

Free energy methods part II

Gareth A. Tribello

(Dated: 4 December 2012)

In this lecture I will cover the following points:

1. Parallel tempering
2. Umbrella sampling
3. Steered MD
4. Metadynamics

Throughout we make use of the following equations from part I.

$$P(\mathbf{x}) = \frac{\exp\left(-\frac{U(\mathbf{x})}{k_B T}\right)}{\int d\mathbf{x}' \exp\left(-\frac{U(\mathbf{x}')}{k_B T}\right)} \quad (1)$$

$$F(s) = -k_B T \log P(s) \quad (2)$$

I. INTRODUCTION

Equation 1 tells us that the easiest way to explore more of phase space is to increase the temperature of the system. As temperature is increased $\exp\left(-\frac{U(\mathbf{x})}{k_B T}\right)$ becomes less strongly peaked at the points in phase space where the energy is low and thus more states become accessible. We can demonstrate this by writing the average energy, $\langle U \rangle$, of the system as:

$$\langle U \rangle = \frac{\int d\mathbf{x} U(\mathbf{x}) \exp\left(-\frac{U(\mathbf{x})}{k_B T}\right)}{Q} \quad (3)$$

$$\text{where } Q = \int d\mathbf{x}' \exp\left(-\frac{U(\mathbf{x}')}{k_B T}\right) \quad (4)$$

If we differentiate the second of the above equations with respect to temperature we arrive at an interesting result:

$$\frac{dQ}{dT} = \frac{1}{k_B T^2} \int d\mathbf{x} U(\mathbf{x}) \exp\left(-\frac{U(\mathbf{x})}{k_B T}\right) \quad (5)$$

$$= \frac{Q \langle U \rangle}{k_B T^2} \quad (6)$$

$$\rightarrow \langle U \rangle = \frac{k_B T^2}{Q} \frac{dQ}{dT} = k_B T^2 \frac{d \log Q}{dT} \quad (7)$$

The derivative in the above is clearly positive so the average energy of the system clearly increases as the temperature increases. Consequently, increasing temperature ensures that the higher energy states become more accessible.

If we perform a simulation at temperature T_1 the Boltzmann distribution tells us that we can express the probability as a function of some collective variable $s(\mathbf{x})$ using:

$$P(s') = \frac{\int d\mathbf{x} \delta(s(\mathbf{x}) - s') \exp\left(-\frac{U(\mathbf{x})}{k_B T_1}\right)}{\int d\mathbf{x}' \exp\left(-\frac{U(\mathbf{x}')}{k_B T_1}\right)} \quad (8)$$

This expression tells us how we can use the results from a high-temperature, T_1 simulation to calculate the free energy at a lower temperature, T_2 . The kernels centered at the s values we visit during the simulation should integrate to $\exp\left(+\frac{U(\mathbf{x})}{k_B T_1}\right) \exp\left(-\frac{U(\mathbf{x})}{k_B T_2}\right)$ rather than 1. Inserting this into the equation we get:

$$H(s') = \frac{\int d\mathbf{x} \delta(s(\mathbf{x}) - s') \exp\left(-\frac{U(\mathbf{x})}{k_B T_1}\right) \exp\left(+\frac{U(\mathbf{x})}{k_B T_1}\right) \exp\left(-\frac{U(\mathbf{x})}{k_B T_2}\right)}{Q'} = \frac{\int d\mathbf{x} \delta(s(\mathbf{x}) - s') \exp\left(-\frac{U(\mathbf{x})}{k_B T_2}\right)}{Q'} \quad (9)$$

In other words the Boltzmann distribution at the lower temperature multiplied by an immaterial constant.

II. PARALLEL TEMPERING

In parallel tempering simulations multiple simulations at different temperatures are run in parallel and the system tries to swap the configurations adopted by adjacent replicas every now and again¹⁻⁶. The notion is that the higher temperature replicas will cross the energetic barriers that prevent the lower temperature replicas from exploring all of phase space. Furthermore, because the temperature gap between adjacent replicas is not that large, there is a substantial overlap between the configurations adopted by two adjacent replicas and thus a substantial probability that their configurations can be swapped.

In parallel tempering the probability for swapping two replicas is calculated using:

$$p = \min\left(1, \frac{\exp\left(-\frac{U_j}{k_B T_i} - \frac{U_i}{k_B T_j}\right)}{\exp\left(-\frac{U_i}{k_B T_i} - \frac{U_j}{k_B T_j}\right)}\right) \quad (10)$$

where U_i and T_i are the potential energy and temperature of replica i respectively and U_j and T_j are the potential energy and temperature of replica j respectively.

There are various ways to set the temperatures of the replicas. Useful arguments as to how to do this can be made by looking at the average energy of the system and the heat capacity. As shown above the average energy is connected to the derivative of the partition function. The heat capacity, C_v , is also related to the partition function because:

$$C_v = \frac{\partial U}{\partial T} = \frac{\partial}{\partial T} \left(\frac{k_B T^2}{Q} \frac{dQ}{dT} \right) \quad (11)$$

$$= \frac{2k_B T}{Q} \frac{dQ}{dT} - \frac{k_B T^2}{Q^2} \left(\frac{dQ}{dT} \right)^2 + \frac{k_B T^2}{Q} \frac{d^2 Q}{dT^2} \quad (12)$$

$$= \frac{2\langle U \rangle}{T} - \frac{\langle U \rangle^2}{k_B T^2} + \frac{k_B T^2}{Q} \frac{d^2 Q}{dT^2} \quad (13)$$

where in the first and third lines we used the relation between the average energy, $\langle U \rangle$, and the partition function, Q , that was derived in the previous section. The second derivative of the partition function function is given by:

$$\frac{d^2 Q}{dT^2} = \frac{d}{dT} \left[\frac{1}{k_B T^2} \int d\mathbf{x} U(\mathbf{x}) \exp \left(-\frac{U(\mathbf{x})}{k_B T} \right) \right] = \frac{d}{dT} \left[\frac{Q \langle U \rangle}{k_B T^2} \right] \quad (14)$$

$$= -\frac{2}{k_B T^3} Q \langle U \rangle + \frac{1}{(k_B T^2)^2} \int d\mathbf{x} [U(\mathbf{x})]^2 \exp \left(-\frac{U(\mathbf{x})}{k_B T} \right) \quad (15)$$

$$= -\frac{2}{k_B T^3} Q \langle U \rangle + \frac{1}{(k_B T^2)^2} Q \langle U^2 \rangle \quad (16)$$

Substituting this result into our equation for C_v gives:

$$C_v = \frac{2\langle U \rangle}{T} - \frac{\langle U \rangle^2}{k_B T^2} + \frac{k_B T^2}{Q} \left[-\frac{2}{k_B T^3} Q \langle U \rangle + \frac{1}{(k_B T^2)^2} Q \langle U^2 \rangle \right] \quad (17)$$

$$= \frac{2\langle U \rangle}{T} - \frac{\langle U \rangle^2}{k_B T^2} - \frac{2\langle U \rangle}{T} + \frac{\langle U^2 \rangle}{k_B T^2} \quad (18)$$

$$= \frac{1}{k_B T^2} (\langle U^2 \rangle - \langle U \rangle^2) = \frac{\sigma(U)}{k_B T^2} \quad (19)$$

In other words, the heat capacity is connected to the fluctuations in the total energy. To have swapping moves between adjacent replicas we need there to be overlap between the distribution of energies on one replica and its neighbor. We thus need to consider the

heat capacity. In parallel tempering calculations the heat capacity is often assumed to be constant so the temperatures according to a geometric sequence. Alternatively, recent works have tried to incorporate the dependence of the heat capacity on temperature⁷.

The biggest problem for parallel tempering is when there are phase transitions. At a phase transition the average energy and/or heat capacity change discontinuously. These discontinuous changes happen because the system samples different parts of phase space above and below the transition temperature. There is thus little overlap in the distributions and there are thus very few swapping moves.

III. SIMULATION BIASES

Configurations with high energies are visited very infrequently in our simulations because the Boltzmann Distribution ensures that the probability of visiting a high-energy configuration is small. Interesting physics/chemistry, such as chemical reactions, involves the formation and destruction of bonds. Configurations with broken bonds have high energies and thus the probability of observing an intermediate state, between the reactants and products is very low. This in turn means that the probability of observing a reaction is low.

To make the probability of observing a chemical reaction larger we introduce a bias $V(x)$ which is designed to lower the energy differences between the low-energy reaction and product states and the higher energy intermediate configurations (the configurations with the broken bonds). This bias makes the Boltzmann distribution become:

$$P'(\mathbf{x}) = \frac{\exp\left(-\frac{U(\mathbf{x})+V(\mathbf{x})}{k_B T}\right)}{\int d\mathbf{x}' \exp\left(-\frac{U(\mathbf{x}')+V(\mathbf{x}')}{k_B T}\right)} = \frac{\exp\left(-\frac{U(\mathbf{x})+V(\mathbf{x})}{k_B T}\right)}{Q'} \quad (20)$$

The bias is designed so that the variations of $U(\mathbf{x})+V(\mathbf{x})$ are not as large as the variations in $U(\mathbf{x})$. This makes that the probability across space more uniform. Generally we write the bias as a function of some CV $s(\mathbf{x})$, which we know describes some interesting transition. We can write the probability as a function of this collective coordinate using:

$$P'(s') = \frac{\int d\mathbf{x} \delta(s(\mathbf{x}) - s') \exp\left(-\frac{U(\mathbf{x})}{k_B T}\right) \exp\left(-\frac{V(s(\mathbf{x}))}{k_B T}\right)}{Q'} \quad (21)$$

$$= \frac{\exp\left(-\frac{V(s')}{k_B T}\right) \int d\mathbf{x} \delta(s(\mathbf{x}) - s') \exp\left(-\frac{U(\mathbf{x})}{k_B T}\right)}{Q'} \quad (22)$$

$$= \exp\left(-\frac{V(s')}{k_B T}\right) \frac{Q}{Q'} P(s) \quad (23)$$

where in the last step we introduce the probability in the unbiased distribution, $P(s)$, which, according to the Boltzman distribution, is equal to the second part of the numerator in equation 22 divided by Q (see equation 4).

IV. UMBRELLA SAMPLING

A bias $V(x)$ can be used to force the system to fluctuate about a particular value of the CV if we set:

$$V(\mathbf{x}) = \frac{1}{2} \kappa (s(\mathbf{x}) - s_0)^2 \quad (24)$$

Using N such simulations with different values of s_0 we can explore the entire range of possible values for s_0 . Furthermore, by reweighting the histograms from these simulations using equation 23 we can extract N pieces of the free energy surface. If there is overlap between the free estimates obtained from each umbrella we can piece these parts together to get the free energy as a function of the coordinate of interest using:

A. Weighted Histogram Analysis Method (WHAM)

When we reweight using equation 23 and take a logarithm we get the value of the free energy modulo an additive constant:

$$F(s) = -k_B T \log P(s) = -k_B T \log \left[\exp\left(+\frac{V(s')}{k_B T}\right) \frac{Q'}{Q} P'(s) \right] \quad (25)$$

$$= -k_B T \log \left[\exp\left(+\frac{V(s')}{k_B T}\right) P'(s) \right] - k_B T \log \left[\frac{Q'}{Q} \right] \quad (26)$$



FIG. 1. Schematic illustration of the result that we would obtain by simply combining the free energy estimates from simulations with different biases.

This is why we cannot directly combine the free energy estimates obtained from all our umbrellas. The factor of $k_B T \log \left[\frac{Q'}{Q} \right]$ will be different in each simulation. As such if we just plot all the reweighted free energies on the same graph we will end up with a free energy surface that looks like that shown in figure 1.

The solution to this problem is to use the weighted histogram method⁸. This method starts by expressing the relationship between the probability observed in each of the biased simulations, $P^i(s)$, with the unbiased probability, $P^0(s)$:

$$P^i(s) = f_i \exp \left(+ \frac{V_i(s)}{k_B T} \right) P^0(s) \quad (27)$$

This equation is identical to equation 26 we have just replaced $\frac{Q'}{Q}$ with f_i . We now insist that the probability in each of the separate simulations is normalized. That is to say we require that:

$$\int ds P^i(s) = 1 \quad (28)$$

For this to be true we need to have:

$$f_i = \frac{1}{\int ds \exp \left(+ \frac{V_i(s)}{k_B T} \right) P^0(s)} \quad (29)$$

Using these equations it is possible to prove that the optimal estimate for $P^0(s)$ is given by:

$$P^0(s) = \frac{\sum_{i=1}^S \int dt \delta(s(t) - s)}{\sum_{i=1}^S f_i N_i \exp \left(+ \frac{V_i(s)}{k_B T} \right)} \quad (30)$$

Where the sums run over the S simulations that have been run and N_i is the number of samples in simulation i . In the WHAM method equations 29 and 30 are solved self-consistently for $P^0(s)$ and the f_i values. This method is very powerful and can be also be used to combine the data from simulations at different temperatures.

V. STEERED MD

This method works by applying a harmonic potential, whose equilibrium position moves at a constant velocity along some reaction coordinate⁹. The system is attached to this moving potential so its motion obviously forces the system to change its geometry. Clearly, the only happens because the potential does some work on the system. It is easy to calculate how much work the potential performs on the system using:

$$W(s, t) = \int_0^t dt k (s'(t) - s(t)) \tag{31}$$

where $s'(t)$ is the equilibrium position for the potential at time t and $s(t)$ is the actual value of the CV at time t . This calculation is useful as the Jarzynski theorem¹⁰ connects the average work performed to the underlying potential of mean force, $F(s)$, by:

$$\exp\left(-\frac{F(s)}{k_B T}\right) = \left\langle \exp\left(-\frac{W(s)}{k_B T}\right) \right\rangle \tag{32}$$

The problem with this method is that it is very difficult to converge this average so you generally have to do a very large number of separate steered MD simulations to get a converged free energy.

VI. METADYNAMICS

Equation 2 suggests that one of the best biases to use would be the negative of the free energy. Were we to use this as a bias we arrive at:

$$P'(s) = \exp\left(-\frac{F(s)}{k_B T}\right) \frac{Q}{Q'} P(s) \quad (33)$$

$$= \exp\left(-\frac{k_B T \log P(s)}{k_B T}\right) \frac{Q}{Q'} P(s) \quad (34)$$

$$= \frac{Q}{Q'} \frac{P(s)}{P(s)} = \frac{Q}{Q'} \quad (35)$$

In metadynamics¹¹⁻¹³ we assume that we can generate such a bias by adding Gaussians at configurations visited during the trajectory:

$$V(s, t) = \sum_{t'=0}^t w G(s - s(t'), \sigma) \quad (36)$$

where $G(s - s(t'), \sigma)$ is a Gaussian of width σ centered at the value of the CVs at time t' , $s(t')$ and w is the rate at which energy is added. In other words the bias is simply the histogram of configurations that was visited.

In recent years, the well-tempered variant of metadynamics¹⁴ has become more popular. In this method the bias, $V(s, t)$ is related to the histogram of accumulated configurations, $P(s, t)$, by:

$$V(s, t) = \Delta T \log\left(1 + \frac{w P(s, t)}{\Delta T}\right) \quad (37)$$

assuming $\frac{dP(s, t)}{dt} = w G(s - s(t), \sigma)$ we can write:

$$\frac{dV(s, t)}{dt} = \frac{w \Delta T G(s - s(t), \sigma)}{\Delta T + w P(s, t)} = w \exp\left(-\frac{V(s(t), t)}{\Delta T}\right) G(s - s(t), \sigma) \quad (38)$$

which, assuming that the bias is initially zero we can integrate numerically to obtain:

$$V(s, t) = \sum_{t'=0}^t w \exp\left(-\frac{V(s(t'), t')}{\Delta k_B T}\right) G(s - s(t'), \sigma) \quad (39)$$

Recall, from equation 23, that there is a relationship between the biased and unbiased distributions so we may write:

$$P'(s) = \exp\left(-\frac{V(s', t)}{k_B T}\right) \frac{Q}{Q'(t)} P(s) = \frac{1}{Q'(t)} \exp\left(-\frac{V(s', t)}{k_B T}\right) \exp\left(-\frac{F(s)}{k_B T}\right) \quad (40)$$

The second part follows given the definition of the free energy. We can use this expression to calculate free energies by reweighing simulations. In addition, we can use this expression to rewrite equation 38 as:

$$\frac{dV(s, t)}{dt} = w \exp\left(-\frac{V(s, t)}{\Delta T}\right) \frac{\exp\left(-\frac{F(s)+V(s)}{k_B T}\right)}{\int ds' \exp\left(-\frac{F(s')+V(s')}{k_B T}\right)} G(s, \sigma) \quad (41)$$

$$= w \frac{\exp\left(-\frac{\Delta T F(s) + (k_B T + \Delta T)V(s)}{k_B T \Delta T}\right)}{\int ds' \exp\left(-\frac{F(s')+V(s')}{k_B T}\right)} G(s, \sigma) \quad (42)$$

$$= w \frac{\exp\left(-\frac{F(s)}{k_B T} - \frac{\gamma V(s)}{\Delta T}\right)}{\int ds' \exp\left(-\frac{F(s')+V(s')}{k_B T}\right)} G(s, \sigma) \quad (43)$$

$$(44)$$

where we have introduced $\gamma = \frac{T+\Delta T}{T}$ ¹⁵. In the later parts of our simulation we assume that $\frac{dV(s, t)}{dt}$ is independent of s . That is to say that the rate of change of the bias is independent of the instantaneous value of s .¹⁶ For this to be true we must have:

$$1 = \exp\left(-\frac{F(s)}{k_B T} - \frac{\gamma V(s)}{\Delta T}\right) \quad (45)$$

$$0 = \frac{F(s)}{k_B T} + \frac{\gamma V(s)}{\Delta T} \quad (46)$$

$$V(s) = -\frac{\Delta T}{\gamma k_B T} F(s) \quad (47)$$

We can substitute this equation into the equation connecting the probability distribution in the biased and unbiased distribution and obtain:

$$P'(s) = \frac{\exp\left(-\frac{F(s)+V(s)}{k_B T}\right)}{\int ds' \exp\left(-\frac{F(s')+V(s')}{k_B T}\right)} = \frac{\exp\left(-\frac{F(s)}{k_B T} \left[1 - \frac{\Delta T}{\gamma k_B T}\right]\right)}{\int ds' \exp\left(-\frac{F(s')}{k_B T} \left[1 - \frac{\Delta T}{\gamma k_B T}\right]\right)} \quad (48)$$

$$= \frac{\exp\left(-\frac{F(s)}{k_B T} \frac{k_B T + \Delta T - \Delta T}{k_B T + \Delta T}\right)}{\int ds' \exp\left(-\frac{F(s')}{k_B T} \frac{k_B T + \Delta T - \Delta T}{k_B T + \Delta T}\right)} = \frac{\exp\left(-\frac{F(s)}{\gamma k_B T}\right)}{\int ds' \exp\left(-\frac{F(s')}{\gamma k_B T}\right)} \quad (49)$$

$$\mathbf{P}'(\mathbf{s}) = \mathbf{P}(\mathbf{s})^{\frac{1}{\gamma}} \quad (50)$$

Given the definition of free energy this implies that the bias at the end of the simulation is equal to:

$$V(s) = -\gamma F(s) \quad (51)$$

A. Reweighting

Free energies along unbiased coordinates can be extracted from metadynamics simulations using the following scheme¹⁷. If you bias along a direction s the probability distribution as a function of \mathbf{x} is given by:

$$P'(\mathbf{x}, t) = \frac{\exp\left(-\frac{U(\mathbf{x})+V(s(\mathbf{x}))}{k_B T}\right)}{\int d\mathbf{x} \exp\left(-\frac{U(\mathbf{x})+V(s(\mathbf{x}))}{k_B T}\right)} \quad (52)$$

we can rewrite this as:

$$P'(\mathbf{x}, t) = \frac{\exp\left(-\frac{U(\mathbf{x})+V(s(\mathbf{x}))}{k_B T}\right)}{\int ds \exp\left(-\frac{V(s,t)}{k_B T}\right) \int d\mathbf{x} \delta(s(\mathbf{x}) - s) \exp\left(-\frac{U(\mathbf{x})}{k_B T}\right)} \quad (53)$$

Recall though:

$$P'(s) = \frac{\int d\mathbf{x} \delta(s(\mathbf{x}) - s) \exp\left(-\frac{U(\mathbf{x})}{k_B T}\right)}{Q} \quad (54)$$

as we can use this to rewrite 53 as:

$$P'(\mathbf{x}, t) = \frac{\exp\left(-\frac{U(\mathbf{x})+V(s(\mathbf{x}))}{k_B T}\right)}{\int ds \exp\left(-\frac{V(s,t)}{k_B T}\right) Q P(s)} \quad (55)$$

$$P(\mathbf{x}, t) = \frac{\exp\left(-\frac{U(\mathbf{x})}{k_B T}\right)}{Q} \frac{\exp\left(-\frac{V(s(\mathbf{x}))}{k_B T}\right)}{\int ds \exp\left(-\frac{V(s,t)}{k_B T}\right) P(s)} \quad (56)$$

$$P'(\mathbf{x}, t) = P(\mathbf{x}) \frac{\exp\left(-\frac{V(s(\mathbf{x}))}{k_B T}\right)}{\int ds \exp\left(-\frac{V(s,t)}{k_B T}\right) P(s)} \quad (57)$$

We now define:

$$c(t) = k_B T \log \left(\int ds \exp \left(-\frac{V(s,t)}{k_B T} \right) P(s) \right) \quad (58)$$

which allows us to rewrite equation 57 as:

$$P'(\mathbf{x}, t) = \exp \left(-\frac{V(s(\mathbf{x}), t) + c(t)}{k_B T} \right) P(\mathbf{x}) \quad (59)$$

This equation connects the probability distribution at any two points in time. That is to say it allows us to write:

$$P(\mathbf{x}, t + \Delta t) = \exp \left(-\frac{V(s(\mathbf{x}), t + \Delta t) + c(t + \Delta t)}{k_B T} \right) P(\mathbf{x}, t) \quad (60)$$

Expanding $V(s(\mathbf{x}), t + \Delta t)$ and $c(t + \Delta t)$ in a Taylor series about t gives:

$$P(\mathbf{x}, t + \Delta t) \approx \exp \left(-\frac{V(s(\mathbf{x}), t) + V'(s(\mathbf{x}), t)\Delta t + c(t) + c'(t)\Delta t}{k_B T} \right) P(\mathbf{x}, t) \quad (61)$$

$$= \exp \left(-\frac{V(s(\mathbf{x}), t) + c(t)}{k_B T} \right) \exp \left(-\frac{V'(s(\mathbf{x}), t) + c'(t)}{k_B T} \Delta t \right) P(\mathbf{x}, t) \quad (62)$$

If $\Delta t=0$ then $P(\mathbf{x}, t + \Delta t) = P(\mathbf{x}, t)$, which means that $\exp \left(-\frac{V(s(\mathbf{x}), t) + c(t)}{k_B T} \right) = 1$. This simplifies the above equation to:

$$P(\mathbf{x}, t + \Delta t) = \exp \left(-\frac{V'(s(\mathbf{x}), t) + c'(t)}{k_B T} \Delta t \right) P(\mathbf{x}, t) \quad (63)$$

To differentiate $c(t)$ we rewrite equation 58 as:

$$c(t) = k_B T \log[u(t)] \quad \text{so} \quad c'(t) = k_B T \frac{1}{u(t)} \frac{du}{dt} \quad (64)$$

$$\text{where} \quad u(t) = \int ds \exp \left(-\frac{V(s,t)}{k_B T} \right) P(s) \quad (65)$$

$$\text{thus} \quad \frac{du}{dt} = -\frac{1}{k_B T} \int ds V'(s,t) \exp \left(-\frac{V(s,t)}{k_B T} \right) P(s) \quad (66)$$

$$\rightarrow \quad c'(t) = -k_B T \frac{1}{\int ds \exp \left(-\frac{V(s,t)}{k_B T} \right) P(s)} \frac{1}{k_B T} \int ds V'(s,t) \exp \left(-\frac{V(s,t)}{k_B T} \right) P(s) \quad (67)$$

$$= -\frac{\int ds V'(s,t) \exp \left(-\frac{V(s,t)}{k_B T} \right) P(s)}{\int ds \exp \left(-\frac{V(s,t)}{k_B T} \right) P(s)} = -\langle V'(s,t) \rangle \quad (68)$$

Hence, the time evolution of the probability in the biased ensemble is given by:

$$P(\mathbf{x}, t + \Delta t) = \exp\left(-\frac{V'(s(\mathbf{x}) - \langle V'(s, t) \rangle)}{k_B T} \Delta t\right) P(\mathbf{x}, t) \quad (69)$$

We now want to extract the probability as a function of some coordinate f that we did not bias. That is to say a coordinate that is not s . We introduce the following:

$$P(f, t) = \frac{\int d\mathbf{x} \delta(f(\mathbf{x}) - f) P(\mathbf{x}, t)}{\int d\mathbf{x} P(\mathbf{x}, t)} = \frac{\int d\mathbf{x} \delta(f(\mathbf{x}) - f) P(\mathbf{x}, t)}{\int df' \int d\mathbf{x} \delta(f(\mathbf{x}) - f') P(\mathbf{x}, t)} = \frac{H(f, t)}{\int df' H(f', t)} \quad (70)$$

where in the last step we define $H(f, t) = \int d\mathbf{x} \delta(f(\mathbf{x}) - f) P(\mathbf{x}, t)$. We can calculate the time dependence of this histogram using equation 69 and get:

$$H(f, t + \Delta t) = \int d\mathbf{x} \delta(f(\mathbf{x}) - f) \exp\left(-\frac{V'(s(\mathbf{x}) - \langle V'(s, t) \rangle)}{k_B T} \Delta t\right) P(\mathbf{x}, t) \quad (71)$$

$$\begin{aligned} &= \int ds \exp\left(-\frac{V'(s(\mathbf{x}) - \langle V'(s, t) \rangle)}{k_B T} \Delta t\right) \int d\mathbf{x} \delta(f(\mathbf{x}) - f) \delta(s(\mathbf{x}) - s) P(\mathbf{x}, t) \\ &= \int ds \exp\left(-\frac{V'(s(\mathbf{x}) - \langle V'(s, t) \rangle)}{k_B T} \Delta t\right) \bar{H}(f, s, t) \end{aligned} \quad (72)$$

We can thus calculate the probability along any coordinate (including those we did not bias) by accumulating the joint histogram $\bar{H}(f, s, t)$.

REFERENCES

- ¹Y. SUGITA and Y. OKAMOTO, *Chem Phys Lett.* **314**, 141 (1999).
- ²U. E. HANSMANN, *Chem Phys Lett.* **281**, 140 (1997).
- ³E. MARINARI and G. PARISI, *Europhys. Lett.* **19**, 451 (1992).
- ⁴N. NAKAJIMA, J. HIGO, A. KIDERA, and H. NAKAMURA, *Chemical Physics Letters* **278**, 297 (1997).
- ⁵P. LIU, B. KIM, R. A. FRIESNER, and B. J. BERNE, *Proceedings of the National Academy of Sciences of the United States of America* **102**, 13749 (2005).
- ⁶F. WANG and D. P. LANDAU, *Phys. Rev. Lett.* **86**, 2050 (2001).
- ⁷M. K. PRAKASH, A. BARDUCCI, and M. PARRINELLO, *Journal of Chemical Theory and Computation* **7**, 2025 (2011).

- ⁸J. D. CHODERA, W. C. SWOPE, J. W. PITERA, C. SEOK, and K. A. DILL, *J. Chem. Theor. Comput.* **3**, 26 (2007).
- ⁹H. GRUBMLER, B. HEYMANN, and P. TAVAN, *Science* **271**, 997 (1996).
- ¹⁰C. JARZYNSKI, *Phys. Rev. Lett.* **78**, 2690 (1997).
- ¹¹A. LAIO and M. PARRINELLO, *Proc. Natl. Acad. Sci. U.S.A.* **99**, 12562 (2002).
- ¹²A. BARDUCCI, M. BONOMI, and M. PARRINELLO, *Wiley Interdisciplinary Reviews: Computational Molecular Science* **1**, 826 (2011).
- ¹³A. LAIO and F. L. GERVASIO, *Reports on Progress in Physics* **71**, 126601 (2008).
- ¹⁴A. BARDUCCI, G. BUSSI, and M. PARRINELLO, *Phys. Rev. Lett.* **100**, 020603 (2008).
- ¹⁵Note that throughout we have assumed that ΔT is in units of energy.
- ¹⁶This is a reasonable assumption the values of $V(s, t)$ will probably end up being much larger than the fluctuations in $F(s)$. Hence, the value of $\exp\left(-\frac{V(s, t)}{k_B T}\right)$ will be pretty much uniform everywhere.
- ¹⁷M. BONOMI, A. BARDUCCI, and M. PARRINELLO, *J. Comput. Chem.* **30**, 1615 (2009).