國立交通大學

生物資訊所

碩士論文

挖掘可語意解讀之知識並
預測蛋白質之殘基與去氧核醣核酸之鍵結

Mining Interpretable Knowledge and
Predicting Residues of DNA-Binding Proteins

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指導教授：何信瑩　教授

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摘要

本論文探討哪一個殘基能夠和去氧核醣核酸形成鍵結的預測問題，並且擷取以可語意解讀鍵結和非鍵結規則來表現的知識。在使用機械學習的方法時，分類器的選擇將會影響預測的結果及知識取得。在生物資訊領域中常用的分類器在預測上有著各種不同的應用並且可產生不錯的結果，但是其中的許多方法缺少可語意解讀的特性。在這篇論文中，使用可語意解讀之分類器，也就是用規則式決策樹系統來研究和去氧核醣核酸鍵結之蛋白質問題，它有下列幾項優點：能直接處理符號式的特徵、可得特徵重要度的排名以及能挖掘可讀的知識。

在過去已有許多預測和去氧核醣核酸鍵結之蛋白質的研究，最近使用類神經網路系統得到 79.1%的正確率 61.1%的淨預測值，在此研究中所使用的決策樹系統，以同樣的和去氧核醣核酸鍵結之蛋白質資料，並使用相同的特徵，可發現不論在正確率或是淨預測值皆有改善。當使用本文所提新特徵的情況下，更可讓正確率達到 79.72%，淨預測值達到 72.90%。因為我們希望挖掘出的規則能更具代表性，所以我們使用了共 982 筆大量的去氧核醣核酸鍵結之蛋白質資料，來進行資料挖掘的工作。結果顯示出除了眾所周知的和溶劑接觸的相對面積外，殘基周圍的電荷分佈和殘基的類別都在預測中扮演重要的角色。同時，這些由決策樹系統挖掘出的規則顯示，其他的特徵也給予我們在處理和去氧核醣核酸鍵結之蛋白質的預測問題提供一定的幫助。

Mining Interpretable Knowledge and Predicting Residues of DNA-Binding Proteins

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Abstract

In the thesis, both prediction of DNA-binding cites in proteins and knowledge acquisition in terms of interpretable binding and nonbinding rules are investigated. The classifier design using machine learning approaches would affect performances of the prediction and knowledge acquisition. The commonly-used prediction methods have a variety of applications and effective results in prediction problems, but their results suffer from low interpretabilities. Therefore, this thesis proposes an interpretable classifier based on a decision tree method to handle the DNA-binding protein problems. It has several advantages: capability of directly dealing with symbol features, ranking importance of features and mining interpretable knowledge.

In the past, a lot of researches studied the prediction problem in DNA-binding proteins. Recently, the existing neural network method has 79.1% accuracy and 61.1% net prediction (*NP*=(*Sensitivity*+*Specificity*)/2)). The proposed decision tree system can obtain better performance in terms of both accuracy and *NP* using the same features in these protein-DNA complex dataset. And when using the proposed feature set, the advanced performance has 79.72% accuracy and *NP* = 72.90%. To obtain more representative rules, we established a large dataset with 982 DNA-binding proteins. From the derived rule base, it reveals that besides well-known relative accessible surface area, the electric charge distribution near the residue and the amino acid groups in the proteins are also significant characteristics in prediction. At the same time, the listed rules mined by the decision tree system explain that other features could assist us in DNA-binding protein prediction.

Acknowledgements

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Chapter 1

Introduction

1.1 Motivation

The problem about DNA-binding proteins is a significant topic for biochemical discussion because the proteins often relate gene regulation. It is mainly controlled via binding of transcription factors to DNA for promoting or repressing gene expression. These transcription factors are mainly DNA-binding proteins coded by 2~3% of the genome in prokaryotes and 6~7% in eukaryotes [1-3]. The thesis would predict which residues are able to bind with DNA and further mining the binding and nonbinding rules. Many researchers in the field of bioinformatics had proposed all kinds of methods. Recently, a better result had been showed in [4]. This paper had used neuron network (NN) system and input four features consisting of solvent accessibility and surrounding residues. However, the disadvantages of the NN method are twofold: 1) the prediction is not linguistically interpretable and 2) it is difficult to deal with a large number of input features [5, 6].

We deem the research have a choice to be improved. Therefore, we propose decision tree (DT) method [7]. It not only obtains the better prediction performance on the problem, but also lists the interpretable knowledge. Besides the above-mentioned advantage, the capability of direct dealing with symbol features, the rank of the major features and knowledge acquisition, DT method could handle higher dimension problem [5-8]. In addition to the same features with [4], we also establish another feature set with 11 candidate features for encouraging prediction by additionally inputting the secondary structure and other information of the residues. Finally, we collect a large data, 982 DNA-binding proteins, in order to mine the representative knowledge in DNA-binding proteins. The knowledge about DNA-binding proteins will be displayed in the thesis later.

1.2 Survey of the Related Works

DNA-binding proteins usually affect the regulation and expression of DNA in organisms. X-ray crystallographic and NMR spectroscopic analysis on DNA-binding proteins have provided valuable information about the general features of these complexes. Computer-aided analysis will be a significant factor when the data is continually growing. It is desirable to analyze DNA-binding proteins via accurate prediction of binding sites and understanding of relations between DNA and protein structures.

Recently, various methods have been proposed to identify valuable features of DNA-binding proteins. Ahmad *et al*. (2005) researched DNA binding sites in proteins according to PSSM-based [9]. Ahmad *et al*. (2004) analyzed and predicted DNA-binding protein based on composition, sequence and structural information by neural network (NN) method [4]. Shanahan *et al*. (2004) identified DNA-binding proteins using structural motifs and electrostatic potential [10]. Luscombe and Thornton (2002) investigated protein-DNA interactions based on amino acid conservation and the effects of mutations on binding specificity [11]. Selvaraj *et al*. (2002) analyzed symmetric/asymmetric and cognate/non-cognate binding by specificity of protein-DNA recognition [12]. Pabo and Nekludova (2000) developed geometrical models for characterizing protein-DNA interfaces [13]. Nadassy *et al*. (1999) analyzed structural features of protein-nucleic acid recognition sites [14]. Kono and Sarai (1999) presented a structure-based method for prediction of DNA target sites by regulatory proteins[15]. According to [16-18], DNA-binding protein problem is a significant topic, but there are a lot of complicated and waiting for be solved difficulties. Consequently, we want to do research in this field further.

1.3 Sketch of the Thesis

The previous research, [4], had provided a successful recognition and statistic in the residues of these proteins. And then, [9] researched DNA binding sites by using PSSM-based. In the thesis, our goal is to mine the knowledge from DNA-binding protein complexes. Consequently, the used model in this thesis is close to [4].

There are two main topics in this thesis. One is to improve the performance of the prediction. Another is knowledge acquisition from DNA-binding proteins. The two objectives could be achieved by proposing an efficient classifier and more useful feature set. Therefore, the step 1 is to propose a rule-based decision tree (DT) method to classify these data with identical feature sets from [4]. According to the results of this part, the performances of the two machine learning methods - NN and DT, for this research could be compared easily. In our work, we find DT method really suits the problem than NN. And step 2, new features are input DT system. Besides original features, we add secondary structure, the electric charge near the residue and the group information. Although the number of candidate features is increased from 4 to 11, DT system has the capability of dealing with the higher dimension problem. These results about using the new feature sets are further improved. In this part of the research, we derive the appropriate feature set from these outcomes to do the advanced experiment, knowledge acquisition.

Step 3 in our research, a large DNA-binding protein data from PDB is obtained in order to mine more creditable knowledge. From these data, the ranked importance of 11 features will be listed, and the significant features include relative accessible surface area (rASA) [19-21], the electric charge distribution near the residue (EC) and its amino acid group. We could discover which features have decisive influence for the growth of the tree and indirectly affect the performance of the prediction. At the same time, the binding and nonbinding rules will be acquired. That function, mining knowledge, is useful property of DT method. The information could give us the verification from biological view. And these rules might be capable to supply the detailed material for us to do advance analysis in biology.

1.4 Organization

The monograph is divided into three major parts. The first part (Chapter 2) is devoted to the used data and feature sets. The second part (Chapter 3) is dedicated to decision tree (DT) method and the processes in the experiment. The third part (Chapter 4) concerns to the prediction results and knowledge discovery. And the detail organization is as follows.

Chapter 2 displays two portions. One is which protein data we are gotten from PDB and their obtained reasons. Another is how the used features are derived from above-mentioned data set.

Chapter 3 presents the proposed decision tree (DT) system in earlier part. Besides the introduction, algorithm, evaluation equation, parameter setting and input data-form will be described. And then, the used accuracy scores and the experimental processes will be also showed.

Chapter 4 contains two major subjects. One shows the prediction performance for DNA-binding proteins by using different parameters or feature sets. Another is to respect with knowledge mining from data, inclusive of the ranked importance of these features, the binding and nonbinding rules for these proteins.

Chapter 5 concludes the thesis. It starts with the summary of the goals and the significance of DNA-binding protein predication problem. The proposed machine learning method, its parameter setting and feature set are concluded for the prediction performance and knowledge acquisition. Finally, we will refer to the advanced research in the topic in future work.

Chapter 2

Materials

2.1 Data sets

There are two datasets which we use to evaluate our DT method in the thesis. However, these two datasets devote to the different function. To compare the accuracy of the prediction results fairly, we must consider the sequence identity in proteins. Therefore, the identity in PDNA-62 is limited, its identity < 25%. But in second part, we must expand the number of the dataset, because we would like to mine representative knowledge and hope that could respond to the importance degree of the rules in DNA-binding protein distribution. For these reasons, the protein identity in PDNA-982 is not limited.

2.1.1 The Source of the PDNA-62

PDNA-62 in the research is the same with the previous research [4, 9, 12]. These used data sets of protein-DNA complexes from the Protein Data Bank (PDB) are given in Table 2.1. Identity among the sequences is < 25%, and the resolution of the structures is 2.5 Å or better.

2.1.2 The Source of the PDNA-982

The more creditable binding and nonbinding rules are desired in order to mine the biological meaning further. And the objective in this part is the significance of these rules could be responded to DNA-binding protein distribution. More DNA-binding protein data are collected in the proportion of the thesis and named as PDNA-982.

Table 2.1. PDB codes of PDNA-62: These protein–DNA complexes selected for prediction of binding sites

1a02	1bl0	1dp7	1hdd	1mdy_a	1per
1tc3	1a74	1c0w_b	1ecr	1hlo	1mey_c
1pnr	1tf3	1aay	1cdw	1gat	1hry
1mhd_a	1pue_e	1tro_a	1azq	1cf7_a	1fjl_a
1hwt	1mnm	1pvi_b	1b3t	1tsr_b	1cjg
1gcc	1if1	1mse	1pyi_a	1ubd	1ber_a
1cma	1gdt	1ign_a	1oct	1rep_c	1xbr_a
1bf5	1d02_a	1hcq	1ihf	1par_b	1srs
1yrn_a	1bhm_a	1d66_a	1hcr	1lmb_4	1pdn
1svc	1ysa	1yui	2bop	2drp_a	2hdc
2gli	3cro_1	-----------	----------	------------	-----------

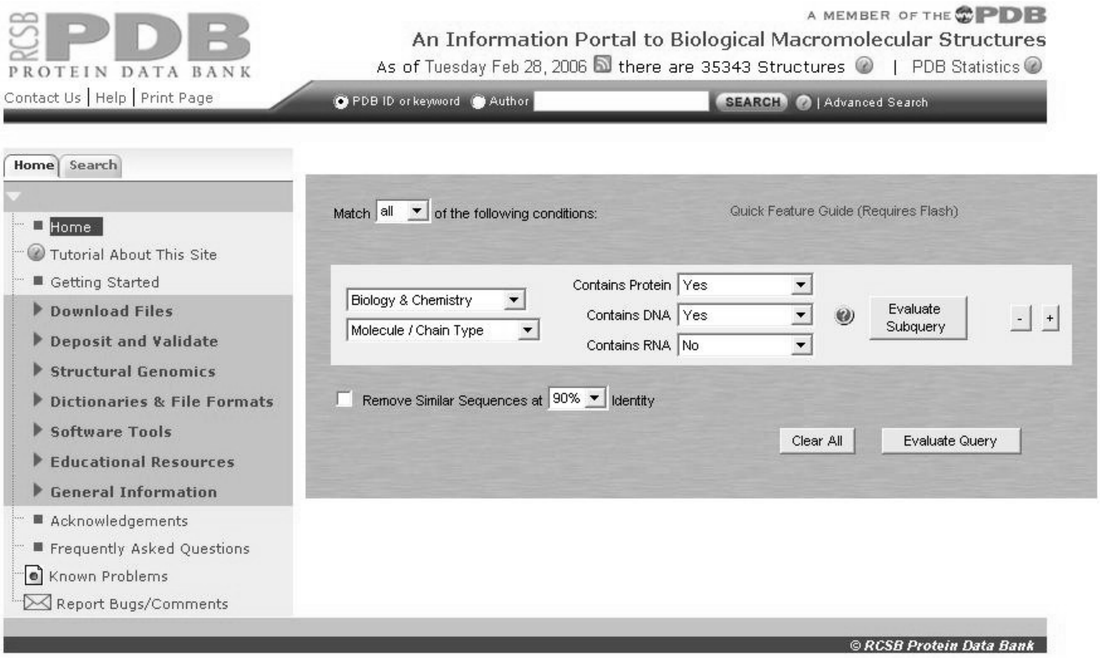
These data are acquired from the processes in PDB database. The advanced search is used and these parameters are set in Figure 2.1 (The website is http://www.rcsb.org/pdb/advSearch.do). These items, “Contains Protein” and “Contains DNA”, in “molecule or chain type” are chosen because we would like to get more data probably. And then, the fragments, the numbers of the residues being less than 10, are taken out from these dataset. Finally, we obtain 982 DNA-binding proteins. PDB codes of PDNA-982 are given in Table 2.2.

2.1.3 To determine the binding and nonbinding criterion

We define the amino acid as a binding residue if its side chain or backbone atoms fell within a cutoff distance of 3.5 Å from any atom within a binding DNA. On the contrary, the data which does not conform to the above definition are nonbinding residues [4, 9, 12]. All binding or nonbinding situations of the residues in the thesis are labeled by this criterion.

2.2 Feature sets

The used features sets in the thesis have two major parts. The application of the feature sets in our proposed method will be expressed in next chapter. In this chapter, we only describe the acquiring method of the feature sets.



A MEMBER OF THE PDB

An Information Portal to Biological Macromolecular Structures

As of Tuesday Feb 28, 2006 there are 35343 Structures | PDB Statistics

Match all of the following conditions:

Biology & Chemistry

Molecule / Chain Type

Contains Protein: Yes

Contains DNA: Yes

Contains RNA: No

☐ Remove Similar Sequences at 90% Identity

Figure 2.1. The parameter setting in PDB advanced search to obtain the PDNA-982: To search for the data, we gave the value of the parameters in PDB database.

Table 2.2. PDB codes of PDNA-982: These protein–DNA complexes selected for knowledge acquisition.

1A0A	1ECR	1J46	1MSF	1PUE	1SL0	1Y6F	2KTQ
1A1F	1EFA	1J47	1MTL	1PUF	1SL1	1Y6G	2KZM
1A1G	1EGW	1J59	1MUH	1PV4	1SL2	1Y8Z	2KZZ
1A1H	1EHL	1J75	1MUR	1PVI	1SRS	1YA6	2LEF
1A1I	1EJ9	1JB7	1MUS	1PVP	1SSP	1YF3	2NLL
1A1J	1EMH	1JE8	1MVM	1PVQ	1STX	1YFH	2OR1
1A1K	1EMJ	1JEY	1MW8	1PVR	1SUZ	1YFJ	2PJR
1A1L	1EO3	1JFI	1MWI	1PYI	1SVC	1YFL	2PUA
1A1V	1EO4	1JFS	1MWJ	1PZU	1SX5	1YNW	2PUB
1A02	1EON	1JFT	1N3A	1Q0T	1SX8	1YO5	2PUC
1A3Q	1EOO	1JGG	1N3C	1Q3F	1SXP	1YQK	2PUD
1A6B	1EOP	1JH9	1N3E	1Q3U	1SXQ	1YQL	2PUE
1A6Y	1EQZ	1JJ4	1N3F	1Q3V	1T2K	1YQM	2PUF
1A31	1ERI	1JJ6	1N4L	1Q9X	1T2S	1YQR	2PUG
1A35	1ESG	1JJ8	1N5Y	1Q9Y	1T2T	1YRN	2PVI
1A36	1EVW	1JK1	1N6J	1QAI	1T03	1YSA	2RAM
1A66	1EWN	1JK2	1N6Q	1QAJ	1T3N	1YTB	2RVE
1A73	1EWQ	1JKO	1N39	1QBJ	1T05	1YTF	2SSP
1A74	1EXI	1JKP	1N48	1QN3	1T7P	1YUI	2STT
1AAY	1EXJ	1JKQ	1N56	1QN4	1T8E	1YUJ	2STW

1AHD	1EYG	1JKR	1NFK	1QN5	1T8I	1YZ8	2UP1
1AIS	1EYU	1JMC	1NG9	1QN6	1T9I	1Z1B	3BAM
1AKH	1F0O	1JNM	1NGM	1QN7	1T9J	1Z1C	3BDP
1AM9	1F0V	1JT0	1NH2	1QN8	1T38	1Z1G	3CRO
1AN2	1F2I	1JWL	1NH3	1QN9	1T39	1Z9C	3CRX
1AN4	1F4K	1JX4	1NJW	1QNA	1TAU	1Z19	3GAT
1AOI	1F4R	1JXL	1NJX	1QNB	1TC3	1Z63	3HDD
1APL	1F4S	1K3W	1NJY	1QNC	1TDZ	1ZAA	3HTS
1AU7	1F5E	1K3X	1NJZ	1QNE	1TEZ	1ZAY	3KTQ
1AWC	1F5T	1K4S	1NK0	1QP0	1TF3	1ZBB	3MHT
1AZ0	1F6O	1K4T	1NK2	1QP4	1TF6	1ZET	3ORC
1AZP	1F44	1K6O	1NK3	1QP7	1TGH	1ZG1	3PJR
1AZQ	1F66	1K7A	1NK4	1QP9	1TK0	1ZG5	3PVI
1B01	1FIU	1K8G	1NK5	1QPI	1TK5	1ZGW	4BDP
1B3T	1FJL	1K61	1NK6	1QPS	1TK8	1ZJM	4CRX
1B8I	1FJX	1K78	1NK7	1QPZ	1TKD	1ZJN	4DPV
1B69	1FLO	1K79	1NK8	1QQA	1TL8	1ZME	4GAT
1B72	1FN7	1K82	1NK9	1QQB	1TN9	1ZQA	4KTQ
1B94	1FOK	1KB2	1NKB	1QRH	1TQE	1ZQB	4MHT
1B95	1FOS	1KB4	1NKC	1QRI	1TRO	1ZQC	4RVE
1B96	1FW6	1KB6	1NKE	1QRV	1TRR	1ZQD	4SKN
1B97	1FYK	1KBU	1NKP	1QSL	1TSR	1ZQE	5CRX
1BBX	1FYL	1KC6	1NLW	1QSS	1TTU	1ZQF	5GAT
1BC7	1FYM	1KDH	1NNE	1QSY	1TUP	1ZQG	5MHT
1BC8	1FZP	1KEG	1NNJ	1QTM	1TV9	1ZQH	6CRO
1BDH	1G2D	1KFS	1NOP	1QUM	1TVA	1ZQI	6GAT
1BDI	1G2F	1KFV	1NOY	1QX0	1TW8	1ZQJ	6MHT
1BDT	1G4D	1KIX	1NVP	1QZG	1TX3	1ZQK	6PAX
1BDV	1G9Y	1KLN	1NWQ	1QZH	1U0C	1ZQL	7GAT
1BF4	1G9Z	1KQQ	1NZB	1R0A	1U0D	1ZQM	7ICE
1BF5	1G38	1KRP	1O3Q	1R0N	1U1K	1ZQN	7ICF
1BG1	1GA5	1KSP	1O3R	1R0O	1U1L	1ZQO	7ICG
1BGB	1GAT	1KSX	1O3S	1R2Y	1U1M	1ZQP	7ICH
1BHM	1GAU	1KSY	1O3T	1R2Z	1U1N	1ZQQ	7ICI
1BJ6	1GCC	1KU7	1O4X	1R4I	1U1O	1ZQR	7ICJ
1BL0	1GD2	1KX3	1OCT	1R4O	1U1P	1ZQS	7ICK
1BNK	1GDT	1KX4	1ODG	1R4R	1U1Q	1ZQT	7ICL
1BNZ	1GJI	1KX5	1ODH	1R7M	1U1R	1ZR2	7ICM
1BP7	1GLU	1L1M	1OE4	1R8D	1U1Y	1ZR4	7ICN
1BPX	1GM5	1L1T	1OE5	1R8E	1U3E	1ZS4	7ICO
1BPY	1GT0	1L1Z	1OE6	1R49	1U4B	1ZTT	7ICP
1BPZ	1GTW	1L2B	1OH5	1R71	1U8B	1ZTW	7ICQ

1BRN	1GU4	1L2C	1OH6	1RAM	1U8R	1ZX4	7ICR
1BSS	1GU5	1L2D	1OH7	1RB8	1U35	1ZYQ	7ICS
1BSU	1GXP	1L3L	1OH8	1RBJ	1U45	1ZZI	7ICT
1BUA	1H0M	1L3S	1OJ8	1RC8	1U47	1ZZJ	7ICU
1BVO	1H6F	1L3T	1OMH	1RCN	1U48	2A0I	7ICV
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1C7Y	1H88	1LAT	1OSL	1RFI	1UA1	2AGO	8ICC
1C8C	1H89	1LAU	1OTC	1RG1	1UAA	2AGP	8ICE
1C9B	1HAO	1LB2	1OUP	1RG2	1UBD	2AGQ	8ICF
1CA5	1HAP	1LCC	1OUQ	1RGT	1UUT	2ALZ	8ICG
1CA6	1HBX	1LCD	1OUZ	1RGU	1V14	2AOQ	8ICH
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1CDW	1HCR	1LE8	1OWG	1RH6	1VAS	2AQ4	8ICJ
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1D2I	1I3J	1M3Q	1P51	1RXV	1WTV	2C2R	9ICB
1D3U	1I6J	1M5R	1P59	1RXW	1WTW	2C5.0R	9ICC
1D5Y	1I7D	1M5X	1P71	1RYR	1WTX	2C7O	9ICE
1D8Y	1I8M	1M06	1P78	1RYS	1WVL	2C7P	9ICF
1D66	1IAW	1M6X	1PA6	1RZ9	1X0F	2C7Q	9ICG
1DC1	1IC8	1M07	1PAR	1RZR	1X9M	2C7R	9ICH
1DCT	1ID3	1M18	1PDN	1RZT	1X9N	2C22	9ICI
1DDN	1IF1	1M19	1PER	1S0M	1X9S	2C28	9ICJ

1DE8	1IG4	1MA7	1PGZ	1S0N	1X9W	2CGP	9ICK
1DE9	1IG7	1MDM	1PH1	1S0O	1XBR	2CRX	9ICL
1DEW	1IG9	1MDY	1PH2	1S6M	1XC8	2CV5	9ICM
1DFM	1IGN	1MEY	1PH3	1S9F	1XC9	2D45	9ICN
1DGC	1IHF	1MHD	1PH4	1S9K	1XF2	2DGC	9ICO
1DH3	1IJS	1MHT	1PH5	1S10	1XHU	2DNJ	9ICP
1DIZ	1IJW	1MJ2	1PH6	1S32	1XHV	2DRP	9ICQ
1DMU	1IMH	1MJE	1PH7	1S40	1XHZ	2EZD	9ICR
1DNK	1IO4	1MJM	1PH8	1S97	1XI1	2EZE	9ICS
1DP7	1IPP	1MJO	1PH9	1SA3	1XJV	2F55	9ICT
1DRG	1IU3	1MJP	1PHJ	1SAX	1XNS	2GAT	9ICU
1DSZ	1IV6	1MJQ	1PJI	1SC7	1XO0	2GLI	9ICV
1DU0	1IXY	1MM8	1PJJ	1SEU	1XPX	2HAP	9ICW
1DUX	1J1V	1MNM	1PM5	1SFU	1XS9	2HDC	9ICX
1E3M	1J3E	1MNN	1PNR	1SKM	1XSD	2HDD	9ICY
1E3O	1J4W	1MOW	1PO6	1SKN	1XSL	2HMI	9MHT
1E7J	1J5K	1MQ2	1PP7	1SKR	1XSN	2IRF	10MH
1EA4	1J5N	1MQ3	1PP8	1SKS	1XSP	2KFN	-----------
1EBM	1J5O	1MSE	1PT3	1SKW	1XYI	2KFZ	-----------

2.2.1 The used feature sets in Ahmad *et al.* (2004)

1) *DNA-binding segments*: Each residue in the data set assigns its closest left residue and right one in the sequence. Every three residues form a segment [4].

2) *Calculation of solvent accessibility or accessible surface area*: Solvent accessibility or accessible surface area (ASA) values of these protein-DNA complexes are obtained by using DSSP program [19]. Absolute values of ASA are normalized and described in [20, 21]. And that solvent accessibility divide its absolute value will get relative accessible surface area (rASA).

2.2.2 The proposed feature sets

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and described in [20, 21]. And that solvent accessibility divide its absolute value will get relative accessible surface area (rASA).

3) *The amino acid group*: The twenty amino acids are classified into five groups [22], listed in Table 2.3..

Table 2.3. The relationship between the twenty amino acids and five groups

Group	**Amino Acid**
Nonpolar, aliphatic R groups	G, A, P, V, L, I, M
Aromatic R groups	F, Y, W
Polar, uncharged R groups	S, T, C, N, Q
Positively charged R groups	K, H, R
Negatively charged R groups	D, E

4) *The secondary structure of the residue*: We could get the secondary structures of the residues in protein complexes from the DSSP file [19].

5) *The electric charge distribution near the residue (EC)*: The electric charge near the surfaces is considered because phosphate outside DNA is negative charge carriers. Therefore, we establish the new feature via the influence of charges. A diagram about above-mentioned idea is given in Figure 2.2. And in amino acid, the property with respect to charge is pI value. However, these values must transform into another form for each residues in proteins. The evaluation function of the feature is as follows.

The referenced pI values of the twenty amino acids are sowed in Table 2.4 [22]. Each pI value subtracting five is regard as its electric charge (e.g. the electric value of Glycine is 0.97). This shift process will make that the residues with negative charge have negative value and those with natural charge have near zero.

The electric charge distribution near the residue (EC) is defined as

$$EC_i = \sum_{i-1,i,i+1} (pI_i - 5) \times (ASA_i / 10) \tag{2.1}$$

i represents a certain residue. And in the sequence, *i-1* and *i+1* show the closest left and right position by *i* residue, respectively. The equation through accumulation estimates the charge near *i* residue.

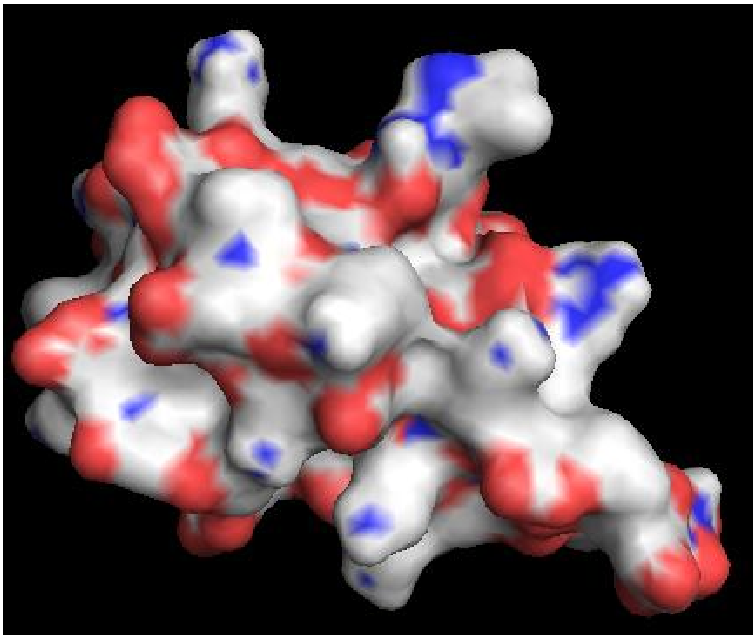


Figure 2.2. An example for electric charge near the surfaces of the residues: The graph shows the atom distribution of the protein surface. Blue and red areas are atoms with positive and negative charge, respectively. We inferred this blue part may bind to DNA. Therefore, we bring up an idea which is to make use of the ASA value of each residue and its pI value for the charge distribution estimation roughly.

Table 2.4. The amino acid and its pI value

Amino Acid	**pI**	**Amino Acid**	**pI**
Glycine	5.97	Serine	5.68
Alanine	6.01	Threonine	5.87
Proline	6.48	Cysteine	5.07
Valine	5.97	Asparagine	5.41
Leucine	5.98	Glutamine	5.65
Isoleucine	6.02	Lysine	9.74
Methionine	5.74	Histidine	7.59
Phenylalanine	5.48	Arginine	10.76
Tyrosine	5.66	Aspartate	2.77
Tryptophan	5.89	Glutamate	3.22

Based on equation (2.1), EC value has the opportunity of being amplified obviously if the *i* residue lies near the surface of the protein, since we multiply ASA value. And in case of buried completely, EC value is zero. The purpose is to get more distinction by the process. Note that ASA values for the calculation of EC values are gotten by

DSSP program directly, not relative ASA (rASA). We hope EC values are influenced more deeply by these bigger residues with absolute larger surfaces, not those smaller residues with relative larger surfaces. Besides this part, relative ASA is used in other parts in our work.

Chapter 3

Methods

3.1 The proposed decision tree method

Decision tree [7] is a popular machine learning method to classify the value of a discrete dependent variable with a finite set. The basic decision tree example and algorithm[23] are given in Figure 3.1 and 3.2, respectively. Decision tree learning is a method for approximating discrete-valued target functions that is robust to noisy data and capable of learning disjunctive expressions [5]. Learned trees can also be re-represented as sets of if-then rules to improve human readability.

A decision tree is constructed by looking for regularities in data. According to entropy calculation, we can select one with the minimum entropy from these features. Given a collection S, if the target attribute can take on c different values, then the entropy of S relative to this c-wise classification is defined as

$$Entropy(S) \equiv \sum_{i=1}^{c} - p_i \log_2 p_i \qquad (3.1)$$

where p_i is the proportion of S belonging to class i [5]. Each level of the trees will be decided by the rule. The distributions of the levels of the tree are important and readable information because we could analyze which feature is more significant than others [5, 7]. In our wok, C5.0 [24], an update version of C4.5 [25] algorithm, is applied in the proposed decision tree method.

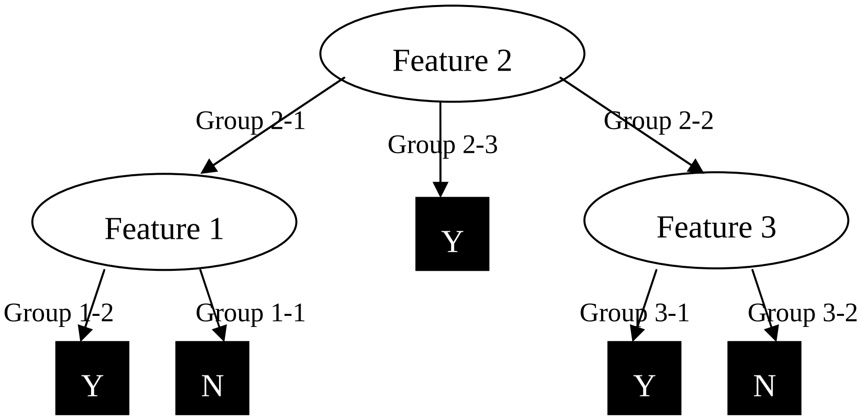
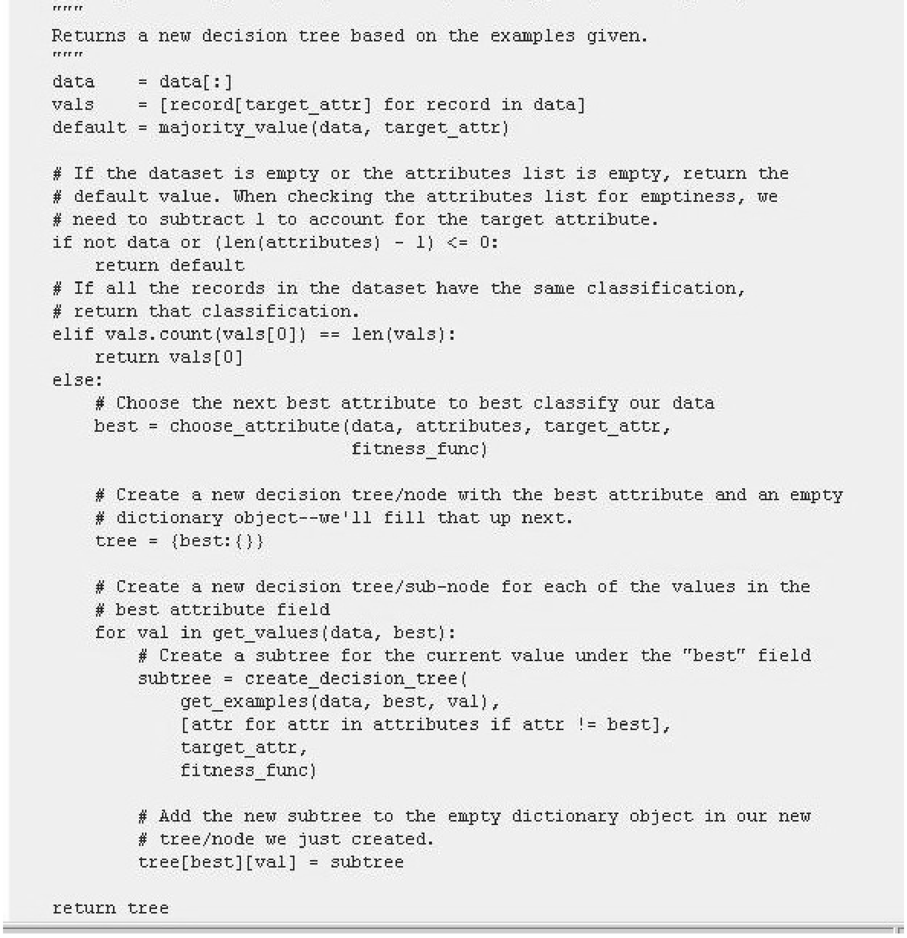


Figure 3.1. An example for decision tree method: A simple is input the system. If its Feature 2 value belongs to Group 2-1, it will leave for Feature 1 node. And then if its Feature 1 value is a portion of Group 1-2, the decision tree system will show it is a member of Class Y. Other classification pathways can be analogized by the above-mentioned mode.



```
def create_decision_tree(data, attributes, target_attr, fitness_func):
    """
    Returns a new decision tree based on the examples given.
    """
    data    = data[:]
    vals    = [record[target_attr] for record in data]
    default = majority_value(data, target_attr)

    # If the dataset is empty or the attributes list is empty, return the
    # default value. When checking the attributes list for emptiness, we
    # need to subtract 1 to account for the target attribute.
    if not data or (len(attributes) - 1) <= 0:
        return default
    # If all the records in the dataset have the same classification,
    # return that classification.
    elif vals.count(vals[0]) == len(vals):
        return vals[0]
    else:
        # Choose the next best attribute to best classify our data
        best = choose_attribute(data, attributes, target_attr,
                                fitness_func)

        # Create a new decision tree/node with the best attribute and an empty
        # dictionary object--we'll fill that up next.
        tree = {best:{}}

        # Create a new decision tree/sub-node for each of the values in the
        # best attribute field
        for val in get_values(data, best):
            # Create a subtree for the current value under the "best" field
            subtree = create_decision_tree(
                get_examples(data, best, val),
                [attr for attr in attributes if attr != best],
                target_attr,
                fitness_func)

            # Add the new subtree to the empty dictionary object in our new
            # tree/node we just created.
            tree[best][val] = subtree

    return tree
```

Figure 3.2. The basic decision tree algorithm

3.1.1 The Parameters Setting

Over-fitting is a significant practical difficulty for the bulk of machine learning methods. Figure 3.3 [5] illustrates the impact of over-fitting in a typical application of decision tree learning. There are two major approaches to avoiding over-fitting in DT. These approaches are to stop growing the tree earlier and post prune [5]. Pruning a decision node consists of removing the sub-tree rooted at that node, making if a leaf node, and assigning it the most common classification of the training examples affiliated that node [5]. To determine the correct final tree size were reported in many researches [26-29]. In this research, we utilize post pruning method [25]. That the pruning parameter, confidence factor (*cf*), certainly affects the performance about error rates is estimated in our experiment later.

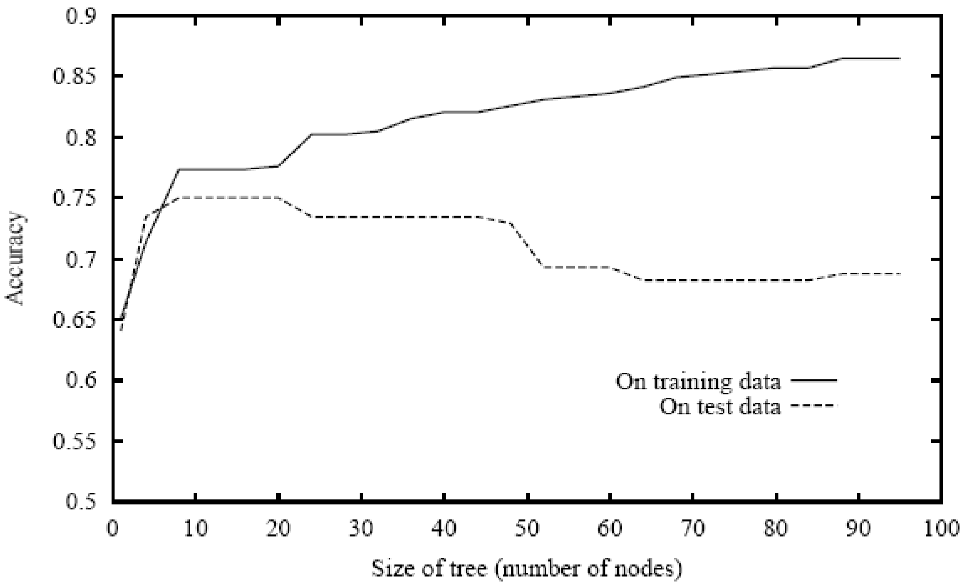


Figure 3.3. Over-fitting in decision tree learning: As DT system adds new nodes to grow the decision tree, the accuracy of the tree measured over the training examples increases monotonically. However, when measured over a set of test examples independent of the training examples, accuracy first increases, then decreases.

As a result of unbalanced distribution of samples, the penalty will be considered to avoid that accuracy about binding ones are sacrificed. The parameter setting is equal to increase the binding influence for the classification results. And it would enhance

NP performance.

Furthermore, the idea of adaptive boosting algorithm [24, 30] to create several decision trees is used in our method. Boosting is a technique for generating and combining multiple classifiers to improve predictive accuracy [24]. When a new case is to be classified, each decision trees vote for its predicted class and the votes are counted to determine the final class. In general, to predict the unknown data by using more decision trees will get a better accuracy than by only using one in our research.

3.1.2 The judgment for the attribute of the features

To select features which have more attribute for classifying example is critical. What is a good quantitative measure of the worth of an attribute? We would define a statistic property that measures how well a given attribute separates the training examples according to their target classification [5]. The best feature choice to build trees generally leads to simple decision at the nodes [6]. A variety of selection attributes measures have been proposed in past researches [31-33]. In the thesis, we would refer three kinds of judgment for the attribute. The source of the part about measuring the attribute comes from [5].

The measure is simply the expected reduction in entropy caused by partitioning the examples according to this attribute. First used judgment function is *Information Gain*. It is defined as

$$Information\ Gain(S,A) \equiv Entropy(S) - \sum_{v \in Value(A)} \frac{|S_v|}{|S|} Entropy(S_v) \tag{3.2}$$

Where *Values(A)* is the set of all possible values for attribute A, and S_v is the subset of S for which attribute A has value v. The first term in Equation (3.2) is just the entropy of the original collection S, and the second term is the expected value of the entropy after S is partitioned using attribute A. The expected entropy described by this second term is the sum of the entropies of each subset S_v, weighted by the fraction of examples $\frac{|S_v|}{|S|}$ that belong to S_v.

However, Equation (3.2) has so many possible values that it is bound to separate the training examples into very small subsets. Because of this, it will have a very high information gain relative to the training examples, despite being a very poor predictor of the target function over unseen instances. Therefore, one alternative measure that has been used successfully is the gain ratio [7]. The gain ratio measure by incorporating a term, called *Potential Information*:

$$\textit{Potential Information(S,A)} \equiv -\sum_{i=1}^{c} \frac{|S_i|}{|S|} \log_2 \frac{|S_i|}{|S|} \tag{3.3}$$

where S_1 through S_c, are the c subsets of examples resulting from partitioning S by the c-valued attribute A. And Gain Ratio measure is defined in terms of the earlier *Information Gain* measure, as well as this *Potential Information*, as follows

$$\textit{Gain Ratio(S,A)} \equiv \frac{\textit{Equation}(3.2)}{\textit{Equation}(3.3)} \tag{3.4}$$

In thesis, these features adopted from the dataset can be chiefly ranked by *Gain Ratio* to prediction. The attributes chosen imply that they own the maximum distinct ability for each split.

3.1.3 Training and Test

The results reported in this thesis mainly show three-fold cross validation (3-CV). It is to say the data are divided into three approximately equal parts. And then, two parts are training data and another is test data by turns. During the training, the nodes of each level in decision tree will be established gradually. And then, the test data are input the system. We could get the first result. Following the process, the three parts take turns the test and training data. On account of using three-fold cross validation, the final results in the thesis are the average of the three times test results.

3.2 Accuracy scores

There are two major evaluations to compare the results in diverse parameter setting in the thesis. First one, total accuracy would supply us with the correct ratios in the whole. Second, the binding and nonbinding data in DNA-binding protein are unbalanced. If we only consider total accuracy, the classification might decide all data are nonbinding since the nonbinding data are most part. But the prediction will lose its meaning. Consequently, *NP* value provides suitable comparing standpoint for the unbalanced data in the experiment.

Total accuracy score is the ratios of the number of correct predictions. (T-True, F-False, P-Positive, N-Negative).

$$accuracy = \frac{(TP + TN)}{(TP + TN + FP + FN)} \times 100\% \tag{3.5}$$

Sensitivity and specificity of the predictions are defined as:

$$sensitivity = \frac{TP}{(TP + FN)} \times 100\% \tag{3.6}$$

$$specificity = \frac{(TN)}{(TN + FP)} \times 100\% \tag{3.7}$$

Net prediction (NP) is the average of the sensitivity and specificity [4].

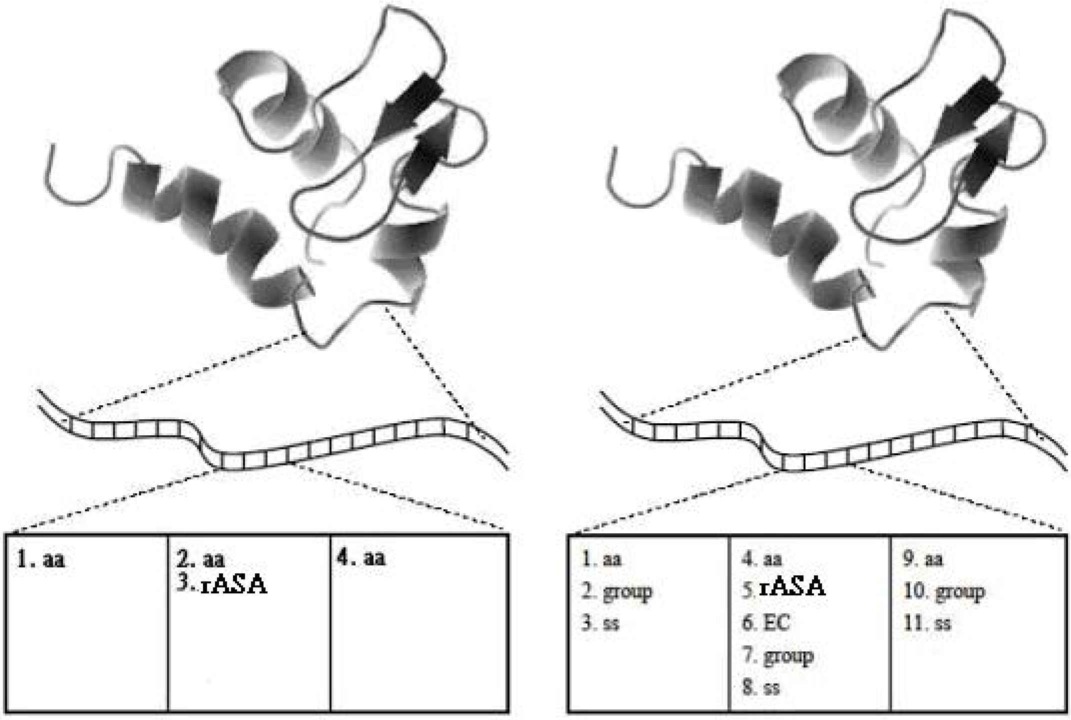
$$NP = \frac{sensitivity + specificity}{2} \tag{3.8}$$

Although total accuracy is certainly judged for the results of predictions, *NP* value is considered in the discussion of the result because binding and nonbinding data sets are unbalanced in this work. We will get biased outcome if we only though about total accuracy scores.

3.3 The process in the experiment

First, the same features with [4] and dataset, PDNA-62, are input DT system. In this process, the used features are the residue, its relative ASA and its two nearest neighbors in the sequence. The models would be considered these regulable parameters, inclusive of boosting, different *cf* values (the extent of the Pruning) and diverse weights. By the way, we are able to compare simply NN method with DT for the influence of the results at the equal condition.

And then, we use PDNA-62 with our proposed features to predict. It means the original features are replaced by new ones, including the residue, its group, secondary structure, relative ASA, EC and its neighbor information. To obtain these original and new feature sets is showed in Figure 3.4. Each vector in the two feature set has 4 and 11 dimensions, respectively, and the decision tree system is sets up via C5.0 model. The model in this part also is used above-mentioned regulable parameters. The performance about the change would easily make the contrast. Thus, we could realize which feature set is better for the DNA-binding protein prediction. Finally, these chosen features will go a step further. A large number of data, PDNA-982, with the proposed features will be utilized to mine knowledge. The framework of the thesis is given in Figure 3.5.



(a) (b)

Figure 3.4. An example for getting the features: The upper level in the figure presents a protein structure. And the middle level shows a portion of the protein sequence. (a) The same feature sets with Ahmad *et al*. (2004) are displayed. (b) We can obtain the proposed features for each residue. (“aa” means its residue and “ss” indicates its secondary structure).

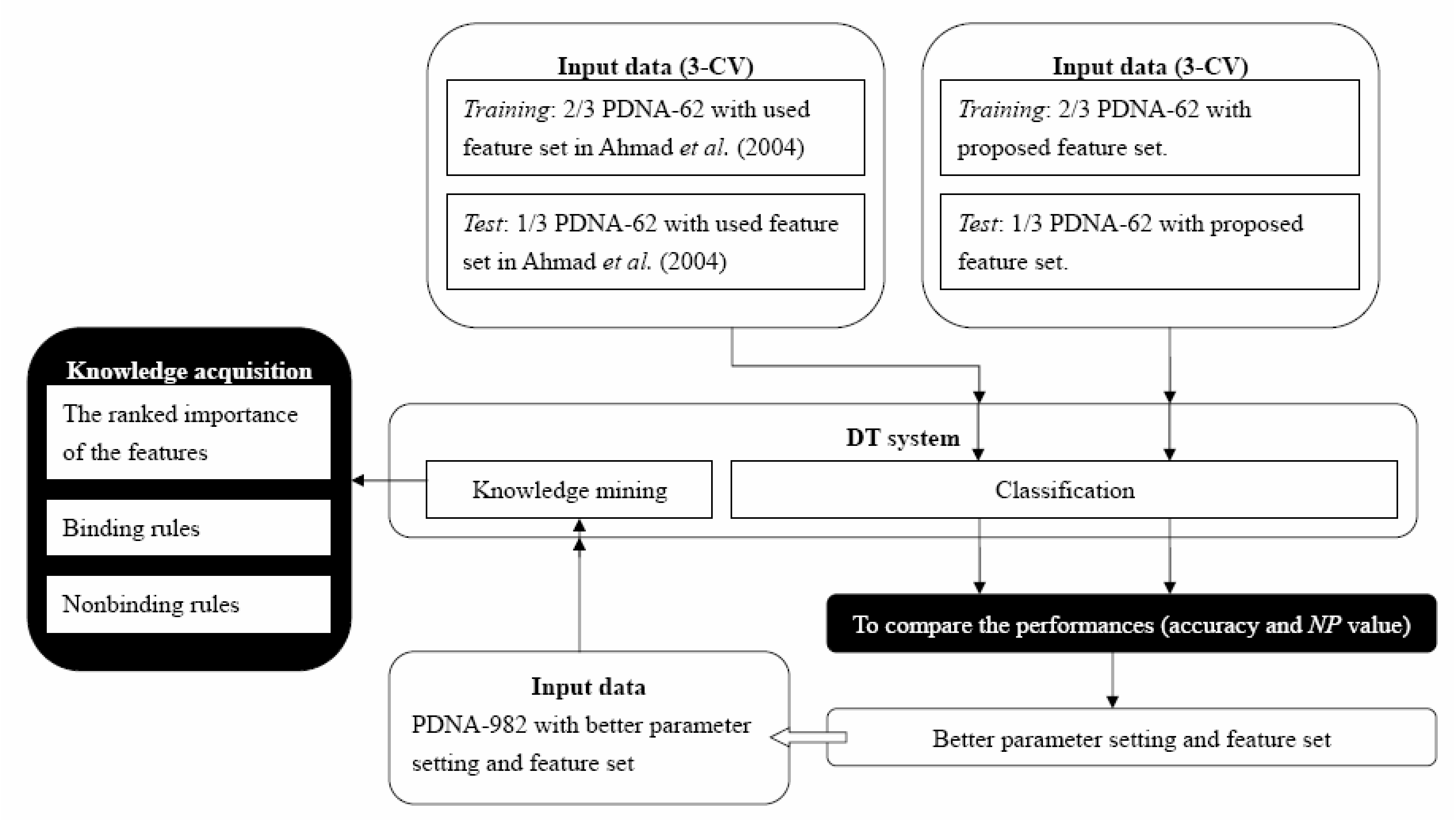


Figure 3.5. Illumination of the framework of the thesis

Chapter 4

Result

4.1 Performance evaluation

4.1.1 Using original feature sets in PDNA-62

The *cf* values are considered combining each weight in early work. We want to know the influence of the *cf* value, and the portion about the research is given in Figure 4.1. Although these lines had similar tendencies, they cause disparity in the results, inclusive of total accuracy, *NP* value and decision tree size. Generally, the smaller *cf* values establish the more brief decision trees with readable characteristic. But we should think about the balance of the performance and the tree size. In Figure 4.1, we discover the over-low *cf* value would make the harmful influence for classifications. However, the influence would progressively decrease when the *cf* value reach certain rang. Therefore, we choose *cf* = 20 to do our later research in the thesis.

Decision trees are built by the same features with [4] research via C5.0 system. The gray lines in Figure 4.2 showing the performance in this process compare with the conclusion of the original paper, represented by the hollow triangle point. Its *NP* value is 61.1% and total accuracy is 79.1%. The two performance values of these parts of our results showed in Figure 4.2 are better than this referenced paper, if the gray points lain in the right-up of the hollow point. The left-up portion of the hollow point express that *NP* value is better than referenced paper, but total accuracy is worse than it. And the mean of the right-down points of the referenced results describe the

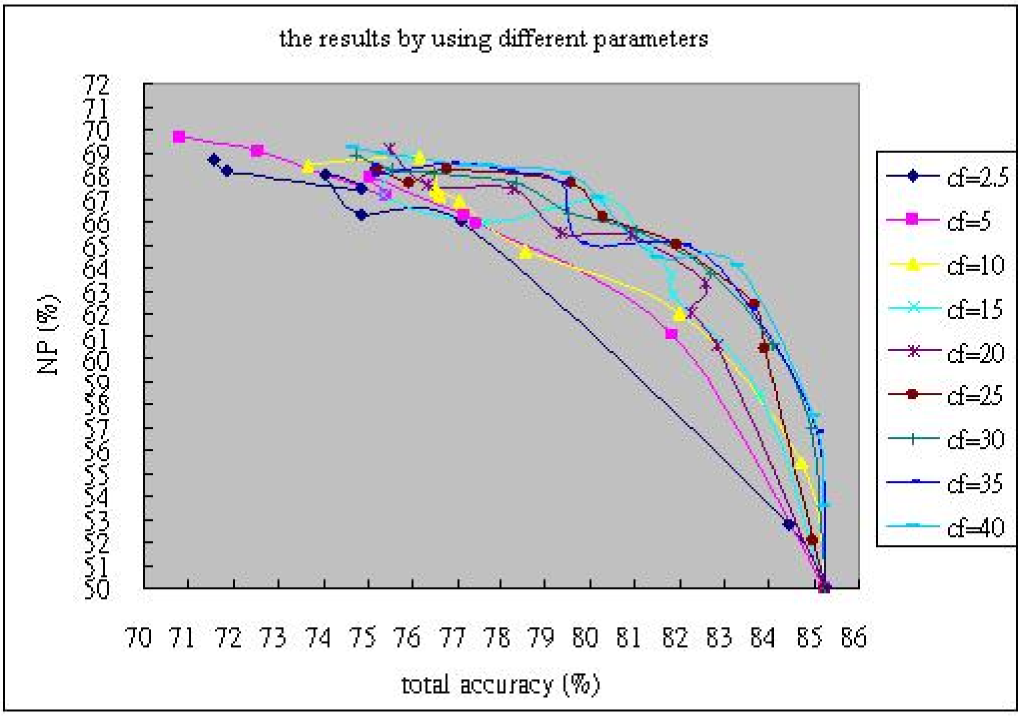


Figure 4.1. To compare *NP* value and total accuracy in different parameters: From right to left in each curve, the weights are gradually increasing.

opposite results to these left-up ones.

We could detect that the added weights would effect the distribution of the results - bigger weights, better *NP* values. The values near the points show its weight parameters in Figure 4.2. The trees are pruned too seriously when lower weight because the binding are regarded as noises. For these reasons, the bigger weights are considered making the binding data, the less part in the total, rather getting the opportunities of the reserve than eliminating. Nevertheless, the total accuracy value would be sacrifice, because one binding datum which gets the correct classification might cause more mistakes, i.e. more nonbinding data are regarded as noises. For the same thought, using the smaller weights, more nonbinding would be classified correctly; but the binding data would be displayed more wrong classification. Even better total accuracy performance is observed. In according to the *NP* function, raising the little judgment of the nonbinding data and losing the much one of the binding data in each relative ratio would make *NP* value decreasing. For the above-mention, we

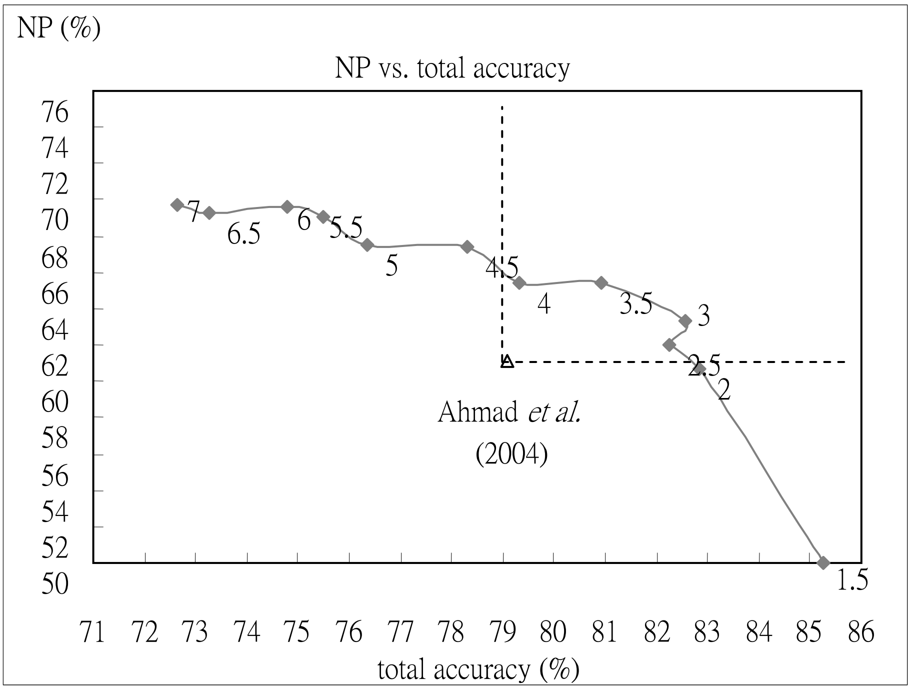


Figure 4.2. To compare the results between Ahmad et al. (2004) and our proposed method: The gray line use original features, the same with the suggestion in Ahmad *et al*. (2004) and the weights are showed beside the points. And the hollow triangle point displays the result of Ahmad *et al*. (2004). The dotted lines purpose to explain conveniently and are unconcerned with the results of the experiment.

could get the appropriate the *NP* value and the total accuracy if we choose the middle weights. These results with middle weights are given in the right-up of in Figure 4.2.

4.1.2 Using the proposed feature sets in PDNA-62

The black lines in Figure 4.3 show the performance of the proposed 11 dimensions into C5.0. We could get more useful results by using the feature set than the original one. No matter what the *NP* value or the total accuracy could lie in the greater grade in the black curve in Figure 4.3. According Table 4.1, we are able to analyze the trend. When the bigger weights added, the sensitivity, the ratio of the accuracy prediction of the binding data, would raise. But the process makes the specificity, the ratio of the accuracy prediction of the nonbinding data, diminish. The total accuracy is reducing and the *NP* value is increasing because the nonbinding data have more part in the whole.

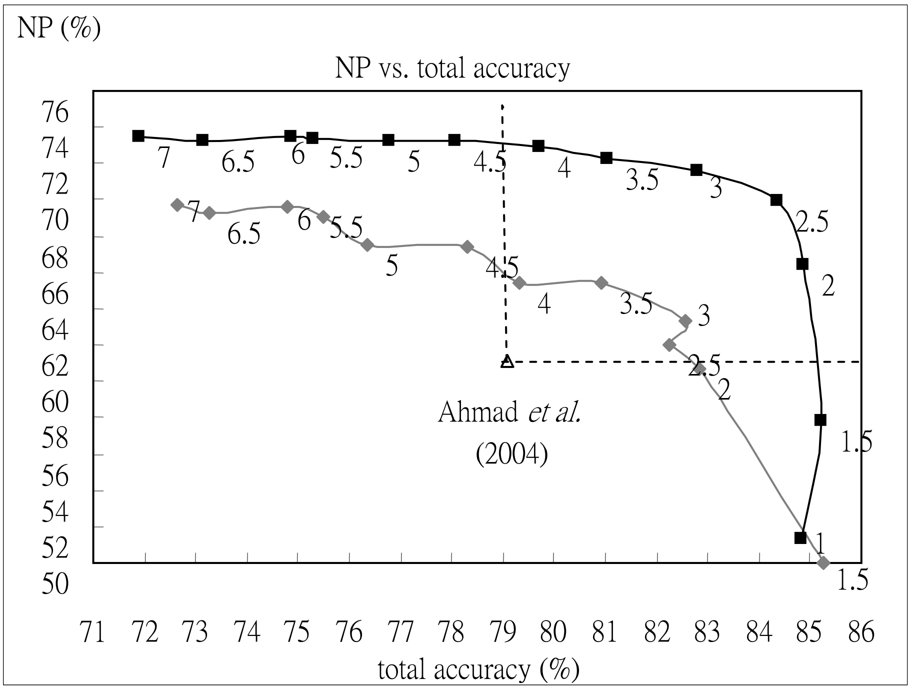


Figure 4.3. To compare the results in different parameters: The black line expresses the result by using proposed feature set, 11 features, the weights are showed besides the point. Other presentation is the same with Figure 4.2.

Table 4.1. Performance of the different feature sets: When *cf* = 20, to use the different weights shows the difference between the original and the new feature performance.

weight	**the original features**		**the new features**	
	total accuracy (%)	NP (%)	total accuracy (%)	NP (%)
1	85.25	50	84.84	51.29
1.5	85.25	50	85.2	57.82
2	82.84	60.64	84.88	66.42
2.5	82.24	61.99	84.35	69.99
3	82.58	63.33	82.81	71.59
3.5	80.93	65.37	81.05	72.29
4	79.32	65.46	79.72	72.9
4.5	78.29	67.42	78.07	73.3
5	76.36	67.56	76.8	73.3
5.5	75.49	69.09	75.29	73.36
6	74.78	69.61	74.85	73.52
6.5	73.27	69.28	73.15	73.3
7	72.64	69.73	71.91	73.47

According to above-mentioned performances, we suggest the classification problem should utilize the middle weights, from 2 to 4, and appropriate *cf* value, near 20. That could provide the suitable results with considered total accuracy, *NP* value and tree size for proposed 11 features by using DT method. In Figure 4.4, we show the comparison of *NP* value by the similar total accuracy in the different conditions. The viewpoint is fair and easily observable for realizing the performance. From Figure 4.4, we are aware that DT method can improve the classification results for the same features. And by C5.0 model, the new proposed features provide a serviceable way for predicting DNA-binding proteins.

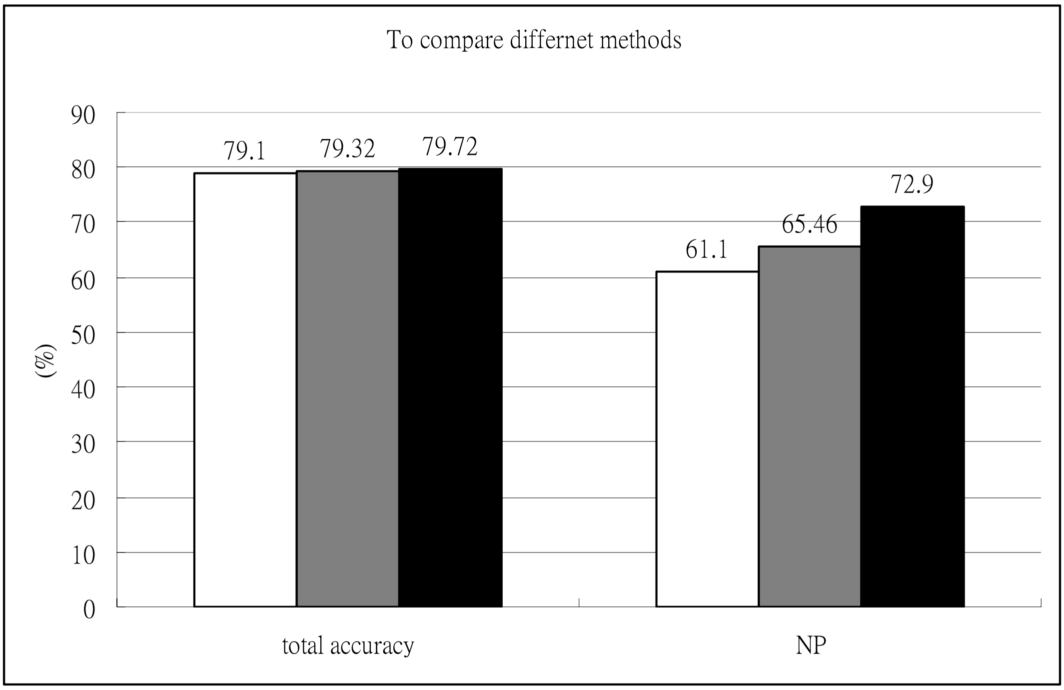


Figure 4.4. To compare our result with previous researches: The white bar shows the result of Ahmad *et al.* (2004). These gray and black bar are our results by using the original and proposed features with *cf* = 20, weight = 4 in DT method, respectively.

4.2 Knowledge acquisition

In early work, we have proved DT system and new proposed features could get better results. In this part of the thesis, the advanced knowledge acquisition from DNA-binding proteins would be a major purpose. And we hope these data are able to more creditable for the rules in biological meaning. For the reason, we input PDNA-982, a large number of dataset, to mine knowledge by C5.0 system and the proposed features in this part of the experiment.

4.2.1 The importance order of the features

According to the levels of the trees, the nodes near the roots are more critical for the establishment of the decision tree. To utilize the decision tree system ranks the importance of these features which is listed in Table 4.3. It shows the best attributes and their corresponding values with high gain ratio at each split in the top 3 tree levels.

The table which depends on the degree of the high ratio by the decision trees would help us to understand which features have important influence for the classification. Gain ratio, the ratio of information gain to potential information, is adopted by DT system. For every tree split, this criterion will select an attribute with the highest gain ration. The chosen attributes imply that they own the maximum distinct ability for each split. Features adopted from the dataset could be ranked by the contribution to predict. By Table 4.3, we could acquaint rASA and the new feature, e.g. EC value and its group, really assist in classifying these data.

4.2.2 Rules mining

Once a decision tree model has been constructed, it is a simple and straightforward matter to convert it into an equivalent set of rules by traversing any given path from the root to any leaf. To discover binding and nonbinding rules would supply the readability and understanding of data for humans.

Table 4.4 and 4.5 represent the important rules for non-binding and binding data, respectively. The foundation of the prediction of the decision tree system is observed by these tables. “Size” in these tables means the length of antecedent sentence. And “Support” of one decision rule refers to the proportion of records in the data set that conform to the rule. For an example, the rule1: if EC <= 5.217 from Table 4.4, the

Table 4.2. The ranked importance of proposed features: Best attributes with high gain ratio at each split and their corresponding values

Tree level	Attributes	Value	Potential information	Information gain	Gain ratio
1	rASA	7.12251	0.857	0.026	0.030
2	rASA	1.27065	0.992	0.010	0.010
2	EC	1.866	0.797	0.014	0.018
3	Group	-------------	1.264	0.001	0.001
3	rASA	2.897	0.975	0.003	0.003
3	EC	-10.891	0.989	0.004	0.004
3	EC	90.847	0.529	0.007	0.013

items of these rules are to explain that 162490 data matched this rule in whole dataset. And then to predict non-binding would get 96.5% in accuracy.

The tendencies about binding and nonbinding rules reveal in Table 4.4 and Table 4.5. We could note the major symbols afterward rASA or EC in Table 4.4 are “<=”, and they are “>” in Table 4.5. We deem these rules fit the fundamental biological knowledge. It means the residues near the surfaces of the proteins with positive charge have more opportunity of binding to DNA, the molecular with negative charge from phosphate. Further, we analyze more information from Table 4.4 and 4.5. These rules also conform to the ranked importance of the attribution in Table 4.3 because rASA and EC value are significant factor for the decision tree to classify.

In Table 4.4, besides the node2 of the rule4, most rules fit the above-mentioned common sense in biochemistry. The rule4 in Table 4.4 means the residues do not prefer to bind to DNA, even these neighbors of the residues having positively charged R groups because of the less surfaces exposed to solvent near the residues.

Table 4.3. The nonbinding rules for DNA-binding proteins: Decision rules with high accuracy and corresponding details for non-binding. (“nbr1_ss” presents the secondary structure of the former neighbor. And “nbr2_aa” shows the residue of the after neighbor. “*” explains nil. The other presentation is analogized.)

Decision rules	Size	Accuracy	Support
if EC <= 5.217	1	96.5	162490
if rASA <= 1.271	1	99.9	66836
if group = Nonpolar, aliphatic R groups and rASA <= 7.835 and nbr1_ss = H	3	99.8	40149
if rASA <= 6.554 and nbr2_group = Positively charged R groups	2	99.3	19718
if aa = L and rASA <= 47.782 and nbr1_ss = H	3	99.7	19601

Table 4.4. The binding rules for DNA-binding proteins: Decision rules with high accuracy and corresponding details for binding

Decision rules	Size	Accuracy	Support
if ss = * and group = Aromatic R groups and rASA > 33.772 and nbr1_aa = R	4	83.09	207
if group = Aromatic R groups and rASA > 37.422 and EC > 105.012	3	76.40	267
if aa = I and ss = * and rASA > 1.271 and rASA <= 6.554 and EC > 5.252 and EC <= 12.6 and nbr2_group = Nonpolar, aliphatic R groups	7	73.56	208
if ss = * and EC > 142.1 and nbr2_group = Polar, uncharged R groups	3	71.84	309
if rASA > 7.123 and rASA <= 43.987 and nbr1_aa = G and nbr2_aa = S and nbr2_ss = H	5	64.19	229

In Table 4.5, we find the aromatic R groups might raise the opportunity of the binding. We reason there are several reasons. First one, the aromatic R groups exits some steric or electronic effects. These effects might cause more attraction with DNA. And another reason, these residues with these groups would be conserved or they are the sections of the domains in DNA-binding proteins. The inference about these reasons will need to do more experiment in biochemistry.

The phenomenon about the cover rate of the data number is extremely discrepant between nonbinding and binding rules. We infer unbalance data and data distribution cause this condition. It is a difficult problem to compact a wide region in data distribution space for only existing binding data except setting up more capable feature set to learning models. On the contrary, the nonbinding data are major part in the whole. It would easily get higher cover rate and accuracy for the nonbinding rules.

When C5.0 system classifies the total data roughly, i.e. the rule sizes are smaller, it is effortless to read for people. However, this manner would make higher cover rate but lower accuracy. However, this method by more detailed rules, more nodes, not only decrease cover rate but also increase the difficulty to interpret for people. Therefore, we choose certain rang of the pruning value, $cf = 20$. It causes the binding rules are interpretable and makes the cover rate and accuracy have a certain level.

Chapter 5

Conclusion

DNA-binding protein problem is an essential issue for studying gene regulation. Consequently, it concerns with metabolism and disease occurring in organisms indirectly. In this thesis, an interpretable machine learning method, DT system, and other features are proposed. We hope the entire classification system could achieve a goal, to decrease the cost and time in biochemical experiment.

5.1 DT for DNA-binding protein prediction

According to performance evaluation, the choice about the weights in C5.0 model could provide a different consideration for the score function, total accuracy and *NP* equation This parameter, weight setting, could give us more elastic for dealing with problems. In general, we suggest the middle weights, nearby 3, be utilized because they would supply the adopted total accuracy and *NP* value at the same time.

Based the results of the performance, decision tree (DT) system is a better classification than neuron network (NN) for this topic. DT method is effectiveness due to its characteristic, inclusive of the ability of immediate coping with symbol features and higher dimension problem. Furthermore, our new feature set also aids for classifying these data. Therefore, the proposed C5.0 model, using these parameter settings and 11 features, provide a useful classifier to deal with DNA-binding protein prediction problem.

5.2 Knowledge acquisition by DT

After prediction, we further want to obtain the knowledge hidden from DNA-binding proteins. To take advantage of the property, one pathway from the root to its leaf being one rule, in DT system, the significant features and rules would have opportunity to be discovered. A large number of data are obtained in order to get representative knowledge.

The ranked importance of the features and the rules about binding or nonbinding with DNA would supply us with interpretable classifying criterion. Nevertheless, the high cover rate in binding rules is not observed. We refer that phenomenon with respect to the characteristic of these data which involves the distribution of the unbalanced data. Although some knowledge from DNA-binding proteins is acquired, we could not deny that the part in the research have a chance of doing better while new features were added.

5.3 Future work

This research could support the predication of the binding or nonbinding with DNA for these unknown and no significant homology proteins. In future work, besides searching for more useful features, to develop more effective machine learning methods and to do advanced analysis in biochemical experiment will help the research in the field.

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