Mechanical quantities

- Temperature (NVE MD):

$$T_{\text{kin}} = \frac{E_{\text{kin}}}{fk_B/2}$$

notation here:
$U = U(r^N)$ = potential energy
$E = E(T, V)$ = internal energy
f = # of degrees of freedom

- Internal energy:

$$E = \langle E_{\text{kin}} + U \rangle \overset{NVT}{=} \frac{f}{2}k_BT + \langle U \rangle \equiv E_{\text{id}} + E_{\text{res}}$$

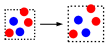
res = residual
see next slide

- Pressure

$\beta = 1/k_BT$

$$p = \frac{N}{V}k_BT - \left\langle \left(\frac{\partial U(V^{1/3}\vec{\xi}^N)}{\partial V} \right)_{\vec{\xi}^N} \right\rangle \equiv p_{\text{id}} + p_{\text{res}}$$

– dimensionless (scaled) coordinates $\vec{\xi}_i$: $\vec{r}_i = V^{1/3}\vec{\xi}_i$
– red derivative is calculated at constant $\vec{\xi}^N$,
whole configurations is uniformly shrank/swelled
– p_{id} = kinetic contribution (=ideal gas), also $p_{\text{id}} = \phi 2E_{\text{kin}}/3V$,
where in periodic b.c. $\phi = N/(N-1)$ takes into acccount 3 zero conserved momenta
– p_{res} = cohesion contribution



Pressure tensor

Also called stress tensor (in solids):

$$\overleftrightarrow{P} = \overleftrightarrow{P}_{\text{id}} + \overleftrightarrow{P}_{\text{res}} = \frac{1}{V}\sum_{i=1}^{N}\left(\phi m_i \vec{v}_i \vec{v}_i + \vec{f}_i \vec{r}_i\right)$$

- Tensor product $\overleftrightarrow{T} = \vec{u}\vec{v}$, also denoted $\overleftrightarrow{T} = \vec{u} \otimes \vec{v}$: $T_{ab} = v_a v_b$.
- $\phi = N/(N-1)$ takes into acccount 3 zero conserved momenta in periodic b.c.
- The scalar pressure is 1/3 of its trace, $p = \text{tr}(\overleftrightarrow{P})/3$.
- In models with rigid (constrained) bonds, the virial of constrained forces has to be included (it depends on velocities).
- Diagonal terms are good for calculating surface tension.
- Off-diagonal terms are good for calculating viscosity.*
- Can be also calculated by the virtual box change:
  – elongation in $\hat{x} \Rightarrow P_{xx}$,
  – simulation cell shape change ⇒ off-diagonal terms.

*Suprisingly, the diagonal terms can be used to calculate viscosity, too.

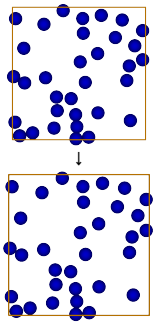
Pressure in the *NVT* ensemble: Derivation

$\text{d}F = -S\text{d}T - p\text{d}V \qquad \langle X \rangle = \frac{1}{Q_N}\int_{V^N} X(\vec{r}^N)\exp[-\beta U(\vec{r}^N)]\text{d}\vec{r}^N$

$$p = -\left(\frac{\partial F}{\partial V}\right)_T, \quad F = -k_BT \ln \frac{Q_N}{N!\Lambda^{3N}}$$

$$Q_N = \int_{V^N} \exp[-\beta U(\vec{r}^N)]\text{d}\vec{r}^N \overset{\vec{r}_i = V^{1/3}\vec{\xi}_i}{=} \int_{1^{3N}} \exp[-\beta U(V^{1/3}\vec{\xi}^N)]V^N \text{d}\vec{\xi}^N$$

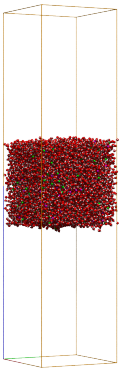
$$\begin{aligned} p &= -\left(\frac{\partial F}{\partial V}\right)_T = k_BT\left(\frac{\partial \ln Q_N}{\partial V}\right)_{\vec{\xi}^N} = \frac{k_BT}{Q_N}\left(\frac{\partial Q_N}{\partial V}\right)_{\vec{\xi}^N} \\ &= \frac{k_BT}{Q_N}\int_{1^{3N}} \exp[-\beta U(V^{1/3}\vec{\xi}^N)]NV^{N-1}\text{d}\vec{\xi}^N \\ &\quad + \frac{k_BT}{Q_N}\int_{1^{3N}} \exp[-\beta U(V^{1/3}\vec{\xi}^N)](-\beta)\left(\frac{\partial U(V^{1/3}\vec{\xi}^N)}{\partial V}\right)_{\vec{\xi}^N} V^N \text{d}\vec{\xi}^N \\ &= \frac{N}{V}k_BT - \left\langle \left(\frac{\partial U(V^{1/3}\vec{\xi}^N)}{\partial V}\right)_{\vec{\xi}^N} \right\rangle = \boxed{\text{ideal part (kinetic)}} + \boxed{\text{residual part (correction)}} \end{aligned}$$



Surface tension of liquid

Using slab geometry – elongated periodic box (2:1 or more)

$$\gamma = \left(\frac{\partial F}{\partial \mathcal{A}}\right)_{V,T} = \left(\frac{\partial G}{\partial \mathcal{A}}\right)_{p,T} = -\frac{1}{4}L_z P_{\text{t}}, \quad \text{where } P_{\text{t}} = P_{xx} + P_{yy} - 2P_{zz}.$$



- It is "mechanical quantity".
- Cannot be used for interfacial energy of crystals (it is "entropic quantity").
- Cutoff corrections – several variants (cf. simen09).
- P_{zz} = saturated vapor pressure;
if small enough, P_{xx}, P_{yy} can be replaced by the usual pressure p.
- Alternative: virtual area change method [Gloor et al.: JCP 123, 134703 (2005)]:
scaling in $\hat{x}, \hat{y}$ and inversely squared in $\hat{z}$ so that volume is preserved:

$$\gamma = \left\langle \left(\frac{\delta U}{\delta \mathcal{A}}\right)_V \right\rangle$$

Residual quantities

= with respect to the standard state of ideal gas at the same temperature, volume (= density), and composition as the given system. Usefull in the canonical (NVT) ensemble.

sometimes "excess"; for solvation Gibbs energy or μ of solute, also "Ben-Naim standard state"

For the Helmholtz energy:

ideal gas: $Q_N = V^N$

$$F = -k_BT \ln Z_N = -k_BT \ln \frac{Q_N}{N!\Lambda^{3N}} = -k_BT \ln \frac{V^N}{N!\Lambda^{3N}} - k_BT \ln \frac{Q_N}{V^N} \equiv F_{\text{id}} + F_{\text{res}}$$

Refresh:
Thermal de Broglie wavelength:

$$\Lambda = \frac{h}{\sqrt{2\pi m k_BT}}$$

chemical potential of ideal gas:

$$\mu_{\text{id}} = \left(\frac{\partial F_{\text{id}}}{\partial N}\right)_{T,V} = k_BT \ln \frac{N\Lambda^3}{V}$$

Fluctuation quantities

$\langle (\Delta X)^2 \rangle = \text{Var}\, X$ = (mean quadratic) fluctuation = variance

$\Delta X = X - \langle X \rangle$

fluctuation = (mech/el/... quantity)′ = (thermodynamic potential)″

Less accurate than mean values!

Perhaps except (observable) = 0. This is the case of permittivity calculated from the fluctuation of the cell dipole moment, $\langle M^2 \rangle$.

- Heat capacity at constant $[V]$:

$$C_V = \left(\frac{\partial E}{\partial T}\right)_V = \frac{1}{k_BT^2}\text{Var}\, E = \frac{1}{k_BT^2}\langle (\Delta E_{\text{kin}} + \Delta U)^2 \rangle$$

It is usually more efficient to measure dependence $E(T)$ or $p(\rho)$ in the *NVT* ensemble, fit it to a suitable function, and calculate a derivative

$\text{Cov}(U, E_{\text{kin}}) = \langle \Delta U \Delta E_{\text{kin}} \rangle = 0$, $\text{Var}\, E_{\text{kin}} = \frac{f}{2}(k_BT)^2$ (see exercise) ⇒

$$C_V = \frac{1}{k_BT^2}\left\langle \left(\frac{fk_BT}{2} + \Delta U\right)^2 \right\rangle = \frac{fk_B}{2} + \frac{1}{k_BT^2}\langle (\Delta U)^2 \rangle \equiv C_{V,\text{id}} + C_{V,\text{res}}$$

- Isothermal compressibility – in the NPT ensemble

$$\kappa = -\frac{1}{V}\left(\frac{\partial V}{\partial p}\right)_T = \frac{\langle (\Delta V)^2 \rangle}{Vk_BT}$$

Pressure – virtual volume change method

$$p = \frac{N}{V}k_BT - \left\langle \left(\frac{\partial U(V^{1/3}\vec{\xi}^N)}{\partial V}\right)_{\vec{\xi}^N} \right\rangle$$

Numerical derivative (for a selected series of configurations)

$$\frac{\partial U}{\partial V} = \frac{U(V+\Delta V) - U(V)}{\Delta V} + \mathcal{O}(\Delta V) \equiv \frac{U(\text{}) - U(\text{})}{\Delta V} + \mathcal{O}(\Delta V)$$

$$\frac{\partial U}{\partial V} = \frac{U(V+\Delta V) - U(V-\Delta V)}{2\Delta V} + \mathcal{O}(\Delta V^2)$$

Implementation: $U(V + \Delta V)$ means that the whole configuration (all distances) is swelled by the same ratio; for molecules w.r.t. a reference point (then, N = # of molecules):

$$\left(\frac{V+\Delta V}{V}\right)^{1/3}.$$

The scaled configuration is not included in the trajectory.

For models with a hard core such that swelling the box cannot cause an overlap, shrinking can be used: $P = Nk_BT/V + \frac{k_BT}{\Delta V}\langle e^{-[U(V-\Delta V)-U(V)]/k_BT} \rangle + \mathcal{O}(\Delta V)$

Exercise

Calculate $\langle E_{\text{kin}} \rangle$ and $\text{Var}(E_{\text{kin}})$ for one degree of freedom, $E_{\text{kin}} = \frac{1}{2}mv^2$.

$$\begin{aligned} E_{\text{kin}} &= \frac{1}{2}mv^2 \\ \boldsymbol{\pi}(v) &= \frac{\exp(-\frac{1}{2}mv^2/k_BT)}{\int \exp(-\frac{1}{2}mv^2/k_BT)\text{d}v} \\ \langle E_{\text{kin}} \rangle &= \int E_{\text{kin}}\boldsymbol{\pi}(v)\text{d}v \\ \text{Var}(E_{\text{kin}}) &= \int (E_{\text{kin}} - \langle E_{\text{kin}} \rangle)^2 \boldsymbol{\pi}(v)\text{d}v \\ &= \frac{1}{2}(k_BT)^2 \end{aligned}$$

```
> restart;
> assume(m>0,k>0,T>0);
> K:=m/2*v^2: kT:=k*T:
> inorm:=int(exp(-K/kT),v=-infinity..infinity);
                    inorm := sqrt(2) k~ T~ sqrt(pi) / sqrt(m~ k~ T~)
> averK:=int(K*exp(-K/kT),v=-infinity..infinity)/inorm;
                    averK := 1/2 k~ T~
> fluctK:=int((K-averK)^2*exp(-K/kT),v=-infinity..infinity)/inorm;
                    fluctK := 1/2 k~^2 T~^2
```

Pressure from the virial of force

The derivative expanded:

$$\frac{\partial U(V^{1/3}\vec{\xi}^N)}{\partial V} = \sum_{i=1}^{N}\frac{1}{3}V^{-2/3}\vec{\xi}_i \cdot \frac{\partial U}{\partial \vec{r}_i} = \frac{1}{3V}\sum_{i=1}^{N}\vec{r}_i \cdot \frac{\partial U}{\partial \vec{r}_i}$$

($-\vec{f}_i$)

The result is

$$p = \frac{N}{V}k_BT + \frac{1}{3V}\langle W_f \rangle, \qquad W_f = -\sum_{i=1}^{N}\vec{r}_i \cdot \frac{\partial U}{\partial \vec{r}_i} = \sum_{i=1}^{N}\vec{r}_i \cdot \vec{f}_i \quad \text{(virial of force)}$$

... cannot be directly applied in the periodic boundary conditions.

- Pair additivity in the periodic boundary conditions ⇒

$$p = \frac{N}{V}k_BT - \frac{1}{3V}\sum_{i<j}\langle r_{ij}u'(r_{ij}) \rangle \equiv p_{\text{id}} + p_{\text{res}}$$

- For molecular models one can use either the atom-frame (N = # of atoms/sites), or molecular frame (N = # of molecules; typically, ref. point = center of mass). Of course, the formulas differ.

Entropic quantities

These include F, G (⇐ partition function), S (number of states W), μ, ΔG,...
They cannot be expressed as a simple $\langle \cdot \rangle$.

Usage: equilibria in general; solubility, ligand–receptor binding, stability of biomolecules, ...

- thermodynamic integration:
  - over a real variable (T, V, P)
  - over a coupling parameter
- reversible work calculated by the integration of force
- Widom particle insertion method;
gradual insertion, alchemical transmutation
- non-Boltzmann sampling:
  - umbrella sampling (various flavors)
  - multiple histogram reweighting
  - metadynamics/Wang–Landau/conformational flooding
- local density method

Formally (for the configurational integral):

$$Q = \frac{\int e^{-\beta U}\text{d}\vec{r}^N}{1}$$

$$= \frac{\int e^{-\beta U}\text{d}\vec{r}^N}{V^{-N}\int e^{-\beta U}e^{+\beta U}\text{d}\vec{r}^N} = \frac{V^N}{\langle e^{\beta U} \rangle}$$

... totally useless

Thermodynamic integration

Physical chemistry: $dF = -SdT - pdV$, $dG = -SdT + Vdp$

$U = U(r^N)$ = potential energy
$E = E(T, V)$ = internal energy

Canonical ensemble ($\beta = 1/k_BT$):

$$\left(\frac{\partial F}{\partial V}\right)_T = -p \;\Rightarrow\; F_1 - F_0 = -\int_{V_0}^{V_1} p\,dV, \quad \left(\frac{\partial(\beta F)}{\partial \beta}\right)_V = E \text{ or } \left(\frac{\partial(\beta F_{\text{res}})}{\partial \beta}\right)_V = \langle U \rangle$$

- Numerically integrated: p, E must be determined at many points
- Start from a suitable reference state (known state, ideal gas, harmonic crystal)

Proof # 1 of $\frac{\partial(\beta F)}{\partial \beta} = E$:

$$\frac{\partial(\beta F)}{\partial \beta} = \frac{\partial(F/T)}{\partial(1/T)} = \frac{\partial(F/T)}{\partial T} \Big/ \frac{\partial(1/T)}{\partial T} = \frac{-ST - F}{T^2} \Big/ \left(\frac{-1}{T^2}\right) = ST + F = E$$

Proof # 2 of $\frac{\partial(\beta F)}{\partial \beta} = E$:

$$\frac{\partial(\beta F)}{\partial \beta} = \frac{-\partial \ln Z}{\partial \beta} = -\frac{1}{Z}\frac{\partial Z}{\partial \beta} = -\frac{\partial \sum_\psi e^{-\beta\mathcal{E}(\psi)}/\partial\beta}{\sum_\psi e^{-\beta\mathcal{E}(\psi)}} = -\frac{\sum_\psi \left[-\mathcal{E}(\psi) e^{-\beta\mathcal{E}(\psi)}\right]}{\sum_\psi e^{-\beta\mathcal{E}(\psi)}} = \langle \mathcal{E} \rangle = E$$

Integration over a coupling parameter

Let us consider any dependence $(\beta U)(\lambda)$, e.g.:

$$(\beta U)(\lambda) = \begin{cases} \beta[U_0 + \lambda(U_1 - U_0)] & \lambda = \text{coupling parameter, } \lambda \in [0,1] \\ \lambda U & \lambda \equiv \beta\text{: see previous slide} \end{cases}$$

then

$$\frac{\partial \beta F_{\text{res}}}{\partial \lambda} = -\frac{\partial \ln Q}{\partial \lambda} = -\frac{1}{Q}\int \frac{\partial e^{-\beta U}}{\partial \lambda} d\vec{r}^N = \frac{1}{Q}\int \frac{\partial(\beta U)(\lambda)}{\partial \lambda} e^{-\beta U(\lambda)} d\vec{r}^N = \left\langle \frac{\partial(\beta U)(\lambda)}{\partial \lambda} \right\rangle_\lambda$$

$$(\beta F_{\text{res}})(\lambda_1) = (\beta F_{\text{res}})(\lambda_0) + \int_{\lambda_0}^{\lambda_1} \left\langle \frac{\partial(\beta U)(\lambda)}{\partial \lambda} \right\rangle_\lambda d\lambda$$

where $\langle\cdot\rangle_\lambda$ = mean value in the ensemble (simulation) with potential $U(\lambda)$

How to integrate: (over a real variable or coupling parameter)

- Several discrete values of λ_i:
  - fit to a suitable function and integrate it
  - use a numerical quadrature method; e.g., the Simpson formula (points with a higher weight should be simulated longer)
- A little change of λ in every MD step (the system is almost in equilibrium) + integration

Examples

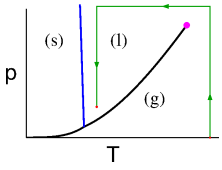
- For $\lambda = \beta$ we get as before:

$$\beta_1 F_{\text{res}}(\beta_1) - \beta_0 F_{\text{res}}(\beta_0) = \int_{\beta_0}^{\beta_1} \langle U \rangle d\beta$$

- Integration from an Einstein crystal to a real crystal.
  NB: Einstein crystal = independent (here classical) harmonic oscillators at lattice sites.
  There are minor solvable problems when the crystal is detached from the fixed sites.
- Integration from ideal gas (e.g., around the critical point to liquid). Because of gas singularity at zero density, one of the integrals is (for NPT):

$$\ln \phi = \frac{\mu - \mu^\circ}{RT} = \int_0^p \left(V_m - \frac{RT}{p'}\right) dp'$$

It helps to use a virial equation of state at low densities.



Zwanzig perturbation method

We want $(\beta U)_1$, but we simulate $(\beta U)_0$ (can change β/U/both)[†]

$$\Delta(\beta U) = (\beta U)_1 - (\beta U)_0$$

$$\langle X \rangle_{(\beta U)_1} = \frac{\int X e^{-(\beta U)_1} d\vec{r}^N}{\int e^{-(\beta U)_1} d\vec{r}^N} = \frac{\frac{1}{Q_0}\int X e^{-(\beta U)_0} e^{-\Delta(\beta U)} d\vec{r}^N}{\frac{1}{Q_0}\int e^{-(\beta U)_0} e^{-\Delta(\beta U)} d\vec{r}^N} = \frac{\langle X e^{-\Delta(\beta U)} \rangle_0}{\langle e^{-\Delta(\beta U)} \rangle_0}$$

Helmholtz energy:

$$\begin{aligned} \Delta(\beta F_{\text{res}}) &= \beta_1 F_{\text{res}}((\beta U)_1) - \beta_0 F_{\text{res}}((\beta U)_0) \\ &= -\ln\left(\frac{Q_1}{Q_0}\right) = -\ln \frac{\int e^{-(\beta U)_1} d\vec{r}^N}{\int e^{-(\beta U)_0} d\vec{r}^N} \\ &= -\ln \frac{\int e^{-(\beta U)_0} e^{-\Delta(\beta U)} d\vec{r}^N}{\int e^{-(\beta U)_0} d\vec{r}^N} = -\ln \langle e^{-\Delta(\beta U)} \rangle_0 \end{aligned}$$

Symmetrically from $0 \leftrightarrow 1$ interchange: $\Delta(\beta F_{\text{res}}) = \ln \langle e^{+\Delta(\beta U)} \rangle_1$

[†]First usage probably Zwanzig (1954) for ΔF, many variants today: umbrella sampling, scaled particle/gradual insertion/alchemical transmutation, non-Boltzmann sampling, ...

Zwanzig perturbation method contd.

- $\Delta(\beta U)$ must not be too large
- the thermodynamic integration is recovered for infinitesimally small $\Delta(\beta U)$:

$e^x = 1 + x + \cdots$
$\ln(1+x) = x + \cdots$

$$\begin{aligned} \Delta(\beta F_{\text{res}}) &= -\ln \langle e^{-\Delta(\beta U)} \rangle_0 \\ &\approx -\ln \langle 1 - \Delta(\beta U) \rangle_0 \\ &= -\ln(1 - \langle \Delta(\beta U) \rangle_0) \\ &\approx \langle \Delta(\beta U) \rangle \\ \text{general } \lambda\text{:} \quad \partial(\beta F_{\text{res}})/\partial\lambda &= \langle \partial \Delta(\beta U)/\partial\lambda \rangle_\lambda \\ \lambda = \beta\text{:} \quad \partial(\beta F_{\text{res}})/\partial\beta &= \langle U \rangle \end{aligned}$$

Umbrella sampling (original)
The system in the middle is sampled: mid = $(\beta U)_0 + \Delta(\beta U)/2 = (\beta_0 U_0 + \beta_1 U_1)/2$:

$$\Delta(\beta F_{\text{res}}) = \ln \langle e^{+\Delta(\beta U)/2} \rangle_{\text{mid}} - \ln \langle e^{-\Delta(\beta U)/2} \rangle_{\text{mid}}$$

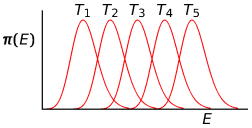
Nowadays, term "umbrella sampling" usually refers to many steps of similar kind and/or many overlapping Gaussian-weighted systems along a collective variable.

Scaled particle: A particle growing step-wise, similar is "alchemic transmutation"

Multiple histogram reweighting I

aka WHAM, weighted histogram analysis method

Building the **density of states** as a funtion of energy in a wide range of temperatures from overlapping histograms of energies obtained in a number of simulations at different temperatures (can be extended to other coupling parameter).



$$\pi(E) = D(E) e^{-\beta E}$$

$$D(E) \propto E^{\text{const}\,N}$$

Configurational integral and residual Helmholtz energy at temperature T_i, $\beta_i = 1/k_BT_i$:

$$Q_i = e^{-\beta_i F_i} = \int e^{-\beta_i U(\vec{r}^N)} d\vec{r}^N = \int D(E) e^{-\beta_i E} dE$$

where $D(E)$ (aka W, Ω) is the density of states:

$$\begin{aligned} D(E) &= \int_{U(\vec{r}^N)=E} 1\, d\vec{r}^N \equiv \int \delta(U(\vec{r}^N) - E)\, d\vec{r}^N \\ &\overset{\text{rectangle}}{\approx} \int_{U(\vec{r}^N) \in (E - \Delta E/2, E + \Delta E/2)} 1 d\vec{r}^N \end{aligned}$$

[Ghoufi et al. (2008)]

Detour: Density of states for a particle in a box

One particle in 1D in a box of length L, energies of eigenstates according to the Schrödinger equation:

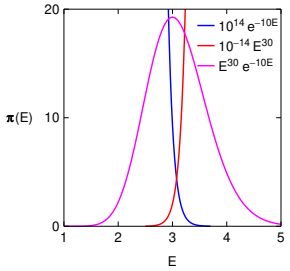
$$E_n = \frac{n^2 h^2}{8L^2} \propto n^2, \; n = 1, 2, \ldots$$

Let's have $f = 3N$ such degrees of freedom. The number of states $\#(E)$ with energy less than E satisfies the equation

$$n_1^2 + n_2^2 + \cdots + n_f^2 < E = [E^{1/2}]^2$$

For large E, $\#(E) = 1/2^f$ of the volume of the $E^{1/2}$-ball in the f-dimendional space:

$$\#(E) = \frac{\pi^{f/2} E^{f/2}}{\Gamma(f/2+1)} \propto E^{f/2} \quad \Rightarrow \quad D(E) = \frac{d\#(E)}{dE} \propto E^{f/2-1}$$



$$\pi(E) = D(E) e^{-\beta E}$$

The Boltzmann factor $e^{-\beta E}$ eventually wins!
For large N, the product converges to a Gaussian with $\text{Var}(E) \propto f \propto N$ ($\sigma = N^{1/2}$)

Multiple histogram reweighting II

In the simulation, we calculate the histogram $h_i(E)$ for a set of (equidistant) energies E, or some equivalent Gaussian-based δ-function approximation. We will use the normalized histogram and the $\int$-form. (To repeat, subscript $_i$ refers to T_i.)

$$\sum_E h_i(E) = \int h_i(E) dE = 1$$

$$h_i(E) = \frac{D(E) e^{-\beta_i E}}{\int D(E) e^{-\beta_i E} dE} = D(E) e^{-\beta_i (E - F_i)}$$

Using one temperature only but F_i is not known (yet):

$$D(E) = h_i(E) e^{\beta_i (E - F_i)} \tag{1}$$

- We will average $D(E)$ from several simulations at different temperatures.
- $D(E)$ does not depend on T_i, but our calculation does ± statistical errors.
- At different T_i different ranges of E are sampled.

⇒ We compose the total $D(E)$ from all data:

$$D(E) = \sum_i w_i(E) h_i(E) e^{\beta_i (E - F_i)}, \quad \sum_i w_i(E) = 1$$

Multiple histogram reweighting III

Determining the weights: minimization of the error $\delta D(E)$ (or some estimate). Using reasonable assumptions, we get

$$w_i(E) = \frac{N_i h_i(E)}{\sum_j N_j h_j(E)} = \frac{N_i e^{-\beta_i (E - F_i)}}{\sum_j N_j e^{-\beta_j (E - F_j)}}$$

where N_i is the number of measurements at temperature β_i. ⇒

$$e^{-\beta_i F_i} = \int D(E) e^{-\beta_i E} dE = \int \sum_j w_j(E) h_j(E) e^{\beta_j (E - F_j)} e^{-\beta_i E} dE$$

$$= \int \frac{\sum_j N_j e^{-\beta_j (E - F_j)} h_j(E) e^{\beta_j (E - F_j)}}{\sum_j N_j e^{-\beta_j (E - F_j)}} e^{-\beta_i E} dE = \int \frac{\sum_j N_j h_j(E) e^{-\beta_i E}}{\sum_j N_j e^{-\beta_j (E - F_j)}} dE$$

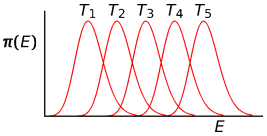
can be solved by iterations (self-consistent solution).
F_i are determined but an additive constant, $D(E)$ but a multiplicative factor

Multiple histogram reweighting IV

Expectation value at temperature β:

$$\langle X \rangle_\beta = \frac{\int X(E) D(E) e^{-\beta E} dE}{\int D(E) e^{-\beta E} dE} = \frac{\int X(E) \frac{\sum_i h_i(E)}{\sum_j N_j e^{-\beta_j (E - F_j)}} e^{-\beta E} dE}{\int \frac{\sum_i h_i(E)}{\sum_j N_j e^{-\beta_j (E - F_j)}} e^{-\beta E} dE}$$

- $\int dE$ is over histograms of width ΔE
- if ΔE is very short, all calculated energies are stored and $\int X(E) h_i(E) dE$ is replaced by a sum of E over $h_i(E) = 1/N_i$
- $\sqrt{\text{Var}E}/\langle E \rangle \approx N^{-1/2} \Rightarrow \beta_i/\beta_{i+1} \approx 1 \pm N^{-1/2}$ (overlapping distributions)



Parallel tempering (replica exchange)

k simulations at temperatures $\beta_1 < \beta_2 \ldots$ are run in parallel.

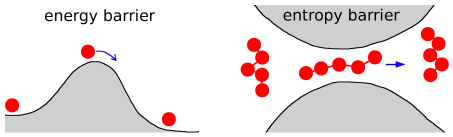
Once a while, 2 subsystems β_i, β_j (normally $|i-j| = 1$) are interchanged, the acceptance probability is

$$\min\left\{1, \frac{\exp(-\beta_i E_j - \beta_j E_i)}{\exp(-\beta_i E_i - \beta_j E_j)}\right\}$$

- ⊕ Easier barrier crossing, improved ergodicity, faster convergence at low temperatures
- ⊖ Correlations between subsystems, difficult error estimation

Conformational flooding, Wang–Landau, metadynamics

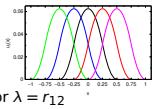
Method suitable for fast **barrier crossing** (bad ergodicity – "bottleneck"), incl. calculation of the free energy profile (ΔF or ΔG), based on decreasing the energy barrier.



- (several predecessors)
- Conformational flooding H. Grubmüller (1995)
- Wang–Landau (MC) F. Wang, D.P. Landau (2001)
- Metadynamics (MD) A. Laio, M. Parrinello (2002)
- Formal equivalence C. Junghans, D. Perez, T. Vogel (2014)

Conformational flooding, Wang–Landau, metadynamics

- Our system is defined by the potential $U_0(\vec{r}^N)$
- **Collective variable** $\lambda = \lambda(\vec{r}^N)$ describes the studied process, e.g.: reaction coordinate, atom–atom distance, group–group distance (of their centers of mass e.g., ligand–receptor). various projections or angles,. . .
  There may be 2 or even more collective variables
- We simulate system with potential $U(\vec{r}^N) = U_0(\vec{r}^N) + \Delta U(\lambda)$, where $\Delta U = 0$ at start
- $\Delta U(\lambda)$ is periodically updated: $\Delta U := \Delta U + \omega \frac{\delta(\lambda)}{h(\lambda)}$, $\lambda = \lambda(\vec{r}^N)$
  δ = aproximation of δ-function (MC: histogram bin, better and MD: Gauss)
  ω = small enough relaxation parameter, $\omega \ll k_B T$
  $h(\lambda)$ = density of Cartesian points on hypersurface λ; e.g., $h(\lambda) = 4\pi r_{12}^2$ for $\lambda = r_{12}$
  ⇒ the probability of visiting the same λ again decreases



- If $h(\lambda)$ is omitted in the update stage, it has to be included later.
- Other weight functions may more eficient (= sample different ranges of λ better) than $h(\lambda)$; e.g., $h(\lambda) = r_{12}$ for $\lambda = r_{12}$. Again, the true density of points must be taken into account later.

Conformational flooding, Wang–Landau, metadynamics

Free energy profile along λ:

- strictly, updating should be turned off in the final run (MC: microreversibility violation, MD: heating)
- then, the residual almost-uniform $p(\lambda)$ is determined and:

$$F(\lambda) = \text{const} - \Delta U(\lambda) - k_B T \ln[p(\lambda)/h(\lambda)]$$

- in practice, with small enough ω and continued updating, we can assume $p(\lambda)/h(\lambda) = \text{const}^\dagger$ so that (in the sampled region of λ)

$$F(\lambda) = \text{const} - \Delta U(\lambda)$$

Free energy of a well-define "basin" of states (e.g., a bond state) is:

$$F = -k_B T \ln \int_{\lambda_1}^{\lambda_2} \mathrm{e}^{-F(\lambda)/k_B T} h(\lambda) \mathrm{d}\lambda$$

integration over region for more collective variables

Two case studies:
- simple MC (next 2 pages)
- potential of mean force in simen08

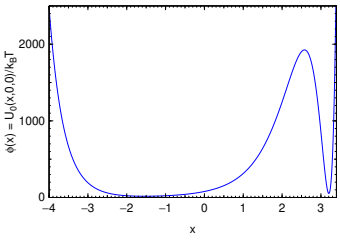
†symbols const are different

Conformational flooding, Wang–Landau, metadynamics: Case study

3D system, interaction energy: online simulation is for T=1 K and T=2 K, type r to reread

$$\frac{U_0(x,y,z)}{k_B\,\mathrm{K}} = \phi(x)(y^2+z^2+1), \text{ where } \phi(x) = \Big[(x+1)(x+2)(x-2)(x-4)+21\Big]\mathrm{e}^{(x+1.5)^2/3}$$

- The barrier is $E^*/k_B = 1910\,\mathrm{K}$, $\mathrm{e}^{-E^*/k_B 1\mathrm{K}} = 10^{-929}$
- Collective variable $\lambda = x$
- Histogram: triangular $\delta(\lambda)$, grid = 1/100
- On purpose short MC step 0.01 in x (≈ MD)
- Initial $\omega = 0.125 k_B T$, decrease to finish
  4me: `arara` in the plot window
- graphs shown:
  – running: $\Delta U - F_{\text{exact}}$, where
  $$F_{\text{exact}}(\lambda) = \phi(\lambda) + k_B T \ln(\phi(\lambda))$$
  – final: ΔU and $\phi(x) = U_0(x, 0, 0)$
  – F and F_{exact} comparison



Note: in real systems, the second term will be a result of many degrees of freedom, not just 2 (y, z)

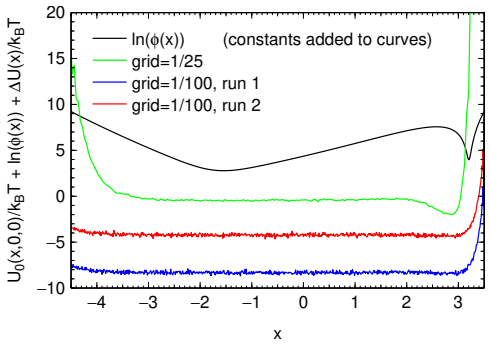
Conformational flooding, Wang–Landau, metadynamics: Case study

The final graph shows $F(x) + \Delta U(x)$ (two independent simulations $T = 1\,\mathrm{K}$, different start)

1/grid	$\Delta F/k_B T$
50	37.85(8)
100	40.52(5)
200	40.98(5)
400	41.08(3)
exact*	41.13

where ΔF is the difference between the right and left basins.

* see Maple



Widom particle insertion method I

Open system

$$\mathrm{d}F = -S\mathrm{d}T - p\mathrm{d}V + \mu\mathrm{d}N$$

$$\beta\mu = \left(\frac{\partial(\beta F)}{\partial N}\right)_{V,T} = -\left(\frac{\partial \ln Z_N}{\partial N}\right)_{V,T}$$

$$\beta\mu_{\text{res}} = \left(\frac{\partial(\beta F_{\text{res}})}{\partial N}\right)_{V,T} = -\left(\frac{\partial \ln(Q_N/V^N)}{\partial N}\right)_{V,T} \approx -\left(\ln\frac{Q_{N+1}}{V^{N+1}} - \ln\frac{Q_N}{V^N}\right)$$

$$\exp(-\beta\mu_{\text{res}}) = \frac{1}{V}\frac{Q_{N+1}}{Q_N}$$

Or for the full chemical potential:

$$\mathrm{e}^{-\beta\mu} = \frac{Z_{N+1}}{Z_N} = \frac{Q_{N+1}/[(N+1)!\Lambda^{3(N+1)}]}{Q_N/[N!\Lambda^{3N}]} = \frac{1}{(N+1)\Lambda^3}\frac{Q_{N+1}}{Q_N} \approx \frac{1}{N\Lambda^3}\frac{Q_{N+1}}{Q_N}$$

then by subtracting $\mu^{\text{id}} = k_B T \ln\left(\frac{N\Lambda^3}{V}\right)$ we get the same $\mu_{\text{res}} = \mu - \mu^{\text{id}}$

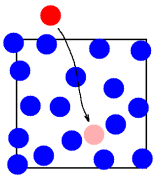
Widom particle insertion method II

$$\exp(-\beta\mu_{\text{res}}) = \frac{1}{V}\frac{Q_{N+1}}{Q_N}$$

$$N \to N+1 \qquad U_{N+1} = U_N + \Psi(N)$$

$$\frac{1}{V}\frac{Q_{N+1}}{Q_N} = \frac{1}{VQ_N}\int \exp(-\beta U_N - \beta\Psi)\mathrm{d}\vec{r}_1 \ldots \mathrm{d}\vec{r}_{N+1} = \frac{1}{V}\int \langle \mathrm{e}^{-\beta\Psi}\rangle_N \mathrm{d}\vec{r}_{N+1}$$

$$\exp(-\beta\mu_{\text{res}}) = \frac{1}{V}\int \langle \mathrm{e}^{-\beta\Psi}\rangle_N \mathrm{d}\vec{r}_{N+1} = \left\langle \langle \mathrm{e}^{-\beta\Psi}\rangle_N \right\rangle_{\text{random } \vec{r}_{N+1}}$$



where $\frac{1}{V}\int X \mathrm{d}\vec{r}_{N+1} = \langle X\rangle_{\text{random } \vec{r}_{N+1}}$ = mean value of X over positions of the $(N+1)$-th particle in volume V, calculated by MC integration (inserting a particle at rancom place)

- $(N+1)$-th particle does not influence the system – it is virtual (fictitious, ghost)
- Problem: dense systems, large solutes
  Remedy: gradual insertion (thermodynamic integration or by finite steps)

Similar: solute insertion ⇒ solubility, Henry constant

Example

We have simulated $N = 500$ Ar atoms (Lennard-Jones: $\sigma = 3.405\,\text{Å}$, $\epsilon/k_B = 119.8$ K) in a box of volume $V = 15.791\,\mathrm{nm}^3$ at temperature $T = 150$ K. By the Widom method, we found that§

$$\exp(-\mu_{\text{res}}/k_B T) = 0.749(3)$$

Calculate μ°, the chemical potential of Ar with respect to the standard state of ideal gas at pressure $p^{\text{st}} = 1$ bar and temperature T.

$\mu^{\text{id}} = k_B T \ln\frac{N\Lambda^3}{V}$

Hints:
$\mu_{\text{res}} = \mu - \mu^{\text{id}}(T, V)$ (N particles in volume V)
$\mu^\circ = \mu - \mu^{\text{id}}(T, V^{\text{id}})$ (V^{id} = volume of ideal gas of N particles at T, p^{st})
$\mu^\circ = \mu_{\text{res}} + \mu^{\text{id}}(T, V) - \mu^{\text{id}}(T, V^{\text{id}})$
$= \mu_{\text{res}} + k_B T \ln\frac{N k_B T}{p^{\text{st}} V}$

$\mu_{\text{res}} = 5.985\cdot10^{-22}\,\mathrm{J}$ (per molecule)
$\sigma(\mu_{\text{res}}) = k_B T \times (0.003/0.749) = 8.3\cdot10^{-24}\,\mathrm{J}$ (std. error)
$V^{\text{id}} = N k_B T/p^{\text{st}} = 10355\,\mathrm{nm}^3$
$\Delta\mu = \mu(15.791\,\mathrm{nm}^3) - \mu(10355\,\mathrm{nm}^3) = -T\Delta S_m$
$= -k_B T \ln(15.791/10355) = 1.3432\cdot10^{-20}\,\mathrm{J}$
$\mu = \mu_{\text{res}} + \Delta\mu = 1.4030(8)\cdot10^{-20}\,\mathrm{J}$
$\mu = 8.449(5)\,\mathrm{kJ\,mol^{-1}}$ (per mole)

§The value in parentheses is the estimated standard uncertainty in the unit of the least significant digit.

Henry constant

Gas (2) dissolved in liquid (1), mole fraction in liquid $x_2 = N_2/(N_1+N_2)$, $x_2 \ll 1$.
One form of the Henry law for partial pressure p_2 of (2) in equilibrium with solution:

$$p_2 = K_H x_2$$

By virtual insertion of one molecule ($N_2 = 1$) of gas (2) to pure liquid (1), we get the residual chemical potential of (2) at $x_2 = 1/(N_1+1) \approx 1/N_1$,

$\mu_{\text{res},2} = \mu_2(x_2) - \mu_2^{\text{id}}(V)$
In equilibrium:
$\mu_2(x_2) \overset{\text{eql.}}{=} \mu^{\text{id}}(V_2) = k_B T \ln\frac{\Lambda_2^3}{V_2}$

$$\Big\} \quad \mu_{\text{res},2} = k_B T \ln\frac{N_2\Lambda^3}{V_2} - k_B T \ln\frac{N_2\Lambda^3}{V} = k_B T \ln\frac{V}{V_2}$$

$\mu^{\text{id}}(V) = k_B T \ln\frac{N\Lambda^3}{V}$

where V_2 is the volume corresponding to pressure p_2 (don't forget that $N_2 = 1$),

$$V_2 = \frac{1 k_B T}{p_2} = \frac{k_B T}{x_2 K_H} = \frac{k_B T N_1}{K_H}$$

where $\boldsymbol{\rho}_1 = N_1/V$ = number density of liquid (1). Finally,

$$K_H = \frac{\boldsymbol{\rho}_1 k_B T}{\mathrm{e}^{-\beta\mu_{\text{res},2}}} = \frac{\boldsymbol{\rho}_1 k_B T}{\langle(\mathrm{e}^{-\beta\Psi})_{N_1}\rangle_{\text{random insertion of (2)}}}$$

Reversible work by integrating the mean force

From thermodynamics:

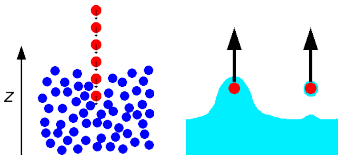
$$\Delta G = W_{\text{other than pressure–volume}} \quad [p, T]$$

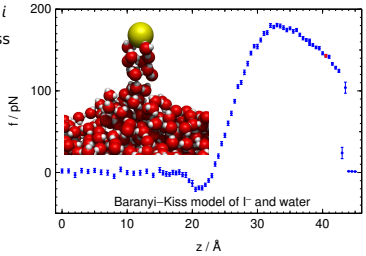
$$\Delta\mu_i = -\int_{\vec{r}_i(1)}^{\vec{r}_i(2)} \langle\vec{f}_i\rangle \cdot \mathrm{d}\vec{r}_i$$

where $\vec{f}_i = -\partial U/\partial\vec{r}_i$ is the force acting on particle i

Molecules: the force applies to the center of mass or other reference point.

Problem: hysteresis





Mean force and its potential

Let us define the **single-particle density** as (also denoted as n_1)

$$\boldsymbol{\rho}_1(\vec{r}_1) = \frac{N}{Q_N}\int \mathrm{e}^{-\beta U(\vec{r}_1,\ldots,\vec{r}_N)}\mathrm{d}\vec{r}_2\ldots\mathrm{d}\vec{r}_N$$

– $\boldsymbol{\rho}_1(\vec{r}_1)\mathrm{d}\vec{r}_1$ is the probability of finding a particle (any one) in $\mathrm{d}\vec{r}_1$
– extension to mixtures: $N/Q_N \to N_{\text{species}}/Q_N$

The **potential of mean force** is defined by

$$\overline{U}_1(\vec{r}_1) = -k_\mathrm{B}T\ln[V\boldsymbol{\rho}_1(\vec{r}_1)]$$

The corresponding force is

$$\overline{\vec{f}}_i = -\left(\frac{\partial\overline{U}_1}{\partial\vec{r}_1}\right) = k_\mathrm{B}T\frac{\partial\boldsymbol{\rho}_1/\partial\vec{r}_1}{\boldsymbol{\rho}_1} = \left\langle -\left(\frac{\partial U}{\partial\vec{r}_1}\right)\right\rangle_{\vec{r}_2,\ldots,\vec{r}_N} = \langle\vec{f}_1\rangle_{\vec{r}_2,\ldots,\vec{r}_N}$$

i.e,. it is indeed the mean force on particle 1 held at fixed position $\vec{r}_1$.

Note: Similarly, for a 2-particle distribution, which for a pair of particles in an isotropic fluid is $g(r)$, one defines the potential of mean force as:

$$\overline{U}_2(r) = -k_\mathrm{B}T\ln[g(r)]$$

Interfacial (surface) energy of solids

Cleaving [Davidchack, Laird: JCP 118, 7651 (2003)]: Thermodynamic integration over a gradually growing "knife" (e.g., Gaussian potential) inserted between crystalographic planes.

Molding [Espinosa, Vega, Sanz: JCP 141, 134709 (2014)]: Thermodynamic integration over a gradually growing "mold" (potential wells) to keep a crystal growing in a part of the system.

- General problem of both methods: hysteresis

Gibbs energy of crystals

- Einstein crystal[¶] at given T as a reference, integration over a coupling parameter [Frenkel, Ladd: JCP 81 3188 (1984), Frenkel, Mulder: Mol. Phys. 55, 1171 (1985)].
- Classical method: harmonic vibrations as a reference, thermodynamic integration of the difference $0 \to T$ [Kolafa JCTC 15, 68 (2019) and references therein]

[¶] independent harmonic oscillators, here treated classically

Local density/concentration method

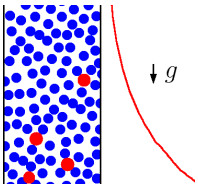
Let a solute i be a subject of external potential $U_i^{\text{ext}}(\vec{r})$ (e.g., "gravity"). In equilibrium:

$$\mu_i(\vec{r}) + U_i^{\text{ext}}(\vec{r}) = \text{const}$$

or

$$\mu_i(\vec{r}_1) - \mu_i(\vec{r}_2) = -[U_i^{\text{ext}}(\vec{r}_1) - U_i^{\text{ext}}(\vec{r}_2)]$$

We determine the concentration or density at $\vec{r}_1$ and know the chemical potential (with respect to a certain reference)

Example:

- reference = infinite dilution approximation ($\gamma = 1$) in the region of small concentration
- the activity coefficient γ in the region of high concentration can be calculated
- problem: slow convergence – diffusion driven