Multi-Self-Overlap Ensemble for protein folding: ground state search and thermodynamics

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Long chains of the HP lattice protein model are studied by the Multi-Self-Overlap Ensemble (MSOE) Monte Carlo method, which was developed recently by the authors \cite{1}. MSOE successfully finds the lowest energy states reported before for sequences of the chain length $N = 42 \sim 100$ in two and three dimensions. Moreover, MSOE realizes the lowest energy state that ever found in a case of $N = 100$. Finite-temperature properties of these sequences are also investigated by MSOE. Two successive transitions are observed between the native and random coil states. Thermodynamic analysis suggests that the ground state degeneracy is relevant to the order of the transitions in the HP model. PACS numbers: 87.15.By, 87.10.+e, 02.70.Lq

Protein folding \cite{2} is one of the most interesting problems in biological science. How amino acid sequences code their native structures, functions, and thermodynamical behavior? To answer these questions, it is useful to study simplified models. Among them, lattice protein models \cite{3,4} have been playing important roles in theoretical studies of protein folding. For relatively short chains, the exact enumerations of all the conformations are possible. In dealing with longer chains, however, we encounter difficulty, because dynamical Monte Carlo methods are not efficient for lattice protein models \cite{5}. One of the reasons why conventional Monte Carlo algorithms are so slow is a rugged free-energy landscape at low temperature due to the heterogeneity of the interactions. For overcoming slow dynamics due to the ruggedness in other random systems such as the spin glasses, extended ensemble Monte Carlo methods have been developed: the multicanonical algorithm \cite{6,7}, the simulated tempering algorithm \cite{8}, the exchange Monte Carlo algorithm \cite{9,10}, and so on. In case of lattice polymers, however, topological barriers due to the self-avoiding condition cause further difficulty, because they are independent of energy and thus cannot be cured by the use of the abovementioned extended ensemble methods. In fact, a work by Shakhnovich et al. \cite{11} suggested that faster dynamics is attained by relaxing the self-avoidingness.

Recently, we proposed a new Monte Carlo method called Multi-Self-Overlap Ensemble (MSOE) \cite{1} by generalizing the idea of the multicanonical ensemble. In this method, the self-avoiding condition is systematically weakened. While the resultant ensemble contains some portions of non-physical self-overlapping configurations, the correct canonical ensemble of the physical conformations can be reconstructed through the histogram reweighting procedure. We observed a considerably fast relaxation for a simple lattice heteropolymer compared with the conventional multicanonical ensemble method.

In this letter, we apply MSOE to long chains of the HP lattice protein model \cite{4} in two and three dimensions. We demonstrate that the low energy states are found successfully and thermodynamic properties are calculated at the same time. It should be noted that the principle of MSOE is independent of specific choices of the interactions between monomers. Although we restrict ourselves to the HP model in the following, extensions to models with other interactions, such as the one with Miyazawa-Jernigan contact matrix \cite{12}, are straightforward.

Let us explain MSOE algorithm briefly. First, we define the degree of violation of self-avoidance $V$ as

\begin{equation}
V = \sum_{i \in G} (n_i - 1)^2
\end{equation}

where $n_i$ is the number of monomers on a lattice point $i$, and $G$ denotes a set of lattice points which are occupied by at least one monomer. For self-avoiding conformations, $V = 0$. We assume that the definition of the original energy function $E$ can be extended to conformations with self-overlaps in a reasonable manner. Then, we determine the weight factor $P_g \propto \exp\left[-g(E, V)\right]$ through preliminary runs as in the case of the conventional multicanonical ensemble \cite{6}, so that the bivariate histogram of $(E, V)$ is sufficiently flat in a prescribed range.
TABLE I. The values of the lowest energy reported by several authors for three sequences of 2D HP model.

| N   | sequence                      | $E_{\text{min}}$ | Ref. |
|-----|-------------------------------|------------------|------|
| 64  | $H_{12}PHPHPHPHPHPHPHPHPHP_{12}$ | $-37$           | [13] |
|     |                               | $-40$           | [14] |
|     |                               | $-42$           | [15] |
|     |                               | $-42$           | [16] |
|     |                               | $-42$           | present study |
| 100 | $P_3H_2P_4P_2H_3(PH_2)_3H_2P_8H_6P_2H_6P_3HHPHPHPH_{11}P_6H_2PH_2PHPHPH_3P_6H_3$ | $-46$   | [20] |
|     |                               | $-49$           | [19] |
|     |                               | $-50$           | present study |
| 100 | $P_6HPH_2P_3H_3PH_2P_2P_2P_2H_3P_2P_2H_3P_{10}HPH_2PH_7P_1H_2P_2PH_3P_6P_6HHP_2$ | $-44$   | [28] |
|     |                               | $-47$           | [19] |
|     |                               | $-47$           | present study |

$E_{\text{min}} \leq E \leq E_{\text{max}}$, $0 \leq V \leq V_{\text{max}}$. We set $E_{\text{min}}$ to a value which is definitely lower than the ground state energy, and set $V_{\text{max}}$ to a value $N/10 \sim N/5$. We actually use the entropic sampling method \[7\] in this paper. After the weight factor $g(E, V)$ is determined, a measurement run is performed. The canonical averages at temperature $T$ is calculated according to the histogram reweighting formula,

$$
\langle A \rangle_T = \frac{\sum_i A(\Gamma_i)P^{-1}_g(\Gamma_i)\exp(-E(\Gamma_i)/T)}{\sum_i P^{-1}_g(\Gamma_i)\exp(-E(\Gamma_i)/T)}, \tag{2}
$$

where $\Gamma_i$ represents a conformation at the $i$th Monte Carlo step and the summations are taken only over the self-avoiding conformations.

How MSOE works? In Fig. 1, observed transitions during a MSOE simulation are plotted on the $(E, V)$ plane. This example is taken from a simulation for the 2D $N = 64$ sequence shown in Table I, of which we will discuss below. We can clearly see bridges (or paths) between self-avoiding low energy states where self-overlapping states are used as stepping stones. That is, while no direct transition is seen between $(E, 0)$ and $(E', 0)$, there are paths that utilize the states with non-zero $V$ as intermediate states. The existence of such paths are a key feature of MSOE, which effectively facilitates the relaxation. The idea behind MSOE can also be extended to off lattice models. For example, one can consider the hard core repulsive part of the energy as an off-lattice counterpart of the self-avoiding conditions. Other types of bivariate extension of the multicanonical algorithm for off-lattice protein models have also been discussed by Higo et al. \[23\]. They, however, did not incorporate unphysical conformations for the purpose of attaining fast relaxations. MSOE also shares some ideas in common with the ghost polymer procedure by Wilding and Müller for dense polymer systems \[14\].

![FIG.1.Observed transitions on the $(E, V)$ plane during a MSOE run of the $N = 64$ HP sequence in Table I. Solid lines connecting two states represent the transitions between them. Only a small part of the entire $(E, V)$ plane near the ground state is shown.](image)

Let us discuss the results of simulations for the HP protein model \[4\], in which a protein consists of a self-avoiding chain on a lattice with two types of amino acids: H(hydrophobic) and P(Polar). The energy $E$ of a chain conformation is determined only by the number of H–H contacts $h$, where $|\epsilon|$ is a positive constant (we measure the energy in the unit of $|\epsilon|$ hereafter). In MSOE, we use the same definition of energy as the original one also for self-overlapping conformations. In principle, MSOE can be implemented with arbitrary dynamics. We use the following elementary moves in this paper: (1)Jacknife move, (2)One bead flip, (3)Pivot operator. A description of the move (1) is given in ref. \[4\] and the moves (2) and (3) are illustrated in ref. \[14\]. All CPU times quote below refer to PCs with 500MHz DEC 21164A chip.

First we consider a two dimensional HP lattice protein with the chain length $N = 64$ in Table I, several methods so far \[13, 16\]. For this sequence, the ground state energy is believed to be $E = -42$; one of the ground state...
conformations is shown in Fig. 5 of ref. [19]. We calculated the weight factor within 30 hours with $E_{\text{min}} = -60$ and $V_{\text{max}} = 10$. Figure 2 shows the marginal distribution of $(E, V)$ obtained by the measurement run. The marginal distribution is sufficiently flat including the state $(-42, 0)$, and we can calculate thermodynamic quantities of the sequence at any temperature using it.

Consider another sequence of $N = 100$ shown in the second row of Table I. Bastolla et al. [19] have found conformations with $E = -49$ ($E = -48$ without the abovementioned assumption on the ground state conformations). On the other hand, we found conformations with $E = -50$ within 50 hours by MSOE taking $E_{\text{min}} = -65$ and $V_{\text{max}} = 10$. Figure 3 shows a typical conformation with $E = -50$. This conformation contains some non-bonded HP neighbor pairs. Thus, it can never be found when these pairs are not allowed. Unfortunately, we have not yet obtained the weight factor that gives a sufficiently flat distribution of $(E, V)$.

Next, we discuss a three dimensional example. Yue and Dill [20] have given a sequence of the chain length $N = 42$, whose ground states are 4-fold degenerate and their conformations resemble the parallel $\beta$-helix found for Pectate Lyase C [21]. The ground state energy has been calculated exactly as $E = -34$ by CHCC method. As far as we know, no attempt have been reported so far to calculate thermodynamic properties of this sequence. We applied MSOE to this sequence. By taking $E_{\text{min}} = -50$ and $V_{\text{max}} = 8$, we successfully obtained appropriate weight factor within 50 hours. Temperature dependence of the specific heat, the entropy and the gyration radius are shown in Fig. 4. We see two peaks in the specific heat curve. The peak at $T \approx 0.28$ and the other one at $T \approx 0.52$ correspond to the transition between the ground states and compact globule states (first-order-like) and one between the compact globule states and the random coil (second-order-like), respectively. The gyration radius is considerably small at $T \approx 0.52$. We also found that (not shown in the figure) the fluctuation

![FIG.2. Bivariate histogram $H(E, V)$ obtained by a measurement run of the $N = 64$ HP sequence shown in Table I.](image)

![FIG.3. A typical conformation with $E = -50$ of the second sequence in Table I. This value of the energy is reached for the first time by MSOE.](image)
of the gyration radius has a peak at temperature significantly higher than $T \sim 0.52$. These observations imply that the coil–globule transition takes place in two steps.

![Graph showing specific heat, entropy, and gyration radius vs. temperature]

FIG. 4. Temperature dependence of the specific heat, the entropy, and the gyration radius for the $\beta$–helix sequence.

We made MSOE simulations for two more HP sequences: another sequence of $N = 100$ on the square lattice given in the third row of Table I and the $N = 48$ sequence on the cubic lattice given as the sequence No.9 in ref. [5]. For both sequences, we easily obtained appropriate weight factors down to the lowest energy states ($E = -47$ and $E = -34$, respectively), and found that no first–order–like transition takes place. Thus, not all the HP sequences exhibit first–order–like transition. The lowest energy states of these sequences are highly degenerated. On the other hand, the lowest energy states of 2D $N = 64$ sequence and the $\beta$–helix sequence, both of which exhibit first–order–like native–globule transitions as we have seen above, have highly regular shapes and have low degeneracy. The above results imply that low degeneracy of the ground states is required for first–order–like native–globule transitions to take place in long HP chains.

We also tested the conventional multicanonical algorithm for all the sequences studied above, but none of the lowest energy states found by MSOE could not be reached within 4–5 days. Thus, for such long chains as treated in the present study, the conventional multicanonical algorithm is of no practical use.

In summary, we applied the Multi-Self-Overlap Ensemble (MSOE) method for long chains of the HP lattice protein model in two and three dimensions. For all five sequences we treated, MSOE successfully reached the lowest energy states reported so far. Especially for the sequence in the second row of Table 1, we found the lowest energy states which any other methods have failed to find. We thus confirmed that MSOE is a powerful tool for searching the ground states of lattice protein models. Moreover, we explored the native–globule transitions at finite temperature by MSOE, and found that the degeneracy of the ground states is relevant for the order of the transition. MSOE is a quite general method so that it can be applied to any types of interactions. It can calculate correct thermodynamic properties within a moderate CPU time (although not fastest in some cases actually) as well as low energy states. Especially, once the proper weight factors are determined, we can calculate thermodynamic properties in an arbitrary wide range of temperature in a single run of MSOE.

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