

International Spring School Statistical Thermodynamics, Santiago de Chile  
Monday, November 27, 2017  
Lecture 15

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# Thermodynamic boundary conditions in molecular simulation

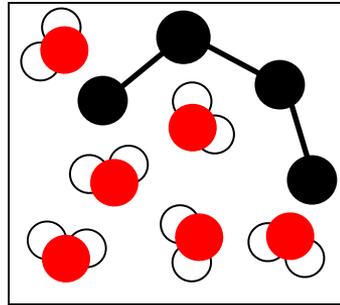
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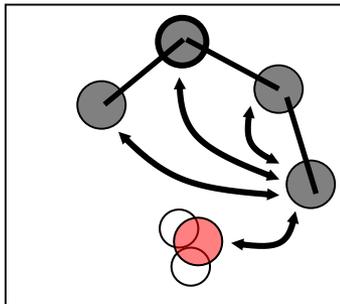
# Definition of a model for a computer simulation

For any system *four choices* have to be made

*Degrees of freedom:*  
what are the elementary  
entities or “particles”

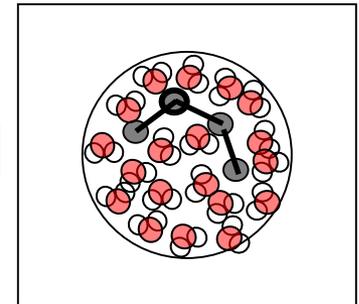


*Interactions or forces between “particles”*



Interaction =  
physico-chemical-  
biological  
knowledge

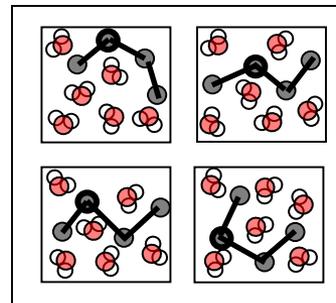
*Boundary conditions or interface to the outside world*



e.g.  
temperature  
pressure  
walls  
external forces

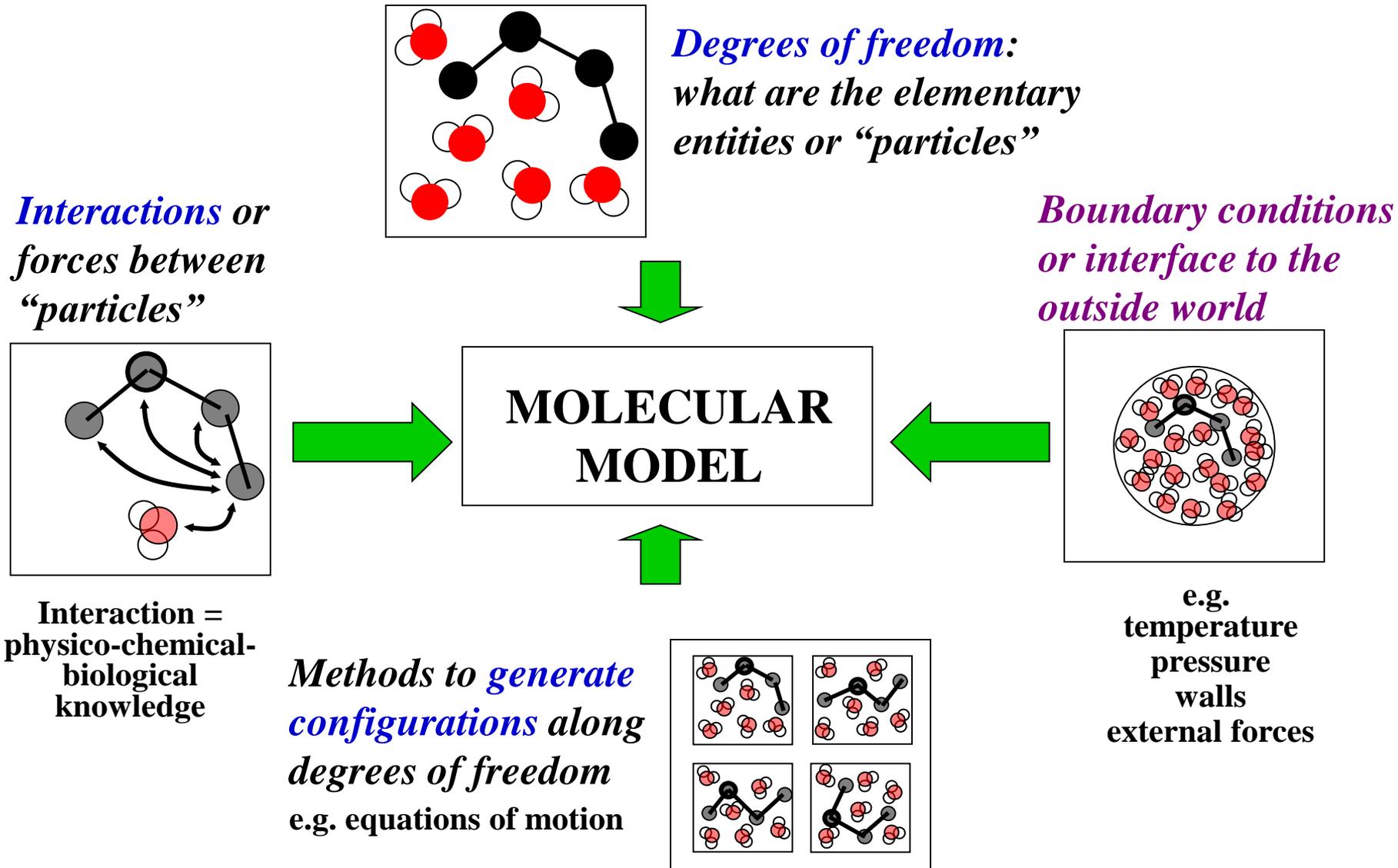
**MOLECULAR  
MODEL**

*Methods to generate configurations along degrees of freedom*  
e.g. equations of motion



# Definition of a model for a computer simulation

For any system *four choices* have to be made



# Molecular simulation: algorithms, boundary conditions and constraints

## 1. Generating configurational ensembles

### a. Integrating equations of motion

1. Newton: molecular dynamics simulation (MD)
2. Langevin: stochastic dynamics simulation (SD)

### b. Monte Carlo type approach

1. Metropolis Monte Carlo simulation (MC)
2. Replica exchange technique (RE)

## 2. Boundary conditions

1. Spatial boundary conditions
2. Thermodynamic boundary conditions
  - temperature
  - pressure
  - other

## 3. Constraints

1. Distance constraints
2. Other constraints

## 4. MD algorithm

# Molecular Dynamics with Coupling to an External Bath

## Standard (micro-canonical) MD:

independent parameters:

number of particles,  $N$

volume,  $V$

total energy,  $E_{tot}$

conserved quantities:

$E_{tot}$

$\vec{P}_{tot}$  = total momentum

$L_{tot}$  = total angular momentum

*(only in vacuo, not with PBC)*

dependent quantities:

temperature =  $T$

pressure =  $P$

## Why apply MD at constant $T$ and/or $P$ ?

-study system properties as a function of  $T$  and  $P$  rather than  $E$  and  $V$

*(normally one measures at constant  $T$  and  $P$ )*

-long-range Coulomb force:  $\sim r^{-2}$

use of cut-off radius introduces heat into the system: } *noise  $\rightarrow$  rising  $T$*

-study of non-equilibrium systems: *maintain a  $P$  or  $T$  gradient.*

**Couple:** *temperature*  
*pressure*

**by scaling the**  
**by scaling the**

*velocities*  
*positions*

# Definition of temperature and pressure

- Macroscopic temperature,  $T$ , is defined from the average kinetic energy per degree of freedom

$$\mathcal{K}(N, \mathbf{p}, \mathbf{q}) = 3N \frac{k_B T}{2}$$

- From this we define an instantaneous temperature

$$T(N, \mathbf{p}, \mathbf{q}) = \frac{2\mathcal{K}(N, \mathbf{p}, \mathbf{q})}{3Nk_B} \quad \text{with} \quad T = \langle T(N, \mathbf{p}, \mathbf{q}) \rangle$$

- Virial theorem

$$K = W_{tot} = W + \frac{3}{2}PV$$

- In terms of instantaneous properties

$$\mathcal{W}(N, \mathbf{q}) = -\frac{1}{2} \sum_{i=1}^N \mathbf{r}_i \otimes \mathbf{F}_i(\mathbf{r})$$

$$\mathcal{P}(N, \mathbf{q}, \mathbf{p}) = \frac{2[\mathcal{K}(N, \mathbf{q}) - \mathcal{W}(N, \mathbf{q})]}{3\mathcal{V}(N, \mathbf{q})}$$

with  $P = \langle \text{Tr}(\mathcal{P}(N, \mathbf{q}, \mathbf{p})) \rangle$

$\mathcal{W}(N, \mathbf{q})$  and  $\mathcal{P}(N, \mathbf{q}, \mathbf{p})$  are tensors  
 $\mathcal{K}(N, \mathbf{p})$  is written as diagonal

$$\mathcal{K}(N, \mathbf{p}) = \sum (2m_i)^{-1} \mathbf{p}_i \otimes \mathbf{p}_i$$

Trace: the sum of the diagonal elements

# Thermostats

Four ways to control the temperature  $T(t)$

1. *Constraint* method (isokinetic simulation)

$$T(t) = T_{ref}$$

2. *Stochastic* method (Langevin dynamics)

$$m_i \frac{d\vec{v}_i(t)}{dt} = \vec{f}_i(t) - m_i \gamma_i \vec{v}_i(t) + \vec{f}_i^{st}(t) \quad \langle \vec{f}_i^{st}(0) \vec{f}_j^{st}(t) \rangle = 6m_i k_B T_{ref} \gamma_i \delta_{ij} \delta(t)$$

Distorts the dynamics of individual particles

3. *Extended system* method (Nosé-Hoover)

$$m_i \frac{d\vec{v}_i(t)}{dt} = \vec{f}_i(t) - m_i \gamma_{NH} \vec{v}_i(t) \quad \frac{d\gamma_{NH}(t)}{dt} = (\tau_{T,NH})^{-2} \left( \frac{T(t)}{T_{ref}} - 1 \right)$$

May introduce spurious oscillations

4. *Weak-coupling* method

$$m_i \frac{d\vec{v}_i(t)}{dt} = \vec{f}_i(t) + m_i (2\tau_T)^{-1} \left( \frac{T_{ref}}{T(t)} - 1 \right) \vec{v}_i(t) \quad \frac{dT(t)}{dt} = \tau_T^{-1} [T_{ref} - T(t)]$$

Statistical-mechanical ensemble ?

# Molecular dynamics with (weak) coupling to a temperature bath

## Variety of methods:

1. **Constraint** method  $\Rightarrow$  **Hamiltonian, but non-physical**
2. **Stochastic** method  $\Rightarrow$  **sizeable effects on atomic trajectories**  
**Langevin equation**
3. **Extended system** method  $\Rightarrow$  **2<sup>nd</sup> order coupling, spurious oscillations**
4. **Weak coupling** method

$$\frac{dT(t)}{dt} = \frac{1}{\tau_T} [T_{bath} - T(t)]$$

$$\begin{aligned} \Delta E_{kin} &= (\lambda^2(t) - 1) \frac{1}{2} N_{df} k_B T(t) \\ &= N_{df} c_V^{df} \Delta T \end{aligned}$$

$$\left. \begin{aligned} \frac{dT(t)}{dt} &= \frac{1}{\tau_T} [T_{bath} - T(t)] \\ \Delta E_{kin} &= (\lambda^2(t) - 1) \frac{1}{2} N_{df} k_B T(t) \\ &= N_{df} c_V^{df} \Delta T \end{aligned} \right\} \lambda(t) = \left[ 1 + \frac{2c_V^{df}}{k_B} \frac{\Delta t}{\tau_T} \left[ \frac{T_{bath}}{T(t)} - 1 \right] \right]^{\frac{1}{2}}$$

$$\frac{dE_{kin}(t)}{dt} = \text{constant} [T_{bath} - T(t)] \Rightarrow$$

**first order, physical, but ensemble ?**

# Energy fluctuations in liquid water as function of the coupling strength $\tau_T$

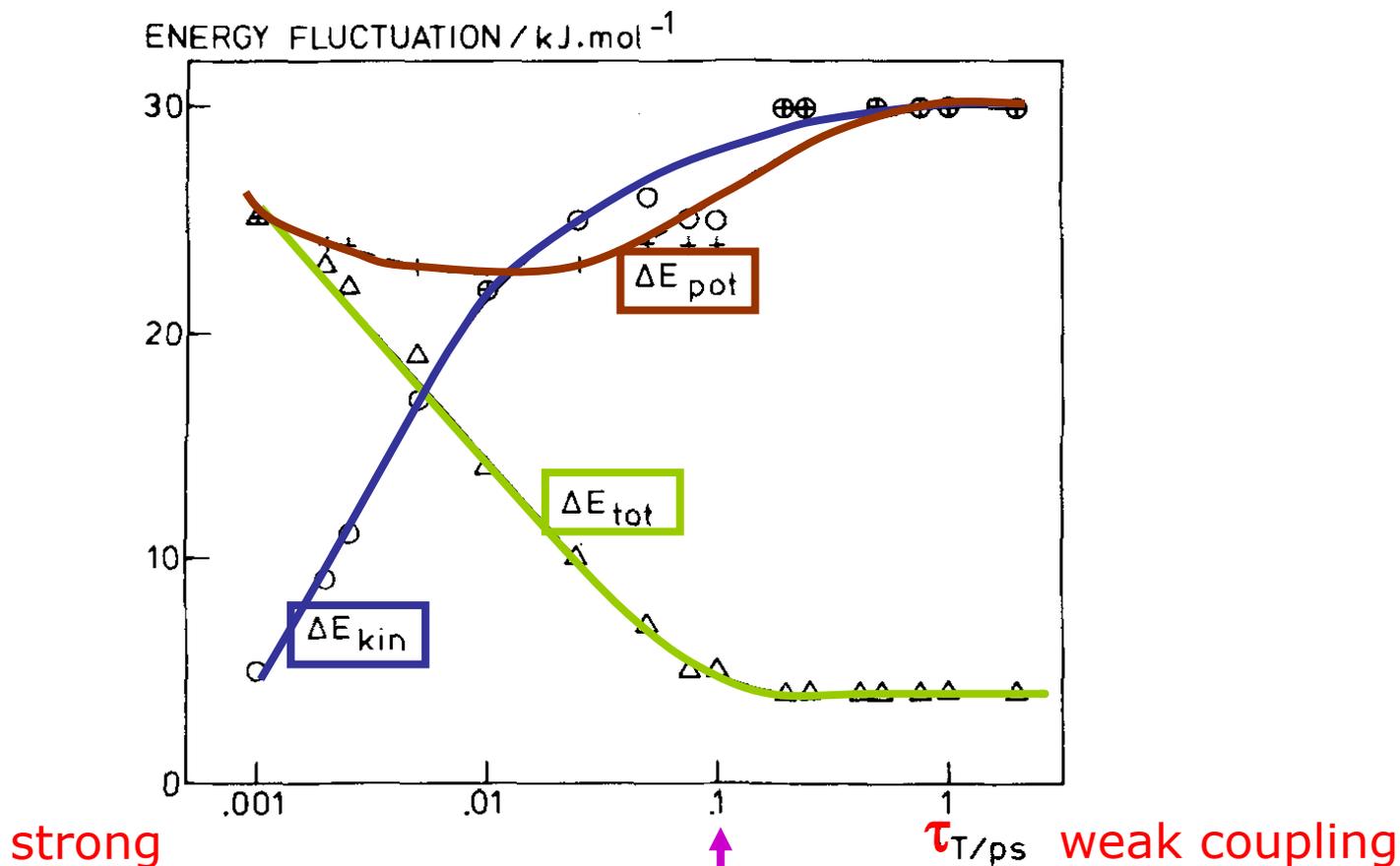


FIG. 2. Root means square fluctuations in kinetic, total, and potential energies, measured over several 0.1 ps simulations of liquid water.

O.K.

H.J.C. Berendsen et al., *J. Chem. Phys.*, 81 (1984) 3684 - 3690

# Coupling to a heat bath at $T = T_{ref}$ : stochastic methods

## 1. Collision model:

The **velocity** of a randomly selected particle after each time period  $\tau_{collision}$  is chosen afresh from a **Maxwell-Boltzmann velocity distribution** at  $T = T_{ref}$

This results in:  $\langle T \rangle = T_{ref}$

## 2. Langevin model:

A frictional force  $-m_i \gamma_i \vec{v}_i$  and a stochastic force  $\vec{f}_i^{st}$  are added to the particle equations of motion:

$$m_i \frac{d\vec{v}_i(t)}{dt} = \vec{f}_i(t) - m_i \gamma_i \vec{v}_i(t) + \vec{f}_i^{st}(t)$$

This results in:  $\langle T \rangle = \frac{\langle (\vec{f}_i^{st})^2 \rangle}{6m_i \gamma_i k_B} = T_{ref}$

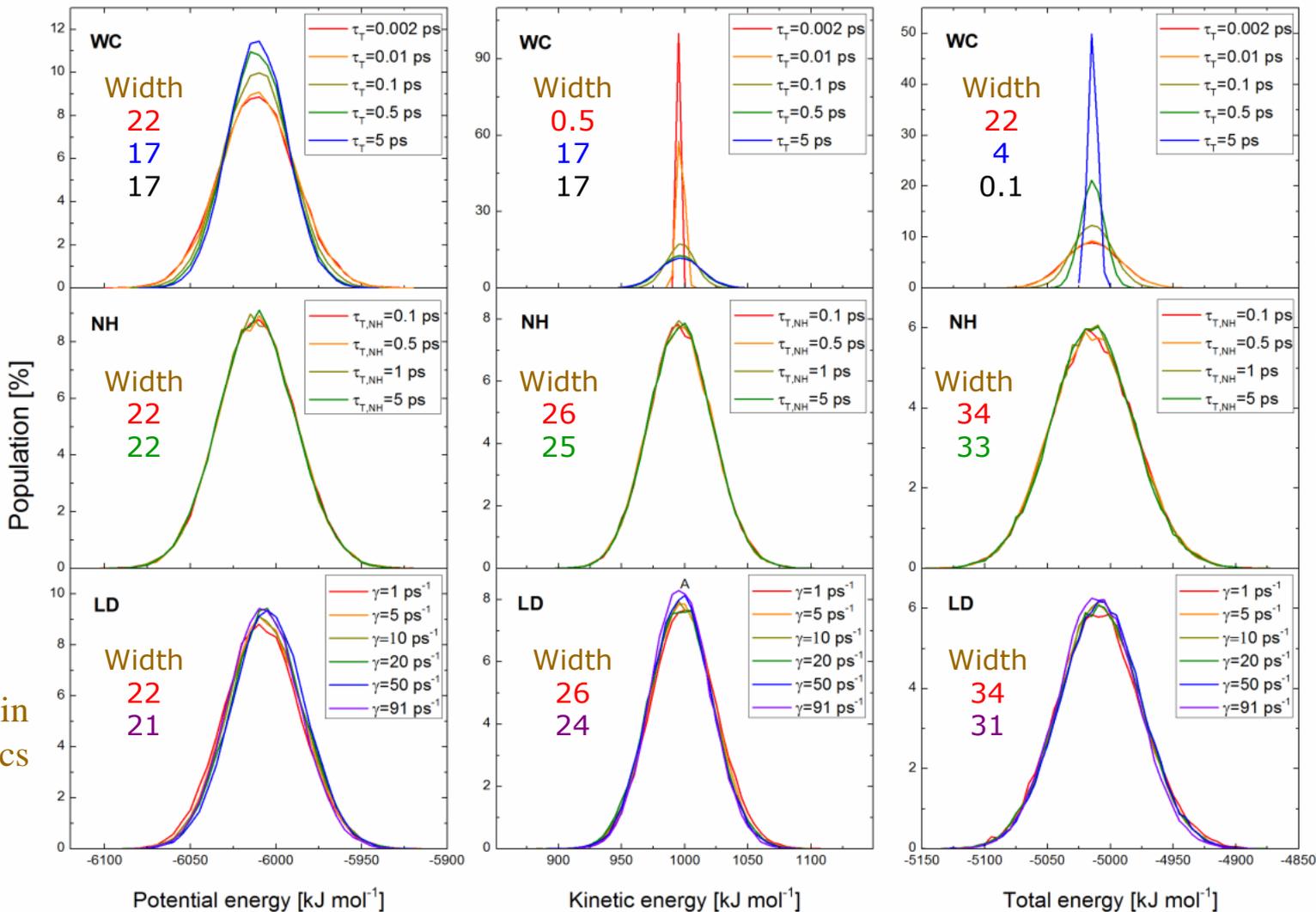
# Energy distributions for different thermostats

Liquid argon (1000 atoms), periodic boundary conditions, 80 K, 1400 kgm<sup>-3</sup>

WC:  
Weak  
coupling

NH:  
Nosé-  
Hoover

LD:  
Langevin  
dynamics



Black:  
micro-  
canonical  
distribution

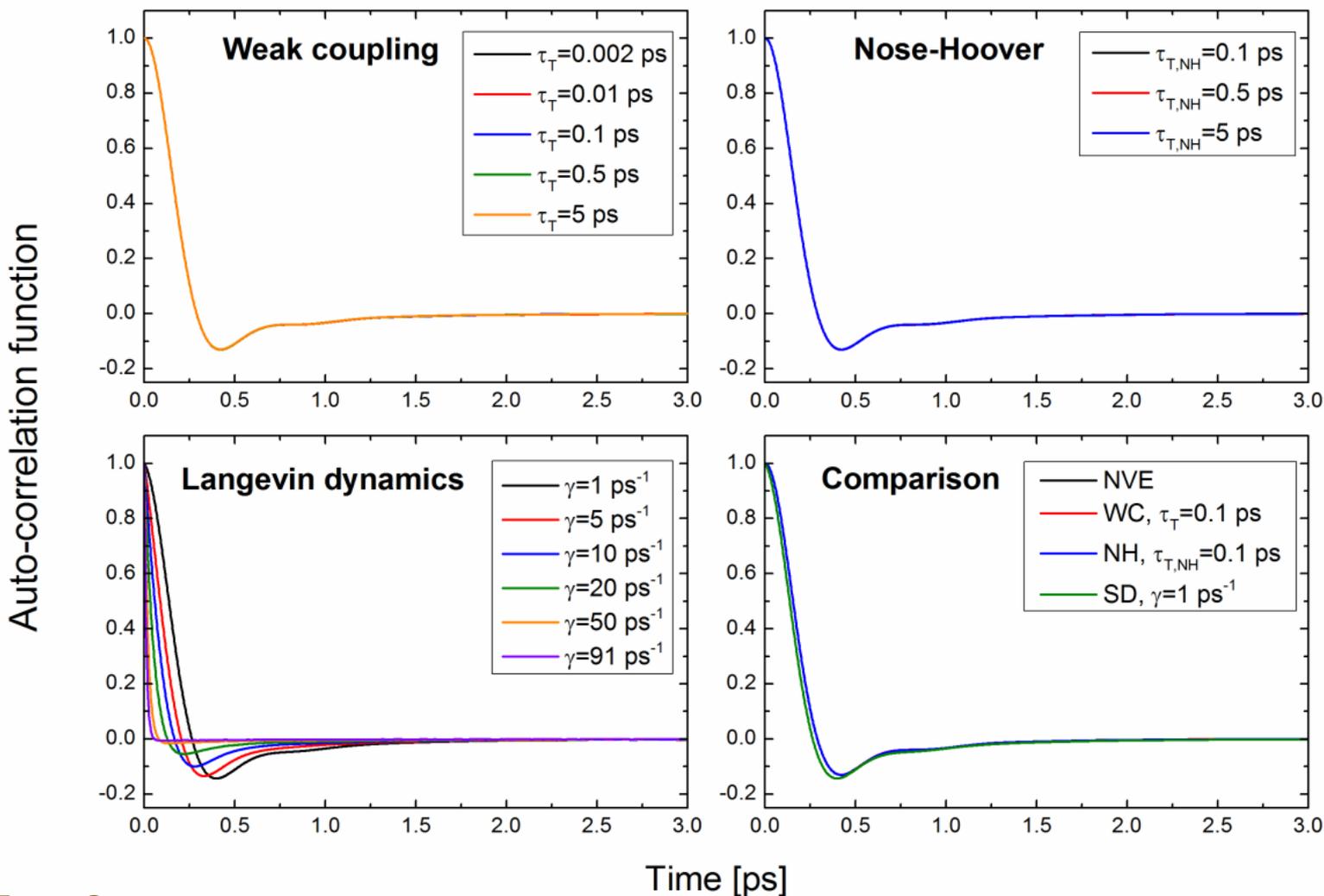
canonical  
distribution

canonical  
distribution

**WC:** small  $\tau_T$ : isokinetic distribution (width  $E_{pot}$  = canonical width)  
 large  $\tau_T$ : micro-canonical distribution (width  $E_{pot}$  < canonical width)  
**NH and LD:** canonical distribution independent of  $\tau_{NH}$  or  $\gamma$

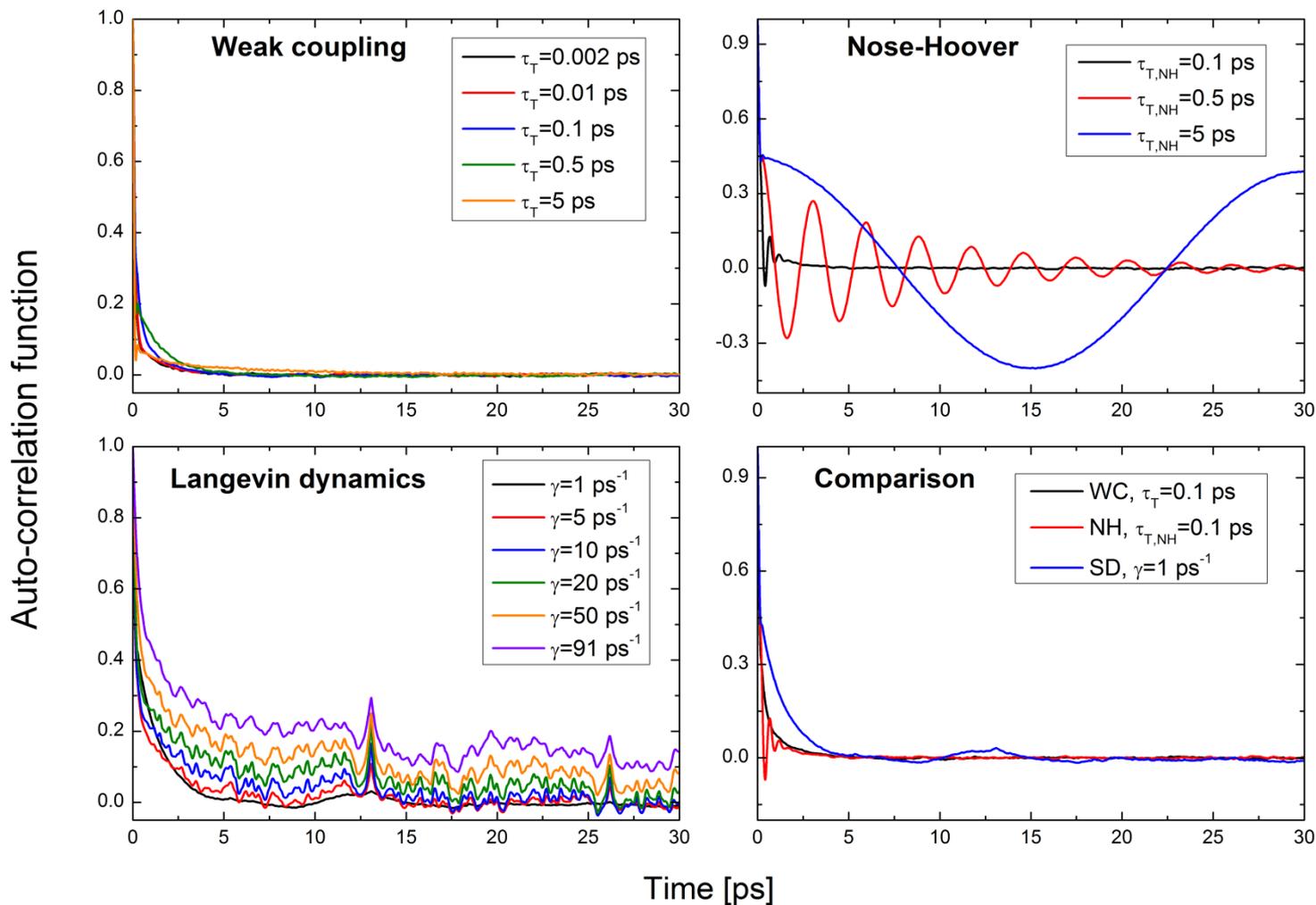
# Atom velocity auto-correlation function for different thermostats

Liquid argon (1000 atoms), periodic boundary conditions, 80 K, 1400 kgm<sup>-3</sup>



# Potential energy auto-correlation function for different thermostats

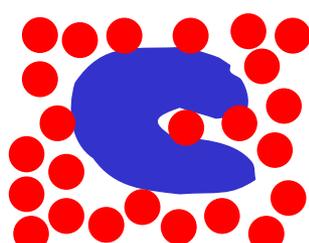
Liquid argon (1000 atoms), periodic boundary conditions, 80 K, 1400 kgm<sup>-3</sup>



**WC:** no correlation irrespective the coupling strength (1st order coupling)  
**NH:** spurious oscillations depending on coupling strength (2nd order coupling)  
**LD:** correlation increases with size of the friction  $\gamma$

# Issues with thermostats

- Temperature is a system property
  - We don't know the temperature of individual particles
- **Hot solvent, cold protein**
  - Solvent consists of many degrees of freedom

$$T_{prot} = 200 \text{ K}$$
$$T_{solv} = 301 \text{ K}$$
$$T_{tot} = 298 \text{ K}$$

$$T_{solv} = \frac{1}{k_B N_{dof}^{solv}} \sum_{i,solv} \frac{\mathbf{p}_i^2}{m_i}$$
$$T_{prot} = \frac{1}{k_B N_{dof}^{prot}} \sum_{i,prot} \frac{\mathbf{p}_i^2}{m_i}$$
$$T_{tot} = \left[ N_{dof}^{prot} T_{prot} + N_{dof}^{solv} T_{solv} \right] / N_{dof}^{tot}$$

- Due to rotational freedom, the solvent molecules are more prone to cut-off noise than the solute molecule
- This leads to stronger heating up of the solvent
- This heat does not leak away to the solute (insufficient solute – solvent collisions)

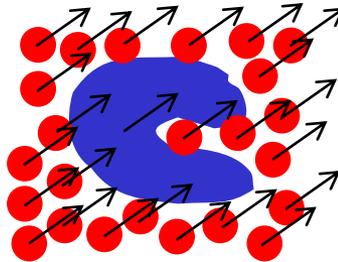
## Remedy

**Separately couple the protein and the solvent to individual heat baths**

# Issues with thermostat

- **Flying ice-cube problem**

- Kinetic energy of uncoupled degrees of freedom accumulates
  - No interconversion of energy through collisions
- Kinetic energy accumulates in translational degrees of freedom and depletes from internal degrees of freedom



*similarly in vacuum simulations:  
the protein turns into a rotating rod*

- **Possible solutions**

- do not apply scaling to (molecular) translational degrees of freedom
- couple translational and internal-rotational degrees of freedom separately
- remove centre-of-mass motion from time to time (discontinuity)
- apply roto-translational constraints to the protein

# Molecular Dynamics with coupling to a pressure bath

## Variety of methods:

1. **Constraint** method

Hamiltonian, but not physical

2. **Extended system** method

2<sup>nd</sup> order coupling  
spurious oscillations

3. **Stochastic** method

1<sup>st</sup> order, physical

$$M_V \ddot{V}(t) = -[P_{bath} - P(t)] - M_V \gamma_V \dot{V}(t) + f_V^{stoch}(t)$$

with

$$\langle f_V^{st}(0) f_V^{st}(t) \rangle = 2M_V k_B T_{bath} \gamma_V \delta(t)$$

4. **Weak coupling** method

1<sup>st</sup> order, physical

$$\left. \begin{aligned} \frac{dP(t)}{dt} &= \frac{1}{\tau_P} [P_{bath} - P(t)] \\ \Delta P &= -\frac{1}{\beta_T V} \Delta V \end{aligned} \right\} \mu(t) = \left[ 1 - \frac{\beta_T \Delta t}{\tau_P} [P_{bath} - P(t)] \right]^{1/3}$$

## Virial theorem:

$$PV = \frac{2}{3} [\langle E_{kin} \rangle - \langle W \rangle] =$$

$$PV = \frac{2}{3} \left[ \left\langle \frac{1}{2} \sum_{i=1}^N m_i \vec{v}_i^2 \right\rangle - \left\langle -\frac{1}{2} \sum_{i<j}^N \vec{r}_{ij} \cdot \vec{f}_{ij} \right\rangle \right] = Nk_B T + \left\langle \frac{1}{3} \sum_{i<j}^N \vec{r}_{ij} \cdot \vec{f}_{ij} \right\rangle$$

$$\vec{r}_{ij} = \vec{r}_i - \vec{r}_j \quad \vec{f}_{ij} = \text{force on atom } i \text{ by atom } j$$

## Derivations:

1.  $P = - \left. \frac{\partial A}{\partial V} \right|_T = k_B T \left. \frac{\partial \ln Z}{\partial V} \right|_T$  , i.e. from the partition function

2. via Newton:  $m_i \dot{v}_i = f_i$

with  $f$  from **external** versus internal forces

3. via **momentum flux** through a surface

*W.G. Hoover, Computational Statistical Mechanics  
(Elsevier, Amsterdam, 1991)*

# Unit cell dimensions as a function of temperature

**Crystals** of a cytidine-derivative

(3',5'-o-(tetra isopropyl-1,3-disiloxanediyl)-cytidine)

**MD at constant temperature and pressure**

Dimension of box (nm)	T <sub>0</sub> =113K		T <sub>0</sub> =289K	
	exp.	MD (50ps)	exp.	MD (160ps)
<b>2a</b>	<b>1.7884</b>	<b>1.792</b>	<b>1.7776</b>	<b>1.790</b>
<b>2b</b>	<b>2.0648</b>	<b>2.050</b>	<b>2.0774</b>	<b>2.064</b>
<b>c</b>	<b>2.7576</b>	<b>2.772</b>	<b>2.8645</b>	<b>2.822</b>
<b>Volume (nm<sup>3</sup>)</b>	<b>10.183</b>	<b>10.180</b>	<b>10.563</b>	<b>10.430</b>

Temperature effect qualitatively reproduced

Atomic van der Waals radii are on average correct (GROMOS)

# MD at constant temperature, pressure

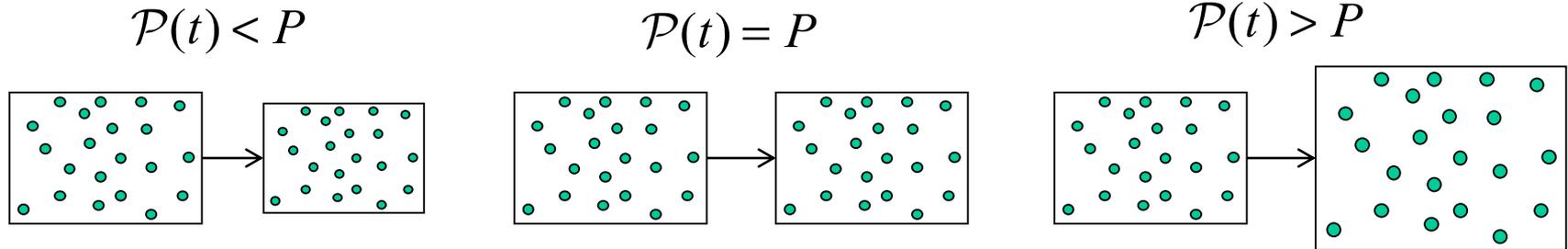
## Temperature

- If there is a small flow of kinetic energy between weakly coupled parts of the system (equipartition not maintained using weak coupling) then  
*couple subsystems separately to T-baths*

## Pressure

- The *pressure* fluctuates much more than the temperature.  
*difference between 2 very large numbers*  
*kinetic energy (expansion) and virial (attractive forces)*
- *Isotropic* coupling (uniform scaling in x,y,z directions)
- *Anisotropic* coupling (e.g. for membrane simulations)
- *Pressure depends on temperature:*  
$$P(t) = 2/3 [E_{kin}(t) - W(t)] / V(t)$$
  
*choose  $T_{pressure} > T_{temperature}$  for couplings to P- and T-baths,*  
*otherwise spurious oscillations may occur*

# Weak-coupling barostat



- The pressure can be given as a tensor, then also  $\mu$ , the spatial scaling factor, is a tensor
- scaling is a matrix multiplication of the vector  $\mathbf{r}$  and the box vector
- isotropic pressure scaling: same pressure in all directions
- anisotropic pressure scaling: different pressure in x, y and z
- fully anisotropic scaling: the box shape can change
- combinations of the above: x and y coupled to one pressure, (semi-isotropic) z coupled separately (membranes)

# Molecular simulation: algorithms, boundary conditions and constraints

## 1. Generating configurational ensembles

### a. Integrating equations of motion

1. Newton: molecular dynamics simulation (MD)
2. Langevin: stochastic dynamics simulation (SD)

### b. Monte Carlo type approach

1. Metropolis Monte Carlo simulation (MC)
2. Replica exchange technique (RE)

## 2. Boundary conditions

1. Spatial boundary conditions
2. Thermodynamic boundary conditions
  - temperature
  - pressure
  - other

## 3. Constraints

1. Distance constraints
2. Other constraints

## 4. MD algorithm

# MD leap-frog algorithm with:

**periodicity**  
**constraints**  
**T-scaling**  
**P-scaling**

} all

**1. Evaluate**  $f_i(t)$  from  $V(\{x_i(t)\})$  (**periodicity**)  
**(put particles in box)** (**calculate**  $P(t)$  **from virial**)

**2. Compute velocities:**  $v_i(t + \Delta t/2) = v_i(t - \Delta t/2) + m_i^{-1} f_i(t) \Delta t$

**3. Scale velocities:**

$$v_i(t + \Delta t/2) = v_i(t + \Delta t/2) \cdot \left[ 1 + \frac{2c_v^{df}}{k_B} \frac{\Delta t}{\tau_T} \left\{ \frac{T_{ref}}{T(t - \Delta t/2)} - 1 \right\} \right]^{1/2}$$

**4. Compute positions:**  $x_i(t + \Delta t) = x_i(t) + v_i(t + \Delta t/2) \Delta t$

**5. Satisfy constraints:**

**SHAKE**

$$\left( \{x_i(t)\}, \{x_i^{uc}(t + \Delta t)\}, \{x_i(t + \Delta t)\} \right) \text{ (periodicity)}$$

**constrained velocities:**  $v_i(t + \Delta t/2) = [x_i(t + \Delta t) - x_i(t)] / \Delta t$

**6. Compute temperature:**  $T(t + \Delta t/2) = \sum_{i=1}^{3N} \frac{1}{2} m_i v_i^2(t + \Delta t/2) / (N_{df} \frac{1}{2} k_B)$

**7. Scale positions: scale box lengths: a, b, c**

$$x_i(t + \Delta t) = x_i(t + \Delta t) \cdot \left[ 1 - \frac{\beta_T \Delta t}{\tau_P} [P_0 - P(t)] \right]^{1/3}$$

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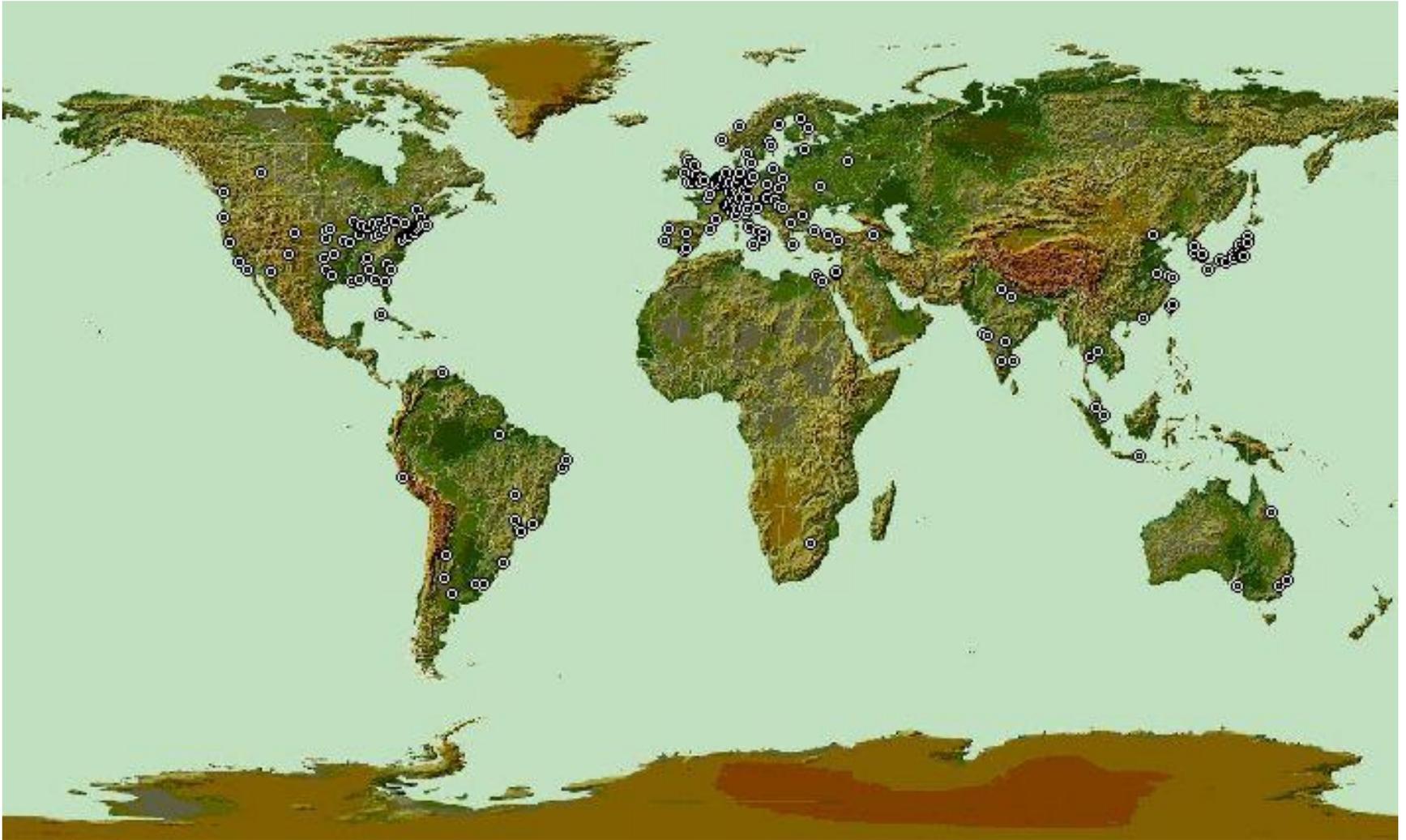
1. Spatial boundary conditions
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  - temperature
  - pressure
  - other

## 3. Constraints

1. Distance constraints
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## 4. MD algorithm

# Spatial distribution of licences GROMOS biomolecular simulation software



**GROMOS = Groningen Molecular Simulation + GROMOS Force Field**

Generally available: <http://www.gromos.net>