Multicanonical Chain Growth Algorithm

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We present a temperature-independent Monte Carlo method for the determination of the density of states of lattice proteins that combines the fast ground-state search strategy of the nPERM chain growth and multicanonical reweighting for sampling the complete energy space. Since the density of states contains all energetic information of a statistical system, we can directly calculate the mean energy, specific heat, Gibbs free energy, and entropy for all temperatures. We apply this method to HP lattice proteins and for the examples of sequences considered, we identify the transitions between native, globule, and random coil states. Since no special properties of heteropolymers are involved in this algorithm, the method applies to polymer models as well.

The simulation of protein folding is extremely challenging, since the interactions between the constituents of the macromolecule and the influence of the environment require sophisticated models. One of the most essential aspects in the description of the folding process is the formation of a compact core of hydrophobic amino acid residues (H) which is screened from water by hydrophilic or polar residues (P). This characteristic property of realistic proteins can be qualitatively studied with simple lattice models such as the HP model [1]. By taking into account the attractive interaction between hydrophobic monomers only, the energy of a lattice protein with certain conformation and sequence is calculated as follows:

\[ E = - \sum_{i,j<i-1} \sigma_i \sigma_j, \]  

where \( i, j < i - 1 \) symbolises that the sum is taken only about any axis through the pivot. Unfortunately, the number of free lattice sites to place the \( n \) th monomer is hydrophobic, \( \sigma_i = 1 \), while for a polar monomer \( \sigma_i = 0 \).

As it is one of the main goals in off-lattice simulations to find low-lying energy states within a rough free energy landscape, good lattice folders are expected to have low-degenerated ground states. Much work has been done on identifying designing sequences with such native states. Ground-state search strategies on three-dimensional lattices range, for example, from enumeration [2,3] over hydrophobic core construction [4,5] and contact interaction [6] to chain growth methods [7–10]. Low-lying energy states for HP sequences with up to 136 monomers were identified with these methods.

In contrast, there were only few attempts to study the thermodynamic properties of the HP model in three dimensions [11]. The main reason is that conventional Monte Carlo methods like Metropolis sampling, but also more sophisticated methods like simulated [12] and parallel [13] tempering as well as histogram reweighting Monte Carlo algorithms such as multicanonical sampling [14] or the Wang-Landau method [15] expose problems in tackling “hidden” conformational barriers in combination with chain update moves which become usually inefficient at low temperatures, where many attempted moves are rejected due to the self-avoidance constraint. One possibility to update the conformation is to apply move sets. Widely used sets usually consist of operations that change a single bond (end flips), two bonds (corner flips), three (crankshaft) or even more bonds, and pivot rotations, where the \( i \) th monomer serves as pivot point and one of the two partial chains connected with it is rotated about any axis through the pivot. Unfortunately, the more dense the conformation, the more inefficient this procedure becomes.

Alternatively, it is possible to let the polymer grow, i.e., the \( n \)th monomer is placed at a randomly chosen next-neighbour site of the \((n - 1)\)th monomer \((n \leq N\) with \(N\) being the total length of the polymer). If this new site is already occupied, the entire chain would have to be discarded to obtain correct statistics. This simple chain growth is not efficient, since the number of discarded chains grows exponentially with the chain length. Rosenbluth chain growth [16] avoids occupied neighbours at the expense of a bias, since the probability of such a chain is \( p_n \sim \left(\prod_{m=2}^{n} m_i^{-1}\right) \), where \(m_i\) is the number of free lattice sites to place the \(i\)th monomer. This bias is balanced out by assigning each conformation a Rosenbluth weight \( W_n^R \sim p_n^{-1}\). Chain growth methods with population control such as PERM (Pruned-Enriched Rosenbluth Method) [8,9] and its recent modifications nPERM* [10] improve this procedure considerably by utilising the counterbalance between Rosenbluth weight and Boltzmann probability. The weight factor \( W_n^R \) is therefore replaced by

\[ W_n^{PERM} = \prod_{l=2}^{n} m_l e^{-(E_l - E_{l-1})/k_B T}, \]  

\( 2 \leq n \leq N \quad (E_1 = 0, \quad W_1^{PERM} = 1), \)

where \( E_l \) is the energy of the partial chain \( X_l = (x_1, \ldots, x_l) \) created with Rosenbluth chain growth and \( T \) is the temperature.

To explain the main ideas, we shall confine ourselves for the moment to the original PERM formulation [8],

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where the sample of chains of length \( n \) is enriched by making identical copies once \( W_n^{\text{PERM}} \) is bigger than a certain threshold value \( W^2 \). In this case, the weight \( W_n^{\text{PERM}} \) is divided among the clones. For \( W_n^{\text{PERM}} \) being smaller than a lower bound \( W^1 \), the chain is pruned with probability 1/2 and the weight of a surviving chain is doubled. The partition sum is proportional to the sum of weight factors (2) for the conformations \( X_{n,t} \) of length \( n \) sampled at “time” \( t \),

\[
Z_n \sim \sum_t W_n^{\text{PERM}}(X_{n,t}). \tag{3}
\]

The PERM algorithms are very successful as ground-state searchers and the canonical distribution at a given temperature \( T \) is well reproduced over some orders of magnitude, but states that are highly suppressed at this temperature are not hit in a reasonable time. Standard reweighting techniques are applicable only in a small region around \( T \). Thus, recording temperature-dependent quantities such as the specific heat requires simulations at different temperatures.

As the partition sum of a polymer or a heteropolymer with fixed sequence can be expressed in terms of the density (or degeneracy) of states \( g(E) \), \( Z = \sum_{\{x\}} e^{-\beta E}\langle x \rangle = \sum_{i} g(E_i)e^{-\beta E_i} \) (\( \beta \equiv 1/k_B T \)), all energetic quantities such as the mean energy \( \langle E(T) \rangle = -(\partial / \partial \beta) \ln Z \), the specific heat \( C_V(T) = (\langle E^2 \rangle - \langle E \rangle^2) / k_B T^2 \), Gibbs free energy \( F(T) = -k_B T \ln Z \), and entropy \( S(T) = (\langle E \rangle - F) / T \) can directly be calculated if the density of states is known. These quantities are of particular interest, since they are indicators of temperature-dependent conformational transitions.

Our method allows within one simulation the direct sampling of the density of states \( g(E) \) over the entire range of the energy space with probabilities ranging over many orders of magnitude, due to combining the advantages of energetic flat histogram reweighting at infinite temperature and chain growth. The flat distribution can then be reweighted to any desired temperature. Rare, i.e. low-lying energy states are also hit and therefore the low-temperature behaviour of the polymer can be reproduced well, in particular the low-temperature transition between compact globules and ground states of lattice proteins with low ground-state degeneracy. Using the HP model, we applied the method to lattice proteins with more than 40 monomers and different ground-state degeneracies and found for examples with low ground-state degeneracy pronounced low-temperature peaks in the specific heat indicating ground-state – globule transitions. Since our method is completely general, it is also applicable to other polymer models.

In order to achieve a flat distribution of energetic states using chain growth, we introduce into the partition sum (3) an additional weight \( W_n^{\text{PERM}}(E_n(X_n)) \) that depends on the energy \( E_n \) of a given conformation \( X_n = (x_1, \ldots, x_n) \):

\[
Z_n \sim \sum_t W_n^{\text{PERM}}(X_{n,t}) \\
\times W_n^{\flat}(E_n(X_{n,t})) \left[ W_n^{\text{flat}}(E_n(X_{n,t})) \right]^{-1}. \tag{4}
\]

Since the histograms at all intermediate stages of the chain growth process are required to be flat, the new reweighting factor is rewritten in product form and we have

\[
Z_n \sim \sum_t \left[ W_n^{\text{flat}}(E_n) \right]^{-1} \\
\times \prod_{l=2}^{n} m_l e^{-(E_l - E_{l-1})/k_B T} W_l^{\text{flat}}(E_l) / W_l^{\text{flat}}(E_{l-1}). \tag{5}
\]

with \( W_n^{\text{flat}} = 1 \). The PERM weight factors (2) lead to a canonical distribution \( P_n^{\text{can,T}}(E_n) \) which shall be deformed to a constant distribution \( P_n^{\text{flat,T}}(E_n) \) over the entire energy space. This requires the weights \( W_n^{\text{flat}} \) to be proportional to the inverse of the canonical distribution, \( W_n^{\text{flat}} \sim 1/P_n^{\text{can,T}}(E_n) \), a condition that can obviously only be satisfied iteratively \([14]\). As we are mainly interested in the density of states, which is proportional to the canonical probability distribution at \( \beta = 1/k_B T = 0, g_n(E_n) \sim P_n^{\text{can}}(E_n) \), we will effectively perform the simulation at infinite temperature. Consequently, \( W_n^{\text{flat}} \sim 1/g_n(E_n) \) and \( Z_n \sim \sum_t g_n(E_n(X_{n,t})) W_n(X_{n,t}) \).

Here we have introduced the combined weight

\[
W_n(X_n) = \prod_{l=2}^{n} \frac{g_l^{-1}(E_l)}{g_{l-1}^{-1}(E_{l-1})}, \quad W_1 = g_1 = 1, \tag{6}
\]

which can also be written recursively, \( W_n = W_{n-1} m_n g_n^{-1}(E_n)/g_{n-1}^{-1}(E_{n-1}) \). The canonical mean value of any quantity \( \langle O \rangle_{n}(X_n) \) is then calculated as follows:

\[
\langle O \rangle_{n/\text{can}} = \frac{\sum_t O_n(X_{n,t}) g_n(E_n(X_{n,t})) W_n(X_{n,t})}{\sum_t g_n(E_n(X_{n,t})) W_n(X_{n,t})} = \frac{\langle O_n g_n(E_n) \rangle_{\text{flat}}}{\langle g_n(E_n) \rangle_{\text{flat}}}. \tag{7}
\]

where we have used mean values according to the flat distribution \( \langle \cdots \rangle_{\text{flat}} = \sum \cdots W_n(X_n)/Z_{n/\text{flat}} \) with the partition sum of the flat distribution \( Z_{n/\text{flat}} = \sum W_n(X_{n,t}) \). The most important technical part of the algorithm is the determination of the weights \( W_n^{\text{flat}} \), since they are directly connected with the desired densities of states \( g_n(E) \). As the weights are completely unknown in the beginning, we evaluate them iteratively, starting from unity, \( W_n^{\text{flat},(0)}(E) = 1 \) \((2 \leq n \leq N)\) for all values of \( E \). This means that the zeroth iteration is a pure chain growth run without reweighting.

Each time, a chain of length \( n \) with energy \( E \) is created, the corresponding histogram value \( h_n(E) \) is increased by the weight \( W_n \) of the chain. If a certain number of chains
with total length $N$ was produced, the iteration is finished and the new weights $W_{n}^{\text{flat},(i)}(E)$ are determined by calculating $W_{n}^{\text{flat},(i)}(E) = W_{n}^{\text{flat},(i-1)}(E)/h_{n}(E)$, $2 \leq n \leq N$. Before the next iteration starts, the histogram is reset, $h_{n}(E) = 0$. The correct weights are found, when $h_{n}(E)$ is “flat”, i.e., it has approximately the same value for all energies. In our actual implementation we employed a suitably adapted multicanonical variant of nPERMIs (new PERM with importance sampling) [10].

Before we present results obtained with this new algorithm, we discuss general properties of heteropolymers exemplified for 14mers which can still be analysed by exact enumeration. Among all $2^{14}$ sequences for 14mers there is only one designing sequence, i.e. a sequence to which a unique ground state belongs (up to a reflection symmetry).

We compared thermodynamic properties of four 14mers with different sequences but same hydrophobicity ($n_H = 8$) and identical lowest energy ($E_{\min} = -8$). Figure 1 shows the specific heat for the 14mers. A pronounced low-temperature peak that indicates the transition between ground states and globule states is only observed for the 14mer with the native ground state, 14.1. These results show qualitatively how the conformational transitions depend on the ground-state degeneracy $g_0$ of the polymer. For the sequences 14.2 and 14.3 it is twice that of the designing sequence, and 14.4 is even four times higher degenerate.

The first example to which we applied our multicanonical chain growth algorithm is a 42mer with the sequence PH$_2$PHPHP$_2$PHPHP$_3$H$_2$PHPHP$_2$PHPHP$_2$PHPHP$_2$P and ground-state properties have similarities with the parallel β-helix of pectate lyase C [17]. The lattice model with only four-fold ground-state degeneracy has a ground-state energy of $E_{\min} = -34$. In order to investigate the low-temperature behaviour of this system it is necessary that the algorithm correctly samples the low-energy states and that it also hits the ground states. The measured density of states ranges over about 25 orders of magnitude and covers the entire energy space $[-34, 0]$, as shown in Fig. 2.

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**FIG. 1.** Specific heat for four 14mers with different sequences. Only the 14mer with the native ground state shows a pronounced low-temperature peak indicating a transition between ground-states and globules.

**FIG. 2.** Density of states of the 42mer, normalised to unity, i.e. $\sum g(E_i) = 1$.

**FIG. 3.** (a) Specific heat and mean energy as functions of the temperature for the 42mer. The ground-state – globule and the globule – random coil transition occur at $T_0 \approx 0.27$ and $T_1 \approx 0.53$, respectively. (b) Reduced free energy $\tilde{F}(T) = F(T) + TS_0$ and entropy $\tilde{S}(T) = S(T) - S_0$.

Figure 3(a) shows the results for the heat capacity and the mean energy. Writing out the raw energies and weights from the simulation, we analysed the data and calculated the statistical error by means of the jackknife blocking method. Due to the low degeneracy of the ground states, the transition between native states and globule states is very pronounced and occurs at a temperature $T_0 \approx 0.27$. The globule – random coil tran-
sition at \( T_1 \approx 0.53 \), on the other hand, is rather weak. This confirms the results of Ref. [11]. From the density of states, we also obtain the Gibbs free energy \( F(T) \) and the entropy \( S(T) \). Since the ground-state degeneracy \( g_0 \) is not accessible by stochastic search algorithms in general, we have plotted in Fig. 3(b) the reduced free energy \( \tilde{F}(T) = F(T) + TS_0 \) and the entropy \( \tilde{S}(T) = S(T) - S_0 \), up to the constant \( S_0 = \ln g_0 \), where \( g_0 \) is the degeneracy of the ground state.

Finally, similar to the consideration of the 14mers, we compare two 48mers with different ground-state properties. The first one, which we denote by 48.1 has the sequence PHPHP₂H₆P₃PHP₃HPHP₂HPHP₂HP₂HP₂H₂P₂H₂P₂HP₃HP₃HP₂H₂P₃HP₃H₂ and its ground state with the energy \(-34\) is 5000-fold degenerate. The ground state of the other 48mer (48.2) with the sequence HPH₂P₃H₃P₃H₂P₃PHP₃HP₂HP₂P₂HP₃HP₂HP₂HP₂HP₃ has the much higher degeneracy of \( 1.5 \times 10^9 \) and possesses the energy \(-32\) [5]. As is demonstrated in Fig. 4, we also observe for these longer chains that the conformational transition between the lowest-energy states and the globules is stronger the lower the ground-state degeneracy is.

![Graph showing specific heat and mean energy for two 48mers](image)

**FIG. 4.** Specific heat and mean energy for the two 48mers with different ground-state properties. The low-temperature conformational transition is more pronounced for the example 48.1 with lower ground-state degeneracy.

In conclusion, we have developed a multicanonical chain growth algorithm that allows the simulation of the thermodynamic properties of polymers and heteropolymers. It is based on energetic flat histogram sampling of the density of states in combination with PERM chain growth. We applied this algorithm to heteropolymers with more than 40 monomers and obtained accurate densities of states over about 25 orders of magnitude that cover the entire energy range, thus yielding very good results for all derived energetic quantities such as mean energy, specific heat, free energy, and entropy. In particular, this enabled us to determine the low-temperature behaviour of the systems with high precision and to observe pronounced low-temperature peaks of the specific heat for lattice proteins with low ground-state degeneracy indicating the ground-state – globule transition.

We thank Peter Grassberger and Hsiao-Ping Hsu for helpful discussions on the new PERM algorithms. This work is partially supported by the German-Israel-Foundation (GIF) under contract No. I-653-181.14/1999.

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