A Step Towards the Explainability of Microarray Data for Cancer Diagnosis with Machine Learning Techniques

Adara S. R. Nogueira[1], Artur J. Ferreira[1,3][a] and Mário A. T. Figueiredo[2,3][b]

[1] *ISEL, Instituto Superior de Engenharia de Lisboa, Instituto Politécnico de Lisboa, Portugal*

[2] *IST, Instituto Superior Técnico, Universidade de Lisboa, Portugal*

[3] *Instituto de Telecomunicações, Lisboa, Portugal*

Keywords: Machine Learning, Feature Selection, Feature Discretization, Microarray Data, Cancer Explainability.

Abstract: Detecting diseases, such as cancer, from from gene expression data has assumed great importance and is a very active area of research. Today, many gene expression datasets are publicly available, which consist of microarray data with information on the activation (or not) of thousands of genes, in sets of patients that have (or not) a certain disease. These datasets consist of high-dimensional feature vectors (very large numbers of genes), which raises difficulties for human analysis and interpretation with the goal of identifying the most relevant genes for detecting the presence of a particular disease. In this paper, we propose to take a step towards the explainability of these disease detection methods, by applying feature discretization and feature selection techniques. We accurately classify microarray data, while substantially reducing and identifying subsets of relevant genes. These small subsets of genes are thus easier to interpret by human experts, thus potentially providing valuable information about which genes are involved in a given disease.

1 INTRODUCTION

The problem of analysing a patient's DNA data to identify the presence/absence of specific genes, indicative of certain diseases, such as cancer, is an active topic of research where machine learning tools play an important role. Many gene expression datasets are publicly available (Alonso-Betanzos et al., 2019)[1], which include microarray data with information on the activation (or not) of thousands of genes, in sets of patients who have (or not) a certain disease. Ideally, one would like to use these datasets to learn to predict the presence of a given disease on new patients, given their microarray data, and to identify the most relevant genes for that purpose. However, these datasets are very high-dimensional, which raises difficulties for human experts to interpret the data. It is laborious to identify the most important genes that explain the presence of a particular disease. In addition to their high dimensionality, these datasets have a small number of instances due to the high cost of acquiring new instances.

Applying classification techniques directly on these datasets poses challenges due to the "curse of dimensionality" issues (Bishop, 1995). The performance of the classifiers is sub-optimal and it is often not possible to determine, in detail, which genes are relevant to detect a given disease. In this paper, we apply *feature discretization* (FD) (Garcia et al., 2013), *feature selection* (FS) (Duda et al., 2001; Guyon et al., 2006), to microarray datasets, to overcome these issues. Moreover, analysing the resulting feature subsets allows identifying the smallest subset of features that are indicative of a given disease. These subsets allow human interpretability of the data. Figure 1 depicts the main steps of the approach taken in this work.

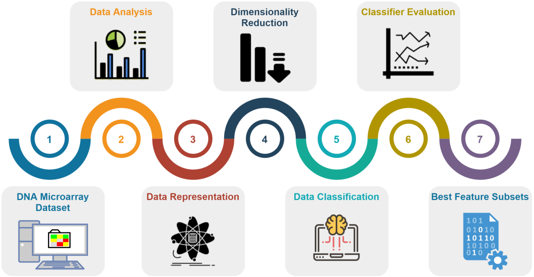


Figure 1: The key steps of the proposed approach.

The remainder of this paper is organized as fol-

[a] https://orcid.org/0000-0002-6508-0932

[b] https://orcid.org/0000-0002-0970-7745

[1] http://csse.szu.edu.cn/staff/zhuzx/Datasets.html

Nogueira, A., Ferreira, A. and Figueiredo, M.
A Step Towards the Explainability of Microarray Data for Cancer Diagnosis with Machine Learning Techniques.
DOI: 10.5220/0010980100003122
In *Proceedings of the 11th International Conference on Pattern Recognition Applications and Methods (ICPRAM 2022)*, pages 362-369
ISBN: 978-989-758-549-4; ISSN: 2184-4313

lows. Section 2 overviews the state-of-the-art on DNA microarray techniques and reviews some approaches. The proposed approach as well as the microarray datasets are presented in Section 3. The experimental evaluation is reported in Section 4. Finally, Section 5 ends the paper with concluding remarks and directions for future work.

2 DNA MICROARRAYS

In this section, we review the key aspects regarding the DNA Microarray technique and data generation (Section 2.1) as well as some approaches to deal with this type of data (Section 2.2).

2.1 The DNA Microarray Technique

Every biological organism has a set of genes encoded in its DNA. These may be expressed, *i.e.*, active, in different cells at different points in time. In the context of biological/medical research, it's important to understand which genes are being expressed (active/inactive) in a given cell, at a given point in time. However, living beings have thousands of genes, *e.g.*, humans have approximately 21000 (Forero and Patrinos, 2020; Weinberg, 2014). Each one of these genes is responsible for encoding a protein, which is in charge of a specific functionality. Given the complexity and amount of information, it is currently infeasible to analyse this data one gene at a time. Even if it were possible, it would take a very long time and the efficiency and accuracy of the analysis would be extremely low.

The DNA microarray technique (Simon et al., 2003) addresses this issue. A DNA microarray allows researchers and healthcare professionals to carry out an investigation on thousands of genes at a time, *i.e.*, in one single experiment [2] and determine which genes are being expressed by a cell. A DNA microarray has the following characteristics:

- a microarray is a solid surface with thousands of spots arranged in well-ordered columns and rows;
- each spot on this microarray characterizes only one gene and contains multiple strands of the same DNA, i.e. the DNA sequence is unique;
- each spot location and its respective DNA sequence is recorded in a database.

DNA microarrays can identify dissimilarities between cancer cells and healthy cells, more specifically, which genes in a cancer cell are being expressed, but not in a healthy cell.

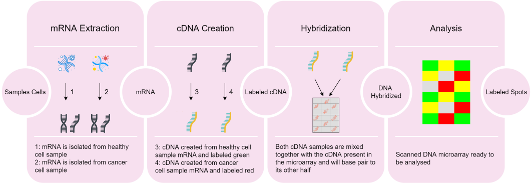

mRNA Extraction
cDNA Creation
Hybridization
Analysis
Samples Cells
1
2
mRNA
3
4
Labeled cDNA
DNA Hybridized
Labeled Spots
1: mRNA is isolated from healthy cell sample
2: mRNA is isolated from cancer cell sample
3: cDNA created from healthy cell sample mRNA and labeled green
4: cDNA created from cancer cell sample mRNA and labeled red
Both cDNA samples are mixed together with the cDNA present in the microarray and will base pair to its other half
Scanned DNA microarray ready to be analysed

Figure 2: Overview of the DNA Microarray Technique.

Figure 2 presents an overview of the DNA microarray technique. First, it's necessary to extract the *ribonucleic acid* (RNA) from the samples cells and then draw out the *messenger RNA* (mRNA) from the existing RNA, because only the mRNA develops gene expression. Then, a DNA copy is made from the mRNA with the aid of the reverse transcriptase enzyme, which will generate the complementary DNA (CDNA). In this process, a label is added in the CDNA representing each cell sample, *e.g.*, a fluorescent red for the cancer cell and a fluorescent green for the healthy cell. This step is necessary because DNA is a more stable molecule than RNA and the labelling allows identifying the genes in each sample later. Both CDNA types previously created are added to the DNA microarray and because each spot of it already has many unique CDNA. When mixed together they will base pair each other due to the DNA property, designated complementary base pairing. This process is denominated "hybridization". Not all CDNA strands will bind to each other, some may not hybridize therefore they need to be washed off. Finally, the DNA microarray is analyzed with a scanner, which can find patterns of hybridization by detecting the fluorescent colors. As a result, we can observe the following:

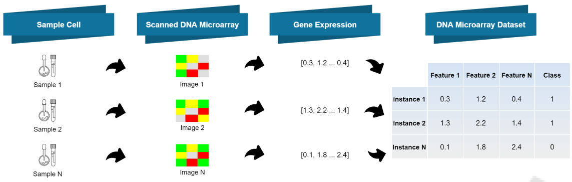
- only a few red CDNA molecules bound to a spot, which means the gene was being expressed only in the red (cancer) cell;
- only a few green CDNA molecules bound to another spot, which means the gene was being expressed only in the green (healthy) cell;
- some of both red and green CDNA molecules bound to a single spot on the microarray (forming a yellow spot), which means the gene was being expressed both in the cancer and the healthy cell;
- several spots of the microarray don't have a single red or green CDNA strand bound to it, because the gene is not being expressed in either cell.

The red color on a spot indicates the higher production of mRNA in the cancer cell compared to the healthy cell. On the other hand, the green color specifies the higher production of mRNA in the healthy

[2] https://learn.genetics.utah.edu/content/labs/microarray/

cell as compared to the cancer cell. However, a yellow spot suggests that the gene is expressed equally in both cells and therefore, they are not relevant as the cause of the disease, because when the healthy cell becomes cancerous its activity does not undergo a change. Using DNA microarray, we can analyze a large amount of genes at the same time, find which genes are being expressed and decide on a better prognosis based on the previous analyzes.

Figure 3 depicts the process of generating a dataset from the use of the DNA microarray technique mentioned in Figure 2. The datasets considered in this work are obtained with this process.



	Feature 1	Feature 2	Feature N	Class
Instance 1	0.3	1.2	0.4	1
Instance 2	1.3	2.2	1.4	1
Instance N	0.1	1.8	2.4	0

Figure 3: Dataset generation from DNA Microarray.

2.2 Related Approaches

In the last decades, there has been considerable research on microarray data classification for cancer diagnosis (Alonso-Betanzos et al., 2019; Yip et al., 2011; Statnikov et al., 2005b). Many unsupervised and supervised FD and FS techniques have been employed on this type of data, before classification takes place. Since microarray datasets are typically labelled, supervised techniques are usually preferred to unsupervised ones. In this section, we briefly review some of the existing related work using FD, FS, and classification techniques.

A survey of common classification techniques and related methods to increase their accuracy for microarray analysis is presented by Alonso-Betanzos et al. (2019); Yip et al. (2011). The experimental evaluation is carried out in publicly available datasets. Saeys et al. (2007) surveyed FS techniques used for this type of data, showing their adequacy.

It has been found that unsupervised FD performs well when combined with several classifiers. For instance, the *equal frequency binning* (EFB) technique with Naïve Bayes (NB) classifier produces very good results (Witten et al., 2016). It has also been reported that applying *equal interval binning* (EIB) and EFB with microarray data, together with *support vector machines* (SVM) classifiers, yields good results (Meyer et al., 2008). The work of Statnikov et al. (2005a) shows that FS significantly improves the classification accuracy of multi-class SVM classifiers and other classification algorithms.

An FS filter for microarray data, with an information-theoretic criterion named *double input symmetrical relevance* (DISR), which measures feature complementarity, was proposed by Meyer et al. (2008). The reported experimental results on one synthetic dataset and 11 microarray datasets show that the DISR criterion is competitive with existing FS filters.

Diaz-Uriarte and Andres (2006) explored FS techniques, such as backwards elimination of features and classification, both using *random forests* (RF). The authors applied the chosen method on one simulated and nine real microarray datasets and found that RF has better performance than other classification methods, such as *diagonal linear discriminant analysis* (DLDA), *K-nearest neighbors* (KNN), and SVM. They also showed that the used FS technique led to a smaller subset of features than alternative techniques, namely Nearest Shrunken Centroids and a combined method of filter and nearest neighbor classifier.

The work by Li et al. (2018) introduced the use of *large-scale linear support vector machine* (LLSVM) and *recursive feature elimination with variable step size* (RFEVSS) as an enhancement to the traditional FS technique based on SVM with *recursive feature elimination* (SVMRFE), which is considered one of the best methods in the literature, but exhibits large computational cost. The improved approach consists in upgrading the RFE by varying the step size with the goal of reducing the number of iterations (the step size is kept higher in the initial stages of this process where non-relevant features are discarded). In addition, the standard SVM is upgraded to a large-scale linear SVM and thus accelerating the method of assigning weights. The authors compare their approach to FS with SVM and RF, and use the SVM, NB, KNN and *logistic regression* (LR) classifiers. These techniques are applied on six microarray datasets and the approach provides better performance with comparable levels of accuracy, showing that SVM and LR outperform the other two classifiers.

Recently, in the context of cancer explainability, Consiglio et al. (2021) considered the problem of finding a small subset of features capable of discerning among six classes of instances. These classes may be healthy or cancerous. The goal was to define a comprehensive set of rules based on the most relevant features (selected by their technique) that can distinguish classes based on their gene expressions. The proposed method combines a *genetic algorithm* (GA) to conduct FS and a fuzzy rule-based system to execute classification on a dataset, with 21 instances, more than 45 thousand features, and 6 classes. Ten rules were devised, each one of them taking into account specific features, which make them crucial in explaining the classification results of ovarian cancer detection.

3 PROPOSED APPROACH

In this section, we present our proposed approach to handle DNA microarray datasets with machine learning techniques. Section 3.1 describes the public domain datasets used in the experimental evaluation. Section 3.2 presents the pipeline of techniques that we apply on the data and the procedures that we follow.

3.1 Microarray Datasets

Table 1 presents the main characteristics of the 11 microarray datasets used in this work. In this table, n denotes the number of instances, d indicates the number of features, and c the number of classes. We also show the $\frac{d}{n}$ ratio.

These datasets exhibit the common characteristic of having many more features than instances, thus $n >> d$, making the $\frac{d}{n}$ ratio quite high for some datasets, which conveys a challenge in applying machine learning techniques in these data (Bishop, 1995; Duda et al., 2001). All datasets have a large number of features, with d ranging from 2000 to 24481. In addition, as evidenced by the n column, all datasets have a small number of instances, with n ranging from 60 to 253.

Table 2 describes the classification task for each of datasets presented in Table 1. We have binary classification and multi-class classification problems. A binary dataset indicates the presence/absence of a specific tumor/cancer (such as in the CNS, Colon, and Ovarian datasets), the re-incidence of a disease (such as in the Breast dataset), or the diagnosis between two types of cancer (such as in the Leukemia dataset). A multi-class dataset distinguishes between different types of cells (such as in the Leukemia_3c, Leukemia_4c and Lymphoma datasets), and tumors/cancer (such as in the Lung, MLL, and SRBCT datasets).

Table 1: Microarray Datasets Characteristics.

Name	n	d	c	d/n
Breast	97	24481	2	252.38
CNS	60	7129	2	118.81
Colon	62	2000	2	32.25
Leukemia	72	7129	2	99.01
Leukemia_3c	72	7129	3	99.01
Leukemia_4c	72	7129	4	99.01
Lung	203	12600	5	62.06
Lymphoma	66	4026	3	61.00
MLL	72	12582	3	174.75
Ovarian	253	15154	2	59.89
SRBCT	83	2308	4	27.80

Table 2: Microarray Datasets Clinical Tasks.

Name	Description
Breast	Breast cancer diagnosis
CNS	Central Nervous System tumor diagnosis
Colon	Colon tumor diagnosis
Leukemia	Acute Lymphocytic Leukemia and Acute Myelogenous Leukemia diagnosis
Leukemia_3c	Distinguishes types of blood cells which became cancerous
Leukemia_4c	Distinguishes types of blood cells which became cancerous
Lung	Lung cancer diagnosis
Lymphoma	Distinguishes subtypes of non-Hodgkin lymphoma
MLL	Distinguishes types of acute leukemia, including Mixed Lineage Leukemia
Ovarian	Ovarian cancer diagnosis
SRBCT	Distinguishes types of of Small Round Blue Cell Tumors

3.2 Machine Learning Pipeline

The connection between our proposal and the related work is that we consider the microarray datasets referred in these studies as well as the most often used classifiers. We also address different data representation techniques, combining FD and FS techniques, before classification. Our aim is not solely the correct classification (regarding the error rate, false negative rate, and false positive rate), but also to find the subsets of features that are more decisive for the classification task. In detail, the steps of our approach are:

- choose which techniques to evaluate, based on the existing literature;
- build a machine learning pipeline using data representation/discretization, dimensionality reduction and data classification techniques;
- compare the performance of each technique;
- and finally, identify the best suited technique as well as the best subset of features to the problem and datasets under consideration.

Figure 4 depicts the machine learning pipeline of the actions that we apply on the datasets.

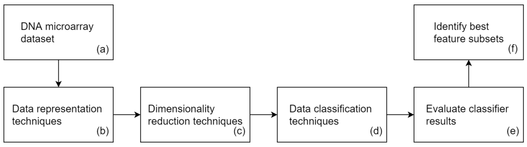

DNA microarray dataset (a)
Data representation techniques (b)
Dimensionality reduction techniques (c)
Data classification techniques (d)
Evaluate classifier results (e)
Identify best feature subsets (f)

Figure 4: The pipeline of the proposed approach.

4 EXPERIMENTAL EVALUATION

This section reports the experimental evaluation of the proposed approach on the 11 microarray datasets described in Table 1 and Table 2. The machine learning pipeline is depicted in Figure 4. The experimental results are organized as follows:

- Section 4.1 describes the baseline classification results without FD and FS techniques, using the SVM and *decision tree* (DT) classifiers (phases (a), (d), and (e) of the pipeline). We chose these classifiers since they take rather different approaches for classification.
- Section 4.2 addresses the use of FD techniques (phases (a), (b), (d), and (e) from the pipeline) and also reports the experimental results of FS techniques (phases (a), (c), (d), and (e) of the pipeline). Finally, it identifies the best parameter configuration found for each dataset.
- Section 4.3 presents experimental results toward the explainability of the classification, by identifying the best subsets of features for some datasets.

4.1 Baseline Classification Results

First, we evaluate the data classification phase of the pipeline, on each dataset. We check the performance of the selected classifiers (SVM and DT) to establish the baseline results. We have chosen the SVM classifier because it is the classification technique that in the literature reports the best results. We have also chosen DT because it is a different classification approach, which is seldom applied to this type of data. As the methodology for training and testing the classifiers, we consider the *leave-one-out cross-validation* (LOOCV) technique for all the evaluations in this paper. Since the number of instances n is small, we achieve a better estimate of the generalization error and the other evaluation metrics, since there is no standard deviation due to the data sampling procedure as it happens on standard 10-fold cross-validation.

Table 3 presents the baseline results (no FD nor FS) with phase (b) of the pipeline being the normalization of all feature values to the range 0 to 1. Table 4 shows a similar evaluation for the DT classifier. In our experiments, we have found that using entropy as a criterion to build the tree is better than using the Gini index; we have also found that the initial random_state parameter set to 42 is the best choice.

These experimental results from Table 3 and Table 4 show that DT does not achieve better results than the SVM classifier (DT only performs better than SVM on the CNS dataset). Thus, from these experiments and from the existing literature, SVM with linear kernel seems to be an adequate classifier for this type of data. It is also preferable to normalize the data before doing any machine learning tasks.

4.2 Feature Discretization Assessment

In the literature of microarray data and for other types of data and machine learning problems, the unsupervised EFB method is know to produce adequate results. Thus, we have carried out some experiments using this discretization method. Table 5 reports the results of the SVM classifier on data discretized by EFB, with different number of bins.

Analyzing these results for all datasets, we conclude that EFB discretization yields a small improvement for the SVM classifier (lower standard deviation in all datasets). Table 6 shows a summary of the results of the best configurations of EFB discretization and SVM/DT classifiers. For each dataset, we select the best configuration found in our experiments.

We now address the use of FS on the normalized features (without discretization). For our experiments, we consider the *Laplacian score* (LS), Spectral, Fisher Ratio (FiR), and *relevance-redundancy feature selection* (RRFS) (Ferreira and Figueiredo, 2012). Table 7 shows the experimental results for the SVM classifier. RRFS works in unsupervised mode using the mean-median (MM) relevance metric and in supervised mode using FiR as metric.

The RRFS method attains the best classification error results. We also achieve considerable dimensionality reduction. For instance, on the Ovarian dataset, we get a reduction to 4% of the original dimensionality: the number of selected features is about 606, from the original set of 15154 features. A similar result is obtained for the Lymphoma dataset, in which we keep 2% of the original features.

We now address the joint effect of all the pipeline phases depicted in Figure 4. Table 8 presents the best configurations for each phase and each dataset.

4.3 Explainability of the Data

In this section, we aim to identify the most relevant features for a given dataset, now that we have acceptable classification results on the previous sections. Figure 5 (top) shows the feature indices that are chosen more often on the LOOCV procedure for the Lymphoma and Ovarian datasets. For a dataset with n instances, each feature can be chosen up to n times. The importance of a feature to (accurately classify) a dataset and to explain the classification results is proportional to the number of times that feature is chosen in this procedure. We show the top 100 features. In the bottom of this figure, we show a similar plot for the Leukemia and Leukemia_3c datasets. We now consider all the features in the dataset, displaying the number of times each feature is chosen. For both

Table 3: Test error rate (Err) of LOOCV for the SVM classifier. For five datasets that have a class label of "no cancer", we also consider the *false negative rate* (FNR) and *false positive rate* (FPR). For the other six datasets, we dont report the FNR and FPR metrics, because the task is to distinguish between cancer types. The best result is in boldface.

	Linear kernel			**Poly kernel**			**RBF kernel**			**Sigmoid kernel**		
Dataset	**Err**	**FNR**	**FPR**	**Err**	**FNR**	**FPR**	**Err**	**FNR**	**FPR**	**Err**	**FNR**	**FPR**
Breast	**0.31**	**0.30**	**0.31**	0.33	0.28	0.37	0.37	0.46	0.29	0.47	1.00	0.00
CNS	**0.33**	**0.62**	**0.18**	0.37	0.62	0.23	0.35	1.00	0.00	0.35	1.00	0.00
Colon	**0.18**	**0.27**	**0.12**	0.27	0.55	0.12	0.21	0.50	0.05	0.39	0.82	0.15
Leukemia	**0.01**	–	–	0.03	–	–	0.15	–	–	0.35	–	–
Leukemia_3c	**0.04**	–	–	0.06	–	–	0.26	–	–	0.47	–	–
Leukemia_4c	**0.07**	–	–	0.10	–	–	0.32	–	–	0.47	–	–
Lung	**0.05**	**0.01**	**0.12**	0.05	0.01	0.18	0.09	0.01	0.24	0.32	0.00	1.00
Lymphoma	**0.00**	–	–	**0.00**	–	–	**0.00**	–	–	0.30	–	–
MLL	**0.03**	–	–	0.06	–	–	0.10	–	–	0.61	–	–
Ovarian	**0.00**	**0.00**	**0.00**	0.004	0.00	0.01	0.02	0.01	0.02	0.36	0.00	1.00
SRBCT	**0.00**	–	–	0.01	–	–	0.07	–	–	0.65	–	–
Average, $\overline{X}$	**0.09**	**0.24**	**0.15**	0.12	0.29	0.18	0.18	0.40	0.12	0.43	0.56	0.43
Std. dev.,σ	**0.12**	**0.23**	**0.10**	0.13	0.26	0.12	0.13	0.37	0.12	0.11	0.47	0.47

Table 4: Test error rate (Err), FNR, and FPR of LOOCV for the DT classifier using entropy as criterion and random_state set to 42, with normalized features in the range 0 to 1. Different values for the max_depth parameter are evaluated (the learned tree maximum allowed depth).

	Max Depth=2			**Max Depth=5**			**Max Depth=7**			**Max Depth=10**		
Dataset	**Err**	**FNR**	**FPR**	**Err**	**FNR**	**FPR**	**Err**	**FNR**	**FPR**	**Err**	**FNR**	**FPR**
Breast	0.40	0.35	0.45	**0.33**	**0.30**	**0.35**	**0.33**	**0.30**	**0.35**	**0.33**	**0.30**	**0.35**
CNS	**0.18**	**0.48**	**0.03**	0.25	0.33	0.21	0.25	0.33	0.21	0.25	0.33	0.21
Colon	**0.18**	**0.36**	**0.08**	0.19	0.23	0.18	0.19	0.23	0.18	0.19	0.23	0.18
Leukemia	**0.26**	–	–	**0.26**	–	–	**0.26**	–	–	**0.26**	–	–
Leukemia_3c	**0.15**	–	–	0.17	–	–	0.17	–	–	0.17	–	–
Leukemia_4c	**0.11**	–	–	0.15	–	–	0.15	–	–	0.15	–	–
Lung	0.13	0.01	0.06	**0.07**	**0.01**	**0.12**	**0.07**	**0.01**	**0.12**	**0.07**	**0.01**	**0.12**
Lymphoma	**0.00**	–	–	**0.00**	–	–	**0.00**	–	–	**0.00**	–	–
MLL	**0.08**	–	–	**0.08**	–	–	**0.08**	–	–	**0.08**	–	–
Ovarian	**0.03**	**0.01**	**0.07**	**0.03**	**0.01**	**0.07**	**0.03**	**0.01**	**0.07**	**0.03**	**0.01**	**0.07**
SRBCT	0.27	–	–	**0.17**	–	–	**0.17**	–	–	**0.17**	–	–
Average, $\overline{X}$	0.16	0.24	0.14	**0.15**	**0.18**	**0.19**	**0.15**	**0.18**	**0.19**	**0.15**	**0.18**	**0.19**
Std. dev., σ	0.11	0.19	0.16	**0.10**	**0.14**	**0.10**	**0.10**	**0.14**	**0.10**	**0.10**	**0.14**	**0.10**

Table 5: Test error rate (Err), FNR, and FPR of LOOCV for the SVM classifier (C=1 and kernel=linear) with EFB discretization. Different values for the n_bins parameter were evaluated (the number of discretization bins).

	Num. Bins=2			**Num. Bins=3**			**Num. Bins=4**			**Num. Bins=5**			**Num. Bins=6**			**Num. Bins=7**		
Dataset	**Err**	**FNR**	**FPR**	**Err**	**FNR**	**FPR**	**Err**	**FNR**	**FPR**	**Err**	**FNR**	**FPR**	**Err**	**FNR**	**FPR**	**Err**	**FNR**	**FPR**
Breast	0.32	0.30	0.33	0.33	0.33	0.33	0.32	0.33	0.31	0.32	0.33	0.31	**0.30**	**0.30**	**0.29**	0.31	0.33	0.29
CNS	0.35	0.71	0.15	**0.30**	**0.62**	**0.13**	0.38	0.71	0.21	0.32	0.62	0.15	0.32	0.62	0.15	0.37	0.67	0.21
Colon	0.18	0.27	0.12	0.18	0.27	0.12	0.16	0.27	0.10	**0.15**	**0.23**	**0.10**	**0.15**	**0.23**	**0.10**	0.16	0.27	0.10
Leukemia	**0.01**	–	–	**0.01**	–	–	**0.01**	–	–	**0.01**	–	–	**0.01**	–	–	**0.01**	–	–
Leukemia_3c	**0.03**	–	–	**0.03**	–	–	**0.03**	–	–	**0.03**	–	–	0.04	–	–	0.04	–	–
Leukemia_4c	0.08	–	–	**0.07**	–	–	**0.07**	–	–	**0.07**	–	–	**0.07**	–	–	**0.07**	–	–
Lung	0.05	0.01	0.18	0.05	0.01	0.18	0.05	0.01	0.18	**0.04**	**0.01**	**0.18**	**0.04**	**0.01**	**0.18**	**0.04**	**0.01**	**0.18**
Lymphoma	**0.00**	–	–	**0.00**	–	–	**0.00**	–	–	**0.00**	–	–	**0.00**	–	–	**0.00**	–	–
MLL	0.04	–	–	**0.03**	–	–	**0.03**	–	–	**0.03**	–	–	**0.03**	–	–	**0.03**	–	–
Ovarian	0.004	0.00	0.01	**0.00**	**0.00**	**0.00**	**0.00**	**0.00**	**0.00**	**0.00**	**0.00**	**0.00**	**0.00**	**0.00**	**0.00**	**0.00**	**0.00**	**0.00**
SRBCT	**0.00**	–	–	**0.00**	–	–	**0.00**	–	–	**0.00**	–	–	**0.00**	–	–	**0.00**	–	–
Average, $\overline{X}$	0.10	0.26	0.16	0.09	0.25	0.15	0.10	0.26	0.16	0.09	0.24	0.15	**0.09**	**0.23**	**0.14**	0.09	0.26	0.16
Std. dev., σ	0.12	0.26	0.10	0.12	0.23	0.11	0.13	0.26	0.10	0.12	0.23	0.10	**0.11**	**0.23**	**0.10**	0.12	0.25	0.10

datasets, we can observe that only one single feature is chosen *n* times (on the LOOCV folds), thus it is identified as the most relevant feature (gene) for cancer detection, to be checked by the clinical staff. Afterward, we observe a decreasing function that shows the relative importance of the features to perform classification. We observe that only a few features are chosen *n* times, being the most relevant in clinical terms.

5 CONCLUSIONS

Cancer detection and classification from high-dimensional DNA microarray data is an important problem, with many techniques having been successfully applied to these problems. However, more than just classifying the data, it is also important to identify the most relevant genes for the classification task,

Table 6: Summary of the best results and respective configurations, for each dataset with normalized features, obtained during the data representation phase with the EFB discretizer. The * symbol denotes an improvement over the baseline classification results of Table 3 and Table 4, without discretization.

		Configurations			
Dataset	**Classifier**	**Num. Bins**	**Err**	**FNR**	**FPR**
Breast	SVM	6	0.30*	0.30	0.29
CNS	DT	5	0.18	0.33	0.10
Colon	SVM	5, 6	0.15*	0.23	0.10
Leukemia	SVM, DT	2, 3, 4, 5, 6, 7	0.01	–	–
Leukemia_3c	SVM	2, 3, 4, 5	0.03*	–	–
Leukemia_4c	SVM	3, 4, 5, 6, 7	0.07*	–	–
Lung	SVM	5, 6, 7	0.04*	0.01	0.18
Lymphoma	SVM	2, 3, 4, 5, 6, 7	0.00	–	–
MLL	SVM	3, 4, 5, 6, 7	0.03	–	–
Ovarian	SVM	3, 4, 5, 6, 7	0.00	0.00	0.00
SRBCT	SVM	2, 3, 4, 5, 6, 7	0.00	–	–
Average, $\overline{X}$	–	–	0.07	0.17	0.13
Std. dev., σ	–	–	0.09	0.14	0.10

Table 7: Test error rate (Err), FNR, and FPR of LOOCV for the SVM classifier (C=1 and kernel=linear) with LS, SPEC, FiR, and RRFS (with MM and FiR relevance and maximum similarity m_s=0.7), with normalized features.

	Unsupervised									**Supervised**					
	LS			**SPEC**			**RRFS (MM)**			**FiR**			**RRFS (FiR)**		
Dataset	**Err**	**FNR**	**FPR**	**Err**	**FNR**	**FPR**	**Err**	**FNR**	**FPR**	**Err**	**FNR**	**FPR**	**Err**	**FNR**	**FPR**
Breast	0.33	0.35	0.31	0.32	0.30	0.33	**0.31**	**0.28**	**0.33**	**0.31**	**0.28**	**0.33**	**0.31**	**0.28**	**0.33**
CNS	0.35	0.52	0.26	0.33	0.62	0.18	**0.27**	**0.48**	**0.15**	0.30	0.57	0.15	0.33	0.67	0.15
Colon	**0.16**	**0.27**	**0.10**	0.19	0.32	0.12	0.21	0.36	0.12	0.19	0.32	0.12	0.18	0.27	0.12
Leukemia	**0.01**	–	–	**0.01**	–	–	**0.01**	–	–	**0.01**	–	–	**0.01**	–	–
Leukemia_3c	0.04	–	–	0.06	–	–	0.04	–	–	0.04	–	–	**0.03**	–	–
Leukemia_4c	0.08	–	–	0.10	–	–	**0.07**	–	–	**0.07**	–	–	**0.07**	–	–
Lung	0.05	0.01	0.12	0.05	0.01	0.12	0.05	0.01	0.12	**0.04**	**0.01**	**0.12**	0.05	0.01	0.18
Lymphoma	**0.00**	–	–	**0.00**	–	–	0.03	–	–	**0.00**	–	–	0.02	–	–
MLL	0.04	–	–	0.06	–	–	**0.03**	–	–	**0.03**	–	–	0.04	–	–
Ovarian	**0.00**	**0.00**	**0.00**	**0.00**	**0.00**	**0.00**	0.004	0.00	0.01	**0.00**	**0.00**	**0.00**	**0.00**	**0.00**	**0.00**
SRBCT	0.02	–	–	**0.00**	–	–	**0.00**	–	–	**0.00**	–	–	**0.00**	–	–
Average, $\overline{X}$	0.10	0.23	0.16	0.10	0.25	0.15	**0.09**	**0.23**	**0.15**	0.09	0.24	0.14	0.09	0.25	0.16
Std. dev., σ	0.12	0.20	0.11	0.12	0.23	0.11	**0.11**	**0.19**	**0.10**	0.11	0.21	0.11	0.12	0.24	0.11

Table 8: Pipeline's best configuration found for each dataset.

	Pipeline Configuration		
Dataset	**Discretization**	**Selection**	**Classification**
Breast	EFB (n_bins=6)	RRFS (with FiR; *ms*=0.7)	SVM (C=1; kernel=linear)
CNS	EFB (n_bins=5)	SPEC	DT (criterion=entropy, max_depth=6, and random_state=42)
Colon	MDLP	LS	DT (criterion=entropy, max_depth=None, and random_state=5)
Leukemia	EFB (n_bins=2)	LS	SVM (C=1; kernel=linear)
Leukemia_3c	EFB (n_bins=2)	RRFS (with FiR; *ms*=0.7)	SVM (C=1; kernel=linear)
Leukemia_4c	EFB (n_bins=3)	RRFS (with FiR; *ms*=0.7)	SVM (C=1; kernel=linear)
Lung	EFB (n_bins=5)	FiR	SVM (C=1; kernel=linear)
Lymphoma	EFB (n_bins=2)	LS	SVM (C=1; kernel=linear)
MLL	EFB (n_bins=3)	RRFS (with MM; *ms*=0.7)	SVM (C=1; kernel=linear)
Ovarian	EFB (n_bins=3)	RRFS (with FiR; *ms*=0.7)	SVM (C=1; kernel=linear)
SRBCT	EFB (n_bins=2)	SPEC	SVM (C=1; kernel=linear)

allowing for the human interpretability of the classification results. In this work, we have proposed an approach using feature selection and feature discretization techniques, able to identify small subsets of relevant genes for the subsequent classifier. The proposed approach is based on standard machine learning procedures, achieves large degrees of dimensionality reduction on several public-domain datasets. By using the LOOCV procedure, identify the features (genes) that are often more relevant for the classifier decision.

In future work, we will explore supervised feature discretization techniques. We will also fine tune the maximum similarity parameter of the RRFS algorithm to further reduce the size of the subsets, allowing medical experts to focus on fewer features.

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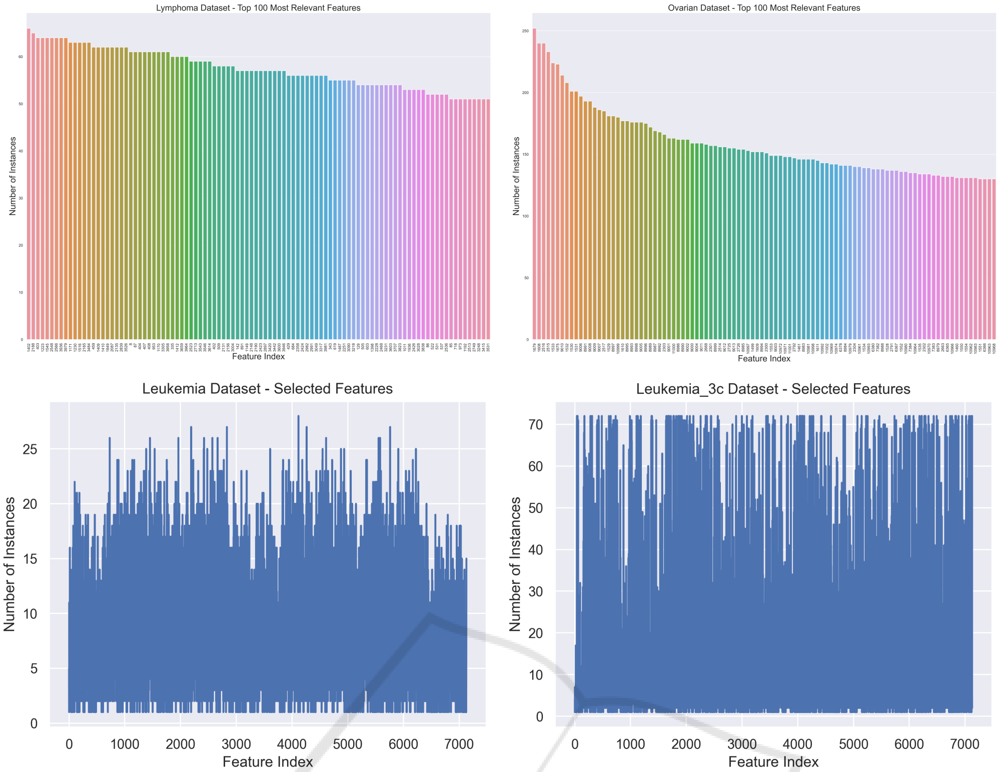

Figure 5: Top: The top-100 of the number of times each feature is chosen/selected on the FS step on the LOOCV procedure for the Lymphoma (n=66, d=4026) and Ovarian datasets (n=253, d=15154). Bottom: The number of times each feature is chosen/selected for the Leukemia (n=72, d=7129) and Leukemia_3c datasets (n=72, d=7129).

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