

Exploiting the Accumulated Evidence for Gene Selection in Microarray Gene Expression Data

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Abstract

Machine Learning methods have of late made significant efforts to solving multidisciplinary problems in the field of cancer classification using microarray gene expression data. Feature subset selection methods can play an important role in the modeling process, since these tasks are characterized by a large number of features and a few observations, making the modeling a non-trivial undertaking.

In this particular scenario, it is extremely important to select genes by taking into account the possible interactions with other gene subsets. This paper shows that, by accumulating the evidence in favour (or against) each gene along the search process, the obtained gene subsets may constitute better solutions, either in terms of predictive accuracy or gene size, or in both. The proposed technique is extremely simple and applicable at a negligible overhead in cost.

1 Introduction

In the last years research in *feature subset selection* (FSS) has become a hot topic, boosted by the introduction of new application domains and the growth of the number of features involved [Liu and Motoda, 1998]. An example of these new domains is web page categorization, a domain cur-

rently of much interest for internet search engines where thousands of terms can be found in a document. Another example is found in cancer classification by gene expression using DNA microarrays, a domain where Machine Learning methods are now extensively used for this task [Duan et al., 2005]. Problems with many features and a limited number of observations are also very common in molecule classification or medical diagnosis, among others.

The selection of a new feature (either to be removed or added to the current set) involves the evaluation of many models. These models typically consist of the addition (deletion) of one feature to (from) the current set. In *wrapper* methods, an inducer is called to build temporary solutions and return their evaluation using some resampling method (e.g. cross-validation) [Kohavi and John, 1997].

In the standard procedure, only the *best* such model evaluation is considered for selecting which feature should be removed or added, and the remaining evaluations are readily *discarded*. Yet there *is* valuable information in the discarded evaluations: the very many evaluated subsets contain information on the relevance of the features that belong to the subset; this relevance does not depend on the subset being selected or not. When an inducer is requested to estimate the predictive accuracy of a model using a given feature subset within a wrapper strategy, no indication is given on which feature is the most recent addition (or deletion): the inducer just sees a feature subset which has to be evaluated *as a whole*.

Since the most difficult part of a FSS process is

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to evaluate the *interactions* between features, the *accumulated* evaluation of a feature in diverse contexts should account for many of these interactions, and ultimately provide with a more informed estimation of usefulness for the chosen inducer. The different *contexts* of a particular feature x are given by all those subsets which are being evaluated along the search process (not necessarily to assess the influence of x , as noted above), either containing or *not* containing x .

Our idea is to accumulate the inducer evaluations as a rich source of information. This information can then be used in conventional existing algorithms, such as the well-known *forward* or *backward* selection. This idea can be applied to any sequential search algorithm and any inducer and, as shown below, at a negligible extra cost.

In this paper we present experimental results showing good performance in a suite of benchmark microarray problems. The proposed modification always achieves improvements when applied to standard backward selection, either in the estimated predictive accuracy, in the size of the delivered gene subsets, or in both.

2 Accumulated Evidence in Feature Subset Selection

2.1 Preliminaries

It is common to see feature subset selection (FSS) in a set Y of size n as an *search problem* where the search space is the power set of Y , $\mathcal{P}(Y)$ [Langley, 1994]. Each state in the search space corresponds to a subset of features. Exhaustive search is usually intractable, and methods to explore the search space efficiently must be employed. These methods are often divided into two main categories: *filter* methods and *subset selection* methods. A major disadvantage of filter methods is that they are performed independently of the classifier, and the same set of features need not be optimal for different classifiers. Most filter methods disregard the dependencies between features, as each feature is considered in isolation.

Without loss of generality, it can be assumed that the evaluation measure $J : \mathcal{P}(Y) \rightarrow \mathbb{R}^+ \cup \{0\}$ is to be maximized. In this setting, the problem is to find the optimal subset $X \in \mathcal{P}(Y)$ as the one max-

imizing J . The evaluation measure may be inducer-independent (as in filter methods) or may be the same inducer being used to solve the task (as in wrapper methods). In either case, we will refer to $J_{\mathcal{L}}(X)$ as the usefulness of $X \subseteq Y$ estimated using the inducer \mathcal{L} . Since the inducer evaluation in a sample varies depending on the resampling method used, we prefer to use the notation $J_{\mathcal{L}}(X)$ instead of simply $\mathcal{L}(X)$ to express such evaluation.

In the literature, several suboptimal algorithms have been proposed for doing this. Among them, a wide family is formed by those algorithms which, departing from an initial solution, iteratively add or delete features by locally optimizing the objective function. The search starts with an arbitrary set of features (e.g. the full set or the empty set) and moves iteratively to neighbor solutions by adding or removing features. Among the most used algorithms for this problem are the *sequential forward generation* (SFG) and *sequential backward generation* (SBG), their generalization *plus l - take away r* or *PTA(l, r)* [Stearns, 1976]¹ or the *floating search* methods [Pudil et al., 1994]. These latter algorithms work by combining SFG and SBG steps.

2.2 Accumulated evidence and feature relevance

The idea consists on accumulating the *evidence* in favor or against a feature, taking into account its *history* of evaluations alongside different feature subsets. A further explanation can be to extract the most of every subset evaluation, normally the most costly part of a FSS process.

Let $Y_x = \{X \in \mathcal{P}(Y) | x \in X\}$ be the set of all feature subsets of the initial set that contain a certain feature x (note that $|Y_x| = 2^{n-1}$ for all $x \in Y$).

Let \mathcal{L}_x^+ and \mathcal{L}_x^- be the average evaluation of all subsets containing and *not* containing x :

$$\mathcal{L}_x^+ = \frac{1}{2^{n-1}} \sum_{X \in Y_x} J_{\mathcal{L}}(X)$$

$$\mathcal{L}_x^- = \frac{1}{2^{n-1}} \sum_{X \notin Y_x} J_{\mathcal{L}}(X)$$

Given an inducer \mathcal{L} (either filter or wrapper) define, for a given feature $x \in Y$, the *relevance* of x as:

¹SFG is PTA(1,0) and SBG is PTA(0,1).

$$R_{\mathcal{L}}(x) = \mathcal{L}_x^+ - \mathcal{L}_x^- \quad (1)$$

The above definition can be more compactly expressed as:

$$R_{\mathcal{L}}(x) = \frac{1}{2^{n-1}} \sum_{X \notin Y_x} \left(J_{\mathcal{L}}(X \cup \{x\}) - J_{\mathcal{L}}(X) \right) \quad (2)$$

Remark 1. Defining feature relevance with expression (2) is very attractive, since it captures feature interactions in all possible ways. We take the freedom of presenting an informal but hopefully illustrative analogy of what this measure captures. Imagine we are willing to evaluate the average influence of a *basketball* player on a team scoring: we can compute the difference in points that the team scores *with* and *without* this player, no matter what other players are playing in the player's team. If this difference is positive, then we can conclude that this player's accomplishments are positive for the team; otherwise we conclude that we should better sell the player at the best possible price! Note that in this example, only subsets X of size 4 are considered and $Y \setminus X$ is the bench².

Remark 2. Full evaluation of expression (2) has an exponential cost in n , making it unfeasible for most practical applications; an estimation is therefore mandatory via Monte Carlo techniques, generating feature subsets randomly from a precise probability distribution determined by the FSS algorithm being used. Oddly, although $R_{\mathcal{L}}(x)$ takes into account all possible feature interactions, by its very nature it does not capture redundancy: two identical features will have the same relevance. This is true even by making $J_{\mathcal{L}}$ cope with redundancy. However, since a search algorithm will impose an order on the evaluated feature subsets, the current state can be used to ascertain redundancy, as will be shown below.

The above expressions can be conveniently generalized by considering a *weighing* function w :

$$R_{\mathcal{L}}^w(x) = \frac{\sum_{X \notin Y_x} \left(J_{\mathcal{L}}(X \cup \{x\}) - J_{\mathcal{L}}(X) \right) w_x(X)}{\sum_{X \notin Y_x} w_x(X)} \quad (3)$$

²Incidentally, this way of ranking players (together with rebounds, assists, etc) is used in the NBA.

For example, the choice $w_x(X) = |X|/|Y| = |X|/n$ gives more importance to improvements in $J_{\mathcal{L}}$ achieved in a scenario with already many features (improving performance in such a case has a certain merit); alternatively, one could choose $w_x(X) = J_{\mathcal{L}}(X)$; this choice expresses the belief that an improved performance when $J_{\mathcal{L}}(X)$ is already high should be rewarded, and less so when it is low (it has a much lower merit). Many alternatives are possible and the best one (if such choice exists at all) is at the moment an open question. Note that eq. (3) reduces to eq. (1) when $w_x(X) = 1$ for all x .

In the following, we present a practical method to approximate this measure of relevance and integrate it in a SBG search algorithm at no additional cost. The idea consists on accumulating the *evidence* in favor or against a feature by taking into account the *history* of evaluations throughout the search process.

2.3 Practical computation of the accumulated evidence

Let X_k denote the current set, where $|X_k| = k$, for notational simplicity (thus $X_0 = \emptyset$ and $X_n = Y$); let X_{n-k} be the set of features not in X_k , i.e. $X_{n-k} = Y \setminus X_k$. Assume first we are in front of performing a *forward* step. Given X_k , in a classical SFG, the set

$$\left\{ J_{\mathcal{L}}(X_k \cup \{x\}) \mid x \in X_{n-k} \right\} \text{ is computed} \quad (4)$$

and the feature $x' = \arg \max_{x \in X_{n-k}} J_{\mathcal{L}}(X_k \cup \{x\})$ is selected. However, all the remaining information:

$$\left\{ J_{\mathcal{L}}(X_k \cup \{x\}) \mid x \in X_{n-k}, x \neq x' \right\} \text{ is discarded,} \quad (5)$$

yet sometime in the future these individual features x (and eventually x' itself) will be considered again for inclusion or exclusion from the current set in forward or backward steps, respectively.

Conversely, in a *backward step* the search algorithm is going to evaluate a feature x for possible exclusion from X_{n-k} in such a way that the set

$$\left\{ J_{\mathcal{L}}(X_{n-k} \setminus \{x\}) \mid x \in X_{n-k} \right\} \text{ is computed} \quad (6)$$

and the feature $x' = \arg \max_{x \in X_{n-k}} J_{\mathcal{L}}(X_{n-k} \setminus \{x\})$ is selected for removal. Again, the information:

$$\left\{ J_{\mathcal{L}}(X_{n-k} \setminus \{x\}) \mid x \in X_{n-k}, x \neq x' \right\} \text{ is discarded.} \quad (7)$$

Yet, sometime in the future these individual features x (and eventually x' itself) will be considered again for inclusion or exclusion from the current set in forward or backward steps, respectively. Reasoning in more general terms, the search algorithm always evaluates a feature x for possible inclusion in (or exclusion from) the current subset using information about x .

Now let $P_{\mathcal{L}}$ denote the set of feature subsets that the search algorithm has evaluated so far (implying a call to \mathcal{L}). Let $P_{\mathcal{L}|x} = \{X \in P_{\mathcal{L}} \mid x \in X\}$. For every $x \in Y$, define the accumulated evaluations (or simply *accumulators*) as the Monte Carlo estimations:

$$\hat{\mathcal{L}}_x^+ = \frac{\sum_{X \in P_{\mathcal{L}|x}} J_{\mathcal{L}}(X) w_x(X)}{\sum_{X \in P_{\mathcal{L}|x}} w_x(X)} \quad (8)$$

$$\hat{\mathcal{L}}_x^- = \frac{\sum_{X \notin P_{\mathcal{L}|x}} J_{\mathcal{L}}(X) w_x(X)}{\sum_{X \notin P_{\mathcal{L}|x}} w_x(X)} \quad (9)$$

which are approximations to the weighted versions of \mathcal{L}_x^+ and \mathcal{L}_x^- , respectively. These two approximated values depend on the search algorithm, which determines the strategy to traverse the search space. Different FSS algorithms (such as SFG or SBG) provide different traces of evaluated subsets at any given number of algorithmic steps. In these conditions, the impact of the considered feature in the *current subset* X can be used to ascertain redundancy and make it influence the search, by modulating the effect of the accumulated evaluations. Consider now, for $\lambda \in [0, 1]$,

$$\hat{R}_{\mathcal{L}}^w(x) = \frac{\lambda}{2} (\hat{\mathcal{L}}_x^+ - \hat{\mathcal{L}}_x^- + 1) + (1 - \lambda) \hat{J}_{\mathcal{L}}(x), \quad (10)$$

where $\hat{J}_{\mathcal{L}}(x) = J_{\mathcal{L}}(X \setminus \{x\})$ in a backward step (the effect of removing x from X) and $\hat{J}_{\mathcal{L}}(x) = J_{\mathcal{L}}(X \cup \{x\})$ in a forward step (the effect of adding

x to X) and λ is a free parameter. This scheme generalizes conventional forward and backward steps (as used by SFG, SBG or any other sequential algorithm) in two ways:

1. By setting $\lambda = 0$, the conventional forward and backward steps are recovered and both relevance and redundancy are evaluated using $\hat{J}_{\mathcal{L}}(x)$. By setting $\lambda = 1$, a pure arithmetic average between $\hat{\mathcal{L}}_x^+$ and $1 - \hat{\mathcal{L}}_x^-$ is computed. For other values of λ , the *search history* makes an influence on the search itself, conditioning the selection of features. In this case, only a $1 - \lambda$ fraction of the importance is assigned to the current subset evaluation.
2. The search history itself is formed by all known contexts in which the considered feature could appear or not (and not only by previous evaluations of the feature), thus conforming a broader picture of its true relevance.

Example. Consider the following feature subset mask ($n = 20$) for a current feature subset $X_8 \subset Y$ where the i -th index is 1 when feature $x_i \in X_8$ and 0 otherwise:

10010010001010100101

signaling the presence of features number 1, 4, 7, etc. An evaluation $J_{\mathcal{L}}(X)$ of this subset is indeed expressing how good is to have the first feature but not the second or the third, also how good is to have the seventh feature but not the one before the last, and so forth. For this reason, all the features in Y (and not only those in X) should have their accumulators updated every time.

3 A practical algorithm

We illustrate the approach on the popular SBG search algorithm (**Algorithm 1**) and give a practical implementation of the previous ideas for it (SBG⁺, **Algorithm 2**). In addition, for simplicity of presentation, we fix $w_x(X) = 1$. In this case, normalization simply amounts to a division by the number of performed accumulations. The initialization of the accumulated relevances is 0 for all $x \in Y$. The results are first accumulated and then used; for this reason, even in the first algorithmic

step (the first discarded feature) the behavior of both algorithms may start to diverge. At the end of the FSS process, n_x^+ (resp. n_x^-) will be the number of times that a feature subset (resp. not) containing x has been evaluated. Note that the computation is done at a negligible overhead in cost; this is due to the fact that the inducer is called *exactly* the same number of times for SBG than for the accumulated counterpart SBG⁺.

Algorithm 1 SBG (inducer \mathcal{L} , feature set Y)

```

1:  $X_n \leftarrow Y$ 
2:  $k \leftarrow 0$ 
3: repeat
4:   for all  $x \in X_{n-k}$  do
5:     compute the set  $\{J_{\mathcal{L}}(X_{n-k} \setminus \{x\})\}$ 
6:   end for
7:    $x' \leftarrow \arg \max_{x \in X_{n-k}} J_{\mathcal{L}}(X_{n-k} \setminus \{x\})$ 
8:    $X_{n-k} \leftarrow X_{n-k} \setminus \{x'\}$ 
9:    $k \leftarrow k + 1$ 
10: until  $k = n$ 
11: return  $\arg \max_{k=1 \div n} J_{\mathcal{L}}(X_k)$ 

```

4 Experimental work

Experimental work is now presented in order to assess the described modifications using two sequential algorithms: SBG and its accumulated counterpart SBG⁺. The algorithms were implemented using the R language for statistical computing [R Development Core Team, 2008].

5 Experimental settings

Each full experiment consists of an *outer* loop of 5x2-cross-validation (5x2cv) for model selection, as proposed by several authors [Dietterich, 1998, Alpaydin, 1999]. This procedure performs 5 repetitions of a 2-fold cross-validation. It keeps half of the examples out of the feature selection process and uses them as a *test set* to evaluate the final quality of the selected features. For every fold and repetition of the outer cross-validation loop, two feature selection processes are conducted with the same examples, one with the original algorithm (SBG) and

Algorithm 2 SBG⁺ (inducer \mathcal{L} , feature set Y , $\lambda \in [0, 1]$)

```

1:  $X_n \leftarrow Y$ 
2:  $k \leftarrow 0$ 
3: {Initialize accumulators and counters}
4:  $\forall x \in Y, \hat{\mathcal{L}}_x^+ \leftarrow \hat{\mathcal{L}}_x^- \leftarrow 0$ 
5:  $\forall x \in Y, n_x^+ \leftarrow n_x^- \leftarrow 0$ 
6: repeat
7:   for all  $x \in X_{n-k}$  do
8:     compute the set  $\{J_{\mathcal{L}}(X_{n-k} \setminus \{x\})\}$ 
9:   end for
10: {Update accumulators and counters}
11: for all  $x \in Y$  do
12:   if  $x \in X_{n-k}$  then
13:      $\hat{\mathcal{L}}_x^+ \leftarrow \hat{\mathcal{L}}_x^+ + \sum_{y \in X_{n-k} \setminus \{x\}} J_{\mathcal{L}}(X_{n-k} \setminus \{y\})$ 
14:      $n_x^+ \leftarrow n_x^+ + 1$ 
15:   else
16:      $\hat{\mathcal{L}}_x^- \leftarrow \hat{\mathcal{L}}_x^- + J_{\mathcal{L}}(X_{n-k} \setminus \{x\})$ 
17:      $n_x^- \leftarrow n_x^- + 1$ 
18:   end if
19: end for
20:  $x' \leftarrow \arg \max_{x \in X_{n-k}} \left\{ \frac{\lambda}{2} (\hat{\mathcal{L}}_x^+ / n_x^+ - \hat{\mathcal{L}}_x^- / n_x^- + 1) \right.$ 
21:    $\left. + (1 - \lambda) \hat{J}_{\mathcal{L}}(X_{n-k} \setminus \{x\}) \right\}$ 
22:    $X_{n-k} \leftarrow X_{n-k} \setminus \{x'\}$ 
23:    $k \leftarrow k + 1$ 
24: until  $k = n$ 
25: return  $\arg \max_{k=1 \div n} J_{\mathcal{L}}(X_k)$ 

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one with the accumulated version (SBG⁺).

Each feature selection iteration uses the 1-*nearest-neighbor* learner implementation in [Venables and Ripley, 2002] (which uses Euclidean distance), *linear discriminant analysis* (LDA) and the *Support Vector Machine* with radial kernel (SVM_r). The parameters of the SVM (the regularization constant or cost and the kernel width) are kept fixed to their default values in all the experiments, since we are only interested in the influence that different feature subsets have on the modelling³.

The evaluation of these inducers is resampled in a second (*inner*) 5x2cv loop for a more informed estimation of usefulness. In all cases, stratification is used to keep the same proportion of class labels across the partitioned sets. After some preliminary experiments, we set $\lambda = \frac{2}{3}$ in expression (10). It is very important to mention that there is no stopping criterion in the algorithms: the two backward methods run until all the features have been removed. Then the *best* subset in the obtained sequence of subsets is returned. This setting avoids the specification of an a priori size for the solution. It also eliminates the possibility that the accumulated algorithm performs differently simply because it merely influences the stopping point.

Once the best feature subset is found (a different one in every outer loop), this subset is evaluated in the corresponding test set. The final test error (the one reported) is the mean of these 10 values.

5.1 Benchmarking microarray data sets

In a microarray gene expression context, there is a wide spectrum of FSS algorithms. Commonly found methods fall into the *filter* category: a list of the top-ranked genes based on some inducer-free figure of merit is generated, followed by an inductive process where a classifier is incrementally evaluated [Ruiz et al., 2006]. This constitutes a fast and low complexity approach. However, considering individual contributions only can hinder the discovery of possible interactions between genes.

Many authors have claimed that the *wrapper* approach, if affordable, is preferable to

³These values are 1 for the cost parameter and the inverse of the number of features for the smoothing parameter in the kernel.

the filter approach (e.g. [Liu and Motoda, 1998, Kohavi and John, 1997]). It is therefore of the greatest importance to take the most of every evaluation of the inducer, which is normally the more costly part.

Validation of the described approach uses five public-domain microarray gene expression data sets, shortly described as follows:

1. *Colon Tumor*: Used originally by [Alon et al., 1999], it consists of 62 samples of colon tissue, of which 40 are tumorous and 22 normal, and contains 2,000 genes.
2. *Leukemia*: Used first by [Golub et al., 1999], the training set consisted originally of 38 bone marrow examples (plus a further test set with 34 examples). This set of examples has been merged to form a data sample of 72 examples, which are described by 7,129 probes: 6,817 human genes and 312 control genes. The goal is to tell acute myeloid leukemia from acute lymphoblastic leukemia.
3. *Lung Cancer*: Studied by [Gordon et al., 2002], the problem consists in distinguishing between malignant pleural mesothelioma and adenocarcinoma of the lung. There are 181 examples available, described by 12,533 genes.
4. *Prostate Cancer*: This data set was used by [Singh et al., 2002] to analyze differences in pathological features of prostate cancer and to identify genes that might anticipate its clinical behavior. There are 181 examples and 12,600 genes.
5. *Breast Cancer*: [Veer et al., 2002] studied 97 patients with primary invasive breast carcinoma; 24,481 genes were analyzed.

These problems are hard for several reasons, in particular the sparsity of the data, the high dimensionality of the feature (gene) space, and the fact that very many features (the genes) are irrelevant or redundant. In these situations, performing feature selection is at best a delicate task that entails a very high risk of overfitting, even when the full set features has been preprocessed to lower the dimensionality of the problem.

We made a preliminary selection of genes on the basis of the ratio of their between-groups to within-groups sum of squares, as in other approaches, to make a wrapper approach computationally feasible [Dudoit et al., 2002]. In this work, the top 200 genes for each dataset were selected as the source of study. It is important to stress that there has been little effort to find the best models among those represented by the considered inducers: in other words, nearest-neighbors is limited to just one neighbour and the SVM parameters have been set to their default values. All the effort is devoted to find good feature subsets and to compare the two search algorithms in similar experimental circumstances.

For comparative purposes, performance results using the whole set of features and the reduced subset of 200 features are displayed in Table 1. In view of these results, it is clear that these subsets constitute a very good departing point for further analysis with wrapper methods.

Problem	1NN		LDA		SVM _r	
	Y	X ₂₀₀	Y	X ₂₀₀	Y	X ₂₀₀
Colon Tumor	23.9	23.2	24.8	20.0	31.0	14.8
Leukemia	9.7	8.3	14.1	3.1	26.7	2.8
Lung Cancer	1.8	2.0	N/A	1.8	4.4	1.0
Prostate Cancer	23.4	19.1	N/A	25.5	38.2	26.9
Breast Cancer	45.1	27.7	N/A	24.5	48.3	24.1

Table 1: Average test error (in %) for the different inducers in the preprocessing phase. Y: using the full set of genes; X₂₀₀: using the top pre-selected 200 genes; N/A: computation unaffordable due to numerical inaccuracies in LDA.

Problem	1NN		LDA		SVM _r	
	SBG ⁺ SBG	SBG	SBG ⁺ SBG	SBG	SBG ⁺ SBG	SBG
Colon Tumor	18.1	20.0	19.0	22.2	18.1	18.7
Leukemia	8.1	10.9	16.7	17.7	7.8	9.2
Lung Cancer	3.3	3.4	2.7	3.4	3.4	3.5
Prostate Cancer	14.0	15.5	24.8	26.4	21.9	22.0
Breast Cancer	26.2	29.3	27.4	36.7	23.7	25.6
Average	13.9	15.8	18.1	21.3	15.0	15.8

Table 2: Average test error (in %) for the different inducers when comparing SBG⁺ to SBG.

Problem	1NN		LDA		SVM _r	
	SBG ⁺ SBG	SBG	SBG ⁺ SBG	SBG	SBG ⁺ SBG	SBG
Colon Tumor	37.4	73.8	70.5	79.2	15.5	14.2
Leukemia	7.2	28.3	30.0	32.5	6.1	37.2
Lung Cancer	17.4	20.0	4.1	13.4	4.5	8.8
Prostate Cancer	18.3	19.3	23.5	44.3	12.9	8.1
Breast Cancer	60.2	34.2	22.4	52.6	13.0	17.5
Average	28.1	35.1	30.1	44.4	10.4	17.2

Table 3: Average gene subset sizes for the different inducers when comparing SBG⁺ to SBG.

6 Discussion

The results of the FSS process are displayed in Tables 2 and 3. The first table shows the (cross-validated) average test error for the two algorithms and the different inducers. The second table shows the (cross-validated) average size of the final selected subsets.

The first fact to note is that the accumulated version outperforms the standard version (though in general by a modest margin) in all cases. This is a very remarkable result, given the big differences among the problems and among the inducers. Second, SBG⁺ finds in general solutions of lower size than SBG does, sometimes by a substantial amount (e.g., 1NN in *Colon Tumor* and *Leukemia*, most of LDA, or *Leukemia* and *Lung Cancer* with the SVM). Given that there is no stopping condition, our explanation is that the standard backward version is *greedier* than the accumulated one. By the (early) inclusion of some (or many) features that are not as good as they look in that moment, and cannot be removed, SBG is driven toward worse local minima of the error function as compared to SBG⁺. The greediness itself is explained by the purely *local* (in the temporal sense) character of SBG and it also explains the worse prediction results of this algorithm.

Feature selection appears to be a viable avenue for dimensionality reduction in this field: a reduction of two orders of magnitude in the number of features by univariate methods shows substantial improvements (Table 1). With a further reduction of another order of magnitude, mean performance of the finally selected classifiers is similar to that achieved using the previously reduced subset. This behavior is important, both for computational and scientific reasons. Even without op-

timization of free parameters (a necessary step in normal conditions), cross-validated wrapper computations with 200 features may take several days of computing time on a modest machine. Scientifically, coping with hundreds of features and pretending interpretability of the role of every feature in the model is out of the question in many cases. This is aggravated in the present situation of data scarcity.

The results diverge for different classifiers, as it may be reasonably expected. This is of the greatest importance when assessing whether an improvement is consistent, or is limited to a certain type of method. In this sense, 1NN seems to be the best method for *Prostate Cancer*, LDA for *Lung Cancer* and the SVM for the other three (in all cases using SBG⁺). The SVM tends to deliver smaller gene subsets, both for SBG and SBG⁺. Given that the SVM parameters were not optimized beyond educated guesses, we think there is room for further improvement in the modeling, specially on the accuracy side.

Comparison to other results in the literature using the same data sets is a delicate undertaking in general. The methodological steps can be very different, especially concerning resampling techniques. We have found that many times there are no true test sets: feature subsets or model parameters (or both) are optimized by means of one or several resampled runs of cross-validation. This procedure is dangerous in that it cannot deliver an unbiased estimation of true error, given that, although test observations have not been used to create the model, they have been used to decide upon competing ones (namely, in the feature selection process itself). The stability of these results is also compromised if only one resample is carried out. On the other hand, the delivered gene subset size is a very important issue to bear in mind, if the solutions are to become interpretable and useful from the clinical point of view. That said, we compare with several references illustrative of recent work:

1. For the *Colon Tumor* data set, [Wang et al., 2008] report an error of 12.7% with 94 genes, while [Bu et al., 2007] report an error of 23.0% with 33 genes, both using radial SVMs. For this dataset, we report a test error of 18.1% using an average of 15

genes.

2. For the *Leukemia* problem, [Bu et al., 2007] report an error of 4.0% with 30 genes using a radial kernel, and an extraordinary 1.4% using only two genes and filter methods for ranking [Hewett and Kijisanayothin, 2008]. For this dataset, we report an average test error of 6.1% using an average of 6 genes.
3. The *Lung Cancer* data set is apparently the easiest to separate. Accuracy values as high as 99% are achieved by [Bu et al., 2007] (using a SVM and 38 genes) and by [Hong and Cho, 2008], this time using 5NN and as much as 135 genes. For this dataset, we report an average test error of 2.7% using an average of 4 genes.
4. In the *Prostate Cancer* problem, as low as 7% error as been reported (half our best result) using a radial SVM and 47 genes (nearly three times our result) [Bu et al., 2007].
5. Finally, for the *Breast Cancer* problem, an error of 21% is reported using a radial SVM and 46 genes [Bu et al., 2007], and an error of 32% using again a SVM and 8 genes [Hewett and Kijisanayothin, 2008]. For this dataset, we report an average test error of 23.7% using an average of 13 genes.

7 Conclusions

This paper has presented a modification suitable for feature subset selection algorithms that iteratively evaluate subsets of features, by making them accumulate all the “log of merit” of the features in quite different contexts. The idea consists in that the current subset evaluation is not used directly to select the feature to add (or remove), but to *accumulate* information on the usefulness of the feature in many contexts. The different contexts of a particular feature x are given by all those subsets that contain x (they express how good is to have x) and do not contain x (they express how good is not to have x). The accumulated information is then used to decide which feature should be added or removed (namely, that feature with the highest (lowest) accumulated usefulness which has not yet been added (removed)). Therefore, the search history makes an

influence on the search itself, conditioning the selection of features. This view is consistent with the definition of a search algorithm as a mapping from its history (including its present state) to the set of possible moves. In these conditions, less importance is assigned to the current subset evaluation than in a classical FSS setting (where it is the *only* source of information). Our experimental results indicate a general improvement in performance, without any additional modelling effort.

Future work includes exploring SFG. The decision to study SBG in the first place is consistent with the goal of discovering feature interactions. Having all the features from the beginning greatly facilitates this task. Nonetheless, the more modest computational demands that SFG entails in practice (if cut before exhaustion of features) may be an appealing characteristic. It is relevant to point out that the presented algorithmic modification may be of little help if an algorithm has many opportunities to rectify its decisions (*e.g.*, the PTA(l, r) family of algorithms). However, even in this case, the forward or backward steps will be more informed, possibly making the search algorithm deliver better solutions at earlier stages. Unfortunately, the $O(n^{l+r+1})$ cost of PTA(l, r) can well make it prohibitively high for microarray data problems in wrapper mode.

A clear avenue for further research is the setting of the free parameter, λ . It is our conjecture that an adaptive value may deliver better results. In this sense, the influence of past evaluations may be different at early or last stages of a search process.

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