# MD Simulations in a nutshell

## Theory and applications

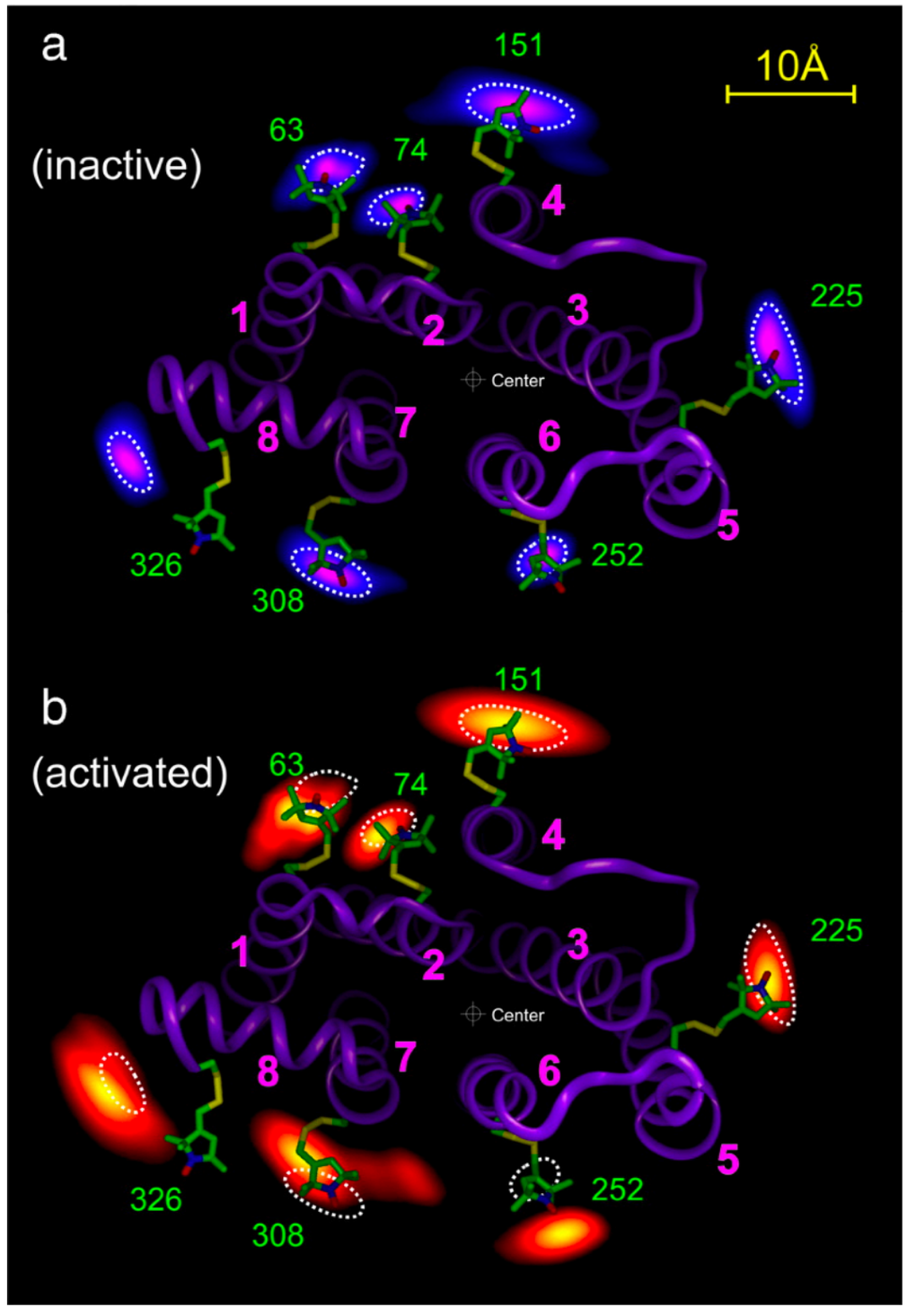
# MD simulations and other methods

## Methods to measure the ‚dynamics‘

- NMR
- Labelling: EPR, DEER
- Labelling: single molecule FRET
- Raman, IR spectroscopy
- X-ray

- MD: provides the time resolved motion of atoms at atomic resolution

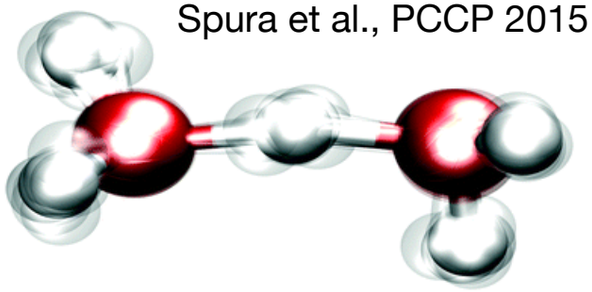
Probable locations of the nitroxide spins

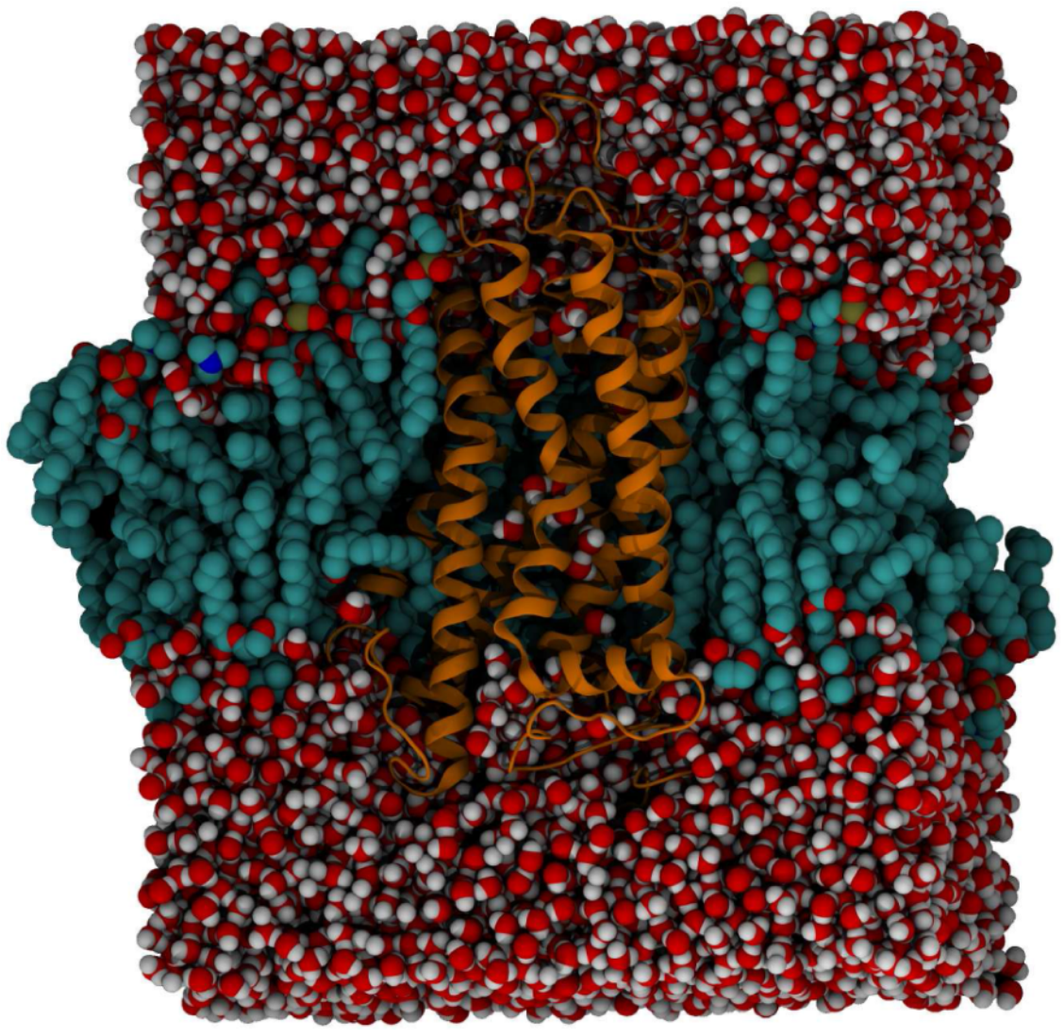



Altenbach et al., PNAS, 2008

# MD simulations: what is it good for?

Spura et al., PCCP 2015





- **replace experiments:**
  e.g. coupled clusters (only < 15 atoms) more accurate than experiments!

- **explain experiments**:
  EPR, NMR, mutations, …

- **drive experiments:**
  by proposing hypothesis

- Generally promotes **interdisciplinary research**

# MD simulations: pro and contra

\+ time resolved physical movements of atoms and molecules

\+ the dynamic evolution of the system —> ‚trajectory‘

\+ study the motions of biological macromolecules

\- Only potential energy is optimized, not the free energy

\- entropic contributions to thermodynamic stability neglected

\- Only crude approximation of electrostatics in all atom force field

# How to calculate interaction energies?

**Calculate to what path a given physical system will take over time:**

Quantum Mechanics (describes physical laws of nature on *an atomic scale*)

**Schrödinger**'s equation: $\mathrm{H}\,\Psi = \mathrm{E}\,\Psi$ (time independent)

$\mathrm{H}$ = Hamiltonian (corresponds to total systems energy)
$\mathrm{E}$ = Energy Eigenvalue
$\Psi$ = wavefunction

Classical Mechanics (describes motion of *macroscopic objects*):

**Newton**‘s second law of motion:

$$\mathbf{F} = m\mathbf{a}$$

**F** = force
**m** = mass
**a** = acceleration

# MD Simulations in a nutshell

**Often used methods**

**Empirical** → ***ab initio***

Molecular Dynamics (**MD**)

- Force fields

Quantum Mechanics (**QM**)

- Semi empirical methods
- Density Functional Theory (DFT)
- Coupled Cluster

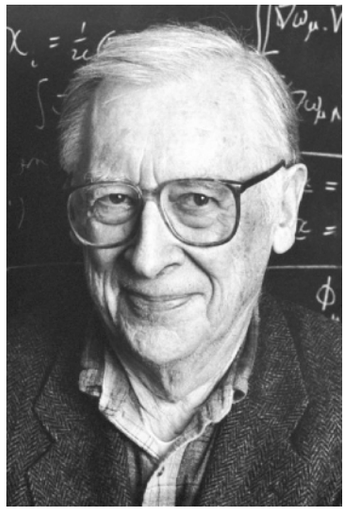
Computationally intensive →

← System size

| Number of atoms: | 1.000.000 | 2000 | 500 | 15 |
|---|---|---|---|---|

# MD is established

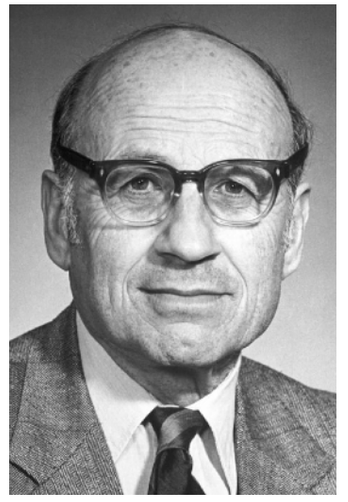
Chemistry 1998

John Pople

-John Pople "for his development of **computational methods in quantum chemistry**"

- Walther Kohn "for his development of the **density-functional theory**"



Walther Kohn

"for the development of **multiscale models for complex chemical systems**"

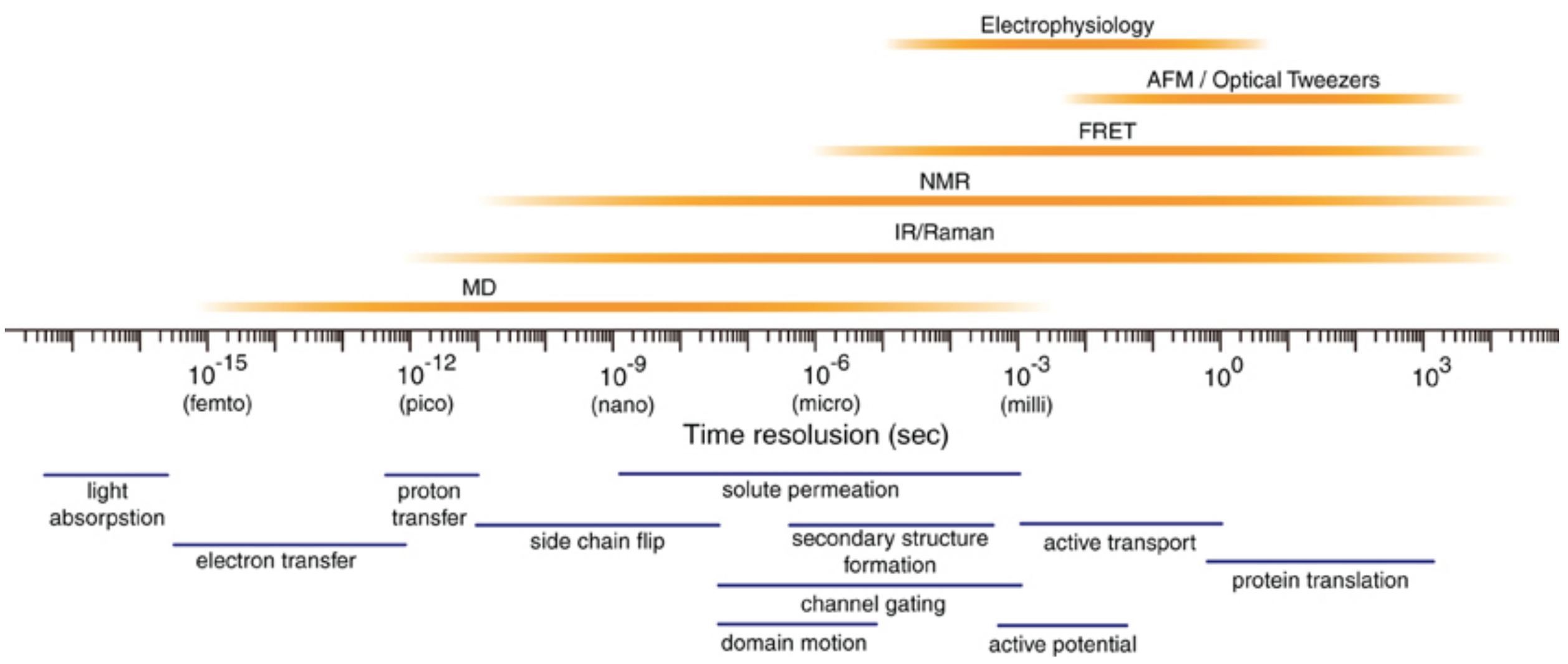
Chemistry 2013


Martin Karplus

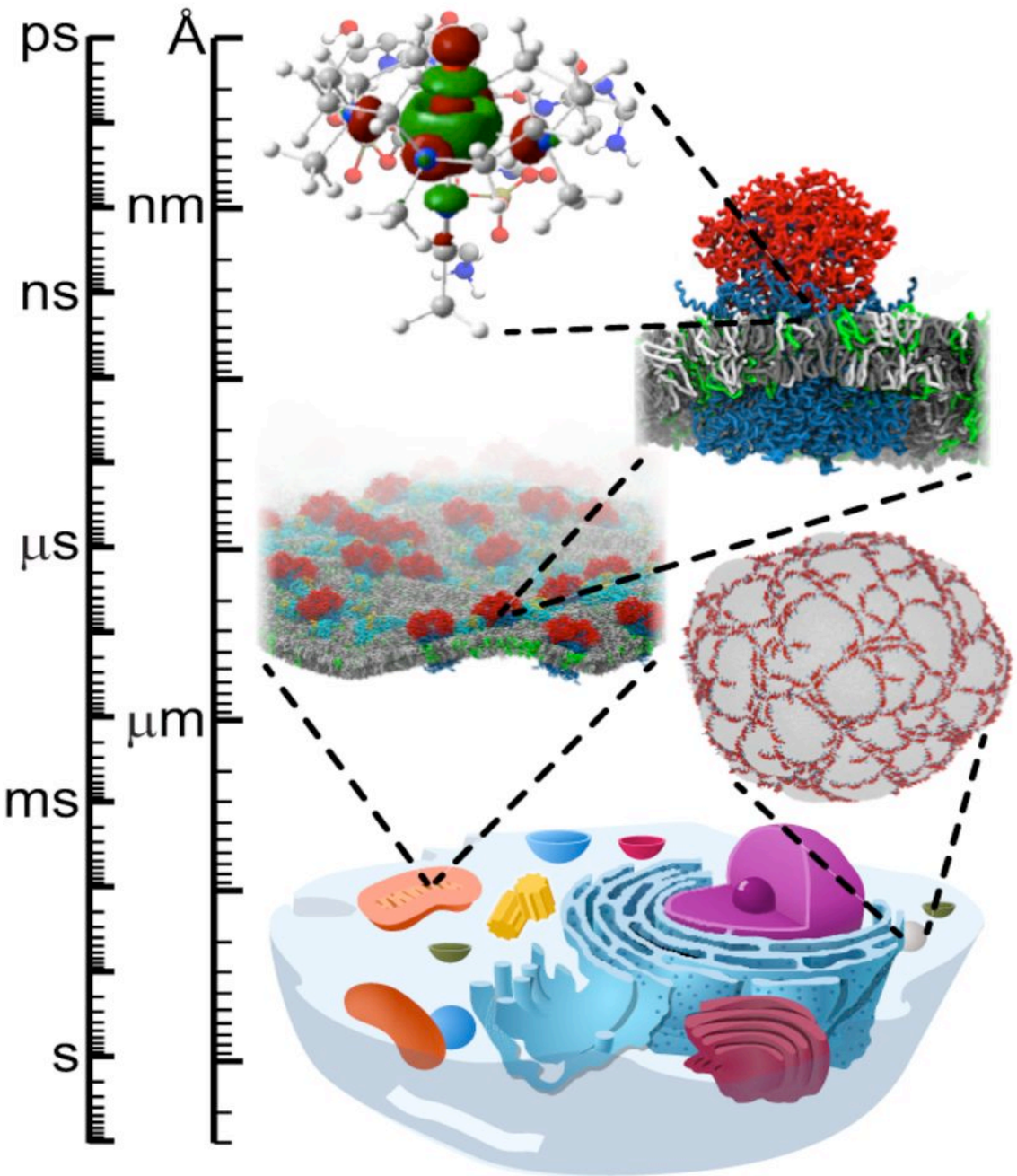
Michael Levitt

Arieh Warshel

# MD simulations: Timescales



# types of MD simulations




**Quantum**
- atoms, electrons and electron clouds included
- explicit solvent
- quantum mechanics

**All-atom**
- all or most atoms present
- explicit solvent
- molecular dynamics

**Coarse-grained**
- beads comprising a few atoms
- explicit or implicit solvent
- molecular dynamics

**Supra-coarse-grained**
- interaction sites comprising many atoms, protein parts or proteins
- implicit solvent
- stochastic dynamics

**Continuum**
- materials as a continuous mass
- implicit solvent
- continuum mechanics

Computational ‘microscopy’ of cellular membranes Helgi I. Ingólfsson, Clément Arnarez, Xavier Periole, Siewert J. Marrink Journal of Cell Science 2016 129: 257-268; doi: 10.1242/jcs.176040

# MD Simulations in a nutshell

**Methods/Force Fields/Packages**

- Molecular Mechanics: empirical force fields: AMBER, OPLS, CHARMM, GROMOS, ...

- Molekular Dynamics Packages (classical Newton-mechanics: GROMACS, NAMD…)

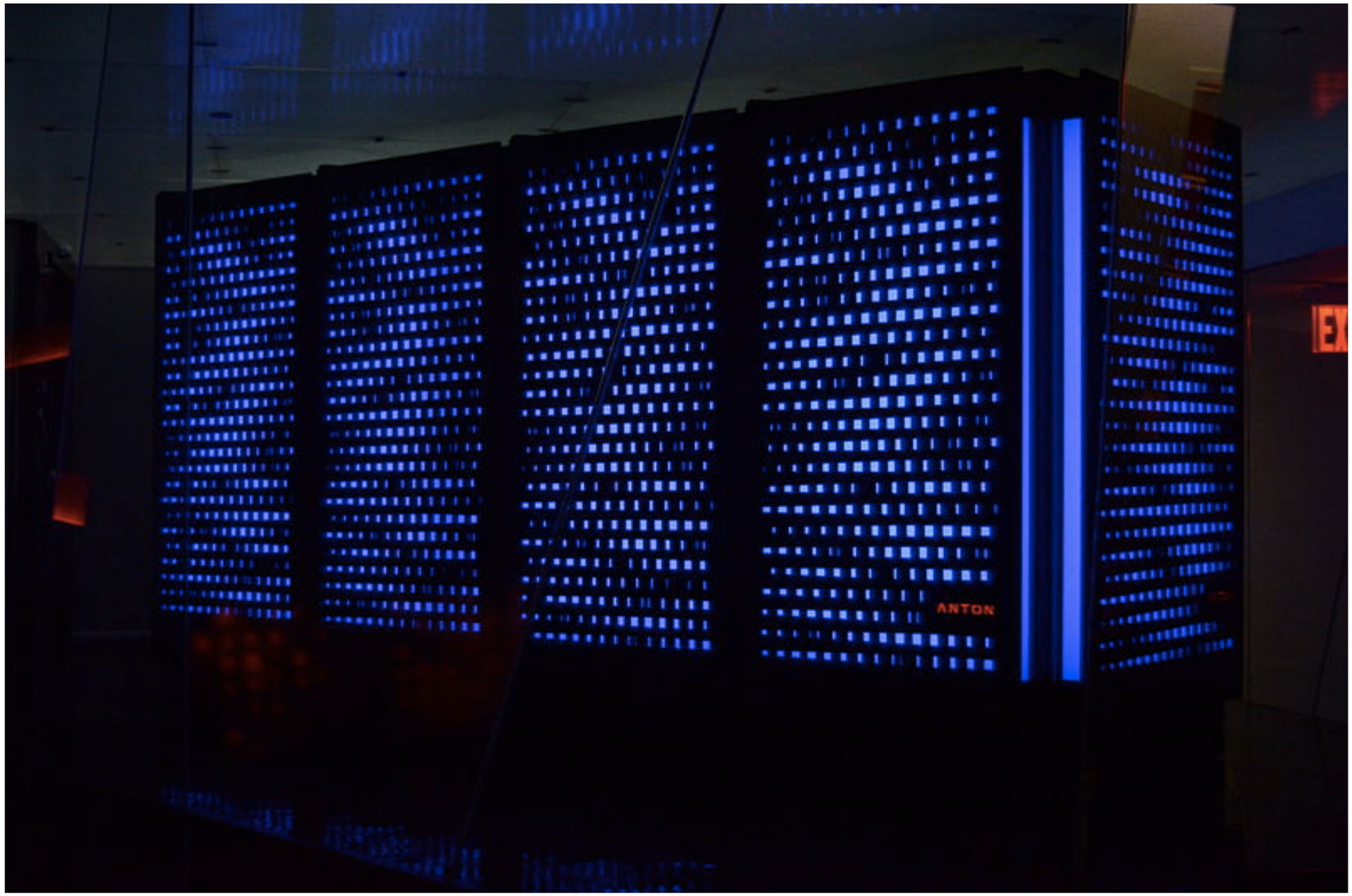
- Semi-empirical Molecular-Orbital-Theorie (MNDO, AM1, PM3, OM2, MNDO/d, …)

- DFT (B3LYP, PW91, BP86, LDA…)

- *ab Initio* Molecular-Orbital-Theorie (Hartree-Fock, Møller-Plesset, Coupled Cluster …)

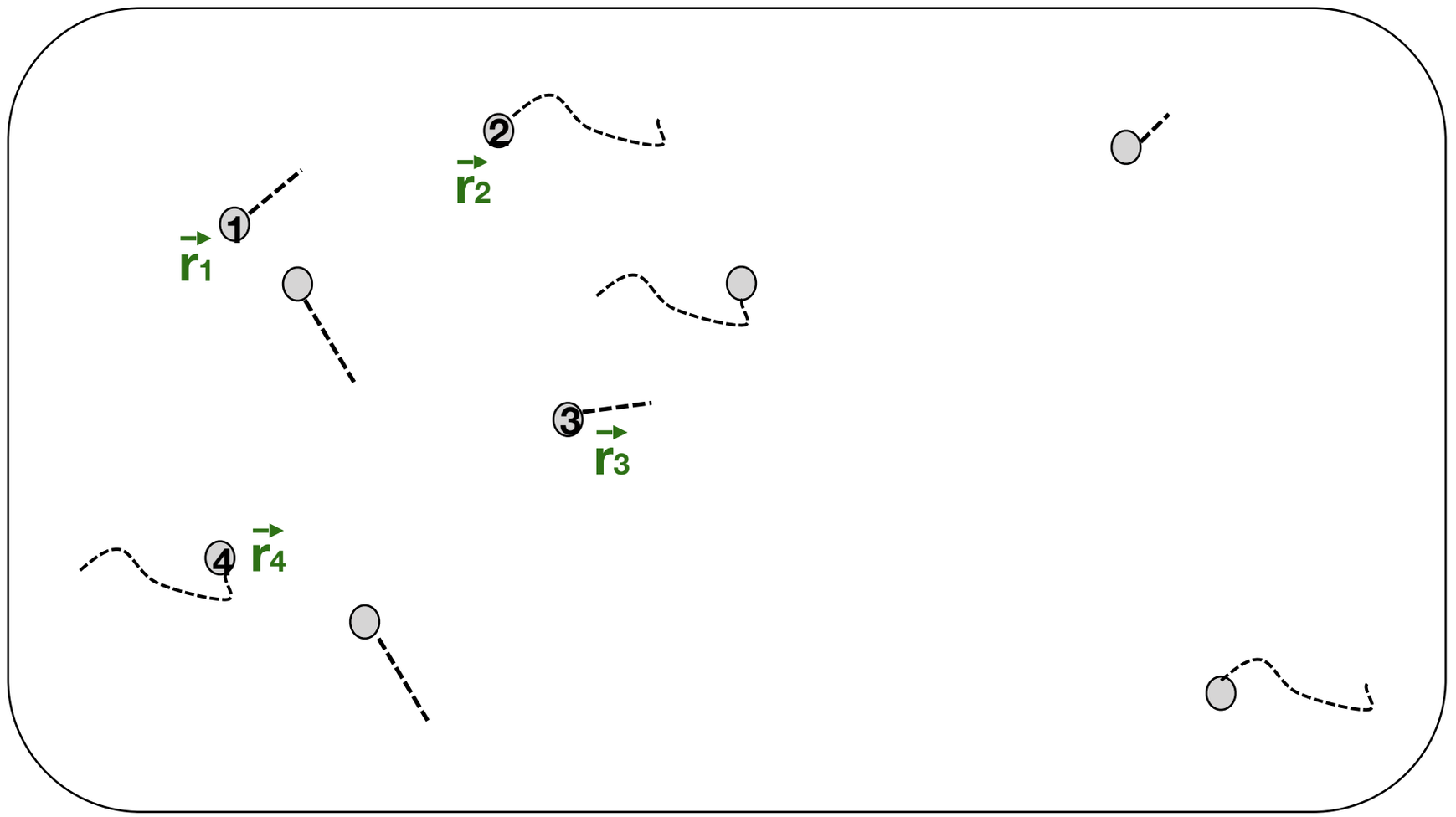
# MD simulations: high computing resources

Anton at DE SHAW



# goal: predict motion of atoms

**many-body system**

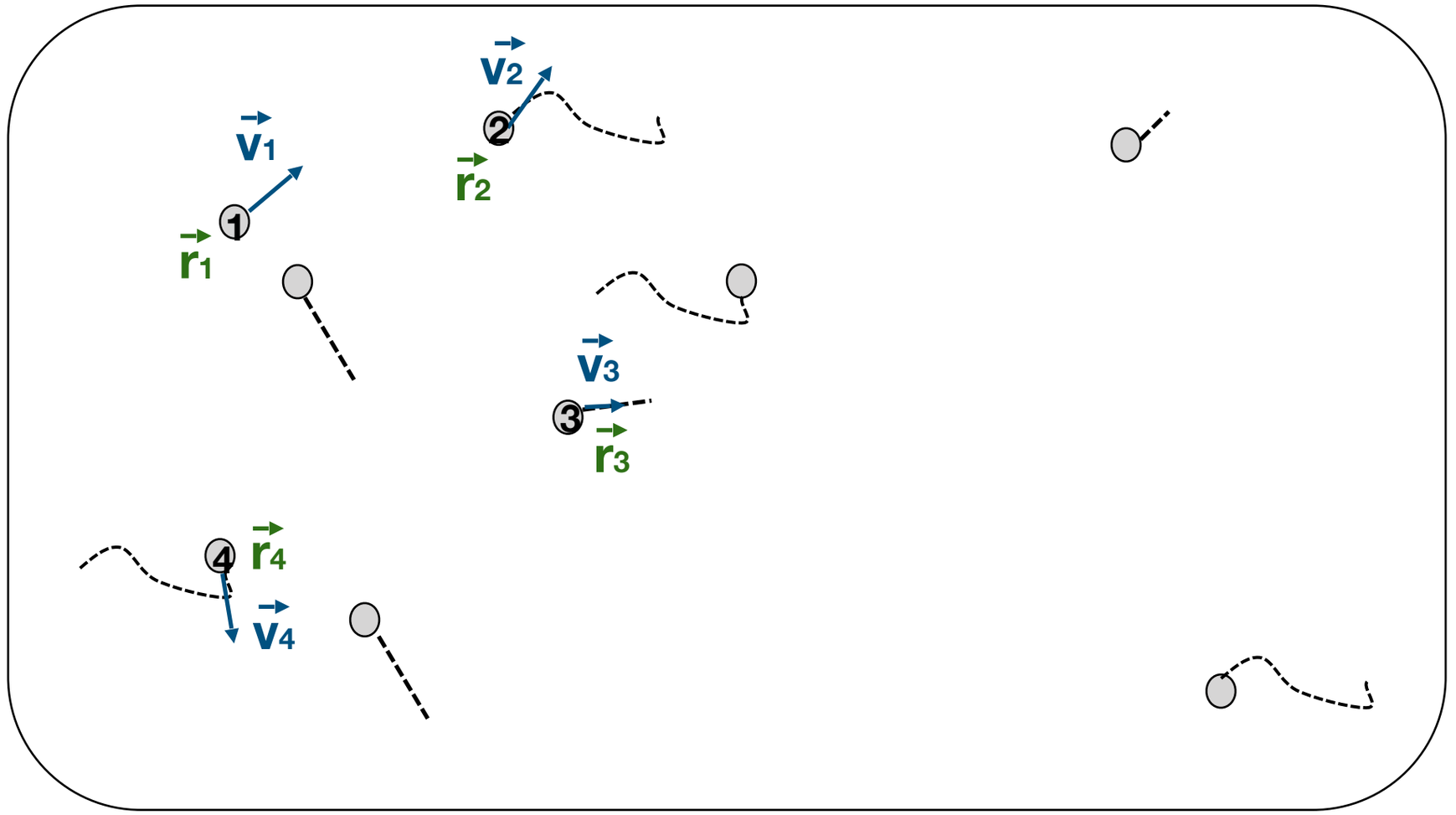



- Atom

- motion

$\vec{r}_{1\text{-}n}$ - Initial position

# goal: predict motion of atoms




- Atom

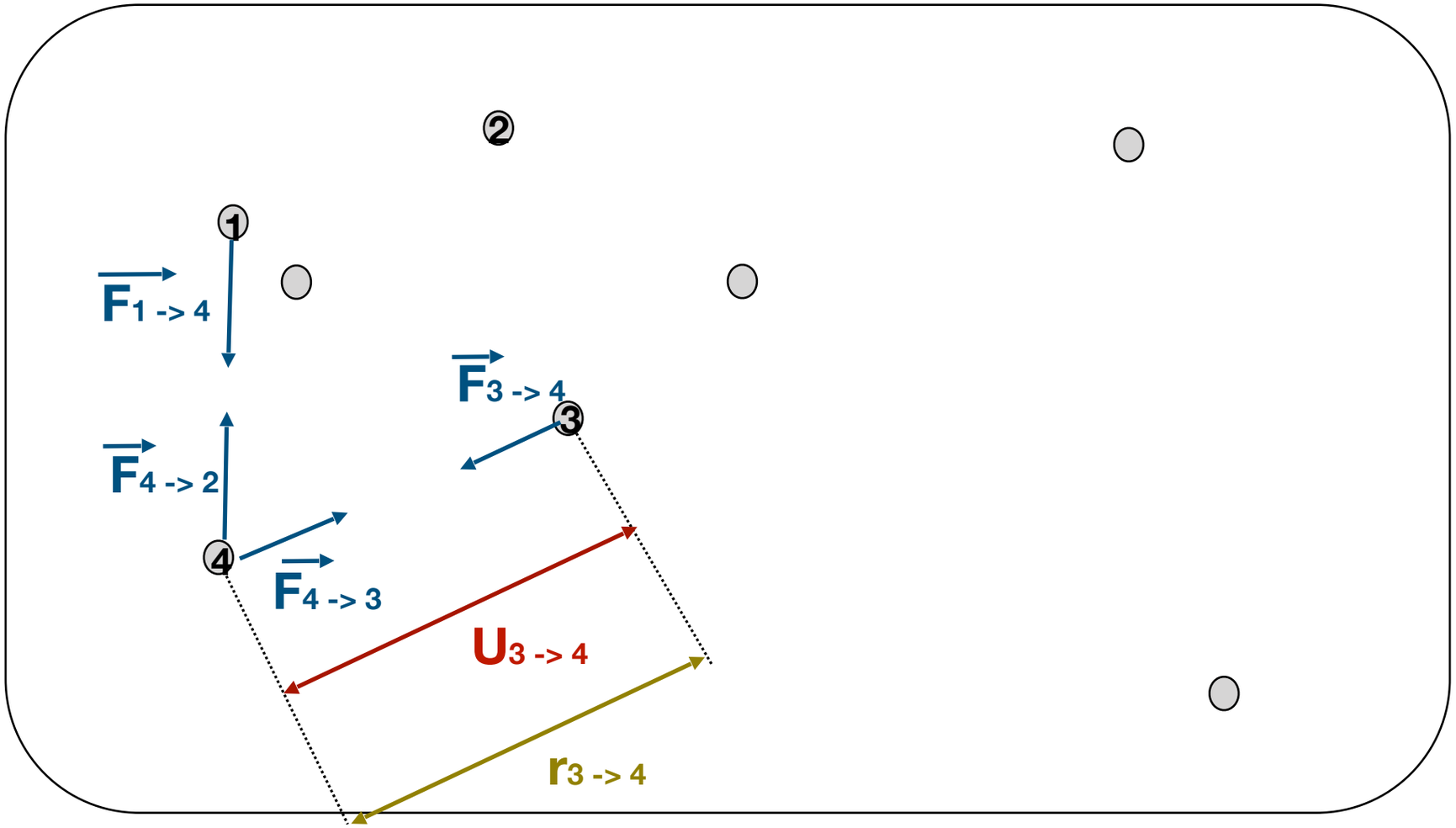
- motion

$\vec{r}_{1\text{-}n}$ - Initial position

$\vec{v}_{1\text{-}n}$ - Initial velocity

# We have to calculate interaction energies

Interaction energies are approximated be the potential energy **U**



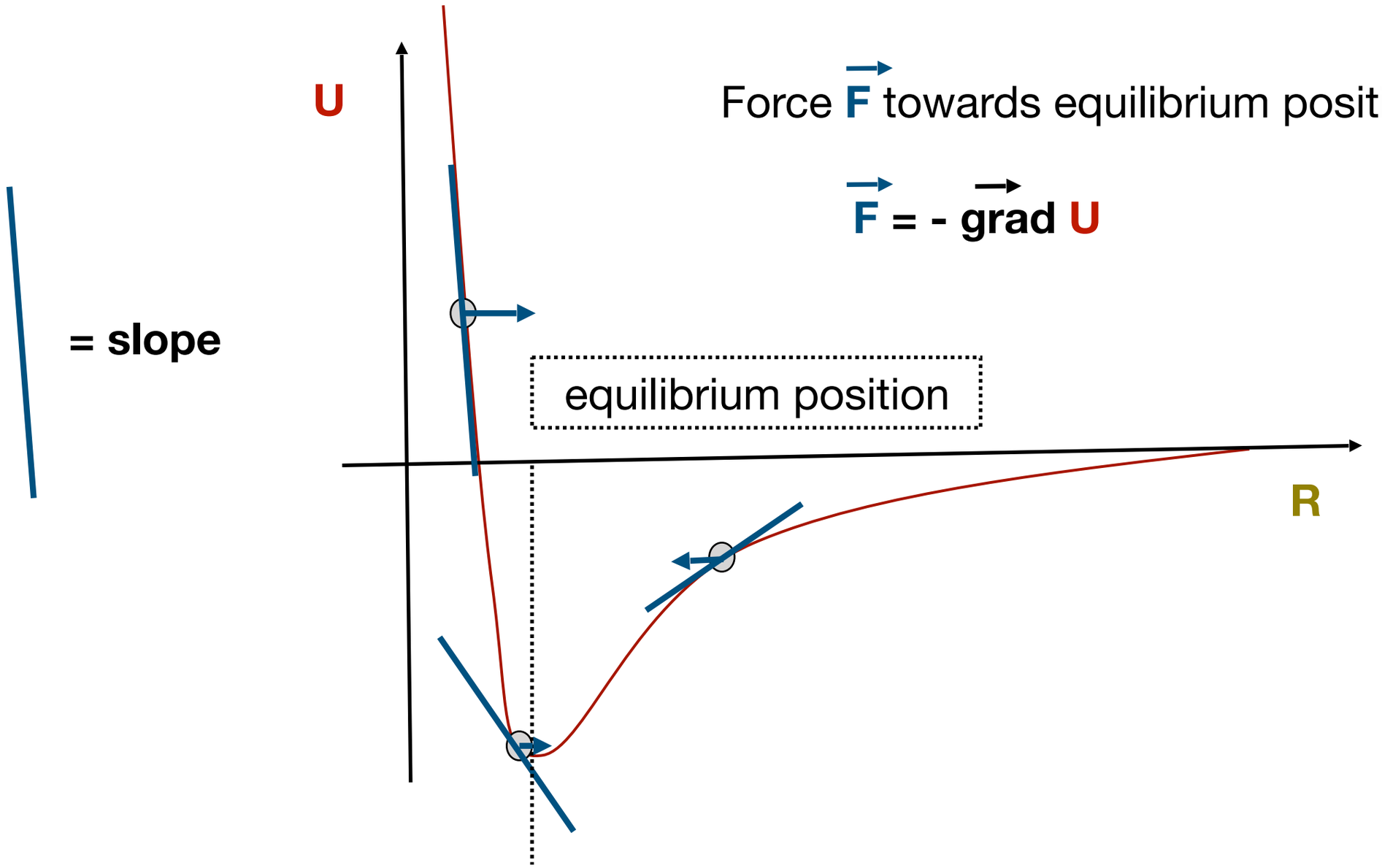

$\vec{F}$ - Force of atom

**U** - potential energy

**r** - distance between atoms

# How to calculate interaction energies?

Approximate the force $\vec{F}$ from the potential Energy **U**

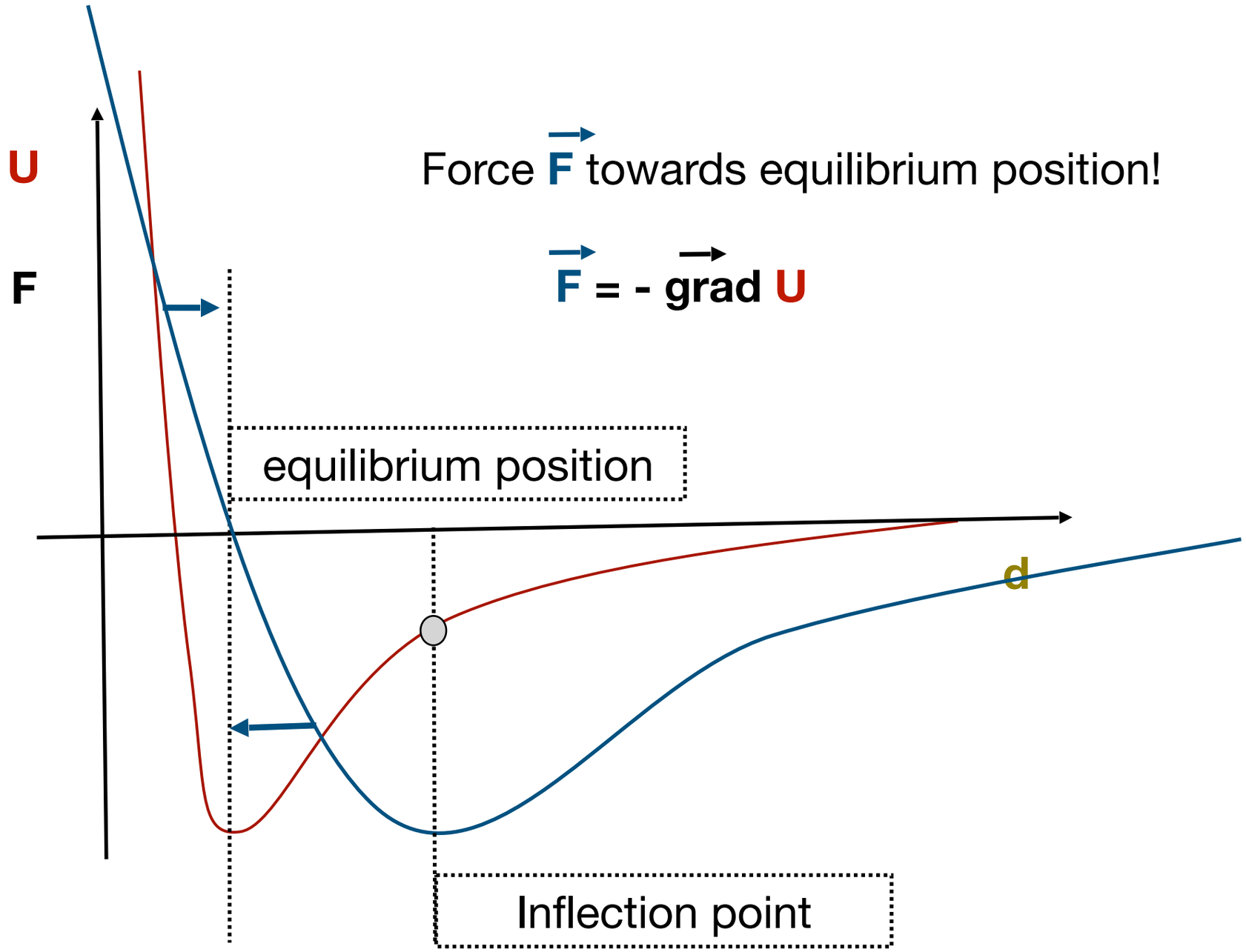



Force $\vec{F}$ towards equilibrium position!

$$\vec{F} = -\,\vec{\text{grad}}\ U$$

# How to calculate interaction energies?

Approximate the force $\vec{F}$ from the potential Energy **U**

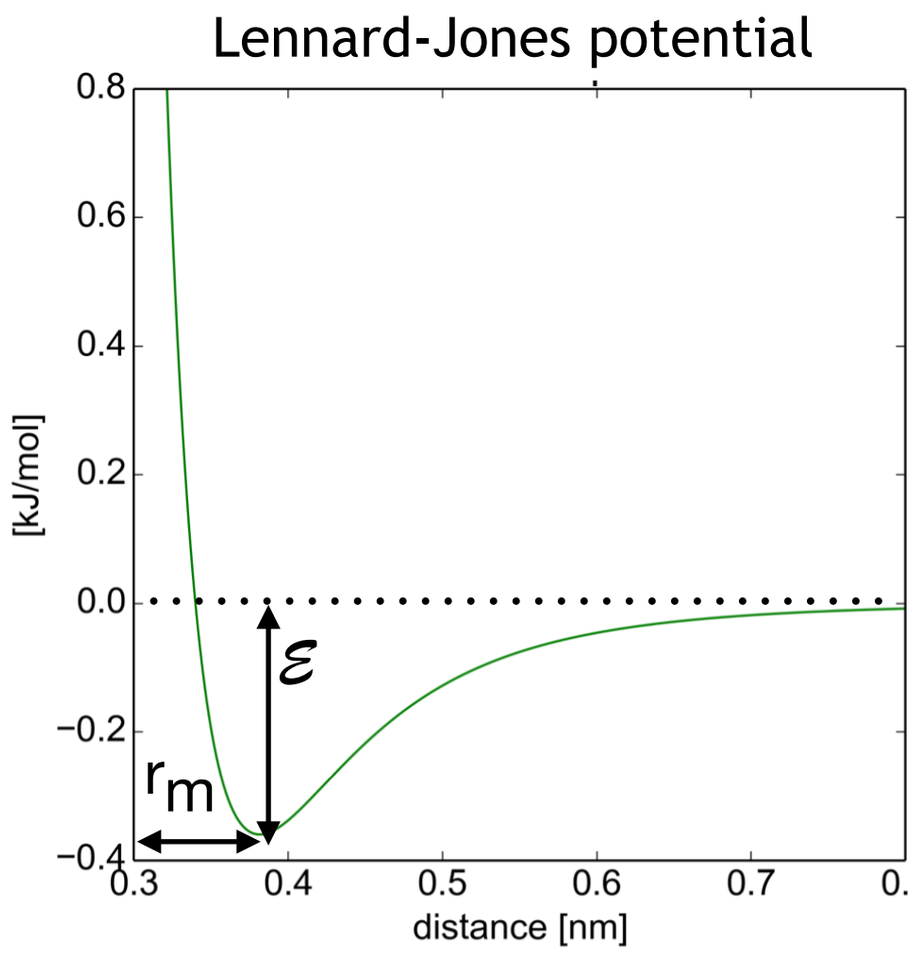



Force $\vec{F}$ towards equilibrium position!

$$\vec{F} = -\,\vec{\text{grad}}\ U$$

# Non-bonded interactions

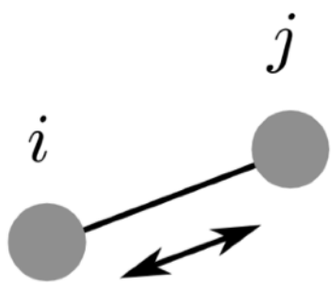
Interaction potential energies approximated by



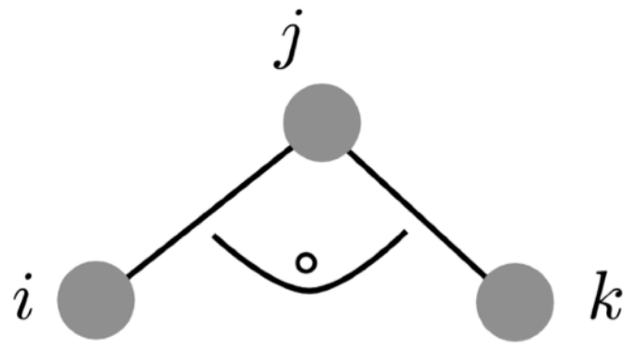

$$U_{vdw} = \sum_{i<j}^{atoms} \varepsilon_{ij} \left[ \left( \frac{r_m}{r_{ij}} \right)^{12} - 2 \left( \frac{r_m}{r_{ij}} \right)^{6} \right]$$

# Bonded interactions

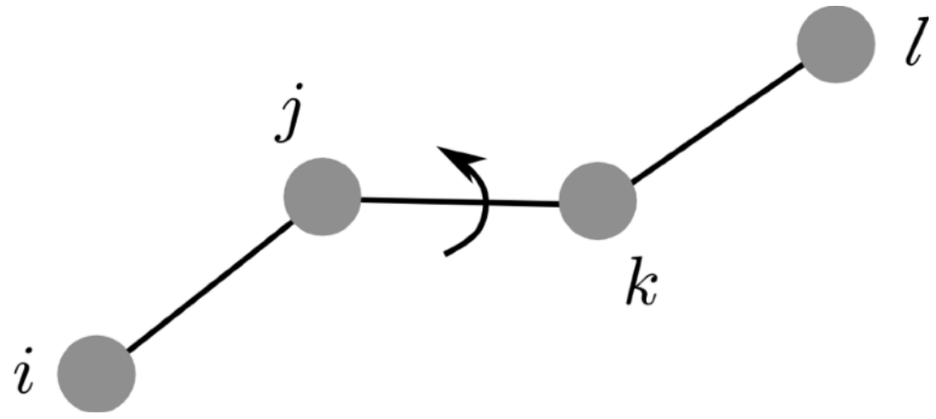
Bond lengths




Bond angles




Torsion angles




$$U_{angles} = \sum_{angles} K_\theta (\theta - \theta_{eq})^2$$

$$U_{Bonds} = \sum_{bonds} K_r (r - r_{eq})^2$$

$$U_{dihedrals} = \sum_{dihedrals} K_\phi (1 + \cos[n\phi - \gamma])^2$$

Allen, NIC 2004

# Complete term of potential energy U

bonded

$$U(r^N) = \left( \left( \sum_{bonds} K_r (r - req)^2 \right) + \left( \sum_{angles} K_\theta (\theta - \theta_{eq})^2 \right) + \left( \sum_{dihedrals} K_\phi (1 + \cos[n\phi - \gamma])^2 \right) \right) +$$

$$\sum_{i=1}^{N} \sum_{j=i+1}^{N} \varepsilon_{ij} \left[ \left( \frac{r_m}{r_{ij}} \right)^{12} - 2 \left( \frac{r_m}{r_{ij}} \right)^{6} \right] + \frac{q_i q_j}{4\pi\varepsilon_0 r_{ij}}$$

non-bonded

# Simplified course of events of MD simulations

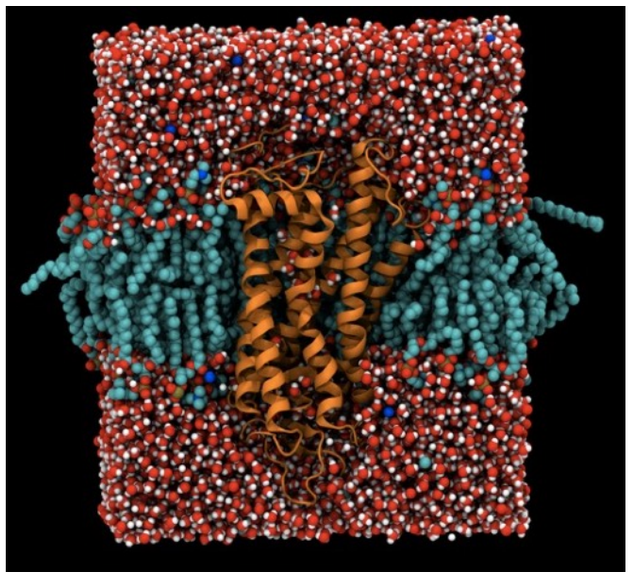
1) define at $t_0$

   all atoms with masses $m_i$

   initial atom positions $r_i$

   small iteration timestep $\Delta t$

   potential energy $U$ (in the forcefield)



2) get accelerations $a_i$ from potential energy $U$

   Newton's equations of motion:

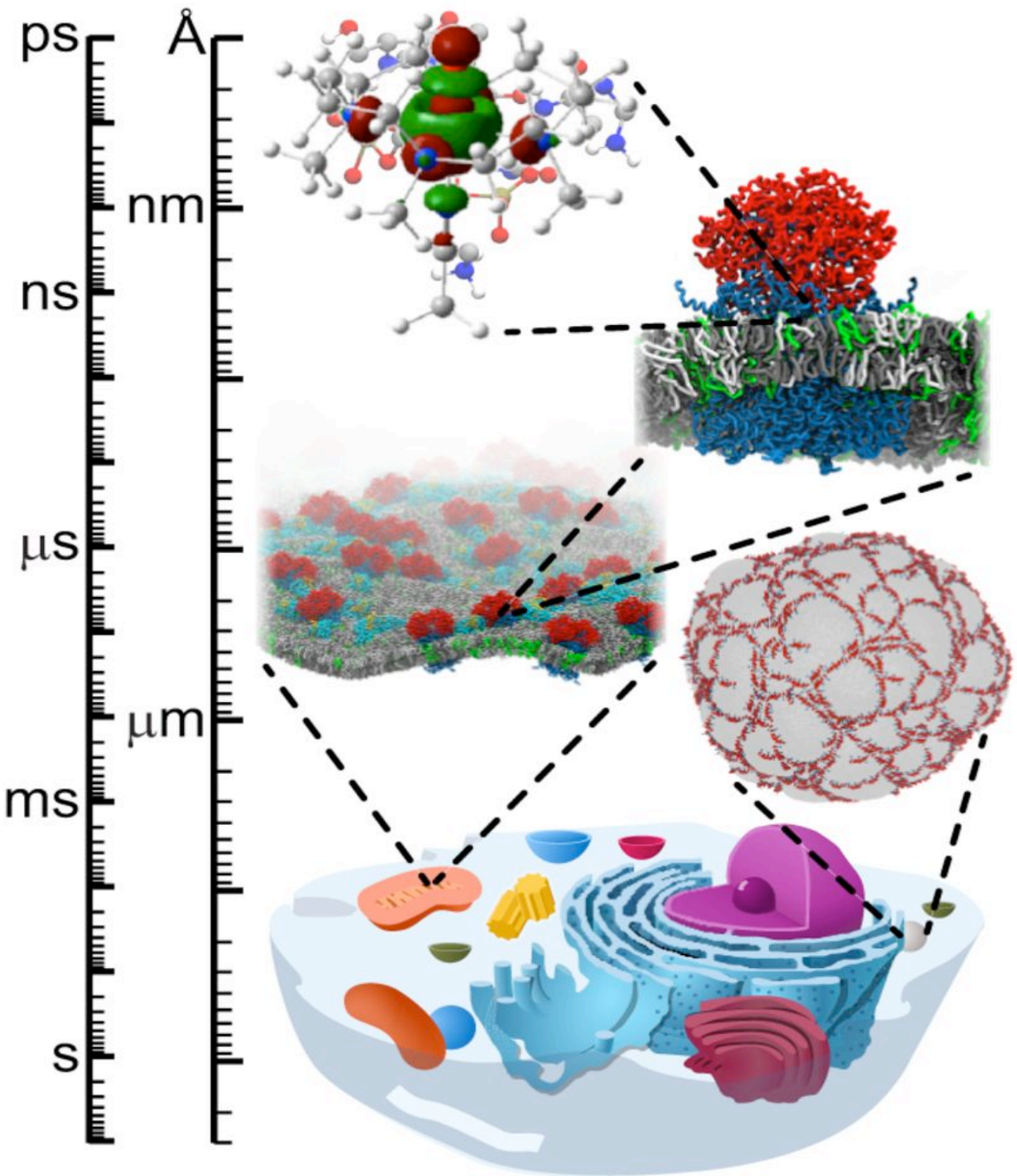
$$f_i = m_i a_i \Rightarrow a_i = \frac{f_i}{m_i} \; ; \qquad f_i = -\frac{\partial}{\partial r_i} U \; ; \qquad U = U_{non\text{-}bonded} + U_{bonded}$$

3) moving atoms

$$r_{i(t+\Delta t)} = r_i + \frac{1}{2} a_i \Delta t^2 \; ; \; a_i = \ddot{r}_i$$

4) repeat from 2) till end of simulation

# types of MD simulations




**Quantum**
- atoms, electrons and electron clouds included
- explicit solvent
- quantum mechanics

**All-atom**
- all or most atoms present
- explicit solvent
- molecular dynamics

**Coarse-grained**
- beads comprising a few atoms
- explicit or implicit solvent
- molecular dynamics

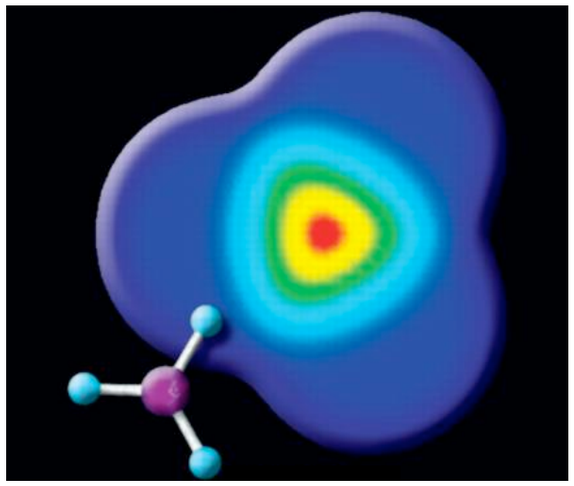
**Supra-coarse-grained**
- interaction sites comprising many atoms, protein parts or proteins
- implicit solvent
- stochastic dynamics

**Continuum**
- materials as a continuous mass
- implicit solvent
- continuum mechanics

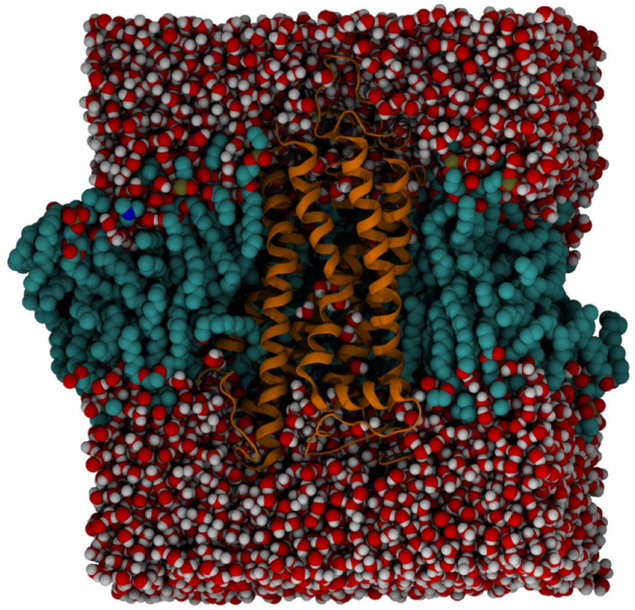
Computational ‘microscopy’ of cellular membranes Helgi I. Ingólfsson, Clément Arnarez, Xavier Periole, Siewert J. Marrink Journal of Cell Science 2016 129: 257-268; doi: 10.1242/jcs.176040

# QM or MM?

- **Quantum mechanics (QM):**
- Electronic structure
- slow and computationally expensive
- up to 1000 atoms can be treated
- Chemical reaction can be calculated

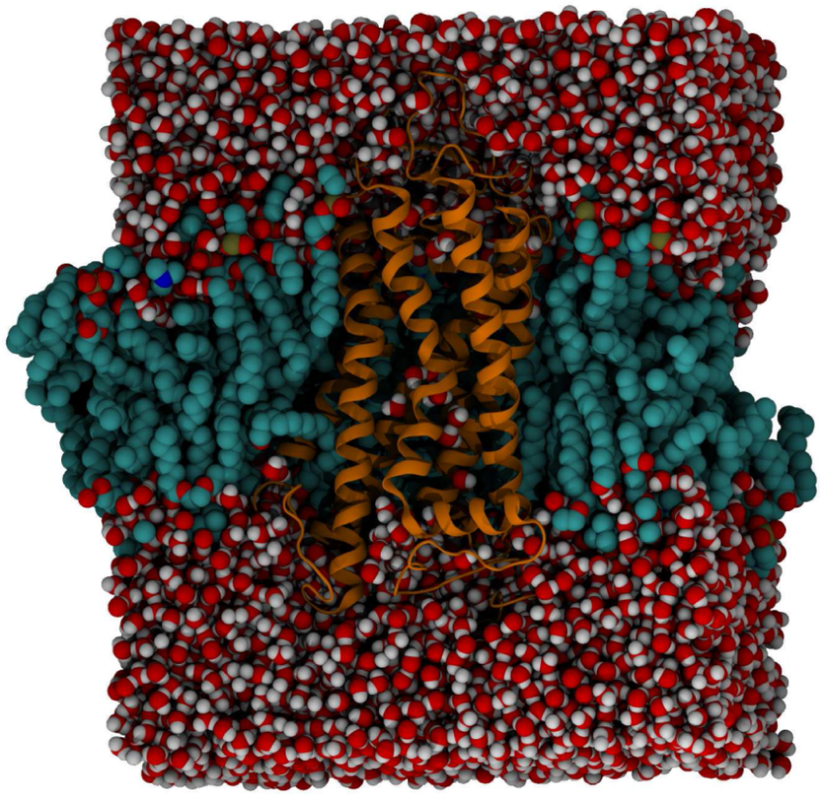


- **Molecular mechanics (MM):**
- Empirical forces, Neglects electronic structure
- computational cheap and fast
- up to 1,000,000 atoms
- Chemical reactions cannot be simulated



Everything Should Be Made as Simple as Possible, But Not Simpler, A. Einstein

# MD simulations plus and minus



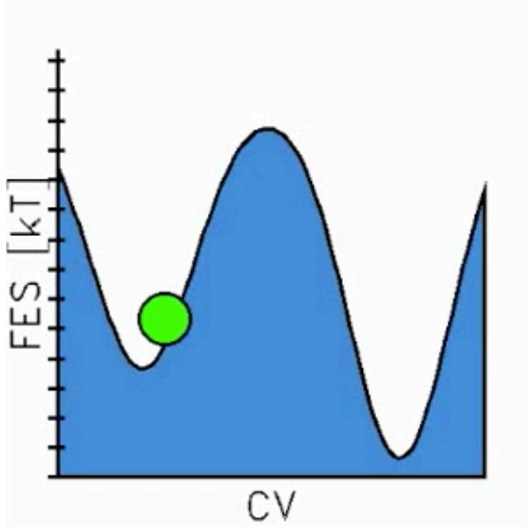
MD simulations overcome several limitations of static computational methods:

+ take explicitly into account solvents and flexibilities
+ apply physical principles + semi-empirical force fields
+ ‚computational microscope‘

- sampling problem: ergodicity is hindered by the form of the system's energy landscape

# sampling problem

the system (e.g. protein in simulation box) only samples a local energy minimum and does not reach functionally meaningful energy minima




Movie by Giovanni Bussi

# MD simulations: Timescales

„If you do **not observe** a specific structural change
it may always be due to **insufficient sampling**“

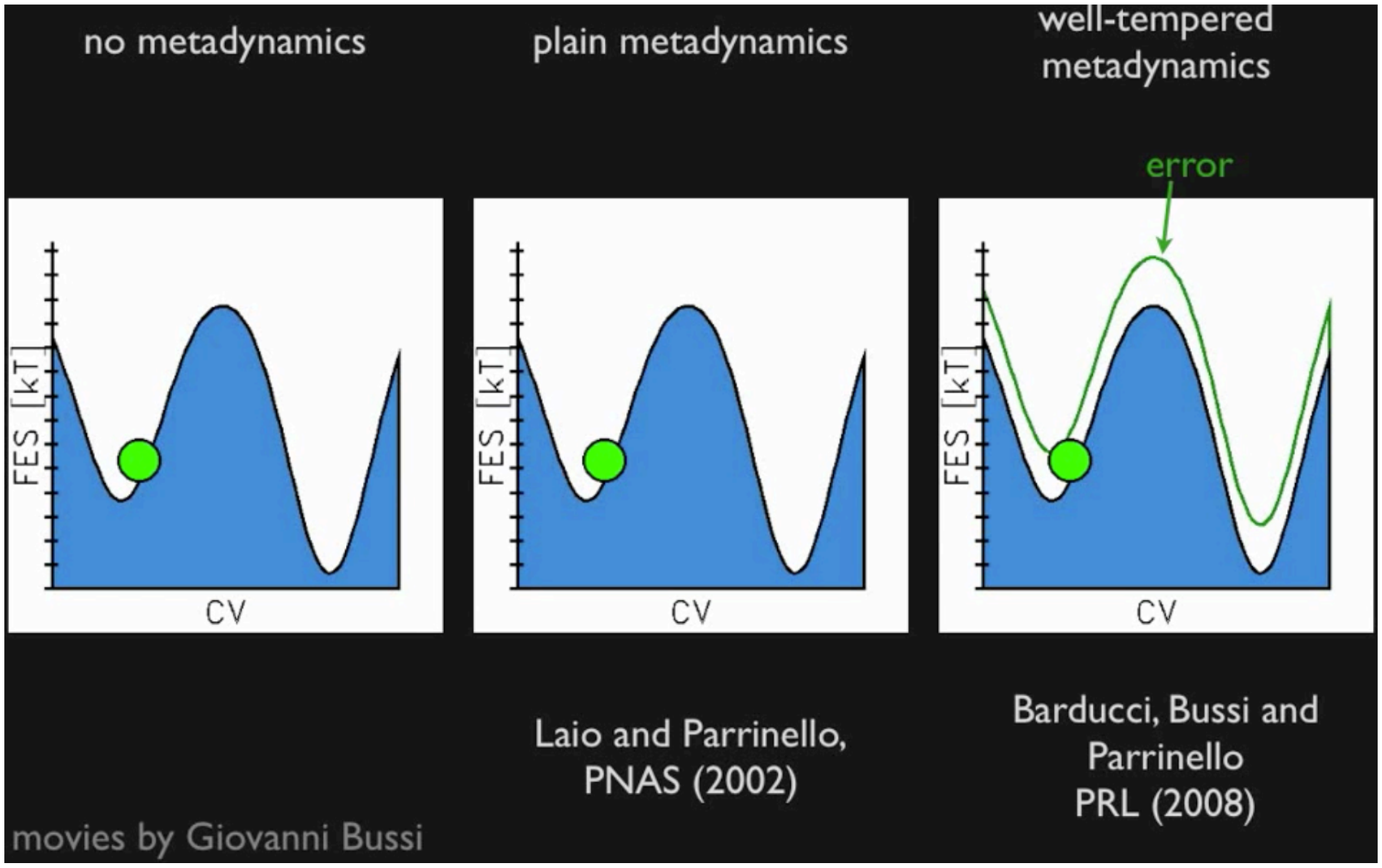
„If you discuss ‚**stability**‘ of a system, always list the limiting
simulation conditions at least **simulation time**“

„If you **observe** a specific structural change only rarely,
always try to **increase sampling**“

**MD simulation is stochastic**
More than one replica is required

# Thermodynamics of ligand binding with metadynamics

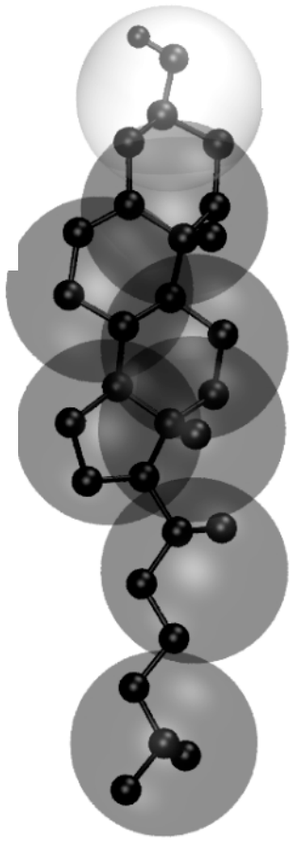
- binding free energies along physically meaningful pathways
- thermodynamics and kinetics of binding
- binding path



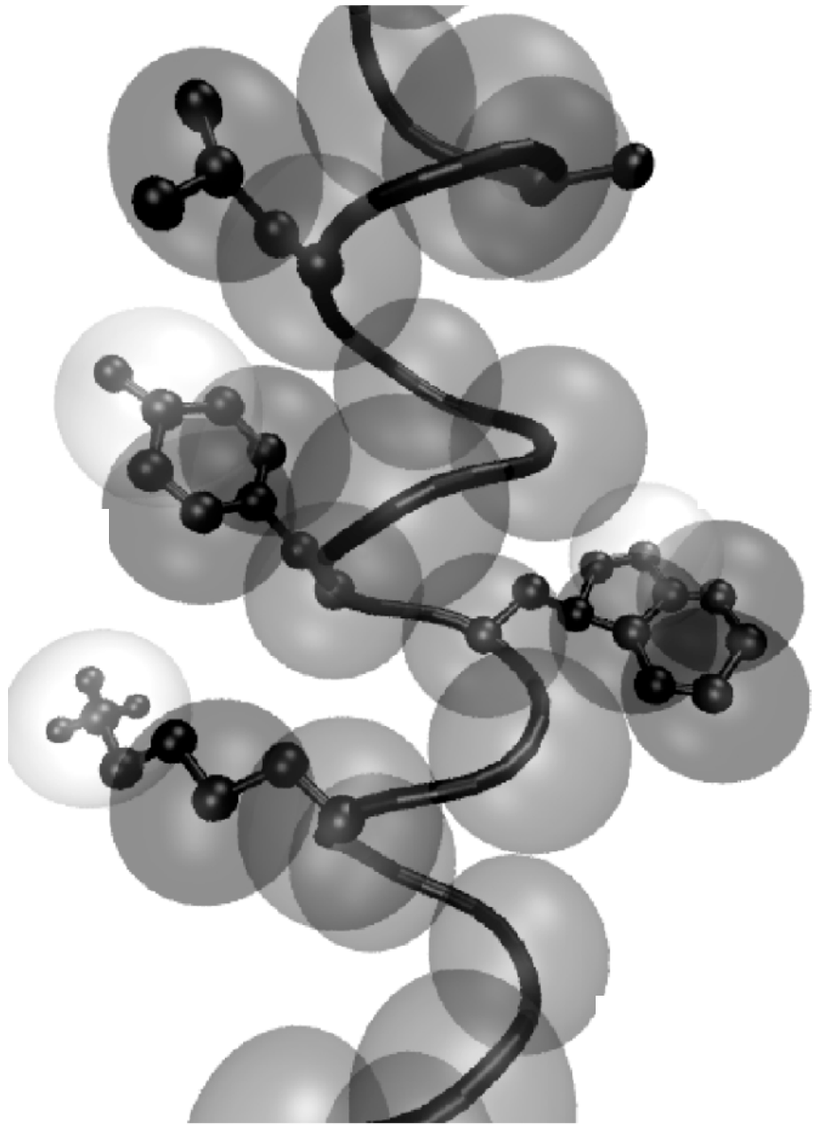
# Course Grained Molecular Dynamics Simulations

DPPC

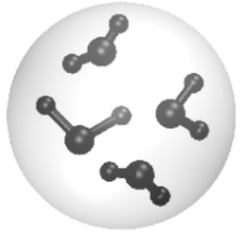
CHOLESTEROL



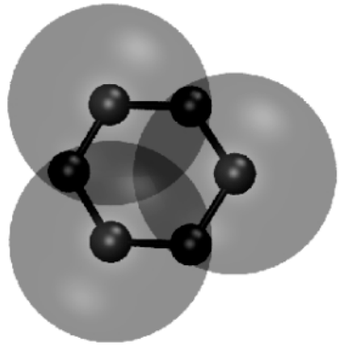
PEPTIDE (ALYWK)



WATER

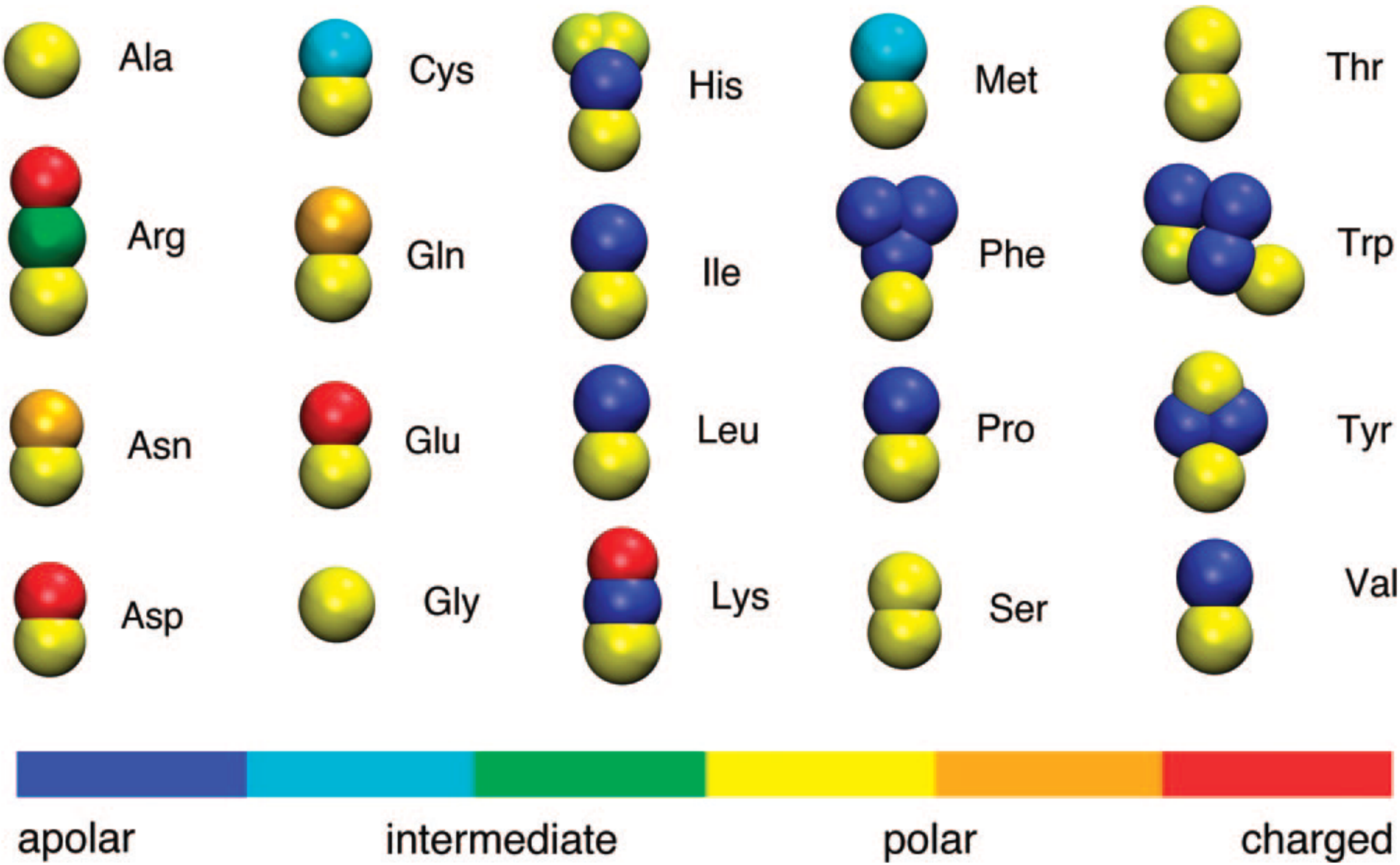


BENZENE



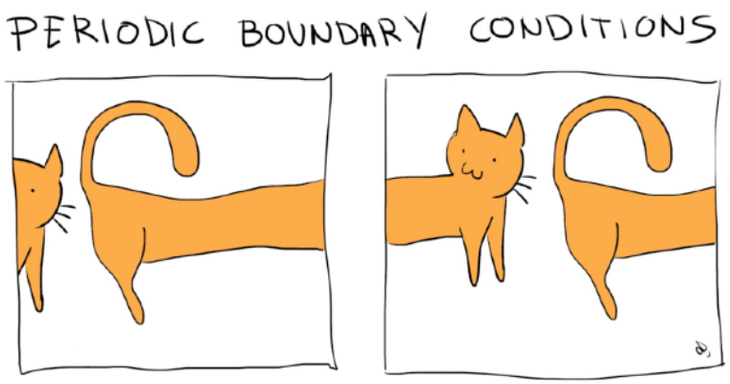
**Martini Homepage (Marrink), http://md.chem.rug.nl/cgmartini/index.php/about**

# Course Grained Molecular Dynamics (CGMD) Simulations




**Monticelli et al., 2008, J. Chem. Theory and Comput.**

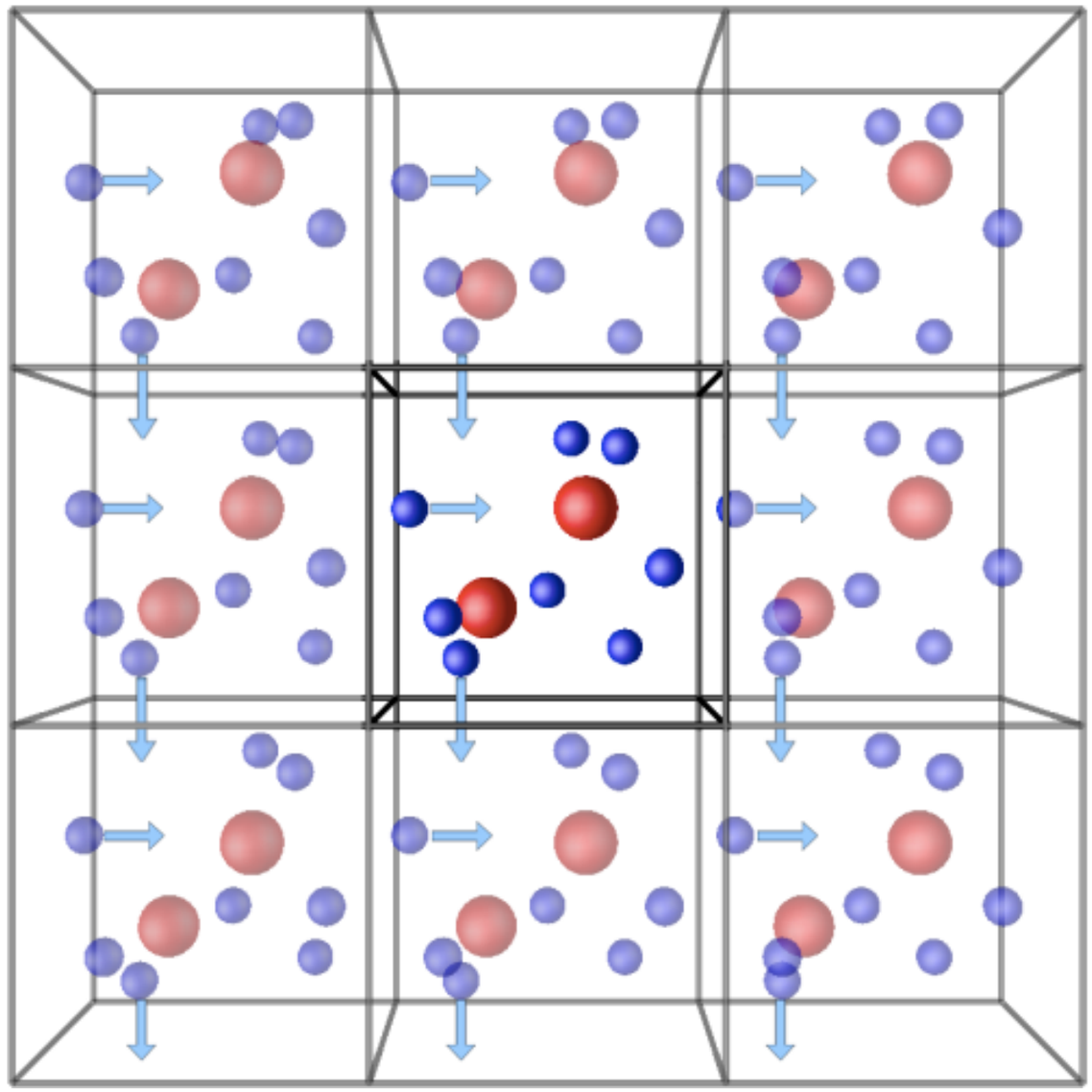
# Periodic boundary conditions (schematic)




a particle leaving the simulation box at one side

-> enters the box at the opposite side

(in the 3 dimensional space)



http://isaacs.sourceforge.net/phys/pbc.html

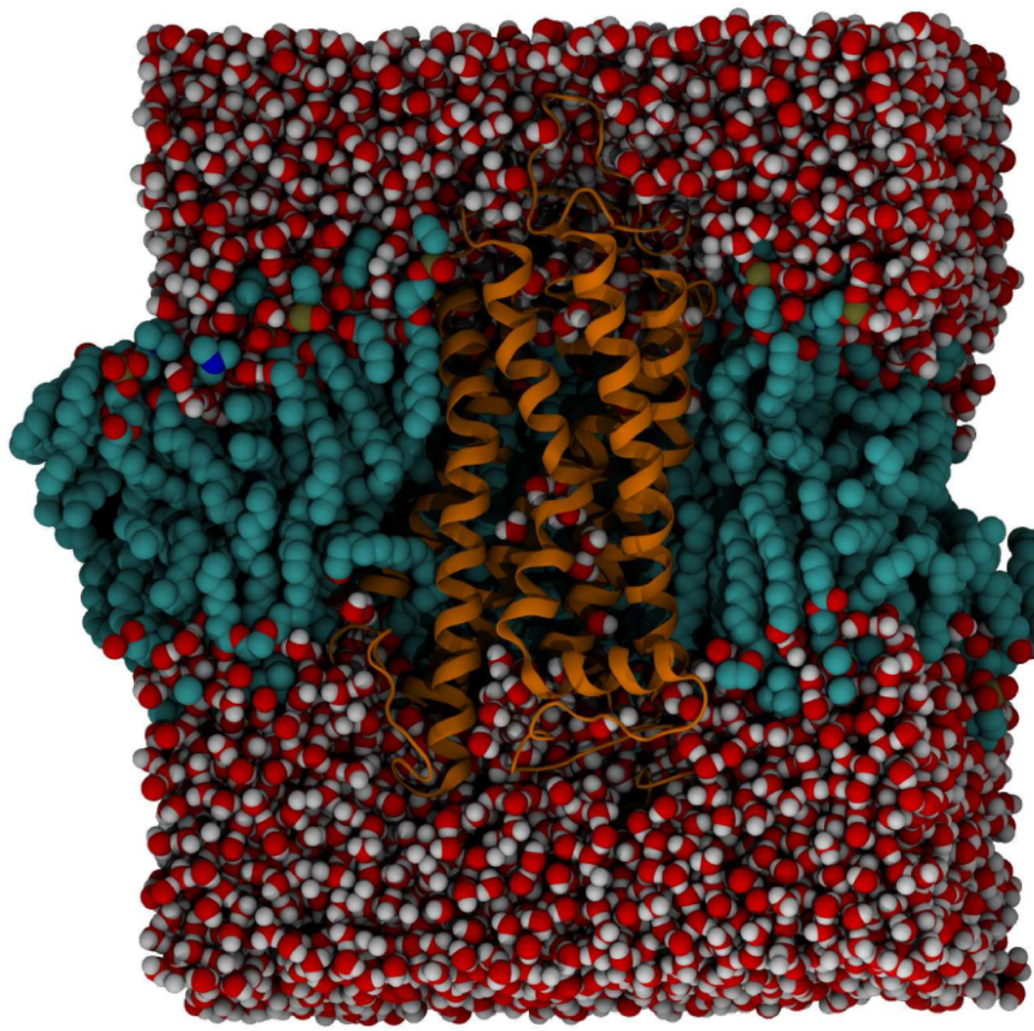
# Periodic boundary conditions (cinematic)

http://isaacs.sourceforge.net/phys/pbc.html

# Simulation box

***approximating the behavior of macro-scale system***

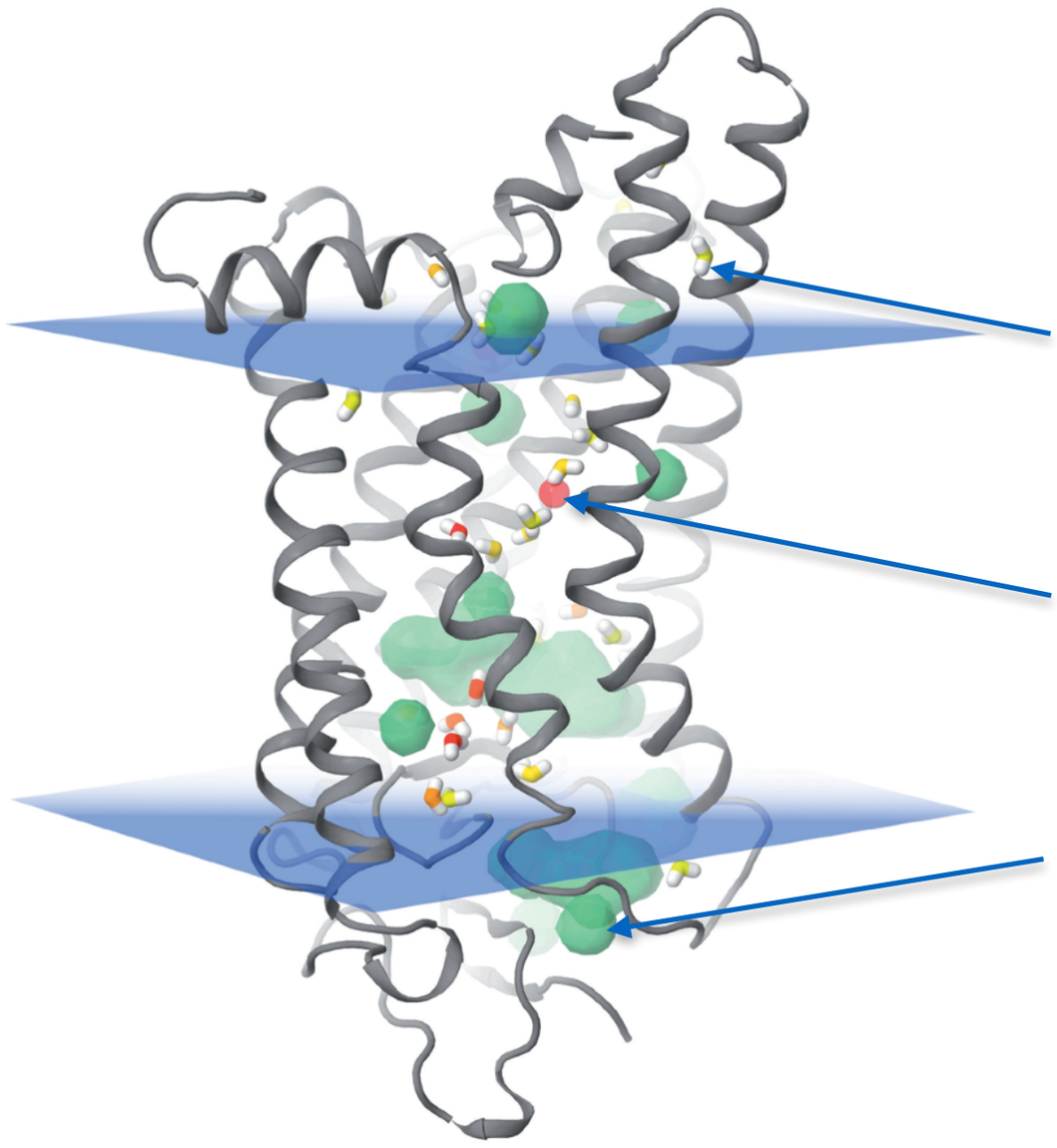
Box size depends on the size of the system e.g. here the solvated receptor embedded in a lipid bilayer



The net electrostatic charge of the system must be zero:

- add Na+ or Cl- to approximate the ionic strength of the solution

# Setup MD simulations: Internal waters / cavities



sticks colored from red (30 kcal/mol) to yellow (10 kcal/mol)

water determined by crystal structure depicted as translucent red ball

,hydrophobic cavities depicted as translucent green surfaces

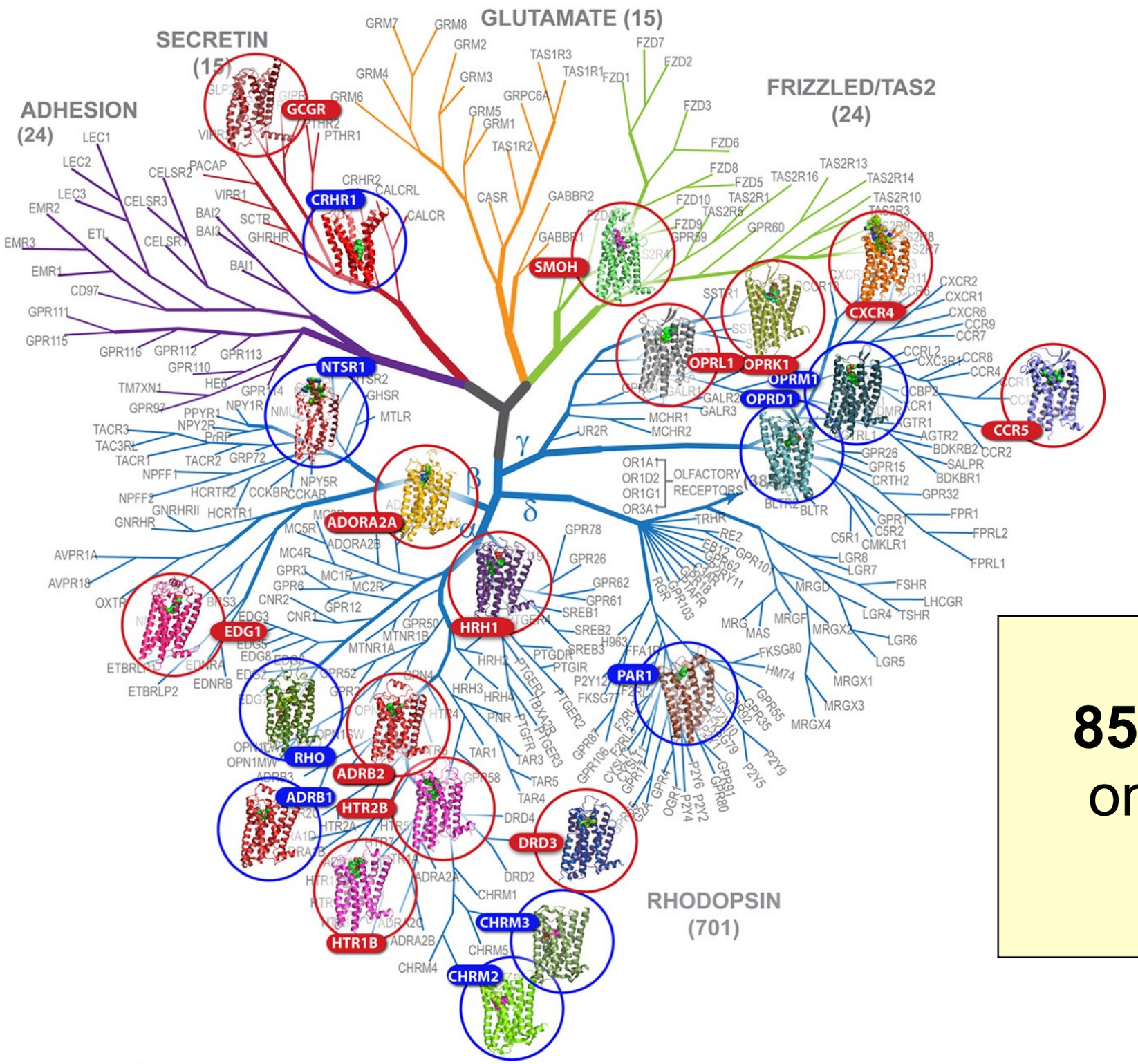
http://proteinformatics.uni-leipzig.de/mppd/

Rose, Theune, Goede & Hildebrand, ***NAR 2009***

http://lmc.uab.es/homolwat

Mayol et al, ***NAR 2020***

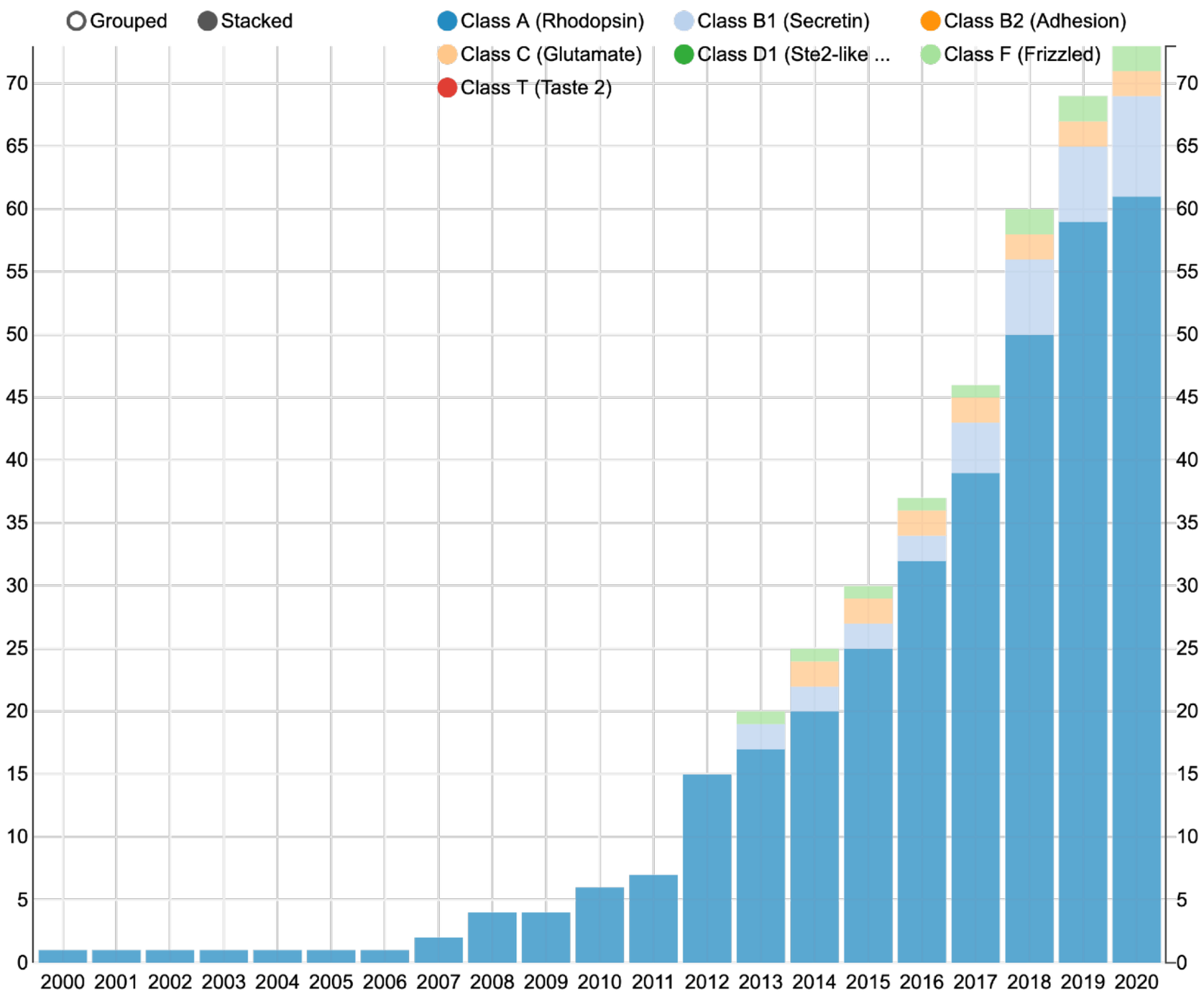
# Titeltext ...many (crystal) structures resolved




**850** receptors but only **73** resolved

GPCR Network: http://gpcr.scripps.edu

# Titeltext ...many (crystal) structures resolved




GPCR DB: https://gpcrdb.org/structure/statistics

# Loopmodelling

-3-2-1-0 +0+1+2+3

1 NKPLITV

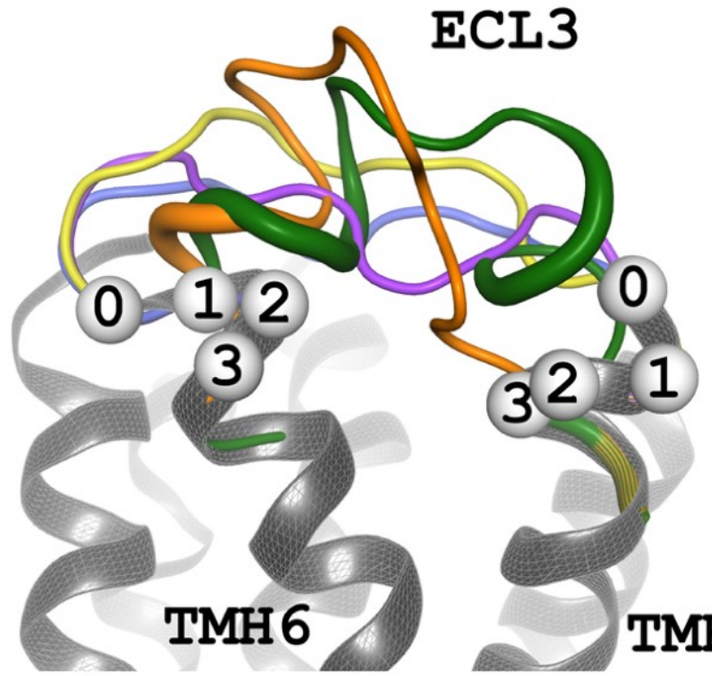
2 AILNKPLITVSNS

3 NKPLITV

4 NKPLITV

5 AILNKPLITVSNS

-3-2-1-0 +0+1+2+3

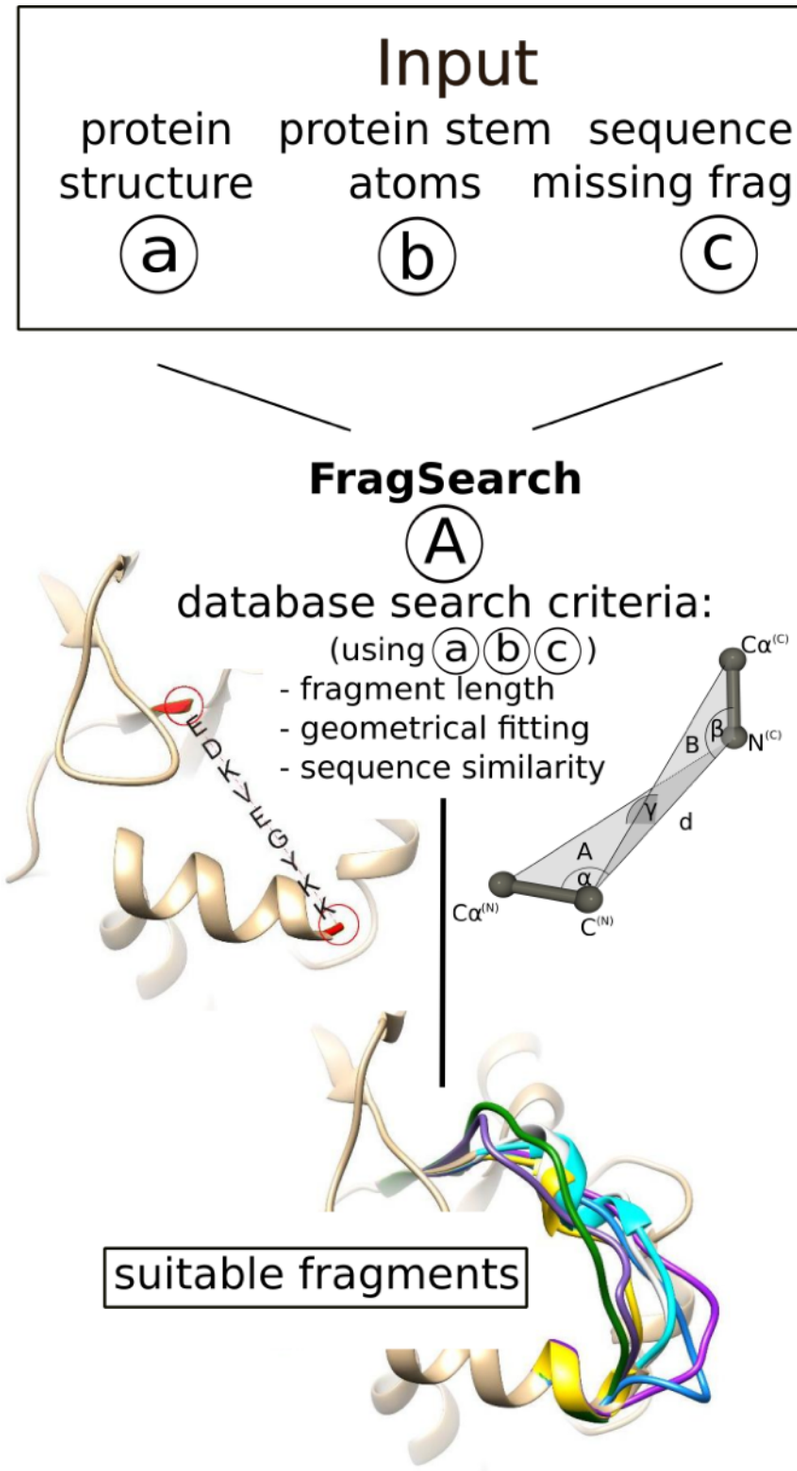



| # | Ext | GPCR | Score | Seq. Ident. | PDB ID |
|---|---|---|---|---|---|
| 1 | 0 | √ | 0.096 | 28.57 | 5C1M |
| 2 | 3 | √ | 0.095 | 30.77 | 3PBL |
| 3 | 0 | √ | 0.083 | 28.57 | 4K5Y |
| 4 | 0 | √ | 0.093 | 28.57 | 4XT1 |
| 5 | 3 | √ | 0.068 | 15.38 | 4Z43 |

http://www.ssfa-7tmr.de/ssfe2/

Worth et al., ***NAR 2009***

# SuperLooper, An Interactive webtool

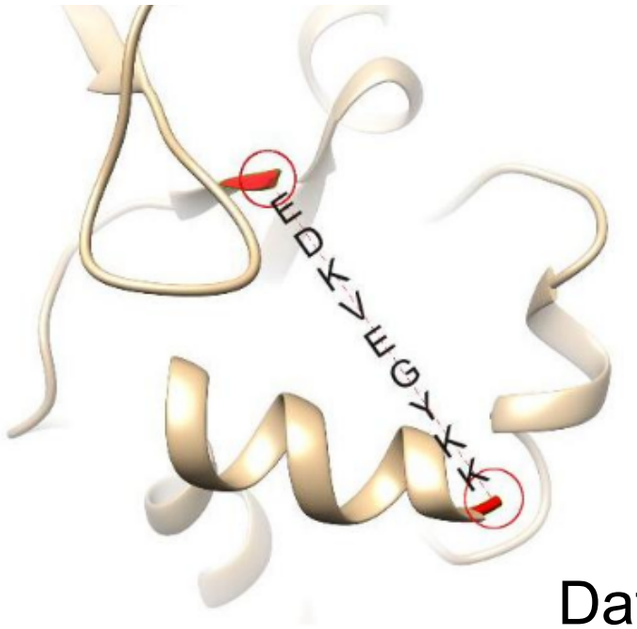



http://proteinformatics.charite.de/sl2

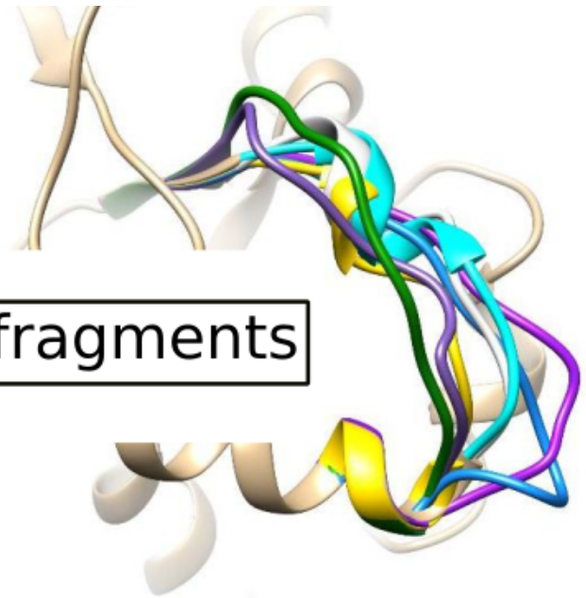
Ismer, Rose, Tiemann, Goede, Preissner & Hildebrand, ***NAR 2016***

# SuperLooper, An Interactive webtool

What we have:



What we want:



suitable fragments

What we need:

Database & Search algorithm

huge

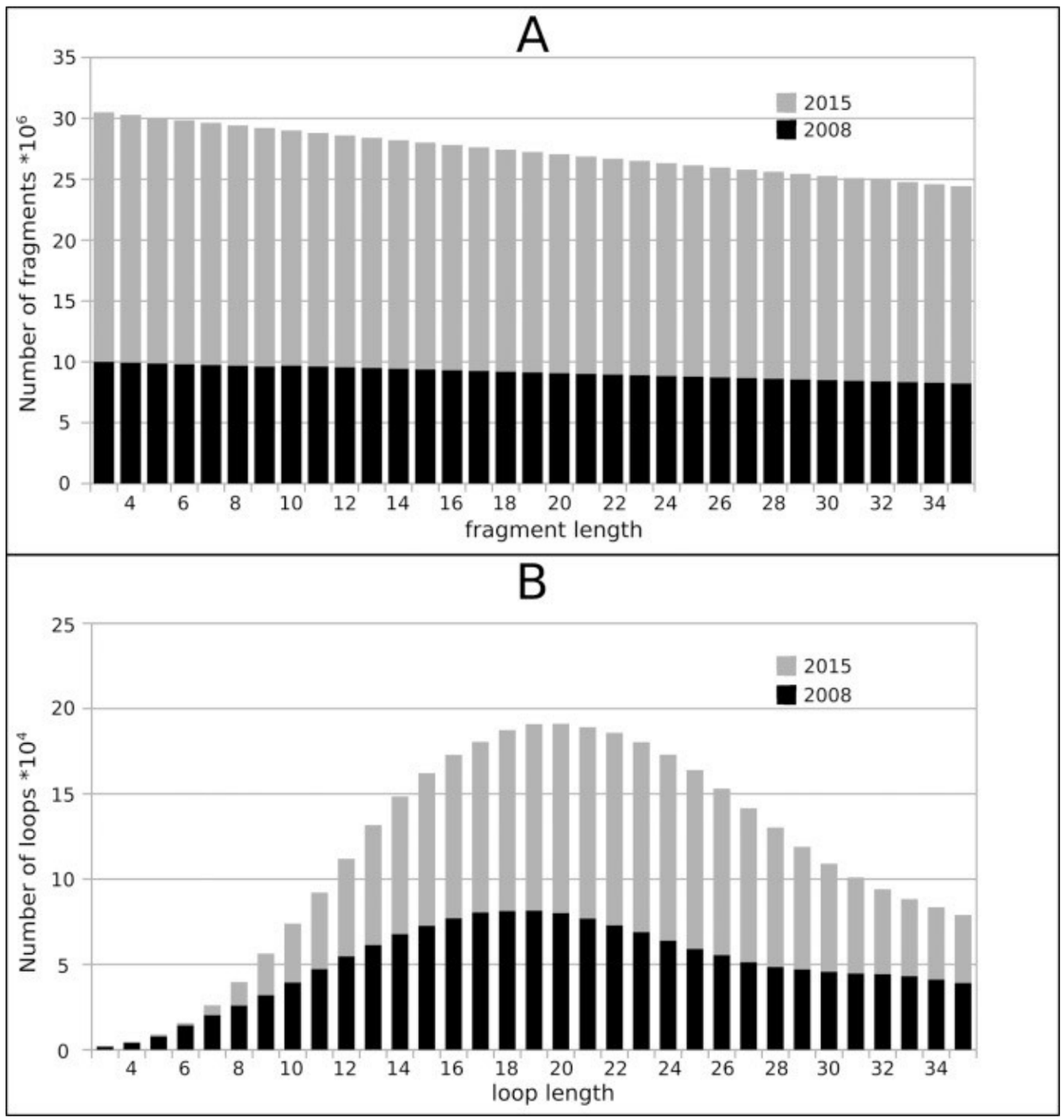
efficient

Suitable as web application

http://proteinformatics.charite.de/sl2

Ismer, Rose, Tiemann, Goede, Preissner & Hildebrand, ***NAR 2016***

# SuperLooper, An Interactive webtool




## SL2 – Database

- 114,693 structures
- 901,609,231 fragments
- 3-35 residue length

http://proteinformatics.charite.de/sl2

Ismer, Rose, Tiemann, Goede, Preissner & Hildebrand, ***NAR 2016***

# SuperLooper, An Interactive webtool

## SL2 – Search algorithm / criteria

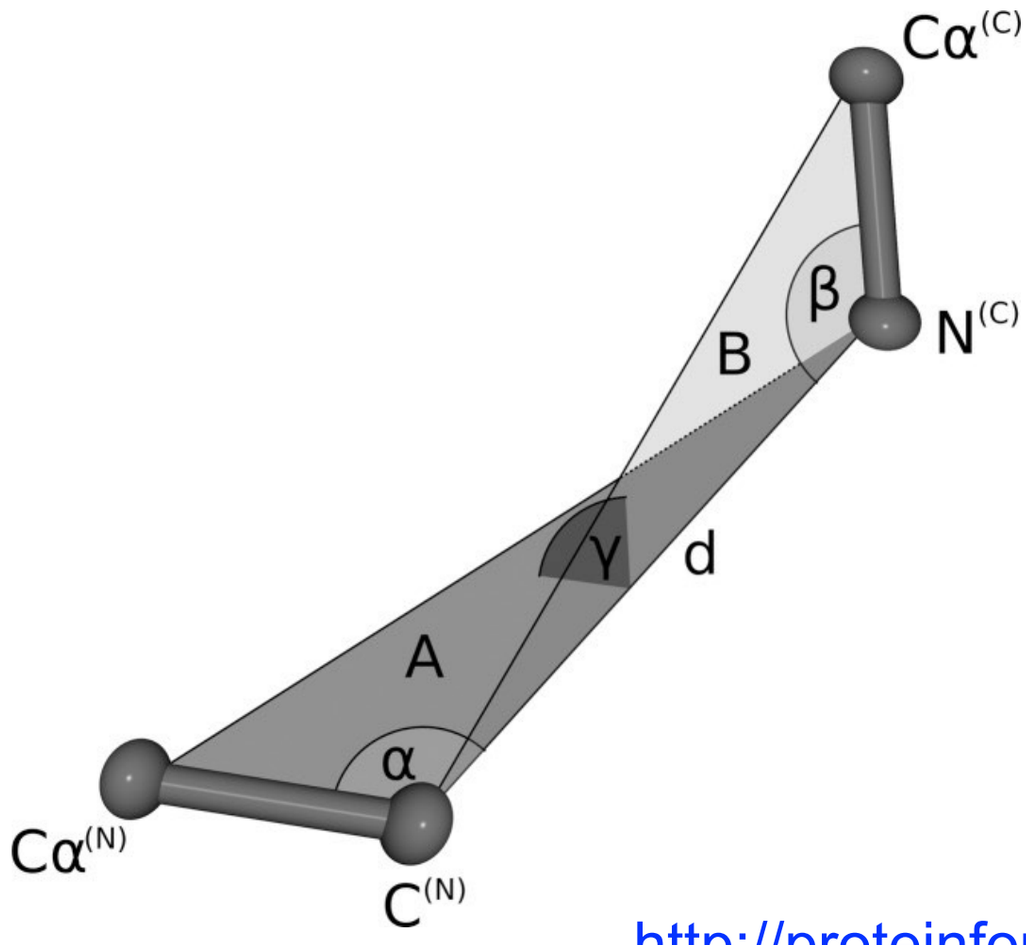
1. Extract fragments with sequence length of missing fragment
2. Weight fragments according to sequence similarity
3. Rank fragments according to geometrical fingerprint matching (RMSD > 0.75 A)
4. Sort similar fragments with backbone RMSD < 0.5 A of top-1000 list out
5. Find clashes
6. Present results to user

http://proteinformatics.charite.de/sl2

Ismer, Rose, Tiemann, Goede, Preissner & Hildebrand, ***NAR 2016***

# SuperLooper, An Interactive webtool

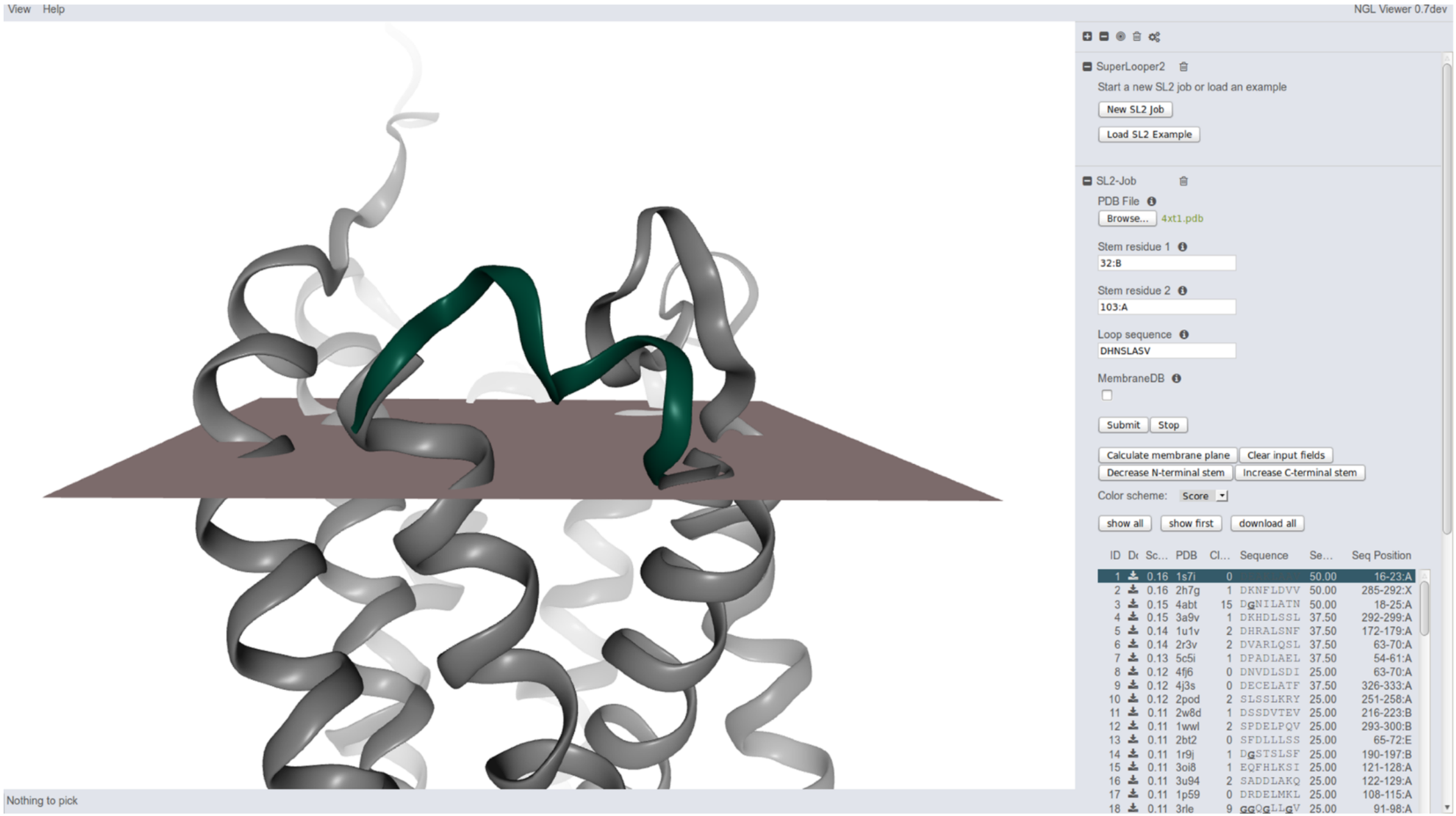
## Geometrical fingerprint




http://proteinformatics.charite.de/sl2

Ismer, Rose, Tiemann, Goede, Preissner & Hildebrand, ***NAR 2016***

# SuperLooper, An Interactive webtool



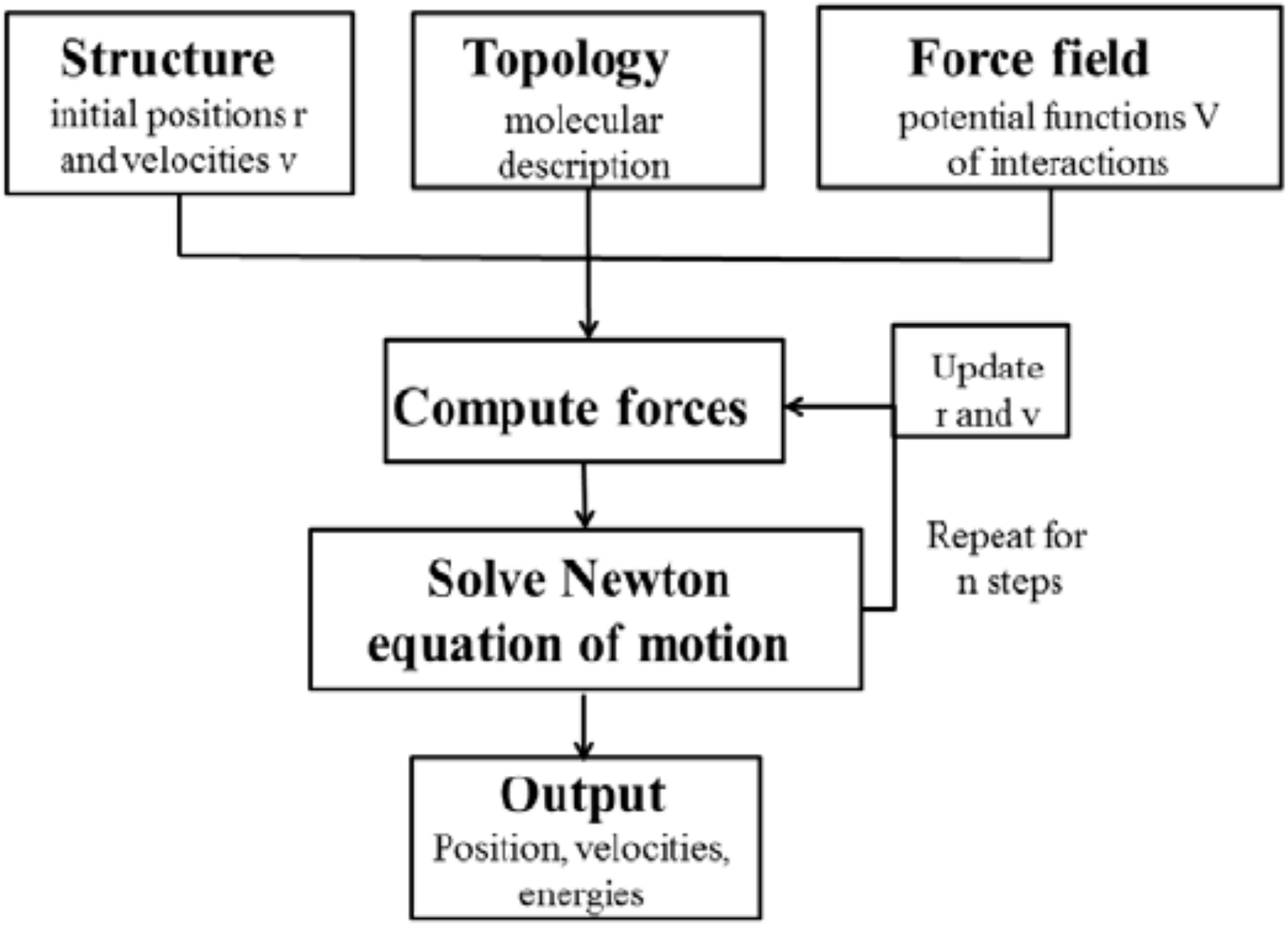

http://proteinformatics.charite.de/sl2

Ismer, Rose, Tiemann, Goede, Preissner & Hildebrand, ***NAR 2016***

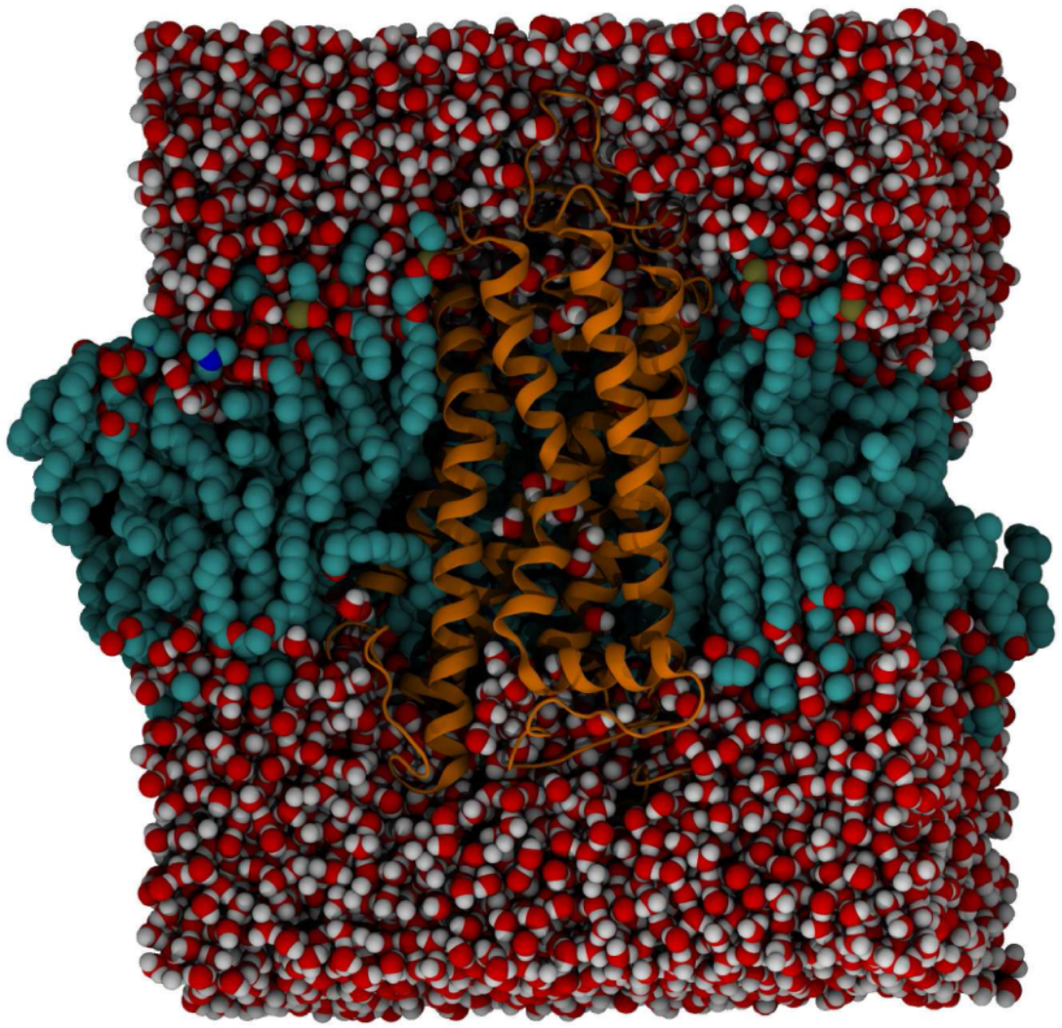
Proteins like to move it

proteinformatics

# Simplified course of events of classical MD simulations



# Setup MD simulations: setup



- Loop modelling with SuperLooper

***www.proteinformatics.charite.de/SL2***

***NAR 2009, 2016, 2018***

- Intra-molecular waters

***www.proteinformatics.charite.de/MPPD***

***NAR 2014; 2020***

- MD simulations with GROMACs
- AMBER99SB forcefield

- Visualization of trajectories in the WEB

***www.proteinformatics.charite.de/MDsrv***

***Nature Methods 2017; TIBS 2019***

Sommer, Elgeti, **Hildebrand**, Szczepek, Hofmann & Scheerer, ***Methods Enzymol 2015***

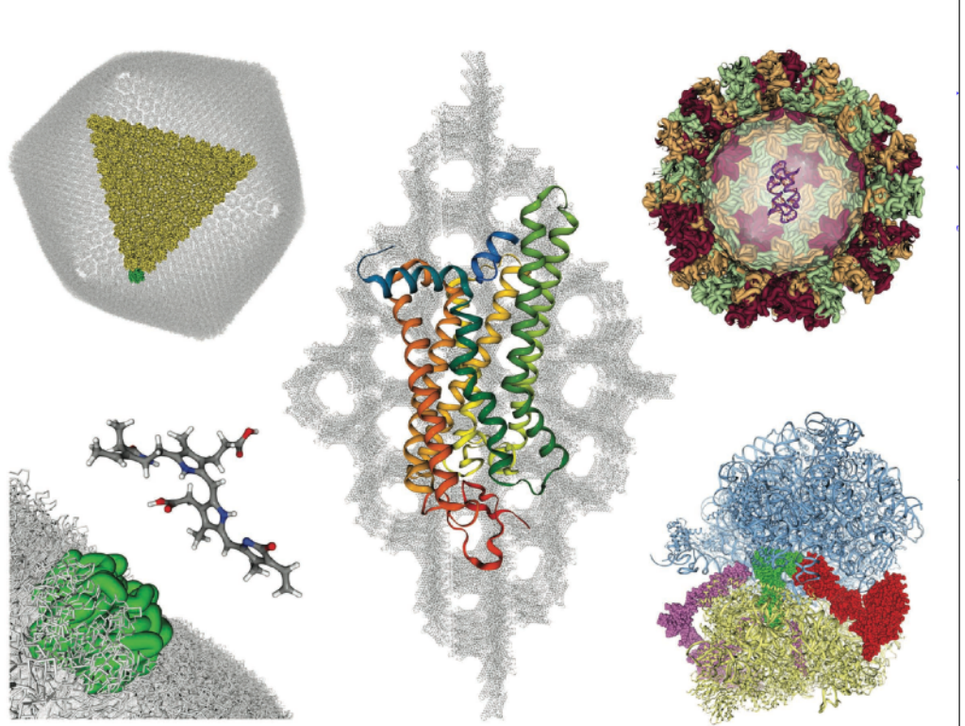
# Sharing



PRINT ISSN: 0305-1048
ONLINE ISSN: 1362-4962

Nucleic Acids Research

VOLUME 43 WEB SERVER ISSUE JULY 1, 2015
www.nar.oxfordjournals.org



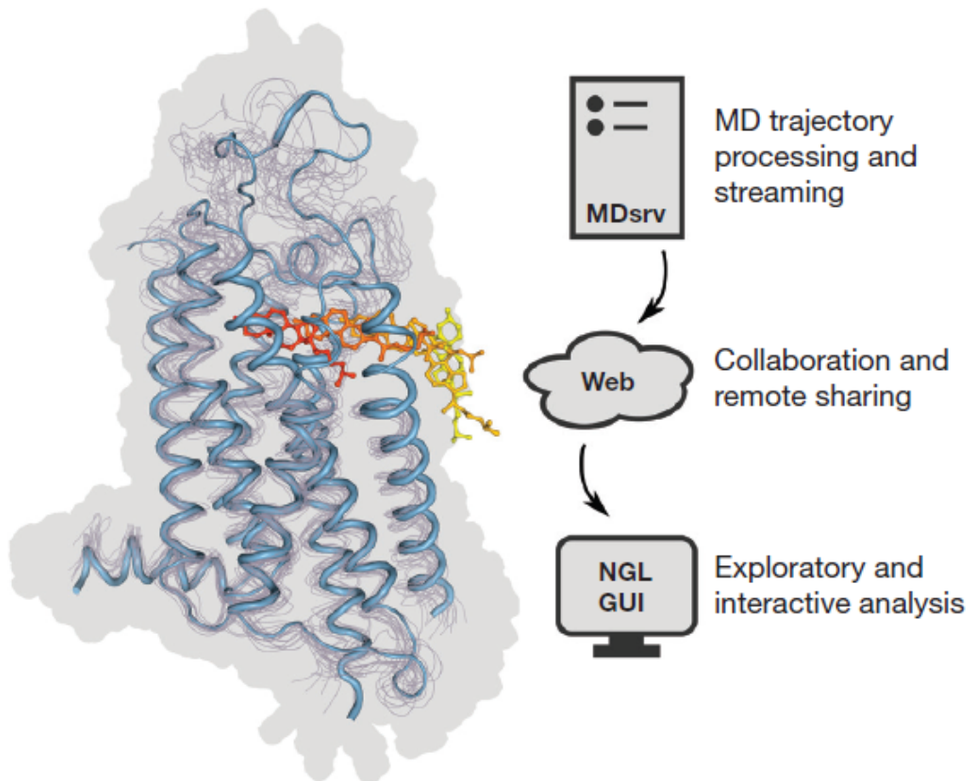
OXFORD UNIVERSITY PRESS

Open Access
No barriers to access – all articles freely available online

MIX
Paper from responsible sources
FSC® C007207

## MDsrv: viewing and sharing molecular dynamics simulations on the web

CORRESPONDENCE



# Thermodynamics

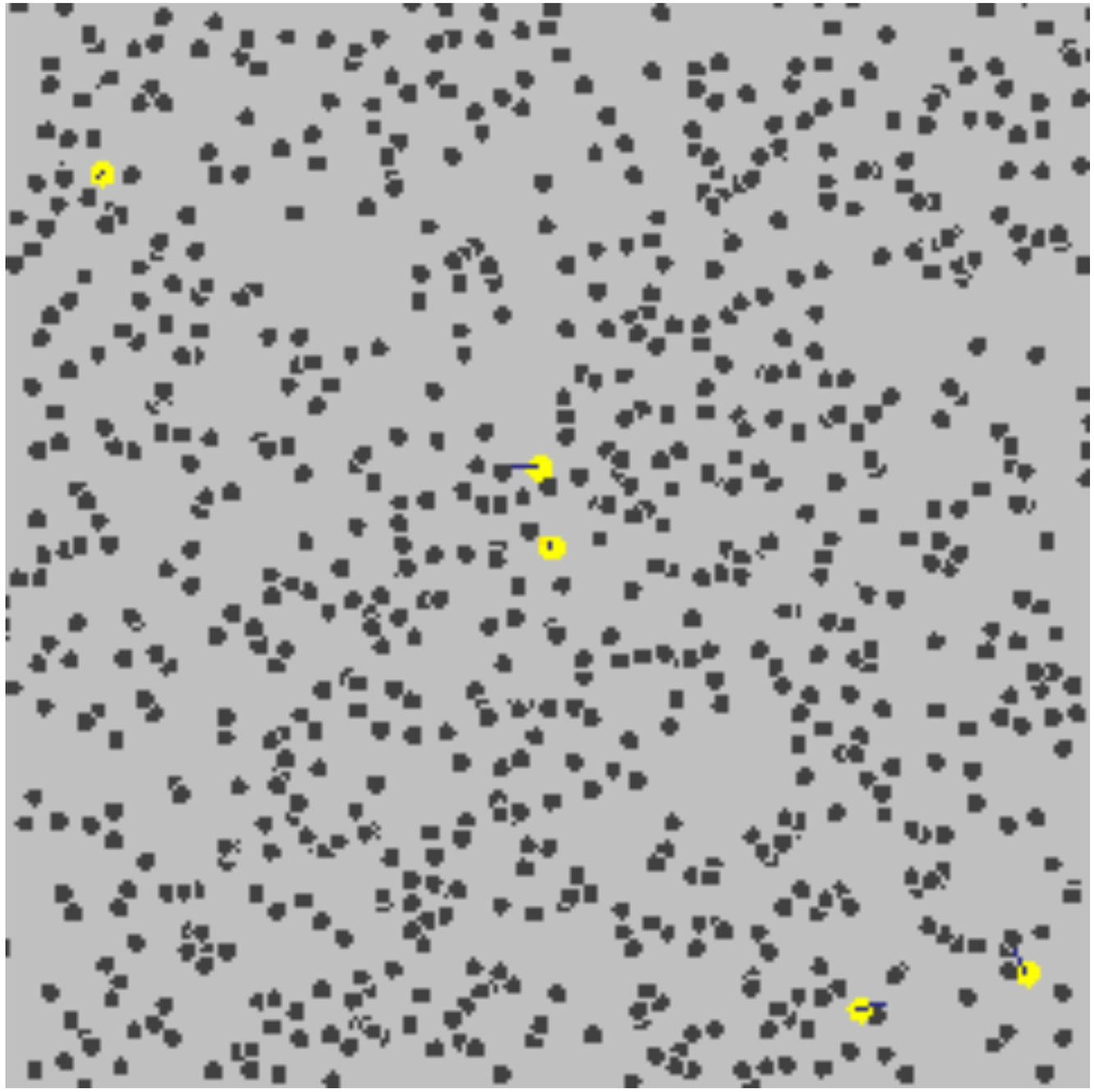
## Brownian Motion

Thermal motion of particles

in liquids or Gases

***By botanics***
***Robert Brown***
***1827***

Thermodynamic temperature



https://commons.wikimedia.org/w/index.php?curid=19140415

# Thermodynamics

**Temperature correlates with kinetic energy**

$$\frac{m}{2}\,\bar{v}^2 = \frac{3}{2}\,k\,T$$

**T - absolute Temperature**

**$k_B$ - Boltzmann-constant**

**$k = 1{,}38 \cdot 10^{-23}$ J/K**

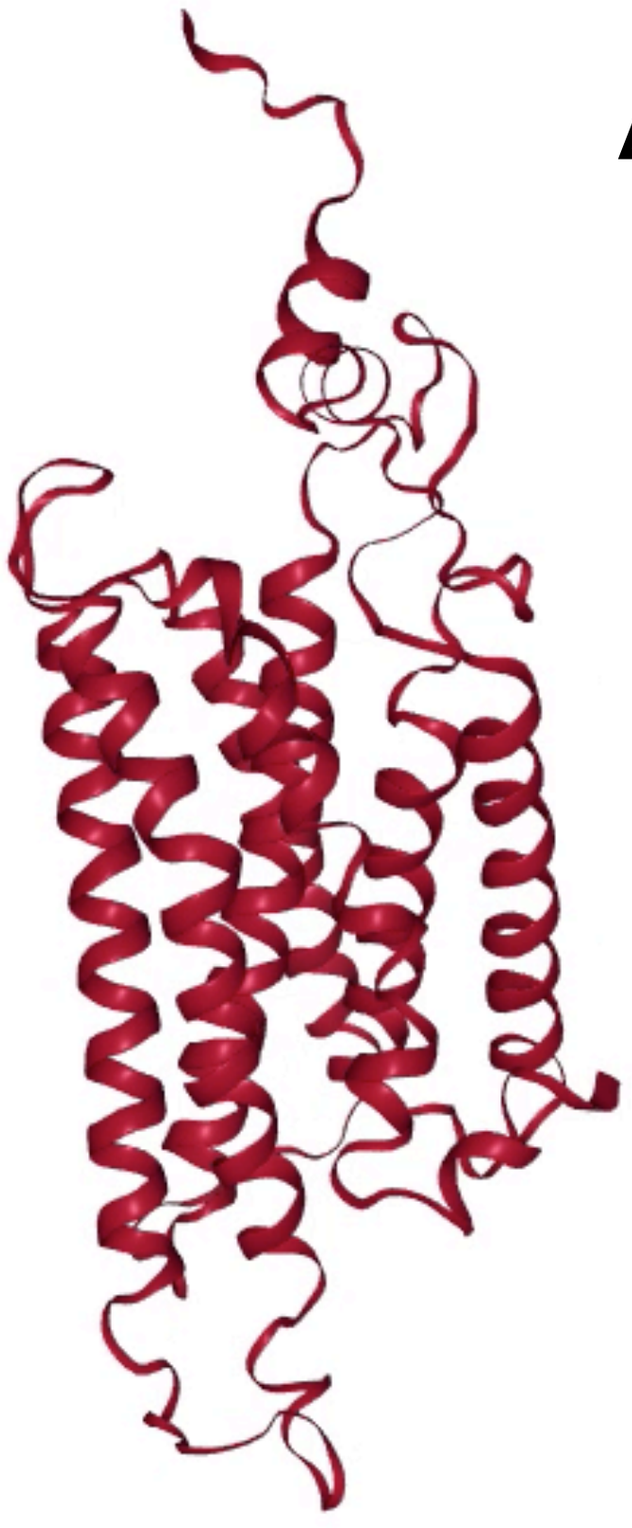
**m = Masse**

refers to an absolute zero according to the properties of the **ideal gas**

$S = k_B \ln W$ **Boltzmann-formula**

entropy **S** and the number of **w**ays the atoms or molecules of a thermodynamic system arrange

# Thermodynamics: Dance of the proteins



$$\Delta G = \Delta H - T*\Delta S$$

Gibbs-Helmholtz
Equation

# Thermodynamics

**Derived from ideal gases**

$$p\,V = n\,R\,T$$

$$\frac{p_1 V_1}{T_1} = \frac{p_2 V_2}{T_2}$$

**Pressure p**

**Temperatur T**

**Volumen V**

n - number of particles

R - Gas constant

$$R = 8{,}314 \ \frac{J}{mol\ K}$$

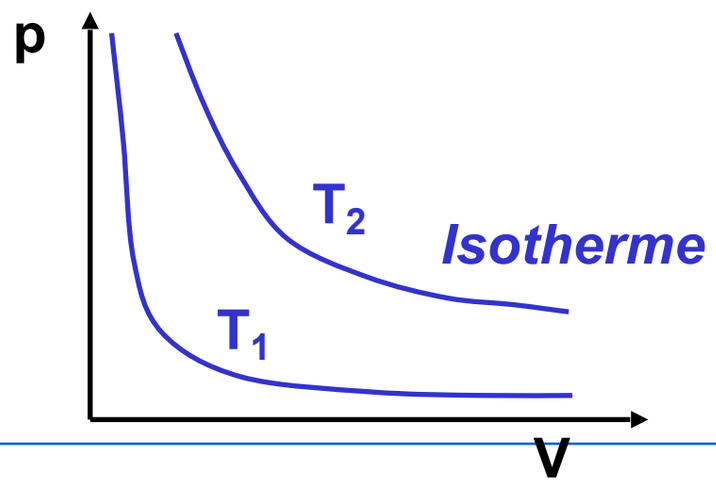
# Thermodynamics

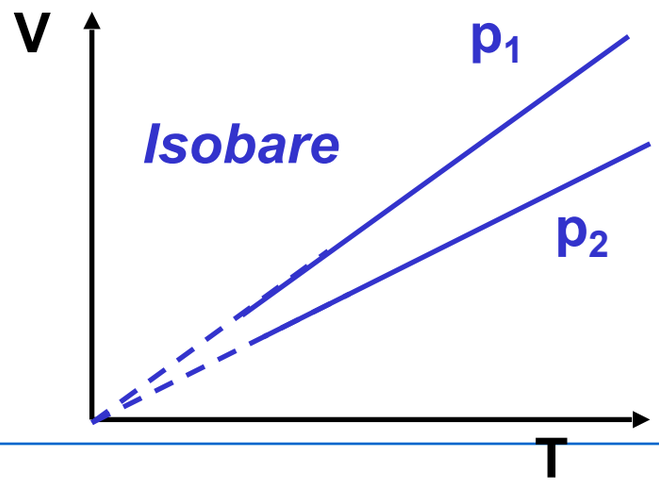


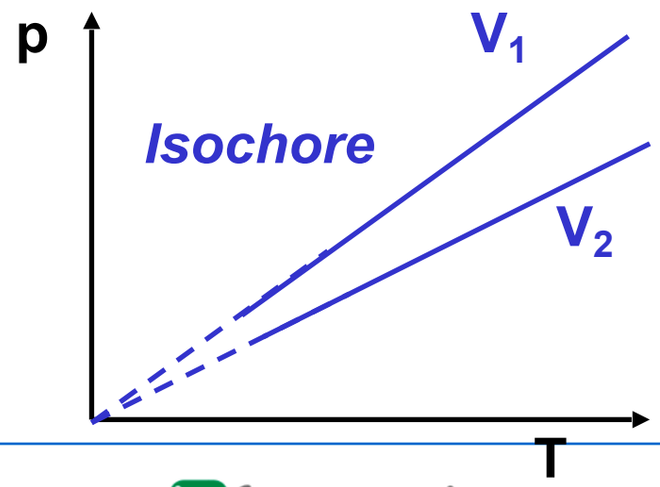
$$p\,V = n\,R\,T$$

| Isothermic | Isobaric | Isochoric |
|---|---|---|
| T = const | p = const | V = const |
| p*V = const | V ~ T | p ~ T |
| Boyle-Mariotte | Gay-Lussac | |

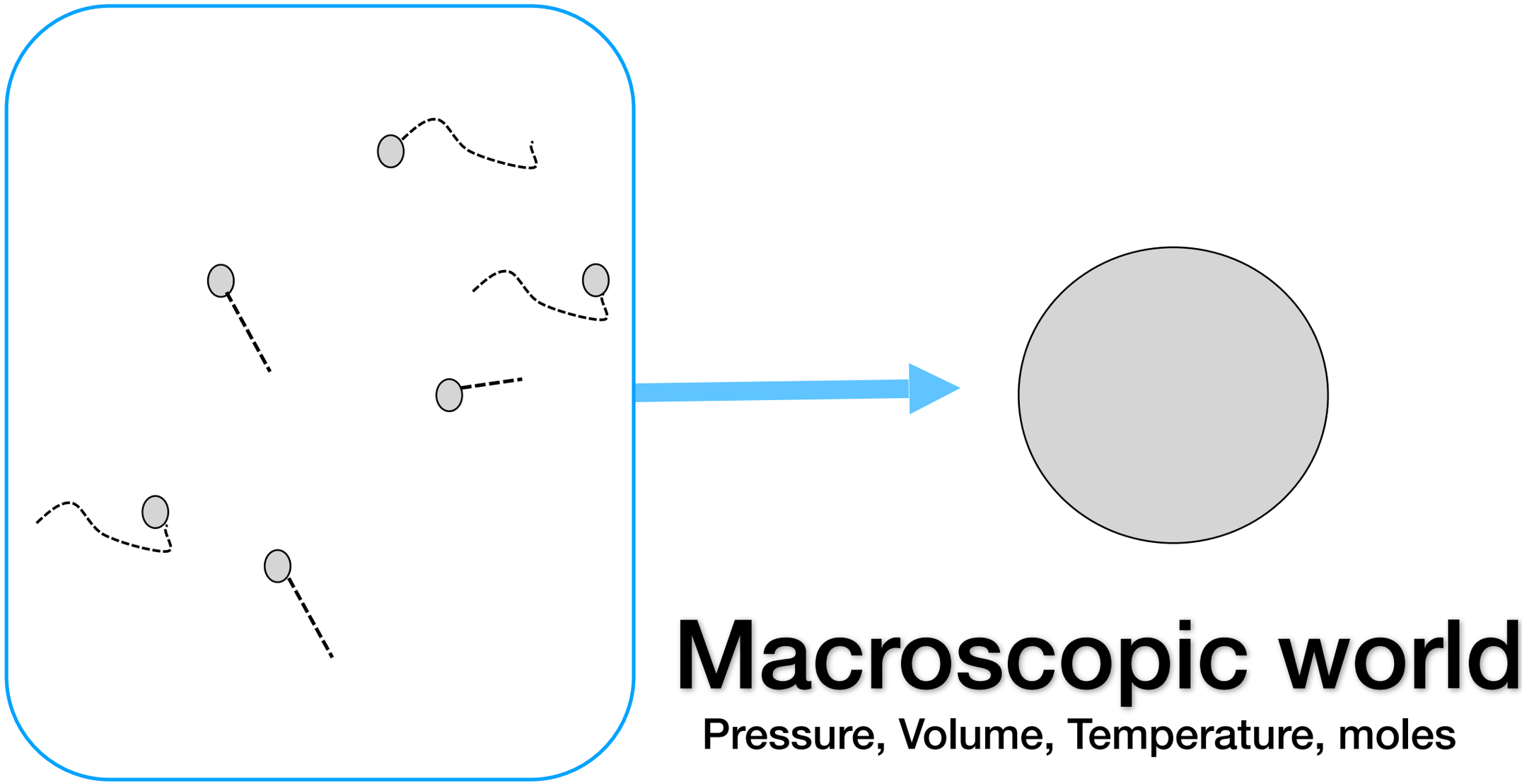
| Compression of gas | Extension of gas | Warming up gas in a closed box |
|---|---|---|



# Microsopic toward macroscopic



**Microscopic world**

Position, velocity, mass

**Macroscopic world**

Pressure, Volume, Temperature, moles

# Molecular Dynamics Ensembles

Constant number of Particle, constant Volume, constant Energy (NVE)

Constant number of Particle, constant Volume, constant Temperature (NVT)

Constant number of Particle, constant Pressure, constant Temperature  (NPT)

**Choose the ensemble that best fits for the system you want to simulate**

# The Ergodic hypothesis states

Experiment

Macroscopic

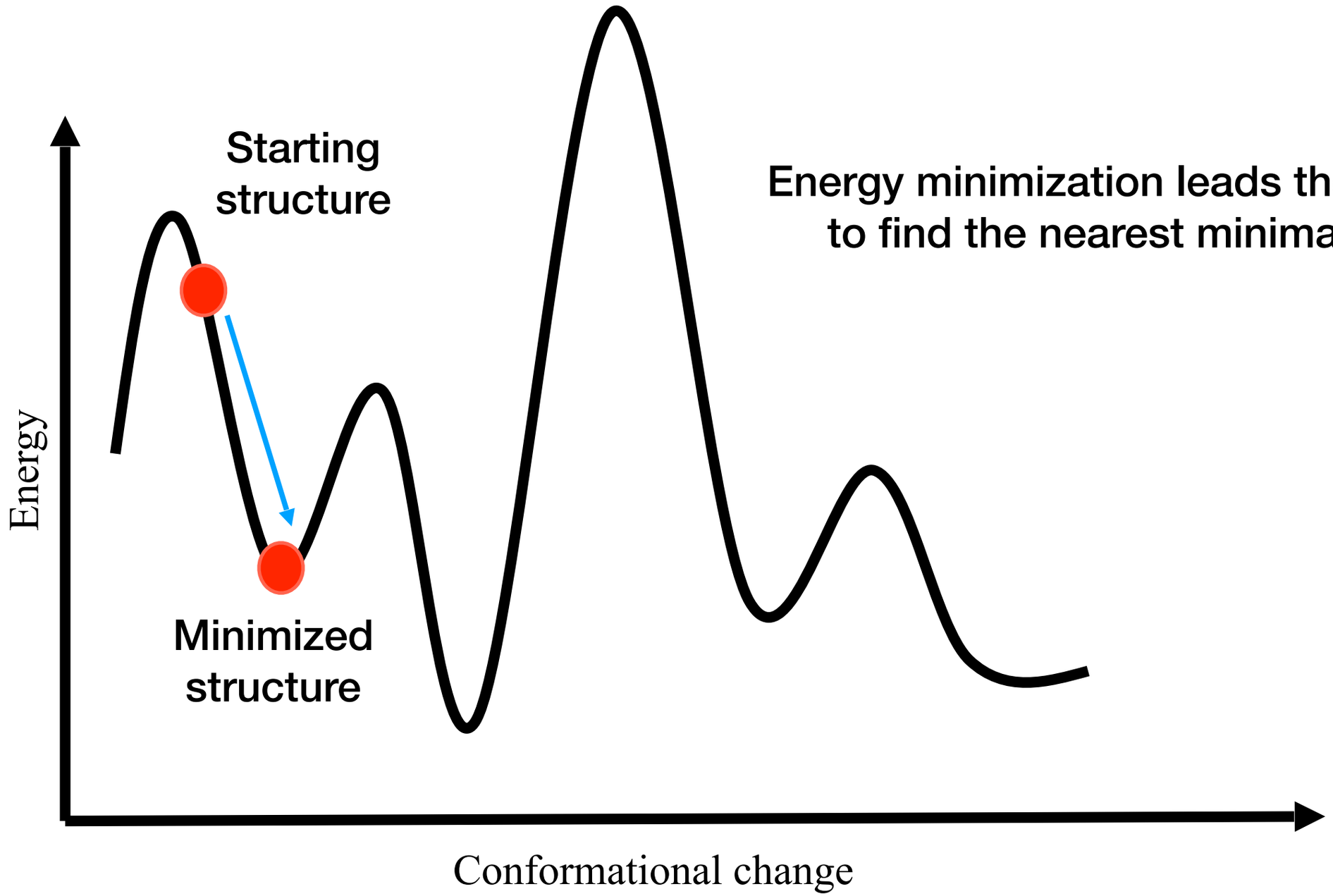
MD Simulation

Microscopic

Allows the system to evolve in time indefinitely, that system will eventually pass through all possible states.

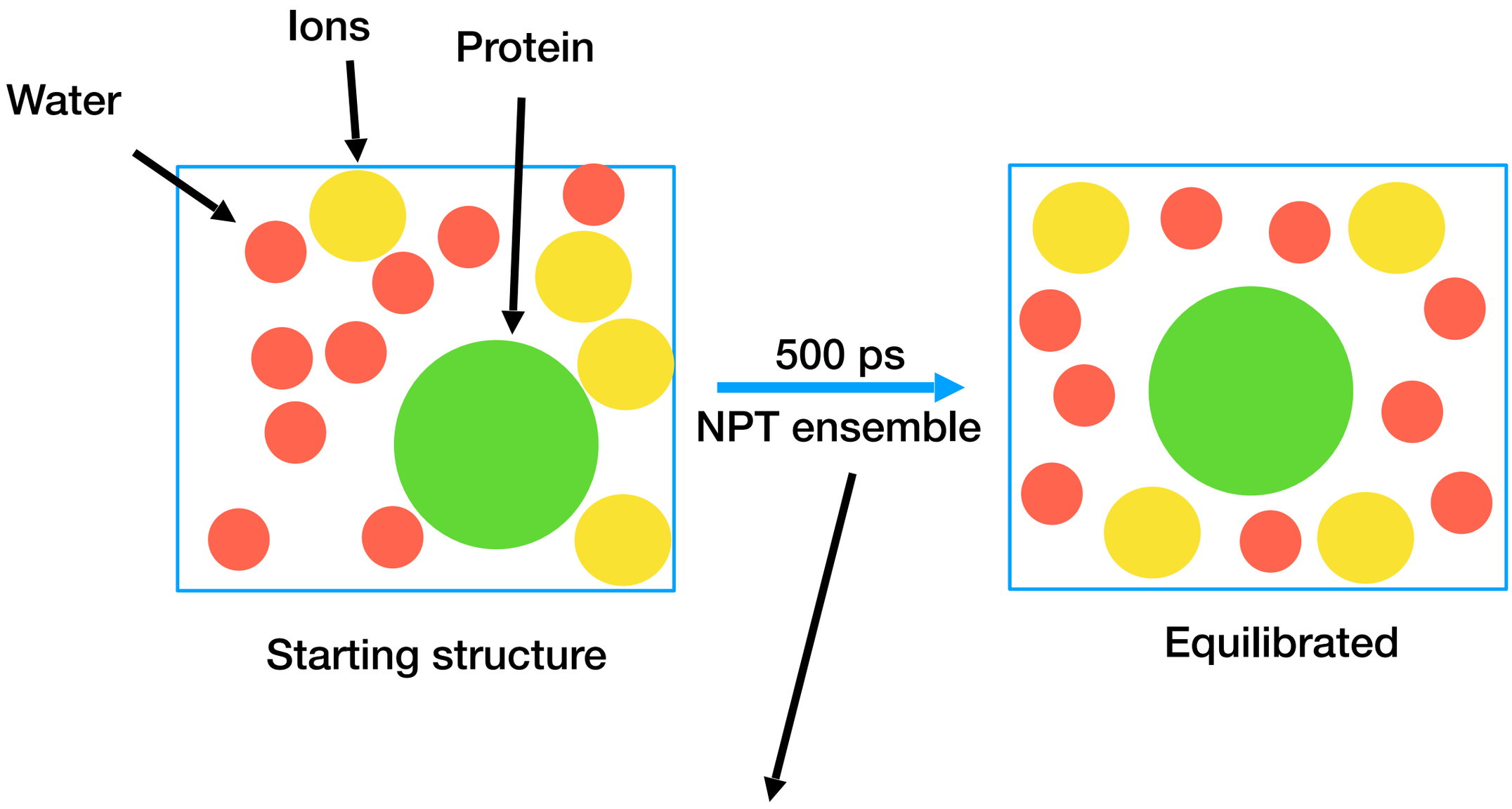
experimentally relevant information concerning structural, dynamic and thermodynamic properties may then be calculated using a feasible amount of computer resources.

# Energy minimization



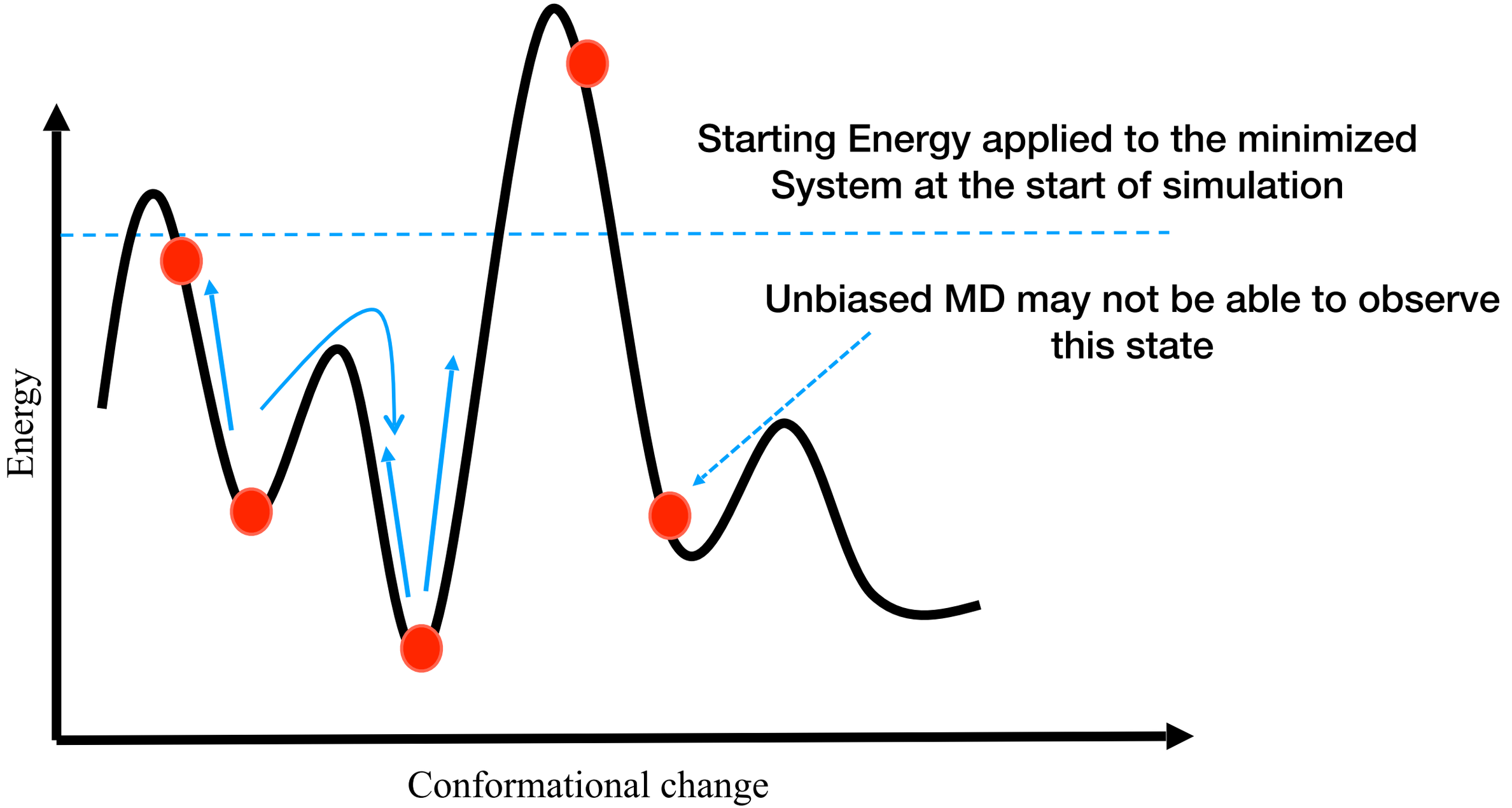

**Energy minimization leads the system to find the nearest minima point**

# Equilibration

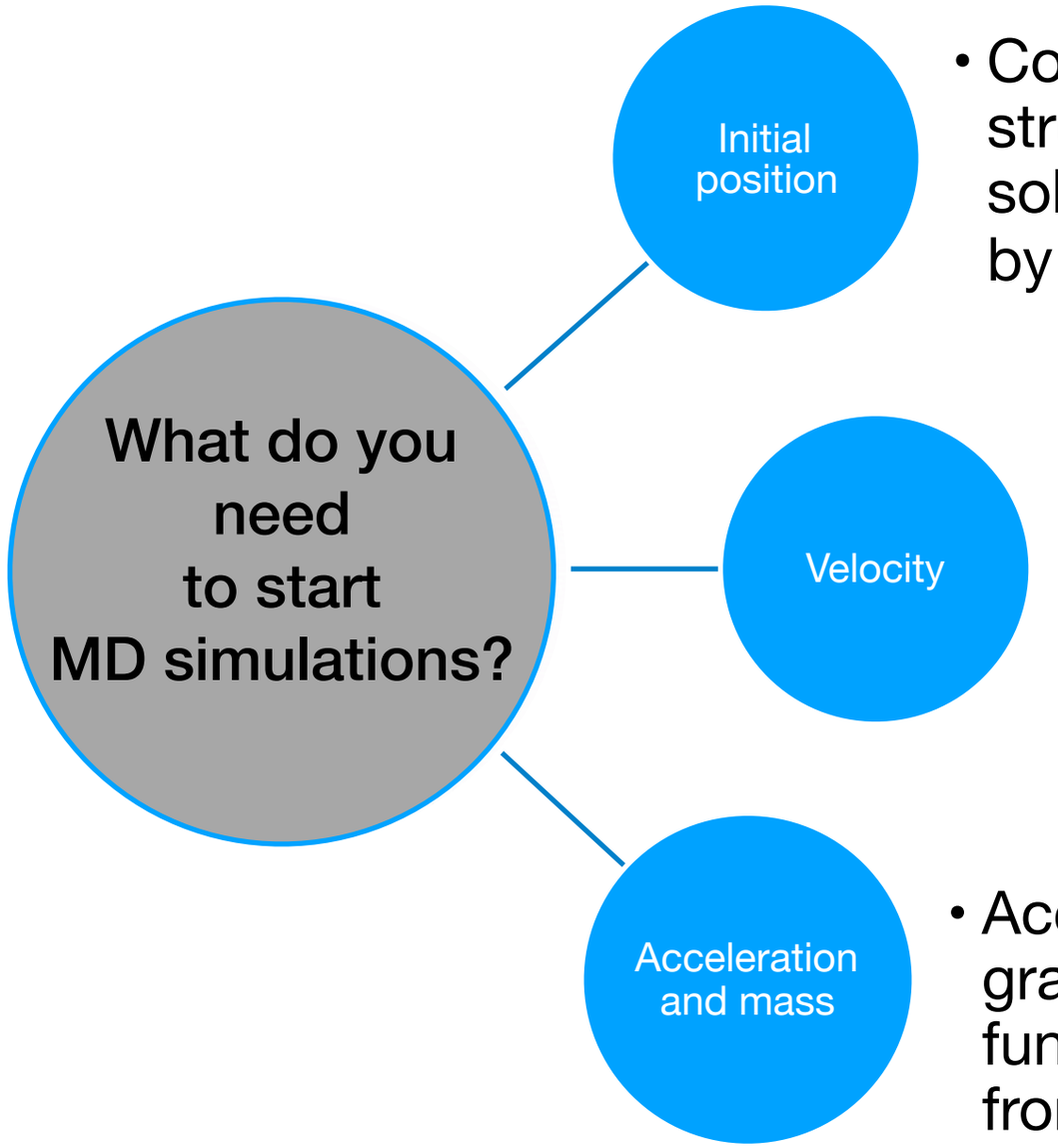



We need Thermostat to control temperature and pressure around the constant level

# MD: Change in conformation over time using a force field



# MD simulations ingredients




- Come from x-ray crystal structure of the protein or the solution structure determined by NMR spectroscopy

- Initial velocity ($V_i$) is chosen randomly from a Maxwell-Boltzmann distribution at a give temperature.

- Acceleration comes from the gradient of the potential energy function and mass can be obtained from a given topology.

# Atomic positions

```
                                        x        Y        Z
ATOM      1   N    GLU A   30       62.650   49.480   18.010
ATOM      2   H1   GLU A   30       62.060   48.690   18.210
ATOM      3   H2   GLU A   30       62.440   49.710   17.050
ATOM      4   H3   GLU A   30       63.650   49.370   18.120
ATOM      5   CA   GLU A   30       62.100   50.540   18.870
ATOM      6   HA   GLU A   30       62.420   51.530   18.550
ATOM      7   CB   GLU A   30       60.580   50.580   18.870
ATOM      8   HB1  GLU A   30       60.160   51.180   19.670
ATOM      9   HB2  GLU A   30       60.300   49.540   19.010
ATOM     10   CG   GLU A   30       59.930   50.950   17.530
ATOM     11   HG1  GLU A   30       60.200   50.260   16.730
ATOM     12   HG2  GLU A   30       60.360   51.910   17.220
ATOM     13   CD   GLU A   30       58.420   51.060   17.580
ATOM     14   OE1  GLU A   30       57.810   51.260   16.500
ATOM     15   OE2  GLU A   30       57.770   50.760   18.610
ATOM     16   C    GLU A   30       62.600   50.340   20.300
ATOM     17   O    GLU A   30       62.390   49.270   20.860
```

# Topology

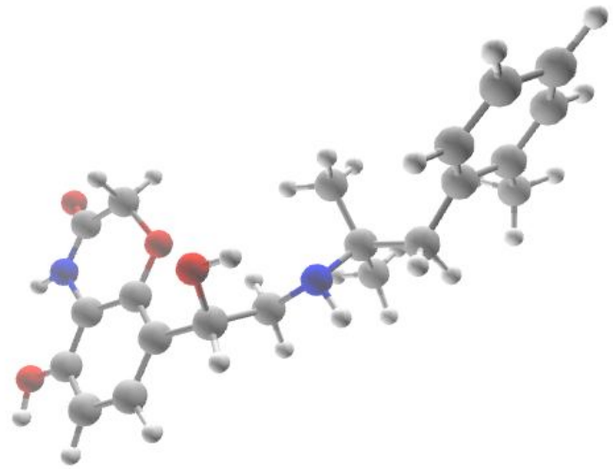
```
RESI p0g            1.000
GROUP           ! CHARGE
ATOM C1     CG331  -0.267
ATOM C2     CG331  -0.272
ATOM C3     CG331  -0.272
ATOM C7     CG2R61 -0.115
ATOM C8     CG2R61 -0.108
ATOM C9     CG2R61 -0.109
ATOM C10    CG2R61 -0.117
ATOM C11    CG2R61 -0.113
ATOM C12    CG2R61 -0.108
ATOM C13    CG321  -0.004
ATOM C14    CG324   0.187
ATOM C15    CG321  -0.179
ATOM C19    CG2O1   0.501
ATOM C20    CG2R61 -0.004
ATOM C21    CG2R61  0.107
ATOM C22    CG2R61 -0.011
ATOM C23    CG2R61  0.003
ATOM C24    CG2R61  0.150
ATOM C25    CG2R61  0.154
ATOM C26    CG311   0.132
ATOM C27    CG301   0.366
ATOM N16    NG3P2  -0.392
ATOM N17    NG2S1  -0.465
ATOM O4     OG2D1  -0.524
ATOM O5     OG311  -0.532
ATOM O6     OG311  -0.636
ATOM O18    OG3R60 -0.312
ATOM H11    HGA3    0.090
```

**Atom type**

**Point charge**

```
BOND H1    C11
BOND H5    O5
BOND O5    C21
BOND C11   C21
BOND C11   C12
BOND H2    C12
BOND C21   C24
BOND C12   C23
BOND H6    O6
BOND O6    C26
BOND C24   N17
BOND C24   C25
BOND C23   C25
BOND C23   C26
BOND H17   N17
BOND N17   C19
BOND C25   O18
BOND C26   H26
BOND C26   C14
BOND H42   C14
BOND C19   O4
BOND C19   C13
BOND C14   H41
BOND C14   N16
```

**How atoms are connected to each other**



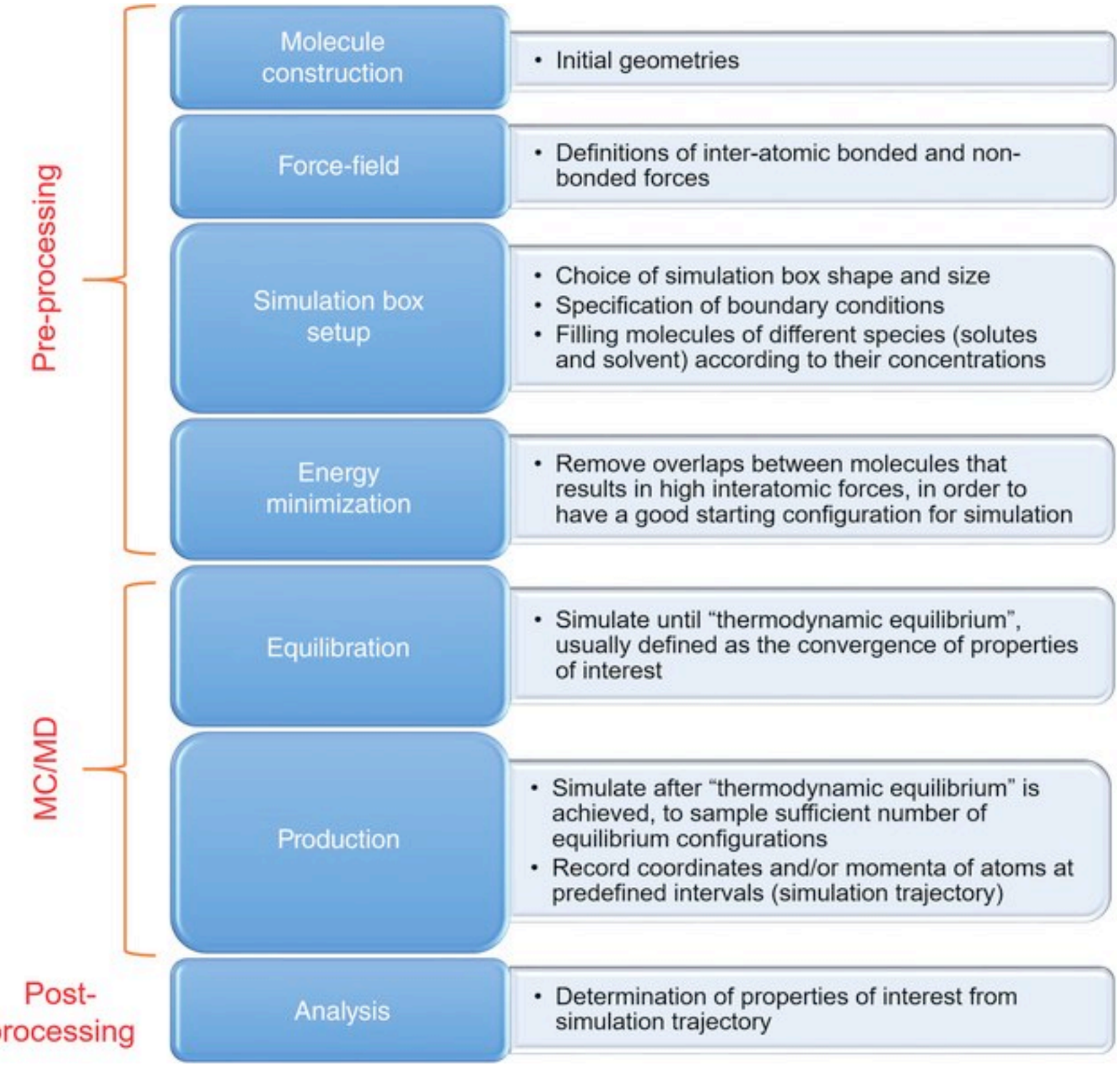
# Parameter

```
BONDS
CG301   NG3P2    200.00      1.4900

ANGLES
CG321   CG301   NG3P2     40.00     110.00
CG331   CG301   NG3P2     40.00     110.00
CG2R61  CG311   CG324     51.80     107.50
CG2R61  CG311   OG311     75.70     110.10
CG2O1   CG321   OG3R60   112.00     111.00
CG2R61  CG321   CG301     51.80     107.50
CG301   NG3P2   CG324     40.00     115.20
CG301   NG3P2   HGP2      30.00     110.80
CG2R61  OG3R60  CG321     20.00      99.00

DIHEDRALS
NG2S1   CG2O1   CG321   OG3R60      0.4000   1      0.00
OG2D1   CG2O1   CG321   OG3R60      0.0000   1      0.00
CG311   CG2R61  CG2R61  OG3R60      2.4000   2    180.00
CG321   CG2R61  CG2R61  CG331       2.4000   2    180.00
NG2S1   CG2R61  CG2R61  OG3R60      2.4000   2    180.00
CG2R61  CG2R61  CG311   CG324       0.2300   2    180.00
CG2R61  CG2R61  CG311   OG311       0.0000   2      0.00
CG2R61  CG2R61  CG321   CG301       0.2300   2    180.00
CG2R61  CG2R61  OG3R60  CG321       1.6200   2    180.00
CG2R61  CG2R61  OG3R60  CG321       0.1900   4    180.00
CG331   CG301   CG321   CG2R61      0.0400   3      0.00
NG3P2   CG301   CG321   CG2R61      0.2000   3      0.00
NG3P2   CG301   CG321   HGA2        0.1950   3      0.00
NG3P2   CG301   CG331   HGA3        0.2000   3      0.00
CG321   CG301   NG3P2   CG324       0.1000   3      0.00
CG321   CG301   NG3P2   HGP2        0.1000   3      0.00
CG331   CG301   NG3P2   CG324       0.1000   3      0.00
CG331   CG301   NG3P2   HGP2        0.1000   3      0.00
CG2R61  CG311   CG324   NG3P2       0.2000   3      0.00
CG2R61  CG311   CG324   HGA2        0.0000   3      0.00
OG311   CG311   CG324   NG3P2       0.1950   3      0.00
CG2R61  CG311   OG311   HGP1        2.1000   1      0.00
CG2R61  CG311   OG311   HGP1        1.4000   2      0.00
CG2R61  CG311   OG311   HGP1        0.7400   3      0.00
CG2O1   CG321   OG3R60  CG2R61      0.7000   3      0.00
HGA2    CG321   OG3R60  CG2R61      0.9000   3      0.00
CG311   CG324   NG3P2   CG301       0.4000   1      0.00
CG311   CG324   NG3P2   CG301       0.2500   2      0.00
CG311   CG324   NG3P2   CG301       0.6000   3      0.00
HGA2    CG324   NG3P2   CG301       0.1000   3      0.00
```

# Scheme of MD simulations




Molecular simulations in drug delivery: Opportunities and challenges,Ratna S. Katiyar Prateek K. Jha, 2019, Computational Molecular Science.