

Free Energy Profiles

(1)

Let's assume we can write a reaction coordinate

$$q = q(\vec{r}_1, \dots, \vec{r}_N)$$

as a function of all the atomic positions.

We can define a probability distribution in q :

$$P(q) = \langle \delta(q(\vec{r}_1, \dots, \vec{r}_N) - q) \rangle$$
$$= \frac{1}{Q} \int d\vec{p}^N \int d\vec{r}^N e^{-\beta H(\vec{p}, \vec{r})} \delta(q(\vec{r}) - q)$$

And a free energy profile

$$A(q) = -k_B T \ln P(q)$$

$P(q)$ is a kind of partition function corresponding to a fixed value of the reaction coordinate:

Globally

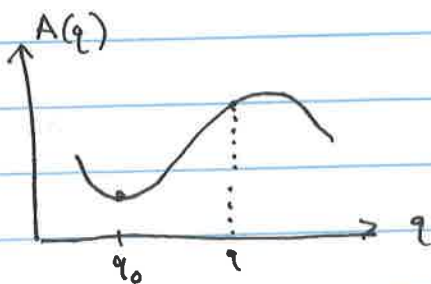
$$A = -k_B T \ln Q$$

Fixed q

$$A(q) = -k_B T \ln P(q)$$

What does $A(q)$ mean?

It is the free energy at some point along the reaction path which means it is an average over all other degrees of freedom (including solvent)!



← suppose we know $A(q_0)$

How might we get $A(q)$?

(2)

Here's How:

$$A(q) = A(q_0) + \int_{q_0}^q dq' \frac{dA}{dq'}$$

$$= A(q_0) - k_B T \int_{q_0}^q dq' \frac{1}{P(q')} \frac{dP}{dq'}$$

Let's figure these out: $\frac{1}{P(q')} = \frac{1}{\langle \delta(q - q') \rangle}$

$$\frac{dP}{dq'} = \frac{1}{Q} \int d\vec{r}^N \int d\vec{p}^N e^{-\beta \mathcal{H}(\vec{r}^N, \vec{p}^N)} \underbrace{\frac{\partial}{\partial q'} \delta(q(\vec{r}_1, \dots, \vec{r}_N) - q')}_{\text{this is hard!}}$$

Here's how to do it:

$$(\vec{r}_1, \dots, \vec{r}_N) \longrightarrow (\underbrace{u_1, \dots, u_n}_{3N-1 \text{ generalized coordinates (unknown!)}, q}_{\text{reaction coordinate}})$$

$$(\vec{p}_1, \dots, \vec{p}_N) \longrightarrow (p_{u_1}, \dots, p_{u_n}, p_q) \leftarrow \text{conjugate momenta}$$

$$d\vec{r}^N d\vec{p}^N \longrightarrow d^n u d^n p_u dp_q dq$$

$$\mathcal{H}(\vec{r}^N, \vec{p}^N) \longrightarrow \mathcal{H}(\vec{u}, \vec{p}_u, q, p_q)$$

$$\frac{\partial}{\partial q'} \delta(q - q') \text{ is anti-symmetric with respect to variables} = -\frac{\partial}{\partial q} \delta(q - q')$$

So:

$$\frac{1}{P(q')} \frac{dP}{dq'} = \frac{-1}{\langle \delta(q - q') \rangle} \frac{1}{Q} \int d^n u d^n p_u \int dq \int dp_q e^{-\beta \mathcal{H}} \frac{\partial}{\partial q} \delta(q - q')$$

We can do integration by parts to move the derivative over to the $e^{-\beta \mathcal{H}}$ part:

$$\frac{1}{P(q')} \frac{dP}{dq'} = \frac{1}{\langle \delta(q-q') \rangle} \frac{1}{Q} \int d^n u d^n p_u dq dp_u \underbrace{\frac{\partial}{\partial q} e^{-\beta \mathcal{H}}}_{-\beta \frac{\partial \mathcal{H}}{\partial q} e^{-\beta \mathcal{H}}} \delta(q-q')$$

$$\frac{1}{P(q')} \frac{dP}{dq'} = -\beta \frac{\langle \frac{\partial \mathcal{H}}{\partial q} \delta(q-q') \rangle}{\langle \delta(q-q') \rangle}$$

$$\equiv -\beta \left\langle \frac{\partial \mathcal{H}}{\partial q} \right\rangle_{q=q'} \leftarrow \text{conditional on reaction coordinate being found at } q'$$

$$\therefore A(q) = A(q_0) + \int_{q_0}^q \left\langle \left(\frac{\partial \mathcal{H}}{\partial q} \right) \right\rangle_{q=q'} dq'$$

This is an important result. The free energy can be obtained at any value of the reaction coordinate by integrating the average change in \mathcal{H} with respect to the r.c.

Connection to work: In Cartesian coordinates,

$$\mathcal{H} = \sum_{i=1}^{3N} \frac{p_i^2}{2m_i} + U(\vec{r}_1, \dots, \vec{r}_N)$$

$$\frac{\partial \mathcal{H}}{\partial q} = \sum_{i=1}^{3N} \left[\frac{\partial \mathcal{H}}{\partial p_i} \frac{\partial p_i}{\partial q} + \frac{\partial \mathcal{H}}{\partial r_i} \frac{\partial r_i}{\partial q} \right]$$

$$= \sum_{i=1}^{3N} \left[\frac{p_i}{m_i} \frac{\partial p_i}{\partial q} + \frac{\partial U}{\partial r_i} \frac{\partial r_i}{\partial q} \right]$$

\uparrow $\sum q$ depends only on \vec{r} force

$$\frac{\partial \mathcal{H}}{\partial q} = \sum_{i=1}^N -\vec{F}_i \cdot \frac{\partial \vec{r}_i}{\partial q} = -F_q \leftarrow \text{generalized force on reaction coordinate}$$

So:

$$A(q) - A(q_0) = - \int_{q_0}^q \underbrace{dq'}_{\text{distance}} \underbrace{F_{q'}}_{\text{force}} = \text{work}$$

Free energy differences are the amount of reversible work it takes to go from one state to another:

$$\Delta A = - \int_{q_0}^q dq' \left\langle \left(\frac{\partial H}{\partial q} \right) \right\rangle_{q=q'}$$

A special version of the reversible work theorem:



What is ΔA between these points?

How can we get ΔA_{subl} exactly?

Suppose we transform our interacting molecular system into some exact system:

$$U_\lambda = (1-\lambda) U_0 + \lambda U$$

$$\lambda = 0 \Rightarrow U_\lambda = U_0 = \text{ideal gas}$$

$$\lambda = 1 \Rightarrow U_\lambda = U = \text{interacting gas}$$

λ is an effective reaction coordinate for the transformation from ideal gas to interacting gas:

$$H(\vec{p}, \vec{r}, \lambda) = \sum_{i=1}^N \frac{\vec{p}_i^2}{2m_i} + \lambda U + (1-\lambda) U_0$$

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$$\frac{\partial \mathcal{H}}{\partial \lambda} = U - U_0$$

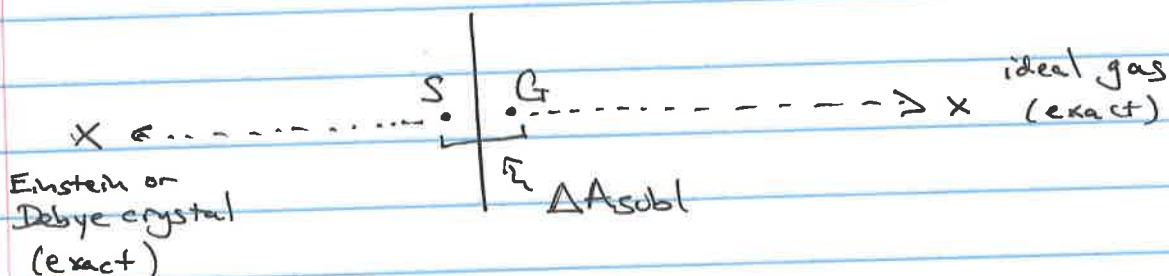
$$\Delta A = A - A_0 = \int_0^1 \left\langle \frac{\partial \mathcal{H}}{\partial \lambda} \right\rangle_{\lambda} d\lambda$$

$$A - A_0 = \int_0^1 \langle U - U_0 \rangle_{\lambda} d\lambda$$

$$A = A_0 + \int_0^1 \langle U - U_0 \rangle_{\lambda} d\lambda$$

exactly known A
for ideal gas

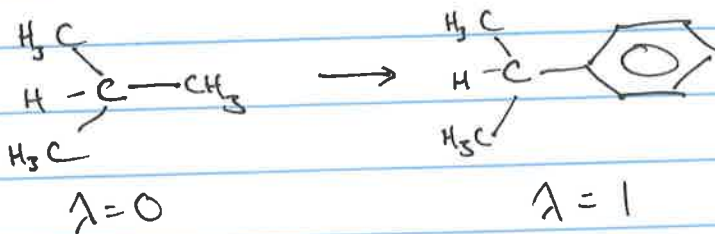
↑
difference between potentials as
simulation progresses with some
value of λ



Thermodynamic Integration is an extremely powerful technique: To use it, we must be able to
1) integrate equations of motion or sample on an intermediate potential energy surface

$$U(\lambda) = (1-\lambda) U_0(\vec{r}) + \lambda(U(\vec{r}))$$

U & U_0 don't even need the same number of atoms!



If we go slowly, we can do TI for alchemical transformations!

The Jarzynski Equality

(6)

Let's recall the Gibbs-Bogoliubov Variational Principle:

$$A \leq A_0 + \langle H - H_0 \rangle_0$$

real free energy reference free energy real Hamiltonian

reference Hamiltonian

average done in reference system

We've spent the last few days talking about Reversible Work & Thermodynamic Integration:

$$A = A_0 + \int_0^1 \langle H - H_0 \rangle_\lambda d\lambda$$

average done in a system with mixed Hamiltonian characterized by λ .

(If the reference Hamiltonian & real Hamiltonian have momenta that depend on λ .)

We've shown previously that

$$A = A_0 + \int_0^1 \underbrace{F_\lambda}_{\text{work}} d\lambda$$

$$A = A_0 + \underbrace{W}_{\text{work integral}}$$

For many years, it was assumed that a GBVP-like inequality holds. That is, unless we do the transformation infinitely slowly, we should have:

$$A \leq A_0 + W$$

$$\text{or: } \Delta A \leq W$$

In 1997, Chris Jarzynski proved this compact statement:

$$\langle e^{-\beta W} \rangle = e^{-\beta \Delta A}$$

This is known as the Jarzynski Equality and it holds no matter how slowly or quickly we do the transformation from reference \rightarrow real

The limitations are all in the average.

There are related proofs of this
Crooks Fluctuation Theorem
Schöll-Paschinger & Dellago's proof
We'll cover some of this now...

$$\Delta A = \int_0^1 \left\langle \frac{\partial H}{\partial \lambda} \right\rangle_{\lambda} d\lambda \quad \leftarrow \text{change in free energy is governed by how Hamiltonian responds to perturbation}$$

$$\frac{\text{Ideal}}{\lambda=0} \longrightarrow \frac{\text{Real}}{\lambda=1}$$

Typically, we want to make this integral discrete or have λ change continuously:

Discrete: $\{ \lambda_0, \lambda_1, \dots, \lambda_n \}$

Continuous: $w = \int_0^{t_s} dt \dot{\lambda} \frac{\partial H_{\lambda}(\vec{r}(t), \vec{p}(t))}{\partial \lambda}$
 \uparrow change in λ with simulation time

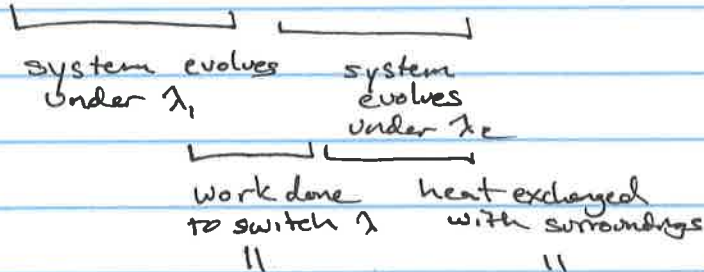
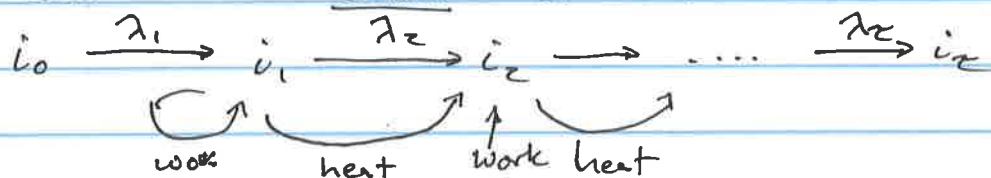
Let's consider the discrete case:

First, the probability of a particular state (j) given a fixed value of λ :

$$P(j|\lambda) = \frac{e^{-\beta E_j(\lambda)}}{\sum_i e^{-\beta E_i(\lambda)}} \quad \leftarrow Q(\lambda) = \sum_i e^{-\beta E_i(\lambda)}$$

$$P(j|\lambda) = e^{\beta[A(\lambda) - E_j(\lambda)]}$$

Now consider a chain of states:



$$E_{i_1}(\lambda_2) - E_{i_1}(\lambda_1) \quad E_{i_2}(\lambda_2) - E_{i_1}(\lambda_2)$$

$$\text{Total Work: } W = \sum_{t=0}^{n-1} E_{i_t}(\lambda_{t+1}) - E_{i_t}(\lambda_t)$$

$$\text{Total Heat: } q = \sum_{t=1}^n E_{i_t}(\lambda_t) - E_{i_{t-1}}(\lambda_t)$$

$$\text{Total Energy: } \Delta E = q + W = E_{i_n}(\lambda_n) - E_{i_0}(\lambda_0)$$

$$\text{Reversible Work: } w_r = \Delta A = A(\lambda_1) - A(\lambda_0) = \int_0^1 \left\langle \frac{\partial H}{\partial \lambda} \right\rangle_{\lambda} d\lambda$$

$$\text{Dissipative Work: } w_d = W - w_r$$

Probability Chains

"Markovian" assumption
(previous history unimportant)

$$P(i_0 \xrightarrow{\lambda_1} i_1 \xrightarrow{\lambda_2} i_2 \dots \xrightarrow{\lambda_\tau} i_\tau)$$

$$= P(i_0 \xrightarrow{\lambda_1} i_1) P(i_1 \xrightarrow{\lambda_2} i_2) \dots P(i_{\tau-1} \xrightarrow{\lambda_\tau} i_\tau)$$

Detailed Balance assumption

$$\frac{P(i \xrightarrow{\lambda} j)}{P(j \xleftarrow{\lambda} i)} = \frac{P(j|\lambda)}{P(i|\lambda)} = \frac{e^{-\beta E_j(\lambda)}}{e^{-\beta E_i(\lambda)}}$$

$$\therefore \frac{P(i_0 \rightarrow i_1 \rightarrow \dots \rightarrow i_\tau)}{P(i_0 \leftarrow i_1 \leftarrow \dots \leftarrow i_\tau)} = \frac{P(i_0 \xrightarrow{\lambda_1} i_1) P(i_1 \xrightarrow{\lambda_2} i_2) \dots}{P(i_0 \xleftarrow{\lambda_1} i_1) P(i_1 \xleftarrow{\lambda_2} i_2) \dots}$$

$$= \frac{e^{-\beta E_{i_1}(\lambda_1)}}{e^{-\beta E_{i_0}(\lambda_1)}} \frac{e^{-\beta E_{i_2}(\lambda_2)}}{e^{-\beta E_{i_1}(\lambda_2)}} \dots$$

$$= e^{-\beta \underbrace{\sum}_{\text{heat}}} = e^{-\beta [E_{i_1}(\lambda_1) - E_{i_0}(\lambda_1)] + \dots}$$

If Both forward & reverse paths start from equilibrium distributions,

$$\frac{P(i_0|\lambda_0) P(i_0 \rightarrow i_1 \rightarrow \dots \rightarrow i_\tau)}{P(i_\tau|\lambda_\tau) P(i_0 \leftarrow i_1 \leftarrow \dots \leftarrow i_\tau)} =$$

$$\frac{e^{\beta A(\lambda_0) - \beta E_{i_0}}}{e^{\beta A(\lambda_\tau) - \beta E_{i_\tau}}} * e^{-\beta Q} = e^{-\beta \Delta A} e^{\beta \Delta E} e^{-\beta Q}$$

$$= e^{-\beta \Delta A} e^{\beta W}$$

$$= e^{-\beta W_r} e^{\beta W} = e^{+\beta W_d}$$

Crooks Equality

(10)

Consider the average value of $\langle e^{-\beta w} \rangle$ from a set of discrete non-equilibrium paths

$$\langle e^{-\beta w} \rangle_{ne} = \sum_{i_0, i_1, \dots, i_T} \underbrace{P(i_0 | \lambda_0) P(i_0 \xrightarrow{\lambda_1} i_1 \xrightarrow{\lambda_2} \dots i_T)}_{\text{probability of a state } i_0 \text{ given } \lambda_0} e^{-\beta w} \quad \begin{matrix} \uparrow \\ \text{for this} \\ \text{path} \end{matrix}$$

Because of what we've derived:

$$\langle e^{-\beta w} \rangle_{ne} = \sum_{i_0, \dots, i_T} P(i_T | \lambda_T) P(i_0 \xleftarrow{\lambda_1} i_1 \xleftarrow{\lambda_2} \dots i_T) \underbrace{e^{+\beta w_d} e^{-\beta w}}_{\substack{e^{-\beta w_r} \\ = \\ e^{-\beta \Delta A}}}$$

So:

$$\langle e^{-\beta w} \rangle_{ne} = \sum_{i_0, \dots, i_T} \underbrace{P(i_T | \lambda_T) P(i_0 \xleftarrow{\lambda_1} i_1 \xleftarrow{\lambda_2} \dots i_T)}_{\substack{= \\ \text{if we sample} \\ \text{lots of paths}}} \underbrace{e^{-\beta \Delta A}}_{\substack{\text{equilibrium} \\ \text{or independent} \\ \text{of path}}}$$

That is:

$$\underbrace{\langle e^{-\beta w} \rangle_{ne}}_{\substack{\text{average over} \\ \text{many paths}}} = e^{-\beta \Delta A} \quad \underbrace{\text{exact reversible}}_{\text{free energy}}$$

work from one non-equilibrium path

NB: This does not imply $w_{ne} = \Delta A$
One ne path is not enough!



$$W(x_0) = H(x_\tau(x_0); B) - H(x_0; A)$$

$$\langle e^{-\beta W} \rangle = \int dx_0 \frac{1}{Z_A} e^{-\beta H(x_0; A)} e^{-\beta W(x_0)}$$

$$= \frac{1}{Z_A} \int dx_0 e^{-\beta H(x_\tau(x_0); B)}$$

$$= \frac{1}{Z_A} \int dx_\tau \left| \frac{\partial x_\tau}{\partial x_0} \right|^{-1} e^{-\beta H(x_\tau; B)} = 1 \text{ (Liouville's thm.)}$$

$$= \frac{Z_B}{Z_A} = e^{-\beta \Delta F}$$

QED