A Model-Free Greedy Gene Selection for Microarray Sample Class Prediction

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Abstract—Microarray data analysis is notoriously challenging as it involves a huge number of genes compared to only a limited number of samples. Gene selection, to detect the most significantly differentially expressed genes under different categories of conditions, is both computationally and biologically interesting, and has become a central research focus in all studies that use gene expression microarray technology. Despite many existing efforts, better gene selection methods that can effectively identify biologically significant biomarkers, yet computationally efficient, are still in need. In this paper, a model-free greedy (MFG) gene selection method is proposed, which implements several intuitive heuristics but doesn’t assume any statistical distribution on the expression data. The experimental results on three real microarray datasets showed that the MFG method combined with a Support Vector Machine (SVM) classifier or a k-Nearest Neighbor (KNN) classifier is efficient and robust in identifying discriminatory genes.

Index Terms—Microarray data analysis, sample class prediction, discriminatory gene, gene selection, greedy.

I. INTRODUCTION

The fast developing microarray technology allows us to monitor the expression levels for thousands of genes simultaneously. This novel technique provides us a large amount of data to understand systematically various gene regulations under different conditions as well as their relation to diseases and treatments. Nevertheless, though microarray technology expands biological and medical information tremendously, it also brings the challenges of how to use the data reasonably and thus to abstract useful information. With respect to a specific application, we may have two categories of genes. For one category of genes, their expression levels are largely unchanged under different conditions, such as housekeeping genes. These genes are less interesting since they do not provide useful information related to the samples. The second category of genes are those that are differentially regulated under certain experimental conditions, that is, their expression levels either increase or decrease across different conditions. These discriminatory genes are very important in delivering information related to experimental conditions and the samples’ property. For instance, they could be highly correlated to certain kinds of diseases or medical conditions. Gene selection is about looking for the second category genes.

Since discriminatory genes are differentially regulated under certain experimental conditions, or in other words they are expected to have very close expression levels in samples of the same condition, or class called in this paper for the sample classification purpose, but significantly different across samples from different classes, there are many gene selection methods proposed to capture this intuitive criterion, for example the F-test [1], [2] and its variants [3], [4]. Basically, these gene selection methods implement the criterion to assign each gene a score and then sort the genes into a non-increasing order, where a higher score indicates a more differential expression [1], [2], [3], [4]. According to Liu and Yu [5],

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they belong to the wrapper-sequential-classification category of feature selection methods. They then set up a score cut-off to report those genes having scores higher than the cut-off. The quality of the subset of reported genes is measured by their class prediction power, when combined with a classifier such as a support vector machine (SVM) classifier or a k nearest neighbor (KNN) classifier, through a leave-one-out cross validation (LOOCV) or an l-fold cross validation.

Microarray data classification is one of the most computationally challenging tasks, which includes previously unrecognized class discovery and sample class prediction. With known classes, the main purpose of gene selection is to identify those discriminatory genes whose expression levels signify the class. In this sense, the classification accuracy of the identified gene subset indeed reflects their biological significance as a whole. The above mentioned gene selection methods only report a certain number of top ranked genes, without consideration of the facts that some genes may have very similar discrimination power as individuals and some genes may have complementary discrimination powers. Obviously, for genes having very similar discrimination powers, if one is top ranked, then the others could also be top ranked. Consequently, using them all in class prediction is redundant. On the other hand, for genes having complementary discrimination powers, they might not be top ranked since as individuals their discrimination powers could be lower than the cut-off. As a result, they would not be used for class prediction and it leads to a loss that could not be made up by the use of other top ranked genes. In this paper, we propose a gene selection method to partially address the above two issues to select a subset of genes that have superior discrimination power as a whole. According to the categorizing framework by Liu and Yu [5], our method might still belong to wrapper-sequential-classification, yet it takes some idea from filter algorithms to exclude or remove certain genes that do not contribute much to the existing selected gene subset.

We note that there are a few previously proposed methods that attempt to address the same issues, to be reviewed in the Methods section. Nevertheless, compared to them, our method implements heuristics that are intuitively sound and is computationally very efficient. For example, our method takes only seconds to minutes on a normal size real microarray dataset. Our method is also model-free in that it does not assume or require any statistical model on the gene expression levels. We review some of the recent related work in the following.

There are a variety of gene selection methods that have been proposed recently, among the rich literature of feature selection algorithms [5]. In general, gene selection methods can be partitioned into two categories, which are model-free and model-based. Model-based gene selection methods assume some specific statistical models on the gene expression data. For example, Baldi et al. [6] developed a Gaussian gene-independent model to process the gene expression data. They implemented a t-test combined with a full Bayesian treatment on the gene expression data. Obviously, the disadvantage of this category of gene selection methods is the lack of adaptability, because it is unlikely to construct a universal probabilistic analysis model that is suitable for all kinds of gene expression data, where noise and variance vary dramatically across different gene expression datasets [7]. Model-free gene selection methods do not assume any specific distribution model on the gene expression data. For example, Xiong et al. [8] suggested two methods, sequential forward selection (SFS) and sequential forward floating selection (SFFS), to select genes through the space of gene subsets using the classification error. We will compare our method with SFS and SFFS, whose more detailed descriptions are included in the next section. Guyon et al. [9] proposed a gene selection approach utilizing support vector machines based on recursive feature elimination (RFE). These model-free gene selection methods, however, have been reported [7] to be possibly influenced by the specific criteria used for scoring the gene discrimination power. According to the categorizing framework by Liu and Yu [5], most of these methods belong to filter/wrapper-sequential-classification category.

The gene selection method proposed in this paper is model-free and implements three greedy heuristics on discrimination power, called the MFG method. The MFG method does not assume statistical model on the gene expression levels, and it adopts the classification accuracy of an individual gene as the score. We have tested two classifiers, a linear kernel support vector machine (SVM) classifier and a k nearest neighbor (KNN) classifier for k = 5, to combine with the MFG method for measuring the classification accuracy. After each gene is assigned a score, they are sorted in non-increasing order and the selection starts with the gene of the highest score. Three heuristics implemented in the selection process are greedy, c-kick and exchange, to be detailed in the Methods section. The MFG method is compared with four recently proposed methods, SFS, SFFS, Cho’s and F-test, on eight real microarray datasets, among which we chose to present results on three datasets in the current report. Note that gene selection is essentially designed to reduce the dimensionality of the gene space, since there are usually much more genes than the number of the microarray chips. To demonstrate the effectiveness of reported genes, we also tested a method to randomly pick the same number of genes from the gene pool and examined their classification accuracy as a whole. We denote this method as Random, whose performance can be regarded as a baseline. The experimental results showed that the MFG method is very efficient and effective in identifying biologically meaningful genes that can be used for class prediction purpose.

The rest of the paper is organized as follows: In the next section, we introduce further details on gene selection and then present the details of the MFG method, F-test, Cho’s, SFS and SFFS. Section III summarizes the experimental results of the MFG method combined with two classifiers, a linear kernel SVM-classifier and a KNN-classifier, on three real microarray datasets that are used for cancer subtype determination. We discuss the results in Section IV on different aspects of the MFG method and their effects. Section V concludes the paper and points out some immediate future works.
II. Methods

Assume in each microarray chip there are in total $n$ genes and in total $m$ chips/samples in the dataset that have been grouped into $L$ classes. In our tested datasets, there are usually multiple classes, typically in those three chosen to be reported. Therefore, the microarray dataset can be represented as a matrix of expression levels $A_{n \times m} = (a_{ij})_{n \times m}$, where $a_{ij}$ denotes the expression level of gene $i$ in sample $j$. Note that every sample is labeled with its class name in the original dataset.

Given a gene selection method, in order to test its performance, the microarray dataset is randomly partitioned into $\ell$ equal parts. Among them, $\ell - 1$ parts are used by the gene selection method to selected a number of discriminatory genes. These selected genes are then fed to a classifier, which is tested on the last part to see how well the classifier can tell the class membership for each sample (whose original class label is erased before the testing). Consequently, those $\ell - 1$ parts form a training dataset and the last part forms a testing dataset. The process is repeated $\ell$ times to have every part as the testing dataset and the average classification accuracy over these $\ell$ ones is called the $\ell$-fold cross validation classification accuracy of the gene selection method combined with the classifier. In this current work, we chose $\ell = 5$ and the random partitioning process was repeated for 20 times. That is, the $\ell$-fold cross validation classification accuracy is the average over a total of 100 ones.

We adopted two classifiers in our study, one is a linear kernel SVM-classifier [9] and the other is a KNN-classifier [1]. Essentially, SVMs compute a decision plane to separate the set of samples (in the training dataset) having different class memberships, and use this plane to predict the class memberships for testing chips. A KNN classifier, in our case $k = 5$, ascertains the class for a testing sample by analyzing its $k$ nearest neighbors in the training dataset and by a majority vote. The interested readers might refer to [9], [1] for more details.

In the following, we present the MFG method on the training dataset in details, with the understanding that this stage only returns a subset of genes. How to build a classifier using these reported genes and the subsequent testing follow the above description and the separate classifiers [9], [1].

A. The MFG Method

In the training dataset, the expression levels of all the samples and their class labels are used for gene selection purpose. In the MFG method, firstly, each gene is used to build a classifier (which could be the SVM-classifier or the KNN-classifier). Adopting the 5-fold cross validation scheme, the performance of the classifier measured by the classification accuracy is the score assigned to the individual gene. In other words, we adopt the cross validation classification accuracy of an individual gene as the scoring function to rank genes. Such a scoring function does not assume any statistical model on the expression data (but the adopted classifier) and thus the MFG method is model-free. We remark that in this stage of scoring genes, the training dataset itself is partitioned into 5 parts for 5-fold cross validation purpose, and the gene scoring has nothing to do with the testing dataset. After each gene is assigned a score, they are sorted in the non-increasing order.

The optimization problem in gene selection is to select a subset of genes that have the highest classification accuracy as a whole, which, however, turns out to be NP-hard. Several heuristics can be applied to rapidly identify a subset of genes that might not have the highest classification accuracy but intuitively very close to the highest. Note that using more genes might not always be a better choice, and thus the set of all genes is generally not the desired solution. One of the simplest heuristics is probably to return the subset of top ranked $x$ genes in the sorted gene order, where $x$ is a number specified by the user. Another simplest heuristics is to randomly select a subset of $x$ genes, even without using the sorted gene order. We denote this latter method as Random, whose performance might be regarded as a baseline of the dataset. That is, every good gene selection algorithm should perform better than Random in order to be recommended.

The Random method certainly is a blind search, without taking advantage of individual gene information. On the other hand, simply reporting the top ranked a few genes does not address the aforementioned two issues: 1) Some similarly expressed genes might all be top ranked and using them all in the classification is redundant; 2) Some genes having complementary discrimination powers might not be top ranked as individuals and thus not included for building classifiers. The proposed MFG method intends to resolve these two issues, through implementation of the following three heuristics. It essentially scans through the sorted gene order to pick up genes which it believes useful, and once every a few iterations it removes some genes which it believes not useful any more.

1) The Heuristics: There are three heuristics implemented in the MFG method:

a) Greedy: The greedy heuristics allows the MFG method to include a gene only when the gene under consideration can improve the classification accuracy, upon appending it to the current selected gene pool. In more details, assume the MFG method is examining the $i$-th gene $g_i$ in the sorted order, and the current selected gene pool is $P$, which is a subset of the first $i - 1$ genes. Let $q$ be the classification accuracy of gene set $P$ as a whole; let $q'$ be the classification accuracy of gene set $P + g_i$. If $q' > q$, then gene $g_i$ is added to the selected gene pool and the MFG method either proceeds to consider the $(i + 1)$-st gene in the sorted gene order, or applies the following $c$-kick heuristics. If $q' \leq q$, then gene $g_i$ is regarded as useless with respect to $P$ and the MFG method proceeds to apply the exchange heuristics.

b) Exchange: At one iteration of the MFG method where the gene under consideration doesn’t improve the classification accuracy, MFG does not discard the gene immediately. Instead, it implements the following heuristics to examine one step backward to see whether or not this gene indeed can be discarded. To this purpose, again assume the notations in the last paragraph and let $q_j$ denote the last gene added to the current selected gene pool $P$. Note that the individual discrimination power of gene $g_j$ is at least as high as that of gene $g_i$. The MFG method tests the classification accuracy
$q'$ of gene set $P - g_j + g_i$, that is, to replace the last added gene $g_j$ by gene $g_i$. If $q' \leq q$, then gene $g_i$ is discarded from further consideration. Otherwise, the replacement is taken and gene $g_j$ is discarded from further consideration. In either case, the MFG method proceeds to consider the next gene in the sorted gene order. Such an exchange heuristics is designed to pick up genes that have complementary discrimination powers to some already selected genes.

(c) $c$-Kick: Once every a few iterations, the MFG method re-examines its selected gene pool and tries to remove some of them that do not contribute to the overall classification. This $c$-kick heuristics is different from the exchange heuristics that only considers to replace the lastly added gene by the current gene. Rather, in more details, once the MFG method has continuously added $c$ fresh genes, say $g_1, g_2, \ldots, g_c$ in the order of addition, it scans if kicking any one of them out of the selected gene pool will increase the classification accuracy. If kicking out one gene does increase the classification accuracy, then the gene is removed from the selected gene pool and would never be considered again. The MFG method continues till no more gene can be kicked out, and then resumes the scanning of the sorted gene order. Inside this heuristics, $c$ is a parameter specified by the user. We have tested several values for $c$ and the best performance seemed achieved at 5. Note that both the $c$-kick and the exchange heuristics take into account a certain portion of the mutual information between genes, and search for the local optimal combinations. In this sense, implementing them into the MFG method expects better performance.

2) The Complete Description: To summarize, upon decision on a classifier and a cross validation scheme, the MFG method works on the training dataset to sort the genes in non-increasing order of their individual classification accuracy and then select a number of top ranked genes according to the three heuristics. These genes are used to build a classifier that can predict the class memberships for the samples in the testing dataset. The cross validation classification accuracy on the testing datasets is taken to measure the performance of the MFG method, combined with the chosen classifier, on the microarray dataset. Figure 1 contains a high level description of the MFG method.

B. The Other Methods

Feature selection is a process to select only a subset of original features whose optimality is measured by an evaluation criterion. Such a process is in general intractable and many related problems have been shown to be NP-hard. Liu and Yu [5] surveyed feature selection algorithms for classification and clustering, and proposed a two dimensional categorizing framework for the algorithms for classification. Most of the gene selection algorithms in the microarray data analysis literature for sample class prediction belong to the wrapper-sequential category, in particular the following four algorithms with which the MFG method is compared in this work.

1) F-test: In F-test, genes that have small intra-class variances and large inter-class variances will be ranked high. Formally, for each gene $g_j$, let $\overline{x}_j$ denote the mean expression value in samples in the $j$-th class and $\overline{\pi}$ denote the mean expression value in all the samples. The score of this gene is calculated as

$$\frac{\sum_{j=1}^{L}(\overline{x}_j - \overline{\pi})^2}{\sum_{j=1}^{n_j}(a_{ij} - \overline{\pi})^2},$$

where $n_j$ is the number of samples in the $j$-th class. The first $x$ top ranked genes are returned as selected genes. We note that though F-test is often reported inferior, it is a classic method to be compared with.

2) Cho’s: Using the same notations used as in the above, Cho’s method [3] defines a weight factor $w_j$ for sample $j$, which is $\frac{1}{n_k}$ if sample $j$ belongs to class $k$, whose size is $n_k$. Let $W = \sum_{j=1}^{m} w_j$. The weighted mean for gene $i$, denoted as $\bar{a}_i$, is defined as

$$\bar{a}_i = \frac{\sum_{j=1}^{m} w_j a_{ij}}{W}.$$

The weighted standard deviation, denoted as $\hat{\sigma}_i$, is defined as

$$\hat{\sigma}_i = \sqrt{\frac{\sum_{j=1}^{m} (a_{ij} - \bar{a}_i)^2}{(m - 1) \sum_{j=1}^{m} w_j}}.$$

Then the score of gene $i$ is calculated as

$$\frac{\bar{a}_i \times \hat{\sigma}_i}{\sigma},$$

where $\sigma$ is the standard deviation of class centroid expression values for gene $i$: $(\overline{\pi}_{1i}, \overline{\pi}_{2i}, \ldots, \overline{\pi}_{Li})$, where $\overline{\pi}_{ki} = \frac{1}{n_k} \sum_{j=1}^{n_k} a_{ij}$. Likewise, the first $x$ top ranked genes are returned as selected genes.

INPUT: A microarray training dataset, a classifier, a cross validation scheme, $c$ and $x$.  
OUTPUT: A subset of $x$ genes.

1) Apply the classifier to determine the cross validation classification accuracies of individual genes on the training dataset, and sort the genes in non-increasing order;
2) For each gene in the sorted order
a) If it improves the classification accuracy
i) Add it to the selected gene pool;
ii) Execute $c$-kick heuristics if applicable;
Else
i) Execute exchange heuristics if applicable;
b) If there are $x$ genes selected or all genes have been considered
i) Stop and return the selected genes;

Fig. 1

A HIGH LEVEL DESCRIPTION OF THE MFG METHOD.
3) SFS: The sequential forward search (SFS) method has been proposed for general feature extraction a long time ago [10], but was only recently investigated for microarray data analysis [8]. Similarly as in the MFG method, each gene is assigned a score indicating its discrimination power — the classification accuracy. The top ranked gene is then selected. Next, this selected gene is combined with every other gene to determine the combination of two genes that achieves the highest classification accuracy. Then, this combination of two genes is combined with every other gene to determine the combination of three genes that achieves the highest classification accuracy, and so on. The process stops when a pre-specified number of genes have been selected, or there is no further improvement on the classification accuracy.

4) SFFS: Adding one more feature called floating to SFS, the sequential forward floating search (SFFS) method was also investigated for microarray data analysis [10], [8]. This was designed to overcome the so-called nesting effect in the SFS method, that is, once a gene is selected, there is no way for it to be discarded later on. In this sense, it is very similar to the c-kick heuristics in the MFG method. SFFS maintains a sequence of subsets of selected genes, which contain $1, 2, 3, \ldots, n$ genes, respectively. The subset of $k$ selected genes is the one that to the moment achieves the highest classification accuracy using $k$ genes. Applying SFS, assume that at the current iteration gene $g_i$ is the one that achieves the highest classification accuracy when added to the current selected gene pool $P$. SFFS examines if there is one gene, say $g_r$, in $P$ such that $P - g_r + g_i$ achieves a higher classification accuracy than $P$. If there is no such gene $g_r$, then SFFS adds $g_i$ to $P$ and moves on to the next iteration. Otherwise, it updates $P$ to be $P - g_r + g_i$, i.e. $P \leftarrow P - g_r + g_i$, and continues on to examine if there is one gene, denoted as $g_r$, in $P - g_r$ such that $P - g_r$ achieves a higher classification accuracy than $P - g_i$, and so on.

III. EXPERIMENTAL RESULTS

A. Overview

We have compared the MFG method with four other gene selection methods, namely F-test [1], Cho’s [3], SFS and SFFS [8] on eight real microarray datasets. We have also used the performance of the Random method as the baseline for comparison. Among these eight datasets, we chose to report the three most difficult datasets, where the difficulty of a dataset is measured by the number of genes versus the number of samples in the dataset, as well as the degree of unbalanced numbers of samples in the classes. As shown in the following, in general, the classification accuracy of the Random method also hints the difficulty of the dataset.

We adopted two classifiers built on the selected genes, one is a linear kernel support vector machines (SVM) classifier [9] and the other is a $k$ nearest neighbor (KNN) classifier [1], where $k = 5$. The SVM we used in MATLAB is from http://theoval.sys.uea.ac.uk/~gcc/svm/toolbox/ and the KNN is coded in MATLAB by ourselves. All the experiments were conducted in MATLAB environment (http://www.mathworks.com) on a cluster of 2.33GHz CPUs. We adopted the 5-fold cross validation to test the classification accuracy of these gene selection methods.

B. Dataset Descriptions

We describe next the three microarray datasets on which the results are reported. Descriptions of the other five datasets are available upon request, as well as the datasets.

The GLIOMA dataset [11] contains in total 50 samples in four classes, classic glioblastoma, nonclassic glioblastoma, classic anaplastic oligodendroglioma and nonclassic anaplastic oligodendroglioma. This dataset is from Affymetrix U95Av2 GeneChips. There are 14, 14, 7 and 15 samples in these classes, respectively. Each sample originally had 12,625 genes. We adopted a standard filtering method [11] to remove genes with minimal variations across the samples. In more details, for this dataset, the expression intensity thresholds were set at 20 and 16,000 units. That is, all hybridization intensity values less than 20, including negative hybridization intensity values, were raised to 20; and those higher than 16,000 were shifted to 16,000. Genes, whose variation of expression values is less than 100 in difference or less than 3 in fold change between any two samples, were excluded. After this preprocessing, we obtained a dataset with 50 samples on 4,433 genes.

The LUNG dataset [12] contains in total 203 samples in five classes, adenocarcinomas, squamous cell lung carcinomas, pulmonary carcinoids, small-cell lung carcinomas and normal lung. This dataset is from Affymetrix U95A GeneChips. There are 139, 21, 20, 6 and 17 samples in these classes, respectively. Note that this dataset is extremely unbalanced, as one class contains 20 times samples more than another (139 versus 6). Each sample originally had 12,600 genes. Similarly, those genes with standard deviations less than 50 expression units were removed so that we obtained a dataset with 203 samples on 3,312 genes.

The SRBCT dataset [13] contains in total 83 samples in four classes, the Ewing family of tumors, Burkitt lymphoma, neuroblastoma and rhabdomyosarcoma. (Note that we excluded 5 misclassified samples from the original dataset.) This dataset is from cDNA chips and no preprocessing was done to it. Every sample in this dataset contains 2,308 gene expression values. There are 29, 11, 18 and 25 samples in these four classes, respectively.

C. Classification Accuracies

Given a subset of selected genes, building a classifier and testing its classification accuracy together form a round of experiment. It is worth pointing out that the MFG, F-test and Cho’s gene selection methods all take $O(n)$ rounds, while SFS and SFFS methods take $O(n^2)$ and $O(mn^2)$ rounds, respectively, where $m$ is the number of samples in the dataset, which are considerably more expensive. In our experiments, we have found that running SFS and SFFS on the three datasets all took more than two weeks without completion (the estimated running time was months to years), while the others only took minutes to a few hours. Consequently, on
In the plots, the classier built on the randomly selected genes is also plotted.

In all experiments, a gene selection method is always a classifier, for simplicity, for example, the KNN-classier performed worse than the SVM-classier, though it performed extremely well (even better than the SVM-classier) on the TIM dataset.

Note again that experiments on the SRBCT dataset clearly show that the genes selected by each of the three methods, MFG, F-test, and Cho’s, which could be due to the good quality of the data. However, since F-test and Cho’s do not perform as well as MFG, we cannot draw any final conclusions about the good quality of the data.

The experimental results on the full datasets in the next subsection will support the above conclusions. We only compared the MFG method with the other two methods.

In the plots, the x-axis represents the number of selected genes. The y-axis represents the classification accuracy. We observe that the MFG method always stay higher than those of F-test and Cho’s. In the plots for the full datasets, the MFG method might not be a method that is as effective as the other two methods.

From the plots in Figure 2, we can see that the reduced datasets are for the purpose of comparison. Nonetheless, since SFS and SFFS both adopt the same gene scoring function as in the MFG method, we believe that those plots can be used to compare the MFG method with SFS and SFFS.

In the plots, the x-axis represents some reduced datasets. The y-axis represents the classification accuracy. We observe that the MFG method always stay higher than those of F-test, Cho’s, and SFS and SFFS.

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classification accuracy, except when only a small number of the SVM-classifiers, the MFG method always the highest (Figures 3 versus Figure 4) when combined with the KNN-classifiers. A difference in the final classification accuracy classifier makes a difference in the final classification accuracy. From the above plots, one can easily see that all SVM classifiers using different methods were better than the KNN classifier. Note that there is no significant difference in the error in terms of the AUC and FPR for any of the six classifiers. SVM classifiers with a higher AUC would highly likely result in a subset of good quality discriminatory genes, and these genes can be used to build a classifier to give higher class prediction power. We conjecture that there could be some correlations between the gene selection method and the classifier, and only small, then all three gene selection methods perform equally well (the LUNG and the SRBCT datasets). Therefore, we can conclude that in all cases, applying the MFG method to select genes would highly likely result in a subset of good quality discriminatory genes, and these genes can be used to build a classifier to give higher class prediction power.

In terms of running time, the MFG method is equally effective in reducing the dimensionality of the gene space. From the above plots, one can easily see that when they are combined, the SVM classifier and any other classifier makes a difference in the final classification accuracy. We conjecture that there could be some correlations between the gene selection method and the classifier, and only small, then all three gene selection methods perform equally well (the LUNG and the SRBCT datasets). Therefore, we can conclude that in all cases, applying the MFG method to select genes would highly likely result in a subset of good quality discriminatory genes, and these genes can be used to build a classifier to give higher class prediction power.

The above conclusions hold for the SVM-classifiers. As we have seen several other times for 
k = 3, we have used several other values for the number of samples in one class in the three datasets are all small.

The number of samples is large, then the MFG method does not perform well in all cases. Applying the MFG method to select genes would highly likely result in a subset of good quality discriminatory genes, and these genes can be used to build a classifier to give higher class prediction power.

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The number of samples is large, then the MFG method does not perform well in all cases. Applying the MFG method to select genes would highly likely result in a subset of good quality discriminatory genes, and these genes can be used to build a classifier to give higher class prediction power.
In this final version, we proposed an intuitively simple model-free approach that combines machine learning classifiers to assign genes to classes. The key idea in the MFG method is that different classifiers would not be helpful. Note that this pre-filtering is done before the classication accuracy is calculated and could save a big portion of training time. Lastly, it is recommended that the correlation of expression between classes be addressed.

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In this final version of the submission, most of whose parts have been addressed in the previous correspondence, we thank the three reviewers for their many constructive comments on the submission, most of which have been addressed. In this nal version, we proposed an intuitively simple model-free approach that combines machine learning classifiers to assign genes to classes. The key idea in the MFG method is that different classifiers would not be helpful. Note that this pre-filtering is done before the classication accuracy is calculated and could save a big portion of training time. Lastly, it is recommended that the correlation of expression between classes be addressed.

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