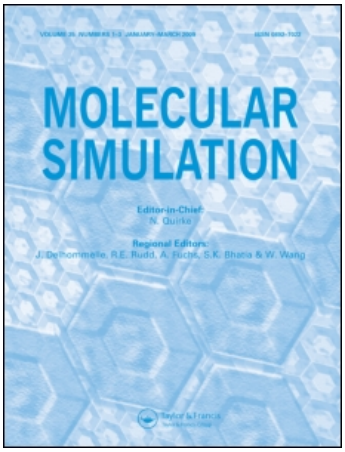

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A new generalized-ensemble algorithm: multicanonical-multioverlap algorithm

S. G. Itoh[a]; Y. Okamoto[a]
[a] Department of Physics, School of Science, Nagoya University, Nagoya, Aichi, Japan

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A new generalized-ensemble algorithm: multicanonical–multioverlap algorithm

S. G. ITOH* and Y. OKAMOTO†

Department of Physics, School of Science, Nagoya University, Nagoya, Aichi 464-8602, Japan

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We introduce a new generalized-ensemble algorithm, which we refer to as the multicanonical–multioverlap algorithm. By utilizing a non-Boltzmann weight factor, this method realizes a random walk in the multi-dimensional, energy-overlap space and explores widely in the configurational space including specific configurations, where the overlap of a configuration with respect to a reference state is a measure for structural similarity. We apply the multicanonical–multioverlap molecular dynamics (MD) method to a penta peptide, Met-enkephalin, in vacuum as a test system. We also apply the multicanonical and multioverlap MD methods to this system for the purpose of comparisons. We see that the multicanonical–multioverlap MD method realizes effective sampling in the configurational space including specific configurations more than the other two methods.

Keywords: Molecular dynamics simulation; Generalized-ensemble algorithm; Protein folding; Transition state

1. Introduction

In complex systems such as proteins, we must realize effective samplings in the configurational space. In usual canonical-ensemble simulations [1–6], however, it is difficult to achieve this. This is because the usual canonical-ensemble simulations tend to get trapped in a few of many local-minimum states. To overcome these difficulties, the generalized-ensemble algorithms have been proposed (for a review, see, for instance, Ref. [7]).

The multicanonical algorithm [8–11] is one of the most well-known methods among the generalized-ensemble algorithms. In the multicanonical ensemble, the probability distribution of the potential-energy is expressed by the product of the density of states and a non-Boltzmann weight factor, which we refer to as the multicanonical weight factor and we have a flat probability distribution of the potential-energy. Therefore, multicanonical-ensemble simulations realize free random walks in the potential-energy space and have effective samplings in the configurational space. This method is suitable to sample widely the configurational space, but not to have samplings that focus on a specific configuration because of the very nature of the algorithm.

The multioverlap algorithm was recently proposed for Monte Carlo (MC) method [12] and molecular dynamics (MD) method [13,14] in order to investigate the stability of specific configurations and transition states among specific configurations. In the multioverlap ensemble, the probability distribution is expressed by the product of the density of states and a non-Boltzmann weight factor, which we refer to as the multioverlap weight factor and we have a flat probability distribution in the overlap space. The method aims at achieving effective samplings that focus on specific configurations. In this method, however, we do not have a random walk in the potential-energy space.

In this article, we introduce a simulation method (see Ref. [15] for details), which we refer to as the multicanonical–multioverlap algorithm, to sample widely the configurational space and effectively the vicinity of specific conformations of a protein. We apply the multicanonical–multioverlap MD method to Met-enkephalin in vacuum and test the effectiveness of the method by comparing the results with those of the multicanonical MD method and the multioverlap MD method.

In Section 2, we summarize the formulation of the multicanonical–multioverlap algorithms. We present the

*Corresponding author. Email: itoh@tb.phys.nagoya-u.ac.jp
†Email: okamoto@phys.nagoya-u.ac.jp

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details of the three simulations that we performed and their results in Section 3. Section 4 is devoted to conclusions.

2. Multicanonical–multioverlap algorithms

2.1 Definition of dihedral-angle distance

We introduce a dihedral-angle distance [12,16] which is a complementary quantity of the overlap, as a reaction coordinate. The dihedral-angle distance d with respect to a reference configuration is defined by

$$d = \frac{1}{n\pi}\sum_{i=1}^{n} d_{\mathrm{a}}\left(v_i, v_i^0\right). \tag{1}$$

Here, n is the total number of dihedral angles, v_i is the dihedral-angle i and v_i^0 is the dihedral-angle i of the reference configuration. The distance $d_{\mathrm{a}}(v_i, v_i^0)$ between two dihedral angles is given by

$$d_{\mathrm{a}}(v_i, v_i^0) = \min(|v_i - v_i^0|, 2\pi - |v_i - v_i^0|). \tag{2}$$

If $d = 0$, from equation (1), all dihedral angles are coincident with those of the reference configuration and the two structures are identical. The dihedral-angle distance is thus an indicator of how similar the conformation is to the reference conformation.

2.2 Effective sampling in the energy-overlap space

In the case of canonical ensemble at a constant temperature T_0, the probability distribution P_{c} of potential energy E is represented by the product of the density of states $n(E)$ and the Boltzmann weight factor $W_{\mathrm{c}}(E, T_0)$:

$$P_{\mathrm{c}}(E, T_0) = n(E)W_{\mathrm{c}}(E; T_0) = n(E)\,\mathrm{e}^{-\beta_0 E}, \tag{3}$$

where β_0 is given by $\beta_0 = 1/k_{\mathrm{B}}T_0$ (k_{B} is the Boltzmann constant). In the multicanonical ensemble at a constant temperature T_0, by employing the non-Boltzmann weight factor $W_{\mathrm{muca}}(E)$, which we refer to as the multicanonical weight factor, a uniform probability distribution of potential energy is obtained:

$$\begin{aligned} P_{\mathrm{muca}}(E) &= n(E)W_{\mathrm{muca}}(E) = n(E)\,\mathrm{e}^{-\beta_0 E_{\mathrm{muca}}(E)} \\ &\equiv \text{constant}, \end{aligned} \tag{4}$$

where $E_{\mathrm{muca}}(E)$ is the multicanonical potential energy. The multicanonical weight factor, or the multicanonical potential energy, is not *a priori* known and has to be determined by short preliminary simulations. There exist many methods for the determination of the weight factor (see, e.g. Refs. [17–26]). Equation (4) implies that multicanonical simulations realize a free random walk in the potential-energy space and are able to sample effectively the configurational space. In this method, however, it is difficult to sample the vicinity of specific configurations because of the very nature of the algorithm.

The multioverlap algorithm, which is developed by generalizing the multicanonical algorithm, is suitable for samplings that focus on specific configurations. In the multioverlap ensemble at a constant temperature T_0, the probability distribution of dihedral-angle distances is defined by

$$\begin{aligned} P_{\mathrm{muov}}(d_1,\ldots,d_N) &= \int \mathrm{d}E\, n(E,d_1,\ldots,d_N)W_{\mathrm{muov}}(E,d_1,\ldots,d_N) \\ &= \int \mathrm{d}E\, n(E,d_1,\ldots,d_N)\mathrm{e}^{-\beta_0 E + f(d_1,\ldots,d_N)} \\ &\equiv \text{constant}, \end{aligned} \tag{5}$$

where d_i is the dihedral-angle distance with respect to reference configuration $i (i = 1, \ldots, N)$, $n(E, d_1, \ldots, d_N)$ is the density of states, $W_{\mathrm{muov}}(E, d_1, \ldots, d_N)$ is the multioverlap weight factor and $f(d_1, \ldots, d_N)$ is the "dimensionless free energy". The dimensionless free energy is not *a priori* known and has to be determined by short preliminary simulations. This method performs a random walk in the N-dimensional dihedral-angle-distance space, in which the simulation visits the N reference configurations often. We can thus obtain accurate information about transition states among these N states. Because the multioverlap method does not realize a free random walk in the potential-energy space, it is difficult to sample widely the potential-energy space.

We want simulations to have effective and wide samplings including the neighborhood of $d = 0$ in the configurational space. Therefore, we consider to carry out a simulation that performs a random walk both in the potential-energy space and in the dihedral-angle distance space (energy-overlap space). In other words, the simulation needs to have a constant probability distribution in the energy-overlap space. In analogy with the multicanonical ensemble in equation (4) or the multioverlap ensemble in equation (5), by employing the non-Boltzmann weight factor $W_{\mathrm{mco}}(E, d_1, \ldots, d_N)$, which we refer to as the multicanonical–multioverlap weight factor, a uniform probability distribution with respect to the potential-energy and dihedral-angle distances is obtained:

$$\begin{aligned} P_{\mathrm{mco}}(E,d_1,\ldots,d_N) &= n(E,d_1,\ldots,d_N)W_{\mathrm{mco}}(E,d_1,\ldots,d_N) \\ &\equiv \text{constant}. \end{aligned} \tag{6}$$

The multicanonical–multioverlap weight factor is not *a priori* known and again has to be determined by short preliminary simulations. The multicanonical–multioverlap weight factor $W_{\mathrm{mco}}(E, d_1, \ldots, d_N)$ at a constant temperature T_0 can be written as

$$W_{\mathrm{mco}}(E, d_1, \ldots, d_N) = \mathrm{e}^{-\beta_0 E_{\mathrm{mco}}(E,d_1,\ldots,d_N)}, \tag{7}$$

where $E_{\mathrm{mco}}(E, d_1, \ldots, d_N)$ is the multicanonical–multioverlap potential-energy.

2.3 Equations of motion in the multicanonical–multioverlap ensemble

The MD algorithm in the multicanonical–multioverlap ensemble naturally follows from equation (7) (see Refs. [10,11] for the case of multicanonical MD). The multicanonical–multioverlap MD simulation is carried out by solving the following modified equations of motion with Gaussian thermostat:

$$\dot{\mathbf{q}}_i = \frac{\mathrm{d}\mathbf{q}_i}{\mathrm{d}t} = \frac{\mathbf{p}_i}{m_i}, \quad \dot{\mathbf{p}}_i = \mathbf{F}_i^{\mathrm{mco}} - \zeta_{\mathrm{mco}}\mathbf{p}_i. \tag{8}$$

The "force" $\mathbf{F}_i^{\mathrm{mco}}$ acting on atom i is calculated from

$$\mathbf{F}_i^{\mathrm{mco}} = -\frac{\partial E_{\mathrm{mco}}}{\partial \mathbf{q}_i}, \tag{9}$$

where E_{mco} is the multicanonical–multioverlap potential-energy in equation (7). The coefficient ζ_{mco} is defined by

$$\zeta_{\mathrm{mco}} = \frac{\sum_i \mathbf{F}_i^{\mathrm{mco}} \cdot \dot{\mathbf{q}}_i}{2\sum_i \frac{\mathbf{p}_i^2}{2m_i}}. \tag{10}$$

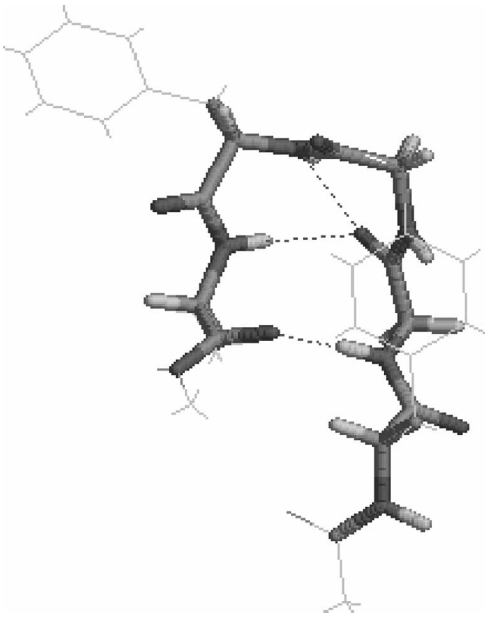

Figure 1. Reference configuration that was used in the multicanonical–multioverlap MD simulation. The dotted lines denote the hydrogen bonds. The N-terminus and the C-terminus are on the right-hand side and on the left-hand side, respectively. The figure was created with RasMol [30].

3. Application to Met-enkephalin in gas phase

3.1 Computational details

In order to demonstrate effectiveness of the multicanonical–multioverlap MD method, we compare a multicanonical–multioverlap MD simulation with multicanonical and multioverlap MD simulations. We apply the three simulations to Met-enkephalin in vacuum. Met-enkephalin is one of the simplest peptides and has the amino-acid sequence Tyr-Gly-Gly-Phe-Met. In our simulations, the N-terminus and the C-terminus were blocked with the acetyl group and the N-methyl group, respectively. This is because we wanted the total charge of the Met-enkephalin system to be neutral. The force field that we adopted is the CHARMM param 22 parameter set [27]. Leap-frog algorithm [28] was employed for the numerical integration and the time step was taken to be 0.2 fs. The reason for using such a small time step is to perform simulations with high accuracy.

In the multicanonical–multioverlap MD simulation, we must have a reference conformation. Therefore, we adopted the conformation in figure 1 as the reference conformation and $N = 1$ in equations (6) and (7).

The backbone dihedral angles are of three types: the rotation angle around the N—C^{α} bond of the backbone (ϕ), that around the C^{α}—C bond (ψ) and that around the peptide bond C—N (ω). Our multicanonical–multioverlap MD simulation was performed using the all-atom model, but we used only ϕ and ψ angles in the definition of the dihedral-angle distances in equation (1). This is because the dihedral angles of the backbone ω have almost the fixed value of 180° for the peptide bond C—N. Furthermore, by using only the backbone dihedral angles (and not side-chain dihedral angles) as the elements of the dihedral-angle distances, we focused on the backbone structures of Met-enkephalin. In equation (1), consequently, the number n of the elements of the dihedral-angle distances is 10 because Met-enkephalin has five pairs of ϕ and ψ.

For the purpose of comparisons we also performed a multicanonical MD simulation and a multioverlap MD simulation for 9 ns at $T_0 = 300$ K. We determined the multicanonical weight factor in equation (4) as follows. We carried out canonical MD simulations at eight temperatures between 300 and 1000 K with equal increment of 100 K and obtained ensemble-averages of the potential energy at each temperature. From the ensemble-averages of the potential energy, we calculated the derivative of the multicanonical potential energy [24–26]:

$$\left.\frac{\partial E_{\mathrm{muca}}(E)}{\partial E}\right|_{E=E_{\mathrm{ave}}} = \frac{T_0}{T(E_{\mathrm{ave}})}, \tag{11}$$

with

$$E_{\mathrm{ave}} = \langle E \rangle_{T(E_{\mathrm{ave}})}. \tag{12}$$

We integrated the derivative of the multicanonical potential energy and obtained multicanonical weight factor. We adopted a random-coil conformation for the initial conformation of the multicanonical MD simulation production run.

In the multioverlap MD simulation, we employed the 2D version of this method. In other words, we used two reference conformations in the multioverlap MD simulation and $N = 2$ in equation (5). One of the two reference conformations was the conformation in figure 1 and the

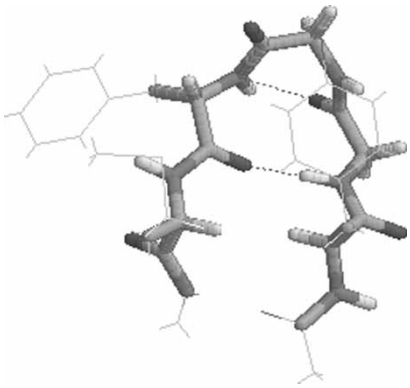

Figure 2. Another configuration that was used in the multioverlap MD simulation. See also the caption of figure 1.

other one is shown in figure 2. We determined the multioverlap weight factor in equation (5) by the following process [17,18]. Suppose that we have the dimensionless free energy $f = f^{(l)}$ in the lth iteration of the short multioverlap MD simulation. In the $l+1$th iteration of the short multioverlap MD simulation, $f^{(l+1)}$ is calculated from

$$f^{(l+1)}(d_1, d_2) = f^{(l)}(d_1, d_2) - \log N^{(l)}(d_1, d_2), \qquad (13)$$

where d_1 and d_2 is the dihedral-angle distance for reference conformation 1 (RC1) in figure 1 and reference conformation 2 (RC2) in figure 2, respectively. $N^{(l)}(d_1, d_2)$ in equation (13) is the histogram obtained from the result of the lth iteration. For this calculation, the dihedral-angle distances were discretized with a bin size of 0.01. Moreover, we interpolated the dimensionless free energy by a polynomial, following the techniques that were introduced in Ref. [29] (see Eq. (94) there). The initial value was set as follows:

$$f^{(1)}(d_1, d_2) = 0. \qquad (14)$$

In first iteration, therefore, we perform a short usual canonical MD simulation. We stopped the iterations after seven short multioverlap MD simulations each for 1.8 ns and we obtained the multioverlap weight factor. The initial conformation for the multioverlap production run was a conformation equilibrated at 300 K by the canonical simulation. Since the multioverlap weight factor has temperature dependence, it is appropriate that we employ this initial conformation.

The multicanonical–multioverlap MD simulation was carried out at $T_0 = 300$ K. We first have to determine the multicanonical–multioverlap weight factor $W_{\mathrm{mco}}(E, d_1)$ in equation (7) to get a flat probability distribution in the energy-overlap space (E, d_1). For this purpose, we used a similar procedure to that in equation (13). Namely, suppose that we have $E_{\mathrm{mco}} = E^{(l)}_{\mathrm{mco}}$ in the lth iteration of the short multicanonical–multioverlap MD simulation. In the $l+1$ th iteration of the short multicanonical–multioverlap MD simulation, $E^{(l+1)}_{\mathrm{mco}}$ is calculated from

$$E^{(l+1)}_{\mathrm{mco}}(E, d_1) = E^{(l)}_{\mathrm{mco}}(E, d_1) + k_{\mathrm{B}} T_0 \log N^{(l)}(E, d_1), \qquad (15)$$

where $N^{(l)}(E, d_1)$ is the histogram obtained from the result of the lth iteration. For this calculation, the potential energy and the dihedral-angle distance were discretized with a bin size of 1.0 kcal/mol and a bin size of 0.01, respectively. We also interpolated the multicanonical–multioverlap potential energy by the polynomial. The initial value was set as follows:

$$E_{\mathrm{mco}}(E, d_1) = E_{\mathrm{muca}}(E), \qquad (16)$$

where $E_{\mathrm{muca}}(E)$ is the multicanonical weight factor that was determined as above. We then performed three iterations of the multicanonical–multioverlap MD simulations in equation (8) for 3 ns. The multicanonical–multioverlap weight factor $E_{\mathrm{mco}}(E, d_1)$ was updated by equation (15) after each multicanonical–multioverlap MD simulation. Finally, the multicanonical–multioverlap MD production run was then performed with this weight factor for 9 ns after equilibration of 1 ns. For the initial conformation of the multicanonical–multioverlap MD simulation production run, we also adopted a random-coil conformation.

3.2 Comparison of the three simulations

We first compared the time series of the potential energy and the dihedral-angle distance obtained from the multicanonical, multioverlap and multicanonical–multioverlap MD simulations. Figure 3 shows the time series of the potential energy of the three simulations. The multicanonical and multicanonical–multioverlap MD simulations cover widely the potential-energy space, as we can see in figure 3(a) and (c). In other words, the two simulations realized free-random walks in the potential-energy space and sampled widely the conformational space. In the multioverlap MD simulation, however, we can sample only a narrow region in the potential-energy space as in figure 3(b). Therefore, in contrast with the other two simulations, multioverlap MD simulations are not suitable to sample widely the conformational space.

In figure 4, we show the time series of the dihedral-angle distance d_1 with respect to conformation RC1 in figure 1. When $d_1 = 0$, the values of the backbone dihedral angles are completely coincident with those of RC1. In the multioverlap and multicanonical–multioverlap MD simulations, we see from figure 4(b) and (c) that the efficient samplings were realized in the neighborhood of $d_1 = 0$. In other words, the multioverlap and multicanonical–multioverlap MD simulations could sample efficiently the vicinity of RC1. The multicanonical MD simulation sampled infrequently the neighborhood of $d_1 = 0$, as we can see in figure 4(a). Thus, it is difficult to sample specific conformations in multicanonical MD simulations.

From figures 3(c) and 4(c), we see that the multicanonical–multioverlap MD simulation sampled widely in the conformational space and efficiently the vicinity of the reference conformation. Therefore, the multicanonical–multioverlap MD method has the advantages of both

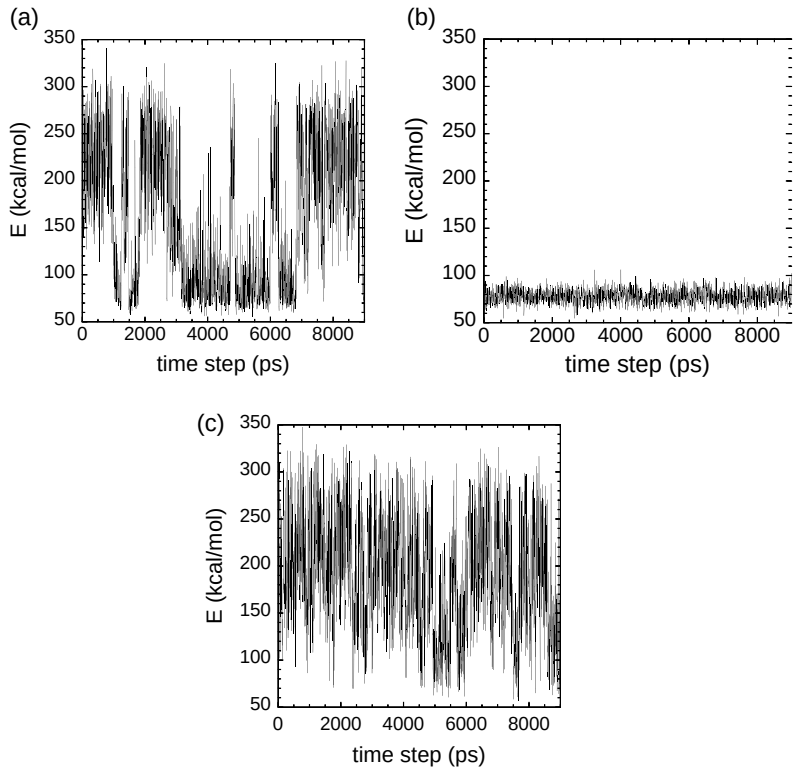

Figure 3. The time series of the potential energy E: (a) is the results from the multicanonical MD simulation; (b) is from the multioverlap MD simulation; and (c) is from the multicanonical–multioverlap MD simulation at $T_0 = 300\,\mathrm{K}$.

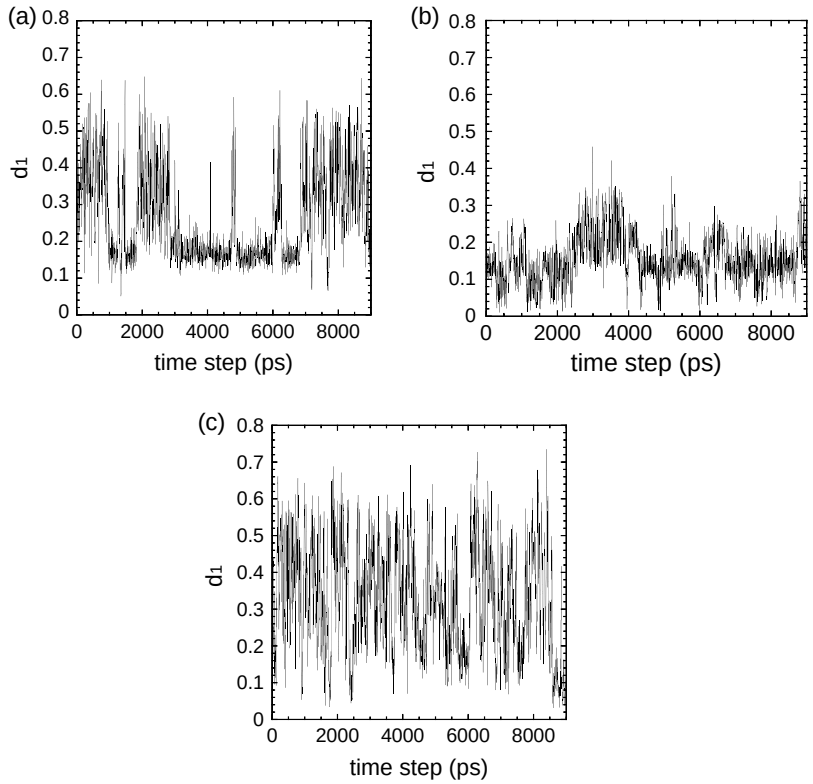

Figure 4. The time series of the dihedral-angle distance d_1: (a) is the results from the multicanonical MD simulation; (b) is from the multioverlap MD simulation; and (c) is from the multicanonical–multioverlap MD simulation at $T_0 = 300\,\mathrm{K}$.

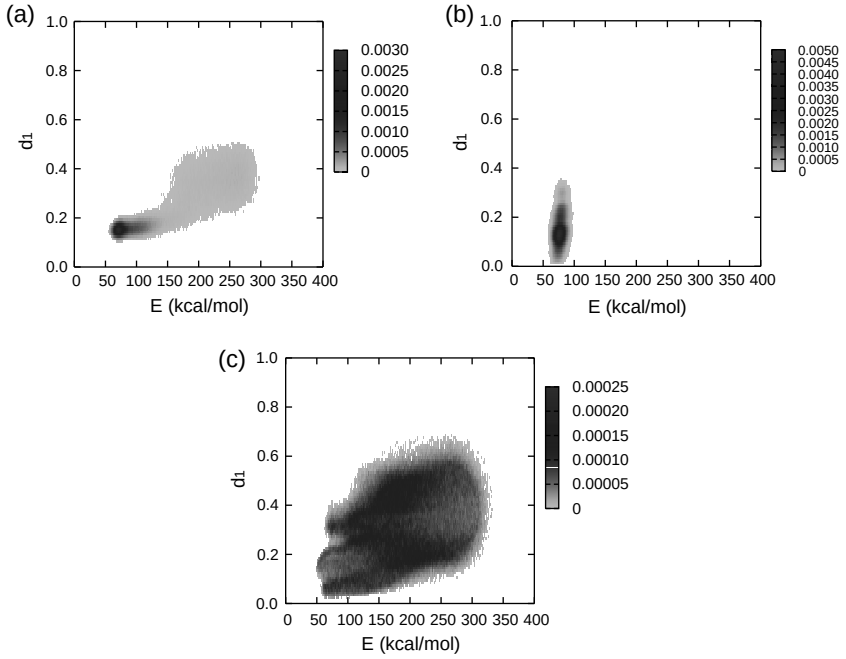

Figure 5. The raw data of the probability distribution with respect to the potential energy and dihedral-angle distance axes: (a) is the results from the multicanonical MD simulation; (b) is from the multioverlap MD simulation; and (c) is from the multicanonical–multioverlap MD simulation at $T_0 = 300\,\mathrm{K}$.

the multicanonical MD method and the multioverlap MD method.

We now discuss the probability distributions of configuration from the three simulations. In figure 5, we show the raw data of the histograms with respect to the potential energy E and dihedral-angle distance d_1. From figure 5(a), it is apparent that the multicanonical MD simulation had only a partial sampling in the vicinity of RC1 (low d_1 regions). Moreover, the multicanonical MD simulation did not sample widely in the conformational space at the low-energy region, although it had a wide sampling in the conformational space at the high-energy region. In the multioverlap MD simulation, on the other hand, the sampling that focuses on RC1 was realized (figure 5(b)). At the high-energy region, however, we could not sample at all in the multioverlap MD simulation. From figure 5(c), we see that the multicanonical–multioverlap MD simulation performed effective sampling in the conformational space in comparison with the other two simulations. In fact, we could sample widely the conformational space at low-energy region as well as high-energy region and the vicinity of RC1 in multicanonical–multioverlap MD simulation.

4. Conclusions

In this article, we have introduced the multicanonical–multioverlap MD algorithm, which is useful to sample the conformational space widely and the vicinity of the reference conformation effectively. We applied this method to a penta-peptide system of Met-enkephalin in vacuum and compared the performance with those of multicanonical and multioverlap MD methods. We showed the effectiveness of the multicanonical–multioverlap MD method over the multicanonical and multioverlap MD methods. The multicanonical MD simulation sampled widely the conformational space at high-energy region but not at low-energy region and did not have the sampling around the reference conformation. The multioverlap MD simulation could sample effectively the vicinity of the reference conformation. In the multioverlap MD simulation, however, we were not able to have the sampling in the high-energy region. On the other hand, the multicanonical–multioverlap MD simulation realized a free-random walk in the energy-overlap space and sampled the conformational space widely and the neighborhood of the reference conformation.

In the protein folding problem, the multicanonical–multioverlap method can be applied to deduce folding pathway in which a protein system has an intermediate state like a molten-globule state. This is because we can obtain free-energy landscapes, which include random-coil states, the native state and the molten-globule state, from the results of multicanonical–multioverlap simulations. Furthermore, we can estimate transition states accurately between the native state (or denatured state) and the molten-globule state by employing the molten-globule state as the reference conformation in multicanonical–multioverlap simulations.

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