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Finding Regularity in Protein Secondary Structures using a Cluster-based Genetic Algorithm

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Abstract: - Secondary structures help in the identification of biological features such as protein classification, protein structure and function, and evolutionary relationships between proteins. However, secondary protein structures are sometimes hard to identify from experimental analysis, therefore researchers are forced to rely on predictive information. In this paper we offer an evolutionary computation approach that combines clustering and genetic algorithms to produce schemata for the visual representations of protein secondary structures. The two major roles of a clustering algorithm are to a) generate parts of initial chromosomes in genetic algorithms and b) assist schemata in predicting secondary protein structures. According to our tests, the new approach improves Q3 accuracy by 12% compared to previous efforts. We also discuss some examples of schemata with interesting biological meaning.

Key-Words: - protein secondary structure, genetic algorithms, clustering, data mining, knowledge discovery

1 Introduction

Determining protein structure in a laboratory is much more difficult than identifying protein sequence, which explains why as of September 23, 2005 the Protein Information Resource (PIR) database contained 2,203,641 protein sequences while the Protein Data Bank (PDB) contained only 32,727 protein structures. Accordingly, independent researchers and an organization known as the Critical Assessment of Techniques for Protein Structure Prediction support the practice of predicting protein structures from previously known sequences [1, 2]. A typical approach is to predict secondary protein structures from a sequence, then use a combination of the secondary information and various biological heuristic functions to improve predictive algorithms [3]. Protein secondary structures also play an important role in protein function discovery, protein classification, and establishing phylogenetic trees. For this reason, we decided to take a closer look at the natural instincts of protein secondary structures and their potential for assisting in protein secondary structure prediction.

Most secondary protein structure prediction methods are incapable of clearly identifying observable regularity. In light of the low Q3 values currently reported by researchers [4], we proposed a schema generated by a steady-state genetic algorithm (SSGA), which are known to outperform association-rule mining methodology in RS130 data sets for these kinds of schemata [5]. In this paper, our schema discovery approach combines SSGA and clustering to identify high confidence schemata and to improve Q3 accuracy by at least 10 percent [6].

1.1 Schema Definition

Protein secondary structures are designated as H (alpha helix, 3/10 helix, pi helix), E (beta bridge, beta ladder), or L (turn, bend) [7]. The regularity of secondary structures (which consist of amino acids and one secondary structure) are usually discussed in terms of factors that cause amino acids to combine in order to form a specific secondary structure. An amino acid that plays a role in certain secondary structures are affected by neighboring amino acids, while secondary structure sheets often require extra consideration for remote amino acids. In the same manner that many researchers de-emphasize the effect of remote amino acids on protein secondary structure [8], we decided to underplay the remote effect in order to simplify schema design.

1.2 Representation

We modified Holland's (1975) one-dimensional schema format

schema $s \in \{1, 0, *\}^l$

(where *l* is a fixed length and * is either 0 or 1) into a two-dimensional format:
schema s $\in$ {an amino acid, *} $^{(l-1)/2}$ X {an amino acid} X {an amino acid, *} $^{(l-1)/2} \rightarrow$ {H, E, L| one kind of secondary structures},
where *l* is a fixed length (an odd number) and * is don't care.

According to our proposed schema, the central amino acid plays a role that corresponds to a specific secondary structure due to non-asterisk amino acids on each of its two sides. In Figure 1, amino acid A is found in the first and last positions and amino acid L is in the center position. Amino acid L is eventually categorized as having a H protein secondary structure—in other words, L is only affected by the first position amino acid on its left side and fourth position amino acid on its right. The other asterisk positions (which have no affect on L) can consist of any amino acid. We focused on the 9 windows in the front part of the schema, since that length is long enough to contain sufficient local structural information for analysis [9].

$$A{*}{*}{*}L\ {*}{*}{*}A \rightarrow H$$

Figure 1. Schema example.

2 Preprocessing the Raw Data

We established a data set according to the PDB_select protein chain list because it is representative of PDB chain identifiers that help researchers save considerable time and effort. The PDB_select protein chain list allows for introductory browsing, protein architecture analysis, prediction method development, and model building via modular construction [10].

2.1 PDB_select constraints

There are many versions, from which no two proteins have more than 25% sequence identity to 95%, in the PDB_select list. Furthermore, it excludes chains according to the following criteria:

- length less than 30 residues;
- number of non-standard amino acid residues (including chain breaks) exceeds 5 percent of chain length;
- resolution exceeds 3.5 angstroms;
- R-factor exceeds 30 percent;
- some chains are known to be of inferior quality;
- number of residues without side chain coordinates < 90 percent chain length;
- number of residues without backbone coordinates < 90 percent chain length;
- content of ALA plus GLY exceeds 40 percent of chain length; and
- data on resolution or R-factor (i.e., NMR-structures) are not available.

2.2 Constraints

We separated the data set into two independent sets (training and testing) and used the most stringent 25% PDB_select list (2,485 chains with 388,067 residues). Next, we located the secondary structures of proteins in the 25% PDB_select list from the Database of Secondary Structure in Proteins (DSSP) of secondary structure assignments for all PDB protein entries. However, due to problems with DSSP secondary structure information, we eliminated some chains from the 25% list for the following reasons:

- incorrect PDB identification in the 25% list;
- no information in the DSSP files;
- broken chains; or
- inclusion of an unknown symbol X.

Our data set consisted of 1,600 chains with 248,984 residues. We randomly selected 1,200 chains for use as a training set for mining schemata; the remainders were used for testing.

2.3 Data Set Analysis

It was assumed that the distribution characteristics of the data set would affect the experimental results. We used the data in Table 1 to inspect a) whether a

Table 1. Statistics for 20 amino acids in the PDB_select chain set.

	Num	%	H 87690	H%	E 55134	E%	L 106160	L%
A	18937	7.60%	9278	**49%**	3216	17%	6443	34%
R	12469	5.01%	5234	**42%**	2585	20.7%	4650	37.3%
N	11335	4.55%	3093	27.3%	1579	13.9%	6663	**58.8%**
D	14300	5.74%	4441	31.1%	1629	11.4%	8230	**57.6%**
C	4497	1.81%	1260	28%	1293	28.8%	1944	**43.2%**
Q	16934	6.80%	7855	**46.4%**	2823	16.7%	6256	37%
E	9989	4.01%	4658	**46.6%**	1643	16.4%	3688	37%
G	17764	7.13%	2952	16.6%	2553	14.4%	12259	**69%**
H	5857	2.35%	1978	33.8%	1254	21.4%	2625	**44.8%**
I	14136	5.68%	5247	**37.1%**	5485	**38.8%**	3404	24.1%
L	21635	8.69%	10053	**46.5%**	5188	24%	6394	29.6%
K	15587	6.26%	6050	38.8%	2837	18.2%	6700	**43%**
M	5550	2.23%	2373	**42.8%**	1174	21.2%	2003	36.1%
F	10109	4.06%	3641	**36%**	3201	31.7%	3267	32.3%
P	11238	4.51%	1960	17.4%	1122	9.98%	8156	**72.6%**
S	15481	6.22%	4193	27.1%	2924	18.9%	8364	**54%**
T	13623	5.47%	3684	27%	3576	26.2%	6363	**46.7%**
W	3705	1.49%	1339	**36.1%**	1115	30.1%	1251	33.8%
Y	8799	3.53%	2936	**33.4%**	2959	**33.6%**	2904	**33%**
V	17039	6.84%	5465	32.1%	6978	**41%**	4596	27%

relationship exists between the amount of a schemata and the percentage of each amino acid in the data set, and b) the individual tendencies of all amino acids in the data set. Data in the first column of Table 1 are for 20 amino acids and second and third column data represent the number of occurrences for each amino acid and their respective percentages. The final column contains data on the corresponding amino acids, number of occurrences, and percentage of secondary helix (H), sheet (E), and Coil (L) structures. The first row presents information on the number of occurrences and percentages of each secondary structure in the data set.

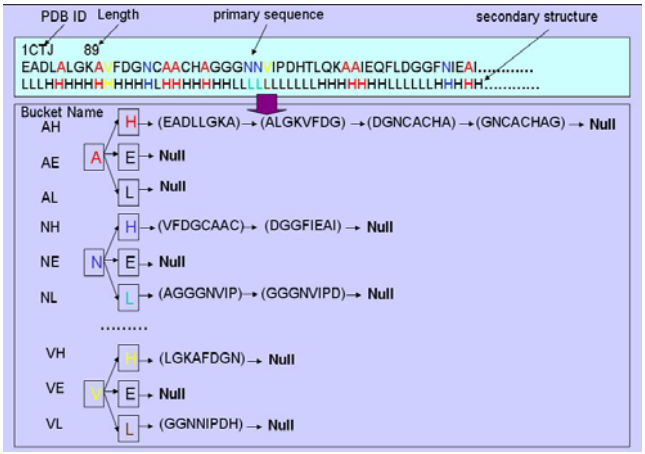

Figure 2. An example of using sequence 1CTJ to make a training set.

2.4 Making Training Sets

For every protein sequence, each amino acid can be viewed as a central amino acid in a schema. We defined amino acids on both sides of a central amino acid as a "neighbor pattern." According to our size choice of 9 windows, neighbor pattern length = 8, or 4 amino acids on each side. To create the training set we placed the neighbor pattern into a corresponding bucket according to the central amino acid and secondary structure; a partially assigned training set is shown in Figure 2. A complete training set consists of 20*3 buckets. Using the fifth amino acid in the 1CTJA protein sequence as an example, the neighbor pattern EADLLGKA should be put into bucket AH, since the central amino acid is A and its secondary structure is H.

3 Cluster-based Genetic Algorithm

Average Q3 accuracy in studies of protein secondary structure prediction using genetic algorithms is only 46 percent. Three issues are considered central to this problem: data set selection, solution search space, and fitness function design. At first, for the data set in previous studies, RS130 cannot represent so far the whole known proteins. Moreover, the number of similarities among DSSP protein families is considered too high. These kinds of problems are not associated with PDB_select.

Based on the 9-window size of the schema we applied, search space size is 20*3*21*8. To reduce search time, the very important thing is let genetic algorithm can search from good start. Therefore, once clustering was completed, we placed cluster centers as chromosomes into the initial population (Fig. 3).

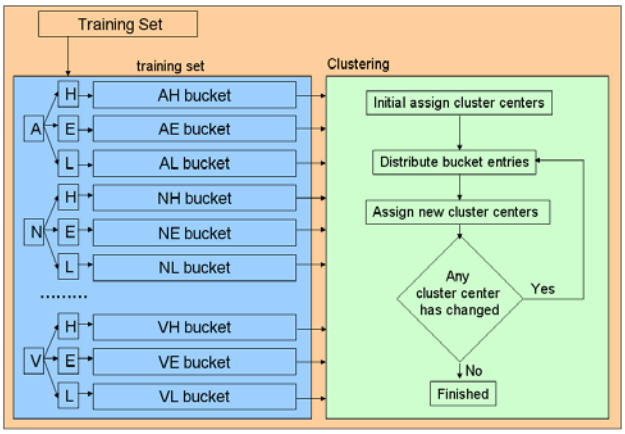

Figure 3. Our proposed clustering strategy.

The fitness function gives evolutionary direction to chromosomes [11]. When designing our fitness function, we assumed that a good schema should have a strong tendency toward a certain secondary structure. Furthermore, our fitness function states that increased chromosome confidence in the training set also increases Q3 accuracy in the protein secondary structure prediction.

As shown in Figure 4, our model includes evolutionary and application phases. With the exception of standard GA steps, during the evolutionary phase we generated some initial chromosomes by clustering. The evolutionary process makes use of a steady-state strategy. In each generation we placed certain high fitness chromosomes into our schemata set. Chromosomes placed in the set were removed from the population; the population consequently generated new chromosomes at random.

For protein secondary structure predictions we cut the sliding windows (9 window lengths) to use as protein sequence patterns for testing. Each pattern aligns with all schemata in the schemata set. After alignment, the secondary structure of the most similar schema was selected as the predictive result. When the fitness of the most similar schema was insufficient, the pattern was aligned with the

neighbor patterns of cluster centers in the training set. The final predictive result was the secondary structure that the most similar cluster center belonged to. Our approach uses blosum62 as a substitution matrix for alignment purposes.

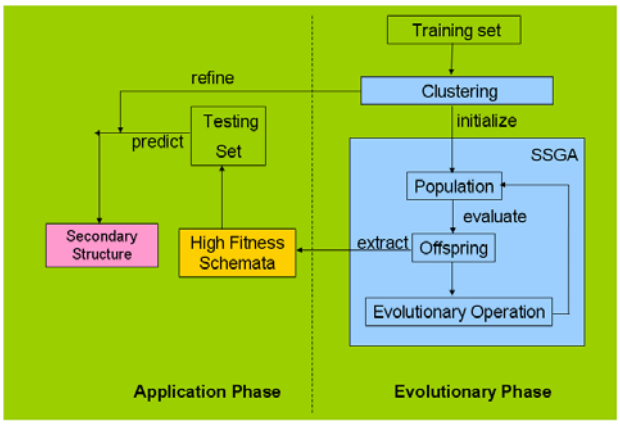

Figure 4. Our cluster-based genetic algorithm for mining schemata and its application for predicting protein secondary structures.

3.1 Population and Evaluation

Our approach uses 20 populations for each amino acid. Each chromosome includes a neighbor pattern and a secondary structure. Initial populations take on the neighbor pattern of the cluster center; all other chromosomes are randomly generated.

To evaluate a chromosome, we used its neighbor pattern for alignment with neighbor patterns in all secondary structure buckets. Alignment scores that exceeded a certain threshold were labeled as one hit. nH, nE, and nL are the respective hit numbers in the H, E, and L buckets. Chromosome secondary structure is determined according to the maximum hit number.

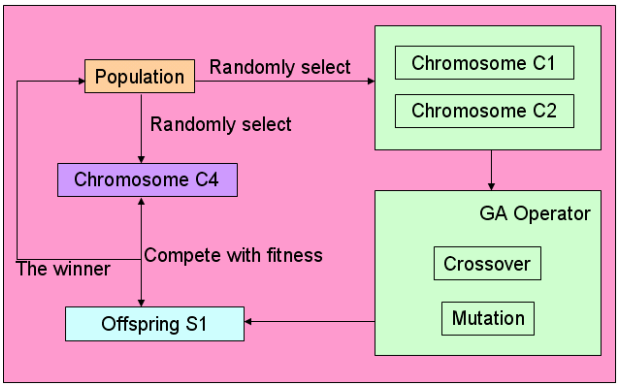

Figure 5. Steady-state strategy for our cluster-based genetic algorithm.

In the following equation,

confidence=nSS/(nH+nE+nL) (1),

nSS is defined as the maximum hit number among nH, nE, and nL. Confidence is relative to Q3; one of our goals was to find schemata with distinct tendencies toward certain secondary structures. We defined the discrimination rate (DR) as

DR=(nHighest-nSecond)/(nH+nE+nL) (2),

where nHighest is equal to nSS and nSecond is the second highest score among nH, nE, and nL. As a result,

fitness=confidence*DR (3)

3.2 Steady-state Strategy

The initial step in the steady-state strategy shown in Figure 5 is to randomly select two chromosomes, C1 and C2. Two offspring are generated by one-point crossover and multi-point mutations of C1 and C2; a single S1 offspring is randomly selected from these two offspring. Another chromosome (C4) is selected from the population for comparison with the S1 offspring in terms of fitness. The best chromosome is used to replace C4 in the population.

4 Experimental Results

Since our approach uses a clustering strategy for the initial population, we ran several trials using cluster numbers between 20 and 70 to predict protein secondary structures; results are shown in Figure 6. At 70 clusters our Q3 accuracy was 58.7 percent—approximately 12 percent better than predictive results from studies using genetic algorithms only.

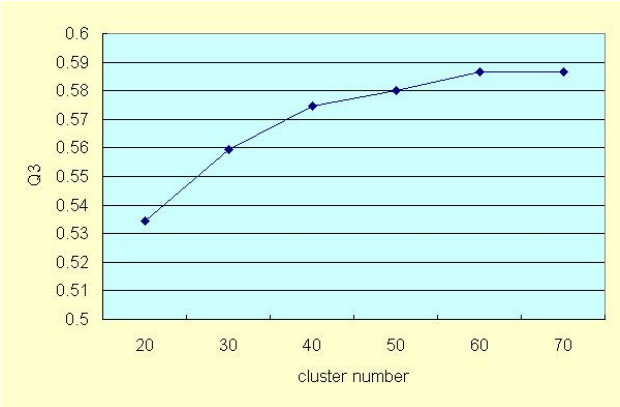

Figure 6. Q3 accuracy in different cluster numbers using our approach.

Table 2 presents a comparison of our Table 1 results with nr-PDB. Several differences are observed when K, W, and Y are in both PDB_select and nr-PDB. This underscores the importance of selecting a suitable data set.

Selected schemata with interesting biological meaning and high fitness are displayed in Table3.

The central amino acid in the first schema is P; when its neighbor pattern is D***P**N, the central amino acid plays an L role in the secondary structure. Note that L is the tendency for D, P, and N in Table 2.

Table 2. Secondary structure tendencies for each amino acid in nr-PDB and PDB_select chain sets.

	A	R	N	D	C	Q	E	G	H	I	L	K	M	F	P	S	T	W	Y	V
nr-PDB	H	H	L	L	L	H	H	L	L	H E	H	H L	H	H	L	L	L	H L	H L	E
PDB_select	H	H	L	L	L	H	H	L	L	H E	H	L	H	H	L	L	L	H	H E L	E

Table 3. Sample schemas of biological interest.

Schema	The tendency of secondary structure
D***PP**N->L	D, P and N are all L
TS**NP**K->L	T, S, P, and K are all L
K***DP**C->L	K, P, and C are all L
****G*P*N->L	P and N are all L
G***AP**P->L	G and P are all L
*F**A*L**H->H	F, L, and H are all H
*EQMRQ*L*->H	E, Q, M, and L are all H
E***E***Q->H	E and Q are all H
I*V*V***Y->E	I, V, and Y are all E
*Y**V*I**E->E	Y, I, and E are all E

5 Conclusion and Discussion

In a previous study we reported that our steady-state genetic algorithm outperformed association rule mining in finding schemata for describing relationships between protein primary and secondary structures. The identified schemata provided biologists with sufficient data for studying protein secondary structure, but they were insufficient for predicting secondary structure. In this paper we addressed the issues of finding high-fitness schemata and improving secondary structure prediction. Although we were able to increase Q3 accuracy by approximately 12 percent, we acknowledge that Q3 accuracy is still inadequate due to the insufficient number of found schemata. Two main reasons for this approach can not find sufficient schemata are the huge search space and incomplete status of current protein structure databases.

Our future plans are to reduce search space by considering some protein evolution information—for example, HMM profile or PSSM. On the other hand, these schemata can be applied to a consensus strategy for secondary structure prediction. When other methods (e.g., SVM, PSIPRED, or PROF) are not reliable for predicting certain protein structures and when exit found schemata can be aligned with these corresponding amino acids, it is possible to determine these protein secondary structures.

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