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# Simulation of Small Peptide Using Combined Wang-Landau-Transition Matrix Monte Carlo Algorithm

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We applied our recently suggested modification of the Wang-Landau algorithm to study the folding thermodynamics of 13-residue peptide P1 from C-terminal  $\alpha$ -helix part of the human Prion Protein (PrP). Temperature dependencies of the average energy, the specific heat, the relative free energy and entropy have been evaluated for the single peptide in gas phase as well as in the implicit water environment. Simulations of single molecule show that this peptide is a good folder and folds into a fully helical conformation. This is consistent with the conformation of this part in the native structure of the mother protein. However, CD spectrum of the water solution of P1 peptide shows only very small amount of  $\alpha$ -helix. This may indicate that in water solution the peptide forms aggregates. We used the simulated annealing algorithm to determine the ground state of the system of two peptides. The results show that the ground state conformation indeed contains a small amount of  $\alpha$ -helix.

## 1 Introduction

The Monte Carlo method has been an effective tool in protein simulations for a long time. Due to the very complicated energy landscape of the proteins with high potential barriers, the conventional Metropolis algorithm does not allow to sample the energy space more or less uniformly, especially in simulations with all-atom potentials. The situation has improved dramatically when several non-conventional (so called generalized-ensemble) algorithms have been introduced<sup>1-4</sup>. However, even the improved algorithms do not meet all challenges in protein simulations, and there is a constant quest for new, more sophisticated and efficient algorithms. Recently we have suggested a new approach which is based on the combination of the Wang-Landau and Transition Matrix Monte Carlo methods<sup>5</sup>. It is well known that the Wang-Landau algorithm allows to easily jump over the energy barriers at the initial stage of simulation and to sample all energy levels uniformly. Nonetheless, at the later stages the statistical errors do not decrease with increasing samples. This is considered as a drawback of the algorithm. At the same time, the transition matrix method

gives a good estimate of the density of states with small statistical errors but it requires a proper initial guess for the density of states which is usually not available. In our algorithm we use the advantages of the two methods within a combined approach whereby the algorithm behaves like the Wang-Landau method in initial stages and uses the transition matrix method to reduce the statistical errors at the later stage. Here we apply our algorithm to simulate a small peptide P1 from the C-terminus of human prion protein (PrP). The biological importance of this peptide is that it has been used as an antigen to produce a monoclonal antibody which recognizes an epitope specific to pathological isoform of PrP from brain samples of Creutzfeld-Jakob disease patients. As a part of the mother protein in the native state this peptide has a fully  $\alpha$ -helical structure whereas the CD spectrum of the water solution shows only a tiny amount of  $\alpha$ -helix. We use the standard geometry model with ECEPP/3 forcefield as implemented in protein simulation package SMMP<sup>6</sup>.

## 2 Calculation of the Thermodynamical Quantities

The advantage of knowing the density of states is that one can calculate directly the partition function and all related quantities

$$Z = \sum_E n(E)e^{-\beta E}, \quad (1)$$

where  $Z$  is the partition function and  $n(E)$  are the density of states. We performed our algorithm to calculate the partition function of P1 peptide both in gas phase and with implicit water environment treated by solvent accessible area method. After calculating the partition function we obtained the temperature dependencies of the potential energy and the specific heat:

$$E(T) = \langle E \rangle_T = Z^{-1} \sum_E E n(E) e^{E/k_B T}$$

$$C(T) = \frac{\langle E^2 \rangle_T - \langle E \rangle_T^2}{k_B T^2}. \quad (2)$$

These quantities are plotted on Fig. (1). One can see that the specific heat has a well defined maximum indicating cooperative transition.

## 3 Modification of the SMMP Code

Since the experiment shows a little amount of the  $\alpha$ -helix the suggestion was made that the molecules of P1 in solution don't behave similar to the single molecule. The most straightforward explanation may be that they aggregate and do not allow each other to undergo helix-coil transition. We have addressed this problem by finding the ground state conformation of the system of two peptides. For this purpose a minor modification of the code was necessary because normally it is impossible to simulate more than one molecule in SMMP. We introduced a "fake" residue which consists only of the backbone bonds and contains atoms which do not interact neither with each other nor with other atoms. Thus they don't contribute into the energy function. The rotations around all bonds of

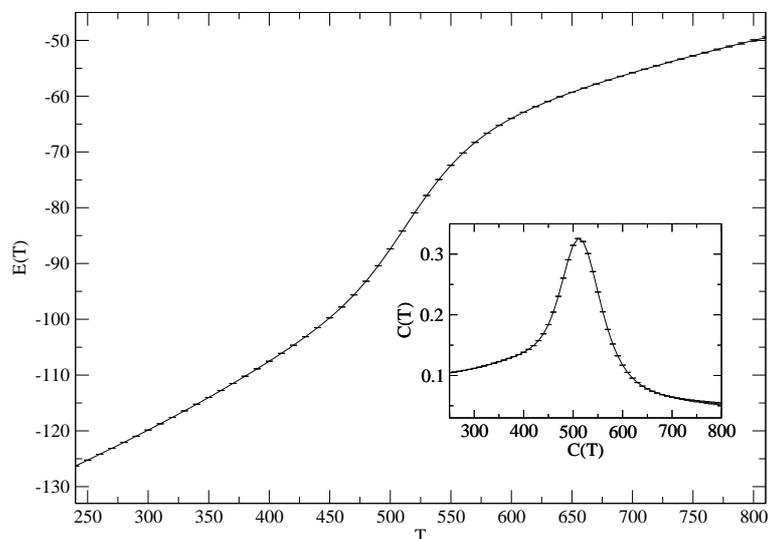


Figure 1. The temperature dependence of the potential energy and the specific heat (inlet) of the peptide P1 in implicit water environment.

virtual residues are completely free. Connecting two peptides with sufficiently long chain of virtual residues allows the two molecules to accept any positions with respect to each other. We have performed a large number of simulated annealing for such a system and obtained that in more than 90% cases the ground state of the system contains only very small amount of  $\alpha$ -helix. In all ground states the two peptides are positioned parallel or antiparallel, creating intermolecular hydrogen bonds instead of intramolecular ones.

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