Quality prediction of proteins models with spherical convolutions on three-dimensional graphs

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Convolutional neural networks have become very popular in recent years, and, in particular, have found widespread application in computer vision. Recently, active work has also begun on graph convolutional networks. In general, the graphs, unlike the pictures, are irregular structures, and in many tasks of learning on graphs sample objects also do not have unified topology. Therefore, the existing operations of convolution on the graphs are very much simplified, and the task of pulling on the graphs remain open in general. The purpose of this work is to research new operations of convolution on three-dimensional graphs within the framework of solving the problem of quality estimation of three-dimensional models of proteins (the problem of regression on the graph nodes). These operations are theoretical mechaincs inspired methods based on the expancion of a function of spherical coordinates as a linear combination of spherical harmonics. It helps solve the problem of capturing some local 3D structure of protein residues.

Key words: *graph convolutional networks, spherical convlutions, three-dimensional graphs learning.*

1 Introduction

Protein molecules are an important part of any biological form. They determine cellular functions and behavior of various biological and chemical structures. It makes the discovery and prediction of proteins structure one of the most important points of medical, chemical and genetic science researches.

Molecules of proteins consist of smaller molecules called amino acids. These amino acids form a chain that is folded and placed in space. Thus, protein functions are determined by their positions in a 3D space. So, having this chain of amino acids we need to identify how they are located. There are ways to do this experimentally, but it can be time-consuming, expensive and not always possible. To solve these disadvantages, computational algorithms [1] [9] [16] were developed that generate different chain foldings. The problem is that no algorithm is the best one. Some of proteins are better modeled by one algorithm, others by others. Therefore, we are facing the problem of quality assessment (QA) of these protein models.

This problem has recently got attention from the machine learning community. Various artificial intelligence methods were applied such as neural networks [15] and support vector machines [13] [14]. More recent approaches mostly include deep learning methods [5] [4] [12] [3]. The newest approach is to use graph machine learning methods such as Graph Convolutional Networks (GCN) [2], where the protein is in some way represented as a graph. This work brings the new idea of capturing the 3D structure of this graph to improve the quality of GCN using convlutions based on spherical harmonics.

2 Problem statement

Consider a 3D model of a protein in space. The protein represents a chain of amino acids rolled up in space. Through dividing space around a protein into cells, for example, by the Voronoi method, we can get a 3D-graph, the vertices of which are amino acids of protein and

edges are carried out between those amino acids that are in adjacent cells. Denote the resulting graph by $G = (V, E)$, where verticles $V = (v_1, \ldots, v_n)$ are a set of amino acids, E are edges. For the i-th vertex we denote for $\mathcal{N}(v_i)$ the set of its neighbors in a graph G and for G an adjacency matrix $\boldsymbol{A}$:

$$A_{ij} = \begin{cases} 1, & (v_i, v_j) \in E \\ 0, & \text{otherwise.} \end{cases}$$

Consider that each vertex v_i is described by some real d-dimensional vector of attributes $x(v_i) = \boldsymbol{x}_i$. In the simplest case, it can be a one-hot representation of an amino acid type. We can form feature matrix $\boldsymbol{X}$ from vectors $x(v_i)$ for every vertex x_i. Using these data we will solve a regression problem: to predict for each vertex v_i a real number - its "score". In other words, how correctly it is placed in the given 3D-model in comparison with the actual conformation of this protein.

3 Graph Convolutional Networks

We will develop approach for machine learning on graphs using Graph Convolutional Network (GCN) [7]. The idea of this approach is aggregation of neighbors features for every vertex and forming new feature vectors on the layer's output. So, for GCN with L layers, $L \geqslant 2$ we have:

$$A_{ij} = \begin{cases} \boldsymbol{H}^{(0)} = \boldsymbol{X} \\ \boldsymbol{H}^{(l)} = \sigma\left(\boldsymbol{A}\boldsymbol{H}^{l-1}\boldsymbol{W}^{(l-1)}\right) \quad \text{for } l \in \{1, \ldots, L-1\} \\ \boldsymbol{H}^{(L)} = \boldsymbol{A}\boldsymbol{H}^{L-1}\boldsymbol{W}^{(L-1)}. \end{cases}$$

In the above $\boldsymbol{H}^{(l)}$ denotes feature matrix at l-th layer and $\boldsymbol{W}^{(l)}$ denotes weight matrix. Common choise for activation function σ is a ReLU activation: $\mathrm{ReLU}(x) := \max(x, 0)$ or an ELU activation: $\mathrm{ELU}(x) := \begin{cases} x, & x \geqslant 0 \\ \alpha(e^x - 1), & x < 0 \end{cases}$. Wheights matrix $\boldsymbol{W}^{(l)}$ are trained by stochastic gradient descend or its modifications.

We rely on this approach because it has already showed outperformance in protein quality assessment problem [2].

The main problem here is that classic GCN is not able to use information about locations of vertices in space. This is because the coordinates in space are given ambiguously: the turned or shifted proteins are actually isomorphic. So our impovement is to capture such information from sequential structure of a protein.

4 Spherical Convolutional Networks

4.1 Spherical harmonics

Let us consider a function $f(\Omega) : [0, \pi] \times [0, 2\pi) \to \mathbb{R}$ — mapping from unit sphere to real numbers. Such function might be unknown or its evaluation might be time consuming. So, we want to expance this function as a linear combination of simplier functions. The common approach that came from theoretical mechaincs is to use spherical harmonics [10]. We will use the following form of spherical functions:

$$Y_l^m(\varphi, \psi) = \sqrt{\frac{(2l+1)}{4\pi}\frac{(l-m)!}{(l+m)!}} P_l^m(\cos\varphi) e^{im\psi},$$

where P_l^m are associated Legendre polynoms [10].

On the unit sphere, any square-integrable function can thus be expanded as a linear combination of these:

$$f(\varphi, \psi) = \sum_{l=0}^{\infty} \sum_{m=-l}^{m=l} f_l^m Y_l^m(\varphi, \psi).$$

We will use this fact to train a function of vertex features using the first few components of this expancion. Since the function is real, the real representation of spherical harmonics can be used:

$$Y_{lm} = \begin{cases} \sqrt{2}(-1)^m \operatorname{Im}\left[Y_l^{|m|}\right] & \text{if } m < 0 \\ Y_l^0 & m = 0 \\ \sqrt{2}(-1)^m \operatorname{Re}\left[Y_l^m\right] & \text{if } m > 0. \end{cases}$$

4.2 Spherical convolution

Consider a vertex v_i. Since all the amino acids in the protein are connected in a peptide chain, it is easy to construct its local coordinate system for the amino acid v_i under consideration — on two dihedral corners, which are unambiguously determined from the geometry of the peptide chain. Write the coordinates of all the neighbors of $v_j \in \mathcal{N}(v_i)$ of the amino acid in the obtained coordinate system. Then proceed to spherical coordinates, and project all vertices onto a unit sphere with the center in v_i. Now, each vertex $v_j \in \mathcal{N}(v_i)$ can be matched with a pair of angles $\Omega_i^j = (\varphi_i^j, \psi_i^j)$ that specify the angular position of the projection of the vertex v_j onto a unit sphere in the local coordinate system of v_i.

Now, having an unambiguous orientation for each vertex of the graph, we can introduce the convolution operation. Let us consider a certain matrix function $f(\Omega) : [0, \pi] \times [0, 2\pi) \to \mathbb{R}^{d \times d'}$ on a single sphere. We can expance it into a series on the basis of spherical functions $\{Y_l^m\}_{l,m}$ and leave the first few components:

$$f(\Omega) \approx f_W(\Omega) = \sum_{l=0}^{L} \sum_{m} \boldsymbol{W}_l^m Y_l^m(\Omega),$$

where $\boldsymbol{W}_l^m$ denotes coefficient matrix in the expancion of matrix function f on the basis of $\{Y_l^m\}_{l,m}$. Then we can introduce the spherical convolution operation for the vertex v_i in the following way:

$$f_W \circ v_i = \sum_{v_j \in \mathcal{N}(v_i)} f_W(\Omega_i^j) x(v_i).$$

Considering $\boldsymbol{W}_l^m$ matrices to be optimized parameters, we will thus train spherical filters.

4.3 Spherical convolution layer

Let us have a 3D model of a protein consisting of N amino acids, the i-th amino acid is described by the trait vector $\boldsymbol{x}_i \in \mathbb{R}^d$. Let us denote all the vertices through the $\boldsymbol{X} \in \mathbb{R}^{N \times d}$ feature matrix. Then one layer of spherical convolution is written down as follows:

$$\boldsymbol{X} \longrightarrow \boldsymbol{X}' = \sigma(f_W \circ \boldsymbol{X}) = \sigma\left(\sum_{l,m} Y_l^m(\boldsymbol{A}_\Omega) \boldsymbol{X} \boldsymbol{W}_l^m\right),$$

where σ is an activation function, Y_l^m are spherical functions, $\boldsymbol{W}_l^m$ are optimized parameters and $\boldsymbol{A}_\Omega$ is the adjacency matrix of graph G, which cells contains the spherical coordinates of

the vertices in the corresponding local coordinate system:

$$[\boldsymbol{A}_\Omega]_{i,j} = \begin{cases} \Omega_i^j, & (v_i, v_j) \in E \\ 0 & \text{otherwise.} \end{cases}$$

5 Experiment

5.1 Dataset

All models are taken from the from CASP competition data (`http://predictioncenter.org`), which is dedicated to the prediction of the 3D structure of proteins by the amino acid sequence. We take data from CASP12 and CASP13 as a test sample, and data from earlier CASPs as a training sample.

For each protein there is one real experimentally obtained 3D structure and many generated 3D structures. Our task is to predict the CAD-score [11] for each of the generated structures i.e. how similar each of the generated structures is to the real one. Graphs are generated using Voronoi diagrams with weights — area of contact.

We have precalculated spherical harmonic of the order of 5 for every pair of incident residues. This took 60GB of HDD space when calculated on CASP8-CASP12. So, this appears to be the main problem there, comparing to the fact that raw data tooks only 15GB and that value grows as n^2, where n is an order of spherical harmonic.

5.2 Metrics

In this task there is a problem of selecting the right quality metric. It was found that MSE's conventional metric used for training were not suitable for the evaluating the quality of the algorithm. This is due to the fact that it does not reflect what the algorithm was created for at all — to select protein folding models. So, we need more suitable metric. Often Pearson correlation between CAD models or residues and algorithm predictions is chosen for this purpose [2]. We will also use **z-score** metric because it represts how good is the model with the maximum predicted score.

We will calculate these metrics for every protein, and then average them. As the result, we will get the global metric value.

5.3 Baseline

For the baseline we will use an architecture inspired by GraphQA [2] network. Firstly, we encode residues features to high-dimensional space using linear layers with a size increasing by a power of two. For the next step we process obtained features through 8 graph convolutional layers to account for the relationships of residues. Finally, we pass the result through a multi-layer perceptron and get single output with sigmoid activation function as the CAD score is from 0 to 1. We have chosen ELU as an activation function for hidden layers. Adam optimizer [6] is used for training with learning rate set to 0.001.

This model was trained on CASP8, CASP9, CASP10, CASP11 datasets for 50 iterations and evaluated on CASP12. We decided to train it on CPU because the slowest part of training was the loading features and adjacency matrices from HDD.

We managed to achieve the maximum Pearson correlation value of 0.57 and maximum z-score value of 0.979. It is significantly lower that many of state-of-the-art algorithms [2] but it can be explained by the fact that we only used geometric structure of proteins. All the high results were obtained only with the use of complex features that represent chemical relations between residues and some biological features that represent protein evalution [2].

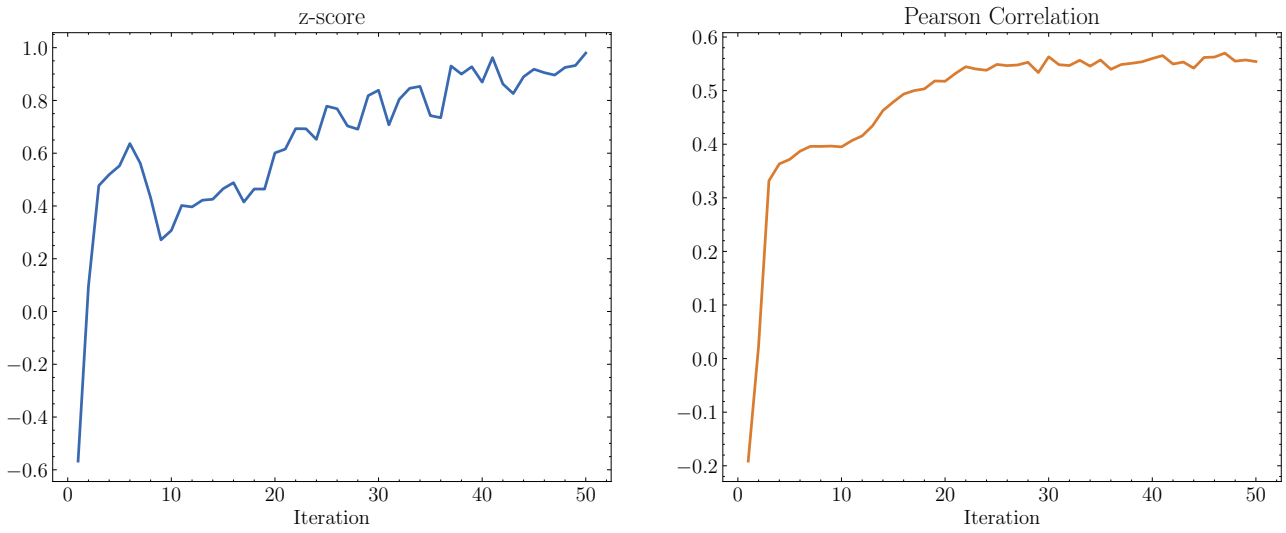

Figure 1 z-score and Pearson correlation coeffient for each iteration on CASP12 dataset.

5.4 Spherical Convolutional Networks

We have ran the same architecture with spherical convolutional layers instead of GCN. The main problem there was the fact, that the number of tained parameters has increased in 25 times because we have used spherical harmonics of the order of 5. So, we have increased learning rate and started learning on GPU because the loading from HDD now is not a bottle neck.

5.5 Comparsion

Table 1 the performance of the state-of-the-art methods of Protein Quality Assessment. The important remark there is the fact that other approaches shown in this table use biological and chemical features but in turn we use only geometric representation of residues graph. Despite that fact Spherical Convolutional Network has shown high performance.

	ρ	r	τ	z-score
ProQ3D	0.806			
ProQ4				
VoroMQN	0.605			
Rwplus	-0.096			
AngularQA				
3D CNN				
Ornate	0.670			
Simple GCN	0.55			0.97
SCN				

Table 1 Comparsion of Pearson, Spearman and Kendell correlation coefficients and z-score of the state-of-the-art algorithms, our GCN baseline and Spherical Convolutional Network on CASP12 dataset.

6 Conclusion

For the first time we applied spherical convolutions for capturing the 3D sctructure of graph. The results shown that it could give a significant imporvement of the quality of the algorithm.

This idea can be combinated with other ideas introduced in other papers [12] [2] [14] so we hope that it can achieve even higher results in the problem of Protein Quality Assessment. We want to notiece that the idea of spherical convlutions is universal and can be applied to various types of tasks of learning on graphs with 3D structure and hope that it will find such applications.

Finally, we wish that this idea will be developed and be applied in more complicated approaches of learning on graphs such as graph variational autoencoders [8] and Quality Assessment will become a popular task in machine learning community.

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