Classifying Microcalcifications in Digital Mammograms using Machine Learning techniques

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Abstract

This paper presents a Computer Aided Diagnosis (CAD) of breast cancer from mammograms. The first part involves several image processing techniques, which extract a set of features from the microcalcifications (μCa) present in a mammogram. The second part applies different machine learning techniques to obtain an automatic diagnosis. The Machine Learning (ML) approaches are: Case-Based Reasoning (CBR) and Genetic Algorithms (GA). We study the application of these algorithms as classification systems in order to differentiate benign from malignant μCa in mammograms, obtained from the mammography database of the Girona Health Area, and we compare the classification results to other classification techniques.

Keywords: Machine Learning, Case-Based Reasoning, Evolutionary Computation, Vision, AI applications in medicine.

1 Introduction

Breast cancer is the most common cancer of western women and is the leading cause of cancer-related death among women aged 15-54 [5]. Survival from breast cancer is directly related to the stage at diagnosis. The earlier the detection, the higher chances of successful treatment [27]. In an attempt to improve early detection, a study has been undertaken to analyse the screening mammograms of breast cancer patients in order to select the microcalcifications features that help to differentiate benignant from malignant cases.

A number of CAD (Computer Aided Diagnosis) techniques have been developed for the detection and classification of microcalcifications [9, 26, 17], in which several image processing techniques are applied ranging from grey-level image analysis [4] to morphological methods [18], as well as a great number of classifiers ranging from Bayesian classifiers [11] to neural networks [26].

In this paper we propose the use of some selected shape-based features in order to classify clustered microcalcifications between benign and malignant. The computerized analysis of mammographic microcalcifications performed in this work can be divided into four steps: 1) digitisation of mammograms and enhancement of images; 2) detection and localization of suspicious areas; 3) extraction of shape-based features for every segmented microcalcification in the digitised mammogram; and 4) analysis of the features using Machine Learning (ML) techniques: Case-Based Reasoning and Genetic Algorithms.

The paper is organized as follows: the next section briefly describes the digitisation of mammograms and the enhancement of images as well as the detection and localization of suspicious areas, by giving an overview of the acquisition and segmentation procedures; section 3 summarizes the process of feature selection and ML techniques analysis which leads to the model proposed, exclusively based on shape-based features. Some experimental results are given in section 4. Finally, we present the conclusions and the further work.

2 Materials and methods

The study is composed by two separate stages: a retrospective and a prospective one. Each mammogram contains one or more clusters of suspicious microcalcifications.

A set of 146 mammograms was used at the retrospective stage with the goal to analyse the incidence of features in the malignant character of the microcalcifications and therefore, to choose the best features in order to build a statistical predictive model for the malignant diagnosis. The real diagnosis was known in advance from biopsies.

The medical diagnosis for the retrospective mammograms, issued by expert radiologists and oncologists, are known.

The predictive model was tested at a prospective stage, composed by 70 mammograms not diagnosed in advance. In order to evaluate the performance of the selected features for characterizing the microcalcifications and the power of the statistical model, the diagnosis provided by the model was compared to the real diagnosis given by the biopsies. Finally, this evaluation was compared to the diagnosis issued by 3 expert radiologists.

2.1 Image Digitisation

Conventional mammograms, in which the positions of clustered microcalcifications were determined by well experienced radiologists, were digitised using a CCD camera at a pixel size ranging from 12 to 37 micrometers and a twelve-bit grey scope, producing a 1524x1012 matrix image. An unshap-mask filter was applied to enhance the high-frequency component on the digitised images, only to make it easier for the observers to recognize the microcalcifications at the stage of annotated image display.

The whole set of digitised mammograms composes an unpublished database formed by patients of the Regional Health Area of Girona, now available upon request, which in the future may contribute to increase the digital mammogram databases.

2.2 Image Segmentation

The microcalcifications are segmented using a region-growing algorithm based on *Shen* segmentation techniques[25]. The algorithm starts with a selected pixel inside every microcalcification, called the seed pixel, which has been manually selected by the expert radiologists. This becomes the first region pixel; then, pixels $p(i,j)$ of every 4-connected neighbour of pixels belonging to the region, are checked for the tolerance-region condition:

$$(1+\tau)(F_{max}+F_{min})/2 \geq p(i,j) \geq (1-\tau)(F_{max}+F_{min})/2 \quad (1)$$

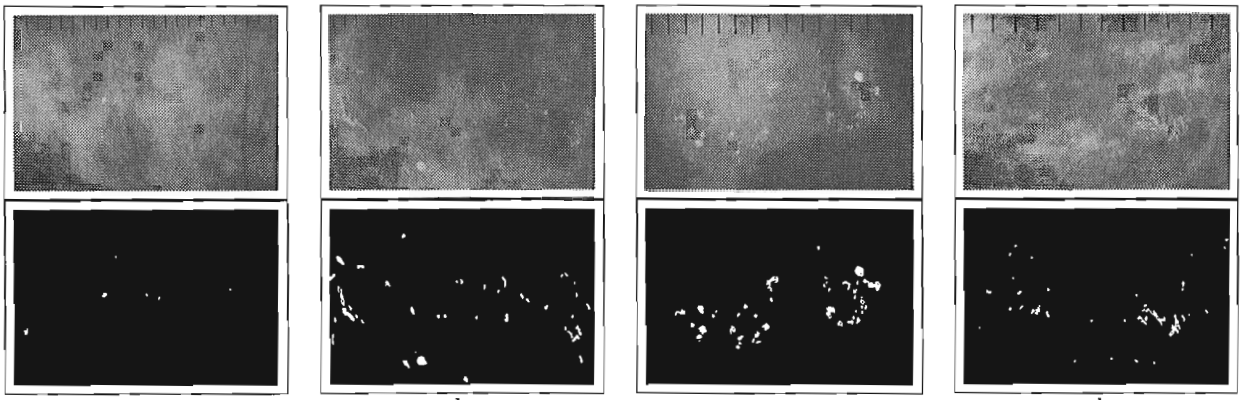
where F_{max} and F_{min} are the current maximum and minimum pixel values of the growing region, and τ is the growth tolerance ($0 \leq \tau \leq 1$). This recursive procedure is continued until no connected pixel meets the condition expressed in (1). Stating that the major difficulty of this method is the determination of the tolerance value for each calcification, a multi-resolution procedure is used, trying to find the most appropriate tolerance value τ for each microcalcification.

A tolerance value τ is selected for each region. The final chosen value is selected among the candidates ranging from 0.01 to 0.4 with a step increment (SS) determined by the seed pixel (SP) value as $SS = 1/SP$. For every region obtained at each tolerance level a feature set is calculated, including shape compactness, centre of gravity (x,y) coordinates, and size (number of pixels). The normalized distance of this feature set among the successive tolerance levels is computed, and the feature set with the minimum distance is selected as the final set in order to choose the value of τ.

Figure 1 shows four examples of microcalcification segmentation, using our implementation of the *Shen* algorithm: the first column depicts the original image after its digitisation, while the second column shows the segmented microcalcification obtained.

2.3 Feature extraction

After segmenting the microcalcifications in every digitised mammogram, a set of binary regions was obtained in each image. The characterization of these regions is not a trivial task, although several methods have been proposed in the literature[30]. Taking into account that shapes and sizes of clustered microcalcifications have been associated with a high risk of carcinoma based on different subjective measures, such as whether or not the calcifications are irregular, linear, vermiform, branched, rounded or ring like, our efforts were addressed to obtain a feature set related to the shape.



a b c d

Figure 1: Four examples of microcalcification segmentation, based on *Shen* algorithm: (a) well defined and big microcalcifications, (b) poor defined and small microcalcifications, (c) with fat tissue, and (d) in a poorly contrasted image.

Feature	Description
Area	The number of pixels in the microcalcification
Perimeter	The total length of boundaries of the microcalcification
Compactness	Derived from the perimeter (P) and area (A) of a microcalcification, it is equal to $\frac{P^2}{4\pi A}$
Box Min. X,Y; Max. X,Y	The coordinates of the extreme left, top, right, and bottom pixels, respectively, of the microcalcification
Feret X,Y	The dimensions of the minimum bounding box of the microcalcification in the horizontal and vertical directions, respectively
Feret Minimum Diameter	The smallest Feret diameter found after checking a certain number of angles (maximum 64)
Feret Maximum Diameter	The largest Feret diameter found after checking a certain number of angles
Feret Mean Diameter	The average Feret diameter at all angles checked
Feret Elongation	A measure of the shape of the microcalcification, it is equal to $\frac{FeretMax.Diameter}{FeretMin.Diameter}$
Number of Holes	The number of holes in the microcalcification
Convex Perimeter	An approximation of the perimeter of the convex hull of the microcalcification
Roughness	A measure of the roughness, it is equal to $\frac{Perimeter}{ConvexPerimeter}$
Length	A measure of the true length of the microcalcification
Breadth	A measure of the true breadth
Elongation	Equal to $\frac{Length}{Breadth}$
Centroid X,Y	The (x, y) position of the centre of gravity of the microcalcification
Principal Axis	The angle at which a microcalcification has the least moment of inertia (the axis of symmetry). For elongated microcalcifications, it is aligned with the longest axis
Secondary Axis	The angle perpendicular to the principal axis

Table 1: Initial feature set used to characterize the segmented microcalcifications.

2.4 Initial Feature Set

The shape features initially chosen for characterizing the binary segmented individual microcalcifications are shown in table 1, where a summary description is provided for every feature.

We must remind that the previous features concern every segmented microcalcification in the mammogram, so it was necessary to modify the features in order to establish reliable comparisons among mammograms. This was accomplished with some statistical parameters associated to some selected features. Moreover, not the complete set of features shown in table 1 has demonstrated to be useful for describing the microcalcifications. Early analysis of the data revealed that the following subset plays a significant role: `Area`, `Compactness`, `Number of holes per area`, `Feret Elongation`, `Roughness`, and `Principal Axis`. Additionally, the number of clusters for each mammogram was added to the subset, stating that a cluster is defined when 4 or more microcalcifications are found in an almost circular area with a diameter = 0.5 cm.

3 Machine learning techniques for feature selection

We are working from different points of view in order to classify -diagnose- the features extracted from each mammogram. We analyse this problem using two Machine Learning approaches: Case-Based Reasoning and Genetic Algorithms.

Following, we present a brief description of each approach, and describe the variants used in the experiments -see section 4- presented in this paper.

3.1 Case-Based Reasoning

Case-Based Reasoning integrates in one system two different characteristics: machine learning and problem solving capabilities. CBR uses a human-inspired philosophy: it tries to solve new cases (i.e. a new mammographic image) by using old previously solved ones [22, 12]. The process of solving new cases also updates the system providing new information and new knowledge to the system. This new knowledge can be used for solving other future cases. The basic method can be easily described in terms of its four phases [1]. The first phase *retrieves* old solved cases similar to the new one. Then, in the second phase, the system tries to *reuse* the solutions of the previously retrieved cases for solving the new case. Next, the third phase *revises* the proposed solution. Finally, the fourth phase *retains* the useful information obtained when solving the new case.

CaB-CS is a *Case-Based Classifier System*, where the *reuse* phase has been simplified. It classifies the new case using the same class of the most similar retrieved one. It was firstly used for medical diagnosis in [7]. One key point in the whole algorithms is the concept of *most similar* case used in the *retrieval* phase of CBR. In CaB-CS, the notion of similarity between two cases is computed using different similarity measures. In this article, we used the *Nearest Neighbour Algorithm (NNA)* computes the similarity between two cases using a global similarity metric. The practical implementation of these distance functions in CaB-CS -for this work- use two main metrics: the *Minkowski's metric* and the *Clark's distance.*

The *Minkowski's metric* is defined as:

$$Similarity(Case\_x, Case\_y) = \sqrt[r]{\sum_{i=1}^{F} w_i \times |x_i - y_i|^r} \quad (2)$$

Where $Case\_x$ and $Case\_y$ are two cases, whose similarity is computed; F is the number of features that describes the case; x_i, y_i represent the value of the ith feature of cases $Case\_x$ and $Case\_y$ respectively; and w_i is the weight of the ith feature.

In this study we test the Minkowsky's metric for three different values of r: *Hamming distance* for $r = 1$, *Euclidean distance* for $r = 2$, and *Cubic distance* for $r = 3$.

The *Clark's distance* is defined as:

$$Similarity(Case\_x, Case\_y) = \sqrt[2]{\sum_{i=1}^{F} \frac{|\,(x_i - y_i)\,|^2}{|\,(x_i + y_i)\,|^2}} \quad (3)$$

Where $Case\_x$ and $Case\_y$ are two cases, whose similarity is computed; F is the number of features that describes the case; and x_i, y_i represent the value of the ith feature of cases $Case\_x$ and $Case\_y$ respectively.

On the other hand, in this paper we also present some results (see section 4) where we incorporate a Data Mining Technique into the Case-Based Reasoning. We use Rough Sets theory introduced by Z. Pawlak [19] in 1982. The idea of Rough Sets consists of the approximation of a set by a pair of sets,

called the upper and lower approximations of this set. We use this theory in two different approaches: (a) as reduction techniques for the case memory [24]; and (b) as weighting methods [23]. BASTIAN system [23] allows to introduce the Rough Sets theory capabilities into CBR.

3.2 Genetic Algorithms

Genetic Algorithms (GA) are general-purpose search algorithms based on evolutionary principles. They evolve a population of individuals (set of feasible solutions) in terms of selective pressure (biasing the search towards good solutions) and sub-symbolic operators for genetic material recombination (knowledge manipulation). The application of GA to Machine Learning has been addressed from two different approaches: the *Pittsburgh* approach and the *Michigan* approach. In this problem we have tested two systems based on the *Pittsburgh* approach (GENIFER and GALE) and another system based on the *Michigan* one, called XCS.

GENIFER [13] is learning system that evolves instance sets induced from the training set of samples. This system achieves a compact knowledge representation (based on instances) that generalises accurately, being robust in the presence of noise. However, GENIFER spends a great amount of time during training, which GALE solves by defining a fine-grained parallel architecture. GALE spreads the population over a 2D grid. Each cell on the grid, which contains up to one individual, is connected to the surrounding cells defining demes, where evolution occurs locally. This architecture [14] can be parallelised massively, thus reducing the computational learning time. Another main contribution of GALE is its knowledge-independent model; it can evolve indistinctly rules, instances, partially-defined instances, and decision trees (orthogonal, oblique, and multivariate based on nearest neighbour).

XCS [28] is a classifier system which evolves a set of rules, based on the *Michigan* approach. This system has two main components: a) the update component, and b) the discovery component. *Update* uses reinforcement learning for computing the quality of the evolved rules. On the other hand, a GA acts as the discovery component searching for promising rules that improve overall performance. XCS has shown a strong tendency to evolve consistent and complete knowledge representations that, moreover, tend to be minimal because of the generalisation bias (see the generalisation hypothesis [28]). This makes XCS particularly interesting for classification tasks.

4 Experiments

First, we evaluate the performance of two ML approaches as the back-end step of the CAD system proposed. The results obtained using a CBR approach [16, 8, 24] and a GA approach [16, 8, 3] are compared with the ones obtained by human experts and the statistical model proposed in [15], as well as with other six well-known classifier schemes provided by machine learning.

4.1 Dataset

The dataset is formed by 216 instances (121 *benignant* and 95 *malignant*) previously diagnosed by surgical biopsy. Each instance of the dataset is the result of the first three steps. First, after an image processing step [15] -using the dataset described at section 2-, a mammographic image is reduced to a $m \times n$ matrix. This matrix contains as many rows, m, as the number of μCa present in the image, and as many columns (n=23) as the number of features that describes one μCa, presented in table 1. Next, this $m \times 23$ matrix is transformed into a vector. This transformation computes the average value for each column (feature) across all the rows (μCas present in the image). Finally, the computed vector is labelled using the class (*benign* or *malign*) obtained from the diagnosis done by surgical biopsy.

4.2 Classifier Schemes

The results presented summarize different studies carried out for this problem.

There are six classifier schemes chosen for the comparison come from different learning theories. All these algorithms are obtained from the *Weka* package [29] developed at the University of Waikato in New Zealand, available from the http address: http://www.cs.waikato.ac.nz/ml/weka. The chosen algorithms are: *a,b*) instance-base learning `IB1` and `IBK` with k=3 [2], *c*) statistical modelling, Naive Bayes (`NB`) [10], *d*) tree induction, `C4.5 revision 8` [21], *e*) rule learning, `PART` [6], and *f*) support vector machines, `SMO` [20]. All these algorithms are run with the default configuration provided by *Weka*.

4.3 Experimental Set-up

We performed two kinds of experiments in order to compare the performance of the different algorithms. First, we maintained the proportion of original images -now, set of features for each image- as training and test sets proposed by human experts. Thus, we compared the results obtained by CBR and GA with those achieved by human experts, and the statistical model [15] in terms of classification accuracy (*accuracy*). We also included in this comparison the true positive (*malign* cases) rate of classified examples (*sensitivity*) and the true negative rate of classified examples (*specificity*). Although *accuracy* is computed using all the available examples, *sensitivity* and *specificity* just take into account the classified examples (the ones marked as *benign* or *malign*).

The second group of experiments computes the *accuracy* using stratified ten-fold cross-validation runs [29]. In other words, we divide the dataset in ten disjoint datasets that contain the same number of instances. These sets also maintain the class distribution presented in the original dataset (*stratificatied folds*). Next, we run the algorithms ten times, holding one different set each time for testing the classification accuracy, whereas the other nine sets are used as the training set of examples. Finally, the *accuracy* is computed averaging the accuracy of the ten runs. We also compute the *sensitivity* and *specificity* obtained across the ten-fold cross-validation runs.

4.4 Results

Table 2 summarizes the results obtained across the different experiments conducted using the original training and test sets. This table includes the results obtained by the CBR approach (CaB-CS - `Hamming`, `Euclidean` and `Cubic`- and BASTIAN - `Clark` and `PRS`-using Rough Sets weighting method-systems) and the GA approach (GENIFER -`MDA` and `RA`- , GALE and XCS systems) as well as the ones obtained by the human experts (`H-E`) and the statistic model (`SM`), both introduced in [15]. Results show that accuracy in our classifier schemes overcomes the accuracy obtained by the human experts and the statistical model. However, human experts and the statistical model show a better sensitivity and specificity than the ones obtained by CBR and GA techniques. This fact is achieved leaving high rates of unclassified cases, and must be addressed in the further work, due to the importance of system's reliability in medical domains.

Variant	Unclas.	Sens.	Spec.	Accuracy
H-E	38.57	70.59	92.59	52.86
SM	52.86	81.82	90.48	40.00
Hamming	0.00	80.95	69.39	72.86
Euclidean	0.00	66.67	75.51	72.86
Cubic	0.00	66.67	77.55	74.29
Clark	0.00	66.66	81.63	77.14
PRS	0.00	66.66	83.67	78.57
MDA	0.00	23.80	93.87	72.86
RA	0.00	47.61	85.71	74.29
GALE	0.00	52.38	85.71	75.71
XCS	1.42	61.90	64.45	62.85

Table 2: Results obtained using the original training and test sets.

Variant	Sens.	Spec.	Accuracy	Std
Hamming	56.84	66.94	62.50	14.47
Euclidean	56.84	69.42	63.89	12.43
Cubic	60.00	68.60	64.81	9.62
Clark	57.10	62.88	60.40	12.73
PRS	63.15	68.60	66.20	11.12
MDA	52.63	70.25	62.50	11.20
RA	43.16	76.86	62.04	9.95
GALE	64.21	76.86	71.30	5.93
XCS	56.84	70.25	64.30	6.40
IB1	56.84	67.77	62.96	12.42
IB3	60.00	69.42	65.28	6.29
C4.5 (r8)	70.53	60.33	64.81	6.36
NB	60.00	68.60	64.81	7.66
PART	80.00	47.93	62.04	4.17
SVM-SMO	52.63	78.51	67.13	7.37

Table 3: Results obtained using stratified ten-fold cross-validation runs.

Machine learning algorithms tend to be more specific than sensitive. Usually, higher specificity rates are obtained. Results summarized in table 3 show this fact. Only, C4.5 and PART present better sensitivity than specificity. Nevertheless, the average accuracy rate, across the stratified ten-fold cross-validation runs, achieved for all machine learning algorithms are quite similar. But, GALE obtains the best accuracy rate.

5 Conclusions and Further Work

This article describes two different machine learning approaches to solve the diagnosis of breast cancer using mammographic microcalcifications. Both approaches, Case-Based Reasoning and Genetic Algorithm, have been compared with the diagnosis proposed by the human experts, statistical model and different well-known machine learning algori-

thms.

The experiments were focused on two issues. The first one analyses the performance of machine learning algorithms when they are applied as the back-end of the CAD system. We want to remark that we have improved the prediction accuracy of the system. However, the machine learning techniques achieve an improvement through eager classification strategies (without leaving any example unclassified). Nevertheless, the human experts and the statistical model obtain better reliability (sensitivity and specificity rates) because they do not classify the uncertain examples. In this sense, our further work, tries to convert the incorrect classified cases as unclassified cases, because it is very important in this domain to obtain a good reliability. The second issue compares the results presented with other well-known machine learning techniques. We want to point out that the accuracy and the reliability obtained by the different tested algorithms are quite similar.

Our future work is focused on improving our techniques in order to increase the reliability of the CAD system. On one hand, further work on Case-Based Reasoning deals with the introduction of decision thresholds into the retrieval functions to classify only the certain cases, as well as improving the usage of the data mining techniques introduced. On the other hand, the further work for Genetic Algorithms approach focuses on two main ideas. First, improving the reliability obtained, designing fitness functions based on sensitivity and specificity rates. Finally, the second idea consists of redefining the classification procedure used by individuals. These changes try to introduce decision thresholds like in the Case-Based Classifier System.

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