

Molecular simulations of biomolecules  
Remote Lecture #6  
reading and homework assignments  
more on free energies

CCB 550, Spring 2020

# Reading assignments

- Please read Chapter 3, “Simulations of Molecular Ensembles”, most of which has been covered in earlier lectures.
- Next, read Chapter 12, “Explicit models for condensed phases”, which will be covered in the next few lectures.
- To give you more time to read these chapters carefully, there will be no new homework assignment this week.
- You are encouraged to use this time period to plan for the term paper.

# Boltzmann distributions and thermodynamics

In earlier lectures we discussed the idea that all of thermodynamics can be computed from knowing the partition function  $Q$ :

$$Q = \sum_{\text{states } i} \exp(-\beta E_i) \simeq \int e^{-\beta V(\mathbf{x})} d\mathbf{x} \quad (1)$$

configuration integral

For gas-phase quantum calculations, we could adopt the RRHO (rigid rotor-harmonic oscillator) approximation, and compute  $Q$  by summing over all of the quantized energy states of the system.

But what if we have many, many atoms, or are in a liquid, and cannot write down the energies needed to compute  $Q$ ? 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.

$$\langle f(\mathbf{x}) \rangle \equiv \int f(\mathbf{x}) e^{-\beta V(\mathbf{x})} d\mathbf{x} / \int e^{-\beta V(\mathbf{x})} d\mathbf{x} \simeq (1/N) \sum_i f(\mathbf{x}_i) \quad (2)$$

This says that the **thermodynamic** average (on the left, over a Boltzmann distribution) is just the **arithmetic** average (on the right) of snapshots taken from an MD simulation.

# Thermodynamic integration

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

$$\frac{\partial A(\lambda)}{\partial \lambda} = -kT \int \frac{\partial}{\partial \lambda} e^{-\beta V(\lambda)} dq / Q = \frac{1}{Q} \int \left( \frac{\partial V}{\partial \lambda} \right) e^{-\beta V(\lambda)} dq = \left\langle \frac{\partial V}{\partial \lambda} \right\rangle_{\lambda} \quad (3)$$

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

$$\Delta A = A(1) - A(0) = \int_0^1 \left\langle \frac{\partial V}{\partial \lambda} \right\rangle_{\lambda} d\lambda \quad (4)$$

12.2.3  
in text

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.

# 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

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

do MD on mixed potential

The simplest numerical approximation to the  $\lambda$  integral is just to evaluate the integrand at the midpoint, 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  $\lambda = 1$ . Another approximate formula uses only the endpoints:

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

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.

# Running thermodynamic integration in sander

→ `mpirun -np 4 sander.MPI -ng 2 -groupfile <filename>` → number of groups always 2 for TI

Since there are 4 total cpu's in this example, each of the two groups will run in parallel with 2 cpu's each. The number of processors must be a multiple of two. The *groups* file might look like this:

2 threads  
1 ←  
2 ←

```
-O -i mdin -p prmtop.0 -c eq1.x -c mdl.o -r mdl.x -inf mdinfo  
-O -i mdin -p prmtop.1 -c eq1.x -c mdlb.o -r mdlb.x -inf mdinfo
```

fine grained

$\left\langle \frac{\partial V}{\partial \lambda} \right\rangle_n$

The input (*mdin*) and starting coordinate files must be the same for the two groups. Furthermore, the two *prmtop* files must have the same number of atoms, in the same order (since one common set of coordinates will be used for both.) The simulation will use the masses found in the first *prmtop* file; in classical statistical mechanics, the Boltzmann distribution in coordinates is independent of the masses so this should not represent any real restriction.

On output, the two restart files should be identical, and the two output files should differ only in trivial ways such as timings; there should be no differences in any energy-related quantities, except if energy decomposition is turned on (*idecomp* > 0); then only the output file of the first group contains the per residue contributions to  $\langle \partial V / \partial \lambda \rangle$ . For our example, this means that one could delete the *mdlb.o* and *mdlb.x* files, since the information they contain is also in *mdl.o* and *mdl.x*. (It is a good practice, however, to check these file identities, to make sure that nothing has gone wrong.)

run on 4 threads

Note: on Amarel, include `$SBATCH -n 4` and replace "`mpirun -np 4`" with "`srun -mpi=pmi2`"

MPI = message passing interface  
coarse-grained parallelization : after MD step,  
same for  $\partial V / \partial x$  :  $U(\lambda) = (1-\lambda)V_0 + \lambda V_1$   
exchange information

# Free energy perturbation theory

Here is an (initially) completely different approach:

$$\Delta A = -kT \ln \left( \frac{Q_1}{Q_0} \right) \quad (7)$$

$$= -kT \ln \left( \frac{\int \exp(-\beta E_1) \exp(\beta E_0) \exp(-\beta E_0) dq}{\int \exp(-\beta E_0) dq} \right) \quad (8)$$

$$\Delta A = kT \ln \left( \frac{Q_0}{Q_1} \right) = -kT \ln \left( \frac{1}{Q_0} \int \exp(-\beta [E_1 - E_0]) \exp(-\beta E_0) dq \right) \quad (9)$$

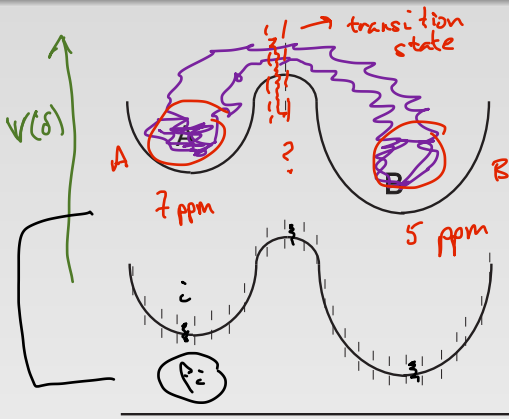
$$= -kT \ln \langle \exp(-[E_1 - E_0]/kT) \rangle_0 \quad (10)$$

$$= kT \ln \langle \exp(-[E_0 - E_1]/kT) \rangle_1 \quad (11)$$

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

# Biased, or umbrella, sampling

TI, FEP  
 $V_0 \leftrightarrow V_1$



only  $V$  (single)

$A \rightleftharpoons B$

doesn't matter  
 much where the  
 dividing surface  
 is.

spectral difference

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

To create a potential of mean force:

$$W(\delta_2)$$

MD simulation

$$\rho_i \equiv \exp(-W(\delta_i)/kT)$$

definition of  $W$   
 free-energy-like function



# Reduced distribution functions

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

$$dx \approx d\delta d\Sigma$$

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

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

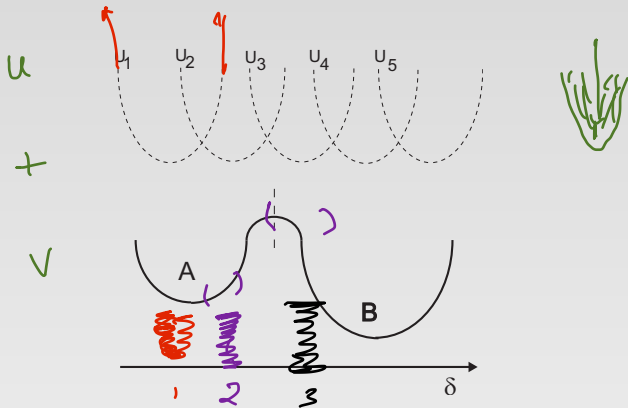
*→ non-physical potential*

*V+U generates MD*

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

*↳ independent of  $\delta$*

# Umbrella sampling

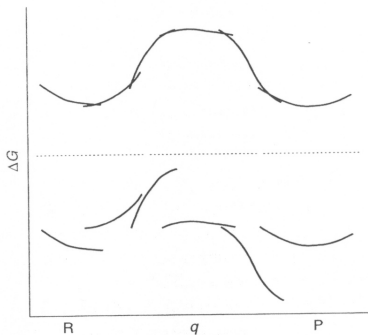


Taking logarithms:  $u + v$   
 MD gives me  $\rightarrow$   $W^*(\delta) = W(\delta) + U(\delta) + kT \ln \langle e^{-\beta U} \rangle$

*want  $\downarrow$   $v$  only*

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

# Thermodynamic cycles

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

# More on thermodynamic cycles