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Comparison of the Parallel Tempering Algorithm and Multicanonical Method as Applied to Coarse-Grained Off-lattice Models for Folding Heteropolymers

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Abstract We have performed Parallel Tempering simulations of hydrophobic-hydrophilic heteropolymers with a simple effective, coarse-grained off-lattice model with the selected monomers and compare the global energy minimums found with Parallel Tempering algorithm with the lowest energy states identified within the multicanonical algorithm.

Keywords Off-lattice protein models · Conformational Sampling · Parallel Tempering

1 Introduction

Predicting the proteins structure and the folding mechanism is an important goal in structural biology. Although the physical principles are known, the complexity of proteins as being macromolecules consisting of numerous atoms makes an accurate analysis of the folding process of realistic proteins extremely difficult.

The configuration space of proteins and peptides presents a complex energy profile consisting of tremendous number of local minima separated by energy barriers. An ideal simulation scheme should freely visit the entire space and predominantly sample the significant conformations. Conventional simulation methods are of little use; because of the energy barriers they tend to get trapped in local minima and the results thus will depend strongly on the initial conditions. To overcome this problem there are two alternatives: generalized ensemble algorithms and Parallel Tempering algorithm which is also known as Replica exchange method.

One of the most well-known, powerful generalized-ensemble methods is the Multicanonical algorithm [1, 2]. But, in multicanonical procedure, the probability weight factors are not a priori known and have to be determined by iterations of trial simulations. This part of simulation can be non-trivial and very tedious for complex systems with many local minimum energy states. The other generalized-ensemble approaches, for example simulated tempering, $1/k$ sampling and Parallel Tempering methods are reviewed in references [3] and [4]

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Application of the Multicanonical approach to peptides was pioneered by Hansmann and Okamoto [5] and followed by others [6–8].

Choosing between the two alternatives of these methods the Parallel Tempering technique has become important for simulation of proteins and other complex systems.

In Parallel Tempering [9, 10] simulations N non-interacting copies, or "replicas", of the system are simultaneously simulated in parallel at a range of values of a control parameter, most often the temperatures $\{T_1, T_2, \ldots, T_N\}$, using a standard version of the Metropolis scheme. After a fixed number of Monte Carlo sweeps conformational energies of the system replicas are compared and neighboring replicas, T_i and T_{i+1}, are swapped according to the probability criterion dependent on energy and temperature:

$$p(E_i, T_i \to E_{i+1}, T_{i+1}) = \min\left(1, \exp(-\Delta\beta \Delta E)\right), \tag{1}$$

where $\Delta\beta = 1/T_{i+1} - 1/T_i$ is the difference between the inverse temperatures and $\Delta E = E_{i+1} - E_i$ is the difference in energy of the two replicas. For a given replica the swap moves induce a random walk in temperature space that allows the replica to cross the complex energy landscape. Thus, the algorithm samples not only conformational space but also different temperatures.

In this paper, we illustrate Parallel Tempering simulation of the coarse-grained off-lattice protein model and compare this results with MUCA results [11] in regards of finding the low energy structures.

2 Model

One of the most prominent minimalistic protein model is the HP model of lattice proteins, which has been exhaustively investigated [12–14]. In this model, only two types of monomers are considered, with hydrophobic (H) and polar (P) character. Chains on the lattice are self-avoiding to account for the excluded volume. The only explicit interaction is between non-adjacent but next-neighbored hydrophobic monomers. This interaction of hydrophobic contacts is attractive to force the formation of a compact hydrophobic core which is screened from the (hypothetic) aqueous environment by the polar residues. Statistical mechanics aspects of this model are being subject of recent studies [15–19]. A manifest off-lattice generalization of the hydrophobic-polar (HP) model is the AB model [20, 21], where the hydrophobic monomers are labelled by A and the polar or hydrophilic ones by B. As on the lattice, the adjacent monomers are connected by rigid covalent bonds. Thus, the distance is fixed and set to unity. The contact interaction is replaced by a more realistic distance-dependent Lennard-Jones type of potential accounting for short-range excluded volume repulsion and long-range interaction; the latter being attractive for AA and BB pairs and repulsive for AB pairs of monomers. An additional interaction accounts for the bending energy of any pair of successive bonds. This model was first applied in two dimensions [20, 21] and generalized to three-dimensional AB proteins [22, 23], with modifications by taking implicitly into account the additional torsional energy contributions of each bond.

AB model as proposed in Ref. [22] has the energy function

$$E = -\kappa_1 \sum_{k=1}^{N-2} \mathbf{b}_k \cdot \mathbf{b}_{k+1} - \kappa_2 \sum_{k=1}^{N-3} \mathbf{b}_k \cdot \mathbf{b}_{k+2} + 4 \sum_{i=1}^{N-2} \sum_{j=i+2}^{N} C(\sigma_i, \sigma_j) \left(\frac{1}{r_{ij}^{12}} - \frac{1}{r_{ij}^{6}} \right), \tag{2}$$

where $\mathbf{b}_k$ is the bond vector between the monomers k and $k+1$ with length unity. In Ref. [22] different values for the parameter set (κ_1, κ_2) were tested and finally set to

$(-1, 0.5)$ as this choice provide both the distributions for the angles between bond vectors $\mathbf{b}_k$ and $\mathbf{b}_{k+1}$ and the torsion angles between the surface vectors $\mathbf{b}_k \times \mathbf{b}_{k+1}$ and $\mathbf{b}_{k+1} \times \mathbf{b}_{k+2}$ giving the best agreement with the distributions obtained for selected functional proteins. Since $\mathbf{b}_k \cdot \mathbf{b}_{k+1} = \cos\vartheta_k$, the choice $\kappa_1 = -1$ makes the coupling between successive bonds "antiferromagnetic". The second term in (2) takes torsional interactions into account. The third term contains a pure Lennard-Jones potential, where the $1/r_{ij}^6$ long-range interaction is attractive whatever types of monomers interact. The monomer-specific prefactor $C(\sigma_i, \sigma_j)$ only controls the depth of the Lennard-Jones valley:

$$C(\sigma_i, \sigma_j) = \begin{cases} +1, & \sigma_i, \sigma_j = A, \\ +1/2, & \sigma_i, \sigma_j = B \text{ or } \sigma_i \neq \sigma_j. \end{cases} \tag{3}$$

For technical reasons, we have introduced in both models a cut-off $r_{ij} = 0.5$ for the Lennard-Jones potentials below which the potential is hard-core repulsive (i.e., the potential is infinite).

3 Computational Details

For updating a conformation, we use the spherical update procedure displayed in Fig. 1 (Details are given in Ref. [24]). Since the length of the bonds are fixed ($|\mathbf{b}_k| = 1$, $k = 1, \ldots, N-1$), the $(i+1)$th monomer lies on the surface of a unit sphere centered on the ith monomer. Therefore, spherical coordinates are the natural choice for calculating the new position of the $(i+1)$th monomer on this sphere. For the reason of efficiency, all the points on the sphere are not selected for updating, but restricted the choice to a spherical cap with maximum opening angle $2\theta_{\max}$ (the dark area in Fig. 1). Thus, to change the position of the $(i+1)$th monomer to $(i+1)'$, we select the angles θ and φ randomly from the respective intervals $\cos\theta_{\max} \leq \cos\theta \leq 1$ and $0 \leq \varphi \leq 2\pi$, which ensure a uniform distribution of the $(i+1)$th monomer's positions on the associated spherical cap. After updating the position of the $(i+1)$th monomer, the following monomers in the chain are simply translated according to the corresponding bond vectors which remained unchanged in this type of update. This is similar to single spin updates in local-update Monte Carlo simulations of the classical Heisenberg model with the difference that, in addition to local energy changes, long-range interactions of the monomers are to be computed anew after the update, due to changing their relative position. In our simulations of the AB models we used a very small opening angle, $\cos\theta_{\max} = 0.99$, in order to be able to sample also very narrow and deep valleys in the landscape of angles. The degrees of freedoms and the updating scheme in the simulations for the two algorithm are the same.

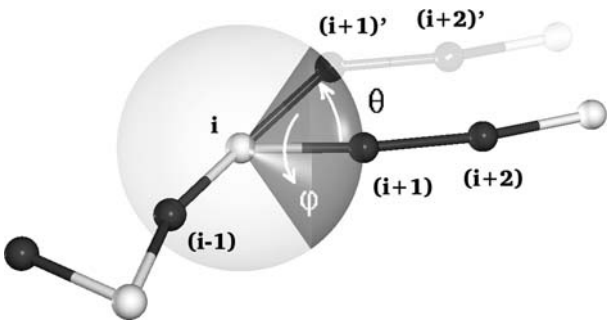

Fig. 1 Spherical update of the bond vector between the ith and $(i+1)$th monomer

The basic idea of Parallel Tempering, as explained in the Introduction is to simulate different copies (replicas) of the system at the same time but at different temperatures. High temperature simulation segments facilitate the crossing of the energy barriers while the low temperature ones give the energy minima in detail. The advantage of swapping between different temperatures is that high temperature replicas help the low temperature replicas to jump across the energy barriers which is the highlight feature of this type systems.

In this study, for Parallel Tempering simulations 12 replicas were used with temperatures 1.5, 1.0, 0.7, 0.5, 0.4, 0.35, 0.3, 0.25, 0.2, 0.15, 0.125, 0.1. Firstly, these temperatures were chosen to span the temperature range between 0.1 and 1.5 which is also used in Multicanonical Simulations [11]. For the Replica-Exchange algorithm the best choice of temperature points should be concentrate around the conformational transition point [25] where is around $T \sim 0.25$ (where the specific heat has a peak known from our previous simulations [11]. To optimize these selection we are now study on a automatic procedure to get the temperature set before doing a long simulation run. The initial conformations were randomly generated. In Replica-Exchange algorithm, after 100000 MC sweeps of equilibration, the production run of 2×10^8 MC sweeps for each replica was made. The conformations were stored every 100 MC sweeps for data analyses. In Multicanonical algorithm 2.5×10^8 sweeps are done in trial run for determination of the weight factors and the production run is 2×10^8 MC sweeps. In this respect, multicanonical simulations seems to be more powerfull, but the probability weight factors are not a priori known and have to be determined by iterations of trial simulations and the trial runs would be usually more than one.

4 Results and Discussions

In order to be able to investigate the low-temperature behaviour of the model, we first assess the capabilities of the Parallel Tempering method to sample the low energy conformations and, especially to approach closely the global energy minimum conformation. In Table 1, there are given the list of sequences that are simulated in this study. In Ref. [11] the ground state energies of these sequences studied with Multicanonical Simulation and other generalized techniques. We compare these results with the respective lowest energies found with Parallel Tempering algorithm. It turns out that the ground-state energies found by Parallel Tempering agree well with what comes out by the MUCA, cf. Table 2 and we are pretty sure that we have found the ground states. Our estimates for the ground state energies lie significantly below the energies quoted with another methods [26]. In Fig. 2 we also compare the mean energy as a function of temperature. The results of both algorithm agree well with each other.

In order to check the structural similarities of the lowest-energy conformations obtained with Multicanonical sampling and those from the Parallel Tempering runs, we calculated here the overlap parameter that enables us to compare conformations [11]. Instead of performing comparisons of positions it is much simpler and less time-consuming to calculate the overlap between two conformations by comparing their bond and torsion angles. As an extension of the torsion-angle based variant [27, 28], the more general overlap parameter defined as

$$Q(\mathbf{X}, \mathbf{X}') = \frac{N_t + N_b - d(\mathbf{X}, \mathbf{X}')}{N_t + N_b}, \tag{4}$$

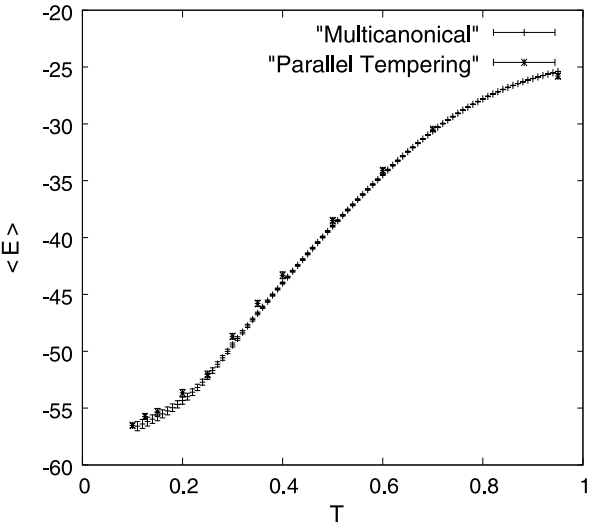

Fig. 2 The mean energy as a function of temperature obtained by both algorithms Multicanonical vs. Parallel Tempering for the sequence $A_4B_2A_4BA_2BA_3B_2A$ (sequence 20.3)

Table 1 Sequences used in the study of thermodynamic properties of heteropolymers by Multicanonical Simulation as introduced in Ref. [11]. The number of hydrophobic monomers is denoted by #*A*

No.	Sequence	#A
20.1	$BA_6BA_4BA_2BA_2B_2$	14
20.2	$BA_2BA_4BABA_2BA_5B$	14
20.3	$A_4B_2A_4BA_2BA_3B_2A$	14
20.4	$A_4BA_2BABA_2B_2A_3BA_2$	14
20.5	$BA_2B_2A_3B_3ABABA_2BAB$	10
20.6	$A_3B_2AB_2ABAB_2ABABABA$	10

Table 2 Minimal energies for the six 20mers obtained by Parallel Tempering algorithm and multicanonical sampling and the overlap values calculated between the minimums

No.	$E_{\min}^{\mathrm{PT}}$	$E_{\min}^{\mathrm{MUCA}}$ [11]	*Overlap*
20.1	−58.300	−58.306	0.991
20.2	−58.930	−58.880	0.971
20.3	−59.751	−59.293	0.977
20.4	−59.221	−59.068	0.981
20.5	−53.513	−51.525	0.994
20.6	−54.435	−53.359	0.985

where (with $N_t = N - 3$ and $N_b = N - 2$ being the numbers of torsional angles Φ_i and bond angles $\Theta_i = \pi - \vartheta_i$, respectively)

$$d(\mathbf{X}, \mathbf{X}') = \frac{1}{\pi}\left(\sum_{i=1}^{N_t} d_t(\Phi_i, \Phi_i') + \sum_{i=1}^{N_b} d_b(\Theta_i, \Theta_i')\right),$$

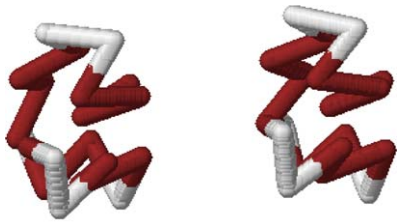

Fig. 3 Global energy minimum conformations of the sequence $A_4B_2A_4BA_2BA_3B_2A$ (sequence 20.3) found with the (**a**) MUCA and (**b**) Parallel Tempering algorithm. The overlap parameter is 0.977 between the conformations. (*dark spheres*: hydrophobic monomers – A, *light spheres*: hydrophilic – B)

$$d_t(\Phi_i, \Phi_i') = \min(|\Phi_i - \Phi_i'|, 2\pi - |\Phi_i - \Phi_i'|),$$
$$d_b(\Theta_i, \Theta_i') = |\Theta_i - \Theta_i'|.$$

Since $-\pi \leq \Phi_i \leq \pi$ and $0 \leq \Theta_i \leq \pi$ it follows immediately that $0 \leq d_{t,b} \leq \pi$. The overlap is unity, if all angles of the conformations $\mathbf{X}$ and $\mathbf{X}'$ coincide, else $0 \leq Q < 1$.

In Table 2 additionally to the minimum energies there are also given the overlap parameter values which are calculated between the MUCA and Parallel Tempering minimums for each sequence. This values are in range 0.97–0.99 which means that the coincidence of the lowest-energy structures found with two algorithms is extremely good and we are sure that the conformations lie in the same or belong to the same attraction basin. In other words, the coincidence of the structures show us that we have found the ground states with both algorithms.

Further, in Fig. 3 there are given the global minimum energy conformations of one of the sequences (sequence 20.3) found with the MUCA and Parallel Tempering algorithm. The overlap parameter is 0.977 which means that these conformations are very close to each other. This can be also seen from the figure. Consequently, the algorithms sample efficiently the same energy valley.

5 Conclusions

The objective of this work has been to investigate the efficiency of MUCA and Parallel Tempering methods for coarse-grained off-lattice heteropolymer models of AB type. In replica-exchange algorithm, after 100000 MC sweeps of equilibration, the production run of 2×10^8 sweeps are made for each replica. In multicanonical algorithm 2.5×10^8 sweeps are done in trial simulations for the determination of the weight factors and the production run is 2×10^8 MC sweeps. In this respect, multicanonical simulations seems to be more powerfull but the probability weight factors are not a priori known and have to be determined by iterations of trial simulations and the trial runs would be usually more than one. This process can be nontrivial and very tedious for complex systems with many degrees of freedom. In the replica-exchange method, the difficulty of weight factor determination is greatly alleviated. The weight factor is just the product of Boltzmann factors, and so it is essentially known. In a test, we checked the ability of the algorithm to find lowest-energy conformations. The results were compared with minimum energy values obtained with the Multicanonical Method. Further, by measuring a generalized overlap parameter for both conformations found from MUCA and Parallel Tempering methods are compared for each sequence. In addition to torsional degrees of freedom the generalized overlap parameter also allows the comparison of bond angles. Therefore we are pretty sure that we found very good coincidences for minimum energies and associated conformations for all sequences under study.

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References

1. Berg, B.A.: Fields Inst. Commun. **26**, 1 (2000)
2. Berg, B.A., Çelik, T.: Phys. Rev. Lett. **69**, 2292 (1992)
3. Hansmann, U.H.E., Okamoto, Y.: Ann. Rev. Comput. Phys. **5**, 129 (1999)
4. Mitsutake, A., Sugita, Y., Okamoto, Y.: Biopolymers (Peptide Sci.) **60**, 96 (2001)
5. Hansmann, U.H.E., Okamoto, Y.: J. Comput. Chem. **14**, 1333 (1993)
6. Hao, M.-H., Scheraga, H.A.: J. Phys. Chem. **98**, 4940 (1994)
7. Hao, M.-H., Scheraga, H.A.: J. Phys. Chem. **98**, 9882 (1994)
8. Kolinski, A., Galazka, W., Skolnick, J.: Proteins **26**, 271 (1996)
9. Trebst, S., Troyer, M., Hansmann, U.H.E.: J. Chem. Phys. **124**(17), 174903 (2006)
10. Nadler, W., Hansmann, U.H.E.: Phys. Rev. E **75**(2), 026109 (2007)
11. Bachmann, M., Arkin, H., Janke, W.: Phys. Rev. E **71**, 031906 (2005)
12. Dill, K.A.: Biochemistry **24**, 1501 (1985)
13. Lau, K.F., Dill, K.A.: Macromolecules **22**, 3986 (1989)
14. Larson, R.G., Scriven, L.E., Davis, H.T.: J. Chem. Phys. **83**, 2411 (1985)
15. Chikenji, G., Kikuchi, M., Iba, Y.: Phys. Rev. Lett. **83**, 1886 (1999) and references therein
16. Hsu, H.-P., Mehra, V., Nadler, W., Grassberger, P.: J. Chem. Phys. **118**, 444 (2003)
17. Hsu, H.-P., Mehra, V., Nadler, W., Grassberger, P.: Phys. Rev. E **68**, 021113 (2003)
18. Bachmann, M., Janke, W.: Phys. Rev. Lett. **91**, 208105 (2003)
19. Bachmann, M., Janke, W.: J. Chem. Phys. **120**, 6779 (2004)
20. Stillinger, F.H., Head-Gordon, T., Hirshfeld, C.L.: Phys. Rev. E **48**, 1469 (1993)
21. Stillinger, F.H., Head-Gordon, T.: Phys. Rev. E **52**, 2872 (1995)
22. Irbäck, A., Peterson, C., Potthast, F., Sommelius, O.: J. Chem. Phys. **107**, 273 (1997)
23. Irbäck, A., Peterson, C., Potthast, F.: Phys. Rev. E **55**, 860 (1997)
24. Aktürk, E., Arkin, H., Çelik, T.: Int. J. Mod. Phys. C **18**(1), 99 (2007)
25. Trebst, S., Troyer, M., Hansmann, U.H.E.: J. Chem. Phys. **124**, 174903 (2006)
26. Liang, F.: J. Chem. Phys. **120**, 6756 (2004)
27. Hansmann, U.H.E., Masuya, M., Okamoto, Y.: Proc. Natl. Acad. Sci. USA **94**, 10652 (1997)
28. Berg, B.A., Noguchi, H., Okamoto, Y.: Phys. Rev. E **68**, 036126 (2003)