Comparing Prediction Accuracy for Machine Learning and Other Classical Approaches in Gene Expression Data

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Abstract

Microarray based gene expression profiling has been emerged as an efficient technique for cancer classification, as well as for diagnosis, prognosis, and treatment purposes. The classification of different tumor types is of great significance in cancer diagnosis and drug innovation. Using a large number of genes to classify samples based on a small number of microarrays remains a difficult problem. Feature selection techniques can be used to extract the marker genes which influence the classification accuracy effectively by eliminating the unwanted noisy and redundant genes. Quite a number of methods have been proposed in recent years with promising results. But there are still a lot of issues which need to be addressed and understood. Diagonal discriminant analysis, regularized discriminant analysis, support vector machines and k-nearest neighbor have been suggested as among the best methods for small sample size situations. In this paper, we have compared the performance of different discrimination methods for the classification of tumors based on gene expression data. The methods are applied to datasets from four recently published cancer gene expression studies. The performance of the classification technique has been evaluated for varying number of selected features in terms of misclassification rate using hold-out cross validation. Our study shows that KNN, RDA and SVM with linear kernel methods have lower misclassification rate than the other algorithms.
Keywords: microarray, gene expression, KNN, DLDA, RDA, SVM

1 Introduction and objectives:

Conventional methods of monitoring and diagnosing cancer rely on a human observer to detect certain features. Cancer diagnosis is usually achieved using an imaging system, such as X-ray, Magnetic Resonance Imaging (MRI), Computed Tomography (CT), and ultrasonography. Microarray technology is a new tool that can automate the diagnostic task and improve the accuracy of the traditional diagnostic techniques (Sarhan, 2009). The classification of DNA micro array data allows the discovery of hidden patterns in expression profiles and opens possibility for accurate cancer classification which has great value in providing better treatment and toxicity minimization on the patients. The gene expression profiles that are obtained from particular microarray experiments have been widely used for differentiating normal or different cancerous states by using selected informative genes (Chuang, 2011). However, studying microarray dataset brings about some complexity due to the huge number of features that contribute to a profile as compared to the very low number of samples. Another challenge is the presence of biological or technical noise in the dataset, which further affects the accuracy of the experimental results. In practice, it has been observed that a large number of features may degrade the performance of classifiers if the number of training samples is small relative to the number of features (Jain, 2000). There are two main procedures in gene expression data classification task: feature selection and classification. Several gene selection methods have been developed to select these predictive genes, such as t-statistics, information gain, towing rule, the ratio of between-groups to within-groups sum of squares (BSS/WSS), Principal Component Analysis (PCA), and Genetic Algorithm (GA). Different classification methods from statistical and machine learning area have been applied to cancer classification such as Fisher Linear Discrimination Analysis (FLDA), Diagonal Discriminant Analysis (DLDA), Regularized Discriminant Analysis (RLDA), Maximum Likelihood Discriminant Rules, Classification Tree, Support Vector Machine (SVM), K-Nearest Neighbor (KNN), and the aggregating classifiers.
Following are the objectives of our study:

- To examine the classification performance of the selected supervised algorithms using delete-d method;
- To reveal the effect of gene selection on different classification methods.

2 Theoretical backgrounds:

2.1 KNN: KNN is a distance-based approach for classification. In order to classify an observation X in the test set, KNN takes the following steps: (i) select an integer K (i.e., by cross-validation) and find the K closest observations in the training set; (ii) classify the observation by majority vote, that is, choose the class that is most

common among those K neighbors (Dudoit et al., 2002; Speed, 2003). The KNN method is the simplest, yet useful approach to general pattern classification. Its error rate has been proven to be asymptotically at most twice that of the Bayesian error rate (R.O. Duda, 2002). However, its performance deteriorates dramatically when the input data set has a relatively low local relevance (J.H. Friedman, 1994).

2.2 DLDA: Diagonal Linear Discriminant Analysis (Dudoit, 2002) is a simplification of classical LDA, which applies the common diagonal covariance matrix to all classes. It is computationally more efficient than other LDA-based algorithms. Interestingly, the "weighted voting scheme" for binary classification proposed by T.R.Golub (1999) can be shown to be a variant of DLDA.

2.3 RDA: Classical Linear Discriminant Analysis (LDA) is not applicable for small sample size problems due to the singularity of the scatter matrices involved. Regularized LDA (RLDA) provides a simple strategy to overcome the singularity problem by applying a regularization term, which is commonly estimated via cross-validation from a set of candidates (Ye, J., 2006). RDA is better able to extract the relevant discriminatory information from training data than the other classifiers tested, thus obtaining a lower error rate (Pima & Aladjem, 2004). The RDA combines strengths of linear discriminant analysis (LDA) and quadratic discriminant analysis (QDA). It solves the small sample size and ill-posed problems suffered from QDA and LDA through a regularization technique (Lee et al., 2010).

2.4 SVM: The SVM has been shown to give superb performance in binary classification tasks. Intuitively, SVM aims at searching for a hyperplane that separates the two classes of data with largest margin which is the distance between the hyperplane and the point closest to it). For multiclass SVM, there are many decomposition techniques that can adapt SVM to identify non-binary class divisions such as one-versus-the rest, pair wise comparison, and error-correcting output coding. SVM was used by Park and Cho (2003) and Li et al. (2004).

3 Microarray Datasets

Four publicly available microarray data sets are used for this study, with sample sizes ranging from 38 to 102 and numbers of genes ranging from 2,308 to 6033. Gene expression values for all the datasets are available from the Bioconductor libraries.

A. Leukemia: This dataset contains gene expression (3051 genes and 38 tumor mRNA samples) levels of n =38 patients either suffering from acute lymphoblastic leukemia (ALL, 27 cases) or acute myeloid leukemia (AML, 11 cases) where ALL and AML classes are coded in 1 and 2 respectively. It was obtained from Affymetrix oligonucleotide microarrays. Following the protocol in Dudoit et al. (2002), it was preprocessed by thresholding, filtering, a logarithmic transformation and standardization, so that the data finally comprise the expression values of p=3051 genes. The data are described in Golub et al. (1999) and can be freely downloaded from http://www-genome.wi.mit.edu/MPR/.

B. Lymphoma: The lymphoma dataset consists of 42 samples of diffuse large B-cell lymphoma (DLBCL), 9 samples of follicular lymphoma (FL), and 11 samples of chronic lymphocytic leukemia (CLL). DBLCL, FL, and CLL classes are coded in 1, 2, and 3, respectively. The total sample size is n=62, and the expression of p =4026 well-measured genes, preferentially expressed in lymphoid cells or with known immunological or oncological importance is documented. Matrix of gene expression data and arrays were normalized, imputed, log transformed, and standardized to zero mean and unit variance across genes as described in Dettling (2004) and Dettling and Beuhlmann (2002). More information on these data can be found in Alizadeh et al. (2000) and can be freely downloaded from http://llmpp.nih.gov/lymphoma

C. SRBCT: This gene expression data (2308 genes for 83 samples) obtained from the microarray experiments of Small Round Blue Cell Tumors (SRBCT) of childhood cancer study. This data set contains 83 samples with 2308 genes: 29 cases of Ewing sarcoma (EWS), 11 cases of Burkitt lymphoma (BL), 18 cases of neuroblastoma (NB), 25 cases of rhabdomyosarcoma (RMS). A total of 63 training samples and 25 test samples are provided in Khan et al. (2001) and was obtained from cDNA microarrays. Five of the test set are non-SRBCT and are not considered here. The training sample indexes correspond to 1to 65 and the test sample indexes (without non-SRBCT sample) correspond to 66 to 83. Each tissue sample is associated with a thoroughly preprocessed expression profile of p= 2,308 genes, already standardized to zero mean and unit variance across genes. Data can be freely downloaded from http://www.thep.lu.se/pub/Preprints/01/lu_tp_01_06_supp.html.

D. Prostate: The prostate dataset consists of 52 prostate tumor and 50 normal samples and obtained using the Affymetrix technology. Normal and tumor classes are coded in 1 and 2, respectively. Matrix of gene expression data and arrays were normalized, log transformed, and standardized to zero mean and unit variance across genes as described in Dettling (2004) and Dettling and Beuhlmann (2002). More information on these data can be found in Chung and Keles (2010) and can be freely downloaded from http://www-genome.wi.mit.edu/cancer.

4 Experimental Results and Discussions:

For the classification job, we have started with the gene expression values existing for cancer disease samples obtained from the DNA microarray experiments. For identifying genes responsible for the classification of different tumor types, the available dataset were divided into two groups: one used for the training purpose and the other used for the testing purpose. The training set of data is utilized for learning the parameters of the classifier, while the test set of data is utilized to measure the misclassification rate.

The essential idea of hold-out cross validation is to split the sample data into separate train and test datasets (Webb, 2002). The classifier is trained on the training set, and its performance is estimated by applying it to the test set. The selection of the train and test sets is done randomly, and the selected proportions are usually 70% for training and 30% for testing. The major disadvantage of this procedure is that the classifier is unable of making use of all data for training; however, if the sample size is large enough this could be accommodated. (Jain et al., 2000).

4.1 Results: To study the impact of the selected gene number on the four classification algorithms, we compare their performances when different numbers of genes are used in the classification. For each data set, experiments are carried out with feature size 50, 200, 500, 1000 and full dataset. We choose the most discriminatory genes according to t-test (two groups) and ANOVA (more than two groups).To reduce the variability each experiment is repeated 500 times, and the average test error rates and their standard variances over the 500 experiments are reported. We now present our experimental results for the four classifiers (KNN, SVM, DLDA, and RDA) with four data sets.

Number selected of genes=50

Method／ Dataset		Leukemia	Lymphoma	SRBCT	Prostate
KNN		0.082(0.062)	0.353(0.056)	**0.284(0.092)**	0.165(0.059)
DLDA		0.098(0.085)	0.551(0.093)	0.459(0.096)	0.267(0.091)
RDA		0.093(0.080)	0.277(0.062)	0.415(0.083)	**0.080(0.041)**
Kernels for SVM	Linear	**0.063(0.066)**	0.447(0.099)	0.333(0.086)	0.109(0.044)
	Polynomial	0.299(0.036)	0.328(0.015)	0.545(0.059)	0.375(0.073)
	Radial	0.115(0.067)	0.297(0.030)	0.353(0.063)	0.098(0.041)
	Sigmoid	0.071(0.061)	**0.249(0.038)**	0.369(0.060)	0.104(0.052)

Table 4.1: *The average misclassification rates(%) and standard deviation based on 500 random partitions into training sets and test set by using delete-d method (where d=0.33) for 50 top ranked genes.*

Number selected of genes=200

Method／ Dataset		Leukemia	Lymphoma	SRBCT	Prostate
KNN		0.014(0.034)	0.333(0.00)	0.276(0.080)	0.232(0.068)
DLDA		0.005(0.021)	0.584(0.088)	0.377(0.097)	0.351(0.071)
RDA		0.070(0.085)	0.261(0.061)	**0.209(0.100)**	**0.065(0.042)**
Kernels for SVM	Linear	**0.002(0.013)**	0.517(0.099)	0.266(0.084)	0.089(0.038)
	Polynomial	0.283(0.044)	0.332(0.005)	0.597(0.044)	0.399(0.061)
	Radial	0.073(0.063)	0.281(0.033)	0.326(0.064)	0.119(0.055)
	Sigmoid	0.002(0.014)	**0.233(0.033)**	0.334(0.064)	0.175(0.060)

Table 4.2: *The average misclassification rates(%) and standard deviation based on 500 random partitions into training sets and test set by using delete-d method (where d=0.33) for 200 top ranked genes.*

Number selected of genes=500

Method／ Dataset		Leukemia	Lymphoma	SRBCT	Prostate
KNN		**0.003(0.016)**	0.334(0.007)	0.212(0.081)	0.226(0.071)
DLDA		0.006(0.021)	0.556(0.091)	0.339(0.094)	0.355(0.089)
RDA		0.071(0.086)	0.257(0.065)	**0.202(0.089)**	0.072(0.043)
Kernels for SVM	Linear	0.004(0.017)	0.453(0.101)	0.217(0.079)	**0.066(0.036)**
	Polynomial	0.277(0.043)	0.333(0.000)	0.593(0.042)	0.285(0.091)
	Radial	0.086(0.073)	0.265(0.040)	0.324(0.055)	0.132(0.057)
	Sigmoid	0.004(0.016)	**0.231(0.033)**	0.282(0.059)	0.204(0.066)

Table 4.3: *The average misclassification rates(%) and standard deviation based on 500 random partitions into training sets and test set by using delete-d method (where d=0.33) for 500 top ranked genes.*
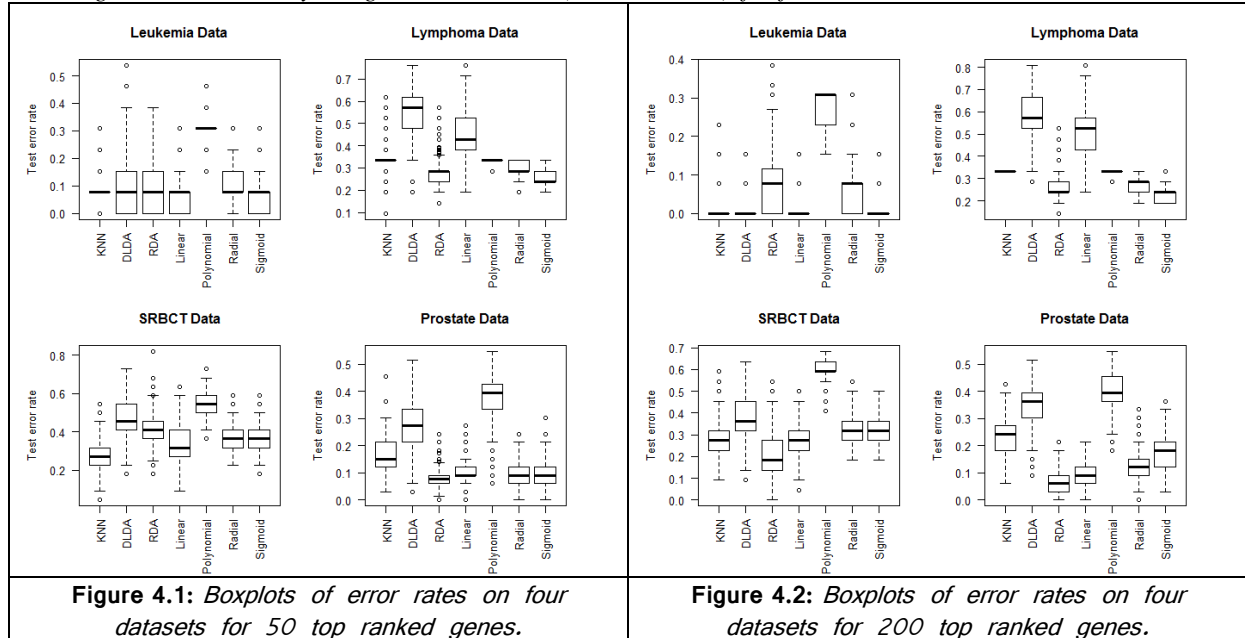
Number selected of genes=1000

Method／ Dataset		Leukemia	Lymphoma	SRBCT	Prostate
KNN		**0.003(0.014)**	0.335(0.020)	0.210(0.089)	0.197(0.066)
DLDA		0.013(0.030)	0.336(0.103)	0.265(0.096)	0.339(0.095)
RDA		0.066(0.077)	0.184(0.075)	**0.120(0.082)**	0.072(0.040)
Kernels for SVM	Linear	0.003(0.015)	**0.165(0.075)**	0.138(0.070)	**0.060(0.034)**
	Polynomial	0.281(0.040)	0.333(0.000)	0.603(0.041)	0.230(0.096)
	Radial	0.070(0.058)	0.231(0.047)	0.315(0.058)	0.115(0.052)
	Sigmoid	0.006(0.020)	0.217(0.033)	0.225(0.054)	0.215(0.068)

Table 4.4: *The average misclassification rates(%) and standard deviation based on 500 random partitions into training sets and test set by using delete-d method (where d=0.33) for 1000 top ranked genes.*

Number of selected genes= full dataset

Method／ Dataset		Leukemia	Lymphoma	SRBCT	Prostate
KNN		0.025(0.042)	0.024(0.030)	0.079(0.059)	0.186(0.063)
DLDA		0.028(0.042)	0.017(.023)	0.075(0.058)	0.376(0.099)
RDA		0.075(0.083)	0.034(0.048)	**0.032(0.039)**	**0.045(.048)**
Kernels for SVM	Linear	**0.008(0.025)**	**0.004(0.013)**	0.033(0.036)	0.095(0.041)
	Polynomial	0.307(0.005)	0.132(0.043)	0.528(0.103)	0.369 (0.063)
	Radial	0.268(0.053)	0.029(0.036)	0.151(0.074)	0.129(0.057)
	Sigmoid	0.014(0.031)	0.005(0.015)	0.050(0.045)	0.140(0.063)

Table 4.5: *The average misclassification rates(%) and standard deviation based on 500 random partitions into training sets and test set by using delete-d method (where d=0.33) for full dataset.*
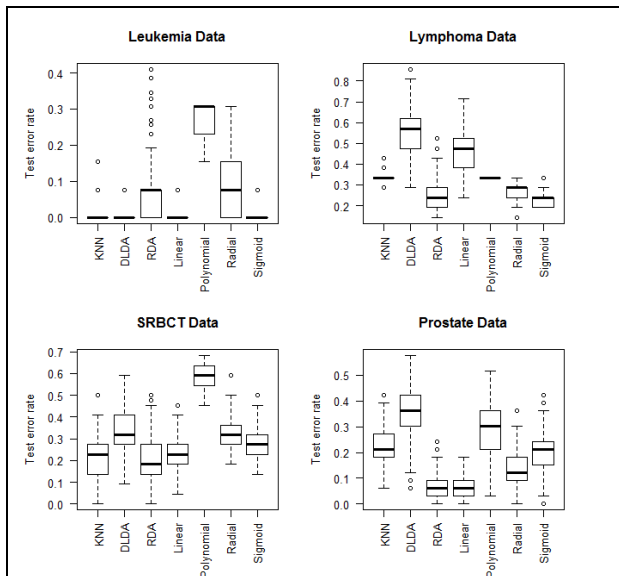

Figure 4.1: *Boxplots of error rates on four datasets for 50 top ranked genes.*	**Figure 4.2:** *Boxplots of error rates on four datasets for 200 top ranked genes.*

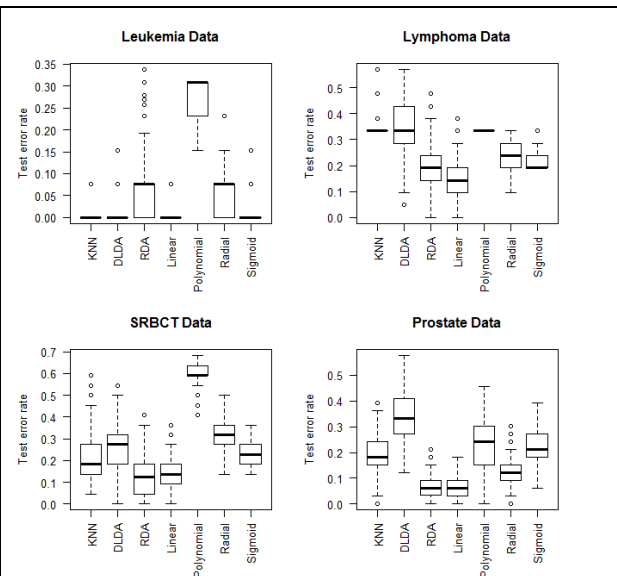**Figure 4.3:** *Boxplots of error rates on four datasets for 500 top ranked genes.*

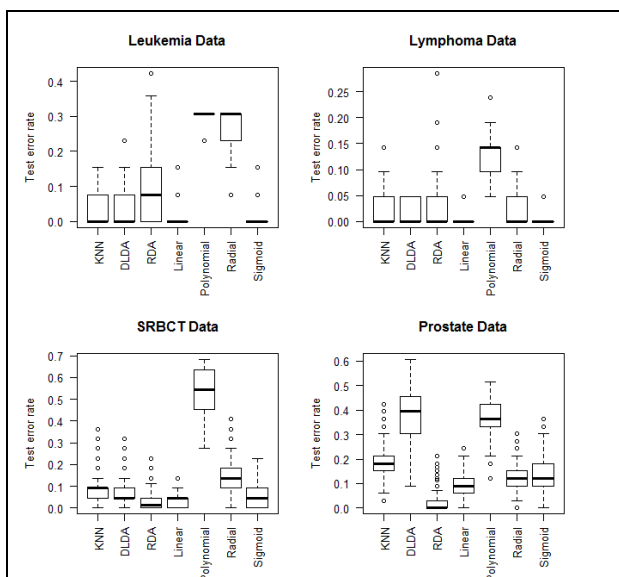**Figure 4.4:** *Boxplots of error rates on four datasets for 1000 top ranked genes.*

Figure 4.5: *Boxplots of error rates on four datasets for full dataset.*

4.2 Discussions: Table 4.1 & Figure 4.1 reveals that, although data points are less disperse for SVM with sigmoid kernel and KNN than SVM with linear kernel but on an average it is better to choose linear (6.3%) kernel because it has lower average misclassification rate than the other classifiers. For lymphoma data, SVM with sigmoid (24.1%) kernel gives the best performance. For SRBCT data, KNN (28.4%) obtains the lowest average misclassification rates and for prostate data, RDA (8.0%) achieves the lowest average misclassification rate among all the classifiers

We see from Table 4.2 and Figure 4.2, on an average it is better to choose SVM with linear (0.2%) kernel function for leukemia data because it achieves the lowest misclassification rate with minimum standard deviation. For lymphoma data, it is observed that SVM with sigmoid kernel function achieves the lowest misclassification rate 23.3%. With SRBCT & prostate data RDA obtains lower average misclassification rate than the other classifiers i.e. 20.9% & 6.5%, respectively.

In Table 4.3 and Figure 4.3, on an average it is better to select KNN (0.3%) which obtains the lowest average misclassification rate. For lymphoma data, SVM with sigmoid (23.1%) kernel function & for SRBCT data RDA (20.2%) yield better result than the others techniques. SVM with linear (6.6%) kernel function achieves the lowest average misclassification rate with minimum standard deviation for prostate data.

In Table 4.4 and Figure 4.4, on an average it is better to use KNN (0.3%) & SVM with linear (0.3%) kernel because they obtain the lowest average misclassification rate. For lymphoma & prostate data SVM with linear kernel functions achieves smaller misclassification rate than others i.e. 16.5% & 6%, respectively. With 1000 top genes RDA (12%) achieves the lowest misclassification rate for SRBCT data.

Table 4.5 represents the average misclassification rate & standard deviation. Figure 4.5 shows the illustration of these results for full datasets. For leukemia & lymphoma datasets, on an average SVM with linear kernel gives

the lowest misclassification rate 0.8% & 0.4%, respectively. For SRBCT & prostate data, RDA achieves the lowest misclassification rate i. e. 3.2% & 4.5%, respectively.

The aim of our exertion was the comparative evaluation of four most used statistical analyses (nearest-neighbor, diagonalized linear discriminant analysis, regularized discriminant analysis & support vector machine with different kernel functions)by testing them on published datasets and measuring their misclassification rate given by hold-out cross validation. Now we briefly addressed the effects of variable selection on the relative performance of the classifiers.
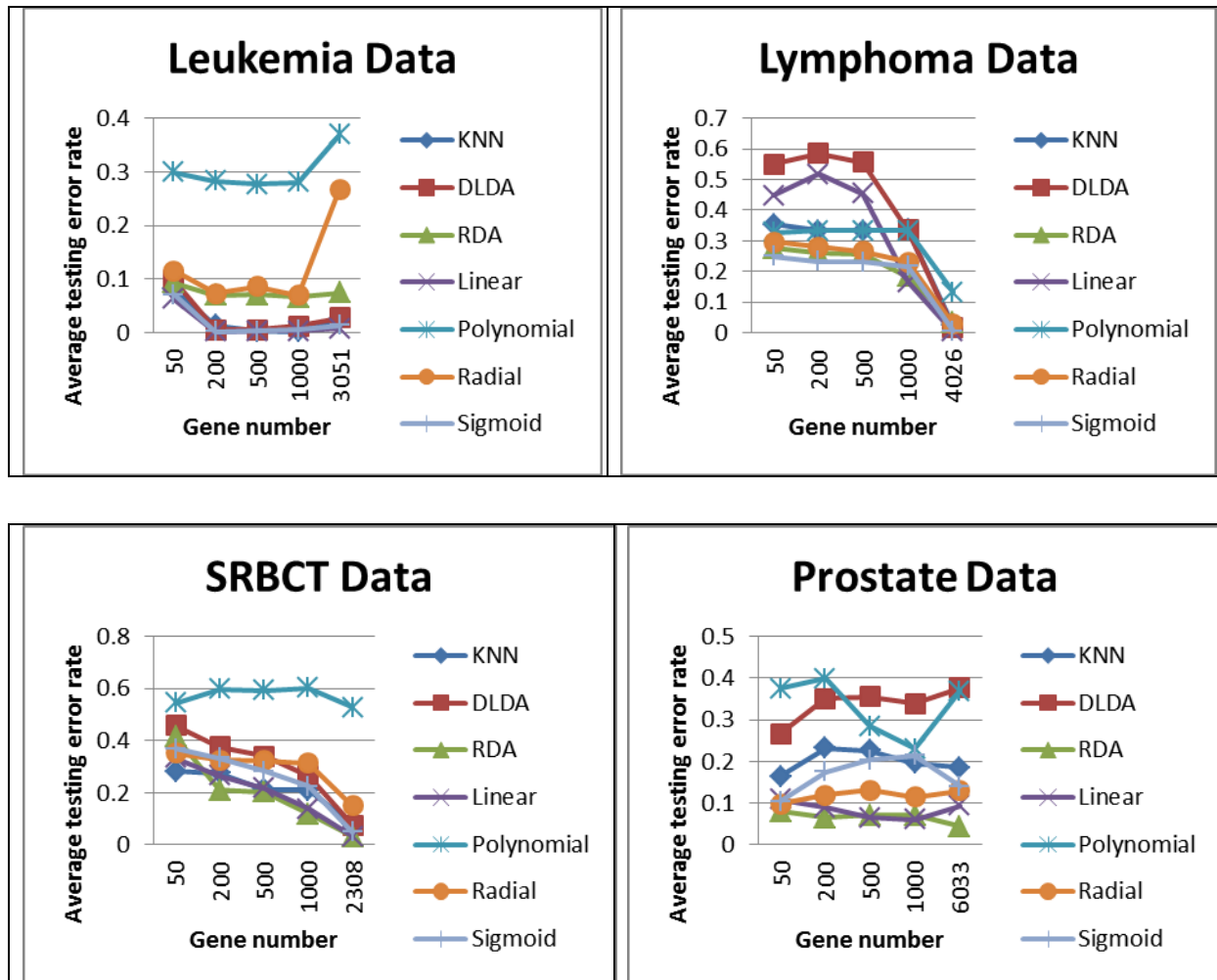

Figure 5.5: *Misclassification trend of the selected statistical technologies on leukemia, lymphoma, SRBCT and prostate gene expression dataset.*

We have observed that all the classifiers show stable results except SVM with polynomial & radial kernel for leukemia data. But for lymphoma and SRBCT data, almost all the selected techniques express different misclassification rates at different numbers of genes. In prostate data, on the contrary, all the chosen statistical algorithms perform better i.e. more or less stable results except SVM with polynomial kernel.

Here, KNN (0.2%) technique reaches its minimum value of misclassification with a selection of top 1000 genes among four datasets. DLDA (0.5%) algorithm gains its minimum value of misclassification with a selection top 200 features among four datasets. RDA (3.2%) technique achieves the lowest misclassification with a selection of more than 2000 genes among four datasets. SVM with linear (0.2%) & sigmoid (0.2%) kernel functions reaches their minimum value of misclassification with a selection of top 200 features. On the other hand, radial (2.9%) & polynomial (13.2%) kernel functions reach their minimum value of misclassification (2.9%) with a selection of more than 4000 features among four datasets.

5 Conclusions:

In this paper, we have shown the comparative results of SVM using different kernels, KNN, DLDA and RDA on four different datasets. Here, we have attempted to explore the best choice among KNN, DLDA, RDA and SVM with different kernel functions. The selected kernels are linear, polynomial, radial basis function (RBF) and sigmoid kernels. Then, focusing on feature selection, we have compared the classification techniques for varying number of selected features and explore the most suitable method in each situation. For different number of informative genes, we have found that KNN, RDA and SVM with linear kernel function achieve the lowest misclassification rate most of the cases. Sometimes other algorithms have provided the lowest misclassification rate. The misclassification rate of the methods has fluctuated when different numbers of informative genes were used.

Through these analyses, we can conclude that classification using gene expression data provides a promising future for cancer research.

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