Re-examination of Structure Optimization of Off-Lattice Protein AB Models by Conformational Space Annealing

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Abstract: The global structural optimization is carried out for off-lattice protein AB models in two and three dimensions by conformational space annealing. The models consist of hydrophobic and hydrophilic monomers in Fibonacci sequences. To accelerate the convergence, we have introduced a shift operator in the internal coordinate system, and effectively reduced the search space by forming a quotient space. With this, we significantly improve our previous results on AB models, and provide new low energy conformations. This work provides insights on exploring complicated energy landscapes by exploiting the advantages and limitations of CSA.

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Introduction

Protein structure prediction is one of the challenging problems of this century in computational sciences. Based on Anfinsen's thermodynamic hypothesis,¹ computational framework for protein structure prediction is well established, defining an appropriate energy function and its optimization. Given an energy function, finding the global minimum of it in the protein folding is a hard combinatorial optimization problem. Recently the importance of optimization in all stages of protein structure prediction using bioinformatics is also investigated.²

Simplified protein models such as AB models³ are devised to study qualitative properties of protein folding. Off-lattice protein AB models consist of hydrophobic monomers labeled by A and hydrophilic ones by B. Interactions between these monomers are composed of a Lennard-Jones type potential term, a bending energy term, and torsional energy contributions.

Although the coarse-grained models of proteins are quite simplified, their free-energy landscapes are quite rugged and finding their global minima is a nontrivial task. Although putative ground-state conformations have been reported, they are continually being updated,^{4–9} and thus it is not clear if they correspond to true ground-state conformations.

In ref. 6, a global optimization method called conformational space annealing (CSA)^{10–12} is applied to find ground-state con-

formations of protein AB models. At that time, optimization by CSA was terminated when a new structure was obtained with lower energy than reported in the literature. Thus systematic and rigorous optimization was not performed. In addition, there was a confusion in signs of energy terms of model2 (see Off-Lattice AB Models section below).

In this article, we study systematically ground-state properties of protein AB models by using CSA. A distinguished point from ref. 6 is that a “shift operator” is introduced to accelerate the convergence. It effectively reduces the search space, and new low energy conformations are reported for four separate cases.

Off-Lattice AB Models

Two effective off-lattice AB models are investigated with Fibonacci sequences. The Fibonacci sequence is defined recursively by

$$\Lambda_0 = A, \quad \Lambda_1 = B, \quad \Lambda_i = \Lambda_{i-2} * \Lambda_{i-1}, \quad (1)$$

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Figure 1. A series of structural changes during minimization in terms of a bond angle is shown. A positive bond angle of (a) goes through a value $\phi = \pi$ at (b), and becomes $\phi > \pi$ (or equivalently $\phi < 0$).

where the asterisk denotes the concatenation operator. We study the cases of $6 \leq i \leq 9$. The sequences of chains are denoted as S_{13}, S_{21}, S_{34} , and S_{55} for $i = 6, 7, 8$, and 9 , respectively, where subscripts indicate chain-sizes.

The first model investigated in this work is the original AB model. It was proposed in ref. 3 with the energy function

$$E_1 = \sum_{i=1}^{N-2} \frac{1}{4} (1 - \cos \theta_{i,i+1}) + 4 \sum_{i=1}^{N-2} \sum_{j=i+2}^N \left[\frac{1}{r_{ij}^{12}} - \frac{C_1(\sigma_i, \sigma_j)}{r_{ij}^6} \right], \quad (2)$$

where $\theta_{i,j}$ is the angle between the i th and j th bond vectors (c.f. it is not a bond angle, but π -bond angle) and r_{ij} is the distance between monomers i and j . The constant $C_1(\sigma_i, \sigma_j)$ is $+1, +1/2$, and $-1/2$ for AA, BB, and AB pairs, respectively, thus introducing strong attraction between AA pairs, weak attraction for BB pairs, and weak repulsion between AB pairs. The bending energy term induces chains to expand, and thus partially competes with the van der Waals energy term. All bond lengths are fixed to unity. We call this model “model1” throughout this article, and simulations are performed in two and three dimensions.

The second model denoted here as model2 was introduced in ref. 13. The energy is given by

$$E_1 = \sum_{i=1}^{N-2} \cos \theta_{i,i+1} - \frac{1}{2} \sum_{i=1}^{N-3} \cos \theta_{i,i+2} + 4 \sum_{i=1}^{N-2} \sum_{j=i+2}^N C_2(\sigma_i, \sigma_j) \times \left(\frac{1}{r_{ij}^{12}} - \frac{1}{r_{ij}^6} \right), \quad (3)$$

where $C_2(\sigma_i, \sigma_j)$ is $+1$ for AA pairs and $+1/2$ for BB and AB pairs. Therefore all nonbonded interactions are attractive with emphasis on stronger AA interactions. The first and second terms prefer chains to zigzag. Thus all terms compete with each other. All bond lengths are fixed to unity. Since the second term was introduced in ref. 13 to mimic a torsional energy term, the model2 is investigated only in three dimensions.

Methods

Shift Operator

In this work, conformations are represented by the internal coordinate I , and there exist trivial symmetries in I . First, after performing local energy minimization of a conformation, a certain bond angle ϕ_i (initially $0 \leq \phi_i \leq \pi$) can be of a negative value ($-\pi \leq \phi_i \leq \pi$). Since any conformation can be represented with bond angles in the range of 0 and π , in this case, we have another representation of the conformation with negative “bond angles.” Performing restrained local minimization is not a remedy to this problem. Since the energy function is continuous in terms of the internal coordinate, the range of “bond angles” should not be restricted to reach a local minimum of a given conformation.

Suppose two bonds are in a shape shown in Figure 1a with a positive bond angle before minimization, and it undergoes the structural change through Figures 1b and 1c in a continuous manner (to make the situation simple, we assume that all the other angles of the rest of the molecule are fixed during minimization). If the local minimization is performed in terms of cartesian coordinates, no special operator is required. However, using the internal coordinate system, the final shape (Fig. 1c) is described with a negative (or $\phi > \pi$) bond angle. To represent the final structure using the bond angle in the range of $[0, \pi]$, we reassign the bond angle of Figure 1 when the shape crosses the flat shape ($\phi = \pi$) of Figure 1b so that the bond angle remains in the range of $[0, \pi]$. This was carried out by introducing the shift operator.

Second, changing signs of all dihedral angles ($-\pi \leq \psi_i \leq \pi$) of a conformation in a simultaneous fashion yields the mirror image with identical energy value.

The idea of forming reduced space is to “glue together” if two points in I represent the same conformation or are mirror images from each other. Mathematically speaking, we define an equivalence relation $\sim$ and obtain a reduced space by forming a quotient space $I/\sim$.

For $p, q \in I$, let $p = (\phi_1^p, \psi_1^p, \phi_2^p, \psi_2^p, \dots, \psi_{n-2}^p, \phi_{n-1}^p)$, and $q = (\phi_1^q, \psi_1^q, \phi_2^q, \psi_2^q, \dots, \psi_{n-2}^q, \phi_{n-1}^q)$, where $\phi_i^{(\cdot)}$ are “bond angles” (which can be negative values, $-\pi \leq \phi_i^{(\cdot)} \leq \pi$), and $-\pi \leq \psi_i^{(\cdot)} \leq \pi$ are dihedral angles. The number of monomers is denoted as n . The index system is that the adjacent dihedral angles of $\phi_i^{(\cdot)}$ become $\psi_{i-1}^{(\cdot)}$ and $\psi_i^{(\cdot)}$. The equivalent relation $\sim$ is defined by the following: $p \sim q$ if (1) $[\phi_i^p = -\phi_i^q, \psi_{i-1}^p = \psi_{i-1}^q + \pi, \text{ and } \psi_i^p = \psi_i^q + \pi]$ for some i , and $[\phi^p = \phi^q \text{ and } \psi^p = \psi^q]$ for the rest of the angles, or (2) $[\phi_i^p = \phi_i^q, \text{ and } \psi_i^p = -\psi_i^q]$ for all i .

The condition (1) comes from the fact that if a bond angle of a conformation is of a negative value, one can represent the identical conformation by converting the bond angle to a positive value and flipping its two adjacent dihedral angles. As a result, all bond angles can be defined between 0 and π . The condition (2) corresponds to gluing mirror images into one.

By the definition of (1), 2^{n-1} points in I are reduced to a single point in $I/\sim$, and by (2) 2 points in I becomes a single point in $I/\sim$. Thus by the “shift operator,” the size of $I/\sim$ is reduced by the factor of 2^n from the size of I .

Although this operator is defined for the specific beads-like protein models, this kind of idea can be applied to any reduced protein

Table 1. The Lowest Energies of Model1 in the Two-Dimensional AB Model by this Work, in Comparison with Those by nPERMis, ACMC, our Previous Work (Old CSA), and STMD.

	nPERMis	ACMC	old CSA	STMD	CSA (this work)
S_{13}	-3.2939	-3.2941	-3.2941	-3.2941	-3.2941(10/10)
S_{21}	-6.1976	-6.1979	-6.1980	-6.1980	-6.1980(10/10)
S_{34}	-8.9749	-10.8060	-10.8060	-10.8060	-10.8060(10/10)
S_{55}	-18.5154	-18.7407	-18.9110	-18.9202	-18.9296 (1/10)

The numbers in the parenthesis in the last column indicates the number of times the lowest energy is found out of ten independent runs. The new lowest energy is shown in bold case. The conformations of the previously reported lowest energy and the current work are shown in Figure 2.

models where virtual bond angles are introduced.^{11,14} The condition (2) is not necessary when dealing with chirally symmetry-broken units such as amino acids of L and D types.

Equipped with this shift operator, we have applied CSA to this reduced internal coordinate space $I/\sim$.

Conformational Space Annealing

The CSA method searches the whole conformational space in its early stages and then narrows the search to smaller regions with low energy as the distance cutoff, D_{cut} , which defines the similarity of two conformations, is reduced. It starts with a preassigned number (50 in this work) of randomly generated and subsequently energy-minimized conformations. This pool of conformations is called the bank. At the beginning, the bank is a sparse representation of the conformational space of local minima.

A number of dissimilar conformations (30 in this work) are then selected from the bank, excluding those that have already been used; they are called seeds. Each seed conformation is modified by replacing consecutive parts (from 10% to 40% of the chain selected in a random fashion) of the seed by the corresponding parts of a randomly selected conformation from the bank. Each conformation is energy-minimized to give a trial conformation. A total of 30 trial conformations are generated for each seed (hence 900 trial conformations). This corresponds to the most time-consuming part of the algorithm, and consequently it is highly suitable for parallel computation,¹⁵ since the energy minimizations are independent from each other.

For each trial conformation, α , the closest conformation A from the bank (in terms of the root mean square deviation, $d(\alpha, A)$) is determined. If $d(\alpha, A) \leq D_{\text{cut}}$ (D_{cut} being the current value of cutoff criterion), α is considered similar to A ; in this case α replaces A in the bank, if it is also lower in energy. If α is not similar to A , but its energy is lower than that of the highest-energy conformation in the bank, B , α replaces B . If neither of the above conditions holds, α is rejected. The narrowing of the search regions is accomplished by setting D_{cut} to a large value initially and gradually reducing it as the search progresses.

Special attention is paid to selecting seeds that are far from each other. One round of the procedure is completed when there is no seed to select (i.e., all conformations from the bank have already been used). At the end of each round, all conformations in the bank are designated as unused as seeds. The value of D_{cut} is also set to

the original value. The round is repeated a predetermined number of times (2 in this work), after which additional random energy-minimized conformations (50 in this work) are added to the bank, and the whole procedure is repeated. In this work, the whole CSA search stops after the complete procedure is finished with 500 bank conformations. More details of CSA can be found elsewhere.^{10,16,17}

Results

In the field of protein structure prediction, carefully prepared knowledge-based energy terms are shown to correlate well with the quality of a model.² Therefore if one can find lower energy conformations, the chances are that the quality of their structures is better. We note that the degrees of freedom of the system S_n in three dimensions increases as $2n$ which corresponds to the number of backbone angles of a protein with n residues.

Model1 in Two Dimensions

Table 1 shows the results of the lowest energy of model1 in two dimensions, along with the values reported in the literature by nPERMis,⁴ ACMC,⁵ our previous work,⁶ and STMD⁷ for comparison. All methods except nPERMis report identical results for S_{13} , S_{21} , and S_{34} . We could almost be sure that the results obtained may correspond to the true ground-state energies. However, for S_{55} , a lower energy conformation is found in this work. Figure 2 shows our lowest energy conformation along with that of STMD. Although its energy is only slightly lower than that found by STMD, hydrophobic cores of our model are more tightly packed in the sense that the number of hydrophobic residues not packed in the cores is one less than that from STMD. We remark that out of 10 independent runs, the new minimum is reached only once, indicating the energy landscape of S_{55} in two dimensions is quite rugged and thus finding the new conformation is a nontrivial task.

Figure 2. The lowest energy conformation from STMD (left) for S_{55} in two dimensions, and the lowest energy conformation of this study (right) is shown. STMD conformation contains hydrophobic residues of four 4As, one 3A, and two single As. Our conformation contains one 5A, three 4As, one 3A, and one single A.

Table 2. The Lowest Energies of Model1 in the Three-Dimensional AB Model by this Work, in Comparison with Those by nPERMis, ELP, our Previous Work (Old CSA), and STA.

	nPERMis	ELP	old CSA	STA	CSA (this work)
S_{13}	-4.9616	-4.967	-4.9746	-4.9746	-4.9746(10/10)
S_{21}	-11.5238	-12.316	-12.3266	-12.3266	-12.3266(10/10)
S_{34}	-21.5678	-25.476	-25.5113	-25.5113	-25.5113(5/10)
S_{55}	-32.8843	-42.428	-42.3418	-42.5781	-44.7983(2/10)

The numbers in the parenthesis in the last column indicates the number of times the lowest energy is found out of ten independent runs. The new lowest energy is shown in bold case.

Model1 in Three Dimensions

Table 2 shows the lowest energies of our model1 in three dimensions, along with the results by nPERMis, ELP,⁸ our previous work, and STA.⁹ Recent three methods report identical results for S_{13} , S_{21} , and S_{34} . However, for S_{55} , our result for the lowest-energy conformation shown in Figure 3 is ~5% lower in energy compared with that by STA. In all 10 independent runs, lowest energies found are lower than that of STA. To investigate low-lying regions in the energy landscape, we chose three “stable” (found several times as the lowest energy in 10 runs) conformations and compared their structures. When we denote them as c1, c2, c3, their energies are -44.7983, -44.4212, and -44.15806, respectively. TM-scores¹⁸ between c1 and the others are about 0.23 meaning c1 is quite different from c2 and c3. However, TM-score between c2 and c3 is 0.67 (roughly speaking, 67% can be superimposable). See the structures in Figure 3. This illustrates a fine structure of low-lying regions in the energy landscape indicating there are two deep basins and one of them has two low-energy meta-stable local minima.

This demonstrates the ability of CSA to cover low-lying energy regions scattered distantly in the energy landscape. This feature of CSA is quite important in the field of protein structure prediction. Low-energy conformations scattered distantly may cover different portions of protein structures, and thus there are more chances to improve the quality of structures by combining the information from diverse low-energy structures.²

In the three-dimensional model1, these results strongly suggest that ground-states for S_{13} , S_{21} , and S_{34} are found. However, the situation is less clear for the case of S_{55} .

Model2 in Three Dimensions

In the three-dimensional model2, the problem appears to be more difficult. Table 3 shows the lowest energies of our results, along with the results by APMC, ELP, our previous work (We acknowledge that there were confusions and mistakes on signs in the energy terms in the previous work for model2, and thus the values in the column of old CSA in Table III should be neglected.), and STA. In this case, even the results in S_{34} do not agree from each other. This observation may indirectly indicate that the energy landscapes of model2 are more rugged than those of model1. This is somewhat expected from the functional form in that there are more competing terms in E_2 . We found the lower energy conformations for S_{34} and S_{55} shown in Figures 4 and 5, respectively. For S_{34} , -98.3571 is reached only

twice out of ten runs. The other 8 runs all reached -98.0757 that is also found as the second lowest energy minimum in the two more successful runs. TM-score between these two conformations is 0.31 indicating they are structurally quite different from each other. This

Figure 3. The lowest energy conformation (c1) for S_{55} of model2 in three dimensions, and two low-energy meta-stable conformations c2 and c3 are shown in stereoview from top to bottom.

Table 3. The Lowest Energies of Model2 in the Three-Dimensional AB Model by this Work, in Comparison with Those by APMC, ELP, our Previous Work (old CSA [18]), and STA.

	APMC	ELP	old CSA	STA	CSA (this work)
S_{13}	-26.506	-26.498	-26.4714	-25.5066	-26.5066(10/10)
S_{21}	-51.7575	-52.917	-52.7865	-52.9339	-52.9339(10/10)
S_{34}	-94.0431	-92.746	-97.7321	-97.6171	-98.3571 (2/10)
S_{55}	-154.505	-172.696	-173.9803	-174.5681	-176.6913 (1/10)

The numbers in the parenthesis in the last column indicates the number of times the lowest energy is found out of ten independent runs. The new lowest energy is shown in bold case.

demonstrates that the energy landscape of S_{34} contains a deep narrow basin and a wider basin. It should be noted that we have found eight distinct conformations whose energy values are all lower than the previous best one by STA. The previous best conformation by STA is also obtained in this study. TM-scores between seven conformations are all less than 0.32 from each other, and the score between two out of eight was 0.5. This illustrates the CSA's ability to find low energy conformations while keeping diversity between conformations, especially in much rugged energy landscapes.

For S_{55} , a conformation with 1.2% lower energy compared to that by STA is found. Again, in all 10 independent runs, all lowest energies found in this work are lower than that by STA. However, the lowest energies in 10 independent runs are not identical from each other except that the second minimum, -176.4706, is reached twice. The lowest minimum energy of -176.6913 is reached only once. This illustrates that finding the global minimum of the energy landscape for S_{55} of model2 is quite difficult even with the state-of-the-art method, and one can not be sure the lowest energy reported here corresponds to the true global minimum. In Table 4, results of 10 runs for the above four cases are summarized.

Summary and Discussions

The ground state energies of two off-lattice AB models are investigated by conformational space annealing (CSA). To accelerate the convergence we have defined an equivalent relation $\sim$, and effectively reduced the internal coordinate space I by forming a quotient space $I/\sim$. By applying CSA to $I/\sim$, lower energy conformations are found for S_{55} of model1 in two dimensions, S_{55} of model1 in

Figure 4. The lowest energy conformation for S_{34} of model2 in three dimensions is shown in stereoview. **Figure 5.** The lowest energy conformation for S_{55} of model2 in three dimensions is shown in stereoview.

three dimensions, S_{34} and S_{55} for model2 in three dimensions. Fine structures of energy landscapes are also discussed.

For S_{13} and S_{21} of model1 and model2, we could be almost sure that their global minima are found. For S_{34} , the ground state conformation of model1 found by this work is more repeatedly visited than that of model2 indicating that the energy landscape of model2 may be more difficult to search than that of model1. It is probably due to one additional competing term in model2. For S_{55} , even with the current method, it is difficult to repeatedly find the reported lowest-energy conformations in this work, and thus finding the true global minimum conformations for S_{55} of model1 and model2 still remains challenging and open to further investigations.

After this work is finished, we have noticed the work of Zhang and Ma,¹⁹ where new putative ground state conformations are reported for four cases, 2D S_{34} , 3D S_{55} of model1, 3D S_{34} of model2, and 3D S_{55} of model2. The energies found by Zhang and Ma are lower than those found here in three out of four cases. Here we aim to provide comparative analysis and discussions.

Interestingly, our results for 3D S_{34} of model2 agree with Zhang and Ma. For this case, previous methods have repeatedly provided new putative global minimum conformations. The agreement from these two separate methods strongly indicates that it could be the true ground-state.

For 2D S_{55} and 3D S_{55} of model1, Zhang and Ma¹⁹ found slightly lower (the energy difference being 0.3274 for 2D, and 0.0782 for 3D, respectively) energy conformations. TM-scores between theirs and the closest one kept in the final bank from CSA was 0.48 for

Table 4. Summary of the Lowest Energies for 10 Independent Runs Found in this Work.

Trial	2D S_{55} , Model1	3D S_{55} , Model1	3D S_{34} , Model2	3D S_{55} , Model2
1	-18.911	-44.1581	-98.076	-176.691
2	-18.911	-44.42124	-98.076	-175.518
3	-18.930	-44.42124	-98.357	-176.211
4	-18.9110	-44.79829	-98.076	-175.721
5	-18.903	-44.29656	-98.076	-176.471
6	-18.9110	-44.15806	-98.076	-175.881
7	-18.9110	-44.79829	-98.076	-175.621
8	-18.889	-44.27933	-98.076	-175.555
9	-18.9110	-44.17801	-98.357	-176.471
10	-18.903	-44.27094	-98.076	-176.067

2D, and 0.53 for 3D indicating structural similarity. It implies that CSA may have reached the big basin where the conformations from Zhang and MA lie.

For 3D S_{55} of model2, however, the energy difference is larger (1.4426) and the structural similarity between the two methods is rather low with TM-score of 0.31.

The failure to obtain lowest energy structures of three protein AB models using CSA is rather disappointing. However, it is important to understand the reason for the failure and to suggest a possible fix for the problem. One important assumption for the success of CSA¹⁰ is that a typical local minimum conformation contains a portion of correct values of internal variables for global minimum solution (combination assumption). In the case of protein structures, most dihedral angles take one of three values denoted as gauche+, gauche– and trans (planar angles take one of the two values, trans and cis). Therefore, a typical local minimum conformation may contain one third of its dihedral angles in agreement with the global minimum conformation (still finding the global minimum remains as a hard combinatorial optimization problem). In CSA, when perturbing a seed conformation, rather than using random variables for random perturbation, randomly chosen locally minimized values from the first bank is used (first bank is the collection of randomly generated and then minimized conformation). We suspect that the current failure is partly from the breakdown of the combination assumption mentioned. Another possibility is that, throughout the CSA procedure, conformations generated are all quite low in energy, especially compared to those by Zhang and Ma.¹⁹ The fact that the Monte Carlo simulations^{19–21} efficiently generate low and quite high energy conformations, appears to enable one to cover more diverse phase space than sampled by CSA, demonstrating the limitation of CSA especially when the first bank fails to provide appropriate candidate values for the global minimum. To overcome this kind of situation, one needs to introduce new measures to CSA when the combination assumption fails. One possibility could be to combine CSA with generalized Monte Carlo ensemble.

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