An Analysis of Gene Expression Variations in Lymphoma, Using a Fuzzy Classification Model

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A B S T R A C T

Introduction: Cancer is a major cause of mortality in the modern world, and one of the most important health problems in societies. During recent years, research on cancer as a system biology disease is focused on molecular differences between cancer cells and healthy cells. Most of the proposed methods for classifying cancer using gene expression data act as black boxes and lack biological interpretability. The goal of this study is to design an interpretable fuzzy model for classifying gene expression data of Lymphoma cancer.

Method: In this research, the investigated microarray contained 45 samples of lymphoma. Total number of genes was 4026 samples. At first, we offer a hybrid approach to reduce the data dimension for detecting genes involved in lymphoma cancer. In lymphoma microarray, six out of 4029 genes were selected. Then, a fuzzy interpretable classifier was presented for classification of data. Fuzzy inference was performed using two rules which had the highest scores. Weka3.6.9 software was used to reduce the features and the fuzzy classifier model was implemented in MATLAB R2010a. Results of this study were assessed by two measures of accuracy and precision.

Results: In pre-processing stage, in order to classify gene expression data of Lymphoma, six out of 4026 genes were identified as cancer-causing genes, and then the fuzzy classifier model was applied on the obtained data. The accuracy of the results of classification was 96 percent using 10 rules with the highest scores and that using 2 rules with the highest scores was about 98 percent.

Conclusion: In the proposed approach, for the first time, a fully fuzzy method named a minimal rule fuzzy classification (MRFC) was introduced for extracting fuzzy rules with biological interpretability and meaning extraction from gene expression data. Among the most outstanding features of this method is the ability of extracting a small set of rules to interpret effective gene expression in cancer patients. Another result of this approach is successfully addressing the problem of disproportion between the number of samples and genes in microarrays with the proposed Filter-Wrapper Feature Selection method (FWFS).

Keywords: Lymphoma Cancer, Cancer Diagnosis, Microarray, Gen Expression, Fuzzy Classifier

Introduction

Lymphoma cancer appears in glands and nodes of the lymphatic system. It consists of glands and vessels which are responsible for purifying body fluids. Lymphocytes are produced in these tissues which have the role of maintaining body immunity. In general, cancer is one the main causes of mortality in the modern world, and an important health problem in societies (1). More than 10 million new cases of cancer and more than 6 million deaths caused by cancer are recorded each year (2). It has been estimated that until 2012, 15 million people will be affected by cancer, 12 million of whom will die of the disease (3).

During recent years, research on cancer as a system biology disease is focused on molecular differences between cancer cells and healthy cells (4). Due to the high number of factors that affect cancer diagnosis as well as the high cost of biological tests, traditional methods are not generally successful. On the contrary, intelligent methods in the domain of bioinformatics have attracted considerable attention. Because diagnosing the disease in its earlier stages is very important and more biological data is available on issues pertaining to cancer diagnosis group, most studies on cancer have used pattern

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recognition methods of the disease-diagnosis type.

Similarly, in this research, our problem is related to cancer diagnosis. By designing a model for classifying gene expression data of cancer, it is possible to address issues such as the interaction of genes and gene products, the impact of differences in gene expression in different cell conditions and different kinds of cells on a disease, and the impact of diseases and different treatment methods on gene expression (5). Studies conducted so far on cancer classification using gene expression data confirm the effectiveness of this approach in cancer diagnosis.

Classifying cancer using microarray data is a challenging problem since, in microarray data, the ratio of the samples to the features (genes) is very low. Therefore, the reduction of data dimensions is very important. In most microarrays including leukemia and lymphoma, the number of samples is fewer than 100. On the other hand, the number of genes for each sample is thousands to ten thousands of genes which is considerably high. The high ratio of unrelated genes to the genes related to cancer in microarray data leads to low precision, speed and generalizability. This also increases the complexity of the classes (6). Here, we briefly discuss all the methods based on reducing dimensions.

In the Relief method, which is based on weights (7), a statistical solution for feature selection was used. In this research, Filter-Wrapper Feature Selection (FWFS) is introduced, wherein a subset of the effective genes in cancer diagnosis is selected by combining different filter and wrapper methods of feature selection.

Different algorithms have been used for the classification of microarray data so far. In a technique proposed by (8), a decision tree was used for cancer classification. The advantages of this technique are its nonparametric nature and very fast construction. These advantages appear in all techniques which use decision tree for cancer classification. Most importantly, such techniques observe the relations among the genes. However, due to the higher number of genes and the small number samples, the application of decision trees results in overfitting and low precision of classification. (9) used the K-Nearest Neighbors (KNN) algorithm, which determines the class of each sample by obtaining votes from its k nearest neighbors. The simplest metric for calculating closeness is the Euclidean distance. The efficiency of this

method is highly dependent on the value of k. Different values for k should be considered so that its optimal value is found. (10) In general, KNN method has a lower sensitivity to the existence of error in data. On the other hand, it is not scalable at all. Furthermore, the distance of each test instance from the training data should be calculated, which lowers the speed of the algorithm.

In (11), Support Vector Machines (SVM) were used for cancer classification. This method has come into attention since the 1990s and has several advantages which make it appropriate for the problem of cancer classification. Overfitting is less likely to occur when faced with samples having large numbers of dimensions. In these methods, it is not possible to extract biological data such as important gene groups in classification and relation between effective genes in cancer. Also, (12, 13) used Fuzzy rules and logics to classify cancer data sets.

In order to increase meaning extraction ability, this paper proposes a fuzzy classification method called (A Minimal Rule Fuzzy Classification) MRFC, using a small set of rules with biological interpretability and meaning extraction from gene expression data cancer diagnosis. Fuzzy theory was used to design this model. (14) In a fuzzy classifier, the relation between gene expression level and type of cancer was interpreted by a set of fuzzy nodes. The ability to extract a small set of rules leading to simpler interpretability is among the strong points of this method. The rest of this paper is organized as follows. In Section 2, we introduce the filter-wrapper feature selection method. After that, in Section 3, a fuzzy classifier with a small set of rules is discussed. Then, the simulation results are presented and analyzed in Section 4. Section 5 briefly discusses the results of this paper, and compares them to those of other studies. Finally, section 6 includes the summary and conclusion of the paper.

Method

A. Wrapper-Filter Feature Selection Method

Feature selection methods are divided into two broad categories of filter and wrapper methods. Filter methods can be easily applied to problems with very high dimensions. In these methods, unlike wrapper methods, feature selection is only performed once by the filter method, and then different classifications can be tested on a selected subset of the features. The proposed approach for selecting a subset of genes is wrapper-filter method. A major drawback in filter methods is ignoring the relation between the selected features and the classifier during algorithm execution which is solved in our proposed approach. This approach uses a number of different filter algorithms for gene selection: Relief, CFS, gain-ratio-based, information gain-based, and symmetric uncertainty coefficient-based.

FWFS algorithm consists of the following steps:

1. Genes existing in the gene expression microarray are separately scored based on the five aforementioned algorithms. The scored genes are placed in sets $S_i, i=1,...,5$, in a descending order (Si is the set of descending ordered genes using ith gene selection algorithm).

2. A constant n is considered as the investigation interval.

3. The n first features of each of S_i sets are placed in the subsets sub-S_i, i=1,... ,5. These n features are then removed from S_i.

4. Common features of the sets sub- S_i, i=1,... ,5 are selected and inserted into the "Common Gene" set.

5. A multilayer perceptron neural network for the classification of gene expression data on the features of the set "Common Gene" is designed and trained.

6. The precision of the designed model is determined by the Leave One out Cross Validation (LOOCV) method.

7. If the precision is acceptable, "Common Gene" set is chosen as the subset of the selected genes, and the algorithm terminates; otherwise, steps 3 to 7 are repeated. Another termination condition involves investigating the

increase in the precision of prediction after re-execution of the algorithm. If the algorithm does not show any noticeable improvement after several iterations, it is terminated. The final subset is the one which has a small increase in precision of prediction after feature addition.

In the first step of this algorithm, filter methods for gene selection are used. Other steps (from 2) are based on the wrapper methods.

Fuzzy Classification Method with the Minimum Rules

In the MRFC method, first, effective genes in cancer are selected using FWFS method as explained in previous section, and then the following steps are taken. Fuzzy classifier model is implemented in MATLAB_{R2010a}.

A. Data Fuzzification

In order to design a fully fuzzy system, fuzzy C-means clustering is used for data fuzzification which is a fully fuzzy algorithm itself. For each of the genes, three fuzzy sets down, neutral and up are considered. Neutral fuzzy set indicates that gene expression level is in its natural state, and the other two fuzzy sets, up and down, show that the gene is higher or lower than its natural state, respectively.

B. Generating Fuzzy Rule Sets

First, the gene expression dataset is divided into two sets: train set and test set. The general structure of each rule, constructed based on the training set, is as follows:

Rule R_j : If x_1 is A(15) and ... and x_n is A_{jn} then Class C_j with CF_j, j=1,2,...,N   (1)

, where R_j is the label of the jth rule, and A_{j1} ..... A_{jn} are fuzzy sets.

In the consequent section of the rule, its class and validity degree are indicated by the two variables i.e. C_j and CF_j. For designing the classifier, three fuzzy sets, namely up, neutral and down, are considered. N Is the initial number of rules, while n is the number of features. If the total number of features in a dataset equals k, and the number of considered fuzzy set for each feature is m, then total number of generated rules will be k^m. The consequent of each rule should be determined using the training dataset. Suppose that the number of training samples equals m, and data are of the form $X_p = X_{p1},...,X_{pm}$,p=1,...,m. Furthermore, assuming the training data have two classes h and h′, we let the value of Cj, which is the class of rule Rj, be h^, and the procedure of generating the rules is as follows:

1) Calculating the value of βh and βh'.

$$\beta_{h(j)} = \sum_{x_p \in class h} \mu_j \, x_p \, ,$$
$$\beta'_{h(j)} = \sum_{x_p \in class h'} \mu_j \, x_p \, ,$$

, where

$$\mu_j(x_p) = \mu_{j1}(x_{p1}) \dots \mu_{jn}(x_{pn}). (2)$$

2) Finding the class of h^ according to the following equation:

$$\beta_{h^\wedge(j)} = \max\{\beta_{h(j)}, \beta'_{h(j)}\}   (3)$$

The degree of certainty of CF_j is calculated as:

$$CF_j = \frac{\beta_{h,j} - \bar{\beta}}{\beta_{h(j)} + \beta'_{h(j)}}, \quad \bar{\beta} = \beta_{h \neq h^\wedge}(j).   (4)$$

C. Ordering Fuzzy Rules

The number of generated rules for the interpretation and extraction of biological concepts is very high. Therefore, in this step, the rules are ordered. Now, we assess the quality of the fuzzy rules.

If X is a non-empty set of objects, and A and B are two fuzzy sets, according to the value of the fuzzy support for certain sets (16), the value for the proposed fuzzy support is as follows:

$$F_{Support}(R_j) = \frac{\sum_{x \in X} T(A(x), CF)}{|X|},$$
$$CF = \begin{cases} CF_j c_j = c_x \\ 1 - CF_j c_j \neq c_x \end{cases}.   (5)$$

In Eq (2), c_j is the value of rule set R_j, and c_x is the value of sample set x.

According to the FclassifierSupport Equation, the precision equation for a fuzzy rule in the fuzzy classifier model is as follows:

$$F_{Accuracy}(R_j) = \frac{FSupport(R\_j)}{support(A)} = \frac{\sum_{x \in X} T(A(x), CF)}{\sum_{x \in X} A(x)}.   (6)$$

According to the size of coverage (17) and Eq (2), coverage size for the fuzzy rule $R_j = A \rightarrow B$ in the fuzzy classifier model is as follows:

$$FCoverage(R_j) = \frac{FSupport(Rj)}{FSupport(B)} = \frac{\sum_{x \in X} T(A(x), CF)}{N}, \quad N = \{x \in X | c_j = c_x\}.   (7)$$

Using the concepts defined above as well as quality measure functions of non-fuzzy rule, several equations are proposed for the evaluation of fuzzy rules. Based on the quality-measurement function of Michalski (18) using the proposed quality measure equation by (19) and according to equations 3, 4 in the fuzzy state, we define a function for ordering fuzzy rules in a fuzzy classifier named Michalski fuzzy function as the innovation of this paper:

$$FuzzyQuality_{Michalski}(r) = \left(\frac{1}{2} + \frac{1}{4} FAaccuracy(r)\right) . FAaccuracy(r) +$$
$$\left(-\left(\frac{1}{2} + \frac{1}{4} FAaccuracy(r)\right)\right) . FCoverage(r). (8)$$

According to the quality measure equation by (20) and Equations 3 and 4, the Bradzil fuzzy function is defined as follows:

$$FuzzyQuality_{Brazdil}(r) = FAaccuracy(r) . e^{FCoverage(r) - 1}.   (9)$$

Fuzzy quality measure function number three is inspired by the function presented by (21) based on the χ^2 distribution with one degree of freedom, and is defined as follows:

$$FuzzyQuality_{G2}(r) = 2(FSupport(r))$$
$$.\ln \frac{FSupport(r).|U|}{n_\alpha(r).n_\beta(r)} + FSupport(r = A \rightarrow -B)$$
$$.\ln \frac{FSupport(r = A \rightarrow -B).|U|'}{n_\alpha(r).n_{-\beta}(r)}$$

, where

$$n_\alpha(r) = \sum_{x \in x} T(A(x), C_x),$$
$$n_\beta(r) = \{x \in X | c_x = c_r\},$$
$$n_{-\beta}(r) = \{x \in X | c_x \neq c_r\}. \qquad (10)$$

We define quality measure function number four based on Kunonkko and (22) and Equation 4 as follows:

$$FuzzyQuality_{Kononenko}(r) = -log_2 F_b + log_2 FAaccuracy(r) \quad (11)$$

D. Fuzzy Inference

Following the selection of an optimal subset of rules, the result of inference on the test dataset $X=(x_1,\ldots,x_n)$ is computed in two steps:

1) Finding the value of $a_h(x)$ for class h, which is computed as follows:

$$\alpha_h(x) = max\{\mu_j(x).CF_j | C_j = h\}. \qquad (12)$$

2) Finding class h' using the following equation:

$$\alpha_{h'}(x) = max_{1 \leq k \leq C}\{\alpha_k(x)\}. \qquad (13)$$

Results

We investigated a microarray containing 45 samples of lymphoma patients, 22 and 23 of whom suffered from the germinal type and activated type, respectively. The total number of genes was 4026 samples . First, FWFS algorithm was implemented on the data. By setting the value of n equal to 5, the algorithm terminated in the third iteration. In the lymphoma microarray, 6 out of 4029 genes were selected. Weka 3.6.9 software was used to implement the FWFS model. Weka is a collection of machine learning algorithms for data mining tasks. The precision of the model using 6 common genes out of 30 genes with the highest score was close to 98 percent. Information about the selected genes, including the number of selected common genes, identifier and the number of selected genes are seen in Table 1. Further details regarding this method are discussed in (23).

Table 1. Information of Selected Genes

SELECTED COMMON GENES	NO. GENES
GENE3332X, GENE3330X, GENE3261X, GENE3335X, GENE3314X , GENE3256X	4026

Afterwards, the MRFC method was implemented using k-fold method, with k=9, and the results were examined. In the examination, the value of 9 for k was considered. The total number of samples was 45; therefore, the algorithm was executed 9 times, and in each step, 40 samples were used for training, while the remaining five

were used for test purposes. In the first step of the MRFC algorithm, three fuzzy sets, namely up, neutral and down, were considered for each gene. In step two, different selection algorithms for s-norm operator in Equation (1) and t-norm operator in Equation 10 existed. In order to reach the optimal result in this method, different operators such as base addition and multiplication, maximum and minimum, Hamacher addition and multiplication, and Einstein addition and multiplication were tested. Finally, 3^6=729 rules were generated. The structure of generated rules based on Hamacher addition is as follows:

Rule R1: If x_1 is down & x_2 is up & x_3 is neutral& x_4 is neutral& x_5 isup & x6 isup then Class C_1=ACL with CF_1=0.99%

In step three, the generated rules were ordered based on quality measure functions. In the final step of the algorithm, fuzzy inference was performed using all of the rules (729 rules). The results are illustrated in Table 2. The precision of this model was 88.88 percent which is acceptable but the high number of rules led to a decrease in interpretability and performance of the model. In order to overcome this problem, fuzzy inference was performed using a subset of the rules.

Table 2. Fuzzy inference with all the rules

result \ Rules	Accuracy	recall		Precision	
		GCL	ACL	GCL	ACL
729	88.88%	81.48%	100%	100%	78.26%

In one study, in the fuzzy inference step, 10 rules with the highest score were used. Table 3 shows the result of this study. As it can be seen, fuzzy inference with the selected rules with quality measure function FuzzyQualityMichalski had a higher precision compared to other functions. The results of Fuzzy QualityBrazdil and FuzzyQualityKononenko were identical, and had good precision.

In another study, fuzzy inference was performed with the two rules having the highest score, as shown in Table 3. According to this table, quality measure function Fuzzy QualityMichalski had the best outcome, followed by Fuzzy QualityBrazdiland Fuzzy QualityKononenkofunctions, respectively. The results of different quality measure functions were compared in Diagram 1. According to this diagram, fuzzy inference with two superior rules which were selected by the function FuzzyqualityMichalski led to the highest result. The precision of this method was approximately 98 percent. As an example, two rules with the highest score selected by each quality measure function are shown in Fig 1.

The accuracy of the proposed model was compared using artificial neural network (ANN) and also the Rough-fuzzy clustering method (23). Neural network method has been implemented using MLP neural network (MLPNN) with the method of "Leave one out cross-validation". This method has been implemented using neural network MATLAB toolbox MATLAB 7.10.0 (R2010a) and using LM training algorithm. As shown in Table 4, the accuracy

of neural networks is high, but the method presented in this paper gives the possibility to extract information about the amount of changes in gene expression; however, the neural network operates like a black box and does not provide any information about the amount of changes in gene expression.

rules for diagnosis of lymphoma cancer of the ACL type, and 5 rules for the GCL type which is 96 percent, and the precision obtained by using 2 rules with the highest scores, consisting of 1 rule for ACL, and one 1 for GCL, is 97.7 percent.

Table 3. Fuzzy inference using effective rules

Number of rules	Estimation Functions	Accuracy	recall		Precision	
			GCL	ACL	GCL	ACL
10 effective rules	Fuzzy Quality Michalski(Q1)	95.55%	100%	92%	90.90%	100%
	Fuzzy Quality Brazdil(Q2)	93.33%	100%	88.46%	86.36%	100%
	Fuzzy Quality G2(Q3)	71.11%	63.63%	91.66%	95.45%	47.82%
	Fuzzy quality Kononenko(Q4)	93.33%	95.23%	91.66%	90.90%	95.65%
2 effective rules	Fuzzy Quality Michalski	97.77%	100%	92%	95.45%	100%
	Fuzzy Quality Brazdil	95.55%	100%	92%	90.90%	100%
	Fuzzy Quality G2	66.66%	60.60%	83.33%	90.90%	47.82%
	Fuzzy quality Kononenko	93.33%	95.23%	91.66%	90.90%	95.65%

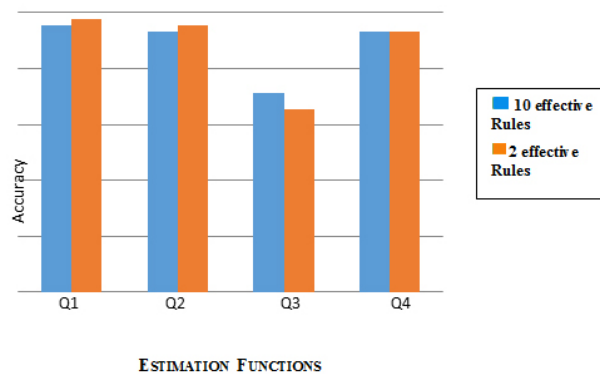**Figure 1.** The effect of estimation functions on performance of rules in classification model

Table 4. The results obtained using similar methods

Method number of rules	Accuracy		
	My method	Rough-fuzzy	ANN
10	95.55	80	97.77
2	97.77	82.22	

Discussion

Due to the importance of diagnosing of disease in its early stages, most studies on cancer have used classification method to diagnose the diseases. This study also discussed the issues related to designing the classifier to detect cancer. The resulting precision from the classification of lymphoma cancer was about 98 percent. Fuzzy quality measure functions were introduced and used in this form for the first time. Using these functions, 729 generated rules were scored. Biological researchers are now able to choose each rule based on its rank, use it in the classification of lymphoma cancer, evaluate its usefulness, and study variations in gene expressions involved in this cancer. The precision obtained by using 10 rules with the highest scores is given in Table 3 and consisted of 5

(24) used a fuzzy classifier for cancer classification. In the proposed method, 4900 rules are obtained, yielding a precision of 100 percent. In an approach which studied leukemia data, (25) first discretized data with fuzzy sets. Interpretable rules were then generated using the minimal method, and their number was reduced using filter methods. (26) used a fuzzy system to generate rules for a fuzzy classifier, and presented 6 rules as the best rules for classification of lymphoma cancer data using a proposed genetic algorithm. The precision of classifying lymphoma cancer with their method is about 92 percent. Recent review of studies show that most researchers attempt to present a model for classification of cancer based on gene expression data with two important features. These features include the design of an interpretable model and

lack of rules for easy interpretation of the results. Methods such as regression (27) and artificial neural network (28-30) are also used by researchers for this problem. These methods act similar to a black box and using them makes it difficult to extract biological information and discover the rules of these models. Therefore, in this study we used fuzzy logic to design the interpretable classifier.

Conclusion

In summary, the success obtained using this approach results from several important factors. The most important one is successfully addressing the problem of disproportion between the number of samples and genes in microarrays with the proposed FWFS method. Furthermore, using ordering functions, the most important fuzzy rules are selected which resulted in an efficient classifier model in addition to making interpretability of gene expression data possible. In future, by expanding this model, it is possible to interpret gene expression data with more than two classes, and it can also be used for interpretation of other gene expression data.

Conflict of Interest
None declared.

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