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Research paper

Optimization of replica exchange temperature ladder under the well-tempered ensemble

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HIGHLIGHTS

- Temperature ladder of the PT-WTE simulations is optimally predicted.
- Other biased CVs in the PT-WTE simulation further enhance the sampling efficiency.
- Larger bias factor retards the convergence of WTE.

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ABSTRACT

Selection of temperature sequence and bias factor is a critical step for the preparation of Parallel Tempering simulations in a Well-Tempered Ensemble (PT-WTE). We provide a scheme in this study to generate the temperature sequence and the corresponding bias factor optimally. The number of replicas for a complete coverage of a specific temperature range is adjustable in this scheme, while keeping the average acceptance probability (AAP) between neighboring replica-pairs unchanged. Two series of PT-WTE simulations were tested with the number of replicas as 16 and 8 respectively. This work leads to a better understanding and application of PT-WTE simulations.

1. Introduction

Molecular dynamics simulations at room-temperature are usually of much interest but easily trapped in the metastable states. Simulations at higher-temperatures with correspondingly higher kinetic energies are able to overcome the energy barrier between different metastable states, however, the free energy surfaces (FES) obtained are different from the one at room temperature. Parallel tempering (PT) has now become a commonly used advanced sampling simulation technique in constructing FES when the simulated systems have rugged energy landscapes [1]. In PT, a series of replicas, whose temperatures are arranged in an incremental ladder, are simulating simultaneously. The enhanced sampling is realized by allowing the exchange of configurations of lower- and higher-temperature replicas. In practice, the exchange is attempted every specified number of simulation time-steps, with an acceptance probability described by [2]:

$$P(T_1 \leftrightarrow T_2) = \min(1, e^{(\beta_1-\beta_2)\cdot(U_1-U_2)}) \quad (1)$$

where $\beta_1 = 1/(k_B T_1)$, $\beta_2 = 1/(k_B T_2)$, k_B is the Boltzmann constant, and U_1, U_2 are the instantaneous potential energies of the two exchanging configurations.

PT achieves the highest sampling efficiency when the average acceptance probability (AAP) between neighboring replica pairs is uniform [3]. In such a case, a well-designed temperature sequence would be required for the optimized performance of PT. Researchers have developed several methods to generate the temperature sequence. For instance, Kofke showed that for systems with a constant heat capacity, a geometric progression of temperature sequence assured the same AAP among all the neighboring replica pairs [4–6]. Rathore et al. found that AAP was relevant to the value of $\frac{U(T_i)-U(T_{i-1})}{\frac{1}{2}(\sigma(T_i)+\sigma(T_{i-1}))}$, where $U(T_i)$ is the average potential of replica at temperature T_i, and $\sigma(T_i)$ is the distribution width of the Gaussian-like potential at that temperature [3]. Before using this algorithm, short simulations for the system at several different temperatures are necessary to estimate the average potential and the potential distribution width. Then the temperatures for PT could be obtained by iteratively solving the equation $\frac{U(T_i)-U(T_{i-1})}{\frac{1}{2}(\sigma(T_i)+\sigma(T_{i-1}))} = \frac{U(T_{i+1})-U(T_i)}{\frac{1}{2}(\sigma(T_{i+1})+\sigma(T_i))}$. Patriksson et al. came up with a much

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friendlier using method [7], on the basis of the assumption of constant heat capacity: description of $U(T_i)$ and $\sigma(T_i)$ in the iterative equation were detailed down to the level of degree of freedom, thus users only needed to provide the information of system size and number of constraints to get the optimal allocation of temperatures with a specified AAP. In another case, Prakash et al. discussed the generation of such a temperature sequence for the system with a variable heat capacity [8].

However, even with the maximum efficiency of PT, there is still a big obstacle that limiting its wider applications. The requirements that the highest temperature must be high enough to keep all the replicas diffusive in phase space and the temperature gap between neighboring replicas must be small enough to keep sufficient exchange, determine the lower bound of the number of replicas, which is usually from dozens to more than one hundred. That is a disaster for researchers with limited computational resources, especially when simulating systems being large. The Well-Tempered Ensemble (WTE) framework can alleviate this issue [9]. Intrinsically, WTE is well-tempered meta-dynamics [10], but using the system potential as a collective variable (CV). When PT is combined with WTE (PT-WTE), the added biases enhance the fluctuations of potential energies of each replica, making it possible to have sufficient exchanges between replicas with larger temperature gaps. This approach has been proved its efficiency in the free energy surface study of peptide-surface interaction [11], peptide oligomerization [12], peptide conformational transition [13], flexible molecules binding [14], and so on. Deighan et al. reported that with a comparable sampling efficiency, the number of replicas could dramatically decrease from 100 in a standard PT to 10 in PT-WTE, and the efficiency in PT-WTE could be further enhanced by adopting a reasonably larger bias factor [15]. However, the criterion of choosing a proper bias factor for WTE has not been established so far.

Inspired by the works of Rathore et al. [3], Patriksson et al. [7] and Prakash et al. [8], we provided an operable scheme to generate reasonable temperature intermediates and a corresponding bias factor for PT-WTE within a given temperature range. By taking different bias factors, the number of replicas could be adjusted in this scheme to keep the desired AAP unchanged. Our method was demonstrated on an explicit solvated mini-protein system. Two series of PT-WTE simulations with different bias factors and number of replicas were carried out. Discussions on the choice of proper bias factors were given.

2. Computational details

2.1. Potential energy probability distribution function in WTE

In WTE, potential energy $U = U(R)$ is used as CV, where R is the full set of atomic coordinates. The bias potential $V(U, t)$ converges to [9,10]:

$$V(U, t \to \infty) = -(1-\gamma^{-1})F(U) \tag{2}$$

where $F(U)$ is the underlying free energy of the system and γ is the bias factor which, by definition, could be expressed as $\gamma = (T + \Delta T)/T$, with T is the temperature of the system and ΔT has the dimension of a temperature. Within an irrelevant constant, $F(U)$ is defined as

$$\begin{aligned} F(U) &= -\beta^{-1}\ln P(U) = -\beta^{-1}\ln \int dR\delta(U-U(R))e^{-\beta U(R)} \\ &= U-\beta^{-1}lnN(U) \end{aligned} \tag{3}$$

where $P(U) = \int dR\delta(U-U(R))e^{-\beta U(R)} = lnN(U)e^{-\beta U}$ is the energy probability distribution function in the canonical ensemble, and $N(U) = \int dR\delta(U-U(R))$ is the number of states of energy U. By combining Eq. (2) and Eq. (3), the biased potential of the system $U_\gamma(R)$ could be written as,

$$U_\gamma(R) = U(R)-(1-\gamma^{-1})(U(R)-\beta^{-1}lnN(U(R))) \tag{4}$$

thus the partition function of the WTE Z_γ is

$$\begin{aligned} Z_\gamma &= \int dRe^{-\beta U_\gamma(R)} \\ &= \iint dRdU\delta(U-U(R))e^{-\beta[U(R)-(1-\gamma^{-1})(U(R)-\beta^{-1}lnN(U(R)))]} \end{aligned} \tag{5}$$

and could be easily simplified as:

$$Z_\gamma = \int dUP(U)^{\gamma^{-1}} \tag{6}$$

If the energy probability distribution function in the canonical ensemble is considered as a Gaussian distribution, which is usually true for the water-dominated systems [16], we have $P(U) \propto e^{-\frac{(U-\mu)^2}{2\sigma^2}}$, where μ is the average potential and σ is the standard deviation of the distribution. In WTE, energy probability distribution function $P_\gamma(U)$ is tuned by the bias factor but still have a Gaussian shape: $P_\gamma(U) = P(U)^{\gamma^{-1}} \propto e^{-\frac{(U-\mu)^2}{2\gamma\sigma^2}}$. This change leads to the same average potential, μ, but $\sqrt{\gamma}$ times larger distributional width in the WTE when compared with the canonical ensemble. These larger potential energy fluctuations guarantee the intact acceptance probability of configurational exchange between replicas with larger temperature gaps in PT-WTE. After normalization, $P_\gamma(U)$ could be written as:

$$P_\gamma(U) = \frac{1}{\sigma\sqrt{2\pi\gamma}}e^{-\frac{(U-\mu)^2}{2\gamma\sigma^2}} \tag{7}$$

2.2. Prediction of temperature sequences and bias factors for PT-WTE

In PT, the AAP between two neighboring replicas $\langle P_{acc}(T_1 \leftrightarrow T_2)\rangle$ could be estimated as:

$$\begin{aligned} \langle P_{acc}(T_1 \leftrightarrow T_2)\rangle = \int_{-\infty}^{+\infty}\Big(\int_{-\infty}^{U_1} P_{(2)}(U_2)\cdot P_{(1)}(U_1)dU_2 \\ + \int_{U_1}^{+\infty} e^{(\beta_1-\beta_2)\cdot(U_1-U_2)}\cdot P_{(2)}(U_2)\cdot P_{(1)}(U_1)dU_2\Big)dU_1 \end{aligned} \tag{8}$$

where $P_{(1)}(U_1)$ and $P_{(2)}(U_2)$ are the probability of having instantaneous potential energy, U_1 and U_2, for replicas at temperature T_1 and T_2, respectively. $P_{(1)}(U_1)$ and $P_{(2)}(U_2)$ should have Gaussian shapes with their normalized expression as: $P_{(1)}(U_1) = \frac{1}{\sigma_1\sqrt{2\pi}}e^{-\frac{(U_1-\mu_1)^2}{2\sigma_1{}^2}}$ and $P_{(2)}(U_2) = \frac{1}{\sigma_2\sqrt{2\pi}}e^{-\frac{(U_2-\mu_2)^2}{2\sigma_2{}^2}}$ respectively, where μ_1, σ_1, μ_2 and σ_2 are the average value and standard deviation of each individual replica. Equivalently, Eq. (8) could be described as [7]:

$$\langle P_{acc}(T_1 \leftrightarrow T_2)\rangle = \int_{-\infty}^{0} P_{(1,2)}(U_{1,2})dU_{1,2} + \int_{0}^{+\infty} e^{(\beta_1-\beta_2)\cdot U_{1,2}}\cdot P_{(1,2)}(U_{1,2})dU_{1,2} \tag{9}$$

where $P_{(1,2)}(U_{1,2})$ is the probability of having energy different $U_{1,2} = U_1-U_2$, with its normalized form: $P_{(1,2)}(U_{1,2}) = \frac{1}{\sigma_{1,2}\sqrt{2\pi}}e^{-\frac{(U_{1,2}-\mu_{1,2})^2}{2\sigma_{1,2}{}^2}}$, where $\mu_{1,2} = \mu_1-\mu_2$ and $\sigma_{1,2} = \sqrt{\sigma_1{}^2 + \sigma_2{}^2}$ are the new average and standard deviation respectively.

Based on the same principle, AAP between replica pairs in PT-WTE is also predictable:

$$\begin{aligned} \langle P_{\gamma,acc}(T_1 \leftrightarrow T_2)\rangle = \int_{-\infty}^{0} P_{\gamma,(1,2)}(U_{1,2})dU_{1,2} + \int_{0}^{+\infty} e^{\frac{1}{\gamma}(\beta_1-\beta_2)\cdot U_{1,2}}\cdot \\ P_{\gamma,(1,2)}(U_{1,2})dU_{1,2} \end{aligned} \tag{10}$$

where

$$P_{\gamma,(1,2)}(U_{1,2}) = \frac{1}{\sigma_{1,2}\sqrt{2\pi\gamma}}e^{-\frac{(U_{1,2}-\mu_{1,2})^2}{2\gamma\sigma_{1,2}{}^2}} \tag{11}$$

It should be noticed that the instantaneous acceptance probability is tuned by γ when compared to the canonical ensemble, since the Boltzmann factor is tuned by γ, based on Eq. (6). In Eq. (10), the AAP is a function of the potential average and potential distributional width of the two replicas, as well as the bias factor. This relationship can be