small molecule force fields

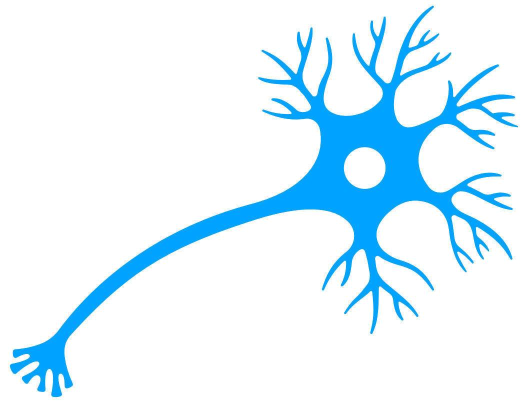


open forcefield

$$E_{pair} = \sum_{bonds} K_r (r - r_{eq})^2 + \sum_{angles} K_\theta (\theta - \theta_{eq})^2 + \sum_{dihedrals} \frac{V_n}{2}\left[1 + \cos(n\phi - \gamma)\right] + \sum_{i<j}\left[\frac{A_{ij}}{R_{ij}^{12}} - \frac{B_{ij}}{R_{ij}^{6}} + \frac{q_i q_j}{\varepsilon R_{ij}}\right]$$

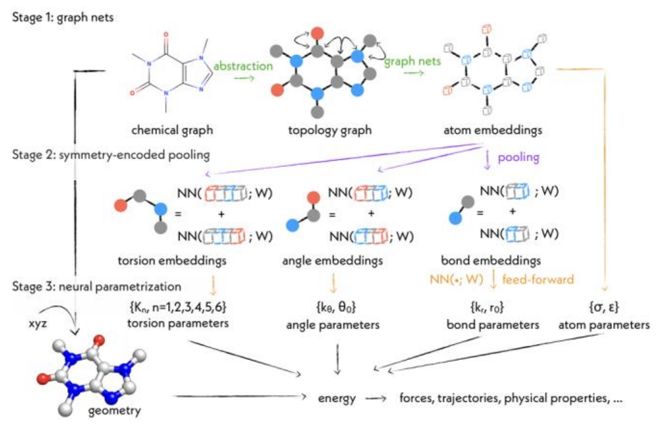
GAFF

Machine learned force fields



Espaloma

Ani-2x



SchNet

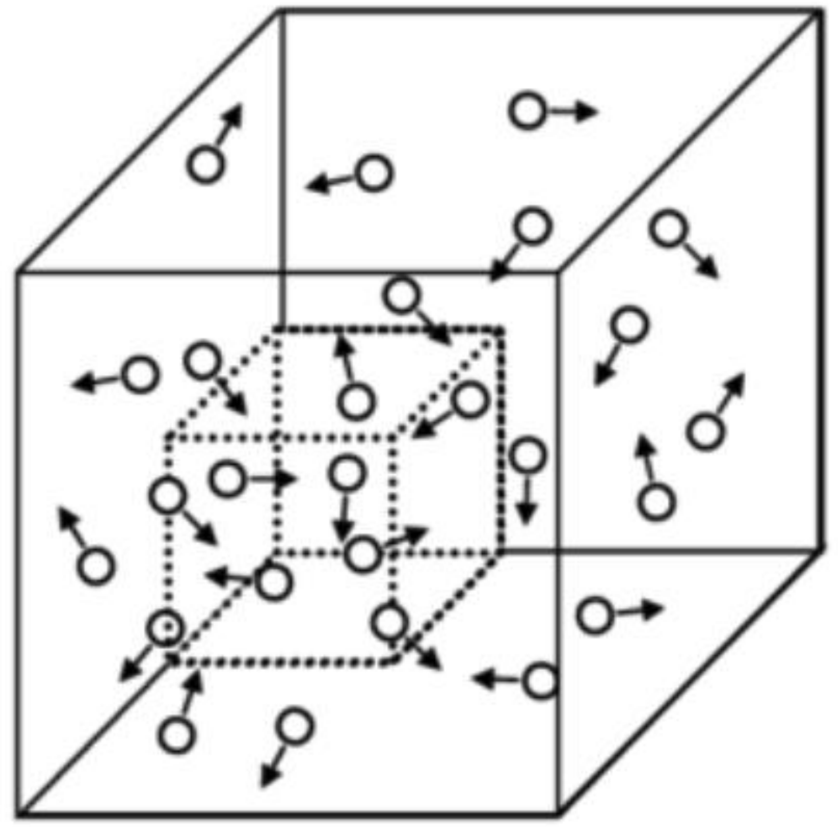
PhysNet

BandNN

Coarse-grained force fields…

Choosing your thermodynamic ensemble

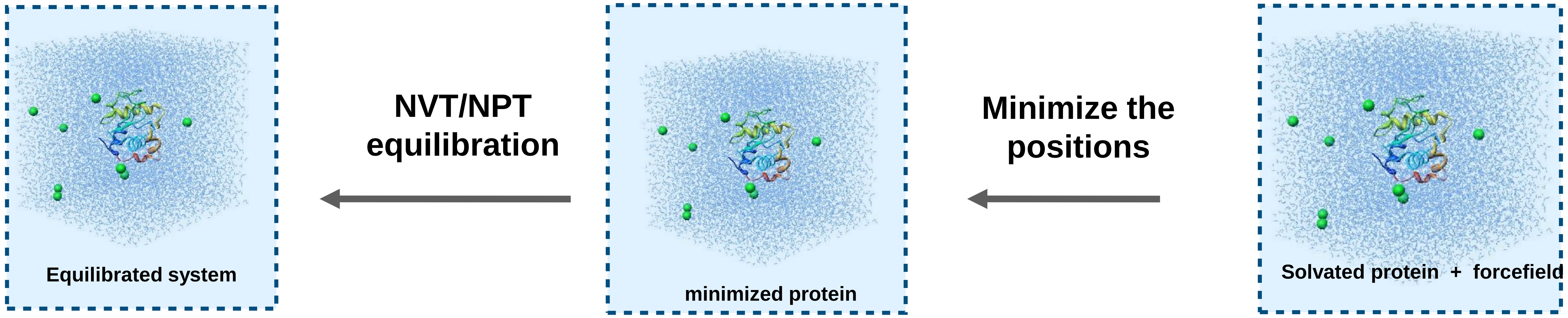
Simulations replicate a specific *thermodynamic ensemble* (typically NVT or NPT), or even grand canonical (μVT)



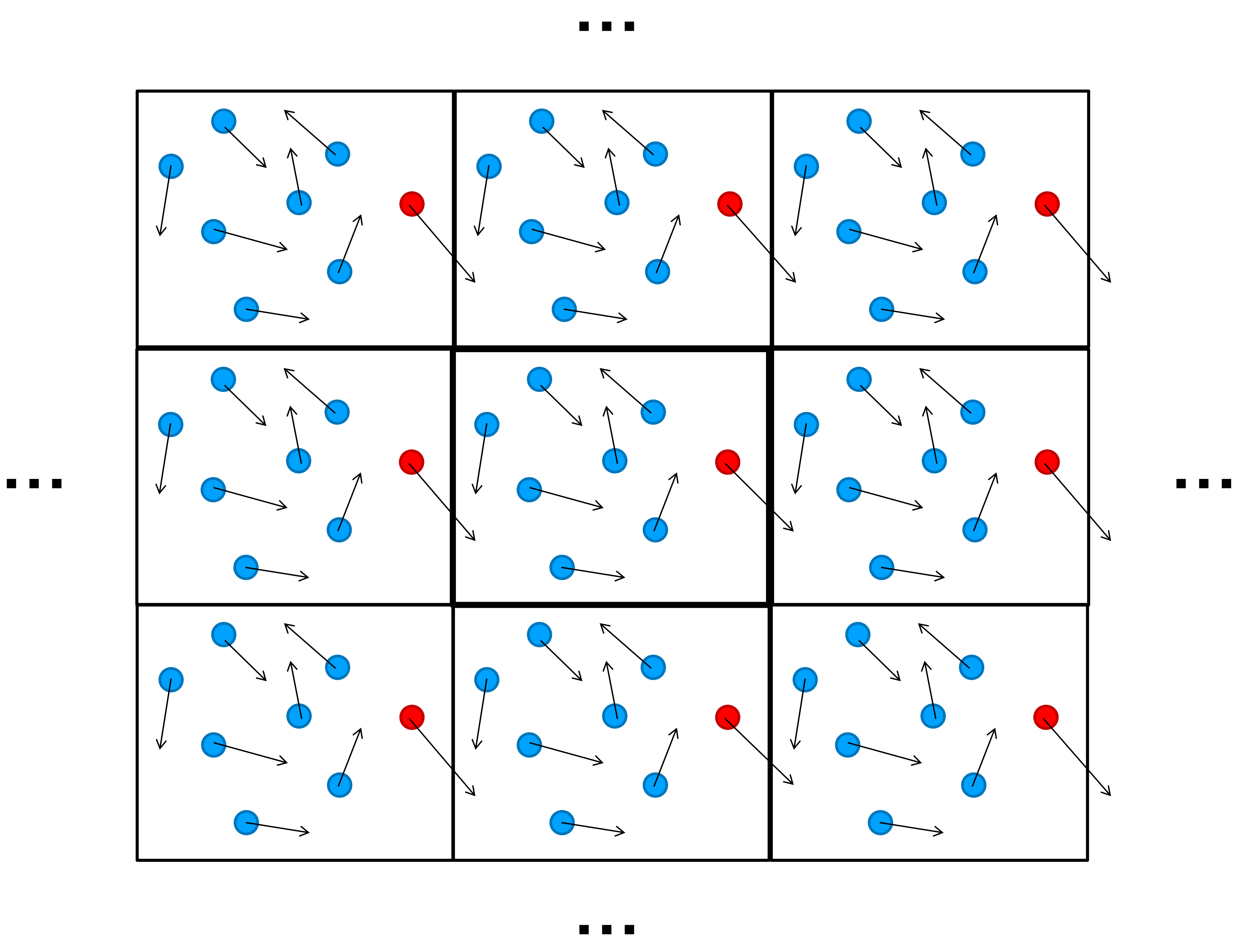
μVT

You will have different options to include *thermostats* (scaling atom velocities) and *barostats* (scaling positions) in your calculations:

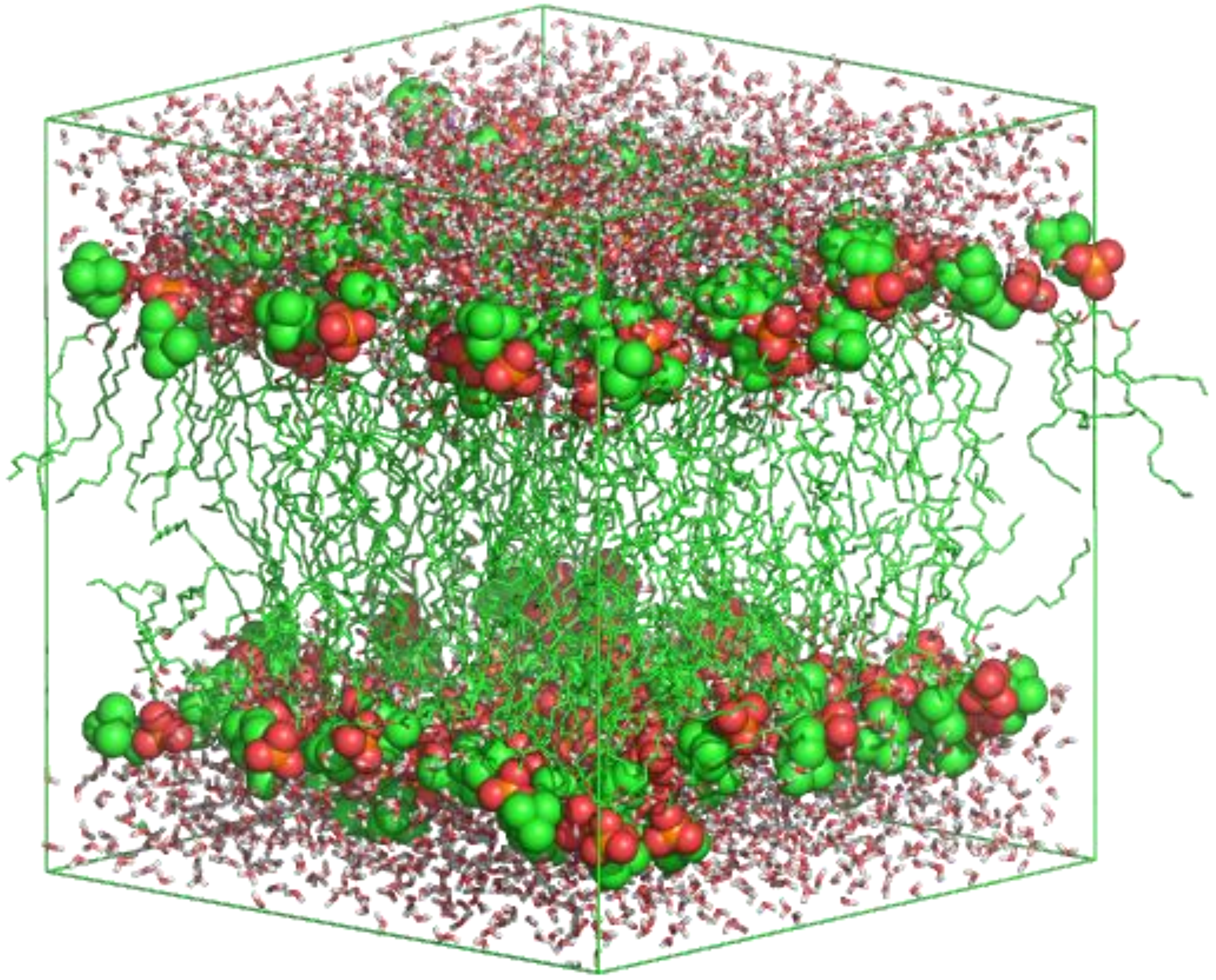
- Nose-Hoover
- Berendsen
- Parrinello-Rahman
- Langevin piston
- …



Periodic boundary conditions (PBC) and pressure coupling



Typically, PBC in x-y-z



If you want to simulate membrane systems, you want to chose semi-isotropic pressure coupling!

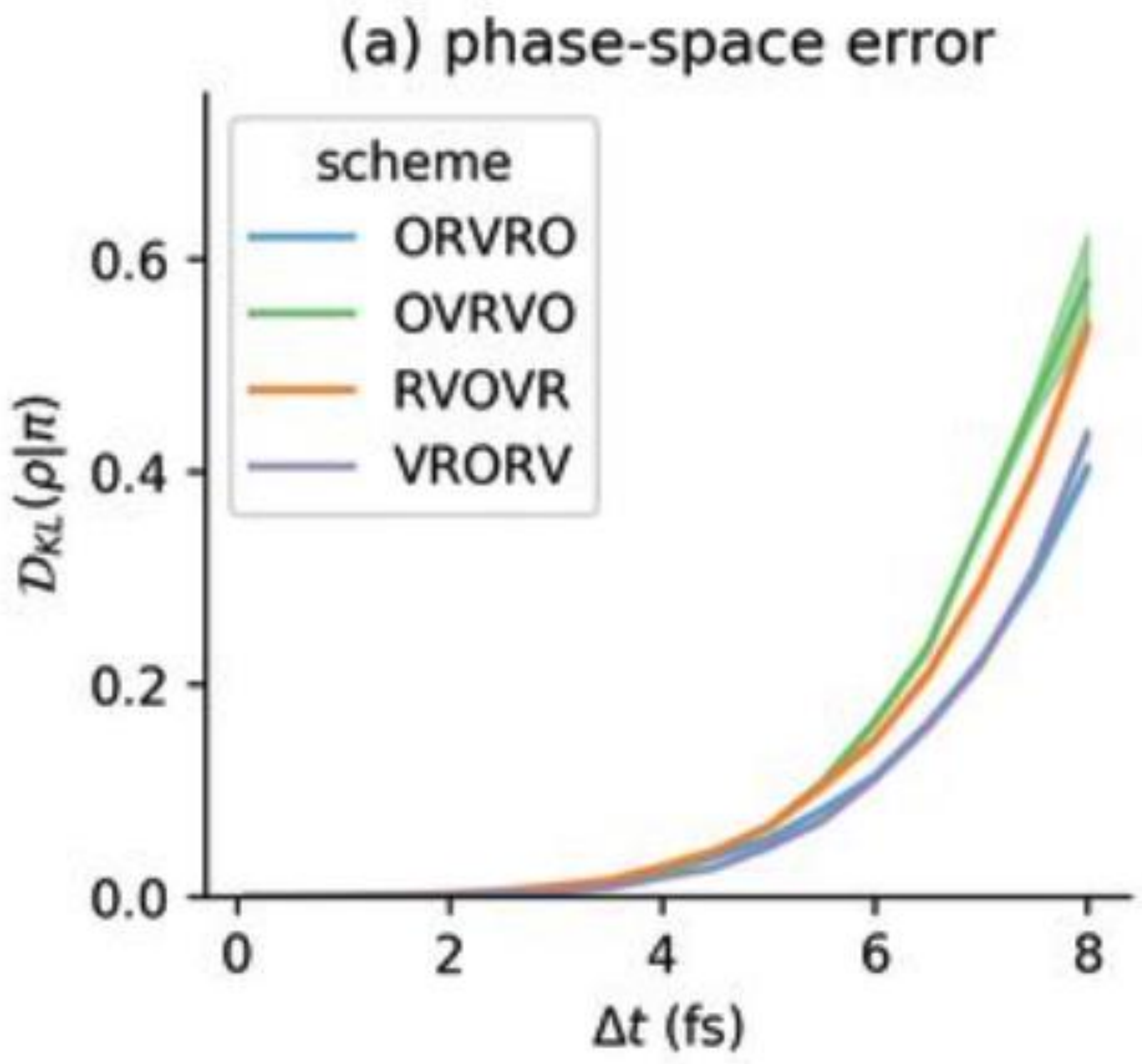
Sampling timescales for protein systems

The steepest gradient determines the smallest timestep:

Timestep size is imposed by the fastest phenomenon we want to observe :

- Covalent bond hydrogen-heavy atom (10^{14} Hz): 0.5 fs
- Covalent bond heavy atom-heavy atom: 1 fs
- Angles fluctuations: 2 fs

Restraining covalent bond distances allows to use 1-2 fs timesteps (restraining methods: SHAKE, RATTLE, LINCS,…)
Hydrogen Mass repartitioning: 4 fs
Other integrators (e.g., Langevin): 4 fs - 6 fs.



“equilibration” and “convergence”, what do they mean?

Equilibration phase: is the system in a “relaxed” state?

Production phase: do we have good sampling and convergence?

Thinking about the problem holistically: an integrated framework for the analysis of equilibration, sampling, and convergence.

Example equilibration protocols

YOU WANT: constant volume, pressure, and temperature, healthy Ramachandran plot, no exotic chemistry, bulk water (if used)

<u>**Suggested equilibration workflow**</u>				<u>**Production Ensemble**</u>
NVT (short simulation to relax to temperature of interest) →			NVE (short equilibration) →	NVE
NVT (short simulation to relax to temperature of interest) →				NVT (at known, fixed density)
NVT (short simulation to relax to temperature of interest) →	NPT (short simulation to relax to density of interest) →	NPT (to calculate average box size) →	NVT (short equilibration) →	NVT (for density defined by pressure or unknown system density distribution, like a homegeneous system)
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

An *example* simulation protocol

YOU WANT: constant volume, pressure, and temperature, healthy Ramachandran plot, no exotic chemistry, bulk water (if used)

Equilibration:

1. Minimize energy, 1000 steepest descent
2. Heat system from 0 to 300 K in 500 ps, NPT, Berendsen barostat 1 atm. α-carbon restrained with 10 kcal/mol harmonic potential. 2 fs timestep, LINCS all bonds
3. 1 ns nVT equilibration with Langevin dynamics, no atom constrained.

Production:

4. 1 μs NPT, Nose-Hoover barostat, PME for electrostatics

DETERMINE HANDLING OF CUTOFFS

- ☐ As a general rule, electrostatics are long-range enough that either the cutoff needs to be larger than the system size (for finite systems) or periodicity is needed along with full treatment of long-range electrostatics (Section 3.4)
- ☐ Nonpolar interactions can often be safely treated with cutoffs of 1-1.5 nm as long as the system size is at least twice that, but long-range dispersion corrections may be needed (Section 4.1)

CHOOSE APPROPRIATE SETTINGS FOR THE DESIRED ENSEMBLE

- ☐ Pick a thermostat that gives the correct distribution of temperatures, not just the correct average temperature; if you have a small system or a system with weakly interacting component choose one which works well even in the small-system limit.
- ☐ Pick a barostat that gives the correct distribution of pressures
- ☐ Consider the known shortcomings and limitations of certain integrators and thermostats/barostats and whether your choices will impact the properties you are calculating

CHOOSE AN APPROPRIATE TIMESTEP FOR STABILITY AND AVOIDING ENERGY DRIFT

- ☐ Determine the highest-frequency motion in the system (typically bond vibrations unless bond lengths are constrained)
- ☐ As a first guess, set the timestep to approximately one tenth of the highest-frequency motion's characteristic period
- ☐ Test this choice by running a simulation in the microcanonical ensemble, and ensure that energy is conserved

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Which MD engine should I use?

Consider:

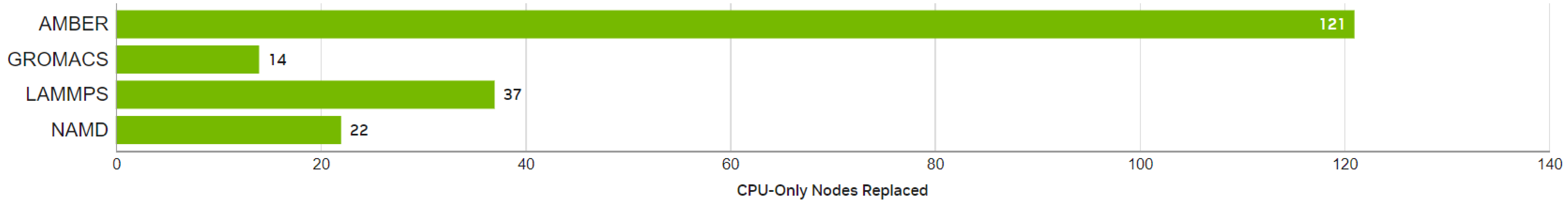
- Support for force field of choice
- Enables running desired simulation protocol
- Performance for available hardware
- Ease of use

depends on number of atoms, hardware, simulation protocol, MD engine

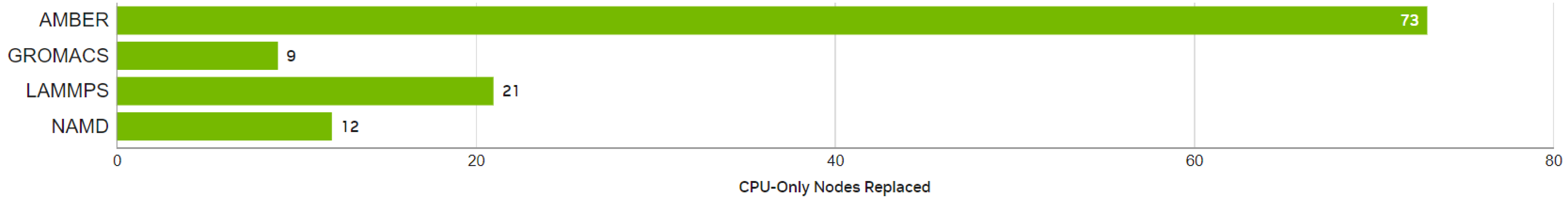
Graphical Processing Units (GPUs) are especially effective for MD

From: developer.nvidia.com/hpc-application-performance

NVIDIA H200

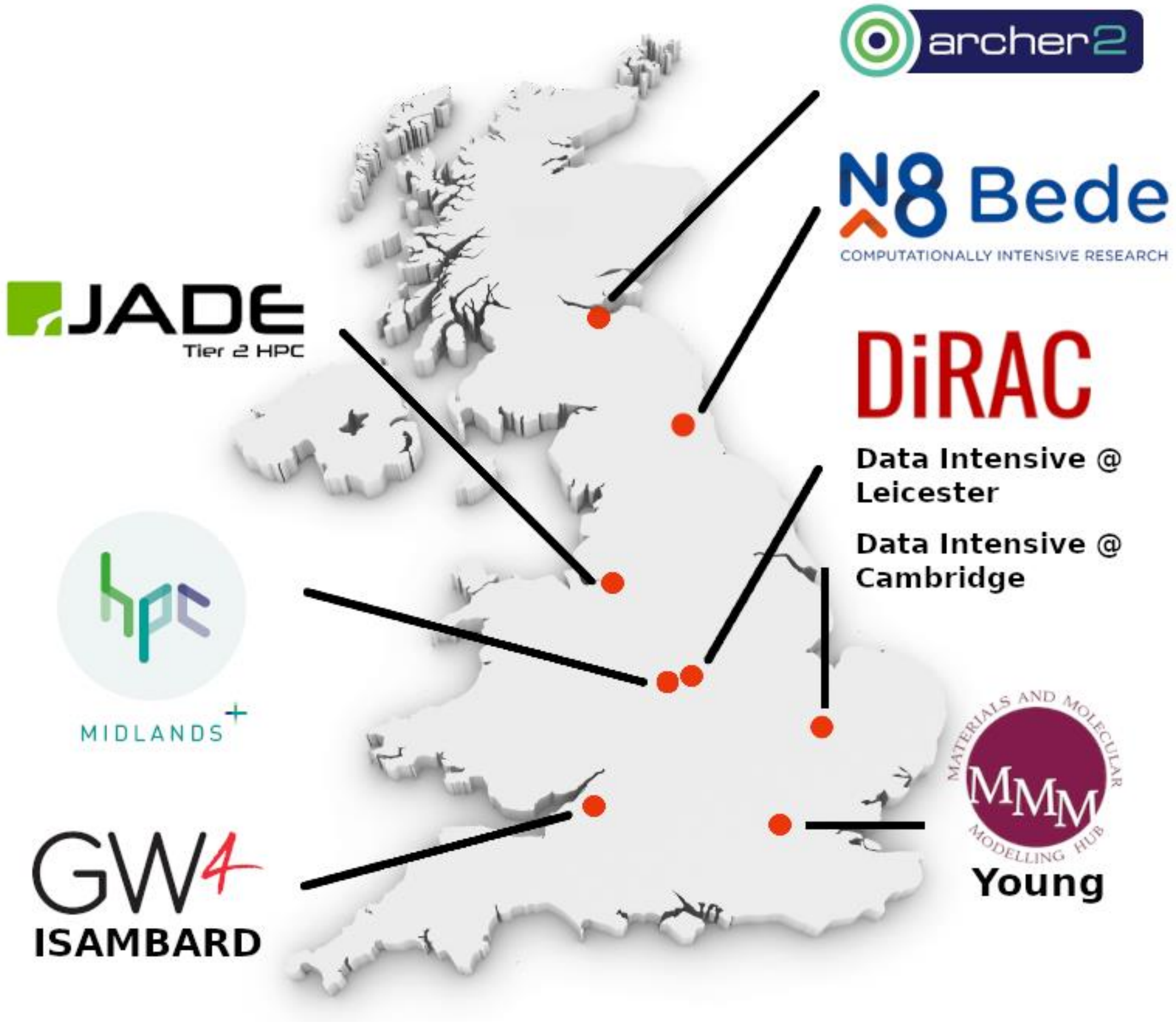


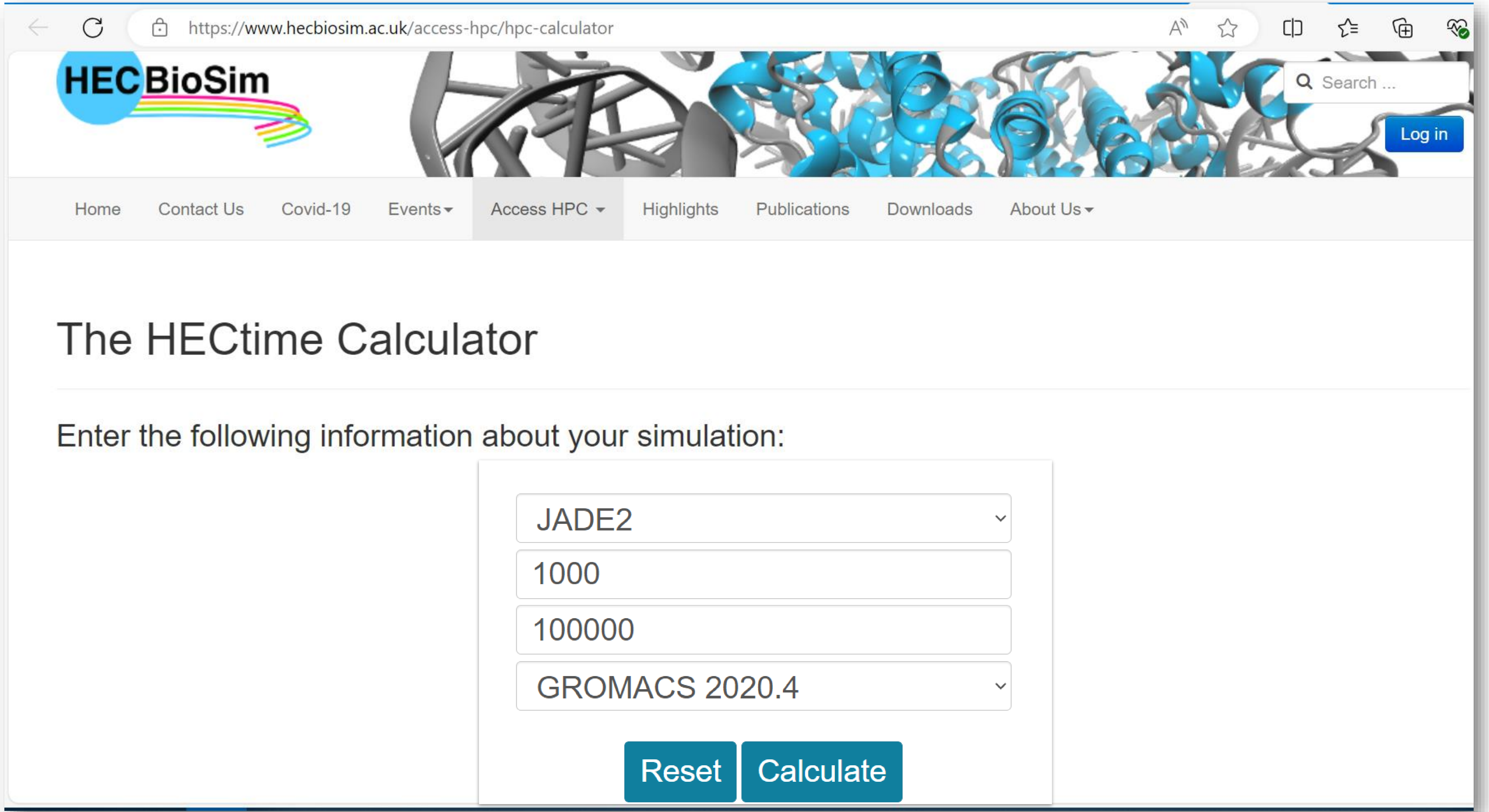
NVIDIA A100



CPU Server: Dual Xeon Platinum 8480+ @2GHz | GPU Server: Dual EPYC 7742@2.25GHz with 4x NVIDIA A100 SXM 80GB | AMBER Benchmark: DC-Cellulose_NVE, CUDA Version: 12.2 | GROMACS Benchmark: ADH Dodec, CUDA Version: 12.4 | LAMMPS Benchmark: Tersoff, CUDA Version: 12.2 | NAMD Benchmark: apoa1_nve_cuda, CUDA Version: 12.2

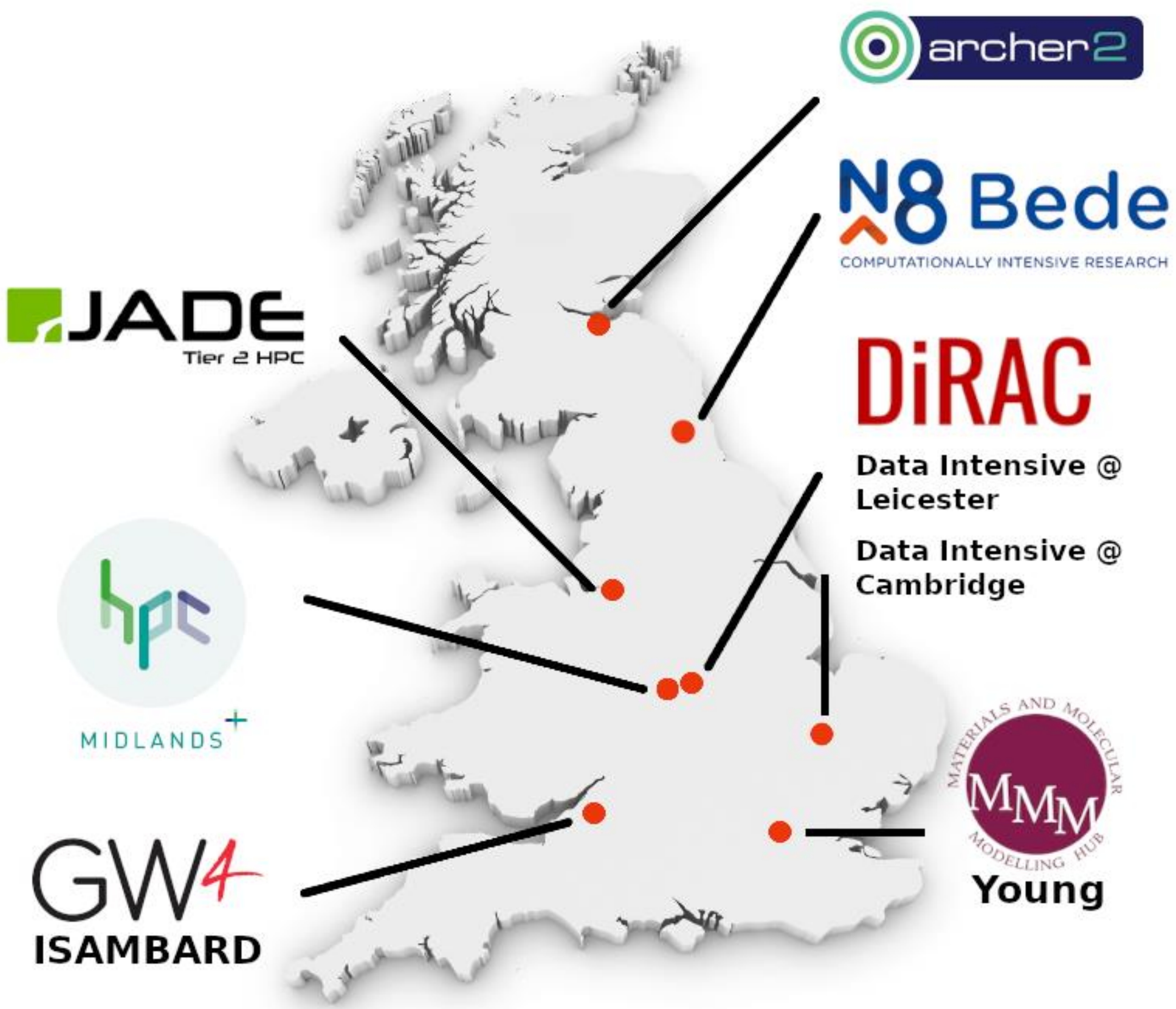
Calculating runtimes: example on UK Tier 2 systems

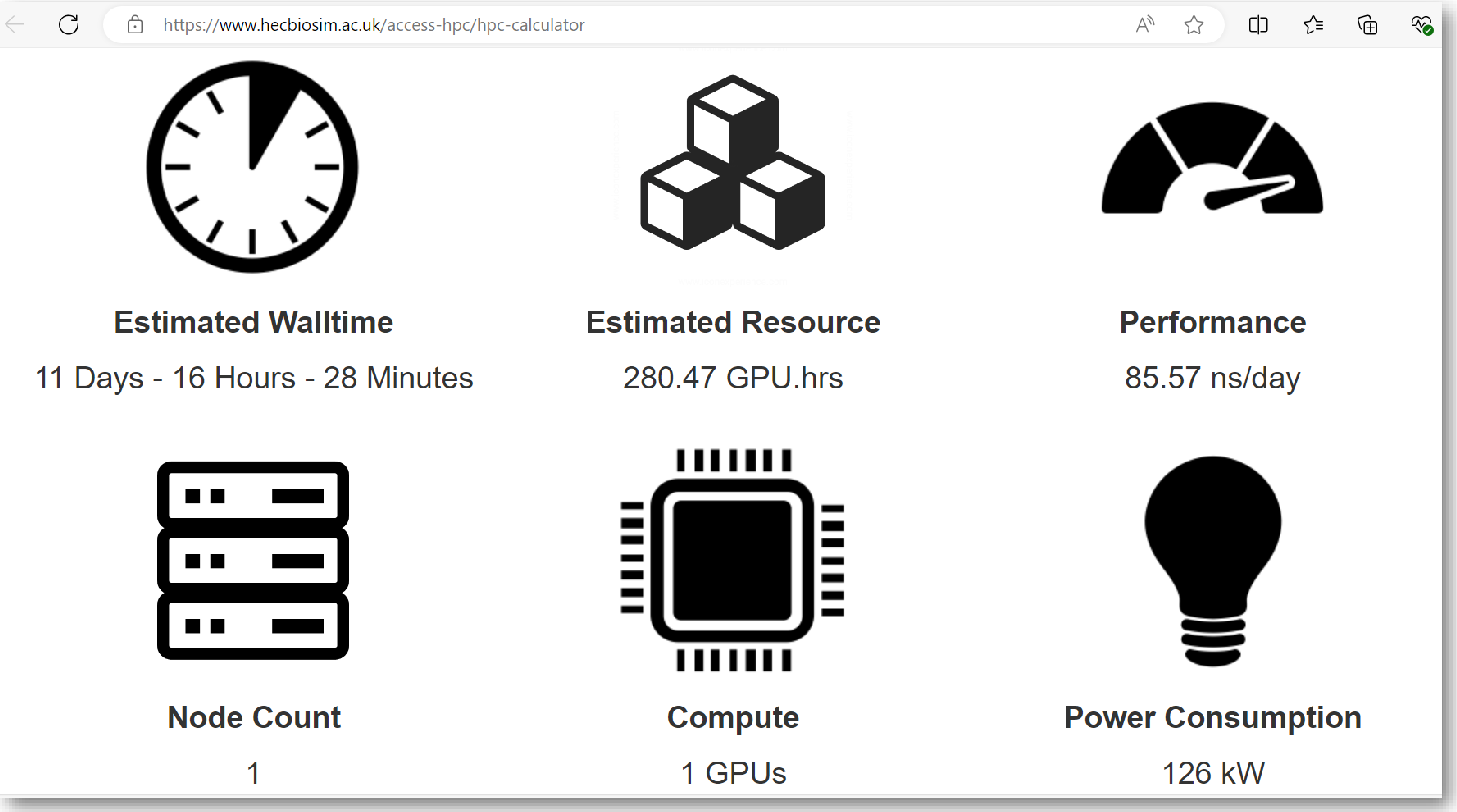




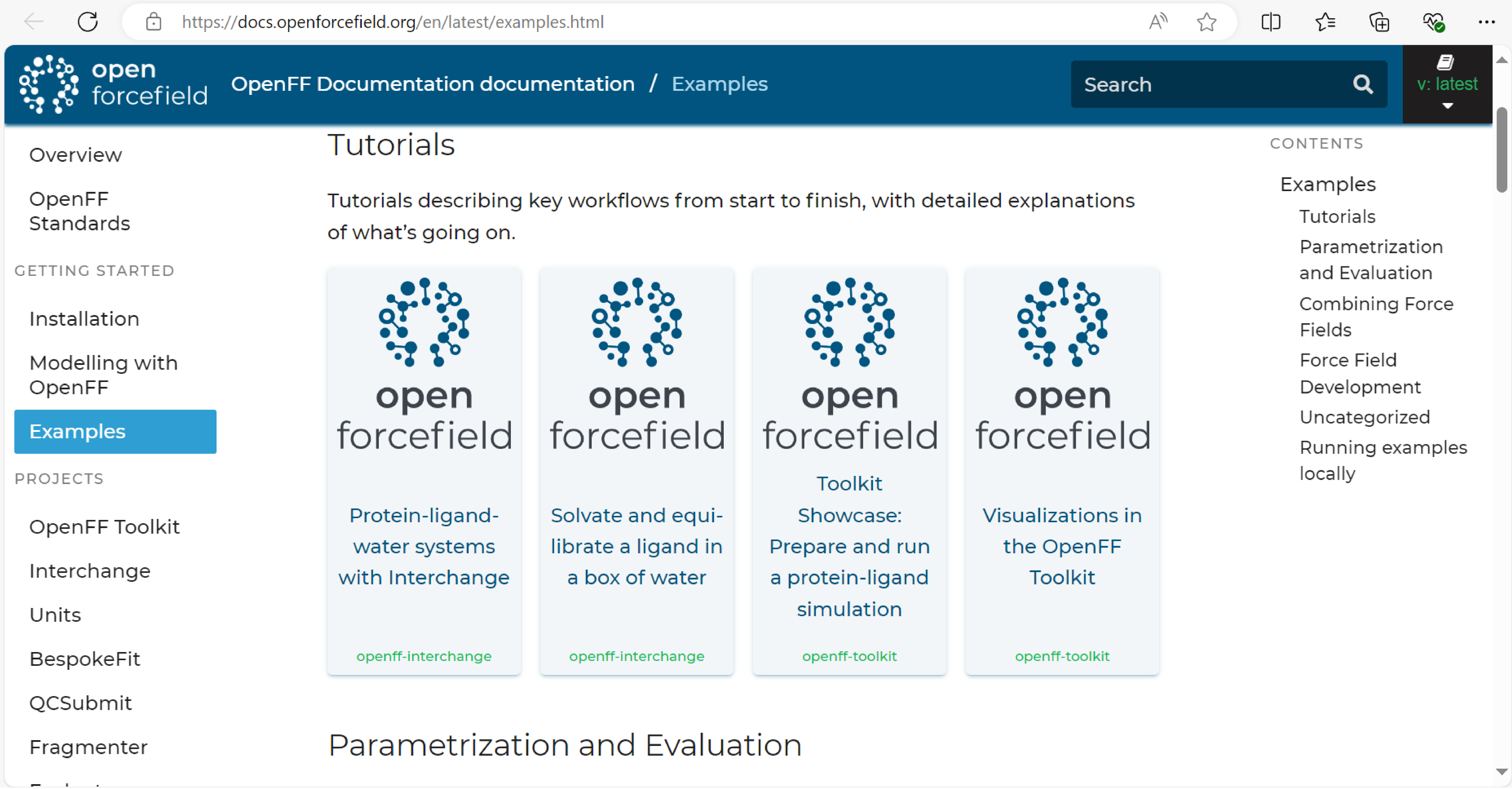
https://www.hecbiosim.ac.uk/access-hpc/hpc-calculator

Calculating runtimes: example on UK Tier 2 systems

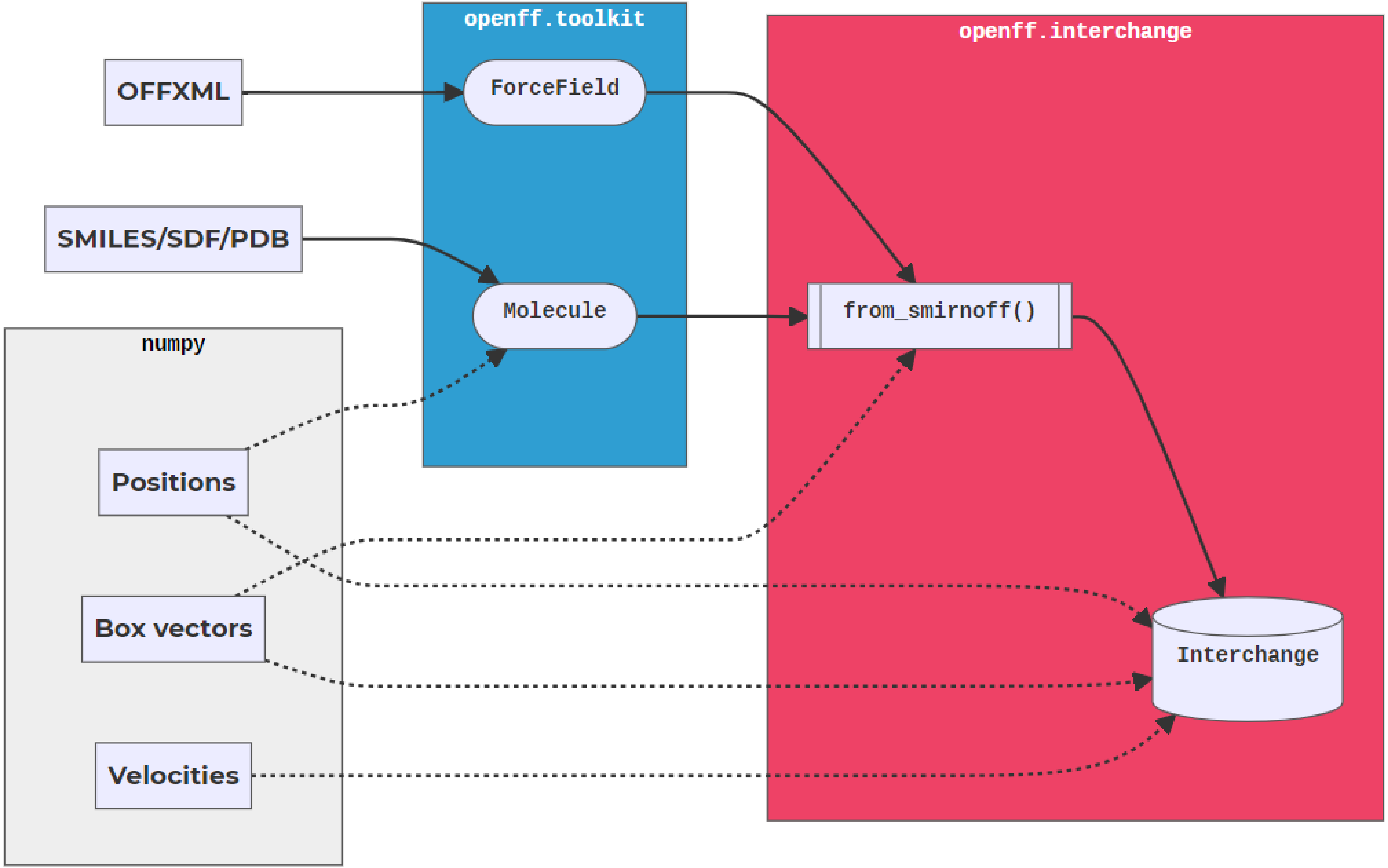




https://www.hecbiosim.ac.uk/access-hpc/hpc-calculator open forcefield



https://docs.openforcefield.org/en/latest/examples.html


openff.toolkit
openff.interchange
OFFXML
ForceField
SMILES/SDF/PDB
Molecule
from_smirnoff()
numpy
Positions
Box vectors
Interchange
Velocities