A MEMETIC ALGORITHM FOR PROTEIN STRUCTURE PREDICTION BASED ON THE 2D TRIANGULAR LATTICE MODEL

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Keywords: Protein structure prediction, HP model, 2D triangular lattice model, Memetic algorithm.

Abstract: Proteins play fundamental and crucial roles in nearly all biological processes, such as, enzymatic catalysis, signaling transduction, embryonic development, and DNA and RNA synthesis. The main function of the protein is decided by its structure. Therefore, many researchers are interested in the prediction of protein structure. The HP model is one of the commonly used models. But most research on the HP lattice model focuses on how to solve the problem of optimization and ignores the purpose of protein structure prediction, namely the prediction of structure similarity between proteins. The 2D triangular lattice model used in this study can predicate protein structure more closely to its topology compared to the 2D square model commonly used in the past. Besides proposing an effective memetic algorithm (MA), this study also investigated structure similarity of natural proteins.

1 INTRODUCTION

The HP model (Lau and Dill, 1989) is a simplified model which has become very popular

However, most researchers define the protein folding or the protein structure prediction problems as optimization problems. Therefore, these researchers have favoured and focused research on the 2D square or 3D cubic lattice model because they have many associated benchmarks, large amounts of data accumulated over the years, and the availability of comparison with different strategies and modeling methods. But what is ignored from their studies is the main purpose of the protein structure prediction: the similarity of protein structures.

This study proposed a memetic algorithm (MA) for protein structure prediction based on 2D triangular lattice model. Our experimental results show that the method developed in this study could get lower free energy more effectively than previous studies by other groups. This study further compared the similarity of the Lattice Mode model and also compared the result with the 3D face-centered-cubic (FCC) lattice model for similarity. From the result of numerical analysis, the 2D triangular lattice model used in this study was shown to be better than the 3D FCC lattice on the prediction of the protein structure with short sequences. This investigation has not been probed into before by other researchers.

2 PRELIMINARIES

2.1 HP Model

In this model, each amino acid is classified based on its hydrophobicity as either an H (hydrophobic or non-polar) or a P (hydrophilic or polar). The HP lattice model allows HP protein sequences to be configured as self-avoiding walks (SAW) on the lattice path favoring an energy free state due to HH interaction. The energy of a given conformation is defined as the number of topological neighboring (TN) contacts between those Hs, which are not adjacent in the sequence. Figure 1 shows an example for the 2D triangular lattice model. The black filled dots denote the hydrophobic amino acid and the red open circles denote the hydrophilic amino acids. The H-H contacts (free energy) in the conformation are assigned the energy value of -1. The free energy is defined as a minimum value; the maximum number of H-H contacts is given in the case of two-dimensional models. Figure 1 illustrates a protein

Tsay J. and Su S..
A MEMETIC ALGORITHM FOR PROTEIN STRUCTURE PREDICTION BASED ON THE 2D TRIANGULAR LATTICE MODEL.
DOI: 10.5220/0003710201310136
In *Proceedings of the International Conference on Bioinformatics Models, Methods and Algorithms* (BIOINFORMATICS-2012), pages 131-136
ISBN: 978-989-8425-90-4

structure with 15 H-H contacts (energy = -15). As a result, the following problem can be formally defined: given an HP sequence $s = s_1, s_2 ... s_n$, find a correct number of matching pairs of the disulfide bonds and energy-minimizing conformation of s; that is: find $c^* \in C(s)$ such that $E(c^*) = \min\{E(c) \mid c \in C\}$, where $C(s)$ is the set of all valid conformations for s (Shmygelska and Hoos, 2005).

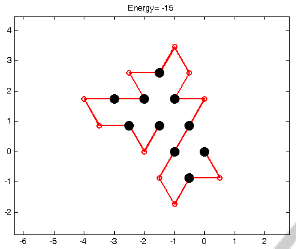


Figure 1: An optimal conformation for the sequence "$(HP)^2PH(HP)^2(PH)^2H\ P(PH)^2$" in a 2D triangular lattice model.

2.2 2D Triangular Lattice Model

In the two-dimensional triangular lattice, each lattice point has six neighbours. Since each residue has two covalent neighbours except the first and the last residues, a residue at a lattice point may be in topological contact with at most four other residues. Thus, each residue may be involved in at most 4 H-H contacts (Joel et al., 2009). The unit vectors shown in Figure 2 are logically defined. Real units require normalization by $\sqrt{2}$ and are (1,0),(-1,0), (-1/2,$\sqrt{3}$/2),(1/2,-$\sqrt{3}$/2),(1/2, $\sqrt{3}$/2),(-1/2, -$\sqrt{3}$/2).

After the unit vectors are obtained in the triangular lattice, it is much easier to model protein conformation on a two-dimensional triangular lattice model without exhibiting the 'parity' problem (Decatur and Batzoglou, 1996).

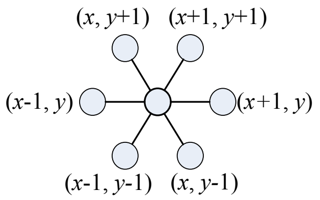
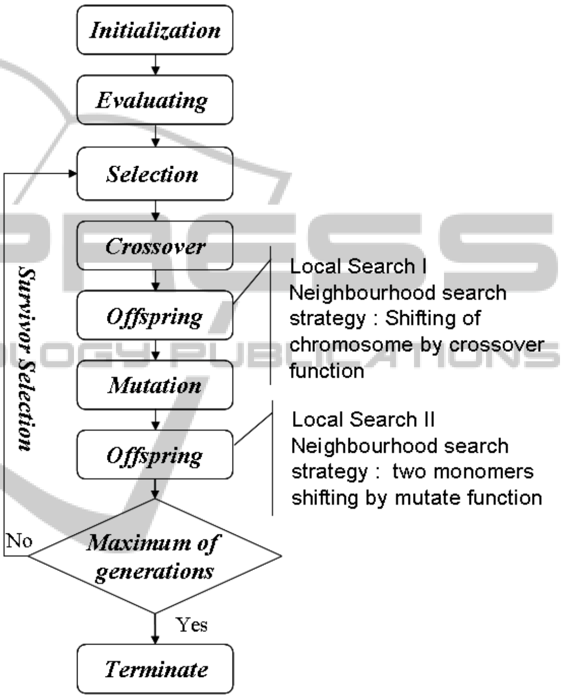


Figure 2: Neighbours of vertex (x, y). Each lattice point has 6 neighbours.

3 MEMETIC ALGORITHM

Memetic algorithms (MA) proposed by Moscato (1999) are powerful algorithms. MA are a class of stochastic global search heuristics in which Evolutionary Algorithms-based approaches are combined with local search techniques to improve the quality of the solutions created by evolution (Hart et al., 2005). In the PSP problem, a better solution is to search for minimum free energy. The details are illustrated in Figure 3. As the evolution continues, the MA is expected to drive the search toward the global optima.



Local Search I
Neighbourhood search strategy : Shifting of chromosome by crossover function

Local Search II
Neighbourhood search strategy : two monomers shifting by mutate function

Figure 3: Flowchart of the proposed MA.

This study proposes the use of a numerical representation for chromosomes. In the PSP problem, if the input amino acid sequence is of length n, then each individual in the population is a string of length n - 1 over the symbols {*1,2,3,4,5,6*}, which represent { *L*; *LD*; *RD* ; *R*; *RU*; *LU* }. The symbols *L*; *LD*; *RD* ; *R*; *RU*; and *LU* are used to denote the fold directions: *L* is for left, *LD* is for left-down, *RD* is right-down, *R* is for right, *RU* is for right-up and *LU* is for left-up in the genotype level encoding scheme, respectively. In the phenotype encoding scheme, coordinate (x,y) is used. {(-1,0);(0,-1);(1,-1);(1,0);(0,1);(-1,1)}is in accordance with the genotype level encoding scheme {*1,2,3,4,5,6*}.

The following subsections describe the operators of MA as in Figure 3.

3.1 Initialization

An initial population was generated randomly and initialized an n - 1 dimensional space within a fixed range. This study applied the method of the random conformation generation by Depth-first search (Hoque et al., 2010) to produce the initial population.

3.2 Evaluation

Each chromosome in the population needs to be evaluated for its fitness. Here we directly used H-H contacts of free energy as the fitness function. The goal for an optimization algorithm like MA is to minimize the fitness value, namely, free energy. The evaluated chromosomes were sorted according to their fitness values. This sorted population served as the basis of subsequent reproduction process.

3.3 Selection

The selection operators include parent selection and survivor selection. In this study, the tournament selection method was used for this reproduction process. Because of the repeatedly selecting, the best individual of a randomly chosen subset is tournament selection. The tournament size is determined by choosing one out of two.

3.4 Crossover

Crossover combines the chromosomes from both parents during the generation of offspring which will inherit part of the genes from their parents. Bazzoli and Tettamanzi (2004) tried a 3D-cube lattice model on the three operators and their results show that 1-point crossover performs better than the other two. Therefore, 1-point crossover operators were used in our study.

3.5 Local Search I

Local search is a method that searches and examines iteratively the set of points in a neighborhood of the current solution and replaces the current solution with a better existing neighbour. In order to improve the offspring, 1-point crossover operators were further developed in our study and a new local search was proposed.

The classical model was proposed by Unger and Moult (1993) as a pivot rotation crossover operation shown in Figure 4.

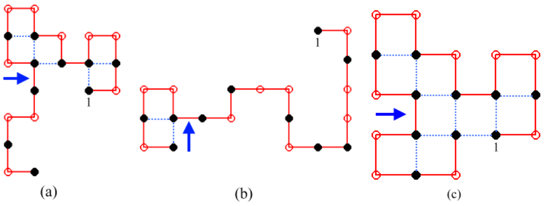


Figure 4: Rotation crossover operation (Unger and Moult 1993). (a) And (b) are parents, (c) is offspring. ‘→’ indicates crossover positions. (a) is the first half of chromosome1. (b) is the latter half of chromosome2. (a) and (b) combination becomes (c) and is also the best structure.

However, our study found that the rotation crossover operation could not fit into some situations, for example, Figure 5. The use of a shift crossover operation might get a better outcome if some kind of structure existed.

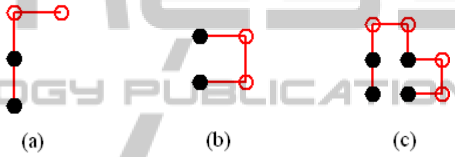


Figure 5: Shift crossover operation. (a) is the first half of chromosome1. (b) is the latter half of chromosome2. (c) is the best structure. In this case (a) and (b) can’t combine by using the method of rotation. On the contrary, it can get the best structure by using the method of shift.

Therefore, this study proposes a new neighbourhood search strategy. It contains the crossover operation of Rotation and Shift as shown in Figure 6.

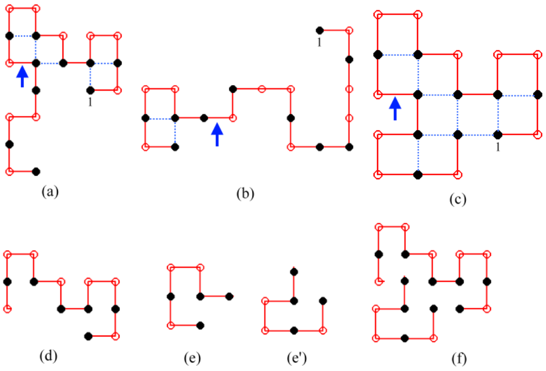


Figure 6: Neighbourhood search strategy. ‘→’ indicates crossover positions. The offspring (d) is the first half of (a). The offspring (e) is the first half of (b). We rotate (e) to (e’) and combine (d) by shift. Then we can get the best solution (f).

In Figure 6, it is found that the best solution can not be obtained by using the Rotation or Shift (the arrowhead pointing to crossover positions). If (e) is rotated to (e') before doing the operation of Shift, the best solution can be achieved.

3.6 Mutation and Local Search II

Mutations can lead GA into genetic structures that have never been searched before. Common mutation operators are bit-flip mutations; however, mutation operators without previous design will lead to invalid conformation.

It is found from our study that two monomers could form a contact only at the bond angle of 60^0 in the 2D triangular lattice model. Based on this feature, a new local search was proposed in our study as illustrated in Figure 7.

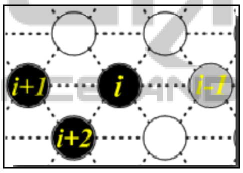


Figure 7: Mutation operators. The *i* is mutation point. The *i* is mutation point ,*i*-1 is the former gene, *i*+1 and *i*+2 are the actual changed genes.

When the mutation operators are in process, one mutation point will be chosen randomly while neighbourhood function uses the information from mutation point genes to mutate in a regular pattern on the following two genes followed by evaluating the chromosomes in the offspring set as shown in Figure 8. The best chromosome will be retained to replace the original one.

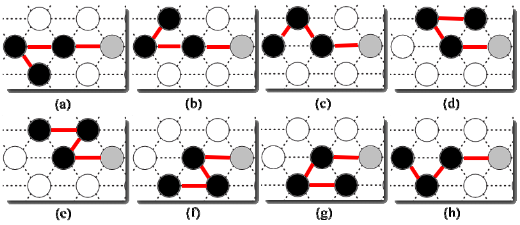


Figure 8: Neighbourhood search strategy. When the mutation operators are proceeding it is found from our study that two monomers could form a contact only at the bond angle of 60^0 in the 2D triangular lattice model.

3.7 Termination

This generational process is repeated until a termination condition has been reached. The termination condition of the study is to adopt the fixed number of generations reached. Finally, the best member of the population is then returned.

3.8 Parameter Settings

The main purpose of the study was to compare the methods. Better results could be obtained if the population size was set larger. Due to limitation on experimental time, the experiment of this part is parameter settings as shown in Table 1.

Table 1: Parameter settings.

Operations/Parameters	Setting
Population size	100
Crossover rate	0.8
Mutation rate	0.4
Parents selection	Tournament selection
Survival selection	$\mu+\lambda$
Termination	200 generations

4 EXPERIMENTAL RESULTS

In order to validate the result of the study, the experiment was divided into two stages.

4.1 General Benchmark

In the past, a few researchers used the 2D Triangular Lattice Model to proceed for the Protein Structure prediction. This study also added three groups of longer sequence. Sequences 1 through 4 used in this study were described in Krasnogor et al., (Krasnogor et al. 2002); Sequence 5-7 was taken from Jiang et al., (2003) and the last three instances were from (Shmygelska and Hoons, 2005). These sequences have been used as the benchmark for the 2D square HP model as shown in Table 2.

This study in comparison with previous studies provided a means of demonstrating the effectiveness of the method described here. The multimeme algorithm (MMA) is the method that Krasnogor et al., (Krasnogor et al., 2002) proposed. The hybrid genetic algorithm (HGA) is the method that Hoque et al., (Hoque et al., 2006) proposed. Further, the hill-climbing and genetic algorithm is the method that this study (Su et al., 2010) proposed previously. Comparing this current method with the method mentioned above, it can be concluded from Table 3 that MA performed more robustly than others.

Table 3 shows the results of 10 sequences after 20 rounds of operations being performed. The format of column entries is 'average / minimum'. Figures in bold indicate the lowest energy.

Table 2: The benchmarks for the 2D triangular lattice HP model.

#	Len.	Protein Sequence
1	24	HHPPHPPHPPHPPHPPHPPHPPHH
2	30a	HHHPPHPPHPPHPPHPHPPHPHPPHPPHHH
3	30b	HHHPPHPPHPPHPHPPHPHPPHPPHPPHHH
4	37	HHHPPHPPHPPHPHPHPPHPPHPPHPPPPPHPHPHHH
5	50	$H^2(PH)^3PH^4PH(P^3H)^2P^4(HP^3)^2HPH^4(PH)^3PH^2$
6	60	$P(PH^3)^2H^5P^3H^{10}PHP^3H^{12}P^4H^6PH^2PHP$
7	64	$H^{12}(PH)^2((P^2H^2)^2P^2H)^3(PH)^2H^{11}$
8	85	$H^4P^4H^{12}P^6(H^{12}P^3)^3HP^2(H^2P^2)^2HPH$
9	100a	$P^3H^2P^2H^4P^2H^3(PH^2)^2PH^4P^8H^6P^2H^6P^9HPH^2PH^{11}P^2H^3PH^2PHP^2HPH^3P^6H^3$
10	100b	$P^6HPH^2P^5H^3PH^5PH^2P^4H^2P^2H^2PH^5PH^{10}PH^2PH^7P^{11}H^7P^2HPH^3P^6HPH^2$

Table 3: Comparison of the proposed approach with the HHGA (Su et al., 2010), MMA (Krasnogor et al., 2002), HGA(Hoque et al., 2006) and TS (Böckenhauer et al., 2008). Figures in bold indicate the lowest energy. MA was run for 200 iterations with the population size 100. For sequence 6, 200 iterations with population size 400.

#	Len.	MA	HHGA	MMA	HGA	TS
1	24	-15.6/**-17**		- /-16		**- /-17**
2	30a	-21.65/-24		- /-24		**- /-25**
3	30b	-22.35/-24		- /-24		**- /-25**
4	37	-25.73/-28		- /-26		**- /-29**
5	50	**-36.2/-38**	-33.15/-35		- /-23	
6	60	-67.65/**-70**	-60.5/-65		- /-46	**- /-70**
7	64	**-61.05/-68**	-53.5/-56		- /-46	- /-50
8	85	**-88.95/-93**	-81.2/-86			
9	100a	**-80.65/-85**	-71.55/-79			
10	100b	**-79.6/-83**	-71.6/-77			

4.2 PDB Benchmark

In this study, the benchmarks are the small proteins. The benchmarks in this study are listed in Table 4. The small protein data were collected from the protein data bank (PDB) (http://www.rcsb.org/pdb/).

In this study, the LatPack Tools – LatFit (Mann et al., 2008) were firstly used to get the best conformation of the 3D FCC lattice model. Then, MA was applied to find the best conformation of the 2D Triangular lattice model and PyMOL followed to proceed to compare structures in order to get the value of RMSD. To compare with the 3D FCC lattice model, this study used the CPSP-web-tools (Mann et al., 2008; 2009) to get the best conformation in the 3D FCC lattice model and also used PyMOL (http://www.pymol.org/) to compare this conformation with benchmark proceeding structure to get the value of RMSD. Based on the value of RMSD, the similarity from different lattice models can be compared objectively. From experimental results, the best conformation of the 2D Triangular lattice model is better than the best conformation of the 3D FCC lattice model in the structure similarity. Table 5 summarizes the result.

Table 4: Benchmarks from PDB.

#	PDB ID	Len.	Protein Sequence
1	1CNL	12	GCCSDPRCAWRC
2	1A0M	16	GCCSDPRCNMNNPDYC
3	1V6R	21	CSCSSLMDKECVYFCHLDIIW
4	1CZ6	25	RSVCRQIKICRRRGGCYYKCTNRPY
5	1EI0	38	DPCQKQAAEIQKCLQANSYLESKCQAVIQELKKCAAQY
6	1CRN	46	TTCCPSIVARSNFNVCRLPGTPEAICATYTGCIIIPGATCPGDYAN
7	1EHS	48	STQSNKKDLCEHYRQIAKESCKKGFLGVRDGTAGACFGAQIMVAAKGC
8	1E8R	50	MGNQQCNWYGTLYPLCVTTTNGWGWEDQRSCIARSTCAAQPAPFGIVGSG
9	1IL8	72	SAKELRCQCIKTYSKPFHPKFIKELRVIESGPHCANTEIIVKLSDGRELCLDPKENWVQRVVEKFLKRAENS

Table 5: RMSD: comparison of the proposed approach with the CPSP-Tools 3D FCC lattice model.

#	PDB ID	Length	MA based on 2D Triangular	CPSP based on 3D FCC
1	1CNL	12	**1.017**	1.203
2	1A0M	16	**1.497**	1.518
3	1V6R	21	**1.661**	2.437
4	1CZ6	25	**3.040**	3.377
5	1EI0	38	**3.187**	3.429
6	1CRN	46	**3.012**	3.533
7	1EHS	48	**2.828**	3.673
8	1E8R	50	**3.218**	4.225
9	1IL8	72	**3.731**	4.158

5 CONCLUSIONS

In the ***ab initio*** technique, the lattice model is one of the most frequently used methods in protein structure prediction.

Some researchers can improve 2D triangular and 3D FCC lattice models to reach 16/30 (53%) (Decatur and Batzoglou, 1996) and 31/36 (86%) (Hart and Istrail, 1997) of approximation ratios and can even achieve a higher structure similarity. However, most researchers define the protein fold problem or the protein structure prediction problem as an optimization problem. Therefore, most of the studies usually use the lower approximation ratios of lattice model, such as the 2D square and 3D cube lattice models.

This study proposed a memetic algorithm (MA) for protein structure prediction based on the 2D triangular lattice model. The result from our experiments showed that the method could get lower free energy in a more effective way than previous studies. In addition, this study further compared the structure similarity of the lattice mode and also compared the result from the 3D FCC lattice model for the structure similarity. From the result of numerical analysis, the 2D triangular lattice model used in this study was better than the 3D FCC lattice on the prediction of the protein structure with short sequences. This means that the 2D triangular lattice model can get more similar simulating results with the HP Lattices Model to predict the protein structure with short sequences. In conclusion, the 2D triangular lattice model is a better choice than the previous approaches. This is the first time that this method has been investigated and its further study in the future will be worthwhile.

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