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AN IMPROVED PARTICLE SWARM OPTIMIZATION ALGORITHM FOR PROTEIN STRUCTURE PREDICTION BASED ON AB MODEL

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ABSTRACT

An improved particle swarm optimization algorithm, which combines the idea of simulated annealing algorithm and opposition-based learning strategy, is presented for NP-hard protein structure prediction based on AB model. Flying grain is used to control the neighborhood structure of particle, so particle can search the global optimum in solution space more finely. An opposition-based learning is used to keep the diversity of swarm and improve the algorithm's ability to escape from local optima. Furthermore, the Metropolis criterion of simulated annealing algorithm is used to balance the exploitation and exploration ability. Simulation results show that those strategies can improve the performance of the proposed algorithm effectively.

Keywords: *Particle Swarm Optimization, AB Model, Protein Structure Prediction, Simulated Annealing Algorithm, Opposition-Based Learning, Flying Grain*

1. INTRODUCTION

Protein structure prediction (PSP) problem is regarded as one of the oldest, most important, yet a highly challenging problem both for the biology and for the computational communities[1]. Solution of this problem would have an enormous impact on medicine and the pharmaceutical industry, since successful tertiary structure prediction, given only the amino acid sequence information, would allow the computational screening of potential drug targets. The main difficult of this problem is the computing complexity for finding the configuration with minimum energy. PSP methods must explore the space of possible protein structures which is astronomically large. Several models, such as hydrophobic/polar (HP) model[2] and off-lattice toy (AB) model[3], were proposed to simplify the structure of proteins. Despite the simplicity of HP model and AB model, both of them are NP-hard problem. Several heuristics algorithm have been successfully applied to AB model, such as simulated annealing (SA) algorithm[4], hybrid evolutionary algorithm[5], genetic annealing algorithm[6], quantum clonal selection algorithm[7], particle swarm optimization (PSO) algorithm[8-11] and differential evolution (DE) algorithm[12] etc.

PSO algorithm is a stochastic population based optimization algorithm, first published by Kennedy and Eberhart in 1995[13, 14]. In PSO, each particle of the population has a position and a velocity, according to which it moves in the search space. Moreover, each particle has a memory, remembering the best position of the search space it has ever visited. Particles fly through hyper-dimensional search space, with each particle being attracted towards the best solution found by the particle's neighborhood and the best solution found by itself. For multi-dimensional function problem, classical PSO algorithm updates all dimensions' data. This strategy may deteriorate PSO's intensification ability because different dimensions may interfere with each other. In order to tackle the dimensions interference problem and to improve algorithm's intensification ability, Zhong et al. proposed a novel PSO algorithm with iterative improvement strategy (PSO_{IIS}) which updates and evaluates velocity and position dimension-by-dimension[15]. Because different problem has different features, evaluating solution dimension-by-dimension and greedy accepting strategy may drive particle into local optima quickly. In order to deal with this problem, this paper proposes an improved PSO algorithm, which is inspired by the idea of SA algorithm and Opposition-based Learning (OBL) strategy. In the proposed algorithm, flying grain (FG) is defined to control the neighborhood structure of particle, Metropolis criterion of SA algorithm is used to decide whether

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to accept new velocity and position, and OBL is used to enhance the chance to escape from local optima. We analyze the performance of our algorithm on 2D PSP based on AB model.

The remainder of this paper is organized as follows: Section 2 provides a short description of PSP problem based on 2D AB model and PSO algorithm. Section 3 presents our proposed PSO algorithm with Metropolis criterion and OBL strategy. Section 4 gives the experimental approach and results of experiments carried on a Fibonacci sequence and four real protein sequences. Finally, section 5 summaries the study.

2. PRELIMINARIES

2.1 Protein Structure Prediction Problem

Although a protein is formed by a combination of 20 possible standard amino acids, AB model incorporates only two "amino acids", to be denoted by A and B, in place of the 20 that occur naturally. In 2D AB model, A represents hydrophobic amino acids and B represents hydrophilic amino acids. They are linked together by rigid unit-length (distance = 1) bonds to form linear unoriented polymers that reside in two dimensions. For any protein structure composed by *N*-monomers represented with the AB model, *N*-2 bend angles will be needed. These angles are defined in the range $-\pi \le \theta_i \le \pi$. Figure 1 is the representation of a hypothetical protein composed by nine amino acids, each one bonded to the next in the chain.

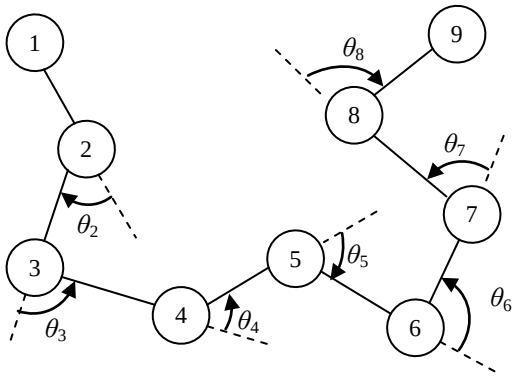

Figure 1: Generic Representation Of A Hypothetic 9-mers Protein Structure With Its Bended Angles

The energy function for a protein structure with *N* monomers (*N*-mers) is given by equation (1):

$$\phi = \sum_{i=2}^{N-1} V_1(\theta_i) + \sum_{i=1}^{N-2} \sum_{j=i+2}^{N} V_2(d_{ij}, \xi_i, \xi_j) \quad (1)$$

This energy function postulates that two kinds of interactions compose the intermolecular potential energy for each molecule: Backbones bend potentials (V_1) and non-bonded interactions (V_2). The former is independent of the *A*, *B* sequence, while the latter vary with that sequence and will receive a contribution from each pair of residues not directly attached by a backbone bond.

The backbone potential (V_1) has a simple trigonometric form as follows:

$$V_1(\theta_i) = 1/4 \cdot (1 - \cos\theta_i) \quad (2)$$

The residue pair interactions (V_2) which only operate between unlinked residues possess a species-dependent Lennard-Jones form as follows:

$$V_2(d_{ij}, \xi_i, \xi_j) = 4 \cdot \left(d_{ij}^{-12} - C(\xi_i, \xi_j) \cdot d_{ij}^{-6}\right) \quad (3)$$

$$C(\xi_i, \xi_j) = 1/8 \cdot (1 + \xi_i + \xi_j + 5 \cdot \xi_i \cdot \xi_j) \quad (4)$$

where d_{ij} is the distance between residues *i* and *j*, and the discrete variables ξ_i denote residue species as follows:

$$d_{ij} = \left\{ \left[1 + \sum_{k=i+1}^{j-1} \cos \sum_{l=i+1}^{k} \theta_l \right]^2 + \left[\sum_{k=i+1}^{j-1} \sin \sum_{l=i+1}^{k} \theta_l \right]^2 \right\}^{\frac{1}{2}} \quad (5)$$

$$\xi_i(A) = +1, \quad \xi_i(B) = -1 \quad (6)$$

Therefore the coefficient $C(\xi_i, \xi_j)$ is +1 for an *AA* pair, +1/2 for a *BB* pair, and -1/2 for an *AB* pair. Consequently the first of these pairs may be regarded as strongly attracting, the second as weakly attracting, and the third as weakly repelling. This diversity mimics in a simple way that of real amino-acid residues, which vary in size, polarity, and degree of hydrophobicity.

2.2 Particle Swarm Optimization Algorithm

There are two variants of the PSO algorithm. One has a global neighbourhood, and the other has a local neighbourhood. In the global variant, each particle moves towards its best previous position and towards the best particle in the whole swarm. In the local variant, each particle moves towards its best previous position and towards the best particle in its specified neighbourhood. Suppose that the search space is *N*-dimensional, then the *i*th particle of the swarm can be represented by an *N*-

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dimensional vector, $\mathbf{X}_i = (x_{i1}, x_{i2}, ..., x_{iN})$. The velocity of this particle, which represents the position change of this particle, can be represented by another N-dimensional vector $\mathbf{V}_i = (v_{i1}, v_{i2}, ..., v_{iN})$. The best previously visited position of the ith particle is denoted as $\mathbf{P}_i = (p_{i1}, p_{i2}, \ldots, p_{iN})$. For the global variant, the best previously visited position of the swarm is $\mathbf{G} = (g_1, g_2, ..., g_N)$, and let the superscripts denote the iteration number, then each particle is manipulated according to the following two equations:

$$v_{ij}^{t+1} = wv_{ij}^{t} + c_1 r_1 (p_{ij}^{t} - x_{ij}^{t}) + c_2 r_2 (g_j^{t} - x_{ij}^{t}) \quad (7)$$

$$x_{ij}^{t+1} = x_{ij}^{t} + v_{ij}^{t+1} \quad (8)$$

where j =1, 2, ..., N; i =1, 2, ..., M, and M is the size of the swarm; w is called inertia weight, which is used to control the impact of the previous history of velocities on the current velocity, thus to influence the trade-off between global and local exploration abilities of the particle; c_1, c_2 are two positive constants, called cognitive and social parameter respectively; r_1, r_2 are random numbers, uniformly distributed in [0, 1]; and t =1, 2, ..., determines the iteration number. Equation (7) is used to calculate the particle's new velocity according to its previous velocity and the distances of its current position from its own best previously visited position and the global best experience. Then the particle flies toward a new position according to equation (8). Parameter w, c_1 and c_2 control particle's learning from its previous velocity, its history best position and the best position of its neighbors respectively.

3. IMPROVED PSO ALGORITHM

3.1 Flying Grain and Metropolis Criterion

We define flying grain (FG) as the number of dimensions which particle updates using equation (7) and (8). In a classical PSO algorithm, FG is equal to the dimension of problem. In PSO_{IIS} algorithm, the FG is equal to 1. After a particle has updated its velocity and position, classical PSO algorithm will accept the new velocity and position blindly, it means that the new values will be accepted always, regardless of whether they are better or worse than their original values. In PSO_{IIS} algorithm, greedy strategy is used to decide whether to accept the new values or not. It means only those better new values will be accepted. Greedy strategy may decrease the explorability, opposite velocity is introduced in PSO_{IIS} to keep the diversity of swarm. Aims to get better balance between explorability and exploitability, we try to find a suitable FG for PSP problem based on AB model. And we use the Metropolis criterion of SA algorithm to decide whether to accept the new velocity and position or not. It means that particle will accept better solutions unconditionally, and it will accept those worse solutions with a probability. Suppose the energy difference between new solution and old solution is ΔE and the current temperature is t, the accepting probability is equal to $\exp(-\Delta E/t)$.

3.2 Opposition Rotation Based Learning

Even though the Metropolis criteria, which allows particle to accept worse solutions, can enhance the explorability of PSO algorithm, flying to particle's best position and the global best position may move all particle to local optima easily and decrease the diversity of swarm quickly. Aims to overcome this shortage and consider that for PSP problem, each data x represents an angle θ in the range $[-\pi, \pi]$, we propose a novel OBL strategy, named as opposition-rotation-based learning (ORBL). Suppose the current position is x and personal best position is p, particle will use velocity equation to calculate angular velocity $c_1 r_1(\theta_p - \theta)$; and then it will rotate to p in counter-clockwise direction as showed in figure 2 (a). In fact, x can rotate to p in two different directions, clockwise or counter-clockwise. Inspired by this, we define an opposite rotation as rotation in clockwise direction as showed in figure 2 (b). Similarly, suppose the global best position is g, beside the angular velocity $c_2 r_2(\theta_g - \theta)$ in counter-clockwise direction, we can define another opposite rotation which rotates to g in clockwise direction as showed in figure 2 (c) and (d).

The combination of $\pm c_1 r_1(\theta_p - \theta)$ and $\pm c_2 r_2(\theta_g - \theta)$ will produce four values. ORBL strategy will take into account those four values at the same time. Unlike in classical OBL strategy, where greedy strategy is used to decide which value is to be selected, ORBL uses a random strategy. Which means ORBL will select a value randomly from the four values. For PSP problem, this strategy can balance intensification and diversification ability of PSO algorithm better. To use ORBL strategy in PSO algorithm, we can use a different strategy to produce random r_1 and r_2. Unlike in classical PSO algorithm, where r_1 and r_2 are random numbers uniformly distributed in [0, 1], in ORBL, they are random numbers uniformly distributed in [-1, 1].

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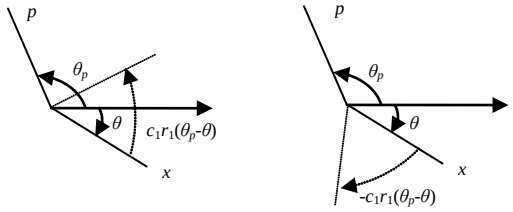

(a) Rotate to personal best in counter-clockwise direction

(b) Rotate to personal best in clockwise direction

(c) Rotate to global best in counter-clockwise direction

(d) Rotate to global best in clockwise direction

Figure 2: Rotation And Opposition Rotation

3.3 Pseudo Code of Improved PSO Algorithm

Algorithm 1 is the pseudo code of our improved PSO algorithm. Where *x*, *v*, and *pb* are all 2-dimensional arrays. The *x* represents positions of all particles, *x*[*i*] represents the position of *i*th particle, and *x*[*i*][*j*] represents the *j*th dimensional position of *i*th particle. Similarly, the *v* represents velocities of all particles, *v*[*i*] represents the velocity of *i*th particle, and *v*[*i*][*j*] represents the *j*th dimensional velocity of *i*th particle. The *pb* represents best previously visited positions of swarm, *pb*[*i*] represents the best previously visited position of *i*th particle, and *pb*[*i*][*j*] represents the *j*th dimensional value of best previously visited position of *i*th particle. Variable *gb* is a 1-dimensional array, which represents the best previously visited position of swarm. Function Energy is used to calculate the energy of a structure specified by the position of particle. For cooling scheme of Metropolis criteria, we use the most often used exponential annealing.

Algorithm 1 Improved PSO algorithm

1. Initialize parameters w, c_1, c_2, fg and t_0;
2. For each particle i = 1 to M
3. Generate position $x[i]$ and velocity $v[i]$ randomly;
4. $pb[i] = x[i]$; //personal best position
5. End for
6. gb = findBest(x); //global best position
7. $t = t_0$; //initial temperature
8. While (End condition is not met)
9. For each particle i = 1 to M
10. For each dimension j =1 to N
11. $k = j$;
12. $nx = x[i]$; //new candidate position
13. For f = 1 to FG //flying grain
14. generate $r1$ and $r2$ between [-1, 1] randomly;
15. calculate the kth dimension velocity $v[i][k]$;
16. calculate the kth dimension position $nx[i][k]$;
17. $k = (k+1) \% N$;
18. End For
19. ΔE = Energy($nx[i]$) – Energy ($x[i]$);
20. If ($\Delta E < 0$ OR random() < exp($-\Delta E / t$)) Then
21. $x[i] = nx[i]$;
22. End if
23. End For
24. If ($x[i]$ is better than $pb[i]$) Then $pb[i] = x[i]$;
25. If ($x[i]$ is better than gb) Then $gb = x[i]$;
26. End for
27. $t = at$ //cooling scheme
28. End while
29. Return gb

4. EXPERIMENTS AND RESULTS

4.1 Analysis on Fibonacci Sequence

We analyze the proposed PSO algorithm using a benchmark Fibonacci sequence with 13 residues as showed in table 1. In this table, there are also results obtained by other authors using different methods. E_{min} is the minimum energy obtained by the conformational space annealing algorithm[16] and annealing contour Monte Carlo algorithm[17]. E_{LAGAA} is obtained by a genetic-annealing algorithm with local adjustment mechanism[6]. E_{Seq} and $E_{DE\text{-}RI}$ is obtained by sequential and parallel DE with ring-island (RI) topology[12]. In order to find the suitable FG and cooling coefficient a, we fix other parameters as follows: w=0.7, c_1=c_2=2.0, t_0=1 and M=10. The maximum iteration times is 3000, so the total function evaluation times is 3000*10*N, which is same as in literature [8] and far less than in literature [12]. In the simulation, we change a from 0.990 to 1.000 at increments of 0.001 and change FG from 1 to 4 at increments of 1. For each combination of a and FG, we run PSO algorithm 30 times. Table 2 and table 3 are the average energy and best energy of the simulation results. In table 2 and table 3, each row means different cooling coefficient and each column means different flying grain. Those results show that: (1) Comparing different FG, our algorithm has best performance when FG is equal to 2. As showed in second column of table 2 and table 3, among the 10 different a, our algorithm has best performance in 7 cases in terms of average solution and best solution respectively, and it found the best known solution in 4 cases; (2) Comparing different a, our algorithm has best performance in terms of average

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solution when *a* is equal to 0.997, and has best performance in terms of best solution when *a* is equal to 0.996. Among 4 different FG, our algorithm found the best known solution in 3 cases when *a* is equal to 0.996.

Table 1: Benchmark Fibonacci Sequence Of Length 13

Sequence	E_{min}	E_{LAGAA}	E_{Seq}	E_{DE-RI}
ABBABBABABBAB	-3.2941	-3.2940	3.1990	-3.2924

Table 2: Average Solution Under Different Cooling Coefficient And Different Flying Grain

a	*FG* = 1	*FG* = 2	*FG* = 3	*FG* = 4
0.990	-2.5813	-3.0588	-3.0506	-2.9350
0.991	-2.5852	-2.9318	-3.0363	-2.9589
0.992	-2.7322	-3.0619	-3.0554	-2.9984
0.993	-2.8013	-3.0953	-3.1359	-3.0494
0.994	-2.8069	-3.1654	-3.1293	-3.0623
0.995	-2.8785	-3.1955	-3.1184	-3.0711
0.996	-3.0268	-3.1967	-3.1892	-3.1416
0.997	-3.1051	-3.2048	-3.2041	-3.1621
0.998	-3.1535	-3.1995	-3.1969	-3.1545
0.999	-3.0498	-3.1318	-3.1323	-3.0930

Table 3: Best Solution Under Different Cooling Coefficient And Different Flying Grain

a	*FG* = 1	*FG* = 2	*FG* = 3	*FG* = 4
0.990	-3.1774	-3.1983	-3.2575	-3.1987
0.991	-3.1666	-3.2941	-3.1990	-3.2234
0.992	-3.1810	-3.2938	-3.2235	-3.1989
0.993	-3.1881	-3.2758	-3.2938	-3.1990
0.994	-3.2877	-3.2941	-3.1990	-3.1990
0.995	-3.2941	-3.2941	-3.2941	-3.1990
0.996	-3.2940	-3.2941	-3.2941	-3.2941
0.997	-3.2939	-3.2938	-3.2939	-3.2935
0.998	-3.2880	-3.2921	-3.2911	-3.1968
0.999	-3.2091	-3.2441	-3.2352	-3.2430

In order to analyze the effect of Metropolis criterion and ORBL, we compare the performance of PSO algorithm with or without those strategies. According to the results of table 2 and table 3, we set *FG*=2 and *a*=0.996. Table 4 is the simulation results of those PSO algorithms. In table 4, PSO is the basic PSO algorithm where FG is equal to *N*. PSO_{SA} is PSO algorithm with Metropolis criterion of SA only, PSO_{ORBL} is PSO algorithm with ORBL strategy only, and $PSO_{SA+ORBL}$ is PSO algorithm with Metropolis criterion and ORBL strategies both. In those tables, ALIG is average last improving generation, which means algorithm will never find better solution after that. Those results show that: (1) although the bigger ALIG means PSO algorithm is not easily trapped into local optima, both average solution and best solution are not good enough. The blind accept strategy and the interference between different dimensions may deteriorate the intensification ability of PSO algorithm; (2) When Metropolis criterion or ORBL strategy is used independently, the performance is not good enough also. The small ALIG means PSO_{SA} and PSO_{ORBL} algorithm are easily trapped into local optimum. When both Metropolis criterion and ORBL strategy are used, $PSO_{SA+ORBL}$ algorithm has best performance.

Table 4: Performance Comparison Of PSO With Different Strategies

Algorithm	Average	Best	Worst	ALIG
PSO	-2.0030	-2.7519	-1.4047	2789
PSO_{SA}	-2.0053	-2.9023	-1.3439	1333
PSO_{ORBL}	-2.3052	-3.1633	1.7157	1854
$PSO_{SA+ORBL}$	-3.1967	-3.2941	-2.4928	2935

Figure 3 is the iteration process of average energy of algorithm PSO, PSO_{SA}, PSO_{ORBL} and $PSO_{SA+ORBL}$. Figure 3 shows that: (1) although basic PSO has persistent optimizing ability, but the convergence speed is slow; (2) PSO_{ORBL} has good convergence speed, but it will lose optimizing ability quickly. $PSO_{SA+ORBL}$ has good persistent optimizing ability; (3) although $PSO_{SA+ORBL}$ is far better than PSO_{SA} and PSO_{ORBL}, its optimizing speed becomes very slow in the late stage.

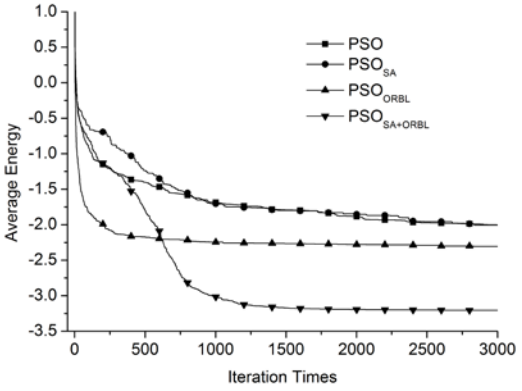

Figure 3: Iteration Process Of Average Energy With Different Strategies

4.2 Performances on Real Protein Sequences

To further analyze the performance and compare the performance with other algorithm, we test PSA algorithm on four real protein sequences as in [8]. Those four sequences are listed in table 5; detail information can be downloaded from PDB (http://www.rcsb.org/pdb/). In the experiments, K-

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D method is used to distinguish hydrophobic and hydrophilic residues of 20 amino acids in real proteins. Briefly speaking, amino acids I, V, L, P, C, M, A, G are hydrophobic and D, E, F, H, K, N, Q, R, S, T, W, Y are polar. Table 5 is the data about those four real protein sequences. In this table, there are also results obtained by other authors using different methods. E_{LAGAA} is obtained by a genetic-annealing algorithm with local adjustment mechanism[6]. E_{SPPSO} is obtained by stochastic perturbation PSO combining with hill climbing algorithm[8].

Table 6 is the simulation results of $PSO_{SA+ORBL}$ algorithm on 1BXP, 1BXL, 1EDP and 1EDN respectively. Table 5 and table 6 show that $PSO_{SA+ORBL}$ algorithm has better performance than E_{LAGAA} and E_{SPPSO} algorithm on all four sequences. It is worth to mention that our algorithm does not use hill climbing algorithm to improve the found solution, so the function evaluation times of our algorithm is less than SPPSO algorithm. The big ALIG means $PSO_{SA+ORBL}$ has persistent optimizing ability.

Table 5: The Four Real Protein Sequence Used In Our Experiment

PDB ID	*N*	Sequence	E_{LAGAA}	E_{SPPSO}
1BXP	13	MRYYESSLKSYPD	-2.2448	-2.4902
1BXL	16	GQVGRQLAIIGDDINR	-8.7469	-8.5731
1EDP	17	CSCSSLMDKECVYFCHL	-5.6072	-6.7081
1EDN	21	CSCSSLMDKECVYFCHLDIIW	-7.0961	-8.6495

Table 6: Results Obtained By $PSO_{SA+ORBL}$ Algorithm

PDB ID	Average	Best	Worst	ALIG
1BXP	-2.2896	-2.4902	-2.1119	2972
1BXL	-8.5161	-8.8126	-7.7829	2949
1EDP	-6.7877	-6.9504	-6.4063	2972
1EDN	-8.1118	-8.6716	-7.7062	2981

In order to evaluate visually the quality of the minimum energy configurations found by this paper, the best results were used to draw the planar form of the sequence. Figure 4 (a), (b), (c) and (d) show the minimum energy configurations found for 1BXP, 1BXL, 1EDP and 1EDN respectively. In figure 4, filled circles represent 'A' monomers and the unfilled circles represent 'B' monomers. It is easy to see that the hydrophobic (A) monomers form one hydrophobic core in the 2D AB model for 1BXP, 1BXL and 1EDP, and form two cores for 1EDN. This can be explained by the fact that hydrophobic monomers are always flanked by the hydrophilic monomers along the sequence.

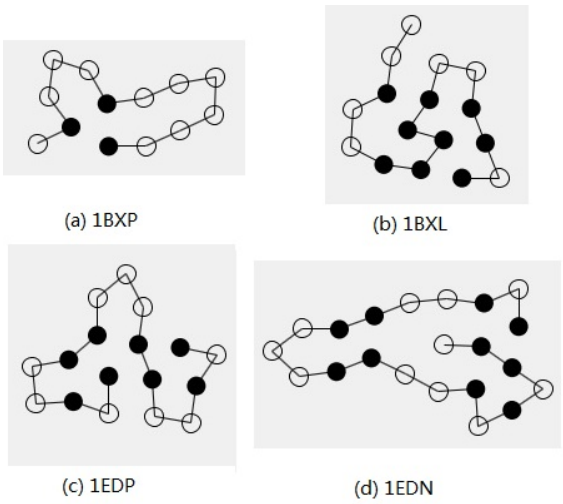

Figure 4: Minimum Energy Configurations Found By The Proposed Algorithms

5. CONCLUSION AND FUTURE WORK

This paper introduces a improved PSO algorithm for 2D protein structure prediction based on AB model. Aims to deal with the interference phenomena between different dimensions, we use flying grain to control the neighborhood structure of particle, so particle can search the solution space more finely. In AB model, the range of each dimension is in $[-\pi, \pi]$, which can be processed as a finite and unbounded circle. Inspired by this feature, we introduce the ORBL strategy to enhance the chance to escape from local optima. Metropolis criterion is combined into our algorithm. Those strategies can improve the balance between intensification and diversification significantly. The experiment simulations, which were carried on four real protein sequences, indicate that the proposed algorithm is promising.

Due to the high complexity of energy function of AB model, we ran the proposed algorithms on short proteins only; further study can be done on the implementation of parallel $PSO_{SA+ORBL}$ algorithms and its application on 2D and more complex 3D AB model for long protein sequences.

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