Simulation of Biomolecules

Molecular Dynamics

- Short Introduction to Statistical Mechanics
- Temperature and pressure in MD: Thermostats and barostats

Introduction to Statistical Mechanics

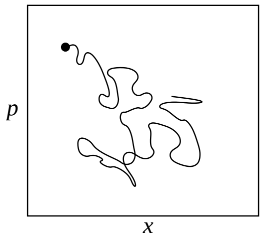
- Statistical mechanics: connection between thermodynamics and the microscopic (classical or quantum) mechanics
- microscopic world: complicated behaviour of a single or few particles governed by the classical Newton equation

$$\frac{\partial U(r_1, r_2, \cdots, r_N)}{\partial r_i} = -m_i \frac{d^2 r_i}{dt^2} \tag{1}$$

and/or the quantum mechanical Schrödinger equation

$$i\hbar \frac{\partial}{\partial t} |\Psi(r_1, r_2, \cdots, r_N, t)\rangle = H(r_1, r_2, \cdots, r_N) |\Psi(r_1, r_2, \cdots, r_N, t)\rangle \tag{2}$$

- Equations (1) and (2) give rise to complicated trajectories in phase space for individual particles (random walks):



Introduction to Statistical Mechanics

- macroscopic world: average over all particles
- Example: energy of an isolated system

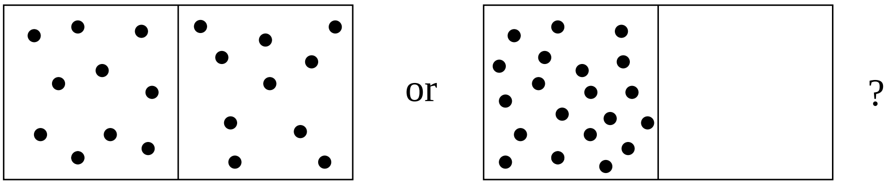
$$E_{\text{tot}}(t) = \sum_{i=1}^{N} E_i(t) = E_{\text{tot}}(t=0) = \text{const.}$$

  where $E_i(t) \neq \text{const.}$ since particles exchange energy with each other
- The behaviour of a macroscopic system more ordered than the behaviour of a microscopic system though the macroscopic system is the sum of many microscopic systems.
- The macroscopic system can be characterised via 3 variables: temperature T, volume V and number of particles N. It is not necessary to know the position and momentum of each of the N particles.

Introduction to Statistical Mechanics

All microstates with the same energy have the same probability.

- Question: What is the most likely macrostate?
- Example: Particles in a box



- Every particle has the same probability to be on the left or right side: $p_{i,\text{left}} = p_{i,\text{right}} = 1/2$.
- The probability to have L ($L \leq N$) particles on the left side is

$$p_{\text{left}} = \prod_{i=1}^{L} p_{i,\text{left}} = (1/2)^L.$$

Introduction to Statistical Mechanics

- The probability for the other $N-L$ particles to be on the right side is then

$$p_{\text{right}} = \prod_{i=L+1}^{N} p_{i,\text{left}} = (1/2)^{N-L}$$

- The total probability to have L particles on the left and $N-L$ particles on the right side is thus

$$p_{\text{left}} \cdot p_{\text{right}} = (1/2)^{N} \qquad \text{independent of } L$$

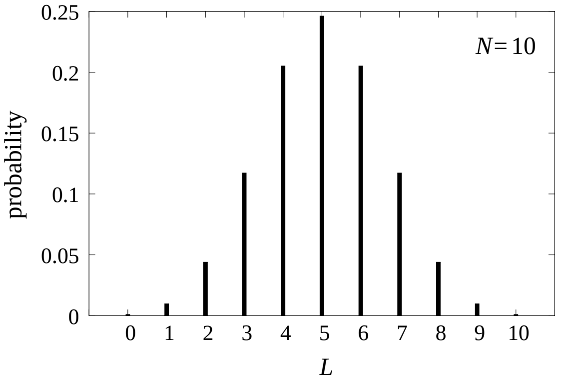
- There are however many possibilities to choose L from N particles (assuming that they are not distinguishable):

$$\frac{N!}{L!(N-L)!} \equiv \binom{N}{L}$$

Introduction to Statistical Mechanics

- The probability to have of the N nondistinguishable particles L on the left and $N-L$ on the right side is thus

$$p_L = \binom{N}{L}\left(\frac{1}{2}\right)^{N}$$



- The average particle number on the left (right) side is

$$\langle L \rangle = \sum_{L=0}^{N} L \cdot p_L = \frac{N}{2}$$

The macrostate with the largest number of microstates is the most probable.

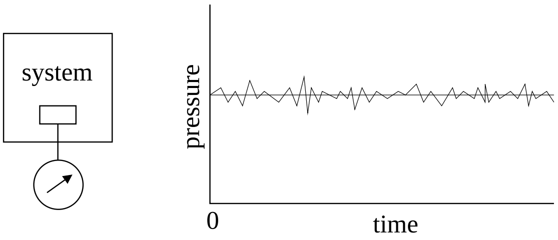
Introduction to Statistical Mechanics

- The conclusion that the macrostate with the largest number of microstates is the most probable follows from the second law of thermodynamics:

Spontaneous natural processes increase entropy overall.

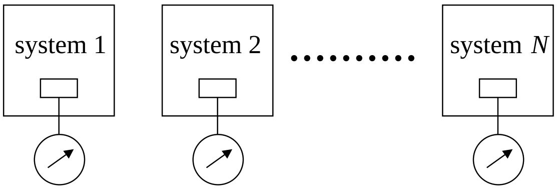
Time *vs* ensemble average

- Time average: one system, thermodynamic quantity, e.g. pressure, measured for a long time:



$$\bar{x} = \frac{1}{t_{\mathrm{obs}}} \int_0^{t_{\mathrm{obs}}} x(t)dt$$

- Ensemble average: thermodynamic quantity measured for N (N must be large) identical systems:



$$\langle x \rangle = \frac{1}{N} \sum_{i=1}^{N} x_i$$

- Ergodicity: ensemble average $\langle x \rangle$ = time average $\bar{x}$

Thermodynamic potentials

- A thermodynamic potential is a scalar function used to represent the thermodynamic state of a system.
- Five common thermodynamic energy potentials are:

Name	Symbol	Formula	Natural variables
Internal energy	U,E	energy of configuration	S, V, N_i
Enthalpy	H	$U + pV$	S, p, N_i
Helmholtz free energy	F,A	$U - TS$	T, V, N_i
Gibbs free energy	G	$U + pV - TS$	T, p, N_i
Grand potential	Φ	$U - TS - \sum_i \mu_i N_i$	T, V, μ_i

where $T =$ temperature, $S =$ entropy, $p =$ pressure, $V =$ volume. Helmholtz free energy is often denoted by F, but the use of A is preferred by IUPAC. N_i is the number of particles of type i in the system and μ_i is the chemical potential for an i-type particle.

Natural variable are the variables that are held constant in the process of question. A thermodynamic potential can be determined as a function of its natural variables by taking partial derivatives of that potential with respect to its natural variables.

Thermodynamic potentials

- Internal energy U is the energy of a configuration of a given system of conservative forces and only has meaning with respect to a defined set of references (or data). It is the capacity to do work plus the capacity to release heat.
- Enthalpy H is the capacity to do non-mechanical work plus the capacity to release heat.
- Gibbs energy G is the capacity to do non-mechanical work.
- Helmholtz free energy F is the capacity to do work (non-mechanical plus mechanical).
- From these definitions we can say that
  - ΔU is the energy added to the system,
  - ΔF is the total work done on it,
  - ΔG is the non-mechanical work done on it,
  - ΔH is the sum of non-mechanical work done on the system and the heat given to it.

Ensembles of statistical thermodynamics

- Different macroscopic environmental constraints lead to different types of ensembles, with particular statistical characteristics. The following are the most important:
  - microcanonical ensemble or NVE[a] ensemble
  - canonical ensemble or NVT ensemble
  - grand canonical ensemble
- The following properties are considered desirable for a classical mechanical ensemble:
  - Representativeness: The chosen probability measure on the phase space should be a Gibbs state of the ensemble, i.e. it should be invariant under time evolution.
  - Ergodicity.

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[a] Change in notation from U to E for the internal energy.

Microcanonical ensemble

- The system is completely isolated:
  - no energy exchange with environment, $dE = 0$
  - no particle exchange with environment, $dN = 0$

System:
N, V, E

- 2nd law of thermodynamics: The macrostate with the largest number of microstates is the most probable for an isolated system.
- $\Omega =$ number of microstates with energy E determines the entropy

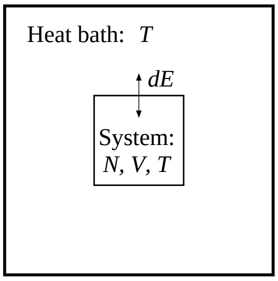
$$S = k_\mathrm{B} \ln \Omega \qquad \text{i.e., entropy tends to its maximum}$$

- From the entropy $S(E, V, N)$ the temperature, pressure and chemical potential can be calculated:

$$\frac{1}{T} = \left.\frac{\partial S}{\partial E}\right|_{V,N} \qquad \frac{p}{T} = \left.\frac{\partial S}{\partial V}\right|_{E,N} \qquad -\frac{\mu}{T} = \left.\frac{\partial S}{\partial N}\right|_{E,V}$$

Canonical ensemble

- The system is in contact with a heat bath of temperature T with which it is in equilibrium:
  - energy exchange between system and bath, internal energy $E \neq \text{const.}$ fluctuates around equilibrium $\langle E \rangle$
  - no particle exchange with environment, $dN = 0$



- The system (s) and bath (b) together are an isolated, i.e., microcanonical ensemble:

$$E_b + E_s = E_{\text{tot}} = \text{const.}$$

- Since

$$E_b \gg E_s$$

  the probability p_i to for the system to be in a certain microstate i with energy $E_s = E_i$ is proportional to:

Canonical ensemble

$$p_i \propto \Omega_b(E_b) = \exp\left(\ln \Omega_b(E_b)\right)$$

i.e., proportional to the number of states of the bath at energy $E_b = E_{\text{tot}} - E_i$.

- Since $E_i \ll E_{\text{tot}}$, a Taylor series expansion can be performed on the logarithm around E_{tot}, keeping the first two terms of the expansion:

$$\ln \Omega_b(E_b) = \sum_{k=0}^{\infty} \frac{(E_b - E_{\text{tot}})^k}{k!} \frac{\partial^k \ln \Omega_b(E_{\text{tot}})}{\partial E_b^k} \approx \ln \Omega_b(E_{\text{tot}}) - E_i \frac{\partial \ln \Omega_b(E_{\text{tot}})}{\partial E_{\text{tot}}}$$

- From the microcanonical ensemble we know that

$$\frac{\partial \ln \Omega_b(E_{\text{tot}})}{\partial E_{\text{tot}}} = \frac{1}{k_{\text{B}}} \frac{\partial S_{\text{tot}}}{\partial E_{\text{tot}}} = \frac{1}{k_{\text{B}} T} \equiv \beta$$

$$\Rightarrow \qquad p_i \propto \exp\left(-\beta E_i\right)$$ Boltzmann factor

Canonical ensemble

- Thus the number of microstates of the bath decreases exponentially as the energy of the system increases.
- Since probabilities must sum to 1, it must be the case that

$$\sum_i p_i = 1 = \sum_i \exp\left(-\beta E_i\right)/Z \qquad \Longleftrightarrow \qquad Z = \sum_i \exp\left(-\beta E_i\right)$$

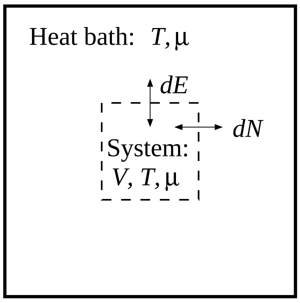
  where Z is known as the **partition function** for the canonical ensemble.
- Knowledge of the partition function allows to calculate thermodynamic quantities of a system under a fixed temperature:

$$F = -\, k_\mathrm{B} T \ln Z \qquad \langle E \rangle = k_\mathrm{B} T^2 \frac{\partial \ln Z}{\partial T}$$

$$S = -\, \left.\frac{\partial F}{\partial T}\right|_{V,N} \qquad p = -\, \left.\frac{\partial F}{\partial V}\right|_{T,N} \qquad \mu = \left.\frac{\partial F}{\partial N}\right|_{T,V}$$

Grandcanonical ensemble

- The system is in contact with a heat and particle bath of temperature T and chemical potential μ, respectively, with which the system is in equilibrium:
  - energy exchange between system and bath, internal energy of system fluctuates around equilibrium $\langle E \rangle$
  - particle exchange between system and bath, particle number of system fluctuates around equilibrium $\langle N \rangle$



- Applying the microcanonical ensemble to the total grandconical system (i.e., system + heat bath + particle bath):

$$E_s + E_b = E_\mathrm{tot} = \mathrm{const.} \qquad N_s + N_b = N_\mathrm{tot} = \mathrm{const.}$$

- Assuming that the system is in a given microstate i with energy $E_s = E_i$ and particle number $N_s = N_i$.

Grandcanonical ensemble

- Since
$$E_b \gg E_i \qquad \text{and} \qquad N_b \gg N_i$$
the probabilty to find the system in microstate i is controlled via the number of microstates of the bath:
$$p_i \propto \Omega_b(E_b, N_b) = \exp(\ln \Omega_b(E_b, N_b))$$
- Performing a Taylor series expansion on the logarithm around E_{tot} and N_{tot} (see canonical ensemble for details) and using the identity
$$\frac{\partial \ln \Omega_b(E_{\text{tot}}, N_{\text{tot}})}{\partial N_{\text{tot}}} = \frac{1}{k_{\text{B}}} \frac{\partial S_{\text{tot}}}{\partial N_{\text{tot}}} = -\frac{\mu}{k_{\text{B}}T}$$
we obtain:
$$p_i = \frac{\exp\left(-\beta(E_i - \mu N_i)\right)}{Z}$$

Grandcanonical ensemble

- The partition function of the grand canonical ensemble is given as a weighted sum of canonical partition functions Z with different number of particles, N_j,
$$\mathcal{Z} = \sum_i \sum_j \exp\left(-\beta(E_i - \mu N_j)\right) \equiv \sum_i \sum_j z^{N_j} \exp\left(-\beta E_i\right) = \sum_j z^{N_j} Z$$
where $z = \exp(\beta\mu)$ is the fugacity, which is a measure for the easiness of adding a new particle into the system.
- Knowledge of the partition function allows to calculate thermodynamic quantities of a system under a fixed temperature T and with the number of particles fixed at N:
$$\Phi = -k_{\text{B}}T \ln \mathcal{Z} \qquad \langle E \rangle = k_{\text{B}}T^2 \frac{\partial \ln \mathcal{Z}}{\partial T} \qquad F = N - k_{\text{B}}T \ln(\mathcal{Z}/z^N)$$
$$S = -\left.\frac{\partial \Phi}{\partial T}\right|_{V,\mu} \qquad p = -\left.\frac{\partial \Phi}{\partial V}\right|_{T,\mu} \qquad \mu = \left.\frac{\partial \Phi}{\partial \mu}\right|_{T,V}$$

Introduction to Statistical Mechanics

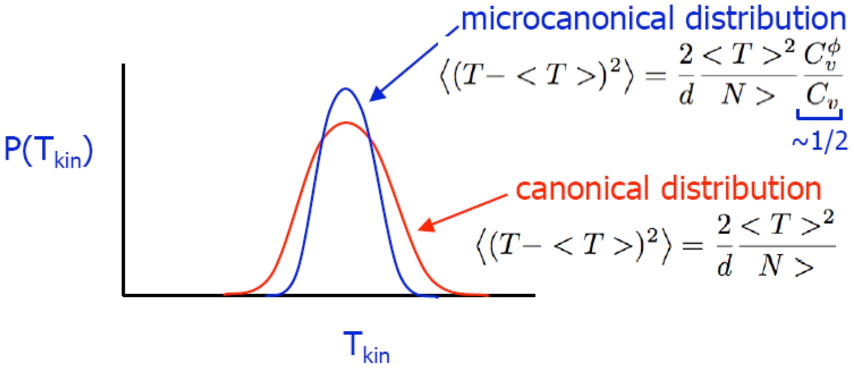
- A molecular dynamics (MD) trajectory corresponds to the microcanonical ensemble: N, V, E are constant.
- A Monte Carlo (MC) simulation corresponds to a canonical ensemble: N, V, T are constant.
- Experiments are usually performed fixing N, p, T.
- Tricks are commonly used to sample the desired ensemble with either MD or MC.

Temperature in Molecular Dynamics

What ensemble is MD? An energy-conserving trajectory gives results for a microcanonical (N,V,E) ensemble (i.e., fixed N, volume, and total energy).

More typically, we are interested in a thermal ensemble, such as the canonical (N,V,T) ensemble (fixed N, volume, and temperature):

$$p(r) \propto \exp\left(-U(r)/k_{\mathrm{B}}T\right) \qquad \text{Boltzmann distribution}$$



microcanonical distribution

$$\left\langle (T - <T>)^2 \right\rangle = \frac{2}{d}\frac{<T>^2}{N>}\underbrace{\frac{C_v^{\phi}}{C_v}}_{\sim 1/2}$$

canonical distribution

$$\left\langle (T - <T>)^2 \right\rangle = \frac{2}{d}\frac{<T>^2}{N>}$$

Thermostats

Thermostat	Brief description	canonical?	stochastic?
Velocity rescaling	E_{kin} fixed to match T_{md}	no	no
Berendsen	E_{kin} fixed to match T_{md}	no	no
Nose-Hoover	extra degree of freedom acts as thermal reservoir	in principle, but caution	no
Nose-Hoover chain	(...(((NH)NH)NH)...)	yes-probably	no
Langevin	noise + frictional drag balances to give correct T	yes	yes
Andersen	occasionally re-randomize momenta	yes	yes

Velocity Scaling

Multiply each atomic velocity by a factor that creates the desired temperature:

$$v^{\mathrm{new}} = \sqrt{T_{\mathrm{md}}/T(t)}v^{\mathrm{old}} \tag{3}$$

Scaling can be done at every time step, or only every few steps..

Advantage:

- Straight-forward to code.

Disadvantages:

- Results do not correspond to any ensemble, though in practice, the amount they deviate from canonical is quite small. Not recommended for use in production MD runs because they do not strictly conform to the canonical ensemble, but fine to use during equilibration.
- Does not remove localized or unwanted correlation motion.
- Not time-reversible or deterministic.

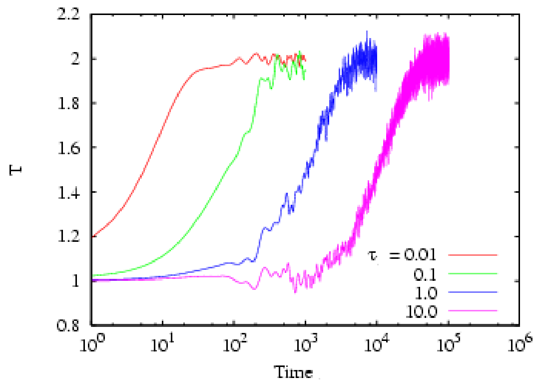
Berendsen Thermostat

Another popular velocity scaling thermostat is that of Berendsen. Here, the scaling is given by

$$\frac{dv}{dt} = \frac{f}{m} + \frac{1}{2\tau}\left(\frac{T_{\mathrm{md}}}{T(t)} - 1\right) v \tag{4}$$

τ is called the 'rise time' of the thermostat. It describes the strength of the coupling of the system to a hypothetical heat bath.

The larger τ, the weaker the coupling, i.e., the longer it takes to achieve a given T_{md} from the current $T(t)$:



Berendsen Thermostat

Advantages:

- Straight-forward to code.
- Robust.

Disadvantages:

- Results do not correspond to any ensemble, though in practice, the amount they deviate from canonical is quite small. Not recommended for use in production MD runs because they do not strictly conform to the canonical ensemble, but fine to use during equilibration.
- Does not remove localized or unwanted correlation motion.
- Not time-reversible or deterministic.

Berendsen et al, J. Chem. Phys. 81, 3684 (1984).

Nosé-Hoover Thermostat

Add one new variable, s, to equations of motion, and scale momenta by $1/s$. With mass Q and friction coefficient ζ, s acts as a thermal reservoir.

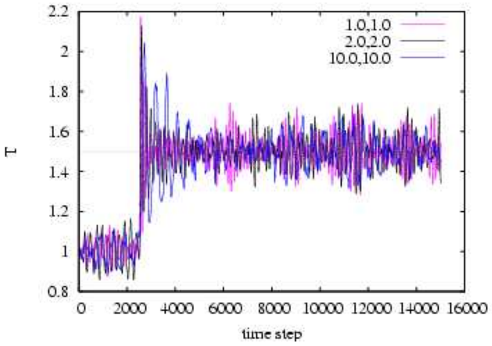
$$H_{\mathrm{Nose-Hoover}} = \sum_{i=1}^{N} \frac{\mathbf{p}_i^2}{2m_i} + U(\mathbf{R}) + \frac{\zeta^2 Q}{2} + (3N)\frac{\ln s}{\beta} \tag{5}$$

- The logarithmic term ($\ln s$) is needed to have the correct scaling of time. Any other scheme that does not have such a logarithmic term will fail to describe the canonical ensemble correctly.
- Built on elegant formalism proposed by Nosé (1984), in which microcanonical dynamics on this extended system is shown to give canonical properties.
- The mass Q determines the strength of the thermostat. The choice of Q is critical in the implementation of this thermostat.
- Deterministic and time-reversible.

Nosé-Hoover Chain

- **Disadvantage of Nosé-Hoover Thermostat:** In some cases, the extended system is not ergodic, becoming trapped in subspace – thus dangerous as a thermostat.
- Martyna, Klein, and Tuckerman (1992): Improve ergodicity in Nosé-Hoover systems by thermostatting the thermostat variable, and then thermostatting that one, and so on.
- Deterministic and time-reversible.
- The effect of increasing the masses Q is to lengthen the decay time of the response to an instantaneous temperature jump.

The temperature controlled by a chain of two Nosé-Hoover thermostats, for various values of the masses Q_1 and Q_2.



Langevin Thermostat

- Each particle i moves as if it is immersed in a bath of much smaller particles (i.e., a viscous fluid). They continuously jostle the particle, giving rise to the stochastic $A_i(t)$ noise term in the force, and provide a viscous drag force proportional to the velocity, $-\Gamma v$:

$$m_i \ddot{r}_i = \underbrace{-\frac{\partial U(\mathbf{R})}{\partial r_i}}_{\text{force}} \underbrace{- m\Gamma \dot{r}_i}_{\text{drag}} + \underbrace{A_i(t)}_{\text{noise}} \tag{6}$$

- The drag and the noise are balanced to give a constant temperature.
- Γ is a friction coefficient with units of s^{-1}, and A_i is a random force that is uncorrelated in time and across particles, with a mean given by

$$\langle A_i(t) A_j(t+\Delta t)\rangle = 2\Gamma m_i k_{\mathrm{B}} T \Delta t \delta_{ij} \delta(\Delta t) \tag{7}$$

Langevin Thermostat

Advantages:

- Langevin dynamics samples from canonical ensemble, i.e., the behaviour is properly thermal for temperature T.
- Can be shown to be ergodic.
- Each particle is coupled to a local heat bath. This can remove heat trapped in localized modes.
- Allows to use a larger time step compared to non-stochastic thermostats.

Disadvantages:

- Momentum transfer is destroyed, i.e., it is unadvisable to use Langevin thermostats for runs in which you wish to compute diffusion coefficients.

Andersen Thermostat

- Perhaps the simplest thermostat which does correctly sample the NVT ensemble is the Andersen thermostat.
- Here, at each step, some prescribed number of particles is selected, and their new velocities are drawn from a Maxwell-Boltzmann distribution corresponding to the desired temperature T_{md}:

$$P(p) = \left(\frac{\beta}{2\pi m}\right)^{3/2} \exp\left[-\beta p^2 / (2m)\right] \tag{8}$$

  where $p = mv$ is the momentum. This is intended to mimic collisions with bath particles at a specified T_{md}.
- The strength of the coupling to the heat bath is specified by a collision frequency, ν. The probability that a particle is selected to undergo a collision with the heat bath in a time step of length Δt is $\nu \Delta t$.

  H.C. Andersen, J. Chem. Phys. 72, 2384 (1980)

Andersen Thermostat

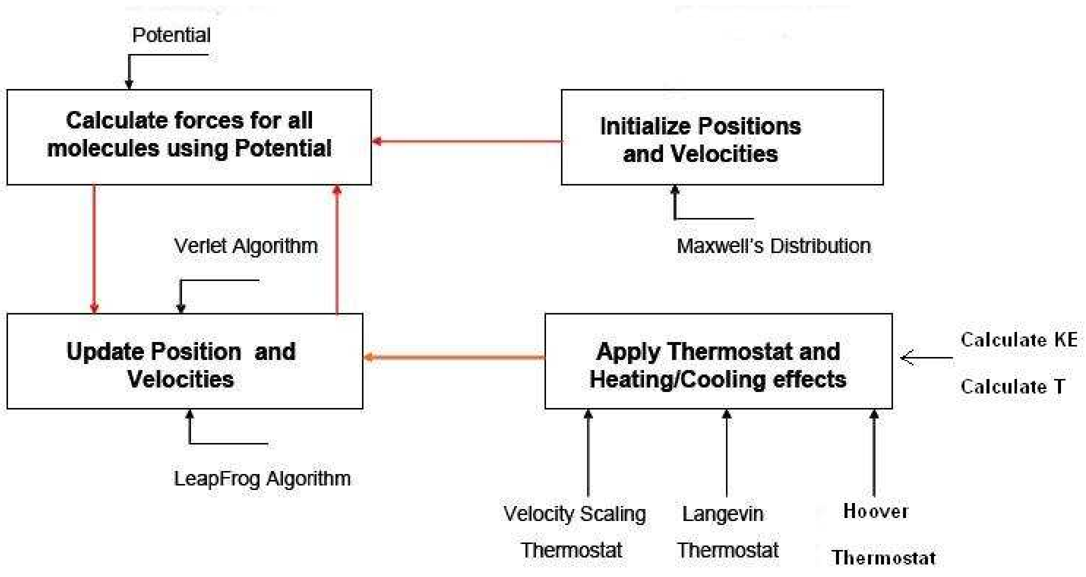
Advantages:

- Samples canonical ensemble.
- While a Langevin trajectory, over time, drifts away from the ‘perfect’ (energy conserving) path due to noise and drag, the Andersen trajectory is perfectly energy conserving.

Disadvantages:

- The mixing of Newtonian dynamics with stochastic collisions turns the MD simulation into a Markov process.
- The Andersen thermostat destroys momentum transport because of the random velocities; hence, there is no continuity of momentum and cannot be used to compute diffusion coefficients.

MD: Final Flow Chart



MD simulations at constant pressure

- Most experiments are performed at constant pressure instead of constant volume
  $\Rightarrow$ **isothermal-isobaric ensemble**
- The volume is thus a dynamical variable that changes during the simulation.
- The pressure of a classical N-body system can be calculated using **Clausius virial theorem,**

$$P = \frac{2}{3V}(E_{\text{kin}} - \Xi) \tag{9}$$

with the box volume V, the kinetic energy E_{kin} and the inner virial for pairwise additive interactions

$$\Xi = \frac{1}{2}\sum_{i<j} \mathbf{r}_{ij} \cdot \mathbf{f}(\mathbf{r}_{ij}) \tag{10}$$

$\mathbf{f}(\mathbf{r}_{ij})$ is the force between particles i and j at a distance $\mathbf{r}_{ij}$.

MD simulations at constant pressure

Derivation of eq. (9): The asymptotic average of the derivative of a bounded function is zero. Intuitively, if you drive around a parking lot (the simulation box) for a long time, your average velocity approaches zero, because as time elapses your net distance traveled does not increase. Formally this can be expressed by noting that, for any constant k and function $r(t)$ bounded such that $|r(t_2) - r(t_1)| < k$ for all t_1 and t_2, the average of the derivative of r over the range from t_1 to t_2 is

$$\langle \dot{\mathbf{r}} \rangle = \left(\frac{1}{t_2 - t_1} \right) \int_{t_1}^{t_2} \frac{d\mathbf{r}}{dt} dt = \frac{\mathbf{r}(t_2) - \mathbf{r}(t_1)}{t_2 - t_1} \tag{11}$$

The magnitude of the numerator is bounded whereas the time interval $t_2 - t_1$ in the denominator can be increased without limit, so the asymptotic average of $d\mathbf{r}/dt$ as the time interval increases is zero, i.e.,

$$\left| \frac{\mathbf{r}(t_2) - \mathbf{r}(t_1)}{t_2 - t_1} \right| < \frac{k}{t_2 - t_1} \longrightarrow 0 \tag{12}$$

If both $\mathbf{r}$ and $d\mathbf{r}/dt$ are bounded functions of t, then so is their product, and it follows from the product rule that

MD simulations at constant pressure

Derivation of eq. (9), continued:

$$\left\langle \frac{d(\mathbf{r} \cdot \dot{\mathbf{r}})}{dt} \right\rangle = \langle \mathbf{r} \cdot \ddot{\mathbf{r}} + |\dot{\mathbf{r}}|^2 \rangle = \langle \mathbf{r} \cdot \ddot{\mathbf{r}} \rangle + \langle |\dot{\mathbf{r}}|^2 \rangle = 0 \tag{13}$$

Now, if $\mathbf{r}$ denotes the spatial position of a particle of mass m, then $m\ddot{\mathbf{r}}$ equals the net force $\mathbf{f}$ on the particle (by Newton's second law), and $m|\dot{\mathbf{r}}|^2$ is twice the kinetic energy E_{kin} of the particle. Thus if we multiply through the above equation by m and consider a set of N particles, we get

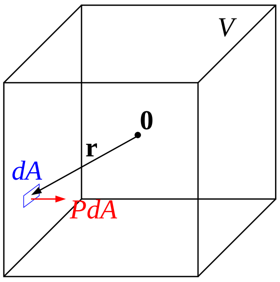
$$\left\langle \sum_{i=1}^{N} (\mathbf{r}_i \cdot \mathbf{f}_{\text{tot},i}) \right\rangle + 2E_{\text{kin}} = 0 \tag{14}$$

The term $\sum_{i=1}^{N} \mathbf{r}_i \cdot \mathbf{f}_{\text{tot},i}$ is called the **virial** and can be decomposed into an outer and inner virial denoted as W and Ξ, respectively. W can be calculated assuming that the particles are trapped in a box with volume V and excert a pressure P onto the walls. That means, that a wall element excerts a force pdA onto nearby particles and is directed inside the box.

MD simulations at constant pressure

Derivation of eq. (9), continued:

$\mathbf{r}$ denotes the vector from the origin to the wall element dA, which excerts a force $P\mathbf{n}dA$ (with $\mathbf{n}$ as the vector normal to the surface element dA) on the **nearby** particles i, thus $\mathbf{r}_i \to \mathbf{r}$.



The contribution of dA to the outer virial can thus be written as

$$\sum_{i=1}^{N} \mathbf{r}_i \cdot \mathbf{f}_{P,i} = \mathbf{r} \cdot \sum_{i=1}^{N} \mathbf{f}_{P,i} = -P\,\mathbf{r} \cdot \mathbf{n}\,dA \tag{15}$$

By integration over the whole surface and using the divergence theorem we then obtain

$$W = -P \int_{\partial V} \mathbf{r} \cdot \mathbf{n} dA = -P \int_{V} \mathrm{div}\,\mathbf{r}\,dV = -3PV \tag{16}$$

where we have used that the divergence of a vector field $\mathbf{F}$ is $\mathrm{div}\,\mathbf{F} = \sum_{i=1}^{n} \partial F_i / \partial x_i$ from which $\mathrm{div}\,\mathbf{r} = 3$ immediately follows.

MD simulations at constant pressure

Derivation of eq. (9), continued:

Combining eqs. (14) and (16) gives

$$\Xi - 3PV + 2E_{\mathrm{kin}} = 0 \qquad \Rightarrow \qquad P = \frac{2}{3V}\left(E_{\mathrm{kin}} + \frac{1}{2}\sum_{i=1}^{N} \mathbf{r}_i \cdot \mathbf{f}_i\right) \tag{17}$$

For pairwise interactions, Ξ is more convenintly expressed in a form which is explicitly independent of the origin of coordinates, yet dependent on interatomic distances. This is done by expressing $\mathbf{f}_i$ as the sum of forces $\mathbf{f}_{ij}$ on atom i due to atom j:

$$\sum_{i} \mathbf{r}_i \cdot \mathbf{f}_i = \sum_{i}\sum_{j\neq i} \mathbf{r}_i \cdot \mathbf{f}_{ij} = \frac{1}{2}\sum_{i}\sum_{j\neq i} \mathbf{r}_i \cdot \mathbf{f}_{ij} + \mathbf{r}_j \cdot \mathbf{f}_{ji}$$

The second equality follows because the indices i and j are equivalent. Newton's third law $\mathbf{f}_{ji} = -\mathbf{f}_{ij}$ is the used to switch indices:

$$\sum_{i}\sum_{i} \mathbf{r}_i \cdot \mathbf{f}_i = \frac{1}{2}\sum_{i}\sum_{j\neq i} (\mathbf{r}_i - \mathbf{r}_j) \cdot \mathbf{f}_{ij} = \frac{1}{2}\sum_{i}\sum_{j\neq i} \mathbf{r}_{ij} \cdot \mathbf{f}_{ij} = \sum_{i}\sum_{j>i} \mathbf{r}_{ij} \cdot \mathbf{f}_{ij} \tag{18}$$

Combining eqs. (18) and (17) gives the expression for the pressure in eq. (9).

MD simulations at constant pressure

- The above derivation is not really valid for infinite periodic systems since there are no container walls and no external forces. Nonetheless, the result is the same!
- The pressure is actually **not a scalar** (as supposed above) but a **second order tensor**:

$$\mathbf{P} = \begin{pmatrix} \mathbf{P}_{xx} & \mathbf{P}_{xy} & \mathbf{P}_{xz} \\ \mathbf{P}_{yx} & \mathbf{P}_{yy} & \mathbf{P}_{yz} \\ \mathbf{P}_{zx} & \mathbf{P}_{zy} & \mathbf{P}_{zz} \end{pmatrix} \quad (19)$$

  where, e.g., the tensor element $\mathbf{P}_{xy}$ is the force in y direction acting on the surface element with its vector normal in x direction.
- Only in isotropic systems, i.e., $P = \mathbf{P}_{xx} = \mathbf{P}_{yy} = \mathbf{P}_{zz}$, can the pressure be expressed as a scalar:

$$P = \mathrm{Tr}(\mathbf{P})/3$$

  which is in this case known as the hydrostatic pressure.

MD simulations at constant pressure

Barostats:

- Correcting the pressure in a simulation can be achieved through a change in the inner virial Ξ by scaling the inter particle distances. This is the common procedure in all barostats described below.
- The ideas in pressure coupling methods are very similar to those in temperature coupling methods.
- Barostats with constant box shape
  - Berendsen barostat
  - Andersen barostat (Nosé-Hoover, Martyna-Tuckerman-Klein, Nosé-Hoover Langevin piston barostats)
- Barostats for changing box shape
  - Parrinello-Rahman barostat

Berendsen barostat

- The Berendsen barostat is very similar to the Berendsen thermostat.
- With the Berendsen barostat the system is made to obey the equation of motion at the beginning of each time step

  $$\frac{dP(t)}{dt} = \frac{P_{\mathrm{md}} - P(t)}{\tau_P}$$

  where $P(t)$ is the instantaneous pressure, P_{md} is the desired pressure, and τ_P is the barostat relaxation time constant.
- This leads to cell size variations, where at each step the MD cell volume is scaled by a factor η, and the coordinates and cell vectors by $\eta^{1/3}$:

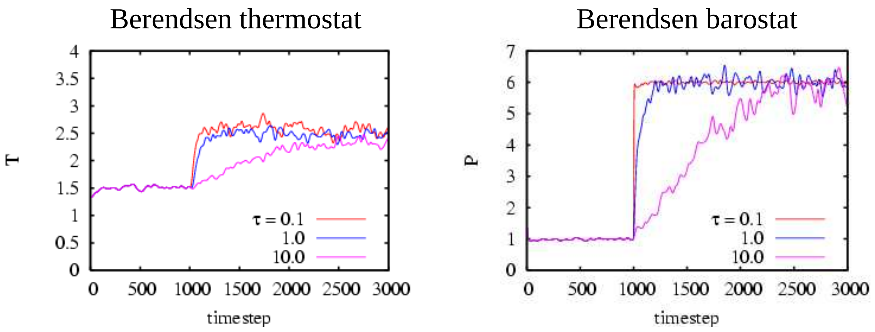
  $$\eta(t) = 1 - \frac{\Delta t}{\tau_P}\gamma(P_{\mathrm{md}} - P(t))$$

  where γ is the isothermal compressibility of the system.

Berendsen barostat

- **Isotropic scaling:** the same η for x, y and z direction
  Anisotropic scaling: different scaling factors for different dimensions (cell shape can change between , e.g., box and cube)
- γ is usually a specified constant which takes to be the isothermal compressibility of liquid water. The exact value is not critical to the algorithm as it relies on the ratio γ/τ_P.
- τ_P is a specified time constant for pressure fluctuations, usually supplied by the user.
- For the strength of the coupling between the system and the "pressure bath", the same applies as for τ in the Berendsen thermostat: The larger τ_P, the weaker the coupling:

Berendsen barostat



- The Berendsen barostat and the thermostat are independent and fully separable.

The same publication for the Berendsen thermostat and barostat: Berendsen et al, J. Chem. Phys. 81, 3684 (1984)

Andersen barostat

- Unlike the Berendsen barostat is the Andersen barostat not similar in idea to the thermostat of the same name.
- The Andersen barostat is an extended system method (compare with the Nosé-Hoover thermostat), which involves coupling the system to an external variable V, the volume of the simulation box.
- This coupling mimics the action of a piston on a real system.
- The piston has a ‘mass’ Q (which actually has the units of (mass)(length)$^{-4}$) and is associated with a kinetic and potential energy:

$$E_{V,\mathrm{kin}} = \frac{1}{2}Q\dot{V}^2 \qquad E_{V,\mathrm{pot}} = P_{\mathrm{md}}V \tag{20}$$

i.e., V is the coordinate of the piston and $P_{\mathrm{md}}V$ is the potential energy resulting from an external pressure P_{md} acting on the piston.

Andersen barostat

- The coordinates of the molecules are given in terms of scaled variables, s_i:

$$\mathbf{r}_i = V^{1/3}\mathbf{s}_i \qquad \mathbf{v}_i = V^{1/3}\dot{\mathbf{s}}_i \tag{21}$$

- The equations of motion are then obtained as

$$\ddot{\mathbf{s}}_i = \frac{\mathbf{f}_i}{m_i V^{1/3}} - \frac{2}{3}\frac{\dot{\mathbf{s}}_i \dot{V}}{V} \qquad \ddot{V} = \frac{P(t) - P_{\mathrm{md}}}{Q} \tag{22}$$

  where the forces $\mathbf{f}_i$ and the instantaneous pressur $P(t)$ are calculated using he unscaled coordinates and momenta of the molecules.

- The Hamiltonian of the system,

$$H = E_{\mathrm{kin}}(\mathbf{R}) + E_{\mathrm{pot}}(\mathbf{R}) + E_{V,\mathrm{kin}} + E_{V,\mathrm{pot}}$$

  is conserved, being equal to the enthalpy of the system plus an additional term of $(1/2)k_{\mathrm{B}}T$ associated with the volume fluctuation (the piston).

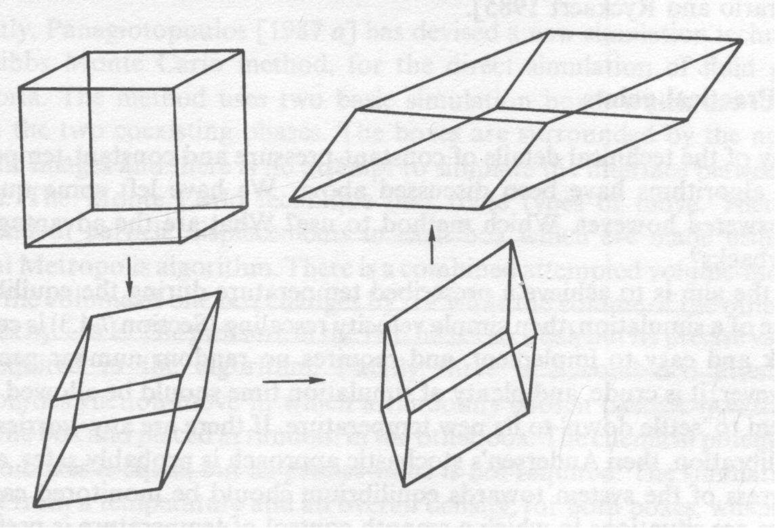
Andersen barostat

- Thus the equations of motion (22) produce trajectories which sample the **isobaric-isoenthalpic ensemble.** The combination with one of the constant-temperature methods allows NPT simulations.
- The parameter Q, the ‘piston mass’, is a user supplied parameter.
- A low ‘mass’ will result in rapid box size oscillations, which are not damped very efficiently by the motions of the molecules.
- A large ‘mass’ will give rise to a slow adjustment of the volume, i.e., the pressure, and infinite mass restores normal MD. (compare with the mass Q in the Nosé-Hoover thermostat).
- The Nosé-Hoover barostat and the Martyna-Tuckerman-Klein barostat are both based on the Andersen barostat.

H. C. Andersen. *Molecular dynamics at constant pressure and/ or temperature.* J. Chem. Phys. 72 (1980), 2384
W. G. Hoover. *Constant pressure equations of motion.* Phys. Rev. A 31 (1986), 1695 G. J. Martyna, D. J. Tobias and M. L. Klein. *Constant pressure molecular-dynamics algorithms* J. Chem. Phys. 101 (1994), 4177

Parrinello-Rahman barostat

- Extension of the constant-pressure method of Andersen by Parrinello and Rahman to allow for the simulation box to change shape as well as size.
- Not of great use in liquid-state simulations but particularly helpful in the study of solids, since it allows for phase changes in the simulation:



Parrinello-Rahman barostat

- The cell can have an arbitrary shape, which can be described by the three vectors $\mathbf{a}$, $\mathbf{b}$, $\mathbf{c}$ representing the sides of the cell. The vectors can be of different lengths.
- The volume is given by

$$V = \det \mathbf{H} = \mathbf{a} \cdot (\mathbf{b} \times \mathbf{c}) \tag{23}$$

  where $\mathbf{H} = \{\mathbf{a}, \mathbf{b}, \mathbf{c}\}$ is a 3×3 matrix.
- The scaled coordinates are now introduced through

$$\mathbf{r}_i = \mathbf{H}\mathbf{s}_i \qquad \text{compare with eq. (21)} \tag{24}$$

- The potential and kinetic energies associated with the fluctuating volume [compare with eq. (22] are

$$E_{\text{pot,V}} = PV \qquad E_{\text{kin,V}} = \frac{1}{2} Q \,\text{Tr}(\dot{\mathbf{H}}^T \dot{\mathbf{H}} \tag{25}$$

  where T stands for transpose and Q is again the cell ‘mass’ (see Andersen thermostat).

Parrinello-Rahman barostat

- The equations of motion are then obtained as

$$\ddot{\mathbf{s}}_i = \frac{\mathbf{H}^{-1}\mathbf{f}_i}{m} - \mathbf{G}^{-1}\dot{\mathbf{G}}\dot{\mathbf{s}} \qquad \ddot{\mathbf{H}} = \frac{(\mathbf{P} - \mathbf{1}P_{\mathrm{md}})V(\mathbf{H}^{-1})^T}{Q} \tag{26}$$

  where $\mathbf{G} = \mathbf{H}^T\mathbf{H}$ is a metric tensor and the pressure tensor (19) was used.
- The similarity between eqs. (26) and the equations of motion for the Andersen thermostat (22) are obvious.

M. Parrinello and A. Rahman:
(i) Phys. Rev. Lett. 45 (1980) 1196
(ii) J. Appl. Phys. 52 (1981) 7182
(iii) J. Chem. Phys. 76 (1982) 2662

Which thermostat and barostat to use?

- Do not use any trivial quenching scaling methods. They suppress fluctuations, and do not provide the correct statistical ensembles.
- Berendsen T and P control are simple to implement and use. In addition, they can steadily drive the system state far from equilibrium toward equilibrated state. This is very handy at the start of the simulation, where significant fluctuations may take place.
- However, if you need to produce the correct statistical ensemble, you will need to use other methods. Nosé-Hoover thermostat with Rahman-Parrinello barostat is a possible option there.
- It also depends on which thermostats and barostats are implemented in the MD package curenty used, for instance,
  - NAMD: Langevin thermostat, Nosé-Hoover Langevin piston barostat
  - GROMACS: Berendsen and Nosé-Hoover thermostats, Berendsen barostat, Parrinello-Rahman barostat
  - AMBER: Berendsen thermostat and barostat