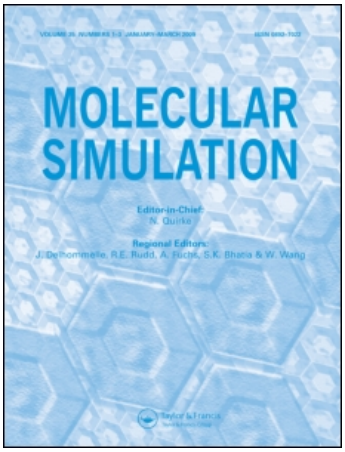


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# Taboo-based Monte Carlo Search as a Method to Improve Sampling Efficiency

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# TABOO-BASED MONTE CARLO SEARCH AS A METHOD TO IMPROVE SAMPLING EFFICIENCY

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Taboo-based Monte Carlo search which restricts the sampling of the region near an old configuration, is developed. In this procedure, Monte Carlo simulation and random search method are combined to improve the sampling efficiency. The feasibility of this method is tested on global optimization of a continuous model function, melting of the 256 Lennard-Jones particles at $T^* = 0.680$ and $\rho^* = 0.850$ and polypeptides (alanine dipeptide and Metenkephalin). From the comparison of results for the model function between our method and other methods, we find the increase of convergence rate and the high possibility of escaping from the local energy minima. The results of the Lennard-Jones solids and polypeptides show that the convergence property to reach the equilibrium state is better than that of others. It is also found that no significant bias in ensemble distribution is detected, though taboo-based Monte Carlo search does not sample the correct ensemble distribution owing to the restriction of the sampling of the region near an old configuration.

*Keywords:* Global optimization; computer simulation; Monte Carlo; sampling efficiency; taboo search

## 1. INTRODUCTION

In recent years, computer simulation methods have become powerful tools to study the variety of systems that are not tractable by formal or numerical approach. The methods are rapidly developed by the increasing speed and

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capacity of computers. The number of particles which can be explicitly treated by current simulational method is typically in the range of $N = 10^3 \sim 10^5$. However, the applicability of simulational method is limited by the computing time which greatly increases with the size of a system. Moreover, there are many kinds of slowing down mechanisms such as the multiple minima problem that can critically lower the convergence rates.

The multiple minima problem is one of the most challenging but also a very difficult subject. Many procedures such as simulated annealing [1, 2], genetic algorithm [3], taboo search [4], diffusion equation method [5, 6], jump-walking method [7] and our methods [8–10] have been suggested to overcome this problem. Nevertheless, there is not a general solution to solve the multiple minima problem yet. There should be much effort to challenge it.

Since the Monte Carlo method simulates the thermal Markovian processes, it should be applicable to the problem of the global optimization and obtaining the equilibrium thermodynamic properties. However Monte Carlo method is hampered by very slow relaxation; when the states are separated by large energy barriers, the relaxation time is greatly increased in proportion to the value of $\exp(\Delta E/k_B T)$. In order to have meaningful results, the observation time should be much greater than the relaxation time of the systems, thus it is difficult to obtain reliable results from the simulation.

Hence it is worthwhile to explore the possibility of accelerating the convergence rate by a more efficient algorithm and numerous attempts have been reported in the literature [9, 11–14]. However their applications are usually dependent on the systems and thus most of them have less general utilities. A new method should satisfy at least two necessary conditions: (1) convergence rate is fast enough to get over the aforementioned difficulty; (2) the method is applicable to most systems accessible by the conventional one.

Recently we have reported the successful results on global optimization of 2-dimensional test functions and the argon clusters by new sampling scheme named restricted random search method [10]. We introduced the concept of taboo region instead of taboo list in Cvijovic and Klinowski's taboo search [4] because the argon clusters were not moved in a fixed domain and had more degree of freedoms than their 2-dimensional test functions. The sampling of a region near an old configuration was restricted by taboo region in the process of Monte Carlo (MC) simulation.

In the present study, as a further application to verify our new method, the convergence rate and the possibility of escaping from the energy minima of our taboo-based Monte Carlo (MC) method are compared with those of Metropolis Monte Carlo method on a 2-dimensional test function. Besides,

in order to show the feasibility to real system, taboo-based Monte Carlo (MC) search is applied to the melting of the Lennard-Jones particles and the global optimization of polypeptides. The thermal equilibration of the 256 Lennard-Jones particles is carried out on the condition of near melting region at $\rho^* = 0.850$ and $T^* = 0.680$ ($Ar(s) \rightarrow Ar(1)$), where $T^*$ and $\rho^*$ denote the reduced temperature and density respectively [15]. The polypeptides which are investigated in this work, are the alanine dipeptide (Ac–Ala–NHMe) and the pentapeptide Met-enkephalin (H–Tyr–Gly–Gly–Phe–Met–OH). From the results of three kinds of systems, it is found that taboo-based MC scheme has the higher convergence rate to equilibrium state, increases the possibility of crossing over the energy barrier. With respect to the equilibrium thermodynamic properties, we can't find any difference of the properties between our new method and conventional Metropolis Monte Carlo procedure. Thus, it is thought to exist little bias in ensemble distribution, in spite of the sampling bias in taboo-based MC procedure.



## 2. METHODS

### 2.1. Taboo-based MC Procedure

The Monte Carlo sampling method is used for the generation of a new configuration. The moving boundary ($\delta$, maximum moving from an old configuration) for random sampling is given as

$$-\delta \leq \Delta q_i \leq \delta, \tag{1}$$

where $q_i$ is the degree of freedom for each system: (1) $x$ and $y$ for the model analytic function; (2) $x$, $y$ and $z$ for Lennard-Jones particles; (3) $\phi$, $\psi$ and so on for polypeptide. The taboo region needed in taboo-based Monte Carlo (MC) scheme is defined as

$$-\delta \cdot f \leq \Delta q_i \leq \delta \cdot f \quad (0 \leq f \leq 1), \tag{2}$$

where $f$ is a factor giving the size of taboo region, named taboo parameter.

If a new configuration is placed within the taboo region, such a configuration is regarded as taboo and so only MC minimization is processed. That is, in the case of the sampling of the taboo region, if the potential energy of new configuration is lower than that of old configuration, the new configuration is accepted. Otherwise the new configuration is rejected. This is the modified aspiration condition [4]. On the other hand, if the new configuration is placed outside the taboo region, the conventional Metropolis

Monte Carlo method is applied, as the following probability,

$$\begin{aligned} p &= \exp[-\Delta U/k_B T], \quad \text{when } \Delta U > 0, \\ p &= 1, \qquad\qquad\quad \text{when } \Delta U \leq 0, \end{aligned} \tag{3}$$

where $U$ is the value of function or potential energy and $k_B$ is the Boltzmann constant. For 2-dimensional model function, $T$–virtual temperature – is used instead of $k_B T$. The old configuration remains with probability of $(1-p)$. Such configurations outside the taboo region would be distributed according to the Boltzmann distribution. Thus, if the taboo region is disregarded ($f = 0$), the present method is reduced to the same adaptive search [16] as Metropolis Monte Carlo method [17]. If the taboo region is enlarged to the entire region ($f = 1$), the present method becomes a sort of pure random search. This procedure is thought to induce that the sampling of the region near an old configuration is restricted, while the sampling of the region far from an old configuration is reinforced relatively. With this procedure, our taboo-based Monte Carlo search is applied to three kinds of systems.



## 2.2. Calculation Details

### *2.2.1. Model Energy Surface*

An analytic equation is employed for the model energy surface as represented in Eq. (4) and Figure 1,

$$f(x,y) = x^2 + y^2 + A\cos(4\pi x) \quad (-2 \leq x, y \leq 2), \tag{4}$$

where the value $A$, the amplitude of cosine part, controls the height of energy barrier between minima. As shown in Figure 1(b), the surface has 8 energy minima including two symmetric global energy minima near $(-(1/4), 0)$ and $((1/4), 0)$. In spite of the simpleness of this surface, it is adequate for the investigation of the efficiency for the global optimization due to its several minima and the possibility to get over the energy barrier owing to the existence of two symmetric global energy minima. Under the various conditions (the energy barrier between minima ($A$), moving boundary ($\delta$) and virtual temperature ($T$)), we examine the convergence rate and the ability to escape from trapping in local energy minimum with diverse taboo parameters ($f$).

### *2.2.2. Lennard-Jones Particles*

In order to confirm the applicability of our new method to real system, we carry out both conventional Metropolis Monte Carlo method (MMC) and

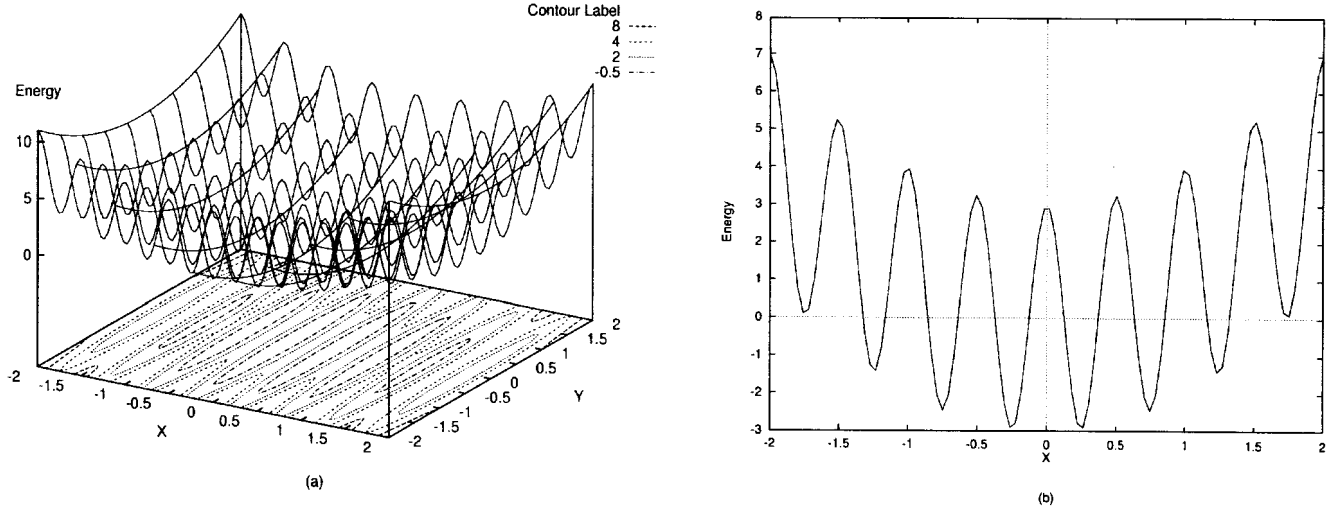


FIGURE 1 Energy map of a continuous model function Eq. (4), where $A$ is equal to 3. (a) 3-dimensional energy surface and contour map and (b) 2-dimensional plot at $y = 0$.

taboo-based Monte Carlo methods on the system of the 256 Lennard-Jones particles (argon) at $T^* = 0.680$ and $\rho^* = 0.850$. The pairwise additive Lennard-Jones potential is used for argon system. The configurational energies $U(r)$ are computed by

$$U(r) = 4\varepsilon\left[\left(\frac{\sigma}{r}\right)^{12} - \left(\frac{\sigma}{r}\right)^{6}\right], \tag{5}$$

where, $\varepsilon$ and $\sigma$ are chosen so that $\varepsilon/k_B = 125.2\,\text{K}$ and $\sigma = 3.405\,\text{Å}$ [18]. The periodic boundary condition is used and the cutoff distance for potential function is $2.5\sigma$ without long-range correction. The face centered cubic configuration is used as the initial configuration. Each run is processed during $1 \times 10^6$ configurations with the moving boundary of $\delta/\sigma = 0.1$.

### *2.2.3. Polypeptides*

In order to compensate for the possible lowering of the transition probabilities between local minima and to make the molecules more flexible so that they move in the conformational space more effectively, the simulations are combined with the simulated annealing. Then the temperature is modified from initial temperature to the target temperature, as the following.

$$T^{k+1} = T^k - \chi^T \cdot T^k, \tag{6}$$

where $\chi^T$ is the temperature annealing factor.

We carry out both the conventional Metropolis Monte Carlo (MMC) simulation and the taboo-based Monte Carlo (MC) search on the alanine dipeptide (Ac–Ala–NHMe) and the pentapeptide Met-enkephalin (H–Tyr–Gly–Gly–Phe–Met–OH). In the case of taboo-based MC, the simulations are processed with the several taboo parameters. All interactions are calculated using the consistent valence force field (CVFF) developed by Hagler *et al.* [19] and the dielectric constant ($D$) of electrostatic interaction is set to the function of the interatomic distance ($r$)($D = 1/r$) to consider the solvent and screening effect [20]. After the full extended structure of alanine dipeptide is minimized for 1000 steps using steepest descents method, $10^5$ configurations of Monte Carlo simulations combined with the simulated annealing procedure are processed. Temperature is gradually reduced from 1000 K to 300 K with the temperature annealing factor of 1% for each 100 configurations. Using this annealing factor, until the temperature becomes the equilibrium temperature of 300 K, about $1.2 \times 10^4$ configurations are

needed. In order to achieve the appropriate acceptance ratio ($\sim 0.5$), the maximum step size of Monte Carlo moving is chosen as 25°. In the case of the Met-enkephalin, the simulations proceeds during $5 \times 10^5$ configurations and the simulated annealing is also applied for each 500 configurations with the same temperature annealing factor. The moving boundary is 15°. Other conditions are analogous to those of alanine dipeptide.

## 3. RESULTS AND DISCUSSIONS

To compare the taboo-based Monte Carlo (MC) search method with the conventional Metropolis Monte Carlo (MMC) simulation, we carry out both MMC and taboo-based MC for three kinds of systems, as already mentioned. At first, in order to investigate the validity of taboo-based MC clearly, the global optimization of a simple analytic function is performed. Then application to the melting of the 256 Lennard-Jones particles system and the structure optimization of polypeptides is processed. In these tests, our emphases are placed mainly on three aspects: (1) the efficiency of our method to move on the configurational space; (2) the ability to escape from trapping in local energy minimum; (3) little or no bias in the equilibrium structure.



### 3.1. Global Optimization of a Model Energy Surface

We employ a model energy surface including the periodic boundary condition, as represented in Eq. (4) and Figure 1. The simulation is performed under various moving boundaries ($\delta$), virtual temperatures ($T$) and energy barriers ($A$) with the initial position of (2,2). The taboo parameters ($f$) are selected from 0.0 to 0.9 at the interval of 0.1. Zero of $f$ means that the taboo region does not exist and therefore the present method is reduced to the conventional Metropolis Monte Carlo method (MMC). In order to compare taboo-based MC with MMC, we investigate the convergence rate and the barrier crossing number in the progression of simulation. The convergence rate is measured as the number of steps arriving at the configuration having 1% error for global energy minimum (GEM). The barrier crossing number is the number of going over the energy barrier at $x = 0$ in Figure 1(b), that is, the number of transverse between two symmetric global energy minima (GEM) during the full process of simulation. Because the high value of barrier crossing number means the high possibility of crossing the barrier, it is used as the criterion for the ability to escape from trapping in local energy minimum.

TABLE I Comparison of the results between Metropolis MC and taboo-based MC

| *Taboo parameter* ($f$[a]) | $A$[b] = 2 ($\delta$[c] = 0.15, $T$[d] = 0.8) *GEM #*[e] | *Cross*[f] | $A$ = 2 ($\delta$ = 0.20, $T$ = 1.2) *GEM #* | *Cross #* | $A$ = 3 ($\delta$ = 0.10, $T$ = 0.8) *GEM #* | *Cross #* | $A$ = 3 ($\delta$ = 0.20, $T$ = 1.2) *GEM #* | *Cross #* |
|---|---|---|---|---|---|---|---|---|
| 0.0 | 4450 | 3 | 1450 | 67 | 83740 | 0 | 56470 | 1 |
| 0.1 | 3060 | 3 | 780 | 61 | 41960 | 1 | 26810 | 6 |
| 0.2 | 2490 | 23 | 1400 | 111 | 45020 | 1 | 8160 | 7 |
| 0.3 | 1950 | 7 | 1020 | 88 | 16780 | 4 | 13060 | 10 |
| 0.4 | 2710 | 7 | 620 | 90 | 44210 | 3 | 14050 | 1 |
| 0.5 | 2820 | 3 | 630 | 77 | 58730 | 12 | 12900 | 9 |
| 0.6 | 4060 | 4 | 360 | 88 | 38880 | 2 | 46110 | 1 |
| 0.7 | 1960 | 2 | 730 | 42 | 36740 | 1 | 96290 | 0 |
| 0.8 | 6200 | 1 | 430 | 35 | 36070 | 0 | – | – |
| 0.9 | 9850 | 0 | 570 | 27 | –[g] | – | – | – |

[a] Taboo parameter controls the size of taboo region. Zero of $f$ means Metropolis MC.

[b–d] Amplitude, moving boundary and virtual temperature, respectively. Amplitude controls the energy barrier between minima.

[e] Monte Carlo step (MCS) arriving at the configuration having 1% error for global energy minimum.

[f] The barrier crossing number during the full process of simulation (total number of MCS: $1 \times 10^4$ when $A = 2$; $1 \times 10^5$ when $A = 3$).

[g] "-" means that the system didn't arrive at global energy minimum during the full process of simulation.

Table I represents the summary of comparison of the results between taboo-based MC and MMC under the various conditions, where 'cross #' is the barrier crossing number and 'GEM #' means the number of Monte Carlo steps (MCS) arriving at the global energy minimum. In the case of $A = 2$ the total number of MCS is $1 \times 10^4$ configurations, while $1 \times 10^5$ configurations are processed when $A = 3$ due to the higher energy barrier. Though the results are varied according to the conditions ($A$, $\delta$ and $T$), as the taboo parameter ($f$) is increased to an appropriate value, 'GEM #' is decreased and 'cross #' is increased. Thus we could expect that our method has higher convergence rate and gives more possibility to escape from trapping in local energy minimum. Examining the results on the condition of $A = 2$, $\delta = 0.15$ and $T = 0.8$ in detail MMC requires 4450 configurations for global optimization, while half nearly of it is needed for taboo-based MC with $f$ of $0.1 \sim 0.6$. Moreover, the barrier crossing number is significantly increased in the case of taboo-based MC with optimum $f$ of 0.2 (from 3 in MMC to 23 in taboo-based MC). We can investigate that the results of taboo-based MC become worse under the extreme high value of $f(0.8 \sim 0.9)$. Thus we can find the existence of the optimum taboo parameter. And we also find that the optimum $f$ on the point of view of 'GEM #' is somewhat different from the optimum value referenced by 'cross #'. On the previous condition, if $f = 0.2$, the maximum value of the barrier crossing number is obtained. But the convergence rate is maximized when $f = 0.3$. On the other hand, comparing the results between $A = 2$ and $A = 3$, convergence rate and the barrier crossing number are remarkably increased relatively to MMC as the energy barrier is increased. In the case of $A = 2$ the convergence rate of taboo-based MC is increased about two times compared with that of MMC, while it is increased about five times when $A = 3$. With respect to the barrier crossing number, the benefit of taboo-based MC is much reinforced as represented in Table I. It is remarkable that the efficiency of taboo-based MC becomes vivid under the extreme condition having the high energy barrier between minima.

### 3.2. Melting of the Lennard-Jones Solids

We also carry out both MMC and taboo-based MC simulations of the 256 Lennard-Jones system under the periodic boundary condition at $\rho^* = 0.850$ and $T^* = 0.680$ which is slightly over the melting temperature. Since the system at those thermodynamic states has been widely studied by many authors to exhibit the efficiencies of their own methods, the results can be easily compared with those of other methods [9, 11, 12].

In the progression of simulations, we take the time evolution of the function $s$ as the criterion for melting of the Lennard-Jones solids as defined by

$$s = \sum_{i}^{N} \sum_{r=x,y,z} \frac{\cos(kr_i)}{3}, \tag{7}$$

where $k = 4\pi/a$, $a$ is a lattice parameter, and $N$ is the number of particles [9]. Then the melting factor $s$ decays from the order of the number of particles to zero and finally fluctuates with an amplitude of about $\sqrt{N}$ around zero during the melting process. Using taboo-based MC the liquid is formed within around $2 \times 10^5$ configurations, while MMC needs at least $5 \times 10^5$ configurations, as depicted in Figure 2. This result shows that taboo-based MC has the higher speed of melting as compared with MMC. In Figure 3, we monitor the mean departures from initial configuration ($d(k)$) as a measure of translational diffusion defined by

$$d(k) = \frac{1}{N} \sum_{i}^{N} |r_i^k - r_i^0|, \tag{8}$$

where $r_i^0$ denotes the initial configuration and $d(k)$ is calculated using the actual movement without considering the periodic boundary condition. As seen from the figure, the taboo-based MC is faster than MMC allowing more rapid movement through the configurational space. The equilibration processes of average energies for every $10^3$ configurations are displayed in

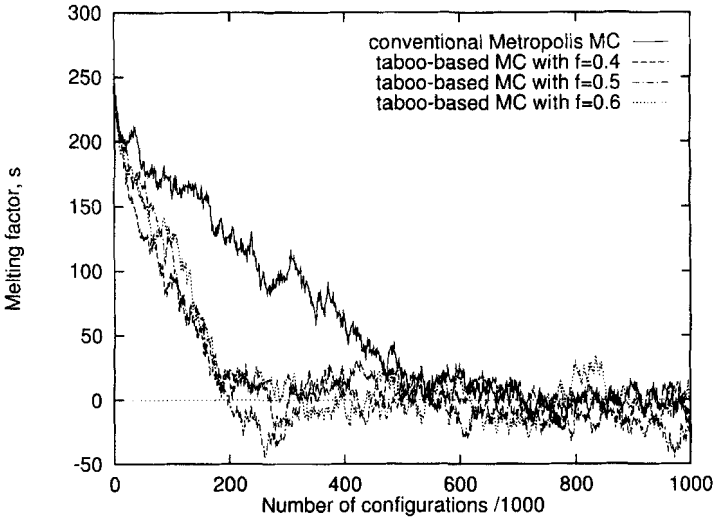


FIGURE 2 Translational order parameters $s$ Eq. (6) as a function of the number of configurations for the Lennard-Jones particles.

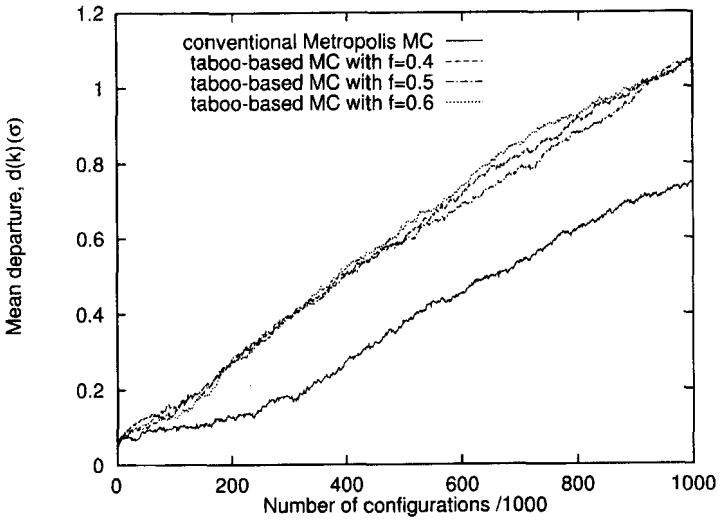


FIGURE 3 Mean departure (Eq. 7) from the initial configuration for the Lennard-Jones system as a function of the number of configurations.

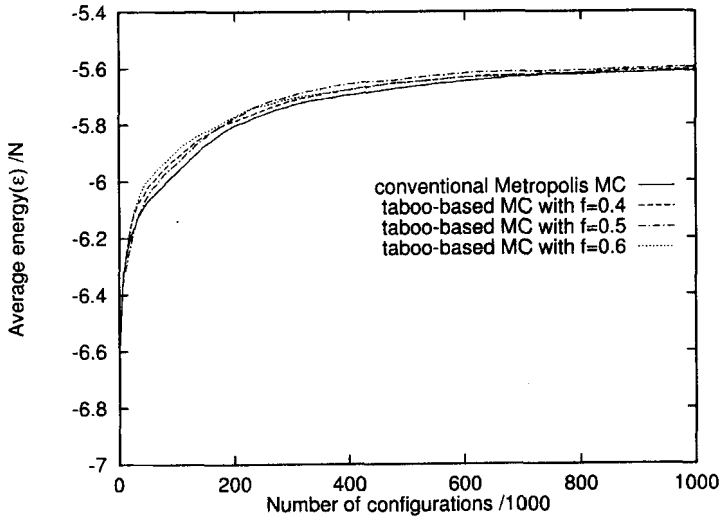


FIGURE 4 Average energy in $\varepsilon$ unit per particle for every $10^3$ configurations as a function of the number of configurations for MMC and taboo-based MC.

Figure 4. Though the convergence rates have a little difference according to $f$, taboo-based MC is faster than MMC for the search of the equilibrium state.

On the other hand, in order to investigate the change of the ensemble distributions by taboo-based MC, we obtained the radial distribution

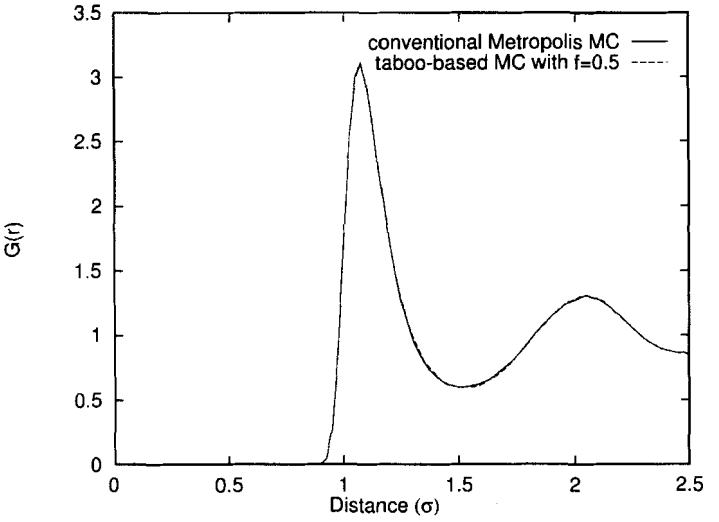


FIGURE 5 Radial distribution functions for the Lennard-Jones fluid. Taboo-based MC data are obtained using $f = 0.5$.



functions (rdfs) of the equilibrated liquid. The rdfs are displayed in Figure 5 and compared with those of MMC. As shown in Figure 5, the two rdfs patterns are very close to each other in phases and intensities. We believe that the two curves represent the identical equilibrium configurations resulting from the similar equilibrium distribution of ensembles. It is doubtful that the equilibrium distribution of ensembles for taboo-based MC is similar with that of MMC in spite of the sampling bias (the restriction of the sampling of the region near an old configuration and the reinforcement of the sampling of the region far from an old configuration). The reason for the similarity in the equilibrium distribution is thought to be due to the small size of taboo region in the process of taboo-based MC. In the case of $f = 0.5$, only $12.5\%(0.5^3)$ of total moving space is restricted in sampling because the particle moves in 3-dimensional space. From this reason, the bias might be very little and couldn't be detected.

## 3.3. Structure Optimization of Polypeptides

### *3.3.1. Alanine Dipeptide*

Though we investigate the equilibration process of energy for the conventional Metropolis Monte Carlo (MMC) method and the taboo-based

Monte Carlo(MC) method with the various taboo parameters ($f$), we do not report here because the convergence rates are very similar and we cannot find the relationship between $f$ and the convergence rate in this system. The similarity of convergence rates is thought to be due to the small size of system, that is, because the small system is quickly converged to the equilibrium structure, we cannot find any difference in convergence rates between them. Anyway, from the comparison between the final conformation of MMC and that of the taboo-based MC, the unique structure is characterized; the principal torsion angles of Ala are $\phi = -88°$ and $\psi = 84°$.

During the full process of simulation, we monitor the averaged conformational change of principal torsion angles ($\phi$ and $\psi$), $\langle \sum_i (\Delta\theta_i)^2 \rangle^{(1/2)}$, for each 1000 configurations as represented in Figure 6. It is used as a indicator of sampling efficiency, which is conceptually very similar to the rms difference of principal torsion angles between the current structure and the next structure [21]. As seen from the figure, though there is a little difference according to the taboo parameter ($f$), we find that the averaged conformational change of the taboo-based MC is slightly increased as compared with that of MMC. And it is also found that the increment of the averaged conformational change is especially large at the initial stage of simulation. This fact will be described in the next part.



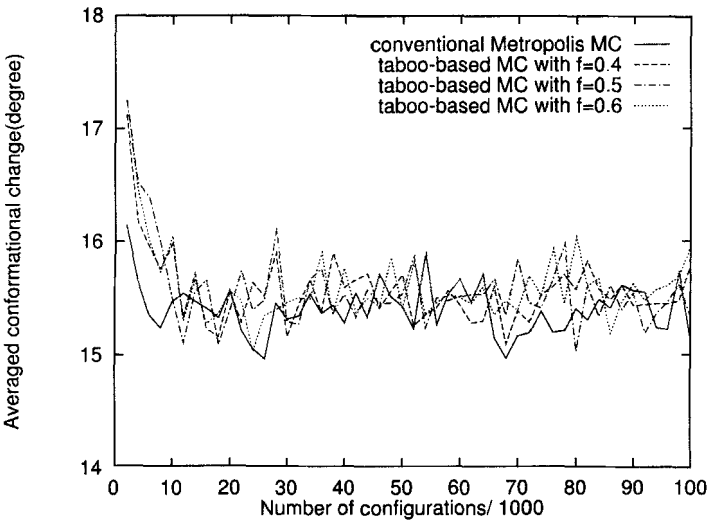


FIGURE 6 Averaged conformational change of the alanine dipeptide $\langle \sum_i (\Delta\theta_i)^2 \rangle^{(1/2)}$, with various taboo parameters. The value is calculated by the principal torsion angles for each 1000 configurations.

### *3.3.2. Met-enkephalin*

The Met-enkephalin ($H-Tyr^1-Gly^2-Gly^3-Phe^4-Met^5-OH$) is an endogenous peptide from the mammalian brain with morphine like activities. Since the system has been widely studied by many authors to exhibit the efficiencies of their own methods, the results can be easily compared with those of other methods [22–24].

Figure 7 displays the energy equilibration processes of the conventional Metropolis Monte Carlo (MMC) method and the taboo-based Monte Carlo (MC) method on the Met-enkephalin. In the case of MMC the energies fluctuate around 88 kcal/mol during the full process of simulation, while the taboo-based MC makes it possible to escape the state having the energy of 88 kcal/mol at about $1.5 \times 10^5$ configurations and converge to another state having the energy of 75 kcal/mol. Actually we can find that the conformations obtained from both methods are very similar mutually when the systems have the similar energy of 88 kcal/mol. Thus it is clear that MMC could not escape the local minima having the energy of 88 kcal/mol during $5 \times 10^5$ configurations. However, using the taboo-based MC, the system could escape the local minima within around $1.5 \times 10^5$ configurations. This difference might stem from the reinforcement of sampling of the region far from an old configuration.

We also investigate the averaged conformational change of principal torsion angles ($\langle \sum_i (\Delta\theta_i)^2 \rangle^{(1/2)}$) for each 5000 configurations. Figure 8 shows

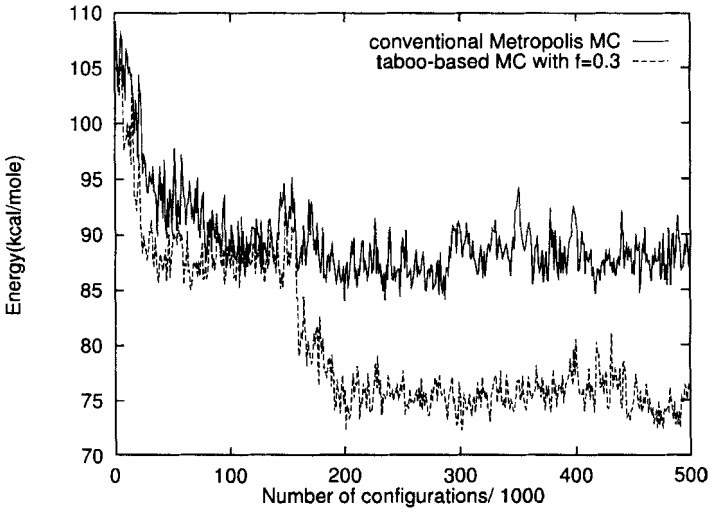


FIGURE 7 Comparison of the energy equilibration process between MMC and taboo-based MC. In the case of taboo-based MC, $f = 0.3$ is selected.

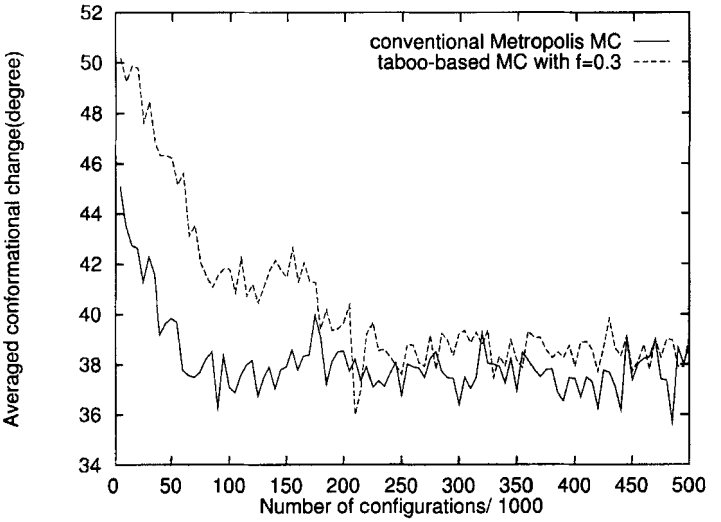


FIGURE 8 Averaged conformational change of the Met-enkephalin for each 5000 configurations.



the comparison of the averaged conformational changes between MMC and the taboo-based MC. Though we didn't mention the averaged conformational change in the case of other values of the taboo parameters ($f$) except $f = 0.3$, the similar tendencies are shown. At the initial stage of simulation (0 to $2.0 \times 10^5$ configurations), the averaged conformational change of the taboo-based MC is much larger than that of MMC. After arriving at the equilibrium state, it is shown that the values of the taboo-based MC is only a little increased. In the case of alanine dipeptide, similar tendency is shown, as depicted in Figure 6. From the comparison of the averaged conformational change of principal torsion angles between two methods, we can guess that the taboo-based MC allows more rapid movement through the configurational space for the search of equilibrium state at the initial stage of simulation compared with MMC, while the averaged conformational changes of MMC and the taboo-based MC converge to the similar value after arriving at equilibrium. This fact indirectly shows that the equilibrium distribution of ensembles by the taboo-based MC is little biased after arriving at the equilibrium state.

There were many studies suggesting the conformational models of enkephalin, both Met- and Leu-, based on experimental and theoretical analysis for the purpose of tracing the effect of folded structures in space on the activities of peptide hormones [22–24]. The resultant structures by those previous works are somewhat different as the solvent composition,

TABLE II Comparison of principal torsion angles for Met-enkephalin[a]

| *Residue* | *Gly*$^2$ | | *Gly*$^3$ | | *Phe*$^4$ | |
|---|---|---|---|---|---|---|
| *Angle (degree)* | $\phi$ | $\psi$ | $\phi$ | $\psi$ | $\phi$ | $\psi$ |
| Our Results | 98 | 71 | 108 | −154 | −79 | −147 |
| Previous Work[b] | 121 | 60 | 114 | −121 | −101 | −153 |

[a] The data reported here is resulted from the taboo parameter of 0.4.
[b] Previous Work is Ref. [23].

the force field and the method of the refinement are varied. Table II shows the comparison of the principal torsion angles of the final conformation compared with the previous report [23]. We exclude the terminal group ($Tyr^1$ and $Met^5$), because terminal group has high conformational flexibility. There is also a little difference in the detailed structures. This may be attributed to the differences in the force field and solvent condition. However, since principal torsion angles $\phi$ and $\psi$ of $Gly^3$ and $Phe^4$ mainly determine the overall structure of Met-enkephalin, we could confirm the structural similarity between our result and previous works.



## 4. CONCLUSION

In this paper, we have developed a search method combined with MMC that restricts the sampling of the region near an old configuration. Though the taboo region in our algorithm is related to the taboo list by Cvijovic and Klinowski [4], the taboo list could not be applicable to the real system, because the real molecules are not moved in a fixed domain and have more degree of freedom than their test function. Therefore we proposed the new procedure including the taboo region.

The result of our work shows the increase of convergence rate and the high possibility to escape from local minima as compared with the conventional method. Furthermore, the bias in the equilibrium distribution of ensembles by our new method cannot be detected. It is thought to be due to the small size of the taboo region compared with total configurational space. And also, the efficiency of our taboo-based Monte Carlo procedure is due to the existence of taboo region. The existence of taboo region would restrict the sampling of a region near an old configuration. Consequently, the sampling of the region far from an old configuration would be increased relatively and this sampling might allow more rapid movement through the configurational space.

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