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# A novel state space representation for the solution of 2D-HP protein folding problem using reinforcement learning methods

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ABSTRACT

In this study, a new state space representation of the protein folding problem for the use of reinforcement learning methods is proposed. In the existing studies, the way of defining the state-action space prevents the agent to learn the state space for any amino-acid sequence, but rather, the defined state-action space is valid for only a particular amino-acid sequence. Moreover, in the existing methods, the size of the state space is strictly depends on the amino-acid sequence length. The newly proposed state-action space reduces this dependency and allows the agent to find the optimal fold of any sequence of a certain length. Additionally, by utilizing an ant based reinforcement learning algorithm, the Ant-Q algorithm, optimum fold of a protein is found rapidly when compared to the standard Q-learning algorithm. Experiments showed that, the new state-action space with the ant based reinforcement learning method is much more suited for the protein folding problem in two dimensional lattice model.



## 1. Introduction

The protein folding problem is a widely studied optimization problem which is known to be NP-complete. Once the proteins are synthesized, they fold a unique three-dimensional structure that makes them functional or biologically active. The mechanism behind the folding process is still unknown, but there are some mathematical models proposed to simulate the folding process and to find the correct fold of a protein from its amino-acid sequence. Perhaps the most widely studied model is the hydrophobic-polar (HP) lattice model, which is firstly proposed by Dill [1]. In this model, each amino-acid is treated either hydrophobic (H) or polar (P) and represented as a point on a two or three dimensional lattice structure.

Lattices are grid like structures that guide the algorithms to form self-avoiding protein configurations, in which each amino-acid in the sequence is mapped to only a particular point on the grid. This mapping process is usually handled in two different ways. In the first one, the amino-acid sequence is considered as a constant chain and folding is performed by iteratively modifying the positions of each amino-acid on the grid without breaking this chain. While in the second one, each amino-acid in the sequence is consecutively added to form continuous and self-avoiding amino-acid chains on the grid which can be considered as a navigation problem or a robot path planning problem.

It is shown that, reinforcement learning methods perform well on the solution of the robot path planning problems [2,3]. Thus, in this study the reinforcement learning methods are used for the solution of the protein-folding problem in two dimensional lattice model. There exist many studies [4–9] in literature that proposed different methods for the solution of this problem, but the use of reinforcement learning methods are quite new. In [10–13], authors used the Q-learning algorithm to solve the protein folding problem in two dimensional hydrophobic-polar (2D-HP) model.

In order to use the reinforcement learning methods for the solution of the protein folding problem in 2D-HP model, first a state-action space should be defined properly. Thus, each move of the agent on the grid could be easily mapped into the defined state-action space.

In the existing studies [10–13], a state-action space is defined for this purpose. However, in these studies the size of the defined state-action space is highly affected by the amino-acid sequence length. As the amino-acid sequence length increases, the size of the proposed state-action space also increases, dramatically. So, even for the small sized amino-acid sequences it is not computationally possible to create the state-action space at the beginning of the algorithm. The only way is to create the state-action space dynamically during the learning process, which is not desirable. Moreover, in these studies the state-action space is created for all amino-acid sequences individually. So, all amino-acid sequences have a unique state-action space and the algorithm must learn all

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of these state-action spaces separately. By this way, after a learning process, the proposed method could not be able to find the optimal fold of another amino-acid sequence, which conflicts with the philosophy of the term "learning".

In this study, to overcome above mentioned drawbacks a new state-action space is proposed. The proposed state-action space allows the agent to find the optimal fold of any amino-acid sequence (protein) with a particular length. This is achieved by incorporating the "learning" concept to the 2D HP protein folding problem by using the newly proposed state-action space. Moreover, by utilizing a swarm based reinforcement method (Ant-Q algorithm) the optimal fold is found rapidly when compared to the traditional Q-learning algorithm.

The remaining part of this paper is organized as follows; in the following section the protein folding problem in 2D-HP model is introduced. In Section 3, existing state space representation of the protein folding problem in 2D-HP model is given. Then, the newly proposed state-action space is introduced. In Section 4, reinforcement learning algorithms, the Q-learning algorithm and the Ant-Q algorithm is given. Section 5 covers the experiments, results and discussions for the proposed method. Finally, Section 6 concludes the work.

## 2. The protein folding problem in two dimensional hydrophobic-polar model

An amino acid sequence (or chain) is known to be the primary structure of a protein which is synthesized by using the information encoded in genes. This primary structure is then folded into a unique three dimensional structure which makes the protein functional. In literature, the challenge of inferring this three dimensional structure (tertiary structure) from the amino acid sequence is known as the "protein folding problem". Since the discovery of the proteins three dimensional structures can provide important clues about the functionalities of the proteins, the protein folding problem is of crucial importance to the biological community.

There are two main methods to experimentally determine the protein three dimensional structure; X-ray crystallography and NMR spectroscopy, both of which can provide information at atomic resolution. Unfortunately, there exist classes of proteins for which three dimensional structure reconstruction is not possible by using these experimental methods. Moreover, these experimental methods are very expensive and it is usually very time consuming to obtain the 3D structure of a protein by using these methods. For these reasons, computational methods are proposed to find out the three dimensional structure of the proteins from their amino acid sequences. However, it is also a problematic task to find the optimum fold a sequence computationally. Because, the number of possible protein conformations dramatically increases with the increased amino acid sequence length. Therefore, the proposed computational methods should explore the search space efficiently in a reasonable time. In order to achieve this, in computational methods the protein folding process is modeled with some mathematical energy functions. It is thought that, the three dimensional structure of a protein is its native state, which has the lowest possible energy conformation. The problem is thus evolved to find out the lowest energy conformation by minimizing these energy functions.

Perhaps the most widely studied model is the hydrophobic–hydrophilic (HP) lattice model in both two and three dimensions, which is firstly proposed by Dill [1]. In this model, each amino acid side chain is classified either as 'H' hydrophobic (repelled by water) or 'P' hydrophilic or polar (liking water). Dill's survey of proteins identified the interactions between hydrophobic residues (amino acids) to be the dominant force in protein folding [14].

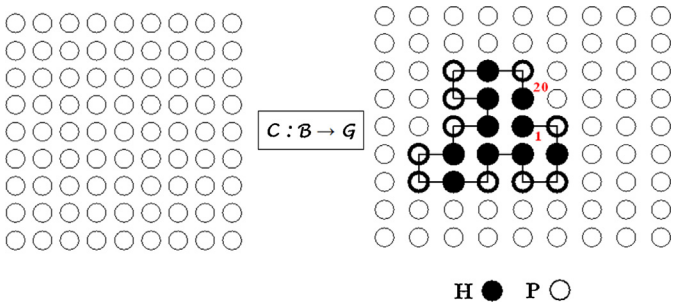


**Fig. 1.** A sample configuration with energy −9 for the protein. $\mathcal{P}$ = HPHPPHHPHPPHPHHPPHPH after mapping process.

Let us, define the primary structure of a protein consists of $n$ amino acid as $\mathcal{P}$. In 2D-HP lattice model this protein could be mathematically defined as below;

$$\mathcal{P} = p_1 p_2 p_3 \ldots . p_n, \quad p_i \in \{H, P\}, \quad \forall 1 \le i \le n \tag{1}$$

Here, $p_i \in \{H, P\}$ represents each amino acid in the chain which are either hydrophobic or hydrophilic (polar). A valid protein structure is defined with a function $\mathcal{C}$, such that each residue of the amino acid chain is mapped to the lattice points in Cartesian coordinates by this function. This could be mathematically defined as in Eq. (2).

$$\begin{aligned} &\mathcal{B} = \{P = p_1 p_2 p_3 \ldots . p_n | p_i \in \{H, P\}, \quad \forall 1 \le i \le n, \quad n \in N\} \\ &\mathcal{G} = \{G = (x_i, y_i) | x_i, y_i \in \Re, \quad 1 \le i \le n\} \\ &\mathcal{C} : \mathcal{B} \to \mathcal{G} \end{aligned} \tag{2}$$

Here, $\mathcal{C} : \mathcal{B} \to \mathcal{G}$ represents the mapping process of a residue $p_i \in \{H, P\}$ to a lattice point $(x_i, y_i)$ in Cartesian coordinates. After this mapping process, for $\forall 1 \le i, j \le n$ with $|i-j| \ge 2$ the energy of the resulting protein structure in 2D-HP lattice model is defined as in Eq. (3).

$$E(C) = \sum_{i,j} I(i,j)$$

$$I(i,j) = \begin{cases} -1, & \text{if } p_i = p_j = H \text{ and } |x_i - x_j| + |y_i - y_j| = 1 \\ 0, & \text{otherwise} \end{cases} \tag{3}$$

where $(x_i, y_i)$ represents the position of the amino acid $p_i \in \{H, P\}$ and $(x_j, y_j)$ represents the position of the amino acid $p_j \in \{H, P\}$ in Cartesian coordinates. More clearly, the energy function is decreased by 1 for each two amino acids that are mapped by $\mathcal{C}$ on neighboring positions in the lattice, but that are not consecutive in the primary structure $\mathcal{P}$. Such two amino acids are called as topological neighbors [12]. In Fig. 1, a sample configuration with energy −9 for the protein $\mathcal{P}$ = HPHPPHHPHPPHPHHPPHPH is given.

## 3. State space representations for the solution of the protein folding problem in two-dimensional hydrophobic-polar lattice model

A valid protein configuration forms a self avoiding path which means, the mapped positions of two different amino acids must not be same in the 2D grid. By considering the resulting self avoiding path, a solution could be represented by an $n-1$ length sequence $\pi = \pi_1 \pi_2 \pi_3 \cdots \pi_{n-1}$, $\pi_i \in \{L, R, U, D\}$, $\forall 1 \le i \le n-1$ of directions, which encodes the relative positions of the current amino acid to the previous one. Let us consider the configuration given in Fig. 1. The resulting sequence for this protein then could be given as $\pi$ = *RDDLULDLLURURULURRD*.