

A Conformational Search Method for Protein Systems Using Genetic Crossover and Metropolis Criterion

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Abstract. Many proteins carry out their biological functions by forming the characteristic tertiary structures. Therefore, the search of the stable states of proteins by molecular simulations is important to understand their functions and stabilities. However, getting the stable state by conformational search is difficult, because the energy landscape of the system is characterized by many local minima separated by high energy barriers. In order to overcome this difficulty, various sampling and optimization methods for conformations of proteins have been proposed. In this study, we propose a new conformational search method for proteins by using genetic crossover and Metropolis criterion. We applied this method to an α -helical protein. The conformations obtained from the simulations are in good agreement with the experimental results.

1. Introduction

To understand functions and stabilities of biomolecules such as DNA and proteins, effective conformational search and accurate estimation of canonical distributions are important. However, because biomolecules have a lot of local minimum-energy states separated by high energy barriers, conventional molecular dynamics (MD) and Monte Carlo (MC) simulations tend to get trapped in states of local minima. In order to overcome this difficulty, various sampling and optimization methods for conformations of biomolecules have been proposed such as generalized-ensemble algorithms (for reviews, see, e.g., [1, 2]). Moreover, we have proposed a conformational search method called the parallel simulated annealing using genetic crossover

(PSA/GAc) [3, 4, 5, 6], which is a hybrid algorithm combining both the simulated annealing (SA) [7] and the genetic algorithm (GA) [8, 9]. In this method, a simulated annealing simulation is combined with genetic crossover, which is one of the operations of genetic algorithm.

In this paper, we propose a new conformational search method that combines the genetic crossover and Metropolis criterion. The operation of the genetic crossover is combined with the conventional MC or MD simulations. In order to examine the effectiveness of our method, we applied our method to a small protein, which is the 10-55 helical fragment B of protein A from *Staphylococcus aureus* (in this paper, just referred to as protein A) [10]. The results of this simulation are found to be in good agreement with the experimental results.

2. Methods

In the present simulation approach, we first prepare M initial conformations of the system in study, where M is the total number of “individuals” in genetic algorithm and is usually taken to be an even integer. We then alternately perform the following two steps:

1. For the M individuals, regular canonical MC or MD simulations at a fixed temperature T are carried out simultaneously and independently for a certain MC or MD steps.
2. $M/2$ pairs of conformations are selected from “parental” group randomly, and the crossover and selection operations are performed. Here, the parental group means the latest conformations obtained in Step 1.

While Step 1 is usually based on local updates of conformations, global updates of conformations are introduced in Step 2 by genetic crossover. The latter greatly enhances the conformational sampling.

In the following, we give the details of Step 2 above. We can employ various kinds of genetic crossover operations such as one-point crossover [3, 4, 5], two-point crossover [6], etc. as in our previous simulation methods. Here, we just present a case of the two-point genetic crossover. The crossover operation in this method exchanges a part of corresponding dihedral angles between two conformations of the protein. In the two-point crossover operation on a parental pair, the following procedure is carried out:

- (i) Consecutive amino acids of length n residues in the amino-acid sequence of the conformation are selected randomly for each pair of selected conformations.
- (ii) Dihedral angles (in only backbone or all dihedral angles) in the selected n amino acids are exchanged between the selected pair of conformations.

Note that the length n of consecutive amino-acid residues can, in general, be different for each pair of selected conformations.

We need to deal with the produced “child” conformations with care. Because the produced conformations often have unnatural structures by the crossover operation, they have high potential energy and are unstable. Therefore, the relaxation process is introduced before the selection operation. In this paper, we use equilibration simulations with restraints as a relaxation process. For instance, short simulations at the same temperature T with restraints on the backbone dihedral angles of only the n amino acids are performed so that the corresponding backbone structures of the n amino acids will approach the exchanged backbone conformation. The initial conformations for these equilibration simulations are the ones before the exchanges. Namely, by these equilibration simulations, the corresponding backbone conformations of the n amino acids gradually transform from the ones before the exchanges to the ones after the exchanges. We then perform short equilibration simulations without the restraints. We select the last conformations in the equilibration simulations as “child” conformations. Note that from a pair of parental conformations we get two child conformations. In the present method, we

consider selection between parent and child for the parent-child pair with the same conformations in the remaining amino acids (other than n consecutive ones).

In the final stage in Step 2, the selection operation is performed. We select a superior “chromosome” (conformation) from the parent-child pair. For this selection operation, we can also employ various criteria. In this study, we employ Metropolis criterion, which selects the new child conformation from the parent with the following probability:

$$w(p \rightarrow c) = \min(1, \exp\{-\beta[E_c - E_p]\}). \quad (1)$$

Here, E_p and E_c stand for the potential energy of the parental conformation and the child conformation, respectively, of the parent-child pair. β is the inverse temperature, which is defined by $\beta = 1/k_B T$ (k_B is the Boltzmann constant).

We remark that if we use different temperatures, we can also introduce the replica-exchange method [11, 12] together with the above method in order to further enhance conformational sampling [13].

3. Results and Discussion

We applied the present method to protein A. Although the whole protein A has 60 amino acids, we used the truncated 46 amino-acid sequence from Gln10 to Ala55. For this simulation, we used the AMBER12 program package and incorporated the two-point genetic crossover procedure. The unit time step was set to 2.0 fs and the bonds involving hydrogen atoms were constrained by the SHAKE algorithm [14]. Each simulation for sampling was carried out for 90.0 nsec (which consisted of 45,000,000 MD steps) with 32 individuals ($M = 32$) and performed the crossover operations 90 times during the simulation. The temperature during the simulations was kept at 300 K by using Langevin dynamics. The nonbonded cutoff of 20 Å was used. As for solvent effects, we used the GB/SA model [15] included in the AMBER12 program package ($igb = 5$). In the crossover operations, we set the length n of consecutive amino-acid residues to be an even integer ranging from 10 to 20. This number was chosen randomly for each pair of parental conformations. As for the equilibration simulations just after each genetic crossover operation, the first simulations with the harmonic restraints on the backbone dihedral angles of n amino-acid residues (the force constants were 600 kcal/mol·Å²) lasted for 20 psec, and the following simulations without restraints also lasted for 20 psec.

We obtained a similar conformation to the experimental native structure, and its root-mean-square distance (RMSD) (for only the backbone atoms) from the native structure was 1.7 Å (see Fig. 1). One of the characteristic analyses of the genetic algorithm is the analysis of data as functions of the generation number. In this paper, the generation number stands for the number of crossover operations. In Fig. 2, we show four kinds of values, the fraction of helix conformations, the average of the potential energy, the average of the RMSD, and the average of the radius of gyration by changing the generation. In Fig. 2(a), we see that the fraction of helix conformations increases as the generation proceeds as a whole. The PDB structure of protein A has three helix regions in the amino-acid sequence of 2–9, 17–29, and 34–46. These helix regions roughly correspond to the high probability regions obtained from the present simulation, and the C-terminal region (Helix III) has the highest helix fraction among the three regions in Fig. 2(a). The stabilities for the three helix structures in protein A have been examined and debated by many researchers [16, 17, 18, 19, 20]. From our simulation results, we consider that Helix III is the most stable, and the central helix is unstable in comparison with the other two helix structures. In Fig. 2(b)–(d), we see that the potential energy, RMSD, and radius of gyration quickly decrease at the early numbers of generations. After that, although these values are roughly convergent, there are some fluctuations. For example, RMSD value has the standard deviation of 1.7 Å around a mean value of about 8.0 Å.

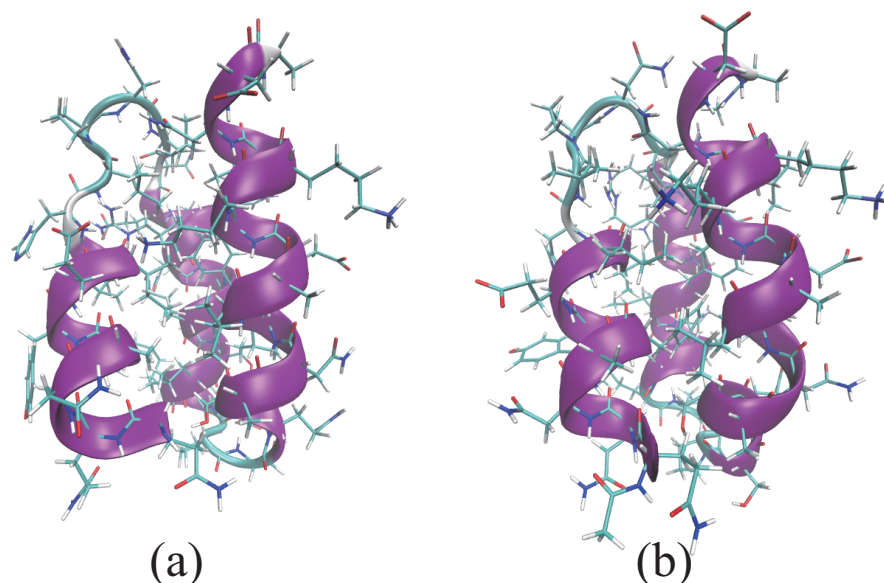


Figure 1. Structures of protein A. (a) PDB structure (PDB ID: 1BDD). (b) A conformation obtained from the present simulation, which has the lowest RMSD value from the PDB structure (RMSD = 1.7 Å).

4. Conclusions

In this work, we proposed a new conformational search method for protein systems. This method combines conventional canonical MC or MD simulations, which are based on local updates of conformations, and genetic crossover, which is based on global updates of conformations. The latter greatly enhances the conformational sampling. In order to examine the efficiency of this method, we applied it to protein A. We found conformations very close to the native structure.

The present method is particularly suitable for highly parallel computers. In the future, we are going to apply this method to larger protein systems.

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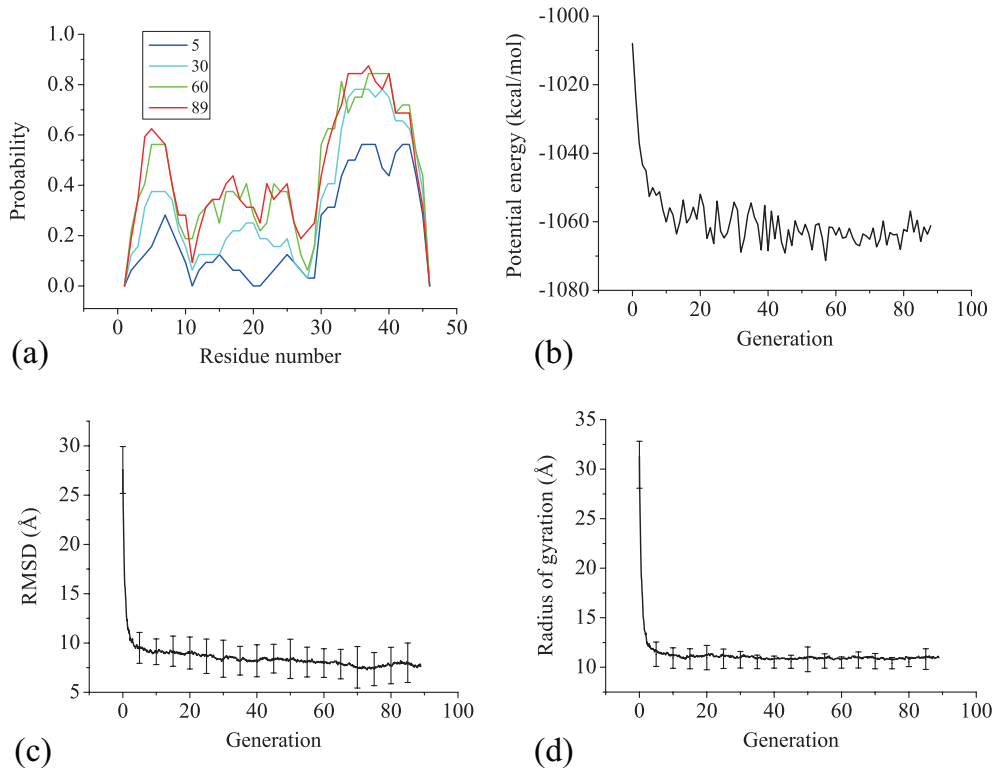


Figure 2. (a) The fraction of helix conformations as a function of residue number at generation numbers 5 (blue), 30 (light blue), 60 (green), and 89 (red), (b) the average of the potential energy, (c) the average of the RMSD, and (d) the average of the radius of gyration, obtained from the present GC simulation results. The helix conformations were examined by using the DSSP program [21]. The error bars in (c) and (d) are standard deviations.

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