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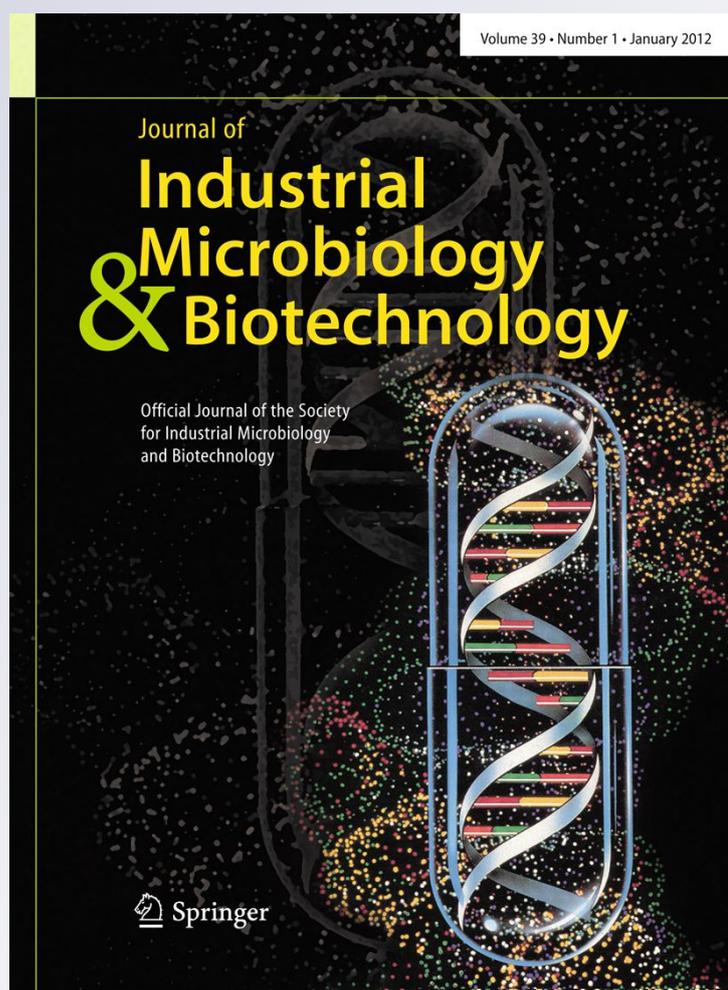
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Prediction of ketoacyl synthase family using reduced amino acid alphabets

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Abstract Ketoacyl synthases are enzymes involved in fatty acid synthesis and can be classified into five families based on primary sequence similarity. Different families have different catalytic mechanisms. Developing cost-effective computational models to identify the family of ketoacyl synthases will be helpful for enzyme engineering and in knowing individual enzymes' catalytic mechanisms. In this work, a support vector machine-based method was developed to predict ketoacyl synthase family using the *n*-peptide composition of reduced amino acid alphabets. In jackknife cross-validation, the model based on the 2-peptide composition of a reduced amino acid alphabet of size 13 yielded the best overall accuracy of 96.44% with average accuracy of 93.36%, which is superior to other state-of-the-art methods. This result suggests that the information provided by *n*-peptide compositions of reduced amino acid alphabets provides efficient means for enzyme family classification and that the proposed model can be efficiently used for ketoacyl synthase family annotation.

Keywords Ketoacyl synthase family · Reduced amino acid alphabet · Support vector machine · *n*-Peptide

Introduction

Enzymes are proteins that catalyze (i.e., increase or decrease the rates of) chemical reactions. Almost all processes in a biological cell need enzymes to occur at significant rates. Enzymes are usually very specific as to which reactions they catalyze and the substrates that are involved in the reactions. Ketoacyl synthases (KSSs) are key members of the fatty acid synthesis cycle used by organisms to form lipids [4]. In fatty acid synthesis, KSSs condense the acyl-X chain with a carboxylated acyl-X chain [where X is either coenzyme A or acyl carrier protein (ACP)] and add two carbon atoms to the growing fatty acid chain by releasing a carbon dioxide and making ketoacyl-ACPs. Based on primary sequence similarity, KSSs are divided into five families, KS1 to KS5 [4]. Knowing to which family an enzyme belongs casts new light on its catalytic specificity and gives clues to the relevant biological function. With the rapid increase in newly found protein sequences, the need for an automated and accurate tool to recognize enzyme families becomes increasingly important.

Over the past decade, many computational methods have been proposed for enzyme family and function prediction. By using the covariant discriminate function algorithm, Chou and Elord [10] predicted the subclasses of oxidoreductases. In follow-up work, Chou [8] improved the predictive accuracy to 70.6% by using amphiphilic pseudo amino acid composition. Afterwards, several other works were developed to predict enzyme subclasses. The GO-PseAA predictor was employed by Chou and Cai [9] to

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predict enzyme subclasses. Later, by using functional domain composition and pseudo amino acid composition, Cai and Chou [2] obtained higher predictive accuracy. Recently, Shen and Chou [43] proposed a top-down approach for predicting enzyme functional classes, obtaining overall success rates ranging from 86.7% to 98.3%. The functions of proteins correlate with their three-dimensional (3D) structures. Based on the information of the 3D structure of proteins, González-Díaz and colleagues developed some models and web servers to discriminate between enzymes and nonenzymes [14, 15, 39], predict enzyme classes [13], and recognize protein kinases [26, 27]. They also developed some quantitative structure–activity relationship (QSAR)-based methods [16, 24, 25] to classify polygalacturonases and nonpolygalacturonases [1], discriminate dyneins from nondyneins [17], and predict RNase scores [23], achieving encouraging results.

However, to the best of our knowledge, there exists no theoretical method for KS family classification. In this article, we propose a support vector machine (SVM)-based method to identify KS families using reduced amino acid alphabets (RAAA) obtained by the protein blocks method [18, 19, 31, 47]. Compared with amino acid composition, RAAA can extract more useful information for protein sequences, eliminate some noise, reduce the dimension of the feature space, and improve the prediction accuracy. The performance of the proposed method was compared with that of other methods. Results demonstrate that this model could be a potentially useful tool for ketoacyl synthase family identification.

Materials and methods

Dataset

A total of 1,304 experimentally confirmed (evidence at transcript level or protein level) KSs were obtained from the ThYme database [4]. Highly similar data will surely lead to overestimation of the performance of the proposed method. To prepare a high-quality dataset, sequences with $\geq 60\%$ identity were removed by using the CD-HIT program [34]. The final dataset contained 225 proteins. According to the database annotation, these proteins are classified into five families: 16 KS1, 30 KS2, 80 KS3, 29 KS4, and 70 KS5. If the sequence identity cutoff is set to a lower percentage (such as 25%), the results will be more objective and reliable. However, in this study we did not use such a stringent criterion because the currently available data do not allow this. Otherwise, the number of proteins for some subsets would be too few to have statistical significance.

Table 1 Scheme for reduced amino acid alphabets based on various protein blocks methods

Size	Protein blocks method
20	G-I-V-F-Y-W-A-L-M-E-Q-R-K-P-N-D-H-S-T-C
13	G- IV-FYW -A-L-M-E- QRK -P- ND-HS -T-C
11	G- IV-FYW -A- LM-EQRK -P- ND-HS -T-C
9	G- IV-FYW - ALM-EQRK -P- ND-HS -TC
8	G- IV-FYW - ALM-EQRK -P- ND-HSTC
5	G- IVFYW - ALMEQRK -P- NDHSTC

Clustered amino acids are shown in bold

Frequency of reduced amino acid alphabet

Reduced amino acid alphabets (RAAA) [21] clustered based on protein blocks [18, 19, 31] have been successfully employed in the area of protein annotation [7, 33, 40, 41, 47]. The RAAA scheme is shown in Table 1. Compared with the traditional amino acid composition, RAAA not only simplifies the complexity of the protein system but also improves the ability to find structurally conserved regions and structural similarity of entire proteins.

In this study, protein sequences are encoded by the frequency of n -peptide composition of RAAA of different sizes. For each value of n , the corresponding feature vector contains the fraction of each possible n -length substring in the sequence. The feature vector dimension (D) of the n -peptide composition obtained from RAAAs of different size (S) is listed in Table 2. The case $n = 1$ can be considered as the first-order approximation to the complete protein sequence. $n = 2$ gives the dipeptide composition, depicting the correlation of proximate residues. As n increases, n -peptides provide progressively more detailed sequential information. However, for $n \geq 3$, the amount of information parameters increases dramatically, and computation becomes not only impractical but also susceptible to the danger of overfitting. So, in the current study, we chose $n = 1$ and 2.

Classification protocol

SVM is a very powerful and popular method for supervised pattern recognition and has been widely used in the realm of bioinformatics [3, 6, 29, 37, 38, 42, 44–46]. To handle a multiclass problem, the one-versus-one (OVO) and one-versus-rest (OVR) approaches are generally applied to extend traditional SVM. In this work, the OVO strategy was employed to make predictions using radial basis functions (RBF). The SVM implementation was based on LibSVM written by Chang and Lin [5]. The grid search method was applied to tune the regularization parameter C and the kernel width parameter γ .

Table 2 Feature vector dimensions of n -peptide compositions with different RAAA sizes

n -Peptide	Dimension of different amino acid alphabet sizes (S)					
	$S = 20$	$S = 13$	$S = 11$	$S = 9$	$S = 8$	$S = 5$
$n = 1$	20	13	11	9	8	5
$n = 2$	400	169	121	81	64	25

Performance assessment

The capability of the method was evaluated using the sensitivity (S_n), specificity (S_p), overall accuracy (OA), average accuracy (AA), and Matthew's correlation coefficient (MCC). These measurements are expressed as follows:

$$S_n(i) = \frac{TP(i)}{TP(i) + FN(i)}, \tag{1}$$

$$S_p(i) = \frac{TN(i)}{TN(i) + FP(i)}, \tag{2}$$

$$OA = \frac{1}{N} \sum_{i=1}^k TP(i), \tag{3}$$

$$AA = \frac{1}{N} \sum_{i=1}^k S_n(i), \tag{4}$$

$$MCC(i) = \frac{TP(i) \times TN(i) - FP(i) \times FN(i)}{\sqrt{(TP(i) + FN(i)) \times (TN(i) + FP(i)) \times (TP(i) + FP(i)) \times (TN(i) + FN(i))}}, \tag{5}$$

where k ($k = 5$) is the number of families and N is the total number of sequences in the final dataset. $TP(i)$, $TN(i)$, $FP(i)$, and $FN(i)$ represent the true positives, true negatives, false positives, and false negatives for family i .

Results and discussion

Three cross-validation methods, namely the subsampling test, independent dataset test, and jackknife test, are often employed to evaluate the predictive capability of a predictor. Among these three methods, the jackknife test is deemed as the most objective and rigorous [12] and can always yield a unique outcome, as demonstrated by a penetrating analysis in a recent comprehensive review [11]; it has been widely and increasingly adopted [20, 28, 30, 32, 35, 36, 43]. Accordingly, the jackknife test was used to examine the performance of the model proposed in this study. In the jackknife test, each sequence in the training dataset is in turn singled out as an independent test sample

and all the rule parameters are calculated without using this one.

Ketoacyl synthase family classification

Each sequence in the dataset was translated into discrete feature vectors described by the frequencies of the n -peptide composition of RAAA. We firstly encoded protein sequences using the frequency of 20 amino acid and 400 dipeptide compositions. The jackknife test results are shown in the first two columns of Table 3. The overall accuracy of dipeptide composition reached 96.44% with average accuracy of 92.80%, which are higher than those of amino acid composition. Especially, all proteins in the KS2, KS3, and KS5 families were correctly recognized by using 400 dipeptides (i.e., sensitivity 100%).

To investigate whether a special class or property of amino acid affects the predictive accuracy and to determine the optimal amount of information, we compared the predictive capability of models trained by using the n -peptide ($n = 1, 2$) composition of RAAA of different sizes. The predictive sensitivity, specificity, average accuracy, and overall accuracy are listed in Table 3. As shown in Table 3, the best predictive results were obtained based on the 2-peptide composition of the reduced amino acid alphabet of size 13 ($n = 2, S = 13$). Although the overall accuracies were equal for the 2-peptide composition of RAAA with sizes $S = 11, 13$, and 20, the best MCC values for each family were obtained for the case $S = 13$ (Fig. 1). When $n = 2$ and $S = 13$, the MCC values for classification of KS1, KS2, KS3, KS4, and KS5 were 0.93, 1, 1, 0.88, and 1, respectively. Besides, the average accuracy of RAAA with $n = 2$ and $S = 13$ is the highest among all parameters. These results indicate that the n -peptide composition of reduced amino acid alphabets could extract more prominent structural and functional

Table 3 Result of SVM model based on different features

Family (%)	<i>n</i> -Peptide composition of RAAA with size <i>S</i> (<i>n</i> , <i>S</i>)											
	(1,20)	(2,20)	(1,13)	(2,13)	(1,11)	(2,11)	(1,9)	(2,9)	(1,8)	(2,8)	(1,5)	(2,5)
KS1												
Sn	50.00	81.25	50.00	87.50	56.25	81.25	62.50	62.50	56.25	68.75	43.75	37.50
Sp	99.47	100.00	98.97	100.00	97.87	100.00	98.92	100.00	99.47	100.00	98.79	99.47
KS2												
Sn	96.67	100.00	93.33	100.00	96.55	100.00	83.33	96.67	86.67	90.00	53.33	70.00
Sp	99.41	99.47	99.43	100.00	97.06	99.47	97.67	98.92	97.69	94.95	95.65	97.75
KS3												
Sn	90.00	100.00	95.00	100.00	88.75	100.00	95.00	100.00	92.50	96.25	88.75	98.75
Sp	87.41	95.14	90.58	100.00	87.14	95.14	83.57	92.31	87.05	92.31	73.88	84.67
KS4												
Sn	65.52	82.76	65.52	79.31	51.72	82.76	41.38	79.31	55.17	82.76	31.03	72.41
Sp	95.70	100.00	95.79	100.00	97.27	100.00	98.37	100.00	96.24	97.88	94.15	97.75
KS5												
Sn	98.57	100.00	100.00	100.00	100.00	100.00	100.00	100.00	100.00	100.00	95.71	97.14
Sp	100.00	100.00	100.00	100.00	100.00	100.00	100.00	100.00	100.00	100.00	99.04	100.00
OA	87.56	96.44	89.33	96.44	85.78	96.44	85.78	94.22	86.67	92.89	75.56	86.67
AA	80.15	92.80	80.77	93.36	78.65	92.80	76.44	87.70	78.12	87.55	62.51	75.16

The best results are shown in bold

information than the original amino acid or dipeptide composition.

Comparison with other methods

It is natural to ask whether the SVM model proposed here is superior to other state-of-the-art methods. For further investigation of the results, we compared the performance of SVM with that of random forest and naïve Bayes classifiers using the same features (2-peptide composition of

the reduced amino acid alphabet of size 13). Random forest and naïve Bayes models were tested on the final dataset containing 225 sequences and implemented in WEKA [22]. The results are presented in Table 4. It is shown that the average accuracy of SVM is approximately 9% and 20% higher than the random forest and naïve Bayes classifiers, respectively. This result demonstrates that SVM can be used to identify ketoacyl synthase family with higher accuracy.

Conclusions

We report a support vector machine-based approach for ketoacyl synthase family classification using reduced amino acid alphabets. The use of reduced amino acid alphabets not only provides an efficient and accurate way of protein vectorization for sequence-based protein classification systems but also achieves a remarkable improvement in terms of computational efficiency. High predictive accuracies show that the reduced *n*-peptide composition clustered based on protein blocks can extract more useful information than original 20 amino acid or 400 dipeptide compositions, and also demonstrate that our proposed method is a potentially useful tool for classification of ketoacyl synthase family. Moreover, as the dimension of the feature space was reduced by using RAAA (from 400 to 169 dimensions in this work), the reduced amino acid alphabet scheme could provide novel insights into proteomic classification tasks.

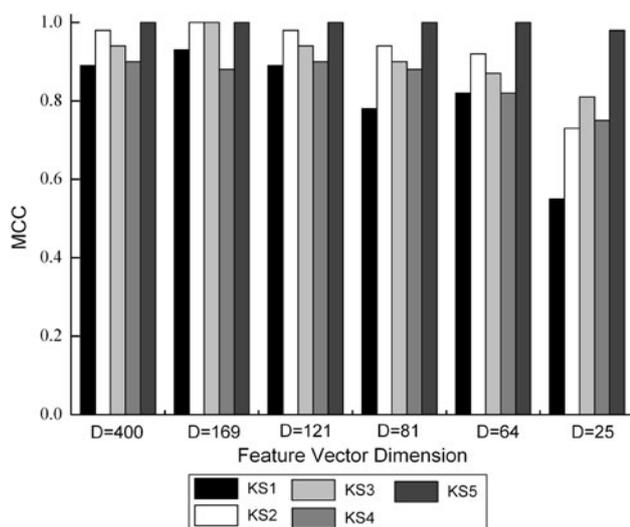


Fig. 1 MCC for five ketoacyl synthase families by using 2-peptide compositions with different RAAA sizes

Table 4 Comparison of SVM with other methods for ketoacyl synthase family classification

Family	SVM			Random forest			Naïve Bayes		
	Sn (%)	Sp (%)	MCC	Sn (%)	Sp (%)	MCC	Sn (%)	Sp (%)	MCC
KS1	87.50	100.00	0.93	43.75	97.33	0.47	62.50	99.44	0.74
KS2	100.00	100.00	1.00	63.33	98.27	0.70	93.33	98.77	0.92
KS3	100.00	100.00	1.00	92.50	85.19	0.76	92.50	89.84	0.81
KS4	79.31	100.00	0.88	65.52	97.14	0.68	72.41	98.25	0.77
KS5	100.00	100.00	1.00	100.00	97.54	0.97	100.00	97.54	0.97
OA (%)		96.44			84.00			90.22	
AA (%)		93.36			73.02			84.15	

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