

# Introduction to Free Energy Methods

# Why Do This?

- The free energy of a system is perhaps the most important thermodynamic quantity, and is usually taken as the Helmholtz or Gibb's free energy
- Techniques to calculate the free energy (or relative free energy) of a system are very useful studying phase transitions, critical phenomena or other transformations
- We can never calculate absolute free energies (since we don't have an appropriate reference state), however relative free energies can be found using several different computational techniques

# Calculating Free Energies

- We know from statistical mechanics that we can calculate the free energy (here the Helmholtz free energy) by evaluating integrals like

$$A = k_B T \ln \left( \iint dp^N dr^N \exp \left[ -\beta H(p^N, r^N) \right] \right)$$

where H is the Hamiltonian.

- In practice it is very difficult to evaluate such integrals using MC or MD since we do not adequately sample high energy regions

# Calculation of Free Energy *Differences*

- Although our simulation methods cannot give us absolute free energies, free energy differences are much more tractable
- Consider two states X and Y
- Since the free energy is a state function, the difference in energy between these two states is simply

$$\Delta A = -k_B T \ln \left( \frac{\iint dp^N dr^N \exp [-\beta H_Y (p^N, r^N)]}{\iint dp^N dr^N \exp [-\beta H_X (p^N, r^N)]} \right)$$

# Free Energy Differences

- If we multiply the numerator by the factor

$$\exp(\beta H_X) \exp(-\beta H_X) \equiv 1$$

we get

$$\begin{aligned}\Delta A &= -k_B T \ln \left( \frac{\iint dp^N dr^N \exp[-\beta H_Y] \exp[\beta H_X] \exp[-\beta H_X]}{\iint dp^N dr^N \exp[-\beta H_X]} \right) \\ &= -k_B T \ln \left( \frac{\iint dp^N dr^N \exp[-\beta(H_Y - H_X)] \exp[-\beta H_X]}{\iint dp^N dr^N \exp[-\beta H_X]} \right)\end{aligned}$$

# Free Energy Difference

- Since we are clever, we notice that this is nothing more than an ensemble average taken over the state  $X$

$$\Delta A = -k_B T \ln \langle \exp [-\beta(H_Y - H_X)] \rangle_X$$

- Equivalently we could write the reverse process

$$\Delta A = -k_B T \ln \langle \exp [-\beta(H_X - H_Y)] \rangle_Y$$

# Overlapping States

- In order to evaluate an ensemble average like

$$\Delta A = -k_B T \ln \langle \exp [-\beta (H_Y - H_X)] \rangle_X$$

we could run a simulation either state X or Y and collect statistics

- Problems arise however when the states X and Y do not overlap such that simulating one state does a poor job of sampling the other

# Intermediate States

- If the energy difference between the two states is large

$$|H_X - H_Y| \gg k_B T$$

we can introduce an intermediate state between X and Y

$$\begin{aligned}\Delta A &= A(Y) - A(X) \\ &= (A(Y) - A(I)) + (A(I) - A(X)) \\ &= -k_B T \ln \left[ \frac{Q(Y)}{Q(I)} \times \frac{Q(I)}{Q(X)} \right]\end{aligned}$$

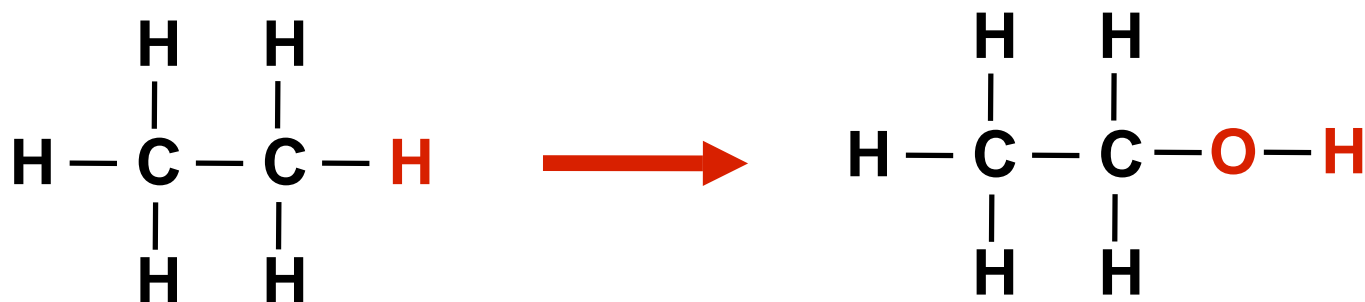
# Intermediate States

- We can obviously extend this treatment to include multiple intermediate states with increasing overlap

$$\begin{aligned}\Delta A &= A(Y) - A(X) \\ &= (A(Y) - A(N)) + (A(N) - A(N-1)) + \dots \\ &+ (A(2) - A(1)) + (A(1) - A(X)) \\ &= -k_B T \ln \left[ \frac{Q(Y)}{Q(N)} \times \frac{Q(N)}{Q(N-1)} \dots \frac{Q(2)}{Q(1)} \times \frac{Q(1)}{Q(X)} \right]\end{aligned}$$

# Intermediate States

- One key to this method is that intermediate states do not need to correspond to actual physical states (consider changing ethane to ethanol)



- Using molecular mechanics we can smoothly interpolate between these two states

# Implementation

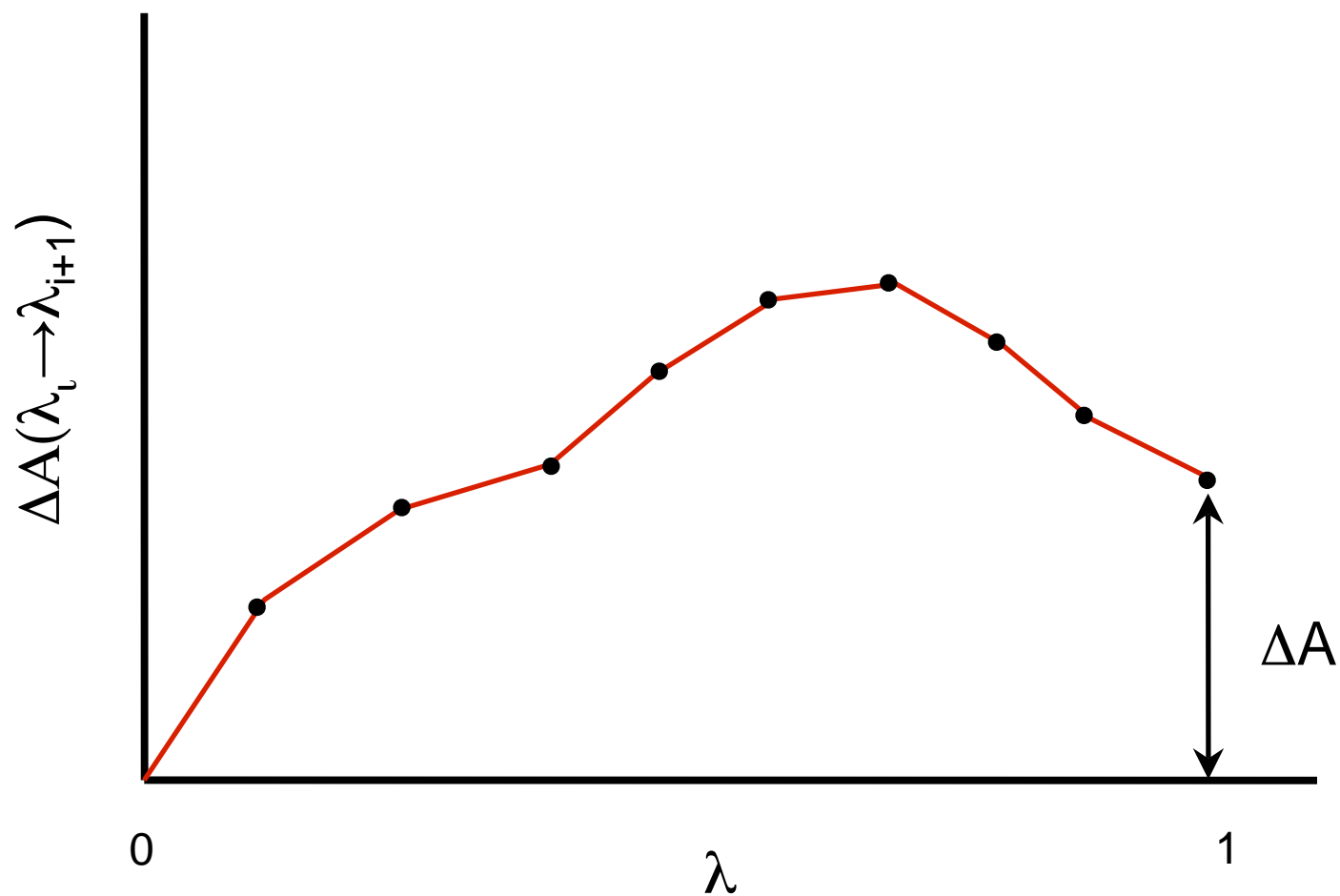
- If we have an empirical force field (like we do in molecular mechanics) we can write all of the force field terms as a linear combination of the values for X and Y
  - Bonds:  $k(\lambda) = \lambda k(Y) + (1-\lambda)k(X)$   
 $l_o(\lambda) = \lambda l_o(Y) + (1-\lambda)l_o(X)$
  - Angles:  $k_\theta(\lambda) = \lambda k_\theta(Y) + (1-\lambda)k_\theta(X)$   
 $\theta_o(\lambda) = \lambda \theta_o(Y) + (1-\lambda)\theta_o(X)$
  - Charges:  $q(\lambda) = \lambda q(Y) + (1-\lambda)q(X)$
  - VDW:  $\varepsilon(\lambda) = \lambda \varepsilon(Y) + (1-\lambda)\varepsilon(X)$   
 $\sigma(\lambda) = \lambda \sigma(Y) + (1-\lambda)\sigma(X)$
  - etc.

# Coupling Parameter

- As we change the coupling parameter  $\lambda$  from 0 to 1, we move from state X to Y
- At each intermediate step  $\lambda_i$  we perform a simulation (Monte Carlo or MD) by first performing a short equilibration run (since our point of equilibrium has changed) and then a “production” run where we calculate

$$\Delta A(\lambda_i \rightarrow \lambda_{i+1}) = k_B T \ln \langle \exp(-\beta \Delta H_i) \rangle$$

# Free Energy Perturbation



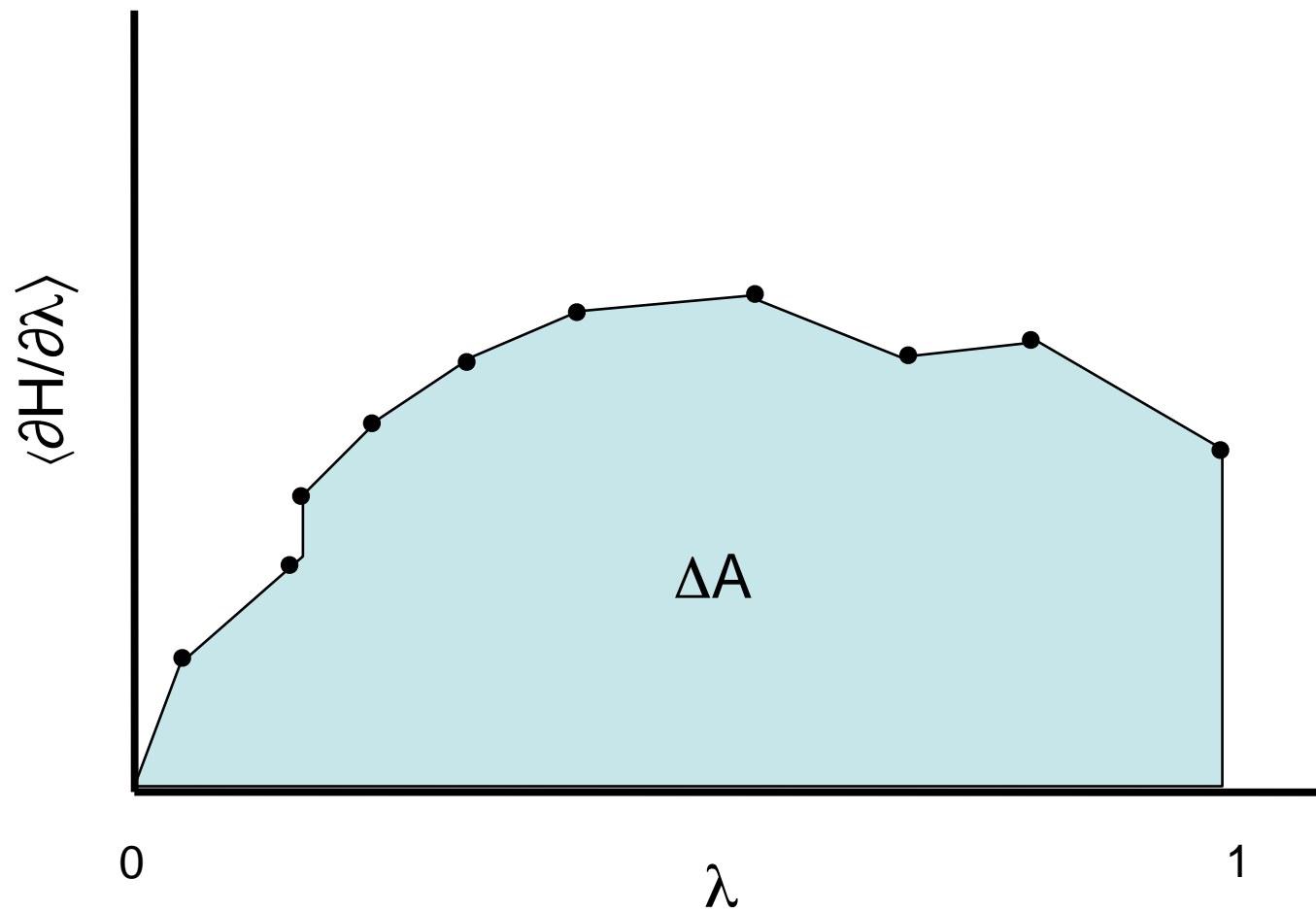
# Thermodynamic Integration

- Instead of evaluating the difference in the free energy between subsequent states, we could also calculate the derivative of the Hamiltonian

$$\Delta A = \int_{\lambda=0}^{\lambda=1} \left\langle \frac{\partial H}{\partial \lambda} \right\rangle_{\lambda} d\lambda$$

- In this case, the free energy difference is the area under the curve

# Thermodynamic Intergration



# Slow Growth Method

- If the changes in the system are gradually made such that the Hamiltonian is nearly constant, we can expand the exponential and ln terms to get

$$\begin{aligned}\Delta A &= -k_B T \sum \ln \langle \exp(-\beta [H(\lambda_{i+1}) - H(\lambda_i)]) \rangle \\ &\simeq -k_B T \sum \ln \langle 1 - \beta [H(\lambda_{i+1}) - H(\lambda_i)] \rangle \\ &\simeq \sum [H(\lambda_{i+1}) - H(\lambda_i)]\end{aligned}$$

# More Reading

- Many references and papers that cover these topics. In the texts for this class consider:
  - Leach Chapter 11 (watch for errors!!)
  - Frenkel & Smit Chapter 7

# Umbrella Sampling and Histogram Methods

# The Sampling Problem

- By now you realize that the major problem in simulations is that of sampling
- We have an exact method of computing a partition function and associated thermodynamic quantities, however this is dependent on us accurately sampling the entire conformational space
- In general (i.e. the way most people run simulations) MD simulations *do not* do an adequate jobs of sampling configurational space unless run for a very, very long time

# Let's Force the System to Sample

- The basic idea behind *Umbrella Sampling* is that we can bias or force the system to sample a particular region(s) (based on some reaction coordinate)
- If we were interested in the free energy difference between two systems  $X$  and  $Y$ , we should sample the conformational space associated with both conformations

# Free Energy Perturbation

- Recall from our discussion of FEP that the free energy difference between two systems can be expressed as

$$\Delta U = -k_B T \ln \left( \frac{\iint dr^N \exp[-\beta U_Y]}{\iint dr^N \exp[-\beta U_x]} \right)$$

or equivalently

$$\langle \exp(-\beta \Delta U) \rangle_X = \frac{\iint dr^N \exp[-\beta U_Y]}{\iint dr^N \exp[-\beta U_x]}$$

# A New Weight Function

- In order to sample both  $X$  and  $Y$  spaces, we now introduce a new weight function  $\pi(r^N)$  to replace the Boltzmann factor

$$\langle \exp(-\beta \Delta U) \rangle_X = \frac{\iint dr^N \pi(r^N) \exp[-\beta U_Y] / \pi(r^N)}{\iint dr^N \pi(r^N) \exp[-\beta U_x] / \pi(r^N)}$$

which using our shorthand notation becomes

$$\langle \exp(-\beta \Delta U) \rangle_X = \frac{\langle \exp(-\beta U_Y) / \pi(r^N) \rangle_\pi}{\langle \exp(-\beta U_X) / \pi(r^N) \rangle_\pi}$$

# Umbrella Sampling Considerations

- In order that both the numerator and denominator are non-zero, the weight function  $\pi(r^N)$  should have considerable overlap between the spaces of  $X$  and  $Y$
- This property gives rise to the name *Umbrella Sampling*
- Although it appears we could sample the entire space with a single choice of  $\pi(r^N)$ , this is not optimal. It is still best to perform several sampling runs using overlapping windows

# Choosing a Weight Function

- In order for Umbrella Sampling to work well we need to make a good choice for  $\pi(r^N)$  – it is not known *a priori*
- A common choice is to make the biasing potential quadratic

$$\begin{aligned}U'(r^N) &= U(r^N) + W(r^N) \\ &= U(r^N) + k_w(r^N - r_o^N)^2\end{aligned}$$

so that the biasing potential is simply

$$\pi(r^N) = \exp[-\beta U'(r^N)]$$

# Weighted Histogram Analysis Method (WHAM)

- Umbrella Sampling is valid in theory, but the implementation is often difficult since the “windows” of overlap must be carefully chosen to minimize the error (since the errors from the individual simulations add quadratically)
- WHAM is a useful method for combining sets of simulations with different biasing potentials in a manner such that the unbiased potential of mean force (PMF) can be found

# A More General Approach

- Instead of a single biasing potential we now consider a group of related models

$$U_i = U_o + W_i (i = 1 \cdots n)$$

where  $U_o$  is the unperturbed potential of the system

- If we consider the case where a specific reaction coordinate or order parameter  $Q(r^N)$  we know that the probability histogram associated with this state is

$$p_i(Q) = \frac{\int dr^N \exp [-\beta(U_o + W_i)] \delta(Q - Q(r^N))}{Z_i}$$

# A More General Approach

- In this case, the  $i^{\text{th}}$  partition function is

$$Z_i = \int dr^N \exp [-\beta(U_o + W_i)]$$

- What we are really interested in is the unperturbed system following this same reaction coordinate

$$p_o(Q) = \frac{\int dr^N \exp [-\beta(U_o)] \delta(Q - Q(r^N))}{Z_o}$$

# Calculating the Histograms

- In order for us to measure  $p_i(Q)$ , we can perform a simulation and keep track of the number of times  $H_i$  that a system with potential energy  $U_o + W_i$  has a value of the order parameter between  $Q$  and  $Q+\Delta Q$
- If we sample  $M_i$  points for each histogram,  $p_i(Q)$  is given by

$$p_i(Q)\Delta Q = \langle H_i(Q) \rangle / M_i$$

# Assessing Errors

- Since we are running finite simulations, the values we measure will fluctuate
- Under the assumption of Poisson statistics we find that the variance of our measurement is

$$\begin{aligned} \frac{\langle H_i^2(Q) \rangle - \langle H_i(Q) \rangle^2}{M_i^2} &= \frac{\langle H_i(Q) \rangle}{M_i^2} \\ &= \frac{p_i(Q) \Delta Q}{M_i} \end{aligned}$$

- We will use this measure as our estimate of  $p_i(Q)$

# Reconstructing the Unbiased Estimate

- Based on our previous results we see that we could in fact reconstruct  $p_o(Q)$  from a single histogram

$$p_o(Q) = \exp(+\beta W_i) \frac{Z_i}{Z_o} p_i(Q)$$

but this rarely works since the regions of  $Q$  that contribute to  $p_i$  likely to do not contribute to  $p_o$  and vice versa

# Weighting Histograms

- Instead of relying on a single measurement, we will construct our estimate of  $p_o$  using a linear combination of all estimates of the histograms

$$p_o^{est}(Q) = \sum w_i(Q) \exp(+\beta W_i) \frac{Z_i}{Z_o} p_i^{est}(Q)$$

where the weight functions  $w_i(Q)$  are not yet determined, but are subject to normalization

$$\sum w_i(Q) = 1$$

# Choosing the Weights

- We want to choose the weights  $w_i$  such that the variance in  $p_o^{est}$  is minimized

$$\begin{aligned} & \langle p_o^{est}(Q)^2 \rangle - \langle p_o^{est}(Q) \rangle^2 \\ &= \sum w_i^2(Q) \exp(+2\beta W_i) \left( \frac{Z_i}{Z_o} \right)^2 (\langle p_i^{est}(Q)^2 \rangle - \langle p_i^{est}(Q) \rangle^2) \\ &= \sum w_i^2(Q) \exp(+2\beta W_i) \left( \frac{Z_i}{Z_o} \right)^2 \frac{p_i(Q)}{M_i} \\ &= p_o(Q) \sum w_i(Q) \exp(+\beta W_i) \frac{Z_i}{Z_o} \frac{1}{M_i} \end{aligned}$$

# Choosing the Weights

- To minimize this expression we differentiate and find the condition

$$w_i(Q) = \alpha \exp(-\beta W_i) M_i \frac{Z_o}{Z_i}$$

where  $\alpha$  is the normalization condition

$$\alpha = \frac{1}{\sum \exp(-\beta W_i) M_i \frac{Z_o}{Z_i}}$$

# Putting it Together

- If we insert these weights back in to our equations we get

$$p_o^{est} = \frac{\sum H_i(Q)}{\sum \exp[-\beta W_i] M_i \frac{Z_o}{Z_i}}$$

- This is now a nice expression, but we still must determine  $Z_i$

# Partition-like Functions

- Recall we had

$$Z_i = \int dr^N \exp [-\beta(U_o + W_i)]$$

- Using expression we had previously we get

$$\begin{aligned} Z_i &= \int dQ Z_o p_o(Q) \exp [-\beta W_i] \\ &= \int dQ \exp [-\beta W_i] \frac{\sum H_j(Q)}{\sum \exp [-\beta W_k] M_k / Z_k} \end{aligned}$$

- This is an implicit equation that must be solved iteratively

# Finally ... a Free Energy

- We in fact cannot solve the previous equation for  $Z_i$ , but only for the ratio of  $Z_i$ 's
- Usually one of the values is fixed as a constant (say  $Z_1$ ) and the rest are solved for self-consistently
- For free energies, however, we typically don't care since the free energy between the start and end states is simply

$$\Delta A = -k_B T \ln (Z_n / Z_1)$$

# Examples and Further Reading

- Leach has some details on Umbrella Sampling in Ch. 11
- Frenkel & Smit discusses Umbrella Sampling and WHAM (disguised as the self-consistent histogram method) in Ch. 7
- There are many papers using these methods. (See Ron Levy paper that uses both techniques)