Basis of molecular dynamics simulations

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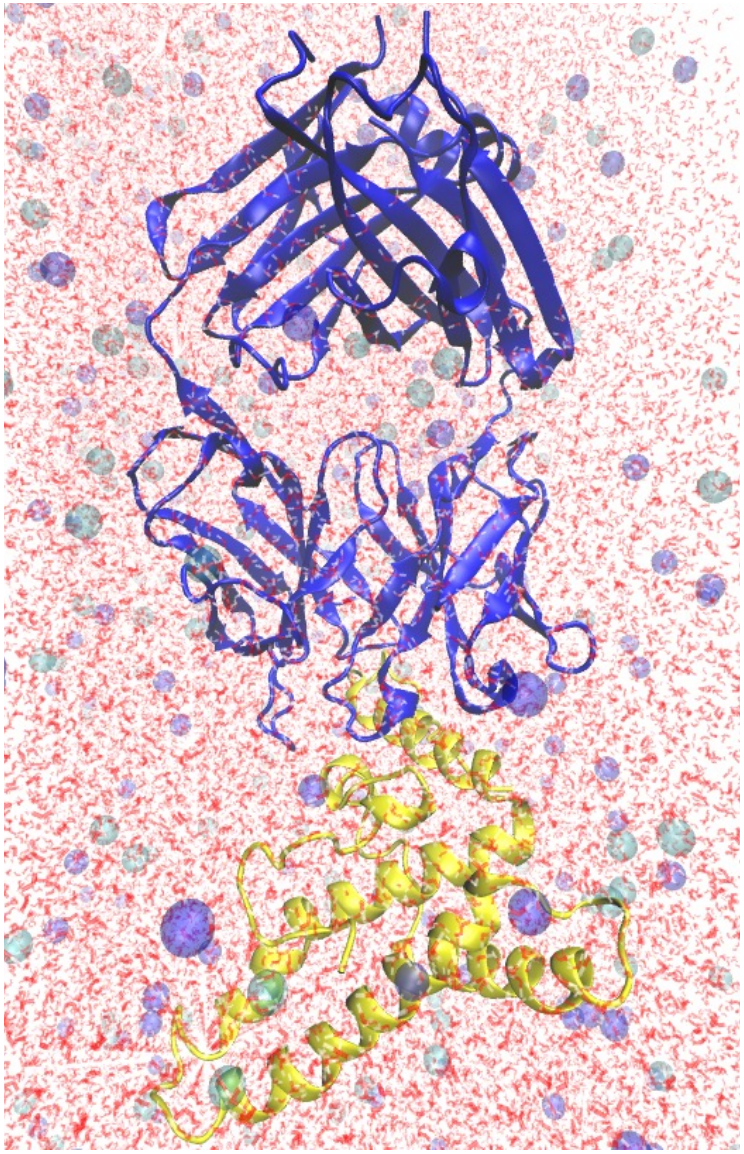
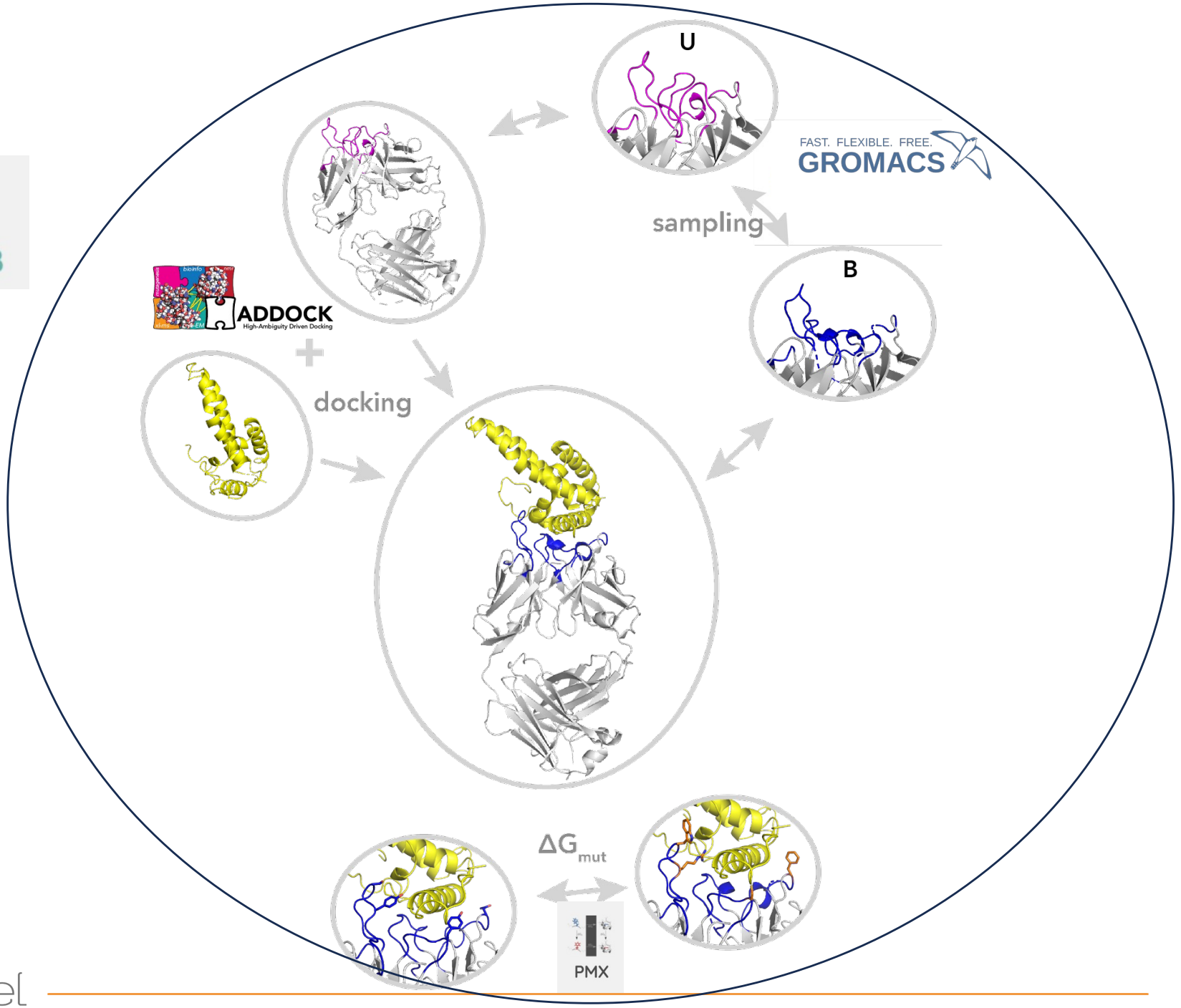
How an antigen interacts with antibody

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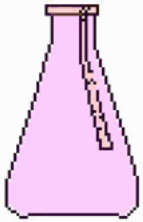
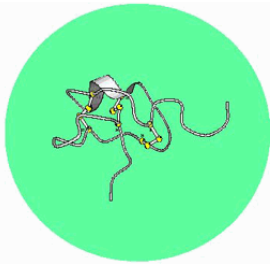
Goal of a Molecular Simulation

One goal of a molecular simulation is to generate enough representative conformations of the molecular system in such a way that accurate values of a property can be obtained.

One method is Molecular Dynamics

Properties





Experimental measurements are made on macroscopic samples. An experiment measures an average property
averaged over a large numbers of molecules (macroscopic sample), usually averaged over the time of measurement.

Molecular Simulations enable us to predict system properties through the generation of several conformations of the systems in such a way that accurate values of a property can be obtained.

The ergodic hypothesis states $\langle A \rangle_{ensemble} = \langle A \rangle_{time}$

Sampling and properties

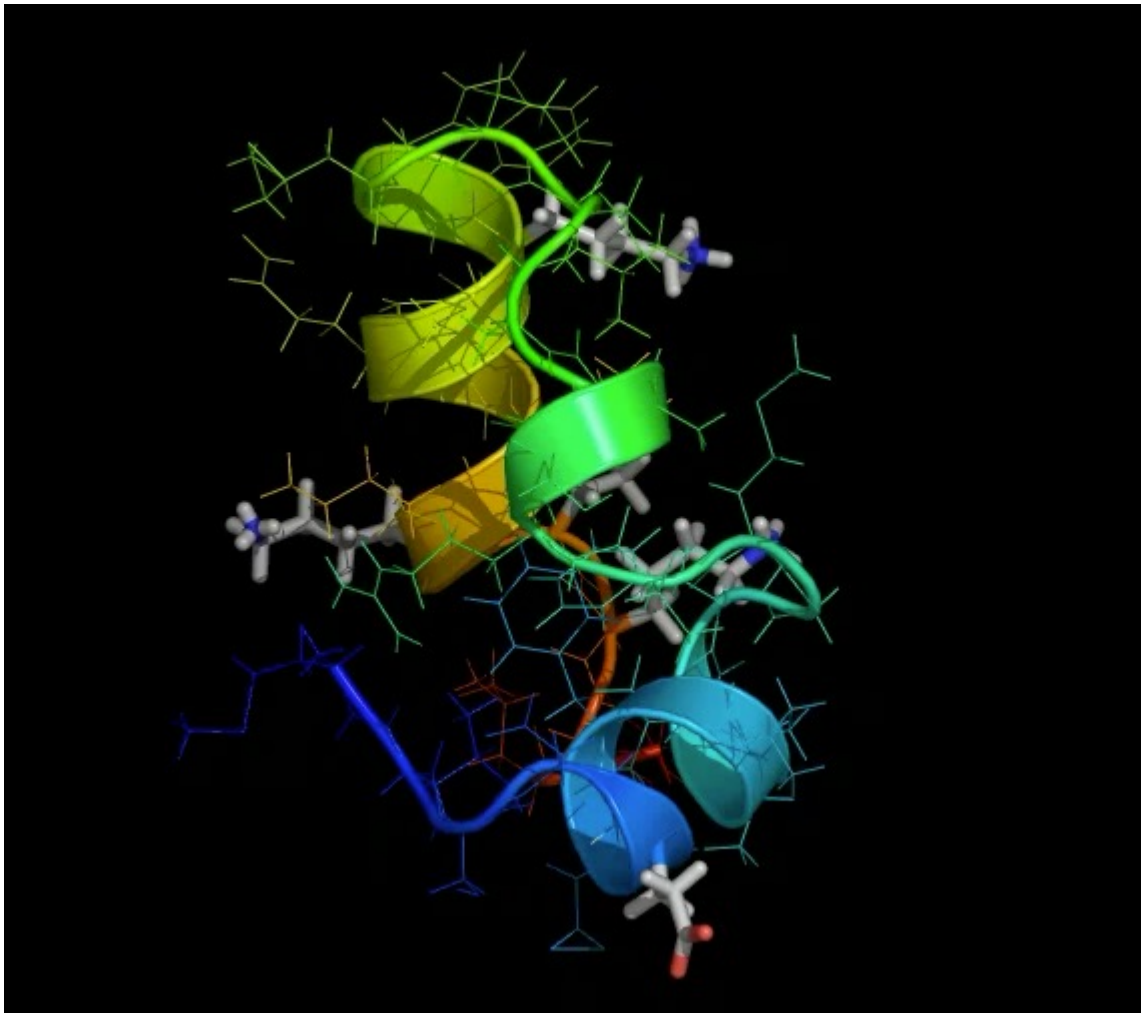
One goal of a molecular simulation is to generate enough representative conformations such the sampling of the conformational ensemble is ergodic. If this is the case, experimentally relevant information may then be calculated

One of the methods is Molecular Dynamics

Different properties have different relaxation time

Molecular dynamics simulations enable also time-dependent behavior of the systems

Phase space sampling



Newton's equation of motion

acceleration = force /mass

$$\frac{d^2 r_i}{dt^2} = \frac{F_i}{m_i}$$

force = -slope of the potential

$$F_i = -\frac{\partial}{\partial r_i} V(r_1, r_2 \ldots\ldots\ldots r_N)$$

$$i = 1 \ldots\ldots\ldots \mathrm{N}_{\mathrm{particles}}$$

One small step for a human,
many small steps for a computer

Challenge for biomolecular simulations

- Biophysical processes involve hundreds of thousands of atoms often in intricate interactions that are difficult to simply
- They span a wide range of time scales: primary events (e.i. photosynthesis) occur within ps, enzymatic and regulatory processes take milliseconds, and structural reorganizations may exceed seconds.
- The small driving forces that cause molecular changes results from large, opposing energetic effect. This required careful fine-tuning of the force fields that describe interatomic interactions.

Molecular Model

One of the factor that governs a MD simulation

Molecular model

A simplify representation of a molecular system should be as simple as possible

- Why?

Have a look at the Nobel lectures in chemistry 2013

(Martin Karplus, Michael Levitt, Arieh Warshel)

Choose the appropriate molecular model

- Degree of freedom (which particles)
- Energy functions or interaction potentials that describe the interactions between the particles

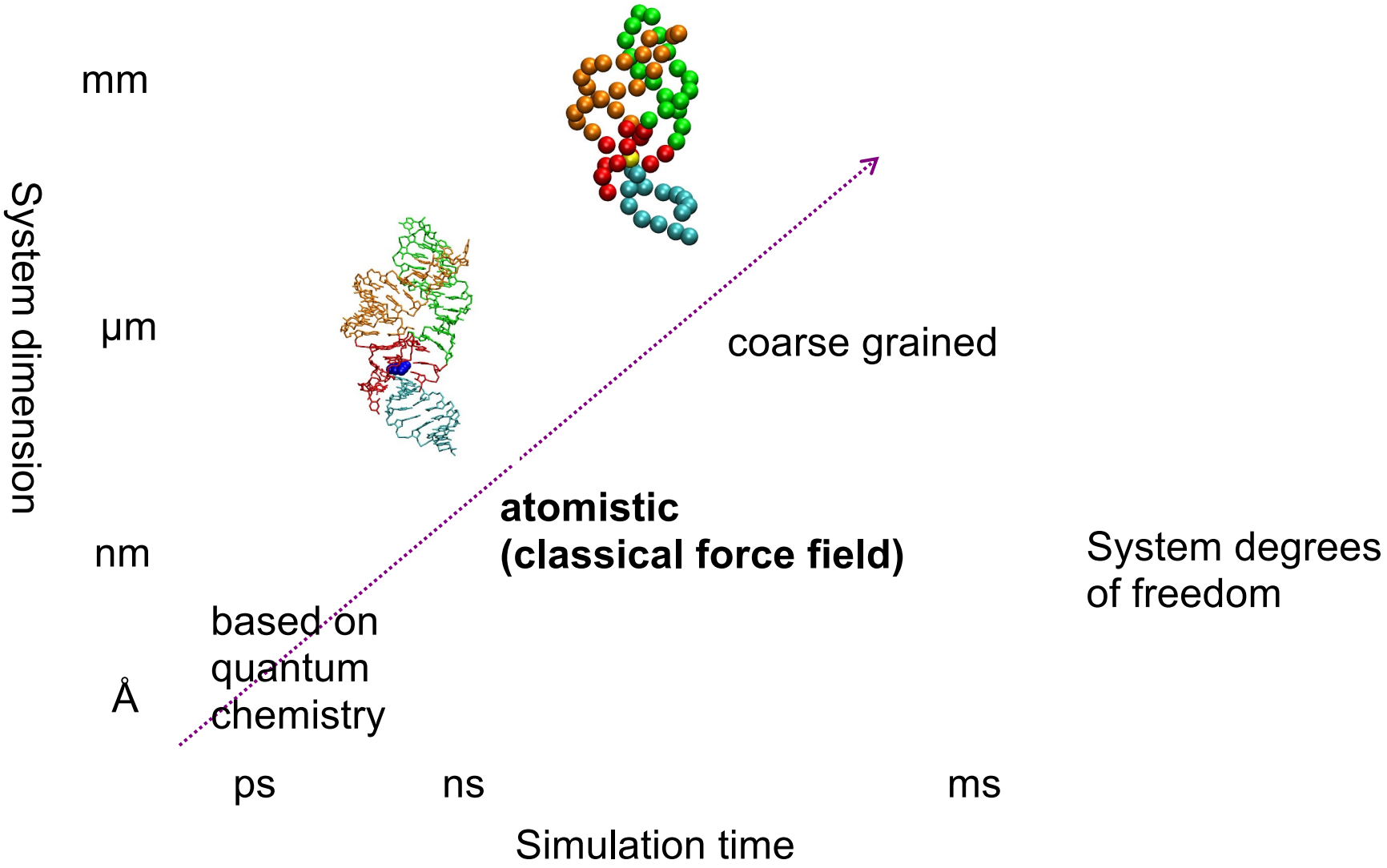
Reliability:

- Model must encompass the properties of interest

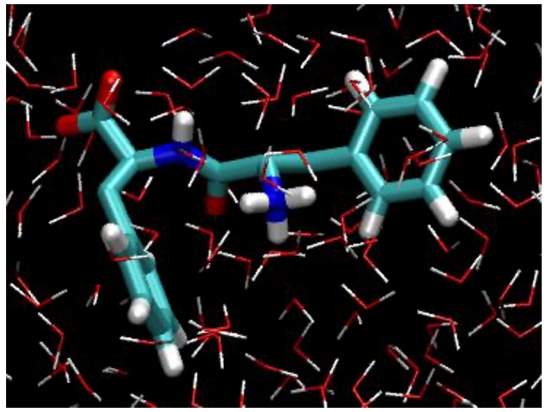
- Simulation time >> time scale of the process to be investigated

- Simulation size >> size of the simulated system[15]

Molecular model and system dimension

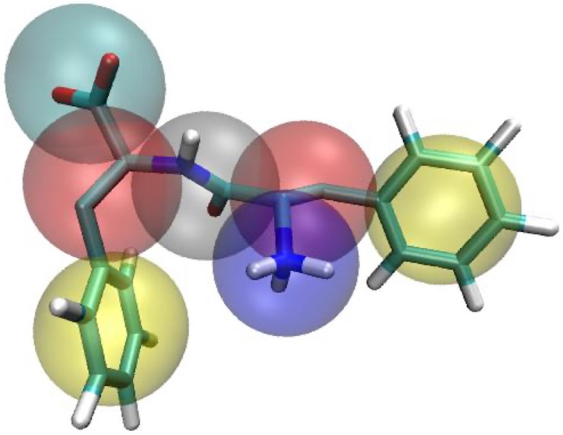


Atomistic vs Coarse grained model



Degree of freedom reduction

Back-mapping to atom



ATOMISTIC
40 particles + water molecules

COARSE GRAINED
7 particles

Villa et al. PCCP 2009

Potential Energy

Potential energy can be divided into terms depending on the position of individual particles, pairs, triplets

more costly

$$V(r) = V(r_1, r_2, \cdots, r_N) =$$

$$\sum_i V^{(1)}(r_i) + \qquad \text{1-body}$$

$$\sum_{i,j} V^{(2)}(r_i, r_j) + \qquad \text{2-body}$$

$$\sum_{i,j,k} V^{(3)}(r_i, r_j, r_k) + \qquad \text{3-body}$$

$$\sum_{i,j,k,l} V^{(4)}(r_i, r_j, r_k, r_l) + \qquad \text{4-body}$$

$$\cdots + \sum_{i_1,\ldots,i_N} V^{(N)}(r_{1\mathrm{i}}, r_1, \cdots, r_N) \qquad \text{N-body}$$

Interactions

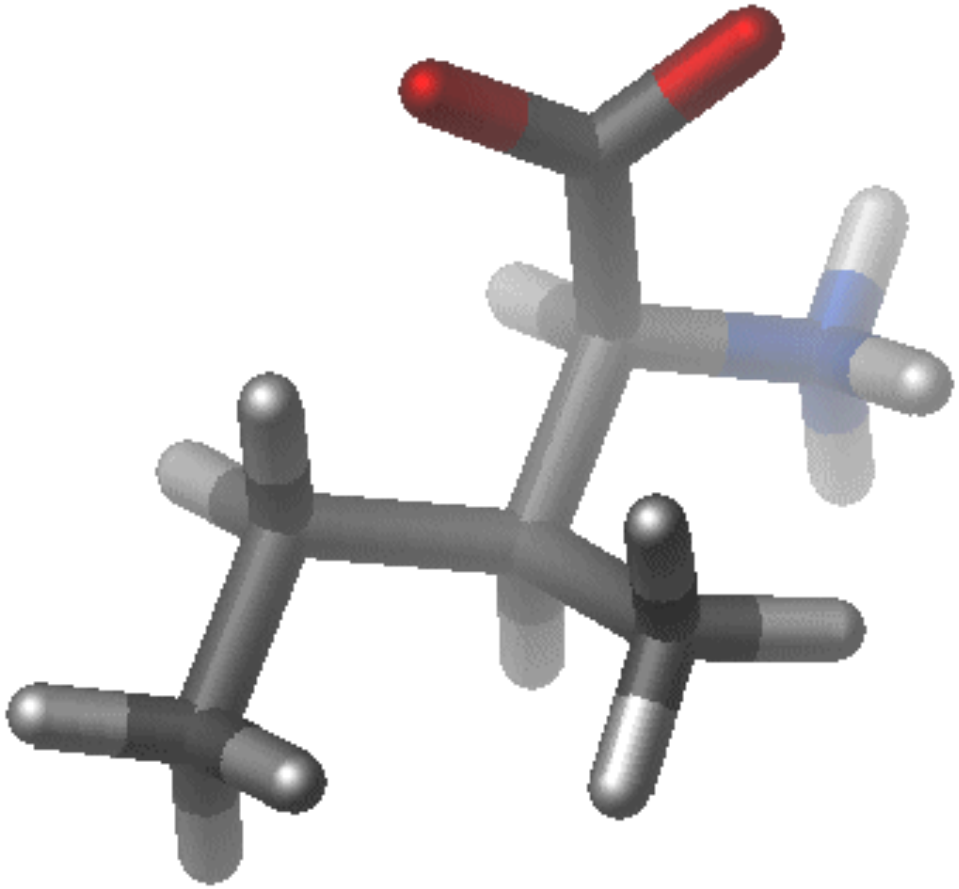
Pair approximation

The pair approximation gives remarkably good description if the average of three-body effects can be partially included by defining an 'effective' pair potential

$$V(r) = V(r_1, r_2, \cdots, r_N)$$
$$= \sum_i V^{(1)}(r_1) + \sum_i Veff^{(2)}(r_1, r_2)$$

Consequence of this approximation: effective potential depends on density and temperature, while the true two-body potential does not.

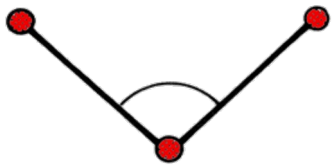
Molecular “movements”



Molecular Mechanics Force field

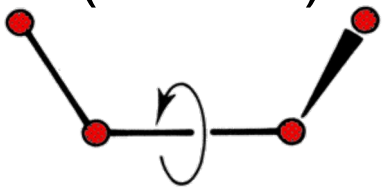
Given a set of particles a force field is the potential function describing the inter-atomic interactions

V = V(bond) **+** V(angle)



From Hooke

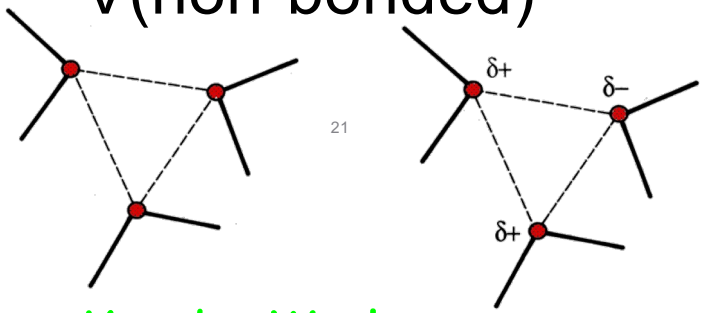
+ V(torsion)



From Fourier

+ V(other term)

+ V(non-bonded)



From Van der Waals

Electrostatic potential

Force field and analytical functions

$$V(r_1, r_2, \ldots, r_N) = \sum_{bonds} \frac{1}{2} K_b (b - b_0)^2 + \sum_{angles} \frac{1}{2} K_\theta (\theta - \theta_0)^2$$

$$+ \sum_{torsions} \frac{1}{2} K_\xi (\xi - \xi_0)^2$$

$$+ \sum_{torsions} \frac{1}{2} K_\phi [1 + \cos(n\phi + \delta)]$$

bonded-interactions

$$+ \sum_{pairs} [C_{12}(i,j) / r_{i,j}^{12} - C_6(i,j) / r_{i,j}^{6}] + q_i q_j / 4\pi\varepsilon_0 \varepsilon r_{i,j}$$

non-bonded interactions

Every force field has his own analytical functions and set of parameters

Force fields and parameters

- Usually based on atom types, often many for each element
- Parameters intimately co-dependent on functional forms and each other
- Do not expect to mix and match force field parameters
- Addition of new parameters in line with parameterization strategy

- Most common biomolecular force field families: AMBER, CHARMM, GROMOS, OPLS, Martini..
- Generalized force field
- Open force field initiative (https://openforcefield.org/)

- Online servers / offline tools where possible (SwissParam, ATB, Antechamber, LEaP, acpype, PRODRG, STaGE, MKTOP, CHARMM-GUI)

https://openforcefield.org/

Non-bonded long-range interactions

–Calculated over every pair of atoms in the system

–~ to N^2 where N is the number of atoms in the system

–More than **90% of the computing time**

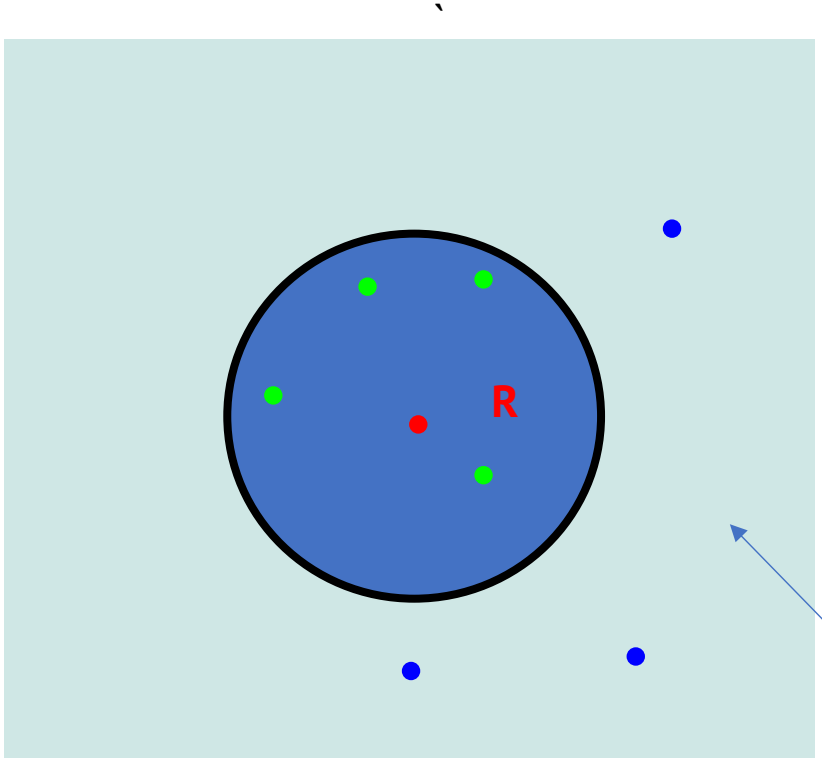
–Decay however relatively fast with the distance:

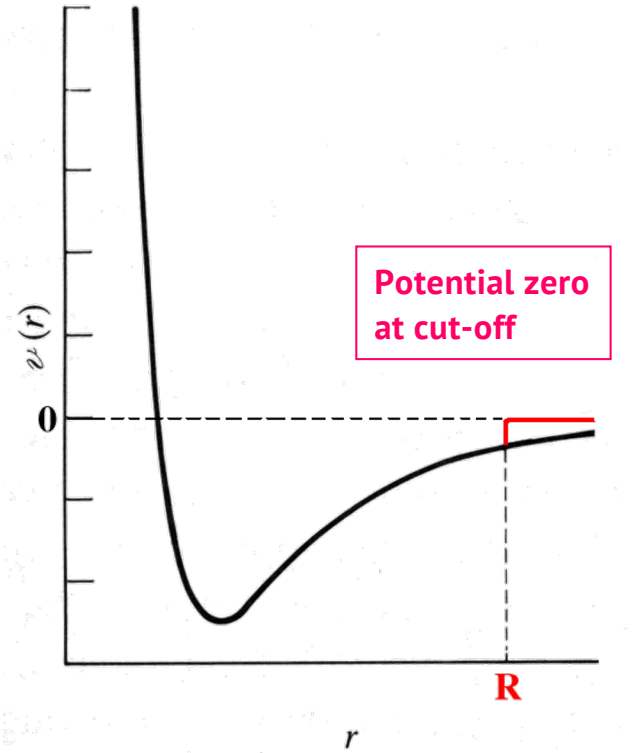
•Lennard-Jones ~ $1/r_{ij}^6$

•Coulomb ~ $1/r_{ij}$

Instead of computing the interactions with all atoms in the system only consider those atoms that are closer than a cut-off distance R_c and reduce thereby the computing time

Treatment of long-range interactions





Particle Mesh Ewald

Reaction field

What governs a MD simulation

- choice of degrees of freedom
- force field parameters
- treatment of non-bonded interactions
- **integration time step**
- **boundary conditions**
- **treatment of temperature and pressure**
- environment (solvation effects, ions and etc)
- starting configuration

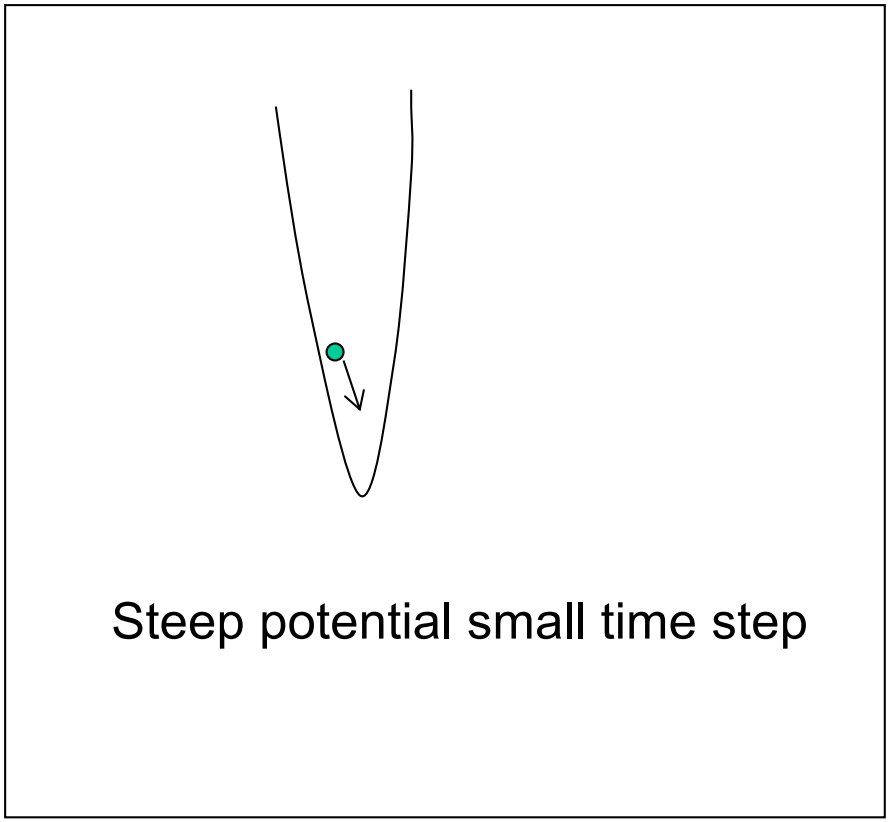
Integration time step

The time step
determines how much time can be simulated.

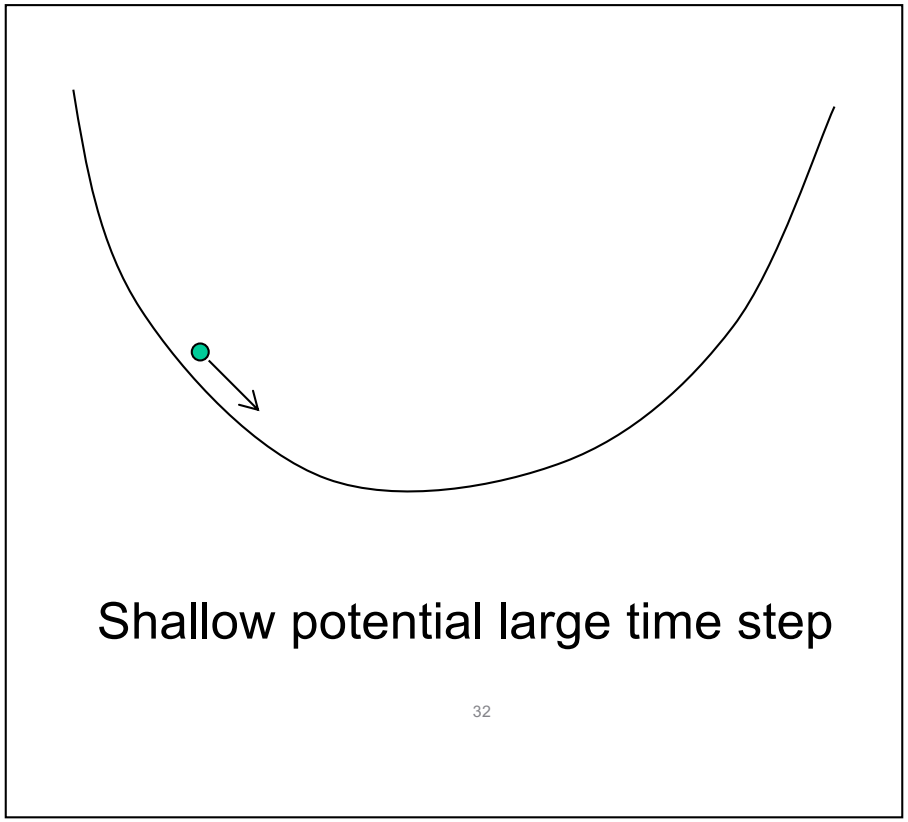
The smaller the time step
 the more expensive the calculation

Choosing the time step

The maximum time step determined by the curvature of the potential



Steep potential small time step



Shallow potential large time step

32

Useful tricks

Δt limited by fast motions - 1fs

=> Remove bond vibrations => 2 fs

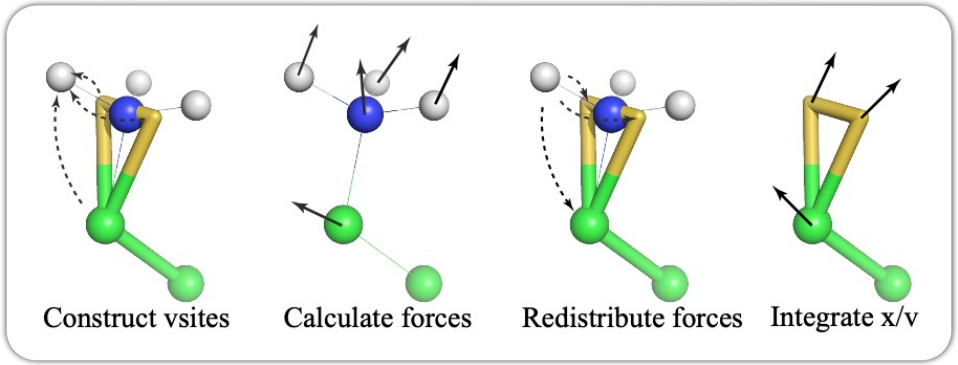
- Constraint algorithms (LINCS, P-LINCS, SHAKE)

- Multi-time step

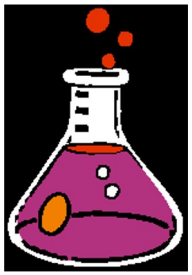
Next fastest motions is H-angle and rotations of CH3/NH2 groups

= > Remove them => upto 5fs

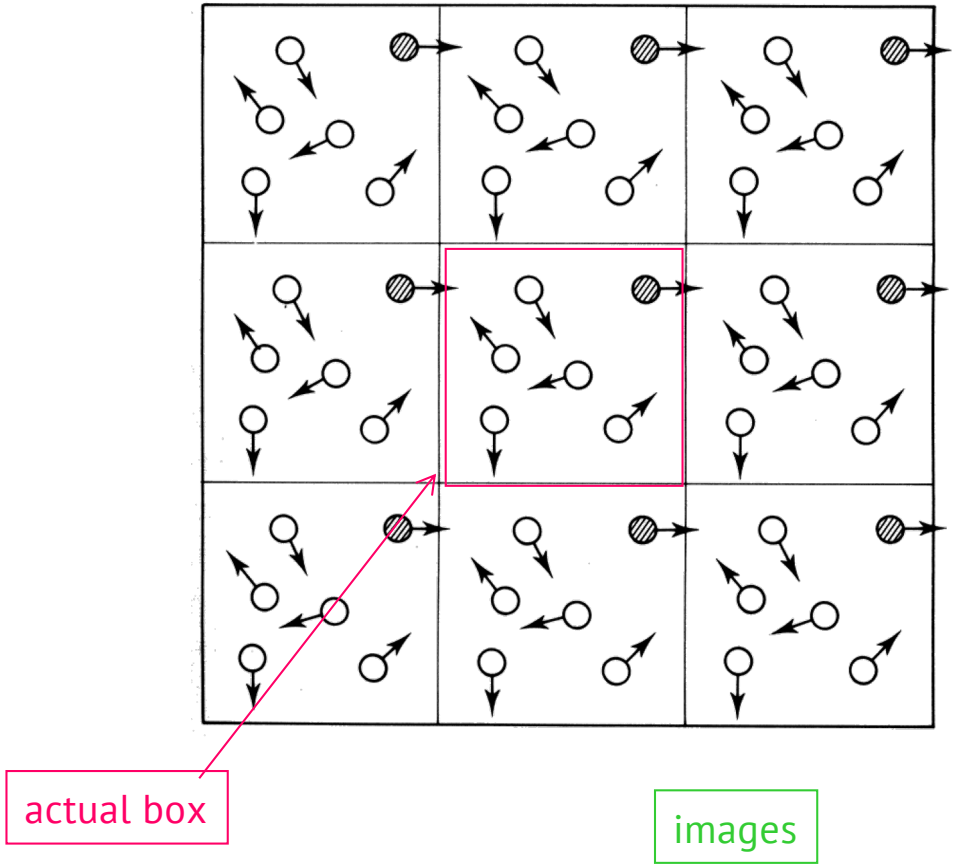
- Virtual interaction sites



Boundary Conditions



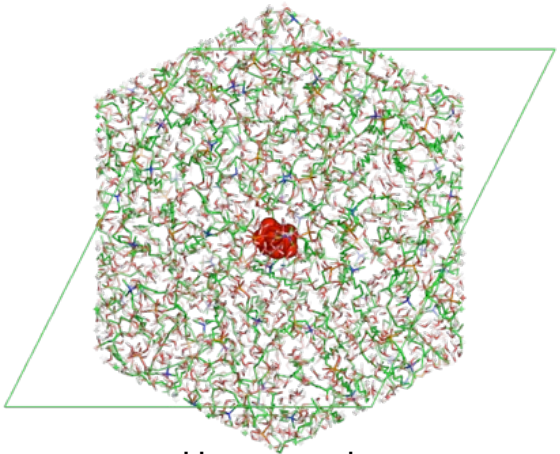
- Simulation box is replicated in all directions
- Particles leaving the central box are reintroduced on the opposite side
- Interactions calculated with particles in neighboring cells
- No vacuum interface anymore!



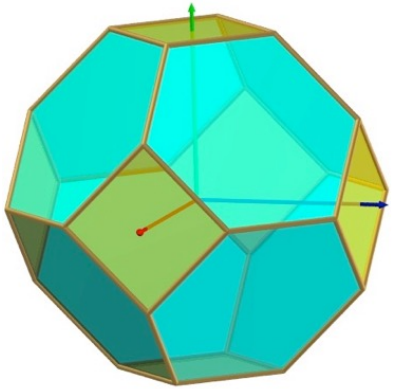
The actual box is surrounded by **26** images of its-self

Common periodic cell shapes

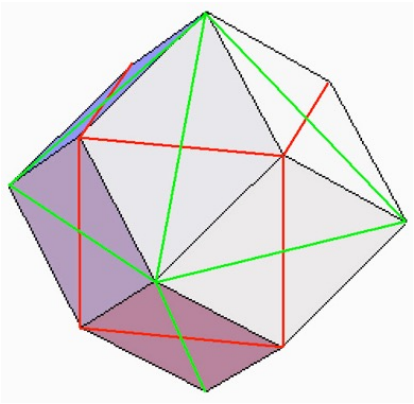
- Cubic / rectangular
- Hexagonal for membrane simulations (volume 87% of cube)
- Truncated octahedron (approximate sphere, volume 77% of a cube)
- Rhombic dodecahedron (most spherical cell, 71%)



Hexagonal



Truncated octahedron



Rhombic dodecahedron

Thermodynamic ensembles

- ***NVE* ensemble**

number of particles *N*, volume *V* and total energy of the system are constant

- ***NVT* ensemble (canonical ensemble)**

number of particles *N*, volume *V* and temperature T of the system are constant

- ***NPT* ensemble**

number of particles *N*, pressure p and temperature T of the system are constant

Temperature in MD simulation

Temperature *T* related to the kinetic energy *K* of the system and therefore to the velocities

$$E_{kin} = \sum_{i=1}^{N} m_i \frac{v_i^2}{2} = \frac{N_{df} k_B T}{2} = \frac{(3N - Nc\ - 3) k_B T}{2}$$

N_{df} is the number of degrees of freedom in the system, N is the number of particles and N_c is the number of constraints on the system

The temperature can thus be controlled by modifying the velocities of particles in the system

Thermostat

The role of a thermostat is to ensure that we have

- the correct average temperature
- fluctuations of the correct size.

Examples of thermostat

Berendsen weak-coupling (Berendsen,1981) -> efficient for relaxing a system to the target temperature but do not correctly reproduce the fluctuations of the kinetic energy.

Velocity-rescaling temperature coupling (Bussi, 2007) -> a Berendsen thermostat with an additional stochastic term that ensures a correct kinetic energy distribution

Nose'-Hoover temperature coupling (Nose', 1984; Hoover, 1985) -> a thermal reservoir and a friction term in the equations of motion is added to system Hamiltonian .

Pressure in MD simulations

The pressure is related to the volume of the system and the interaction between particles

$$P = N_{df} k_b T / V - \frac{1}{3 \mathrm{k}_b V T} \sum_{i=1}^{N} \sum_{j=i+1}^{N} \vec{r}_{ij} \vec{f}_{ij}$$

The second term is the virial describing the contribution due to the forces between the particles and it can easily be calculated in MD when calculating the forces.

Pressure can be controlled by varying the volume of the system and scaling the position of the molecules

Barostat

Pressure coupling can be isotropic, semi-isotropic or anisotropic.

Surface-tension coupling is also possible.

Examples of barostat

Berendsen (Berendsen,1984) -> scales coordinates and box vectors every step

Stochastic cell rescaling (Bernetti, 2020) -> add a stochastic term to Berendsen algorithm

Parrinello-Rahman (Parrinello, 1981; Nose', 1984) -> similar to the Nosé-Hoover temperature coupling

Thermostats & barostats

FAST. FLEXIBLE. FREE. GROMACS

For thermostats and barostats we need to compute the temperature or pressure. This requires global communication and is currently not done on the GPU => expensive

•To reduce these costs, we now set nsttcouple and nstpcouple to 100 by default, unless needed more frequently:

- For v-rescale and c-rescale: ≥ 5 steps per tau_t/p
- For Nose-Hoover and Parrinello-Rahman: ≥ 20 steps per tau_t/p

recommendation, use:

•v-rescale for temperature coupling, with tau_t = 1 ps

•c-rescale for pressure coupling, with tau_p = 5 ps

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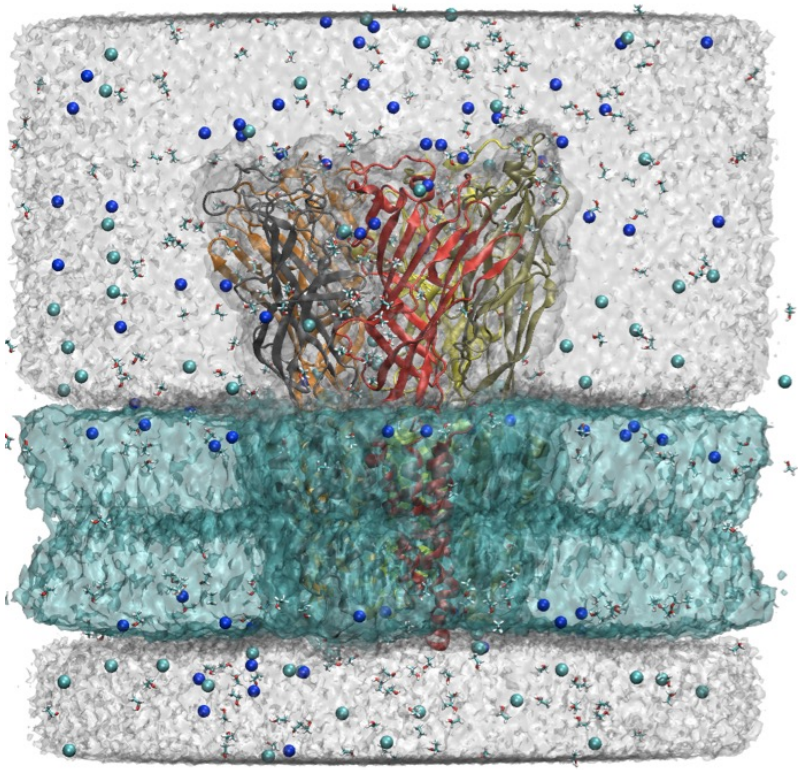
What governs a MD simulation

- choice of degrees of freedom
- force field parameters
- treatment of non-bonded interactions
- **integration time step**
- **boundary conditions**
- **treatment of temperature and pressure**
- environment (solvation effects, ions and etc)
- starting configuration

System setting-up

Environment – Solvent - Ions

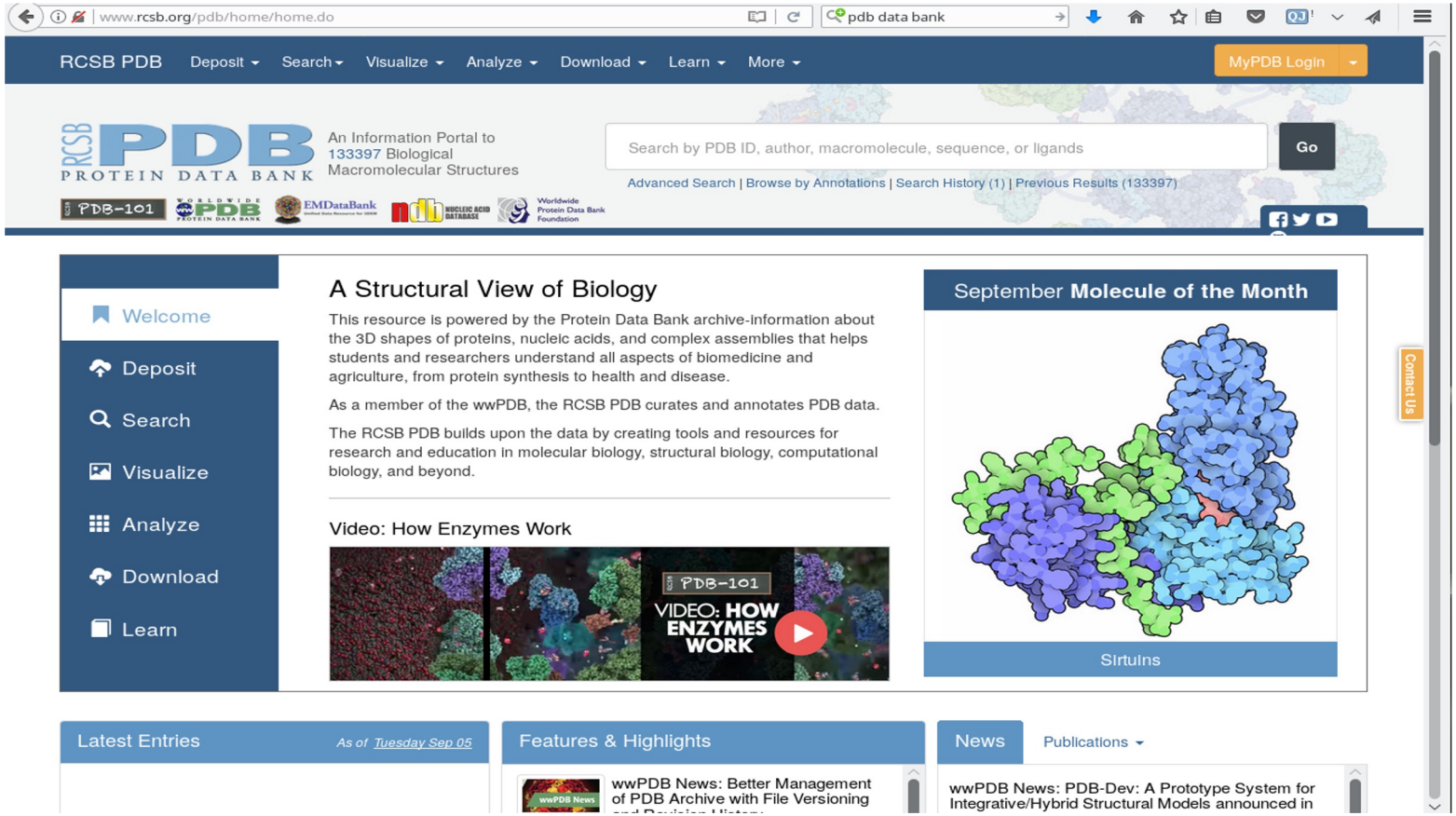


Starting configuration

Initial coordinates

- Experimental structures from database (coming from X-ray crystallography, NMR spectroscopy, cryo-electron microscopy)
- Self-built model three-dimensional structure (e.i homology modelling, docking model, Alpha fold)
- Pre-built solvent box

3-D structures Database



http://www.rcsb.org/

Possible issues

- Not all the atoms are available in the experimental structure (i.e. flexible loops)

- H positions:

- not always experimentally available
- pKa shift due to pocket environment
- account for possible tautomeric states

- Water positions (kinetically trapped water). Water or ion ?

- Extra molecules (i.e. co-factors, ligands, surfactant, etc) or special conditions used to promote the observation of the experimental structure

Initial velocities

The velocities at time t=0 $v_i(0) = \frac{dr_i}{dt}$, i = 1.....$N_{particles}$

Usually the velocities are taken from random (Maxwell) distribution with the kinetic energy corresponding to desired temperature (T)

$$E_{kin} = \sum_{i=1}^{N} m_i \frac{v_i^2}{2} = \frac{N_{df} k_B T}{2}$$

Molecular Dynamics Simulations and

www.gromacs.org

What is the name of the bird in GROMACS logo?

Simulation options

- Simulated annealing
- Walls
- COM pulling
- AWH adaptive biasing
- Enforced rotation
- Free energy calculations
- Expanded ensemble calculations
- Non-equilibrium MD
- Electric fields
- Computational Electrophysiology
- Density-guided simulations
- QM/MM simulations with CP2K interface

In the future

- pH simulations

https://manual.gromacs.org/current/user-guide/mdp-options.html

Restraints and simulations

Here special potentials are used for imposing restraints on the motion of the system

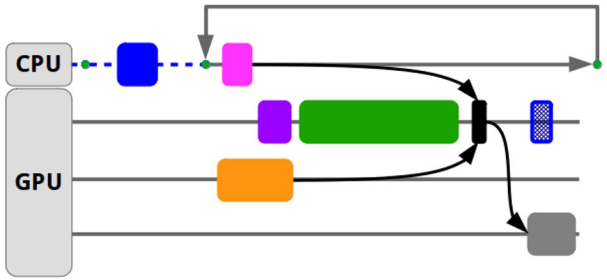
Type of restraints :

- **Position** restraints
- **Flat-bottomed position** restraints: sphere, cylinder, layer
- **Angle and dihedral** restraints
- **Distance restraints**: simple harmonic, piecewise linear/harmonic, complex NMR distance
- **Orientation** restraints

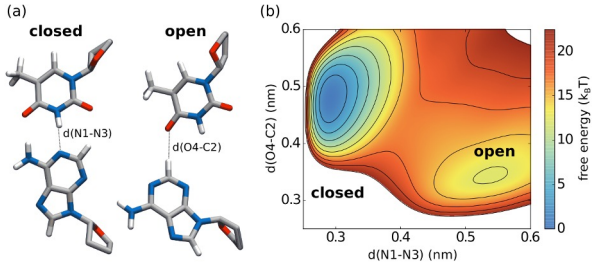
The tool gmx genrestr may be useful here

Highlights

[Heterogeneous parallelization and GPU acceleration]

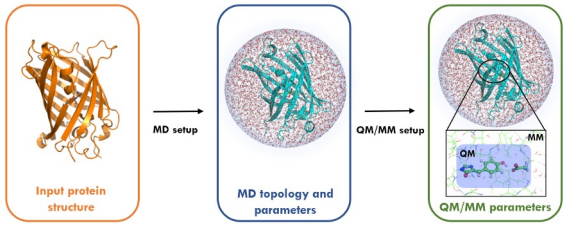


[Accelerating sampling with the AWH method]

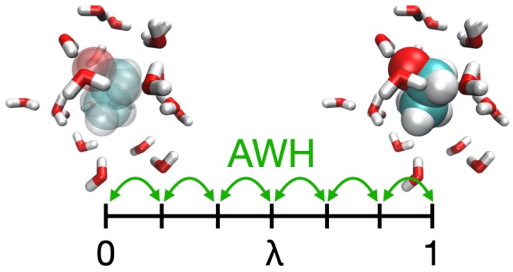


[gmxapi Python interface for GROMACS]

[Hybrid Quantum-Classical simulations (QM/MM) with CP2K interface]



[Applying the Accelerated Weight Histogram method to alchemical transformations]



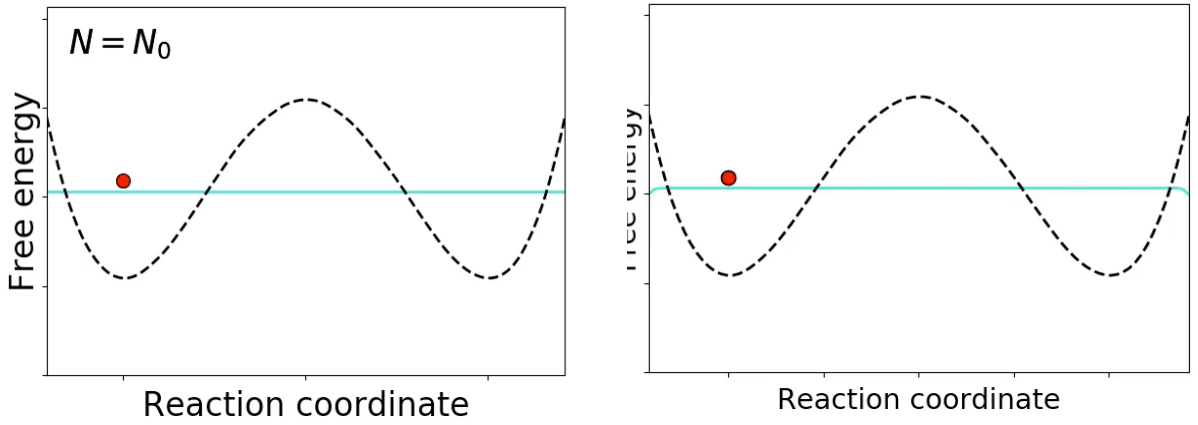
[Ions in Action! Studying ion channels by Computational Electrophysiology]

https://www.gromacs.org/highlights.html

Accelerated Weight Histogram method

an efficient and easy to use adaptive biasing method for sampling reaction coordinates

- Trick: add a bias potential to make the effective potential flat
- AWH can give exponential acceleration of barrier crossings
- Only one, uncritical parameter to set and we can also use multiple walkers
- Can act on pull reaction coordinates and the alchemical lambda

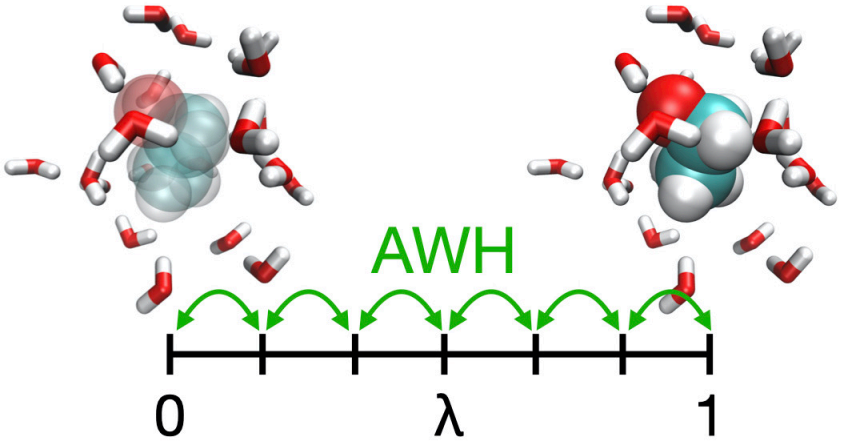


https://tutorials.gromacs.org/awh-tutorial.html

Webinar: Accelerating sampling in GROMACS with the AWH method (2019-09-24)

Accelerated Weight Histogram method alchemical transformations

lambda is varied dynamically in a single simulation, and the free energy difference can be obtained directly



https://tutorials.gromacs.org/awh-free-energy-of-solvation.html

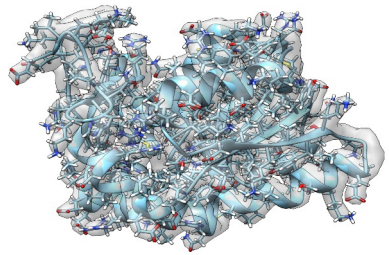
[Webinar Applying the Accelerated Weight Histogram method to alchemical transformations]

Density-guided simulations

Here additional forces are applied to atoms that depend on the gradient of similarity between a simulated density and a reference density.

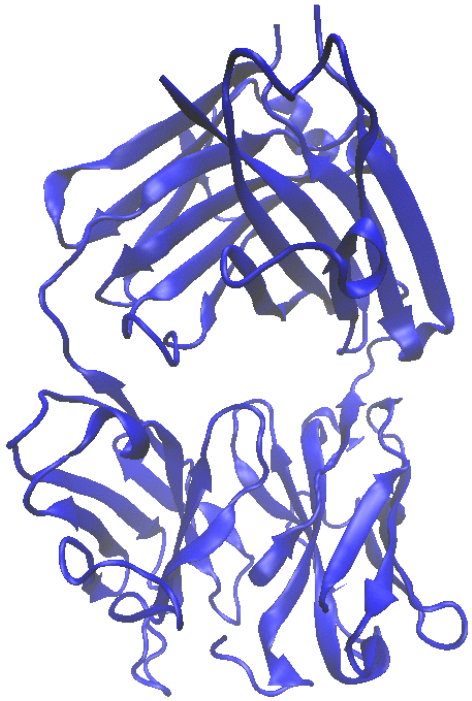
Steps:

- set up a standard molecular dynamics simulation
- have a reference density (.mrc or .ccp4 file) in working_dir and put the name in the mdp file
- add density-guided simulations parameter **to mdp file**
- perform the simulation



Webinar: Density guided simulations – combining cryo-EM data and molecular dynamics simulation
https://bioexcel.eu/webinar-density-guided-simulations-combining-cryo-em-data-and-molecular-dynamics-simulation-2020-04-28/

Visualization and Analysis



Most used GROMACS analysis tools:

gmx energy – to process energy

gmx trjconv – to convert trj files

gmx select / gmx make_ndx – for selection

gmx rms

gmx cluster

gmx distance/gmx mindist /gmx pairdist

for trajectory analysis

Example of visualization software:

VMD http://www.ks.uiuc.edu/Research/vmd/

Rasmol http://www.openrasmol.org/

Pymol http://www.pymol.org/

Chimera https://www.cgl.ucsf.edu/chimera/

All GROMACS commands are command-line and require an option before any arguments.

Use option –h to show help

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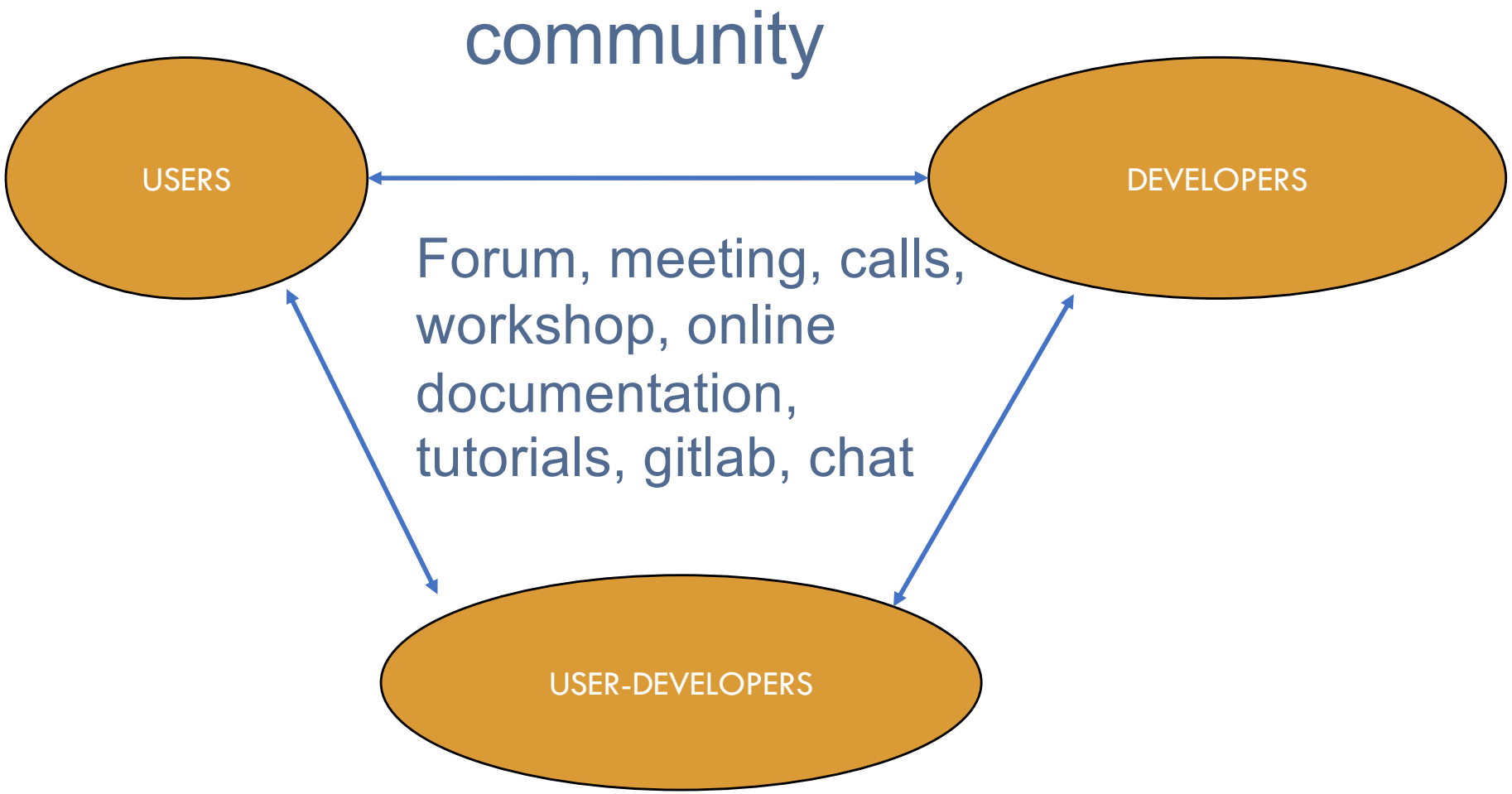

User information and communication channel

GROMACS documentation -> https://manual.gromacs.org/

GROMACS forum -> https://gromacs.bioexcel.eu/

GROMACS tutorials -> https://tutorials.gromacs.org/

GROMACS webpage -> http://www.gromacs.org/

GROMACS GitLab -> https://gitlab.com/gromacs

BioExcel Survey -> https//bioexcel.eu

Developer communication

- Developer forum -> gromacs.bioexcel.eu :
- Bi-weekly video meeting (see developer forum)
- Quaternary meeting
- Slack channel -> https://gromacs.slack.com
- File and follow issues on GitLab
  - also for users, if you think you found a bug you can file an issue (see https://www.gromacs.org)
- Workshops: e.i "learn to code in GROMACS"

Forum: gromacs.bioexcel.eu

Here you can

- ask questions on the usage and installation,
- follow GROMACS announcements,
- discuss your ideas and intentions related to the GROAMCS development,
- share third party tools and files useful the GROMACS community,
- help the developer to understand which feature/tool is used or un-used -> via polls

- look for a new position

What's new in 2023?

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No major new functionality

Lots of performance improvements:

- Update now run by default on the GPU
  => can give 10-20% performance improvement
- Pairlist construction frequency decoupled from other things
- nsttcouple and nstpcouple are now 100 by default

=> improves parallel and GPU performance

- SYCL support has been extended
- Support for CUDA graphs (experimental)
- Support for PME using multiple GPUs

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Note: GROMACS versions are always defined by two numbers:
Year.Release => version 2023.2 2022.6

Molecular simulation: Input files

Information on the positions (and velocities) of the atoms

structure file (*pdb *gro)

Information about the molecular model

topology file (*top *itp)

Information on how we want to run the simulation

molecular dynamics parameter file (*mdp)

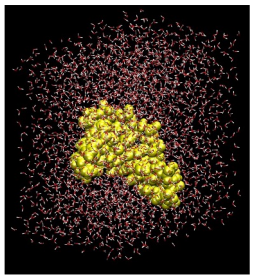
Molecular simulation in GROMACS

Input files

Structure
(*.gro, *.pdb)

Simulation parameter
(*.mdp)

Topology (*.top)



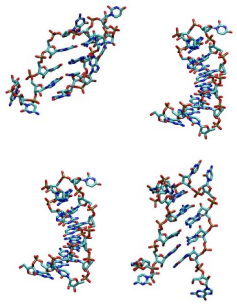
gmx grompp

*.tpr file

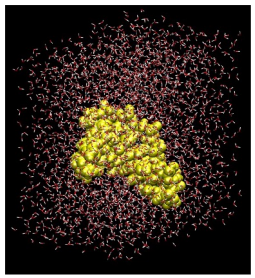
gmx mdrun

Output files

Ensemble of structures, called configurations:
.xtc/.trr -> trajectory,
*.edr -> energy file,
*.log -> log file



Simulation step



Energy minimization

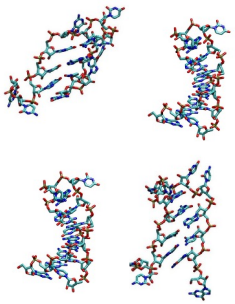
*.mdp

*.mdp

Solvent and ion relaxation, system equilibration

*.mdp

Data production



Ensemble of structures (called configurations)

thermodynamic properties

structural properties

kinetic properties

dynamic information

For each step a dedicated simulation parameter file (*mdp) has to be created

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GROMACS

Authors/Contributors

These people have contributed to the 2023 release of GROMACS:

Mark Abraham; Andrey Alekseenko; Cathrine Bergh; Christian Blau; Eliane Briand; Mahesh Doijade; Stefan Fleischmann; Vytautas Gapsys; Gaurav Garg; Sergey Gorelov; Gilles Gouaillardet; Alan Gray; M. Eric Irrgang; Farzaneh Jalalypour; Joe Jordan; Christoph Junghans; Prashanth Kanduri; Sebastian Keller; Carsten Kutzner; Justin A. Lemkul; Magnus Lundborg; Pascal Merz; Vedran Miletić; Dmitry Morozov; Szilárd Páll; Roland Schulz; Michael Shirts; Alexey Shvetsov; Bálint Soproni; David van der Spoel; Philip Turner; Carsten Uphoff; Alessandra Villa; Sebastian Wingbermühle; Artem Zhmurov; Paul Bauer; Berk Hess; Erik Lindahl

Thank you

In future for any questions on

go to

GROMACS forum:
gromacs.bioexcel.eu

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