Mechanical quantities

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

- Temperature (NVE MD):

$$T_{\mathrm{kin}} = \frac{E_{\mathrm{kin}}}{f k_{\mathrm{B}}/2}$$

- Internal energy:

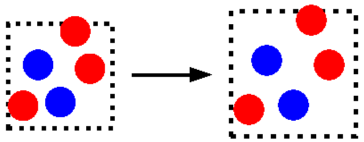
$_{\mathrm{res}}$ = residual
see next slide

$$E = \langle E_{\mathrm{kin}} + U \rangle \overset{NVT}{=} \frac{f}{2} k_{\mathrm{B}} T + \langle U \rangle \equiv E_{\mathrm{id}} + E_{\mathrm{res}}$$

- Pressure

$\beta = 1/k_{\mathrm{B}}T$

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



- 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 $p_{\mathrm{id}} = \phi 2 E_{\mathrm{kin}}/3V$,
  where in periodic b.c. $\phi = N/(N-1)$ takes into acccount 3 zero conserved momenta
- p_{res} = cohesion contribution

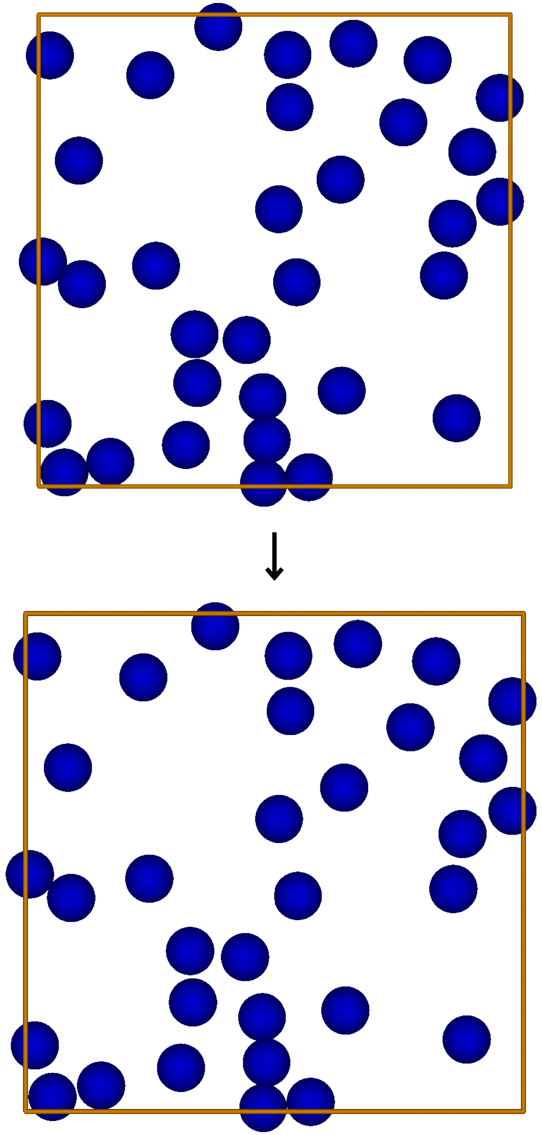
Pressure in the *NVT* ensemble: derivation

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

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

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

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



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: $Q_N = V^N$

$$F = -k_\mathrm{B}T \ln Z_N = -k_\mathrm{B}T \ln \frac{Q_N}{N!\Lambda^{3N}} = -k_\mathrm{B}T \ln \frac{V^N}{N!\Lambda^{3N}} - k_\mathrm{B}T \ln \frac{Q_N}{V^N} \equiv F_\mathrm{id} + F_\mathrm{res}$$

Refresh:

de Broglie thermal wavelength:

$$\Lambda = \frac{h}{\sqrt{2\pi m k_\mathrm{B}T}}$$

chemical potential of ideal gas:

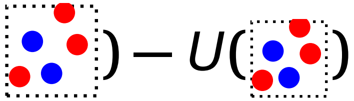
$$\mu_\mathrm{id} = \left(\frac{\partial F_\mathrm{id}}{\partial N}\right)_{T,V} = k_\mathrm{B}T \ln \frac{N\Lambda^3}{V}$$

Pressure – virtual volume change method

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

Numerical derivative (for a selected series of configurations)

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



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

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: $P = Nk_{\mathrm{B}}T/V + \frac{k_{\mathrm{B}}T}{\Delta V}\langle \mathrm{e}^{-[U(V-\Delta V)-U(V)]/k_{\mathrm{B}}T}\rangle + \mathcal{O}(\Delta V)$

Pressure from the virial of force

The derivative expanded:

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

The result is

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

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

- Pair additivity in the periodic boundary conditions ⇒

$$p = \frac{N}{V} k_\mathrm{B} T - \frac{1}{3V} \sum_{i<j} \langle r_{ij} u'(r_{ij}) \rangle \equiv p_\mathrm{id} + p_\mathrm{res}$$

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

Pressure tensor

Also called stress tensor (in solids):

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

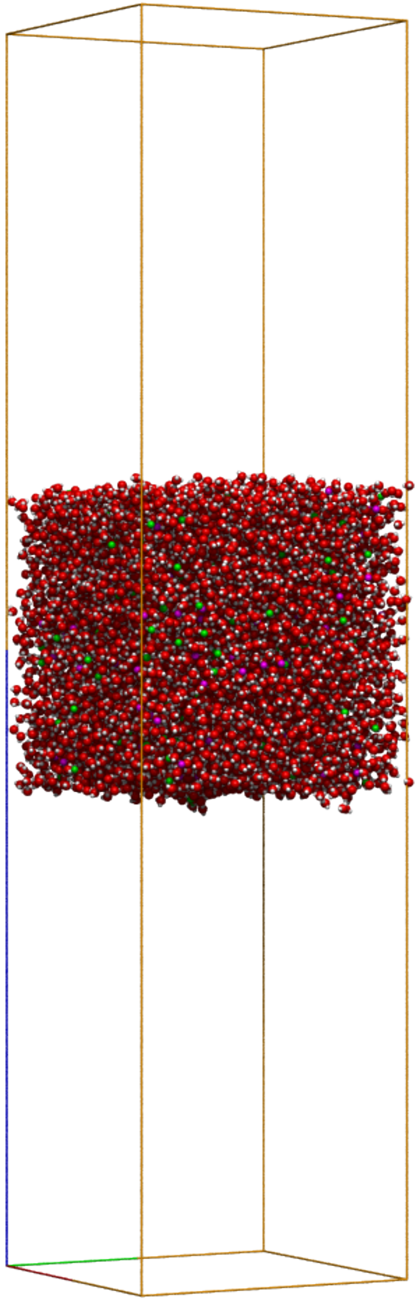
- Tensor product $\overleftrightarrow{T} = \vec{u}\vec{v}$, also denoted $\overleftrightarrow{T} = \vec{u} \otimes \vec{v}$: $T_{ab} = v_a v_b$.
- $\phi = N/(N-1)$ takes into acccount 3 zero conserved momenta in periodic b.c.
- The scalar pressure is 1/3 of its trace, $p = \mathrm{tr}(\overleftrightarrow{P})/3$.
- 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.

Surface tension of liquid

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

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



- 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:

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

Fluctuation quantities

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

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

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

Less accurate than mean values!

E.g. (NVT): $P = -\left(\frac{\partial F}{\partial V}\right)_T$, $E = \left(\frac{\partial \beta F}{\partial \beta}\right)_V$, then:

- Heat capacity at constant $[V]$:

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

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

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

- Isothermal compressibility – in the NPT ensemble

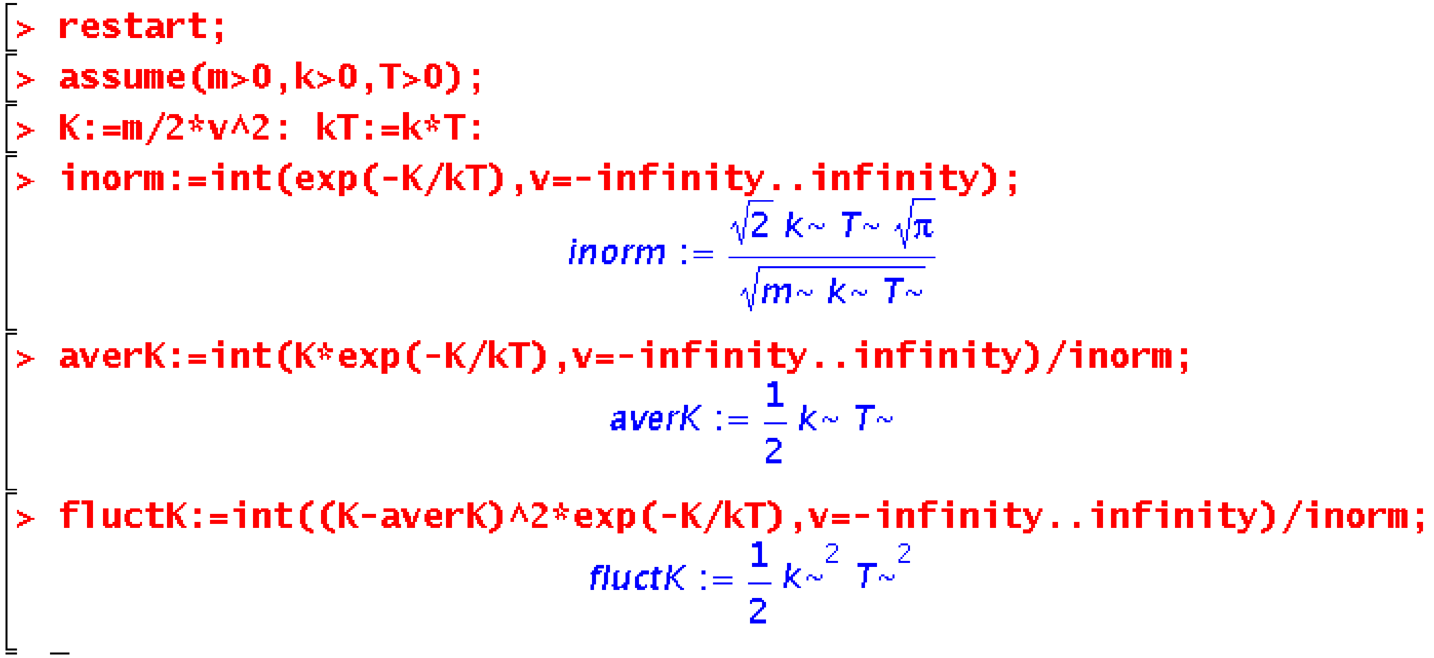
$$\kappa = -\frac{1}{V}\left(\frac{\partial V}{\partial P}\right)_T = \frac{\langle (\Delta V)^2 \rangle}{V k_B T}$$

Permittivity can be calculated from the fluctuation of the cell dipole moment, $\langle M^2 \rangle$, (more later).

Exercise

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

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



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

$$inorm := \frac{\sqrt{2}\,k\sim\,T\sim\,\sqrt{\pi}}{\sqrt{m\sim\,k\sim\,T\sim}}$$

```
> averK:=int(K*exp(-K/kT),v=-infinity..infinity)/inorm;
```

$$averK := \frac{1}{2}\,k\sim\,T\sim$$

```
> fluctK:=int((K-averK)^2*exp(-K/kT),v=-infinity..infinity)/inorm;
```

$$fluctK := \frac{1}{2}\,k\sim^2\,T\sim^2$$

Isochoric heat capacity C_V in the NVE ensemble

In the **canonical** ensemble:

$$\mathrm{Var}\,X = k_\mathrm{B}T^2\frac{\partial X}{\partial T} \equiv k_\mathrm{B}T^2 X' \quad (X = U,\, E_\mathrm{kin}) \tag{1}$$

$$\mathrm{Cov}\,(U, E_\mathrm{kin}) = 0$$

$$C_V = U' + E'_\mathrm{kin}, \quad E'_\mathrm{kin} = \frac{f k_\mathrm{B}}{2}$$

Unnormalized probability distribution for temperature T:

$$w(U, E_\mathrm{kin}) \sim \exp\left[-\frac{(\delta U)^2}{2\,\mathrm{Var}\,U} - \frac{(\delta E_\mathrm{kin})^2}{2\,\mathrm{Var}\,E_\mathrm{kin}}\right]$$

where the deviations are linearized: $(U, E_\mathrm{kin}) = (U_0 + \delta U, E_{\mathrm{kin},0} + \delta E_\mathrm{kin})$

Unnormalized probability distribution taking into account change in temperature, $T = T_0 + \delta T$:

$$w(T, U, E_\mathrm{kin}) \sim \exp\left[-\frac{(\delta U - U'\delta T)^2}{2\,\mathrm{Var}\,U} - \frac{(\delta E_\mathrm{kin} - E'_\mathrm{kin}\delta T)^2}{2\,\mathrm{Var}\,E_\mathrm{kin}}\right]$$

Isochoric heat capacity C_V in the NVE ensemble II

In the **MD NVE** ensemble it holds $U + E_{\text{kin}} = E = \text{const}$ or $U = E - E_{\text{kin}}$, and of course $\delta E_{\text{kin}} = -\delta U$, so that let us choose δE_{kin} as the independent variable

$$w(T, E_{\text{kin}}) \sim \exp\left[-\left(\frac{1}{2k_{\text{B}}T^2U'} + \frac{1}{2k_{\text{B}}T^2E'_{\text{kin}}}\right)\delta E_{\text{kin}}^2 - \left(\frac{U'}{2k_{\text{B}}T^2} + \frac{E'_{\text{kin}}}{2k_{\text{B}}T^2}\right)\delta T^2\right]$$

where the variances were replaced by derivatives, see (1).

NB: term $\delta E_{\text{kin}}\delta T$ cancels out!

From term at δT^2:

$$\operatorname{Var} T = \frac{k_{\text{B}}T^2}{U' + E'_{\text{kin}}} = \frac{k_{\text{B}}T^2}{C_V}$$

which is a known expression for the temperature in the NVE ensemble, however, T here is **not** the kinetic temperature, but T in formula $\mathrm{d}E = T\mathrm{d}S\,[V]$. The average temperature is the same, but not the fluctuation.

Isochoric heat capacity C_V in the NVE ensemble III

From the term at δE^2:

$$\operatorname{Var} E = \operatorname{Var} U = \operatorname{Var} E_{\text{kin}} = \frac{k_{\text{B}} T^2}{1/U' + 1/E'_{\text{kin}}} = \frac{k_{\text{B}} T^2}{1/(C_V - E'_{\text{kin}}) + 1/E'_{\text{kin}}}$$

Since E'_{kin} is known:

$$C_V = \frac{fk}{2} \left[\left(\frac{2\,T^2}{f \operatorname{Var} T_{\text{kin}}} - 1 \right)^{-1} + 1 \right]$$

where $T_{\text{kin}} \equiv E_{\text{kin}}/(fk/2)$ is the kinetic temperature.

Final expression applicable in simulations:

$$C_V = \frac{fk}{2} \left[\left(\frac{2\,\langle T_{\text{kin}} \rangle^2}{f\,\langle (\Delta T_{\text{kin}})^2 \rangle} - 1 \right)^{-1} + 1 \right]$$

Entropic quantities

These include F, G (($\Leftarrow$ 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
  - multiple histogram reweighting
  - metadynamics/Wang–Landau/conformational flooding
- local density method

Formally (for the configurational integral):

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

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

... totally useless

Thermodynamic integration

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

Physical chemistry: $\mathrm{d}F = -S\mathrm{d}T - p\mathrm{d}V,\ \mathrm{d}G = -S\mathrm{d}T + V\mathrm{d}p$

Canonical ensemble ($\beta = 1/k_\mathrm{B}T$):

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

- 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 $\frac{\partial(\beta F)}{\partial\beta} = E$:

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

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

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

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

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:

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

- Integration from an Einstein crystal to a real crystal.

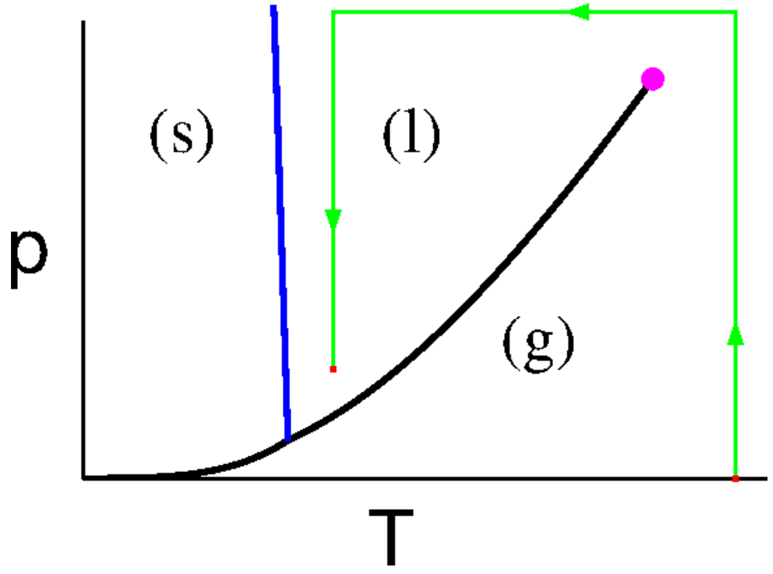
  NB: Einstein crystal = independent (here classical) harmonic oscillators at lattice sites.

  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):

$$\ln\phi = \frac{\mu - \mu^\circ}{RT} = \int_0^p \left(V_{\rm m} - \frac{RT}{p'} \right) \mathrm{d}p'$$

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



Non-Boltzmann sampling

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

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

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

Helmholtz energy:

$$\begin{aligned}
\Delta(\beta F_{\text{res}}) &= \beta_1 F_{\text{res}}((\beta U)_1) - \beta_0 F_{\text{res}}((\beta U)_0) \\
&= -\ln\left(\frac{Q_1}{Q_0}\right) = -\ln \frac{\int \mathrm{e}^{-(\beta U)_1} \mathrm{d}\vec{r}^N}{\int \mathrm{e}^{-(\beta U)_0} \mathrm{d}\vec{r}^N} \\
&= -\ln \frac{\int \mathrm{e}^{-(\beta U)_0}\, \mathrm{e}^{-\Delta(\beta U)} \mathrm{d}\vec{r}^N}{\int \mathrm{e}^{-(\beta U)_0} \mathrm{d}\vec{r}^N} = -\ln\langle \mathrm{e}^{-\Delta(\beta U)}\rangle_0 \\
&= \ln\langle \mathrm{e}^{+\Delta(\beta U)}\rangle_1
\end{aligned}$$

where the last equation follows from 0 ⟷ 1 interchange

[†] First usage probably Zwanzig (1954) “thermodynamic perturbation method”, loosely also “umbrella sampling”

Non-Boltzmann sampling contd.

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

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

https://positiveoutlooksblog.com/2015/01/30/surviving-the-storm-together

$$\begin{aligned} \Delta(\beta F_{\text{res}}) &= -\ln\langle e^{-\Delta(\beta U)}\rangle_0 \\ &\approx -\ln\langle 1-\Delta(\beta U)\rangle_0 \\ &= -\ln(1-\langle\Delta(\beta U)\rangle_0) \\ &\approx \langle\Delta(\beta U)\rangle \end{aligned}$$

$$\text{general } \lambda: \quad \partial(\beta F_{\text{res}})/\partial\lambda = \langle\partial\Delta(\beta U)/\partial\lambda\rangle_\lambda$$

$$\lambda = \beta: \quad \partial(\beta F_{\text{res}})/\partial\beta = \langle U\rangle$$

Umbrella sampling

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

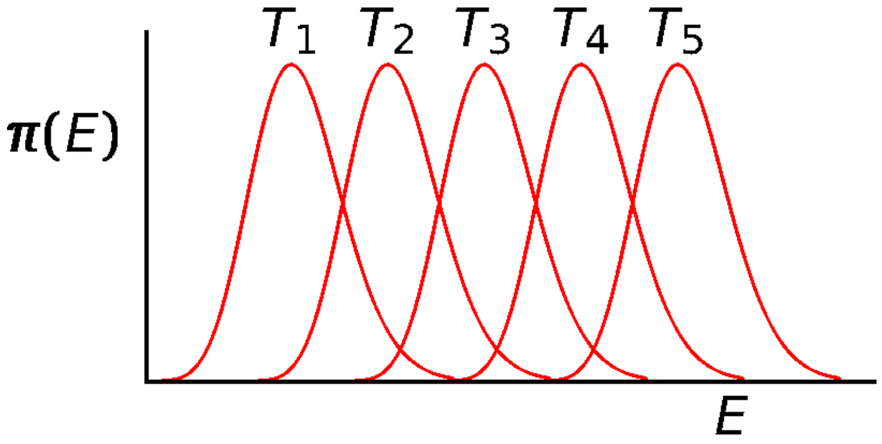
$$\Delta(\beta F_{\text{res}}) = \ln\langle e^{+\Delta(\beta U)/2}\rangle_{\text{mid}} - \ln\langle e^{-\Delta(\beta U)/2}\rangle_{\text{mid}}$$

Nowadays, term “umbrella sampling” usually refers to many steps of similar kind.

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).



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

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

Configurational integral and residual Helmholtz energy at temperature T_i, $\beta_i = 1/k_\mathrm{B}T_i$:

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

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

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

[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:

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

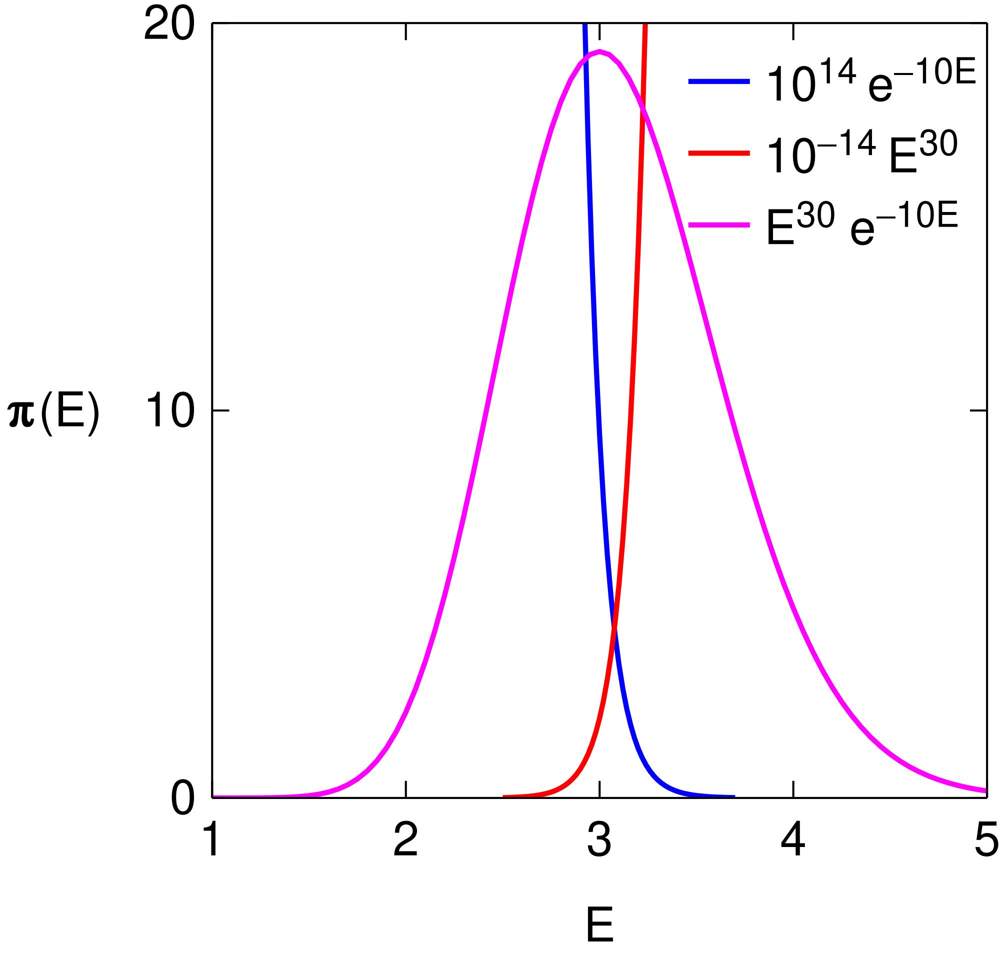
Let’s have $f = 3N$ such degrees of freedom. The number of states $\#(E)$ with energy less than E satisfies the equation

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

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

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

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



The Boltzmann factor $\mathrm{e}^{-\beta E}$ eventually wins!

For large N, the product converges to a Gaussian with $\mathrm{Var}(E) \propto f \propto N$ ($\sigma = N^{1/2}$)

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.)

$$\sum_E h_i(E) = \int h_i(E)\mathrm{d}E = 1$$

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

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

$$D(E) = h_i(E)\mathrm{e}^{\beta_i(E-F_i)} \tag{2}$$

- 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:

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

Multiple histogram reweighting III

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

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

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

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

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

can be solved by iterations (self-consistent solution).

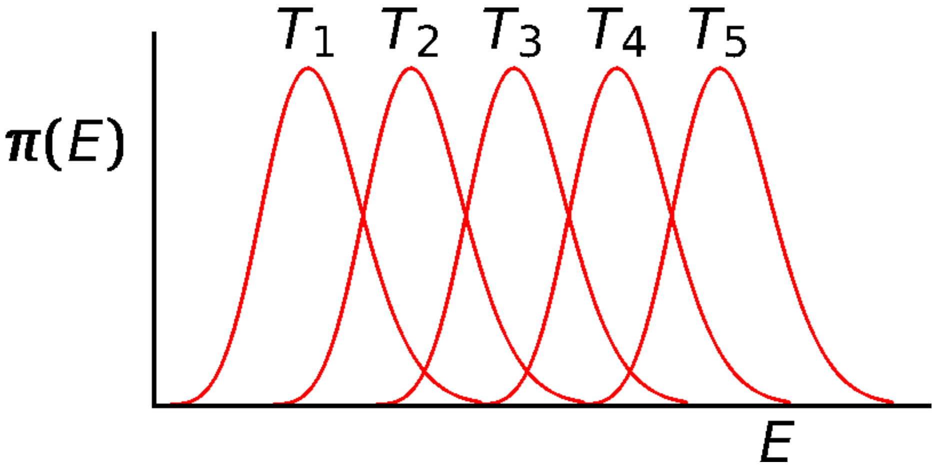
F_i are determined but an additive constant, $D(E)$ but a multiplicative factor

Multiple histogram reweighting IV

Expectation value at temperature β:

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

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



Parallel tempering (replica exchange)

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

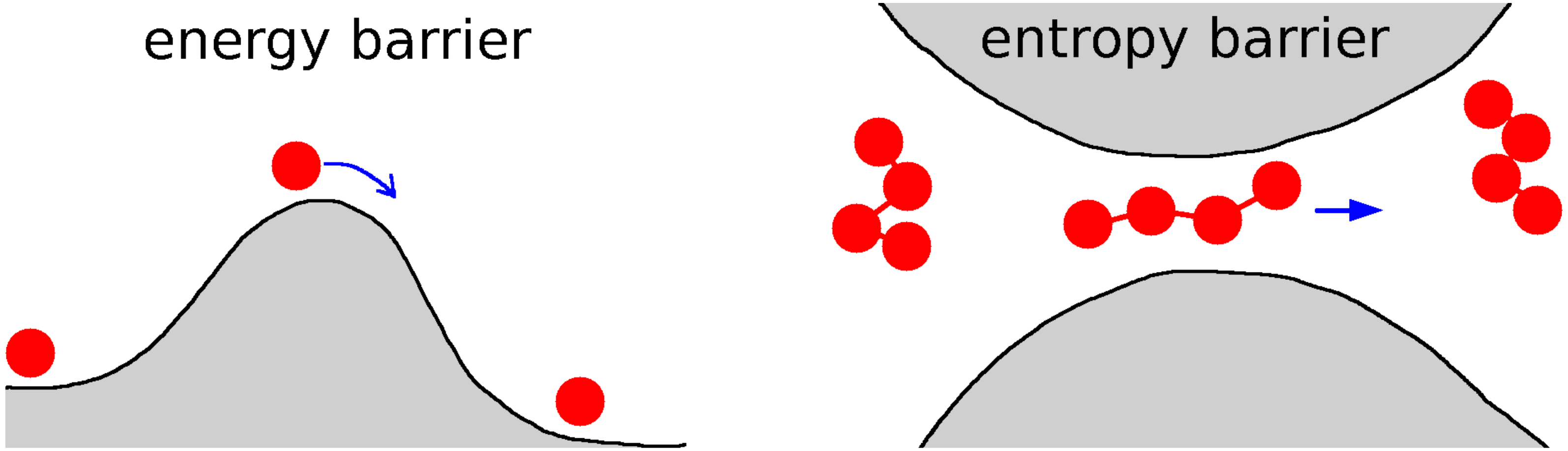
Once a while, 2 subsystems β_i, β_j (normally $|i-j| = 1$) are interchanged, the acceptance probability is

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

- Pros: easier barrier crossing, improved ergodicity, faster convergence at low temperatures
- Cons: 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, distance ligand–receptor (optionally + orientation), etc.
  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:

$$\Delta U := \Delta U + \omega \frac{\delta(\lambda)}{h(\lambda)}, \quad \lambda = \lambda(\vec{r}^N)$$

δ = aproximation of δ-function (MC: histogram bin, better and MD: Gauss)
ω = small enough relaxation parameter, $\omega \ll k_\mathrm{B}T$
$h(\lambda)$ = density of Cartesian points on hypersurface λ; e.g., $h(\lambda) = 4\pi\lambda^2$ for $\lambda = r_{12}$

⇒ the probability of visiting the same λ again decreases

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:

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

- in practice, with small enough ω and continued updating, we can assume $p(\lambda)/h(\lambda) = \text{const}^{\ddagger}$ 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:

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

integration over region for more collective variables

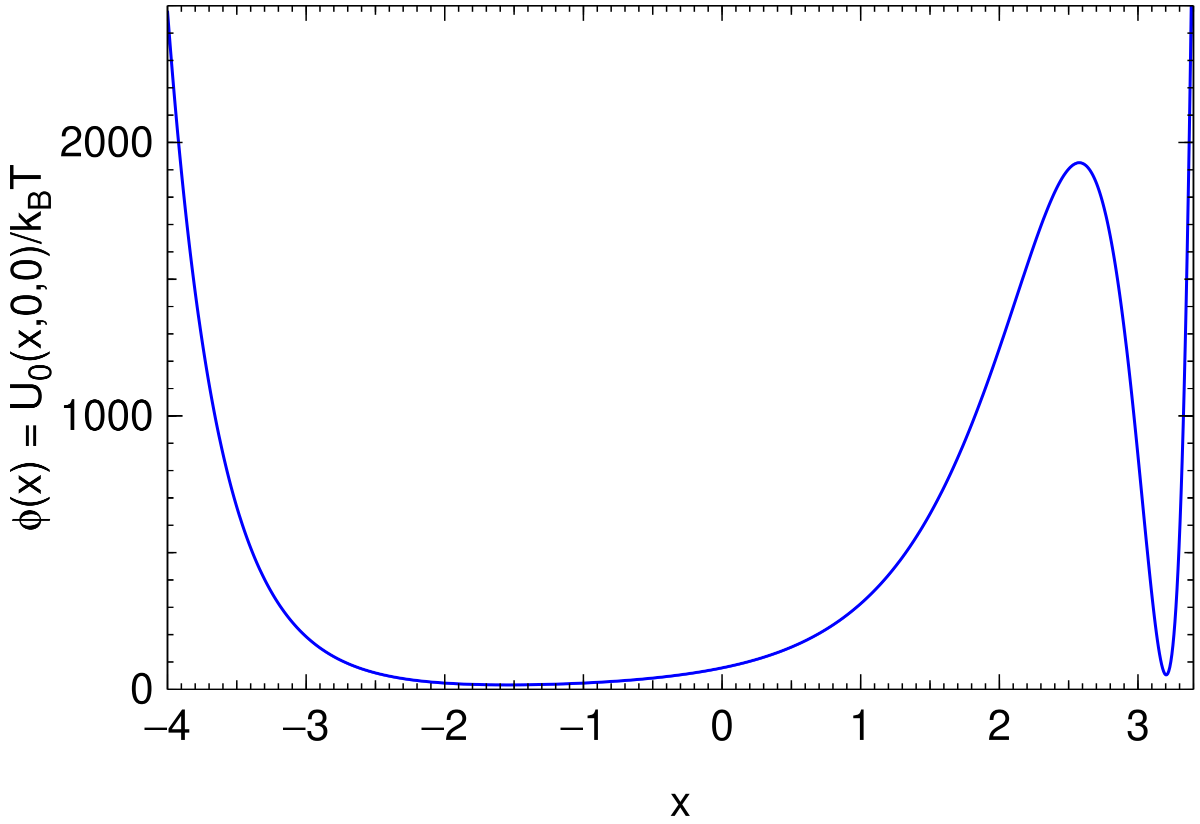
[‡] symbols const are different

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 in x ($\approx$ MD)
- Initial $\omega = 0.25 k_B T$, decrease to finish
  fine + stop ($\omega \equiv \alpha < 0$): aaaV 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)

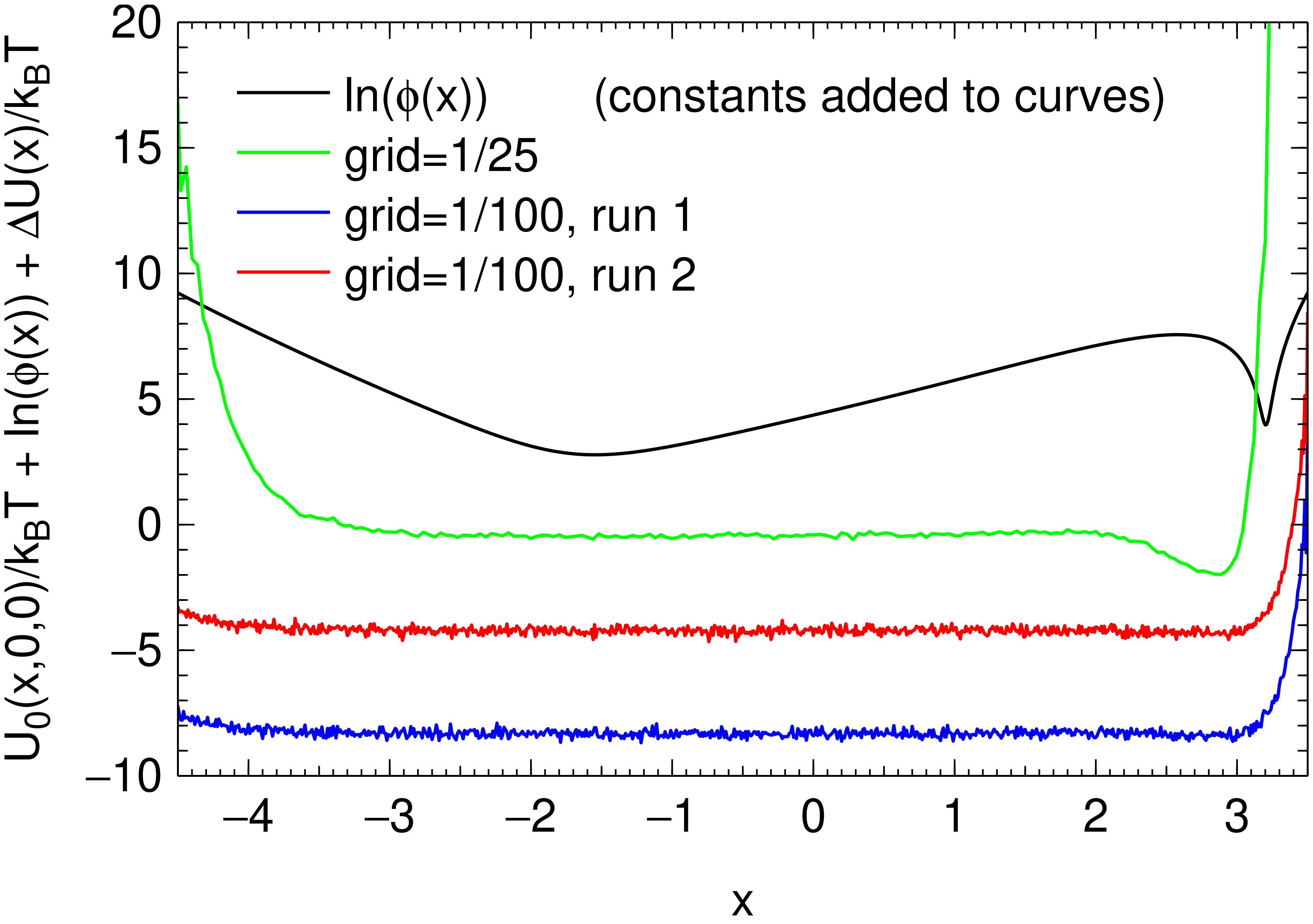
Conformational flooding, Wang–Landau, metadynamics: Case study

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

1/grid	$\Delta F/k_\mathrm{B}T$
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

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

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

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

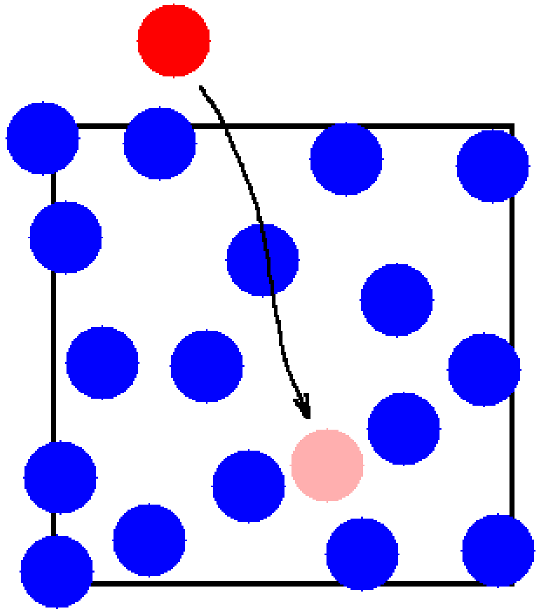
$$\exp(-\beta\mu_{\mathrm{res}}) = \frac{1}{V}\frac{Q_{N+1}}{Q_N}$$

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 $\mu^{\mathrm{id}} = k_{\mathrm{B}}T\ln\left(\frac{N\Lambda^3}{V}\right)$ we get the same $\mu_{\mathrm{res}} = \mu - \mu^{\mathrm{id}}$

Widom particle insertion method II



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

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

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

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

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

`cd ../maple; xmaple simul07+18+Widom.mw`

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 $V = 15.791\,\text{nm}^3$ at temperature $T = 150$ K. By the Widom method, we found that[§]

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

Calculate $\mu°$, 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:

$$\begin{aligned}
\mu_{\text{res}} &= \mu - \mu^{\text{id}}(T, V) \quad (N \text{ particles in volume } V) \\
\mu° &= \mu - \mu^{\text{id}}(T, V^{\text{id}}) \quad (V^{\text{id}} = \text{volume of ideal gas of } N \text{ particles at } T, p^{\text{st}}) \\
\mu° &= \mu_{\text{res}} + \mu^{\text{id}}(T, V) - \mu^{\text{id}}(T, V^{\text{id}}) \\
&= \mu_{\text{res}} + k_B T \ln \frac{N k_B T}{p^{\text{st}} V}
\end{aligned}$$

$$\begin{aligned}
\mu_{\text{res}} &= 5.985 \times 10^{-22}\,\text{J (per molecule)} \\
\sigma(\mu_{\text{res}}) &= k_B T \times (0.003/0.749) = 8.3 \times 10^{-24}\,\text{J (std. error)} \\
V^{\text{id}} &= N k_B T / p^{\text{st}} = 10355\,\text{nm}^3 \\
\Delta\mu &\equiv \mu(15.791\,\text{nm}^3) - \mu(10355\,\text{nm}^3) = -T\Delta S_m \\
&= -k_B T \ln(15.791/10355) = 1.3432 \times 10^{-20}\,\text{J} \\
\mu &= \mu_{\text{res}} + \Delta\mu = 1.4030(8) \times 10^{-20}\,\text{J} \\
\mu &= 8.449(5)\,\text{kJ mol}^{-1}\ \text{(per mole)}
\end{aligned}$$

[§] 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:

$$p_2 = K_\mathrm{H} x_2$$

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 $x_2 = 1/(N_1+1) \approx 1/N_1$,

$$\mu^\mathrm{id}(V) = k_\mathrm{B}T \ln \frac{N\Lambda^3}{V}$$

$$\left.\begin{array}{l} \mu_{\mathrm{res},2} = \mu_2(x_2) - \mu_2^\mathrm{id}(V) \\ \text{In equilibrium:} \\ \mu_2(x_2) \overset{\text{eql.}}{=} \mu^\mathrm{id}(V_2) = k_\mathrm{B}T \ln \dfrac{\Lambda_2^3}{V_2} \end{array}\right\} \mu_{\mathrm{res},2} = k_\mathrm{B}T \ln \frac{N_2\Lambda^3}{V_2} - k_\mathrm{B}T \ln \frac{N_2\Lambda^3}{V} = k_\mathrm{B}T \ln \frac{V}{V_2}$$

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

$$V_2 = \frac{1 k_\mathrm{B}T}{p_2} = \frac{k_\mathrm{B}T}{x_2 K_\mathrm{H}} = \frac{k_\mathrm{B}T N_1}{K_\mathrm{H}}$$

where $\rho_1 = N_1/V$ = number density of liquid (1). Finally,

$$K_\mathrm{H} = \frac{\rho_1 k_\mathrm{B}T}{\mathrm{e}^{-\beta\mu_{\mathrm{res},2}}} = \frac{\rho_1 k_\mathrm{B}T}{\left\langle \langle \mathrm{e}^{-\beta\Psi} \rangle_{N_1} \right\rangle_{\text{random insertion of (2)}}}$$

Reversible work by integrating the mean force

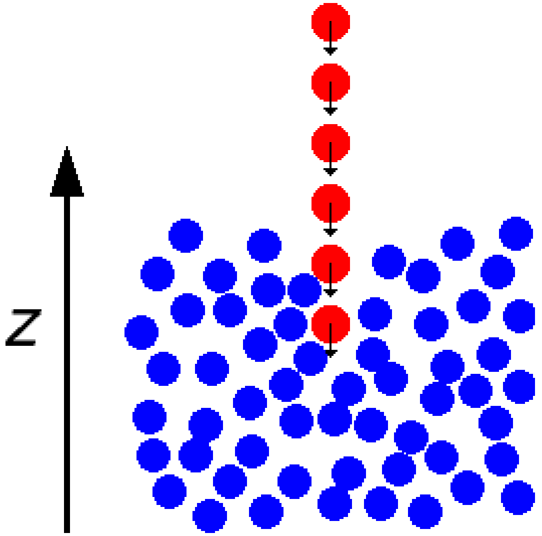
From thermodynamics:

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

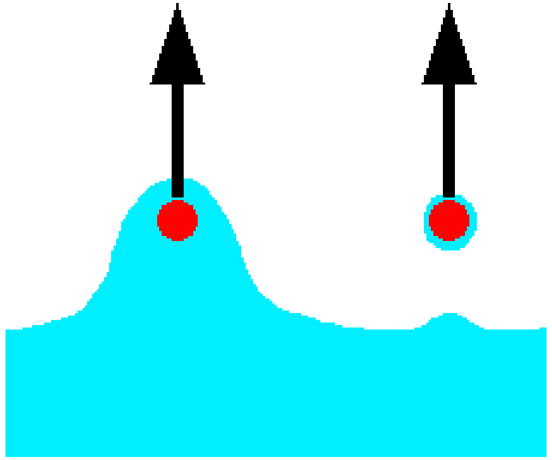
$$\Delta \mu_i = - \int_{\vec{r}_i(1)}^{\vec{r}_i(2)} \langle \vec{f}_i \rangle \cdot \mathrm{d}\vec{r}_i$$

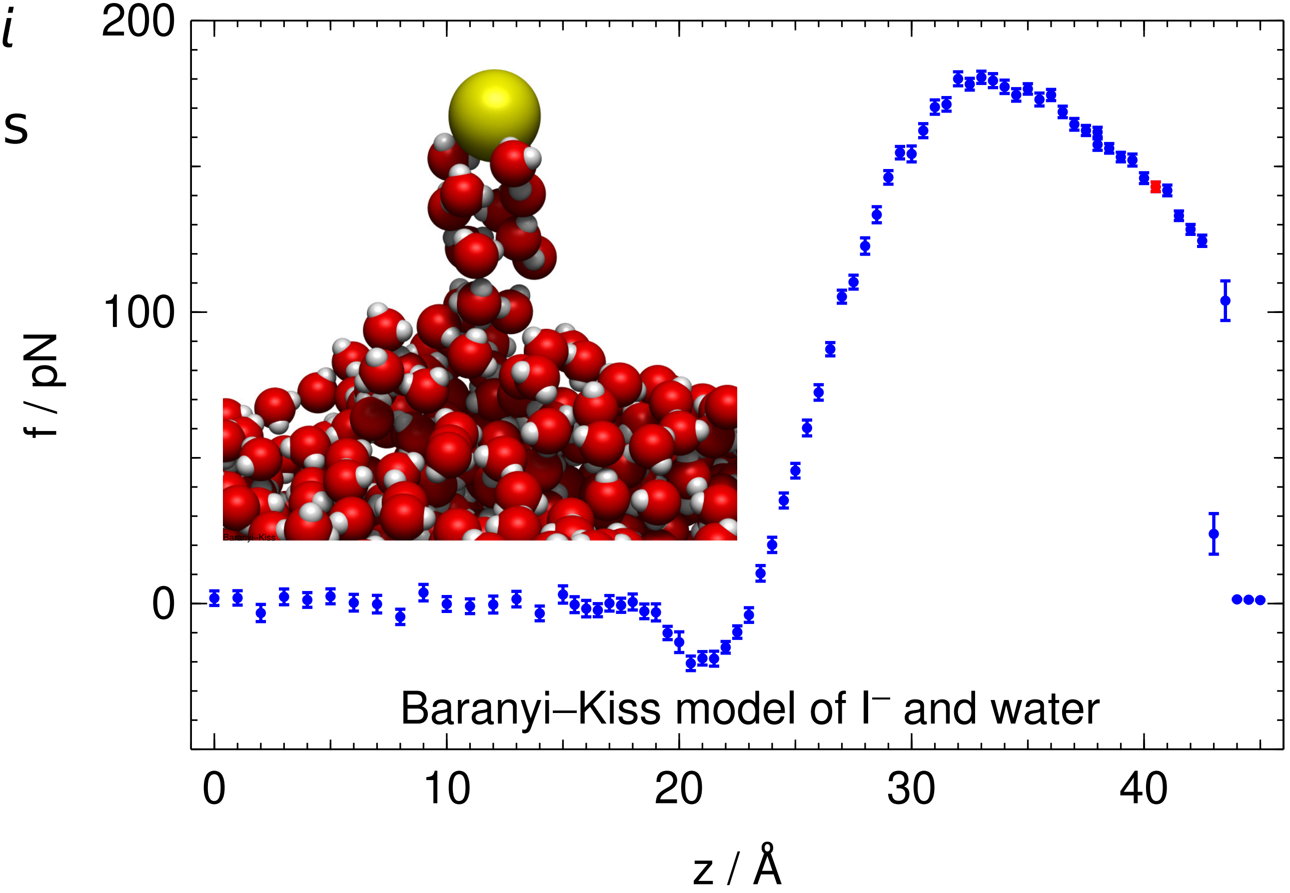
where $\vec{f}_i = -\partial U / \partial \vec{r}_i$ is the force acting on particle i

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)

$$\rho_1(\vec{r}_1) = \frac{N}{Q_N} \int \mathrm{e}^{-\beta U(\vec{r}_1,\ldots,\vec{r}_N)} \mathrm{d}\vec{r}_2 \ldots \mathrm{d}\vec{r}_N$$

– $\rho_1(\vec{r}_1)\mathrm{d}\vec{r}_1$ 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

$$\overline{U}_1(\vec{r}_1) = -k_\mathrm{B}T \ln[V\rho_1(\vec{r}_1)]$$

The corresponding force is

$$\bar{f}_i = -\left(\frac{\partial \overline{U}_1}{\partial \vec{r}_1}\right) = k_\mathrm{B}T \frac{\partial \rho_1/\partial \vec{r}_1}{\rho_1} = \left\langle -\left(\frac{\partial U}{\partial \vec{r}_1}\right)\right\rangle_{\vec{r}_2,\ldots,\vec{r}_N} = \langle \vec{f}_1 \rangle_{\vec{r}_2,\ldots,\vec{r}_N}$$

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 → 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