NVT Umbrella Sampling and Free Energy Profiling using WHAM

Zeng Wu

This illustrates the concept of umbrella sampling under the NVT ensemble and demonstrates how to compute the energy profile from the sampling data.

1. Umbrella Sampling

When investigating a process with a high energy barrier using molecular dynamics simulations, a more efficient sampling method is to divide the reaction coordinate (ξ) into multiple windows, each denoted as ξ_i. In each window, a harmonic biasing potential ($\omega(\xi_i)$) is applied to enhance sampling and help the system overcome the barrier. Umbrella sampling is then used to reconstruct the unbiased potential of mean force A^u (PMF) from the biased distributions.

$$A_i^b = A_i^u + \omega(\xi_i) \tag{1}$$

$$A_i^b = A_i^u + k(\xi_i - \xi_{i,0}) \tag{2}$$

Here, A_i^b and A_i^u represent the biased and unbiased free energies for each window, respectively. The term $\omega(\xi_i)$ denotes the harmonic biasing potential, ξ_i is the reaction coordinate, and $\xi_{i,0}$ is the equilibrium position (center) of the harmonic potential in window i.

We can compute the biased probability distribution P_ξ^b along the reaction coordinate from the MD simulation. Our goal is to calculate the unbiased free energy ($A^u(\xi)$) or PMF from biased probability distribution $P^b(\xi)$.

$$A^u(\xi) = f\left(P^b(\xi)\right) \tag{3}$$

1.1 Canonical ensemble (NVT)

In the NVT the Helmholtz energy can be compute from probability distribution :

$$A^u(\xi) = -K_B T \ln P_\xi^u \tag{4}$$

The probability distribution along the reaction coordinate ξ can be compute by integrating out all degrees of freedom except the ξ in Boltzmann distribution :

$$P^u(\xi) = \frac{\int \delta\left[\xi(q) - \xi\right] e^{-\beta A^u(q)} dq}{\int e^{-\beta A^u(q)} dq} \tag{5}$$

where $\delta\left[\xi(q) - \xi\right] = 1$, when $\xi(q) = \xi$. In this case, the $P^b(\xi)$ can be compute in same way as adding the bias potential to the previous equation 5.

We can compute the $P^u(\xi)/P^b(\xi)$ as following :

$$\frac{P^u(\xi)}{P^b(\xi)} = \frac{\int \delta\left[\xi(q)-\xi\right] e^{-\beta A^u(q)} dq}{\int e^{-\beta A^u(q)} dq} \cdot \frac{\int e^{-\beta[A^u(q)+\omega(\xi(q))]} dq}{e^{-\beta\omega(\xi)} \int \delta\left[\xi(q)-\xi\right] e^{-\beta A^u(q)} dq} \tag{6}$$

$$P^u(\xi) = P^b(\xi) e^{\beta\omega(\xi)} \left\langle e^{-\beta\omega(\xi)} \right\rangle \tag{7}$$

we replacing the equation 7 into equation 4 :

$$A^u(\xi) = -K_B T \ln P^b(\xi) - \omega(\xi) - K_B T \ln \left\langle e^{-\beta\omega(\xi)} \right\rangle \tag{8}$$

$$= -K_B T \ln P^b(\xi) - \omega(\xi) + F \tag{9}$$

where $F = -K_B T \ln \left\langle e^{-\beta\omega(\xi)} \right\rangle$, it is constant in each window. This equation 9 allows computation of unbiased free energy from biased probability distribution in each window.

WHAM Analysis

It is worth mentioning that the free energy we calculated earlier is defined with respect to a well-characterized probability distribution. In the context of umbrella sampling, this means that for each window i, we can compute a local free energy profile $A_i^u(\xi)$. The key challenge is then to combine these individual profiles into a global free energy landscape over the entire reaction coordinate ξ.

Previously, we often did not concern ourselves with the value of parameter F, because what typically matters is the free energy difference ΔA^u. However, when combining data from multiple windows, the values of F become important, since they determine the relative weights $w_i(\xi)$ associated with each window. These weights influence how each window contributes to the reconstruction of the unbiased global free energy profile.

$$A^u(\xi) = \sum_i^{n_w} w_i(\xi) A_i^u(\xi) \tag{10}$$

where i is index of window, n_w is total number of windows, $A^u(\xi)$ is unbiased global free energy profile and $A_i^u(\xi)$ is unbiased free energy for each windows. Here the $w_i(\xi)$ can be calculated as [1], Then we can iterate through the following process :

$$W_i(\xi) = \frac{a_i(\xi)}{\sum_{j=0}^{n_w} a_j} \tag{11}$$

$$a_i(\xi) = N_i e^{-\beta\omega_i(\xi)+\beta F_i} \tag{12}$$

$$P^u(\xi) = \sum_i^{n_w} W_i(\xi) P_i^u(\xi) \tag{13}$$

$$e^{-\beta F_i} = \int P^u(\xi) e^{-\beta\omega_i(\xi)} d\xi \tag{14}$$

Références

[1] Shankar Kumar, John M Rosenberg, Djamal Bouzida, Robert H Swendsen, and Peter A Kollman. The weighted histogram analysis method for free-energy calculations on biomolecules. i. the method. *Journal of computational chemistry*, 13(8) :1011–1021, 1992.