Combination of genetic crossover and replica-exchange method for conformational search of protein systems

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We combined the genetic crossover, which is one of the operations of genetic algorithm, and replica-exchange method in parallel molecular dynamics simulations. The genetic crossover and replica-exchange method can search the global conformational space by exchanging the corresponding parts between a pair of conformations of a protein. In this study, we applied this method to an α-helical protein, Trp-cage mini protein, which has 20 amino-acid residues. The conformations obtained from the simulations are in good agreement with the experimental results.

I. INTRODUCTION

The search of the stable states of biomolecules, such as DNA and proteins, by molecular simulations is important to understand their functions and stabilities. However, as the 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. To overcome this difficulty, various sampling and optimization methods for conformations of biomolecules have been proposed such as generalized-ensemble algorithms which include the multicanonical algorithm (MUCA)1–3, simulated tempering (ST)4–5 and replica-exchange method (REM)6,7. We have also proposed a conformational search method referred to as the parallel simulated annealing using genetic crossover (PSA/GAc)8–11, which is a hybrid algorithm combining both simulated annealing (SA)12 and genetic algorithm (GA)13,14. In this method, parallel simulated annealing simulations are combined with genetic crossover, which is one of the operations of genetic algorithm. Moreover, we proposed a method that combines parallel MD simulations and genetic crossover with Metropolis criterion.15

In this study, we applied this latest conformational search method using the genetic crossover to Trp-cage mini protein, which has 20 residues. The operation of the genetic crossover is combined with the conventional MD and REM. The obtained conformations during the simulation are in good agreement with the experimental results. This article is organized as follows. In Section 2 we explain the present methods. In Section 3 we present the results. Section 4 is devoted to conclusions.

II. METHODS

A. Parallel molecular dynamics using genetic crossover

We briefly describe our method15. 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.

If we employ MC simulations in Step 1 above, we can refer the method to as parallel Monte Carlo using genetic crossover (PMC/GAc) and if MD simulations, parallel molecular dynamics using genetic crossover (PMD/GAc). In Step 2, we can employ various kinds of genetic crossover operations. Here, we just present a case of the two-point crossover (see Ref.11).

The following procedure is carried out (see Fig. 1):

1. Consecutive amino acids of length n residues in the amino-acid sequence of the conformation are selected randomly for each pair of selected conformations.
2. 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, a relaxation process is introduced before the selection operation. 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.

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 employ Metropolis criterion, which selects the new child conformation from the parent with the following probability:

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

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

### B. Combination with replica-exchange method

The sampling method using genetic crossover in the previous subsection can be easily combined with other sampling methods such as generalized-ensemble algorithms. Firstly, the conventional MC or MD in Step 1 above can be replaced by other sampling methods such as MUCA and ST. Secondly, the above method can be combined with REM in Step 2 above.

As an example, we introduce a method that combines genetic crossover and REM. We first prepare \( M \) initial conformations of the system in study, where \( M \) is the total number of “individuals” (in genetic algorithm) or replicas (in REM) and is usually taken to be an even integer. While only one temperature value was used in the previous method, we prepare \( M \) different temperature values \( (T_1, \ldots, T_M) \) here. Without loss of generality, we can assume that \( T_1 < \cdots < T_M \). We then alternately perform the following two steps:

1. For the \( M \) individuals, regular canonical MC or MD simulations at the fixed temperature \( T_m \) \((m = 1, \cdots, M)\) are carried out simultaneously and independently for a certain MC or MD steps.

2. \( M/2 \) pairs of conformations at neighboring temperatures are selected from “parental” group, and one of the following two operations is performed.

   (a) Two-point genetic crossover is performed for each pair of parents to produce two children, and new child conformations are accepted with the probability in Eq. (1).

   (b) each pair of replicas \( i \) and \( j \) (with coordinates \( q_i \) and \( q_j \)) corresponding to neighboring temperatures \( T_m \) and \( T_{m+1} \), respectively, is exchanged with the following probability:

\[
w(i \leftrightarrow j) = \min(1, \exp(-\Delta)) , \tag{2}\]

where

\[
\Delta = (\beta_m - \beta_{m+1})(E(q_j) - E(q_i)) . \tag{3}\]

Here, \( \beta_m \) is the inverse temperature \((\beta_m = 1/k_B T_m)\) and \( E(q_i) \) is the potential energy of replica \( i \) before replica exchange. If MD is employed in Step 1, we also have to rescale momenta after replica exchange.

If we employ MC simulations in Step 1 above, we can refer the method to as replica-exchange Monte Carlo using genetic crossover (REMC/GAc) and if MD simulations, replica-exchange molecular dynamics using genetic crossover (REMD/GAc). In the above formulation, we chose pairs of the parent individuals (replicas) that correspond to neighboring temperatures. This is to make the acceptance of replica exchange high. Hence, as far as the crossover operations are concerned, we could select pairs of parents randomly.
We applied the present methods, namely, PMD/GAc and REMD/GAc, to Trp-cage. Trp-cage is known to be one of the smallest protein-like model systems and has 20 amino-acid residues. This mini protein was studied experimentally by NMR measurements at 282 K (PDB ID: 1L2Y).

We incorporated our genetic crossover sampling methods by modifying the TINKER program package. The unit time step was set to 1.0 fs. Each simulation for sampling was carried out for 10.0 nsec (hence, it consisted of 10,000,000 MD steps) with 16 individuals ($M = 16$). Namely, the total simulation time for sampling was 160.0 nsec. We performed 200 crossover operations, which selected consecutive amino-acid residues of length between 2 to 10, during the simulations. The temperature during MD simulations was controlled by Nosé-Hoover method. The temperature was set at 282 K for the PMD/GAc simulation (the same as the experimental condition). For REMD/GAc, the number of replicas were also set to $M = 16$. The temperatures were distributed exponentially: 650, 612, 577, 544, 512, 483, 455, 428, 404, 380, 358, 338, 318, 300, 282, and 266 K. During the REMD/GAc simulation, we performed 100 genetic crossover operations and 10,000 replica-exchange operations. As for the computational potential energy calculations, we used the AMBER ff99SB force field. As for solvent effects, we used the GB/SA model included in the TINKER program package. In order to test the effectiveness of the present method more quantitatively, we have to include more rigorous solvation models, which we will do in a future work. The individuals (replicas) for the simulations had different sets of randomly generated initial velocities. We also performed conventional MD and REM simulations for comparisons. The simulation conditions were the same as above except the crossover and selection operations. In order to balance the computational cost, we performed independent 16 simulation runs of 10.0 nsec in length for the conventional MD.

In Fig. 2, we compare the structure of PDB (1L2Y model) and the lowest-RMSD conformations obtained from the conventional MD simulation and the PMD/GAc simulation. The room-mean-square-distance (RMSD) values of Cα atoms with respect to the native structure for the conventional MD simulation and the PMD/GAc simulation are 4.06 Å and 1.78 Å, respectively. Obviously, the conformation obtained from PMD/GAc is more similar to the native structure than that from the conventional MD. Moreover, we also compared the structures with a native-like structure, which was the lowest-energy conformation obtained from iso-thermal canonical simulations at 282 K. This native-like conformation was obtained from 16 canonical simulations of 2.0 nsec with different sets of randomly generated initial velocities. The RMSD values with respect to the native-like structure for the conventional MD simulation and the PMD/GAc simulation are 3.48 Å and 1.62 Å, respectively. The conformation obtained from PMD/GAc is in better agreement with the native-like structure than that from the conventional MD.

In Fig. 3, the probability distributions of RMSD of all conformations obtained from the conventional MD simulation and the PMD/GAc simulation are shown. RMSD values obtained from PMD/GAc are lower than those of the conventional MD as a whole. The averages of RMSD values obtained from the conventional MD and PMD/GAc are 7.06 Å and 5.50 Å, respectively. Hence, PMD/GAc can search the conformational space around the native structure efficiently in comparison with the conventional MD.

We now examine the results of REMD/GAc simulation. In Fig. 2, we compare the lowest-RMSD conformations obtained from the conventional REMD simulation and REMD/GAc simulation. The RMSD values with respect to the PDB structure for the conventional REMD simulation and the REMD/GAc simulation are 2.03 Å and 1.93 Å, respectively. Hence, these conformations are almost the same and similar to the PDB structure. Moreover, the RMSD values with respect to the native-like structure for the conventional REMD simulation and the REMD/GAc simulation are 1.78 Å and 1.27 Å, respectively. The conformation obtained from REMD/GAc is in slightly better agreement with the native-like structure than that from the conventional REMD.

In Fig. 3, the probability distributions of RMSD of all conformations obtained from the conventional REMD simulation and the REMD/GAc simulation are shown. The obtained ranges of the RMSD values of both conventional REMD and REMD/GAc simulations are broad. The averages of RMSD values obtained from the conventional REMD simulation and the REMD/GAc simulations are 6.32 Å and 6.58 Å, respectively. Hence,
there is almost no difference of the two average values. However, there are some differences in the distribution of conventional REMD and REMD/GAc simulations. The peak values of the probability distributions of the conventional REMD simulation and the REMD/GAc simulation are 7.28 Å and 6.68 Å, respectively. Moreover, there is another small peak around 3.26 Å for the conventional REMD simulation. On the other hand, there are not any peaks except for the highest peak in the case of the REMD/GAc simulation. These results suggest that the REMD/GAc simulation did not get trapped in any local minima in comparison with the conventional REMD simulation.

In order to further examine the sampling efficiency of the conventional REMD simulation and the REMD/GAc simulation, we counted the number of tunneling events. A tunneling event means a random walk from the lowest-energy region to the highest-energy region and back, and is observed when a system goes from an energy minimum to another minimum via a high-energy region. If the number of the tunneling events is large, the conformational sampling is considered to be more efficient. The numbers of the tunneling events obtained from the conventional REMD simulation and the REMD/GAc simulation are 54 and 107, respectively (these numbers are the total for all the 16 replicas). We see that REMD/GAc can perform more efficient conformational search by using the crossover operation. Here, the average of the acceptance ratio of crossover operations was 0.26. However, the ratio must depend on the system and the length $n$ of the crossover operations.

IV. CONCLUSIONS

In this work, we introduced two conformational sampling methods based on genetic crossover and applied them to a mini protein, Trp-cage. One method is a combination of conventional molecular dynamics and genetic crossover, and the other is a further combination with the replica-exchange method. These methods realize a broader conformational search by the genetic crossover, which is based on global conformational updates. Conformations close to the native structure were successfully obtained by these methods.

The genetic crossover sampling methods have a big advantage of being highly parallelizable on parallel computers. In the future, we are going to apply these methods to various large proteins in explicit solvent.

ACKNOWLEDGEMENTS

The computations were performed on the computers at the Research Center for Computational Science, Institute for Molecular Science and Information Technology Center, Nagoya University. This work was supported, in part, by the Grants-in-Aid for Scientific Research (A) (No. 25247071), for Scientific Research on Innovative Areas (“Dynamical Ordering & Integrated Functions”), for the Computational Materials Science Initiative, and for High Performance Computing Infrastructure from the Ministry of Education, Culture, Sports, Science and Technology (MEXT), Japan.

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