Energy Minimization of Protein Tertiary Structures by Local Search Algorithm and Parallel Simulated Annealing using Genetic Crossover

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Abstract- In this paper, the local search algorithm to improve the searching capability of Parallel Simulated Annealing using Genetic Crossover (PSA/GAc) for the energy minimization of protein tertiary structures is proposed. Our previous research shows that PSA/GAc is effective for the energy minimization of the small proteins. However, because the energy minimization of larger proteins requires larger number of calculations, it is essential to reduce the amount of calculations required to reach the global optimum. In this paper, the local search algorithm to search α-helix efficiently is proposed and is applied to the energy minimization of proteins. Also, for the verification of the algorithm, the test function which has a similar characteristic to the energy function of proteins that have α-helix structures is proposed. Finally, PSA/GAc with the proposed local search is applied to the same proteins and its capability is discussed. The result indicates that as for the target proteins of this paper, PSA/GAc with local search has obtained the more accurate solutions and additionally, total number of evaluations required to reach the optimum can be reduced. From the results, the possibility of effectiveness of proposed local search algorithm on the energy minimization of the proteins with α-helices has been verified.

1 Introduction

The prediction of tertiary structures of proteins from only its amino acid sequence is called the prediction from the first principle. This problem, known as the protein folding problem, is an important problem due to the fact that the biological functions of proteins are derived from its tertiary structure. Tertiary structure of proteins is believed to correspond to the conformation with the lowest energy. Therefore as one of the methods to predict the tertiary structure of proteins, the optimization methods such as Simulated Annealing (SA)[1], Genetic Algorithms (GA)[2], and Multicanonical Algorithms[3] have been employed. However, the energy function that determines the tertiary structure is very complicated with large numbers of global and local minima that it is difficult to predict the tertiary structure by simple minimization algorithms. As one of the optimization method, Parallel Simulated Annealing using Genetic Crossover (PSA/GAc) that is the hybrid algorithm of Parallel SA and an operator of GA is reported to be effective on the energy minimization of small proteins[4].

However, because the energy minimization of larger proteins require larger number of calculations, finding its global optimum require vast amount of time. Therefore it is essential to reduce the amount of calculations required to reach the global optimum in the energy minimization of large proteins. It is conceivable that if some kind of a local search algorithm can be applied to the energy minimization of proteins, then the total amount of calculations can be reduced. As an object to apply the local search algorithm, in this research, we apply an α-helix structure, which is a secondary structure of the protein tertiary structures. In this paper, we propose the local search algorithm based on the characteristic of α-helices. This local search is combined with PSA/GAc. The effectiveness is confirmed through the numerical examples.

2 Energy Minimization of Proteins by PSA/GAc

Parallel Simulated Annealing using Genetic Crossover (PSA/GAc) is the optimization method to exchange

the information of solutions among SAs running in parallel by the genetic crossover[5]. In case the optimum values of some design variables are obtained by the SAs running in parallel, the crossover operation works to transfer the values to other individuals. Thus, the convergence of the annealing is precipitated. In this algorithm, the total number of SAs running in parallel is defined as population size and each SA is defined as individual[5].

In this article, the energy minimization of proteins is the gas-phase simulation based on the energy parameters of ECEPP/2[6, 7, 8]. The dihedral angles of backbone and side chains are applied as design variables. Values of the dihedral angles are in the range of [-180°, 180°]. Each dihedral angle is generated and given the accept criterion sequentially, and then the temperature is cooled. We define this series of operations as a Monte Carlo Sweep (MCsweep).

Our previous research shows that PSA/GAc has higher searching capability than SSA on the energy minimization of a small protein called Met-enkephalin[4]. However, because our simulation is based on the energy parameters of ECEPP/2, the amount of calculation required for an evaluation of the energy strongly depends on the number of amino residues that make up the protein. Thus, it is obvious that the calculation time required for the energy minimization by PSA/GAc increases rapidly as the target protein becomes larger. Therefore it is essential to develop an algorithm to reduce the amount of calculations required to reach the optimum range. So in the next section, the algorithm, based on the characteristic of a secondary structure of protein called α-helix, is proposed to search the α-helix efficiently.

3 PSA/GAc with Local Search Algorithm

In this section, we propose the local search algorithm to reduce the total amount of calculations required to reach the global optimum in the energy minimization of proteins. As an object to apply the local search algorithm, in this research, we apply α-helix structure, which is a secondary structure of the protein tertiary structures. In this research, we propose the local search algorithm based on the characteristic of the α-helices.

3.1 α-helix Structure

The α-helix is the most abundant helical conformation found in the globular proteins. An amino residue is in the α-helix configuration when the dihedral angles (ϕ, ψ) fall in the range $(-70 \pm 30°, -37 \pm 30°)$[9]. The α-helix consists of plural numbers of this α-helical residues. Since there are 3.6 residues per turn in the α-helix[10] we consider a conformation as helical when the length of the helical residues is greater than four.

The α-helix is maintained by hydrogen bonding between backbone peptide chain, and therefore it is a stable structure.

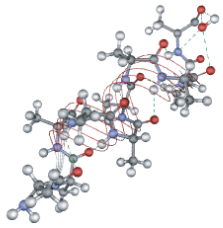

Figure 1: The α-helix structure of proteins. The illustration is the lowest energy conformation $(\mathrm{Ala})_{10}$ which consists of 10 Alanynes. $(\mathrm{Ala})_{10}$ has α-helices in residues (2-9), that is 2.2 turns of helices.

3.2 Local Search Algorithm Based on α-helix

As stated in the previous section, α-helix is formed when there are plural number of amino residues which have certain value in its dihedral angles (ϕ, ψ). Thus, we propose an algorithm that searches the α-helix efficiently using this characteristic of α-helix. In the proposed algorithm, when a part of the α-helix is found during the search of the energy function, the α-helix is expanded to the adjacent residues. As an effect of this local search operation, the α-helix is hoped to form in the early stage of the searching, and as a result the total amount of calculations can be reduced.

In this research, the local search algorithm is introduced in the energy minimization by PSA/GAc. In the algorithm of PSA/GAc with local search, after certain number of MCsweeps, a determination whether there are α-helical residues in the target protein is made. If the α-helical residues that reduce the total energy are found, values of the dihedral angles (ϕ, ψ) of corresponding residue are copied to the ones of the adjacent residues. Figure 2 describes the detail of the algorithm. The figure describes the case of PSA/GAc with three SAs running in parallel. First, after certain number of MCsweeps, genetic crossover is performed among the individuals. This operation does not differ from the crossover operation of conventional PSA/GAc. After another certain number of MCsweeps, the local search is performed on each SA independently. In Figure 2, optimum tertiary structure has an α-helix in the residues (2-6). In the left hand SA, there is α-

helical residue in the fourth residue and its energy is $5.2kcal/mol$. After local search is performed and the values of the residues (ϕ, ψ) are copied to the adjacent residues, its energy is reduced to 0.2 $kcal/mol$. If the energy reduces like in this case, the operation of local search is accepted. The local search is then continuously performed while the energy lowers. In the case of middle SA of the figure, there is no α-helical residues, therefore the local search will not be performed. In the right hand SA, the local search is performed on the fifth residue, however, copied dihedral angles of the adjacent residues are rejected because the energy has increased from 3.4 $kcal/mol$ to 9.2 $kcal/mol$.

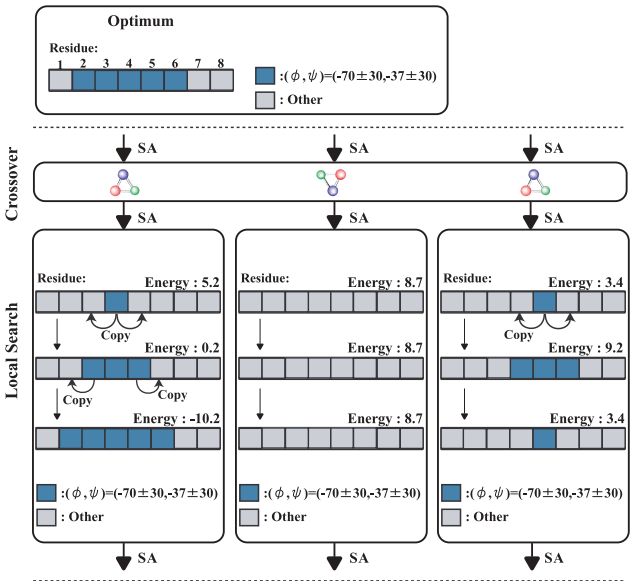

Figure 2: PSA/GAc with local search. The illustration describes the case of three SAs running in parallel. Crossover operation is performed after certain number of annealing. After another certain number of annealing, each SA performs local search independently.

4 Simplification of the Energy Function of Proteins

In the previous section, we proposed the local search algorithm that works to search α-helix structures efficiently. That is, by expanding the part of the α-helix to the adjacent residues, total amount of calculations to obtain the lowest energy conformation can be reduced. In this section, we propose a test function that imitates the energy function of proteins, especially the characteristic of α-helix structure. We adopt this test function to verify the effectiveness of the proposed local search algorithm. That is, because the minimization of the actual energy function of proteins requires high calculation cost, it is inefficient to verify the new algorithm using the actual energy function. If somekind of a test function with a similar characteristic to the energy function of proteins and low calculation cost is available, it can be used effectively to verify the algorithm to search the energy function of proteins. In this research, we proposed the algorithm to search for the α-helix structures. Therefore we develop the test function that has the similar characteristic to the α-helix structures.

4.1 Specification of the Test Function

The test function we develop here is required to have the characteristics of the proteins, especially the α-helix structures. To meet the requirement, the test function must have the following specifications:

- Among the plural design variables that make up the test function, the energy of the function decreases by copying the value of some design variable to the adjacent variables.
- The test function should have a plural number of local minima. The search may be trapped to the local minima by applying the local search on the improper design variables.

The first specification corresponds to the characteristic of α-helix structure of proteins. Thus the proposed local search algorithm works to lower the energy of the test function. The second specification corresponds to the local minima of the energy function of proteins. When the α-helix is formed in the improper part of the proteins by the local search algorithm, the search may be trapped by the local minima.

4.2 Mechanism of the Test Function

The test function we develop here has the following characteristics:

1. The function is composed of 20 design variables and each design variable has a continuous value between -180 and 180 which is same as the design variables of proteins.
2. Using an evaluation function described in (1), an evaluation value for each design variable x is calculated. Sum of the evaluation values is the temporary evaluation value of the test function.
3. A bit pattern is generated according to the values of the design variables. For each design variable x_I, 0 is given when the value is in the range of

$(-180^\circ \leq x_I < -60^\circ)$ or $(60^\circ < x_I \leq 180^\circ)$ and 1 is given when the value is in the range of $(-60^\circ \leq x_I \leq 60^\circ)$.

4. By referring a database of the bit patterns, a bonus point for the bit pattern generated in 3 is determined.

5. The sum of the temporary evaluation value calculated in (2) and the bonus point determined in (4) is the evaluation value of the proposed test function.

An outline of the test function is illustrated in Figure 3.

$$F(x) = \begin{cases} -\frac{1}{120}x - \frac{3}{2} & if \quad -180 \leq x < -60 \\ -\frac{1}{15}x - 5 & if \quad -60 \leq x < 0 \\ \frac{1}{15}x - 5 & if \quad 0 < x \leq 60 \\ \frac{1}{120}x - \frac{3}{2} & otherwise \end{cases} \tag{1}$$

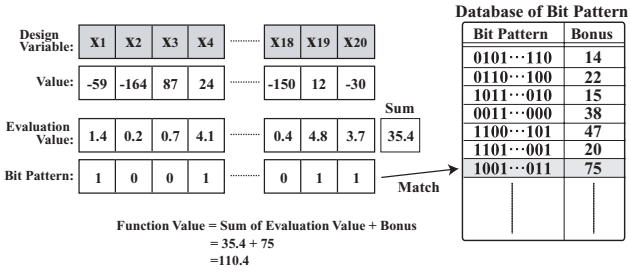

Figure 3: The evaluation of the test function. Database of bit patterns and the bonus points has to be prepared beforehand. The evaluation value of the test function is calculated from the evaluation values of the design variables and the bonus point.

In the tertiary structure of proteins, the α-helix structure is formed when the values of the dihedral angles (ϕ, ψ) fall in the range $(-70 \pm 30^\circ, -37 \pm 30^\circ)$[9]. To give the test function this characteristic, a bit pattern is generated according to the value of the design variable x_I. The I th element of the bit pattern is set to 1 when the value of the design variable x_I is in the range of $(-60^\circ \leq x_I \leq 60^\circ)$ and set to 0 otherwise. In the generated bit pattern, elements with 1 coresspond to the α-helix structure of protein and elements with 0 correspond to other structures.

For each design variable, the evaluation value is calculated using the evaluation function. The evaluation function is designed to return high evaluation value when the value of x_I is in the range of $(-60^\circ \leq x_I \leq 60^\circ)$. Therefore, the design variables with 1 as the bit pattern have the high evaluation values. For each of the 20 design variables, the evaluation values is calculated and sum of these values become a temporary evaluation value of the test function.

In the test function, a database of the bit patterns has to be prepared beforehand. The bit patterns registered in the database each possess a bonus point. The bit pattern generated according to the values of the desing variables is then checked with the bit patterns registered in the database. Then the database returns the corresponding bonus point when the matching bit pattern was found in the database. Sum of the temporary evaluation value and the bonus point is the evaluation value of this test function. By registering a number of bit patterns in the database, one optimum and a number of local minima can be created.

In the algorithm of local search for the test function, after certain number of MCsweeps, a determination whether there are design variables x_I with the value of $(-60^\circ \leq x_I \leq 60^\circ)$ is made. If found, values of the corresponding design variables are copied to the ones of the adjacent design variables. If the function value lowers by the local search, the copied design variables will be accepted. By this operation, values of the design variables with 1 as the bit pattern will be copied to the adjacent design variables. Since the design variables with one as the bit pattern have higher evaluation value, it is conceivable that the local search works to lower the value of the test function. However, because the number of bit patterns are registered in the database as local minima, there is a possibility of being trapped in the local minima by accepting the local search operation performed on the improper design variables.

4.3 Experiment

Here, we apply PSA/GAc with local search on the proposed test function. The purpose of the experiment here is to compare the searching capability of conventional PSA/GAc and PSA/GAc with local search algorithm.

Parameters of the experiment are shown in Table 1. The result of the experiment is shown in Figure 4.

The figure shows the average of 5 runs of both PSA/GAcs. From the figure, it is obvious that the local search algorithm is working properly. That is, the figure of PSA/GAc with local search indicates that the

Table 1: Parameters of PSA/GAc on the test function

Parameter	Value
Initial Temperature	2.0
Last Temperature	0.1
Number of MCsweeps	10,000
Crossover Interval	30 MCsweeps
Local Search Interval	20 MCsweeps

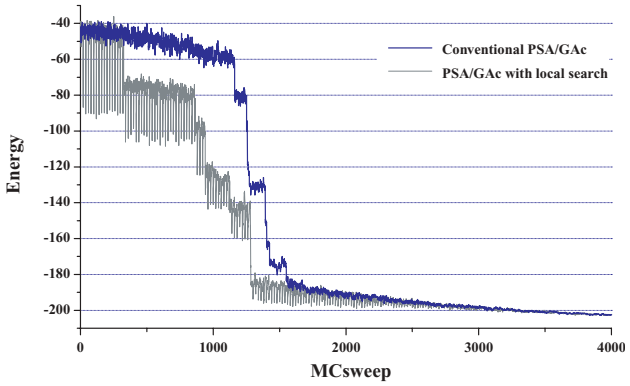

Figure 4: Energy transition of PSA/GAc with local search compared with the conventional PSA/GAc applied on the test function.

function value decreases rapidly in every local search interval. This is because every time the local search is performed, design variables with the high evaluation values are copied to their adjacent design variables. Although both PSA/GAcs have reached the optimum range (in this test function, -200) in about the same number of MCsweeps, the local search algorithm was confirmed to work properly to lower the energy of the test function that has the characteristic of the α-helix structures.

From the experiment using the proposed test function, PSA/GAc with local search was revealed to have a possibility of showing faster convergence to the optimum range than the conventional PSA/GAc. So in the next section, PSA/GAc with local search is applied to the energy minimization of proteins and its searching capability is compared to the conventional PSA/GAc.

5 Energy Minimization of Proteins by PSA/GAc with Local Search

Here, we apply PSA/GAc with local search on the energy minimization of proteins. The target proteins are $(Val)_{10}$, C-peptide, and PTH(1-34). Parameters of the experiment are shown in Table 2. In Table 2, initial temperature and last temperature are the same values as the Reference[11]. We used the parameters of Okamoto's to compare the performance of PSA/GAc with the Okamoto's results. For PSA/GAc, we set the interval of each genetic crossover to 32 MCsweep.

Table 2: Parameters of PSA/GAc

Parameter	Value
Initial Temperature	2.0
Last Temperature	0.1
Crossover Interval	32 MCsweeps
Local Search Interval	50 MCsweeps

5.1 Target Proteins

The target proteins of this paper are $(Val)_{10}$, C-peptide, and Parathyroid Hormone Fragment(1-34)(PTH(1-34)). The local search algorithm proposed in this research is based on the characteristic of the secondary structure called α-helix. In order to examine the performance of the algorithm, the target proteins must contain the α-helices. Therefore in this research, we adopt the stated proteins, which are known to have the α-helices in its lowest energy conformation[12, 10, 13] as target proteins. Number of amino residues, dihedral angles, and atoms of each protein are described in Table 3.

Table 3: Target proteins

	# amino residues	# dihedral angles	# atoms
$(Val)_{10}$	10	50	163
C-peptide	13	64	218
PTH(1-34)	34	178	582

Thus, 50 Metropolis criterions are performed in one MCsweep in the case of $(Val)_{10}$, 64 in the case of C-peptide, and 178 in the case of PTH(1-34).

Okamoto's experiments, using the energy function that adopts ECEPP/2 energy parameters, shows that $(Val)_{10}$ has the lowest energy conformation when eight residues (2-9) form an α-helix. The energy of this lowest energy conformation was -0.8 $kcal/mol$[9].

Likewise, C-peptide has the lowest energy conformation when eight residues (4-11) form an α-helix and its energy was -42 $kcal/mol$[10]. Also, the lowest energy conformation of C-peptide obtained in this experiment corresponds to the structure deduced from the X-ray crystallography experiment[3].

It is known by the NMR experiment that PTH(1-34) has two α-helices[14]. The lowest energy conformation

of PTH(1-34) deduced from Okamoto's experiment also had two α-helices and its energy is -210.0 $kcal/mol$[13].

From the above statements, we define the optimum energy range of $(\mathrm{Val})_{10}$ as $< -0.8kcal/mol$, C-peptide as $< -42kcal/mol$, and PTH(1-34) as $-210kcal/mol$.

5.2 Results

Figure 5, Figure 6, and Figure 7 show the results of the energy minimization of $(\mathrm{Val})_{10}$, C-peptide, and PTH(1-34) by PSA/GAc with local search. We made 30 runs of PSA/GAc with local search on each protein. Each line of the figures indicate the Best, Worst, and Average of the energy transition. For comparison, along with the results of PSA/GAc with local search, average energy transition of conventional PSA/GAc is also indicated in the figures.

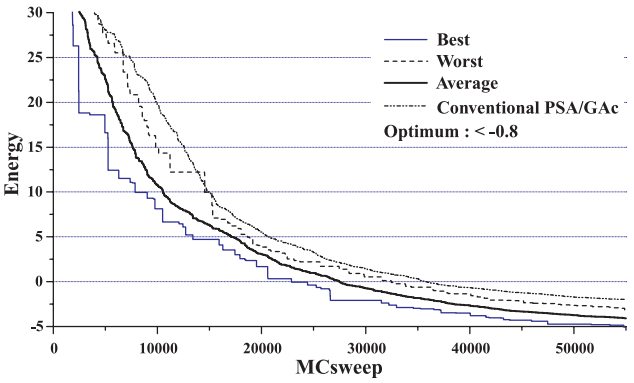

Figure 5: Energy transition of PSA/GAc with local search applied on the energy minimization of $(\mathrm{Val})_{10}$.

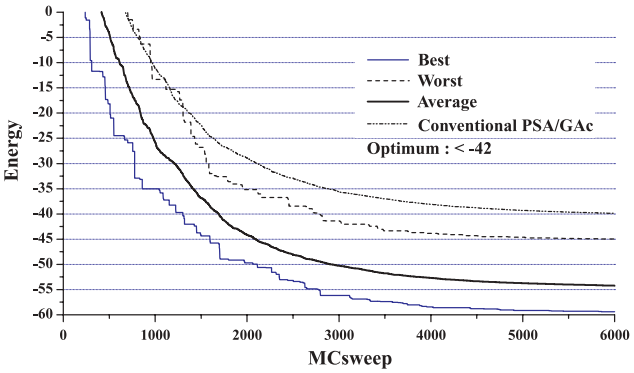

Figure 6: Energy transition of PSA/GAc with local search applied on the energy minimization of C-peptide.

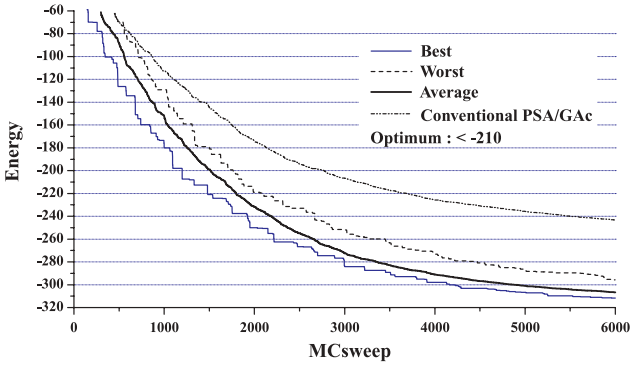

Figure 7: Energy transition of PSA/GAc with local search applied on the energy minimization of PTH(1-34).

5.3 Discussion of the Results

In this section, two discussions are made from the results of the experiment. First discussion is about the accuracy of the solution. Figure 5, Figure 6, and Figure 7 indicate that in either proteins, PSA/GAc with local search has obtained lower energies than conventional PSA/GAc. Comparing the Averages of the figure, in $(\mathrm{Val})_{10}$ of Figure 5, energy of PSA/GAc with local search at the end of the run differs from the energy of conventional PSA/GAc in approximately 2 $kcal/mol$. Likewise, C-peptide of Figure 6 differs in approximately 15 $kcal/mol$ and PTH(1-34) of Figure 7 differs in approximately 63 $kcal/mol$. From these results, in either protein, the proposed algorithm is working effectively to reduce the energies. This result is due to the characteristic of α-helices stated in Section 3.1. That is, because α-helix is a stable secondary structure, longer α-helix derives more stable structure with lower energy. The proposed local search algorithm is based on this characteristic of α-helix and is the algorithm to accelerate the development of the α-helices. Therefore with the proposed algorithm, longer α-helix has formed in the structure than the conventional PSA/GAc, and as the result lower energies were obtained.

Second discussion is about the amount of calculation required to reach the optimum energy range. The result is obvious from Figure 5, Figure 6, and Figure 7. That is, in either proteins the required MCsweeps to reach the optimum energy range by PSA/GAc with local search are less than the conventional PSA/GAc. From the result of $(\mathrm{Val})_{10}$ in Figure 5, the optimum energy range is reached approximately 11,000 MCsweeps faster than the conventional PSA/GAc. The result of C-peptide in Figure 6 indicates that the conventional PSA/GAc has not reached the optimum range. On the

other hand, PSA/GAc with local search has reached the optimum range in approximately 1,500 MCsweeps. Likewise, the result of PTH(1-34) in Figure 7 indicates that PSA/GAc with local search has reached the optimum range approximately 1,500 MCsweeps faster than the conventional PSA/GAc.

We also discuss the total number of evaluation required to reach the optimum range in each protein. In PSA/GAc, as stated in Section 5.1, number of evaluations in 1 MCsweep is equal to the number of dihedral angles. Therefore the total number of evaluations in PSA/GAc can be described as :

$$\#\ DihedralAngles \times Total\ \#\ MCsweeps + \alpha \quad (2)$$

Here, α is the number of evaluations required for the genetic crossover and can be described as :

$$\#\ of\ individuals \times \frac{\#\ of\ MCsweeps}{Crossover\ interval} \quad (3)$$

For example, when minimizing the energy of PTH(1-34) with 16 individuals × 6,000 MCsweeps and crossover interval of 32, the number of evaluations required for the genetic crossover is $16 \times (6,000/32) = 3,000$. On the other hand number of evaluations for the MCsweeps is $178 \times 6,000 = 1,068,000$. Figure 8 describes the ratio of total number of evaluation required to reach the optimum range by PSA/GAc with local search when the total number of evaluation required by the conventional PSA/GAc is described as 1. However, since the conventional PSA/GAc did not reach the optimum range of C-peptide, as for C-peptide the total number of evaluation required until the end of the run is described as 1. The number of evaluations required in the local search can be described as :

$$\frac{\#\ of\ MCsweeps}{LS\ interval} \times \#of\ evaluation\ in\ 1\ LS \quad (4)$$

$$LS : Local\ search$$

The number of evaluations required in a single local search is not fixed, however depends on the number of dihedral angles. So we set this value to $[\#\ of\ dihedral\ angles]/2$. That is using the example stated above, number of evaluations required in a single local search is $(6000/50) \times (178/2) = 10,680$.

Figure 8 indicates that the total number of evaluations required in PSA/GAc with local search is less than the conventional PSA/GAc. As for PTH(1-34) required number of evaluations is approximately half, and as for C-peptide required number of evaluations is approximately 1/3. From the results, the local search

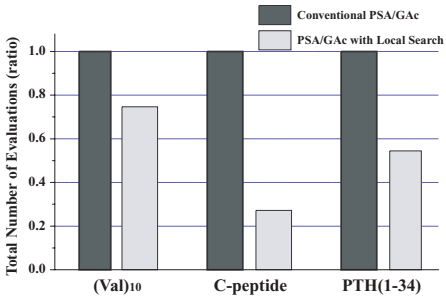

Figure 8: The ratios of the numbers of evaluations required to reach the optimum. For each protein, numbers of evaluations required to reach the optimum by the conventional PSA/GAc is described as 1.

is working effectively to reduce the number of evaluations required in the energy minimization of the target proteins. This denotes that by applying the local search to the energy minimization of proteins, the α-helix is formed in the early stage of the run, and as a result faster convergence than the conventional PSA/GAc was achieved. Also, as for the target proteins of this research, every run have reached the optimum energy range without trapped to the local minima of the energy function.

From the above discussions, PSA/GAc with local search based on the characteristic of α-helix is effective on the energy minimization of proteins.

6 Conclusion

In this paper, the local search algorithm based on the characteristic of α-helix, which is a secondary structure of proteins, is proposed and is introduced to Parallel Simulated Annealing using Genetic Crossover (PSA/GAc). In the proposed algorithm, when a part of the α-helix is found during the search of the energy function, α-helix is expanded to the adjacent residues.

Before applying the proposed algorithm to the energy minimization of proteins, the test function with the characteristic of the energy function of proteins was proposed for an efficient verification of the algorithm. The proposed test function has two characteristics of the energy function of proteins: the characteristic of α-helices and a number of local minima. By applying PSA/GAc with local search to the proposed test function, the effect of the local search algorithm was confirmed.

Then, PSA/GAc with the proposed local search was applied to the energy minimization of $(Val)_{10}$, C-peptide, and PTH(1-34). From the comparison of the results of PSA/GAc with local search and the conven-

tional PSA/GAc, two effects of the local search were confirmed. One is the accuracy of the solution. That is, in either protein PSA/GAc with local search has obtained lower energies than the conventional PSA/GAc. Second effect is about the total number of evaluations required to reach the optimum energy range. That is, PSA/GAc with local search has reached the optimum range in less number of evaluations than the conventional PSA/GAc.

From the results, the possibility of the effectiveness of the proposed local search algorithm on the energy minimization of the proteins with α-helices has been verified.

Bibliography

[1] Hikaru Kawai, Takeshi Kikuchi, and Yuko Okamoto. A prediction of tertiary structures of peptide by the Monte Carlo simulated annealing method. *Protein Engineering*, Vol. 3, No. 2, pp. 85–94, 1989.

[2] Osamu Takahashi, Hajime Kita, and Shigenobu Kobayashi. Protein Folding by A Hierarchical Genetic Algorithm. *Proceeding of the Fourth International Symposium on Artificial Life and Robotics*, pp. 19–22, 1999.

[3] Ulrich H. E. Hansmann and Yuko Okamoto. Tertiary Structure Prediction of C-Peptide of Ribonuclease A by Multicanonical Algorithm. *J. Phys. Chem. B*, Vol. 102, No. 4, pp. 653–656, 1998.

[4] Tomoyuki Hiroyasu, Mitsunori Miki, Maki Ogura, and Yuko Okamoto. Examination of Parallel Simulated Annealing using Genetic Crossover. *Journal of Information Processing Society of Japan*, Vol. 43, No. SIG7(TOM6), pp. 70–79, 2002.

[5] Tomoyuki Hiroyasu, Mitsunori Miki, and Maki Ogura. Parallel simulated annealing using genetic crossover. *Proceedings of the 44th Institute of Systems, Control and Information Engineers*, pp. 113–114, 2000.

[6] F.A. Momany, R.F. McGuire, A.W. Burgess, and H.A. Scheraga. Energy parameters in polypeptides. vii. geometric parameters, partial atomic charges, nonbonded interactions, hydrogen bond interactions, and intrinsic torsional potentials for the naturally occurring amino acids. *J. Phys. Chem.*, Vol. 79, pp. 2361–2381, 1975.

[7] G. Nemethy, M.S. Pottle, and H.A. Scheraga. Energy parameters in polypeptides. 9. updating of geometric parameters, nonbonded interactions and hydrogen bond interactions for the naturally occurring amino acids. *J. Phys. Chem.*, Vol. 87, pp. 1883–1887, 1983.

[8] M.J. Sippl, G. Nemethy, and H.A. Scheraga. Intermolecular potentials for crystal data 6. determination of empirical potentials for 0-h—o=c hydrogen bonds for packing configurations. *J. Phys. Chem.*, Vol. 88, pp. 6231–6233, 1984.

[9] Ayori Mitsutake and Yuko Okamoto. Helix-coil transitions of amino-acid homo-oligomers in aqueous solution studied by multicanonical simulations. *JOURNAL OF CHEMICAL PHYSICS*, Vol. 112, No. 23, pp. 10638–10646, 2000.

[10] Yuko Okamoto, Masataka Fukugita, Takashi Nakazawa, and Hikaru Kawai. α-Helix folding by Monte Carlo simulated annealing in isolated C-peptide of ribonuclease A. *Protein Engineering*, Vol. 4, No. 6, pp. 639–647, 1991.

[11] Yuko Okamoto, Takeshi Kikuchi, and Hikaru Kawai. Prediction of Low-Energy Structures of Met-Enkephalin by Monte Carlo Simulated Annealing. *CHEMISTRY LETTERS*, pp. 1275–1278, 1992.

[12] Yuko Okamoto and Ulrich H.E. Hansmann. Thermodynamics of Helix-Coil Transitions Studied by Multicanonical Algorithms. *J. Phys. Chem.*, Vol. 99, No. 28, pp. 11276–11287, 1995.

[13] Yuko Okamoto, Takeshi Kikuchi, Takashi Nakazawa, and Hikaru Kawai. α-Helix structure of parathyroid hormone fragment (1-34) predicted by Monte Carlo simulated annealing. *INTERNATIONAL JOURNAL OF PEPTIDE & PROTEIN RESEARCH*, Vol. 42, pp. 300–303, 1993.

[14] W. Klaus, T. Dieckmann, V. Wray, D. Schomburg, E. Wingender, and H. Mayer. *Biochemistry*, Vol. 30, pp. 6936–6942, 1991.