Multicanonical molecular dynamics algorithm employing an adaptive force-biased iteration scheme

Jae Gil Kim,[1,*] Yoshifumi Fukunishi,[2] and Haruki Nakamura[3]
[1]*Japan Biological Information Research Center, JBIC, Aomi 2-41-6, Koto-ku, Tokyo, 135-0064, Japan*
[2]*Biological Information Research Center, AIST, Aomi 2-41-6, Koto-ku, Tokyo, 135-0064, Japan*
[3]*Laboratory of Protein Informatics, Research Center for Structural Biology Institute for Protein Research, Osaka University 3-2 Yamadaoka, Suita, Osaka 565-0871, Japan*
(Received 7 June 2004; published 17 November 2004)

We present one effective multicanonical molecular dynamics (MCMD) algorithm accelerating the convergence of rough energy landscapes simulations via an adaptive force-biased iteration scheme. Our method utilizes several short MCMD simulations with dynamically updated weights and combines them to estimate the density of states via multiple histogram technique. The key step of our algorithm is the adaptive refinement for the derivative of multicanonical weight, which allows the system to enlarge the sampling energy range maintaining the statistical accuracy. The performance of our method has been validated for atomic Lennard-Jones clusters.

DOI: 10.1103/PhysRevE.70.057103 PACS number(s): 05.70.−a, 02.50.−r, 64.60.−i

Recently, multicanonical sampling (MUCA) has become one of the primary tools to study equilibrium properties of diverse complex systems, exhibiting a quasiergodic behavior [1]. Since configurational spaces of complex systems are effectively partitioned into basin attractions surrounded by high energy barriers, conventional simulations employing the Boltzmann weight often fail to sample thermally accessible phase space due to a trapping in one of local minima. To circumvent this quasiergodicity, MUCA uses a non-Boltzmann weight, which is iteratively modified to allow the system to visit high energy barrier regions more frequently [2]. Combined with Monte Carlo (MC) or molecular dynamics (MD) algorithm, MUCA has been proved to be very effective for studies of phase transitions of lattice spins [2] and folding problems of small peptides [3]. One limitation of MUCA is its unknown weight dependence. Since the weight is inversely proportional to the density of states, i.e., $\Omega(E)$, the determination of weight becomes very difficult for large size systems having a huge dynamic range of $\Omega(E)$. Therefore, many theoretical efforts [4–7] have been devoted to accelerate the convergence for the determination of weight in MUCA.

In this Brief Report, we developed one effective method to accelerate the convergence of multicanonical MD (MCMD) by combining an adaptive force-biased iteration with an umbrella sampling scheme. In contrast to conventional MCMD associated with a long production run with predetermined weight, we performed several short MCMD simulations with dynamically updated weights, and then combines them to estimate the density of states through multiple histogram technique [8]. The critical feature of our method is the adaptive refinement for the derivative of multicanonical weight, which enables a considerable enhancement for the rate of convergence maintaining the statistical accuracy of the simulation. The effectiveness of our method has been validated for atomic Lennard-Jones (LJ) clusters.

Let us begin by briefly reviewing the conventional MCMD, in which multicanonical potential $\alpha(E)$ is iteratively determined using

$$\alpha^{k+1}(E) = \alpha^k(E) + \frac{1}{\beta_0} \ln P^k(E), \tag{1}$$

where $P^k(E)$ is the probability density function (PDF) at kth iteration and β_0 is an arbitrarily chosen reference temperature [3]. As the iteration proceeds, $\alpha(E)$ approaches $T_0\mathcal{S}(E)$, $\mathcal{S}(E)$ being the microcanonical entropy of $k_B \ln \Omega(E)$. The multicanonical ensemble associated with the weight $w_k(E) = e^{-\beta_0 \alpha^k(E)}$, is sampled by the constant temperature MD at β_0 with the energy-dependent force scaling as $\dot{\mathbf{p}}_i = \nu^k(E)\mathbf{f}_i$, $\nu^k = \partial_E \alpha^k(E)$. Here, $\mathbf{p}_i$ and $\mathbf{f}_i$ correspond to the momentum and force of the particle i on the original potential energy E, respectively [3].

One drawback of the potential-biased MCMD using Eq. (1) is that the simulation requires human interventions in the iteration to represent $\alpha(E)$ as a smooth function. However, the smoothing process is actually redundant since the trajectory of the particle is not determined by $\alpha^k(E)$, but $\nu^k(E)$. Based on this, we developed the force-biased multicanonical MD (FB-MCMD) employing

$$\nu^{k+1}(E) = \nu^k(E) + \mathcal{F}^k(E), \tag{2}$$

where $\beta_0 \mathcal{F}^k(E) = \partial_E \ln P^k(E)$. The derivation of Eq. (2) is straightforward denoting that it is obtained by differentiating both sides of Eq. (1), but the exact physical meaning of the force-biased iteration can be appreciated in the stochastic formulation of MUCA [5]. According to our analysis [5,9], the iteration procedures in Eq. (2) are equivalent to the dynamical processes approaching a free Brownian motion via the cancellation of the deterministic force in corresponding Langecvin equation, and the uniform sampling weight $\nu_{\mathcal{S}}(E) = T_0 / T_{\mathcal{S}}(E)$, $T_{\mathcal{S}}(E) = [\partial \mathcal{S}(E) / \partial E]^{-1}$, can be estimated by

*Corresponding author. Email address: jaegil@bu.edu

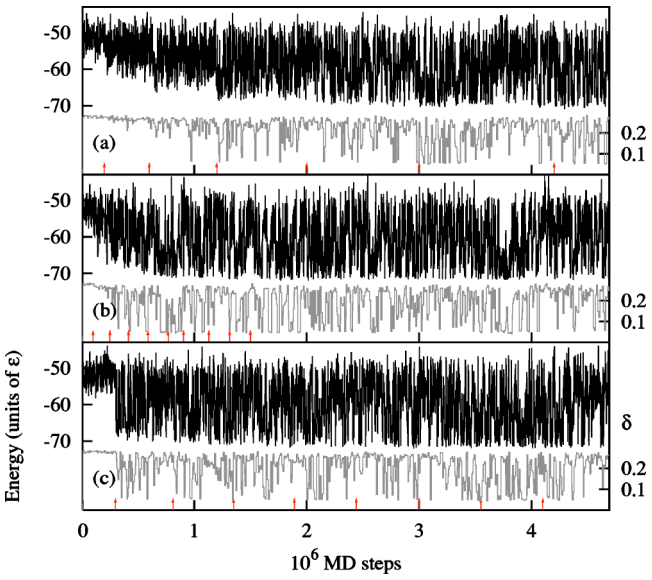

FIG. 1. Energy trajectory (black) and bond length fluctuation δ (gray) for (a) FB-MCMD, (b) AdFB1, and (c) AdFB2 for LJ19. Arrows in all figures represent the weight updates. Further updates in (b) are not represented beyond 10th iteration.

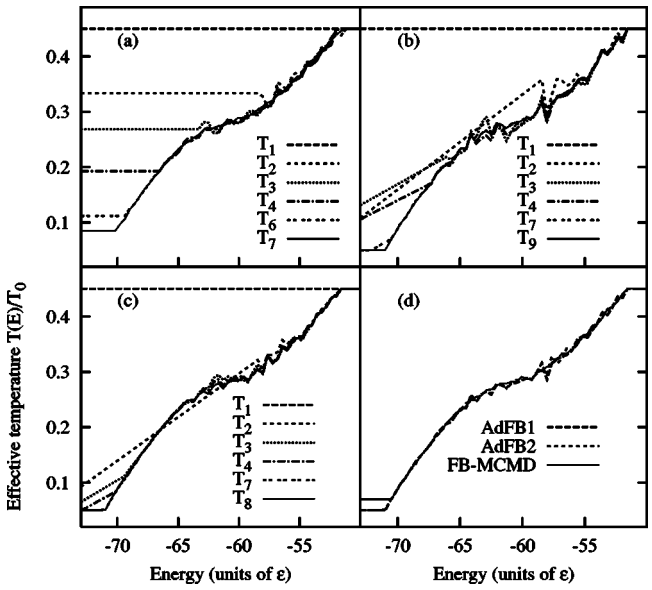

FIG. 2. Effective temperature $\tilde{T}_k(E)$ as a function of the iteration for (a) FB-MCMD, (b) AdFB1, and (c) AdFB2 for LJ19. (d) Convergent effective temperatures of $\tilde{T}_7$ in FB-MCMD, $\tilde{T}_9$ in AdFB1, and $\tilde{T}_7(E)$ AdFB2.

inverting the functional relationship between the average energy $U(T)$ and the temperature as $\nu_S = U^{-1}(E)$.

In FB-MCMD, the system moves away from previous sampled regions by the force biasing $\mathcal{F}^k(E)$ and wanders another unexplored regions via the canonical samplings at both energy ends [9]. Since the sampling range is extended as a function of the iteration, the number of sampling in each iteration step has been also increased to maintain the statistical accuracy as $N_k^{FB} = kN_1$, N_1 being the number of sampling in the first iteration. The typical feature of FB-MCMD has been demonstrated in the simulation of 19-atoms LJ cluster (LJ19) of $E = 4\epsilon\Sigma_{i<j}^N[(\sigma/r_{ij})^{12} - (\sigma/r_{ij})^6]$ with $\sigma = 3.4$ Å and $\epsilon = 0.2472$ kcal/mol corresponding to Ar atom. The LJ cluster has been widely used to test many sampling algorithms due to its topographical feature of rough energy landscapes [10–12]. The simulation has been done using the program PRESTOX [13] with 10 fs time step, 0.1 kcal/mol bin size, and $N_1 = 2 \times 10^5$ MD steps at $T_0 = 0.45\epsilon$. To prevent a cluster evaporation, a repulsive spherical wall $U_c(\mathbf{r}) = k_0(r - R_c)^2$ has been imposed on $r \geqslant R_c = 1.75\sigma$ with $k_0 = 50$ kcal/mol. As observed in Fig. 1(a), the simulation shows a typical random walk in energy space and extends the sampling range to a low energy region with the updates of the weight indicated by arrows along x axis. The effective temperature $\tilde{T}_k(E) = 1/\nu^k(E)$ in Fig. 2(a) converges to the valid one at 7th iteration, allowing the system to swap an entire energy space several times without further refinements for the weight. The conformational state of LJ cluster has been checked by calculating the bond length fluctuation $\delta = [2/N(N-1)]\Sigma_{i<j}^N \sqrt{\Delta r_{ij}/\langle r_{ij}\rangle}$ where $\Delta r_{ij} = \langle r_{ij}^2\rangle - \langle r_{ij}\rangle^2$, $\langle \ldots \rangle$ being the time average over 10^4 MD steps [14]. The average mobility of atoms indicated by δ in Fig. 1(a) is very small in a solidlike phase of low energy region and large in a liquidlike phase above the melting point identified by a plateau in Fig. 2(a).

For systems having a small degrees of freedom, FB-MCMD works very well through the automatic determination of the weight. However, the convergence has not been improved compared to the potential biased MCMD due to the multiple increment of the sampling data as $N_k^{FB} = kN_1$, that is intractable for complex systems having a large dynamic range. To accelerate the convergence of the simulation, here we modified FB-MCMD in various aspects. First, we use the adjusted number of sampling as $N_k^{Ad} = N_1 S_{k-1}/S_1$ $(k > 1)$, $S_k = E_h^k - E_l^k$ being the sampled energy range at kth iteration. Both E_h^k and E_l^k are updated every iteration step using $\min[E_1^k, E_1^{k-1}]$ and $\max[E_2^k, E_2^{k-1}]$, respectively, E_1^k and E_2^k being the lowest and highest energies sampled at kth iteration. Notice that N_k^{Ad} is monotonically increasing as a function of the iteration, but much smaller than N_k^{FB} since $S_k \geqslant S_{k-1}$. For example, $N_7^{Ad}/N_7^{FB} \sim 0.5$ in Fig. 2(a). However, FB-MCMD with an adjustable N_k^{Ad} has one problem that the force scaling function might be exposed to a statistical noise due to a poor sampling statistics of $P^k(E)$. To solve this problem, we developed an adaptive iteration scheme for the force scaling function as

$$\nu^{k+1}(E) = \nu_T^k(E) + \mathcal{F}_T^k(E), \tag{3}$$

where

$$\nu_T^k(E) = \frac{\sum_{j=1}^k f_j(E)\nu_j(E)}{\sum_{j=1}^k f_j(E)},$$

$f_j(E) = N_j^{Ad} w_j(E)/Z_j$, and $\beta_0 \mathcal{F}_T^k(E) = \partial_E \ln P_T^k(E)$, $P_T^k(E)$ being the total PDF defined as $\Sigma_{j=1}^k N_j^{Ad} P_j(E)$. The relative partition function Z_j is self-consistently determined as $Z_i = \Sigma_E w_i(E)\Omega^k(E)$, $\Omega^k(E)$ being the approximate density of

states determined from multiple histogram analysis for simulations with weights $w_j(E)$ and resulting PDFs $P_j(E)$ as $\Sigma_{j=1}^{k} N_j^{Ad} P_j(E) / \Sigma_{j=1}^{k} f_j(E)$. Notice that differentiating both sides of the logarithm of $\Omega^k(E)$ and identifying $\beta_0 \nu^{k+1}(E) = \partial \ln \Omega^k(E) / \partial E$ gives Eq. (3). The adaptive force-biased iteration in Eq. (3) has two contributions of the weighted average $\nu_I^k(E)$ of all previous force scaling functions $\nu_j(E)$ and the mean force $\mathcal{F}_I^k(E)$ derived from the total PDF. Since all previous simulations are adaptively combined to estimate next weight, the iteration becomes very robust and the statistical uncertainty by a poor statistics of $P^k(E)$ can be significantly reduced.

Our next modification is to combine the adjusted FB-MCMD (AdFB-MCMD) with an umbrella sampling scheme. Contrary to conventional MCMD associated with a long production run with predetermined weight, here we performed several short MCMD simulations with dynamically updated weight $\nu_j(E)$ and then combined them to estimate the density of states $\Omega(E)$ via multiple histogram technique. The necessary condition for the success of this approach is that the number of sampling N_k^{Ad} is relatively long enough for the system to sample the ensemble $w_j(E)$, and the perturbation due to the update of the weight should be negligible. The former condition is realized by choosing an appropriate large N_1 and the latter one is also effectively achieved since the weight rapidly converges to the unique one and does not change with further iterations. The detailed simulation scheme is outlined as follows. (i) Perform MCMD at β_0 with $\nu^1(E)=1$. (ii) By calculating $\nu_I^k(E)$ and $\mathcal{F}_I^k(E)$ from the energy histogram, update the force scaling function using

$$\nu^{k+1}(E) = \begin{cases} \text{Eq . (3)} & \text{for } E_l^k \leqslant E \leqslant E_h^k, \\ \dfrac{1}{\tilde{T}^{k+1}(E_l^k) + \xi(E - E_l^k)} & \text{for } E < E_l^k, \end{cases} \tag{4}$$

where $\xi = [\tilde{T}^{k+1}(E_h^k) - \tilde{T}^{k+1}(E_l^k)] / [2(E_h^k - E_l^k)]$. In Eq. (4), we used the linear extrapolation having the slope ξ for the estimation of the effective temperature $\tilde{T}^{k+1}$ for $E < E_l^k$. Notice that $\tilde{T}^{k+1} = 1/\nu^{k+1}$ is well defined for the sampled region of $E_l^k \leqslant E \leqslant E_h^k$. (iii) Repeat steps (ii) to obtain a flat energy distribution. (iv) Calculate $\Omega(E)$ by joining all simulation results of $\alpha^j = \int \nu^j(x) dx$ and P^j using multiple histogram technique. The canonical PDF and the ensemble average of any observable O are obtained as $P_0(E,T) = \int dE \Omega(E) e^{-\beta E}$ and $\langle O \rangle_T = \int dE P_0(E,T) O(E)$, respectively.

The validity of AdFB-MCMD has been first examined by monitoring N_1 dependence for LJ19. Actually, N_1 should be chosen not to be small since the success of AdFB-MCMD relies on the fidelity of the sampling statistics in each iteration step. We compared two simulations of $N_1 = 10^5$ MD steps (AdFB1) and 3×10^5 MD steps (AdFB2) with FB-MCMD result. The energy samplings in Figs. 1(b) and 1(c) show the same characteristic of FB-MCMD with subsequent enlargements of the sampling ranges to an unexplored low energy region via automatic determinations of weights. However, the updates of the weight indicated by arrows in Figs. 1(b) and 1(c) are more frequent due to an optimal adjustment of N_k^{Ad} compared to FB-MCMD. The effective temperature for AdFB1 in Fig. 2(b) shows some fluctuations at low energy ends in early iterations, but rapidly converges to the vaild one at 9th iteration. On the other hand, the statistical uncertainty of AdFB2 with a large N_1 is noticeably reduced and the weight reaches the convergent one at 7th iteration. All convergent weights of $\tilde{T}_9(E)$ in AdFB1 at 1.4 ns and $\tilde{T}_7(E)$ in AdFB2 at 3.0 ns are in a good agreement with $\tilde{T}_7(E)$ in FB-MCMD at 4.2 ns as in Fig. 2(d), demonstrating the acceleration of the convergence of AdFB-MCMD. The accuracy of simulations has been checked by comparing thermodynamic quantities in Fig. 3. The differences in the average energy $U(T)$ are indistinguishable and the specific heats $C_v(T)$ also show a good agreement except for low temperature region, in which the sampling statistics of FB-MCMD is bad.

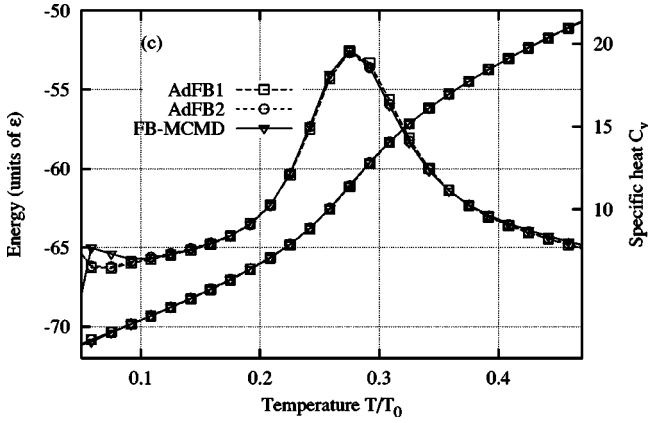

FIG. 3. Average energy $U(T)$ and specific heat $C_V(T)$ for FB-MCMD, AdFB1, and AdFB2.

Next, we examined our method for LJ31 having a more complicated topography associated with low lying multiple minima [11,12]. Conventional multicanonical MC shows an anomalous behavior in thermodynamic properties such as an extra peak or bump in the specific heat at low temperature region below $T \sim 0.17$ [12]. The simulation has been done for 18 ns using $N_1 = 2 \times 10^5$ MD steps and $T_0 = 0.45\epsilon$ with the bin size of 0.1 kcal/mol and $R_c = 2.2\sigma$ (LJ31-I). As expected, the energy trajectory in Fig. 4(a) shows a characteristic random walk including the phase transition region and the neighborhood of the global minimum of −133.58. The lowest sampled energy is identified as −133.12 and the weight converges to the valid one at 10th iteration corresponding to 3.2 ns in Fig. 4(b). Both thermodynamic properties of $U(T)$ and $C_v(T)$ in Fig. 5 show a well defined smooth behavior without any anomaly of a peak or bump at low temperature region. However, the specific heat displays an oscillation for a very low temperature region below 0.05 due to a poor sampling statistics, in which another narrow phase change associated with the coexistence of multiple minima has been predicted around $T \sim 0.03$ by the entropic tempering and harmonic superposition approximation methods [12]. To examine this, another AdFB-MCMD simulation (LJ31-II) has

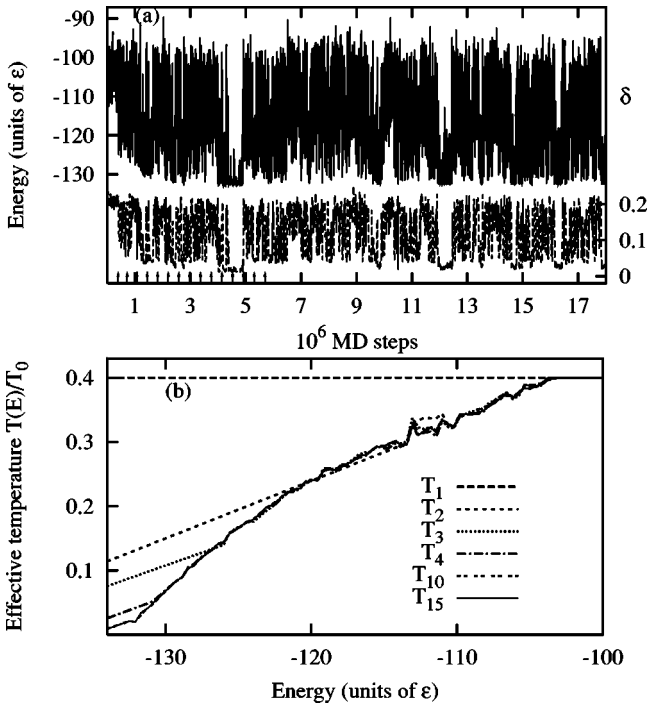

FIG. 4. (a) Energy trajectory (solid) and bond length fluctuation δ (dashed), and (b) effective temperature $\tilde{T}_k(E)$ for LJ31-I.

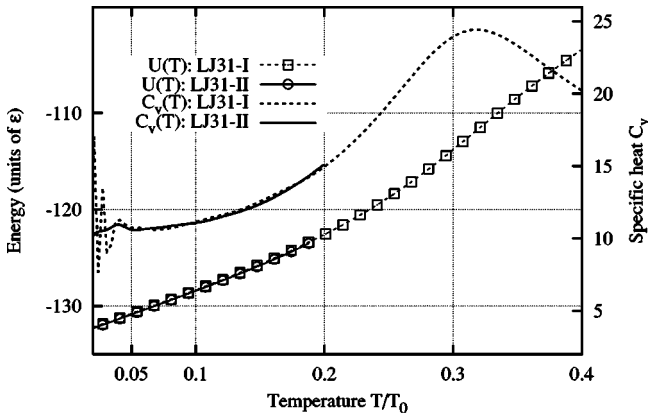

FIG. 5. Average energy $U(T)$ and specific heat $C_V(T)$ for LJ31-I and LJ31-II.

been performed for 15 ns with bin size of 0.05 kcal/mol, focusing on low temperature region of $0.01<T<0.2$. As observed in Fig. 5, we found a small peak in the specific heat around $\tilde{T}\sim 0.035$ consistent to previous study [12]. Except for this narrow temperature region, both simulations of LJ31-I and LJ31-II give the same thermodynamics.

In summary, we developed the adaptive force-biased multicanonical molecular dynamics algorithm, which enables a considerable enhancement for the rate of convergence of rough energy landscape simulations by combining the adaptive refinement for the weight with multiple histogram technique. We expect that AdFB-MCMD can be also applied to other complex systems such as spin glasses or protein folding problem.

We acknowledge that this work was supported by NEDO and METI.

[1] B.J. Bern and J.E. Straub, Curr. Opin. Struct. Biol. **7**, 181 (1997); A. Mitsutake, Y. Sugita, and Y. Okamoto, Biopolymers **60**, 96 (2001); U.H.E. Hansmann, Comput. Sci. Eng. **5**, 64 (2003).

[2] B.A. Berg and T. Celik, Phys. Rev. Lett. **69**, 2292 (1992); J. Lee, *ibid.* **71**, 211 (1993).

[3] N. Nakajima, H. Nakamura, and A. Kidera, J. Phys. Chem. B **101**, 817 (1997); U.H.E. Hansmann, Y. Okamoto, and F. Eisenmenger, Chem. Phys. Lett. **259**, 321 (1996).

[4] S. Kumar, P. Payne, and M. Vasquez, J. Comput. Chem. **17**, 1269 (1996).

[5] J.G. Kim, Y. Fukunishi, and H. Nakamura, Phys. Rev. E **67**, 011105 (2003).

[6] T. Terada, Y. Matsuo, and A. Kidera, J. Chem. Phys. **118**, 4306 (2003).

[7] A. Mitsutake, Y. Sugita, and Y. Okamoto, J. Chem. Phys. **118**, 6664 (2003); **118**, 6676 (2003).

[8] A.M. Ferrenberg and R.H. Swendsen, Phys. Rev. Lett. **63**, 1195 (1989).

[9] J.G. Kim, Y. Fukunishi, A. Kidera, and H. Nakamura, Phys. Rev. E **68**, 021110 (2003); **69**, 021101 (2004).

[10] H. Xu and B.J. Berne, J. Chem. Phys. **112**, 2701 (2000).

[11] J.P.K. Doye, M.A. Miller, and D.J. Wales, J. Chem. Phys. **111**, 8417 (1999).

[12] F. Calvo and J.P.K. Doye, Phys. Rev. E **63**, 010902 (2000).

[13] Y. Fukunishi, Y. Mikami, and H. Nakamura, J. Phys. Chem. B **107**, 13201 (2003).

[14] J. Jellinek, T.L. Beck, and R.S. Berry, J. Chem. Phys. **84**, 2783 (1986).