Umbrella sampling

We consider here an alternative approach to compute free energy differences of states, which is called umbrella sampling. We assume a transition from two states A and B (can be folded and unfolded proteins if we really want to be concrete). The reaction coordinate for that transition is q and the potential for this system, $U(R,q)$ is a function of the reaction coordinate and (in principle) all other complementing coordinates stored in the vector R. The free energy as a function of q is

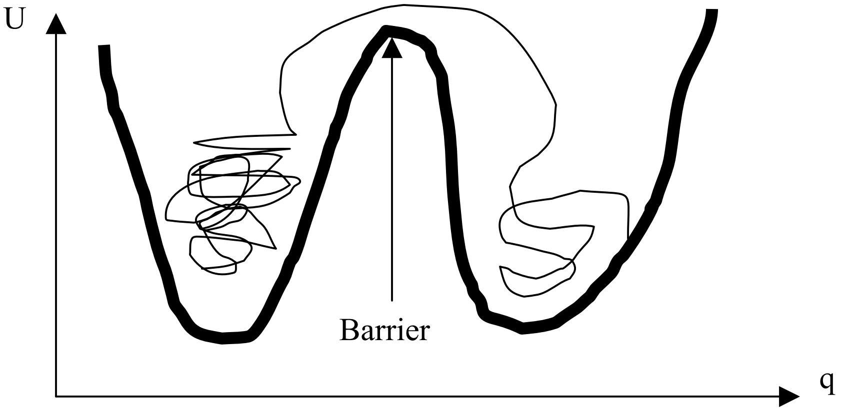
$$F(q_0) = -T\log\left[\int \delta(q-q_0)\exp\left[-U(R,q)/T\right]dRdq\right]$$

We are usually interested in free energy differences such as $F(q_0)-F(q_1)$. For the calculations of differences it is possible to add a constant to the free energy without changing its value. The constant that we are adding below is the free energy of the whole system F_{total} which is independent of q, the variable we are interested in. We re-define the free energy to be

$$F(q_0) = -T\log\left[\frac{\int \delta(q-q_0)\exp\left[-U(R,q)/T\right]dRdq}{\int \exp\left[-U(R,q)/T\right]dRdq}\right] = -T\log\left[\left\langle \delta(q-q_0)\right\rangle_U\right]$$

The above expression is accessible (in principle) to computation by randomized algorithms and Markov chains, since it is written as an average of a function (the Dirac's delta function in q) with a weight of $\exp\left[-U/T\right]$. Since our weights always will be of the exponential form we write only the potential as a subscript of the corresponding average.

A Markov chain could be initiated sampling configurations from the relevant space. However, if some of the q configurations are highly improbable it will be difficult to obtain appropriate statistics for these q. A projection of a potential along the reaction coordinate which is problematic to sample is schematically drawn below



The thick line is the potential energy and the thin line presents position sampled by a Markov chain. Sampling in the neighborhood of the barrier is difficult since the expected statistics of configuration selected with the Metropolis algorithm is expected to be very small (it is exponentially smaller with positive energy difference).

At the core of the umbrella sampling procedure there is a distortion mechanism for the original potential in such a way that significant sampling can be obtained at desired reaction coordinate configuration. Consider the following addition to the original potential

$$U(R,q) \rightarrow U(R,q)+V(q)$$

where $V(q)$ is independent on R and is chosen such that it is centered near a specific q value. A possible realization of the added potential is

$$V(q) \equiv V^{(k)}(q) = k\left(q-q^{(k)}\right)^2$$

where $q^{(k)}$ is a constant that we may shift following our desires to focus on different q values. It is clearly advantageous to generate Markov chains with the modified potentials since we can force our sampling to be the largest at particular values we are interested in. The obvious problem is however, that the modified potential is not the true potential and we must find a way of converting sampling data obtained with the biased potential to statistical data without the bias (which is the turth). To show how this can be done we start with the integrals

$$\frac{\int \delta(q-q_0)\exp\left[-U(R,q)/T\right]dRdq}{\int \exp\left[-U(R,q)/T\right]dRdq} =$$

$$\frac{\int \delta(q-q_0)\exp\left[V/T\right]\exp\left[-\left(U(R,q)+V(q)\right)/T\right]dRdq}{\int \exp\left[-\left(U(R,q)+V(q)\right)/T\right]dRdq}\frac{\int \exp\left[-\left(U(R,q)+V(q)\right)/T\right]dRdq}{\int \exp\left[-\left(U(R,q)\right)/T\right]dRdq} =$$

Both sides are clearly equal since we have done nothing more than adding and subtracting $V(q)$ from the exponent and multiplying and dividing by the same integral. Le us consider one ratio at a time we have

$$\frac{\int \delta(q-q_0)\exp\left[V/T\right]\exp\left[-\left(U(R,q)+V(q)\right)/T\right]dRdq}{\int \exp\left[-\left(U(R,q)+V(q)\right)/T\right]dRdq} = \left\langle \delta(q-q_0)\exp\left[V/T\right]\right\rangle_{U+V}$$

$$= \exp\left[V(q_0)\right]\left\langle \delta(q-q_0)\right\rangle_{U+V}$$

The interesting result here is that we replaced an average done with a weight of $\exp\left[-U/T\right]$ by an average with our new weight which is $\exp\left[-(U+V)/T\right]$ that can be tuned to get optimal sampling.

However, we have another pair of integrals to perform (which in principle can be written as an average as well).

$$\frac{\int \exp\left[-\left(U\left(R,q\right)+V\left(q\right)\right)/T\right]dRdq}{\int \exp\left[-\left(U\left(R,q\right)\right)/T\right]dRdq} =$$

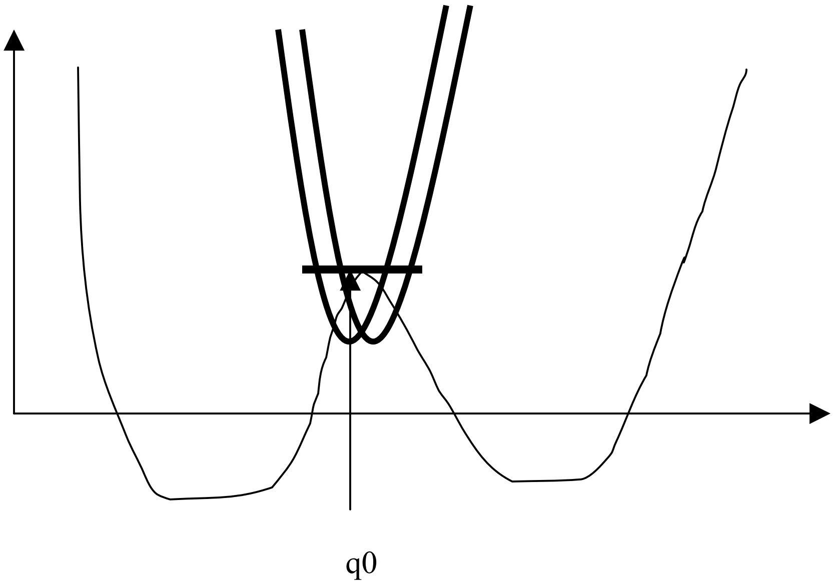
$$\frac{\int \exp\left[-\left(U\left(R,q\right)+V\left(q\right)\right)/T\right]dRdq}{\int \exp\left[V\left(q\right)/T\right]\exp\left[-\left(U\left(R,q\right)+V\left(q\right)\right)/T\right]dRdq} = \frac{1}{\left\langle \exp\left[V\left(q\right)/T\right]\right\rangle_{U+V}}$$

The average in the denominator is (again) performed with the adjusted potential. In sum, we have

$$\left\langle \delta\left(q-q_0\right)\right\rangle_U = \frac{\exp\left(V\left(q_0\right)/T\right)\left\langle \delta\left(q-q_0\right)\right\rangle_{U+V}}{\left\langle \exp\left(V\left(q\right)/T\right)\right\rangle_{U+V}}$$

The nominator is accessible to straightforward calculations. The denominator is (however) not. This is since we sample configuration with a weight of $\exp\left[-\left(U+V\right)/T\right]=\exp\left[-U/T\right]\exp\left[-V/T\right]$ while the entity we attempt to average is $\exp\left[V/T\right]$. The weight is exponentially small in V while the function we attempt to average is exponentially large in the same variable. This guarantees that most of the sampled points will be a miss, most of the times either the function or the weight will be essentially zero. It is therefore highly desirable to find a way to avoid the calculation of the denominator.

Here is how it can be done. Consider two biasing potential $V^{(k)}$ and V^{k+1}, both with minimum near but not identical to q_0



Both potentials $V^{(k)}$ and $V^{(k+1)}$ leads to a significant sampling in the neighborhood of q_0 so in principle we can compute the average $\left\langle\delta\left(q-q_0\right)\right\rangle_U$ in more than one way (using two different biasing potentials

We have

$$\left\langle\delta\left(q-q_0\right)\right\rangle_U=\frac{\exp\left(V^{(k)}\left(q_0\right)/T\right)\left\langle\delta\left(q-q_0\right)\right\rangle_{U+V^{(k)}}}{\left\langle\exp\left(V^{(k)}\left(q\right)/T\right)\right\rangle_{U+V^{(k)}}}$$

and

$$\left\langle\delta\left(q-q_0\right)\right\rangle_U=\frac{\exp\left(V^{(k+1)}\left(q_0\right)/T\right)\left\langle\delta\left(q-q_0\right)\right\rangle_{U+V^{(k+1)}}}{\left\langle\exp\left(V^{(k+1)}\left(q\right)/T\right)\right\rangle_{U+V^{(k+1)}}}$$

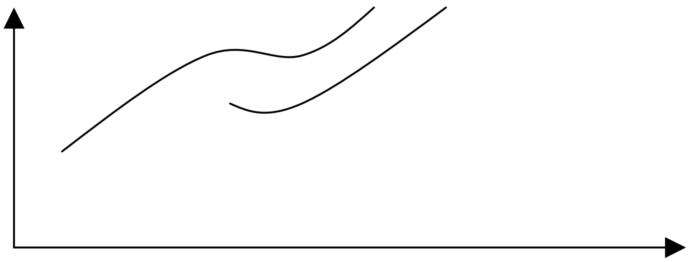
Divide the two equations above and take the log of the division

$$\begin{aligned}&\log\left[\left\langle\delta\left(q-q_0\right)_{U+V^{(k)}}\right\rangle\right]+V^{(k)}\left(q_0\right)/T-\log\left[\left\langle\delta\left(q-q_0\right)_{U+V^{(k+1)}}\right\rangle\right]-V^{(k+1)}\left(q_0\right)/T=\\&=\log\left[\left\langle\exp\left(V^{(k+1)}/T\right)\right\rangle_{U+V^{(k+1)}}\right]-\log\left[\left\langle\exp\left(V^{(k)}/T\right)\right\rangle_{U+V^{(k)}}\right]\end{aligned}$$

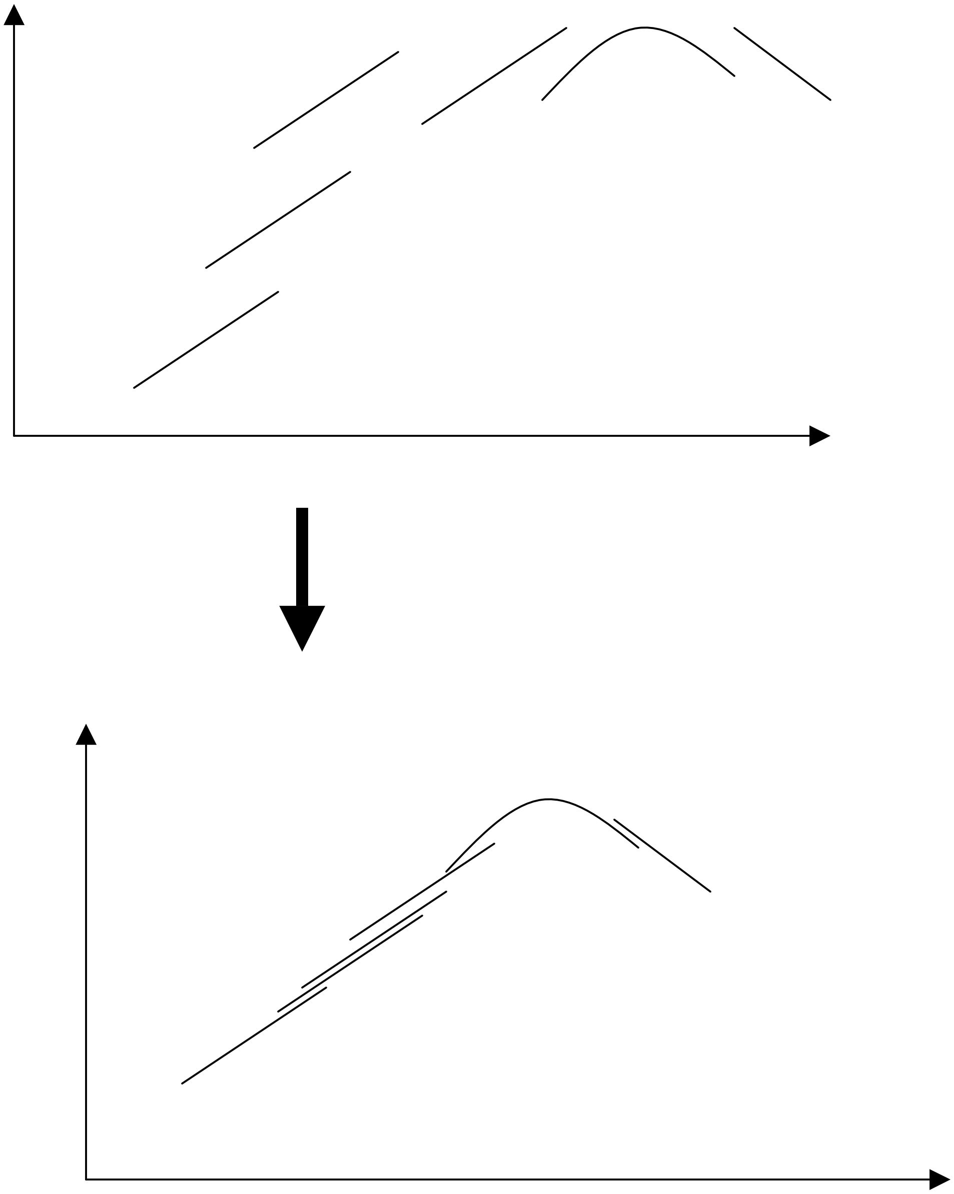
Note that the right hand side of the equation includes only terms that are independent of q_0. So miraculously all the q_0 dependence on the left hand side must cancel out to yield a constant. If we use now the same potentials to consider free energy difference of set of points that are still sampled adequately (the thick parallel line in the above plot). We can write as an example the same equation for another point say q_1 in which the right hand side of the equation will remain the same constant.

$$\begin{aligned}&\log\left[\left\langle\delta\left(q-q_1\right)_{U+V^{(k)}}\right\rangle\right]+V^{(k)}\left(q_1\right)/T-\log\left[\left\langle\delta\left(q-q_1\right)_{U+V^{(k+1)}}\right\rangle\right]-V^{(k+1)}\left(q_1\right)/T=\\&=\log\left[\left\langle\exp\left(V^{(k+1)}/T\right)\right\rangle_{U+V^{(k+1)}}\right]-\log\left[\left\langle\exp\left(V^{(k)}/T\right)\right\rangle_{U+V^{(k)}}\right]\end{aligned}$$

We can therefore determines this constant by considering a range of q that are adequately sampled by the two potential (usually the interval between the two minima of the different biasing potential when they are sufficiently closed). Pictorially we may plot the function $\log\left[\left\langle\delta\left(q-q_i\right)_{U+V^{(k)}}\right\rangle\right]+V^{(k)}\left(q_i\right)/T$ for the two $k-s$ that will look something like



The two curves are different by a constant value that we can determine by least square fit or by manual plotting. Note that the matching will help us determine the <u>difference</u> between the two curves which is the difference between $C^{(k)}$ and $C^{(k+1)}$. In the most graphical solution to the constants problem we compute a sequence of distributions by sliding out biased potential along numerous positions of the reaction coordinate. Since every curve that we compute must match nearby curves (up to shifting by a constant), and is related to the true free energy by a constant as well (different curves however are related to the true free energy by different constant. So the process may look pictorially something like



The last figure is the same as the true free energy profile up to an overall constant (which does not matter if we primarily interested in free energy differences.