

Mechanical quantities

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- 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:

$$E = (E_{\text{kin}} + U) \stackrel{NVT}{=} \frac{f}{2} k_B T + (U) \equiv E_{\text{id}} + E_{\text{res}}$$
 res = residual
 see next slide
- Pressure

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

$$\beta = 1/k_B T$$
 - dimensionless (scaled) coordinates $\xi_i: r_i = V^{1/3} \xi_i$
 - red derivative is calculated at constant ξ^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 account 3 zero conserved momenta
 - p_{res} = cohesion contribution

Pressure tensor

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Also called stress tensor (in solids):

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

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

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

Pressure in the NVT ensemble: derivation

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$$dF = -SdT - pdV \quad (X) = \frac{1}{Q_N} \int_{V^N} X(r^N) d \exp[-\beta U(r^N)] r^N$$

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

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

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

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

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

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

Surface tension of liquid

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

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

- It is "mechanical quantity".
- Cannot be used for interfacial energy of crystals (it is "entropic quantity").
- Cutoff corrections – several variants (cf. simenon9).
- 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:

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

Residual quantities

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= 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:

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

Fluctuation quantities

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$\langle (\Delta X)^2 \rangle = \text{Var } X = (\text{mean quadratic fluctuation} = \text{variance})$
 $\langle \Delta X \rangle = X - \langle X \rangle$
 fluctuation = (mech/el/... quantity)' = (thermodynamic potential)''

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

- Heat capacity at constant [V]:

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

$$\text{Cov}(U, E_{\text{kin}}) = \langle \Delta U \Delta E_{\text{kin}} \rangle = 0, \text{Var } E_{\text{kin}} = \frac{1}{2} (k_B T)^2 \text{ (see exercise)} \Rightarrow$$

$$C_V = \frac{1}{k_B T^2} \left\langle \left(\frac{f k_B T}{2} + \Delta U \right)^2 \right\rangle = \frac{f k_B}{2} + \frac{1}{k_B T^2} \langle (\Delta U)^2 \rangle \equiv C_{V,\text{id}} + C_{V,\text{res}}$$
- Isothermal compressibility – in the NPT ensemble

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

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

Pressure – virtual volume change method

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

Numerical derivative (for a selected series of configurations)

$$\frac{\partial U}{\partial V} = \frac{U(V + \Delta V) - U(V)}{\Delta V} + \mathcal{O}(\Delta V) \equiv \frac{U(\xi^N, V + \Delta V) - U(\xi^N, V)}{\Delta V} + \mathcal{O}(\Delta V)$$

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

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: $P = Nk_B T/V + \frac{k_B T}{\Delta V} (e^{-[U(V-\Delta V)-U(V)]/k_B T}) + \mathcal{O}(\Delta V)$

Exercise

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

$$E_{\text{kin}} = \frac{1}{2} m v^2$$

$$\pi(v) = \frac{\exp(-\frac{1}{2} m v^2 / k_B T)}{\int \exp(-\frac{1}{2} m v^2 / k_B T) dv}$$

$$\langle E_{\text{kin}} \rangle = \int E_{\text{kin}} \pi(v) dv$$

$$\text{Var}(E_{\text{kin}}) = \int (E_{\text{kin}} - \langle E_{\text{kin}} \rangle)^2 \pi(v) dv = \frac{1}{2} (k_B T)^2$$

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> 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(k*T)/sqrt(m);
> 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:

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Pressure from the virial of force

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The derivative expanded:

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

The result is

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

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

- Pair additivity in the periodic boundary conditions \Rightarrow

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

Entropic quantities

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These include F, G (\Leftarrow partition function), S (number of states W), $\mu, \Delta G, \dots$
 They cannot be expressed as $\langle \cdot \rangle$.

Formally (for the canonical partition function) but totally useless:

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

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

Thermodynamic integration

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

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

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

notation here:
 $U = U(T, V)$
= potential energy
 $E = E(T, V)$
= internal energy

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

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

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

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

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

Integration over a coupling parameter

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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

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

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

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

How to integrate:

- 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

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- 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 harmonic oscillators at lattice sites. There are minor problems (\Rightarrow correction) when the crystal is detached from the fixed sites.
- Integration from ideal gas around the critical point to liquid. Because of gas singularity at zero density, one of the integrals is (for NPT):

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

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

Non-Boltzmann sampling

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

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

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

Helmholtz energy:

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

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

Non-Boltzmann sampling contd.

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

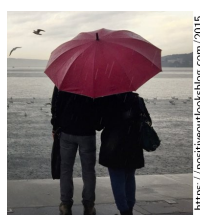
$$\begin{aligned} \Delta(\beta F_{\text{res}}) &= -\ln \langle e^{-\Delta(\beta U)} \rangle_0 \\ &\approx -\ln(1 - \Delta(\beta U))_0 \\ &= -\ln(1 - \langle \Delta(\beta U) \rangle_0) \\ &\approx \langle \Delta(\beta U) \rangle_0 \\ \Rightarrow \partial(\beta F_{\text{res}})/\partial \lambda &= \langle \partial(\beta U)/\partial \lambda \rangle \end{aligned}$$

Umbrella sampling

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

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

Often, term "umbrella sampling" is extended to using many steps of similar kind



<https://preshonebooks.com/2015/01/30/surviving-the-storm-together/>

Multiple histogram reweighting I

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Building the **density of states** as a function of energy in a wide range of temperatures from overlapping histograms of energies obtained in a number of simulations at different temperatures.

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

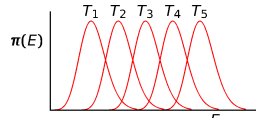
$$Q_i = e^{-\beta_i F_i} = \int e^{-\beta_i U(\mathcal{P}^N)} d\mathcal{P}^N = \int D(E) e^{-\beta_i E} dE$$

where $D(E)$ is the density of states:

$$D(E) = \int_{U(\mathcal{P}^N)=E} 1 d\mathcal{P}^N \equiv \int \delta(U(\mathcal{P}^N) - E) d\mathcal{P}^N$$

$$\approx \int_{U(\mathcal{P}^N) \in (E - \Delta E/2, E + \Delta E/2)} 1 d\mathcal{P}^N$$

[Ghouri et al. (2008)]



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

$$D(E) \propto E^{kN}$$

where k is a constant

Detour: Density of states for a particle in a box

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

$$E_n = \frac{n^2 \hbar^2}{8L^2} \propto n^2, \quad n = 1, 2, \dots$$

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

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

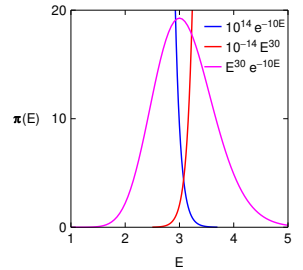
For large E , $\#(E) = 1/2^f$ of the volume of the $E^{1/2}$ -ball in f -dimensional space:

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

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

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

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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):

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

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

\Rightarrow 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

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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 . \Rightarrow

$$\begin{aligned} e^{-\beta_i F_i} &= \int D(E) e^{-\beta_i E} dE = \int \sum_j w_j(E) h_j(E) e^{\beta_j (E - F_j)} e^{-\beta_i E} dE \\ &= \int \frac{\sum_j N_j e^{-\beta_j (E - F_j)} h_j(E) e^{\beta_j (E - F_j)}}{\sum_j N_j e^{-\beta_j (E - F_j)}} e^{-\beta_i E} dE = \int \frac{\sum_j N_j h_j(E) e^{-\beta_i E}}{\sum_j N_j e^{-\beta_j (E - F_j)}} dE \end{aligned}$$

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

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

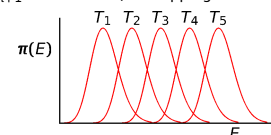
Multiple histogram reweighting IV

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Expectation value at temperature β :

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

- $\int dE$ 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 $h_i(E) = 1/N_i$
- $\sqrt{\text{Var}(E)} \approx N^{-1/2} \Rightarrow \beta_i/\beta_{i+1} \approx 1 \pm N^{-1/2}$ (overlapping distributions)



Parallel tempering (replica exchange)

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k simulations at temperatures $\beta_1 < \beta_2 \dots$ 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, metadynamics, Wang-Landau: Case study

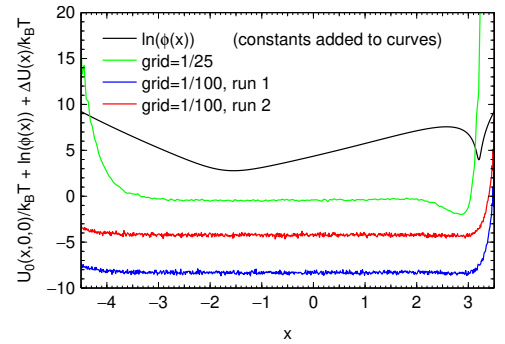
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The final graph shows $F(x) + \Delta U(x)$ (two independent simulations $T = 1$ K, different start)

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.

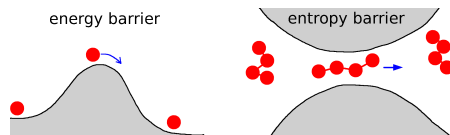
* see Maple



Conformational flooding, metadynamics, Wang-Landau

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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)

Widom particle insertion method I

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Open system

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

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

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

$$\exp(-\beta\mu_{res}) = \frac{1}{V} \frac{QN+1}{QN}$$

Or for the full chemical potential:

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

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

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- Our system is defined by the potential $U_0(r^N)$
- Collective variable** $\lambda = \lambda(r^N)$ 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 $U(r^N) = U_0(r^N) + \Delta U(\lambda)$, where $\Delta U = 0$ at start
- $\Delta U(\lambda)$ is periodically updated:

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

δ = approximation 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., $h(\lambda) = 4\pi\lambda^2$ for $\lambda = r_{12}$

→ the probability of visiting the same λ again decreases

Widom particle insertion method II

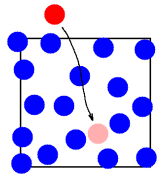
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$$\exp(-\beta\mu_{res}) = \frac{1}{V} \frac{QN+1}{QN}$$

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

$$\frac{1}{V} \frac{QN+1}{QN} = \frac{1}{VQN} \int \exp(-\beta U_N - \beta \Psi) d\mathbf{r}_{N+1} \dots d\mathbf{r}_{N+1} = \frac{1}{V} \int \langle e^{-\beta \Psi} \rangle_N d\mathbf{r}_{N+1}$$

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



where $\frac{1}{V} \int X d\mathbf{r}_{N+1} = \langle X \rangle_{\text{random } \mathbf{r}_{N+1}}$ = 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 → solubility, Henry constant

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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 $p(\lambda)/h(\lambda) = \text{const}$ 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:

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

integration over region for more collective variables

! symbols const are different

Example

[cd.../maple; xmapple simul07+18+Widom.mw] 29/34
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We have simulated $N = 500$ Ar atoms (Lennard-Jones: $\sigma = 3.405 \text{ \AA}$, $\epsilon/k_B = 119.8 \text{ K}$) in a box of volume $V = 15.791 \text{ nm}^3$ at temperature $T = 150 \text{ K}$. By the Widom method, we found that¹

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

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

Hints: $\mu_{res} = \mu - \mu^{id}(T, V)$ (N particles in volume V)

$$\mu^o = \mu - \mu^{id}(T, V^{id}) \quad (V^{id} = \text{volume of ideal gas of } N \text{ particles at } T, p^{st})$$

$$\mu^o = \mu_{res} + \mu^{id}(T, V) - \mu^{id}(T, V^{id})$$

$$= \mu_{res} + k_B T \ln \frac{Nk_B T}{p^{st} V}$$

$$\begin{aligned} \mu_{res} &= \mu - \mu^{id}(T, V) \\ \mu^o &= \mu_{res} + \mu^{id}(T, V) - \mu^{id}(T, V^{id}) \\ &= \mu_{res} + k_B T \ln \frac{Nk_B T}{p^{st} V} - k_B T \ln \frac{Nk_B T}{p^{st} V^{id}} \\ &= \mu_{res} + k_B T \ln \frac{V^{id}}{V} \end{aligned}$$

¹The value in parentheses is the estimated standard uncertainty in the unit of the least significant digit.

Conformational flooding, metadynamics, Wang-Landau: Case study

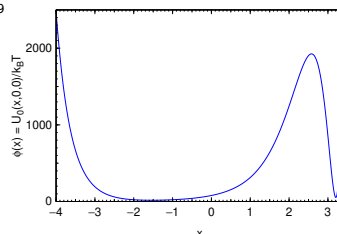
[plot/metadynamics.sh 1-2] 25/34
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3D system, interaction energy:

online simulation is for $T=1$ K and $T=2$ K, type [] to reread

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

- The barrier is $E^*/k_B = 1910 \text{ K}$, $e^{-E^*/k_B} = 10^{-929}$
- Collective variable $\lambda = x$
- Histogram: triangular $\delta(\lambda)$, grid = 1/100
- On purpose short MC step in x (\approx MD)
- Initial $\omega = 0.25k_B T$, decrease to finish
fine + stop ($\omega \equiv \alpha < 0$): aaaV in the plot window
- graphs shown:



running: $\Delta U - F_{exact}$, where

$$F_{exact}(\lambda) = \phi(\lambda) + k_B T \ln(\phi(\lambda))$$

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)

Henry constant

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

$$\mu_{res,2} = \mu_2(x_2) - \mu_2^{id}(V)$$

In equilibrium:

$$\mu_2(x_2) \stackrel{eq.}{=} \mu_2^{id}(V_2) = k_B T \ln \frac{\Lambda^3}{V_2}$$

$$\left. \begin{aligned} \mu_{res,2} &= \mu_2(x_2) - \mu_2^{id}(V) \\ \mu_{res,2} &= k_B T \ln \frac{\Lambda^3}{V_2} - k_B T \ln \frac{\Lambda^3}{V} = k_B T \ln \frac{V}{V_2} \end{aligned} \right\} \mu_2^{id}(V) = k_B T \ln \frac{N\Lambda^3}{V}$$

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

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

where $p_1 = N_1/V$ = number density of liquid (1). Finally,

$$K_H = \frac{p_1 k_B T}{e^{-\beta\mu_{res,2}}} = \frac{p_1 k_B T}{\langle (e^{-\beta\Psi})_{N_1} \rangle_{\text{random insertion of (2)}}$$

Reversible work by integrating the mean force

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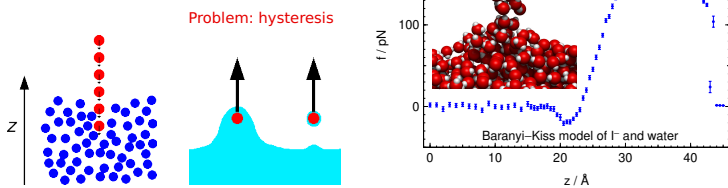
From thermodynamics:

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

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

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.



Mean force and its potential

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

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

- $\rho_1(\vec{r}_1) d\vec{r}_1$ is the probability of finding a particle (any one) in $d\vec{r}_1$

- extension to mixtures: $N/Q_N \rightarrow N_{\text{species}}/Q_N$

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

$$\bar{U}_1(\vec{r}_1) = -k_B T \ln[\rho_1(\vec{r}_1)]$$

The corresponding force is

$$\vec{f}_i = - \left(\frac{\partial \bar{U}_1}{\partial \vec{r}_1} \right) = k_B T \frac{\partial \rho_1 / \partial \vec{r}_1}{\rho_1} = \left\langle - \left(\frac{\partial U}{\partial \vec{r}_1} \right) \right\rangle_{\vec{r}_2, \dots, \vec{r}_N} = \langle \vec{f}_1 \rangle_{\vec{r}_2, \dots, \vec{r}_N}$$

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:

$$\bar{U}_2(r) = -k_B T \ln[g(r)]$$

Interfacial (surface) energy of solids

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Cleaving [Davidchack, Laird: JCP 118, 7651 (2003)]: Thermodynamic integration over a gradually growing "knife" (e.g., Gaussian potential) inserted between crystallographic 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 $0 \rightarrow T$ [Kolafa JCTC 15, 68 (2019) and references therein]

[§]independent harmonic oscillators, here treated classically

Local density/concentration method

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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

