

The free energies } A (Helmholtz, variables N, V, T)
 } G (Gibbs, variables N, P, T)

are key for analyzing phase equilibria, adsorption, binding of drugs to receptors, protein folding etc.

Unfortunately $A = -k_B T \ln Q$ } cannot be
 $S = k_B \ln Q$ } obtained
 } directly

[If we could get S , $A = U - TS$
 $\uparrow$ easy to get
 $G = U - TS + PV$]

However, derivatives of A can be obtained by simulation:

$$\left(\frac{\partial A}{\partial V} \right)_{N, T} = -P \quad \left(\frac{\partial A / T}{\partial (1/T)} \right)_{V, N} = U$$

Thermodynamic Integration (T.I.)

This is a very general approach to obtain free energy differences between two states:

→ Construct reversible path linking them

→ If final state has a known free energy (e.g., ideal gas), complete thermodynamic properties can be recovered

Free Energies

CBE 422

(2)

Systems I and II:

$$U(\lambda) = (1-\lambda)U_I + \lambda U_{II} = U_I + \lambda(U_{II} - U_I)$$

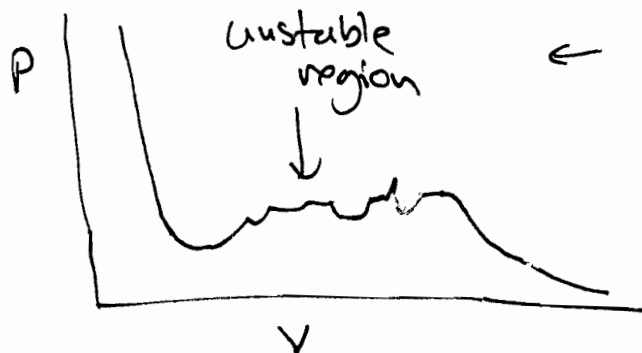
$$Q(N, V, T; \lambda) = \frac{1}{N!} \int d\vec{r}^N \exp[-\beta U(\lambda)]$$

$$\left(\frac{\partial A(\lambda)}{\partial \lambda} \right)_{N, V, T} = - \frac{\partial}{\partial \lambda} k_B T \ln Q = - \frac{k_B T}{Q} \frac{\partial Q}{\partial \lambda} =$$

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

$$\boxed{A(\lambda=1) - A(\lambda=0) = \int_0^1 d\lambda \left\langle \frac{\partial U(\lambda)}{\partial \lambda} \right\rangle_\lambda} \quad \text{general T.I. relationship}$$

Note that there may be practical difficulties with some coordinates λ , if there is a phase transition that intervenes - e.g.,



← system with vapor-liquid equil., $T < T_c$

$$\Delta A = - \int_{V_1}^{V_2} P dV \quad \left. \vphantom{\int_{V_1}^{V_2}} \right\} \text{not reliable}$$

$$\left(\frac{\partial (A/T)}{\partial (1/T)} \right) = U \Rightarrow \Delta \left(\frac{A}{T} \right) = - \int U d(1/T) \quad \left. \vphantom{\int U d(1/T)} \right\} \text{works}$$

Widom Test Particle Insertions

This can be considered as a special case of T.I., even though it was not derived as such.

Ref.: Widom, B. J. Chem. Phys. 39: 2802 (1963)

$$dA = -SdT - PdV + \sum_i \mu_i dN_i \Rightarrow \mu_i = \left(\frac{\partial A}{\partial N_i} \right)_{T, V, N_{j \neq i}} \quad (1)$$

$$Q(N, V, T) = \frac{V^N}{N!} \int_0^1 \int_0^1 \dots \int_0^1 d\vec{s}_1 d\vec{s}_2 \dots d\vec{s}_N e^{-\beta U_N} \quad (2)$$

$\vec{s}_i$: scaled coordinates, $\vec{s}_i = \vec{r}_i / L$

$$A = -k_B T \ln Q = \underbrace{-k_B T \ln \frac{V^N}{N!}}_{\text{ideal part}} - \underbrace{k_B T \ln \left(\int d\vec{s}^N e^{-\beta U_N} \right)}_{\text{excess part}}$$

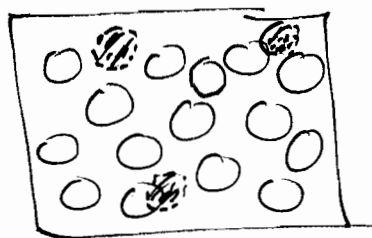
From (1) we can approximate μ_i for large N_i

$$\text{as: } \mu_i = \frac{A(N+1) - A(N)}{1} = -k_B T \ln \frac{Q_{N+1}}{Q_N} \quad (2)$$

$$-k_B T \ln \left(\frac{V}{N+1} \right) - k_B T \ln \left[\frac{\int d\vec{s}^{N+1} e^{-\beta U_{N+1}}}{\int d\vec{s}^N e^{-\beta U_N}} \right] \Rightarrow$$

$$\boxed{\mu_{\text{ex}} = -k_B T \ln \left\langle e^{-\beta \Delta U} \right\rangle_N}$$

ΔU : energy to add a single particle to system, ignoring other particle positions



○ : "real" particles,
participate in simulation

⊗ : "test" particles -
random positions

The excess chemical potential is related to the ensemble average of the test particle energy: $\langle e^{-\beta U_{\text{test}}} \rangle = e^{-\beta \mu_{\text{ex}}}$

Example - hard spheres :

$$e^{-\beta U_{\text{test}}} = \begin{cases} 0 & \text{if overlap } U_{\text{test}} = \infty \\ 1 & \text{if no overlap, } U_{\text{test}} = 0 \end{cases}$$

$\langle e^{-\beta U_{\text{test}}} \rangle =$ fraction of non-overlapping
random insertions $= \phi$
("free volume")

$$\mu_{\text{ex}} = -kT \ln \phi$$

Limitations of T.I.

Thermodynamic integration methods are often used to calculate free energy changes for "mutations" of chemical structures, e.g. to find better pharmaceuticals. However, it is frequently difficult to obtain reliable results,

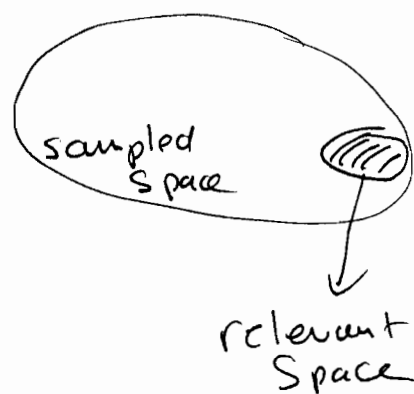
Free Energies

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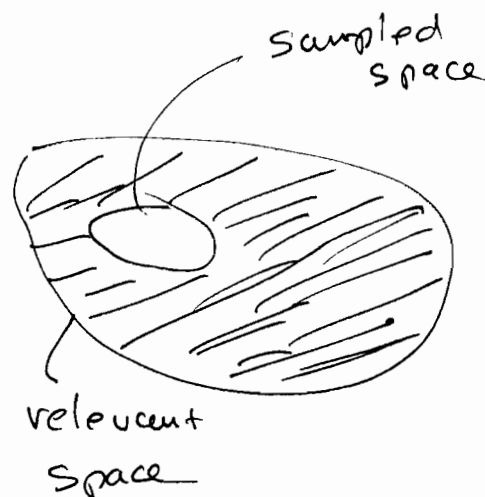
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for two reasons

1. The configuration space "relevant" for a free energy change may be a small part of overall phase space - e.g., μ calculations at high density using Widom insertions



2. The relevant space may be entirely (or mostly) outside the sampled space - e.g. there is a theoretically correct "reverse widom" expression,



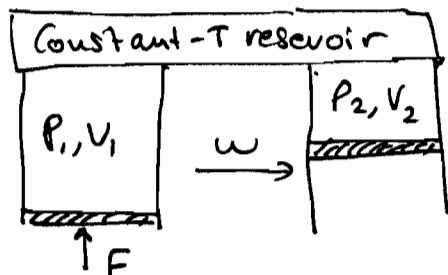
$$\mu_{ex} = +k_B T \ln \langle e^{+\beta U_{trial}} \rangle \quad \text{that fails}$$

almost all systems / conditions (e.g., predicts $\mu_{ex} = 0$ for hard spheres, independent of density)

See Lutkofke J. Chem. Phys. 114:7303 (2001)
for general principles of accurate sampling
using free energy calculation methods.

Non-Equilibrium Work Theorem

aka "Jarzynski's equality": $\left\{ \begin{array}{l} \text{Jarzynski, PRL } \underline{78}:2690(1997) \\ \text{Crooks, J. Stat. Phys. } \underline{90}:1481(1998) \end{array} \right.$



$$w = \int F dx = \Delta U - Q$$

for slow, reversible processes:

$$\Delta A = \Delta U - \underbrace{T \Delta S}_{Q_{\text{rev}}} = w_{\text{rev}}$$

For irreversible processes, $\overline{w_{\text{irr}}} > w_{\text{rev}}$ (otherwise - violation of 2nd Law). The overbar "-" denotes averages over all possible paths.

Jarzynski's equality states that

$$\boxed{\overline{e^{-\beta w}} = e^{-\beta \Delta A}}$$

for any process, reversible or irreversible!

Proof: Consider switch of Hamiltonians over time t_s

So that at $t=0$ $\lambda=0$ $H=H_0$ State $\Gamma(0) = \{\vec{p}^N, \vec{r}^N\}_0$
 $t=t_s$ $\lambda=1$ $H=H_1$ State $\Gamma(t_s) = \{\vec{p}^N, \vec{r}^N\}_{t_s}$

$$\text{Probability } P_0[\Gamma(0)] = \frac{\exp(-\beta H_0(\Gamma(0)))}{Q_0}$$

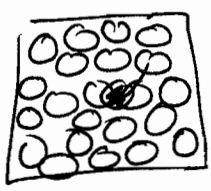
$$\begin{aligned} \overline{\exp[-\beta w(t_s)]} &= \underbrace{\int d\Gamma(0) P_0[\Gamma(0)] \exp[-\beta w(t_s, \Gamma(0))]}_{\text{over all init states}} = \int d\Gamma(0) \frac{\exp(-\beta H_0(\Gamma(0)))}{Q_0} e^{-\beta w(t_s, \Gamma(0))} \\ &= \int d\Gamma(0) \frac{\exp(-\beta H_0(\Gamma(0)))}{Q_0} e^{-\beta w(t_s, \Gamma(0))} = \int d\Gamma(0) \frac{e^{-\beta H_0}}{Q_0} \cdot \underbrace{e^{-\beta H_1 + \beta H_0}}_{\text{work} = H_1 - H_0} \end{aligned}$$

Now using that Hamiltonian equations of motion are area-preserving, $d\Gamma(t_s) = d\Gamma(0) \Rightarrow$

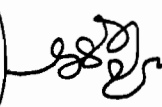
$$\overline{\exp(-\beta W(t_s))} = \int d\Gamma(t_s) e^{-\beta H_1(\Gamma(t_s))} / Q_0 = \frac{Q_1}{Q_0} = \exp(\beta \Delta A)$$

Limiting case (of ∞ fast switching) $\rightarrow$ wildom insertion ^(see)

Key limitation: If fluctuations in W over different paths are $\gg kT$, average is dominated by rare events that are almost never sampled!

E.g.  $\rightarrow$ large $\Delta \tilde{r}$  $\Delta A = 0$,
dense liquid but $w \gg 0$
for most attempts!

Experimental Validation: Lipshaw et al.,
Science, 296:1832 (2002)

bead  bead

Stretch RNA using optically trapped beads;
variable switching rate

