Dynamical origin of uniform sampling in multicanonical ensemble

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The stochastic model describing the sampling process in multicanonical ensemble has been derived by considering the sampling process as an overdamped Brownian motion on the free energy surface. The essential dynamics of the multicanonical sampling has been characterized by a Langevin equation in a piecewise multivalleyed free energy landscape, modulated by a temperature-dependent curvature. Based on the stochastic model we showed that the multicanonical weight can be determined by interpolating maximum probability energy points of the canonical samplings at different temperatures.

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I. INTRODUCTION

The potential energy surfaces of many important physical processes, such as protein folding [1], cluster melting [2], and spin glasses [3], are characterized by a large number of the local minima separated by high energy barriers. Thus conventional simulations based on Monte Calro (MC) or molecular dynamics (MD) algorithm will become trapped in one of local energy basins and fail to sample broad regions of thermally accessible phase space.

During the past decade, several sampling methods have been proposed to overcome quasiergodicity in the simulation of rough energy landscape. One effective way is to use a non-Boltzman weight generating a random walk on the energy space, allowing the system to cross high energy barriers more frequently. This idea is employed in the multicanonical sampling [4] and an equivalent entropic sampling [5]. The other alternative is to perform several canonical simulations simultaneously and allow the system to communicate with each other at different temperatures as in the parallel tempering also known as the replica exchange method [6–8]. The parallel tempering has been proved to be very effective when it is combined with the multiple histogram technique [9,10]. Recently, Wang and Landau [11] have developed a very powerful new Monte Carlo sampling technique based on the independent random walks for a different range of energy. In those studies, they first determined the density of state accurately by using a random walk generating a flat histogram in energy space. The resulting pieces of the density of states estimated from multiple random walks were joined together and were used to produce thermodynamic quantities of canonical ensemble at an arbitrary temperature.

The multicanonical ensemble method [4,5] combined with MC simulation shows a substantial progress to improve the ergodic behavior in the studies of the first-order phase transitions [12] and the protein folding problem [13]. Recently, multicanonical algorithm has also been implemented to MD by performing an isokinetic MD on the modified potential energy surface [14]. Since then multicanonical MD has been applied to a variety of systems showing a considerable enhancement of the sampling efficiency [15]. More recently, Nose-Hoover MD protocol has also been applied to generate multicanonical ensemble [16]. Despite successful applications of multicanonical sampling it has one substantial problem. Contrary to the canonical ensemble, the weight factor, which is inversely proportional to the density of state, i.e., $\Omega(E)$, is not known *a priori* and has to be determined by an iterative procedure. However, the determination of the exact weight via an iterative process in conventional multicanonical MD is very difficult and nontrivial because $\Omega(E)$ of the complex system has a very large dynamic range. Even though several attempts have been applied to accelerate the convergence [17], the unknown weight factor is still limiting the use of the multicanonical sampling.

In this paper, the characteristic feature of the sampling dynamics in multicanonical MD has been analyzed in terms of the stochastic model describing an overdamped Brownian motion. By considering the sampling process as a stochastic diffusion in a free energy potential, we derive a stochastic differential equation (SDE) governing the sampling process in canonical and multicanonical ensemble. Based on the stochastic model, we reveal that the uniform sampling in multicanonical ensemble is achieved by transforming a complex free energy surface into a piecewise multivalleyed landscape structure driven by a stepwise temperature modulation. Our analysis also provides one natural way to determine the multicanonical weight for the uniform sampling, which does not resort to the iteration scheme. The detailed dynamics of the multicanonical MD has been verified in the model systems of $(\mathrm{Ala})_2$ dipeptide in a gas and an explicit water phase.

In Sec. II, the basic theory of the sampling process has been explained in terms of SDE. The correspondence between the sampling process and the stochastic dynamics has been demonstrated by identifying the transition probability of the Markovian stochastic process. In Sec. III, the dynamics of multicanonical sampling has been analyzed by a Langevin equation subject to a staircase temperature modulation. Through this analysis we showed that the fixed points

constructed from the average energy and the dynamical temperature play a critical role in the uniform sampling of the multicanonical ensemble method. The conclusion and a brief summary are presented in Sec. IV.

II. STOCHASTIC DIFFERENTIAL EQUATION GOVERNING SAMPLING PROCESS

A. Canonical sampling

In the canonical ensemble at the temperature $\beta_0 = 1/k_B T_0$, the sampling weight of each state with energy E is given by the Boltzmann factor

$$w_B(E) = e^{-\beta_0 E}. \tag{1}$$

The probability density function (PDF) in the energy is obtained by multiplying the Boltzmann weight w_B by the density of state of the system, $\Omega(E)$, as

$$P_0(E) = \Omega(E) e^{-\beta_0 E}/Z_0 = e^{-\beta_0 A(E)}/Z_0, \tag{2}$$

where Z_0 is the partition function and $A(E)$ is the free energy density defined by $E - T_0 S(E)$, $S(E)$ being the entropy defined in the microcanonical ensemble as $k_B \ln\Omega(E)$. In a thermodynamic limit, Eq. (2) reduces to a Gaussian distribution centered about the average energy U_0 with the width equal to $\sigma_0 = k_B T_0^2 C_V(T_0)$ [18], C_V being the specific heat of the system, as

$$P_0(E) = \frac{1}{\sqrt{2\pi\sigma_0}} \exp\left\{ -\frac{(E-U_0)^2}{2\sigma_0} \right\}. \tag{3}$$

Our present study starts from the well-known fact that the PDF of Eq. (2) can be obtained as a stationary solution of the Langevin equation [19]

$$\partial_t E = \Gamma(E) + \sqrt{f}\,\eta(t), \tag{4}$$

where $f = 2/\beta_0$ and $\Gamma(E) = -\partial_E A = T_0/T_S(E) - 1$, $T_S(E) = [\partial S/\partial E]^{-1}$. The definition of T_S is identical to the statistical temperature defined in the microcanonical ensemble. In Eq. (4), thermal fluctuations are approximated by unbiased δ-correlated Gaussian white noise with $\langle \eta(t)\eta(t')\rangle = \delta(t - t')$. Then, the sampling process in the canonical ensemble can be considered as a stochastic diffusion modeled by the overdamped Brownian motion in the free energy potential $A(E)$. The time-dependent probability distribution of Eq. (4) is determined by solving corresponding Fokker-Planck equation (FPE) as

$$\partial_t P = \partial_E[-\Gamma(E)P(E,t) + k_B T_0 \partial_E P(E,t)]. \tag{5}$$

The Gaussian distribution of Eq. (3) can be obtained by expanding $T_S(E)$ at E_0 satisfying $T_S(E_0) = T_0$ in Eq. (4) as

$$\partial_t E = -\xi(T_0)(E - E_0) + \sqrt{f}\,\eta(t), \tag{6}$$

where $\xi = 1/T_0[\partial T_S/\partial E]_{E=E_0} = [T_0 C_V(T_0)]^{-1}$, C_V being $[\partial T_S/\partial E|_{E=E_0}]^{-1}$. It should be noted that E_0 becomes identical to an average energy U_0 in a thermodynamic limit given by the definition of $\partial_E S|_{E=E_0} = 1/T_0$ [18]. Here we truncate the Taylor series of $T_S(E)$ up to first order by assuming that the specific heat is a smooth function around T_0. Notice that the coefficient of nth-order term ($n > 1$) in the Taylor expansion is proportional to $(n-1)$th derivative of the specific heat. The PDF of Eq. (6) becomes identical to Eq. (3) by solving the FPE governing Ornstein-Uhlenbeck process [19].

When the specific heat of the system shows a rapid variation or a divergence occurring for the van der Waals loops of the finite system [20], higher-order terms in the Taylor series cannot be neglected. Furthermore, the relation of $T_S(E_0) = T_0$ may not have a unique solution in that case. This means that the PDF of the canonical sampling shows a nonGaussian distribution. The approximate form of the PDF is determined by the number of these optimum points E_i and the values of local curvatures $\xi(E_i)$. Notice that the solutions E_i satisfying $T_S(E_i) = T_0$ correspond to the optimum points of the free energy potential $A(E)$.

The dynamics of Eq. (6) is characterized by identifying corresponding transition probability governing the stochastic process. From the solution of the FPE subject to an initial condition $P(E',t) = \delta(E' - E)$, the transition probability from (E,t) to (E',t') is given by

$$W[E't';Et] = \frac{1}{\sqrt{2\pi\sigma(\Delta)}} \exp\left\{ -\frac{[X + Y(E)]^2}{2\sigma(\Delta)} \right\}, \tag{7}$$

where $X = E' - E$, $Y(E) = (E - E_0)(1 - e^{-\xi\Delta})$, and $\sigma(\Delta) = f/2\xi(1 - e^{-2\xi\Delta})$, Δ being the time difference $t' - t$. For a fixed time step Δ, Eq. (7) determines the dynamics of the Markov chains in the canonical ensemble. The PDF at time t' is obtained by integrating the probability of all possible paths from the energy E to E' multiplied by the probability being at E at time t as

$$P(E + X, t + \Delta) = \int dE \;\; W[X, Y(E); \Delta] P(E,t), \tag{8}$$

where $P(E,\infty) = P_0(E)$.

The basic postulate underlying Eq. (8) is the independence of the transition X of any previous history of the dynamics. Here we assume that the Markov postulate can be attained in MD as an approximation valid when the dynamics of many-body system is considered on a relatively coarse time scale. The validity of this assumption can be demonstrated by examining the correspondence between the stochastic process and real sampling process. For that purpose, we define some statistical quantities. Assuming that $\xi\Delta \ll 1$ as in usual MD simulation, the energy increment X shows a Gaussian distribution as

$$Q(X) = \frac{\int dE \;\; W[X,Y] P_0(E)}{\int dX dE \; W[X,Y] P_0(E)} \approx \frac{e^{-X^2/2\sigma_x}}{\sqrt{2\pi\sigma_x}}, \tag{9}$$

where $\sigma_x \approx f\Delta$. Notice that the statistical property of X is uniquely determined by the property of the stochastic noise $\eta(t)$. Next, first and second moments of X are calculated at each energy E as

$$\overline{X_1} = -Y(E) \approx -\xi\Delta(E-E_0),$$

$$\overline{X_2} = \sigma(\Delta) + Y(E)^2 \approx f\Delta,$$

respectively, where $\overline{X_n} = \int_{-\infty}^{\infty} X^n W[X,Y]dX$. Finally, by integrating $W[X,Y]$ with respect to X in the limit from 0 to ∞, we define the probability for the dynamics to move to a right (energy-increasing) direction from E as

$$R(E) = 0.5\left\{1 - \mathrm{erf}\left[-\frac{Y(E)}{\sqrt{2\sigma(\Delta)}}\right]\right\}, \tag{10}$$

where $\mathrm{erf}(z) = 2/\sqrt{\pi}\int_0^z e^{-y^2}dy$. On the other hand, the probability moving to a left (energy-decreasing) direction becomes $L(E) = 1 - R(E)$. The quantity $R(E)$ or $L(E)$ represents a randomness of the dynamics in one-dimensional energy space.

To show the correspondence, we performed the canonical simulations with varying the temperature for $(\mathrm{Ala})_2$ dipeptide system in a gas phase whose N and C termini were blocked with acetyl and N-methyl groups, respectively. The simulation was performed by the program PRESTO [21] and the force-field parameters were taken from the all-atom version of AMBER [22]. From the simulation we first evaluate the values of Δ and $\xi(=f/2\sigma_0)$ by computing the variance of the distributions $Q(X)$ and $P_0(E)$, respectively. As can be seen in Fig. 1(a) the distributions $Q(X)$ are well approximated by a Gaussian shape. With fixed Δ and ξ, numerical values of $\overline{X_1}$ and $R(E)$ were plotted with their theoretical predictions in Figs. 1(b) and 1(c), respectively. In Fig. 1(c), we also plot canonical energy distributions for a comparison. The numerical value of $R(E)$ was calculated from the simulation by counting a right transition at each energy histogram E. For all temperatures, the simulation results show a good agreement with the stochastic predictions.

The characteristic feature of the canonical sampling can be seen in the profiles of $R(E)$. Notice that the maximum peaks of each canonical distribution exactly correspond to the points of E_0 satisfying $R(E_0) = 0.5$. Within a small energy window around E_0, the value of $R(E)$ shows a linear behavior as $0.5[1 - \gamma_0(E-E_0)]$, $\gamma_0 = \sqrt{f\Delta/8\pi\sigma_0}$. This means that the transition from E becomes biased to a left or right direction in one-dimensional energy space depending on whether E is greater than E_0 or not, respectively. The bias in $R(E)$ causes the sampling to be concentrated on the average energy E_0.

B. Multicanonical sampling

In multicanonical ensemble, the uniform sampling can be obtained by weighing each state of an energy E by the weight w_{mc} that is inversely proportional to $\Omega(E)$, as

$$w_{mc}(E) = 1/\Omega(E) = e^{-\beta_0 \alpha_{mc}(E)}, \tag{11}$$

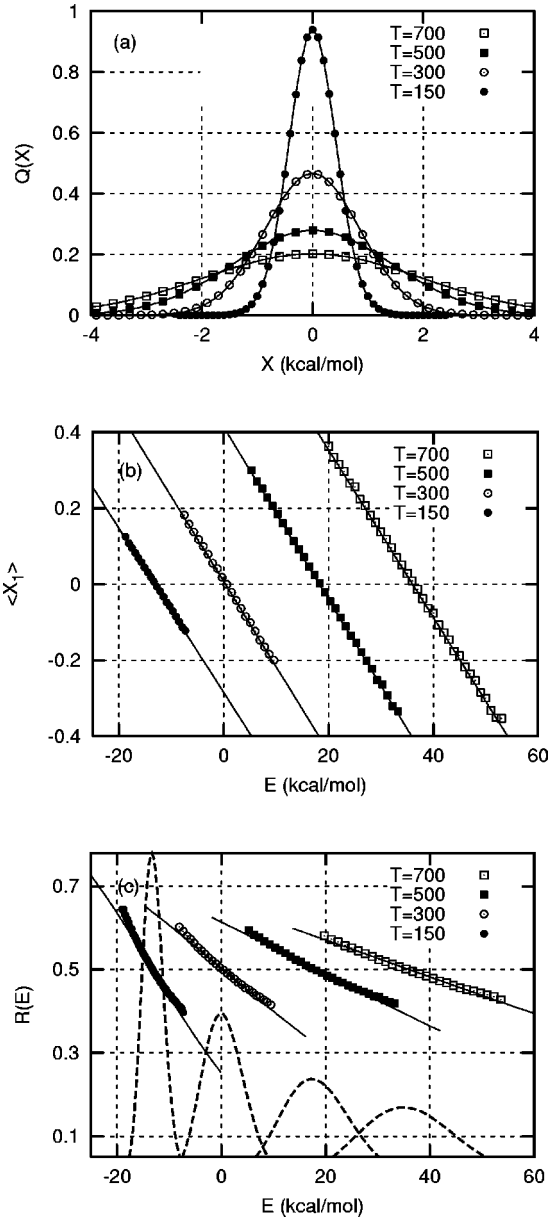

FIG. 1. (a) The distribution of an energy increment X, $Q(X)$, (b) the first moment $\overline{X_1}$, and (c) the right transition probability $R(E)$ in canonical ensembles at $T = 150$, 300, 500, and 700 K for $(\mathrm{Ala})_2$ in a gas phase. In (b) and (c), theoretical predictions are plotted as solid lines. The canonical distributions $P_0(E)$ in (c) are magnified by four times for comparison.

where $\alpha_{mc}(E)$ is the multicanonical potential function. In Eq. (11), the multicanonical sampling was considered as the canonical one on the modified potential energy surface $\alpha_{mc}(E)$. Thus the energy trajectory in multicanonical ensemble can be generated by performing an isokinetic MD at T_0 with a scaled Newton's equation [14]

$$\dot{\mathbf{p}}_i = -\frac{\partial \alpha_{mc}(E)}{\partial \mathbf{q}_i} = \frac{\partial \alpha_{mc}(E)}{\partial E}\mathbf{f}_i, \tag{12}$$

where $\mathbf{q}_i$, $\mathbf{p}_i$, and $\mathbf{f}_i$ correspond to the coordinate, momentum, and force of the particle i on the original potential en-

ergy surface E, respectively. Notice that the derivative of the multicanonical potential α_{mc} corresponds to the force scaling factor in Eq. (12). In the usual case, the simulation proceeds by determining the weight w_{mc} iteratively from previous simulations since $\Omega(E)$ is not known *a priori*.

The connection between the sampling dynamics and the corresponding stochastic process in a multicanonical ensemble can be shown by considering the simulation with an arbitrary weight $w(E)=e^{-\beta_0\alpha(E)}$. For a given weight $w(E)$, the PDF becomes

$$P_\alpha(E)=e^{-\beta_0 A_\alpha(E)}/Z_\alpha[\beta_0], \tag{13}$$

where $A_\alpha(E)=\alpha(E)-T_0S(E)$ and Z_α is the partition function defined by $\int e^{-\beta_0 A_\alpha(E)}dE$. The stochastic differential equation governing the multicanonical sampling can be derived by replacing $\Gamma_\alpha(E)=-\partial_E A_\alpha$ for Γ in Eq. (4) as

$$\begin{aligned}\partial_t E&=\{T_0/T_S(E)-\partial\alpha(E)/\partial E\}+\sqrt{f}\,\eta(t)\\&=\{1/\tilde{T}_S(E)-1/\tilde{T}_\alpha(E)\}+\sqrt{f}\,\eta(t),\end{aligned} \tag{14}$$

where $\tilde{T}_S(E)=T_S(E)/T_0$ and $\tilde{T}_\alpha(E)=[\partial\alpha(E)/\partial E]^{-1}$. Notice that the drift term in Eq. (14) is uniquely determined by the derivative of $\alpha(E)$ corresponding to the force scaling factor.

The role of $\tilde{T}_\alpha$ in the sampling process of multicanonical MD can be clearly understood when $\tilde{T}_\alpha(E)$ is constant for a whole range of E. If $\tilde{T}_\alpha(E)=\lambda$ in Eq. (14) where λ is an arbitrary positive constant, the Taylor expansion of T_S at E_0' satisfying $T_S(E_0')=\lambda T_0=T_0'$ gives the canonical PDF at a scaled temperature T_0'. Therefore, the inverse of the derivative of $\alpha(E)$ can be considered as a scaling factor for the temperature. This interpretation can also be seen in MC version of the multicanonical ensemble [23]. The acceptance ratio for a given single MC step from E to E' for the multicanonical sampling is given by $A(E)=\exp\{S(E)-S(E')\}$. In a large system where $S(E)/N$ is a smooth function of the energy density E/N, the expansion of $S(E)$ with respect to $E'-E$ gives acceptance ratio $A(E)=\exp\{-(E'-E)/T_S(E)\}$. Thus the multicanonical sampling at the energy E has exactly the same acceptance ratio as the simulated annealing at a temperature $T_S(E)$. In this respect, the sampling subject to the weight $\alpha(E)$ can be considered as a repeated annealing with an energy dependent heating and cooling schedule modulated by $\tilde{T}_\alpha(E)$.

The transition probability describing the multicanonical sampling cannot be defined since it is difficult to obtain the time-dependent solution of FPE corresponding to Eq. (14) for general Γ_α. However, for an infinitesimal time interval Δ, the FPE gives an approximate transition probability [19] as

$$W_\alpha[X,Y_\alpha(E)]=\frac{1}{\sqrt{2\pi\sigma_\alpha}}\exp\left\{-\frac{[X+Y_\alpha(E)]^2}{2\sigma_\alpha}\right\}, \tag{15}$$

where $Y_\alpha(E)=-\Gamma_\alpha(E)\Delta$ and $\sigma_\alpha=f\Delta$. The first and second moments of X are calculated by putting Y_α and σ_α in the canonical formulation. Also, the right transition probability is given by

$$R_\alpha(E)=0.5\left\{1-\mathrm{erf}\left[\frac{\sqrt{\Delta}\Gamma_\alpha(E)}{\sqrt{2f}}\right]\right\}. \tag{16}$$

The uniform sampling can be obtained from a generation of a random walk on the energy space by forcing a condition of $R_\alpha=L_\alpha$, i.e., $\Gamma_\alpha=0$. Thus the stochastic process modeling multicanonical sampling corresponds to a free Brownian motion on the energy space by coinciding $\tilde{T}_\alpha$ with $\tilde{T}_S$. However, the problem still remains unsolved because $\tilde{T}_S$ is not known *a priori*.

III. STAIRCASE TEMPERATURE MODULATION

The essential point of the multicanonical sampling is the weight-dependent temperature modulation of $\tilde{T}_\alpha(E)$ as was seen in Eq. (14). Then, how does the temperature modulation realize the uniform sampling in the energy space? The characteristic dynamics of Eq. (14) can be captured by approximating $\tilde{T}_\alpha(E)$ by a following staircase function:

$$\tilde{T}_\alpha^M(E)=\sum_{i=1}^{M-1}\tilde{T}_i h_i(E), \tag{17}$$

where $\tilde{T}_i=[\tilde{T}_S(E_i)+\tilde{T}_S(E_{i+1})]/2$ and $h_i(E)=\theta(E-E_i)\theta(E_{i+1}-E)$, $\theta(E)$ being the Heaviside step function. Here, E_i is an arbitrary chosen discrete energy in ascending order of $E_1<\cdots<E_M$ within a prescribed energy range $[E_1,E_M]$. To eliminate a boundary effect we set $\tilde{T}_\alpha^M(E)=\tilde{T}_1$ and $\tilde{T}_M$ for $E<E_1$ and $E>E_M$, respectively. Here it should be noted that the effective temperature $\tilde{T}_\alpha(E)$ is a constant $\tilde{T}_i$ for each energy range $[E_i,E_{i+1}]$. This means that the sampling dynamics generates an energy trajectory that samples a canonical ensemble at a temperature $T_i=\tilde{T}_iT_0$ for each energy basin $[E_i,E_{i+1}]$. Next, by approximating $\tilde{T}_S(E)$ with its Taylor expansion at E_i^* satisfying $\tilde{T}_S(E_i^*)=\tilde{T}_i$ for each energy basin $[E_i,E_{i+1}]$, we have

$$\Gamma_\alpha^M(E)=\sum_{i=1}^{M-1}-\xi(T_i)(E-E_i^*)h_i(E). \tag{18}$$

The stationary solution associated with $\tilde{T}_\alpha^M(E)$ becomes

$$P_\alpha^M(E)\sim\exp\left\{-\sum_{i=1}^{M-1}\frac{(E-E_i^*)^2}{2\sigma_i}\,h_i(E)\right\}, \tag{19}$$

where $\sigma_i=k_BT_i^2C_V(T_i)$. Taking an infinite limit of $M\to\infty$ we can recover the uniform distribution. The key point of the staircase approximation is to transform a complex free energy surface into a multivalleyed landscape structure. Dividing the energy space into smaller canonical basins all valleys are parametrized to have a parabolic shape with a curvature

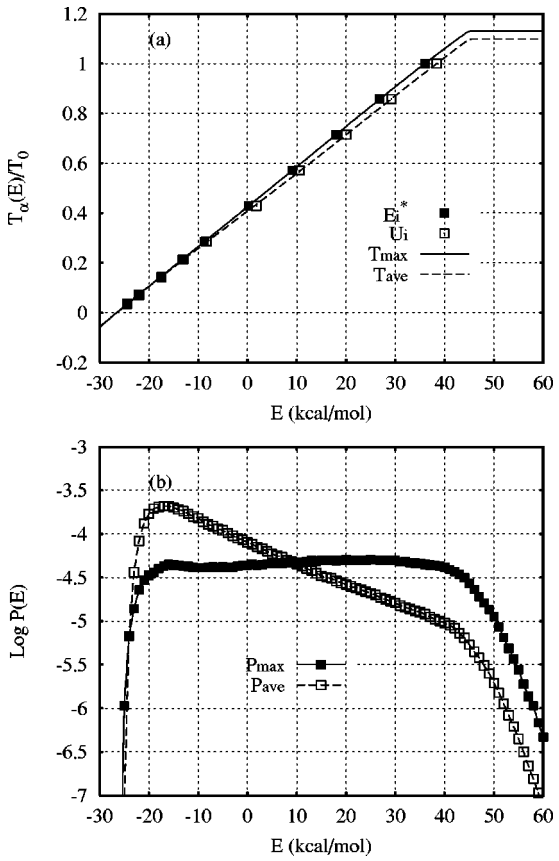

FIG. 2. (a) The effective temperature $\tilde{T}_{max}$ (solid line) and $\tilde{T}_{ave}$ (dashed line) constructed from the maximum probability energy E_i^* and the average energy U_i, respectively, for $(\mathrm{Ala})_2$ in a gas phase. (b) The probability distributions P_{max} and P_{ave} obtained from the multicanonical simulation ($T_0=700$ K) based on $\tilde{T}_{max}$ and $\tilde{T}_{ave}$, respectively.

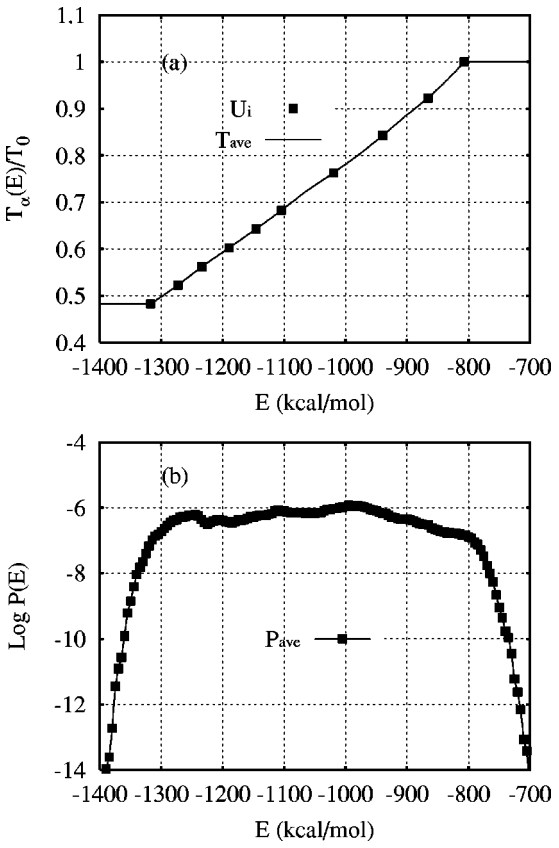

FIG. 3. (a) The effective temperature $\tilde{T}_{ave}$ and (b) the resulting probability distribution P_{ave} of $(\mathrm{Ala})_2$ in an explicit water phase. The filled squares in (a) represent the average energies at each canonical temperature. The multicanonical simulation was performed at $T_0=500$ K.

being σ_i^{-1} and position of the center being E_i^*. The free energy barriers between the valleys become small to be comparable with thermal fluctuations with an increase of M, allowing the dynamics to sample all over energy basins.

Our analysis based on the staircase approximation gives a natural way to realize an uniform sampling. Denoting $\tilde{T}_S(E_i^*)=\tilde{T}_i$, an explicit form of $\tilde{T}_S(E)$ can be estimated by interpolating a maximum probability energy set $[E_i^*,\tilde{T}_i]$ from preliminary canonical simulations. Notice that E_i^* corresponds to the maximum probability energy for each canonical basin in Eq. (19). In the present $(\mathrm{Ala})_2$ system in a gas phase, we construct the multicanonical weight $\tilde{T}_{max}(E)$ [see Fig. 2(a)] by interpolating E_i^* obtained from the canonical simulations at $T_i=25$, 50, 100, 150, 200, 300, 400, 500, 600, and 700 K. By substituting $\tilde{T}_{max}^{-1}$ for the force scaling function in Eq. (12), we performed multicanonical MD at $T_0=700$ K. Resulting energy distribution $P_{max}(E)$ in Fig. 2(b) shows an uniform sampling for all energy range. We would like to emphasize that our result is obtained directly from the estimation of $\tilde{T}_\alpha(E)$, contrary to conventional approaches correcting the multicanonical potential $\alpha(E)$ via iterative simulations.

By noting that E_i^* converges to an average energy $U[\tilde{T}_i]$ in the thermodynamic limit, a necessary condition for the uniform sampling is derived as

$$E=U[\tilde{T}_S(E)], \tag{20}$$

from the extension of the staircase approximation to a continuous limit in Eq. (19). Determining $\tilde{T}_S=h^{-1}(E)$ by inverting a functional relationship $U=h(\tilde{T})$ of the canonical simulations, the fixed point condition of Eq. (20) can be satisfied for all E. This means that in a large system, we can obtain an uniform sampling by constructing $\tilde{T}_\alpha$ from an average energy set $[U_i,\tilde{T}_i]$. To confirm this, we applied our method to the solvated $(\mathrm{Ala})_2$ system in which the dynamic energy range is very large. The multicanonical weight in Fig. 3(a) is constructed from the average energy set obtained from the canonical simulations at $T_i=240$, 260, 280, 300, 340, 380, 420, 460, and 500 K. Even though the sampling energy range is huge the result shows an impressive uniform distribution over the whole energy region as in Fig. 3(b). However, for a small system like $(\mathrm{Ala})_2$ in a gas phase, the maximum probability energy E_i^* has to be used for an estimation of $\tilde{T}_\alpha$. Even though there is a small difference be-

tween $\tilde{T}_{max}$ and $\tilde{T}_{ave}$ [see Fig. 2(a)], the resulting P_{ave} shows a significant deviation from P_{max} in Fig. 2(b).

When we approximate $\tilde{T}_S$ by $\tilde{T}_\alpha$ in Eq. (20), the fixed point $E^*=U[\tilde{T}_\alpha(E^*)]$ plays a very important role in sampling dynamics. Notice that the free energy potential $A_\alpha(E)$ has stationary points at E^* corresponding to crossing points of $\tilde{T}_\alpha$ and $\tilde{T}_S$. Qualitative properties of the sampling can be characterized by identifying the stability of each fixed point, which is determined by [24]

$$\kappa(E^*)=\left|\frac{\partial U}{\partial T_\alpha}\frac{\partial T_\alpha}{\partial E}\right|_{E^*}=\frac{C_V(E^*)}{C_\alpha(E^*)}, \tag{21}$$

where $C_\alpha=\partial E/\partial T_\alpha$. The value of κ determines a local curvature of the free energy potential A_α at E^*. The stable fixed points corresponding to $\kappa(E_S^*)<1$ attract nearby probability currents toward it since A_α is concave at E_S^*. Crossing E_S^*, R_α that was greater than L_α for $E<E_S^*$ becomes less than L_α for $E>E_S^*$. Near unstable fixed points of $\kappa(E_U^*)>1$, the probability currents flow away from E_U^*, showing an opposite behavior in R_α due to the convexity of A_α. Consequently, the sampling concentrates on the isolated stable fixed points. The role of the fixed points can be demonstrated numerically in the multicanonical simulation of the staircase weight function. In Fig. 4(b), the probability distributions P_α^M obtained from an artificially constructed $\tilde{T}_\alpha^M$ [see Fig. 4(a)] are plotted for $M=6$ and 11, respectively. Notice that the peaks of P_α^M in each canonical basin exactly correspond to the stable fixed points E_i^* determined by horizontal crossing points of $\tilde{T}_\alpha^M$ and $\tilde{T}_{max}$ in Fig. 4(a). On the other hand, P_α^M shows a local minimum at the unstable fixed points corresponding to the basin boundaries E_i of $\tilde{T}_\alpha^M$. Here we regard $\tilde{T}_{max}$ as an exact weight because it gives the uniform PDF as was shown in Fig. 3(b).

The efficiency of the sampling depends on how easily the dynamics escapes from one basin attraction and transits to another one. The transition rate can be quantified by calculating the bias of R_α at each basin attraction. In the staircase approximation, R_α shows a ratchet structure [see Fig. 4(c)] as

$$R_\alpha^M(E)\approx 0.5\sum_{i=1}^{M-1}[1-\gamma_i(E-E_i^*)]h_i(E), \tag{22}$$

where $\gamma_i=\sqrt{f\Delta/8\pi\sigma_i}$. The slope of $R_\alpha(E_i^*)$, i.e. γ_i, becomes very steep at low temperature energy region because it is inversely proportional to the temperature T_S. Severely biased R_α becomes an obstacle to the transition between the canonical basins around the stable fixed points, causing a localization of the sampling in the low-energy region [25]. To avoid a trapping of the sampling in low-energy region, the basin attraction has to be reduced comparable with the statistical fluctuations of k_BT_0 by creating more fixed points. As expected, the increase of M enhances the transitions between the canonical basins by lowering the free energy barriers between the basins and results in a broader sampling as can be seen in Fig. 4(b). The discontinuities in R_α^M at basin boundaries E_i originate in the stepwise jumps in $\tilde{T}_\alpha^M$. On the other hand, R_{max} shows a typical random walk producing uniform distribution of P_{max}.

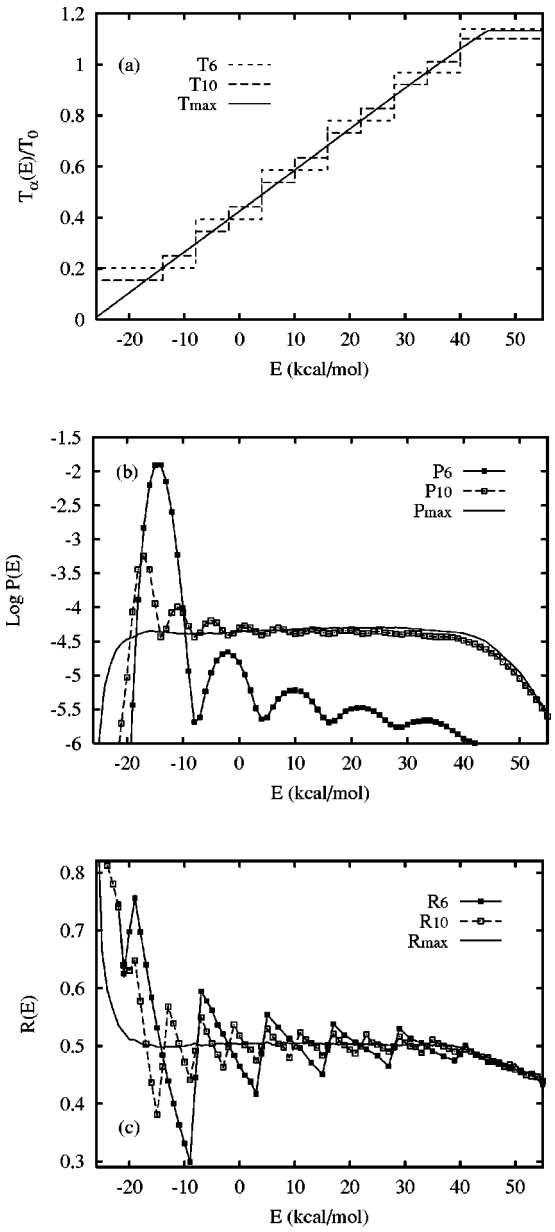

FIG. 4. (a) $\tilde{T}_\alpha^M(E)$ for $M=6$ (dotted line) and 11 (dashed line) scaled by $T_0=700$ K for $(Ala)_2$ in a gas phase. The crossing points of $\tilde{T}_{max}$ (solid line) and $\tilde{T}_\alpha^M(E)$ correspond to the fixed points in Eq. (20). (b) The energy distributions $P_\alpha^M(E)$ based on $\tilde{T}_\alpha^M(E)$ show maximum peaks at the stable fixed point E_i^* in each canonical basin. (c) Ratchet structure of the right transition probabilities of $R_\alpha^M(E)$.

IV. CONCLUSION

The sampling process of molecular dynamic simulation in a multicanonical ensemble has been analyzed by considering the sampling process as a stochastic diffusion modeled by a

Langevin equation. The characteristic features of the sampling dynamics have been identified by computing the transition probability of the Markovian stochastic process. The correspondence between the sampling and the stochastic process has been demonstrated numerically by comparing the simulation results with the theoretical predictions. The necessary condition for the uniform sampling has been derived by analyzing the sampling dynamics in terms of the stochastic model subject to the staircase temperature modulation. Our analysis reveals that the dynamical origin of the uniform sampling in multicanonical MD is the formation of the infinite number of the fixed points, which makes the dynamics move constantly between the canonical basin attractions by lowering the free energy barriers. Finally, we showed that the weight factor in multicanonical MD can be determined by interpolating the maximum probability energy points of the canonical samplings at different temperatures. In contrast to the previous multicanonical MD updating the multicanonical potential $\alpha(E)$ iteratively [14], our method is based on the direct estimation of the derivative of the multicanonical potential, i.e., $\tilde{T}_{\alpha}(E)$.

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