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# Molecular dynamics

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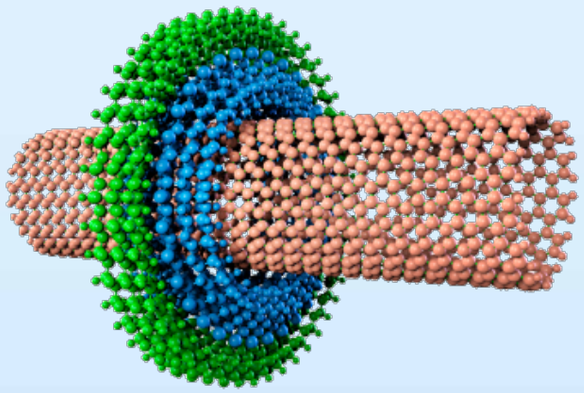
# Outline

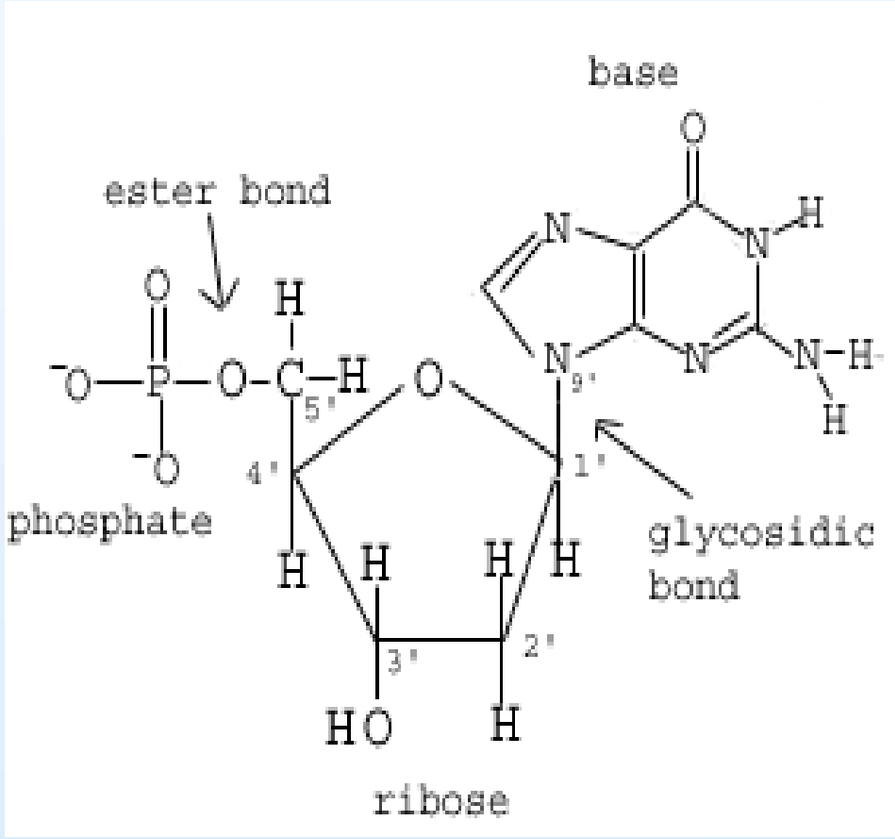
- The idea
- Approximations and validity
- Molecular mechanics, force fields
- Numerical simulations
- Technical details
- High performance computing
- Examples

# Motivation

## Matter at the nano scale



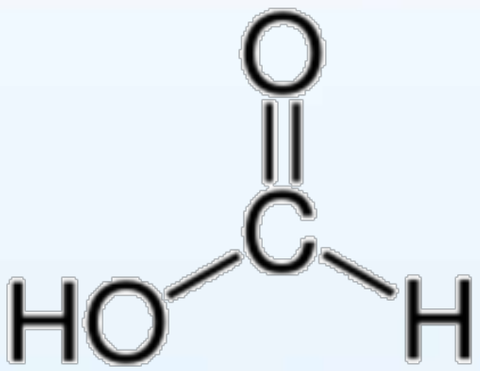
Atom scale ~ $10^{-10}$ m



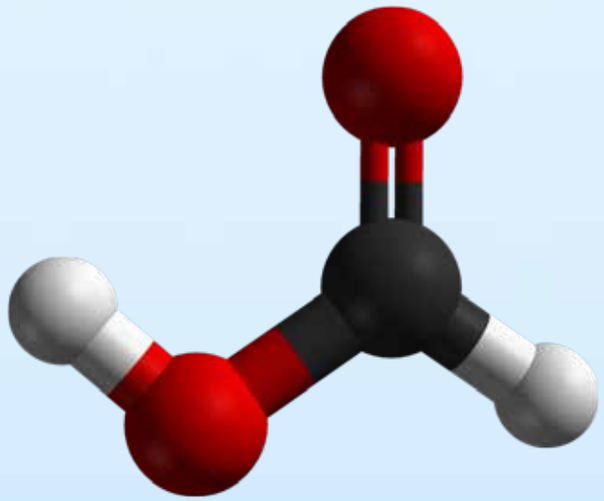

Molecules = atoms connected with bonds

# The idea

## Molecular dynamics simulations




**Formic acid**

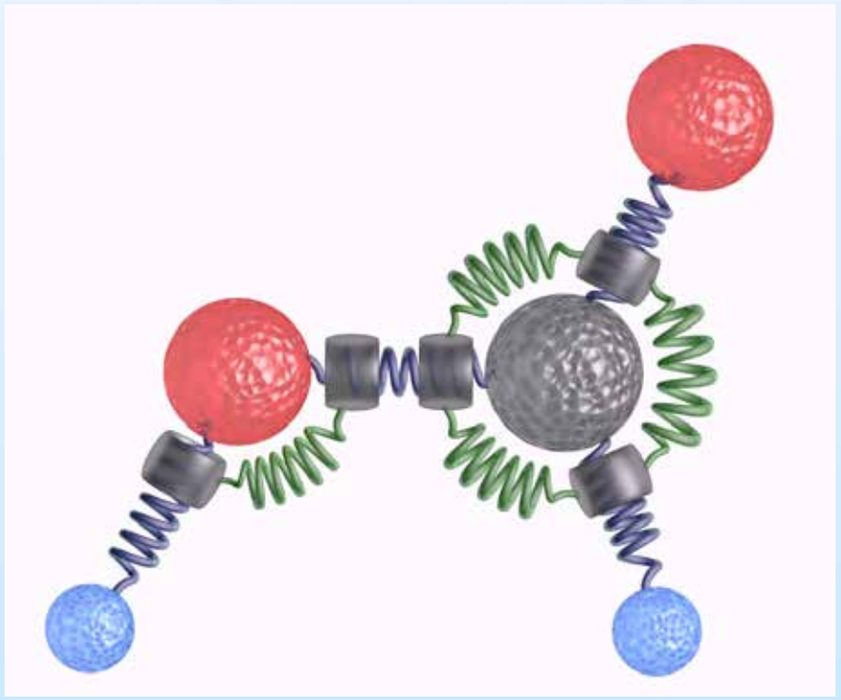


Laws of classical mechanics

$$\vec{F} = m * \vec{a}$$

Principles of statistical physics

$$P \propto exp(-E/kT)$$



# Fundamentals: from quantum to classical

$$i\hbar\frac{\partial}{\partial t}\Psi = \hat{H}\Psi$$

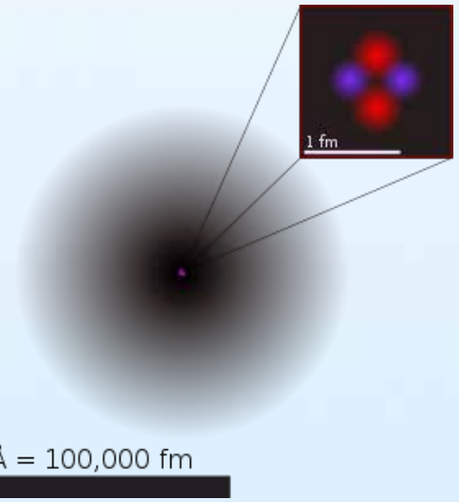
Time dependent non-relativistic Schrödinger equation

$$E\Psi(\mathbf{r}) = \frac{-\hbar^2}{2m}\nabla^2\Psi(\mathbf{r}) + V(\mathbf{r})\Psi(\mathbf{r})$$

Time independent Schrödinger equation for a single particle

$$\Psi_{\text{total}} = \psi_{\text{electronic}} \times \psi_{\text{nuclear}}$$

Born-Oppenheimer approx.



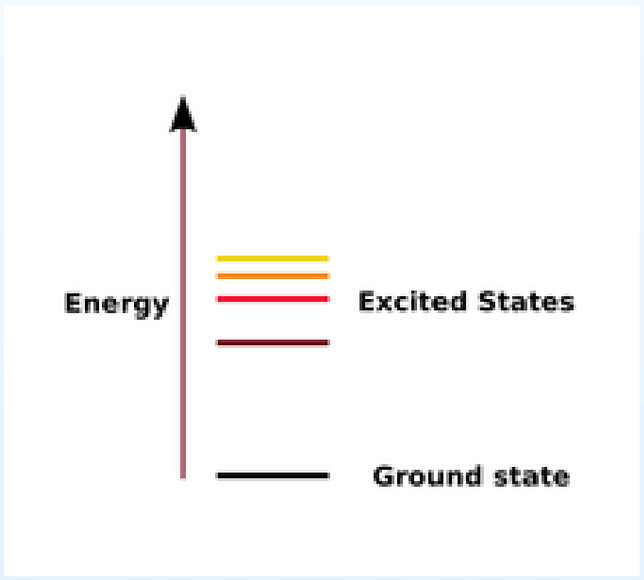

electron mass approx. 1/1836 that of the proton

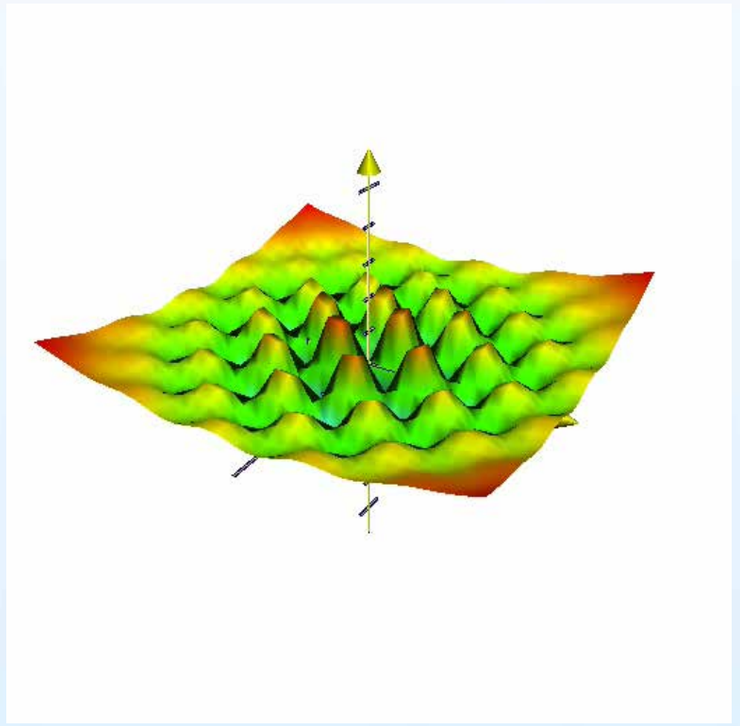
$$H_{\text{e}}(\mathbf{r},\mathbf{R})\ \chi(\mathbf{r},\mathbf{R}) = E_{\text{e}}\ \chi(\mathbf{r},\mathbf{R})$$

$E_{\text{e}}(\mathbf{R})$ - potential energy surface

# Fundamentals: from quantum to classical

$E_{\mathrm{e}}(\mathbf{R})$ - potential energy surface



Ground state of
electronic wave function

The nuclei movements are considered classical

$$i\hbar\frac{\partial}{\partial t}\Psi = \hat{H}\Psi \quad \Rightarrow \quad \frac{d\mathbf{p}}{dt} = -grad(E_{\mathrm{e}}(\mathbf{R}))$$

# Approximations, restrictions and gains

1. BO approx. (adiabatic approx.)
   No nonadiabatic processes (charge-transfer reactions, photochemistry)
2. Ground state
   No electronic excitations, no electron-phonon coupling, etc
3. Classical approx. for nuclei movement
   No proton transfer, atom tunneling, etc

On the good side – big systems, long evolution times, nice parallelization and scaling

TD Schrödinger eq. – 3 atoms

MD – 10^9 atoms, up to milliseconds

# Mechanics: main concepts

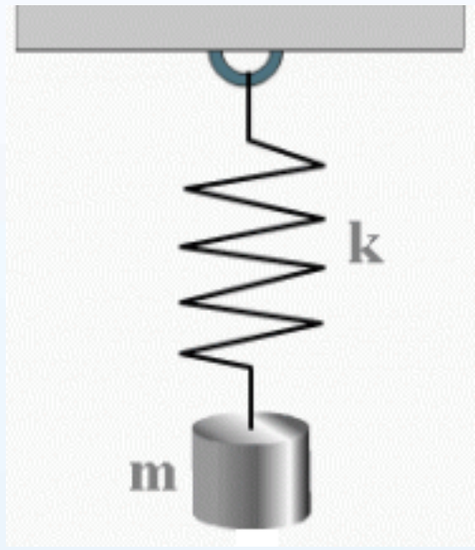
Newton laws

$$\vec{F} = m * \vec{a}$$

$$\vec{a} = \frac{d\vec{v}}{dt} = \frac{d^2\vec{r}}{dt^2}$$

$$\vec{F} = -grad(U)$$

$$\vec{p} = m\vec{v}$$




$$U = \frac{kx^2}{2}$$

U – potential energy
T – kinetic energy
H – full energy, Hamiltonian

$$\frac{d^2\vec{r}}{dt^2} = \vec{F}/m$$

$$T = \frac{mv^2}{2}$$

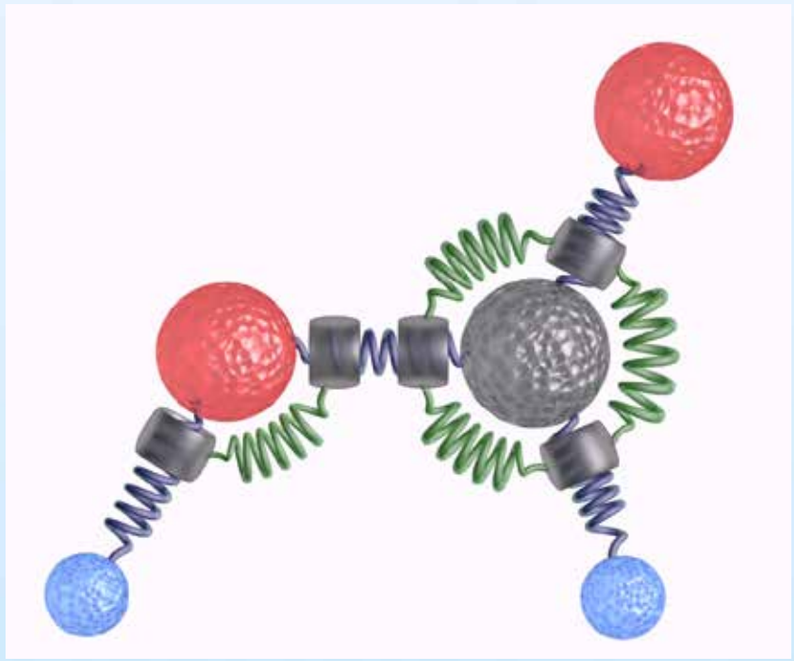
$$H = T + U$$

# PES, force field

$$\frac{d^2\vec{r}}{dt^2} = -grad(U) \qquad U = E_e(\vec{r}) \qquad H_e\,\chi = E_e\,\chi$$

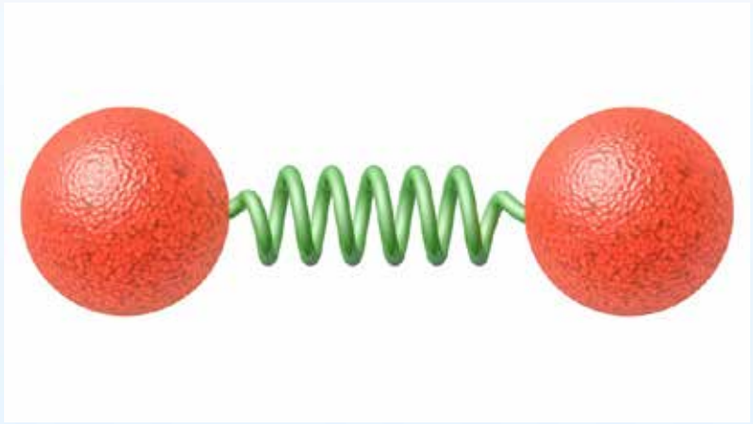
Empirical potential energy functions
– force fields

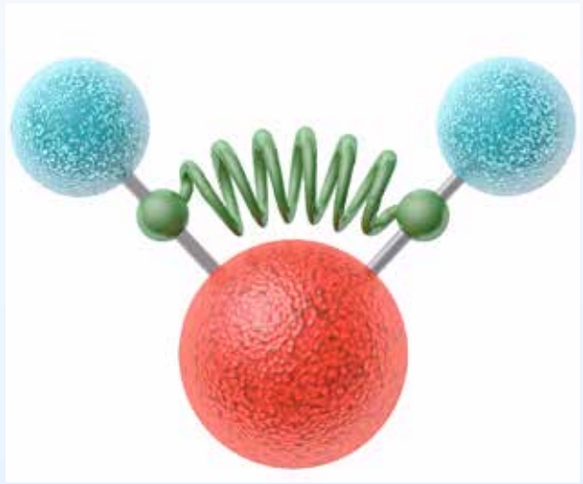
1. Knowledge of chemical structure
2. Combination of typical simple interaction terms
3. Often pair wise additive
4. Empirical parameters fit to experimental or ab initio data



# Typical force field

## Bonded terms



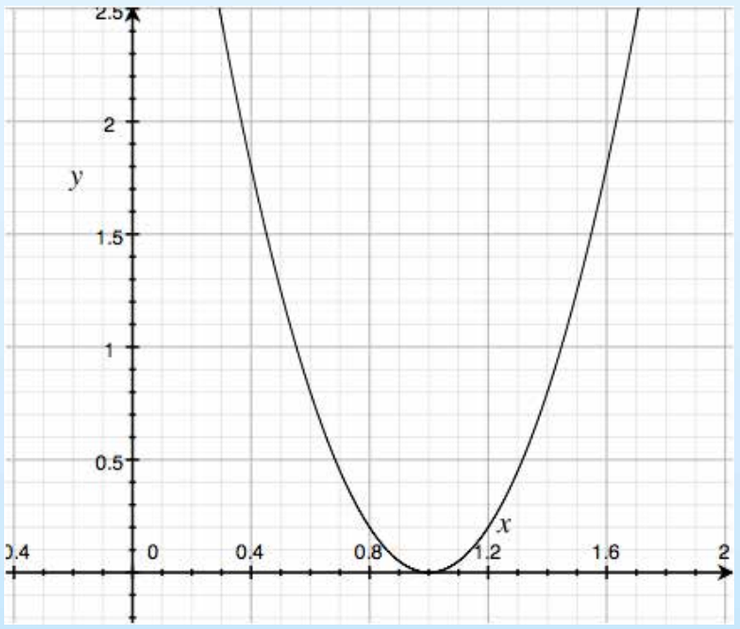


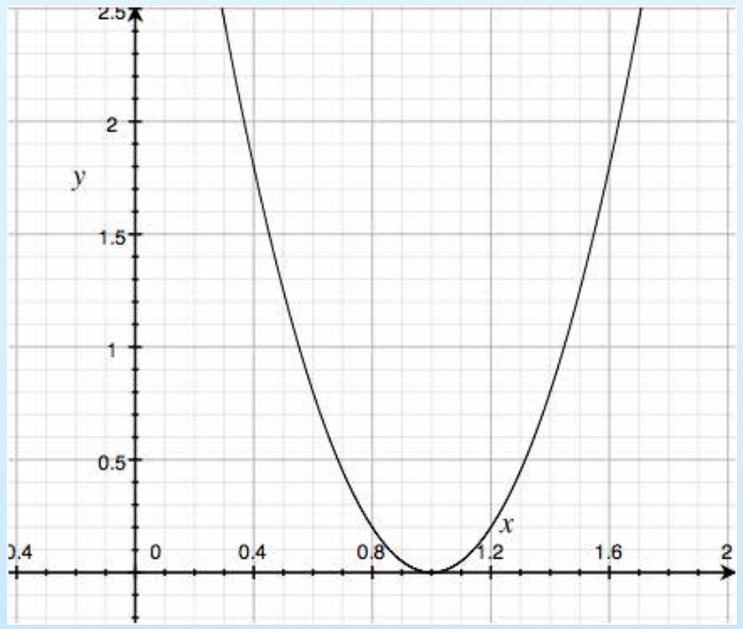


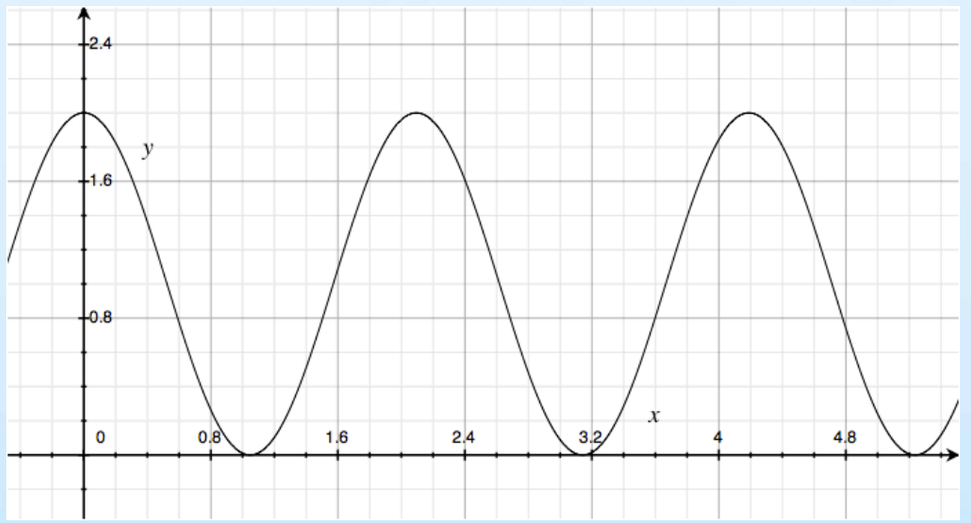
$$U_{bond} = \frac{k(l - l_0)}{2}$$

$$U_{ang} = \frac{k(\theta - \theta_0)}{2}$$

$$U_{tor} = V[1 + cos(n\phi - \phi_0)]$$



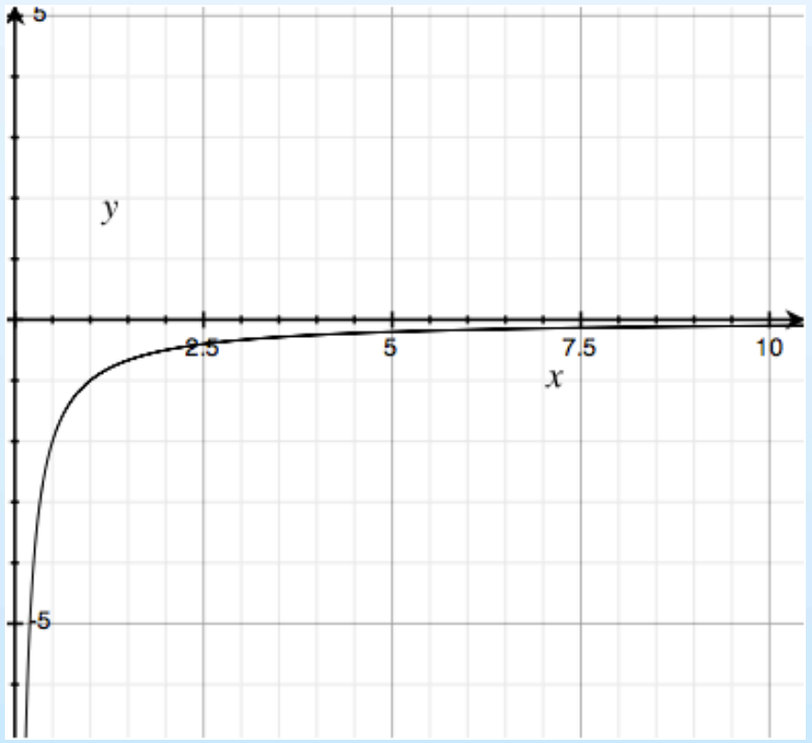



# Typical force field

## Non-bonded terms

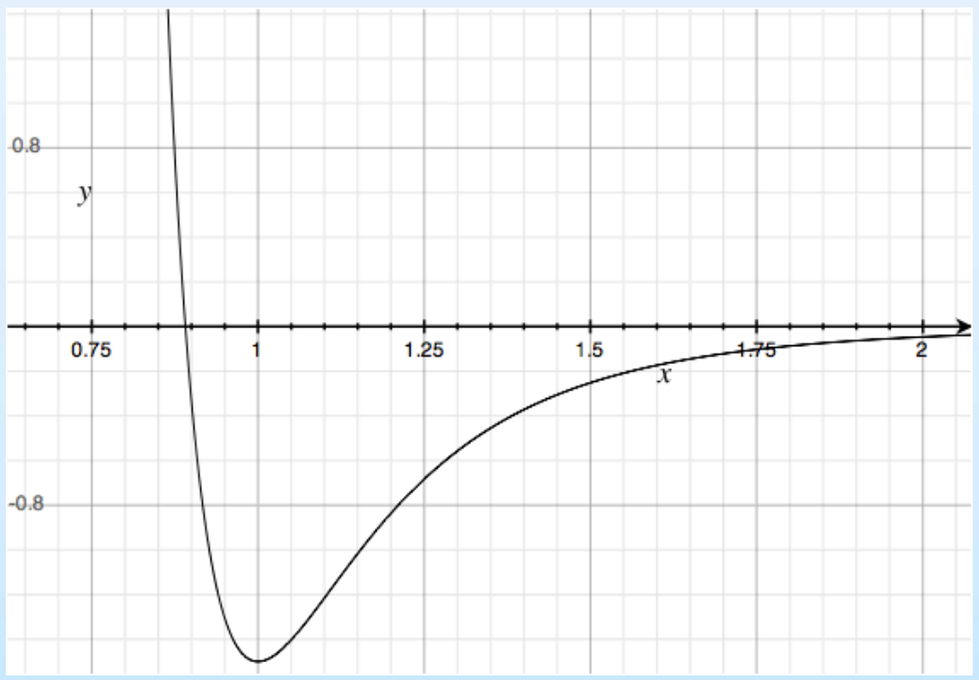
### Coulomb

$$U_q = \frac{q_i q_j}{r}$$

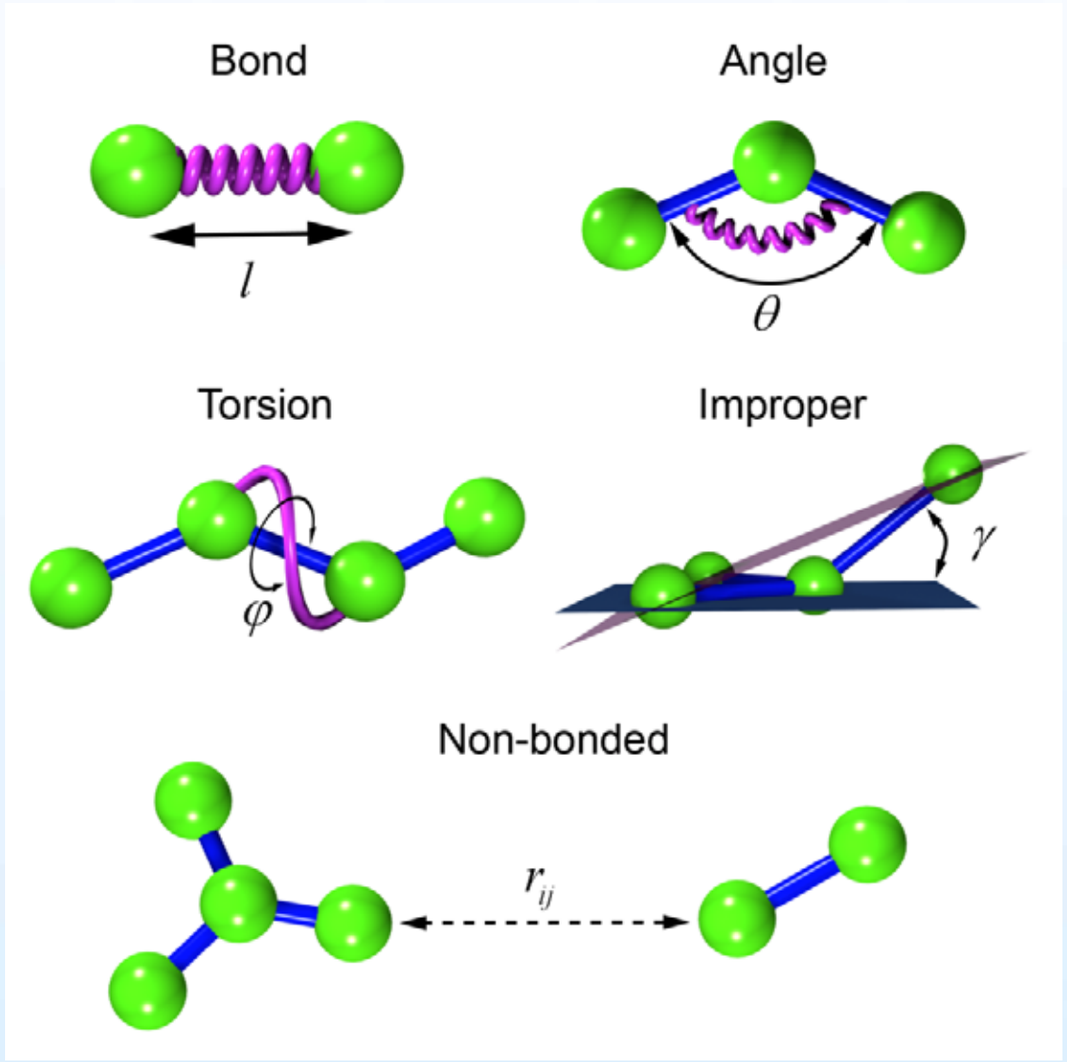



### Lennard-Johnes

$$U_{LJ} = 4\epsilon \left[ \left( \frac{\sigma}{r} \right)^{12} - \left( \frac{\sigma}{r} \right)^{6} \right]$$



# Typical force field




$$U(\{\vec{r}_i\}) = \sum_{bonds} \frac{1}{2} k_b (l - l_0)^2 + \sum_{angles} \frac{1}{2} k_\theta (\theta - \theta_0)^2 + \sum_{torsions} \frac{1}{2} V_n [1 + \cos(n\varphi - \varphi_0)]$$

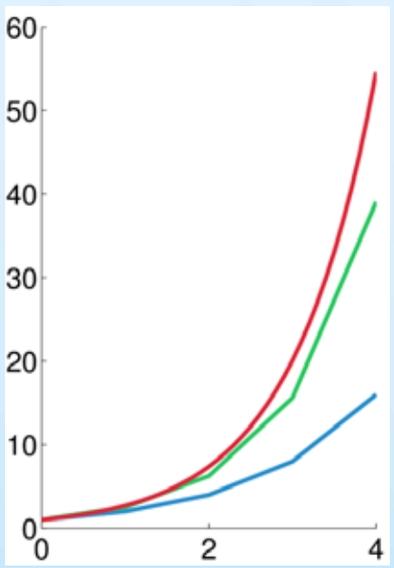
$$+ \sum_{impropers} \frac{1}{2} k_\gamma (\gamma - \gamma_0)^2 + \sum_{j=1}^{N-1} \sum_{i=j+1}^{N} \left\{ 4\epsilon_{ij} \left[ \left( \frac{\sigma_{ij}}{r_{ij}} \right)^{12} - \left( \frac{\sigma_{ij}}{r_{ij}} \right)^{6} \right] + \frac{q_i q_j}{4\pi\epsilon_0 r_{ij}} \right\} f_{ij}$$

# Integrating equations of motion

$$\begin{cases} \frac{d\vec{r_i}}{dt} = \vec{v}_i \\ \frac{d\vec{v_i}}{dt} = \vec{F}_i/m_i \end{cases} \Longrightarrow \begin{cases} \frac{\vec{r_i}(t+\Delta t)-\vec{r_i}(t)}{\Delta t} = \vec{v}_i \\ \frac{\vec{v_i}(t+\Delta t)-\vec{v_i}(t)}{\Delta t} = \vec{F}_i(t)/m_i \end{cases}$$

Euler Scheme

$$\left\{ \begin{array}{c} \vec{r_i}(t) \\ \vec{v_i}(t) \end{array} \right\} \Rightarrow \left\{ \begin{array}{c} \vec{r_i}(t+\Delta t) = \vec{r_i}(t) + \vec{v_i}(t) * \Delta t \\ \vec{v_i}(t+\Delta t) = \vec{v_i}(t) + \frac{\vec{F_i}(t)}{m_i} * \Delta t \end{array} \right\}$$




- First order algorithm
- Instable
- High energy drifts
- No time reversibility
- Not area preserving (non-symplectic)

# Integrating equations of motion

## Störmer-Verlet scheme

$$\frac{\frac{\vec{r_i}(t+\Delta t)-\vec{r_i}(t)}{\Delta t} - \frac{\vec{r_i}(t)-\vec{r_i}(t-\Delta t)}{\Delta t}}{\Delta t} = \frac{\vec{F_i}(t)}{m_i}$$

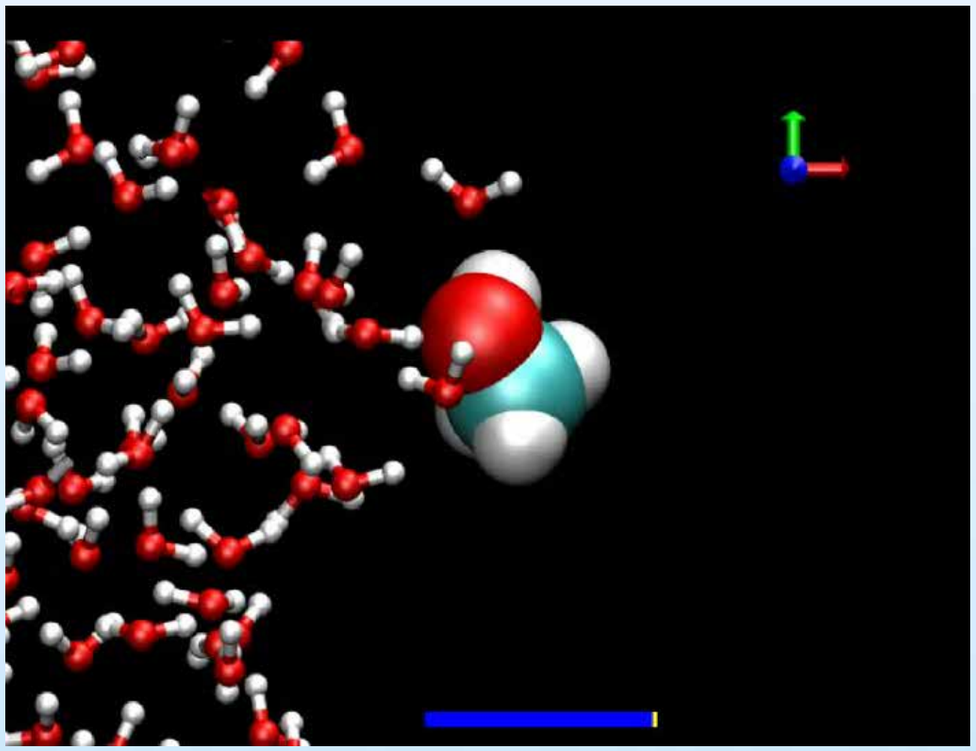
$$\vec{r_i}(t+\Delta t) = 2\vec{r_i}(t) - \vec{r_i}(t-\Delta t) + \frac{\vec{F_i}(t)}{m_i} * \Delta t^2$$

- No long term energy drift (except for rounding errors)
- Nice stability
- Time reversible
- Global error of order O(t^2)

# Integrating equations of motion

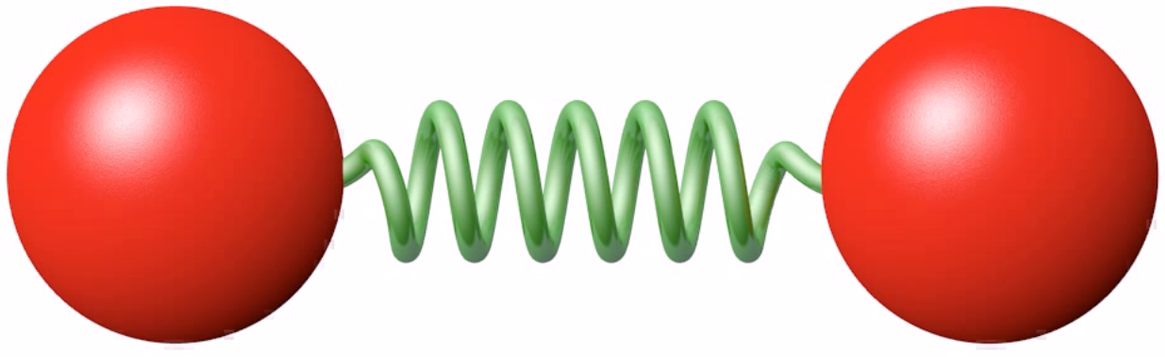
Velocity verlet scheme (leap frog)

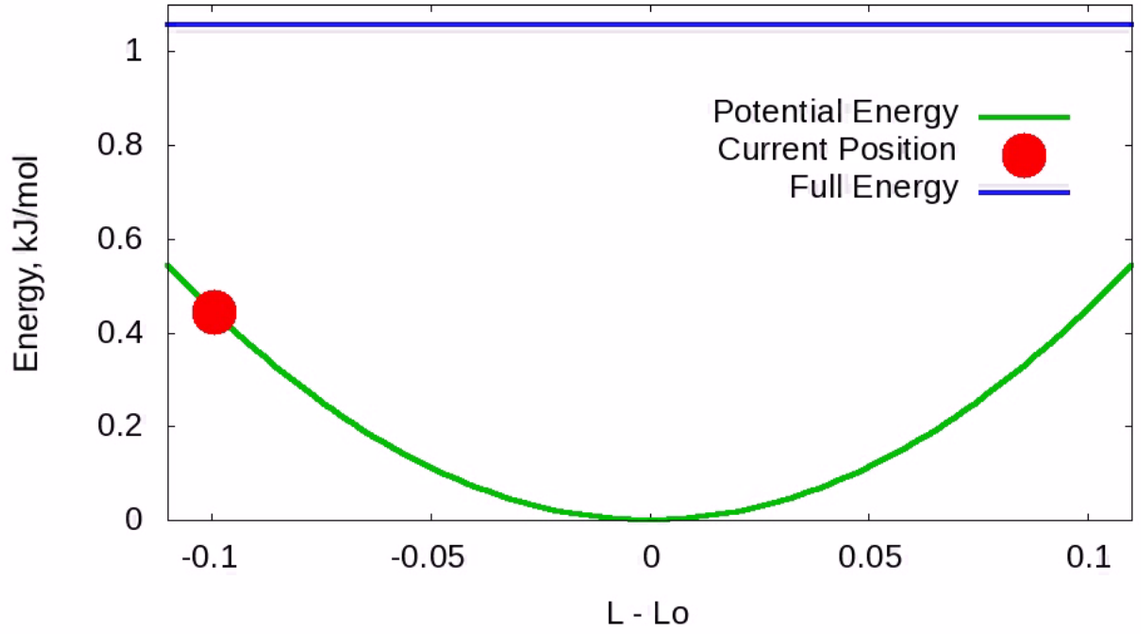
$$\begin{cases} \vec{r_i}(t+\Delta t) = \vec{r_i}(t) + \vec{v_i}(t)\,\Delta t + \frac{1}{2}\vec{a_i}\Delta t^2 \\ \vec{v_i}(t+\Delta t) = \vec{v_i}(t) + \frac{\vec{a_i}(t)+\vec{a_i}(t+\Delta t)}{2}\Delta t \end{cases}$$



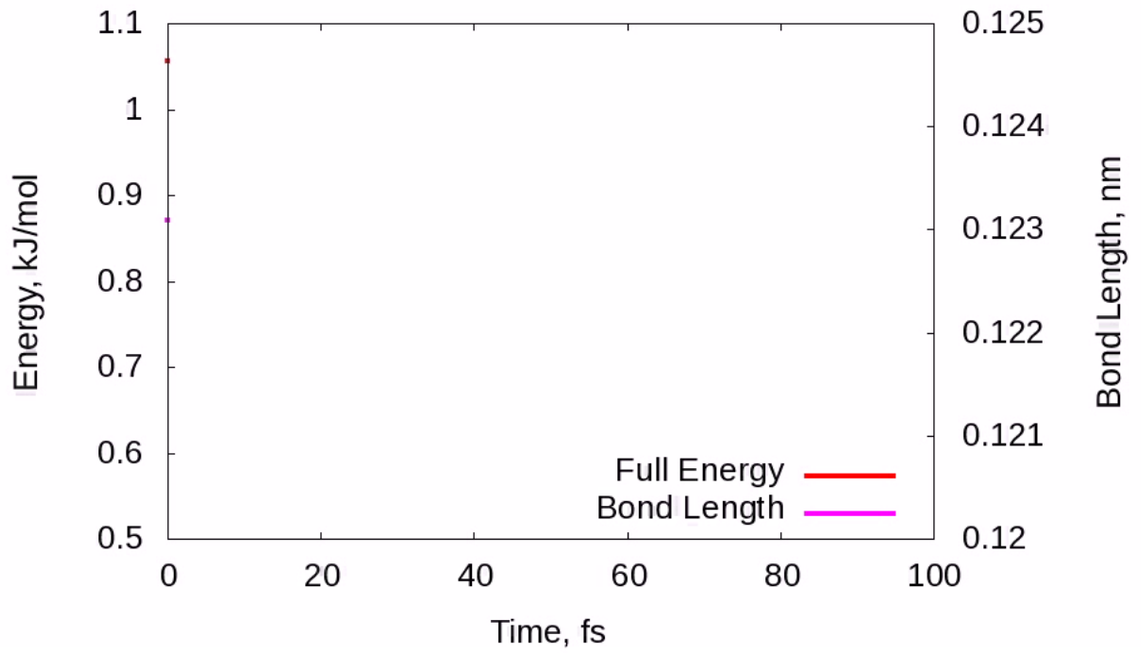
Example of MD simulation

# Integrating equations of motion






Oxygen molecule
NVE simulation
Leap-frog integrator
Integration step 1 fs

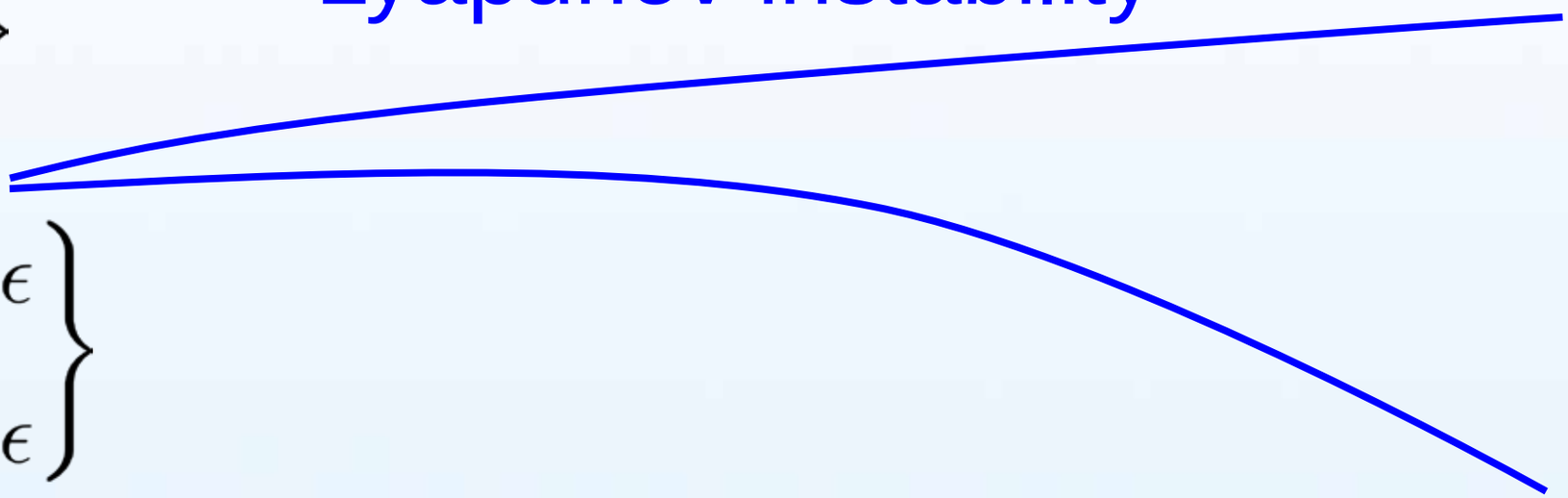


# MD picture vs reality?

$$\left\{ \begin{array}{c} \vec{v_i^0} \\ \vec{r_i^0} \end{array} \right\}$$

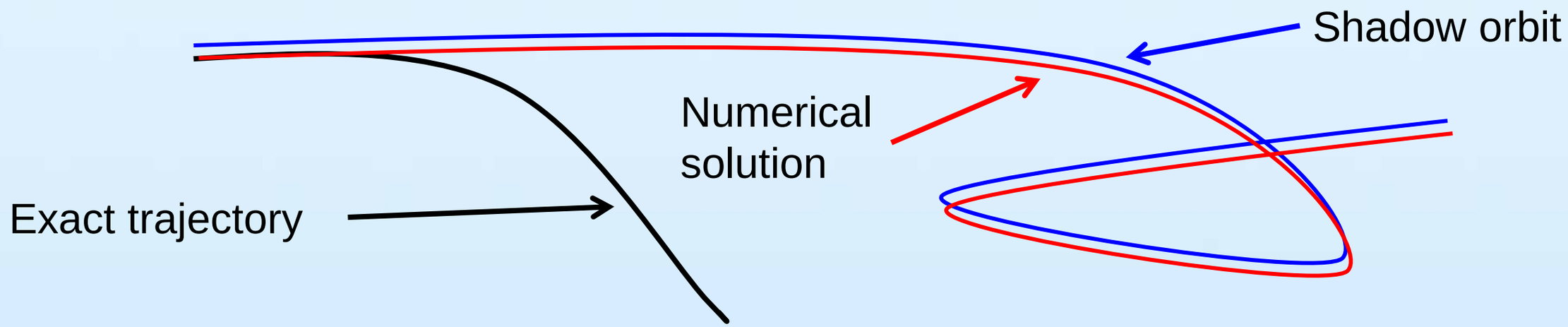
$$\left\{ \begin{array}{c} \vec{v_i^0} + \epsilon \\ \vec{r_i^0} + \epsilon \end{array} \right\}$$

Lyapunov instability



How can we know that we generate correct results in MD?

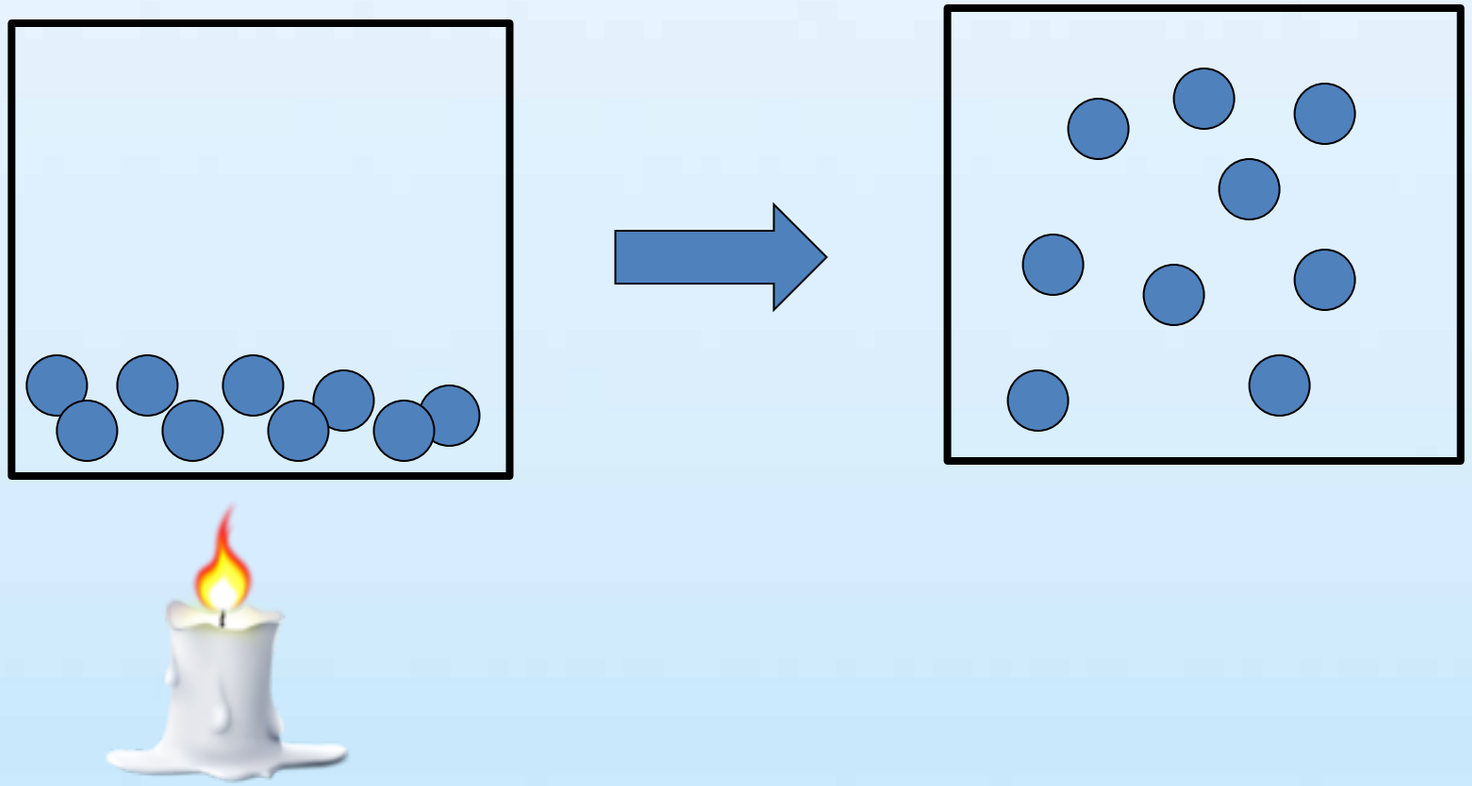
- We can not know for sure, but there is hope ...




A *shadow orbit* is an exact trajectory for the system, that starts from a slightly different initial point

# MD picture vs reality?

The aim of MD is not to predict precisely what will happen to a system that has been prepared in precisely known initial conditions – but to predict average behavior of the system prepared in an initial state about which we know something but not everything.



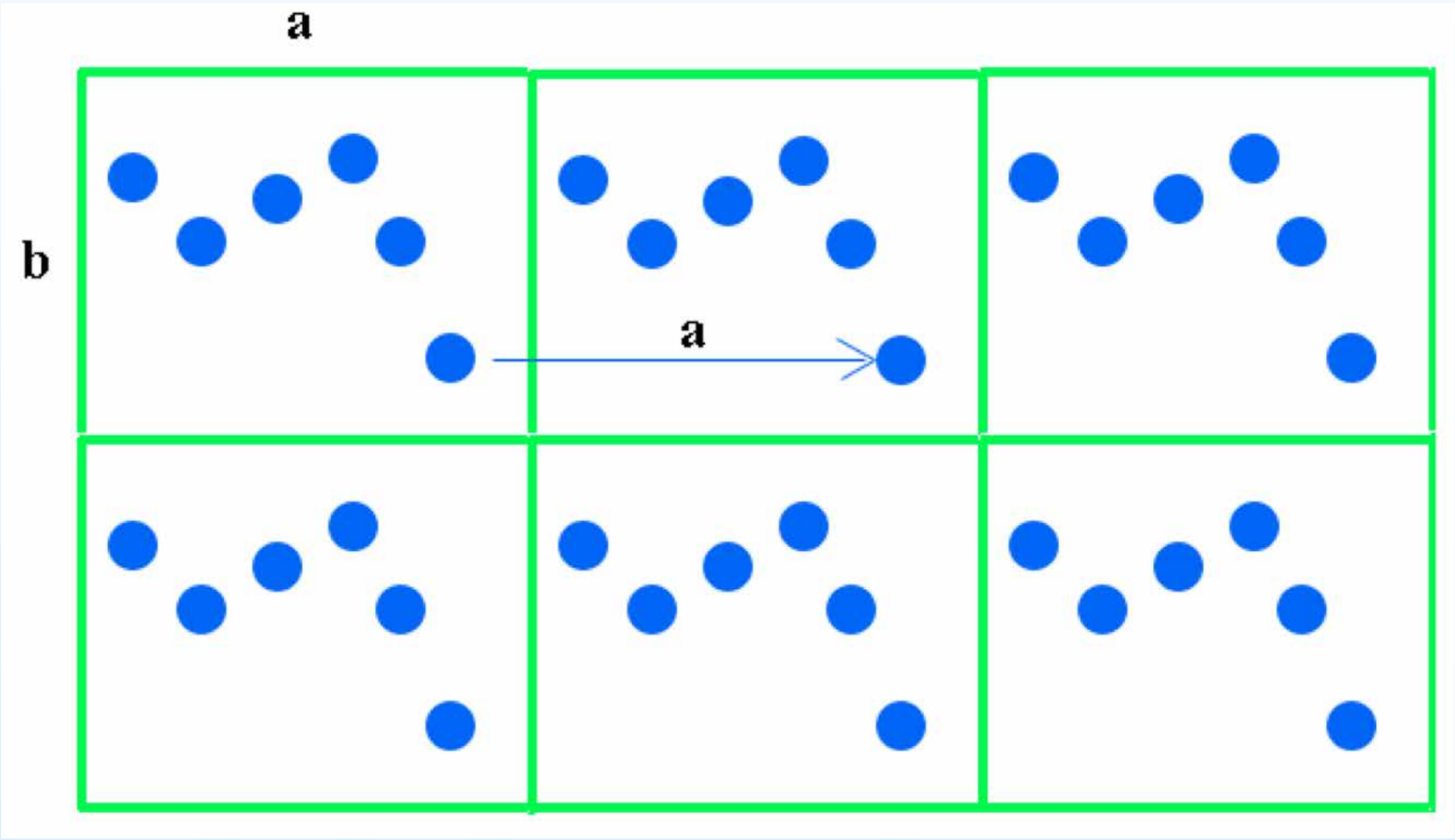
# MD tricks: level 1

Needed almost in every simulation

- Periodic boundary conditions
- Interaction cut off
- Constant temperature/pressure simulations
- Parallelization and HPC computing

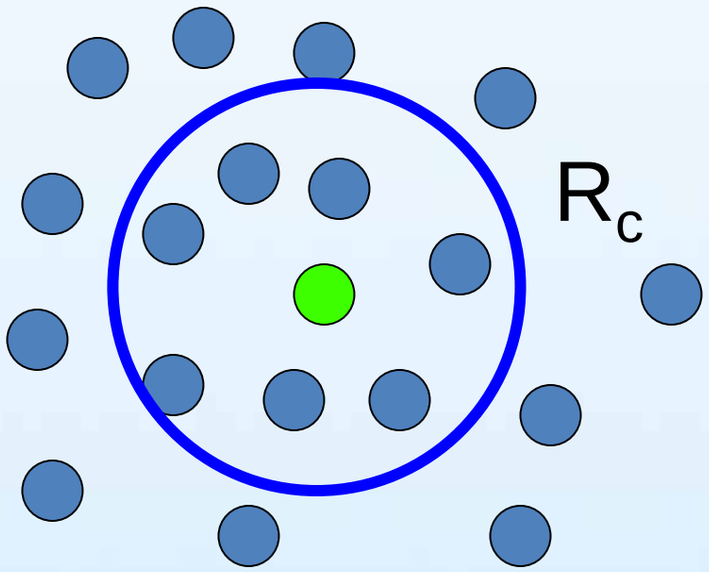
# Periodic boundary conditions

## A trade off against boundary effects

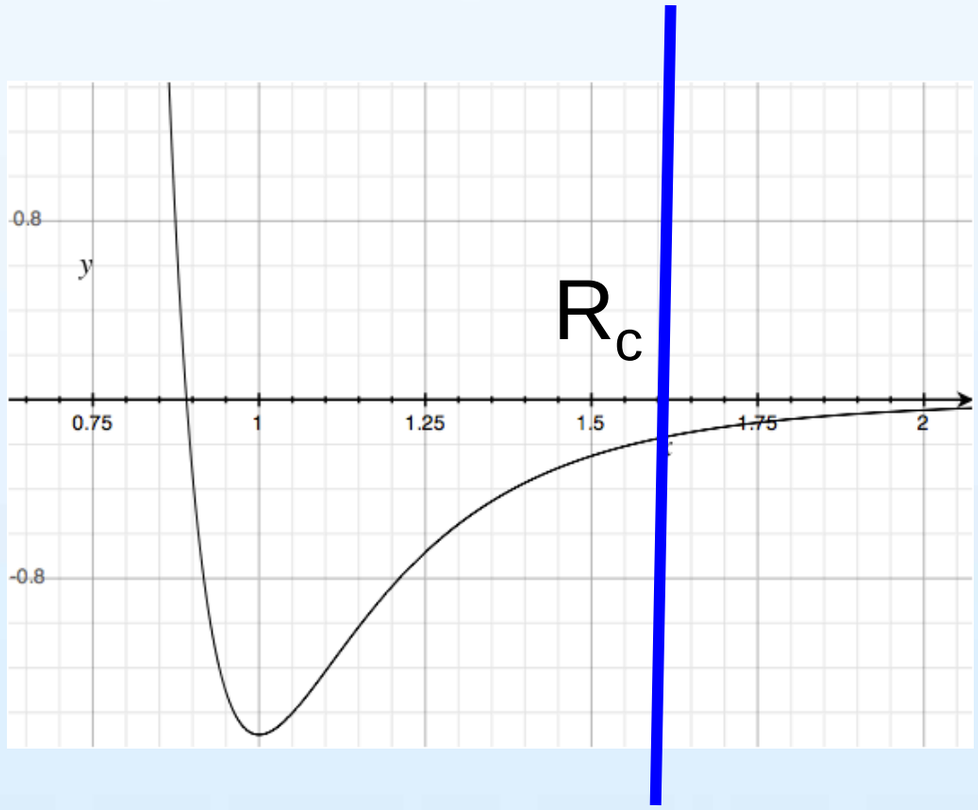



$$\vec{r}_{klm} = \vec{r} + k * \vec{a} + l * \vec{b} + m * \vec{c}$$

# Cutoff schemes



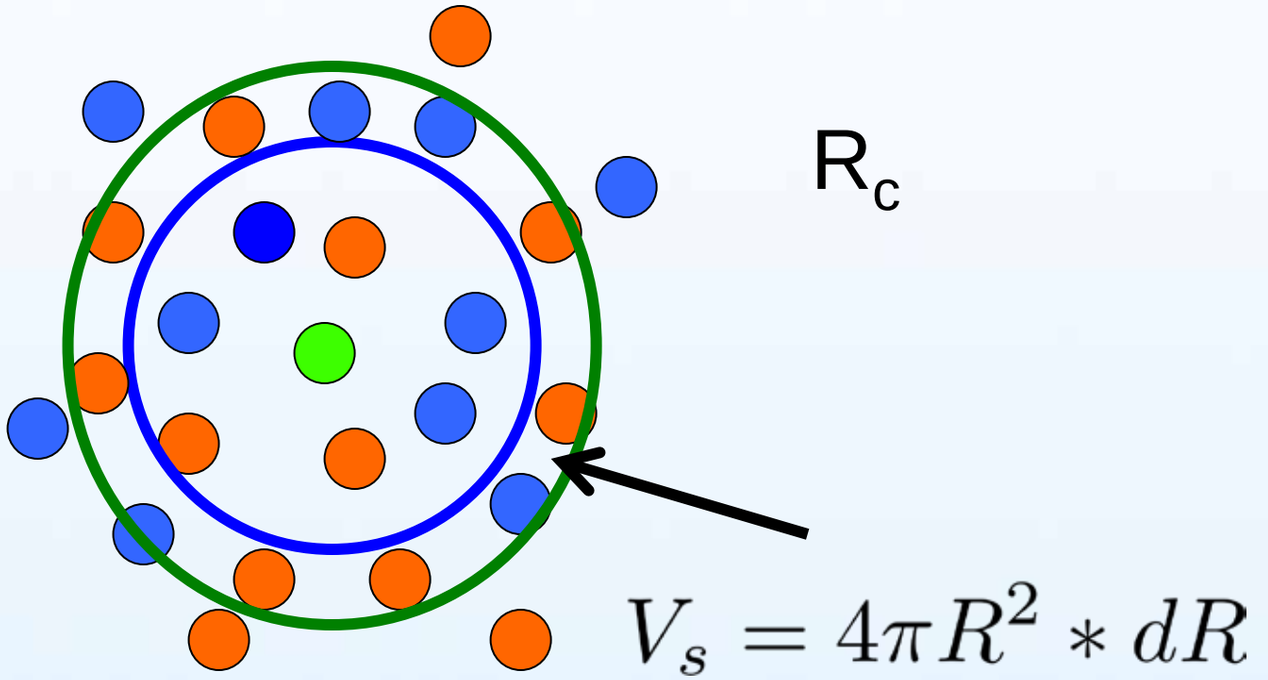

Simple cutoff radius



# Electrostatics

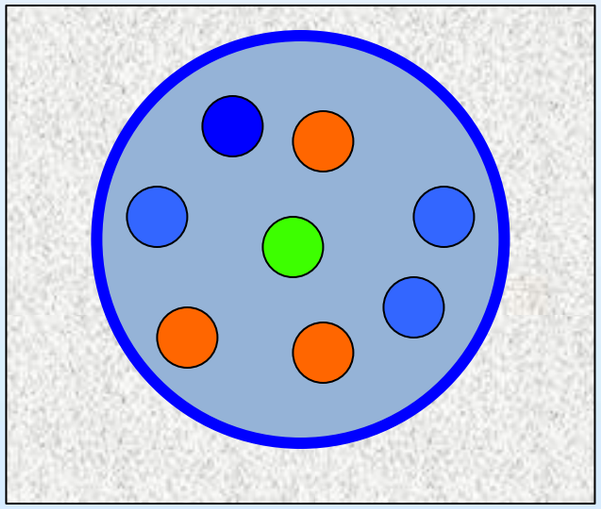
$$U_q = \frac{q_i q_j}{r}$$

Coulomb potential



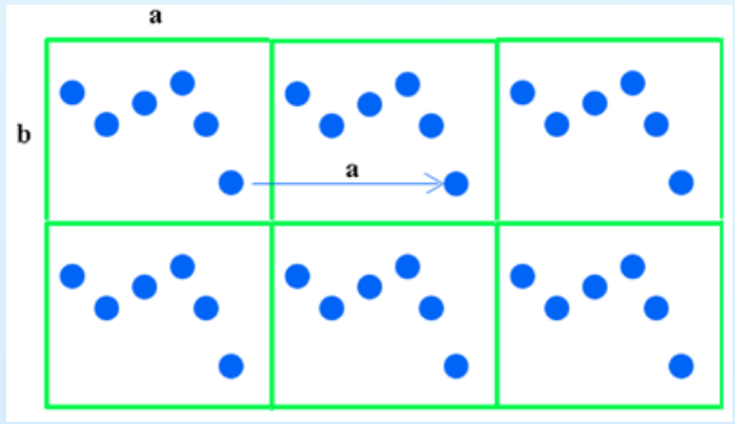

$$\phi(r_i) = q\sum_{j+}^{\infty}\frac{1}{|r_i - r_{j+}|} - q\sum_{j-}^{\infty}\frac{1}{|r_i - r_{j-}|}$$

## Reaction field



Make use of Poisson-Boltzmann equation

## Ewald summation



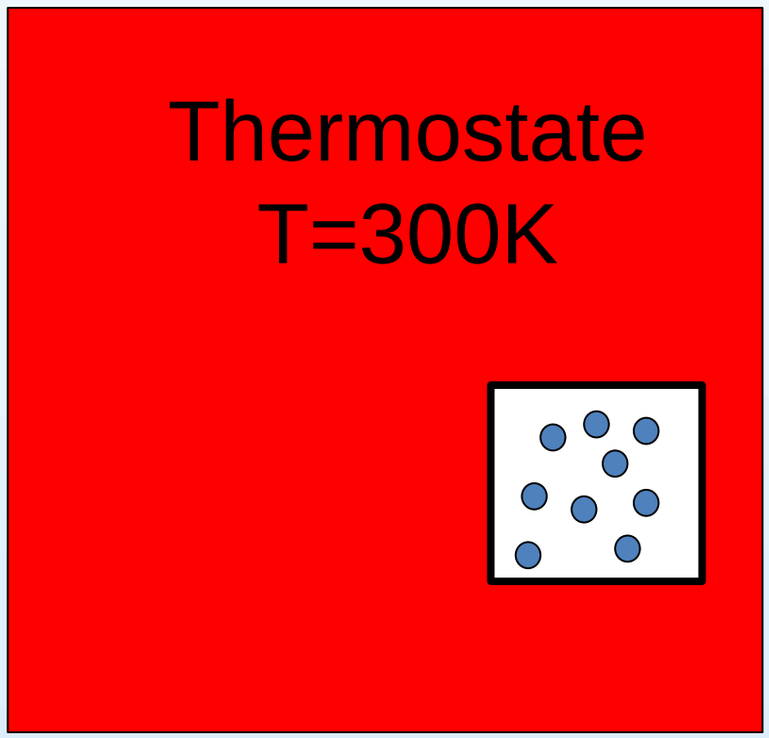

Make use of periodicity and reciprocal space summation

# Constant temperature simulations

- Why use temperature coupling?
- -Compensate energy drift
- -NVT ensemble

$$P_{microstate} \propto e^{-\frac{H}{kT}}$$

Gibbs distribution




Two possibilities:
1)Add stochastic interactions
2)Use modified equations of motion

# Constant temperature simulations 2

## Stochastic approach

Andersen thermostat
-random collision with virtual particles

$$P(t) = \nu e^{-\nu t}$$

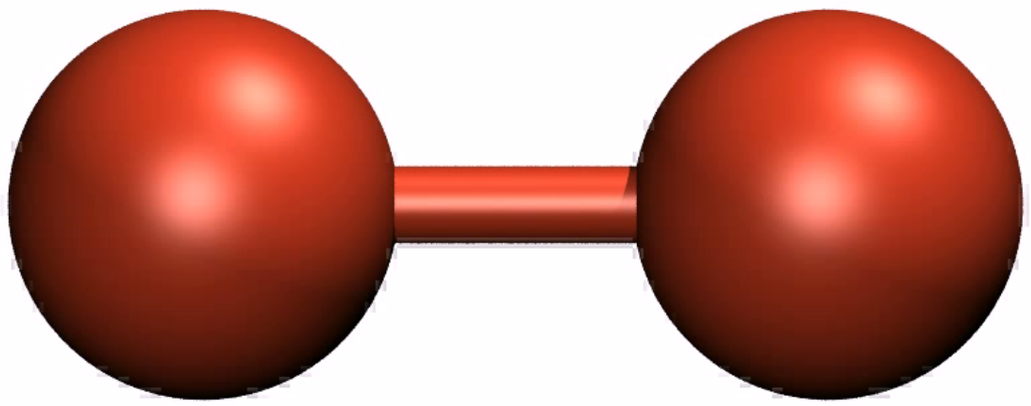
Langevin stochastic dynamics
-add friction and stochastic term

$$m\frac{d^2\vec{r_i}}{dt^2} = \vec{F_i} - \lambda\frac{d\vec{r_i}}{dt} + \boldsymbol{\eta}\left(t\right)$$

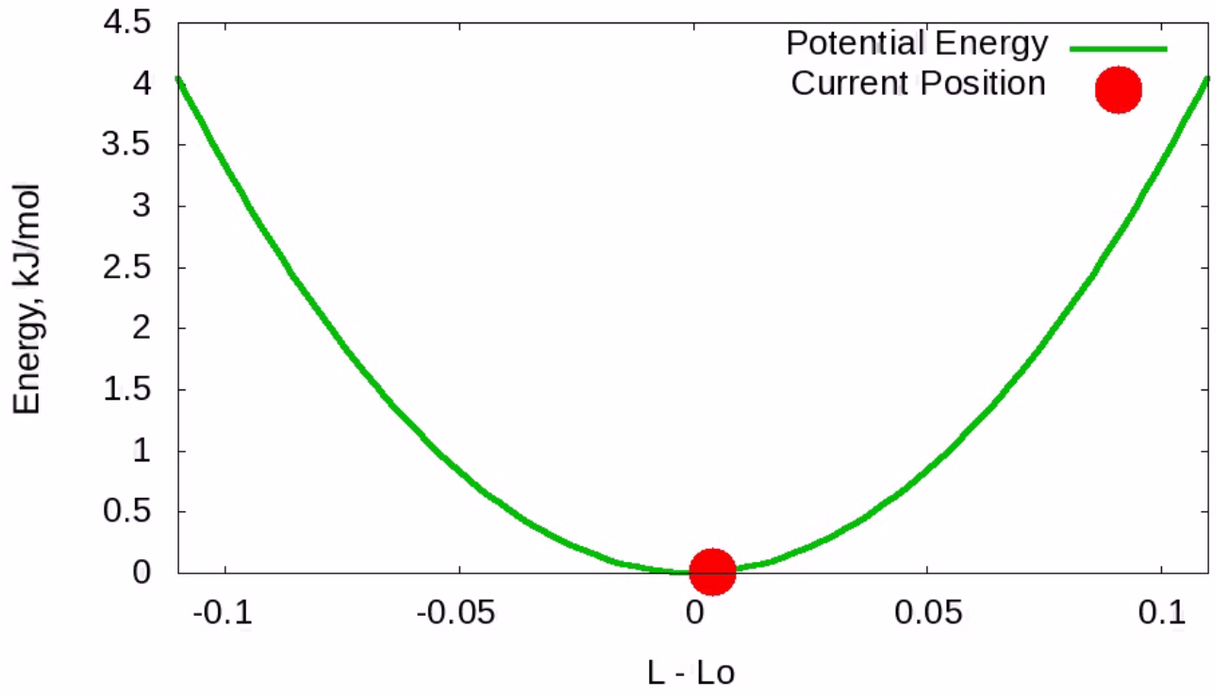
$$\left\langle \eta_i\left(t\right)\eta_j\left(t'\right)\right\rangle = 2\lambda k_B T\delta_{i,j}\delta\left(t-t'\right)$$

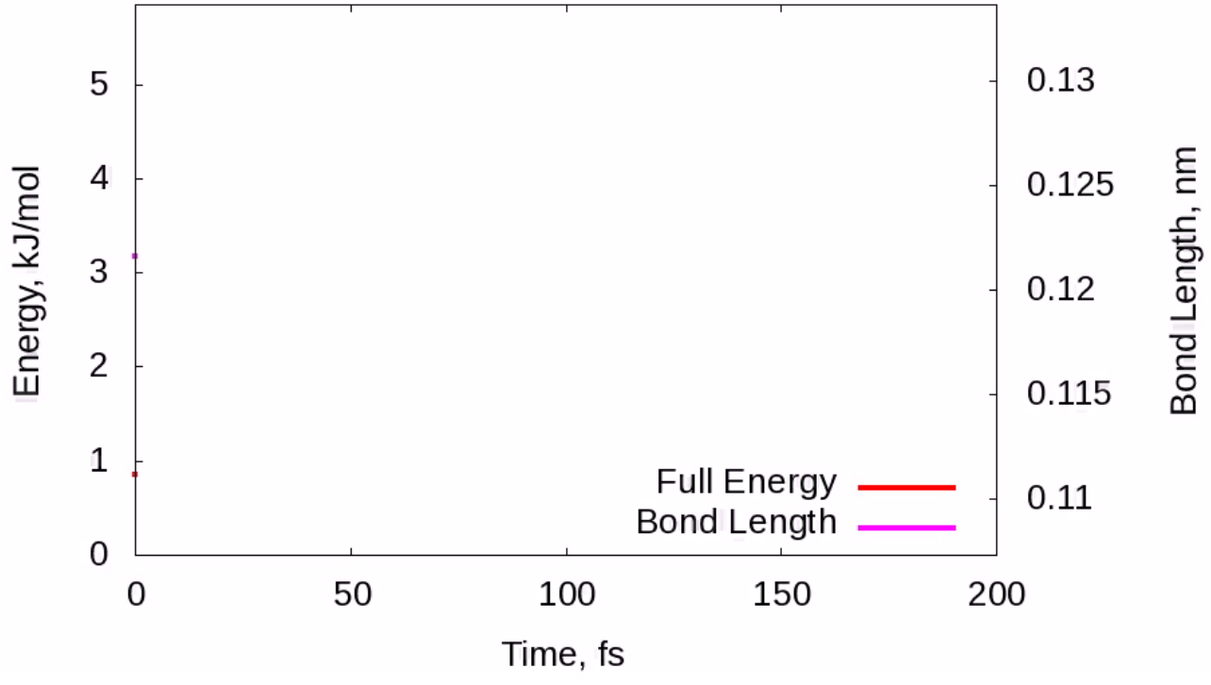
# Constant temperature simulations 2

## Langevin dynamics



Oxygen molecule
Stochastic dynamics simulation



# Constant temperature simulations 3

## Berendsen thermostat

$$\frac{kT}{2}(3N - N_c) = \sum_{i=1}^{N} m_i \vec{v_i}^2$$

-instantaneous temperature

Modify equations of motion

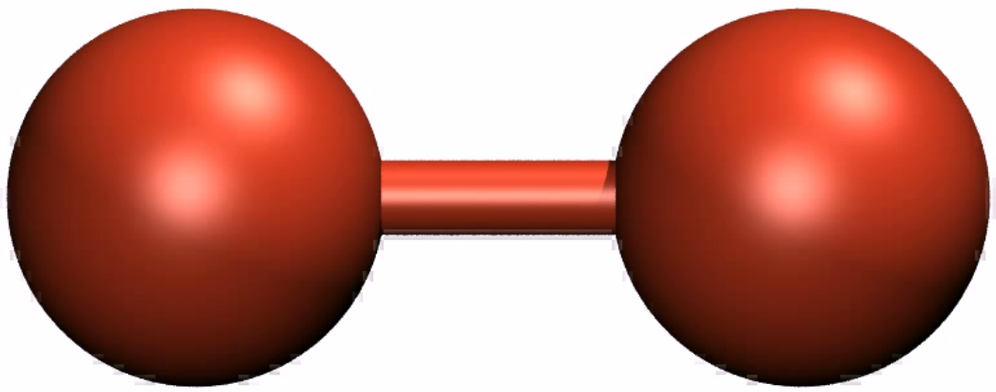
-re-scale the velocities of particles, multiply by

$$\lambda = \sqrt{T_0/T(t)}$$

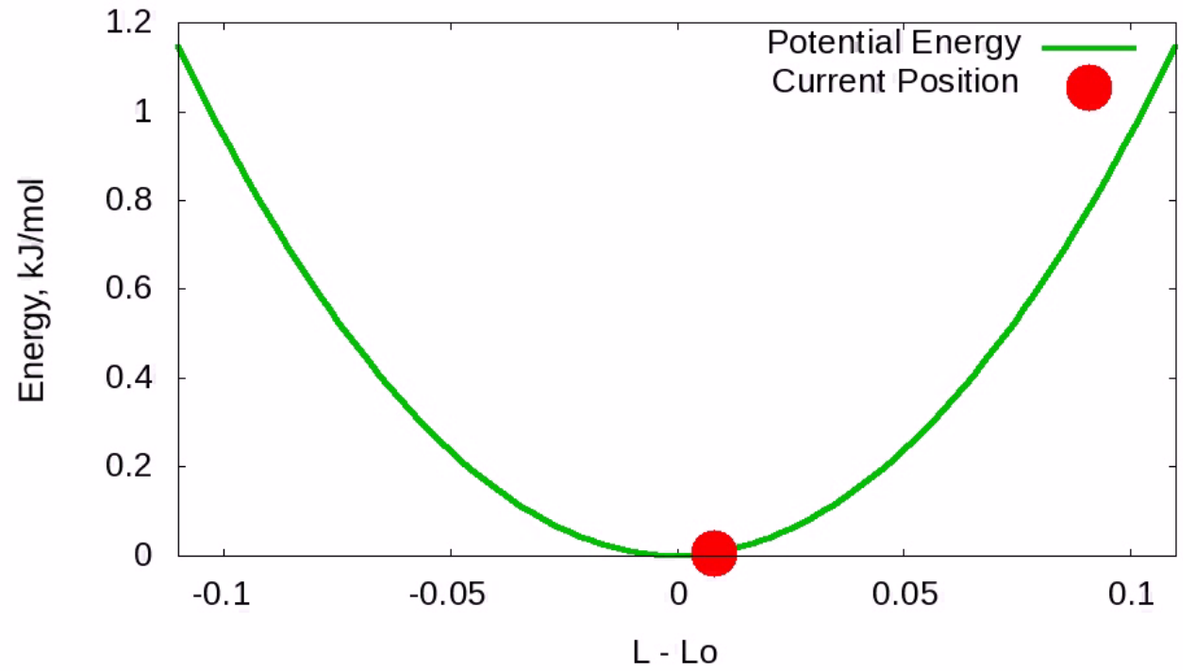
(!) incorrect ensemble, flying ice cube effect

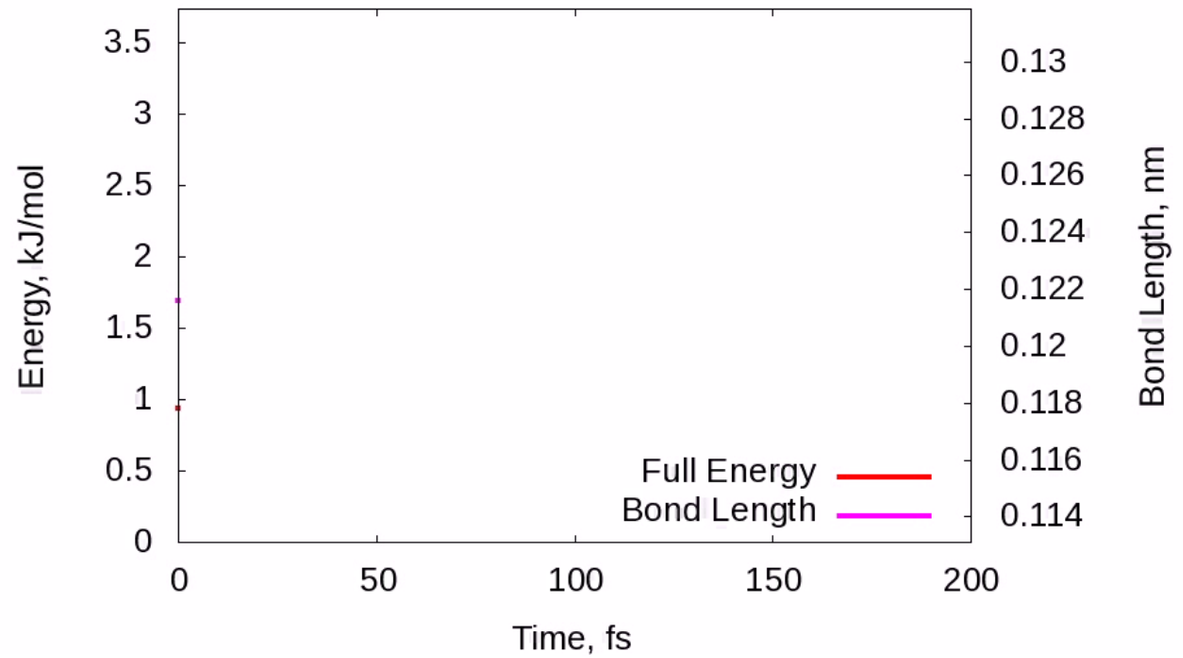
# Constant temperature simulations 3

## Berendsen thermostat



Oxygen molecule
NVT simulation
Leap-Frog integrator
Integration step 1 fs
Berendsen thermostat



# Constant temperature simulations 3

## Nose-Hoover thermostat

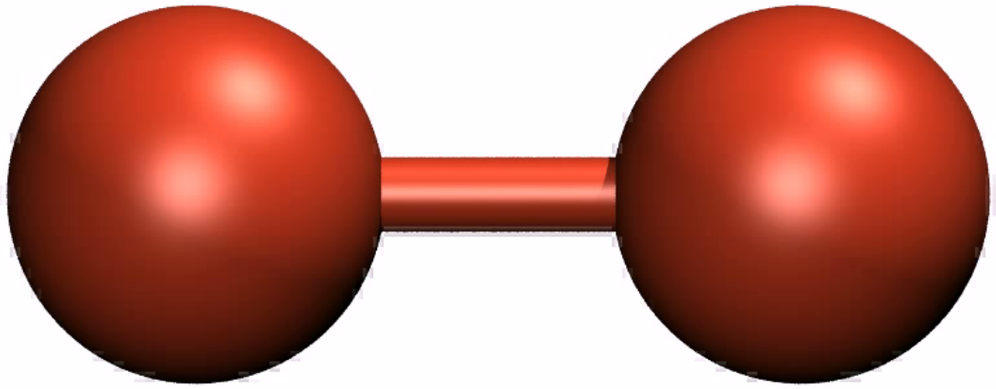
Extended system approach
-add a “bath particle”
-modify equations of motion, Non-Hamiltonian dynamics
-gives NVT ensemble if:
1) No external forces, 2) there is only one conservation law, 3) the system is ergodic

$$\begin{cases} \dfrac{d^2\vec{r_i}}{dt^2} = \dfrac{F_i}{m_i} - \dfrac{d\xi}{dt}\dfrac{d\vec{r_i}}{dt} \\ \dfrac{d^2\xi}{dt^2} = \dfrac{N_f k}{Q}\left[T - T_0\right] \end{cases}$$

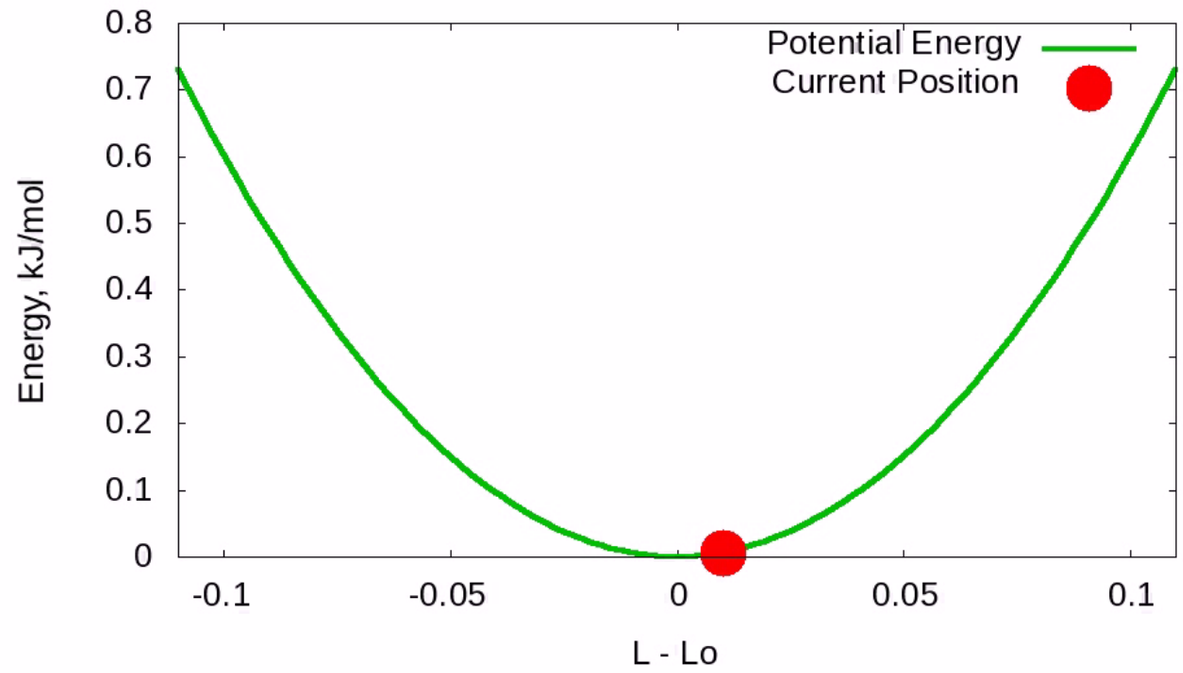
$$E_{NH} = E_k + U + \frac{1}{2}Q\dot{\xi}^2 + N_f k T \xi$$

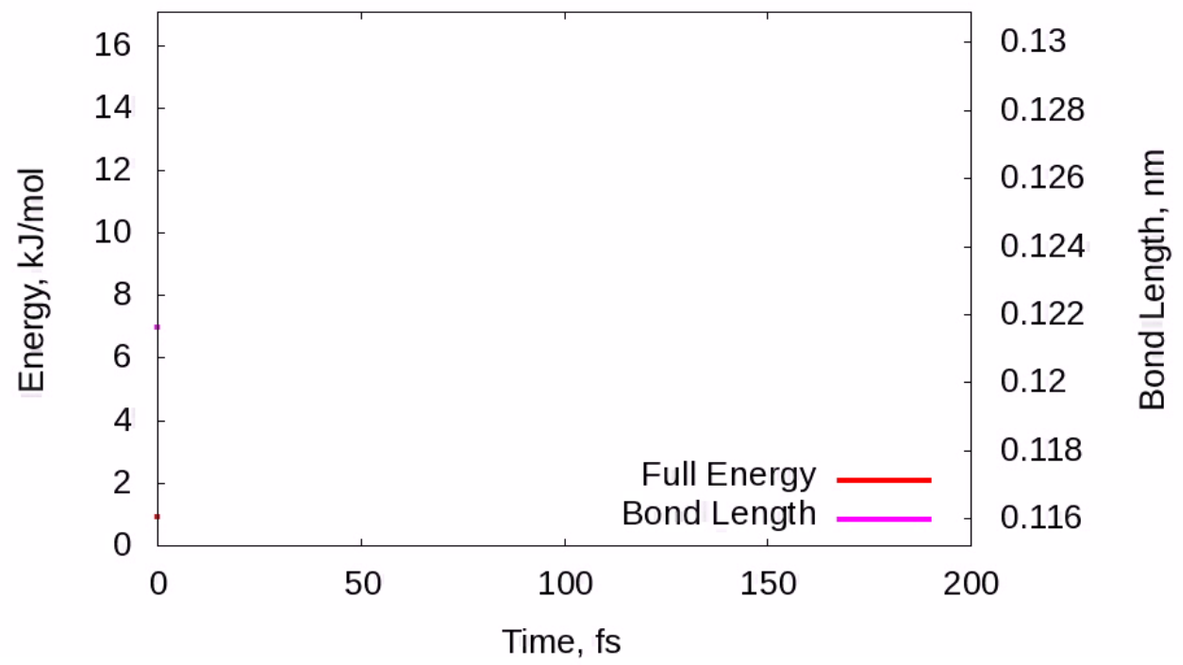
# Constant temperature simulations 3

## Nose-Hoover thermostat



Oxygen molecule
NVT simulation
Verlet integrator
Integration step 1 fs
Nose-Hoover thermostat



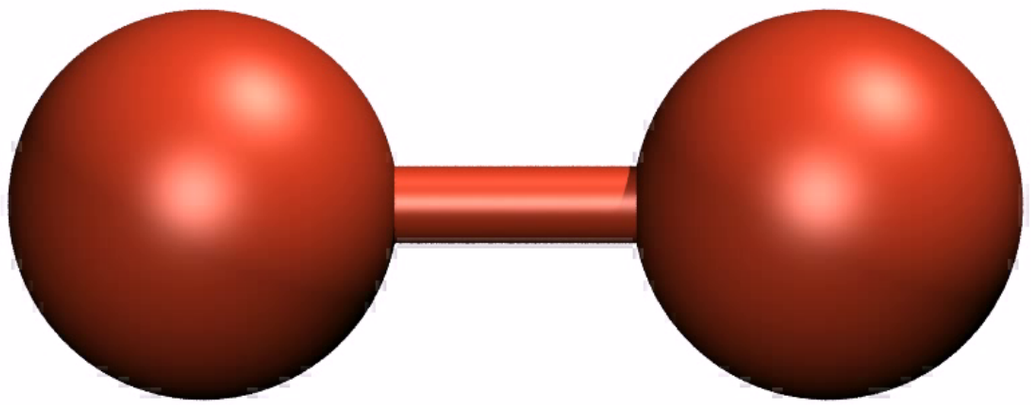
# Constant temperature simulations 3

## Nose-Hoover chains

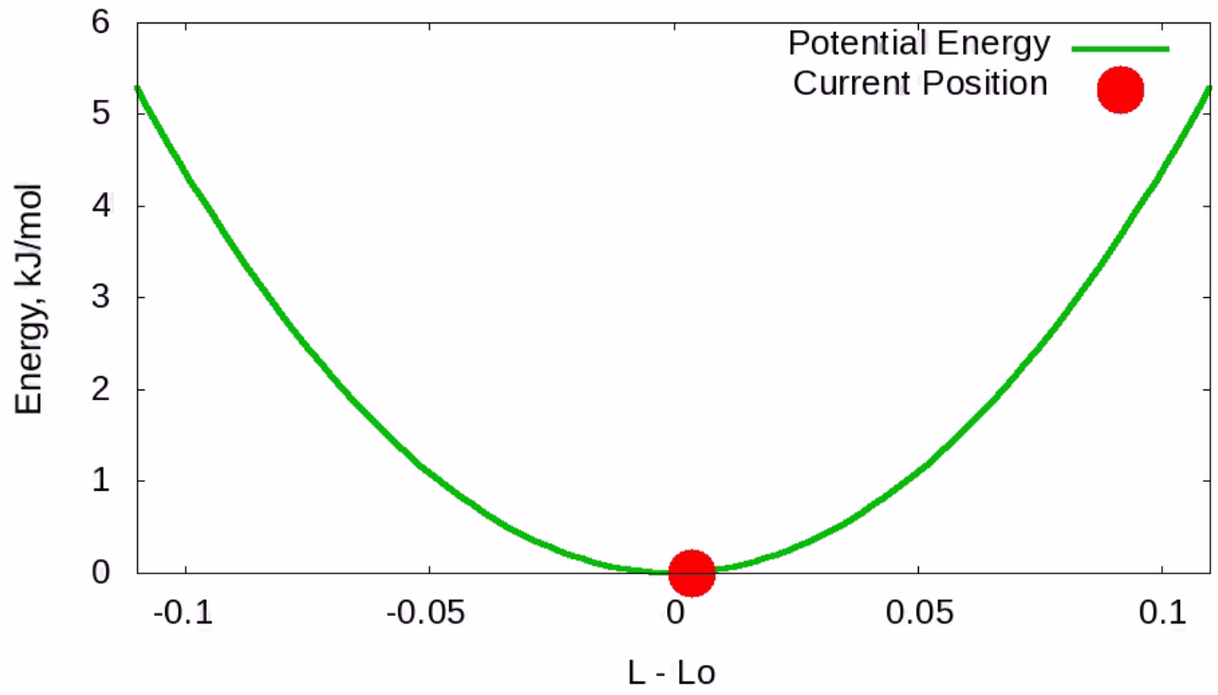
$$
\begin{aligned}
\dot{\boldsymbol{r}}_i &= \frac{\boldsymbol{p}_i}{m_i} \\
\dot{\boldsymbol{p}}_i &= \boldsymbol{F}_i - \boldsymbol{p}_i \dot{\xi}_1 \\
\ddot{\xi}_1 &= \frac{1}{Q_1}\left[\sum_{i=1}^{N} m_i \boldsymbol{v}_i^2 - N_f k_B T_{set}\right] - \dot{\xi}_1 \dot{\xi}_2 \\
\ddot{\xi}_j &= \frac{1}{Q_j}\left[Q_{j-1}\dot{\xi}_{j-1}^2 - k_B T_{set}\right] - \dot{\xi}_j \dot{\xi}_{j+1} \quad , j = 2, \ldots, M-1 \\
\ddot{\xi}_M &= \frac{1}{Q_M}\left[Q_{M-1}\dot{\xi}_{M-1}^2 - k_B T_{set}\right] \quad ,
\end{aligned}
$$

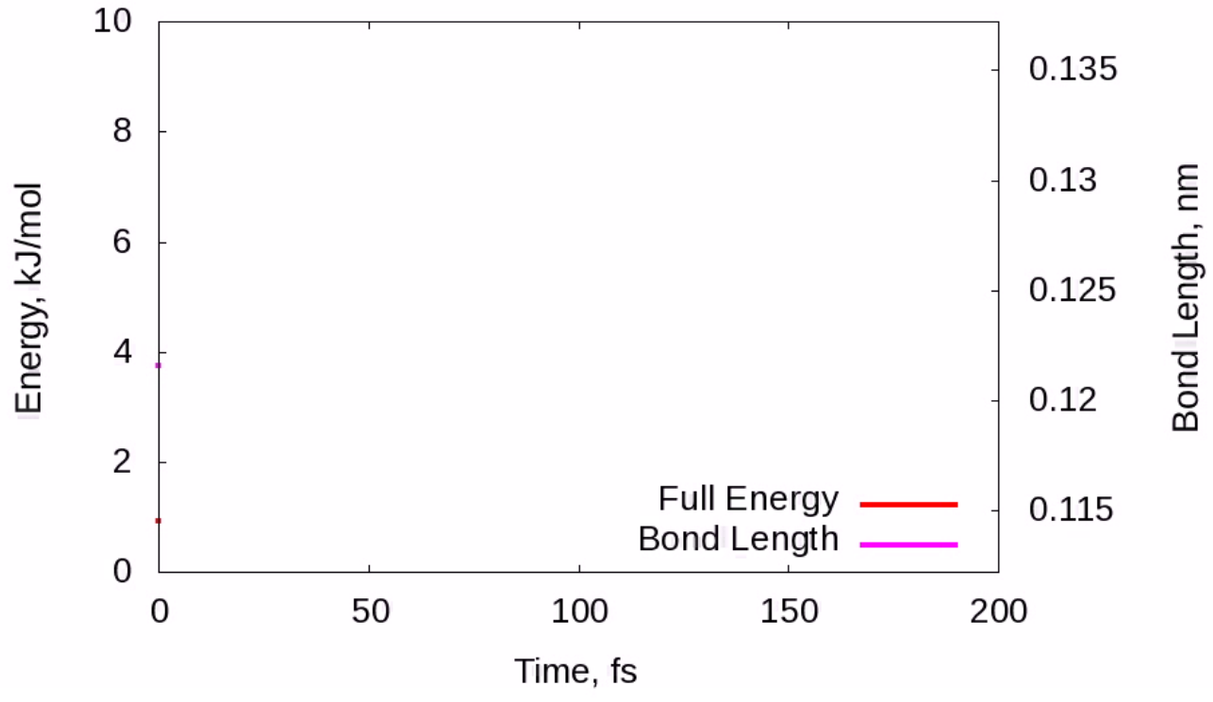
# Constant temperature simulations 3

## Nose-Hoover chains



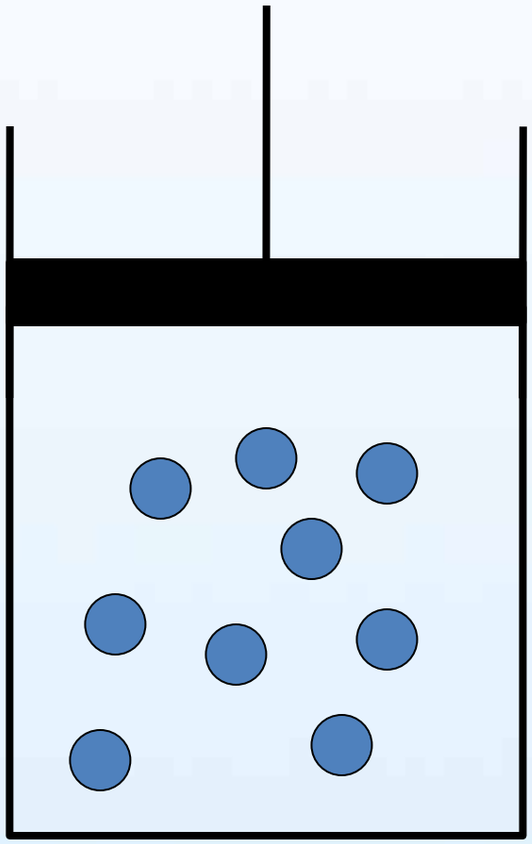
Oxygen molecule
NVT simulation
Verlet integrator
Integration step 1 fs
Nose-Hoover + chains thermostat



# Constant pressure simulations

## Berendsen Barostat



NPT-ensemble

$$P = nkT + vir/V$$

$$vir = \frac{1}{3}\sum \vec{f_{ij}}\vec{r_{ij}}$$

$$\begin{cases} \vec{r_i} \Longrightarrow \mu\vec{r_i} \\ L \Longrightarrow \mu L \end{cases}$$

$$\mu = \left[1 - \frac{\Delta t}{\tau_p}(P - P_0)\right]$$

# Computational costs

Initial coordinates

Force calculation

$$\boldsymbol{F}_i = -\frac{\partial V}{\partial \boldsymbol{r}_i} \qquad \boldsymbol{F}_i = \sum_j \boldsymbol{F}_{ij}$$

Coordinate update

$$\frac{\mathrm{d}^2 \boldsymbol{r}_i}{\mathrm{d}t^2} = \frac{\boldsymbol{F}_i}{m_i}$$

Data output

Computational time

$$\sum_\theta K_\theta(\theta - \theta_0)^2 +$$
$$\sum_\phi K_\phi(1 + cos(n\phi - \phi_0))$$

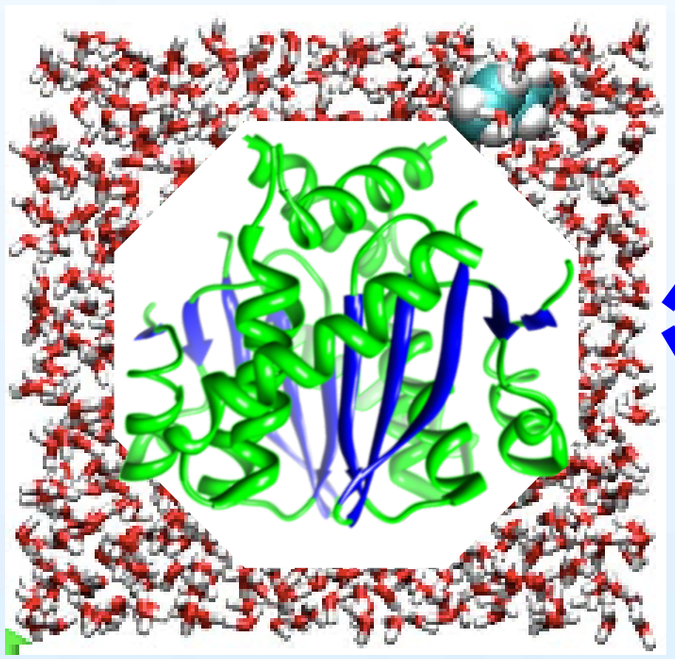
~2 %

$$\sum \epsilon \left[\left(\frac{\sigma}{r}\right)^{12} - \left(\frac{\sigma}{r}\right)^{6}\right] +$$
$$\sum_{ij} \frac{q_i q_j}{r_{ij}}$$

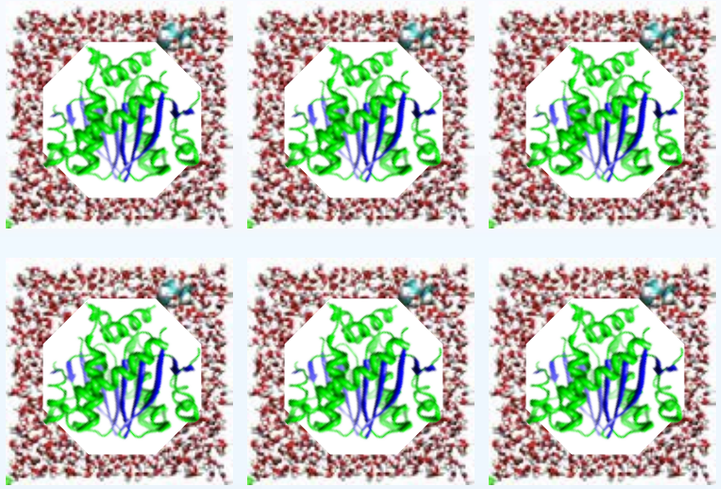
~90 %

~0.1 %

# Parallel computing

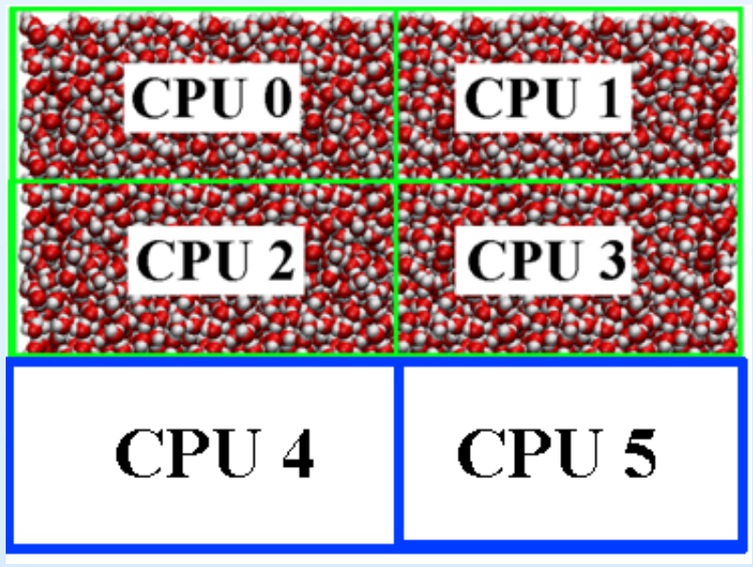


System under study



Multiple replica calculation

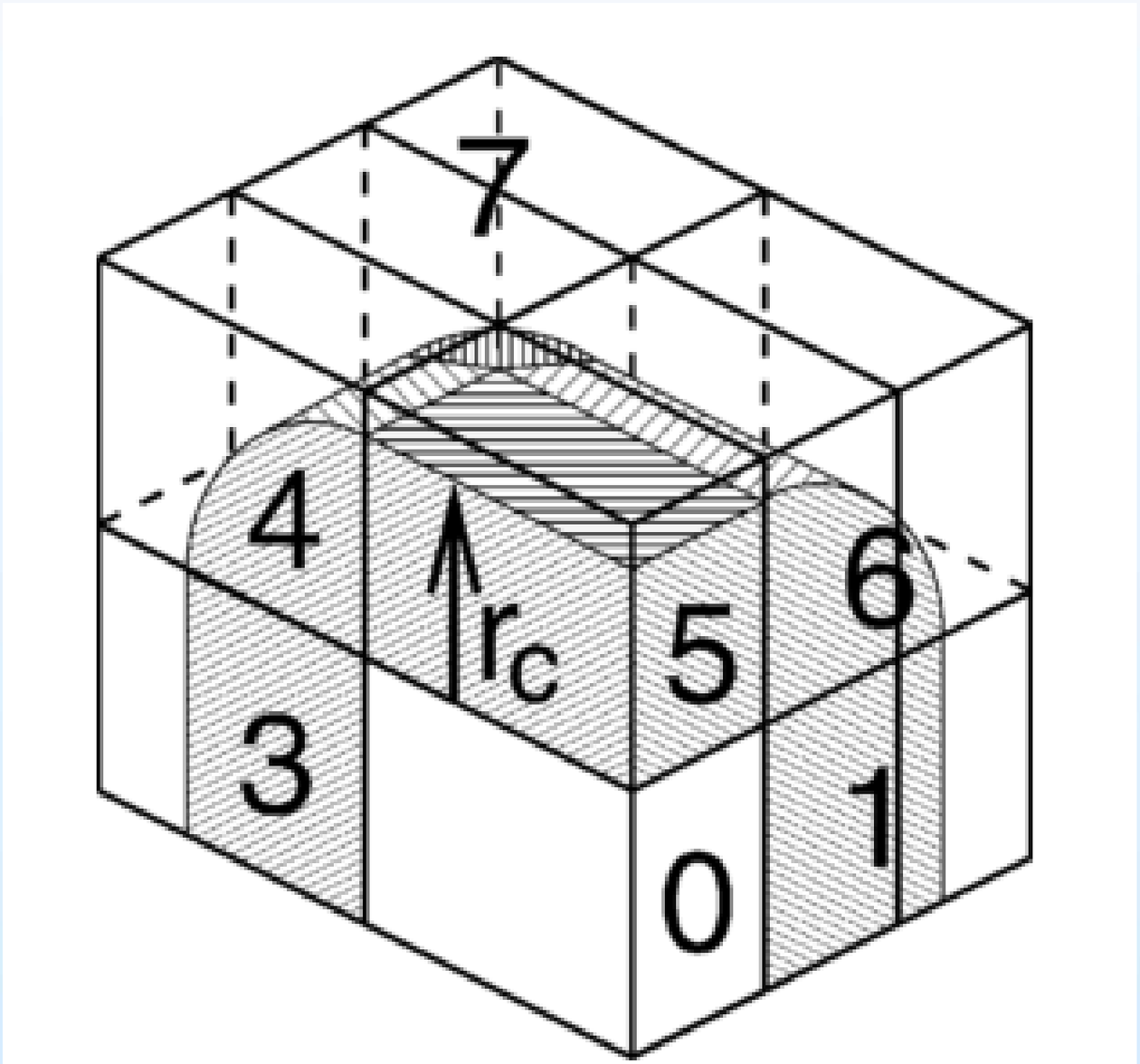
GRIDs, distributed computing, etc



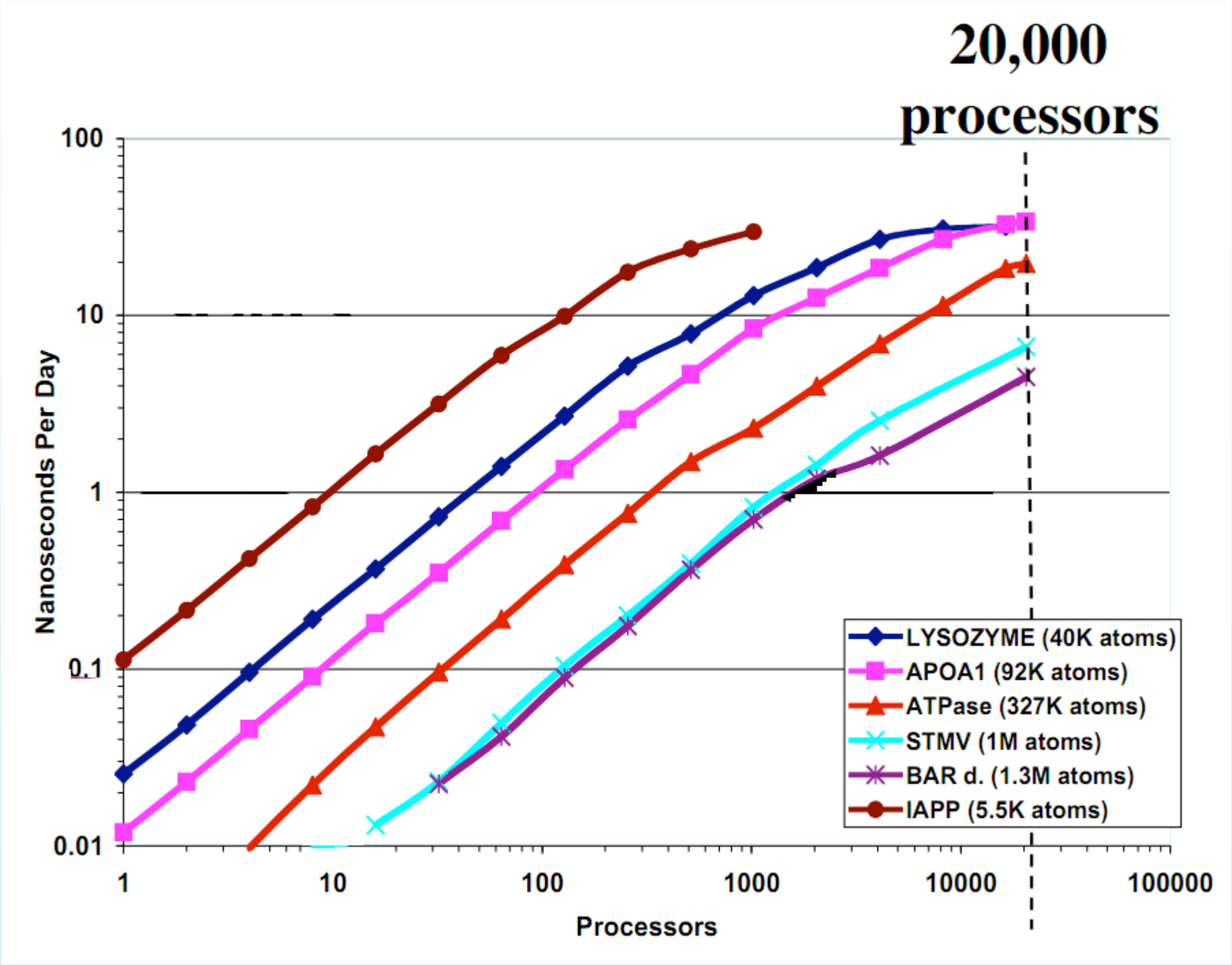

Domain/task decomposition

supercomputing (general, with GPU, ASIC, etc)

# Domain decomposition

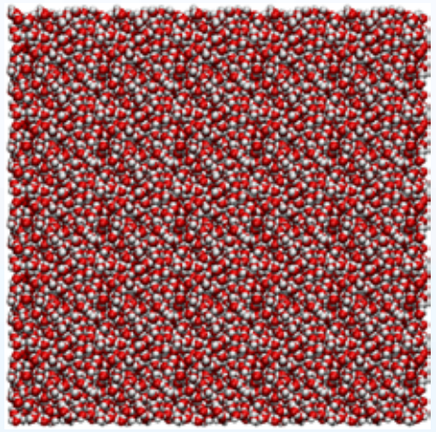


# Parallel computing

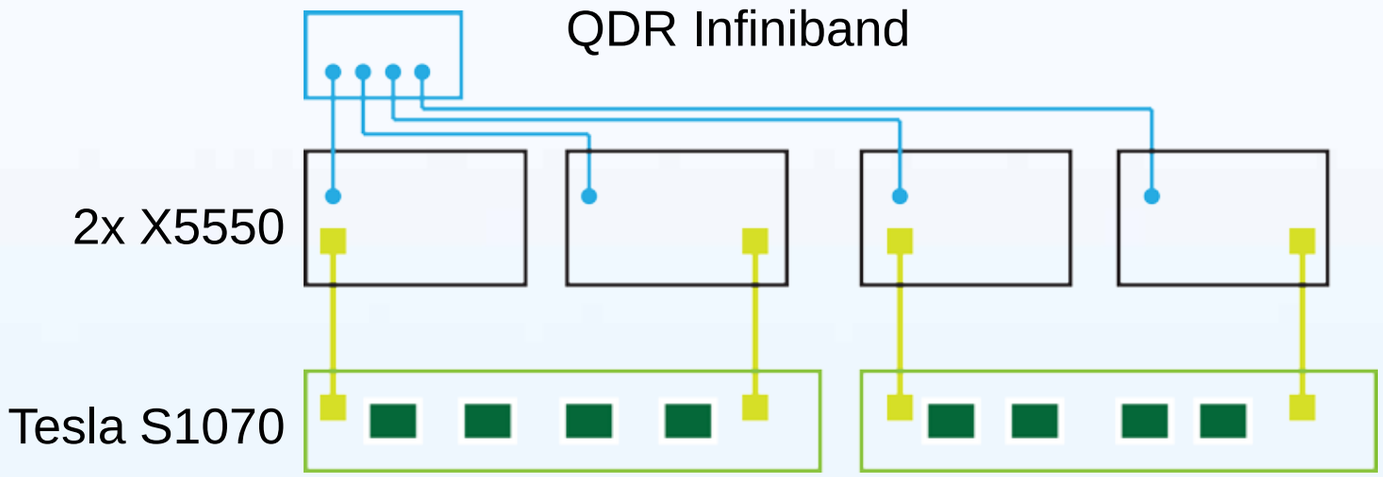


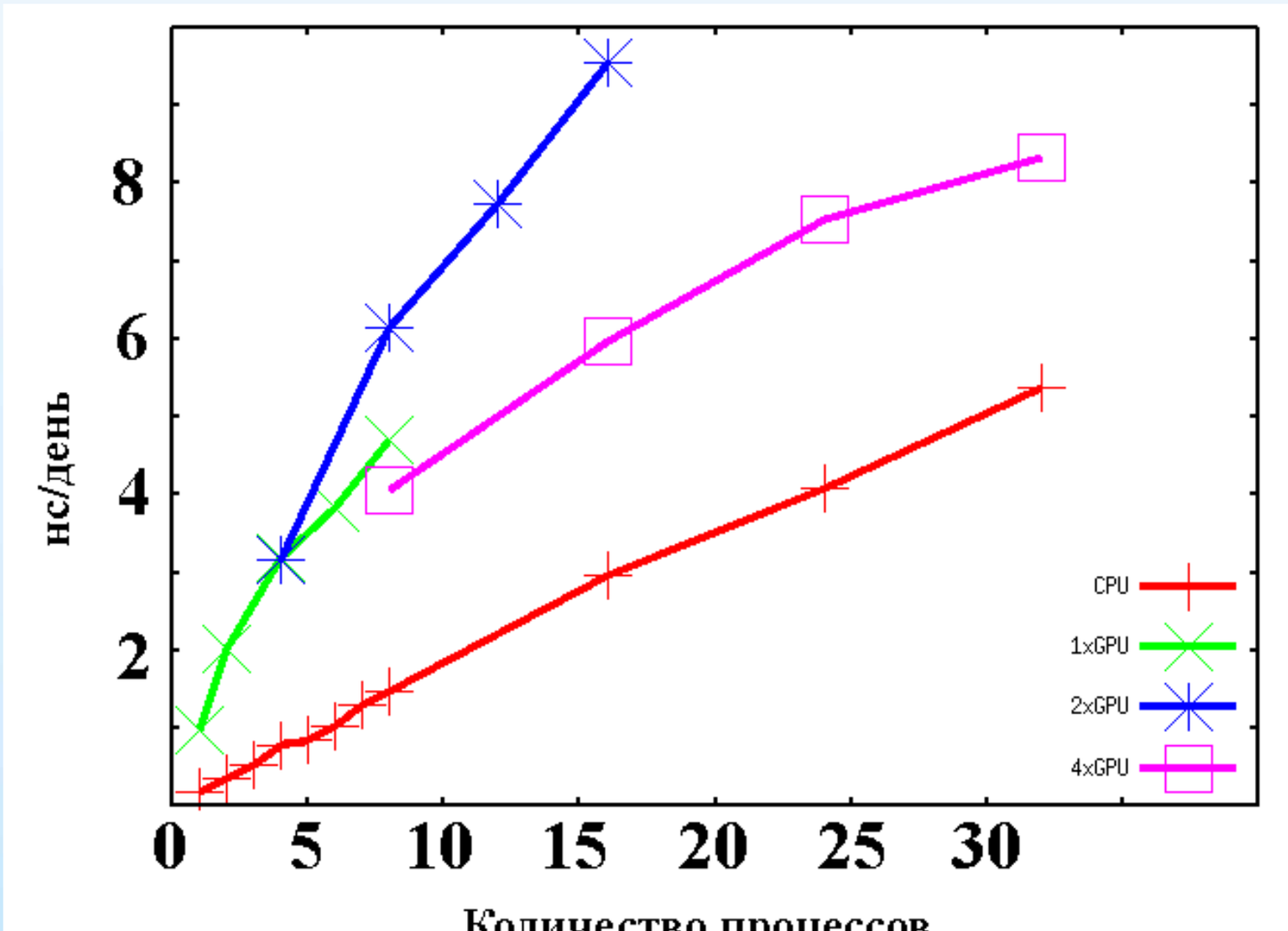

NMAD scaling (from the NAMD website)

# Scaling example



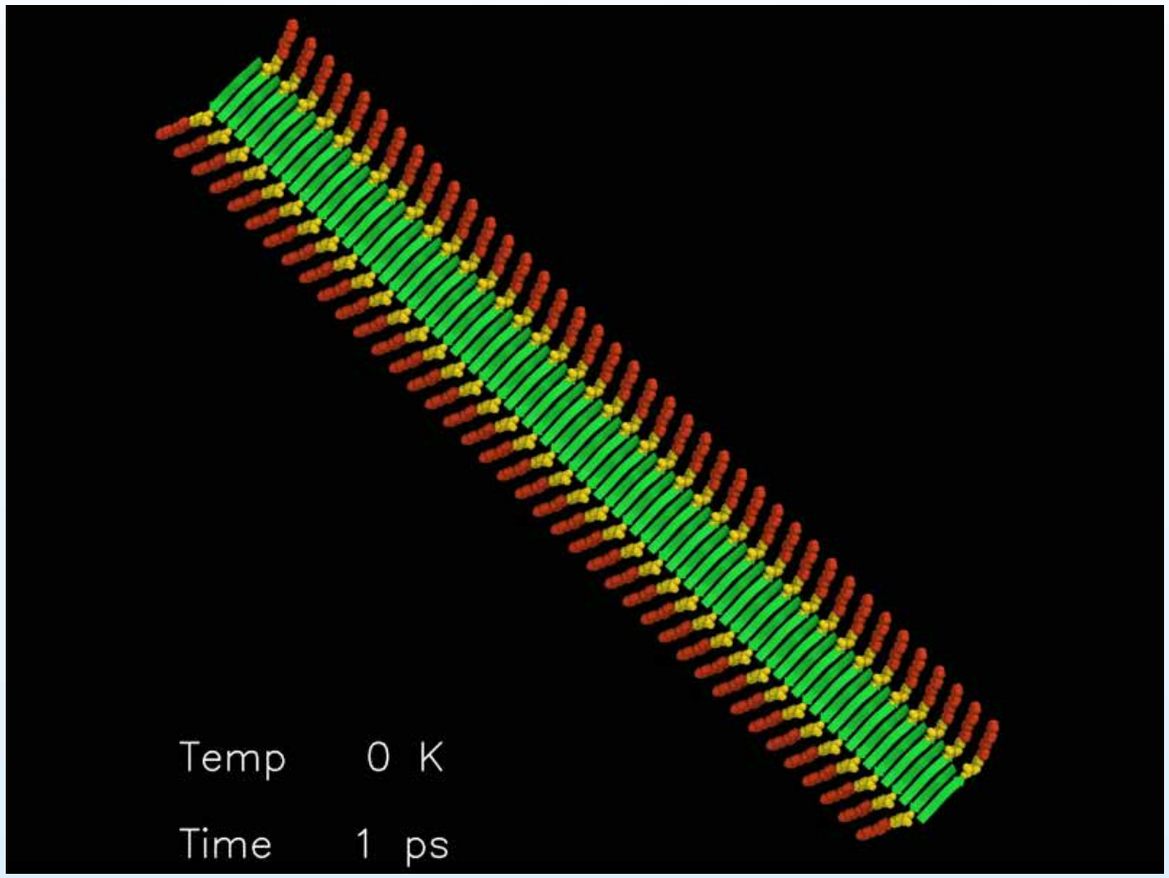
100K atoms
32K waters



# Time and scale examples


DNA-protein complex in salt solution.
200 000 atoms




40 nm hybrid nanowire from thiophenes and peptides.
50 000 atoms

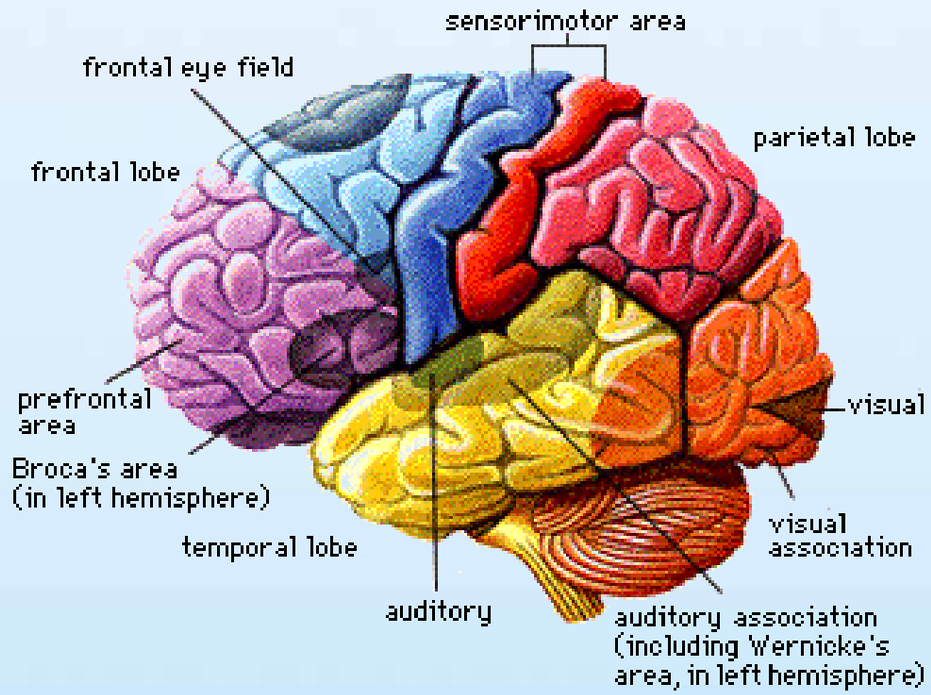
# Time and scale examles


Potassium voltage gated channel
~250 µs
~200 000 atoms

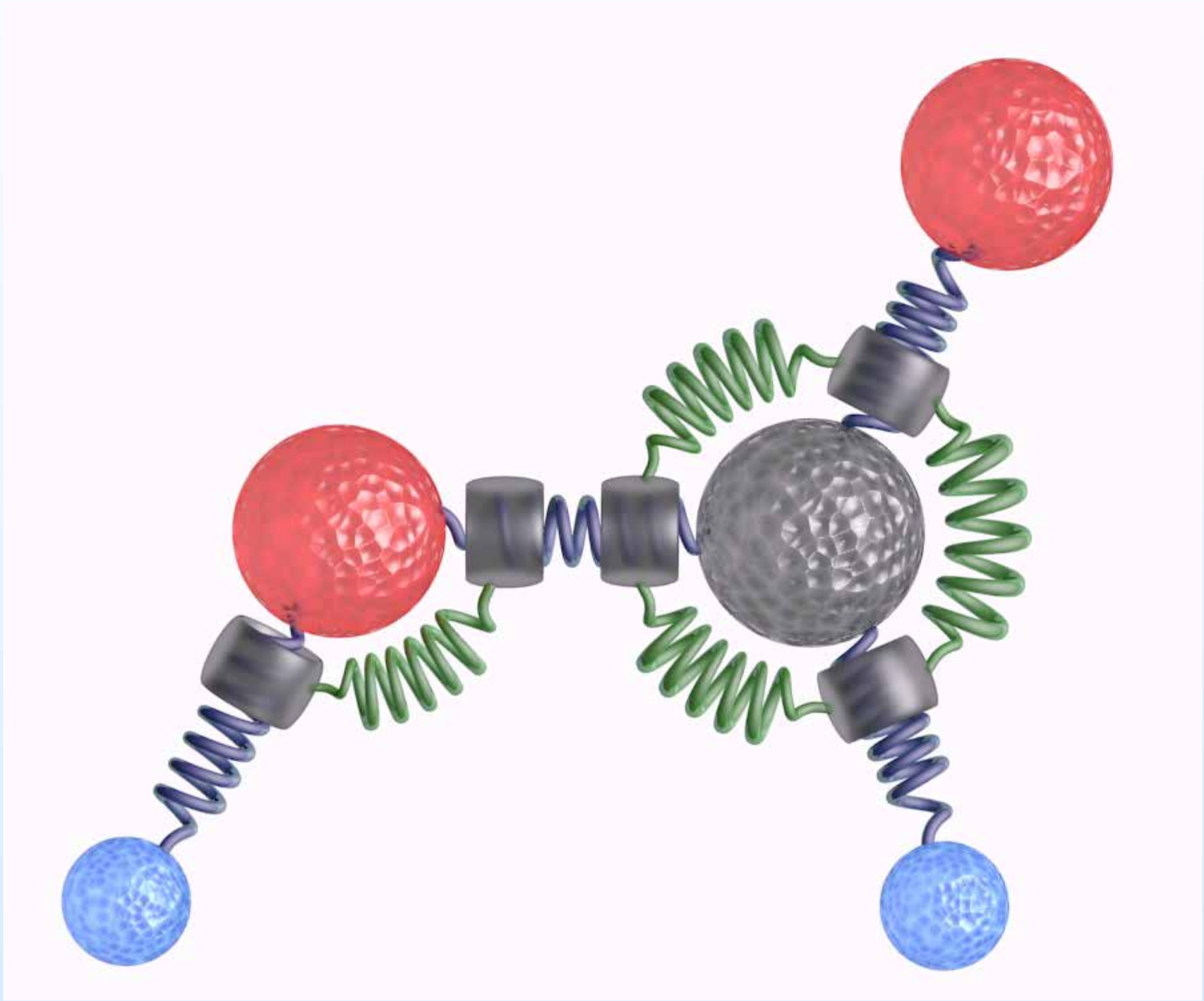
Science 2012, Morten Ø. Jensen et al.  “Mechanism of Voltage Gating in Potassium Channels”

# Advanced approaches

- Multiscale modeling: coarse graining, QM/MM etc.
- Advanced sampling: parallel tempering, meta dynamics, adaptive algorithms
- Thermodynamics: free energy profiles, reaction coordinates, alchemical transformations, etc



# Thanks for attention!



http://molsim.org/

http://www.youtube.com/molsimmsu