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Gene Selection for Microarray Cancer Data Classification by a Novel Rule-Based Algorithm

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Abstract: Due to the disproportionate difference between the number of genes and samples, microarray data analysis is considered an extremely difficult task in sample classification. Feature selection mitigates this problem by removing irrelevant and redundant genes from data. In this paper, we propose a new methodology for feature selection that aims to detect relevant, non-redundant and interacting genes by analysing the *feature value* space instead of the feature space. Following this methodology, we also propose a new feature selection algorithm, namely Pavicd (Probabilistic Attribute-Value for Class Distinction). Experiments in fourteen microarray cancer datasets reveal that Pavicd obtains the best performance in terms of running time and classification accuracy when using *Ripper-k* and *C4.5* as classifiers. When using SVM (Support Vector Machine), the Gbc (Genetic Bee Colony) wrapper algorithm gets the best results. However, Pavicd is significantly faster.

Keywords: gene selection; feature selection; microarray classification

1. Introduction

Microarray is a multiplex technology used in molecular biology and medicine that enables biologists to monitor expression levels of thousands of genes [1]. Many microarray experiments have been designed to investigate the genetic mechanisms of cancer [2] and to discover new drug designs in the pharmaceutical industry [3]. According to the World Health Organization, cancer is among the leading causes of death worldwide accounting for more than 8 million deaths. Therefore, finding a mechanism to discover the genetic expressions that may lead to an abnormal growth of cells is a first order task today. To build a microarray, short sequences of genes tagged with fluorescent materials are printed on a glass surface for hibridization [4]. Then, the slice is scanned and goes through various data processing steps including image data collection, quality control and normalization. The resulting dataset is a two-dimensional array $\mathbf{D}$ with thousands of columns (genes) and several rows (instances):

$$\mathbf{D} = \begin{bmatrix} x_1^1 & \cdots & x_1^n & c_1 \\ \vdots & \ddots & \vdots & \vdots \\ x_m^1 & \cdots & x_m^n & c_m \end{bmatrix}.$$

Every instance x_j (a row in $\mathbf{D}$) is described by a row vector $[x_j^1, \ldots, x_j^n, c_j]$ that represents a labeled genetic expression: x_j^i refers to the expression level of gene f_i, and $c_j \in C$ is the classification for the j-th sample. C may represent different types of cancer or a binary label for cancerous and non-cancerous tissue.

Analysis of microarray data presents unprecedented opportunities and challenges for data mining in areas such as: sample classification and gene selection [5,6]. For sample classification, the microarray matrices serve as training sets to a given classifier, to find a classification function $\ell : \mathbf{D} \rightarrow v(c)$ that

is able to classify an arbitrary sequence of genes with unknown class from $v(c) \in C$. Classification function ℓ is built from analysing the relation between labeled sequence of genes in $\mathbf{D}$. The performance of supervised classifiers is often measured in three directions: efficiency, representation complexity and accuracy. The efficiency refers to the time required to learn the classification function ℓ, while the representation complexity often refers to the number of bits used to represent the classification function [7]. One of the most common metrics to measure the accuracy of a supervised classifier is the error rate defined as:

$$Err(\ell, \mathbf{D}) = \frac{1}{m} \sum_{j=1}^{m} \overline{\delta}(\ell(x_j), c_j), \tag{1}$$

where m is the number of sequence of genes in $\mathbf{D}$ and $\overline{\delta}$ is the complement of the Kronecker's delta function, which returns 0 if both arguments are equal and 1 otherwise.

The main obstacle in microarray datasets arises from the fact that the genes greatly outnumber the sample observations. As a popular example, in the "Leukemia" dataset, there are only 72 observations of the expression level of 7129 genes [8]. It is clear that, in this extreme scenario sample, classification methods cannot perform well because of the "curse of dimensionality" phenomena, where excessive features may actually degrade the performance of a classifier if the number of training examples used to build the classifier is relatively small compared to the number of features [7].

Feature selection plays an essential role in microarray data classification since its main goal is to identify and remove irrelevant and redundant genes that do not contribute to minimize the error of a given classifier [9]. Basically, the advantages of feature selection include selecting a set of genes $\tilde{F} = \{f_{i_1}, \ldots, f_{i_k}\} \subsetneq F$ with:

$$Err(\ell, \mathbf{D}_{\tilde{F}}) \leq Err(\ell, \mathbf{D}), \tag{2}$$

where $\mathbf{D}_{\tilde{F}}$ is the result of projecting $\tilde{F}$ over $\mathbf{D}$. In addition, when a small number of genes are selected, their biological relationship with the target diseases is more easily identified. These "marker" genes thus provide additional scientific understanding of the causes of the disease [6]. Feature selection plays a fundamental role for increasing efficiency and enhancing the comprehensibility of the results.

In gene selection, genes are evaluated based on (i) their individual relevance to the target class, (ii) the redundancy level respect to other genes, and (iii) how the gene interacts to other genes [10]. The relevance and the redundancy level of a gene are often measured by correlation coefficients such as: Pearson's correlation [11], Mutual Information (*MI*) [12], Symmetrical Uncertainty [13] and others. On the other hand, it is said that a gene interacts with other genes if, when combined, it becomes more relevant [14]. Most of the feature selection algorithms in the literature evaluate features by only using one or two of these aspects, but not using all three of them as a whole. This may lead the algorithm to output low-quality solutions, especially when redundant genes and interacting genes are abundant in the problem. In addition, we have detected that most of feature selection algorithms in the literature suffer from what we call the *integrality problem* (to be defined). Roughly speaking, the *integrality problem* occurs when the relevance of a gene is measured by the average of the correlation of their values with the target class. We will further analyse this problem in Section 3.

While not losing sight of the fact that microarray cancer datasets are large and abundant in "noisy" genes, the first goal of this paper is to present a new algorithm able to efficiently detect and select relevant, non-redundant and interacting genes to improve the accuracy of classification algorithms. In order to reach this task:

- We first introduce a new feature selection methodology that can avoid the *integrality problem.*
- Second, we present a new simple algorithm that can detect irrelevant, redundant and interacting genes in an efficient way.
- Finally, the new algorithm is compared with five state-of-the-art feature selection algorithms in fourteen microarray datasets, which include leukemia, ovarian, lymphoma, breast and other cancer data.

2. Feature Selection for Microarray Cancer Data

Feature selection can be accomplished in a variety of ways depending on the characteristics of the data. In this section, we review most popular algorithms used in microarray cancer data, taking into account two basic group of algorithms: gene ranking and pairwise evaluation methods.

2.1. Gene Ranking Methods

In order to find the optimal subset of features that maximize some feature selection criterion function, an exhaustive search is required, which is a classic NP (non-polynomial) hard problem. Various heuristics and greedy algorithms have been proposed to find suboptimal solutions. The individual relevance score $r(f_i; C)$ of a gene f_i is a common term that refers to the power of a single gene to predict the class feature C. Assuming independence between genes, the individual relevance score can be used as a metric to select the genes that better predict the class (target disease or phenotype) under certain thresholds. That is, genes are ranked using their individual relevance score and then the top genes are selected. These algorithms are called gene ranking methods and often use correlation, distance and information measures between a single gene and the target class to find genes with high discriminatory power among diseases or phenotypes.

As an instance, the Recursive Feature Elimination algorithm evaluates a gene f_i by computing the added error when f_i is removed from the current set [15]:

$$RFE(f_i; C) = \Big(\sum_k \alpha_k \, c(x_k) \, x_k^i \Big)^2, \tag{3}$$

where $c(x_k) = \{+1, -1\}$ returns the class corresponding to the instance x_k. α_k is the optimal weight of the k-th instance, which is computed with a linear discriminatory classifier such as the Support Vector Machine (SVM). Different from most of the gene ranking algorithms, in the Recursive Feature Elimination approach, a greedy search is performed to add at the end of the ranking the gene f_i that minimize $RFE(f_i; C)$. Although this atypical way of building a ranking leads to a relatively high computational complexity, the quality of the output is high [15]. Fisher Score [16] is a distance-based gene ranking algorithm. Let n_c be the number of instances with class c and let μ_{ic} and σ_{ic}^2 be the mean and variance of the i-th value of all instances in the data, respectively. The Fisher Score represents the average of the distances among instances with different classes when the data are projected with the gene f_i. The Fisher score metric is defined as follows:

$$FS(f_i; C) = \frac{\sum_{c=1}^{|C|} n_c (\mu_{ic} - \mu_i)^2}{\sum_{c=1}^{|C|} n_c \sigma_{ic}^2}. \tag{4}$$

Another example is RELIEF [17], which computes the relevance score of a gene f_i based on the capability of f_i to discriminate among instances of different classes. Assuming instance x_k with class c_+ is randomly sampled from the data, and H_k and M_k are two sets of instances (in the neighborhood of x_k) with class c_+ and c_-, respectively, then a gene has high separability power if it has similar values (expression) in instances from H_k and different values in instances from M_k. RELIEFF is an extension of RELIEF that handles multiple classes by splitting the data into series of two-class data [18]. The individual relevance of each gene f_i is assessed by computing the average of its separability power in l instances randomly sampled. That is,

$$RF(f_i; C) = \frac{1}{|C|} \sum_{k=1}^{l} \Big(-\frac{1}{|M_k|} \sum_{x_j \in M_k} d(x_k^i, x_j^i) + \sum_{c \neq c(x_k)} \frac{p(c)}{|H_k|(1 - p(c))} \sum_{x_j \in H_k} d(x_k^i, x_j^i) \Big),$$

where $p(c)$ is the probability that an instance is labeled with class c and $d(x_k^i, x_j^i) = (x_k^i - x_j^i)/(max(f_i) - min(f_i))$, with $max(f_i)$ and $min(f_i)$ being the maximum and minimum value of gene f_i.

It is well known that the assumption of independence between genes leads to the selection of redundant genes and over simplifies the complex relationship between genes [19]. Genes are well known to interact with each other [20]. Several recent research papers on feature selection, especially gene selection [19,21,22], took into consideration the correlation between genes explicitly by genes' pairwise evaluation.

2.2. Pairwise Evaluation Methods

Oppositely to the gene ranking algorithms, pairwise evaluation algorithms are able to remove redundant genes. The way most of these algorithms operate is as follows. First, the relevance score $r(f_i, C)$ of each gene $f_i \in F$ is computed, and, second, pairwise evaluations $r(f_i, f_j)$ between genes are performed to detect genes that are highly correlated to others (redundant genes). Finally, following some criteria, only relevant and non-redundant genes are selected. As an example, the algorithm Fcbf (*Fast Correlation based-Filter*) [23] first ranks all genes $\{f_1, \ldots, f_n\}$ in the descending order of the Symmetrical Uncertainty scores. Then, starting from the best/first gene in the ranking f_i (with $i = 1$), it applies a redundancy filter to all of the genes f_j with $j > i$ as follows. If $SU(f_i; f_j) > SU(f_j; C)$ holds, then gene f_j is removed. Since the overall complexity of algorithm Fcbf is $O(mn \log n)$, where m is the number of instances in the data, this algorithm is scalable to large microarray data.

CFS(*Correlation-based Feature Selection*) is one of the most well-known feature selection algorithms that take advantage of a redundancy filter [24]. Cfs use a *Sequential Forward Search* to generate candidate sets. Every candidate set $\tilde{F}$ is heuristically evaluated as follows:

$$Cfs(\tilde{F}, C) = \frac{|\tilde{F}|\,\overline{r_{cf}}}{\sqrt{|\tilde{F}| + |\tilde{F}|(|\tilde{F}| - 1)\,\overline{r_{ff}}}}, \tag{5}$$

where $\overline{r_{cf}}$ represents the average of the relevance score of each gene in $\tilde{F}$ and $\overline{r_{ff}}$ is the average of the redundancy score of all possible pair of genes in $\tilde{F}$. Finally, from all the candidate sets, the one with higher *Cfs*() value is selected. The time complexity of this algorithm is quadratic in terms of number of genes. Therefore, Cfs is not recommended for high-dimensional microarray data classification problems.

The *Minimum Relevance Maximum Relevance* (mRMR) algorithm uses a very similar process to select sets of genes [22]. In each iteration, the gene $f^* \in F \setminus \tilde{F}$ that optimizes certain evaluation functions is selected. Again, the evaluation function corresponds to a balance between the averages of the relevance score and redundancy score of the set of genes already selected $\tilde{F}$:

$$f^* = \underset{f_i \in F \setminus \tilde{F}}{\operatorname{argmax}} \left\{ \frac{MI(f_i, c)}{\frac{1}{|\tilde{F}|} \sum_{f_j \in \tilde{F}} MI(f_i, f_j)} \right\}. \tag{6}$$

Assuming that the optimal number of features is not known a priori, one of the disadvantages of mRMR is that the number of features to select must be specified.

Genetic Bee Colony (Gbc) [25] is a well known algorithm in the field of microarray data analysis. Gbc combines the advantages of two naturally inspired algorithms: *Genetic Algorithm* and *Artificial Bee Colony*. Since evolutionary algorithms are time-consuming, in Gbc algorithm, the search space is drastically reduced in the first step by discarding the features eliminated by MRMR. In the reduced dataset, *Artificial Bee Colony* for feature selection is then run with additional crossover and mutation operations, borrowed from *Genetic Algorithms*, to enhance the exploration process. Although this

algorithm is not so fast, it can have a high accuracy since a *Support Vector Machine* algorithm is used to evaluate the candidate sets by cross validation.

Although feature ranking and pairwise evaluation methods are quite fast and easy to implement, they are not able to detect complex relations among genes. This is why, in high-dimensional microarray data, they may output low-quality sets. To illustrate, consider the class target function $c = f_1 \oplus f_2$ where $\{f_1, f_2, \ldots, f_n\} \in F$ are binary genes and $\oplus$ denotes the *xor* operator. Beforehand, we may expect that $\{f_1, f_2\}$ won't be selected because both genes by themselves are uncorrelated with c. If we consider that genes in $F \setminus \{f_1, f_2\}$ can not accurately describe the class, then we can not expect a good performance of the classifier after reducing F by any of the feature ranking or pairwise evaluation algorithms. Figure 1 depicts a numerical version of the aforementioned example.

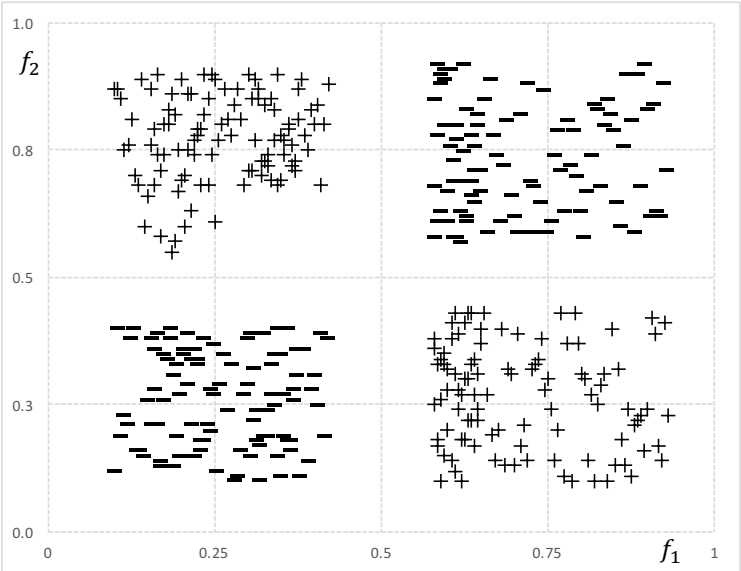


Figure 1. Numerical features f_1 and f_2 are represented in a two-dimensional space to demonstrate their interaction to discriminate between class $+$ and class $-$.

The main motivation of this paper is to present an efficient gene selection algorithm able to detect complex relation among relevant genes that yields a significant improvement in the sample classification problem. In the next section, we present a novel methodology for gene selection and a new algorithm derived from such methodology.

3. Materials and Methods

In this section, we introduce a new methodology to create feature selection algorithms that take advantage of feature value information to avoid the *integrality problem* mentioned in Section 1. For a better understanding of the *integrality problem*, consider the dataset depicted in Figure 2.

Note that the *Symmetrical Uncertainty* of f_1, f_2, f_3 and f_4 with respect to class C is 0.729, 0.57, 0.71 and 0.628, respectively. Therefore, most of the feature selection algorithms described in Section 2, will select f_1 as the best feature, and the rest of the features might be selected or not according to their correlation (redundancy score) with f_1. However, it is clear that class C is perfectly predictable by three one-precedent rules when $\{f_2, f_3, f_4\}$ is selected.

This problem occurs because features in $\{f_2, f_3, f_4\}$ have at least one value that is highly correlated with a class label and its other values are not correlated with the class. Consequently, if the relevance of these features (genes) is measured by averaging the prediction power of all its *feature values*, then this feature may be considered irrelevant. We call this phenomena the *integrality problem*. Note that we call the correlation of a *feature value* f_i^j with respect to a class label of C, to the existing correlation between the binary feature obtained from the respective feature f_i and a given class label. As an example,

the feature value f_3^a of feature $f_3 = \{b, c, b, c, b, b, b, a, a, a\}$ is $\{0, 0, 0, 0, 0, 0, 0, a, a, a\}$. Note that the correlation between f_3^a and the target class C, given that $C = c$, is maximal.

f_1	f_2	f_3	f_4	C
0	B	b	0	a
0	B	c	0	a
0	A	b	0	a
1	A	c	0	a
1	C	b	1	b
1	C	b	2	b
1	C	b	1	b
3	A	a	2	c
2	B	a	1	c
2	B	a	1	c

Figure 2. Dataset with interacting-genes.

3.1. New Methodology for the Gene Selection Problem

Several feature selection methodologies have been proposed in the literature [9,23]. However, the methodology we introduce in this section is designed so that the search is performed over *the expressions of genes* (*feature values*) and not over genes (features). For simplicity, from now on, we refer to an *expression of a gene* as a *feature value*, and we refer to a gene as a feature.

As stated above, when a feature has only a *feature value* that is highly correlated with a class label, then the average of the relevance of all the *feature values* may be small. Consequently, this feature is often removed by most of the current feature selection algorithms, leading to the loss of important information to predict certain class labels. In order to avoid the *integrality problem*, our methodology is as follows:

- First, for each class label $c_k \in C$, the *feature values* that are highly correlated with the class label c_k (according to some evaluation function) are stored in $\mathscr{G}_k$. Optionally, a filter process may be carried out, by eliminating *feature values* in $\mathscr{G}_k$, whose correlation score does not exceed a certain threshold. From now on, we call this step the Relevance Analysis. Note that $\mathscr{G}_k$ is a cluster of *feature values* with the highest correlation score with respect to c_k.
- Second, *feature values* in $\mathscr{G}_k$ are evaluated/tested among them to determine their redundancy and interaction level. *Feature values* that are redundant and do not interact with other *feature values* are removed from $\mathscr{G}_k$. From now on, we call this step the Integration Analysis.
- Third, the set of features that correspond to the *feature values* in each $\mathscr{G}_k$ is returned as the solution.

This methodology is very simple and easy to reproduce. The only entries required are: an evaluation function (that estimates how good an individual *feature value* is to predict a class label) and a threshold for the Relevance Analysis; and an evaluation function (to measure how good two or more *feature values* are to predict a class label) for the Integration Analysis. However, the main property that distinguishes this methodology from other feature selection algorithms relies on the fact that the selection process is carried out over the *feature value* space and not over the feature space. This property may enhance the quality of the feature selection process because features are discriminated according to their contribution to predict only one class label and they are not forced to contain all the necessary information to predict the entire set of class labels, in order to be classified as "good" features. The methodology is depicted in Figure 3.

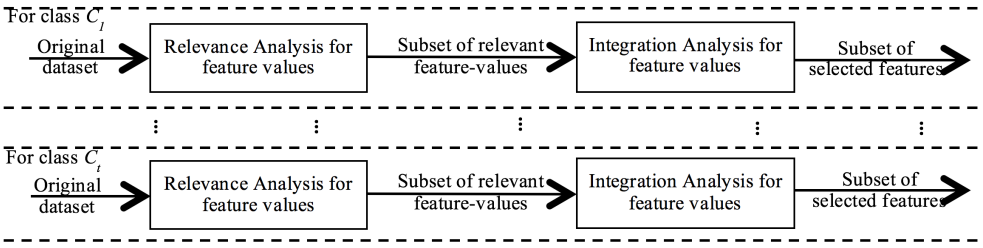


Figure 3. New feature selection methodology, based on the search of *feature values*, to avoid the *integrality problem*.

3.2. Pavicd: A Probabilistic Rule-Based Algorithm

We now introduce a new algorithm, namely Pavicd (Probabilistic Attribute-Value Integration for Class Distinction), which is based on the methodology aforementioned. In order to develop the algorithm, we take into account three aspects: first, how to deal with non-binary datasets, second, how to build $\mathscr{G}_k$ for each class label c_k, and third, to develop functions to measure the relevance, redundancy and interaction score of *feature values*.

The first step in Pavicd is the preparation of data. Since the proposed methodology is based on the evaluation of *feature values*, instead of features, dealing with non-binary data can be difficult. However, to deal with non-binary data, Pavicd builds a new space of binary features through the decomposition of each feature f_i in (v number of *feature values* of f_i) new binary features where each one of them take value "1" in the position, where the respective *feature value* appears in the original feature and takes value "0" in the other positions. Note that this conversion is reversible because the original feature could be obtained through the union of its binary features. With this transformation, a feature is analysed piecemeal, so that its most intrinsic useful information to predict a given class label is easily identified.

The second step is to determine, and store in $\mathscr{G}_k$ which of the entire sets of *feature values* are relevant for a given class label c_k. Here, we adopt a very simple approach that consists of selecting the covering or reliable *feature values* for a given class label c_q. Note that we use two thresholds, namely λ and δ, to fix the lower bound value for the selection of covering and reliable values, respectively.

Definition 1. *A feature value f_i^j is said to be **covering** with respect to the class label c_q if $c_q \in \text{argmax}_{c_k \in C} P(f_i = f_i^j | C = c_k)$ and $P(f_i = f_i^j | C = c_k) > \lambda$.*

Definition 1 suggests that a *feature value* f_i^j is covering with respect to the class c_q if the conditional probability of f_i^j given c_k is the largest among all the class labels in C. Note that all *features values* in **D** are covering for at least one class label. Therefore, we use the threshold $0 \leq \lambda < 1$ to discriminate between "good" covering values and "bad" covering values for a given class label.

Definition 2. *A feature value f_i^j is said to be **reliable** with respect to the class label c_q if $c_q \in \text{argmax}_{c_k \in C} P(C = c_k | f_i = f_i^j)$ and $P(C = c_k | f_i = f_i^j) > \delta$.*

According to Definition 2, a *feature value* is likely to be reliable for a given class c_q if it occurs many times in c_q and almost does not occur in the rest of the class labels. Note that, again, we introduce a new threshold $0 \leq \delta < 1$ to filter the *feature* values.

In the third step, we carried out the Integration Analysis by means of a *sequential forward search*. The *sequential forward search* is twofold. First, the best feature value in $mathscrG_k$ is identified and included in the current solution set $\tilde{\mathcal{F}}_k$; and second, the *sequential forward search* itself is performed. To select the best feature value in $mathscrG_k$, we use the following evaluation function:

$$\mu(f_i^j, c_k) = \frac{P(f_i = f_i^j | C = c_k) + P(C = c_k | f_i = f_i^j)}{2}. \quad (7)$$

This measure is equal to 1 when f_i^j completely covers c_k and does not occur in any other instance with different class (as *feature values* f_2^C, f_3^a and f_4^0 in the example of Figure 2), and it takes value 0 if the feature value does not occur in any of the instances labelled with class c_k. In other words, we may expect that the best *feature value* is a highly-covering and highly-reliable one. For the *sequential forward search*, we start with $\tilde{\mathcal{F}}_k$ equal to the *feature value* in $\mathcal{G}_k$ that maximizes Equation (7), and, then, in each iteration, we explore $\mathcal{G}_k$ so that *feature value* $f_i^j \in \mathcal{G}_k$ that maximizes $\mu(\tilde{\mathcal{F}}_k, f_i^j, c_k)$ is selected, and *feature value* f_i^j such that $\mu(\tilde{\mathcal{F}}_k, f_i^j, c_k) < \mu(\tilde{\mathcal{F}}_k, c_k)$ holds, is removed from $\mathcal{G}_k$ and never tested again. Note that, since Pavicd deals with binary features (or *feature values*), the current solution $\tilde{\mathcal{F}}_k$ is also a binary feature because it is the result of one of "AND" or "OR" operators between two binary features. This is briefly explained below.

To evaluate how good a *feature value* $f_i^j \in \mathcal{G}_k$ is with respect to the already selected set $\tilde{\mathcal{F}}_k$, we use the following set of rules:

- **Rule 1.** If both f_i^j and $\tilde{\mathcal{F}}_k$ are covering *feature values*, then $\mu(\tilde{\mathcal{F}}_k; f_i^j; c_k) = P(\tilde{\mathcal{F}}_k \cap f_i^j | c_k) + P(c_k | \tilde{\mathcal{F}}_k \cap f_i^j)$
- **Rule 2.** If both f_i^j and $\tilde{\mathcal{F}}_k$ are reliable *feature values*, then $\mu(\tilde{\mathcal{F}}_k; f_i^j; c_k) = P(\tilde{\mathcal{F}}_k \cup f_i^j | c_k) + P(c_k | \tilde{\mathcal{F}}_k \cup f_i^j)$
- **Rule 3.** If neither Rule 1 or Rule 2 hold, then apply the **Rule** (**1** or **2**) that maximizes $\mu(\tilde{\mathcal{F}}_k; f_i^j; c_k)$.

Note that $\tilde{\mathcal{F}}_k$ is treated as a *feature value* (or a binary feature) because every time a *feature value* $f_i^j \in \mathcal{G}_k$ is "added" to $\tilde{\mathcal{F}}_k$, $\tilde{\mathcal{F}}_k$ is transformed to $\tilde{\mathcal{F}}_k \cap f_i^j$ or $\tilde{\mathcal{F}}_k \cup f_i^j$, if **Rule 1** or **Rule 2** holds, respectively. Algorithm 1 shows the pseudo code of Pavicd.

Algorithm 1: Algorithm of Pavicd

Input:
D: dataset
λ: threshold for covering *feature values*
δ: threshold for reliable *feature values*
Output:
the features corresponding to the selected *feature values*
Binarize **D**
foreach *class* c_k *in* **D do**
  Find the covering and reliable *feature values* and store them in $\mathcal{G}_k$
  Let f^* be the best *feature value* in $\mathcal{G}_k$
  $\tilde{\mathcal{F}}_k = f^*$
  $\gamma = \mu(f^*; c_k)$
  $\mathcal{G}_k = \mathcal{G}_k \setminus \{f^*\}$
  repeat
    $f^* = NULL$
    foreach f_i^j *in* $\mathcal{G}_k$ **do**
      $\gamma_{temp} = \mu(\tilde{\mathcal{F}}_k; f_i^j; c_k)$ (see **Rules**)
      if $\gamma_{temp} > \gamma$ **then** $\gamma = \gamma_{temp}, f^* = f_i^j$;
      else
        $\mathcal{G}_k = \mathcal{G}_k \setminus \{f_i^j\}$
      end
    end
    if $f^* \neq NULL$ **then** Update $\tilde{\mathcal{F}}_k$ to $\tilde{\mathcal{F}}_k \cap f^*$ or $\tilde{\mathcal{F}}_k \cup f^*$ depending on the rule (**Rule 1** or **Rule 2**) used in line 11 ;
  until $\mathcal{G}_k = \emptyset$;
end

3.3. Complexity Analysis

The first part of Pavicd has a linear time complexity with respect to the number of features n. In this step, instead of computing the mean relevance of each feature as the common feature selection algorithms do, Pavicd analyses all the feature values, which is equivalent in terms of complexity.

On the other hand, assuming that each feature has v feature values, the computational complexity in the second step is $O(nv \log nv)$ on average, that is, when the half of the remaining *feature values* are removed in each iteration.

3.4. Preliminary Evaluation

It is well known that microarray datasets contain interacting genes. In order to test the proposed algorithm, we run some benchmark algorithms in four datasets where the optimal solution is known. Table 1 shows the features selected by each algorithm and the number of errors (#*Error*) for each algorithm. In Table 1—means that a feature that should be selected was not selected, and features in **bold** letters represent the features that do not belong to the optimal solution.

Table 1. Features selected by some benchmark algorithms in artificial datasets with known solutions.

Dataset	Relevant Features	FCBF	Cfs	INTERACT	GBC	PAVICD
Corral	A_0, A_1, B_0, B_1	A_0, A_1, B_0, B_1, **R**	A_0, —, —, —, **R**	A_0, A_1, B_0, B_1	A_0, A_1, B_0, B_1, **R**	A_0, A_1, B_1, **R**
Monk1	A_1, A_2, A_5	A_1, —, $\mathbf{A_3}$, $\mathbf{A_4}$, A_5	—, —, A_5	A_1, A_2, A_5	A_1, A_2, $\mathbf{A_3}$, $\mathbf{A_4}$, A_5	A_1, A_2, A_5
Monk2	A_1, A_2, A_3, A_4, A_5, A_6	—, —, —, A_4, A_5, A_6	—, —, —, A_4, A_5, A_6	A_1, A_2, A_3, A_4, ,A_5, A_6	A_1, A_2, A_3, A_4, A_5, A_6	A_1, A_2, —, A_4, —, A_6
Monk3	A_2, A_4, A_5	A_2, —, A_5, $\mathbf{A_6}$	A_2, —, A_5	$\mathbf{A_1}$, A_2, A_4, A_5	$\mathbf{A_1}$, A_2, $\mathbf{A_3}$, A_4, A_5	A_2, A_4, A_5
	#Error	9	10	1	5	3

4. Empirical Study

To evaluate the proposed algorithm, we conduct experiments in fourteen microarray cancer datasets. We compare Pavicd with some of the state-of-the-art feature selection algorithms such as: ReliefF [17], mRMR [22], Fcbf [23], Cfs [24], Interact [26] and Gbc [25]. To run experiments, we implemented mRMR and Gbc algorithms in weka. The rest of the algorithms are available on the weka framework. The experiments were conducted as follows. Given a dataset, we perform the feature selection with all the algorithms listed above to obtain seven reduced datasets, one for each algorithm. At this point, the number of features selected and the running time of each algorithm is compared. To evaluate the accuracy of each algorithm, a ten-fold cross validation is performed over the reduced sets, using four different classifiers: *Support Vector Machine* (*SVM*) [27], *C4.5* [28], *Ripper-k* [29] and *Naïve Bayes* [30]. Classification accuracy is computed and then compared. The classification accuracy depends on the number of instances correctly classified t (*true positive* + *true negative*) and is computed by the following formula:

$$acc = \frac{t}{m} * 100, \tag{8}$$

where m is the number of instances of the dataset.

As a final step, non-parametric statistical tests are performed to detect significant differences among the feature selection algorithms. The experiment was performed on the machine learning suite, namely weka [31]. When running Pavicd, we fix the parameters to $\lambda = \delta = 0$. For the rest of the algorithms, we use the default values for their parameters. For Svm, we use an Rbf (Radial basis function) kernel with $C = 1$ and $\gamma = 0.5$. To evaluate a feature set, the Gbc algorithm requires training and testing the *SVM* classifier by cross-validation. After running extensive experiments we decided to train and test the *SVM* using all the instances in the datasets. In our experiments, there was no difference (in the selected set) between this approach and the leave-one-out cross-validation, except for the running time. Table 2 shows the characteristic of each dataset, which can be found in the OpenML machine learning repository [32].

Table 2. Datasets used in the experiments.

Data	Acronym	# Features	# Instances	#Classes	Available at:
Leukemia	LEU	7130	72	2	https://www.openml.org/d/1104
Anthracycline	ANT	61,360	159	2	https://www.openml.org/d/1085
BreastCancer	BRE	24,482	97	2	http://mldata.org/repository/data/viewslug
BurkittLymphoma	BUR	22,284	220	3	https://www.openml.org/d/1084
Central Nervous System	CEN	7130	60	2	http://eps.upo.es/bigs/datasets.html
Lymphoma	LYM	4027	96	11	http://eps.upo.es/bigs/datasets.html
Difusse B Cell	STAN	4027	47	2	http://eps.upo.es/bigs/datasets.html
ECML	ECM	27,680	90	43	http://eps.upo.es/bigs/datasets.html
Global Cancer Map	GCM	16,064	144	14	http://eps.upo.es/bigs/datasets.html
HepatitisC	HEP	22,278	123	4	https://www.openml.org/search?q=hepatitisC&type=data
Leukemia MLL	MLL	12,583	72	3	http://mldata.org/repository/data/viewslug/leukemia-mll/
MouseType	MOU	45,102	214	7	https://www.openml.org/d/1083
Ovarian Cancer	OVA	54,622	283	3	https://www.openml.org/d/1086
Various Cancer	VAR	54,676	383	9	https://www.openml.org/d/1088

4.1. Accuracy Evaluation

Tables 3–6 represent the classification accuracy computed for each classifier after their application on the reduced data. AVG. denotes averaged classification accuracy. It can be seen that Pavicd performs consistently better for *Ripper-k* and *C4.5*. We attribute this to the fact that Pavicd detects gene interaction while *Naïve Bayes* assumes independence between genes. For SVM, Pavicd does not perform so well. However, non-parametric tests reveal that there are not significant differences between the best algorithm when using *SVM* (Gbc) and Pavicd. For *Naïve Bayes*, Pavicd has comparable results with the other algorithms in all datasets. One interesting thing to notice is that in many cases the best classification results correspond to *Naïve Bayes*. The best answer we find by investigating the results more deeply is that in these datasets there are a lot of genes highly-correlated with the target class. However, according to the results, Pavicd is able to detect these type of genes, but the interacting genes found by Pavicd may be useless for *Naïve Bayes*. Tables 3–6 also show the averaged ranking of the results.

Table 3. Classification accuracy with *Support Vector Machine*.

Data	LEU	ANT	BRE	BUR	CEN	COM	STAN	ECM	GCM	HEP	MLL	MOU	OVA	VAR	AVG.
SVM															
Fcbf	100	83.6	87.4	95.5	91.7	85.7	100	76.7	69.6	93.9	94.2	87.4	92.0	90.1	89.1
RF	98.6	59.7	70.2	96.0	65.0	82.4	97.3	87.8	58.5	91.0	96.7	78.4	92.2	88.4	83.0
Cfs	94.8	65.8	84.2	93.8	87.4	87.8	96.8	100	63.2	93.0	97.2	72.6	94.2	98.3	87.8
mRMR	98.6	78.0	80.1	96.0	88.3	84.3	93.2	75.6	55.6	91.8	100	77.1	94.0	93.8	79.1
INT	94.3	63.5	75.2	92.3	78.3	89.2	92.9	91.1	59.0	82.9	91.7	63.6	95.4	93.9	83.1
GBC	100	59.1	87.6	95.5	78.3	86.4	97.1	100	86.8	96.2	97.5	57.9	95.0	97.4	87.4
PAV	95.7	66.0	84.2	96.0	83.3	86.4	97.3	89.7	64.4	94.3	97.2	74.8	94.5	94.8	86.9
Ranking															
Fcbf	1.5	1.0	2.0	4.5	1.0	5.0	1.0	6.0	2.0	3.0	5.0	1.0	7.0	6.0	3.29
RF	3.5	6.0	7.0	2.0	7.0	7.0	2.5	5.0	6.0	6.0	4.0	2.0	6.0	7.0	5.07
Cfs	6.0	4.0	3.5	6.0	3.0	2.0	5.0	1.5	4.0	4.0	2.5	5.0	4.0	1.0	3.68
mRMR	3.5	2.0	5.0	2.0	2.0	6.0	6.0	7.0	7.0	5.0	7.0	3.0	5.0	5.0	4.68
INT	7.0	5.0	6.0	7.0	5.5	1.0	7.0	3.0	5.0	7.0	6.0	6.0	1.0	4.0	5.04
GBC	1.5	7.0	1.0	4.5	5.5	3.5	4.0	1.5	1.0	1.0	1.0	7.0	2.0	2.0	3.04
PAV	5.0	3.0	3.5	2.0	4.0	3.5	2.5	4.0	3.0	2.0	2.5	4.0	3.0	3.0	3.21

Table 4. Classification accuracy with *Naïve Bayes*.

Data	LEU	ANT	BRE	BUR	CEN	COM	STAN	ECM	GCM	HEP	LEU	MOU	OVA	VAR	AVG.
Naive Bayes															
Fcbf	100	78.0	54.6	96.0	73.3	93.2	99.5	66.7	96.1	92.7	97.4	94.9	93.7	96.3	88.0
RF	95.8	59.7	66.0	87.7	65.0	90.9	99.2	66.7	87.6	89.4	100	86.6	80.6	93.2	83.5
Cfs	96.4	77.5	76.2	92.8	71.7	92.8	99.5	69.3	96.1	87.8	93.4	93.8	93.9	95.5	88.3
mRMR	97.2	88.7	56.7	95.0	71.7	93.4	99.5	67.2	96.1	90.2	100	94.2	98.2	95.7	88.8
INT	94.4	84.0	52.6	90.0	81.7	88.7	98.9	67.1	88.1	87.8	97.4	87.1	84.3	90.0	85.2
GBC	95.8	80.2	84.5	93.6	70.0	90.2	96.4	67.0	95.2	91.9	97.4	91.0	94.2	94.1	88.7
PAV	97.2	86.9	76.2	94.1	75.0	93.9	99.3	67.2	96.3	91.9	97.4	94.9	94.5	95.6	90.0
Ranking															
Fcbf	1.0	5.0	6.0	1.0	3.0	3.0	2.0	6.5	3.0	1.0	4.5	1.5	5.0	1.0	3.11
RF	5.5	7.0	4.0	7.0	7.0	5.0	5.0	6.5	7.0	5.0	1.5	7.0	7.0	6.0	5.75
Cfs	4.0	6.0	2.5	5.0	4.5	4.0	2.0	1.0	3.0	6.5	7.0	4.0	4.0	4.0	4.11
mRMR	2.5	1.0	5.0	2.0	4.5	2.0	2.0	2.5	3.0	4.0	1.5	3.0	1.0	2.0	2.57
INT	7.0	3.0	7.0	6.0	1.0	7.0	6.0	4.0	6.0	6.5	4.5	6.0	6.0	7.0	5.50
GBC	5.5	4.0	1.0	4.0	6.0	6.0	7.0	5.0	5.0	2.5	4.5	5.0	3.0	5.0	4.54
PAV	2.5	2.0	2.5	3.0	2.0	1.0	4.0	2.5	1.0	2.5	4.5	1.5	2.0	3.0	2.43

Table 5. Classification accuracy with C4.5.

Data	LEU	ANT	BRE	BUR	CEN	LYM	DIF	ECM	GCM	HEP	LEU	MOU	OVA	VAR	AVG.
C4.5															
Fcbf	80.6	68.6	67.0	78.6	68.3	92.8	68.2	76.3	78.7	87.0	97.4	81.3	70.2	86.0	78.6
RF	79.2	59.7	52.6	82.7	65.0	75.4	73.9	88.7	66.4	80.5	92.1	79.0	65.5	88.7	75.0
Cfs	85.6	70.6	81.7	85.8	69.5	73.2	87.1	88.5	78.4	84.7	95.0	85.9	71.9	81.2	81.4
mRMR	80.6	77.4	70.1	82.7	80.0	81.9	70.2	75.5	75.2	83.7	89.5	75.1	71.6	82.9	78.3
INT	90.3	78.9	73.2	87.7	76.7	83.4	85.9	72.3	77.1	80.5	97.4	84.2	74.9	83.3	81.8
GBC	84.7	73.9	68.0	85.9	72.7	81.9	83.4	91.8	77.3	88.7	81.6	84.6	66.3	81.4	80.2
PAV	87.5	71.5	82.4	87.2	73.3	82.2	87.9	88.9	78.6	86.2	97.4	86.6	78.4	90.3	84.2
Ranking															
Fcbf	5.5	6.0	6.0	7.0	6.0	7.0	5.0	1.0	2.0	2.0	5.0	5.0	3.0	5.0	4.68
RF	7.0	7.0	7.0	5.5	7.0	6.0	5.0	3.0	7.0	6.5	5.0	6.0	7.0	2.0	5.79
Cfs	3.0	5.0	2.0	4.0	5.0	7.0	2.0	4.0	3.0	4.0	4.0	2.0	3.0	7.0	3.93
mRMR	5.5	2.0	4.0	5.5	1.0	4.5	6.0	6.0	6.0	5.0	6.0	7.0	4.0	5.0	4.82
INT	1.0	1.0	3.0	1.0	2.0	2.0	3.0	7.0	5.0	6.5	2.0	4.0	2.0	4.0	3.11
GBC	4.0	3.0	5.0	3.0	4.0	4.5	4.0	1.0	4.0	1.0	7.0	3.0	6.0	6.0	3.96
PAV	2.0	4.0	1.0	2.0	3.0	3.0	1.0	2.0	2.0	3.0	2.0	1.0	1.0	1.0	2.00

Table 6. Classification accuracy with Ripper-k.

Data	LEU	ANT	BRE	BUR	CEN	COM	STA	ECM	GCM	HEP	LEU	MOU	OVA	VAR	AVG.
Ripper-k															
Fcbf	84.7	59.7	75.3	83.6	71.7	79.6	87.3	89.0	77.1	82.1	97.4	82.5	86.7	83.4	81.4
RF	87.5	59.7	68.0	80.0	65.0	81.5	81.2	87.8	70.4	75.6	76.3	77.9	76.8	81.5	76.4
Cfs	91.2	67.3	77.4	83.5	76.8	77.7	92.4	87.8	81.5	86.3	95.1	84.2	74.2	86.2	83.0
mRMR	86.1	61.6	73.2	83.2	66.7	84.3	93.7	89.8	74.8	78.0	81.6	84.1	72.9	76.9	79.1
INT	94.4	67.4	74.2	86.4	75.0	79.2	89.1	89.5	74.3	78.0	97.4	77.9	75.9	81.6	81.5
GBC	87.5	63.9	63.9	86.8	65.0	84.1	94.1	90.4	76.6	82.1	84.2	82.3	70.0	76.5	79.1
PAV	91.6	69.3	79.4	86.4	80.0	85.9	89.9	89.9	83.2	90.2	97.4	84.5	87.9	87.2	85.9
Ranking															
Fcbf	7.0	6.5	3.0	4.0	4.0	5.0	6.0	5.0	3.0	3.5	2.0	4.0	2.0	3.0	4.14
RF	4.5	6.5	6.0	7.0	6.5	4.0	7.0	6.5	7.0	7.0	7.0	6.5	3.0	5.0	5.96
Cfs	3.0	3.0	2.0	5.0	2.0	7.0	3.0	6.5	2.0	2.0	4.0	2.0	5.0	2.0	3.46
mRMR	6.0	5.0	5.0	6.0	5.0	2.0	2.0	3.0	5.0	5.5	6.0	3.0	6.0	6.0	4.68
INT	1.0	2.0	4.0	2.5	3.0	6.0	5.0	4.0	6.0	5.5	2.0	6.5	4.0	4.0	3.96
GBC	4.5	4.0	7.0	1.0	6.5	3.0	1.0	1.0	4.0	3.5	5.0	5.0	7.0	7.0	4.25
PAV	2.0	1.0	1.0	2.5	1.0	1.0	4.0	2.0	1.0	1.0	2.0	1.0	1.0	1.0	1.54

For *Ripper-k*, Pavicd found the best reduced sets in ten out of fourteen datasets, which is a promising result. For *C4.5*, Pavicd found the best results for the fifty percentage of datasets. Figure 4 shows the Critical Distance chart. The Critical Distance was computed using Nemenyi's equation [33] with $\alpha = 0.1$.

The post hoc Nemenyi test shows significant differences among the algorithms for the four classifiers. For *SVM* (Figure 4a), Gbc and Pavicd have significant differences with ReliefF

and INTERACT. Moreover, there are not significant diferences among Gbc and Pavicd. For *Naïve Bayes* (Figure 4b), algorithms Fcbf, Pavicd, Cfs and mRMR have no differences among them. However, Fcbf and Pavicd show significantly better results than RELIEFF and INTERACT. Speaking about *Ripper-k* (Figure 4d), Pavicd is significantly better with respect to the rest of the algorithms, and the rest of the algorithms do not have significant differences among them. For *C4.5* (Figure 4c), Pavicd is significantly better to all of the algorithms except for INTERACT.

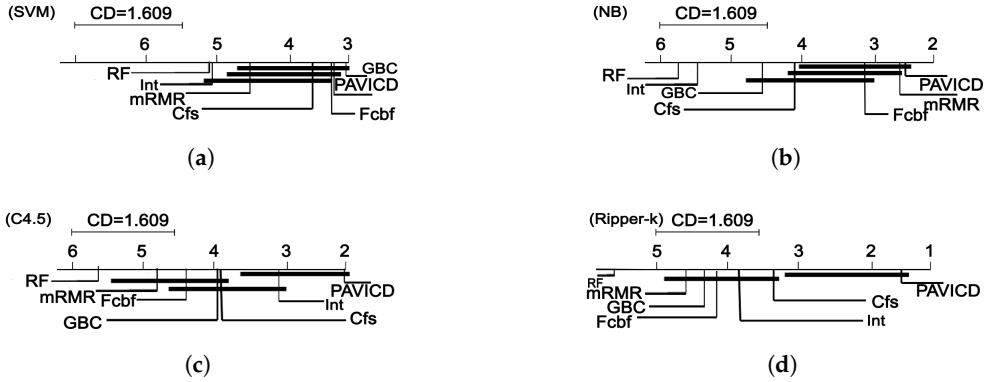


Figure 4. Critical Distance charts that show the average ranking of the feature selection algorithms and their significant differences with $\alpha = 0.1$. (**a**) Critical Distance chart for *SVM*; (**b**) Critical Distance chart for *Naïve Bayes*; (**c**) Critical Distance chart for *C4.5*; (**d**) Critical Distance chart for *Ripper-k*.

Next, we examine the performance of the algorithms in terms of number of features selected and running time.

4.2. Number of Features Selected and Running Time

The main goal of feature selection is to reduce the data so that machine learning algorithms can improve their performance. Table 7 shows the running time and the number of genes selected by each feature selection algorithm.

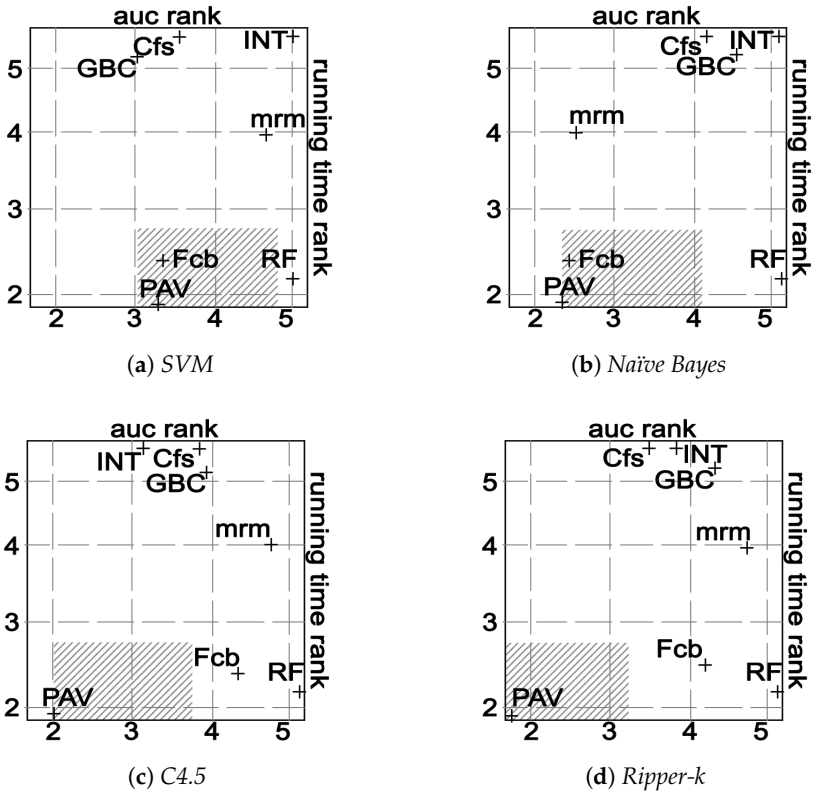
Table 7. Running time (in seconds) and number of features selected by the algorithms.

	Running Time (in Seconds)							#Feat. Selected						
Data	**Fcbf**	**RF**	**Cfs**	**mrm**	**INT**	**GBC**	**PAV**	**Fcbf**	**RF**	**Cfs**	**mrm**	**INT**	**GBC**	**PAV**
LEU	1.1	0.76	206	7.49	22.1	14.5	0.79	51	130	51	50	3	5	6
ANT	6.27	10.8	14763	853	11653	5091	4.73	67	1	78	50	15	2	29
BRE	1.81	4.8	437	69.4	304	321	1.28	90	3	89	50	9	5	16
BUR	8.3	6.76	3215	83.1	765	233	3.44	208	201	314	50	9	8	27
CEN	0.27	0.52	104	6.9	14.9	12.4	0.20	28	1	36	50	8	3	11
Lym	0.08	0.11	501	2.9	10.6	9.7	0.07	14	5	154	50	11	3	4
STAN	0.16	0.17	30	2.48	4.76	7.9	0.10	60	54	33	50	3		5
ECM	1.81	7.26	709	98.8	303	572	2.23	74	2750	97	50	7	2	25
GCM	4.63	5.96	428	33.3	264	256	3.27	67	173	63	50	13	4	37
HEP	6.73	5.13	2981	57.1	485	188	2.48	239	626	189	50	6	8	12
MLL	2.38	1.71	1520	19.1	83.2	34.3	0.77	97	580	82	50	3	7	5
MOU	11.93	10.43	5652	264	2989	2739	8.32	127	112	233	50	10	4	33
OVA	53.12	14.67	11412	464	5849	6932	9.63	734	934	781	50	16	17	13
VAR	144	23.08	13902	515	9920	7664	37.53	934	1528	827	50	17	19	54
AVG.	17.3	6.58	3990	177	2333	1720	5.35	199	507	216	50	9.29	6.69	19.8

Speaking about the number of genes selected, it is clearly revealed that INTERACT and Gbc select a small number of genes. However, when we look at the performance of INTERACT in terms of accuracy (see Section 4.1), we reach the conclusion that INTERACT might be removing genes with important information for classification. The same applies to Gbc in all the classifiers except *SVM*. Nevertheless,

Pavicd selects a similar number of features with respect to INTERACT and Gbc, but its performance in terms of accuracy is high. Another conclusion to reach is that the algorithms Cfs and RELIEFF select a huge number of features with respect to the rest of the algorithms.

Speaking about running time, surprisingly, Pavicd is the fastest in all datasets except in VAR, ECM and LEU. We further investigated this result and realized that Pavicd removes a lot of genes in early iterations. In addition, we tested two types of implementations of Pavicd: (1) without *binarizing* the genes and (2) with the *binarization* process mentioned in Section 3.2. With the first implementation, the running time of Pavicd was slightly larger to Fcbf. However, with the *binarization* process that transforms the gene space in a binary genes space, the algorithm is extremely fast as shown in Table 7. To better understand the trade-off between the efficiency and effectiveness of the algorithms, Figure 5 depicts a visual comparison between these aspects.



(**a**) *SVM* (**b**) *Naïve Bayes*

(**c**) *C4.5* (**d**) *Ripper-k*

Figure 5. Visual comparison of the accuracy and the running time of each algorithm. The figure plots a cross for each algorithm. Each cross is centered on its averaged ranks (for accuracy and running time parameters). The shadowed region represents the area of non-significant difference according to the *Nemenyi* test with $\alpha = 0.1$ (critical distance is 1.609).

In Figure 5, every algorithm is placed according to their averaged ranks for both running time (vertical axis) and classification accuracy (horizontal axis). Again, the Nemenyi test is performed to compute the critical distance ($CD = 1.609$) with $\alpha = 0.1$. The shadowed area represents the region where there are not significant differences between Pavicd and the rest of the algorithms in terms of both the accuracy and running time. In the context of this experiment, and speaking about the balance between the efficiency and accuracy, we reach the conclusion that Pavicd and Fcbf are the best algorithms for *Naïve Bayes* and *C4.5*. While Pavicd performs the best for *Ripper-k*, Gbc obtains the best results for *SVM* in terms of accuracy, but the running time is very large in the datasets with the largest dimensions.

We also more deeply investigate the statistical significance of the obtained results, specifically, the observed difference of Pavicd from the other benchmark algorithms by conducting the

Benjamini–Hochberg (BH) test [34]. The BH test controls the false discovery rate (*FDR*) instead of the family wise error rate (*FWER*). *FWER* is the probability of rejecting one or more null hypotheses assuming that all of the null hypotheses are true, while *FDR* is the conditional probability that a null hypothesis is true when the test indicates rejecting the null hypothesis. The inequality $FDR \leq FWER$ implies a test that controls *FDR* may be less conservative than a test that controls *FWER*. In our investigation, we run the BH test on the maximum values across the classifiers. Fcbf, Cfs, MRMR, Gbc and Pavicd form the top group, and the BH test showed that the difference is not significant. For the maximum values across the classifiers, we can conclude that all of five of these algorithms are comparable with respect to accuracy, while Fcbf and Pavicd are comparable with respect to time efficiency.

5. Conclusions

Due to the intrinsic distribution of the data population of microarray datasets, where genes greatly outnumber the sample observations, feature selection has proven to be a crucial step for further data analysis such as sample classification. In this paper, we propose a new feature selection algorithm based on a novel methodology, which aims to mitigate the *integrality problem*. The proposed algorithm, Pavicd, works on the space of *feature values* instead of the features' space. This gives the algorithm the opportunity to better detect relevant, non-redundant and interacting features. Experiments in fourteen microarray cancer datasets reveal that Pavicd obtains the best performance in terms of running time and classification accuracy when using *Ripper-k* and *C4.5* as classifiers. When using SVM, the Gbc wrapper algorithm gets the best results. However, Pavicd is significantly faster. In future work, we will evaluate the incidence of the parameters λ and δ in the algorithm of Pavicd.

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