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Monte Carlo Simulations of Energy Surface and conformation of Complex Systems

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ABSTRACT

The energy surfaces of complex systems such as spin glass and proteins are characterized by a large number of local minima and few global minima which correspond to many slightly different conformations that a complex system can assume. This complex energy landscape which specifies the dynamic and the conformation of the system have been described by highly frustrated interactions between components in the systems. In order to obtain the energy surface of these systems, we use Monte Carlo simulation techniques based on Markov chains which are very effective and distinct among many approaches to describe the behaviour of complex systems. We demonstrate our approach through Ising spin glasses and lattice protein model. In the Edwards-Anderson spin glass, we are able to produce the thermodynamic results of the densities of states for magnetization, specific heat and magnetic susceptibility using metropolis-biased Monte Carlo simulation. In hydrophobic-polar (HP) lattice model, we put forward a move-biased Monte Carlo simulation (MBMC) method based on self-avoiding walk in combination with the neighborhood (diagonal-pull) moves search strategy on the 2D square lattice on a set of benchmark protein sequences which produce optimal conformations with compact hydrophobic core surrounded by

polar residues when compared with the state-of-the-art local search algorithm for protein structure prediction.

Keywords: Energy landscape, Ising model, Lattice Protein, Monte Carlo, H-P model

1. INTRODUCTION

Complex systems can be categorized broadly into passive (e.g. Glasses, Ising spin glass and spin glasses) and active (e.g. Protein) [1] systems. The energy surface of a complex system such as glass, spin glass and proteins show very large number of minima which corresponds to many slightly different conformations that a complex system can assume. The complex energy landscape of these systems which specify their conformation and dynamic has long been a subject of discussion by many authors in different fields of science. These complex systems have been described by highly frustrated interactions between components in the systems. The most commonly studied frustrated passive is "Ising spin glass" while in the case of active it is "Protein" [2,3,4]. The Ising spin model is a simple and standard model of statistical physics that has a phase transition between a ferromagnetic and paramagnetic state and typical models to investigate the rough energy landscape of frustrated systems. The model in 2D has been solved to show a phase transition at the critical temperature by Onsager [5]. According to Wust et al. and Iveta et al. [3, 6] Ising spin glass is a disordered magnetic system with frustration and is quite challenging using local methods, both in statistical mechanics and computer simulation; because its free energy landscape is quite complicated with nontrivial properties and demands a lot of time with freezing transition at low temperature. As a result of this, Monte Carlo (MC) simulation with Metropolis algorithm has been viable to circumvent this challenge. The other extended MC methods are: Multicanonical Monte Carlo sampling [7] which preweight the evolution of the MC Markov chain

in order to sample the interface configuration, cluster algorithm [8,9], Wang-Landau sampling [10] which is very potent in computing the density of state, Parallel tempering MC method [8] where multiple systems are simulated simultaneously at different temperature, simulated annealing algorithm (SA) [11], and replica exchange Monte Carlo method (REMC) [12].

Proteins on the other hand, which borrowed some concepts and techniques from physics of spin glass field are viewed as a system with minimal frustration in its native conformation. It exhibits similar complexity with spin glass for which many different folding configurations may have almost the same energy. Also, the concept of two-state transitions (conformational transition) from unfolded (denatured) state to the folded (Native) state [13] is synonymous to spin glass phase transition [14]. There are two remarkable problems in the study of proteins. The first one is protein folding problem which is how the 20 natural amino acid monomers coupled with other physiological conditions ended up spontaneously in a unique tertiary structure [2,3,15,16,17,18]. The second problem is protein design (inverse of protein folding) i.e. finding the amino acid sequence from a given protein conformation which is stable and fold fast in the target conformation. These two problems have triggered the effort of many researchers experimentally and computationally in the past 20 decades [18,19,20,21].

The main goal of this paper is to use heuristic approaches to study the energy surface of complex systems via Ising spin glass and Hydrophobic-polar lattice model. The rest of the paper is organized as follows. In section 2, we describe the method used. In section 3, we describe the energy surface in an Ising spin glass and lattice protein model with the results of our simulation. A conclusion is given in section 4.

2. **Methodology**

2.1 The Ising Model

In the Ising model, the Metropolis algorithm starts with an arbitrary spin configuration to generate a new one (trial) and then calculate the energy. If the energy of the trial is less than or equal to the old, we accept the trial, but if the energy of the trial is greater than the old, we accept with probability $P = \exp(-\Delta E / KT)$ which depends on the random number $0 \le r \le 1$, where K is the Boltzmann constant, T is the temperature and ΔE is the change in energy.

2.2 The HP Model

In HP model, we put forward a move-biased Monte Carlo simulation (MBMC) method and the neighborhood search strategy (diagonal-pull moves) in our algorithm. Stochastic Local search algorithm according to Shatabda and Cebrian [22, 23], is known for its effectiveness with quality solutions. It starts from an initial conformation and moves from one conformation to another to find a better conformation. Stochastic sampling like Monte Carlo method driven by random numbers and probability statistic is a veritable tool to sample conformational space when it is infeasible or impossible to compute an exact result with a deterministic algorithm [24, 25]. Our approach involves the simulation of a protein conformation as a self avoiding walk (SAW) on a square lattice to model the folding process; we vary the probabilities of the four possible directions (North, west, south and east) along which a self-avoiding walker may move. The procedures are as follows

1. The adopted method generates an initial conformation 'ξ' following a SAW on square lattice points. It places the first amino acid at (0, 0) followed by a random selection of a basis vector to place the amino acid at a neighboring free lattice point. The mapping proceeds until a SAW is found in the whole protein sequence.

2. We compute the energy $\Psi(\xi)$ as a SAW on square lattice point for each conformation using equation 3.3.
3. We let $i = 1$
4. We execute coupled (diagonal-pull) moves for all legal move positions of the *ith* amino acid of the current conformation ξ. If the coupled move is executed successfully, we compute the energies of the corresponding legal conformations obtained by coupled moves and pick out the conformation with the lowest energy as a newly updated conformation of, ξ expressed as ξ^*
5. We compute $\Psi(\xi^*)$
6. If the $\Psi(\xi^*) < \Psi(\xi)$, then let $\xi = \xi^*$, $\Psi(\xi) = \Psi(\xi^*)$ and go to the last procedure; otherwise go to (7)
7. If $(0 \le \Re \le 1) < \exp\{[\Psi(\xi) - \Psi(\xi^*)]/k_B T\}$, where $\Re(0,1)$ denotes a random number between 0 and 1, then we let $\xi = \xi^*$, $\Psi(\xi) = \Psi(\xi^*)$, and go to (9); otherwise we go to (8)
8. From the current conformation ξ, we produce the new conformation ξ^* by coupled move search strategy. If ξ^* is a legal conformation, then we update the current conformation ξ with, ξ^*, i.e we let $\xi = \xi^*$ and $\Psi(\xi) = \Psi(\xi^*)$
9. Stop if the move is ergodic; otherwise we go to step (2)

3.0 Results and Discussion

3.1 Ising Spin Glass

The study of spin glasses is an active and controversial area of statistical Physics. In particular the properties of these systems at zero temperature have been intensively studied in the last years. The problem of finding the ground states (G Ss) is a very difficult subject because of the quenched disorder and frustration that are present in most realistic spin glass models [26]. A simple spin glass model is the Edwards- Anderson model which consists of a set of N Ising spins $\zeta_i = \pm 1$ placed in a square or cubic lattice of linear dimension L, with periodic boundary conditions in all directions. Its Hamiltonian for 2D is

$$\mathrm{H} = -\sum_{\langle i,j \rangle} J_{ij} \zeta_i \zeta_j - E \sum_i \zeta_i \qquad 3.1$$

Where $\langle i, j \rangle$ indicates a sum over nearest neighbors. The coupling constants between nearest neighbor followed a bimodal distribution, i.e., $J_{ij} = \pm 1$, with equal probability, E is an external magnetic field. For simplicity, we take E = 0. For relatively large system sizes, and due to the fact that the coupling constant is the independent variables, only configurations with half of the bonds of each sign are statistically significant. To preserve this feature for small sizes, we explicitly enforce the constraint

$$\sum_{i,j} J_{ij} = \begin{cases} 0 & for \quad even \quad number \quad of \quad bonds \\ \pm 1 & for \quad odd \quad number \quad of \quad bonds \end{cases} \qquad 3.2$$

For systems with an odd number of bonds, we enforce the constraint $\sum_{\langle i,j \rangle} J_{ij} = 1$ for the half of the samples and $\sum_{\langle i,j \rangle} J_{ij} = -1$, for the other half.

At high temperature, we expect a random assortment of spin and so a vanishing magnetization, while at low temperature it is expected to approach N/2 as all the spin get aligned.

$$M = \sum_{i=1}^{N} \varsigma_i \qquad 3.3$$

The specific heat energy (C) is obtained by knowing the fluctuation in energy (U) occurring during a number of simulation

calculated as:

$$C_v = {}^{1}\!\!\diagup\!\!{}_{T^2}\left[< H^2 > - < H >^2\right]$$

3.4

The magnetic susceptibility (χ) gives the information about how much the magnetization changes by increasing the temperature

$$\chi = {}^{1}\!\!\diagup\!\!{}_{T}\left[< M^2 > - < M >^2\right] \qquad 3.6$$

The magnetic moments of the ferromagnetic materials domains are aligned along the direction of the applied magnetic field with equal magnitude resulting in a large net magnetic moment. Their crystalline structures allow for direct coupling interactions between the moments, which may strongly enhance the flux density. The materials are composed of domains, each containing large numbers of atoms whose magnetic moments are parallel producing a net magnetic moment of the domain that points in the same direction due to unpaired electrons which still retain its magnetization after the external magnetic field has been removed (spontaneous magnetization) as a result of the residual magnetic moment. Any materials that retain permanent magnetization in

the absence of an externally applied magnetic field are known as hard magnets. Good examples are: iron, nickel and cobalt [27, 28]. The magnetic moments of the atoms of a paramagnetic material are align along the direction of the applied magnetic field resulting to a weak net magnetic moment and small positive magnetic susceptibility $(\chi \approx 0)$ This material has magnetic moment with no long-range order because above the *Ne′el* temperature, thermal energy is sufficient to cause the equal and oppositely aligned atomic moments to randomly fluctuate, leading to a disappearance of their long-range order. The atom of the materials has a net magnetic moment due to unpaired electrons, but magnetic domains are absent, a sequel to this, the material does not retain magnetic moment at the removal of the externally applied magnetic field. Good examples are: lithium, magnesium, gadolinium, tantalum and pyrite [27, 28, 29, 30]. In diamagnetic, the atom of the materials has a zero net magnetic moment and negative susceptibility $(\chi < 0)$ due to the nonexistence of the unpaired electrons. Also, as a result of their weak response against the applied magnetic field (repel an applied magnetic field), the material does not retain the magnetic moment when the externally applied magnetic field is removed. Good examples are: silver, gold, copper, quartz and SiO_2 [27, 28]. The magnetization was determined as shown in figure 1a, since at critical temperature the spontaneous magnetization vanishes, but above T = 2.60 of zero field the magnetization rapidly decreases. Below this temperature, the system is in a ferromagnetic state and above it, is in a paramagnetic state of the 2D Ising model. The specific heat as shown in figure 1b shows how much the energy changes with increasing temperature. Also, the magnetic susceptibility as shown in figure 1c shows that below and above the critical temperature (T_C) the magnetic susceptibility is about zero and around T_C it goes to infinity [31].

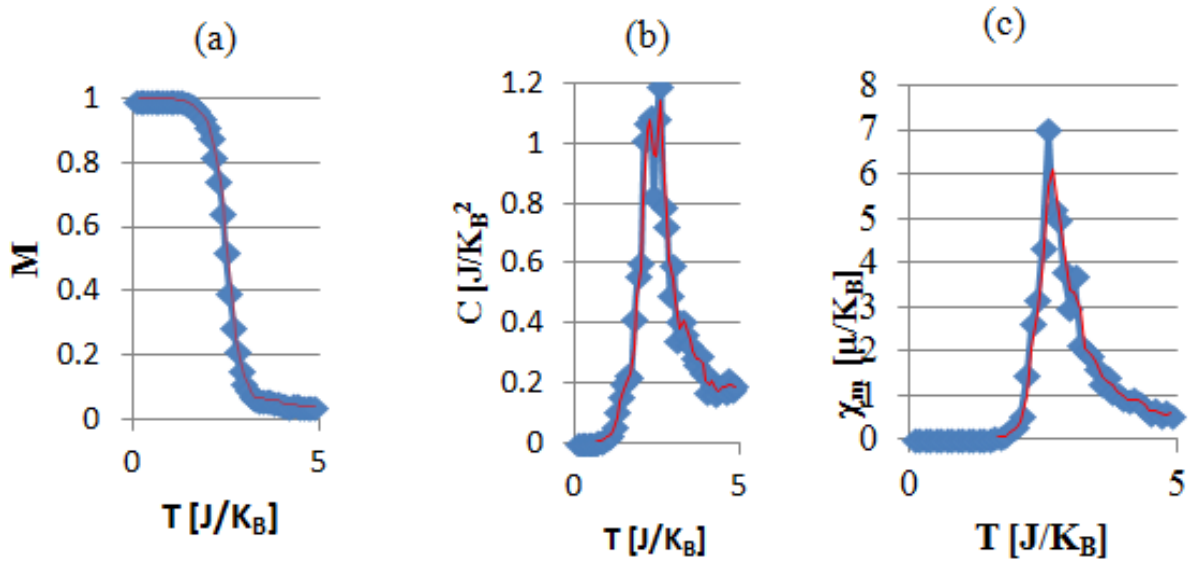

Figure 1: (a) Magnetization (b) Specific Heat and (c) Magnetic Susceptibility at zero fields for 2D Ising model

3.2 HP Lattice Protein Model

Currently, the investigation of the folding process of real proteins via full simulation or deterministic approaches is not feasible. Consequently, a stochastic heuristic lattice protein model which abstract from real protein and has the ability to extract minimal energy conformations efficiently has come to a full-fledged stage to address this complexity [3, 32]. Lattice models have proven to be extremely useful tools to address the complexity of the protein structure prediction problem (PSP) that has been proven to be NP-complete by many authors [33, 34, 35]. This model can be used to extract essential principles, make predictions and harmonize our understanding of many different properties of proteins. Istrail et al. [36], classified Lattice models into two types: The first type is "designed to understand the basic physics governing the protein folding process," The second type used real proteins as templates by statistical sampling of the available structures.

The HP lattice model of Dill [37] is a standard model which abstract from real proteins and shows rich thermodynamic behaviors. This model is the most frequently used among the lattice model,

based on the observation that the hydrophobic interaction between amino acids is the main driving force for protein folding and is restricted to only the backbone structure. In HP model, amino acids are represented as a reduced set of H (Hydrophobic) and P (Polar) according to the hydrophobicity of a single amino acid [3, 35, 38]. A folding of a protein in this model means that amino acids are ported in the lattice such that adjacent amino acids in the sequence occupy adjacent grid points in the lattice and no grid point in the lattice is occupied by more than one amino acid, a process known as the self avoiding walk. The HP lattice model has been described by many authors as the Ising model of protein folding [38, 39].

In this paper, we worked on selected benchmark sequences in the literature for

N = 24 (HHPPHPPHPPHPPHPPHPPHPPHH),

N = 36 (PPPHHPPHHPPPPPHHHHHHHHPPHHPPPPHHPPHPP),

N = 48 (PPHPPHHPPHHPPPPPHHHHHHHHHHPPPPPPHH PPHHPPHPPHHHHH) and

N = 64 (HHHHHHHHHHHHPHPHPPPHHHHPPHPPHHPPHHPPHPPHHHHPPPPHPHPHH HHHHHHHHHH) [40, 41, 42]. This is done on 2D-square HP lattice backbone-only model with two monomer types, H (hydrophobic) and P (polar) for 250 iterations. We calculated the energy function $\Psi(\vartheta,\xi)$ using equation 3.3 for each of the best conformation; that is the number of topological neighbouring contacts between the H-H monomers that are not sequential with respect to the sequence.

$$\Psi(\vartheta,\xi)=\sum_{1\le i<j\le N}\in_{\vartheta i\vartheta j}(q_i-q_j)\Delta_{ij} \qquad 3.3$$

Where ϑ_i and ϑ_j are amino acids at position q_i and q_j on the lattice site respectively. While the contact matrix $\Delta_{ij}(q_i-q_j)=1$, if monomers at q_i and q_j are nearest neighbour sites that are non-

bonded and zero otherwise. The function $\in_{\vartheta i \vartheta j}$ is -1 if the monomers are (H, H) and 0 if the monomers are (H, P) and (P, P).

A Monte Carlo simulation of 1000 steps was performed for the chain to find the global energy minimum. The main goal is to separate the non-degenerated sequences into the two sets good and bad folders. According to Mazzoni et al. [43], good folders are presume to be the more protein-like sequences as a result of the ability to fold into their native conformation in a quick succession i.e "a given conformation "ξ" is said to be good or designable if there is at least one sequence " ϑ " out of the possible 2^N that has the "ξ" as its nondegenerate ground state" while the bad folders represent random protein sequences that are able to form a random coil but with no stable functional native structure [20,21].

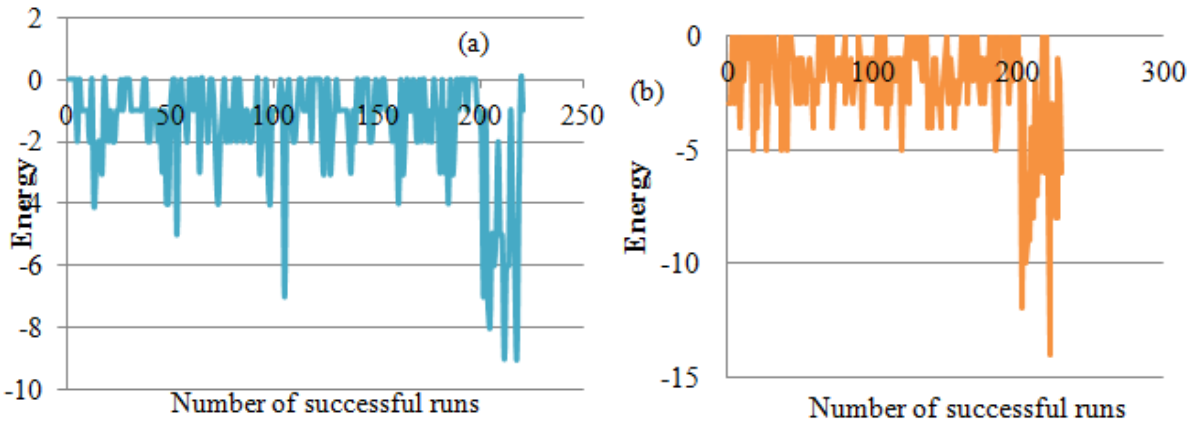

Figure 2: the energy landscape (a) N = 24 (b) N = 36 for 250 iterations

The properties of good and bad folders are related to the attribute of the energy landscape, often called folding funnel as seen in figure 2. In the case of good folders, the folding funnels dominated the landscape and engineered the folding process downwards to the native fold [44]. The energy

landscape as shown in figure 2 with a randomly chosen order of amino acids is very rugged and has been smoothed to resemble a funnel, with many high energy and few low energy conformations.

Figure 3: (Color online) The grid line coupled with the simulated residues gives the native conformation for N = 24, (HHPPHPPHPPHPPHPPHPPHPPHH) is equivalent to (-1,1,2,3,4,5,6,7,8,9,10,11,12,13,14,15,16,17,18,19,20, 21,22,23) where (-1,1,4,7,10,13,16,19,22,23) are hydrophobic and (2,3,5,6,8,9,11,12,14,15,17,18,20,21,22) are polar residues. The ground state energy is -9. The blue and red circles are the polar and the hydrophobic residues, respectively, while -1 is the starting point.

Table 1: This table shows the performance comparison of MBMC with other heuristic methods. The comparison of the lowest energy conformation with four other algorithms, which include CMC, GA, ACO and ENLS. The number in each cell is the minimum energy obtained by the corresponding method for the respective HP sequence.

Length	#	MBMC	CMC	GA	ACO	ENLS
24	-9	-9	-9	-9	-9	-9
36	-14	-14	-12	-12	-14	-14
48	-23	-23	-20	-22	-23	-23
64	-42	-42	-35	-37	-32	-39

is the putative energy value, CMC: Conventional Monte Carlo, GA: Genetic algorithm, ACO: Ant Colony Optimization, ENLS: Hybrid elastic net algorithm

This funnel topology makes predicting the mechanism of folding easy once the structure is known. The intermediate conformations which constitute the high energies (non-compact structure) are essential stepping-stones that guide a protein through the folding process to the native state. These

intermediates are the critical species in misfolding processes (i.e an aberration from the native state) that lead to aggregation and diseases; because they expose sticky interfaces that are normally buried in the native states. The common one is the 'molten globule', i.e. a state possessing native-like secondary structure elements, but lacking the tight packed tertiary structure of the native state.

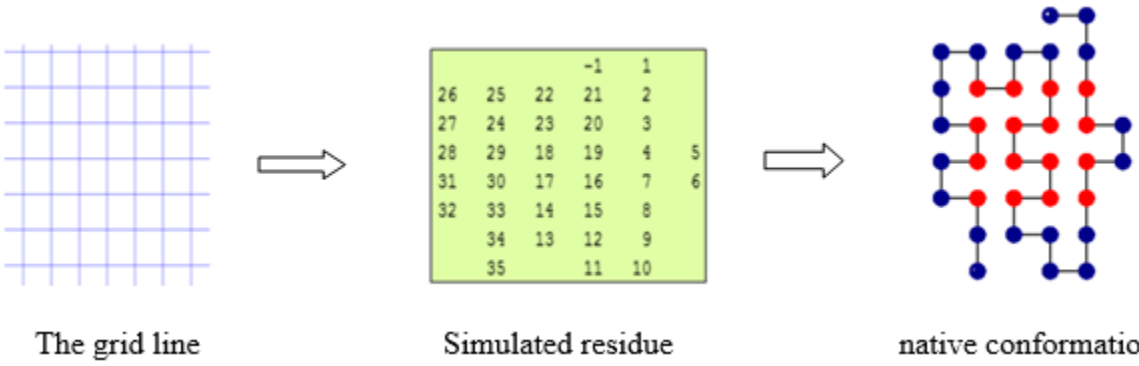

Figure 4. (Color online) The grid line coupled with the simulated residues gives the native conformation for N = 36, (PPPHHPPHHPPPPPHHHHHHHPPHHPPPPHHPPHPP) is equivalent to (-1,1,2,3,4,5,6,7,8,9,10,11,12,13,14,15,16,17,18,19,20,21,22,23,24,25,26,27,28,29,30,31,32,33,34,35) where (3,4,7,8,14,15,16,17,18,19,20,23,24,29,30,33) are hydrophobic and (-1,1,2,5,6,9,10,11,12,13,21,22,25,26,27,28,31,32) are polar residues. The ground state energy is -14. The blue and red circles are the polar and the hydrophobic residues, respectively, while -1 is the starting point.

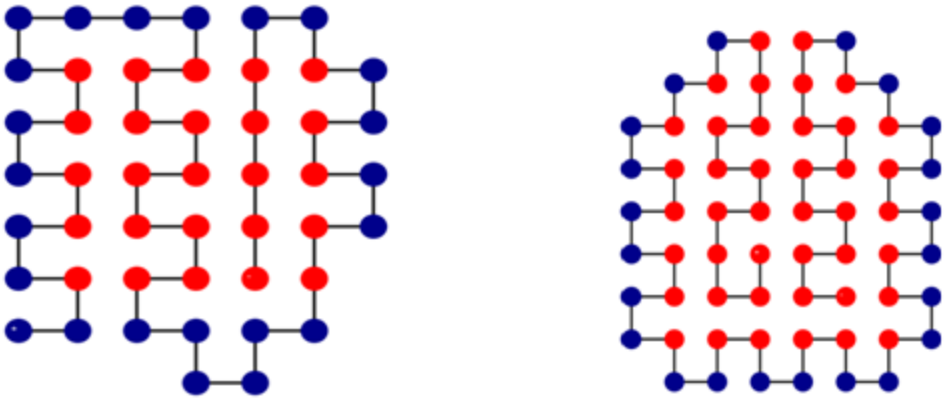

Figure 5. (Color online) the native conformation for N = 48 and 64. The ground state energy is -23 and -42 respectively. The blue and red circles are the polar and the hydrophobic residues respectively while -1 is the starting point.

Figures 3 and 4 described how the simulated residues are embedded in the lattice grid to obtain the native conformation. The conformations in figures 3, 4 and 5 are the ground state (native) conformations obtained by MBMC for the instances considered. It is obvious that each of these conformations possesses a compact hydrophobic core surrounded by polar residues. The results obtained compared to other methods using 2-D as shown in table 1 indicate that MBMC is competitive with the Conventional Monte Carlo (CMC), Genetic algorithm (GA), Evolutionary Monte Carlo (EMC) and Ant colony Optimization (ACO) methods described in the literature. And even outperform them at the highest sequence with the lowest energy value.

4.0 Conclusion

Ising spin glass, and HP lattice model are in the forefront of computational physics of system with Complex energy landscapes. We have demonstrated using Monte Carlo (MC) simulation method which is very distinct among many methods like Wang-Landau sampling, parallel tempering and multicanonical sampling for complex systems. Firstly, we used Metropolis MC Simulation to obtain the thermodynamic properties with Ising model and secondly we used move-biased MC simulation with HP lattice protein model based on self-avoiding walk using diagonal-pull moves on the 2D square lattice to obtain optimal protein conformations that obey thermodynamic and kinetics hypothesis.

Conflict of interest: The authors declare that they have no conflict of interest

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