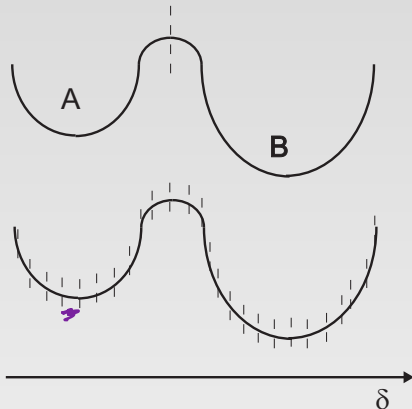


Molecular simulations of biomolecules  
Remote Lecture #7  
free energies, take 2

CCB 550, Spring 2020

- Updated due date is May 7, submit as a PDF file via email.
- Greatest effort should be on parts 1,2,3 and 5 of the instructions; don't neglect item 4, but don't let it take over the project either; you should limit both the CPU time *and* limit the personal time you spend on this.
- I will certainly (try to) help as I'm able if you hit snags in the computations.
- You can use programs other than Amber or Gaussian.

# Biassed, or umbrella, sampling



$$\frac{\rho_B}{\rho_A} = K_{eq} = \exp(-\Delta A/kT) \quad (1)$$

To create a *potential of mean force*:

$$\rho_i = \exp(-W(\delta_i)/kT) \quad (2)$$

# Reduced distribution functions

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

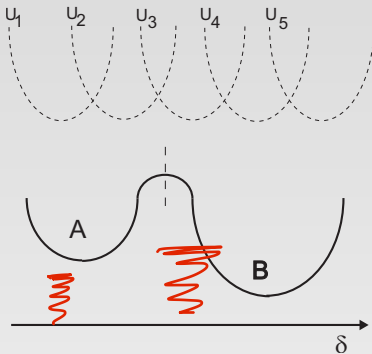
$$\rho(\delta) = \frac{\int \exp(-\beta V) d\Sigma}{\int \exp(-\beta V) d\delta d\Sigma} \quad (3)$$

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

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

→ independent of  $\delta$

# Umbrella sampling



Taking logarithms from end of last slide:

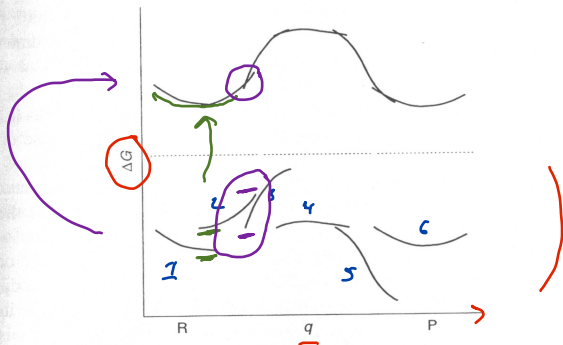
*we don't actually need this*

(12.26)

$$W^*(\delta) = W(\delta) + U(\delta) + kT \ln \langle e^{-\beta U} \rangle \quad (4)$$

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).

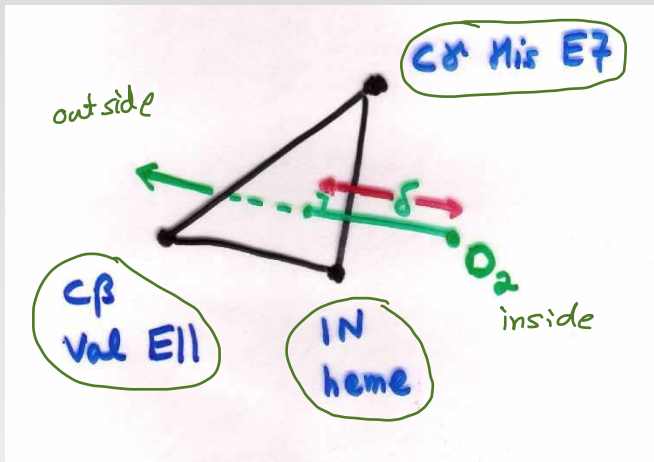
# Putting things back together



**Figure 12.5** A reaction coordinate  $q$  constructed piecewise from reactants R to products P as a series of PMFs determined using different umbrella functions. The individual PMFs determined using Eq. (12.26), shown below the dashed line and taking each left endpoint as the relative zero, are held within their respective regions of the reaction coordinate by the umbrella function. Their overlap on a common energy scale generates the complete PMF shown above the dashed line

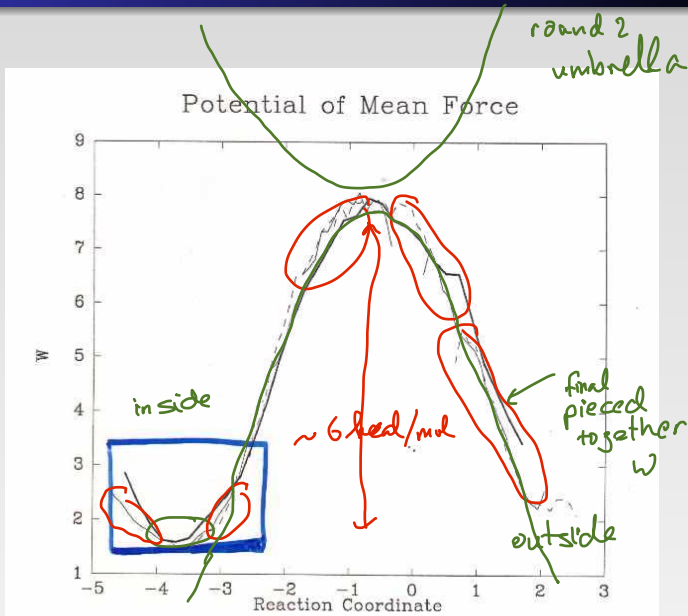


# Reaction coordinate that we used

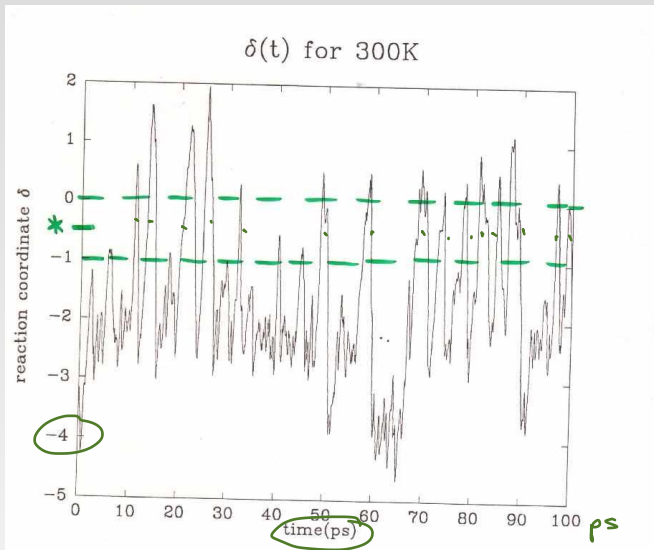




# Construction a potential of mean force



See if we have indeed flattened the potential



# Types of thermodynamic calculations

- "alchemical" changes:  $V_0 \rightarrow V_1$ , using TI or FEP
  - end states can have different chemistry or different environments; or just different force fields
- conformational free energy changes: using umbrella sampling or other enhanced sampling techniques
- "end-point" methods:  $\Delta G = G_1 - G_0$

$$G \approx \langle H_{MM} \rangle - TS_{chain} + \langle \Delta G_{solvation} \rangle + \cancel{E}$$

$\Delta H = \Delta E + \Delta(pV) \rightarrow 0$  in condensed phases

$$A = E - TS \quad NVT$$

$$G = H - TS \quad NPT$$

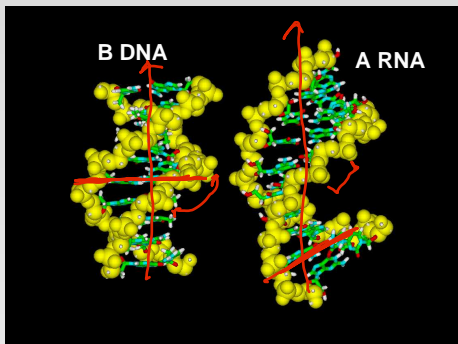
$$\Delta A \approx \Delta G$$

$\langle H_{MM} \rangle =$  average potential energy [gas-phase]

$-TS_{chain}$

$\langle \Delta G_{solvation} \rangle$  (sCRF, Cosmo)

# B-A energy differences for r,d(CCAACGTTGG)<sub>2</sub>



|              | B-A DNA      | B-A RNA     |
|--------------|--------------|-------------|
| Coulomb      | -293.3       | -266.9      |
| PB           | 286.6        | 240.2       |
| vdW          | -7.7         | 18.7        |
| bad          | -7.0         | 17.6        |
| $-T\Delta S$ | 0.5          | 3.0         |
| <b>total</b> | <b>-20.9</b> | <b>12.6</b> |
| 0.1M salt    | -15.7        | 16.0        |
| 1.0M salt    | -14.9        | 16.5        |

Srinivasan, Cheatham, Kollman, Case, JACS 120, 9401 (1998)

- ✓ Coulomb + PB electrostatic  $\langle H_{\text{int}} \rangle$  P<sub>OH</sub>-P<sub>OH</sub> reaction
- ✓ vdW  $\leftrightarrow$  LS " size of 2 OH
- ✓ bad " " sugar, phosphate

DNA B is favored ~ -2 kcal/bp  
 RNA A " " 1 kcal/bp

# Thermodynamic cycles

- See Figs. 12.3, 12.4 and 11.9, 11.10 in your text