

- Temperature (NVE MD):

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

notation here:

$U = U(r^N)$ = potential energy

$E = E(T, V)$ = internal energy

f = # of degrees of freedom

- Internal energy:

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

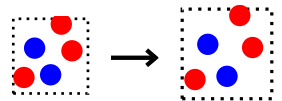
res = residual
see next slide

- Pressure

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

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

- 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)
- p_{res} = cohesion contribution



$$dF = -SdT - pdV$$

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

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

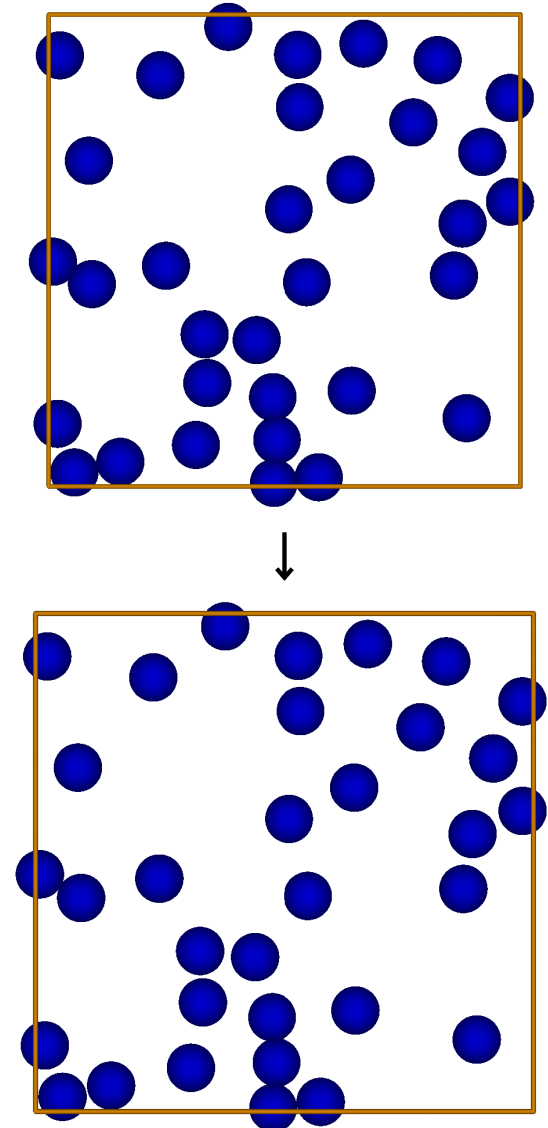
$$Q_N = \int_{V^N} \exp[-\beta U(\vec{r}^N)] d\vec{r}^N \quad \vec{r}_i = V^{1/3} \xi_i \quad \int_{1^{3N}} \exp[-\beta U(V^{1/3} \xi^N)] V^N d\xi^N$$

$$p = - \left(\frac{\partial F}{\partial V} \right)_T = k_B T \left(\frac{\partial \ln Q_N}{\partial V} \right)_{\xi^N} = \frac{k_B T}{Q_N} \left(\frac{\partial Q_N}{\partial V} \right)_{\xi^N}$$

$$= \frac{k_B T}{Q_N} \int_{1^{3N}} \exp[-\beta U(V^{1/3} \xi^N)] N V^{N-1} d\xi^N$$

$$+ \frac{k_B T}{Q_N} \int_{1^{3N}} \exp[-\beta U(V^{1/3} \xi^N)] (-\beta) \left(\frac{\partial U(V^{1/3} \xi^N)}{\partial V} \right)_{\xi^N} V^N d\xi^N$$

$$= \frac{N}{V} k_B T - \left\langle \left(\frac{\partial U(V^{1/3} \xi^N)}{\partial V} \right)_{\xi^N} \right\rangle = \boxed{\text{ideal part (kinetic)}} + \boxed{\text{residual part (correction)}}$$



= 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 called “excess”

For the Helmholtz energy:

ideal gas: $Q_N = V^N$

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

Refresh:

de Broglie thermal wavelength:

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

chemical potential of ideal gas:

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

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

Numerical derivative (for a selected series of configurations)

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

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

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):

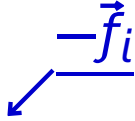
$$\left(\frac{V + \Delta V}{V} \right)^{1/3} .$$

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

The derivative expanded:

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



The result is

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

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

● Pair additivity in the periodic boundary conditions \Rightarrow

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

● 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.

These include F , G (partition function needed), S (number of states W), μ , ΔG , ...

Useless approach:

$$Q = \frac{\int e^{-\beta U} d\mathbf{r}^N}{1} = \frac{\int e^{-\beta U} d\mathbf{r}^N}{V^{-N} \int e^{-\beta U} e^{+\beta U} d\mathbf{r}^N} = \frac{V^N}{\langle e^{\beta U} \rangle}$$

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

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

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

Canonical ensemble ($\beta = 1/k_B T$):

$$\left(\frac{\partial F}{\partial V}\right)_T = -p, \quad \left(\frac{\partial(\beta F)}{\partial \beta}\right)_V = E, \quad \text{or} \quad \left(\frac{\partial(\beta F_{\text{res}})}{\partial \beta}\right)_V = \langle U \rangle$$

notation here:

$$U = U(r^N)$$

= potential energy

$$E = E(T, V)$$

= internal energy

● Numerically integrated: p , E must be determined in many points

● Start from a suitable reference state (ideal gas, hard spheres, Lennard-Jones, Einstein crystal)

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

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

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

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

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 $U(\lambda)$

Example 1: for $\lambda = \beta$ we get as before:

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

Example 2: integration from an Einstein crystal to a real crystal.

NB: Einstein crystal = independent harmonic oscillators at lattice sites

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

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

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

Helmholtz energy:

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

where the last equation follows from $0 \leftrightarrow 1$ interchange

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

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

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

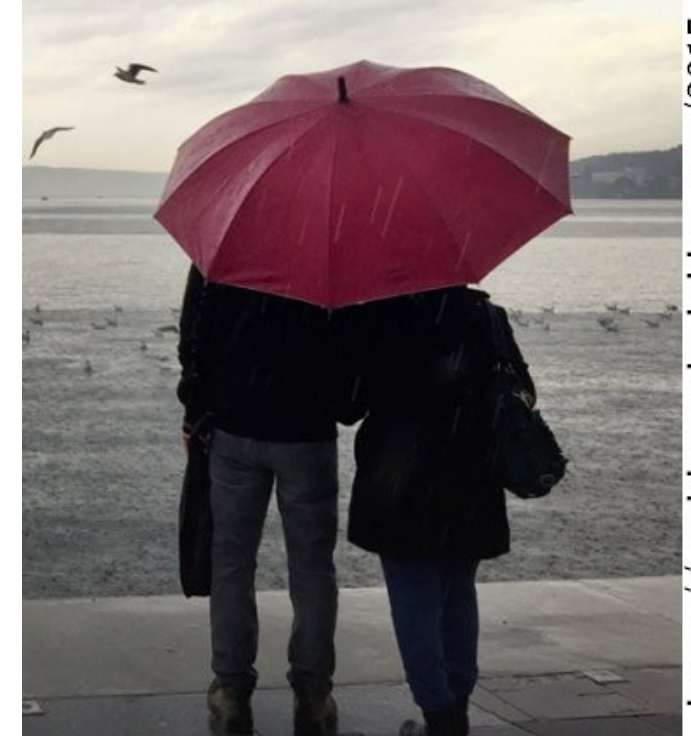
- Several discrete λ : a) Fit + integrate; b) Simpson or similar rule
- Slow change of λ every MD step and integrate

Umbrella sampling

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

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

$$\begin{aligned}e^x &= 1 + x + \dots \\ \ln(1 + x) &= x + \dots\end{aligned}$$



Open system

$$dF = -SdT - pdV + \mu dN$$

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

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

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

Or for the full chemical potential:

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

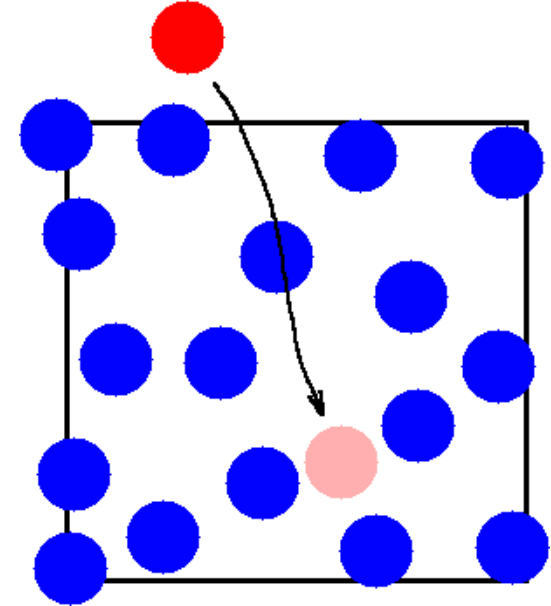
then by subtracting $\mu^{\text{id}} = k_B T \ln \left(\frac{N\Lambda^3}{V} \right)$ we get the same $\mu_{\text{res}} = \mu - \mu^{\text{id}}$

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

$$N \rightarrow N + 1 \quad U_{N+1} = U_N + \Psi(N)$$

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

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



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

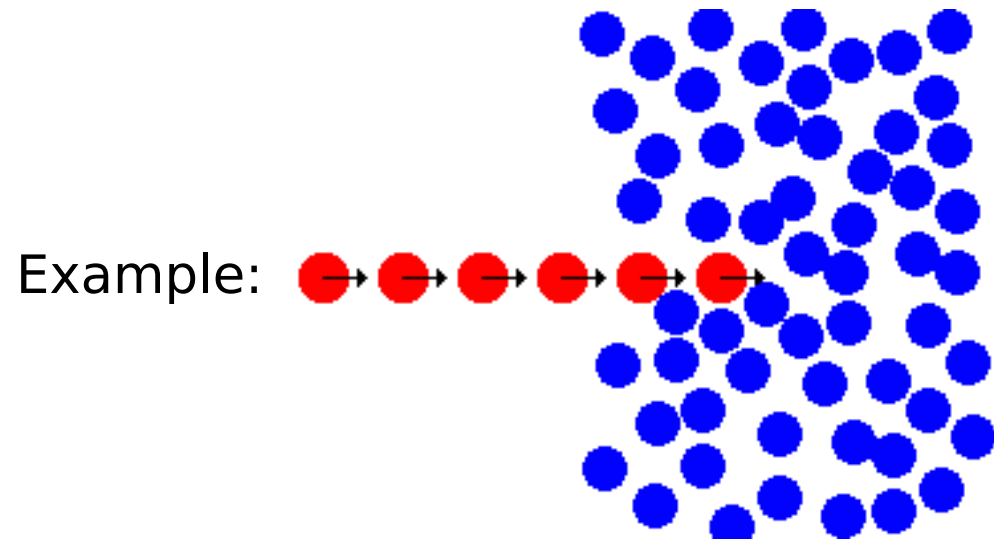
From thermodynamics:

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

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

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

