

PROSIMA: Protein Similarity Algorithm

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Abstract

In this article we present a novel algorithm for measuring protein similarity based on their three dimensional structure (protein tertiary structure). The PROSIMA algorithm using suffix tress for discovering common parts of main-chains of all proteins appearing in current NCSB Protein Data Bank (PDB). By identifying these common parts we build a vector model and next use classical information retrieval tasks based on the vector model to measure the similarity between proteins - all to all protein similarity. For the calculation of protein similarity we are using tf-idf term weighing schema and cosine similarity measure. The goal of this work to use the whole current PDB database (downloaded on June 2009) of known proteins, not just some kinds of selections of this database, which have been studied in other works. We have chose the SCOP database for verification of precision of our algorithm because it is maintained primarily by humans. The next success of this work is to be able to determine protein SCOP categories of proteins not included in the latest version of the SCOP database (v. 1.75) with nearly 100% precision.

1 Introduction

Analyzing three dimensional protein structures is a very important task in molecular biology. The solution more and more nowadays for protein structures is the

use of state-of-the-art technologies such as nuclear magnetic resonance (NMR) spectroscopy techniques or X-Ray crystallography as seen in the increasing number of Protein Data Bank (PDB) [16] entries: 57944 as of June 8, 2009. Protein Data Bank is a database of 3D structural data of large biological molecules, such as proteins and nucleic acids. It was proved that structurally similar proteins tend to have similar functions even if their amino acid sequences are not similar to each other. Thus it is very important to find proteins with similar structures (even in part) from the growing database to analyze protein functions. Yang et al. [25] exploited machine learning techniques including variants of Self-Organizing Global Ranking, a decision tree, and a support vector machine algorithms to predict the tertiary structure of transmembrane proteins. Hecker et al. [10] developed a state of the art protein disorder predictor and tested it on a large protein disorder dataset created from Protein Data Bank. The relationship of sensitivity and specificity is also evaluated. Habib et al. [8] presented a new SVM based approach to predict the subcellular locations based on amino acid and amino acid pair composition. More protein features can be taken into consideration and consequently improves the accuracy significantly. Wang et al. [22] discussed an empirical approach to specify the localization of protein binding regions utilizing information including the distribution pattern of the detected RNA fragments and the sequence specificity of RNase digestion.

In this paper we present a novel method for analyzing three dimensional protein structure using suffix trees and classical information retrieval methods and schemes. Several studies were developed for indexing protein tertiary structure [5, 20]. These studies are targeted mainly at some kind of selection of the PDB database. The goal of this work is that we are taking into account the whole current PDB database and calculating the similarities of each protein in comparison to each other protein. The suffix tree is a very useful data structure which can discover common substructures of proteins in a reasonable time (linear or logarithmic time), depending on the implementation of the construction algorithm.

When the generalized suffix tree is constructed for all proteins appearing in the entire PDB database, we are using similar methods which were previously studied [27, 9, 3, 13, 23] for measuring the similarity of proteins based on their three dimensional structure definition. Our work arises from the relations of amino acid residues defined by its dihedral angles rather than the relations between just the Alpha Carbon atoms. The relations between alpha carbons use DALI for example, when computing the distance matrix between alpha carbon atoms of a given protein. In the final stage we are building a vector space model which is very suitable for various information retrieval tasks and can be used for future studies of proteins relations. Mainly we want to focus on protein hierarchical clustering and make comparison with existing protein hierarchical databases such as CATH.

2 Background

2.1 Protein Structure

Proteins are large molecules. In many cases only a small part of the structure - *an active site* - is directly functional, the rest existing only to create and fix the spatial relationship among the active site residues [11].

Chemically, protein molecules are long polymers typically containing several thousand atoms, composed of a uniform repetitive backbone (or mainchain) with a particular sidechain attached to each residue. The amino acid sequence of a protein records the succession of sidechains.

The polypeptide chain folds into a curve in space; the course of the chain defining a **folding pattern**. Proteins show a great variety of folding patterns.

Underlying these are a number of common structural features. These include the recurrence of explicit structural paradigms - for example, α - *helices* and β - *sheets* and common principles or features such as the dense packing of the atoms in protein interiors. Folding may be thought of as a kind of intramolecular condensation or crystallization [11].

2.2 Vector Space Model

The vector model [1] of documents is dated back to 70th of the 20th century. In vector model there are documents and users queries represented by vectors.

We use m different terms $t_1 \dots t_m$ for indexing N documents. Then each document d_i is represented by a vector:

$$d_i = (w_{i1}, w_{i2}, \dots, w_{im}),$$

where w_{ij} is the weight of the term t_j in the document d_i .

An index file of the vector model is represented by matrix:

$$D = \begin{pmatrix} w_{11} & w_{12} & \dots & w_{1m} \\ w_{21} & w_{22} & \dots & w_{2m} \\ \vdots & \vdots & \ddots & \vdots \\ w_{n1} & w_{n2} & \dots & w_{Nm} \end{pmatrix},$$

where i -th row matches i -th document, and j -th column matches j -th term.

The similarity of two documents is given for example by following formula (cosine measure):

$$\text{sim}(d_i, d_j) = \frac{\sum_{k=1}^m (w_{ik}w_{jk})}{\sqrt{\sum_{k=1}^m (w_{ik})^2 \sum_{k=1}^m (w_{jk})^2}}$$

For more information see [12, 15, 1].

2.3 Suffix Trees

A suffix tree is a data structure that admits efficient string matching and querying. Suffix trees have been studied and used extensively, and have been applied to fundamental string problems such as finding the longest repeated substring [24], strings comparisons [4], and text compression [17]. Following this, we describe the suffix tree data structure - its definition, construction algorithms and main characteristics. One major difference is that we treat documents as sequences of words, not characters. A suffix tree of a string is simply a compact trie of all the suffixes of that string. In more precise terms [26] Citation:

Definition 2.1. A suffix tree T for an m -word string S is a rooted directed tree with exactly m leaves numbered 1 to m . Each internal node, other than the root, has at least two children and each edge is labeled with a nonempty sub-string of words of S . No two edges out of a node can have edge labels beginning with the same word. The key feature of the suffix tree is that for any leaf i , the concatenation of the edge labels on the path from the root to leaf i exactly spells out the suffix of S that starts at position i , that is it spells out $S[i \dots m]$.

In cases where one suffix of S matches a prefix of another suffix of S then no suffix tree obeying the above definition is possible since the path for the first suffix would not end at a leaf. To avoid this, we assume the last word of S does not appear anywhere else in the string. This prevents any suffix from being a prefix to another suffix. To achieve this we can add a terminating character, which is not in the language that S is taken from, to the end of S .

In a similar manner, a suffix tree of a set of strings, called a generalized suffix tree [7], is a compact trie of all the suffixes of all the strings in the set [26]:

Definition 2.2. A generalized suffix tree T for a set S of n strings S_n , each of length m_n , is a rooted directed tree with exactly $\sum m_n$ leaves marked by a two number tuple (k, l) where k ranges from 1 to n and l ranges from 1 to m_k . Each internal node, other than the root, has at least two children and each edge is labeled with a nonempty sub-string of words of a string in S . No two edges out of a node can have edge labels beginning with the same word. For any leaf (i, j) , the concatenation of the edge labels on the path from the root to leaf (i, j) exactly spells out the suffix of S_i that starts at position j , that is it spells out $S_i[j \dots m_i]$.

Several linear time algorithms for constructing suffix trees exist [14, 21, 24]. To be precise, these algorithms also exhibit a time dependency on the size of the vocabulary (or the alphabet when dealing with character based trees): they actually have a time bound of $O(L \times \min(\log |V|, \log L))$, where L is the length of the string and $|V|$ is the size of the language. These methods are more difficult to implement than the simple method. In this work we have made some implementation improvements of the naive method to achieve better than the $O(L^2)$ worst-case time bound [13].

3 Preparing the Data

In this section we describe the process of retrieving the data for protein indexing. We are using the whole

current PDB database which consists of approximately 58000 known proteins.

3.1 Creating Proteins Collection

In the current PDB database we can find proteins, nucleic acids and complex assemblies. Our study is focused just on relations between proteins. We have filtered out all nucleic acids and complex assemblies from the entire PDB database. Next we have filtered out proteins which have incomplete N-C α -C-O backbones (e.g. some of the files have C atoms in the protein backbone missing, etc.).

After this cleaning step we have obtained a collection consisting of 53069 files. Each such that the file contains a description of one protein and its three dimensional structure and contains only amino acid residues with complete a N-C α -C-O atom sequence.

From each such that the file we have retrieved has at least one main chain (some proteins have more than one main chain) of at least one model (in some cases PDB files contains more models of three dimensional protein structure). In cases when the PDB file contains more main chains or more models we take into account all main chains of all models.

3.2 Encoding the 3D Protein Main Chain Structure for Indexing

To be able to index proteins by IR techniques we need to encode the 3D structure of the protein backbone into some sequence of characters, words or integers (as in our case). Since the protein backbone is the sequence of the amino acid residues (in 3D space) we are able to encode this backbone into the sequence of integers in the following manner.

For simple example let's say the protein backbone consists of four amino acid residues $M V L S$ (abbreviations for methionie, valine, leucine and serine). The relationship between the two following residues can be described by its dihedral angles ϕ , ψ and ω [11]. Since ϕ and ψ are taking values from the interval $\langle -180^\circ, 180^\circ \rangle$ we have to do some normalization. From this interval we have obtained 36 values (the interval was divided into 35 equal parts, by 10° degrees) i.e. $-180^\circ, -170^\circ, \dots, 0^\circ, 10^\circ, \dots, 180^\circ$. Each of these values was labeled with a positive number (00, 01, 02, \dots , 35). Now, let's say that ϕ is -21° , the closest discrete value is -20° which has the label 02, so we have encoded this dihedral with the string

'02'. The same holds for ψ . The ω was encoded as the two characters A or B since the ω tends to be almost in every case 0° or 180° . After concatenation of these three parts we get a string which looks something like this 'A0102' which means that $\omega \approx 180^\circ$, $\phi \approx -10^\circ$, $\psi \approx -20^\circ$

3.3 Indexing

The major objective of this stage is to prepare the data for indexing by suffix trees. The suffix tree can index sequences. The resulting sequence in our case is a sequence of integers (positive numbers). For simple example let's say we have a protein with a backbone consisting of 6 residues e.g. M V L S E G with its three dimensional properties. The resulting encoded sequence can be for example:

{A3202, A2401, A2603, A2401, A2422}

After obtaining this sequence of 5 words, we create a dictionary of these words (each unique word receives its own unique integer identifier). The translated sequence will look like this:

{0, 1, 2, 1, 3}

In this way we encode each main chain of each model contained into one PDB file. This task is done for every protein included in our filtered PDB collection. Now we are ready for indexing proteins using suffix trees.

4 PROSIMA - Protein Similarity Algorithm

In this section we describe the algorithm for measuring protein similarity based on their tertiary structure. A brief description of the algorithm follows:

1. Prepare the data as was mentioned in section 3.
2. Insert all encoded main chains of all proteins in the collection into the generalized suffix tree data structure.
3. Find all maximal substructures clusters in the suffix tree.
4. Construct a vector model of all proteins in our collection.
5. Build proteins similarity matrix.
6. For each protein find top N similar proteins.

4.1 Inserting All Main Chains into the Suffix Tree

In this stage of the algorithm we will be constructing a generalized suffix tree of all encoded main chains.

As was mentioned in section 3, we obtain the encoded forms of three dimensional protein main chains - sequences of positive numbers. All of these sequences are inserted into the generalized suffix tree data structure (section 2.3).

4.2 Finding All Maximal Substructure Clusters

To be able to build a vector model of proteins we have to find all maximal phrase clusters. The **phrase** in our context is an encoded protein main chain or any of its parts (words of the phrase is encoded dihedral angles). The document in our context can be seen as a set of encoded main chains of the protein. Now we can define a maximal phrase cluster (the longest common substructure) [27]:

Definition 4.1. A phrase cluster is a phrase that is shared by at least two documents, and the group of documents that contain the phrase. A maximal phrase cluster is a phrase cluster whose phrase cannot be extended by any word in the language without changing (reducing) the group of documents that contain it. Maximal phrase clusters are those we are interested in.

Now we simply traverse the generalized suffix tree and identify all maximal phrase clusters (i.e. all of the longest common substructures).

4.3 Building a Vector Model

In this section we describe the procedure of building the matrix representing the vector model index file (section 2.2). In a classical vector space model the document is represented by the terms respectively by the weights of the terms. **In our model the document is represented not by the terms but it is represented by the common phrases (maximal phrase clusters)!**

In the previous stage of the algorithm we have identified all maximal phrase clusters - all of the longest common substructures. From the definition of the phrase cluster we know that the phrase cluster is the group of the documents sharing the same phrase (group of proteins sharing the same substructure). Now we can obtain the matrix representing the vector model index file directly from the generalized suffix tree. Each document (protein) is represented by the maximal phrase clusters in which it is contained. For computing the weights of the phrase clusters we are using a $tf - idf$ weighting schema:

$$w_{ij} = tf_{ij} \times idf_j = tf_{ij} \times \log \frac{n}{df_j} \quad (1)$$

where tf_{ij} is the frequency of term t_j in document d_i and df_j is count of documents where term t_j appears in, and n is the total count of documents in collection.

Simple example: let's say we have a phrase cluster containing documents d_i . These documents share the same phrase t_j . We compute w_{ij} values for all documents appearing in a phrase cluster sharing the phrase t_j . This task is done for all phrase clusters identified by the previous stage of the algorithm.

Now we have a complete matrix representing the index file in a vector space model (section 2.2).

4.4 Building a Similarity Matrix

In the previous stage of the algorithm we have constructed a vector model index file. To build a protein similarity matrix we use standard information retrieval techniques for measuring the similarity in a vector space model. As was mentioned in section 2.2 we have used cosine similarity which looks quite suitable for our purpose. The similarity matrix will be:

Documents (proteins) similarity matrix:

$$S = \begin{pmatrix} 0 & sim(d_1, d_2) & \dots & sim(d_1, d_n) \\ sim(d_2, d_1) & 0 & \dots & sim(d_2, d_n) \\ \vdots & \vdots & \ddots & \vdots \\ sim(d_n, d_1) & sim(d_n, d_2) & \dots & 0 \end{pmatrix},$$

where the i -th row matches the i -th document (protein respectively), and the j -th column matches the j -th document (protein). The similarity matrix is diagonally symmetrical. Note that on the diagonal we have put zeros to eliminate $sim(d_i, d_i)$ which is always equal to 1 and for the simplification of the last step of the algorithm.

As this task is the most time consuming, we have developed a multi-threaded variant of computing this similarity matrix. We have simply divided the similarity matrix into n equal parts and for each n_i thread computed its own part of the similarity matrix. By this little enhancement we have achieved a very good reduction of the time needed to compute the similarity matrix - multiprocessors or multi-core processors computers required.

4.5 Finding Similar Proteins

This step is quite simple. When we have computed the similarity matrix S , we simply sort the documents (proteins) on each row according to its scores. The

higher score the more similar protein is. This is done for each protein in our protein collection.

5 Evaluation and Testing

5.1 Structural Classification of Proteins

To evaluate the accuracy and effectiveness of our algorithm we are using a comparison with the SCOP database [19]. It is maintained primarily by humans in contrast with for example CATH [2], which uses some automated methods. We are using the current version of the SCOP database (v. 1.75 released on June 2009) which contain 38221 of proteins classified. We have chose SCOP because we wanted to evaluate our algorithm to manually classified proteins rather than to automated methods.

5.2 Evaluation

For each protein P in our collection C we did the following:

1. For protein P determine the class, folding pattern group, super-family, family and domain.
2. Based on the similarity matrix, find N most similar proteins P_S according to their score of similarity to protein P .
3. For each protein P_S determine the class, folding pattern group, super-family, family and domain.
4. For all proteins in our collection compute the percentage of correctly classified proteins P_S to protein P .

We did this for each protein in our collection and computed the overall percentage accuracy over our filtered collection. There are approximately 20000 unclassified proteins because they do not appear in current SCOP database.

In more precise terms: let's say we have protein P . Based on the calculated similarity matrix we sort all other proteins P_S in our protein collection in descending order according to their scores. The greater the score the more similar the protein is to protein P . We take only the top N highest scoring proteins (the top N most similar proteins to the given protein). We set N to the value of 20. After that we obtain a list such that the similar proteins for every protein in our collection we have determined the SCOP classification of those proteins.

5.3 Experiments

Here we present our first results with this new method of measuring protein similarity based on their tertiary structure and int comparison with the SCOP database. All experiments were run on computer with 32 GBytes of RAM and 4 AMD 64 bit Opteron dual core CPUs. The whole PDB database indexed by our version of the suffix tree construction algorithm takes about 3.2 GBytes of RAM and about 55 minutes of time (section 4.1). The calculation of the similarity matrix 4.4 takes about 54 hours of time and 12 Gbytes of RAM since the similarity matrix is computed in memory.

First we have computed a percentage accuracy of all proteins in the entire SCOP database (32509 proteins classified), next we have computed the accuracy only for proteins for which our algorithm found proteins with at least some given score of similarity (e.g. we have protein A and for this protein exists at least one protein which has a score of similarity with protein A of at least 0.2 - we cut off all proteins which do not satisfy this assumption) - this is some kind of threshold or cutoff.

The description of the following table 1 is as follows (Figures 1, 2, 3, 4, 5 show these results in a graph representation). Column **No.** means the ordering of similar proteins (e.g. No. 1 means the most similar protein to a given protein, No. 10 means the 10th most similar protein to a given protein). Column **sim** was mentioned above. Line **Count** means for how many proteins with this cutoff were found in our collection. For example line 1 of the table 1 (not considering the header of the table) means that all the proteins placed in the 1st place (i.e. the most similar protein to given a protein) has a 89.36909% accuracy in the classification of class with no cutoff, a 89.62752% accuracy with the cutoff of proteins scoring less than 0.1, etc...

We have also identified class, fold, super-family, family and domain of proteins which are not classified by the SCOP with almost 100% membership accuracy. Table 2 shows these results. Let's examine line 4 of this table. Column $sim = 0.2$ means that we have chosen only proteins which have at least one structurally similar protein with a score of similarity of at least 0.2. Column mpa_{Class} means *minimal membership percentage accuracy to the scop protein class* (same for Fold, Superfamily, Family and Domain). Column UPC - *Unclassified proteins count* is the count of proteins

No.	sim 0.0	sim 0.10	sim 0.15	sim 0.20	sim 0.25
1	87.45	87.72	95.29	98.89	99.40
2	83.33	83.56	91.22	95.23	96.28
3	81.35	81.58	88.67	93.06	94.49
4	79.80	80.03	86.66	90.82	92.56
5	78.07	78.28	85.08	89.05	90.70
6	77.41	77.63	83.92	87.88	89.50
7	76.25	76.48	82.38	86.66	88.07
8	75.29	75.49	81.25	85.10	86.59
9	75.03	75.22	80.77	84.59	85.97
10	73.75	73.95	79.65	83.43	85.09
Count	35951	35663	23962	15408	10507

Table 1. Class classification percentage accuracy.

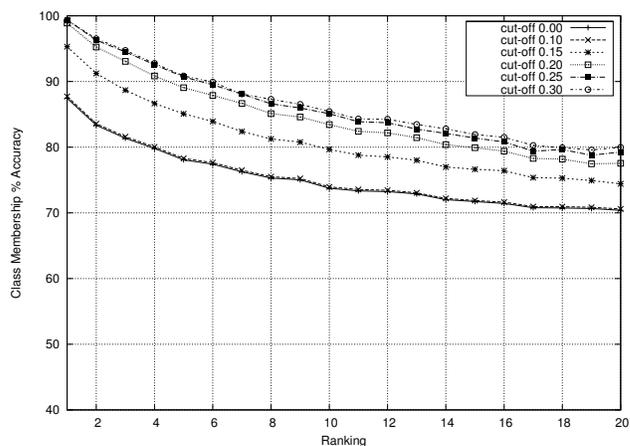


Figure 1. Protein Class Membership Percentage Accuracy.

which are not classified by SCOP and which appear in the first place in the list of similar proteins to a given protein. Column TPC - *Total proteins count* is the total count of proteins which have at least one structurally similar protein with a score of similarity of 0.2. In summary this means that we have found 784 unclassified proteins by using SCOP out of 15408, such that proteins have a 98.89% class membership accuracy, a 98.46% fold membership accuracy, etc.

6 Conclusion

In this article we have presented a novel method for measuring protein similarities using suffix tree data structure and information retrieval techniques. The method is fully automated and in comparison with the human maintained database SCOP has achieved very good results. We have also proved that we can use

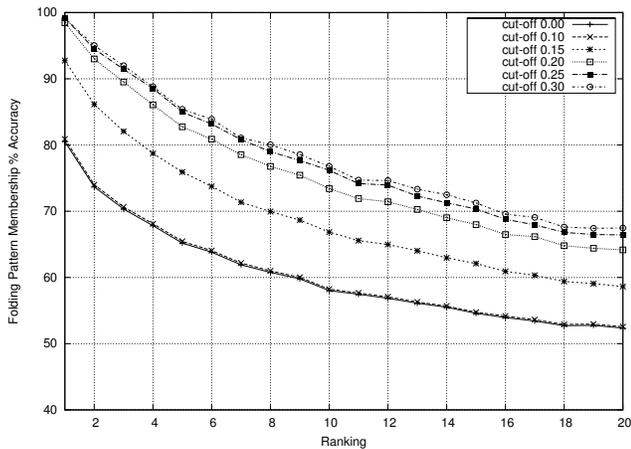


Figure 2. Protein Folding Pattern Membership Percentage Accuracy.

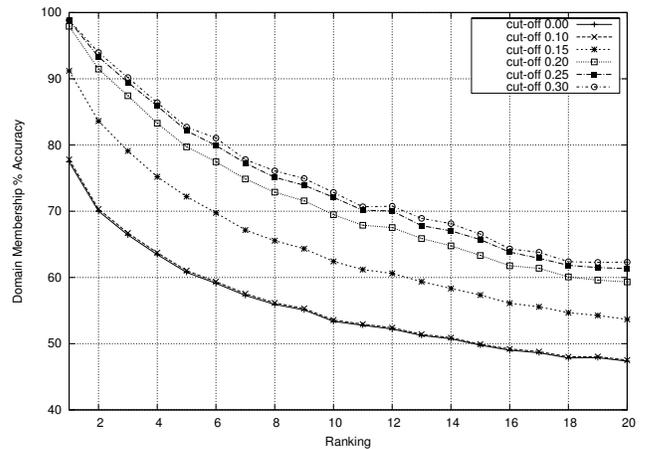


Figure 5. Protein Domain Membership Percentage Accuracy.

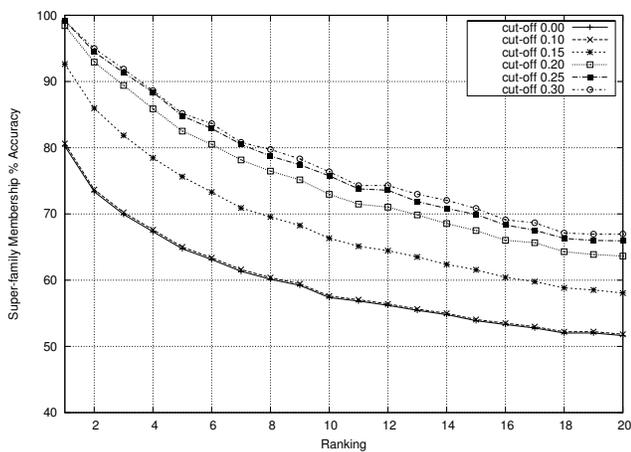


Figure 3. Protein Super-Family Membership Percentage Accuracy.

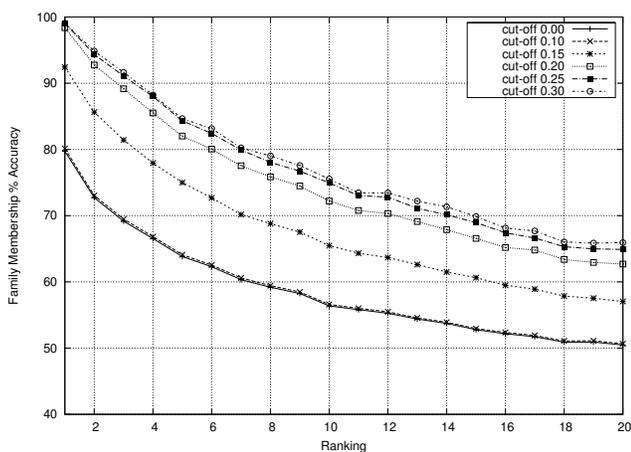


Figure 4. Protein Family Membership Percentage Accuracy.

sim	<i>mpa_C</i>	<i>mpa_F</i>	<i>mpa_{SF}</i>	<i>mpa_D</i>	UPC	TPC
0.00	87.45	80.51	80.23	79.75	77.44	4793
0.10	87.72	80.90	80.62	80.13	77.81	4712
0.15	95.29	92.74	92.62	92.42	91.20	1846
0.20	98.89	98.46	98.44	98.37	97.92	784
0.25	99.40	99.17	99.17	99.07	98.79	460
0.30	99.32	99.14	99.14	99.05	98.85	296

Table 2. Proteins unclassified by using SCOP found by our algorithm and their membership percentage accuracy (*mpa*) to a given Class, Fold, Super-family, Family and Domain.

common information retrieval models and methods for measuring similarity of proteins. With these methods we have achieved very good results.

We are also able to determine classes, folds, super-families, families and domains of many unclassified proteins contained in the current SCOP database with almost 100% membership accuracy. By the simple observation that when the unclassified protein is most similar to the protein which is classified and have at least some given score, than in 99% cases the unclassified protein has a similar SCOP categories as known proteins.

In future work we want to use the similarity matrix for other information retrieval tasks such as clustering. The clustering of proteins is one of the first steps in the homology modeling of proteins, which we want to develop in the future.

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