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HOW TO USE BOOSTING FOR TUMOR CLASSIFICATION WITH GENE EXPRESSION DATA

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HOW TO USE BOOSTING FOR TUMOR CLASSIFICATION WITH GENE EXPRESSION DATA

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Abstract

Motivation: Microarray experiments generate large datasets with expression values for thousands of genes but not more than a few dozens of samples. Accurate supervised classification of tissue samples in such high-dimensional problems is difficult but often crucial for successful diagnosis and treatment. A promising way to meet this challenge is by using boosting in conjunction with decision trees.

Results: We demonstrate that the generic boosting algorithm needs some modifications to become an accurate classifier in the context of gene expression data. In particular, we present a feature preselection method, a more robust boosting procedure and a new approach for multi-categorical problems. This allows for slight to drastic increase in performance and yields competitive results on several publicly available datasets.

Availability: Software for the modified boosting algorithms as well as for decision trees is available for free in *R* at <http://stat.ethz.ch/~dettling/boosting>.

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1 Introduction

The recently developed microarray technology allows for measuring expression levels of thousands of genes simultaneously. We focus on the case where the experiments monitor gene expression values of different individuals or tissue samples, and where each experiment is equipped with an additional categorical outcome variable describing a cancer (pheno)type. In such a supervised setting, our goal is to predict the unknown class label of a new individual on the basis of its gene expression profile, since precise diagnosis of cancer type is often crucial for successful treatment. Given the availability of efficient classification techniques, bio-molecular information could become as, or even more important than traditional clinical factors.

Classification of different phenotypes, predominantly cancer types, using microarray gene expression data has been considered by Golub et al. (1999), Alon et al. (1999), Ben-Dor et al. (2000), Furey et al. (2000), Slonim et al. (2000), Dudoit et al. (2001), West et al. (2001) and Zhang et al. (2001), among others. The methods used in these studies range from classical discriminant analysis over Bayesian approaches and clustering methods to flexible tools from machine learning such as bagging, boosting and support vector machines. Explicitly, boosting decision trees has been applied for the classification of gene expression data in Ben-Dor et al. (2000) and Dudoit et al. (2001). Both studies compare the original AdaBoost algorithm that was proposed by Freund & Schapire (1997) against other classifiers, and both recognize that boosting does not yield very impressive results.

In this paper we demonstrate that the performance of boosting for classification of gene expression data can often be drastically improved by modifying the algorithm as follows: First, we perform feature preselection with the nonparametric scoring method of Park et al. (2001). Then, we apply the LogitBoost procedure introduced by Friedman et al. (2000) instead of the AdaBoost procedure, since the former usually performs better on noisy data or when there are misspecifications or inhomogeneities of the class labels in the training data, which is frequently the case with microarray gene expression data. Finally, if discrimination has to be done for more than two tumor types, we reduce multiclass to multiple binary problems so that different gene subsets and different model complexity for discriminating different tumor types are allowed. This multiclass approach turns out to be much more accurate than the direct multiclass LogitBoost algorithm of Friedman et al. (2000). On six publicly available datasets and with a simulation study we show that the sum of these modifications leads to a classification procedure which performs very competitively, does not require sophisticated fine tuning and is fairly easy to implement.

2 Methods

2.1 The Stochastic framework

We assume that we are given n training data pairs

$$(x_1, y_1), \dots, (x_n, y_n), \text{ with } x_i \in \mathbb{R}^p \text{ and } y_i \in \{0, \dots, J-1\},$$

which are independent and identically distributed realizations of a random vector (X, Y) . The interpretation is that the feature or input vector X models the p -dimensional gene

expression profile and the response or output variable Y denotes the class label. Today, the sample size n is typically in the range of 20 to 80 and the number of monitored genes p varies between 2'000 and 20'000.

In the standard classification problem, the goal is to predict the class label Y , based on the expression vector X . This amounts to construct a classifier function

$$\mathcal{C} : X \mapsto \mathcal{C}(X) \in \{0, \dots, J-1\},$$

which can subsequently be used to predict the unknown class label of a *new* tissue sample based on its expression vector. The optimal classifier is such that the misclassification risk

$$\mathbb{P}[\mathcal{C}(X) \neq Y] \text{ is minimal.} \quad (2.1)$$

Note that this quantity is most often different from zero. The solution of (2.1) requires knowledge of the true, but generally inaccessible conditional probability distribution $\mathbb{P}[Y = j|X]$ and is called *Bayes classifier*,

$$\mathcal{C}_{Bayes}(X) = \operatorname{argmax}_{j \in \{0, \dots, J-1\}} \mathbb{P}[Y = j|X]. \quad (2.2)$$

In practice, it can be constructed via estimated conditional probabilities $\hat{\mathbb{P}}[Y = j|X]$. This is a classical task for $p \ll n$, but expression data with many more features than samples ($p \gg n$) create a new challenge. A promising way to meet it is by using boosting in conjunction with decision trees.

2.2 Binary Classification of Gene Expression Data

We focus first on binary problems with response $Y \in \{0, 1\}$. The best way to handle multi-categorical problems is explained later in section 2.3.

2.2.1 Feature Preselection

The intrinsic problem with classification from microarray data is that sample size n is much smaller than the dimensionality of the feature space, i.e. the number of genes p . Many genes are non-differentially expressed across the samples and irrelevant for phenotype discrimination. Dimensionality reduction of the feature space has been performed by many authors, see for example Golub et al. (1999), Ben-Dor et al. (2000) and Dudoit et al. (2001), among others. It drastically eases the computational burden and for many problems improves class prediction due to the reduced amount of noise. Our feature selection is based on scoring each individual gene g , with $g \in \{1, \dots, p\}$, according to its strength for phenotype discrimination. We use a nonparametric method that is based on ranks and was presented by Park et al. (2001). It is in fact equivalent to the test statistic of Wilcoxon's two sample test,

$$\text{Score}(g) = s(g) = \sum_{i \in \mathcal{N}_0} \sum_{j \in \mathcal{N}_1} 1_{[x_j^{(g)} - x_i^{(g)} \leq 0]},$$

where $x_i^{(g)}$ is the expression value of gene g for individual i and \mathcal{N}_m represents the set of the n_m indices $\in \{1, \dots, n\}$ having response in $m \in \{0, 1\}$. The score function can

be interpreted as counting for each individual having response value zero, the number of instances with response one that have smaller expression values, and summing up these quantities. This captures to what extent a gene g discriminates the response categories and it is easy to notice that both values near the minimum score zero and the maximum score n_0n_1 indicate a differentially expressed, informative gene. The quality measure

$$q(g) = \max(s(g), n_0n_1 - s(g))$$

thus gives the highest values to those genes whose expression levels have the best strength for phenotype discrimination. We then simply take the $\tilde{p} \leq p$ genes with the highest values of $q(g)$ as our top features and restrict the boosting classifier to work with this subset. The number of predictor variables is a tuning parameter whose optimal value varied across different datasets. A formal choice of \tilde{p} is possible via cross validation on the training data or by bootstrap methods and significance testing as in Park et al. (2001).

Many more variable selection criteria for gene expression data have been proposed in the literature. We tried the methods of Golub et al. (1999), Ben-Dor et al. (2000) and Dudoit et al. (2001). We observed that their gene subsets strongly overlap with ours, and that they produced similar effects on the performance. In our experience, the quickly computable and simple score criterion shows very good overall performance, but other criteria may be similarly accurate.

2.2.2 Binary LogitBoost with Decision Trees

Boosting, first introduced by Freund & Schapire (1996) has been found to be a powerful classification technique with remarkable success on a wide variety of problems, especially in higher dimensions. It aims at producing an accurate combined classifier from a sequence of *weak* (or *base*) classifiers, which are fitted to iteratively reweighted versions of the data. In each boosting iteration m , with $m \in \{1, 2, \dots, M\}$, the observations that have been misclassified at the previous step have their weights increased, whereas the weights are decreased for those that were classified correctly. The m th weak classifier $f^{(m)}$ is thus forced to focus more on individuals that have been difficult to classify correctly at earlier iterations. The combined classifier is equivalent to a weighted majority vote of the weak classifiers for shifted labels $\in \{-1, 1\}$,

$$\mathcal{C}^{(M)}(X) = \text{sign} \left(\sum_{m=1}^M \alpha_m f^{(m)}(X) \right).$$

Three elements need to be chosen: (i) the type of weak learners $f^{(m)}$, (ii) the reweighting of the data and the aggregation weights α_m , and (iii) the number of boosting iterations M . Regarding issue (i), we exclusively focus on decision trees, see Breiman et al. (1984). These are the most popular learners in conjunction with boosting. In fact, we even further restrict here to *stumps*, which are trees with two terminal nodes only, since in the context of gene expression data, this always yielded better or equal performance than boosting larger trees. Concerning issue (ii), the reweighting of the data and the choice of aggregation weights can be coherently motivated by the principle of functional gradient descent (Breiman, 1999; Friedman et al., 2000), from which several versions of boosting for classification emerge. We build here on the LogitBoost introduced by Friedman et al. (2000): compared to

AdaBoost, it seems more robust in noisy problems where the misclassification risk of equation (2.1) is substantial, and also in situations where mislabeled training data points or inhomogeneities in the training samples are present, all of which can be the case with gene expression data, see Hastie et al. (2001). Finally regarding (iii), the choice of the stopping parameter is often neglected and the boosting process is stopped at a usually large, but arbitrarily fixed number of iterations. Alternatively, we consider an empirical approach for the choice of M in the next section. The binary LogitBoost with decision stumps as weak learner works then as follows:

Step 1: Initialization

Start with an initial committee function $F^{(0)}(x) \equiv 0$ and initial probabilities $p^{(0)}(x) \equiv 1/2$; $p(x)$ is an abbreviation for $\hat{\mathbb{P}}[Y = 1|X = x]$.

Step 2: LogitBoost iterations

For $m = 1, 2, \dots, M$ repeat:

A. Fitting the weak learner

(i) Compute working response and weights for all $i = 1, \dots, n$

$$w_i^{(m)} = p^{(m-1)}(x_i) \cdot \left(1 - p^{(m-1)}(x_i)\right),$$

$$z_i^{(m)} = \frac{y_i - p^{(m-1)}(x_i)}{w_i^{(m)}}.$$

(ii) Fit a regression stump $f^{(m)}$ by weighted least squares

$$f^{(m)} = \operatorname{argmin}_{f \in \{\text{stumps}\}} \sum_{i=1}^n w_i^{(m)} (z_i^{(m)} - f(x_i))^2.$$

B. Updating and classifier output

$$F^{(m)}(x_i) = F^{(m-1)}(x_i) + \frac{1}{2} f^{(m)}(x_i).$$

$$\mathcal{C}^{(m)}(x_i) = \operatorname{sign}\left(F^{(m)}(x_i)\right),$$

$$p^{(m)}(x_i) = \left(1 + \exp\left(-2 \cdot F^{(m)}(x_i)\right)\right)^{-1}.$$

To increase understanding of the LogitBoost algorithm, we point out that each committee function $F^{(m)}(x)$ is an estimate of half of the log-odds ratio

$$F(x) = \frac{1}{2} \log \left(\frac{p(x)}{1 - p(x)} \right).$$

LogitBoost thus fits an additive logistic regression model by stagewise optimization of the binomial log-likelihood. More details can be found in Friedman et al. (2000).

A very useful property of our classification method is that it directly yields probability estimates $\hat{\mathbb{P}}[Y = j|X = x]$. This is crucial for constructing classifiers respecting non-equal

misclassification costs. Moreover, it allows to build classifiers which have the option to assign the label “no class” (or “doubt”) for certain regions in the space of gene expression vectors x , see for example Ripley (1996).

An important advantage of LogitBoost compared to methods like neural nets or support vector machines is that it works well without fine tuning and no sophisticated non-linear optimization is necessary. Provided that a decision tree algorithm is available, e.g. versions of CART (Breiman et al., 1984) or C4.5 (Quinlan, 1993), LogitBoost with trees can be implemented very easily. Software for decision trees is widely available: for example for free as an R-Package called `rpart`, at <http://www.stat.math.ethz.ch/CRAN>.

2.2.3 Choice of the Stopping Parameter

The stopping parameter M is often simply fixed at a large number in the range of dozens or hundreds. This, because boosting is generally quite resistant against overfitting so that the choice of M is typically not very critical, see also figure 3.1. An alternative is to use an empirical approach for estimation of M by leave-one-out cross validation on the training data. The idea is to compute the binomial log-likelihood

$$\ell(m) = \sum_{i=1}^n \left(\log \left(\hat{p}^{(m)}(x_i) \right) \cdot 1_{[Y_i=1]} + \log \left(1 - \hat{p}^{(m)}(x_i) \right) \cdot 1_{[Y_i=0]} \right), \quad (2.3)$$

for each boosting iteration m across the samples and to choose the stopping parameter as the m for which $\ell(m)$ is maximal. However empirically, we could not exploit significant advantages of estimated stopping parameters against a choice of $M = 100$ in the gene expression data we considered.

2.3 Reducing Multiclass to Binary

Here we explain how multi-response problems ($J > 2$) can be handled in conjunction with boosting. We recommend to compare each response class separately against all other classes. This *one-against-all* approach for reduction to J binary problems is very popular in the machine learning community, since many algorithms are solely designed for binary problems. It works by defining the response in the j th problem as

$$Y^{(j)} = \begin{cases} 1, & \text{if } Y = j, \\ 0, & \text{else} \end{cases}$$

and running j times the entire procedure including feature preselection, binary LogitBoost and stopping parameter estimation on the data $(x_1, y_1^{(j)}), \dots, (x_n, y_n^{(j)})$. This yields estimates $\hat{\mathbb{P}}[Y^{(j)} = 1|X]$ for $j \in \{0, \dots, J-1\}$, which can be converted into probability estimates for $Y = j$ via normalization,

$$\hat{\mathbb{P}}[Y = j|X] = \frac{\hat{\mathbb{P}}[Y^{(j)} = 1|X]}{\sum_{k=1}^J \hat{\mathbb{P}}[Y^{(k)} = 1|X]}.$$

This expression can be plugged into the Bayes classifier of equation (2.2) and it is easy to see that this yields

$$\mathcal{C}(X) = \operatorname{argmax}_{j \in \{0, \dots, J-1\}} \hat{\mathbb{P}}[Y^{(j)} = 1|X]$$

as our final classifier in multiclass problems. More sophisticated and computationally more expensive approaches for reducing multiclass to binary problems also exist, see Hastie & Tibshirani (1998) or Allwein et al. (2000) for a thorough discussion.

The one-against-all approach allows for different preselected features, different chosen variables for the decision trees in the LogitBoost algorithm, and for different model complexity via different stopping parameters for every class discrimination. This adaption seems to be very important with gene expression data. We observed, that the multiclass LogitBoost of Friedman et al. (2000), which treats the multiclass problem more simultaneously, performed much worse in our study. In the NCI dataset, comprising $J = 8$ different tumor types, it yielded an error rate of 36.1%, whereas with the one-against-all method, the error-rate was only 22.9%. For the Lymphoma dataset with $J = 3$ response classes, the one-against-all approach is also superior with 1.61% versus 8.06%.

3 Results

3.1 Real Data

We explored the performance of our classification technique on six publicly available datasets.

Leukemia

This dataset contains gene expression levels of $n = 72$ patients either suffering from acute lymphoblastic leukemia (ALL, 47 cases) or acute myeloid leukemia (AML, 25 cases) and was obtained from Affymetrix oligonucleotide microarrays. More information can be found in Golub et al. (1999); the raw data are available at <http://www.genome.wi.mit.edu/MPR>. Following the protocol in Dudoit et al. (2001), we preprocess them by thresholding, filtering, a logarithmic transformation and standardization, so that the data finally comprise the expression values of $p = 3571$ genes.

Colon

In this dataset, expression levels of 40 tumor and 22 normal colon tissues for 6500 human genes are measured using the Affymetrix technology. A selection of 2000 genes with highest minimal intensity across the samples has been made by Alon et al. (1999), and these data are publicly available at <http://www.molbio.princeton.edu/colondata>. As for the leukemia dataset, we process these data further by carrying out a base 10 logarithmic transformation and standardizing each tissue sample to zero mean and unit variance across the genes.

Estrogen & Nodal

These datasets were first presented in recent papers of West et al. (2001) and Spang et al (2001). Their common expression matrix monitors 7129 genes in 49 breast tumor samples. The data were obtained by applying the Affymetrix gene chip technology. We thresholded the raw data with a floor of 100 and a ceiling of 16000 and then applied a base 10 logarithmic transformation. Finally, each experiment was standardized to zero mean and unit variance across the genes. Two different response variables are available: The first one describes the status of the estrogen receptor (ER). 25 samples are ER+, whereas the remaining 24 samples are ER-. The second response variable describes the lymph nodal (LN) status, which is an indicator for the metastatic spread of the tumor, a

very important risk factor for disease outcome. Also here, 25 samples are positive (LN+) and 24 samples are negative (LN-).

Lymphoma

This dataset is available at <http://llmpp.nih.gov/lymphoma/data/figure1> and contains gene expression levels of the $J = 3$ most prevalent adult lymphoid malignancies: 42 samples of diffuse large B-cell lymphoma, 9 observations of follicular lymphoma and 11 cases of chronic lymphocytic leukemia. The total sample size is $n = 62$, and the expression of $p = 4'026$ well-measured genes, preferentially expressed in lymphoid cells or with known immunological or oncological importance is documented. More information on these data can be found in Alizadeh et al. (2000). We imputed missing values and standardized the data as described in Dudoit et al. (2001).

NCI

This dataset comprises gene expression levels of $p = 5'244$ genes for $n = 61$ human tumor cell lines from cDNA microarrays, which can be divided in $J = 8$ classes: 7 breast, 5 central nervous system, 7 colon, 6 leukemia, 8 melanoma, 9 non small cell lung carcinoma, 6 ovarian and 9 renal tumors. A more detailed description of the data can be found on the website <http://genome-www.stanford.edu/nci60> and in Ross et al. (1999). We work with preprocessed data as described in Dudoit et al. (2001).

3.1.1 Empirical Study

We performed leave-one-out cross validation to explore the classification potential of our method. This means that we set aside the i th observation and carry out feature selection, stopping parameter estimation and classifier fitting by considering only the remaining $(n - 1)$ data points. We then predict \hat{Y}_i , the class label of the i th observation and repeat this process for all observations in the training sample. Each observation is held out and predicted exactly once. We determine the test set error using symmetrically equal misclassification costs

$$Error = \frac{1}{n} \sum_{i=1}^n 1_{[Y_i \neq \hat{Y}_i]}.$$

Table 3.1 reports test set errors with different gene subset size from feature selection for several classifiers. LogitBoost, is reported with minimum error across the iterations, error after a fixed number of 100 iterations as well as with error using our stopping parameter estimate from equation (2.3). To illustrate the benefit of boosting, we also ran the (optimally tuned) CART algorithm to produce single classification trees. Boosting uses them as weak learners and leads to massive improvements in all except the estrogen and nodal datasets. As a benchmark method we applied the nearest neighbor classifier, a simple rule known to perform reasonably well on gene expression data. In all but the leukemia dataset, boosting clearly outperforms the benchmark.

The effect of gene subset size on the boosting error-rates varies across the datasets. The colon data are more accurately classified by using all predictor variables, whereas the leukemia and estrogen data show nearly optimal performance with all features, but also for a wide range of subsets. On the other hand, the classification of lymphoma and NCI data strongly benefits from feature preselection, which improves the error-rate from 8.06%

<i>Leukemia</i>	10	25	50	75	100	200	3571
LogitBoost, optimal	4.17%	2.78%	4.17%	2.78%	2.78%	2.78%	2.78%
LogitBoost, 100 iter.	5.56%	2.78%	4.17%	2.78%	2.78%	2.78%	2.78%
LogitBoost, estimated	6.94%	5.56%	5.56%	4.17%	4.17%	5.56%	5.56%
Nearest Neighbor	4.17%	1.39%	4.17%	5.56%	4.17%	2.78%	1.39%
Classification Tree	22.22%	22.22%	22.22%	22.22%	22.22%	22.22%	23.61%
<i>Colon</i>	10	25	50	75	100	200	2000
LogitBoost, optimal	14.52%	16.13%	16.13%	16.13%	16.13%	14.52%	12.90%
LogitBoost, 100 iter.	14.52%	22.58%	22.58%	19.35%	17.74%	16.13%	16.13%
LogitBoost, estimated	22.58%	19.35%	22.58%	20.97%	22.58%	19.35%	19.35%
Nearest Neighbor	17.74%	14.52%	14.52%	20.97%	19.35%	17.74%	25.81%
Classification Tree	19.35%	22.58%	29.03%	32.26%	27.42%	14.52%	16.13%
<i>Estrogen</i>	10	25	50	75	100	200	7129
LogitBoost, optimal	4.08%	4.08%	2.04%	2.04%	2.04%	4.08%	2.04%
LogitBoost, 100 iter.	8.16%	6.12%	6.12%	4.08%	4.08%	8.16%	6.12%
LogitBoost, estimated	6.12%	6.12%	6.12%	6.12%	6.12%	6.12%	6.12%
Nearest Neighbor	4.08%	8.16%	18.37%	12.24%	14.29%	14.29%	16.33%
Classification Tree	4.08%	4.08%	4.08%	4.08%	4.08%	4.08%	4.08%
<i>Nodal</i>	10	25	50	75	100	200	7129
LogitBoost, optimal	16.33%	18.37%	22.45%	22.45%	22.45%	18.37%	20.41%
LogitBoost, 100 iter.	18.37%	20.41%	26.53%	42.86%	42.86%	18.37%	22.45%
LogitBoost, estimated	22.45%	30.61%	30.61%	34.69%	28.57%	26.53%	24.49%
Nearest Neighbor	18.37%	30.61%	30.61%	42.86%	36.73%	36.73%	48.98%
Classification Tree	22.45%	20.41%	20.41%	20.41%	20.41%	20.41%	20.41%
<i>Lymphoma</i>	10	25	50	75	100	200	4026
LogitBoost, optimal	1.61%	3.23%	1.61%	1.61%	1.61%	3.23%	8.06%
LogitBoost, 100 iter.	1.61%	3.23%	1.61%	1.61%	1.61%	3.23%	8.06%
LogitBoost, estimated	3.23%	3.23%	3.23%	1.61%	3.23%	3.23%	-%
Nearest Neighbor	11.29%	4.84%	4.84%	6.45%	6.45%	3.23%	1.61%
Classification Tree	25.81%	25.81%	30.65%	29.03%	27.42%	25.81%	25.81%
<i>NCI</i>	10	25	50	75	100	200	5244
LogitBoost, optimal	32.79%	31.15%	27.87%	22.95%	26.23%	24.59%	31.15%
LogitBoost, 100 iter.	37.70%	44.26%	34.43%	29.51%	26.23%	24.59%	36.07%
LogitBoost, estimated	36.07%	44.26%	36.07%	39.34%	44.26%	47.54%	-%
Nearest Neighbor	60.66%	54.10%	49.18%	40.98%	40.98%	29.51%	27.87%
Classification Tree	65.57%	78.69%	85.25%	86.89%	90.16%	86.89%	62.30%

Table 3.1: Test set error rates based on leave one out cross validation for leukemia, colon, estrogen, nodal, lymphoma and NCI data with gene subsets from feature selection ranging between 10 to all genes for several classifiers. LogitBoost error rates are reported with optimal stopping, after a fixed number of 100 iterations as well as with the estimated stopping parameter. The cross validation with estimated stopping parameters for the lymphoma and NCI data with all genes was not feasible.

to 1.61% and from 31.2% to 22.9%, respectively. Finally, the nodal data are accurately classified with few or many features, whereas a mid-size number of genes performs worse.

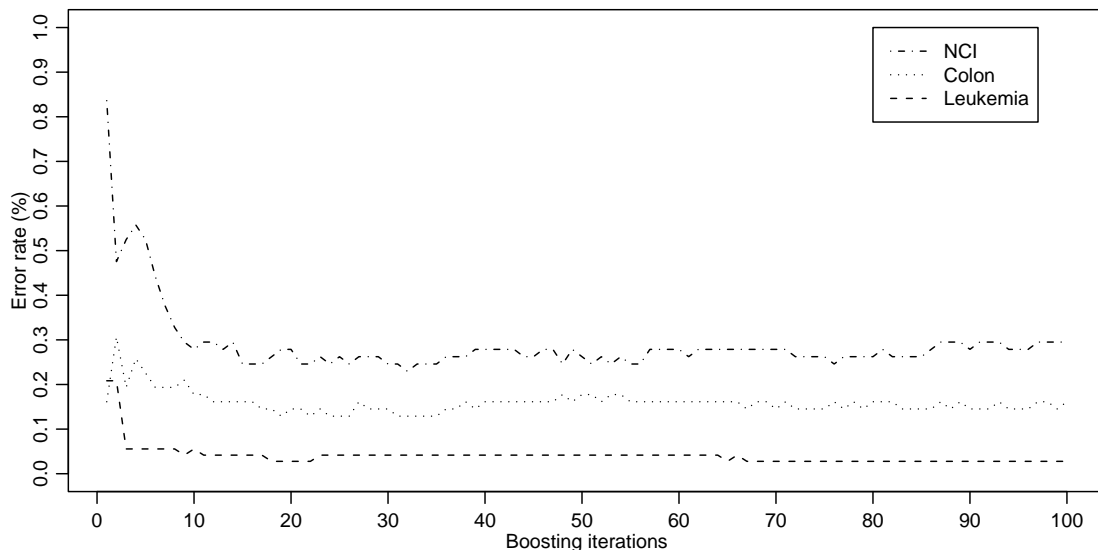


Figure 3.1: Test set error curves for leukemia, colon and NCI data. The number of genes was chosen such that the performance was optimal: 75 for leukemia and NCI data, and 2'000 for the colon data. The error curves for estrogen, nodal and lymphoma data look similar and are not displayed for reasons of clarity.

The choice of the stopping parameter for boosting is not very critical in all six datasets. Our classifier did not overfit much and figure 3.1 shows that the error-rates are at, or close to the minimal error-rate for many boosting iterations. We conjecture that stopping after a large, but arbitrary number of 100 iterations is a reasonable strategy in the context of gene expression data. Our data-driven approach for estimating the stopping parameters by cross validation on the training data does not improve, but most often yields slightly worse results.

3.1.2 Validation of the Results

The leukemia dataset has been considered by many authors. On the original test set comprising 34 observations, LogitBoost assigns the correct label to 33 of the 34 patients. This can be directly compared to the study in Golub et al. (1999), where 29 observations were classified correctly by their weighted voting scheme. Furey et al. (2000), working with support vector machines, report results ranging between 30 to 32 correct classifications. Ben-Dor et al. (2000) applied AdaBoost and carried out cross validation. They obtained an optimal error rate (including unclassified instances) of 4.17% without feature preselection, and of 1.39% with several gene subsets, both after 10'000 boosting iterations.

The colon dataset has been cross validated by Ben-Dor et al. (2000) with various classifiers as well as with and without precedent feature selection. AdaBoost performed comparably bad and consistently led to error-rates of more than 20%. Our best result here are 12.9% wrongly classified observations. We gain evidence that LogitBoost can be

clearly superior over AdaBoost. The best support vector machine of Furey et al. (2000) misclassified only 6 tissue samples in the full cross validation cycle, being equivalent to an error-rate of 9.68%, whereas our error-rate of 12.9% corresponds to 8 misclassifications.

The NCI dataset has been extensively analyzed by Dudoit et al. (2001). They tried several classification methods including AdaBoost on a precedently reduced feature space. Also in their study, AdaBoosting was not among the best classifiers with a median error of about 48% in 150 random divisions in training and test set. Our method with reduction to binary problems and LogitBoost shows a considerable improvement to an error of only 22.9%, but a part of this reduction could be caused by the two different setups, i.e. random divisions versus cross validation for estimating the test set error.

For the estrogen and nodal datasets, we obtain better predictions than West et al. (2001) with their Bayesian approach, even without omitting the most difficult cases as they do. A validation of the results for the lymphoma dataset in comparison to other studies is not possible. Since our classifier does well with respect to the benchmarks, we assume that it yields competitive results here too.

3.2 Simulation

Due to the scarcity of samples in real datasets, relevant differences between classification methods may be difficult to detect. We consider here simulated gene expression data: by generating large test sets, the performance of our modified LogitBoost classifier can be much more accurately compared against the benchmark classifiers and assessing significant differences becomes possible. We start by producing gene expression profiles from a multivariate normal distribution, $X \sim \mathcal{N}_p(0, \Sigma)$, where the covariance structure Σ is from the colon dataset. We continue by assigning one out of two response classes to the simulated expression profiles according to $Y \mid X = x \sim \text{Bernoulli}(p(x))$, where the conditional probabilities are from the model

$$\log \left(\frac{p(x)}{1 - p(x)} \right) = \sum_{j=1}^{10} \beta_j \bar{x}^{(C_j)} \left(1 + \gamma_j \bar{x}^{(C_j)} \right) \left(1 + \delta_j \bar{x}^{(C_j)} \right).$$

The $\bar{x}^{(C_j)} = \sum_{g \in C_j} x^{(g)} / |C_j|$ are mean values across random gene clusters $C_j \subseteq \{1, \dots, p\}$ of uniformly random size between 1 and 10 genes. The model coefficients β_j , γ_j and δ_j were randomly drawn from normal distributions with zero mean and standard deviation $\sigma = 2, 1$ and $1/2$, respectively. This leads to a complex non-additive decision boundary, where LogitBoost with stumps, which fits an additive model, is not in favor of the benchmark classifiers¹.

The training sample size was chosen to be $n = 200$ and we considered the performance of the classifiers on single but large test sets comprising 1'000 new observations. The process was independently repeated 20 times, which enables to explore whether LogitBoost yields significantly better test set error-rates than the benchmark classifiers by performing paired Wilcoxon signed rank tests for the hypothesis of equal misclassifications against the two-sided alternative. The test always points towards better accuracy of LogitBoost, results are given in table 3.2.

¹LogitBoost with larger trees would allow to pick up non-additive decision boundaries.

	Nearest Neighbor	Classification Tree
LogitBoost, optimal	12.37%, $p = 1.7 \cdot 10^{-4}$	10.21%, $p = 1.1 \cdot 10^{-3}$
LogitBoost, 150 iter.	7.54%, $p = 1.4 \cdot 10^{-3}$	5.27%, $p = 1.7 \cdot 10^{-2}$

Table 3.2: Percentual improvement and p-values of LogitBoost (stopped optimally and after a fixed number of 150 iterations) against the nearest neighbor method and classification trees in 20 independent realizations from our simulation model. The p-values are from paired two-sided Wilcoxon signed rank tests for equal test set error and are always in favor of LogitBoost.

Not only when the LogitBoost algorithm was optimally stopped, but also after a fixed number of 150 iterations (which was found to be a reasonable ad-hoc choice for this problem) it significantly outperformed the benchmark methods. This confirms our findings from real data, where our classifier was most often more accurate than the benchmarks.

4 Conclusions

We propose modifications and extensions of boosting classifiers for microarray gene expression data from several tissue or cancer types. We applied precedent feature selection and used the more robust LogitBoost combined with an alternative approach for binary problems. The results on six real and a simulated dataset indicate that these modifications are successful and make boosting a competitive player for predicting expression data. While feature preselection speeded up the computing substantially, its effect on the classification performance remained somewhat obscure, since it was a real benefit for two datasets only, did hardly affect two other datasets and worsened the results on a fifth. We observed superior performance of LogitBoost compared to other studies where AdaBoost was applied on the same data, and we thus recommend the use of the former for classification in microarray experiments. Finally, we propose to reduce multiclass problems to multiple binary problems which are solved separately. This was found to have a great potential for more accurate results on gene expression data, where the choice of predictor variables is crucial.

Our LogitBoost classifier is very suitable for application in a clinical setting. In comparison to other methods, it yields good results, is easy to implement and does not require sophisticated tuning and model or kernel selection as with neural networks or support vector machines. Unlike several other classifiers, it directly provides class membership probabilities. They are essential to quantify the uncertainty of a class label assignment and allow decisions under unequal misclassification costs which are often encountered in practice.

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