Well Sliced Metadynamics Explained

John H. Hymel

October 2022

1 Free Sampling

If we want to determine the free energy of a system as a function of some coordinate, **s**, all we need is the probability distribution along that coordinate. From there the free energy with respect to **s** can be computed by...

$$A(\mathbf{s}) = -k_b T ln P(\mathbf{s}) \tag{1}$$

While straightforward, freely sampling P(**s**) is quite difficult in many cases due even small barriers (¿ 1 k_bT). In these cases, free/unbiased sampling is insufficient and enhanced/biased sampling is the name of the game. The purpose of this document is to describe the formalism for an enhanced sampling method called well-sliced metadynamics which is a hybrid method of umbrella sampling and well-tempered metadynamics. I'll begin by describing the biases involved in standard umbrella sampling and how it is re-weighted using the WHAM equations using bond breaking as an example. Next, I'll describe the time-dependent bias used in metadynamics and how it is re-weighted using a solvent specific coordination number as an example. Finally, I'll describe how these methods are combined in well-sliced metadynamics. The vast majority of the content of this document comes from two sources, Laio et al. Nat. Rev. Phys. 2020, 2 (4), 200–212. (a review paper on metadynamics) and Nair et al. J. Comput. Chem. 2016, 37 (16), 1413–1424. (the paper which defines well-sliced metadynamics) If you want to know the ground truth, those papers are the first place to look. A historical piece that is nice to mention is Valleau et al. J. Comput. Phys. 1977, 23 (2), 187-199., the paper which coined the name umbrella sampling.

2 Umbrella Sampling

Umbrella sampling works by applying a series of harmonic biases to the potential energy surface in order to force the system to sample a desired region of phase space. For the electrosynthesis project, this involves adding harmonic potentials at particular C-C bond distances, $\mathbf{r_h}$, where h = 1, 2, ..., M, for M total independent simulations. For standard umbrella sampling with respect to **r**, the bias potentials take the form...

$$W_h(\boldsymbol{r}) = \frac{1}{2} k_h (\boldsymbol{r} - \boldsymbol{r_h})^2, h = 1, ..., M \tag{2}$$

From this series of simulations, we get a series of biased probability distributions which need to be re-weighted and stitched together in order to get back P(**r**). This is done using the weighted histogram analysis method (WHAM) which requires self-consistently solving the WHAM equations. A key piece to the WHAM equations is a set of constants, **f**, which are offsets used to stitch the re-weighted probabilities from each simulation together. Initial guesses for these need to be given at the start of the WHAM SCF procedure. Below are the standard 1D WHAM equations.

$$P(\boldsymbol{r}) = \frac{\sum_{h=1}^{M} n_h P_h(\boldsymbol{r})}{\sum_{h=1}^{M} n_h \exp[\beta \boldsymbol{f}_h] \exp[-\beta W_h(\boldsymbol{r})]} \tag{3}$$

and

$$\exp[-\beta \boldsymbol{f}_h] = \int d\boldsymbol{r} \exp[-\beta W_h(\boldsymbol{r})] P(\boldsymbol{r}) \tag{4}$$

By iteratively solving equations 3 and 4 for convergence of **f**, the final guess for P(**r**) can be plugged into equation 1 to compute the potential of mean force (PMF) / free energy surface (FES) with respect to the C-C bond distance, **r**.

3 Metadynamics

Umbrella sampling works well in case where the collective variable that needs to be sampling along is known and low dimensional. This is the case with a bond distance, but is intractable if we want to study the effect of some high dimensional solvent coordinate. Metadynamics was developed to solve this issue. In metadynamics, a time-dependent bias potential is built up by placing down Gaussian's at previously visited regions of CV space. By doing this, the system is driven away from lower energy regions and biased towards higher energy regions without need of prior knowledge of the underlying potential energy surface. This bias potential take the form...

$$V(\boldsymbol{N_X}, t) = \sum_{\tau<t} w_\tau \exp\left[-\frac{\{\boldsymbol{N_X} - \boldsymbol{N_X(\tau)}\}^2}{2(\delta s)^2}\right] \tag{5}$$

Where w_τ and δs are the height and width of the Gaussian's added to the bias potential at some time τ. Standard metadynamics, where the weights w_τ are constant, is no commonly used. This is because standard metadynamics simulations do not have a clear endpoint since as time, $t \to \infty$ the bias potential, $V(\boldsymbol{N_X}, t) \to \infty$. To address this issue, well-tempered metadynamics was developed where the weights associated with the Gaussian biases are themselves time-dependent, reducing in size during the simulation such that they reach convergence. The time-dependence of the weights is defined by...

$$w_\tau = \omega_0 \tau_0 \exp\left[-\frac{V(\boldsymbol{N_X}, t)}{k_B \Delta T}\right] \tag{6}$$

Where ω_0 is the initial rate of deposition of the bias, τ_0 is the time step at which the Gaussian potentials are modified, and ΔT is a parameter that controls how quickly the Gaussian height is decreased. Often, ΔT is written in terms of a so called bias factor, γ,

$$\gamma = \frac{T + \Delta T}{T} \tag{7}$$

This bias factor controls the height to which the bias potential flattens and converges. The bias factor controls the "effective temperature" at which the chosen CV (here coordination number, N_X) is sampled. Upon convergence of the metadynamics bias potential, V($\mathbf{N_X}$, t), the PMF/FES is computed by...

$$A(\boldsymbol{N_X}) = -\frac{T + \Delta T}{\Delta T} \lim_{t\to\infty} V(\boldsymbol{N_X}, t) \tag{8}$$

4 Well-sliced Metadynamics

Well-sliced metadynamics (WSMD) uses a combination of the two aforementioned methods, umbrella sampling and metadynamics. This method is more efficient than performing standard well-tempered metadynamics over two collective variables since it can be trivially parallelized in 1D over umbrella simulations. The combined bias potential used for WSMD in the electrosynthesis system is the following...

$$W_h(\boldsymbol{r}) + V_h(\boldsymbol{N_X}, t), h = 1, ..., M \tag{9}$$

Where $W_h(\mathbf{r})$ and $V_h(\mathbf{N_X},t)$ are biases defined in equations 2 and 5, respectfully. Appropriately re-weighting this bias potential is complicated since it consists of time-independent and time-dependent factors. During the re-weighting procedure, the biased probabilities are all first re-weighted with respect to the time-dependent metadynamics biases, then the WHAM procedure is used to re-weight the time-independent bias with from the umbrella potentials. The equation used to re-weight the time-dependent biasing is...

$$P_h^u(\boldsymbol{r'}, \boldsymbol{N'_X}) = \frac{\int_{t_{min}}^{t_{max}} d\tau \exp[\beta\{V_h(\boldsymbol{N_X}(\tau), \tau) - c_h(\tau)\}]\ \ \delta(\boldsymbol{r}(\tau) - \boldsymbol{r'})\ \ \delta(\boldsymbol{N_X}(\tau) - \boldsymbol{N'_X})}{\int_{t_{min}}^{t_{max}} d\tau \exp[\beta\{V_h(\boldsymbol{N_X}(\tau), \tau) - c_h(\tau)\}]} \tag{10}$$

The key to re-weighting with respect to the time-dependent bias $V(N_X,t)$ in equation 10 is c(t), which is essentially a time-dependent correction to the partition function (since the bias in changing in time, so is the partition function, this must be corrected for). c(t) is defined below...

$$c(t) = \frac{1}{\beta}\left[\frac{\int d\boldsymbol{N_X} \exp\left[-\beta F(\boldsymbol{N_X})\right]}{\int d\boldsymbol{N_X} \exp\left[-\beta\{F(\boldsymbol{N_X}) + V(\boldsymbol{N_X}, t)\}\right]}\right] \tag{11}$$

Where $F(\mathbf{N_X})$ is the Tiwary–Parrinello time-independent free energy estimator. c(t) is quite complicated to compute, but thankfully, it can be easily computed using Plumed by setting the CALC_RCT flag true when using the metadynamics engine. Once $P_h{}^u(\mathbf{r}, \mathbf{N_X})$ has been computed across all M simulations, the WHAM procedure can be applied to re-weight the umbrella biasing. In this case, the WHAM equations have to be slightly modified in order to re-weight a 2D probability distribution with respect to only one of the coordinates...

$$P(\boldsymbol{r}, \boldsymbol{N_X}) = \frac{\sum_{h=1}^{M} n_h P_h^u(\boldsymbol{r}, \boldsymbol{N_X})}{\sum_{h=1}^{M} n_h \exp[\beta \boldsymbol{f}_h] \exp[-\beta W_h(\boldsymbol{r})]} \tag{12}$$

and

$$\exp[-\beta \boldsymbol{f}_h] = \int d\boldsymbol{r} \exp[-\beta W_h(\boldsymbol{r})] P(\boldsymbol{r}, \boldsymbol{N_X}) \tag{13}$$

Once again, as in equations 3 and 4, self-consistently solving these equations yield an accurate approximate of the 2D probability distribution $P(\mathbf{r}, \mathbf{N_X})$, which is properly re-weighted to remove the biases imposed by equation 9. Using this probability distribution, the PMF/FES can be computed using the 2D equivalent of equation 1...

$$A(\mathbf{r}, \mathbf{N_X}) = -k_b T ln P(\mathbf{r}, \mathbf{N_X}) \tag{14}$$

Initially, I had two scripts for running WSMD, one code which used c(t)'s computed using Plumed to compute the biased probabilities in equation 10 and then write those out into M csv files. This was followed by a second script which used those csv's as input to solve self-consistently solve equations 12 and 13. Since then I've written up an object-oriented version of the code that is contained to one file, this has been benchmarked against the Grossfield lab's WHAM code with good results.