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Abstract

Microarray technology allows for the monitoring of thousands of gene expressions in various biological conditions, but most of these genes are irrelevant for classifying these conditions. Feature selection is consequently needed to help reduce the dimension of the variable space. Starting from the application of the stochastic meta algorithm "Optimal Feature Weighting" (OFW) for selecting features in various classification problems, focus is made on the multiclass problem that wrapper methods rarely handle. From a computational point of view, one of the main difficulties comes from the commonly unbalanced classes situation when dealing with microarray data. From a theoretical point of view, very few methods have been developed to minimize any classification criterion, compared to the 2-class situation (*e.g.* SVM, l_0SVM, RFE...).

The OFW approach is developed to handle multiclass problems using CART and *one-vs-one* SVM as classifiers. The results are then compared with those obtained with other multiclass selection algorithm (Random Forests and the filter method F-test), on five public microarray data sets with various complexities. Statistical relevancy of the results is assessed by measuring and comparing the performances of these different approaches. The aim of this study is to heuristically evaluate which method would be the best to select genes classifying the minority classes. Application and biological interpretation are then given in the case of a pig folliculogenesis study.

Key words: Feature Selection, Stochastic Algorithm, Classification, Unbalanced Multiclass Microarray

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1 Introduction

When dealing with microarray data, one of the most important issues to improve the classification task is to perform feature selection. Thousands of genes can be measured on a single array, most of which are irrelevant or uninformative for discriminative methods and dimensionality thus must be reduced without losing information.
In this context, our objective was to look for predictors (the genes) that would classify the observed cases (the microarrays) into their known classes. The selection of these discriminative variables can be performed in two ways: either explicitly (filter methods) or implicitly (wrapper methods). The filter methods measure the usefulness of a feature by ordering it with statistical tests such as t- or F-tests. These gene-by-gene approaches are robust against overfitting and computationally fast. However, they disregard the interactions between the features and may fail to find the "useful" set of variables: they usually select variables with redundant information. On the other hand, the aim of the wrapper methods is to measure the usefulness of a subset of features in the set of variables. However, when dealing with a large number of variables as it is the case here, it is computationally impossible to do an exhaustive search among all subsets of features and these methods are prone to overfit. One solution to benefit from the wrapper approach is to perform a search using stochastic approximations that still cover a large portion of the feature space to avoid local minima. The "Optimal Feature Weighting" algorithm (OFW) proposed by Gadat and Younes (2007) allows for the selection of an optimal discriminative subset of variables. This meta algorithm can be applied independently with any classifier. Classifiers such as Support Vector Machines (SVM, Vapnik 1999) and Classification And Regression Trees (CART, Breiman et al. 1984) were passed up to this stochastic meta algorithm in Lê Cao et al. (2007) for 2-class microarray problems. The aim was to make a comparative study of OFW+SVM/CART with other wrapper methods (Recursive Feature Elimination, Guyon et al. 2002, l_0 norm SVM, Weston et al. 2003, Random Forests, Breiman 2001) and the filter method t-test on public microarray data sets. The relevancy of the results was assessed in a statistical manner by measuring the performance of each gene selection, and with a biological expertise related to the biological experiment. The results showed that the selections made with OFW were statistically competitive and biologically relevant, even with complex data sets.
From this point, we investigate this stochastic algorithm with multiclass microarray data sets. Multiclass problems are often considered as an extension of 2-class problems. However this extension is not always straightforward as the data sets are often characterized by unbalanced classes with a small number of

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cases in at least one of the classes. Furthermore, this "rare" minority class is often the one of interest for the biologists who would like to diagnose a disease for example. Nevertheless, most algorithms do not perform well for such problems as they aim to minimize the overall error rate instead of focusing on the minority class. Moreover, the classification accuracy appears to degrade very quickly as the number of classes increases (Li et al., 2004). Several methods have been proposed in the recent years. Chen et al. (2004) proposed balanced or weighted random forests, McCarthy et al. (2005) compared sampling methods and cost sensitive learning with however no clear winner in the results, and more recently Eitrich et al. (2007); Qiao and Liu (2008) also addressed the unbalanced multiclass issue with cost sensitive machine learning technique or SVM.

In the specific context of multiclass microarray data, Li et al. (2004) applied various classifiers with various feature selection methods and conclude that the accuracy is highly dependent on the choice of the classifier, rather than the choice of the selection method- although this would be more natural. Chen et al. (2003) applied four filter methods with low correlation between selected genes, Yeung and Burmgarner (2003) applied uncorrelated or error-weighted Shrunken Centroid.

In this study we compare two ways of handling multiclass data: with or without an internal weighting procedure in OFW. We do not intend to optimize the size of the gene subset. We rather focus on the assessment criteria to measure the performance of the different methods on the first selected genes.

Biological interpretation that is one of the main key to evaluate the relevancy of the biological results will not be given in this paper when analyzing the five public data sets, but the reader can refer to Lê Cao et al. (2007) that highlight the importance of biological interpretation in the analysis.

We apply the multicategory classifier CART and the *one-vs-one* SVM approach with OFW on five public microarray data sets. Numerical comparisons are done with Random Forests, known to perform efficiently on such data sets, and one filter method (F-tests), by computing the e.632+ bootstrap error from Efron and Tibshirani (1997) for each feature selection method, the stability of the results with Jaccard Index and by comparing the different gene lists. The weighted and no weighted approaches are then compared in OFW+CART and OFW+SVM with the same tools. Finally, application and biological analysis are performed on a pig folliculogenesis data set.

The first section introduces the theoretical adaptation of the OFW model to the multiclass framework. In next section we consider the computational aspects of the application of CART and SVM in OFW and describe the different tools to assess the performance of the results. Application on public data sets and on a practical data set follow. The paper ends with further elements of discussion.

2 The model

We introduce our model of feature selection in the framework of multiclass analysis. As we focus here on microarray data, we will mostly refer to "genes" instead of "variables".

2.1 Measure of the classification efficiency

Let $\mathcal{G}$ be a large set of genes numbered from 1 to N that describes a signal $\mathcal{I}$ to belonging to one of the classes $\{\mathcal{C}_1, \ldots, \mathcal{C}_k, \ldots, \mathcal{C}_K\}$, $k = 1, .., K$. A classification algorithm $\mathbb{A}$ will be chosen according to the problem type (2-class, multiclass), as OFW does not depend on the classification procedure $\mathbb{A}$.
Let us define a positive weight parameter $\mathbb{P}$ on each of the genes in $\mathcal{G}$. After a normalization step, $\mathbb{P}$ can be considered as a discrete probability on the N genes. The goal is to learn a probability that fits the efficiency of each gene for the classification of $\mathcal{I}$ in $\{\mathcal{C}_1, \ldots, \mathcal{C}_K\}$, so that important weights are given to genes with high discriminative power and lower weights to those that have a poorest influence on the classification task. Denote p any small integer compared to N, a gene subset of size p has to be extracted from $\mathcal{G}$ using $\mathbb{P}$. We then define how to measure the goodness of $\mathbb{P}$ for the set of genes $\mathcal{G}$ and the classes $\{\mathcal{C}_1, \ldots, \mathcal{C}_K\}$ (*i.e.* the objective function).

Definition 1 *Given a probability $\mathbb{P}$ on $\mathcal{G}$ and $\epsilon(\omega)$ the measure of classification efficiency with any p-uple $\omega \in \mathcal{G}^p$, the energy of the system at point $\mathbb{P}$ is the mean classification performance where ω is drawn with respect to $\mathbb{P}^{\otimes p}$ in $\mathcal{G}^p$*

$$\mathcal{E}(\mathbb{P}) = \mathbb{E}_{\mathbb{P}}[\epsilon] = \sum_{\omega \subset \mathcal{G}^p} \mathbb{P}(w)\epsilon(w). \tag{1}$$

Remark 1 *Remark here that genes selected with respect to $\mathbb{P}$ in (1) are drawn with replacement although it looks more reasonable to use subsets of genes without replacement. This mainly comes from the mathematical derivations to optimize $\mathcal{E}$ that will be described below.*

Note that the energy $\mathcal{E}$ depends on the way we measure the classification efficiency on ω, that we denote $\epsilon(\omega)$. Given any standard classification algorithm $\mathbb{A}$, $\epsilon(\omega)$ will actually be the error rate of $\mathbb{A}$ computed on the training set using the set of extracted features ω. The more $\mathbb{P}$ enables us to hold good genes g for classification (important weight on g and $\epsilon(\omega)$ small each time ω contains this gene g), the less $\mathcal{E}$. Minimizing $\mathcal{E}$ with respect to $\mathbb{P}$ will thus permit to exhibit the most weighted and consequently the most highly discriminative genes. Hence, a natural importance ranking will be read on the weight $\mathbb{P}^\star$ minimizing $\mathcal{E}$.

2.2 Stochastic optimization method

The energy $\mathcal{E}$ can be minimized with a stochastic version of the standard gradient descent technique. More details about the theoretical derivations can be found in Gadat and Younes (2007)
The function $\mathcal{E}$ has to be minimized up to the constraints defined by a discrete probability measure on $\mathcal{G}$. Thus, the more natural way to optimize (1) is to use a gradient descent of $\mathcal{E}$ projected to the set of constraints. The set of constraints $\mathcal{S}$ is the simplex of probability map on $\mathcal{G}$. We also denote by $\Pi_{\mathcal{S}}$ the Affine projection of any point of $\mathbb{R}^N$ on the simplex $\mathcal{S}$. This natural projection $\Pi_{\mathcal{S}}$ of any point x can be computed in a finite number of steps as mentioned in Gadat and Younes (2007). Using this former projection $\Pi_{\mathcal{S}}$, the Euclidean gradient of $\mathcal{E}$ is

$$\forall g \in \mathcal{G} \qquad \nabla\mathcal{E}(\mathbb{P})(g) = \sum_{\omega \in \mathcal{G}^p} \frac{C(\omega, g)\mathbb{P}(\omega)}{\mathbb{P}(g)}\epsilon(\omega), \tag{2}$$

where $C(\omega, g)$ is the number of occurrences of g in ω. The iterative procedure to update $\mathbb{P}$ is then given by

$$\mathbb{P}_{t+dt} = \mathbb{P}_t - \nabla\mathbb{P}_t dt. \tag{3}$$

The main clue is that the Euclidean gradient expression (2) can be seen as an expectation as stated in the next proposition.

Proposition 1 *For any $\mathbb{P}$ probability map on $\mathcal{G}$ and if $\nabla_{\mathcal{S}}$ denotes the gradient of $\mathcal{E}$ with respect to constraints $\mathcal{S}$, $\nabla_{\mathcal{S}}\mathcal{E}$ is given by*

$$\forall g \in \mathcal{G} \qquad \nabla_{\mathcal{S}}\mathcal{E}(\mathbb{P})(g) = \Pi_{\mathcal{S}}\left(\mathbb{E}_\omega\left[\frac{C(\omega, g)}{\mathbb{P}(g)}\epsilon(\omega)\right]\right).$$

This last expression is numerically intractable since it requires the computation of ϵ over all possible p-uple of $\mathcal{G}$. To deal with such gradient, a computable Robbins-Monro algorithm can be used, which gets similar asymptotic behavior as (3) (see for instance Gadat and Younes (2007), Kushner and Clark 1978). With this stochastic method, the updated formula of $\mathbb{P}_n$ becomes:

$$\mathbb{P}_{n+1} = \Pi_{\mathcal{S}}\left[\mathbb{P}_n - \alpha_n \frac{C(\omega_n, .)\epsilon(\omega_n)}{\mathbb{P}_n(.)}\right], \tag{4}$$

where ω_n is any set of p genes sampled with respect to $\mathbb{P}_n$. Note that the last expression is always defined since when $\mathbb{P}_n(g) = 0$ as we cannot draw this gene in ω_n and the integer $C(\omega_n, g)$ vanishes. The next theorem precisely describes the asymptotic behavior of (4).

Theorem 1 *Defining the discretisation time* $\tau_k = \sum_{i=0}^{k} \alpha_i$ *and its associated dual reversion* $I(t) = \sup\{k \quad | \quad \tau_k \leq t\}$, *then the interpolated process* $P^k(t) = \mathbb{P}_{I(\tau_k+t)}$ *is an asymptotic pseudo-trajectory of the ordinary differential equation (3) provided that the sequence of steps* (α_i) *satisfies the two conditions:*

$$\sum_i \alpha_i = \infty \qquad \textit{and} \qquad \exists\, \nu > 0 \quad \sum_i \alpha_i^{1+\nu} < \infty.$$

This last result insures that the stochastic algorithm computing $\mathbb{P}_n$ is asymptotically equivalent to the real gradient descent (3). Several derivations of this theoretical point can be found in Gadat and Younes (2007). In our experiments, we have decided to use a step sequence $\alpha_i = A/(B+i)$ for calibrated constants A and B.

2.3 Detailed algorithm.

We detail the application of the algorithm in the case of a given classifier $\mathbb{A}$:

Let $\mathcal{G} = (\delta_1 \dots \delta_{|\mathcal{G}|})$, $\mu \in \mathbb{N}^*$ and η the stopping criterion.
- For iteration $n = 0$ define $\mathbb{P}_0$ as the uniform distribution on $\mathcal{G}$.
- While $|\mathbb{P}_{(n+\mu)} - \mathbb{P}_n|_\infty > \eta$:
  - extract ω_n from $\mathcal{G}^p$ with respect to $\mathbb{P}_{n,p} = \mathbb{P}_n^{\otimes p}$,
  - construct $\mathbb{A}_{\omega_n}$ and compute $\epsilon(\omega_n)$,
  - compute the drift vector $d_n = C(\omega_n, \cdot)\epsilon(\omega_n)/\mathbb{P}_n(\cdot)$,
  - update $\mathbb{P}_{n+1} = \Pi_{\mathcal{S}}[\mathbb{P}_n - \alpha_n d_n]$,
  - $n = n + 1$.

3 Application of OFW and performance evaluation

We discuss here the applications in the field of multiclass problems. The application of OFW+CART and the comparisons of OFW+CART/SVM in the binary case can be found in Lê Cao et al. (2007).

3.1 CART and SVM multiclass applied to OFW

CART

OFW is applied with the classifier CART (Classification And Regression Trees Breiman et al. 1984) that is well adequate for multiclass problems.

CART is constructed via a recursive partitioning routine. It builds a classification rule to predict the class label of the microarrays based on the feature information following the Gini criterion. To avoid overfitting, trees are then generally pruned using a cross validation procedure. In our special case, the trees were not pruned and a node was declared terminal when all the cases landing in this node belonged to the same class.
Note that CART is unstable by nature: a slight change in the features can lead to a very different construction of the tree. Following the example of Breiman (1996), the trees were aggregated (*bagging*) to overcome this instability. As in Breiman (1996), the trees were unpruned, but there is no overfitting, thanks to the aggregation technique.
To compute the efficiency criterion ϵ at iteration n we launched B trees on B bootstrap samples on different ω_n^b drawn with respect to $\mathbb{P}_n$, where $b = 1, \ldots, B$. We then defined ϵ as the mean classification error rate on the out-of-bag samples. The detailed bagging version of OFW+CART is described in 3.3.

SVM Multiclass

We applied OFW with the *one-vs-one* SVM approach that is implemented in the `e1071 R` package. Other SVM multiclass approaches could have been applied, such as the *one-vs-rest* approach, the approach proposed by Lee and Lee (2003), by Joachims (1999) or the multiclass version from Weston and Watkins (1999). Unlike CART, SVM is very stable and ϵ was hence computed on only one bootstrap sample ($B = 1$).

3.2 Different computations of the approximate gradient

In contrary to Gadat and Younes (2007), we made some slight modifications of the gradient descent to improve the speed of the algorithm with OFW+CART. We propose an averaged time version of the initial OFW as follows:

$$D_n = \frac{\sum_{i=1}^{n} \alpha_i \bar{d}_i}{\sum_{i=1}^{n} \alpha_i} \quad \text{with} \quad \bar{d}_i = \sum_{b=1}^{B} \frac{C(\omega_i^b, .)\epsilon(\omega_i^b)}{\mathbb{P}_i(.)},$$

where b is the bootstrap sample on which each CART tree is constructed and $\alpha_i = A/(B + i)$ is the step sequenced referred in section 2.2.
This enables the stochastic algorithm to better approximate the mean drift (2) than in the standard case. With CART, the approximation of $\nabla\mathcal{E}$ is actually much more difficult than in the SVM case since the variance of the stochastic algorithm seems higher using CART classifier. This averaging step is hence

crucial for the algorithm.

3.3 Detailed OFW+CART algorithm

Here is the detailed version of OFW+CART with bagging.

Let $\mathcal{G} = (\delta_1 \dots \delta_{|\mathcal{G}|})$, $\mu \in \mathbb{N}^*$ and η the stopping criterion. $\mathbb{A}$ is the unpruned classifier CART.

- For iteration $n = 0$ define $\mathbb{P}_0$ as the uniform distribution on $\mathcal{G}$
- While $|\mathbb{P}_{(n+\mu)} - \mathbb{P}_n|_\infty > \eta$:
  - For $b = 1..B$:
    extract ω_n^b from $\mathcal{G}^p$ with respect to $\mathbb{P}_{n,p} = \mathbb{P}_n^{\otimes p}$,
    draw a bootstrap sample b_{samp} and construct $\mathbb{A}_{\omega_n^b}^{b_{samp}}$,
    compute $\epsilon(\omega_n^b)$ on the out-of-bag sample $\bar{b}_{samp}$.
  - compute the averaged drift vector D_n as in 3.2,
  - update $\mathbb{P}_{n+1} = \Pi_{\mathcal{S}}[\mathbb{P}_n - \alpha_n D_n]$,
  - $n = n + 1$.

The last lines introduce a projection Π_S which corresponds to the natural affine projection into the simplex S of discrete probability measures. More precisely, we have

$$\Pi_S(q) = \arg\min_{p \in S} \|q - p\|^2.$$

Note that since $\mathbb{P}_n - \alpha_n D_n$ may have some negative coordinates, this projection is slightly different from a simple normalization step. Several details are provided in Gadat and Younes (2007).

3.4 Weighting procedure

An efficient way to take into account the unbalanced characteristics of the data set is to weight the internal error rate $\epsilon(\omega)$ according to the number samples of each class in the learning set. This would penalize a classification error made on the minority class and hence put more weight on the variables that help classifying this class instead of the majority class.
Let n be the total number of cases and m_k, $k = 1..K$ the number of cases in class k. We define the (normalized) weight of *each* case in class k by $w_k = \frac{1}{m_k \times K}$.
Then for each out-of-bag test case (*i.e.* the sample not drawn in the bootstrap sample), we note mis_k the number of misclassified cases from class k and the

weighted internal error rate is defined as:

$$\epsilon(\omega) = \sum_{k=1}^{K} mis_k \times w_k,$$

instead of $\frac{\sum_k^K mis_k}{n}$ in the no weighting case. This weighting procedure also stands for the evaluation step, see following section 3.5.

3.5 Performance measurement

Comparison of the prediction performance

Error rates of all methods on each data set were computed with the e.632+ bootstrap error estimate from Efron and Tibshirani (1997) that is adequate for small sample sizes data sets. Each algorithm will be learned on a bootstrap sample to avoid any overfitting during the gene selection evaluation (see Ambroise and McLachlan 2002). However, note that this performance evaluation does not dictate the optimal number of genes to select. The e.632+ only allows for the comparison of the performances of the different selection methods.

Stability

One can define the feature stability as the level of agreement between the set of selected genes chosen in each bootstrap sample with the set of selected genes using the full training set. The Jaccard index (Yeung and Burmgarner, 2003) then computed lies between 0 (low level of agreement) and 1 (high level of agreement) and will be used to compare the stability of all four ranking methods.

Definition 2 *Let $S(\Delta)$ be the set of the Δ selected genes from the entire training set and $S(nb, \Delta)$ the set of selected genes from the nb bootstrap sample. The number of true positives (TP) is the number of selected genes that were chosen in both $S(\Delta)$ and $S(nb, \Delta)$:*

$$TP = |S(\Delta) \cap S(nb, \Delta)|.$$

Similarly, we define as the false positives (FP) the number of selected genes that were chosen in $S(nb, \Delta)$ but not in $S(\Delta)$:

$$FP = |S(nb, \Delta) \setminus_{S(\Delta)}|,$$

and the number of false negatives (FN) the number of genes that were selected

in $S(\Delta)$ *but not in* $S(nb, \Delta)$*:*

$$FN = |S(\Delta) \setminus_{S(nb,\Delta)}|.$$

The Jaccard index $J(nb, \Delta)$ *is defined as* $TP/(TP + FP + FN)$ *and is high and close to 1 when there are many true positives and few false positives and false negatives. We then compute the averaged Jaccard index* J_Δ *over all nb samples for* Δ *varying between 1 selected gene and* Δ_{max} *selected genes.*

We expect therefore to rank the stability of each feature selection procedure with this Jaccard index.

3.6 Ranking methods

Multicategory ranking methods are still rare in the context of classification, especially in microarray data context. A comparative study is performed with the well-known Random Forests (RF, Breiman 2001). The three wrapper methods (OFW+CART, OFW+SVM and RF) were also compared to the F-test filter method, that is still widely used for selecting genes in the context of microarrays.
Although Random Forests can also be performed with a weighting approach such as Balanced Random Forests (BRF) or Weighted Random Forests (WRF) from Chen et al. (2004), we chose to compare all these methods with no weighting procedure.

4 Statistical assessment on public data sets

A short description of the five public data sets is first given. We then compare the results obtained with OFW+CART, OFW+SVM, RF and F-test with no weighting procedure. During the evaluation performance, the F-test selection was assessed with a *one-vs-one* linear SVM.
We finally focus on OFW and compare the weighted *vs.* non-weighted procedure and give some elements of discussion.

4.1 Multiclass data sets

We present the results obtained on five public multiclass data sets.

Table 1
Summary of the five data sets.

	Lymphoma	Leukemia	SRBCT	Brain	Multiple Tumor
# genes	4026	3000 [1]	2308	1963 [1]	2000 [1]
# classes	3	3	4	5	11
# obs.	62	72	63	42	90
# obs. per class	42/9/11	38/9/25	23/20/12/8	10/10/10/4/8	8/4/7/26/ 4/15/3/7/ 6/5/5

[1]pre-filtered with a very large F-test p-value.

(1) Lymphoma (Alizadeh et al., 2000) compares 3 classes of cells (42, 9 and 11 cases per class) with 4026 gene expressions.
(2) The 3-class Leukemia version (Golub et al., 1999) with 7129 genes compares the lymphocytes B and T in ALL (Acute Lymphoblastic Leukemia, 38 and 9 cases) and the AML class (Acute Myeloid Leukemia, 25 cases). The classes AML-B and AML-T are known to be biologically very similar.
(3) The Small Round Blue-Cell Tumor Data of childhood (SRBCT, Khan et al. 2001) includes 4 different types of tumours with 23, 20, 12 and 8 microarrays per class and 2308 genes.
(4) The Brain data set compares 5 embryonal tumours (Pomeroy et al., 2002) with 5597 gene expression. Classes 1, 2 and 3 count 10 microarrays each, the remaining classes 4 and 8.
(5) The Multiple Tumor data set initially compared 14 tumors (Ramaswamy et al., 2001) and 7129 gene expressions. We used the normalized data set from Yeung and Burmgarner (2003) with 11 types of tumor. To fit into a usual microarray framework (*i.e.* a small number of samples), we randomly selected 90 samples (out of 192) that have tumor types coming from breast (8), central nervous system (4), colon (7), leukemia (26), lung (4), lymphoma (15), melanoma (3), mesotheolima (7), pancreas (6), renal (5) and uterus (5).

The Brain and the Leukemia data sets were pre-filtered with a very large F-test p-value (0.1 and 0.2, leaving 1963 and 3000 genes). The Multiple Tumor data set was also pre-filtered with an F-test, leaving 2000 genes, to reduce the computation time of the algorithms. These data sets are succinctly described in Table 1.
All these data sets were chosen for their unbalanced characteristics as the minority class represents for each data set a small percentage of the total number of cases.All data sets were assumed to be correctly normalized.

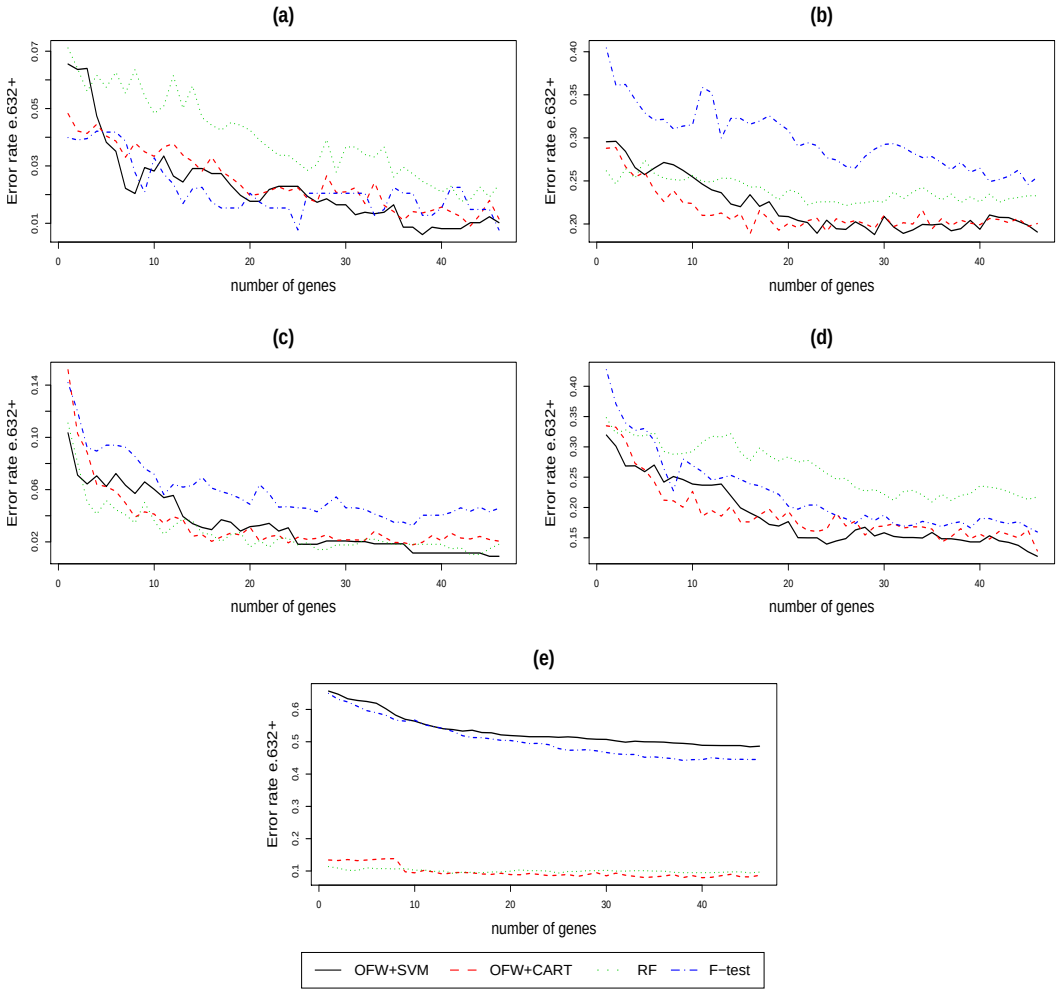

Fig. 1. Error e.632+bootstrap of several algorithms with respect to the number of genes on Lymphoma (a), Leukemia (**b**), SRBCT (**c**), Brain (**d**) and Multiple Tumor (**e**) .

4.2 Comparison of the ranking methods with no weighting procedure

Performance comparison

Figures 1 display the e.632+ error rates obtained on all data sets with respect to the number of selected genes with the different ranking methods.
The classification complexity of the data sets is easy to identify as Lymphoma **(a)** and SRBCT **(c)** display an evaluated error rate less than 7% for a selection of 10 genes, whereas for Leukemia **(b)**, Brain **(d)** and Multiple Tumor **(e)** , the error rates vary between 25 to 50 % for a selection of 10 genes.
OFW is generally among the best performers, and the error rates of OFW+CART and OFW+SVM are often very close, except for Multiple Tumor, where OFW+SVM gives a poor performance. We suspect that the aggregation of this type of binary SVM (*one-vs-one*) may not be adapted in this extreme multi-

class setting.
RF achieves good results on Leukemia, SRBCT and Multiple Tumor, whereas on Lymphoma and Brain, the performance of the RF selection is the worst. RF might therefore not succeed in selecting genes with information relevant enough, especially in Lymphoma, where all classes are easy to classify with too many informative variables.
On the contrary, the F-test achieves good results on Lymphoma and Brain. This filter method orders genes that are differentially expressed (*i.e.* significant) for at least one of the classes. If genes are differentially expressed for more than one class (or for all classes), the selected genes will all be informative enough and the performance will be good. With Leukemia, the F-test performs the worst. This data set is more difficult to classify as the 2 classes ALL-B and AL-LT are very similar (Golub et al., 1999). The difficulty is reinforced as ALL-B is the majority class while ALL-T is the minority class in this 3-class problem. The F-test thus first ordered significant genes that discriminated the easiest class (ALL-B), to the detriment of the other classes. In any case, these results show that one cannot draw general conclusions on the best method to apply. In general, OFW+SVM and OFW+CART were the best performers, especially OFW+CART in a high multiclass setting.

Remark on the performance assessment with e.632+ bootstrap error rate

The e.632+ error rate was chosen as it is the most adequate to compute the performance of the different methods on small sample data sets (Ambroise and McLachlan, 2002). However we did observe some weaknesses and the interpretation of the results should be done with caution. One would expect the error rate to increase when the number of evaluated variables becomes too big (as more noise enters the selection). This is not the case for any method using the SVM classifier and RF, which are known to base their classification task on the good variables among numerous and possibly noisy variables. The results that we obtain are in agreement with this fact. We did not observe this tendency with OFW+CART, as during the evaluation step, each aggregated tree is constructed on a small variable subset from the selection (see Lê Cao and Chabrier 2008 for the details of the algorithm).
The evaluation error rate should thus be solely used to compare the ranking methods between each others, and not to give an accurate classification error rate of a given variable selection.

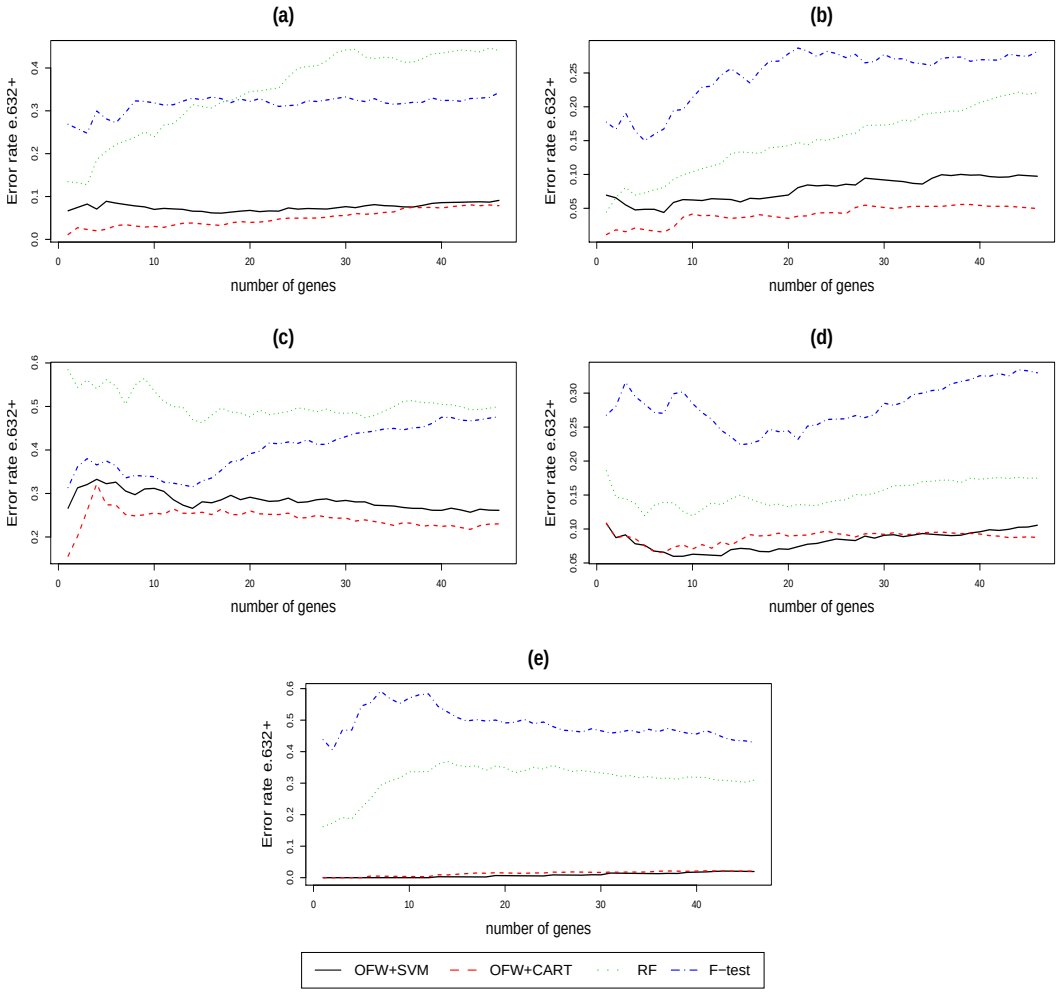

Fig. 2. Jaccard index of OFW+SVM, OFW+CART, RF and F-test with respect to the number of genes on Lymphoma (**a**), Leukemia (**b**), SRBCT (**c**), Brain (**d**) and Multiple Tumor (**e**).

Stability

Computation of the Jaccard index with respect to the number of selected genes are displayed in Figures 2. Maximum stability is obtained on easy data sets (Lymphoma **(a)** and SRBCT **(c)**) with a Jaccard index reaching 0.45 and 0.6. The F-test is undoubtedly the most stable method on complex data sets (Leukemia **(b)**, Brain **(d)**, Multiple Tumor **(e)**), although the performance is very poor (see section 4.2). RF is in general very stable compared to OFW+SVM and OFW+CART.
The good stability results of the filter method is easy to explain as the F-test selects redundant information usually only on the majority class, whereas the other methods select genes with relevant information on all classes. As the gene selection might be strongly dependent on the cases drawn in the bootstrap sample, especially if one of the classes is small, the methods focusing on the minority classes will consequently be less stable.

OFW+SVM and OFW+CART are stochastic methods and are hence less stable for all data sets. When the number of classes becomes large (Brain, SRBCT, Multiple Tumor), the stability results seem largely affected. A compromise needs hence to be taken between information (on all classes) and stability.

Table 2
Number of genes shared by several feature selection algorithms on Leukemia or Lymphoma for a selection of 50 genes.

Leukemia \ Lymphoma	OFW+SVM	OFW+CART	RF	F-test
OFW+SVM	#	12	11	12
OFW+CART	7	#	22	24
RF	17	18	#	30
F-test	3	6	11	#

Table 3
Number of genes shared by several feature selection algorithms on Brain or SRBCT for a selection of 50 genes.

Brain \ SRBCT	OFW+SVM	OFW+CART	RF	F-test
OFW+SVM	#	25	31	11
OFW+CART	8	#	29	15
RF	12	22	#	9
F-test	7	2	2	#

Insight into the different selections

Tables 2 and 3 provide more insight of the different 50 gene lists selected with all methods on each data set (not shown for Multiple Tumor). For example in Table 2 for the Lymphoma data set (upper triangle), OFW+SVM and OFW+CART selected 12 common genes among the 50 selected.
The most striking point is the very few number of shared genes between all methods, that highlights the characteristics of each ranking method. Generally, as they are constructed with the same classifier, RF and OFW+CART share a fair amount of genes (22 and 18 on Lymphoma and Leukemia, Table 2). Table 2 also shows that RF selected more significant genes (*i.e* differentially expressed with F-test) than OFW+CART/SVM (30 and 11 on Lymphoma and Leukemia). In Table 3, where the number of classes is bigger than 3 (SRBCT, Brain), the 3 methods RF, OFW+CART and OFW+SVM generally shared more genes together than with the F-test. This highlights the poor relevancy of a selection made with an F-test in this context.

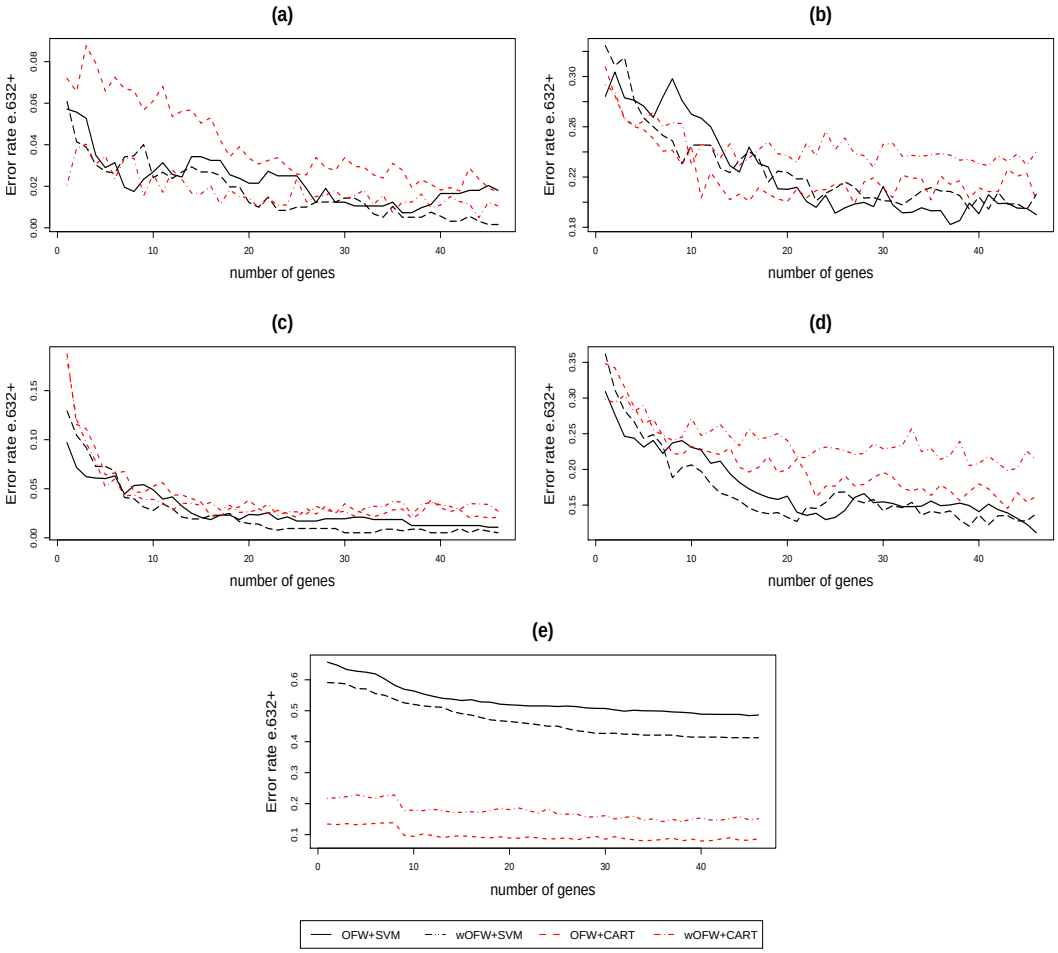

Fig. 3. Weighted e.632+ bootstrap error of OFW+CART and OFW+SVM with both procedures weighted and non weighted with respect to the number of genes on Lymphoma (**a**), Leukemia (**b**), SRBCT (**c**), Brain (**d**) and Multiple Tumor (**e**).

On all data sets except SRBCT, OFW+CART and OFW+SVM shared very few genes. This can be explained as the construction of these two classifiers is completely different: CART searches in the feature space the best variable and the best split to divide each node in the tree while SVM looks for the optimal hyperplane between two classes. For SRBCT where all methods except F-test seemed to share numerous genes, this can be explained as all methods seemed to perform equally well with the same relevant genes (see Fig. 1 (**c**)).
Note that the same tendency was observed if we reduced the size of the selection (*e.g.* from 50 to 10): the top selected genes were not necessarily the same from one selection to another.
The difficulty of the Multiple Tumor data set was strongly highlighted as no method shared more than 4 common genes. Given the poor performances of the F-test and OFW+SVM (section 4.2), this small overlapping result is to be expected.

4.3 Comparisons of the weighted and non-weighted procedures of OFW

The aim of this section is to compare the weighted and non-weighted versions of OFW only, as the other ranking methods do not share the same weighting procedure (especially WRF/BRF for RF, Chen et al. 2004), the F-test having no weighting procedure).

Performance comparison

In order to compare the internal weighting procedure in OFW+CART or SVM, we computed the e.632+ error rate for both approaches: weighted (wOFW) or non-weighted (OFW). We remind that the weighted procedure implies an internal weighted error rate in the gradient.
For the e.632+ computations, the learning of the *nb* bootstrap samples of wOFW or OFW for each classifier was performed. Then, during the testing phase, both types of learning were evaluated with a *weighted* e.632+. This was necessary in order to compare the improvement of the performance with the weighting approach. A non-weighting approach in e.632+ would indeed favour the majority class to the detriment of the minority class and would still give a (wrongly) low error rate.
Figures 3 display the weighted e.632+ error rate of OFW and wOFW with the application of either CART or SVM for the five data sets.
There is often a strong difference between the performances of OFW+CART and wOFW+CART, showing that CART seems affected by unbalanced classes, whereas there is no difference between the two variants of OFW+SVM. The *one-vs-one* SVM approach seems hence extremely well adequate for unbalanced classes. wOFW+CART seems to improve the error rate compared to OFW+CART on the easy data set Lymphoma (**a**). For SRBCT **(c)**, all methods perform similarly, whereas for Multiple Tumor **(e)**, wOFW+SVM is still affected by the high number of classes.
These graphs show that the weighting procedure in OFW+SVM seems not necessary in the multiclass case as the *one-vs-one* SVM aims to classify each class, even minority, as long as the number of classes remains reasonable (≤ 5 here). On the contrary, for OFW+CART, the weighting procedure might be needed as by construction, CART tends to favour the majority classes.

Stability

The comparisons of the Jaccard index for both versions of the algorithm is displayed on Figures 4. wOFW+SVM seems to improve the stability of the results of the 3-class data sets Lymphoma (**a**) and Leukemia (**b**). When the

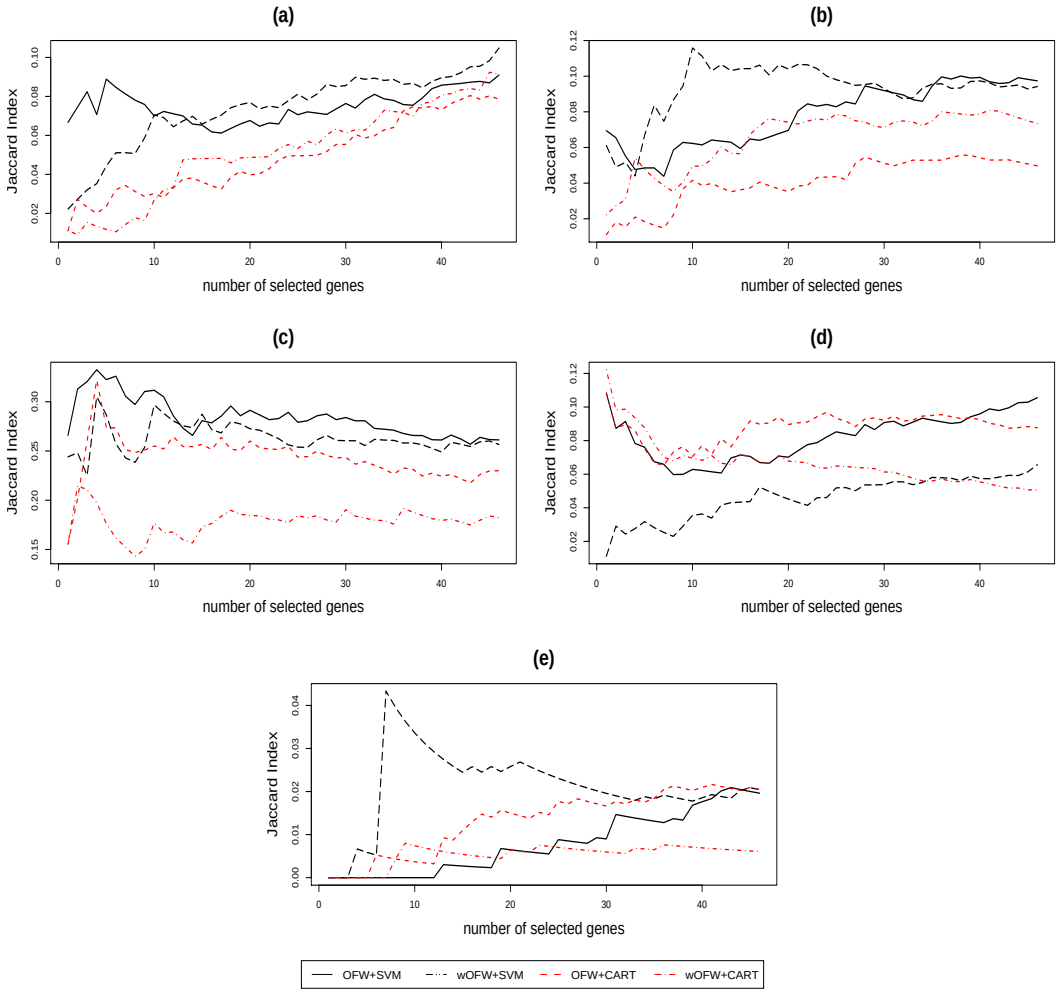

Fig. 4. Comparison of the Jaccard index with the weighted and non-weighted versions of OFW+SVM and OFW+CART on Lymphoma (**a**), Leukemia (**b**), SRBCT (**c**), Brain (**d**) and Multiple Tumor (**e**) .

number of classes is larger, the non-weighted versions are the most stable. These Jaccard indexes are very low as the proportion of the minority cases is often diminished during the bootstrap sampling and the selected variables discriminating the minority classes must strongly depend on each bootstrap sample. This explains the poor results obtained in Multiple Tumor (**e**).

Comparisons of the lists (weighted vs. non-weighted)

We compared the lists given by the weighted *vs.* the non-weighted procedures in OFW+CART or SVM in Table 4. There is a difference in the gene selections between the weighted and non-weighted version of OFW. For example on Lymphoma, OFW+SVM and wOFW+SVM shared 13 genes out of the 50 selected. This is surprising as section 4.3 showed that there was not a strong difference in the performance of both methods (Fig. 3 **(a)**). However,

Table 4
Number of genes shared by the weighted and non-weighted versions of OFW+SVM or OFW+CART for each data set (selection of 50 genes).

	Lymphoma	Leukemia	SRBCT	Brain	Multiple Tumor
OFW+SVM ∩ OFW+CART	12	7	29	8	0
wOFW+SVM ∩ wOFW+CART	16	5	24	4	0
OFW+SVM ∩ wOFW+SVM	13	13	31	18	5
OFW+CART ∩ wOFW+CART	27	11	25	13	2

with SRBCT, where all performances of the four tested version were similar (Fig. 3 **(c)**), the number of shared genes was quite close and high compared to the other data sets (from 24 to 31 in Table 4).
The less numerous the genes that are shared between OFW and wOFW, the better the improvement of the selection in terms of relevancy (as wOFW aims to favour minority classes). For example the selections of wOFW+SVM in Lymphoma might be more informative than the OFW+SVM selection, the same stands for wOFW+CART *vs.* OFW+CART in Leukemia and Brain. However, the high complexity of the Multiple Tumor data set show the limitation of the algorithm OFW, as well as a strong difference between all proposed versions of this meta algorithm.

5 Application and biological interpretation.

When developing feature selection algorithms for microarray data, we believe it useful to show if the actual gene selection is biologically relevant for the study. The biological interpretation is hence valuable to show the applicability of such algorithms.

5.1 The pig folliculogenesis data set

This experiment was designed to compare different sizes of healthy follicles granulosa cells during the last stages of antral phase. Large (L), Medium-sized (M) and Small (S) follicles from three different sows per size category were used. After extraction, the RNA isolated from these cells was used to hybridise 42 microarrays that includes duplicates, resulting in 20 Large, 14 Medium-sized and 8 Small follicle cases (GEO accession number: GSE5798). After a normalizing and a filtering steps, the expression of 1564 clones remain on each microarray.

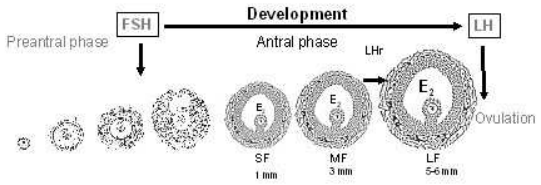

Fig. 5. The three follicle classes: Small, Medium-sized and Large.

The main characteristic of this data set is the obvious difference between the Large follicles and the others. This is due to the biological properties of the data mainly including the appearance of LH receptors between the Medium and Large follicles (Figure 5). Medium-sized and Small follicles are still in the growth process whereas the Large follicles are completely differentiated to produce steroid hormones. Moreover, during the measurements that assign each follicle its class, the diameters of the Small and the Medium-sized follicles are very similar (1-2mm and 3 mm) whereas the Large ones cannot be mistaken (5-6mm). Another factor to consider is the vast majority of regulated cDNAs (clones) over-expressed in the Large follicles and hence the minority of regulated cDNAs (referred to as *genes* instead of clones) that are over-expressed in the Small ones.
We are clearly here in the practical case where classes are unbalanced, and where the number of original samples is extremely small, as some of the microarray experiments were duplicated.

5.2 Results and biological interpretation

The analysis of this data set with Random Forests and F-test was performed in Bonnet et al. (2008) and gave biologically relevant results. We focus here on the application of OFW+CART/SVM and their weighted variants.

Application of OFW

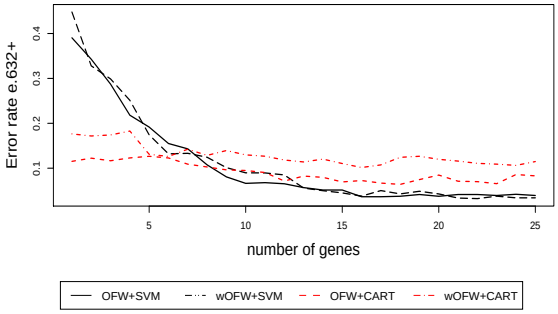

Fig. 6. Weighted e.632+ bootstrap error of OFW+CART and OFW+SVM with both procedures weighted and non weighted with respect to the number of genes on the follicle data set.

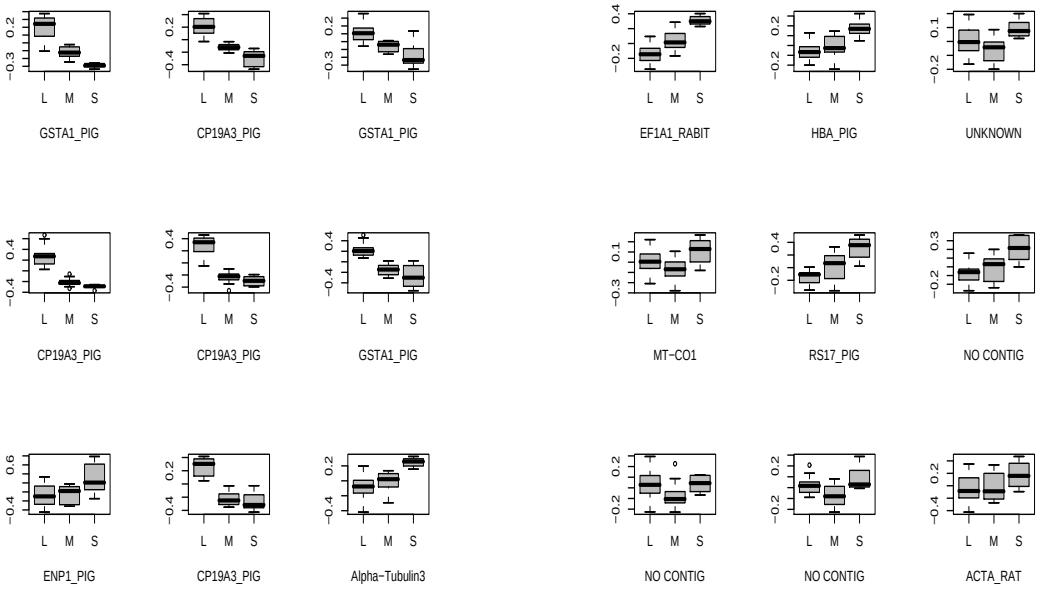

Fig. 7. Boxplots of the 9 top genes selection with OFW+CART (left) or with OFW+SVM (right) on the follicle growth data set. Boxplots are displayed for each class (L, M and S).

When the number of original samples is extremely small, the e.632+ bootstrap error rate must be considered with caution and should not be the only argument to favour a gene selection coming from a feature selection method rather than another. Fig. 6 displays the weighted e.632+ error rate for all approaches. Both OFW+SVM and wOFW+SVM seem to give the best performance.

However, our experience show that the most biologically relevant results do not always give the best statistical performance (Lê Cao et al., 2007). This is why biological interpretation is a crucial step when analyzing microarray data.

Interpretation of the results

In these four gene lists we identified the genes GSTA1 and Cyp19A3 which are known to be over-expressed during follicular development (Keira et al., 1994; Slomczynska et al., 2003) and nexin, ACTA2, ATF7, UBC, that were not selected by F-test and Random Forest in the previous analysis.
Figure 7 displays the boxplots of the 9 top genes selected either with OFW+CART or OFW+SVM for each class (L, M or S). They show that while a minority of selected genes are over-expressed in the S class with OFW+CART (left), a majority of them are over-expressed in the S class in the OFW+SVM selection (right). This tendency can be generalized for a larger list of genes. It seems here that the construction of the *one-vs-one* SVM tends to mostly favour genes discriminating the minority class S rather than the majority class L, as L seems too easy to classify.
When applying wOFW+CART and wOFW+SVM, this tendency is still observed, with more genes that are over-expressed in S for the wOFW+CART selection (not shown).
The biological analysis shows that most of the over-expressed genes in the S class code for ribosomic proteins that may be associated with a decrease of proliferation during follicular growth from Small to Medium follicles. The wOFW+SVM selection seems hence to give a better discrimination between S and M classes. However, we also identify in this selection a great number of unknown genes that will need further investigation. The wOFW+CART selection seemed not appropriate here since two negative controls were selected and the OFW+SVM selection missed the known discriminative gene CYP11A3.
This section shows that depending on the experimental design, as well as the precise biological questions, the statistician might not answer the study's aim if the conclusions are only drawn from statistical results.

6 General remarks

6.1 Computation time.

The experiments were performed with `R` with a 1.6 GHz 960 Mo RAM AMD Turion 64 X2 PC for OFW+SVM (implementation in `R`) and OFW+CART (implementation in C in a `R` package). The learning time of OFW mostly depends on the initial number of variables in the feature space and the step of the stochastic scheme, as well as the size of ω and the number of trees aggregated for OFW+CART. For Brain (Lymphoma) that contains 1963 (4026) genes,

the learning took about 1 (1.5) hour for OFW+SVM for 200 000 iterations.It took 1 (3.5) hour for OFW+CART for 5000 iterations.

6.2 Complexity of OFW.

The complexity of the meta algorithm OFW depends on two points. The first one is the nature of the algorithm used with SVM. The second point is the convergence speed of the stochastic scheme towards a minimum of the energy $\mathcal{E}$.

The complexity of each algorithm used with OFW (CART, SVM, Multiclass SVM, ...) may be very variable and depends on the choice of the user. For instance, with this meta algorithm, each iteration computes a SVM with N_s samples described by p variables and the complexity of each step is at most $p \times N_s^2$ since $p > N_s$ in this study (see detailed computation of this complexity in Burges 1998).

Regarding the second points, the convergence to an optimal state x^* using a standard (non averaged) Robbins-Monro stochastic approximation scheme $(X_n)_{n\in\mathbb{N}}$ is described by the following assessment:

$$\sqrt{\frac{n}{\log n}}(X_n - x^\star) \to \mathcal{N}(0, \Lambda^*). \tag{5}$$

This last theoretical derivation can be found in Duflo (1997). In this last statement, Λ^* is the trace of Hessian matrix of $\mathcal{E}$ computed on the optimal state x^*. If n iterations are run in the initial version of OFW Gadat and Younes (2007), the convergence speed is bounded by $O\left(\frac{\log n}{n} Tr(\Lambda^*)\right)$. The interest of the OFW meta algorithm is significant since an exhaustive search of p-uple among N features would required C_N^p iterations.

The interest of the averaging step introduced in section 3.2 is to improve the rate of convergence of the stochastic scheme reducing the variance of the estimate D_n. The theoretical derivations concerning the rate of convergence is at the moment an open issue but it is likely to reduce the $Tr(\Lambda^*)$ term introduced in (5).

6.3 General remarks

This study shows that microarray data sets have various levels of difficulty and are quite unpredictable if there is not a solid biological knowledge background of the data set. The analysis of several public data set shows that there

is no data set that seems to behave like the other. Without biological expertise, it is extremely difficult to assess the relevancy of the results. Simulating a set of data would not help giving more insight in the applied methodologies, as simulating a data set like microarray is an extremely complex work.
The performance assessment of the methods could be computed, but had sometimes serious limits, due to the evaluation method and the applied algorithms, or the small number of samples. This study shows that the evaluation part has to be taken with caution by the user in search of the "best" method. Furthermore, although there seemed to be no improvement of the performance of the method when applying wOFW+SVM, the resulting gene selection seemed to contain more biological information on the minority class. Our evaluation performance method might hence not be adequate in this context, especially for OFW+CART where a "double bootstrap sampling" is performed during the evaluation step. We also believe that the performance of wOFW+CART can be improved by directly including weights during the construction of the trees.
Both multicategory classifiers CART and *one-vs-one* SVM that were applied with OFW seemed to perform better than the other tested methods, except when the number of classes was very high (here ≥ 5). In this case, aggregating binary *one-vs-one* SVMs seems limited. Lee and Lee (2003) mentioned that the *one-vs-rest* SVM can also give bad results if several classes are similar, as it is often the case with biological data. One should investigate instead the implementation of a multiclass SVM, as was proposed by Weston and Watkins (1999), to solve the multiclass optimization quadratic problem into the SVM directly rather than aggregating binary SVMs.
Regarding the performances, choosing between these two methods seems difficult. If the user is interested in biological relevancy of the gene selection, or if the number of classes is high, then OFW+CART might be adequate as the construction of CART really fits this requirement (*i.e* finding genes with differential expression in different classes at each node of the tree). However if the interest mostly lies in the classification task and finding predictive genes, then OFW+SVM might be appropriate. By construction, it searches the best hyperplane between two of the classes. In contrary to CART, SVM optimizes a cost criterion based on the classification performance.

7 Conclusion

Starting from Lê Cao et al. (2007) that provided interesting results for binary problems, we extended the application of OFW+CART and OFW+SVM *one-vs-one* for multiclass microarray problems. These data sets are known to be difficult because of their high dimensionality with a small sample size and at least one of the classes that is under represented. For most classifiers, this

often results in a good overall classification accuracy even though the minority classes are misclassified.
We first compared OFW+CART and OFW+SVM with two other methods, Random Forests and the still widely used F-test in gene selection. All methods were performed with no weighting procedure. Our results showed that our two methods generally gave good results in terms of error rate estimation. The filter method F-test seemed not appropriate for multiclass datasets and the stability of the results tended to be better in OFW+SVM than CART.
We then compared the weighted version of wOFW+CART or SVM. There seemed to be no difference in the performance evaluation between the weighted and the non-weighted version of OFW+SVM, which generally performed the best. The performances of the two versions of OFW+CART differed largely, due to the extensive use of bootstrap samples during the learning step. The relevancy of the selected genes with wOFW should however be improved as they aim at discriminating the minority classes.
In the case where the classes were numerous (≥ 5) and unbalanced, OFW+CART clearly outperformed OFW+SVM. These poor results were due to the type of binary SVMs that were aggregated for the multiclass purpose. The implementation of OFW with a multiclass SVM might improve these results.
Application and biological interpretation on a real world data set (pig folliculogenesis data set) show that the wOFW+SVM selection might give relevant results that are complementary with a previous analysis.

Availability

OFW is implemented in an `R` package called `ofw`.

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