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Structure optimization by heuristic algorithm in a coarse-grained off-lattice model*

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A heuristic algorithm is presented for a three-dimensional off-lattice AB model consisting of hydrophobic (A) and hydrophilic (B) residues in Fibonacci sequences. By incorporating extra energy contributions into the original potential function, we convert the constrained optimization problem of AB model into an unconstrained optimization problem which can be solved by the gradient method. After the gradient minimization leads to the basins of the local energy minima, the heuristic off-trap strategy and subsequent neighborhood search mechanism are then proposed to get out of local minima and search for the lower-energy configurations. Furthermore, in order to improve the efficiency of the proposed algorithm, we apply the improved version called the new PERM with importance sampling (nPERMis) of the chain-growth algorithm, pruned-enriched-Rosenbluth method (PERM), to face-centered-cubic (FCC)-lattice to produce the initial configurations. The numerical results show that the proposed methods are very promising for finding the ground states of proteins. In several cases, we found the ground state energies are lower than the best values reported in the present literature.

Keywords: protein folding, off-lattice model, heuristics, FCC-lattice
PACC: 8715B, 3620E, 3120A

1. Introduction

Predicting the native structure of a protein from its amino acid sequence is one of the most challenging problems in biophysics and bioinformatics. Although some substantial advances in *ab initio* prediction have recently been made, especially in the area of the "fragment assembly" method,[1] there are presently no practical methods that can reliably deliver a good approximation to a protein's three-dimensional structure. Although the general belief that structure is indeed determined in a lawlike way by sequence remains unchallenged, it seems that whatever the detailed form of these laws may be, they are not easily uncovered.[2] In *ab initio* prediction, the difficulty of the folding problem lies in two major aspects. One is the determination of the potential energy function. The effective energy function can generally distinguish the native states from non-native states of protein molecules. The other is that the potential energy landscape of the system can be characterized by a multitude of local minima separated by high-energy barriers. The first of these issues needs to be addressed primarily by biochemists who study and model protein folding process; the second, however, is a rich source of interesting and challenging computational problems in local and global optimization.

Since solving such a problem is very difficult for realistic protein models, in recent years the theoretical community has introduced and examined some highly simplified but still nontrivial models, which make the following assumptions: instead of considering all the 20 different kinds of amino acids in real protein, the models comprise only two prototypes of amino acid residues: the hydrophobic (H) and the hydrophilic (or polar, P) residues, respectively. This is to account for the fact that most of the naturally occurring amino acids can be classified in this way and that the atomic interactions are drastically simplified. These models include a large family of HP lattice models[2−6] and HP off-lattice models.[7,8] Even though these models are highly simplified, to solve the corresponding folding problem remains to be NP-hard, which means that it is not solvable in polynomial time. In recent years, a wide variety of approximate algorithms[9−13] have been employed to analyze these models. Though they

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work well, their efficiency still needs to be improved.

Among a large family of simplified models, one of the most prominent examples is the HP lattice model by Dill *et al*,[2−4] in which each amino acid is treated as a point particle on a regular (quadratic or cubic) lattice, and sequences consisting of two types of amino acids, hydrophobic and hydrophilic, are configured as self-avoiding walks on square and simple cubic lattices. The energy between any two neighboring non-bonded H residues (H–H) is defined as –1, but otherwise is 0. Being the most simplified and most popular model, the HP model only considers the interactions between neighboring non-bonded H residues, neglecting the other non-local effects caused by P–P, H–P and non-neighbored H–H pairs, which also exert significant statistical influence on the conformation of the residues in the properly folded state. To illustrate the influence of non-local effects on protein folding, Stillinger *et al* [14,15] studied a similar off-lattice AB protein model, where the hydrophobic residues were labeled by A and the polar or hydrophilic ones by B. Fibonacci sequences of A and B residues were studied using potentials including bending energy and Lennard–Jones energy. Though this model has no explicit representation of side chains or hydrogen bond, and provides only a coarse-grained approximation to the complexities of real proteins, its off-lattice construction and the use of both Lennard–Jones and bending energy contributions still enable it to capture some of the basic features of protein structure.

Based on the minimum free-energy theory,[16] many authors have developed various techniques to find the low-energy states of AB proteins, including neural networks,[14] conventional Metropolis type Monte Carlo procedures,[15] annealing contour Monte Carlo method,[17] simulated tempering,[18] biologically motivated methods,[19,20] multicanonical sampling,[21−23] the conformational space annealing[24] and off-lattice new pruned-enriched-Rosenbluth method with importance sampling.[25] For its two-dimensional (2D) version, the putative ground states for various AB sequences with various chain lengths are given in Refs.[14], [15], [17], [19] and [25], and for its three-dimensional (3D) version, the putative ground states for the four Fibonacci sequences with lengths of 13–55 amino acids have also been obtained in Refs.[23]–[25].

In this article, we study the 3D version of this model and propose a quite different class of heuristic algorithm for predicting the ground states of the AB proteins. The proposed algorithm integrates the well-known gradient method and some effective off-trap strategies including the neighborhood search mechanism. In order to improve the efficiency of our algorithm, a novel strategy of generating promising initial configuration is put forward. The numerical results show that the proposed methods are very effective for finding the ground states of AB proteins. Compared with other algorithms in the literature, our algorithm can find lower-energy states in several cases and each of the four resulting configurations has a single hydrophobic core.

2. The model

The AB model consists of hydrophobic (A) and hydrophilic (B) residues in Fibonacci sequences. The Fibonacci sequences are defined recursively by S_0=A, S_1=B, $S_{i+1} = S_{i-1} * S_i$. Here the asterisk denotes the concatenation operator. For example, the first few sequences are S_2=AB, S_3=BAB, S_4=ABBAB, and so on. They have lengths given by $n_{i+1} = n_{i-1} + n_i$, that is, given by the Fibonacci numbers. The present work will focus on the cases of $n = 13$, 21, 34 and 55.

In the AB model, n amino acid residues linked by rigid bonds of unit length form linear chain living in three-dimensional Euclidean space. The shape of n-mer is specified by the $n-2$ angles $\theta_2, \ldots, \theta_{n-1}$, where θ_i $(2 \le i \le n-1)$ denotes the supplementary angle of the bond angle at residue i and satisfies $-\pi \le \theta_i < \pi$. The energy function[23−25] is given as

$$\begin{aligned} E &= E_{\text{bend}} + E_{\text{nonb}} \\ &= \frac{1}{4}\sum_{i=2}^{n-1}(1-\cos\theta_i) \\ &\quad + 4\sum_{i=1}^{n-2}\sum_{j=i+2}^{n}[r_{ij}^{-12} - C(\zeta_i,\zeta_j)r_{ij}^{-6}]. \end{aligned} \tag{1}$$

Here r_{ij} is the distance between residues i and j (with $i < j$). Each ζ_i is either A or B, and $C(\zeta_i, \zeta_j)$ is $+1$, $+1/2$, and $-1/2$, respectively, for AA, BB, and AB pairs, giving strong attraction between AA pairs, weak attraction between BB pairs, and weak repulsion between A and B. The first sum runs over the $(n-2)$ angles θ_i $(2 \le i \le n-1)$ of successive bond vectors, and it is the bending energy. The second term partially competes with bending barrier by a potential of Lennard–Jones type, depending on the distance between residues nonadjacent along the chain.

The protein folding problem for the AB model can be formally defined as follows: given a amino acid residue chain $s = \zeta_1\zeta_2\zeta_3\ldots\zeta_n$, we try to find an energy-minimizing configuration of s, i.e., find $X^* \in C(s)$ so that $E(X^*) = \min\{E(X) \mid X \in C(s)\}$, where $C(s)$ is the set of all the valid configurations of s.

3. The methods

3.1. The gradient method

Imagine that all n residues involved in the model are smooth solids with the radius of 1/2 for each, marked by 1, 2,... , n and cast randomly in 3D Euclidean space. So the potential energy E is a known function of the coordinates $X = (x_1, y_1, z_1,\ldots, x_n, y_n, z_n)$ of all n residues with the constraint:

$$r_{i,i+1} = 1, \quad i = 1, 2, \ldots, n-1. \tag{2}$$

In order to remove constraint (2) and convert the constrained optimization problem into the unconstrained optimization problem, we conceive that there exists a spring with the original length 1 between the centers of the i-th and the $(i+1)$-th residues (i=1, 2,... , $n-1$). According to Hooks' law, the spring's elastic potential energy between two adjacent residues is proportional to the square of the length of the spring transformation. So the spring's elastic potential energy is as follows:

$$E_1 = \sum_{i=1}^{n-1} \frac{1}{2} k_1 (r_{i,i+1} - 1)^2,$$

where k_1 is physical coefficient characterizing the rigidities of all the springs.

In order to speed up the search for the ground states, we imagine that all n residues involved in the model are smooth elastic solids. When two different elastic residues are embedded into each other, the extrusive elastic potential energy between them is proportional to the square of the depth of their mutual embedment according to elasticity mechanism. So the extrusive elastic potential energy of this system constituted by n elastic residues is

$$E_2 = \sum_{i=1}^{n-1} \sum_{j=i+1}^{n} \frac{1}{2} k_2 d_{ij}^2 \ ,$$

where k_2 is a physical coefficient characterizing the rigidities of all the residues. d_{ij} is the embedding depth between the i-th and the j-th residues. If $r_{ij} < 1$, $d_{ij} = 1 - r_{ij}$, otherwise $d_{ij} = 0$.

By adding the spring's elastic potential energy and the extrusive elastic potential energy to the whole system, we can indicate the sum of potential energy as $U = E + E_1 + E_2$, where E_1 and E_2 are the penalty terms in the potential energy U. When the physical coefficients k_1 and k_2 are large enough, the optimal solution to the unconstrained optimization problem min $U(X)$ is also the optimal solution to the constrained optimization problems (1) and (2). At this time, constraint (2) is satisfied approximately and no two residues are embedded into each other. Thus, the protein folding problem of the AB model is converted into an unconstrained optimization problem of the known function $U(X)$.

For the unconstrained optimization problem min $U(X)$, we can employ a well-known optimization method, the gradient method, or the steepest descent method, to find low-energy configurations for a given amino acid chain. Assume that $X^{(0)}$ is the initial configuration for iterations. If the configuration $X^{(t)}$ $(t \geq 0)$ is not a local minimum, a new configuration $X^{(t+1)} = X^{(t)} - \lambda_t \nabla U^{(t)}$ is obtained in the anti-gradient direction of the energy function $U(X)$ at $X^{(t)}$, where λ_t is the iterative step length factor and $-\nabla U^{(t)}$ is the iterative search direction. Let $t = t+1$. From the updated configuration $X^{(t)}$, we repeat this course of iterations until a global energy minimum configuration $X^{(t+1)}$ is found, or a trap of local minimum $X^{(t+1)}$ ($\left|E^{(t+1)} - E^{(t)}\right| < 10^{-6}$, where $E^{(t+1)}$ denotes the energy at $X^{(t+1)}$) occurs. In the latter case, if the energy $E^{(t+1)}$ is not less than target energy, a completely new round of the gradient descent minimization should be initiated from a new initial configuration. In our simulation of computation, we let $\lambda_0 = 0.5 \times 10^{-6}$, $k_1 = k_2 = 1000$.

In order to foster tight hydrophobic core, when calculating the gradient ∇U in iterations, we modify the Lennard–Jones potential through multiplying it by a physical constant $k_3 = 10000$, meaning the Van Del Waals interaction coefficient. In the beginning of the calculation, a large value of k_3 is taken so as to increase the Van Del Waals interaction force of the system and make A residues 'embrace' tightly together. Along with the increment in the calculating steps, its value decreases gradually through multiplying it by the factor 0.7 per 50000 iterative steps until $k_3 < 2$. In the course of execution, another trick is to modify the physical coefficients k_1, k_2 through

multiplying each by the factor 1.3 per 50000 iterative steps, and in the later stage of calculation, or when $\left|E^{(t+1)} - E^{(t)}\right| < 10^{-3}$, to modify k_1, k_2 through multiplying each by the factor 1.1, and to decrease step size λ_t through multiplying it by a step shrinking factor 0.9 per 50000 iterative steps. So, during the beginning of the calculation, the physical coefficients of all the springs and residues are small enough so that all residues can move freely and attain easily low-energy states. Thereafter, along with the execution of calculation, the physical coefficients k_1, k_2 increase gradually so as to increase the "penalty", and make constraint (2) satisfied gradually and no two residues imbedded into each other. Finally, the interactions of springs disappear and constraint (2) is satisfied naturally. At this time, an optimum or approximate solution to the AB model is found.

3.2. The heuristic gradient algorithm

It is often possible for the gradient method to get struck in the course of execution, that is, the calculation falls into the trap of local energy minima. To jump out of local minima, enlightened by the configurations of real protein molecules, where all A residues foster tight hydrophobic cores, we can pick out all B residues squeezed among A residues, and place them in certain spots in 3D space to speed up the lowest-energy state search. The concrete description of the off-trap strategy is as follows: (i) Calculate the center of all A residues; (ii) Compute the distance from the center to every A residue, signing the greatest distance as d; (iii) Calculate respectively the distance from every B residue to the center. Our strategy is that for every B residue, as long as the distance $< d$, it will be picked and placed somewhere three times the distance away from the center, along the vector direction from the center to the B residue picked. Keeping all A residues and the rest of B residues at their current positions, we can obtain a new configuration, where in addition to the changes of bending energy and elastic potential energy, long-range Lennard–Jones interactions of the residues, with the changing of their relative position to each other, have to be computed anew after the update.

By integrating the off-trap strategy into the gradient method, we gain a heuristic gradient algorithm. The calculation is executed by using the gradient algorithm until a certain minimum configuration is reached. The local minimum energy E is saved. If now the energy E is lower than the target value and the system is satisfied with constraint (2), the computation will terminate, otherwise the calculation point will jump to a new position through the off-trap strategy and the computation will proceed with the gradient method until a new local minimum or optimal configuration is found. If the off-trap strategy is repeated up to ten times and the simulation does not find states with lower energy than the target value, we execute the following neighborhood search mechanism near the lowest-energy state X^* found by ten rounds of the heuristic gradient minimization.

3.3. Neighborhood search mechanism

In order to search for the lower-energy states near local minimum point X^*, we compute respectively the potential energy of each A residue and assume the mark of the residue with the highest energy is i. Then we change randomly the positions of residue i and one of its two adjacent residues along the chain by probability $|u_k|/(|u_{i-1}| + |u_{i+1}|)$, $k = i-1$, $i+1$, where u_k denotes the potential energy of residue k. Without the loss of generation, we suppose that the chose residue is $i-1$. The concrete procedure of the neighborhood search mechanism is to construct a neighboring configuration $X' = (x_1^*, y_1^*, z_1^*, \ldots, x'_{i-1}, y'_{i-1}, z'_{i-1}, x'_i, y'_i, z'_i, \ldots, x_n^*, y_n^*, z_n^*)$ of the configuration $X^* = (x_1^*, y_1^*, z_1^*, \ldots, x_{i-1}^*, y_{i-1}^*, z_{i-1}^*, x_i^*, y_i^*, z_i^*, \ldots, x_n^*, y_n^*, z_n^*)$, where $X'_j = (x'_j, y'_j, z'_j)$ $(j = i-1, i)$ in the configuration X' is the replacement of the position vector $X_j^* = (x_j^*, y_j^*, z_j^*)$ of residue j in the configuration X^*. $X'_j = X_j^* + m \times s$, where m is the random number between –1 and +1, and $s = 1/100$ is the scale of the neighborhood of X_j^*.

From the updated configuration X', we execute the gradient algorithm until a new local minimum or optimal configuration is found. The neighborhood search mechanism is repeated until the simulation cannot find lower-energy states. If the lowest energy found is lower than the target energy and the system is satisfied with constraint (2), the energy will be scored and the simulation will terminate. Otherwise we randomly choose another initial configuration and execute a new round of the heuristic gradient algorithm with neighborhood search mechanism, which is called the HG algorithm for short.

4. The calculating results and comments

We implement the HG algorithm in C++ language on a Pentium IV, 2.0 GHz computer. Following Refs.[23]–[25], in this article we consider the sequences with lengths n = 13, 21, 34, and 55, which are listed in Table 1.

Table 1. The four Fibonacci sequences in the AB model.

n	sequence ("B_2" for BB)
3	$AB_2AB_2ABAB_2AB$
21	$BABAB_2ABAB_2AB_2ABAB_2AB$
34	$AB_2AB_2ABAB_2AB_2ABAB_2ABAB_2AB_2ABAB_2AB$
55	$BABAB_2ABAB_2AB_2ABAB_2ABAB_2AB_2ABAB_2AB_2ABAB_2ABAB_2AB_2ABAB_2AB$

To locate the global energy minimum for a given amino acid residue chain, we apply the improved version called new PERM with importance sampling (nPERMis)[11] of the celebrated chain-growth algorithm, pruned-enriched-Rosenbluth method (PERM),[26] to the face-centered-cubic (FCC) lattice to produce initial configuration.

nPERMis has been applied successfully to the HP model on the square and simple cubic (SC) lattices.[11] Reference [25] gives an off-lattice nPERMis variant that is efficient for energy minimization in the AB model. Now we apply nPERMis to the FCC-lattice to acquire initial configurations, which are close to the wanted off-lattice ones. FCC-lattice nPERMis is a simple generalization of SC-lattice nPERMis.[11] Their difference only consists of lattice type. A single FCC-lattice contains not only every corner common to SC-lattice type but also the center of each of the six cube faces. So, on FCC-lattice, the residue to be placed has at most 12 "candidate directions" for the next step, but on SC-lattice, at most 6.

After employing FCC-lattice nPERMis to produce the initial configuration for each amino acid residue chain, we execute the HG algorithm to optimize low-energy configurations. The calculating results show that along with the increment in the calculation steps, at last all residues will tend to be stable. For each of the four configurations that are the solution to the problem, constraint (2) is satisfied approximately. The error margin is smaller than 10^{-6}, that is: $\mid r_{i,i+1} - 1 \mid < 10^{-6}$ $(i = 1, 2, \ldots, n-1)$.

For each sequence, the HG algorithm is run for ten times independently. The lowest energies found by HG for all four Fibonacci sequences are listed in Table 2, along with the values reported in the literature by off-lattice nPERMis (PERM+),[25] multicanonical (MUCA) sampling[23] and the energy landscape paving (ELP) method[23] for comparison. Our results are better than those of the PERM+ for all cases, with the energy difference increasing gradually for longer chains, and are also slightly better than those by MUCA and ELP. We also compare our results with minimum energies listed in Ref.[24] obtained by the conformational space annealing (CSA) method. Table 2 shows that HG runs slightly lower energies for the sequence with 55 residues, while the results for those with 13–34 residues are consistent with the corresponding results by CSA with a difference of less than 0.1%. Furthermore, we execute the gradient (GRAD) algorithm with the neighborhood search mechanism but without off-trap strategy. The lowest energies found by GRAD over ten independent runs are also listed in Table 2, in comparison with those by PERM+, MUCA, ELP, CSA, and HG. Table 2 shows that GRAD obtains worse results than MUCA, ELP, CSA, and HG, but better than PERM+.

Table 2. Estimates for global energy minima obtained by HG and GRAD for the AB model with the four Fibonacci sequences, in comparison with those by PERM+, MUCA, ELP, and CSA, respectively.

n	$E_{\min}^{\mathrm{PERM+}}$ (Ref.[25])	$E_{\min}^{\mathrm{MUCA}}$ (Ref.[23])	$E_{\min}^{\mathrm{ELP}}$ (Ref.[23])	$E_{\min}^{\mathrm{CSA}}$ (Ref.[24])	$E_{\min}^{\mathrm{GRAD}}$	$E_{\min}^{\mathrm{HG}}$
13	–4.9616	–4.967	–4.967	–4.9746	–4.9644	–4.9746
21	–11.5238	–12.296	–12.316	–12.3266	–11.9612	–12.3238
34	–21.5678	–25.321	–25.476	–25.5113	–22.7516	–25.5063
55	–32.8843	–41.502	–42.428	-42.3418	–40.9713	–42.4817

Figure 1 displays the lowest-energy configurations produced by the HG simulations. It should be noted that the configuration for $n = 55$ obtained by PERM+ contains two clearly disjointed hydrophobic cores, while our results form a single hydrophobic core, and agree well with what comes out in Refs.[23] and [24]. With it, we can draw out a conclusion that the AB model in three dimensions with Fibonacci sequences displays the important feature of forming a single hydrophobic core as observed in real proteins.

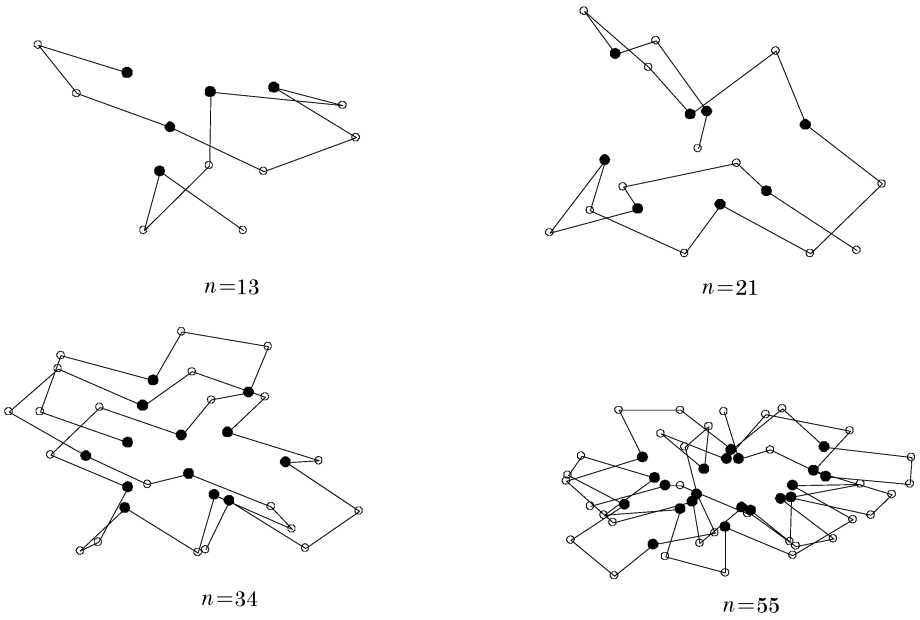


Fig.1. Stereographic views of the putative ground states of the four Fibonacci sequences listed in Table 1, found by applying the HG algorithm to the 3D AB model. Full dots and empty circles indicate hydrophobic and hydrophilic residues, respectively.

5. Summary and anticipation

In this article, we study a coarse-grained off-lattice protein AB model consisting of two types of residues, A and B, which behave as hydrophobic and hydrophilic residues, respectively. The spring's elastic potential energy and the extrusive elastic potential energy are introduced into the original potential function to convert the protein folding problem of the AB model into an unconstrained optimization problem which can be solved by the gradient method. Since the gradient method is only a local search algorithm, it is possible for the gradient method to fall into the trap of local minima. The effective off-trap strategy and neighborhood search mechanism are then proposed to get out of local minima and search for the lower-energy states. The proposed methods are applied to the AB model with Fibonacci sequences to optimize low-energy configurations. It is found that the putative ground state energies obtained by HG are lower than or comparable to the best values reported in the literature. In all cases, the ground state configurations obtained by the HG simulation form single hydrophobic cores. Based on this, it is concluded that the AB model with Fibonacci sequences in three dimensions mimics the real protein reasonably well.

In our future work, we hope to apply the methods proposed in this article to all-atom models with realistic potential by combining it with simulated annealing or with genetic methods, and design various kinds of more high-performance heuristic algorithms for the protein folding problem.

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