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Novel 2D Graphic Representation of Protein Sequence and Its Application

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Abstract

In recent years, more and more researchers presented their graphic representations for protein sequence. Here, we present a new 2D graphic representation of protein sequence based on four physicochemical properties of 20 amino acids. By this graphic representation we define a distance calculation formula to quantificationally calculate the similarity degree of different protein sequences. Then we apply the proposed graphical curve and new distance in the similarity/dissimilarity comparison of 10 ND5 proteins and the protein sub-cellular localization prediction about two common test datasets, ZD98 and CL317. The results show the proposed method is easy and effective.

Keywords: Graphic Representation; Protein Sequence; Sequence Similarity; Sub-cellular Location

1 Introduction

As bio-molecular sequences are rapidly growing, it is of great importance for people to reveal their meaning of life by analyzing these bio-molecular data. Now, people have developed many information methods to research the huge amounts of bio-molecular sequences. The graphic representation of biology sequences such as DNA or protein sequence has been a useful method to get important information from the primary sequences.

In 1983 [1], Hamori first tried to use graphical technique to research and analyze the DNA sequences. Thereafter, many researchers followed this research method and proposed some other graphic representations of DNA sequences [2-11]. For instance, Randić [7-9], Qi [5] and Yuan [10] introduced 2D or 3D graphic representations of DNA sequences. Liao [11] and Chi [3] presented higher dimensional methods to graphically represent DNA sequences. Moreover, researchers like Randić [7-9] presented some graphic representations to analyze protein sequences. Considering the physicochemical properties of amino acids Yao [12] proposed a graphical method based on the PK_α values of $COOH$ and NH_3^+ of the 20 amino acids. Xiao [13] and Wu [13] also developed their 2D graphic representations considering the physicochemical properties of 20 amino acids.

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An important application of the proposed graphic representations of DNA or protein sequences is to get the similarities or dissimilarities among different biological sequences but not considering the alignment [12]. Based on the graphic representation of sequence, some mathematical descriptors like E, M/M, L/L [7, 8, 14] are developed to quantificationally compute the evolution distance among sequences. Recently, Liao et al. [15] proposes a new 2D graphic representation. They defined a distance computing formula to calculate the similarities or dissimilarities among different protein sequences. Then the method was used for protein sub-cellular localization prediction and got satisfactory results.

In this paper we propose a new graphic representation of protein sequences considering four main physicochemical properties of amino acids. According to the graphic representation we give a 20D characteristic vector to represent the corresponding protein sequence. The vector method can deal with sequences with different length. Then we use the characteristic vector extracted from graphic representation of protein sequence to analyze the similarities or dissimilarities of ten ND5 protein sequences. The test results show that the proposed method is a useful method in finding the similarities or dissimilarities among different protein sequences. Then, we utilized the similarity evaluation ability of the proposed method to take a prediction of sub-cellular localization of proteins. It is well-known that if two proteins are more similar, the two proteins are more likely to exist in the same sub-cellular location. We take two test datasets, the apoptosis proteins ZD98 and CL317. The prediction accuracy in jackknife test shows that the proposed method is effective on protein sub-cellular localization prediction.

2 Novel 2D Graphic Representation of Protein Sequences

Although proteins have many types and are different in nature and functions, they are composed of 20 native amino acids, which everyone knows have a variety of properties. People can study the structures and functions of proteins by these properties of amino acids. Some graphic representations of protein sequence are presented according to the physicochemical properties of amino acids. For example, Randić in [16] proposed a 2D graphic representation of protein. This method considered a pair of physicochemical properties of 20 amino acids, the pKa values of —NH$_3$ and —COOH. Yao et al. in [12] also proposed a dynamic 2D graphic representation of protein sequence based on the pKa values. In this paper, we present a novel 2D graphic representation based on four main physicochemical characteristic properties of 20 amino acids. They are relative molecular mass, isoelectric point, hydropathy index and melting point. The relative molecular mass can reflect the composition of the side chain. The isoelectric point is the pH value at which a particular surface or molecule carries no net electrical charge. The hydropathy index is a number representing the hydrophobic or hydrophilic properties of side chain of an amino acid. The melting point of amino acid is considered to be that temperature at which its crystalline substance becomes unreliable. The four physicochemical characteristic properties are essential for the protein structure and the catalytic activities of enzymes. The detailed data of the four physicochemical properties are listed in Table 1.

Observing Table 1, we find that similar amino acids have similar physicochemical properties. To clearly know the similarities/dissimilarities among amino acids, we take a similarity analysis of the 20 amino acids based on the four main physicochemical properties. However, the different physicochemical property values in Table 1 have different orders of magnitude. The different magnitude is likely to take bad effect on the similarity analysis of the amino acids. To eliminate

Table 1: Four main physicochemical properties associated with the 20 basic Amino acids

Amino acid	Symbol	MR	PI	HI	MP (°C)	Amino acid	Symbol	MR	PI	HI	MP (°C)
Glycine	G	75.07	5.97	−0.4	290	Serine	S	105.09	5.68	−0.8	228
Alanine	A	89.09	6.01	1.8	297	Threonine	T	119.12	5.87	−0.7	253
Proline	P	115.13	6.48	−1.6	222	Cysteine	C	121.16	5.07	2.5	178
Valine	V	117.15	5.97	4.2	292-295	Asparagine	N	132.12	5.41	−3.5	236
Leucine	L	131.18	5.98	3.8	337	Glutamine	Q	146.15	5.65	−3.5	185
Isoleucine	I	131.18	6.02	4.5	284	Lysine	K	146.19	9.74	−3.9	224-225
Methionine	M	149.21	5.74	1.9	283	Histidine	H	155.16	7.59	−3.2	277
Phenylalanine	F	165.19	5.48	2.8	284	Arginine	R	174.20	10.76	−4.5	238
Tyrosine	Y	181.19	5.66	−1.3	344	Aspartate	D	133.10	2.77	-3.5	270
Tryptophan	W	204.23	5.89	-0.9	232	Glutamate	E	147.13	3.22	−3.5	249

the negative we firstly normalize each property value of 20 amino acids into the range from −1 to 1. The normalization formula is as follows,

$$a' = (a - a\_mean)/a\_var \tag{1}$$

where a_mean is the average value of the corresponding property, and a_var is the variance of this property. The a is the original value of the property of each amino acid, and a' is the normalized value.

Then we can construct a characteristic vector to represent the 20 amino acids, consisting of the four normalized property values by the formula (1). Now, let V_1 and V_2 denote the characteristic vectors of two amino acids, respectively. Let $C(V_1, V_2)$ denote the correlation between two amino acids. It is computed as the *Cosine* function of the angle of the two vectors V_1 and V_2,

$$C(V_1, V_2) = \sum_{i=1}^{4} v_1(i) \times v_2(i) \Bigg/ \sqrt{\sum_{i=1}^{4}[v_1(i)]^2 \times \sum_{i=1}^{4}[v_2(i)]^2} \tag{2}$$

The *Cosine* value of the angle is from -1 to 1 when the angle changes from 180° to 0°. To get a more clear description, we normalize the $C(V_1, V_2)$ value to the range from 0 to 1. Then we define the distance $Dis(V_1, V_2)$ between two amino acids as follows.

$$Dis(V_1, V_2) = \frac{1 - C(V_1, V_2)}{2} \tag{3}$$

Then two amino acids are more similar if the distance D is smaller. Based on all the distances among 20 amino acids we use the *linkage* and *dendrogram* functions of Matlab to achieve their cluster analysis. The clustering result of the 20 amino acids is shown in Fig. 1.

Observing the Fig. 1, we can map the 20 amino acids into a series of numbers if we assign 1 to amino acid K,

$$\begin{array}{lllll}
K \rightarrow 1, & R \rightarrow 2, & H \rightarrow 3, & P \rightarrow 4, & G \rightarrow 5, \\
Y \rightarrow 6, & S \rightarrow 7, & T \rightarrow 8, & D \rightarrow 9, & E \rightarrow 10, \\
N \rightarrow 11, & Q \rightarrow 12, & W \rightarrow 13, & A \rightarrow 14, & V \rightarrow 15, \\
I \rightarrow 16, & L \rightarrow 17, & M \rightarrow 18, & F \rightarrow 19, & C \rightarrow 20.
\end{array}$$

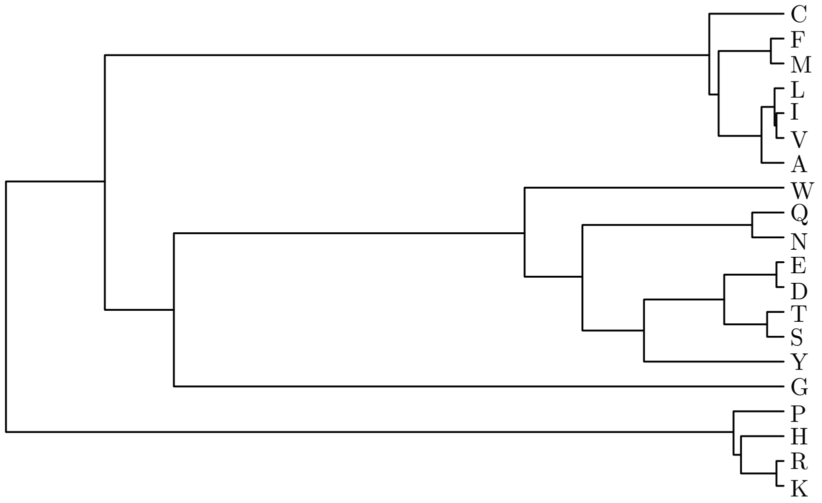


Fig. 1: Clustering results of the 20 amino acids considering the four main physicochemical properties

The two amino acids with closer number have more similar physicochemical properties. Based on the number mapping we give a new graphic representation of protein sequence. Now let S be a protein sequence with N amino acids, $S = s_1 s_2, \cdots, s_N$. For each amino acid s_i in S, according to the number mapping we can map it into the Cartesian coordinate system as follows,

$$\begin{array}{lllll} K \rightarrow (i,1), & R \rightarrow (i,2), & H \rightarrow (i,3), & P \rightarrow (i,4), & G \rightarrow (i,5), \\ Y \rightarrow (i,6), & S \rightarrow (i,7), & T \rightarrow (i,8), & D \rightarrow (i,9), & E \rightarrow (i,10), \\ N \rightarrow (i,11), & Q \rightarrow (i,12), & W \rightarrow (i,13), & A \rightarrow (i,14), & V \rightarrow (i,15), \\ I \rightarrow (i,16), & L \rightarrow (i,17), & M \rightarrow (i,18), & F \rightarrow (i,19), & C \rightarrow (i,20). \end{array}$$

Then we can get N points in the 2D space. Connecting these points by the order of the amino acid in the protein sequence, we can obtain a graphic curve. The protein sequence S is represented by the graphic curve in a 2D space. Here we give a random sequence MMYALFLLSVGLVMG as an example to illustrate the proposed method. The 2D graphic curve of the random sequence is shown in Fig. 2.

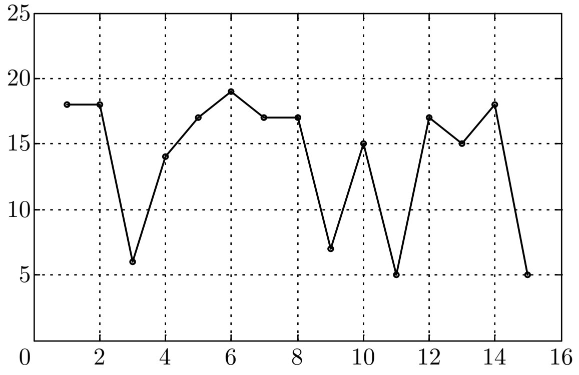


Fig. 2: The 2D curve of the sequence MMYALFLLSVGLVMG

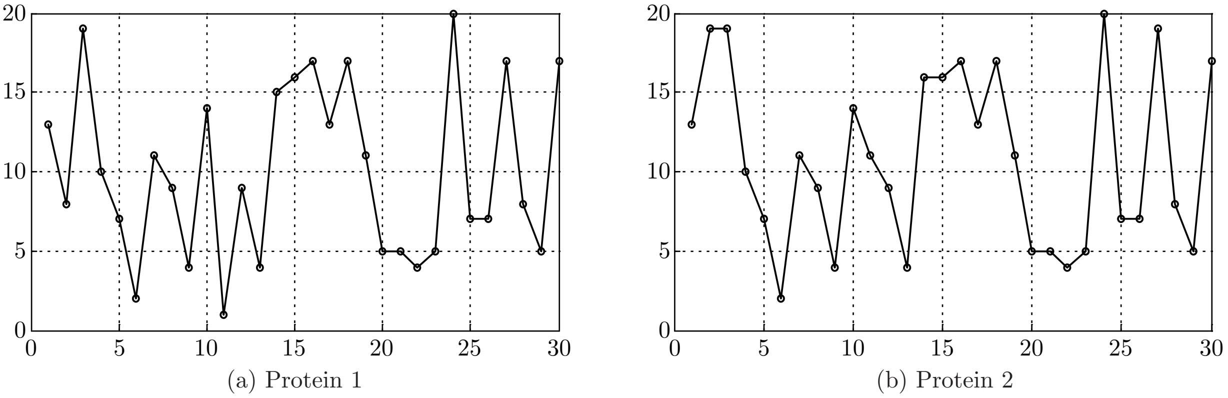
3 Similarities and Dissimilarities of Protein Sequences

Here we first consider two short segments of a protein of yeast Saccharomyces cerevisiae, which was gotten from the Handbook of Chemoinformatics by Randić [16]. As an example, we find some of characterization from the 2D graphic curve with the proposed approach. The two protein sequences are illustrated as follows,

Protein 1, WTFESRNDPAKDPVILWLNGGPGCSSLTGL

Protein 2, WFFESRNDPANDPIILWLNGGPGCSSFTGL

Fig. 3 (a) and (b) show the 2D graphic curves of Protein 1 and Protein 2, respectively. From Fig. 3 we can see that the two curves are very similar. It indicates that the two protein sequences may be highly similar.



(a) Protein 1

(b) Protein 2

Fig. 3: The 2D graphic curves of Protein 1 and Protein 2

In Fig. 4 we show the Y-components of the 2D graphic representation of the two segments. From the figure, we can see that the amino acids corresponding to those points are different when the Y_ Protein 1 and Y_ Protein 2 are not overlapped closely. From the figure, we find that the two protein sequences are generally similar except at some special points. The two proteins are different at the 2-th, 11-th, 14-th, 27-th amino acids.

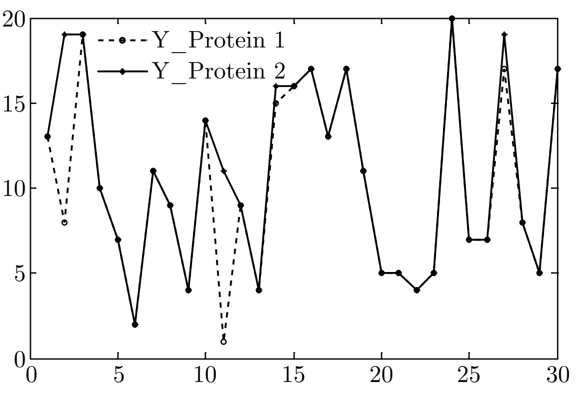


Fig. 4: The Y-components of the graphic curves of Protein 1 and Protein 2

In order to take quantitative similarities/dissimilarities analysis of protein sequences we define a new distance calculating method based on the proposed graphic curve. Observing the curve in

Fig. 3 we find that different vertexes of the curve have different y-axis values. According to the number mapping of 20 amino acids there are 20 different y-axis values. Now let k_i be the amount of y-axis value i. Then for a protein sequence S we can construct a 20D vector V_S as follows,

$$V_S = (k_1, 2k_2, \ldots, 20k_{20}) \tag{4}$$

Then we can define a new distance computing method based on the 20D vector derived from the proposed graphic curve. The calculating formula is as follows:

$$D(S_1, S_2) = \sqrt{\sum_{i=1}^{20} [V_{S_1}(i) - V_{S_2}(i)]^2} \quad i = 1, 2, \cdots, 20 \tag{5}$$

The S_1 and S_2 refer to any two protein sequences, respectively. The $V_{S_1}(i)$ in the formula means the i-th element of the vector V_{S_1} of the sequence S_1. And the $V_{S_2}(i)$ denotes the i-th element of the vector V_{S_2} of the sequence S_2.

Based on the 2D graphic representation and the distance calculation formula, we can analyze the similarity of protein sequences. The similarity analysis is based on the assumption that two protein sequences are similar if their computing distance has similar magnitude. That is to say, the smaller is the distance, the more similar are the two protein sequences. Now in order to test the utility of the proposed method, we use it to analyze ND5 proteins of the 10 species. These species include human, chimpanzee, Norway rat, house mouse, North American opossum, chicken, cattle, dog, fruit fly and zebrafish [17]. The computing distance matrix of 10 species is listed in Table 2. For convenience, all elements of the distance matrix are reduced 10000 times.

Table 2: Distance matrix of ND5 proteins of 10 species

Species	Human	Chimpanzee	Rat	House mouse	Opossum	Chicken	Cattle	Dog	Fruit fly	Zebrafish
Human	0	0.2795	1.0729	1.1670	1.5989	0.8055	1.0333	0.8925	2.1053	1.4258
Chimpanzee		0	1.0839	1.1860	1.5860	0.8692	1.1135	0.8662	2.0116	1.5224
Rat			0	0.4538	1.0463	1.0784	0.6523	0.6846	1.9292	1.1356
House mouse				0	1.0614	1.1804	0.7083	0.8023	1.9867	1.0510
Opossum					0	1.5147	1.0377	0.9753	1.6373	1.1981
Chicken						0	1.1654	1.0267	2.3659	1.2091
Cattle							0	0.6561	1.8198	0.8218
Dog								0	1.5786	1.1031
Fruit fly									0	2.1436
Zebrafish										0

From Table 2, we find that the pair human - chimpanzee has the smallest entries. So the ND5 protein of chimpanzee is the most similar to that of human than other species. The smaller distance shows the two sequences are more similar. What's more, the largest entry comes from the pair of fruit fly - zebrafish. This reveals that there are significant dissimilarities between the two species. Similar results were obtained [17].

For comparison, we denote the similarity degree of the pair human - chimpanzee as 1. And in Fig. 5 we list the results of the similarity degree of human and other several species. In Fig. 5

we only consider the four pairs, human - chimpanzee, human - rat, human - house mouse and human - opossum, because only the five ND5 proteins are analyzed by all authors. From Fig. 5 we find that there is a consistent variation tendency by different methods although there is some variation. The results are not occasional, but reveal that the species have much closer evolutionary relationship.

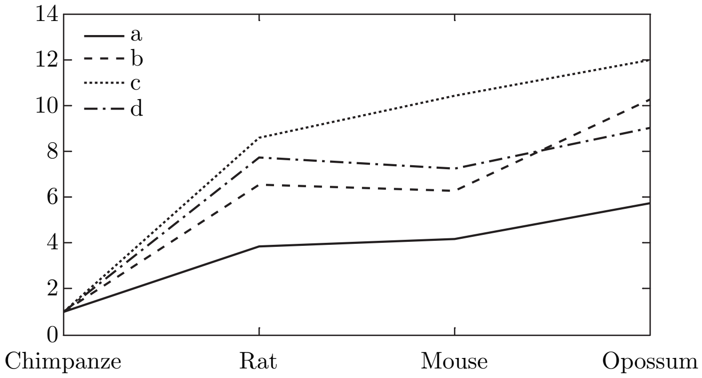


Fig. 5: Comparison of similarity degree of DN5 proteins of several species with the ND5 protein of human (a: This work; b: Table 3 from Liao [15]; c: Table 4 from Yao [12]; d: Table 4 from He [18])

4 Application in Prediction for the Protein Sub-cellular Localization

Protein sub-cellular localization refers to their specific locations in cells. A certain protein or substance of protein expression is likely to exist in different locations of cells, such as in the nucleus (NU), cytoplasm (CY), membrane (ME), and so on [19, 20]. The different locations of proteins in cell are related to the structure and function of biological cell. We can usually get the protein function and structure information by the prediction for the protein sub-cellular localization. In addition, the more similar proteins are more likely to exist in the same sub-cellular localization of cell. Thus, generally by analyzing the similarities/dissimilarities and classification of protein sequences, we can predict the protein sub-cellular localization.

To predict the protein sub-cellular localization, we use the proposed 2D representation method and the distance calculation formula to take the similarity analysis of protein sequences. Here we consider two apoptosis protein data sets, the 98 apoptosis protein data set (ZD98) suggested by Zhou and Doctor [19], and the 317 apoptosis protein data set (CL317) suggested by Chen and Li [20]. The 98 apoptosis proteins includes 43 cytoplasm proteins (CY), 13 mitochondrial inner and outer proteins (MI), 12 other proteins (OTHER), and 30 plasma membrane-bound proteins (ME). The 317 apoptosis protein data set has 112 cytoplasm proteins (CY), 47 endoplasmic reticulum proteins (EN), 52 nuclear proteins (NU), 55 membrane proteins (ME), 34 mitochondrial proteins (MI), and 17 secreted proteins (SE).

Generally, for any prediction method, it is necessary to evaluate its performance using some evaluation index and test methods. Here, we test the prediction accuracy by the jackknife test method [21, 22].

At present, the following four evaluating indicators are commonly used in bioinformatics to evaluate and compare the prediction effects by different classification prediction methods. They are ACC (prediction accuracy), SEN (individual sensitivity), SPE (individual specificity) and MCC (Matthew′s correlation coefficient). Now, given a test protein data set, there are N protein sequences and k protein categories. Then the four evaluating indicators are defined as follows,

$$ACC = \left(\sum_{k=1}^{N} TP_k\right) \Big/ N \tag{6}$$

$$SEN_k = \frac{TP_k}{TP_k + FN_k} \tag{7}$$

$$SPE_k = \frac{TP_k}{TP_k + FP_k} \tag{8}$$

$$MCC_k = \frac{TP_k \times TN_k - FP_k \times FN_k}{\sqrt{(TP_k + FP_k)(TP_k + FN_k)(TN_k + FP_k)(TN_k + FN_k)}} \tag{9}$$

where TP_k is the amount of the sequences in the k-th protein category correctly classified as the k-th category, FP_k is the amount of the sequences in other protein categories classified as the k-th category, TN_k is the amount of the sequences in other protein categories correctly classified as their corresponding categories, and FN_k the numbers of the sequences in the k-th protein category falsely classified as other categories.

We use the four evaluating indicators to perform the prediction effect of the proposed method for the dataset ZD98 and the dataset CL317. Table 3 and 4 list the evaluation results. From the two tables we find that the proposed method is useful in prediction for the protein sub-cellular localization.

Table 3: Evaluation results for the dataset ZD98 by the proposed method

Protein category	SEN (%)	SPE (%)	MCC (%)	ACC (%)
CY (43)	93.02	90.91	85.31	90.82
ME (30)	93.33	96.55	92.55	
MI (13)	92.31	85.71	87.06	
OTHER (12)	75	81.82	75.33	

Table 4: Evaluation results of the dataset CL317 by the proposed method

Protein category	SEN (%)	SPE (%)	MCC (%)	ACC (%)
CY (112)	91.07	91.07	85.84	89.27
ME (55)	90.91	89.29	87.79	
MI (34)	88.24	81.08	82.48	
SE (17)	76.47	81.25	77.55	
NU (52)	88.46	86.79	84.96	
EN (47)	89.36	97.67	92.23	

Then, in order to compare our method with others, in Table 5 and 6 we show the results of evaluating indicators SEN and ACC for the two datasets. Observing Table 5, we find that the *ACC* (prediction accuracy) for the dataset ZD98 by the proposed method achieves 90.8% in jackknife test. This value is higher than the BC method [23], the HensBC method [23], the covariant method [19], the ID_SVM method [24] and the method Liao [15]. Besides, the individual sensitivity *SEN* for CY, ME and MI reaches 93%, 93.3% and 92.3%, respectively. Although the lowest *SEN* value for other proteins (OTHER) only arrives in 75%, the percentage compared with other methods is also high.

Table 5: Evaluating indicators SEN and ACC for the datasets ZD98

Methods	Individual sensitivity (SEN) (%)				ACC (%)
	CY (43)	ME (30)	MI (13)	OTHER (12)	
Covariant [19]	97.7	73.3	30.8	25.0	72.5
BC [23]	90.7	90.0	92.3	50.0	85.7
HensBC [23]	95.3	90.0	92.3	66.7	89.8
EBGW_SVM [26]	97.7	90.0	92.3	83.3	92.9
ID_SVM [24]	95.3	93.3	84.6	58.3	88.8
LABSVM [25]	97.7	96.7	92.3	75.0	93.9
The method in [15]	88.4	96.7	92.3	75.0	89.8
Our method	93.0	93.3	92.3	75.0	90.8

Table 6: Evaluating indicators SEN and ACC for the datasets CL317

Methods	Individual sensitivity (SEN) (%)						ACC(%)
	CY(112)	ME(55)	MI(34)	SE(17)	NU(52)	EN(47)	
ID [20]	81.3	81.8	85.3	88.2	83	82.7	82.7
ID_SVM [24]	91.1	89.1	79.4	58.8	87.2	73.1	84.2
LABSVM [25]	92.9	85.5	76.5	76.5	93.6	86.5	88.0
The method in [15]	88.4	85.5	76.5	58.8	78.9	91.5	83.6
Our method	91.1	90.9	88.2	76.5	88.5	89.4	89.3

Moreover, Table 6 shows that for our method the overall prediction accuracy *ACC* for the dataset CL317 achieves 89.3%, which is the highest among the compared methods, including ID [20], ID_SVM [24], LABSVM [25] and the method Liao [15]. The individual sensitivity *SEN* for *ME* and *MI* are highest, and reach 90.9% and 88.2%, respectively.

The results in Table 5 and 6 show that the proposed method and the SVM methods are better than others although they also have different prediction results for different test dataset. For example, in Table 5 our overall prediction accuracy *ACC* for the dataset ZD98 is 2.1% lower than EBGW_SVM [26] and 3.1% lower than LABSVM [25]. This shows that for the dataset ZD98 the machine-learning methods, such as EBGW_SVM and LABSVM, have better overall prediction effect. But in Table 6 our *ACC* value for the dataset CL317 is the highest among the methods including the SVM methods. From a statistical standpoint, the difference is negligible. The proposed method is as good as the SVM methods. However, our method has other advantages, easiness and less time consuming.

5 Conclusions

In this paper, we proposed a novel 2D graphic representation of protein sequences considering four main physicochemical properties of 20 amino acids. Based on the proposed graphical curve we define a new distance calculating method and its application in the similarity or dissimilarity comparison of ND5 proteins of 10 species. The similarity/dissimilarity results by the new distance computing method derived from the proposed graphical curve are consistent with the results obtained from other methods.

Then we use the proposed method in another important application using similarity comparison, the protein sub-cellular localization prediction. Two common test datasets, ZD98 and CL317, are used to evaluate the prediction performance. The results show that the proposed prediction method are more efficient than most of the other methods. Its prediction performance is almost as good as the machine-learning methods. It is a simple method with lower computing complexity.

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