Feature Selection and Combination Criteria for Improving Accuracy in Protein Structure Prediction

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***Abstract*—The classification of protein structures is essential for their function determination in bioinformatics. At present, a reasonably high rate of prediction accuracy has been achieved in classifying proteins into four classes in the SCOP database according to their primary amino acid sequences. However, for further classification into fine-grained folding categories, especially when the number of possible folding patterns as those defined in the SCOP database is large, it is still quite a challenge. In our previous work, we have proposed a two-level classification strategy called hierarchical learning architecture (HLA) using neural networks and two indirect coding features to differentiate proteins according to their classes and folding patterns, which achieved an accuracy rate of 65.5%. In this paper, we use a combinatorial fusion technique to facilitate feature selection and combination for improving predictive accuracy in protein structure classification. When applying various criteria in combinatorial fusion to the protein fold prediction approach using neural networks with HLA and the radial basis function network (RBFN), the resulting classification has an overall prediction accuracy rate of 87% for four classes and 69.6% for 27 folding categories. These rates are significantly higher than the accuracy rate of 56.5% previously obtained by Ding and Dubchak. Our results demonstrate that data fusion is a viable method for feature selection and combination in the prediction and classification of protein structure.**

***Index Terms*—Combinatorial fusion analysis (CFA), data fusion, diversity rank/score graph, hierarchical learning architecture (HLA), neural network (NN), protein structure prediction, radical basis function network (RBFN), rank/score functions.**

Manuscript received December 20, 2005; revised September 6, 2006. This work was supported by the National Science Council (NSC) under Contract NSC 93-2321-B-007-001. The work of of C.-Y. Lin was supported by the NSC under Contract NSC93-3112-B-007-008. The work of D.F. Hsu was supported in part by the National Science Foundation under DIMACS Grant STC-91-1999 and in part by the NJ Commission. *Asterisk indicates corresponding author.*

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Digital Object Identifier 10.1109/TNB.2007.897482

I. Introduction

HIGH-TECHNOLOGY large-scale sequencing projects have produced a massive number of proteins with putative amino acid sequences but much less is known in terms of their 3-D structure. Several popular structure databases, such as the Structural Classification of Proteins (SCOP) [1] and the Class, Architecture, Topology, and Homologous superfamily (CATH) [2], contribute only no more than 32 000 entries in the Protein Data Bank (PDB) (SCOP release version 1.65 [3]: 20619 PDB entries, PDB: 31 217 entries on 7 June 2005). This number constitutes only about 20% of collections in the Swiss-Port (Swiss-Port release version 47.2: 184 304 entries on 7 June 2005). Physically, x-ray diffraction or NMR is used to determine the 3-D structure for a protein. However, each has its limitation [4]. As such, extracting structural information from the sequence databases becomes an important and complementary alternative, especially for swiftly determining protein functions or discovering new compounds for medical or therapeutic purposes.

The classification of protein structures has, more recently, been facilitated with some computer-aided algorithms. Previous research [4], [5] have shown that an accuracy rate of 70%–80% has been achieved to classify most of proteins into four classes according to their amino acid sequence information (i.e., all-alpha (α), all-beta (β), alpha/beta (α/β) and alpha + beta ($\alpha + \beta$)) [6]. In summary, these four classes contain 82.5% folding patterns, 84.7% superfamilies and 88.1% families in the SCOP database (SCOP release version 1.65 [3]). However, less optimal results are obtained if a more complicated category is used such as the one with protein folding patterns in [7].

In [7], Ding and Dubchak proposed a taxonmetric approach for protein folding classification (into 27 folding patterns) beyond four simple classes with a neural network (NN) and support vector machine (SVM) [8]. Their approach attempts to predict the 3-D structure of a protein from its primary amino acid sequence under the assumption that only limited folding patterns are formed in most of these four protein classes and can be used as template. They predicted protein folds according to six single-parameter features C, S, H, P, V, and Z (see Section II-B for details) first, then a combinatorial multiple-parameter features were formed and checked for their prediction accuracy in protein folding classification. They then demonstrated that one multiple-parameter feature CSHP had the highest overall prediction accuracy rate at 56.5% by SVM.

In Huang *et al.* [9], extra features were defined. We proposed two additional indirect coding features B and SB (see Sections II-B and II-C for detail) to correlate neighboring di-peptide pairs with protein structure classification. In addition to NN and SVM, we also constructed a new computational architecture called hierarchical learning architecture (HLA). In HLA, which was the first two-level classification strategy, a protein is classified into one of four classes at first, and then further classified into a folding structure (into one of 27 folding patterns). We combined the six single-parameter features proposed by Ding and Dubchak [7] and the outcomes of our two indirect coding features to form two new multiple-parameter features CSHPVZ + B and CSHPVZ + B + SB. With the latter features, Huang *et al.* [9] improved the prediction accuracy rate by 9%, compared with the result from Ding and Dubchak [7].

In this paper, we apply the technique of data fusion [10]–[14], in particular the combinatorial fusion analysis described in Hsu *et al.* [13], to perform better protein structure classification and better feature selection and combination. Using data fusion, results from various features are combined to obtain predictions with higher accuracy rate. In addition, the notion of diversity rank/score function is used to select the most suitable features for combination. We start with eight features, six from Ding and Dubchak (C, CS, CSH, CSHP, CSHPV, and CSHPVZ) [7] and two from our previous work (CSHPVZ + B and CSHPVZ + B + SB) [9] to assign protein class and folding pattern. Then, some explicit rules from data fusion in information retrieval (IR) and virtual screening (VS) (see [10]–[14]) are used together with a special diversity rank/score graph to choose the best discriminating features for further combination. It has been demonstrated in IR and VS that using a combination of distinctive features may result in higher prediction accuracy rate than using single features. The proposed rules for proper feature selection are to reduce the complexity at the beginning. Then, we systematically choose the best discriminating features according to the diversity (see Section II-F for detail) of these features, which is represented in a diversity rank/score graph. Our experimental results achieve an overall prediction accuracy rate at 87% for predicting protein classes and 69.6% for predicting protein folding patterns which are higher than the previous work at 83.6% and 65.5% by Huang *et al.* [9], respectively.

Section II of this paper introduces the protein data sets, the features, and the computational architecture used in this paper. Section II also describes the method of data fusion, the rules, and the diversity rank/score graph used to enhance the process of feature selection and combination. Experimental results are included in Section III, while discussions and conclusion are given in Section IV.

II. Materials and Methods

A. Protein Data Sets

We use the data sets from Ding and Dubchak [7] which were originated from the SCOP database for training and testing. Training data set is selected from the database built for the prediction of 128 folding patterns in the SCOP database [15]. It is ensured that any pair of two proteins in the training set is less than 35% identical in any aligned subsequence longer than 80 residues. The independent testing set is selected from the PDB-40D set [1], [6], [15], [16]. Moreover, all proteins in the testing set are less than 40% identical to each other. No protein in the testing set is more than 35% identical to any protein in the training set. The total number of proteins is 698 with 313 and 385 for training and testing, respectively. These proteins will be divided into four classes and 27 folding patterns all together according to their structures. Table I shows the number of proteins in different classes and folding patterns used for training and testing in this paper.

B. Features

Features extraction from the data is critical for meaningful results before these features can be subjected to machine learning techniques. Different features may result in different classifications. Two major approaches including direct and indirect coding have been used to extract features from the data. The direct one contains a vector for each peptide residue in the chain that characterizes the position, sequence length and so on. In indirect coding, the vector is assigned for each sequence which is position and length independent [9]. Ding and Dubchak [7] proposed six direct coding features for protein structure classification. These single-parameter features are global descriptions of a peptide chain representing the proteins. These features are based on physical, chemical and structural properties of the constituent amino acids.

The proposed six single-parameter features are amino acid composition (C), predicted secondary structure (S), hydrophobicity (H), normalized van der Waals volume (V), polarity (P), and polarizability (Z). The proposed five multiple-parameter features, CS, CSH, CSHP, CSHPV, and CSHPVZ were constructed to classify protein folding patterns. Ding and Dubchak [7] finally determined one multiple-parameter feature CSHP with the highest overall accuracy rate for protein structure prediction with SVM. The above 11 single and multiple-parameter features all emphasize more on the global properties and structures of amino acid sequences than on the local interactions among neighboring peptides.

In Huang *et al.* [9], we used the N-gram concept while extracting features from the amino acid sequence of proteins. Two other indirect coding features, generated from the bigram (B) and the spaced-bigram coding (SB) scheme, respectively, were proposed. These features reflect the local interactions among neighboring peptides within the 3-D structure of a protein. We combined the six single-parameter features proposed by Ding and Dubchak [7] and the outcomes of our two indirect coding features to form two new multiple-parameter features CSHPVZ + B and CSHPVZ + B + SB'. We showed that using the feature CSHPVZ + B + SB together with NN outperformed all single- or multiple-parameter features used by Ding and Dubchak [7] in terms of prediction accuracy rate for protein structure classification.

In this paper, we start with eight features, C, CS, CSH, CSHP, CSHPV, CSHPVZ, CSHPVZ + B, and CSHPVZ + B + SB to assign protein classes or folding patterns. Then, we use the method of data fusion for feature selection and combination in order to improve classification accuracy.

C. The HLA Computational Architecture

The NNs have been commonly used in many machine learning and data mining applications, such as input–output

TABLE I
THE VARIETY IN PROTEIN STRUCTURES FOR TRAINING AND TESTING

Classes	Folding patterns	Number of proteins (Training)	Number of proteins (Testing)
1. all-α	1. α_1: Globin-like	13	6
	2. α_2: Cytochrome *c*	7	9
	3. α_3: DNA-binding 3-helical bundle	12	20
	4. α_4: 4-helical up-and-down bundle	7	8
	5. α_5: 4-helical cytokines	9	9
	6. α_6: Alpha; EF-hand	7	9
2. all-β	7. β_1: Immunoglobulin-like β-sandwich	30	44
	8. β_2: Cupredoxins	9	12
	9. β_3: Viral coat and capsid proteins	16	13
	10. β_4: ConA-like lections/glucanases	7	6
	11. β_5: SH3-like barrel	8	8
	12. β_6: OB-fold	13	19
	13. β_7: Trefoil	8	4
	14. β_8: Trypsin-like serine proteases	9	4
	15. β_9: Lipocalins	9	7
3. α/β	16. $(\alpha/\beta)_1$: (TIM)-barrel	29	48
	17. $(\alpha/\beta)_2$: FAD (also NAD)-binding motif	11	12
	18. $(\alpha/\beta)_3$: Flavodoxin-like	11	13
	19. $(\alpha/\beta)_4$: NAD(P)-binding Rossmann-fold	13	27
	20. $(\alpha/\beta)_5$: P-loop containing nucleotide	10	12
	21. $(\alpha/\beta)_6$: Thioredoxin-like	9	8
	22. $(\alpha/\beta)_7$: Ribonuclease H-like motif	10	14
	23. $(\alpha/\beta)_8$: Hydrolases	11	7
	24. $(\alpha/\beta)_9$: Periplasmic binding protein-like	11	4
4. $\alpha+\beta$	25. $(\alpha+\beta)_1$: β-grasp	7	8
	26. $(\alpha+\beta)_2$: Ferredozin-like	13	27
	27. $(\alpha+\beta)_3$: Small inhibitors, toxins, lectins	12	27

mapping and bioinformatics [17], [18]. We use NN as a multiclass classifier to build HLA for the purpose of protein structure prediction. The multilayer perceptron (MLP) and the radial basis function network (RBFN) are two popular NN models. The RBFN is a three-layer network with Gaussian function that is suitable to be a classifier [19] since the weights of RBFN are measured and adjusted according to the distance of data. The RBFN is constructed as a kind of hybrid NN network that combines the self-organized-map (SOM) and the back-propagation (BP) [9]. It was shown [9] that the overall prediction accuracy rate for protein structure classification using RBFN is better than that using MLP. Therefore, we adopted the RBFN model in this paper where one hidden layer and nodes will be generated automatically. The hidden layer nodes show the coordinate of training sample clusters.

The HLA framework, proposed in Huang *et al.* [9] consists of a two-level procedure. In the first level, a protein is classified into one of four classes by a multiclass classifier (classifier 1 in Fig. 1). Then, in the second level, it is further classified into one of f_i folding patterns by the corresponding multiclass classifier (f_1, f_2, f_3 and f_4 is equal to 6, 9, 9 and 3 in classifier 1, 2, 3, and 4 respectively in Fig. 1).

In Huang *et al.* [9], it has been shown that the HLA framework is an effective learning structure which reduces the number of classifiers, avoids the voting scheme, and directly indicates the reliability or confidence of the result predicted. Our current study incorporates data fusion in HLA for the testing data set, as shown in Fig. 1. For the training data set, HLA is used without data fusion. To predict which of four classes a protein belongs to with HLA, we use eight individual features to assign class to each protein in the testing data set at first. Then, we use the technique of data fusion to select the best feature and to combine results for the protein class discrimination. Finally, the protein class is predicted with the combined feature. For protein folding patterns associated with each protein class, the eight individual features are used once more to assign protein folding patterns to each protein in the class. Similarly, data fusion is applied again for feature selection and combination in order to improve the prediction of protein folding patterns.

D. Data Fusion and The Diversity Rank/Score Graph

The approach we take to properly select and combine features in protein structure classification is analogous to those used in information retrieval [10], [11], [14], [20], [21], pattern recognition [22], molecular similarity searching and structure-based screening [12], [23], and microarray gene expression analysis [24]–[26]. In addition, we adopt some of the notations and terminologies from [11]–[13]. Moreover, each feature is viewed as

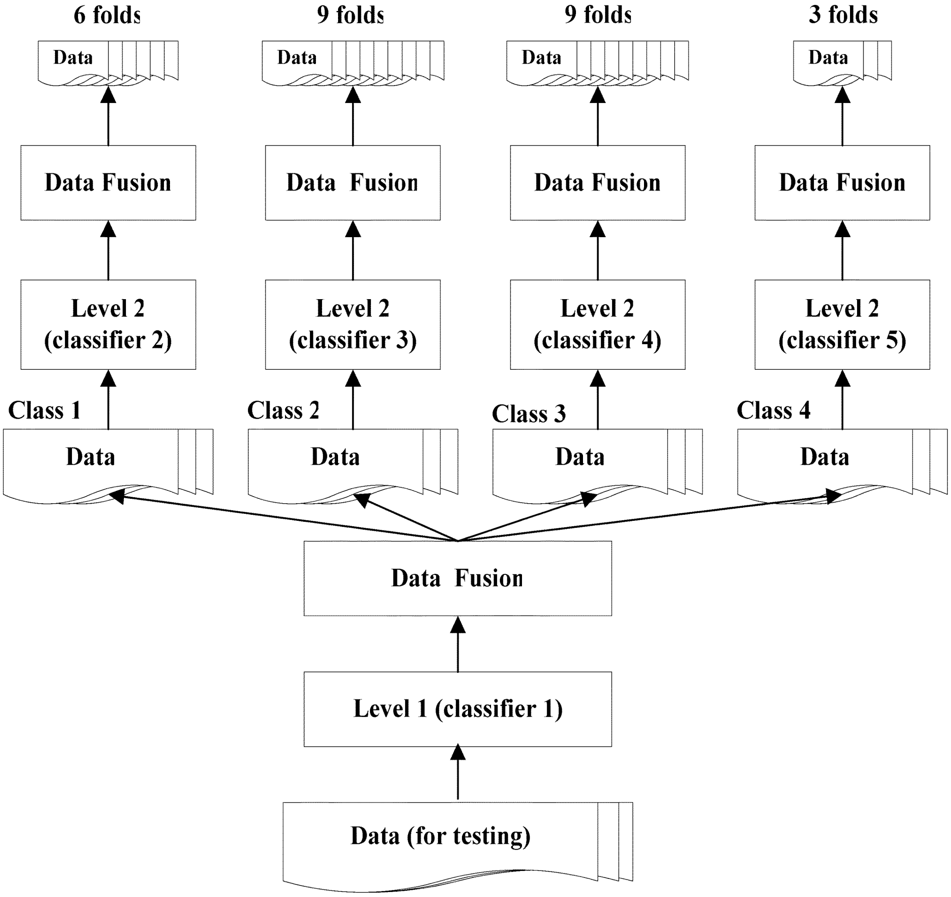


Fig. 1. The architecture of HLA using data fusion.

a **scoring system** F containing a **score function** s_F and a **rank function** r_F on the set of classes.

Our previous work in information retrieval, molecular similarity searching, structure-based virtual screening and microarray gene expression study have demonstrated the following:

Remark 1: For a set of multiple scoring systems, each with a score function and a rank function, we have: (a) the combination of multiple scoring systems would improve the prediction accuracy only if: (1) each of the systems has a relatively high performance, and (2) the individual systems are distinctive (or diversified), and (b) rank combination performs better than score combination under certain conditions.

Given a protein sequence and for each feature A, let $s_A(x)$ be a function that assign a real number to the class (or folding pattern) x in the set of all n classes (or folding patterns) $D = \{c_1, c_2, \ldots, c_n\}$. We view the function $s_A(x)$ as the score function from D to R (the set of real numbers) with respect to the feature A. When treating $s_A(x)$ as an array of real numbers, it would lead to a rank function $r_A(x)$ after sorting the $s_A(x)$ array into descending order and assigning a rank to each of their classes (folding patterns). The resulting rank function $r_A(x)$ is a function from D to $N = \{1, 2, \ldots, n\}$.

In order to properly compare and correctly combine score functions from multiple features, the function values have to be normalized. The normalization we used is the transformation from $s_A(x)$: $D \rightarrow R$, to $s_A^*(x)$: $D \rightarrow [0, 1]$, where $s_A^*(x) = (s_A(x) - s_{\min})/(s_{\max} - s_{\min})$, x in D and $s_{\max} = \max\{s_A(x)|x \text{ in } D\}$ and $s_{\min} = \min\{s_A(x)|x \text{ in } D\}$.

Suppose we have m features (i.e., m scoring functions). There are combinatorially $2^m - 1$ combinations for all m individual features ($\sum_{k=1}^{m} \binom{m}{k} = 2^m - 1$) with rank or score functions. The total number of combinations to be considered for predicting protein class and protein folding pattern are $2^{m+1} - 2$ and $2^{2m+2} - 2^{m+3} + 4$ respectively in the HLA architecture. These numbers can become huge when the number of features m is large. Moreover, we have to evaluate the predictive power of each combination across all proteins. Because of this complexity, the current paper would start with combining only two features which still retain fairly good prediction power. Combination of more than two features will be considered in our future work.

E. Methods of Combination and Feature Selection

Suppose m features A_i, $i = 1, 2, \ldots, m$, are given with score function s_{Ai} and rank function r_{Ai}, there are several different ways of combination. Among others, there are **score combination, rank combination, voting, linear average combination and weighted combination** [10]–[12], [14], [20]–[27]. Voting is computationally simple and better than simple linear combinations when applied to the situation with large number of features. However, a better alternative is to reduce the number of features to a smaller number and then these features are combined. In this paper, we reduce the set of features to those which

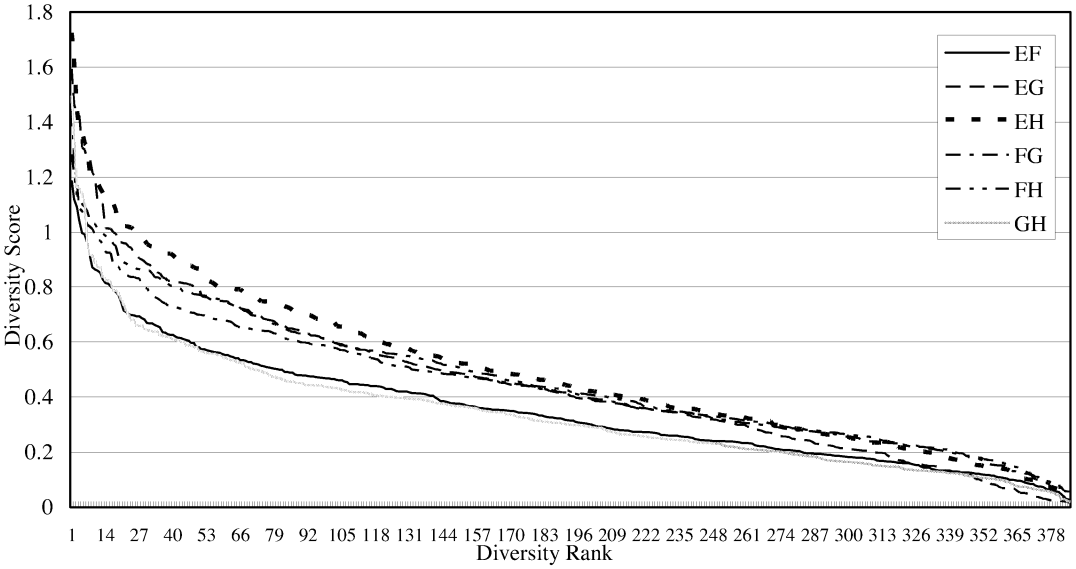


Fig. 2. The diversity rank/score graph for each pair of features from {E,F,G,H} for classifying protein classes.

perform relatively well and then use the diversity rank/score function to decide whether to combine by rank or by score. For the m features A_i, rank functions r_{Ai}, and score functions s_{Ai}, we have the score function s_R and s_S of the rank combination and score combination respectively defined as

$$s_R(x) = \sum_{i=1}^{m} \left[\left(r_{Ai}(x) \right) / m \right], \text{ and } s_S(x) = \sum_{i=1}^{m} \left[\left(s_{Ai}(x) \right) / m \right].$$

As we did before, $s_R(x)$ and $s_S(x)$ are then sorted into ascending and descending order to obtain the rank function of the rank combination $r_R(x)$ and the score combination $r_S(x)$, respectively.

In this paper, we use the rules (a)(1), (a)(2), and (b) stated in Remark 1 as our guiding principle to select features and to decide on the method of combination. We started with eight features and, in each case, use rule (a)(1) to reduce the number of features to four. A diversity function $d(A,B)$ between features A and B is then computed using the concept of the rank/score function defined by Hsu *et al.* [10], [11], [13].

F. The Rank/Score Function and The Diversity Rank/Score Graph

Given a protein sequence and for each feature A, we have the score function s_A and rank function r_A. Both s_A and r_A are functions from D to [0,1] and N respectively, where $D =$ the set of classes. As in other application domains [10]–[13], we explore the scoring (and ranking) characteristics of feature A by calculating the **rank/score function**, $f_A\colon N \rightarrow [0,1]$ as follows:

$$f_A(j) = \left(s_A^* \circ r_A^{-1} \right)(j) = s_A^* \left(r_A^{-1}(j) \right).$$

We note that the set N is different from the set D which is the set of classes (or fold patterns). The set N is used as the index set for the rank function value and $|N| = n$ is indeed the cardinality of D. The rank/score function so defined signifies the scoring (or ranking) behavior of the feature A and is independent of the classes (or folding patterns) under consideration.

For protein p_i in $P = \{p_1, p_2, \ldots, p_t\}$ and the pair of features A and B, **the diversity score function** $d_i(A,B)$ is defined as: $d_i(A,B) = \Sigma |f_A(j) - f_B(j)|$, where j is in $N = \{1, 2, \ldots, n\}$ and n is the number of classes (or folding patterns). When there are q features selected (in this paper, $q = 4$), there are $\binom{q}{2} = q(q-1)/2$ (in this paper, this number is 6) diversity score functions. If we let i vary and fix the feature pair (A,B), then $\boldsymbol{d_i(A,B)}$ **is the diversity score function** $\boldsymbol{s_{(A,B)}(x)}$ **from** $\boldsymbol{P = \{p_1, p_2, \ldots, p_t\}}$ **to** $\boldsymbol{R}$. Sorting $s_{(A,B)}(x)$ into descending order would lead to **the diversity rank function** $\boldsymbol{r_{(A,B)}(x)}$. Consequently, the **diversity rank/score function** $f_{(A,B)}(x)$ is defined as

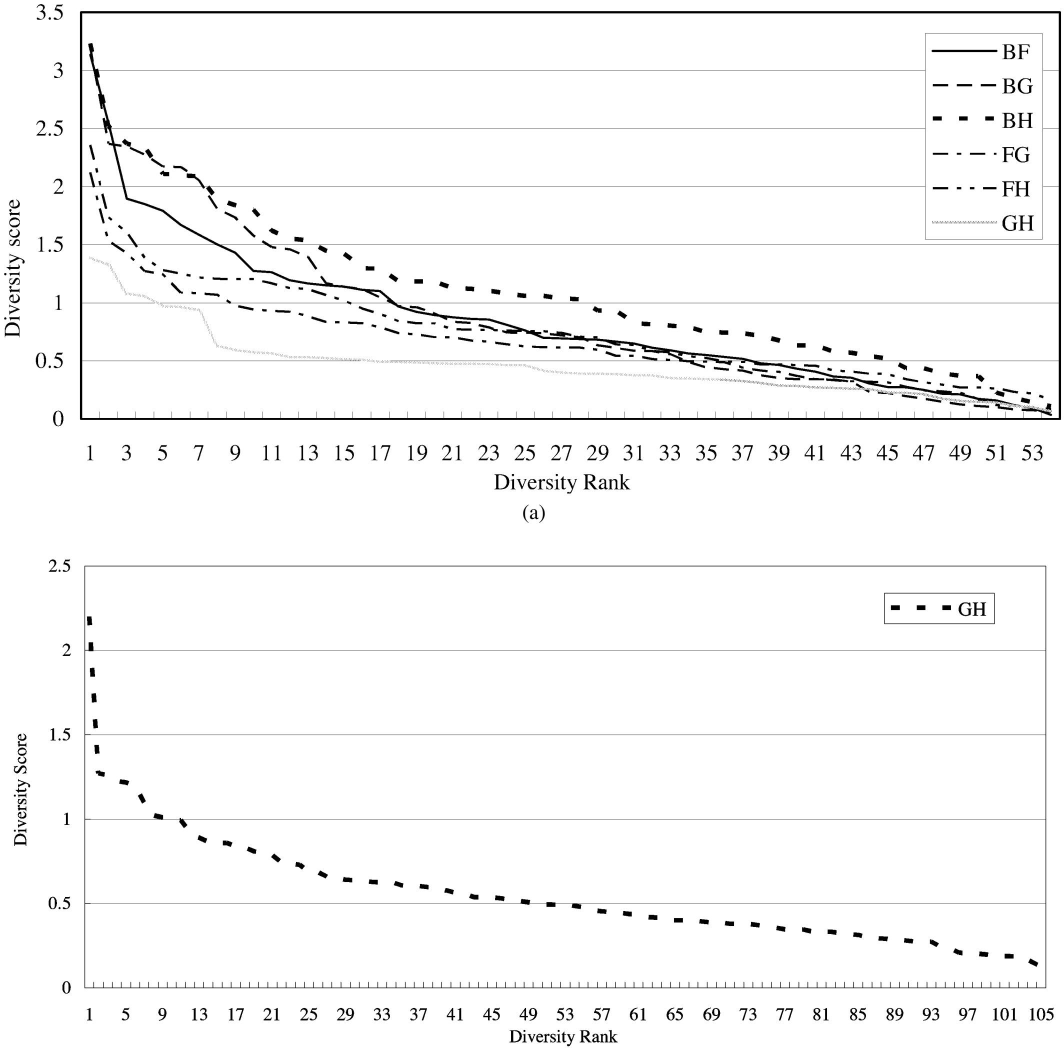
$$f_{(A,B)}(j) = \left(s_{(A,B)} \circ r_{(A,B)}^{-1} \right)(j) = s_{(A,B)} \left(r_{(A,B)}^{-1}(j) \right),$$
$$\text{where } j \text{ is in } T = \{1, 2, 3, \ldots, t\}.$$

We note that the set T is different from the set P which is the protein set considered. The set T is used as the index set for the diversity rank function value and $|T| = t$ is indeed the cardinality of P. The diversity rank/score function $f_{(A,B)}(k)$ so defined exhibits the diversity trend of the feature pair (A,B) across the whole spectrum of input set of t proteins and is independent of the specific protein under study.

For two features A and B, the graph of the diversity rank/score function $f_{(A,B)}(j)$ is called the **diversity rank/score graph** (or **diversity graph** in short). Our current study aims to examine all the $q(q-1)/2$ diversity rank/score graphs to see which pair of features would give the highest diversity measurement. Following rules (a)(2) and (b) in Remark 1, the rank combination of these two features is then calculated to give the final rank function and to choose the class (or folding pattern).

III. Results

The technique of combinatorial fusion (see [13]) is used for protein structure classification on a testing data set with NN using RBFN under the HLA architecture. Initially, we use eight features, C (reworded as A), CS (as B), CSH (as C), CSHP (as



(a)

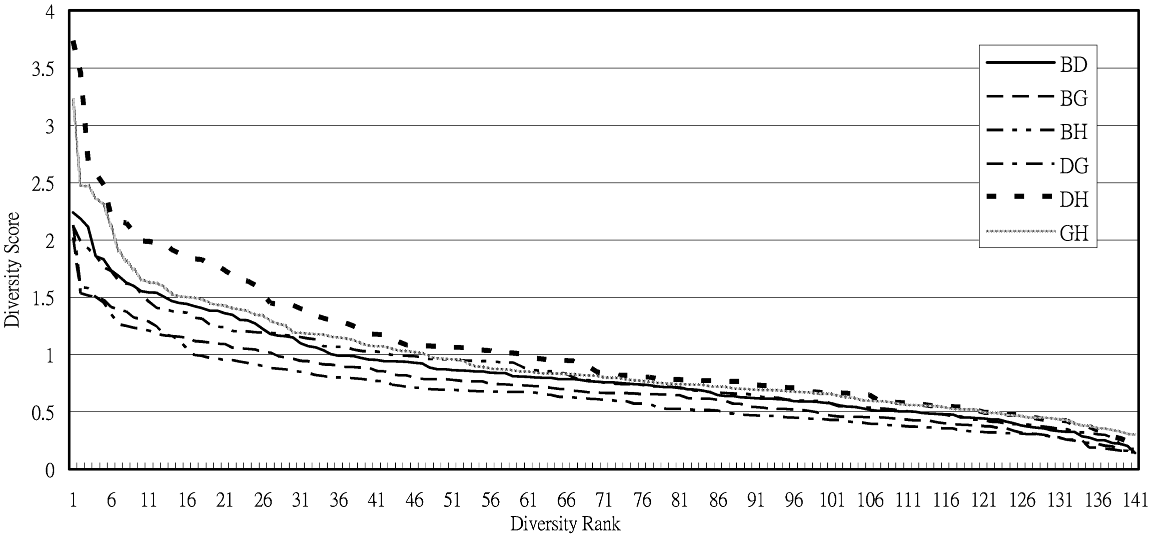
(b)

Fig. 3. The diversity rank/score graph for each pair of features in {B,F,G,H} for classifying protein folding patterns in class1; in {G,H} for classifying protein folding patterns in class2; in {B,D,G,H} for classifying protein folding patterns in class3; and in {G,H} for classifying protein folding patterns in class4. (a) Class 1. (b) Class 2.

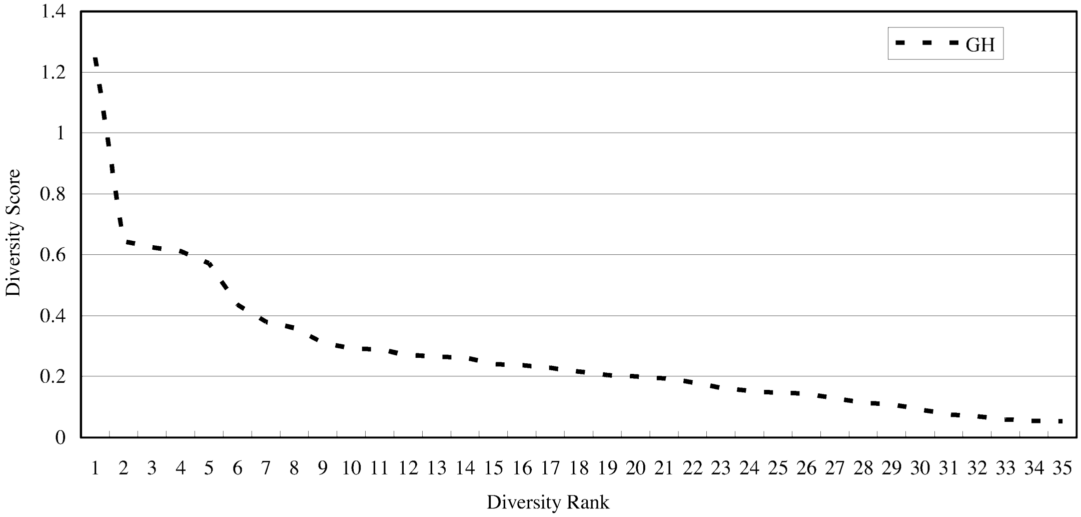
D), CSHPV (as E), CSHPVZ (as F), CSHPVZ + B (as G), and CSHPVZ + B + SB (as H), to assign protein classes for all proteins tested. Following the rule (a)(1) in Section II-D, we select four features E, F, G, and H, for further fusion (or combination) because of their higher accuracy rate than others as demonstrated in [9]. With the help of rule (a)(1), we can reduce $2^8 - 1$ combinations to $2^4 - 1$ combinations. Following the rules (a)(2) and (b) in Section II-D, we shall use the rank combination of the features to predict the protein class.

As stated in Section II-F, the diversity of any two of features E, F, G, and H can be calculated for all proteins tested and features E and H are found to have the highest diversity, as shown in Fig. 2, among all six ($\binom{4}{2} = 6$) feature combinations. In conjunction with (b) in Remark 1, we use the rank combination of features E and H to predict protein classes for all proteins tested. After the protein classes for all proteins tested have been predicted and categorized, the prediction of protein folding patterns follows in the HLA architecture. We use the same rules and a diversity graph to choose the best combined two features in each class for the purpose. Accordingly, we choose a rank combination of features BG, GH, DH, and GH to predict protein folding patterns in classes 1, 2, 3, and 4, respectively. The diversity graph to pick the pair of features (B,G), (G,H), (D,H) and (G,H) for combination and to predict folding patterns in class 1, 2, 3, and 4 are depicted in Fig. 3(a), (b), (c), and (d), respectively. In Fig. 3(b) and (d), only the pair of features (G, H) is selected since its accuracy rate is more higher than others. It implies that the features G and H are more suitable than others for classifying proteins, which belong to class 2 or class 4, into folding patterns.

We use the standard percentage accuracy rate Q_i [7], [9], [28] to evaluate our work. $Q_i = p_i/n_i \times 100$, where n_i is the number of testing proteins in the ith class or folding pattern and p_i is the number of proteins being correctly predicted in the ith class or folding pattern. The overall prediction accuracy rate Q is given by $Q = \sum_{i=1}^{k} q_i Q_i$, where $q_i = n_i/K$, where K is the total number of proteins tested, and n is the number of classes or folding patterns. We compare the overall prediction accuracy rates Q for protein classes in our previous [9] and current work. These are shown in Table II. The current overall prediction accuracy rate is 87%, 3.4% higher than that of our previous work. Table III shows that for prediction of folding pattern, our current



(c)



(d)

Fig. 3. (*Continued.*) The diversity rank/score graph for each pair of features in {B,F,G,H} for classifying protein folding patterns in class1; in {G,H} for classifying protein folding patterns in class2; in {B,D,G,H} for classifying protein folding patterns in class3; and in {G,H} for classifying protein folding patterns in class4. (c) Class 3. (d) Class 4.

TABLE II
THE COMPARISONS OF OVERALL PREDICTION ACCURACY RATES Q FOR PROTEIN CLASSES

Method	HLA, NN 'CSHPVZ'*	HLA, NN 'B'*	HLA, NN 'CSHPVZ+B'*	HLA, NN 'CSHPVZ+B+SB'*	HLA + data fusion, NN
Q	81.6	79.2	83.1	83.6	**87**

* Data from Huang et al. [9]

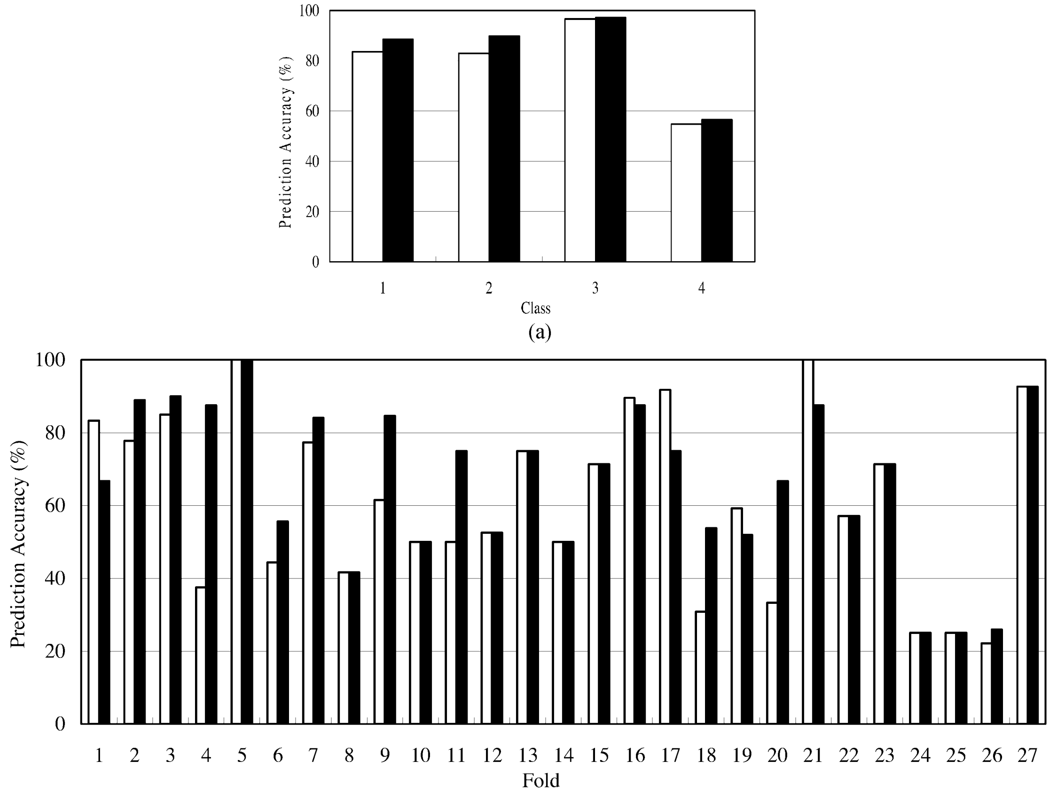
work has an overall prediction accuracy rate of 69.6%, which is 13.1% higher than that of Ding and Dubchak [7], 4.1% higher than that of our previous work.

We summarize the comparisons of prediction accuracy rates Q_i of our previous work [9] and our current work in Fig. 4. Our results give prediction accuracy rates (>80%) in 3 classes, especially in class α/β with accuracy rate reaches 97.2%, all higher than what we achieved previously, shown in Fig. 4(a). For protein folding patterns prediction, the current work gives prediction accuracy rates (>80%) in 9 folding patterns, more than what in our previous work, 7, as shown in Fig. 4(b). Also, the current work outperforms our previous work in ten folding patterns, especially (>30% improvement) in folding patterns: α_4 (4-helical up-and-down bundle), β_3 (viral coat and capsid proteins), β_5 (SH3-like barrel), $(\alpha/\beta)_3$ (flavodoxin-like) and $(\alpha/\beta)_5$ (P-loop containing nucleotide). Our previous work has slightly better results only in 5 folding patterns [especially in fold α_1 (globin-like)]. Overall, there is an improvement with our current method using the HLA framework and data fusion techniques. In summary, the current method has achieved an accuracy rate of 69.6% for folding pattern classification, which is a significant improvement over the result of Ding and Dubchak ([7], 2001) of 56.5%.

TABLE III
THE COMPARISONS OF OVERALL PREDICTION ACCURACY RATES Q FOR PROTEIN FOLDING PATTERNS

Feature / Method	'C'	'CS'	'CSH'	'CSHP'	'CSHPV'	'CSHPVZ'	'CSHPVZ+ B'	'CSHPVZ+ B+SB'
OvO[1], NN**	20.5	36.8	40.6	41.1	41.2	41.8	—	—
OvO[1], SVMs**	43.5	43.2	45.2	43.2	44.8	44.9	—	—
uOvO[2], SVMs**	49.4	48.6	51.1	49.4	50.9	49.6	—	—
AvA[3], SVMs**	44.9	52.1	56.0	**56.5**	55.5	53.9	—	—
HLA, NN*	44.9	53.8	53.3	54.3	55.3	56.4	63.7	**65.5**
HLA+data fusion, NN	**69.6**							

[1] one-versus-others method [7]; [2] unique one-versus-others method [7]; [3] all-versus-all method [7]
* Data from Huang et al. [9]
** Data from Ding and Dubchak [7]



(a)

(b)

Fig. 4. The comparisons of prediction accuracy rates Q_i of our previous work (Huang et al. [9]) (in white) and the current work (in black) (a) for 4 protein classes and (b) for 27 protein folding patterns.

IV. CONCLUSION AND FUTURE WORK

Methods of combining multiple classification systems or multiple scoring systems have been used in a variety of applications domains including information retrieval, pattern recognition, microarray gene expression analysis, and molecular similarity searching [10], [14], [20]–[27]. More recently, criteria to select the classification systems or scoring systems for combination and to decide ways to combine these systems have been discussed and studied [11]–[14], [27]. It has been demonstrated in Combinatorial Fusion Analysis (see [13] and its references) that (a) the combination of multiple systems (or features) would improve the performance only if (1) each of the individual systems (features or functions) has a relatively high performance, and (2) each individual systems are distinctive (or different), and (b) combination by rank outperform combination by score under certain conditions.

In this paper, we have applied the concept of Combinatorial Fusion (see Remark 1) to improve accuracy in protein structure prediction. In particular, we have successfully improved the overall predictive accuracy rate of 87% for the second structure (the four classes) and 69.8% for the folding patterns (the 27 folding categories). We improve previous results by Huang *et al.* [9] (65.5% for folding structure) and Ding and Dubchak [7] (56.5% for folding structure) by incorporating the method of combinatorial fusion in their approach using NN with the RBFN using the HLA.

One of the novelties of our current work is the notion of a diversity rank/score function $d_i(A, B)$ between a pair of features A and B (Figs. 2 and 3). This function characterizes the diversity of ranking (or scoring) behavior between features A and B across the whole spectrum of all protein sequences under consideration. This parameter is then used to select appropriate and diverse features for combination. The current work is the first of a series of on-going projects towards the protein structure prediction problem using HLA, NN-RBFN, and combination fusion analysis. Following the current work, we have observed the following.

The method of combinatorial fusion we used in this paper is computational efficient, able to adapt to different situations and approaches, and scalable to a large number of classes (or folding patterns) and a large number of proteins.

In this paper, we considered only combination of a pair of two features in order to improve the performance. It may be possible to achieve better results with combination of more than two features. However, it is indicated in criteria (a)(1) and (2) that each of these three or more features would have relatively high performance and individual features should be different. As such, the diversity between three or more features should be defined. This will be studied in a latter work.

Although it has been shown (e.g., [31]) that combining multiple predictors or servers improves fold recognition, we note here that combining all the features or multiple scoring systems together may not guarantee optimal performance (see [12] and [13]).

We used rank combination due to criterion (b) which was demonstrated to be better under certain conditions analytically and by simulation in Hsu and Taksa [11]. We observed that score combination does have its merit when the two features combined are similar and homogeneous with respect to their scoring functions, rank function, or rank/score function. We decided to use the rank combination because the pair of features to be combined satisfies criteria (a)(1) and (a)(2) and these two items are precisely the conditions stipulated in [11], [12], [14], [25], and [26].

In our feature selection process, we selected top four performers out of the original eight features. The ideal case is to select those features which perform much better than the others. That means there is a big difference on the performance between those selected and those not selected.

Our current work represents the first of a series of investigations on the protein structure prediction problem using HLA and combinatorial fusion. It has generated several issues and topics worthy of further study. We summarize some of them here.

Our diversity rank/score function d_i(A,B) for the feature pair (A,B) with respect to protein p_i is defined using the variation of the rank/score functions between A and B. As indicated in [11], [13], and [14], variation of the rank functions or the score function between A and B can be used also to define the diversity score function. We will explore these two other options in a latter work.

The effectiveness of our fusion of multiple features is limited by the set of eight original chosen features. It might be worthwhile to study the content of original set of features. For example, we would like to explore the diversity among the original features such as local versus global, physical versus chemical, and bigram versus trigram scheme.

Related to observation (D) above, one might ask if it is better to expand the scope and the number of features. In this paper, we started with eight features and four are selected using the CFA criteria. In a separate paper [30], eleven features are collected and three features are selected according to the criteria (a)(1) and (a)(2) in Remark 1. We have obtained a slightly better overall accuracy rate of 87.8% for four classes and 70.9% for 27 folding categories.

Our results improve previous results by Huang *et al.* [9] and Ding and Dubchak [7] which used NN with radial basis function in an HLA. Work has been performed to improve those results which used other machine learning technique such as kernel method, SVM and genetic algorithm. For example, Yu *et al.* [29] has obtained good accuracy rate using SVM with n-peptide coding schemes and jury voting. Ongoing work has been performed to improve these results using our combinatorial fusion approach. These results will be reported in the future.

Due to its importance, protein structure prediction and classification has been studied extensively in the past decade. In particular, protein structure classification using databases of proteins with known structures have been studied (See [32] and [33] and their references). As stated before, our work does not use or rely on any databases of known structures

ACKNOWLEDGMENT

D. F. Hsu would like to thank National Tsinghua University and the Ministry of Education for their support and hospitality during his visit to NTHU, Hsinchu, Taiwan, R.O.C., in Spring 2004.

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