PROGNOSIS OF BREAST CANCER BASED ON A FUZZY CLASSIFICATION METHOD

L. Hedjazi[1,2], T. Kempowsky-Hamon[1,2], M.-V. Le Lann[1,2] and J. Aguilar-Martin[1,3]

[1]*CNRS, LAAS, 7, avenue du Colonel Roche, F-31077 Toulouse, France*

[2]*Université de Toulouse, UPS, INSA, INP, ISAE, LAAS, F-31077 Toulouse, France*

[3]*Universitat Politècnica de Catalunya, grup SAC;Rambla de Sant Nebridi, 10, E-08222 Terrassa (Catalunya), Spain*

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Abstract: Learning and classification techniques have shown their usefulness in the analysis of ana-cyto-pathological cancerous tissue data to develop a tool for the diagnosis or prognosis of cancer. The use of these methods to process datasets containing different types of data has become recently one of the challenges of many researchers. This paper presents the fuzzy classification method LAMDA with recent developments that allow handling this problem efficiently by processing simultaneously the quantitative, qualitative and interval data without any preamble change of the data nature as it must be generally done to use other classification methods. This method is applied to perform breast cancer prognosis on two real-world datasets and was compared with results previously published to prove the efficiency of the proposed method.

1 INTRODUCTION

In the cancer treatment domain, there are two distinct purposes: diagnosis of cancer and the prognosis of survival or relapse/recurrence in the case of a previously diagnosed cancer. This work focuses on developing a methodology for the prognosis to better assess the potential risk of relapse based on the analysis of ana-cyto-pathological data. Among many works performed in the cancer diagnosis field, classical classification methods often give satisfactory results (Ryu et al.,2007). However, in the prognosis field, they have shown a real difficulty in obtaining accurate predictions in terms of the relapse risk (Holter, 1993). This is due firstly to the fact that the potential prognostic factors remain still partially known (Deepa et al., 2005) and, secondly, the data contained in prognosis datasets are heterogeneous: they can be quantitative or qualitative and even take the form of intervals. In this work, the fuzzy classification method LAMDA based on learning (Learning Algorithm for Multivariable Data Analysis) (Aguilar-Martin & López de Mantaras, 1982) was used. LAMDA can handle datasets that contain simultaneously features of different type: quantitative, qualitative (Isaza et al., 2004). In the

present paper, this method is also extended in order to handle another type of data: interval.

The paper is organized as follows: in section 2, a brief presentation of the general classification procedure based on the LAMDA method is given with the treatment of different types of data (quantitative, qualitative, intervals). In section 3, an application on two Breast Cancer Prognosis datasets illustrates the effectiveness of the proposed methodology. Finally the paper is concluded and perspectives on future works are given in section 4.

2 CLASSIFICATION PROCEDURE BY LEARNING

For any classification and analysis method based on learning, there are two principal phases (Figure 1): training and recognition (or test). In the training phase the objective is to find the set of classes (with their features or their parameters: number, shapes,...) which represents at best a set of known data. In the recognition phase new cases (other than those used for learning) are examined and matched to the classes obtained during the training phase.

During the training phase, the first step is to select the features that best discriminate the different classes (Figure 1). This selection may relate to the raw data as the results from filtering, principal components analysis (PCA),.... The next step is to determine the parameters of each class.
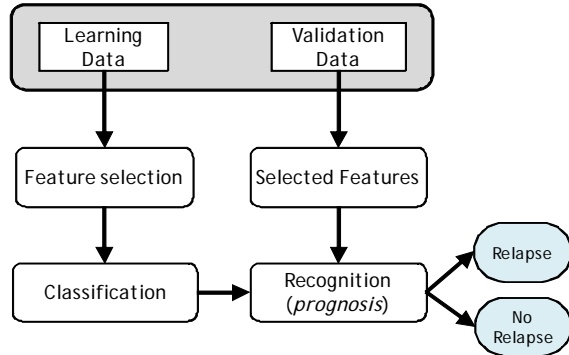

Figure 1: Data processing by classification.

2.1 LAMDA Classification Method

LAMDA is a fuzzy methodology of conceptual clustering and classification. It is based on finding the global membership degree of an individual to an existing class, considering all the contributions of each of its features. This contribution is called the *marginal adequacy degree* (*MAD*). The MADs are combined using "fuzzy mixed connectives" as aggregation operators in order to obtain the *global adequacy degree* (*GAD*) of an element to a class. LAMDA can simultaneously handle qualitative and quantitative data (Isaza et al., 2004) and has been recently extended to interval data.

LAMDA offers the possibility to make a supervised learning (with classes assigned a priori) and/or unsupervised (self-learning). Learning is done in an incremental and sequential way, thus reducing the learning phase to one or very few iterations. The assignment of an individual to a class follows always the same procedure; the present individual initializes a class or contributes to the modification of an existing class. Figure 2 illustrates the procedure for assigning an individual to a class.

LAMDA states upon the assumption that the features of the elements to be classified are independent of each other, i.e. there is no correlation between the variables (features).

2.2 MAD: Marginal Adequacy Degree

The marginal adequacy degree (MAD) is expressed as a function of marginal relevance to the C_k class:

$$\mu_k^i(x_i) = \text{MAD}(x_i / i^{th} \text{ parameter of class } C_k)$$

This function depends on the ith feature x_i of the individual X and on parameter θ_{ki} of class C_k:

$$\mu_k^i(x_i) = f_i(x_i, \theta_{ki})$$

The parameter θ_{ki} is calculated iteratively from the ith feature of all individuals belonging to class C_k.

The procedure to calculate the MAD when the feature is qualitative, quantitative or interval is detailed in the following subsections.
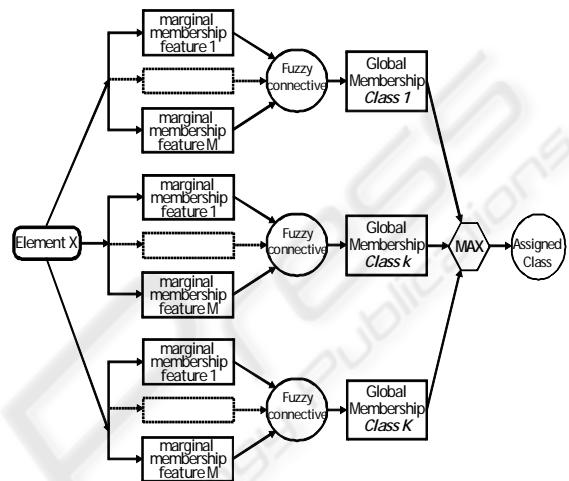

Figure 2: LAMDA structure for 3 classes.

2.2.1 Qualitative Type Features

In the qualitative case, the possible values of the ith feature form a set of modalities:

$$D_i = \{Q_{i1}, ... Q_{ij}, ... Q_{iMi}\}$$

Let Φ_{ij} be the probability of Q_{ij} in the class C_k, estimated by its relative frequency, then the membership function of x_i is multinomial:

$$\mu_k^i(x_i) = \Phi_{i1}^{q_{i1}} * \cdots * \Phi_{iMi}^{q_{iMi}} \qquad (1)$$

where:

$$q_{ij} = \begin{cases} 1 & si\ x_i = Q_{ij} \\ 0 & si\ x_i \neq Q_{ij} \end{cases}$$

2.2.2 Quantitative Type Features

When the feature is quantitative, its numerical values are firstly normalized (2) within the interval $[x_{imin}, x_{imax}]$, where the bounds can be the extremes of a given dataset or independently imposed.

$$\alpha(x_i) = (x_i - x_{imin})/(x_{imin} - x_{imax}) \qquad (2)$$

The MAD is calculated by selecting one of the different possible membership functions proposed

by (Aguado et Aguilar-Martin, 1999). To take into account the correlation between all the quantitative features, a pre-treatment of the data was performed in order to express the features in the new basis where they are linearly independent (appendix A). Therefore, the Gaussian membership function has been used:

$$\mu_k^i = e^{-\frac{1}{2}(y_i - v_k)^2 / \lambda_i} \qquad (3)$$

Where y_i, v_k and λ_i correspond respectively to the projected value of the feature, the mean value of class C_k and the variance in the new basis obtained after the transformation rendering the features uncorrelated to each other.

2.2.3 Interval Type Features

To take into account the various uncertainties (noises) or to reduce large datasets, the interval representation of data has seen widespread use in recent years (Billard, 2008). In this work, an interval data classification is proposed using a new fuzzy similarity measure in such a way that LAMDA can handle this type of features.

To establish a similarity measure S between two intervals A=[a⁻,a⁺] and B=[b⁻,b⁺] defined on the universe of discourse $U=[min(x^-),\ max(x^+)]$ where the distance between A and B is given by $D=[min(a^+,b^+),\ max(a^-,b^-)]$, each interval is considered as a fuzzy subset, so that the similarity measure is given by:

$$S(A,B) = \frac{1}{2}\left[\left(\frac{\sum_{x_n}(\mu_{A \cap B}(x_n))}{\sum_{x_n}(\mu_{A \cup B}(x_n))} \right) + \left(1 - \frac{\sum_{x_n}(\mu_D(x_n))}{\sum_{x_n}(\mu_U(x_n))} \right) \right] \qquad (4)$$

The class parameters for the interval type features are represented by a vector of intervals and are given by the arithmetic mean of its bounds:

$$\rho_{1k}^i = \frac{1}{m}\sum_{j=1}^{m} x_{ij}^-, \qquad \rho_{2k}^i = \frac{1}{m}\sum_{j=1}^{m} x_{ij}^+ \qquad (5)$$

Where m is the number of individuals assigned to class C_k.
A normalisation within the interval [0,1] is also necessary:

$$x_i^- = \frac{\hat{x}_i^- - \hat{x}_{iMIN}^-}{\hat{x}_{iMAX}^+ - \hat{x}_{iMIN}^-}, \qquad x_i^+ = \frac{\hat{x}_i^+ - \hat{x}_{iMIN}^-}{\hat{x}_{iMAX}^+ - \hat{x}_{iMIN}^-} \qquad (6)$$

Where $x_i = [x_i^-, x_i^+]$ is the normalized value of feature $\hat{x}_i = [\hat{x}_i^-, \hat{x}_i^+]$.

Finally the marginal adequacy degree is taken as the similarity between the data interval x_i and the interval $\rho_k^i = \left[\rho_{1k}^i, \rho_{2k}^i \right]$ representing class C_k.

$$\mu_k^i(x_i) = MAD\ (x_i, \rho_k^i) = S(x_i, \rho_k^i) \qquad (7)$$

2.3 GAD: Global Adequacy Degree

Once all the MADs are calculated, the concept of mixed connective is used to compute the overall membership (GAD) of the individual X to class C_k. This is valid even if the features are of different types (intervals, qualitative or quantitative).

The global level of adequacy (GAD) can be also expressed as the membership function of an individual X to a class C_k, which is interpreted as a fuzzy set:

$$\mu_k(X) = \text{GAD(individual } X/ \text{ class } C_k)$$

This function depends on each of the n features of the individual X through the MADs μ_k^i computed in the previous step and combining them by a marginal aggregation function generally chosen as a linear interpolation between fuzzy *t-norm* (γ) and *t-conorm* (β) (Piera et Aguilar, 1988).

$$\begin{aligned}\mu_k(X) = &\ \alpha\gamma\,(\mu_k^1(x_1) \cdots \mu_k^n(x_n)) \\ &+ (1-\alpha)\beta\,(\mu_k^1(x_1) \cdots \mu_k^n(x_n))\end{aligned} \qquad (8)$$

where parameter α, $0 \le \alpha \le 1$, is called *exigency*.

3 APPLICATION TO CANCER PROGNOSIS

The two real-world datasets used to assess the effectiveness of the presented methodology are obtained from the publicly available machine learning repository from Irvine University (Murphy & Aha, 1995) and concern the relapse prediction of patients with breast cancer: the first one provided by the Centre of Clinical Sciences at the University of Wisconsin, the second one comes from the Institute of Oncology of the University Medical Centre of Ljubljana, dedicated also for prognosis including only qualitative and interval features. These datasets have been widely used to test and compare the performance of different learning algorithms and classification methods.

3.1 Prognosis Wisconsin Dataset

This dataset of prognosis was obtained from the well known Wisconsin Breast Cancer Diagnosis (WBCD)

which contains 569 patients divided into 2 subsets: 357 with fibrocystic breast masses and 212 with cancer. The later one contains 166 patients with primary invasive breast cancer for whom necessary information for studying prognosis was available. The remaining 46 patients either had in situ cancers, or had distant metastasis in the time of presentation (Wolberg & al, 1995). Only 118 of the 166 patients, excluding patients with missing data, developed metastases sometime following surgery (i.e. relapse) or were followed a minimum of 24 months without developing distant metastases (i.e. no relapse). This dataset contains 32 features, 30 were obtained by image processing. These features describe the characteristics of cell nuclei present in the image:

1. Radius (average distance from the centre to points on the perimeter).
2. Texture (standard deviation of the values of "gray-scale").
3. Perimeter
4. Area
5. Smoothness (local variation in radius lengths).
6. Compactness (perimeter^2 / area - 1.0).
7. Concavity (severity of concave parts of the contour).
8. Concave points (number of concave portions of the contour).
9. Symmetry.
10. Fractal dimension (coastline approximation - 1).

The average value, the "worst" (average of the three larger ones), and standard deviation of each feature were calculated for each image, resulting in a total of 30 features. In addition, the dataset includes the tumour size and the number of affected lymph nodes.

3.1.1 Feature Selection and Extraction

Feature selection is the problem of choosing a small subset of features that ideally is necessary and sufficient to describe the target concept (Kira and Rendell, 1992). There are 32 features for the Wisconsin prognosis dataset. Two feature selection methods and one extraction method have been compared to assess the performance of the proposed classification method during the training phase: T-Test, Entropy and Principal Component Analysis (PCA).

The T-Test method determines if two groups are statistically different from their characteristics. By reverse reasoning, it is clear that the characteristics that make them different can be determined. Similarly, the entropy (entropy of the information

according to Shannon) is a measure of the quality of information. The PCA seeks a projection of d-dimensional data onto a lower-dimensional subspace in a way that is optimal in a sum-squared error sense.

In all three cases, the first 10 ranked features have been selected. In the case of T-Test and entropy, it was found that although the ranking order was different seven out of the first 10 features appeared within the two methods. The list of these 10 features is given in Table1.

Table 1: Feature selection for Wisconsin dataset according to the T-test and Entropy methods. M=mean, W=worst, SE= standard deviation.

T-TEST	ENTROPIE
W Perimeter	W fractal dimension
W Radius	M fractal dimension
M Perimeter	M Area
M Radius	W Perimeter
M Area	M Perimeter
W Area	M Radius
M Fractal dimension	W Radius
SE Area	W Area
M concave points	SE Fractal dimension
SE Perimeter	M Symmetry

As regards to the PCA, the 32 features were used to identify the main directions that best represent the data. Figure 3 shows the amount of information represented by each component and the cumulated information given by the first 10 components. It can be seen that these components enable to represent 93% of the total information in the training set.
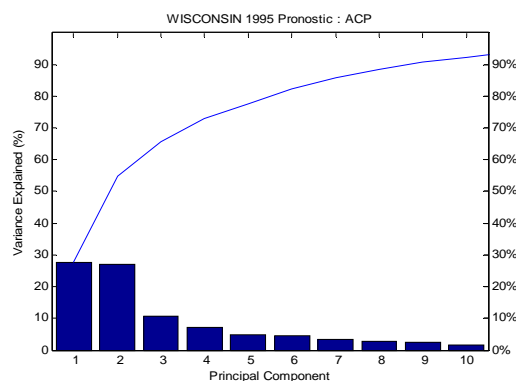

Figure 3: 10 principal components obtained by ACP and their power of data representation.

126

3.1.2 Method and Results

In this study, due to the limited number of relapsed patients, a Leave-One-Out Cross Validation (LOO CV) strategy has been performed to estimate the rate of accuracy. This consists of removing one sample from the dataset, constructing the predictor only on the basis of the remaining samples, and then testing its performance on the removed example. The 118 patients have been ordered: the first 96 have not relapsed after 24 months and the last 22 relapsed (ordered in Figure 4 from left to right).

The fuzzy classification results obtained by using the Gaussian membership function are presented in Table 2.

A first classification has been performed using the 32 features and the results are shown in Figure 5. It can be noted that the overall prognosis is quite good (85.59%) with a prediction of relapse of 72.73% (which is acceptable given the reduced amount of relapsed patients in the dataset). In Figure 4 it can be seen that 7 patients (points starting from patient number 97) who effectively relapsed have not been well recognized. It is clear that a good analysis of the results must not only consider the total recognition score but focus on the false negatives since these patients will not receive an appropriate treatment.
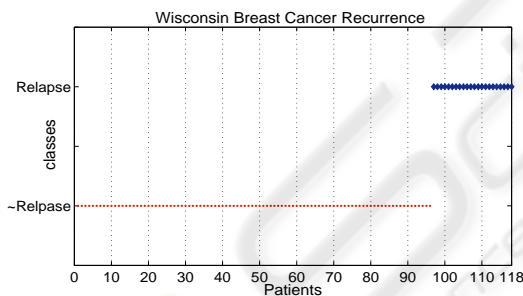

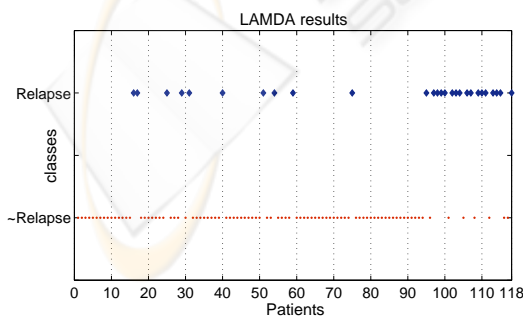Figure 4: Wisconsin Breast Cancer ordered dataset.

Figure 5: LAMDA results with 32 features.

A comparison of these results can be made with those obtained by Wolberg et al. (Wolberg et al., 1995) using a variant of MSM (MultiSurface Method) known as MSM-Tree (MultiSurface Tree Method): 86.3%. This method uses linear programming iteratively to place a series of separating planes of the feature space of the examples (Wolberg et al., 1995). MSM-T is similar to other decision tree methods such as CART and C4.5 but has been shown to be faster and more accurate on several real-world data sets (Bennett, 1992). Although in the reported studies a T-test feature selection was performed it was not finally used to build the classifier. On the contrary all possible combinations of the 32 features were tested to determine the best set of features leading to the best class separation. Only four features were selected: M texture, W area, W concavity, W fractal dim. The best obtained result (86%) using this method is comparable to ours. Moreover it is shown that the introduction of the tumour size and the lymph nodes as supplementary features did not improve the performance (77.40%). Nevertheless, it is impossible to go further in the comparison since the authors did not give the rate of the false negatives.

Complementary studies with preliminary feature selection step were performed: T-test, entropy and PCA. The results are given in Table 2. These results confirm that the features that correspond to the morphology of the tumour are directly related to the prediction of relapse. Nevertheless this information is not sufficient to obtain a comparable accuracy (the accuracy of general prediction is less than 75% for T-test and entropy). These results confirm as stated by (Wolberg et al., 1995), that this kind of feature

Table 2: WBCP recognition results for the 3 feature selection methods with/without Tumour size and positive lymph nodes.

Feature selection	Total	~Relapse	Relapse
T-Test: 10 features	74.58%	77.09%	63.64%
T-Test: 10 features + tumour size & lymph nodes	78.81%	82.29%	63.64%
Entropy: 10 features	72.88%	77.08%	54.55%
Entropy: 10 features + tumour size & lymph nodes	76.27%	81.25%	54.55%
PCA: First 10 components	83.05%	93.75%	36.36%
Nuclei cell 30 features	83.05%	85.42%	72.73%
Nuclei cell 30 features + tumour size & lymph nodes	85.59%	88.54%	72.73%
MSM-T Results (M texture, W area, W concavity, W fractal dim.)	86.3%	~	~
MSM-T Results + tumour size & lymph nodes	77.4%	~	~

selection procedure does not allow identifying the best class separation. When the tumour size and the number of infected lymph nodes are added to these 10 selected features, an increase of 4% is achieved in both cases but it remains under the 86% obtained with the 32 features. In the case of PCA, the results given in Table 2 seem better. Nevertheless, even if the overall rate of prediction is more than 83%, the prediction of relapse (poor prognosis) is very low (36.36%).

3.2 Ljubljana Prognosis Dataset

For roughly 30% of the patients who undergo an operation on breast cancer, the disease reappears after five years. Regarding this dataset, the aim is to predict whether patients are likely to relapse, which may influence the treatment they will receive. The Ljubljana Prognosis dataset contains a total of 286 patients for whom 201 have not relapsed after five years and 85 who have relapsed (Clark & Niblett, 1987). For these patients, 9 features are available (six qualitative and three interval types):

1. Age: 10-19, 20-29, 30-39, 40-49, 50-59, 60-69, 70-79, 80-89, 90-99
2. Menopause: >40, <40, pre-menopause.
3. tumour size: 0-4, 5-9, 10-14, 15-19, 20-24, 25-29, 30-34, 35-39, 40-44, 45-49, 50-54, 55-59.
4. invaded nodes: 0-2, 3-5, 6-8, 9-11, 12-14, 15-17, 18-20, 21-23, 24-26, 27-29, 30-32, 33-35, 36-39.
5. Ablation ganglia: yes, no.
6. malignancy Degree: I, II, III
7. Breast right, left
8. Quadrant: sup. left, inf. left sup. right, inf. right, center.
9. Irradiation: yes, no

3.2.1 Methods and Results

A cross-validation (50% training, 50% test) has been performed to estimate the accuracy of the proposed methodology. Patients with missing data were excluded from this analysis (9 patients). The results are given in Table 3. In order to compare these results with those cited in earlier works (Clark & Niblett, 1987), a first study consisted in classifying

Table 3: LAMDA results with Ljubljana dataset.

Feature selection	Training	Test
Whole original dataset	91%	89.89%
8 features with interval grade	91.33%	90%
Without irradiated patients	93%	92.1%

the 277 patients with 9 features as given in the original dataset: 6 qualitative features including the degree of malignancy (feature No. 6 given by modalities I, II or III) and 3 interval features. A second study was done by treating the grade data as intervals (I: [3,5], II: [6,7], III: [8,9]). This allows expressing the linguistic distance between grades, such as oncologists do naturally.

Table 4: Ljubljana comparative results.

Method	Accuracy
MEPAR-miner	92.8%
LAMDA	90%
Isotonic separation	80%
EXPLORE	76.5%
C4.5	72%
AQR	72%
Assist 86	68%
NaiveBayes	65%

The results obtained by considering the grade type as an interval show the effectiveness of this method, which gives an accuracy of 91.33% in training and 90% in test. Figure 6, 7 and 8 show the class parameters of interval features obtained in these two studies. It can be observed that the interval features "Tumour size" and "Lymph nodes" are more discriminatory between classes in the two studies than the "Age" feature. This fact was established in many previous studies (Deepa et al., 2005), where it was noted that these two features still to date are considered as important prognostic factors. While for the feature "Grade" which makes the difference between the two studies, even if in the first study (Figure 7, where it was considered as qualitative) the difference in the three modalities frequencies between the two classes can be observed, the interpretation is still quite ambiguous since the two classes contains the three grades with a slight difference. In the second study (Figure 8, when the grade is considered as interval feature) the interpretation becomes easier and straightforward.

A third part of the study was to consider only patients who have not yet undergone an irradiation treatment (215). This treatment had been applied systematically to patients with a positive number of lymph nodes. This implies that the two features: "irradiation" and the "number of affected lymph nodes" are correlated with each other. The objective here is to validate the method precisely to help physicians on the decision of treatment based on the results of prognosis beyond 5 years. The results (3rd line of Table 3) are quite satisfactory, 93% of accuracy for learning and 92.1% for test. Comparing these results (Table 4) with those obtained with
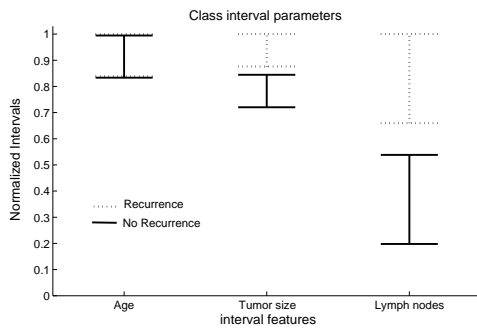
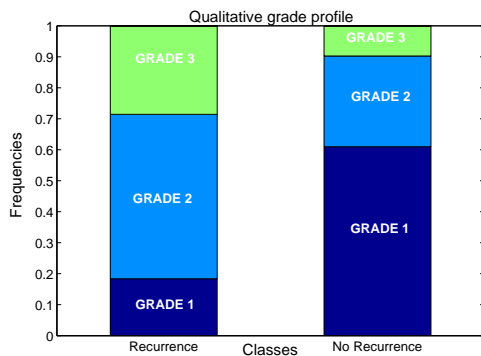Figure 6: Classes parameters of interval features (1ststudy).

Figure 7: Classes of the feature "grade" (1st study).
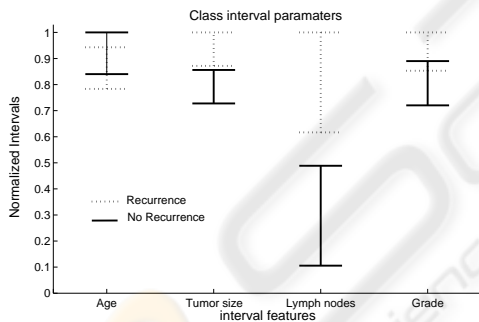

Figure 8: Classes parameters of interval features(2ndstudy).

other techniques AQR (Michalski & Larson, 1983), Assistant (Cestnik et al., 1987), CN2 (Clark & Niblett, 1989), C4.5 (Quinlan, 1993), Boosters (Bernhard et al., 2001), Isotonic separation (Ryu et al., 2007) and EXPLORE (Kors et al., 1997), LAMDA classification results appear to be as good as the best results reported previously and gives comparable results to MEPAR-miner algorithm (Aydogan et al.) which achieves 92.8% of accuracy.

4 CONCLUSIONS

This study has shown that the fuzzy classification provides satisfactory results in the prognosis of breast cancer. Comparing these results with those of the literature shows that they are either very similar or higher. The improvement of the quality of these results is based primarily on the recent development of a method that handles efficiently interval data as well as both quantitative and qualitative data; this property is one of the main features of the LAMDA method. Although other methods may yield results that are equal to those obtained with the LAMDA method, the advantage of using LAMDA is the significant gain in the interpretation simplicity. This is particularly useful in the medical context where a significant insight into the nature of the problem under investigation is recommended.

Future works will be devoted to develop a feature selection procedure based on a wrapper method which consists in using the classification algorithm itself to evaluate the goodness of a selected feature subset.

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APPENDIX

As it has been described, in the LAMDA approach the *GAD* is obtained by using a fuzzy aggregation function applied to the *MAD*s considered independently. In the present work the *MAD* function used is:

$$MAD[x_i / C_k] = \exp\left(-\tfrac{1}{2}\left(\frac{x_i - \rho_{ik}}{\sigma_{ik}}\right)^2\right) \qquad (A.1)$$

where the parameters of class C_k are respectively the mean ρ_{ik} and the standard deviation σ_{ik} of the elements of this class. Therefore, if the aggregation function chosen is Γ, for an object $X=[x_1,...,x_i...x_n] \in R^m$, its global membership to class C_k is

$$GAD[X/C_k]=\Gamma(MAD[x_1/C_k],..., MAD[x_i/C_k],... MAD[x_n/C_k]) \qquad (A.2)$$

Nevertheless by using the Gaussian type function it is possible to take into account the correlation between features in the definition of the *GAD*, as follows:

$$GAD[X/C_k] = \exp\left(-\tfrac{1}{2}(X-\rho_k)^T \sigma_k^{-1}(X-\rho_k)\right) \qquad (A.3)$$

where the parameters of class C_k are ρ_k and σ_k, respectively the mean vector and the covariance matrix of the elements of this class. To take into account the features correlation it is proposed a transformation to calculate the *MAD*s in a new basis such as they are uncorrelated to each other. This transformation relies on the following theorem:

Theorem: given a set of vectors $\{X_n | n=1,\cdots N\}$, its mean vector is M (A.4) and its covariance (correlation) matrix is P (A.5) assumed to be invertible.

$$M = \frac{1}{N}\sum_{n=1,\cdots N} X_n \qquad (A.4)$$

$$P = \frac{1}{N-1}\sum_{n=1,\cdots N}(X_n - M)(X_n - M)^T \qquad (A.5)$$

There exists always a linear transformation T such that the covariance matrix of $Y_n = TX_n$ is diagonal.

Proof: A square regular matrix P is diagonalizable if and only if there exists a basis consisting of its eigenvectors. The matrix B having these basis vectors as columns is such that $R = B^{-1}PB$ will be a diagonal matrix. The diagonal entries of this matrix are the eigenvalues of P. Therefore the transformation $T=B^{-1}$ such that $Y_i=T.X_i$ transforms the mean of the set $\{Y_n|n=1,...,N\}$ into:

$$K = \frac{1}{N}\sum_{n=1,\cdots N} TX_n = TM \qquad (A.6)$$

and the covariance matrix into:

$$\begin{aligned} R &= \frac{1}{N-1}\sum_{n=1,\cdots N} T(X_n - M)(X_n - M)^T T^{-1} \\ &= TPT^{-1} \\ &= B^{-1}PB \end{aligned} \qquad (A.7)$$

So that

$$\begin{aligned} &\exp\left(-\tfrac{1}{2}(Y_n - K)^T R^{-1}(Y_n - K)\right) \\ &= \prod_{i=1,\cdots m}\exp\left(-\tfrac{1}{2}\frac{(y_{ni} - k_i)^T(y_{ni} - k_i)}{r_i}\right) \end{aligned} \qquad (A.8)$$

where r_i is the ith eigenvalue of R, and the mean $k_i = \frac{1}{N}\sum_{n=1,\cdots N} y_{ni}$.

By analogy this property is extended further than the product towards any fuzzy aggregation function Γ.