

$$A^{\text{excess}} = -kT \ln Q$$

$$V = \frac{1}{2} kx^2 \leftarrow$$

$$Q = \int_{-\infty}^{+\infty} e^{-\beta V(x)} dx = \text{analytical formula}$$

## Getting free energies from simulations

CCB 422/522, Spring, 2021

$$\underline{\tilde{F}} = - \frac{\partial \tilde{U}}{\partial \tilde{x}} = m \underline{\tilde{a}} = m \frac{d^2 \tilde{x}}{dt^2} \Rightarrow \tilde{x}(t)$$

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:

$$\langle f(x) \rangle = \frac{1}{Q} \int f(x) e^{-\beta V(x)} dx \approx \frac{1}{N} \sum_{i=1}^{10,000} f(x_i) \quad (1)$$

### 1 Thermodynamic integration

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

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

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

$$A = \int_0^1 \frac{\partial A}{\partial \lambda} d\lambda$$

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

This is called thermodynamic integration, and is a fundamental connection between macroscopic free energies, and microscopic simulations. The integral over  $\lambda$  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

$$V_1(x) - V_0(x) = \Delta V \quad (4)$$

$$\Delta A = \int_0^1 \langle \Delta V \rangle_{\lambda} d\lambda \quad (5)$$

The simplest numerical approximation to the  $\lambda$  integral is just to evaluate the integrand at the midpoint, so that  $\Delta A \approx \langle \Delta V \rangle_{1/2}$ . 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  $\lambda = 1$ .

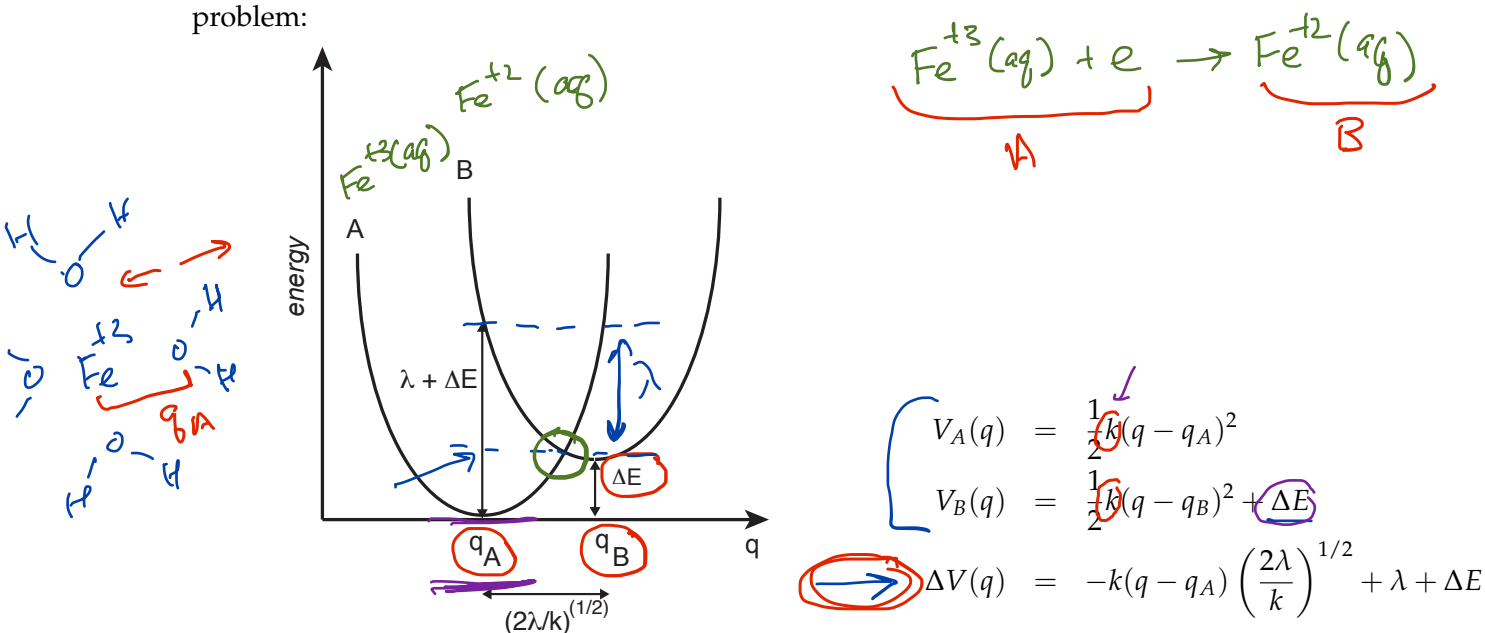
It is often convenient for other purposes to perform simulations only at the endpoints. In this case, a convenient formula would be:

$$\Delta A \simeq \frac{1}{2} \langle \Delta V \rangle_0 + \frac{1}{2} \langle \Delta V \rangle_1 \quad (6)$$

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:



### 2.1 Analyze this with thermodynamic integration:

exercise →

$$\langle V_B - V_A \rangle_A = Q_A^{-1} \int_{-\infty}^{\infty} \left[ -k(q - q_A) \left(\frac{2\lambda}{k}\right)^{1/2} + \lambda + \Delta E \right] e^{-\beta V_A(q)} dq = \lambda + \Delta E \quad (7)$$

$$\langle V_B - V_A \rangle_B = -\lambda + \Delta E; \quad \Delta A \simeq \frac{1}{2} [\langle \Delta V \rangle_A + \langle \Delta V \rangle_B] = \Delta E - \Delta(TS) \quad (8)$$

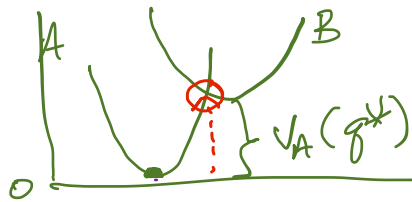
= 0 only for simple model

What is the distribution of  $\Delta V$  in the  $V_A$  state?

$$\rho(\Delta V) = \rho(q) \left| \frac{dq}{d\Delta V} \right| \quad \text{where} \quad q(\Delta V) = - \left[ \frac{(\Delta V - \lambda - \Delta E)}{(2k\lambda)^{1/2}} \right] + q_A \quad (9)$$

$$\rho(\Delta V) \sim \frac{1}{\sqrt{2k\lambda}} \exp \{ -\beta V_A [q(\Delta V)] \} \simeq \exp \left\{ -\frac{(\Delta V - \lambda - \Delta E)^2}{2\sigma^2} \right\} \quad \text{with} \quad \sigma^2 = 2\lambda/\beta \quad (10)$$

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



## 2.2 Connection to kinetics of electron transfer

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

exercise: derive

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

equation 12 is valuable way beyond this model. simple

(11)

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

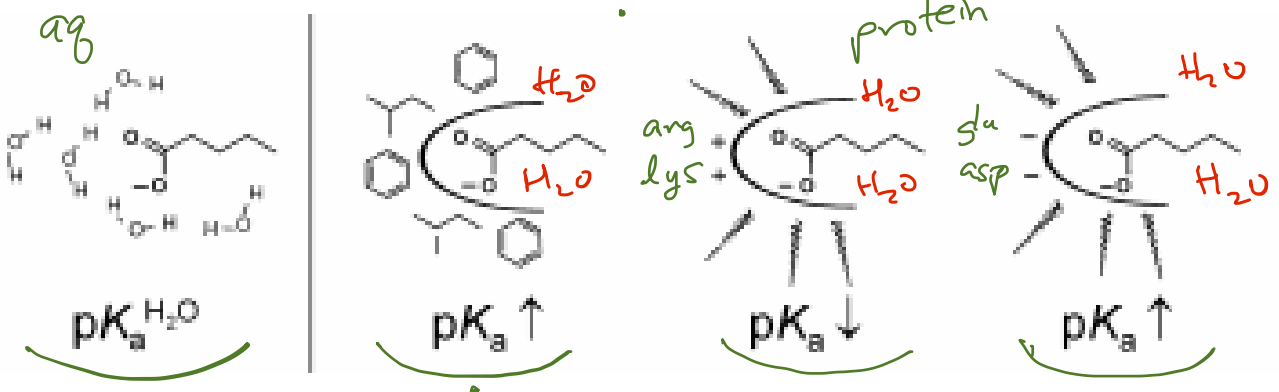
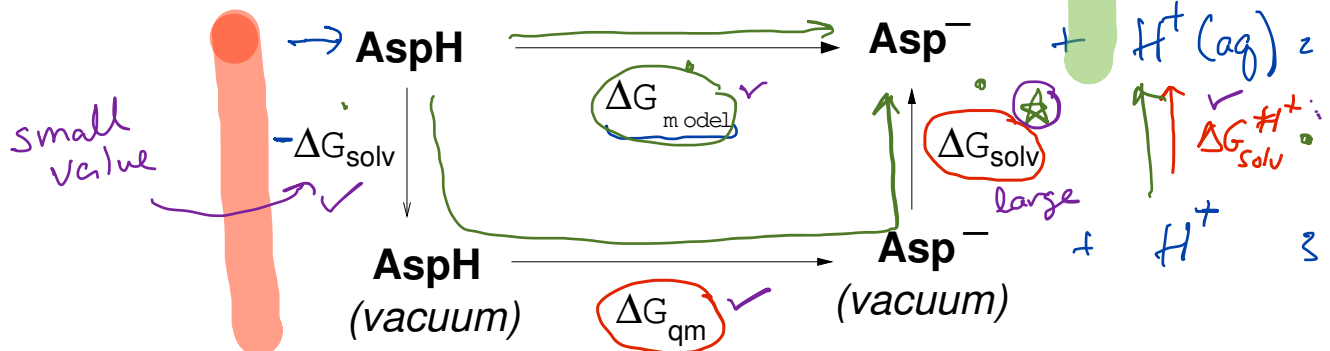
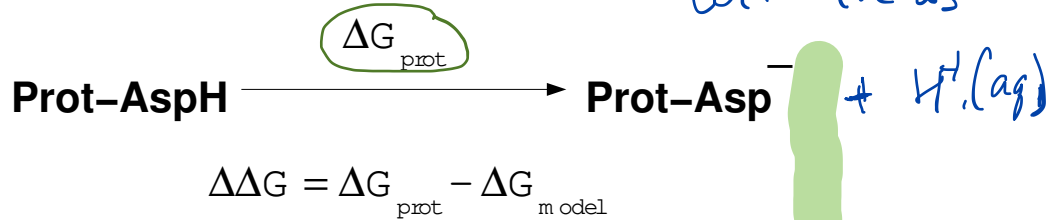
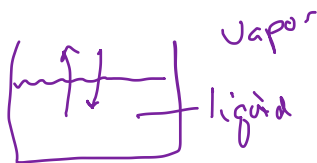
activation energy

$$V_A(q^*) = \frac{1}{2}k(q^* - q_A)^2 = \frac{1}{2}k \frac{\lambda^2(1 + \Delta E/\lambda)^2}{(2\lambda k)} = \frac{\lambda}{4} \left(1 + \frac{\Delta E}{\lambda}\right)^2 \quad (12)$$

Note that terms in  $k$  cancel.

useful observations come not just with single system, but with trends

## 3 Application: pKa behavior in proteins



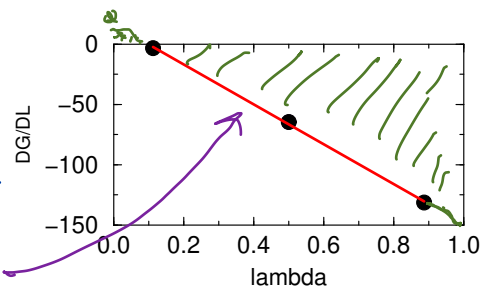
To apply any of these models, we need to know the average energy gap at different  $\lambda$  values, and it also helps to know its distribution.

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

neut
anion

$$\int_0^1 \left\langle \frac{\partial V}{\partial \lambda} \right\rangle_\lambda d\lambda \cong \Delta G$$

$\left\langle \frac{dV}{d\lambda} \right\rangle_\lambda$   
electrostatic change



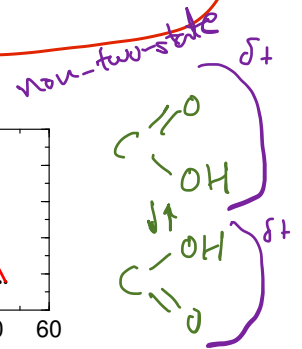
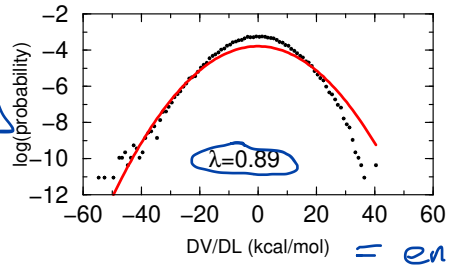
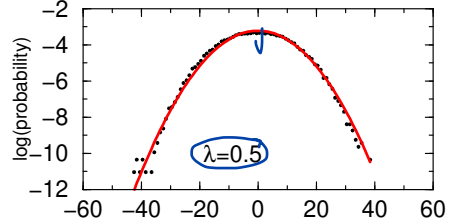
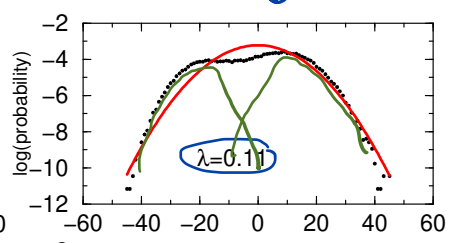
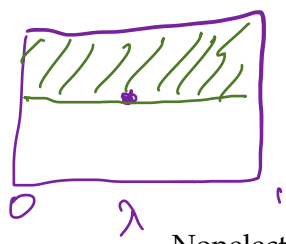
Lambda	DG/DL (kcal/mol)
0.11270	-3.1
0.50000	-64.5
0.88729	-131.4

thioredoxin  
Asp 26

$$\langle \Delta V \rangle_{1/2} \cong \Delta G$$

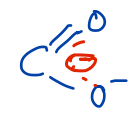
single-point quadrature almost enough

$\ln[p(\Delta V)]$



very close to 2-state system

neg state

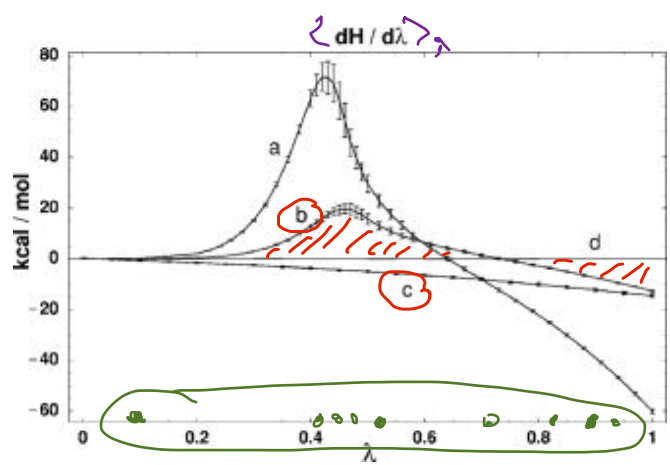


= energy gap

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

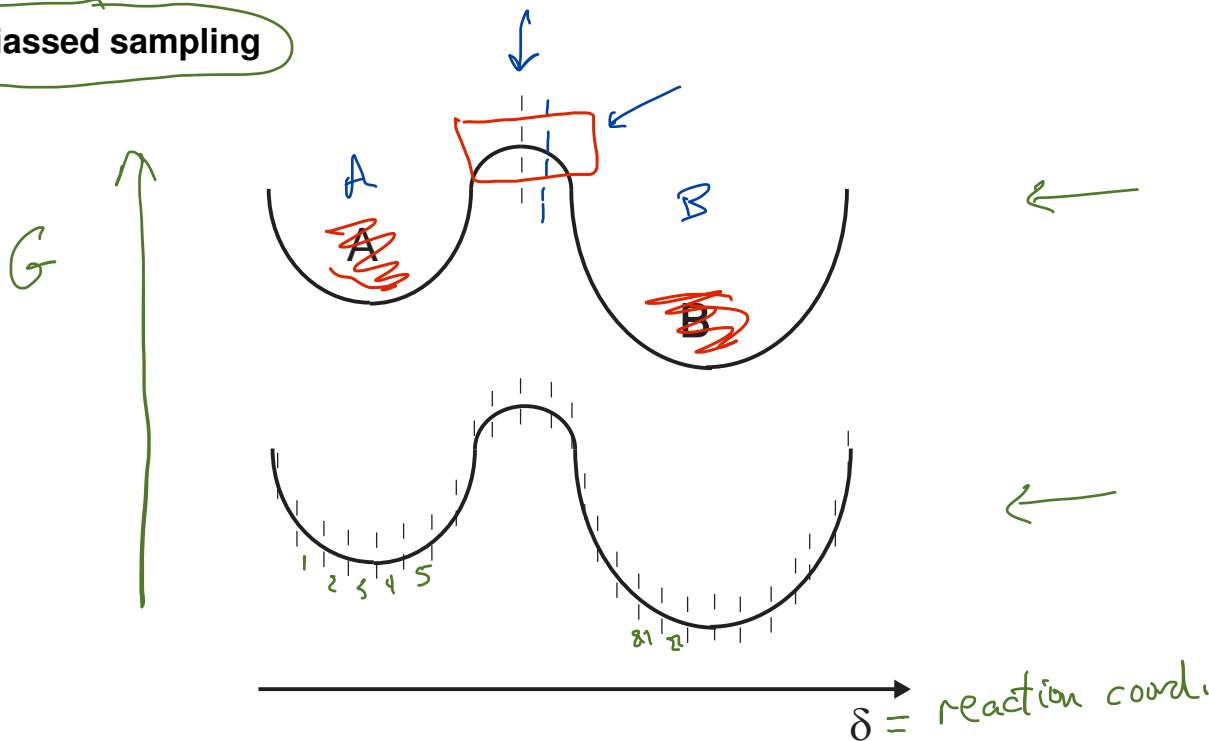
Nonelectrostatic contributions are generally much more complex:

- electrostatics - linear
- shape change - more complex



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

# 4 Biassed sampling



$$\frac{\rho_B}{\rho_A} = K_{eq} = \exp(-\Delta A/kT) \quad (13)$$

To create a potential of mean force:  
 $W$

$$\rho_i = \frac{\exp(-W(\delta_i)/kT)}{\int \exp(-W(\delta)/kT) d\delta} \quad (14)$$

definition of  $w(\delta)$

## 4.1 Reduced distribution functions:

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

$$dx_{\sim} = d\delta d\Sigma$$

$$\rho(\delta) = \frac{\int \exp(-\beta V) d\Sigma}{\int \exp(-\beta V) d\delta d\Sigma} \quad (15)$$

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

\* = with the biassing potential

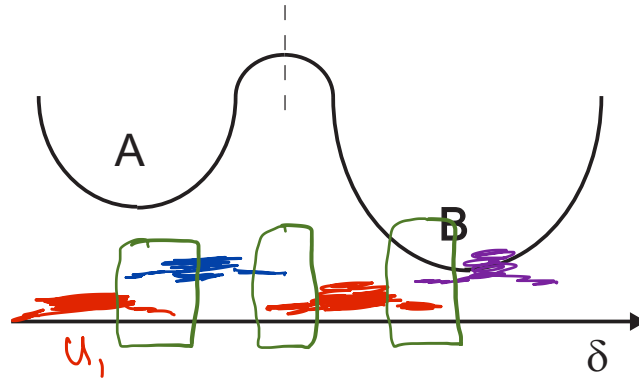
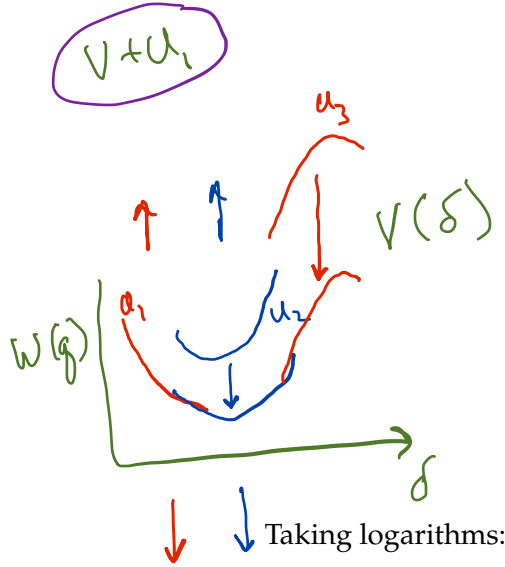
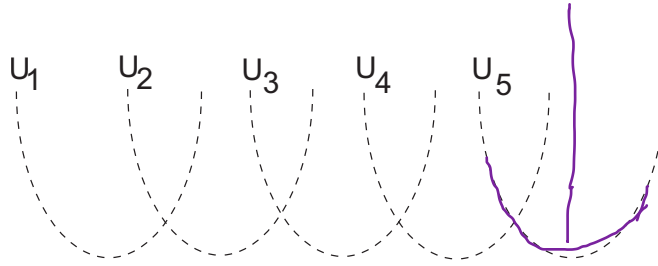
$$\begin{aligned} \rho^*(\delta) &= \frac{e^{-\beta U(\delta)} \int \exp(-\beta V) d\Sigma}{\int \exp(-\beta(U+V)) d\delta d\Sigma} \\ &= \frac{e^{-\beta U(\delta)} \int \exp(-\beta V) d\Sigma}{\int \exp(-\beta(V)) d\delta d\Sigma} \frac{\int \exp(-\beta V) d\delta d\Sigma}{\int \exp(-\beta U) \exp(-\beta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

reciprocal

constant, independent of  $\delta$   
 get this independtly

$$\langle e^{-\beta U} \rangle = \frac{\int e^{-\beta U} e^{-\beta V} d\delta d\Sigma}{\int e^{-\beta V} d\delta d\Sigma}$$

## 4.2 Umbrella sampling

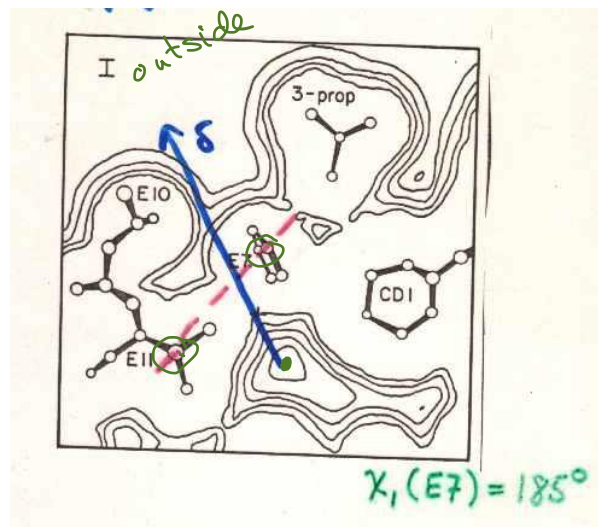
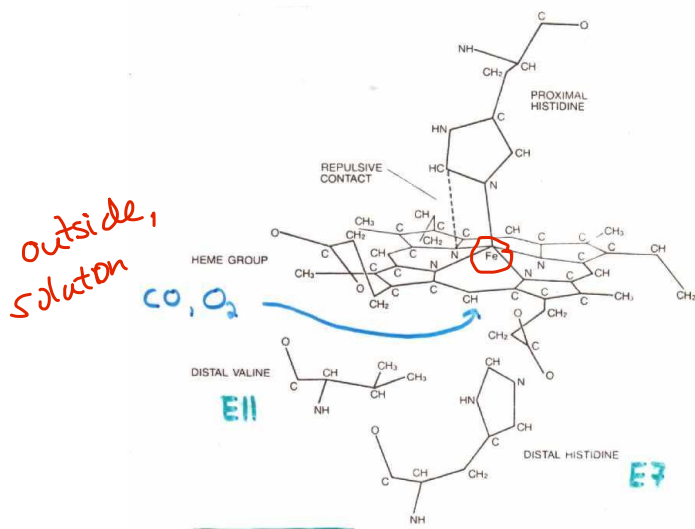


$$W^*(\delta) = W(\delta) + U(\delta) + kT \ln \langle e^{-\beta U} \rangle$$

determined by analyzing the overlap regions (16)

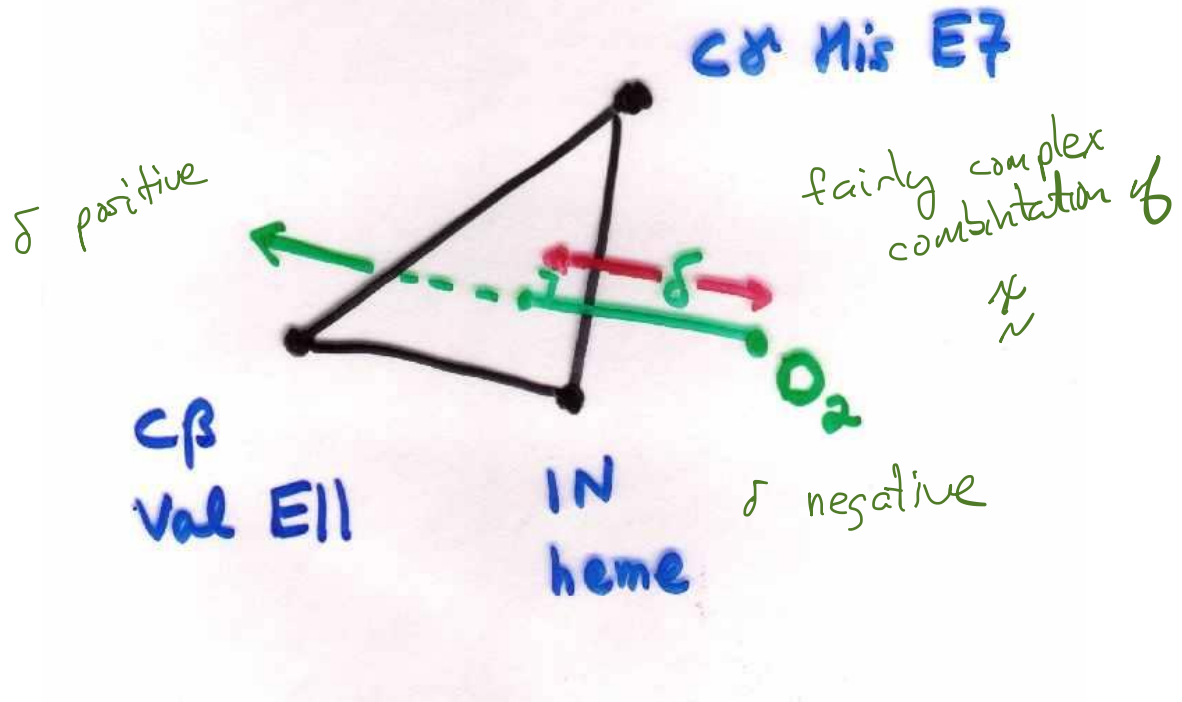
Note that the final term is independent of  $\delta$ . These can be treated as adjustable parameters, determined so that the  $W(\delta)$  values from adjacent windows agree in their overlap region. See *J. Comput. Chem.* 16, 1339 (1995).

## 4.3 Example: oxygen binding to myoglobin



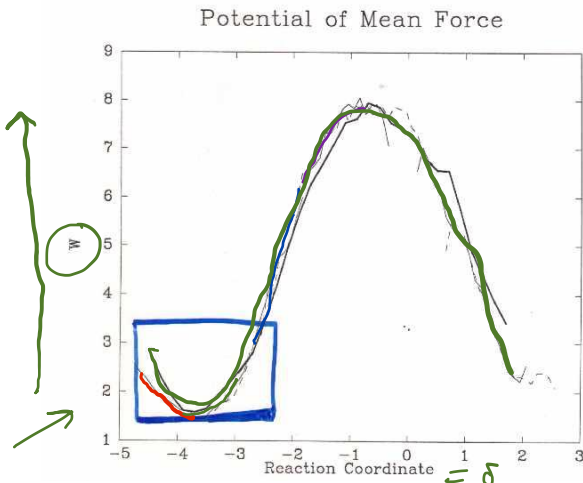
plane perpendicular to heme group

One possible reaction coordinate



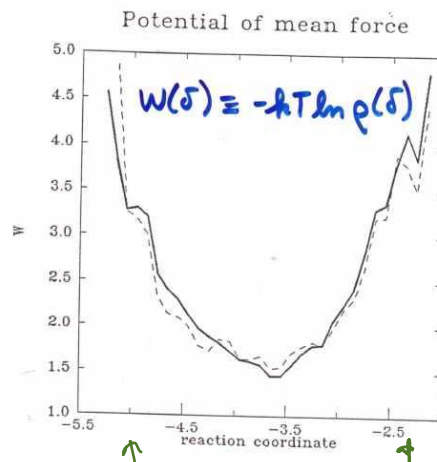
Kottalam & Case, JACS 110, 7690 (1988) ←

Computing a pmf



inside

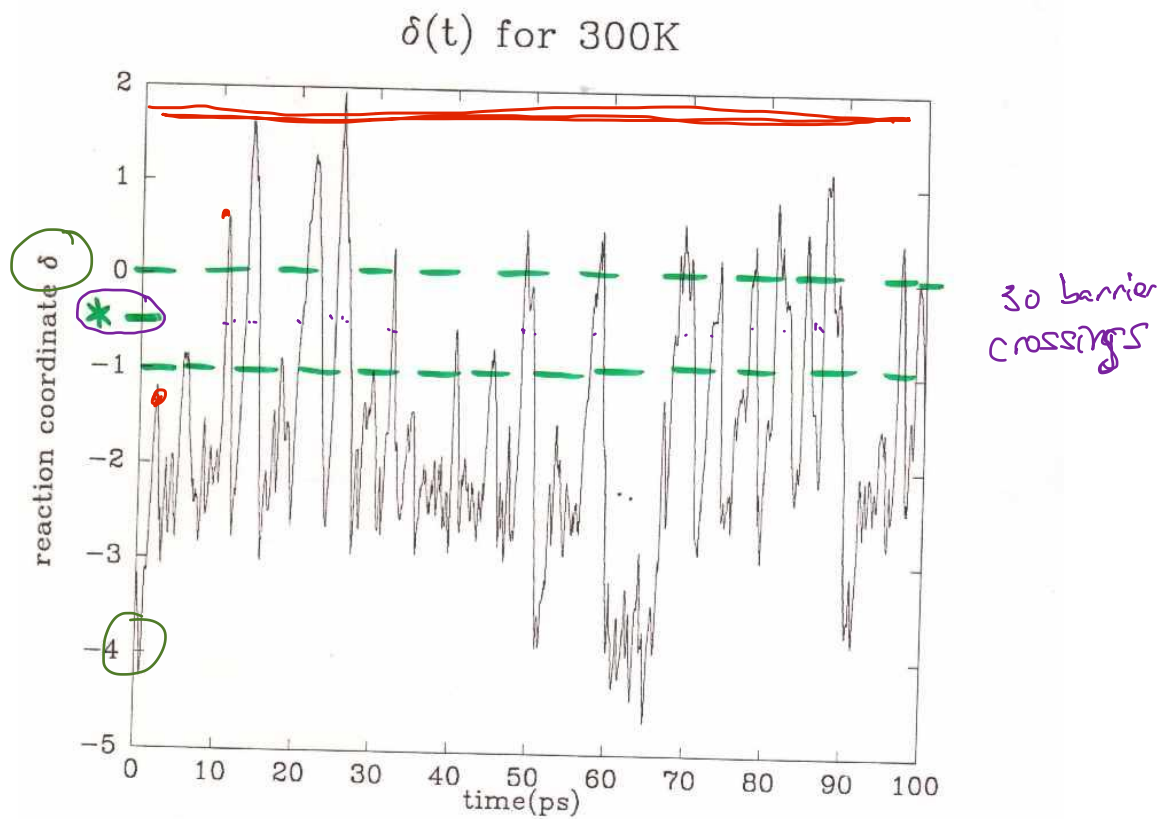
outside



step 2 : we took  $\times$  Green curve at a new umbrella  $U_{new}(\delta)$   
 expect  $U_{new}(\delta) + V(\delta)$  should be flat

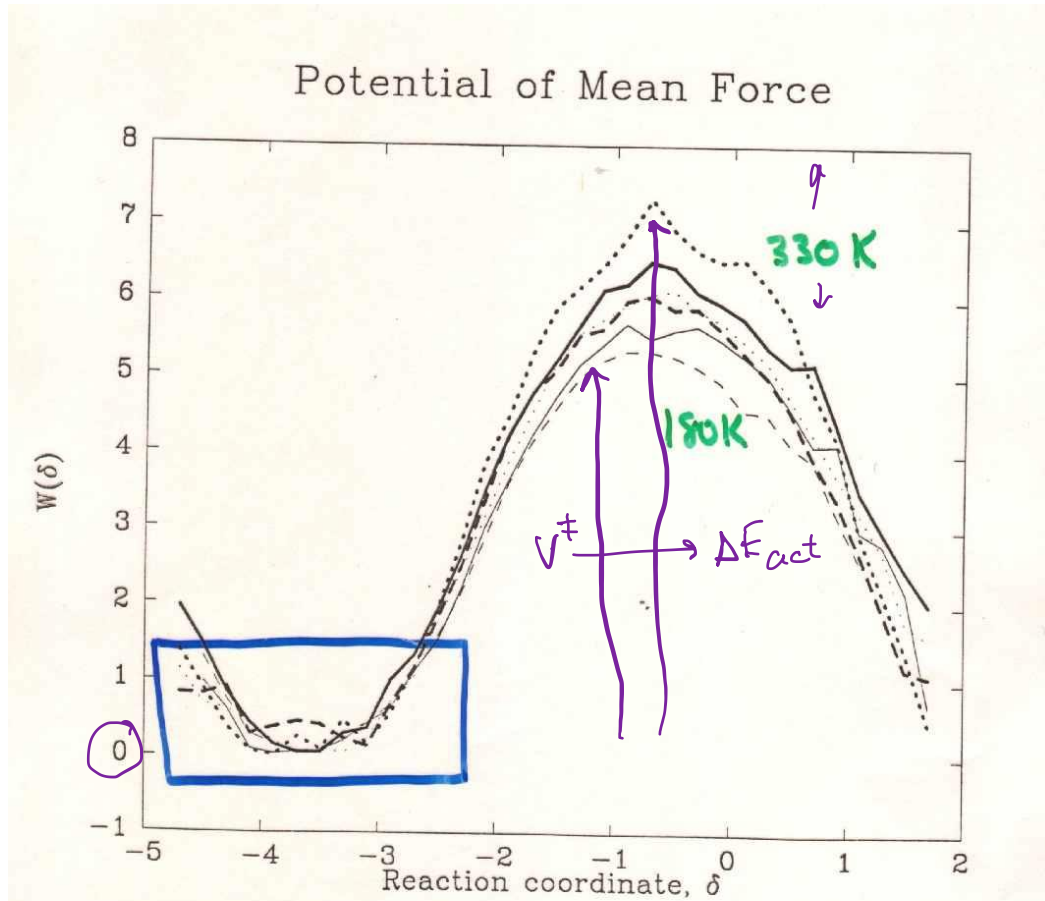


Now try to flatten the potential





Look at different temperatures



leads non-Arrhenius temperature dependence of rate constant

### 5 Free energy perturbation theory

Here is an (initially) completely different approach: to free energies from simulation

$$E \leftrightarrow V$$

$$\Delta A = -kT \ln \left( \frac{Q_1}{Q_0} \right) \tag{17}$$

$$= -kT \ln \left( \frac{\int \exp(-\beta E_1) \exp(\beta E_0) \exp(-\beta E_0) dq}{\int \exp(-\beta E_0) dq} \right) \tag{18}$$

$$= -kT \ln \left( \frac{1}{Q_0} \int \exp(-\beta[E_1 - E_0]) \exp(-\beta E_0) dq \right) \tag{19}$$

$$= -kT \ln \langle \exp(-[E_1 - E_0]/kT) \rangle_0 \tag{20}$$

$$= kT \ln \langle \exp(-[E_0 - E_1]/kT) \rangle_1 \tag{21}$$

exercise derive:

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

TI

FEP

$\langle \Delta V \rangle$   
(don't numerically try to average  $e^{-\beta \Delta V}$ )

$\langle e^{-\beta \Delta V} \rangle$   
converges slowly with simulation time

$\exp(-\Delta V/kT)$

