Move set, algorithm, and folding kinetics of Monte Carlo simulations for lattice polymers

Yu-Pin Luo, Ming-Chang Huang† and Yen-Liang Chou
Department of Physics, Chung-Yuan Christian University, 32023 Chungli, Taiwan

Tsong-Ming Liaw
Computing Centre, Academia Sinica, 11529 Taipei, Taiwan

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The effect of different move sets on the folding kinetics of the Monte Carlo simulations is analysed based on the conformation-network and the temperature-dependent folding kinetics. A new scheme of implementing Metropolis algorithm is given. The new method is shown to satisfy the detailed balance and converge efficiently towards thermal equilibrium. A new quantity, employed from the continuous time Monte Carlo method, is introduced to identify effectively the kinetic traps of foldings.

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The problem how proteins fold, in milliseconds to seconds, into unique and stable structures with definite biological functions has recently become intriguing to the biophysicists. The kinetic feature of such problem amounts to the characteristics of the folding paths. Subject to this, considerable progress have been achieved through numerical studies of lattice heteropolymers in two or three dimensions. Although oversimplified, characteristic features obtained from the simulations, such as folding funnel, folding bottleneck and kinetic traps, have provided much insights to the kinetic process. However, there exists some suspicions about the simulation methodology and few ambiguities in the move sets adopted for the simulations. For the former, question about implementing the kinetic Monte Carlo algorithm was raised and some implementations were shown to violate the condition of detailed balance. For the latter, Chan and Dill and Hoang and Cieplak stressed the strong dependence of the folding landscape on the choice of move sets. Consequently, further clarification and improvement for the methodology remain essential. In Ref. , proposals of refining the Monte Carlo algorithm were discussed. In addition, move steps other than the conventional ones, such as the snake move, have also become of interest.

In this Letter we attempt a systematic analysis for the move set, algorithm, and folding kinetics of Monte Carlo simulations for lattice polymers. A specific model system is used to carry out the study. Based on the considerations given by Ref. , we consider the H-P model on a 2D square lattice with the “protein-like” sequence of 16 monomers specified as P H P P H P P H P P H P P H P P H P P H. As the consequence of assigning the contact energies with $E_{H,H} = -3.3$, $E_{H,P} = -2$ and $E_{P,P} = -1$, the energy of the native state, shown in the inset of Fig. 1(b), appears to be $E_g = -13.3$. In addition, the mean energy gap $\Delta E_g = 1.97$ is obtained by averaging out all the energy differences between the lowest 10 excited states and the ground state. The specific-heat curve $C_v(T)$ possesses a single peak, representing the phase transition from the molten globule to the native state, as well as a shoulder at a higher temperature, signifying the transition from random coil to molten globule. Moreover, the folding temperature $T_f$, defined as the temperature at which the probability of the native conformation is 1/2, is at $T_f = 0.50$ which is near to the specific-heat peak.

We are concerned with move sets consisting of typical move steps, say the end flip (ef), corner shift (cs), crankshaft (cr) and the rigid rotation (rr). The conventional move set $S_1$ only allows for ef, cs and cr based on locality. However, the ergodicity is shown to fail for $S_1$. To be concrete, in two dimensions the move set $S_1$ prohibits the reaching of one conformation from the other ones for the folding with 16 monomers and, considerably, the number of such conformations rapidly increases for more monomers and/or dimensions. The problem can be remedied by involving moves of $rr$ type which have been realised in some simple diffusive motions for groups of...
monomers. While $ef$ itself can be viewed as short-scale rigid rotation, an ergodic move set, say $S_2$, can be achieved by simply combining $ef$ with $rr$. Finally, involving all the four types, an $S_3$ move set is also known to be ergodic.

Different move sets generate different conformation-networks for which, each conformation is a node and two nodes are connected by an edge if and only if the two can be transformed to each other via an elementary move of the move set. The nodes for the conformation-network are unambiguously given as long as the ergodicity is fulfilled. For the case at hand, the number of monomers $M = 16$ and the total node number $K = 802,075$. On the other hand, the edge distributions among nodes remain sensitive to the choice of the move sets. Heuristically, few measures for the edge distributions are shown to provide the global properties of the conformation networks as folding in the high temperature limit.

Define the number of edges $k_i$ associated with any node $i$ by means of one elementary move. The corresponding mean values per node $\langle k \rangle$ are 9.2, 20.7 and 26.3 for $S_1$, $S_2$ and $S_3$, respectively. The $\langle k \rangle$ value for $S_2$ or $S_3$ is twice more than the value for $S_1$. Thus, the larger $\langle k \rangle$ value provides more through-way accessibility to the native state and reduce the possibility of being trapped in local minimum. The minimal edge number $l_i$ for a node $i$ to connect with the native state is also of interest. Upon enumerating this for the model sequence with respect to various move sets and taking average, we obtain $\langle l \rangle = 26.4$ for $S_1$ and 8.4 for both $S_2$ and $S_3$. The $\langle l \rangle$ value for $S_2$ or $S_3$ is about one-third of that for $S_1$. More thorough informations are provided by the distributions $P(k)$ and $P(l)$, where $P(k)$ equips each node with the probability of accessing $k$ nodes and $P(l)$ corresponds to the probability associated with minimal edge number $l$ between a node and the native state. In Fig. 1(a), the results of $P(k)$ are given with respect to different move sets. In Fig. 1(b), the $P(l)$ curves develop very narrow widths of the distributions for $S_2$ and $S_3$, sharply contrasting to the case for $S_1$. The results for $P(k)$ and $P(l)$ assure us that, at high temperature, the kinetic features of $S_2$ and $S_3$ are similar but are drastically different from that of $S_1$. Meanwhile, for finite temperatures, the structure peculiar to problem setting remains important.

The method of Monte Carlo simulation is constrained by the condition of detailed balance held on the transition between any of two connected nodes, say from $c_k$ to $c_m$,

$$P_{eq}(c_k)W(c_k \rightarrow c_m) = P_{eq}(c_m)W(c_m \rightarrow c_k), \quad (1)$$

where $P_{eq}(c_k)$ is the equilibrium probability for the conformation $c_k$, and the transition probability rate $W(c_k \rightarrow c_m)$ can be factorized as

$$W(c_k \rightarrow c_m) = p(c_k \rightarrow c_m) \cdot P_{acc}(c_k \rightarrow c_m), \quad (2)$$

with the probability of applying the corresponding update $p(c_k \rightarrow c_m)$ and the acceptance rate $P_{acc}(c_k \rightarrow c_m)$. For the randomly chosen target node $c_m$ from the $k_{eq}$ connected nodes, we have $p(c_k \rightarrow c_m) = 1/k_{eq}$. While the acceptance ratio is $R = P_{acc}(c_k \rightarrow c_m)/P_{acc}(c_m \rightarrow c_k)$, the condition of detailed balance of Eq. (1) and the factorized form of $W(c_k \rightarrow c_m)$ of Eq. (2) lead to

$$R = r_{k,m} \exp\left[-(E_{c_m} - E_{c_k})/T\right], \quad (3)$$

with $r_{k,m} = k_{c_k}/k_{c_m}$, where the Boltzmann constant is set to unity and $T$ is the temperature. Consequently,

$$P_{acc}(c_k \rightarrow c_m) = \frac{R}{1 + R}, \quad (4)$$

the acceptance rate depends on both the energy difference and the edge numbers of two nodes. Therefore, our scheme bears interesting correspondence to the embedding structure of the conformation-network. This is different from the method suggested by Collet who employed $p(c_k \rightarrow c_m) = 1/(2M - 5)$ but adopted $r_{k,m} = 1$ for the acceptance ratio $R$ of Eq. (3) above of the basis of the move set $S_1$. Noteworthy is also the conventional scheme equipped with randomly updating $c_k \rightarrow c_m$ and $r_{k,m} = 1$ may violate the condition of detailed balance. Subsequently, the reliability as well as the efficiency of the algorithm and the dynamic features with respect to move sets are of concern.

Consider the standard deviation of probability distribution from the equilibrium probability, $D(t) = (\sum_{k=1}^{K} (P_{eq}(c_k) - \Pi(c_k,t))^2 / K)^{1/2}$, where $\Pi(c_k,t)$ is the occurrence probability of the state $c_k$ during the time steps $t$. By generating the Monte Carlo trajectories of 300 billion steps at $T = 2.50$ starting from the completely extended chain, the values of $D(t)$ can be sampled at each 100,000 Monte Carlo steps. The results depicted in Fig. 3 reveal interesting issues. First of all, as seen from Fig. 2(a), Monte Carlo simulations with randomly updating $c_k \rightarrow c_m$ and $r_{k,m} = 1$, which violates the detailed balance, cannot converge toward thermal equilibrium. Relative to this, employing the non-ergodic set $S_1$ plays minor role for the unachievable thermal equilibrium since only one isolated node exists for $M = 16$. In addition, the Collet’s method, for which one spend additional time in determining whether an update is applied or not, tends to slow down the convergence toward the thermal equilibrium in contrast to our new scheme. Meanwhile, Fig. 2(b) also shows up even more rapid convergence for the move sets $S_2$ and $S_3$ by means of our new scheme. But the choice of move sets appears to be insensitive to the asymptotic behaviours of the standard deviation of probability distribution, the corresponding scaling rule reads then $D(t) \sim t^{-1/2}$. Thus, we conclude the reliability and efficiency for simulations based on our scheme. The price to pay is that for each update the edge numbers of the present and target nodes have to be known.

For analyzing the perspectives of folding kinetics in relation to move sets, we refer to the CTMC method proposed by Gillespie. The CTMC method can be
and the probability of the occurrence of a transition from the current node \( c_k \) at the time \( \tau \) is

\[
P_{c_k}(\tau) = [W_S(c_k)] \exp[-\tau W_S(c_k)],
\]

where \( W(c_k \to c_m) \) is given by Eq. 2 and \( W_S(c_k) = \sum_{j=1}^{c_k} W(c_k \to c_j) \). Accordingly, we update the node \( c_k \) and determine its time duration \( \tau \) by using two random numbers \( r_1 \) and \( r_2 \) ranging between 0 and 1. With the transition probability of Eq. 5, we calibrate the estimate of the transition probability \( \tau \) by setting \( r_2 = \exp[-\tau W_S(c_k)] \) to yield \( \tau = -\ln(r_2)/W_S(c_k) \).

We first employ the CTMC method described in the last paragraph to measure the first passage time \( t_f \), defined as the required time from a stretched chain to the first arrival of native state. The mean values, \( \langle t_f \rangle \), at various temperatures for different move sets are obtained by averaging over the results of 1000 simulations. The curves of log \( \langle t_f \rangle \) versus \( 1/T \) are parabolic for all move sets. Hence, there exists the fastest folding temperature \( T_{min} \) with the value 1.74 for \( S_1 \), and 1.70 for \( S_2 \) and \( S_3 \). The corresponding \( \langle t_f \rangle \) at \( T_{min} \) is 1.2E5 for \( S_1 \), 3.5E4 for \( S_2 \), and 2.8E4 for \( S_3 \). Moreover, there exists a linear behaviour for log \( \langle t_f \rangle \) against \( 1/T \) at the region of low temperatures, and this gives rise to the Arrhenius law as \( \langle t_f \rangle \sim \exp((E_b)/T) \) with the mean activation energy \( \langle E_b \rangle = 6.72 \) for \( S_1 \), 5.04 for \( S_2 \), and 4.44 for \( S_3 \). All these results are consistent with the geometric features of the conformation-networks, namely that the network associated with \( S_2 \) or \( S_3 \) owns a larger value of the mean number of edges associated with a node and a smaller value of the mean minimal edge number between a node and the native state in comparison with those for \( S_1 \).

The kinetic traps, referred to the states strongly prohibiting the folding into the native one but locating at only few steps away from it, are important for understanding the folding kinetics. Their identifications often rely on the distinction of local energy minima without taking account of the entropy effect. To make the criterion more effectively, we introduce the measure, the average time duration of a state, in the frame of the CTMC method to distinguish obstacle states. The average time duration of a state \( c_k \) is, from Eq. 6, given as \( \langle \tau_{c_k} \rangle = \int_0^\infty \tau P_{c_k}(\tau) d\tau \), and it yields \( \langle \tau_{c_k} \rangle = 1/W_S(c_k) \).

By defining the ratio of \( \tau_{c_k} / \tau_{ave} \) to the average value of all states, \( \eta_{c_k} = (\tau_{c_k})/\tau_{ave} \), with \( \tau_{ave} = \sum_{k=1}^{K} (\tau_{c_k})/K \), as the viscosity-factor associated with the state \( c_k \), we can signify an obstacle state of foldings by means of \( \eta > 1 \).

The root mean square deviation (RMSD) of the location of a node \( c_k \) from that of the native state \( c_0 \) is defined as

\[
d_{\text{RMSD}}(c_k) = \left[ \frac{1}{M} \sum_{i=1}^{M} (\vec{r}_i(c_k) - \vec{r}_i(c_0))^2 \right]^{1/2},
\]

where \( \vec{r}_i(c_k) \) is the position vector of the \( i \)-th monomer of the state \( c_k \). The \( d_{\text{RMSD}}(c_k) \) is adopted as the conformational distance of \( c_k \) from the native state. Note that the other alternative is to take the minimal number of edges between two nodes as the conformational distance, but this suffers from the ambiguity owing to the choice of move sets. By taking the average of the \( \eta \) values, \( \langle \eta \rangle \), of the states associated with the given \( d_{\text{RMSD}} \) as the viscosity-factor of the \( d_{\text{RMSD}} \), we show the results of \( \langle \eta \rangle \) versus \( d_{\text{RMSD}} \) at the fastest folding temperatures \( T_{min} \) of different move sets in Fig. 3. The results indicate that the folding process can be divided into two stages. One is the folding from the denatured to the semicompact states for which, it corresponds to \( d_{\text{RMSD}} \geq 2 \) and the viscosity-factor variations among different move sets are very small. Owing to the large scale change caused by rigid rotation, the folding time for \( S_2 \) and \( S_3 \) can be expected to be much shorter than that for \( S_1 \). The other stage is the adjustment to the native from the semicompact states corresponding to the range \( d_{\text{RMSD}} \leq 2 \). Because of the high \( \langle \eta \rangle \) values, the searching of the native state is a very slow process for all move sets. For a given \( d_{\text{RMSD}} \leq 2 \), the inequality \( \langle \eta \rangle_{S_2} > \langle \eta \rangle_{S_3} > \langle \eta \rangle_{S_1} \) indicates that the local moves are more effective for the searching. The strongest obstacles of foldings for different move sets all occur at \( d_{\text{RMSD}} \simeq 0.5 \) which contains 9 conformations. Among these, the state with the largest \( \eta \) value, shown in the inset of Fig. 3, is the same for different move sets, and the corresponding \( \eta \) value is 21.4 for \( S_1 \), 50.9 for \( S_2 \), and 37.6 for \( S_3 \). From the numerical results of other sequences, we notice that the strongest obstacle is not necessary the same for different move sets, it may also vary with the sequence; but the inequality \( \eta_{S_2} > \eta_{S_3} > \eta_{S_1} \) for the strongest obstacle of a sequence is always true.

In summary, we present a detailed study on the methodology of lattice Monte Carlo method, including the implementation of the algorithm and the move set adopted in the simulations. A new method of implementing the Metropolis algorithm, which is shown to satisfy the condition of detailed balance, is proposed, and the characteristic features of different move sets in the folding kinetics are given. In particular, we combine the CTMC method with the new implementation to introduce a more effective quantity, called viscosity-factor, to identify the kinetic traps.

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Fig. 1. (a) The distribution function of the edge number associated with a node, $P(k)$, versus the edge number, $k$; and (b) the distribution function of the distance $l$ from a conformation to the native conformation, $P(l)$, versus the distance $l$ for the move sets, $S_1$ (circles), $S_2$ (triangles), and $S_3$ (crosses). The inset shown in (b) is the native conformation of the model sequence.

Fig. 2. The standard deviation of probability distribution from the equilibrium probability, $D(t)$, as a function of the number of Monte Carlo steps $t$, at $T = 2.50$: (a) the results of conventional implementation (circles), Collet’s method (triangles), and the new proposed method (crosses) with the move set $S_1$; and (b) the results of the new proposed method with the move sets $S_1$ (circles), $S_2$ (triangles), and $S_3$ (crosses) with the straight lines given by $D(t) \sim t^{-1/2}$.

Fig. 3. The average value of viscosity-factors, $\langle \eta \rangle$, versus the distance to the native conformation, $d_{RMSD}$, at the fastest folding temperatures $T_{min}$ for the move sets $S_1$ (circles), $S_2$ (triangles), and $S_3$ (crosses). The inset shows the conformation with the largest $\eta$ value for the peak in the curve of $\langle \eta \rangle$ versus $d_{RMSD}$. 
fig. 1(a)
fig. 1(b)
fig. 2(a)
fig. 2(b)
fig. 3