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A Cytokine Protein Identification Model Based on the Compressed PseKRAAC Features

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ABSTRACT Cytokine proteins, which form a complex cytokine regulatory network, participate in a variety of important physiological functions of the human body. Identification of cytokine proteins is very important and has attracted the attention of many researchers. In this paper, we propose a MRMD-cosine model based on the PseKRAAC features to identify the cytokine proteins. First, the PseKRAAC feature extraction method is used to extract four kinds of feature sets from the cytokine proteins, named type1 g-gap, type1 lambda, type2 g-gap and type2 lambda feature sets. Then the MRMD algorithm is used to remove the redundant features from the feature sets. Three kinds of metrics are used by the MRMD algorithm to measure the redundancy of a feature set, which are the Euclidean distance, Cosine similarity and Tanimoto coefficient. Bagging and random forest algorithms are used to construct the classification models based on the compressed feature set. The experimental results show that the MRMD-cosine model based on the type1 lambda feature set constructed by the random forest algorithm can achieve the best performance among all models. Finally, we compare the performance of the MRMD-cosine model with another state-of-art model, named greedy based feature compression model based on the CNT features. It shows that the MRMD-cosine model uses only 15% features of the greedy based model to achieve a better accuracy.

INDEX TERMS MRMD, feature compression, cytokine identification.

I. INTRODUCTION

Cytokine is a kind of low molecular weight soluble protein induced by immunogen, mitogen or other stimulants. It can regulate innate immunity and adaptive immunity, hematopoiesis, cell growth and repair of damaged tissues. Cytokines can be divided into interleukin, interferon, tumor necrosis factor superfamily, colony stimulating factor, chemokines, growth factors and so on. Cytokines have multiple physiological characteristics, such as pleiotropy, overlap, antagonism, synergy and so on. They form a complex regulatory network and participate in a variety of important physiological functions of the human body.

Identification of cytokine proteins is very important and researchers have proposed several kinds of machine learning based models to identify the cytokine proteins [1]–[16]. As the number of features extracted from the cytokine data set is large, some kinds of feature selection methods are used to compress the feature set [23]–[35]. In paper [36], a greedy based feature compression model based on the CNT feature set is proposed to classify the cytokine proteins. The greedy based model, constructed by the SVM (Support Vector Machine) algorithm [37]–[53], is composed of 167 features and can achieves the accuracy of 87.3%.

In this paper, we utilize the PseKRAAC methods [54] to extract features from the cytokine proteins to construct the classification models. Four kinds of feature sets are extracted by the PseKRAAC methods, which are the type1 g-gap feature set, the type1 lambda feature set, the type2 g-gap feature set and the type2 lambda feature set. There are 155 features in the original feature set, which means some redundant features are contained in the feature set. Then the MRMD (Max Relevance Max Distance) based dimensionality reduction algorithm [55] is used to compress the four feature sets. MRMD wants to find the feature subset with maximum relevance with the classification, and the maximum distance between features in the subset at the same time. Such kind of feature set has strong correlation with classification and low redundancy within the feature set. MRMD utilizes three kinds of metrics to evaluate the redundancy of features in the feature set, which are the Euclidean distance, Cosine similarity and Tanimoto coefficient. Then two machine learning algorithms, bagging and random forest, are used to construct the classification models to identify the cytokines based on the compressed

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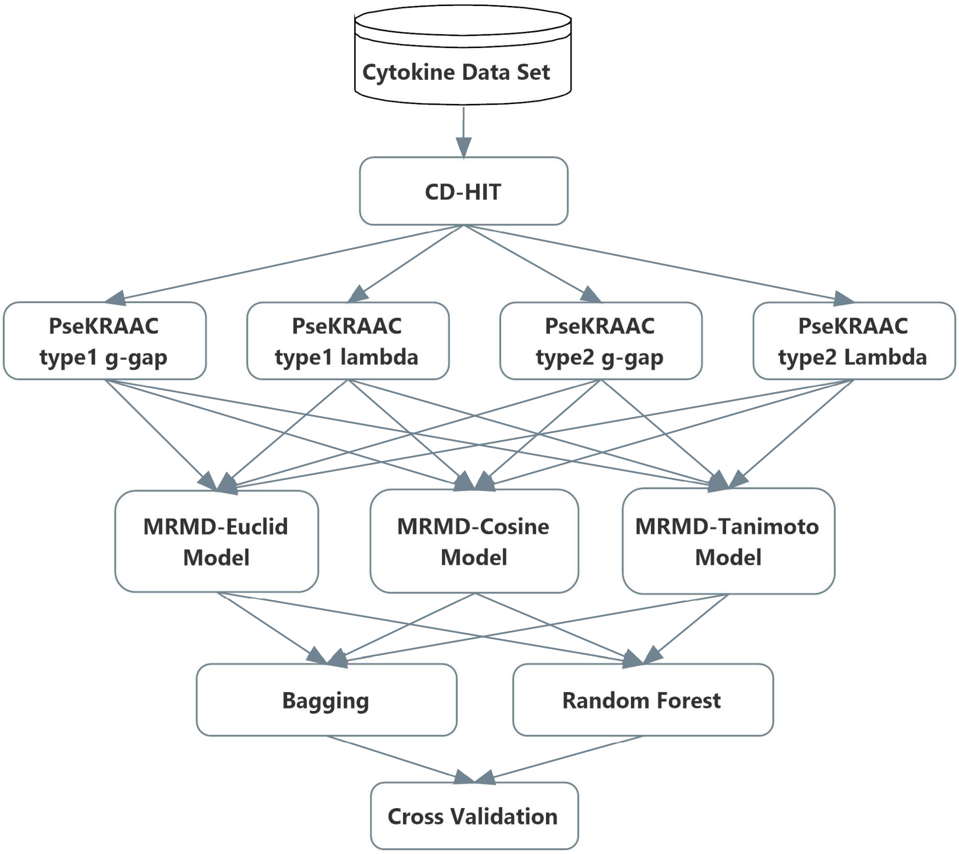


FIGURE 1. Framework for cytokine protein identification.

PseKRAAC feature set. Finally, a MRMD-Cosine model based on the type1 lambda feature set constructed by the random forest algorithm achieves the best performance among all models. Finally, we compare the performance of the MRMD-cosine model with the greedy based model based on the CNT feature set. It shows that the accuracy of the MRMD-cosine model is 87.7%, which is better than that of the greedy based model. Furthermore, the number of features used by the MRMD-cosine model is only 25, which is much smaller than that of the greedy based model.

The contributions of the paper are as follows. (1) A MRMD-cosine model based on the type1 lambda feature set constructed by the random forest algorithm is proposed to classify the cytokine proteins. (2) Compared with a state-of-art greedy based model, the MRMD-cosine model uses only 15% features of the greedy based model to achieve a better accuracy.

The organization of the paper is as follows: in section 2, we introduce the methods to construct the cytokine identification model. In section 3, five groups of experiments are done to evaluate the performance of models proposed in this paper. Finally, conclusions are drawn.

II. METHODS

Figure 1 shows the construction procedure of the cytokine identification model. First, the cytokines data set are processed by the CD-HIT algorithm [56], which remove the redundant instances to balance the number of positive and negative instances in the data set. Then the PseKRAAC method is used to extract four kinds of features from the cytokine data set, which are the type1 g-gap feature set, the type1 lambda feature set, the type2 g-gap feature set and the type2 lambda feature set. There are 155 features contained in each kind of feature set. Then the MRMD feature compression algorithm is used to compress the four feature sets. MRMD utilizes three kinds of metrics to evaluate the redundancy of features in the feature set, which are the Euclidean distance, Cosine similarity and Tanimoto coefficient. After the four feature sets are compressed by the MRMD algorithm, bagging and random forest algorithm are used to construct the machine learning model to classify the cytokines. Finally, the cross validation method is used to evaluate the performance of the classification models.

A. DATASET

The positive instances of cytokine data set are downloaded from the Uniprot [57]–[59] database. The negative instance data set is constructed according to the PFAM families of the positive instance. The longest proteins of all PFAM families, except the PFAM families of the positive instances, are extracted from the Uniprot database to form the negative instance data set. To balance the number of positive and negative instances in the data set, the CD-HIT algorithm is used to delete the redundant negative instances from the data set. There are 9299 negative instances and 9645 positive instances in the cytokine data set.

B. PseKRAAC FEATURE EXTRACTION METHOD

As we all know, there are 20 kinds of amino acids that make up proteins. It is a common feature extraction method to classify protein sequences based on their structural characteristics [60]–[65]. However, due to the large number of features caused by 20 kinds of amino acids and their combinations, people hope to classify 20 kinds of amino acids according to their physical and chemical characteristics. Since each class contains many amino acids with similar properties, the amino acids belonging to one class can be treated as a whole, which is called RAAC (Reduced AAC), so the number of features can be reduced [66]. Such kind of feature extraction method is called PseKRAAC (Pseudo K-tuple Reduced Amino Acids Composition) descriptor [67], [68]. 16 kinds of classification methods are listed in [69]. In this paper, two classification methods, type1 and type2, were used to extract features from cytokine protein. Two methods, g-gap and lambda correlation [70], have been proposed to describe the structural character of RAAC in proteins. Therefore, based on the above two RAAC types and two structural character description methods, we can extract the four feature sets: type1 g-gap, type1 lambda, type2 g-gap and type2 lambda.

C. MRMD FEATURE COMPRESSION ALGORITHM

Feature selection is widely used to select important features aiming to improve the predictive performance [71]–[75]. The main idea of MRMD (Max Relevance Max Distance based dimensionality reduction) is as follows. First, it calculates the correlation between each feature and classification by Pearson coefficient, which means Max Relevance. Second, the distance between features in the feature set is calculated to find the feature set with low redundancy. The larger the distance between features, the lower the correlation between them and the lower redundancy of the selected feature set. MRMD provides three methods to calculate the distance between features: Euclidean distance1, Cosine similarity2 and Tanimoto coefficient3. The feature subset selected based on the above idea has strong correlation with classification and low redundancy within the feature set.

$$ED(\vec{X}, \vec{Y}) = \sqrt{\sum_{k=1}^{N} (x_k - y_k)^2} \tag{1}$$

$$\mathrm{COS}(\vec{X}, \vec{Y}) = \frac{\vec{X} \cdot \vec{Y}}{\|\vec{X}\| \cdot \|\vec{Y}\|} \tag{2}$$

$$\mathrm{TC}(\vec{X}, \vec{Y}) = \frac{\vec{X} \cdot \vec{Y}}{\|\vec{X}\|^2 + \|\vec{Y}\|^2 - \vec{X} \cdot \vec{Y}} \tag{3}$$

D. BAGGING AND RANDOM FOREST ALGORITHMS

For a given training set S, m training samples are extracted from S by boosting sampling in each round. After N rounds are conducted and N sample sets are obtained. It should be noted that the N training sets are independent of each other. A sample set is used to construct a prediction model by some kinds of machine learning algorithm each time. And we get N prediction models. To solve the classification problem, the N models vote to get the classification results. All kinds of machine learning algorithms can be used to construct the prediction models for bagging. Random Forest is a special case of bagging, which use the decision tree as the machine learning algorithm to construct the prediction model [76]–[83].

III. EXPERIMENTS

In this section, five groups of experiments are done to test the performance of models constructed by combining different kinds of feature sets, feature redundancy metrics and machine learning algorithms. The four feature sets extracted by PsekRAAC methods are type1 g-gap, type1 lambda, type2 g-gap and type2 lambda. For each feature set, three kinds of feature redundancy metrics are used, which are the Euclidean distance, Cosine similarity and Tanimoto coefficient. Finally, the bagging and random forest algorithm are used to construct the classification model.

TABLE 1. Parameters set for the experiments.

Algorithm	Parameter Name	Value
Bagging	bagSizePercent	100
	calcOutOfBag	False
	numExecutionSlots	1
	numIterations	10
	classifier	REPTree
REPTree	maxDepth	-1
	minNum	2
	minVarianceProp	0.001
	numDecimalPlaces	2
Random Forest	maxDepth	0
	numTrees	100
	numFeatures	0

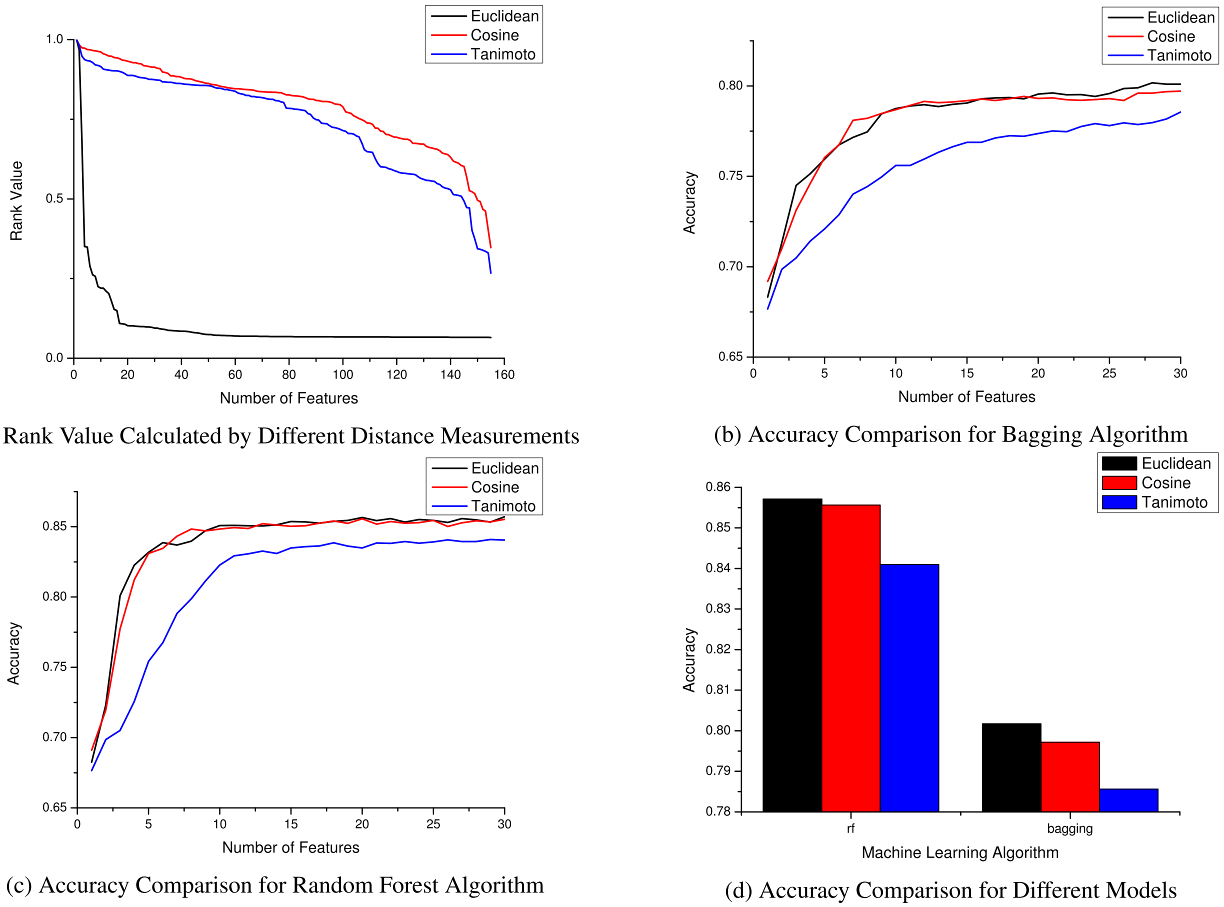
Accuracy (ACC), defined by Formula (4), is used to evaluate the performance of all classification models. The 10-fold cross-validation is used to calculate the accuracy for each model. Weka [84] is used to do all the experiments. Details of the parameters used in the experiments are shown in table 1.

$$ACC = \frac{TN + TP}{TN + FP + TP + FN} \tag{4}$$

where TP represents the True Positive, FP represents False Positive, TN represents true negative, and FN represents False Negative.

A. PERFORMANCE FOR THE PseKRAAC FEATURE SET OF TYPE1 G-GAP

Firstly, the MRMD feature compression method utilizes the Euclidean distance, the Cosine similarity and the Tanimoto



(a) Rank Value Calculated by Different Distance Measurements

(b) Accuracy Comparison for Bagging Algorithm

(c) Accuracy Comparison for Random Forest Algorithm

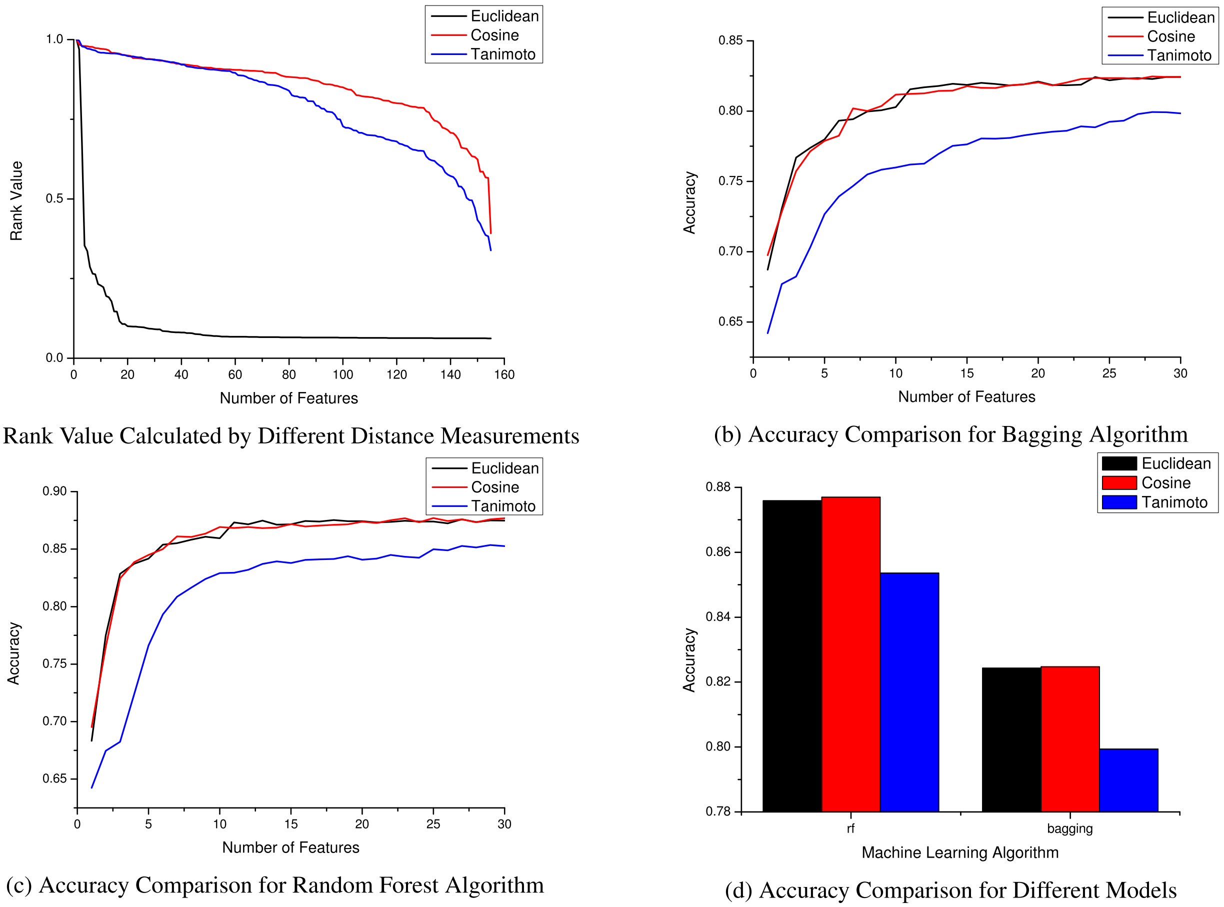
(d) Accuracy Comparison for Different Models

FIGURE 2. Performance comparison for PseKRAAC feature set of type1 G-gap.

coefficient to measure the redundancy among features. The results are shown in Figure 2. The rank values of the 155 features calculated by MRMD method are shown in Figure 2a. The experimental results show that the range of rank values calculated by the three methods for each feature is between 0 and 1, and the more important the feature, the larger the rank value. When Euclidean distance is used as the measurement method, the rank value of features decays rapidly. The rank value of the first 17 features decays rapidly from 1 to 0.109. When the feature number exceeds 24, the change rate of rank values is very small. However, the change rate of rank values calculated by cosine similarity and Tanimoto coefficient is much gentler than that of the Euclidean distance. With the increase of the feature number, the rank values of the features decrease approximately linearly. The rank values after 100 features show accelerated decay. At the same time, the rank values calculated by Cosine similarity are slightly larger than those calculated by Tanimoto coefficient.

Secondly, according to the rank values of each feature calculated by the three distance methods, we select the features from 1 to 30 in order, and form the feature set. Bagging and random forest algorithms are used to identify cytokine proteins, and accuracy is used as the metric to evaluate different classification models. The experimental results are shown in Figure 2b and Figure 2c. As shown in Figure 2b, in which bagging is used as the classification algorithm, when the feature number in the feature set is small, the classification accuracy is poor. With the increase of the feature number, the classification accuracy has been improved significantly. When the feature number in the feature set reaches a certain number, the improvement of classification accuracy is very limited by adding new features to the feature set. The performance comparison among the three distance methods is as follows. The classification models using Euclidean distance and Cosine similarity as the measurement achieves similar classification accuracy. The results also show that the model using the Tanimoto coefficient method is the worse than the other two models, and there is a big gap between it and the other two methods. The experimental results also show that increasing the feature number in the feature set has a great impact on the improvement of the classification performance of the Tanimoto based model. However, if there are too many features in the feature set, the running time of the classifier will be greatly affected in the face of the classification task with large amount of data.

As shown in Figure 2c, when random forest is used as the classification algorithm, the overall performance of models with different distance measurements is similar to that of



(a) Rank Value Calculated by Different Distance Measurements

(b) Accuracy Comparison for Bagging Algorithm

(c) Accuracy Comparison for Random Forest Algorithm

(d) Accuracy Comparison for Different Models

FIGURE 3. Performance comparison for PseKRAAC feature set of type1 lambda.

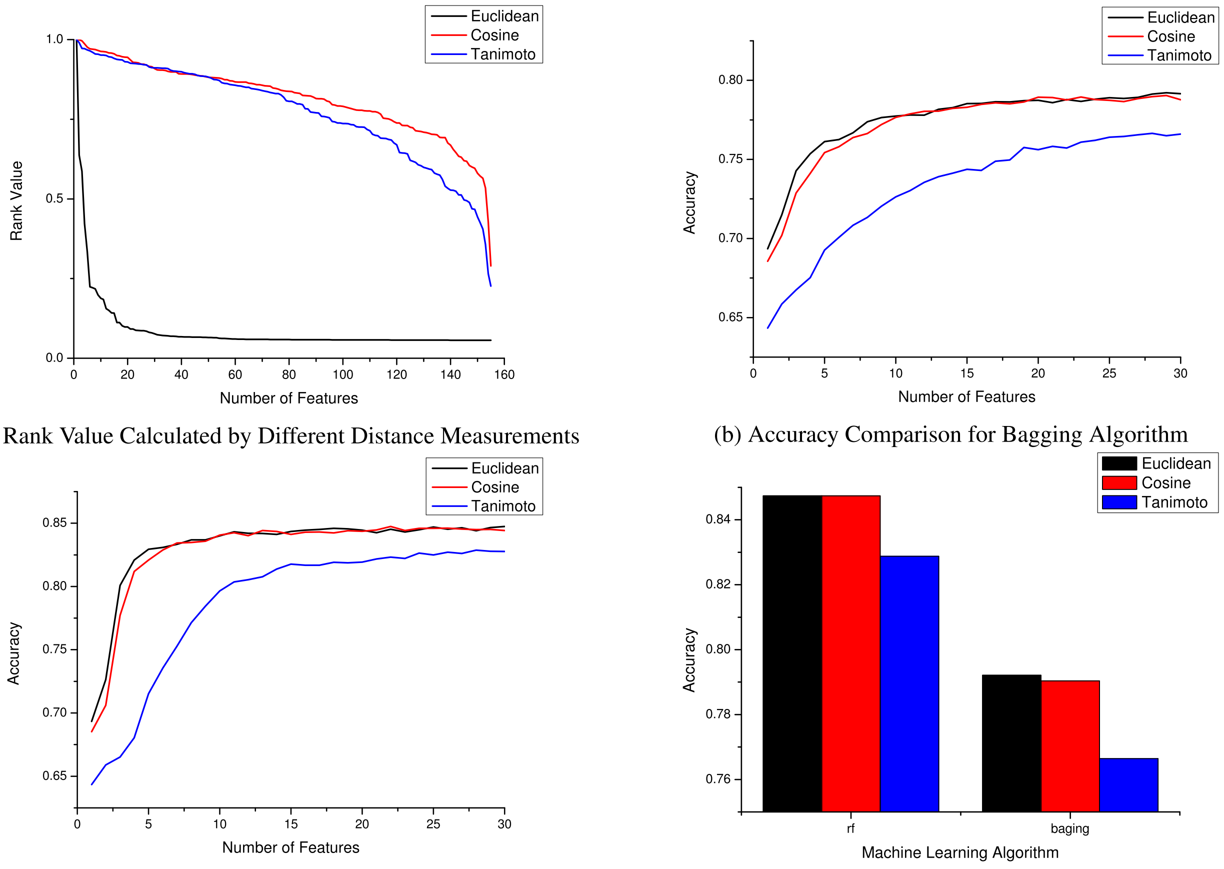
bagging algorithm. It should be noted that when using random forest algorithm, with the increase of the feature number in the feature set, the classification accuracy of the random forest algorithm is significantly better than that of the bagging algorithm. For example, when the feature number is 9, the classification accuracy of Euclidean model and Cosine model using random forest classification algorithm can reach 84.7%. While the classification accuracy of Euclidean model and Cosine model using bagging classification algorithm is only 78.5%, with a difference of 6.2%. In terms of classification accuracy, the accuracy of the classification models using random forest algorithm is significantly better than that of the classification models using bagging algorithm.

In order to compare the impact of the two machine learning algorithms on classification accuracy, we compare the highest accuracy achieved by all the Euclidean, cosine and Tanimoto based models constructed with random forest and bagging algorithm as classifier respectively. The comparison results are shown in Figure 2d. It shows that the classification accuracy of random forest based model is obviously better than that based on bagging algorithm. At the same time, the model using Euclidean distance as the redundancy measurement among features is the best, the model using cosine similarity takes the second place, and there is a small gap with Euclidean distance. The performance of Tanimoto coefficient is the worst, and there is a big gap between it and the other two models. Therefore, for the feature set extracted by type1 g-gap method, the random forest based model with the Euclidean distance achieves the best accuracy.

B. PERFORMANCE FOR THE PseKRAAC FEATURE SET OF TYPE1 LAMBDA

The experimental results for the PseKRAAC Feature Set of Type1 Lambda are shown in Figure 3. The rank values of the 155 features calculated by MRMD method are shown in Figure 3a. The experimental results show that the rank value of the first 18 features decays rapidly from 1 to 0.107. When the feature number exceeds 22, the change rate of rank values is very small. The change rate of rank values calculated by cosine similarity and Tanimoto coefficient decrease approximately linearly. After 100 features, the rank values drop accelerately. At the same time, the rank values of Cosine similarity are slightly larger than those of Tanimoto coefficient.

The experimental results by using Bagging and random forest algorithms are shown in Figure 3b and Figure 3c. As shown in Figure 3b, in which bagging is used as the classification algorithm. The classification models using Euclidean



(a) Rank Value Calculated by Different Distance Measurements

(b) Accuracy Comparison for Bagging Algorithm

(c) Accuracy Comparison for Random Forest Algorithm

(d) Accuracy Comparison for Different Models

FIGURE 4. Performance comparison for PseKRAAC feature set of type2 G-gap.

distance and Cosine similarity as the measurement achieves similar classification accuracy. The model using the Tanimoto coefficient method is worse than the other two models, and there is a big gap between it and the other two methods.

As shown in Figure 3c, when random forest is used as the classification algorithm, the classification accuracy of the random forest algorithm is significantly better than that of the bagging algorithm. When the feature number is 7, the classification accuracy of Cosine model using random forest classification algorithm can reach 86.1%. While the classification accuracy of Euclidean model using bagging classification algorithm is only 80.2%, with a difference of 5.9%. In terms of classification accuracy, the accuracy of the classification models using random forest algorithm is significantly better than that of the classification models using bagging algorithm.

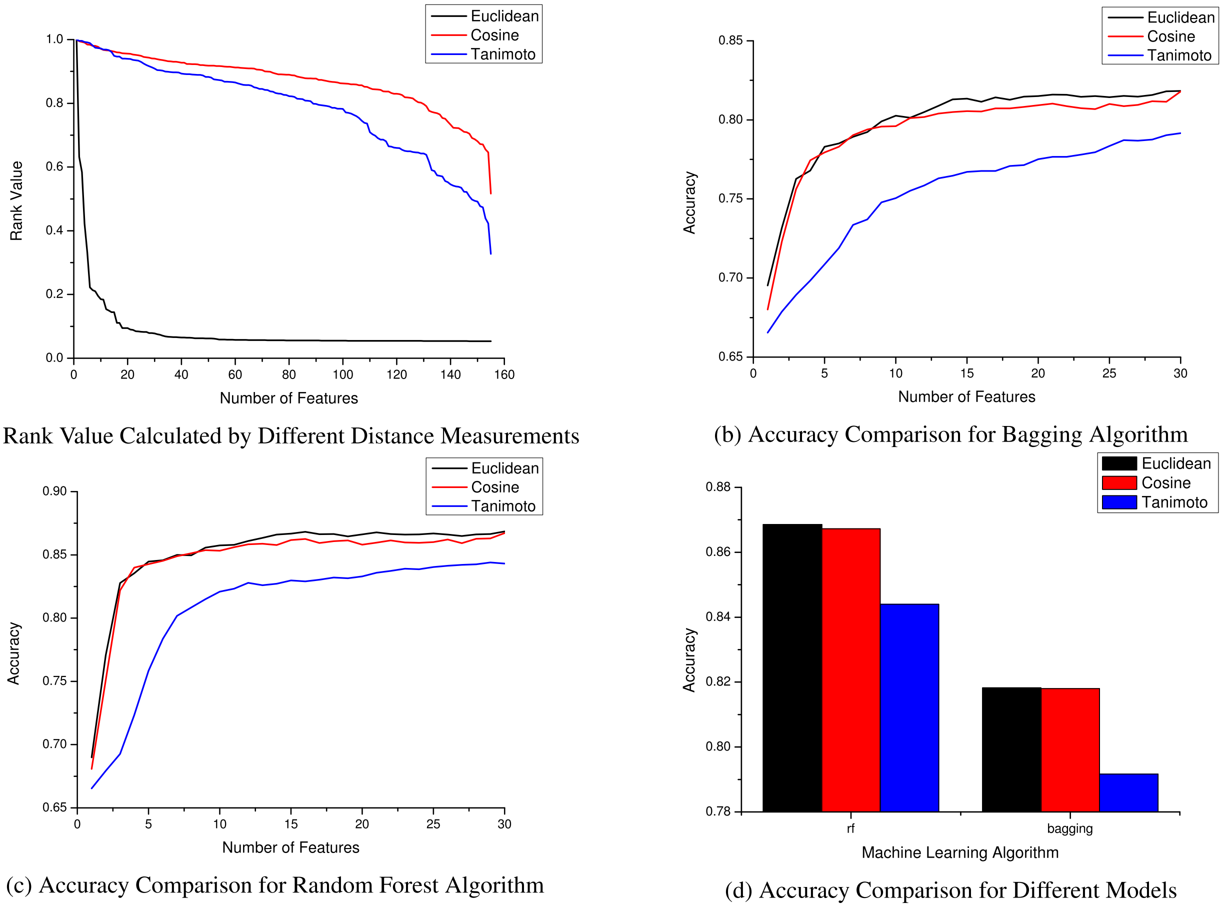
The highest accuracy achieved by the Euclidean, cosine and Tanimoto based models constructed with random forest and bagging algorithm as classifier are compared in Figure 3d. It shows that even the worst model of random forest, which is the Tanimoto based model, is better than the best model of bagging algorithm. Therefore, for the feature set extracted by type1 lambda method, the random forest based model with the Cosine similarity achieves the best accuracy.

C. PERFORMANCE FOR PseKRAAC FEATURE SET OF TYPE2 G-GAP

The experimental results for the PseKRAAC Feature Set of Type2 G-gap are shown in Figure 4. The rank values of the 155 features calculated by MRMD method are shown in Figure 4a. It shows that the rank value drops rapidly from 1 to 0.101, that takes only 18 features. With the increase of the feature number, the change rate of rank values becomes very small. The change rate of rank values of cosine similarity and Tanimoto coefficient decrease smoothly at first. After 140 features, the rank values drop significantly.

The experimental results by using Bagging and random forest algorithms are shown in Figure 4b and Figure 4c. As shown in Figure 4b, in which bagging is used as the classification algorithm. The classification accuracy of Euclidean based models are better than that of the Cosine based models when the feature number is small. When the feature number exceeds 10, the accuracy of the two kinds of models are very similar. The model based on the Tanimoto coefficient method is worse than the other two models.

As shown in Figure 4c, when random forest is used as the classification algorithm, the classification accuracy of the random forest algorithm is significantly better than that of the bagging algorithm. The classification accuracy of Euclidean



(a) Rank Value Calculated by Different Distance Measurements

(b) Accuracy Comparison for Bagging Algorithm

(c) Accuracy Comparison for Random Forest Algorithm

(d) Accuracy Comparison for Different Models

FIGURE 5. **Performance comparison for PseKRAAC feature set of type2 lambda.**

based models are very similar. The model based on the Tanimoto coefficient method is worse than the other two models.

The highest accuracy achieved by the Euclidean, Cosine and Tanimoto based models constructed with random forest and bagging algorithm as classifier are compared in Figure 4d. It shows that the random forest based model with the Euclidean distance achieves the best accuracy.

D. PERFORMANCE FOR THE PseKRAAC FEATURE SET OF TYPE2 LAMBDA

The experimental results for the PseKRAAC Feature Set of Type2 G-gap are shown in Figure 5. The rank values of the 155 features calculated by MRMD method are shown in Figure 5a. It shows that the rank value drops rapidly from 1 to 0.095, that takes only 18 features. With the increase of the feature number, the change rate of rank values becomes very small. The change rate of rank values of cosine similarity and Tanimoto coefficient decrease smoothly at first. After 130 features, the rank values drop accelerately.

The experimental results by using Bagging and random forest algorithms are shown in Figure 5b and Figure 5c. As shown in Figure 5b, in which bagging is used as the classification algorithm. When the feature number is below 9, the accuracy of the two kinds of models are very similar. The accuracy of Euclidean based models are better than that of the Cosine based models when the feature number exceeds 9. The model based on the Tanimoto coefficient method is worse than the other two models.

As shown in Figure 5c, when random forest is used as the classification algorithm, the accuracy of the random forest algorithm is significantly better than that of the bagging algorithm. The accuracy of the Euclidean based model is the best.

The highest accuracy achieved by the Euclidean, Cosine and Tanimoto based models constructed with random forest and bagging algorithm as classifier are compared in Figure 5d. It shows that the random forest based model with the Euclidean distance achieves the best accuracy.

E. COMPARISON OF DIFFERENT KINDS OF CLASSIFICATION MODELS

In this section, we compare the performance of the classification models for the four feature sets with the best accuracy. The four experiments above show that, for all feature sets, the models constructed by the random forest algorithm is better than that constructed by the bagging algorithm. Furthermore, for the type1 g-gap, type2 g-gap and type2 lambda feature sets, the Euclidean distance metric

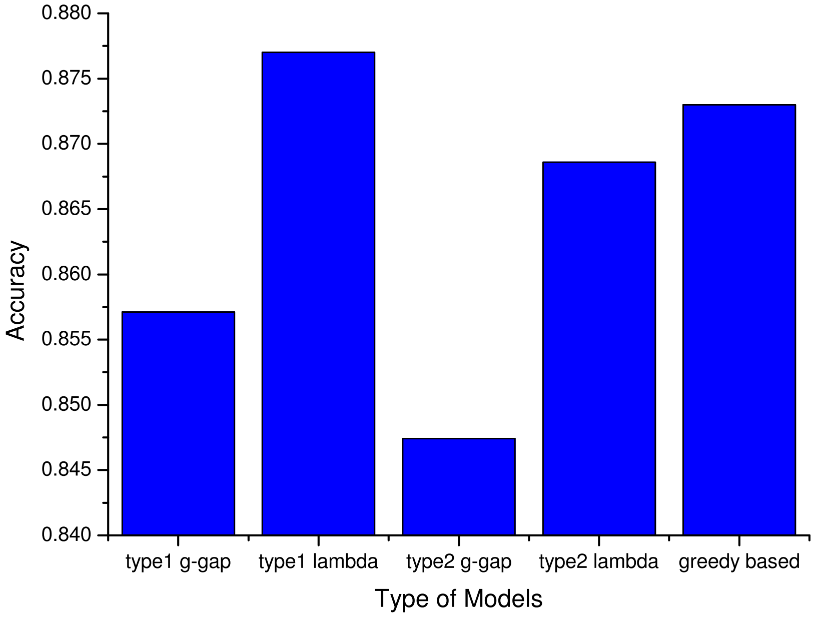


FIGURE 6. Comparison among different kinds of classification models.

achieves the best accuracy. For type1 lambda feature set, the Cosine similarity metric achieves the best accuracy. The four accuracy are compared in Figure 6, which shows that the feature set of type1 lambda is the best among all the models. We can conclude that the type1 lambda model processed by MRMD-cosine compression and random forest algorithm is the best model.

In paper, a greedy based feature compression model based on the CNT feature set is proposed to classify the cytokine proteins. The greedy based model, constructed by the SVM (Support Vector Machine) algorithm, is composed of 167 features and can achieves the accuracy of 87.3%. The accuracy of MRMD-cosine model proposed in this paper is 87.7%, which is composed of 25 features. It means that the MRMD-cosine model uses only 15% features of the greedy based model to achieve a better accuracy.

IV. CONCLUSION

In this paper, four kinds of PseKRAAC based feature sets are extracted from the cytokine data set. Three kinds of feature redundancy calculation metrics, which are the Euclidean distance, Cosine similarity and Tanimoto coefficient, are used to compress the features in the feature set by the MRMD feature compression algorithm. The bagging and random forest algorithm are used to construct the machine learning model to classify the cytokines. The experimental results show that the MRMD-cosine model based on type1 lambda feature set is the best model, which uses only 15% features of the greedy based model to achieve a better accuracy.

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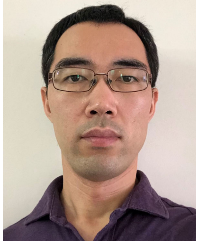

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