A New Combined Filter-Wrapper Framework for Gene Subset Selection with Specialized Genetic Operators

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Abstract. This paper introduces a new combined filter-wrapper gene subset selection approach where a Genetic Algorithm (GA) is combined with Linear Discriminant Analysis (LDA). This LDA-based GA algorithm has the major characteristic that the GA uses not only a LDA classifier in its fitness function, but also LDA's discriminant coefficients in its dedicated crossover and mutation operators. This paper studies the effect of these informed operators on the evolutionary process. The proposed algorithm is assessed on a several well-known datasets from the literature and compared with recent state of art algorithms. The results obtained show that our filter-wrapper approach obtains globally high classification accuracies with very small number of genes to those obtained by other methods.

Keywords: Microarray gene expression, Feature selection, Genetic algorithms, Linear Discriminant Analysis, Filter, Wrapper.

1 Introduction

The DNA Microarray is a tool that permits to monitor and to measure gene expression levels for tens of thousands of genes simultaneously under hundreds of biological conditions. This technology enables to consider cancer diagnosis based on gene expressions [1,2,3,6]. This microarray technology enables clinicians and biologists to obtain the gene expression profile of tissue samples rapidly.

Microarray data is characterized with thousands of genes but with only a small number of samples available for analysis. Microarray data often contains many irrelevant and redundant features, which affect the speed and accuracy of most learning algorithms. The task of selecting the “best” feature subset is known as feature selection, sometimes as variable selection or subset selection [4].

Feature selection consists to select a minimal subset of m features from the original set of n features ($m \ll n$). Normally, a feature selection method consists of four components: a search mechanism, an evaluation function, a stopping criterion, and a validation procedure.

In this paper, we propose a new combined filter-wrapper approach for gene subset selection for microarray data classification in two stages. In the first stage is proposed a filter for individual gene ranking. In the second stage a wrapper is proposed where Fisher's Linear Discriminant Analysis (LDA) is used to provide useful information to a Genetic Algorithm (GA) for an efficient exploration of gene subsets space. LDA has been used for several classification problems and recently for microarray data [7,10,11].

This paper is organized as follows: Section 2 describes the state of the art of feature selection. In Section 3 The General Genetic algorithm procedure is discussed in detail. Experimental results are shown in Section 4 and conclusions are drawn in Section 5.

2 State of the Art

Feature selection methods are separated into three main families [12]: 1) the filter approach, 2) the wrapper approach and 3) the embedded approach.

The filter approach uses statistical information to filter out irrelevant features. All features are first ranked and then a classifier is build by selecting the highest ranking features. In most cases, the selection relies on an individual evaluation of each feature [6,13], therefore this method ignores interactions among genes.

The wrapper approach relies on a classification algorithm that is used as a black box to explore the space of features subset to evaluate each candidate subset; the quality of a candidate subset is measured by the performance of the classifier obtained on the training data, using, for example a cross validation process. Finally, the feature subset that achieves highest performance is chosen. Wrapper methods are generally computation intensive since the classifier must be trained for each candidate subset. For this reason, several strategies can be considered to explore the space of possible subsets. In the context of microarray data, several wrapper methods have been proposed using uncorrelated discriminant analysis [10], generalized discriminant analysis [31], null space [11], diagonal covariance matrices [24] and linear discriminant analysis using pseudo-inverse [5].

Finally, in embedded methods, a inductive algorithm is used as feature selector and classifier. A representative work of this approach is the method that uses support vector machines with recursive feature elimination (SVM/RFE) [18]. The selection is based on a ranking of the genes and, at each step, the gene with the smallest ranking criterion is eliminated. The ranking criterion is obtained from the weights of a SVM trained on the current set of genes. In this sense, embedded methods are similar to wrapper methods. There are other variants of these approaches, see [19,20] for two examples. In [21], the authors propose a forward search approach based in two steps. In the first a filter method is used as a pre-selection step, all features are ranked. In the second step a wrapper method is used for feature selection by building N attributes subsets. These subsets are evaluated using the so-called Rank-Search algorithm, which is very fast, but gives very large feature subsets.

3 General GA Procedure

Our approach first extracts a set of interesting genes (about $p = 150$ genes) by a filter method in order to limit the search space. Then we use a dedicated Genetic Algorithm (GA) to determine a small subset of genes that allows high classification accuracy. Contrary to most existing GAs for gene selection that rely essentially on random genetic operators, we devised a problem specific GA that takes into account useful knowledge of the gene selection and classification problem. Indeed, our GA uses a LDA classifier to assess the fitness of a given candidate gene subset and LDA's discriminate coefficients in its crossover and mutation operators.

This paper first studies the impact of these informed operators on the evolutionary process. We present experimental evidence about the performance of our dedicated crossover operator when compared with two conventional crossover operators.

To evaluate the usefulness of the proposed approach, we carry out extensive experiments on seven public datasets and compare our results with 13 best performing algorithms from the literature. We observe that our approach is able to achieve a high prediction accuracy (from 81% to 100%) with a very small number of informative genes (from 2 to 19).

3.1 Filter Method

Different feature selection approaches have been applied to gene selection for cancer classification (Fisher ratio, Wilcoxon test, Information Gain, Relief-F, T-statistics, entropy-based, BW ratio, etc.).

The **BW ratio**, introduced by Dudoit *et al.* [7], is the ratio of between-group to within-group sums of squares. For a gene j , the ratio is formally defined by:

$$BW(j) = \frac{\sum_i \sum_k I(y_i = k)(\bar{x}_{kj} - \bar{x}_j)^2}{\sum_i \sum_k I(y_i = k)(x_{ij} - \bar{x}_{kj})^2} \quad (1)$$

where $I(\cdot)$ denotes the indicator function, equaling 1 if the condition in parentheses is true, and 0 otherwise. $\bar{x}_j$ and $\bar{x}_{kj}$ denote respectively the average expression level of the gene j across all samples and across samples belonging to class k only and finally y_i denotes a class label. This filter method considers the most discriminatory genes those that have the highest scores. We use this ranking-based method to identify differentially expressed genes in two tissue types.

In our filter-wrapper framework, we use three filters : between-group to within-group sums of squares (BW), t-statistic (TT), and Wilcoxon test (WT) for a comparative analysis.

3.2 Wrapper Method

We describe now the wrapper method based in a genetic algorithm and a classifier LDA (GALDA) of the general model for gene selection and classification. The

GA is designed for discovering good gene subsets by using genetic operators specialized. The LDA-based classifier is used to ensure the fitness evaluation of each candidate gene subset. The basic components of our GA are detailed in this section.

Encoding representation and initialization. In our GA, a chromosome encodes more information than a classic GA, because the chromosomes are formed by two parts of same length: 1) a binary vector and 2) a real-valued vector (as shown in Figure 1). The first part represents a candidate gene subset (150), where each allele (bit) of the chromosome represents a gene. If an allele is “1” it means that this gene is kept in the gene subset and “0” indicates that the gene is not included. Each chromosome represents thus a gene subset. The chromosome length is equal to the number of p genes pre-selected by the filter t-statistics (3.1). The second part of the chromosome is a real-valued vector that corresponds to the discriminant coefficients obtained by a LDA classifier for a gene g_i which are useful for designing powerful crossover and mutation operators (described below).

Fig. 1. Representation of a chromosome in our GA

The individual of the initial population are generated randomly according to a uniform distribution in such a way that each chromosome contains a number of genes ranging from $p = 0.60$ to $p = 0.75$. The population size is fixed at 100 in this work. The chromosomes of the current population P are sorted according to the fitness function (see subsection 3.2). The best 10% chromosomes of P are directly copied to the next population P' and removed from P . The remaining 90% chromosomes of P' are then generated by using specialized genetic operators.

Double fitness function. The fitness of a chromosome, i.e. a subset of genes, is assessed by two fitness functions: 1) the classification rate (f_1), and 2) the number of selected genes in the each chromosome (f_2). In the first part of the double fitness function, a subset of genes leading to a high classification rate is considered to be better than a subset leading to a low classification rate. In our case, the LDA classifier ensures this classification task. We apply a 10 fold cross validation to calculate the performance of the classifier LDA for a candidate gene subset. The second part of the fitness (f_2) is calculated by the formula:

$$f_2 = \left(1 - \frac{m_\omega}{p}\right) \quad (2)$$

Where m_ω is the number of bits having the value “1” in the candidate gene subset ω , p is the length of the chromosome corresponding to the number of the pre-selected genes from the filter ranking. Then the fitness function f is defined as the weighted aggregation of f_1 and f_2 as follows:

$$f(I) = \alpha f_1(I) + (1 - \alpha) f_2 \text{ subject to } 0 < \alpha < 1 \quad (3)$$

Where α is a parameter that allows us to allocate a relative importance factor to f_1 or f_2 . Assigning to α a value greater than 0.5 will push the genetic search toward solutions of high classification accuracy (probably at the expense of having more selected genes). In contrast, using a small values of α helps the search toward small sized gene subsets. So varying α will change the search direction of the genetic algorithm.

Specialized genetic operator of crossover. We use the discriminant coefficients from a LDA classifier to design our specialized genetic operator of crossover. The crossover combines two parent chromosomes $I1$ and $I2$ to generate a new chromosome I_{new} in such a way that 1) top ranking genes in both parents are preserved in the child and 2) the number of selected genes in the child I_{new} is not greater than the number of selected genes in the parents. The first point ensures that “good” genes are transmitted from one generation to another while the second property is coherent with the optimization objective of small-sized gene subsets.

Specialized genetic operator of mutation. The mutation operator is used as a source of genetic variation in the population by introducing new genetic information by making local changes in a given chromosome. For binary coded GAs, this is typically realized by flipping the value of some bits ($1 \rightarrow 0$, or $0 \rightarrow 1$). In our case, mutation is used for dimension reduction; each application of mutation eliminates a single gene ($1 \rightarrow 0$). To determine which gene is removed, we use discriminant coefficients obtained from LDA classifier [5]. Given a candidate gene subset, we identify the smallest LDA discriminant coefficient and remove the corresponding gene that is the least informative gene among the current candidate gene subset.

4 Experiments on Microarray Datasets

In this section, we use seven public microarray datasets for our experiments (more details in table 1). In this table is shown the number of genes, the number of samples and the first publication that has presented an analysis of this dataset.

Our filter-wrapper approach was implemented in octave for Linux O.S. A Fisher LDA classifier is used. In order to test each dataset we conduce 10 independent runs and we retain the best solution found during these 10 executions to have statistically meaningful conclusions. In the first experiment, we focus on the accuracy, so the fitness function is defined with $\alpha = 0.50$ (results shown in Figure 2).

We show in Table 2 the best accuracies (in bold) obtained by other methods and by our filter-wrapper approach on the seven datasets presented previously. An entry with the symbol (–) in this table means that the paper does not treat the corresponding dataset. All the methods reported in this table use a process of cross validation. Each cell contains the classification accuracy and the number of genes when this is available.

Table 1. Description of seven microarray datasets

Dataset	Genes	Samples	Training set	Test set	References
Leukemia	7129	72	38	34	Golub et al. [6]
Colon	2000	62	32	32	Alon et al. [2]
Lung	12533	181	102	101	Gordon et al. [22]
Prostate	12600	109	54	55	Singh et al. [23]
CNS	7129	60	30	30	Pomeroy et al. [25]
Ovarian	15154	253	91	162	Petricoin et al. [26]
DLBCL	4026	47	23	24	Alizadeh et al. [1]

Fig. 2. Comparison of the best fitness averaged over 10 independent runs with the classical genetic algorithms: uniform crossover and single point crossover. In this experiment was used a $\alpha = 0.50$.

According to these observations, it seems clear that our filter-wrapper approach is very competitive in comparison with some top-performing methods. It is difficult to assess this statement by statistical tests since many methods only deal with two datasets.

Table 2. Comparison of our filter-wrapper approach with the most relevant works on cancer classification

Reference	Leukemia	Colon	DLBCL	Lung	Prostate	CNS
[10]	97.5	85.0	–	–	92.5	–
[27]	100(30)	91.9(30)	98(30)	100(30)	97(30)	–
[28]	91.1	95.1	–	93.2	73.5	88.3
[29]	100	93.5	–	97.2	–	–
[30]	95.9(25)	87.7(25)	93(25)	–	–	–
[31]	73.2	84.8	–	–	86.8	–
[33]	98.6(5)	87(4)	–	100(3)	–	–
[34]	95.8(20)	100(20)	95.6(20)	–	–	–
[35]	94.1(35)	83.8(23)	–	91.2(34)	–	65(46)
[36]	97.1(20)	83.5(20)	93.0(20)	–	91.7(20)	68.5(20)
[37]	100(30)	90.3(30)	92.2(30)	100(30)	95.2(30)	80(30)
[11]	83.8(100)	85.4(100)	–	–	–	–
[38]	100(4)	93.6(15)	–	–	–	–
BW-GALDA with $\alpha=0.50$	99.3(± 2.4)	94.1(± 3.2)	99.6(± 1.0)	98.6(± 2.0)	99.3(± 1.5)	97.8(± 1.0)

We show in table 3 and table 4 the most frequent genes obtained by our model for the Leukemia and Colon by using the filters TT, BW and WT. In the first column we show the ID number for each dataset, in the second column we show their frequency and finally in third column is shown the references where is reported these gene in the literature by other well-know models.

Table 3. Summary of 10 first-genes with highest frequency for Leukemia dataset

FILTER-BW			FILTER-TT			FILTER-WT		
Gene-id	Frequency	References	Gene-id	Frequency	References	Gene-id	Frequency	References
1834	915		3847	823		3847	933	
4847	535	[6,9,8,32]	1882	582	[38,9,32]	1779	709	[9]
1239	466		3252	507	[9]	1882	693	[38,9,32]
312	383	[8]	4847	368	[6,8,9,32]	4847	584	[6,8,9,32]
1829	290		5122	367		5122	497	
2242	279		5039	312		4377	386	[9]
5501	279		1834	281	[9]	1829	318	[9]
4373	278		6041	277	[9]	4373	314	
2288	274	[8,9]	1779	223	[9]	1807	295	
6041	230	[9]	6169	182		2020	279	[9]

Table 4. Summary of 10 first-genes with highest frequency for Colon dataset

FILTER-BW			FILTER-TT			FILTER-WT		
Gene-id	Frequency	References	Gene-id	Frequency	References	Gene-id	Frequency	References
739	694		1836	532		493	879	[8]
164	670		548	526		1836	737	
576	513		792	407	[8]	1873	284	
625	464	[38]	377	392		765	277	
399	391		493	381	[8]	377	276	
1472	384		18	362	[8]	897	252	[38]
26	297		67	330		792	227	[8]
619	296		765	301		180	216	
451	294		517	288		267	205	
249	280	[38]	823	287		689	203	

In table 5 are shown the number of genes selected by our model in the seven microarray datasets. In this way we could obtain a smaller number of genes with

a perfect classification accuracy in 5 of seven datasets. Those minimum set of genes can be used to differentiate the two types of diseases(p.e. ALL/AML for the Leukemia dataset). For the others datasets we obtain a very good classification for the Colon, CNS and Lung cancer.

Table 5. Best classification rates for seven public dataset using small gene subset with the filters: BW, TT and WT

Data sets	filter-BW Accuracy(Number of genes)	filter-TT Accuracy(Number of genes)	filter-WT Accuracy(Number of genes)
Leukemia	99.3(± 2.3)	99.3(± 3)	99.3(± 2.6)
Colon	94.1(± 3)	93.1(± 3.1)	94.1(± 2.6)
DLBCL	99.6(± 1)	99.3(± 3.1)	99.3(± 1)
CNS	97(± 1)	97.3(± 1)	98.6(± 1)
Lung	98.6(± 2)	98.6(± 2)	98.6(± 2.1)
Prostate	99.3(± 2)	99.3(± 1.7)	99.3(± 1.9)
Ovarian	97.8(± 1)	99.3(± 2.2)	96.3(± 1.0)

5 Conclusions

In this paper we propose a new combined filter-wrapper with specialized genetic operators for the gene selection and classification of microarray gene expression. The propose approach begins with a filter that pre-selects a first set of genes (about $p = 150$ in this paper). To further explore the combinations of these genes, we rely on a hybrid Genetic Algorithm combined with Fishers Linear Discriminant Analysis. In this LDA-GA, LDA is used not only to assess the fitness of a candidate gene subset, but also to inform the crossover and mutation operators. This GA and LDA hybridization makes the genetic search highly efficient for identifying small and informative gene subsets.

We use a double function fitness that provides an interesting way for the LDA-GA to explore the gene subset space either for the minimization of the selected genes or for the maximization of the prediction accuracy.

We have extensively evaluated our filter-wrapper approach on seven public datasets using a rigorous 10-fold cross-validation process. A large comparison was carried out with 13 state-of-art algorithms that are based on a variety of methods. The results clearly show the competitiveness of our filter-wrapper approach. For all the datasets, our approach is able to select small gene subsets while ensuring the best or the second best classification rate. The proposed approach has another practically useful feature for biological analysis. In fact, instead of producing a single solution (gene subset), our approach can easily and naturally provide multiple non-dominated solutions that constitute valuable candidates for further biological investigations.

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