Motivation

Lots of interesting properties require knowledge of free energies:

- Phase diagrams/coexistence.
- Drug binding affinities.
- Rates of reactions.
- Equilibrium constants.
- Solvation properties.
- Acid-base equilibria.
- Isotope effects.





Recap

Partition function in classical mechanics,

$$Q = h^{-3N} \int d\mathbf{p} \int d\mathbf{r} e^{-\beta H(\mathbf{r},\mathbf{p})} = h^{-3N} \int d\mathbf{p} \ e^{-\beta \sum_{j} \frac{p_{j}^{2}}{2m_{j}}} \int d\mathbf{r} \ e^{-\beta V(\mathbf{r})}$$

$$\beta = 1/k_{B}T$$

Position and momentum integrals are separable,
Momentum part Position part

$$Q = \int d\mathbf{p} \ e^{-\beta \sum_{j} \frac{p_{j}^{2}}{2m_{j}}} \int d\mathbf{r} \ e^{-\beta V(\mathbf{r})} = \left(2\pi m/\beta h^{2}\right)^{3N/2} \int d\mathbf{r} \ e^{-\beta V(\mathbf{r})}$$

Yielding the configuration integral, $Z = \int d\mathbf{r} \ e^{-\beta V(\mathbf{r})}$ Today we will primarily deal this

with this.

Observables obtained performing trajectories which sample points in the ensemble and averaging the observables over them (assuming ergodic hypothesis),

$$< O >= \frac{\int d\mathbf{r} \int d\mathbf{p} \ O(\mathbf{r}, \mathbf{p}) e^{-\beta H(\mathbf{r}, \mathbf{p})}}{\int d\mathbf{r} \int d\mathbf{p} \ e^{-\beta H(\mathbf{r}, \mathbf{p})}} \implies < O >= \frac{\int d\mathbf{r} \ O(\mathbf{r}) e^{-\beta V(\mathbf{r})}}{\int d\mathbf{r} \ e^{-\beta V(\mathbf{r})}}$$

Expectation value of observable O If observable depends only on position.

Simulations

Basic simulation scheme



How to obtain free energy?

$$A = -k_B T \ln Q \qquad Q = h^{-3N} \int d\mathbf{p} \int d\mathbf{r} e^{-\beta H(\mathbf{r},\mathbf{p})}$$

For simplicity everything will be presented in terms of Helmholtz energy A (i.e. working in the NVT ensemble) but extension to Gibbs (NPT) is straightforward.

- Not good news: to get an absolute free energy of a system we need to know the entire partition function i.e. to count all the states for a given N,V,T!
- → In practice calculating the partition function is impossible for a system of more than a few degree of freedom (with the exception of special cases).

• However, calculating <u>differences</u> in free energies is possible. $Z = \int d{f r} \ e^{-\beta V({f r})}$

$$\Delta A = A_1 - A_0 = -k_B T \ln\left(\frac{Q_1}{Q_0}\right) = -k_B T \ln\left(\frac{Z_1}{Z_0}\right)$$

$$\Delta A = -k_B T \ln\left(\frac{Z_1}{Z_0}\right) \qquad Z_0 = \int d\mathbf{r} \ e^{-\beta V_0(\mathbf{r})} \quad Z_1 = \int d\mathbf{r} \ e^{-\beta V_1(\mathbf{r})}$$

• The above expression is not in a nice form to extract from a simulation.

$$\Delta A = -k_B T \ln\left(\frac{Z_1}{Z_0}\right)$$

$$= -k_B T \ln \left\langle e^{-\beta (V_1(\mathbf{r}) - V_0(\mathbf{r}))} \right\rangle_0$$

What does this translate to?

- Do a simulation of system 0.
- During the simulation accumulate the average: $e^{-eta(V_1(\mathbf{r})-V_0(\mathbf{r}))}$
- At the end take the natural logarithm of the observable and multiply by $-k_BT$ and you obtain the free energy difference between system 1 and 2.

Example:

I want to develop a new drug that binds into an active site more strongly than my current drug.

Can I do this by replacing a Hydrogen by a Methyl Group?

→ Potential V_0 is force field with H and V_1 is that with Me. Hence can use FEP to calculate the <u>difference</u> in free energy of binding.





Unfortunately FEP is not perfect



• Consider in 1D two systems with different potentials:





Massive jumps in expectation value correspond to the rare events of entering a region where

potential V_2 - V_1 is small giving rise to a massive contribution to $e^{-\beta(V_1(\mathbf{r}) - V_0(\mathbf{r}))}$



FEP fails when the difference potential $V_1(\mathbf{r}) - V_0(\mathbf{r})$ shows a large <u>standard deviation</u> compared to β .

Simulation time/ MC steps

How to avoid this problem?

• Good news: free energies are <u>state functions</u>.

i.e. they only depend on the current state of the system and not how the system acquired that state.

• This allows us to take <u>any</u> path between the two states we are interested in whether or not the intermediates represent anything "real".



Hence we can break the journey from transforming from potential V_0 to V_2 by splitting it into M sections:

$$V_0 \longrightarrow V_1$$
 Here M=5
 $V_{0.2} \quad V_{0.4} \quad V_{0.6} \quad V_{0.8}$

We can then calculate the free energy change for each section and add them together to generate the total free energy change on going from 1 to 2:

$$\Delta A_{0\to 1} = \Delta A_{0\to 0.2} + \Delta A_{0.2\to 0.4} + \Delta A_{0.4\to 0.6} + \Delta A_{0.6\to 0.8} + \Delta A_{0.8\to 1}$$

$$\Delta A_{0\to 0.2} = -k_B T \ln \left\langle e^{-\beta(V_{0.2}(\mathbf{r}) - V_0(\mathbf{r}))} \right\rangle_0 \qquad \Delta A_{0.4\to 0.6} = -k_B T \ln \left\langle e^{-\beta(V_{0.6}(\mathbf{r}) - V_{0.4}(\mathbf{r}))} \right\rangle_0.$$

Free energy from statistical mechanics

General expression for making M steps between start and end-point

$$\Delta A_{0\to 1} = -k_B T \sum_{i=1}^{M} \ln \left\langle e^{-\beta (V_{i/M}(\mathbf{r}) - V_{(i-1)/M}(\mathbf{r}))} \right\rangle_{(i-1)/M}$$

How does one pick intermediate potentials ($V_{0,2}$, $V_{0,4}$ etc.)?

- In principles could pick anything.
- However, if intermediates are widely spaced or take a long path between the two end potentials then evaluation will be inefficient.
- Hence a wise choice might be a linear interpolation between V_0 and V_1 .



Thermodynamic Integration

Another approach is to use thermodynamic integration

As before we want to calculate the free energy change between two potentials V_0 and V_1 .

Define a potential:
$$V_{\lambda}(\mathbf{r}) = f(\lambda)V_0 + g(\lambda)V_1$$

Where f(λ) and g(λ) switch between the potentials V₀ and V₁ and satisfy:
f(0)=1, f(1)=0, g(0)=0 and g(1)=1

<u>Note</u>: Although $f(\lambda) = (1 - \lambda)$ and $g(\lambda) = \lambda$ are a valid choice one can pick other forms that satisfy the above constraint.

• The free energy is now a function of the phase point (N,V,T) and the parameter λ

$$A(\lambda) = -k_B T \ln Q(\lambda)$$

• Taking derivative of A w.r.t. λ yields:

$$\frac{\partial A(\lambda)}{\partial \lambda} = -\frac{k_B T}{Q} \frac{\partial Q(\lambda)}{\partial \lambda} = -\frac{k_B T}{Z} \frac{\partial Z(\lambda)}{\partial \lambda}$$

Thermodynamic Integration

What is
$$\frac{\partial Z(\lambda)}{\partial \lambda}$$
?

$$Z_{\lambda} = \int d\mathbf{r} \ e^{-\beta V_{\lambda}(\mathbf{r})}$$

$$\sum \frac{\partial Z(\lambda)}{\partial \lambda} = \int d\mathbf{r} \ \frac{\partial e^{-\beta V_{\lambda}(\mathbf{r})}}{\partial \lambda} = \int d\mathbf{r} \ \left(-\beta \frac{\partial V_{\lambda}}{\partial \lambda}\right) e^{-\beta V_{\lambda}(\mathbf{r})}$$
Combining gives

$$\beta \text{ cancels } k_{B}T$$

$$\frac{\partial A(\lambda)}{\partial \lambda} = -\frac{k_{B}T}{Z} \frac{\partial Z(\lambda)}{\partial \lambda} \stackrel{\checkmark}{=} -\frac{\int d\mathbf{r} \ \left(\frac{\partial V_{\lambda}}{\partial \lambda}\right) e^{-\beta V_{\lambda}(\mathbf{r})}}{Z}$$

$$= \frac{\int d\mathbf{r} \ \left(\frac{\partial V_{\lambda}}{\partial \lambda}\right) e^{-\beta V_{\lambda}(\mathbf{r})}}{\int d\mathbf{r} \ e^{-\beta V_{\lambda}(\mathbf{r})}} = \left\langle \frac{\partial V_{\lambda}}{\partial \lambda} \right\rangle_{\lambda}$$
Recognize this is of form:

$$\langle O \rangle = \frac{\int d\mathbf{r} \ O(\mathbf{r}) e^{-\beta V(\mathbf{r})}}{\int d\mathbf{r} \ e^{-\beta V(\mathbf{r})}}$$

$$\frac{\partial A(\lambda)}{\partial \lambda} = \left\langle \frac{\partial V_{\lambda}}{\partial \lambda} \right\rangle_{\lambda}$$
Relates change in potential with change in free energy.

Thermodynamic Integration

$$\frac{\partial A(\lambda)}{\partial \lambda} = \left\langle \frac{\partial V_{\lambda}}{\partial \lambda} \right\rangle_{\lambda} \xrightarrow{\text{Integrate}} \Delta A = \int_{0}^{1} \left\langle \frac{\partial V_{\lambda}}{\partial \lambda} \right\rangle_{\lambda} d\lambda$$

Thermodynamic integration: Kirkwood (1935)

If we choose: $V_{\lambda} = (1 - \lambda)V_0 + \lambda V_1$

$$\frac{\partial V_{\lambda}}{\partial \lambda} = V_1 - V_0 \qquad A(\lambda) = \int_0^1 \left\langle V_1 - V_0 \right\rangle_{\lambda} d\lambda$$

Implementation

- Perform a series of simulations at different values of λ to get the gradients: $\left\langle \frac{\partial V_{\lambda}}{\partial \lambda} \right\rangle$
- Perform the integral of the gradients by midpoint rule or other numerical integration schemes.

More advanced techniques (beyond this course): Adiabatic free energy dynamics

• Allow λ to evolve continuously in the simulation by including it as an additional coordinate which is dynamically, As long as this coordinate moves much slower than the system relaxes (adiabatic separation) one can obtain the free energy from one simulation.

Free energy along collective variables

- In many cases in chemistry one is interested in the probability of finding a particle at some particular point along a single coordinate of the system called a collective variable, $R(\mathbf{r})$.
- The collective variable can be defined as a general function of any of the positions in the system **r**.
- For example in transition state theory a key input is knowing the probability of reaching the top of the barrier along the "reaction coordinate".
- Although we will refer to R(**r**) as a collective variable (CV) it can also be called an order parameter or reaction coordinate.



Collective variable

Example: to calculate a transition stat theory prediction of the rate of hydrogen diffusion through ice one can compute the free energy associated with moving the H between the 6 O's defining ice's hexagonal lattice.



Probability of obtaining a given configuration: $(\mathbf{r}^*, \mathbf{p}^*)$

$$P(\mathbf{r}^*, \mathbf{p}^*) = \frac{e^{-\beta H(\mathbf{r}^*, \mathbf{p}^*)}}{\int d\mathbf{r} \int d\mathbf{p} \ e^{-\beta H(\mathbf{r}, \mathbf{p})}}$$

Consider a system where one coordinate R (which can be a complex function of all coordinates in the system i.e. $R(\mathbf{r})$) is constrained to hold a particular value R* but all other coordinates are distributed according to Boltzmann,

$$Q_R(R^*) = \int d\mathbf{r} \int d\mathbf{p} \ \delta(R^* - R(\mathbf{r})) e^{-\beta H(\mathbf{r},\mathbf{p})}$$

It follows the probability distribution along the coordinate is given by,

$$P_R(R^*) = \frac{\int d\mathbf{r} \int d\mathbf{p} \, \delta(R^* - R(\mathbf{r})) e^{-\beta H(\mathbf{r},\mathbf{p})}}{\int d\mathbf{r} \int d\mathbf{p} \, e^{-\beta H(\mathbf{r},\mathbf{p})}} Q$$

Free energy along collective variables

$$P_R(R^*) = \frac{\int d\mathbf{r} \int d\mathbf{p} \,\,\delta(R^* - R(\mathbf{r}))e^{-\beta H(\mathbf{r},\mathbf{p})}}{Q} = \frac{Q_R(R^*)}{Q} \qquad \qquad \text{Constrained} \text{ partition function.}$$

Recall,
$$A=-k_BT\ln Q\,$$
 and hence $\,A_R(R^*)=-k_BT\ln Q_R(R^*)$

$$\Rightarrow A_R(R^*) = -k_B T \ln P_R(R^*) - k_B T \ln Q$$
 Potential of mean force

In practice we are (like before) more interested in <u>differences</u> in free energy in going from one position along the coordinate R to another e.g. R_0 to R_1 .

$$\Delta A_R = A_R(R_1) - A_R(R_0) = -k_B T \ln\left(\frac{P(R_1)}{P(R_2)}\right)$$

$$\Delta A_R = -k_B T \ln\left(\frac{T(R_1)}{P(R_2)}\right)$$

Really useful equation: allows one to convert a histogram of probabilities along a particular coordinate to the free energy change associated with moving along that coordinate.

Figure: Ann. Rep. in Comput. Chem. 6, 280–296 (2010)

Example 1:

Radial distribution gives probability of being found a given distance away from a particle at the center.



Can convert probability to a free energy change as a function of particle separation.

Note: The free energy as a function of particle separation, A(R) is not the same as pair potential, V(R) <u>unless</u> only two particles are present.

Free energy along collective variables

Example 2:

Can also extend to more constrained dimensions e.g. the Ramachandran plot of alanine dipeptide shows the free energy as a function of two torsions angles of the molecule.

Red regions are low free energy, blue is high free energy.



In both this and the previous case the problem is sufficiently simple that one can run for long enough to see point in all regions of interest \rightarrow suppose there is a high barrier?

Free energy along order parameters

Methods of obtaining free energy when high barriers are present

Umbrella sampling

 Add an additional force to the potential to keep the system close to a particular value of the CV, R* e.g. a harmonic force.

$$V'(\mathbf{r}) = V(\mathbf{r}) + k(R(\mathbf{r}) - R^*)^2$$

• The biased simulation can then be converted into an unbiased probability by using techniques such as WHAM¹ or umbrella integration².

Hard constraints



- The free energy is then obtained by integrating the average force in the direction of the collective variable.
- This gives rise to the name "Potential of mean force" for ΔA_R



1.) Kumar et. al. J. Comp. Chem. 13, 1011 (1992)
 2.) Kästner and Thiel, J. Chem. Phys. 123, 144104 (2005)

Caveat: Can also get an additional term due to the Jacobian of the change into generalized coordinates (depends on form of R).

Metadynamics

A more recent approach to obtaining the free energy along an order parameter is metadynamics.

Basic idea

- Each time a position along the order parameter is visited place down a Gaussian to "fill up" the potential.
- The Gaussians placed bias against revisiting the same region over and over.
- At the end of the simulation the probability density can be obtained simply by looking at the density of the Gaussians placed at each position along the collective variable.



Note: to obtain the free energy accurately the rate at which the Gaussians are dropped must be slow compared to the rate at which the other coordinates move.

Collective variable

Video by Giovanni Bussi showing metadynamics in action:

https://www.youtube.com/watch?feature=player_embedded&v=IzEBpQ0c8TA

Phase coexistence

• Suppose we know a coexistence point of two phases.



• Can we trace the rest of the phase diagram from one coexistence point?

 \rightarrow Yes, by Gibbs-Duhem integration

• Integrate the Clapeyron equation numerically:

$$\frac{dP}{dT} = \frac{\Delta H}{T\Delta V}$$

Run NPT simulations of each phase at the current point and calculate difference in enthalpy and volume. Use that to obtain new coexistence point and repeat.



Thanks for listening.

Books:

D. Frenkel and B. Smit, Understanding molecular simulation: from algorithms to applications

M. E. Tuckerman, Statistical mechanics: theory and molecular simulation

M.P. Allen and D.J. Tildesley, Computer simulation of liquids