Protein folding in 3D lattice HP model using heuristic algorithm

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Abstract: - The proteins play a key role in many vital functions in living organisms. The tertiary structure of the proteins determines their functions. Predicting of a protein's tertiary structure can be the base for development of treatments for diseases such as Alzheimer's disease and cystic fibrosis. Therefore, the predicting of a protein's tertiary structure from its amino acid sequence from long time is one of the fundamental problems in computational biology, molecular biology, biochemistry, and physics. The prediction of a protein's tertiary structure from its amino acid sequence is known as Protein Folding Problem. This is the NP-complete problem. In this article we propose extension of the heuristic algorithm that solves the problem in 2D (described by some of authors on this article) to solve the protein folding problem in 3D lattice HP model.

Key-Words: - NP-complete problem, protein folding problem, HP folding, HP model, 3D lattice, integer programming, bioinformatics, heuristics.

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1 Introduction

The proteins are large biomolecules, which play a key role in many vital functions in living organisms. The protein functions depend on its tertiary structure (3D structure), which in turn depends on the protein's primary structure. So, the 3D structure of proteins is the major factor that determines their biological activity. The determination of the functionality of a protein from its amino acid sequence is one of the fundamental problems in computational biology, molecular biology, biochemistry, and physics. The synthesis of new proteins and the crystallographic analysis of their 3D structure is very slow and very expensive process. So, if we can predict the 3D structure of many proteins, than only proteins with expected properties have to be synthesized.

To date, the number of experimentally determined 3D protein structures in Protein Data Bank (www.rcsb.org) is >125 000. The number of these structures increases day by day.

The mistakes, arising in the protein folding process lead to occurrence of proteins with unusual forms, which are the main causes of many diseases such as cystic fibrosis, Alzheimer's disease and mad cow. If we can predict, with high accuracy, the tertiary structures of proteins from their primary structure, we will be able to better treat these diseases. The knowledge of the tertiary structures of proteins, there are other applications, such as in drug design [1].

The common practice for predicting of the tertiary structure of the proteins is to use models that simplify the possible conformations search space. These models reflect the different global characteristics of the proteins structure. In the Hydrophobic-Polar (HP) model the amino acids sequence of the protein (which may be represented as a string over twenty-letters alphabet) is simplified to a sequence of Hydrophobic (H) and Polar/ Hydrophilic (P) amino acids and thus the amino acids sequence is presented as a sequence over {H,P} alphabet [2].

Hydrophobic-Polar (HP) model describes a protein sequence based on the fact that hydrophobic amino acids must have less contact with water as opposed to the polar amino acids [2]. The way of folding is determined by the polarity or the hydrophobicity of different amino acids, so the 3D structure with minimum energy is the real case, i.e. the optimal conformation of a protein in HP model is the one that has the maximum number of contacts between the H amino acids which are not neighbors in the protein structure (H-H contacts) (Figure 1). This leads to formation of hydrophobic core in the tertiary structure of protein and gives the lowest energy value [3].

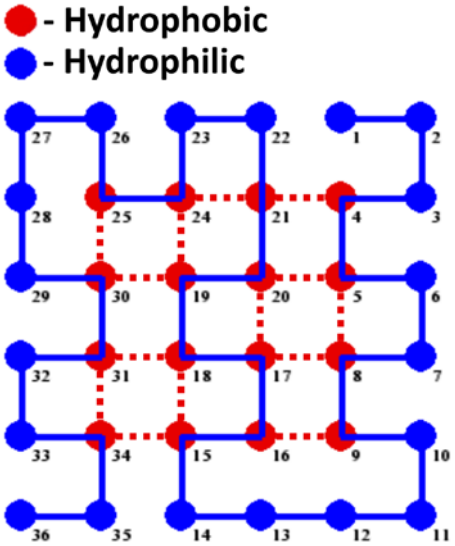


Fig. 1 Optimal conformation for HP sequence with length 36 amino acids in 2D lattice (14 contacts – the dashed red lines).

The prediction of the 3D structure of proteins, from their primary structure (the amino acid sequence), is known as Protein folding problem. It is proved that the Protein folding problem in HP model for 2D and 3D is *NP*-hard [4, 5].

In 2D, the heuristic algorithm described by Traykov et al. in [17] generates folds that are better than the folds obtained by approximate algorithms as Monte Carlo Algorithm, Newman's algorithm, Hart-Istrail algorithm, and close to the folds obtained by the Mixed Search Algorithm, and Genetic Algorithm [6, 7, 8, 9]. Here, we will present extension on this heuristic to solve the protein folding problem in 3D lattice HP model.

2 HP Folding in lattice method

The processes, related with the protein folding are very complex and only minority of them are explained and understood from the scientists. For this reason the simplified models such as Dill's HP model, have become one of the main tools for study of proteins.

In 1985, Ken Dill suggested Hydrophobic-Polar (HP) model, which is described in a huge amount literature because this model play key role in protein folding models. HP model is based on the observation that the hydrophobic interaction between the amino acid is the driving force in the protein folding process. Hydrophobic effect of

amino acids contributes significant part of the total energy function so that is the most important force in determining the structure of the proteins [2].

In the HP model, the energy of the conformation is defined as the number of contacts between hydrophobic amino acids, which are not neighbors in the protein sequence, the so-called H-H contacts. More specifically conformation c with n H-H contacts have energy value $E(c) = n$ [10].

In the HP lattice model, 20-th amino acids are reduced to two types – H (Hydrophobic) and P (Polar/Hydrophilic). In the lattice model, each sequence is presented as **self-avoiding walk**.

The self-avoiding walk is a sequence of moves in the lattice, which do not pass through the same position more than once. Table 1 show the number of self-avoiding walks between two diagonal vertices in 2D lattice with size n x n.

n* x *n	**The number of self-avoiding walks**
1	2
2	12
3	184
4	184
5	1262816
6	575780564
7	789360053252
8	3266598486981642
9	41044208702632496804
10	1568758030464750013214100
11	182413291514248049241470885236
12	645280393432700189633571851584821 18
13	69450664761521361664274701548907358996488
14	227449714676812739631826459327989863387613323440
15	22667455688626727463745673967130989348663248854083190 28
16	68745445609149931587631563132489232824587945968099457285419306
17	63448146112379639713102975407955244004494439868664806936463693878553 36
18	17821128408420651298933849466523252751678380657047676559314524746058266927825 32
19	10^{88}
20	10^{97}
21	10^{107}

Table 1 The number of self-avoiding walks between two diagonal vertices in 2D lattice with size n x n.

The connections between the H-H amino acids (H-H contacts) are constructive [11]. The natural conformation of the HP sequence is defined as the conformation with the largest number of H-H contacts. Basing on the number of H-H contacts, we calculate the energy value of the conformation. The energy value should be minimized in order to obtain the best 3D structure. Figure 2 shows a schematic representation of the 3D HP lattice model.

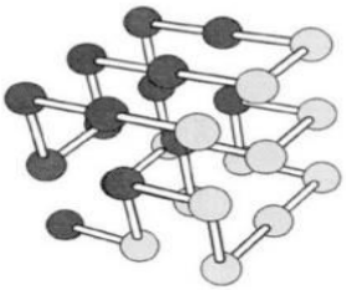


Fig. 2 HP lattice model in 3D [11].

The protein folding problem in 3D HP lattice model can be defined as follows. Given an amino acid sequence, $S = s_1, s_2, ..., s_n$ (sequence of letters over the {H,P} alphabet) and a lattice. The goal is to find conformation of S with lowest energy value, i.e. Maximize:

The number of H-H contacts

Subject to:

1. (*Assignment*) Each amino acid must occupy one lattice point.
2. (*Non-overlapping*) No two amino acids may share the same lattice point.
3. (Connectivity) Each two amino acids that are consecutive in the protein's sequence must also occupy adjacent lattice points.

For solving the protein folding problem in 3D HP lattice model, are proposed a number of known heuristic optimization methods, including Evolutionary Algorithms (EA), Monte Carlo (MC)

algorithms, Ant Colony Optimization (ACO) algorithms, Genetic algorithms [12, 13, 14, 15].

3 Integer programming formulation

Let n to be the length of the protein sequence. Let $L(i, k)$ to be 3D lattice, with side N:

- $N = n$;
- $N = 2\sqrt{n}$;
- $N = \frac{n}{2}$.

So, the size of the lattice $L(i, k)$ is N^3.

We define HP model in 3D lattice. For simplification we convert 3D lattice model in 1D as follows [16]: we present the three-dimensional coordinates (x, y, z) as one $i = N^2(z-1) + N(y-1) + x$.

Each cell in column $i \in L$ and row $k \in L$ on the lattice may be occupied by element of the protein sequence. We define the following variables

$$x_{i,k} = \begin{cases} 1, if\ the\ k^{th}\ amino\ acid\ is\ in\ the\ cell\ i \\ 0, otherwise, \end{cases}$$

where $i = 1 \dots N^3$, $k = 1 \dots n$.

$$y_{i,k,j,l} = \begin{cases} 1, if\ we\ have\ H-H\ contact \\ 0, otherwise, \end{cases}$$

where $i, j = 1 \dots N^3$, $k, l = 1 \dots n$.

Our goal is to maximize the number of H-H contacts, i.e.

$$\max \sum y_{i,k,j,l}.$$

Each element k can be placed in only one cell of the lattice (*Assignment*):

$$\sum_{i=1}^{N^3} x_{i,k} = 1, \quad \forall k, \qquad (1)$$

where $k = 1 \dots n$.

Each cell i can contain only one element of the input sequence (*Non-overlapping*):

$$\sum_{k=1}^{n} x_{i,k} \le 1, \quad \forall i, \qquad (2)$$

where $i = 1 \dots N^3$.

Each two neighboring elements of the protein sequence should be placed in the adjacent cells in the lattice (*Connectivity*):

$$x_{i,k} \le \sum_{j \in G(i)} x_{j,k+1}, \qquad (3)$$

where $i = 1 \dots N^3$, $k = 1 \dots n$. These constraints define **self-avoiding walk** (Figure 3).

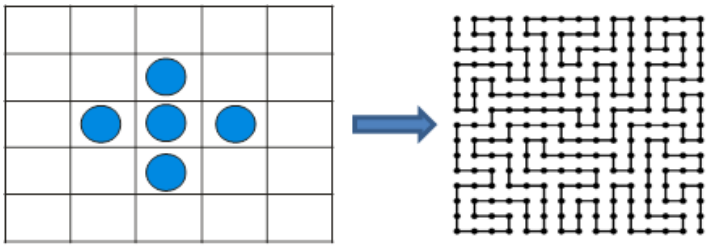


Fig. 3 Self-avoiding walk.

The variable $y_{i,k,j,l}$ has value 1, if two adjacent cells are occupied by hydrophobic amino acids that are not adjacent in the protein sequence and 0 otherwise [16]:

$$x_{i,k} \ge \sum_{j \in G(i)} y_{i,k,j,l}, \quad \forall i, k, \qquad (4)$$

$$x_{j,l} \ge \sum_{i \in G(j)} y_{i,k,j,l}, \quad \forall j, l, \qquad (5)$$

where

$i, j = 1 \dots N^3$,

$k, l = 1, \dots, n$,

$G = \{l - k > 2 \cap S_k = H \cap S_i = H\}$,

$G(j)$ – set of cells, which are neighbor of j-th cell

So, mathematical model is as follow

$$\max \sum y_{i,k,j,l}$$

Subject to

$$\sum_{i=1}^{N^3} x_{i,k} = 1, \quad \forall k, k = 1 \dots n,$$

$$\sum_{k=1}^{n} x_{i,k} \le 1, \quad \forall i, i = 1 \dots N^3,$$

$$x_{i,k} \le \sum_{j \in G(i)} x_{j,k+1}, \quad i = 1 \dots N^3, k = 1 \dots n,$$

$$x_{i,k} \ge \sum_{j \in G(i)} y_{i,k,j,l}, \quad \forall i, k, i = 1 \dots N^3, k = 1 \dots n,$$

$$x_{j,l} \ge \sum_{i \in G(j)} y_{i,k,j,l}, \quad \forall j, l, j = 1 \dots N^3, l = 1 \dots n,$$

$$G = \{l - k > 2 \cap S_k = \mathrm{H} \cap S_i = \mathrm{H}\},$$

$$x_{i,k} \in \{0,1\}, \quad y_{i,k,j,l} \in \{0,1\}$$

4 Algorithm for solving the problem

The process for protein folding prediction in 3D lattice HP model must satisfy the following constraints: the amino acid sequence must be

continuous; the folding process must be in the range of the cubic lattice and must follow self-avoiding path.

The heuristic algorithm described by Traykov et al. in [17] uses sequence of moves to generate self-avoiding walk in 2D HP lattice model. To solve the problem in 3D HP lattice model we extend this set of moves to generate self-avoiding walk in a cubic lattice, i.e. in 3D case the possible directions for the movement of amino acids in the lattice are six: L (Left), R (Right), U (Up), D (Down), F (Forward) and B (Back). The main idea of algorithm is as follow.

We consider a sequence S with length n in a cubic lattice. The size of the cubic lattice is selected so that the first two amino acids of the sequence to be fixed in center of the lattice, or with 1 cell displacement from it. We divide the sequence S on parts with predefined size, i.e. $S = S_1 \cup S_2 \cup \ldots \cup S_m$, $S_i \cap S_{i+1} = \varnothing$. After that, we take i-th part from S and generate all possible folds. On the next step we choose the fold with maximum number of contacts and put it in a cubic lattice. To already obtained fold, we add (i+1)-th part from S and find all possible folds against already selected fold. From the obtained new folds we choose the fold with maximum number of H-H contacts and put it in a cubic lattice. The main flowchart of the algorithm is shown on figure 4.

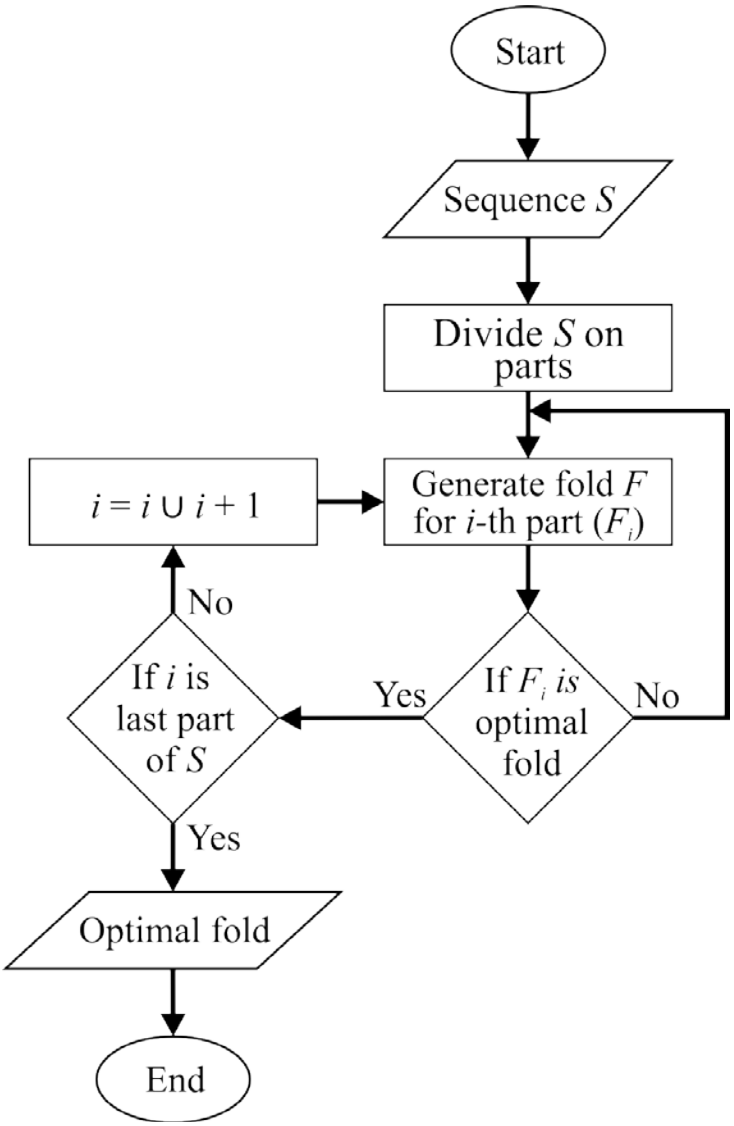
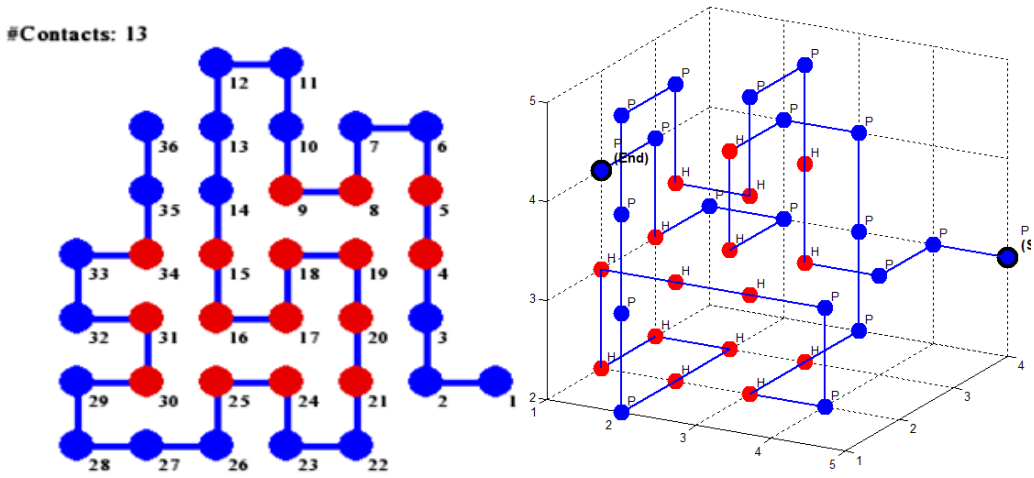


Fig. 4 The main flowchart of the algorithm.



(a) (b)

Fig. 5 Protein folding with length 36 amino acids in: (a) 2D HP lattice model (13 contacts), (b) 3D HP lattice model (18 contacts).

This concept allows us to reach a solution for protein with any length. Figure 5 shows the protein fold with length 36 amino acids generated by the heuristic algorithm described by Traykov et al. in [17] (Figure 5a) and the extended heuristic algorithm (Figure 5b).

5 Computational experiments

In this chapter we compare Extended Heuristic Algorithm with Genetic Algorithm, Ant Colony Optimization Algorithm and Evolutionary Algorithm with Backtracking in 3D lattice. For computational experiments we use eight HP sequences that are known in the literature benchmarks for 3D lattice in HP model (Table 2) [18, 19].

Length	Protein Sequence
20	$(HP)_2PH(HP)_2(PH)_2HP(PH)_2$
24	$H_2P_2(HP_2)_6H_2$
25	$P_2HP_2(H_2P_4)_3H_2$
36	$P(P_2H_2)_2P_5H_5(H_2P_2)_2P_2H(HP_2)_2$
46	$P_2H_3PH_3P_3HPH_2PH_2P_2HPH_4PHP_2H_5P$ $HPH_2P_2H_2P$
48	$P_2H(P_2H_2)_2P_5H_{10}P_6(H_2P_2)_2HP_2H_5$
50	$H_2(PH)_3PH_4PH(P_3H)_2P_4(HP_3)_2HPH_4(P$ $H)_3PH_2$
60	$P(PH_3)_2H_5P_3H_{10}PHP_3H_{12}P_4H_6PH_2PHP$

Table 2 HP benchmarks for 3D lattice.

The symbols H_i, P_i and $(\ldots)_i$ in table 2 shows *i* repeats of character or sequence.

For the realization of the algorithm we use the programming language Python. This programing language has built-in complex data types such as flexible arrays and dictionaries, and provides good structure and support for the development of complex applications.

In table 3 we compare the obtained results by Extended Heuristic Algorithm (the column EHA) with known in the literature results obtained by Meta-Heuristic Ant Colony Optimization Algorithm (the column ACO-Metaheuristic), Genetic Algorithm (the column GA), and Evolutionary Algorithm with Backtracking (the column Backtracking-EA) [14, 20, 21, 22]. The column BKS show best known solution for these HP sequences.

Length	Contacts				
	BKS	GA	Backtracking-EA	EHA	ACO-metaheuristic
20	11	11	11	11	10
24	13	13	13	13	8
25	9	9	9	9	6
36	18	18	18	18	10
46	32	–	–	29	21
48	29	25	25	31*	–
50	26	23	23	26	–
60	49	37	39	55*	–

Table 3 Computational results obtained for 8 HP sequences in 3D.

With * we note the protein sequence for which we improve the best know energy value.

From table 3 we can see that the EHA generates the best know solution for sequences with length 20, 24, 25, 36 and 50 amino acids. For sequences with length 48 (Figure 6), and 60 amino acids (Figure 7), Extended Heuristic Algorithm generates folds that are better than the best know solutions for these protein sequences.

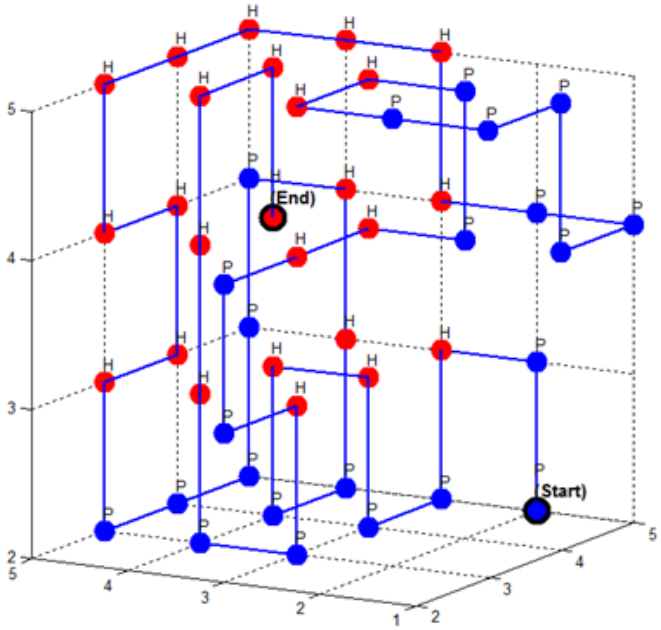


Fig. 6 Protein folds with length 48 amino acids (31 contacts).

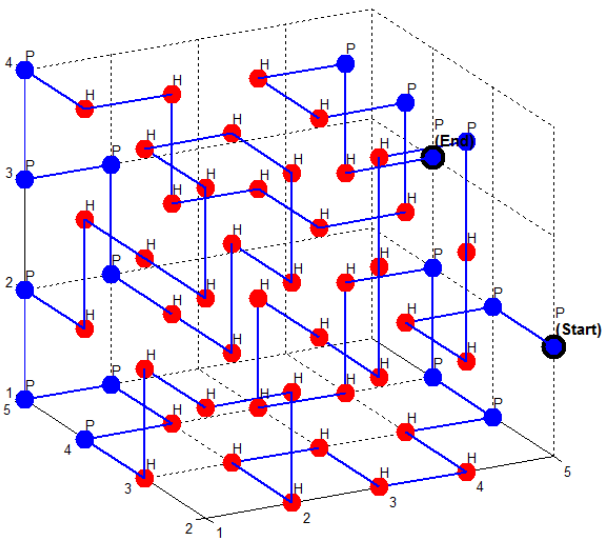


Fig. 7 Protein folds with length 60 amino acids (55 contacts).

1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
P	P	H	H	H	P	H	H	H	H	H	H	H	H	P	P	P	H	H	H
	y	x	y	z	z	x	z	z	y	y	z	x	z	x	z	y	x	y	x

21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40
H	H	H	H	H	H	H	P	H	P	P	P	H	H	H	H	H	H	H	H
y	x	y	z	x	y	z	y	x	y	x	z	y	z	y	y	z	y	x	y

41	42	43	44	45	46	47	48	49	50	51	52	53	54	55	56	57	58	59	60
H	H	H	H	P	P	P	P	H	H	H	H	H	H	P	H	H	P	H	P
z	y	z	y	y	z	x	z	y	x	z	x	y	x	z	x	y	x	z	x

Fig. 8 Analytical solution for protein sequence with length 60 amino acids.

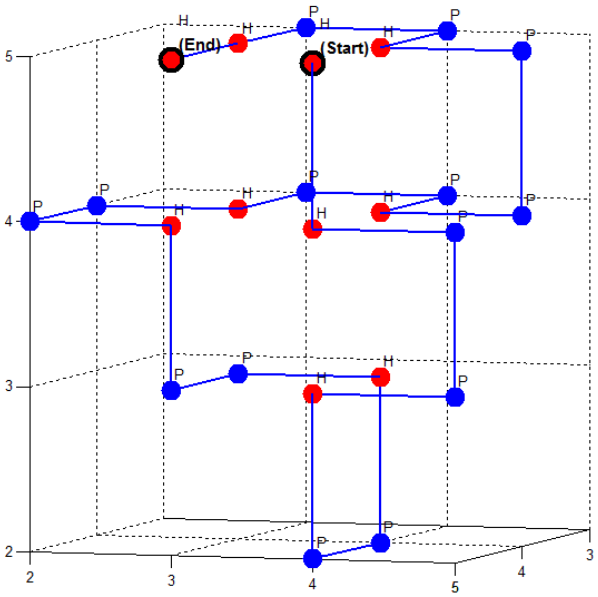


Fig. 9 Protein folds with length 24 amino acids (13 contacts).

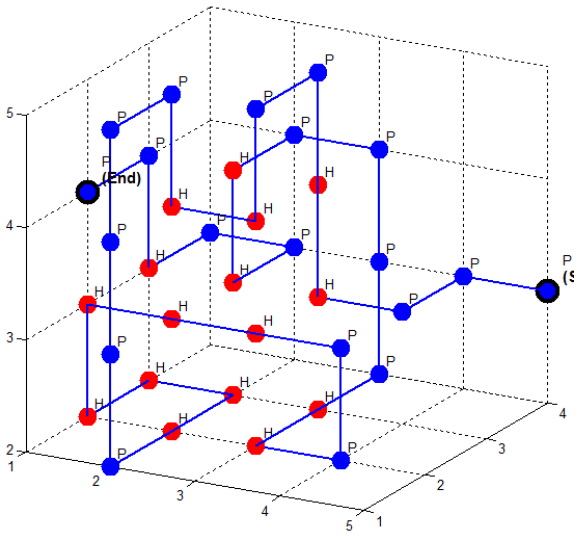


Fig. 10 Protein folds with length 36 amino acids (18 contacts).

On figure 8 we show the solution for protein sequence with length 60 amino acids in analytical form, where $x/\bar{x}, y/\bar{y}, z/\bar{z}$ represents "plus/minus one" to the corresponding coordinate of the previous amino acid.

The next figures show the optimal conformations obtained by the Extended Heuristic Algorithm for protein sequences with length 24 amino acids (Figure 9) and 36 amino acids (Figure 10).

Table 4 shows the execution time for each of the tested sequences.

Length	HP Sequence	CPU time (sec.)
20	$(HP)_2PH(HP)_2(PH)_2HP(PH)_2$	44
24	$H_2P_2(HP_2)_6H_2$	410
25	$P_2HP_2(H_2P_4)_3H_2$	103
36	$P(P_2H_2)_2P_5H_5(H_2P_2)_2P_2H(HP_2)_2$	82
46	$P_2H_3PH_3P_3HPH_2PH_2P_2HPH_4P$ $HP_2H_5PHPH_2P_2H_2P$	216
48	$P_2H(P_2H_2)_2P_5H_{10}P_6(H_2P_2)_2HP_2$ H_5	93
50	$H_2(PH)_3PH_4PH(P_3H)_2P_4(HP_3)_2$ $HPH_4(PH)_3PH_2$	369
60	$P(PH_3)_2H_5P_3H_{10}PHP_3H_{12}P_4H_6P$ H_2PHP	811

Table 4 CPU time for run on extended heuristic algorithm.

The machine that we use for realization of the computational experiments is laptop with Intel Core i5 430M (2.26 GHz, 3MB L3 cache) processor and 4GB RAM. We not compare the execution time with the other algorithms because they have different mode of operation.

6 Conclusion

In this work is shown that the heuristic algorithm for 2D lattice HP model, described by Traykov et al. in [17], can be successfully applied to solve the protein folding problem in 3D. Simulation results indicate that the Extended Heuristic Algorithm is performs better than Evolutionary Algorithm with Backtracking, Meta-Heuristic Ant Colony Optimization Algorithm and Genetic Algorithm. Also, from the computational experiments we can see that Extended Heuristic Algorithm is very effective in protein structure predicting, and provides good folds for the each of the tested protein sequences. The idea of decomposing the problem into subproblems works well in 3D for proteins sequence with length up to 100 amino acids (not only in 2D [17]). Ahead of us stands the challenge to implement the algorithm on proteins with a larger size (≥ 100 amino acids) and with other lattices as triangular lattice, diamond lattice, Bravais lattice (not only square and cubic lattices). We can improve the quality of folds, obtained from the proposed method by insertion of other techniques for analysis of protein structure.

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