Learning co-evolution information with natural language processing for protein folding problem[*]

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Many problems in bioinformatics are related to protein folding. Most of the techniques aimed to solve such problems usually begin by building protein sequence descriptors. One of the most significant parts of such descriptors is co-evolution information which computation is based on Multiple Sequence Alignments (MSA). This technique requires significant computational efforts, moreover, it does not guarantee precise results since it fully relies on finite databases. Besides, this method fails for sequences with shallow alignment. In this work, we will consider pre-trained language models (LMs) as a potential alternative to this increasingly time-consuming database search. Specifically, our main focus is fold classification problem. We will examine several state-of-the-art methods and modify them by replacing MSA-based feature-generation parts with pre-trained LMs.

1 Introduction

Protein properties are determined by its shape which is specified by its amino acid sequence [13]. Therefore it is important to learn how to analyze this sequence. Any analysis usually begins by constructing protein sequence descriptors whose essential part is a co-evolution information. This information can be obtained by searching for homologues of the target protein in large databases and further computing multiple sequence alignment (MSA) on it.

Co-evolution-based methods assume that a mutation of one amino acid very often leads to mutations of others. Therefore given an amino acid sequence it is natural to look for other similar sequences. That is usually performed with MSA [5]. The problem arises when we're dealing with the sequences that did not evolve a lot. They will have shallow alignments, i.e. there will be only a few similar sequences. Therefore, information extracted from these alignments will be insignificant.

Besides, computing MSA is a heavy task. Moreover, alignment databases are finite. If for a given sequence there are no matches in the database, MSA-based methods fail to produce reliable results.

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16   In this work, we will consider pre-trained language models (LMs) [8] as a potential alterna-
17 tive to traditional MSA approaches. It is assumed that protein sequences are not random [4],
18 that there is logic in amino acids structure. Therefore, a set of all amino acids could be seen as
19 a language with complicated inner rules. With the invention of BERT [6] it has become possible
20 to learn the structure of any abstract language. It is natural to assume that by learning amino
21 acids structure, BERT will be able to implicitly learn co-evolution information.

22   Our main aim is to study the efficiency of pre-trained LMs in application to the fold classi-
23 fication problem. To start with, we will consider the state-of-the-art method DeepSF [9] which
24 solves the protein fold classification problem. By replacing its MSA-based feature-generation
25 part with a pre-trained LM, we will study how NLP approach affects on learning the fold-related
26 information. The whole framework is schematically represented in Figure 1. Further, we can
27 do the same with other fold classification algorithms [7, 14] as well as with end-to-end protein
28 structure prediction methods [10, 15].

29 2   Problem statement

30 2.1   General description

31 Proteins that share similarities in their structure are divided into classes – folds [12]. In this
32 work we investigate a fold classification problem.

33   We use the following notation: S is a set of all known classes, X is a set of all proteins with
34 known folds and $f : X \rightarrow S$ is a mapping between proteins and their classes.

35   Suppose, $x \notin X$ is a protein with unknown fold. We aim to build a model capable of either
36 classifying x as an element of one of the present classes, extending f on the set $X \cup \{x\}$ or
37 concluding that x does not share enough similarities with any of known classes.

38 2.2   Data

39 We use SCOP2 [1,2] dataset. It contains information about proteins whose structure is already
40 known. All the proteins in the database have classes assigned to them (folds). At present, there
41 are 1501 known folds [2].

42   In SCOP2 proteins are represented by their amino acid sequences. Each sequence is stored
43 as a string in the 20 letter alphabet and an ID. The length of the string varies from one protein
44 to another. Search by ID allows database users to extract information about target proteins,
45 including their fold classes.

46 2.3   Baseline solution

47 Our solution is a modification of the DeepSF [9] method. The designers of DeepSF use PSI-
48 BLAST [3] to generate features from MSA as well as SCRATCH [11] to extract secondary

structure (3 classes) and solvent accessibility (2 classes). In the core of this classification method PSI-BLAST is used during the first stage of prediction [11].

Hoe et al. then use these features as an input to the deep convolutional neural network. The depth of CNN used in DeepSF is 10. The output of the model is a vector of fold probabilities. Fold with the maximal probability is accepted as a target protein fold.

2.4 Proposed solution

DeepSF feature generation is entirely based on MSA. The main point of this work is to suggest another approach to feature generation which is independent of MSA.

We apply BERT to the language of amino acids. We take the representation of acid sequences BERT creates as a new set of features. Then we train DeepSF model on these features

It shall be noted that we do not reject co-evolution information in our research. Instead of directly applying MSA we let BERT learn information about amino acid language. We suppose that the model learns evolution information implicitly.

2.5 Evaluation

We use standard cross-validation procedure to compute accuracy of our model. We then compare it to the accuracy score of DeepSF method based on MSA feature generation as well as several other state-of-the-art techniques.

3 Structure of the article

Divide your article into clearly defined and numbered sections and paragraphs.

3.1 Paragraph

Sections and paragraphs are numbered and have a brief heading.

4 Concluding Remarks

This section should provide the summary and explore the significance of the results achieved and list problems not yet solved. Results should be clear and concise.

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