

Getting free energies from simulations

Spring, 2019

The basic question here: what if we cannot write down expressions for the partition function (or configurational integral) Q ? Of course, we have to know *something*! We will assume that we can extract samples from the Boltzmann distribution: this fundamentally implies that we can evaluate averages of mechanical properties, that is, of variables that are functions just of the structures we sample. To establish some notation:

$$\langle f(\mathbf{x}) \rangle \equiv \int f(\mathbf{x}) e^{-\beta V(\mathbf{x})} d\mathbf{x} \simeq \sum_i f(\mathbf{x}_i) \quad (1)$$

1 Thermodynamic integration

Suppose that the potential energy, V (and hence Q and A), are parameterized by $\lambda : V \rightarrow V(\lambda)$. Then, since $A = -kT \ln Q$:

$$\frac{\partial A(\lambda)}{\partial \lambda} = -kT \int \frac{\partial}{\partial \lambda} e^{-\beta V(\lambda)} dq / Q = \frac{1}{Q} \int \left(\frac{\partial V}{\partial \lambda} \right) e^{-\beta V(\lambda)} dq = \left\langle \frac{\partial V}{\partial \lambda} \right\rangle_{\lambda} \quad (2)$$

The total change in A on going from $\lambda = 0$ to $\lambda = 1$ is:

$$\Delta A = A(1) - A(0) = \int_0^1 \left\langle \frac{\partial V}{\partial \lambda} \right\rangle_{\lambda} d\lambda \quad (3)$$

This is called thermodynamic integration, and is a fundamental connection between macroscopic free energies, and microscopic simulations. The integral over λ can be done by quadrature, and the Boltzmann averages $\langle \partial V / \partial \lambda \rangle_{\lambda}$ can be carried out by molecular dynamics or Monte Carlo procedures.

1.1 Linear mixing

Consider the special case of *linear mixing*, where

$$V(\lambda) = (1 - \lambda)V_0 + \lambda V_1$$

Then $\partial V / \partial \lambda = V_1 - V_0 \equiv \Delta V$ (often called the *energy gap*), and

$$\Delta A = \int_0^1 \langle \Delta V \rangle_{\lambda} d\lambda \quad (4)$$

The simplest numerical approximation to the λ integral is just to evaluate the integrand at the mid-point, so that $\Delta A = \langle \Delta V \rangle_{1/2}$. This says that the free energy difference is approximately equal to the

average potential energy difference, evaluated for a (hypothetical) state half-way between $\lambda = 0$ and $\lambda = 1$.

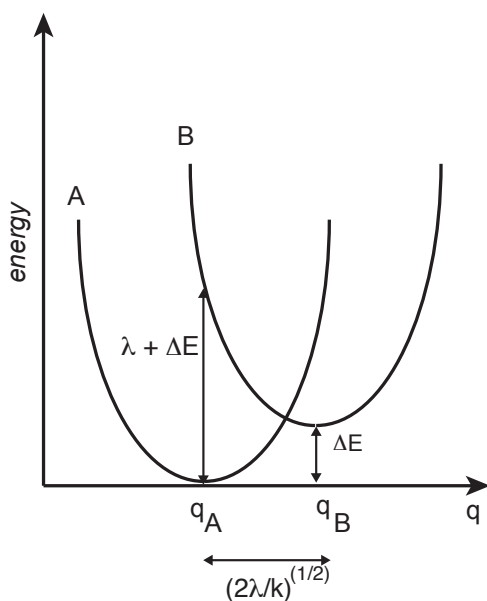
It is often convenient for other purposes to perform simulations only at the endpoints. In this case, a convenient formula would be:

$$\Delta A \simeq \frac{1}{2} \langle \Delta V \rangle_0 + \frac{1}{2} \langle \Delta V \rangle_1 \quad (5)$$

And more elaborate formulas (e.g. from Gaussian integration) are feasible (and often used). See Hummer & Szabo, *J. Chem. Phys.* **105**, 2004 (1996) for a fuller discussion.

2 A simple model: “Marcus theory”

Rudy Marcus did many interesting things, but the most famous was to analyze a very simple two-state problem:



$$\begin{aligned} V_A(q) &= \frac{1}{2}k(q - q_A)^2 \\ V_B(q) &= \frac{1}{2}k(q - q_B)^2 + \Delta E \\ \Delta V(q) &= -k(q - q_A) \left(\frac{2\lambda}{k} \right)^{1/2} + \lambda + \Delta E \end{aligned}$$

2.1 Analyze this with thermodynamic integration:

$$\langle V_B - V_A \rangle_A = Q_A^{-1} \int \left[-k(q - q_A) \left(\frac{2\lambda}{k} \right)^{1/2} + \lambda + \Delta E \right] e^{-\beta V_A(q)} dq = \lambda + \Delta E \quad (6)$$

$$\langle V_B - V_A \rangle_B = -\lambda + \Delta E; \quad \Delta A \simeq \frac{1}{2} [\langle \Delta V \rangle_A + \langle \Delta V \rangle_B] = \Delta E \quad (7)$$

What is the distribution of ΔV in the V_A state?

$$\rho(\Delta V) = \rho(q) \left| \frac{dq}{d\Delta V} \right| \quad \text{where} \quad q(\Delta V) = - \left[\frac{(\Delta V - \lambda - \Delta E)}{(2k\lambda)^{1/2}} \right] + q_A \quad (8)$$

$$\rho(\Delta V) \sim \frac{1}{\sqrt{2k\lambda}} \exp \{ -\beta V_A [q(\Delta V)] \} \simeq \exp \left\{ -\frac{(\Delta V - \lambda - \Delta E)^2}{2\sigma^2} \right\} \quad \text{with} \quad \sigma^2 = 2\lambda/\beta \quad (9)$$

Hence, the **mean** of the distribution gives $\lambda + \Delta E$, and the **width** of the distribution gives λ (the “relaxation”); knowing both allows you to get ΔE and λ separately.

2.2 Connection to kinetics of electron transfer

Now we can find the point q^* where $\Delta V(q^*) = 0$:

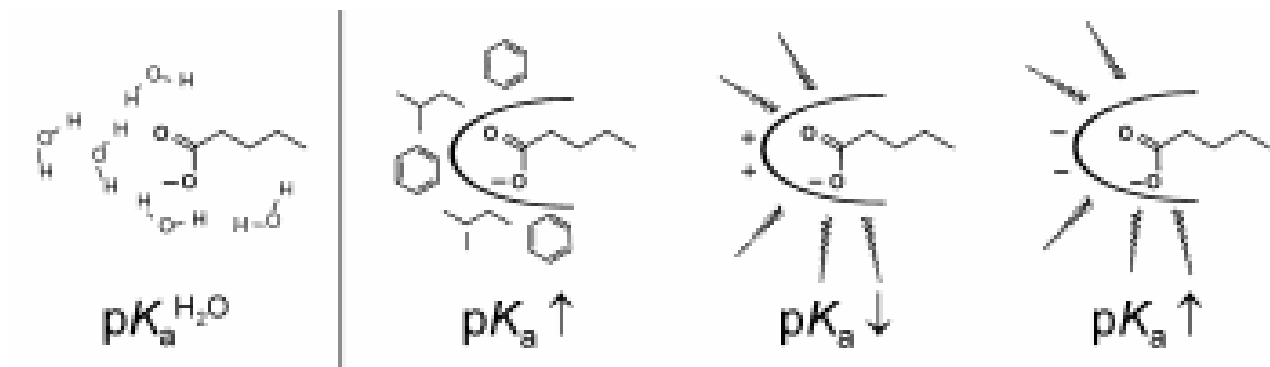
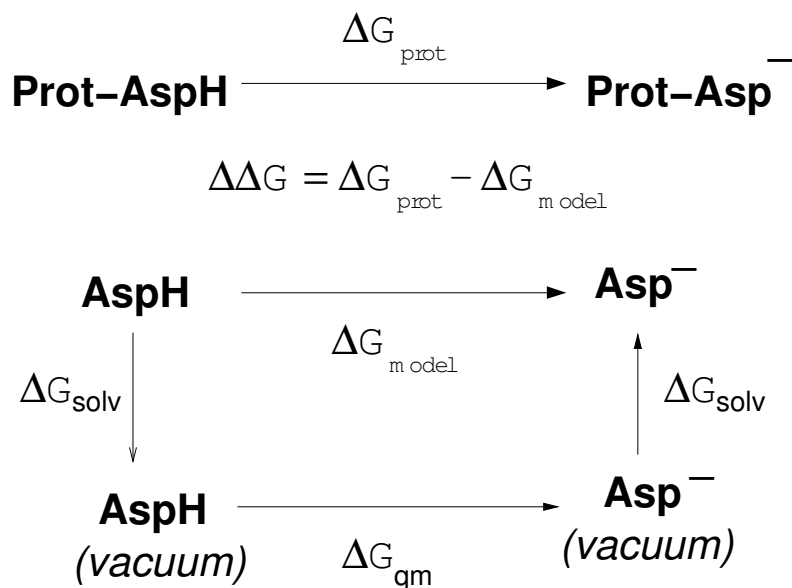
$$(q^* - q_A) = \frac{(\lambda + \Delta E)}{(2\lambda k)^{1/2}} = \frac{\lambda(1 + \Delta E/\lambda)}{(2\lambda k)^{1/2}} \quad (10)$$

Next, we can compute the activation energy, which is the value of $V_A(q^*)$:

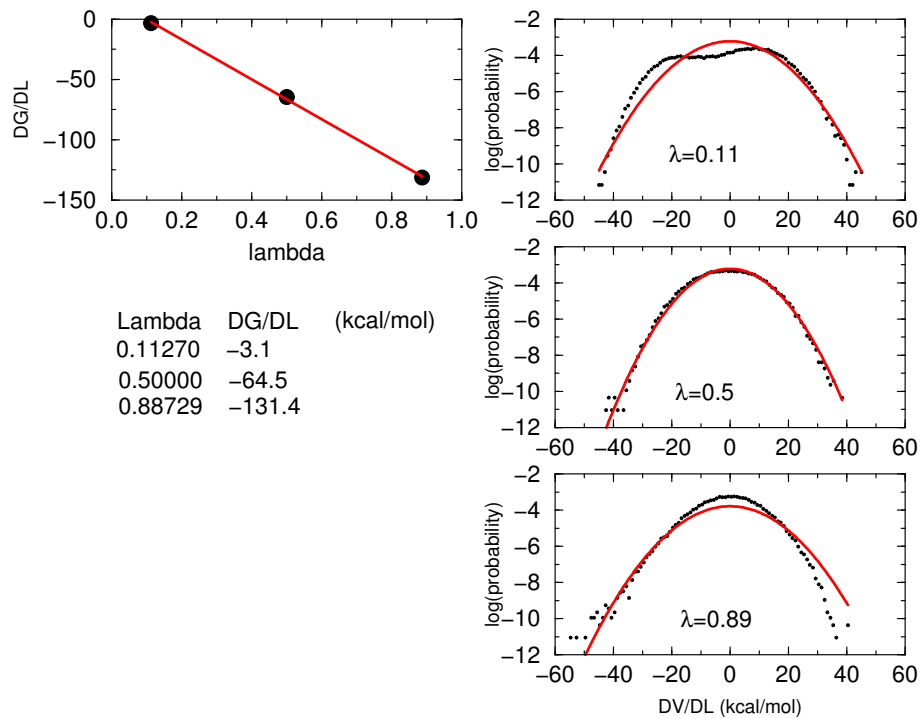
$$V_A(q^*) = \frac{1}{2}k(q^* - q_A)^2 = \frac{1}{2}k \frac{\lambda^2(1 + \Delta E/\lambda)^2}{(2\lambda k)} = \frac{\lambda}{4} \left(1 + \frac{\Delta E}{\lambda}\right)^2 \quad (11)$$

Note that terms in k cancel.

3 Application: pKa behavior in proteins

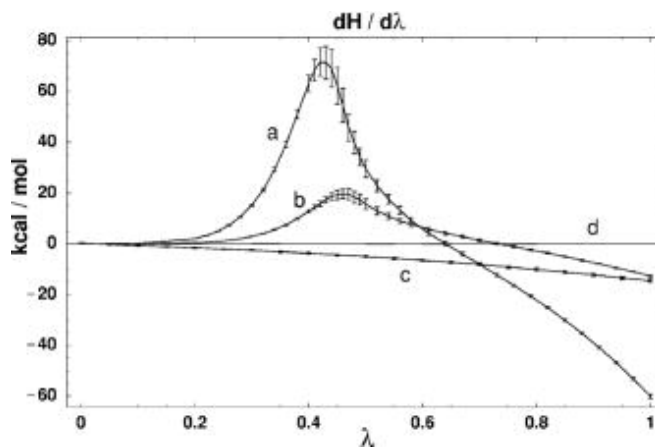


To apply any of these models, we need to know the average energy gap at different λ values, and it also helps to know its distribution.



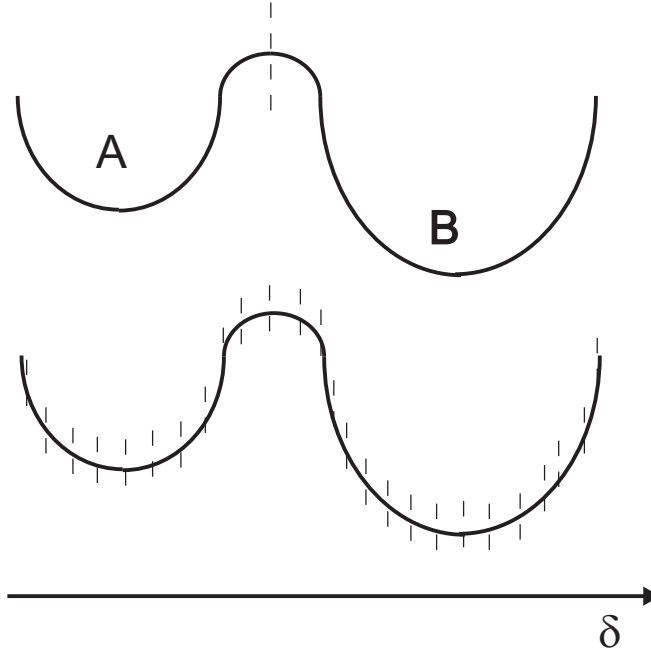
Simonson, Carlson, Case, JACS 126:4167 (2004)

Nonelectrostatic contributions are generally much more complex:



Shirts, Pitner, Swope, Pande, J. Chem. Phys. 119, 5740 (2003).

4 Biassed sampling



$$\frac{\rho_B}{\rho_A} = K_{eq} = \exp(-\Delta A/kT)$$

To create a *potential of mean force*:

$$\rho_i = (-W(\delta_i)/kT)$$

4.1 Reduced distribution functions:

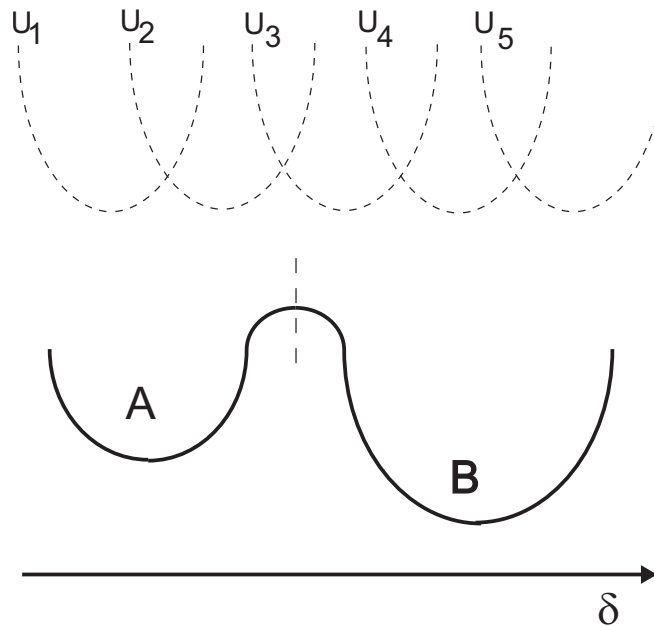
Now $\rho(\delta)$ is a reduced distribution function:

$$\rho(\delta) = \frac{\int \exp(-\beta V) d\Sigma}{\int \exp(-\beta V) d\delta d\Sigma}$$

In order to improve sampling in high-energy regions, add a biasing (umbrella) potential $U(\delta)$. Then the observed (simulated) reduced distribution will be:

$$\begin{aligned} \rho^*(\delta) &= e^{-\beta U(\delta)} \frac{\int \exp(-\beta V) d\Sigma}{\int \exp(-\beta(U+V)) d\delta d\Sigma} \\ &= e^{-\beta U(\delta)} \frac{\int \exp(-\beta V) d\Sigma}{\int \exp(-\beta(V)) d\delta d\Sigma} \frac{\int \exp(-\beta V) d\delta d\Sigma}{\int \exp(-\beta U) \exp(-\beta V) d\delta d\Sigma} \\ &= e^{-\beta U(\delta)} \rho(\delta) / \langle e^{-\beta U} \rangle \end{aligned}$$

4.2 Umbrella sampling

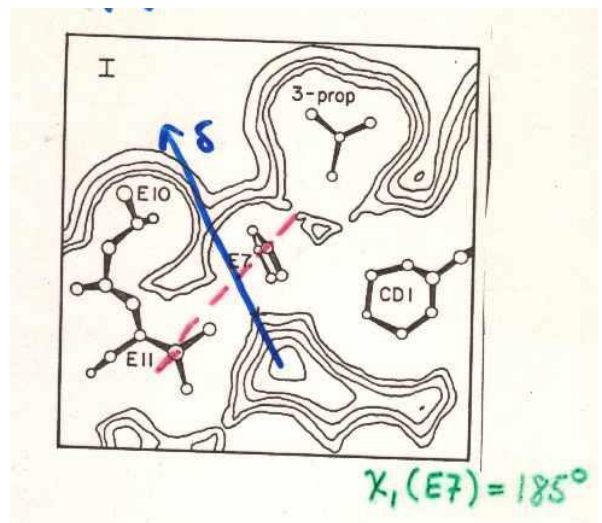
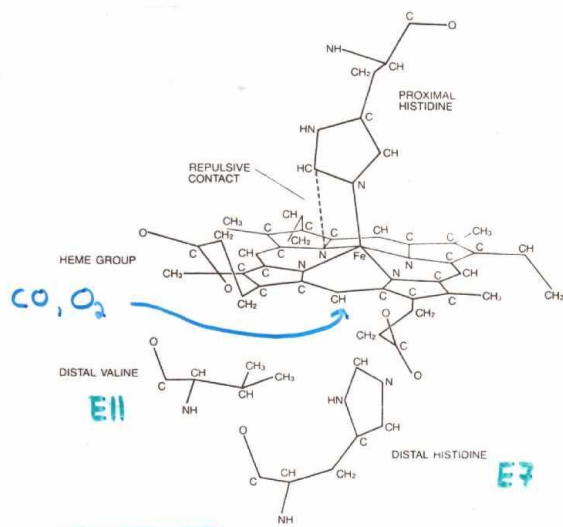


Taking logarithms:

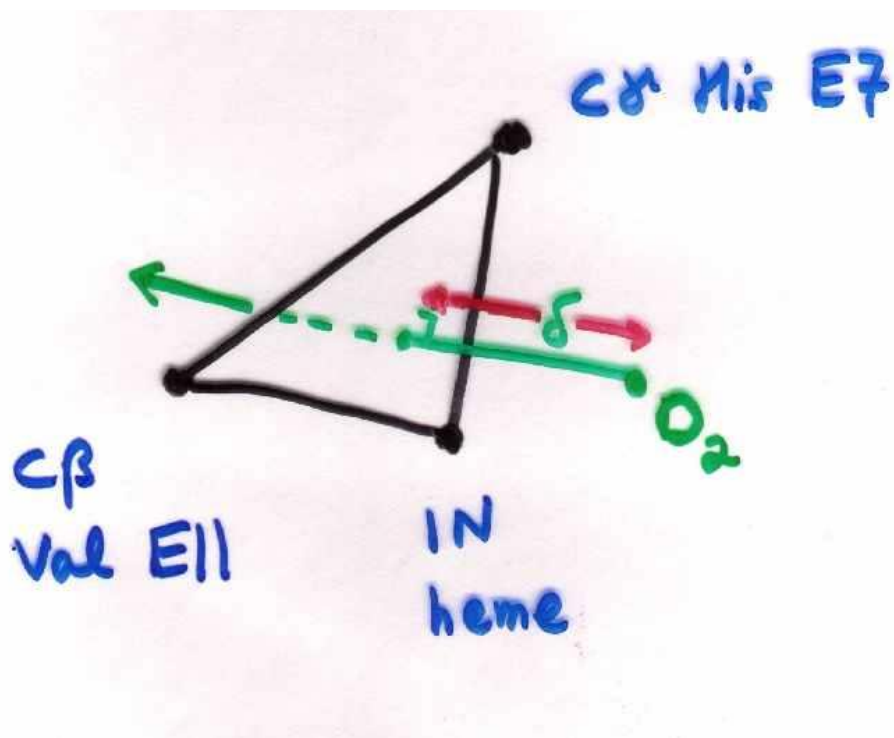
$$W^*(\delta) = W(\delta) + U(\delta) + kT \ln \langle e^{-\beta U} \rangle$$

Note that the final term is independent of δ . These can be treated as adjustable parameters, determined so that the $W(\delta)$ values from adjacent windows agree in their overlap region. See *J. Comput. Chem.* 16, 1339 (1995).

4.3 Example: oxygen binding to myoglobin

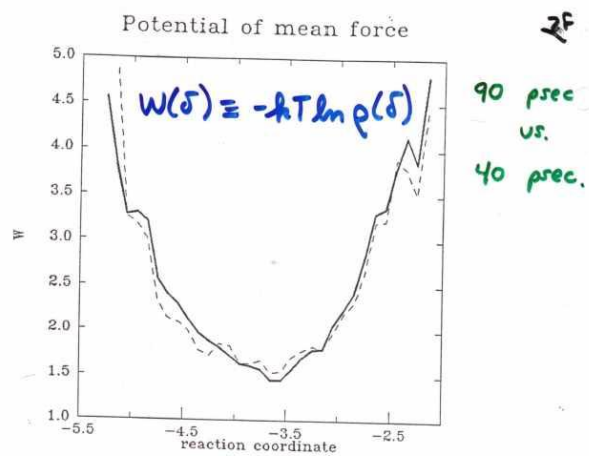
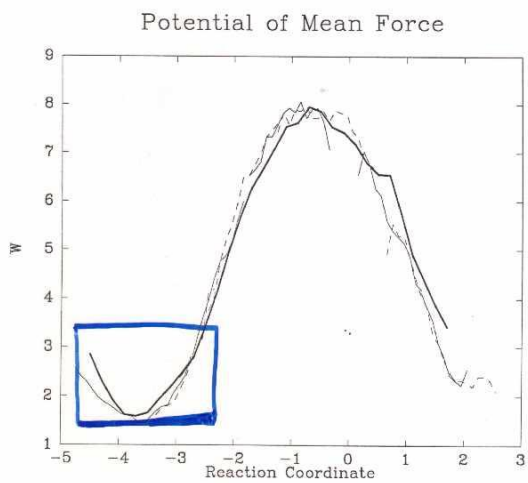


One possible reaction coordinate

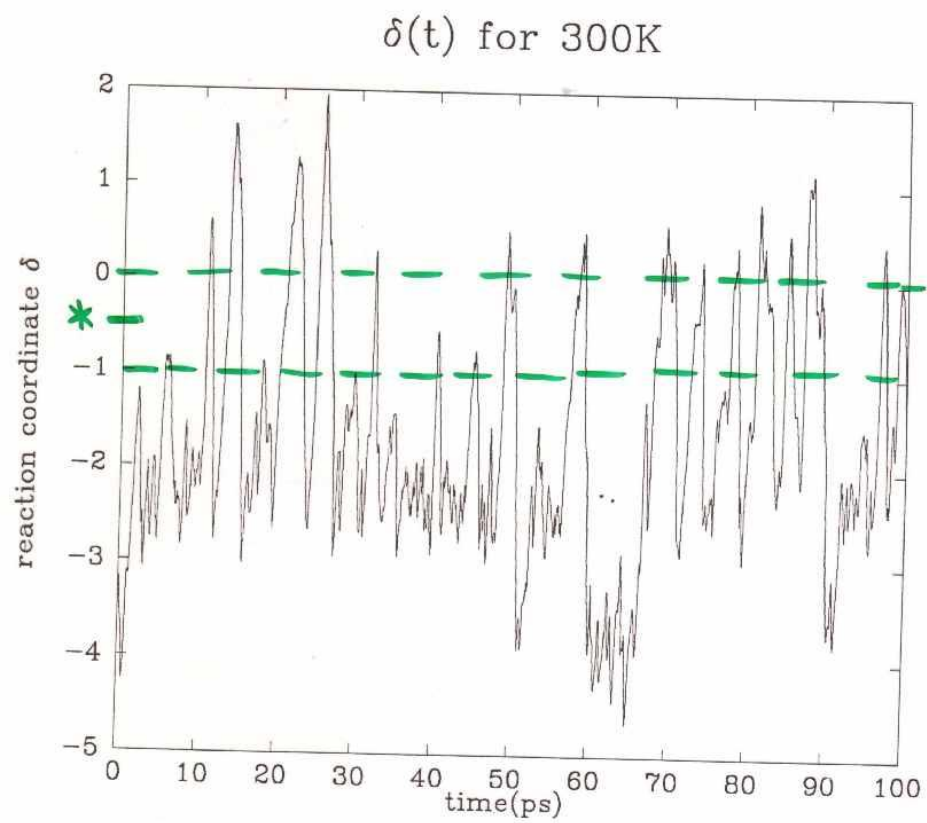


Kottalam & Case, JACS 110, 7690 (1988)

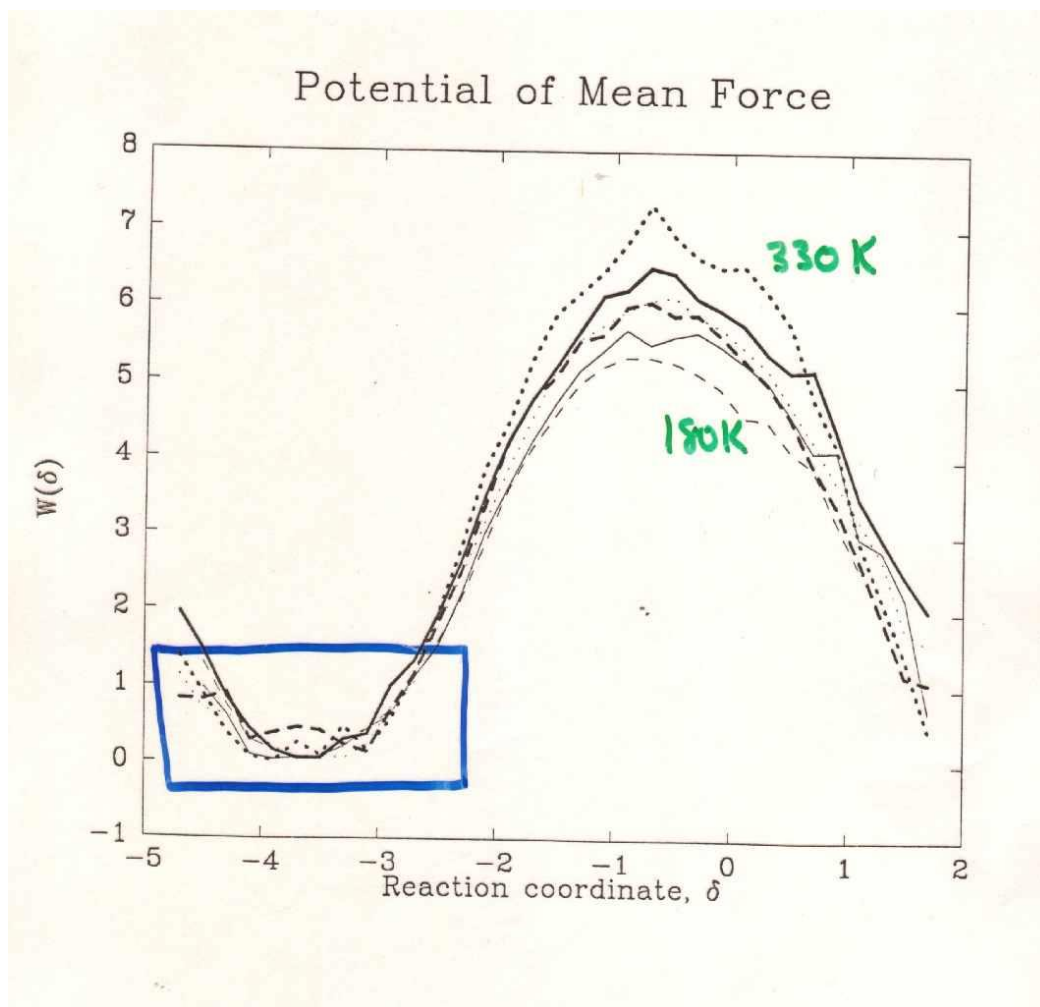
Computing a pmf



Now try to flatten the potential



Look at different temperatures



5 Free energy perturbation theory

Here is an (initially) completely different approach:

$$\Delta A = -kT \ln \left(\frac{Q_1}{Q_0} \right) \quad (12)$$

$$= -kT \ln \left(\frac{\int \exp(-\beta E_1) \exp(\beta E_0) \exp(-\beta E_0) dq}{\int \exp(-\beta E_0) dq} \right) \quad (13)$$

$$= -kT \ln \left(\frac{1}{Q_0} \int \exp(-\beta [E_1 - E_0]) \exp(-\beta E_0) \right) \quad (14)$$

$$= -kT \ln \langle \exp(-[E_1 - E_0]/kT) \rangle_0 \quad (15)$$

$$= kT \ln \langle \exp(-[E_0 - E_1]/kT) \rangle_1 \quad (16)$$

This is generally called "perturbation theory", and involves averaging the exponential of the energy gap, rather than the energy gap itself.