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A Second Opinion System for Microcalcification Diagnosis

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Abstract: An important early sign of breast cancer is the presence of microcalcification clusters in mammograms. To assist radiologists in the diagnosis of mammographic clusters a Computer Aided System for breast cancer diagnosis is presented. In particular, the procedure first detects microcalcifications having a cluster pattern and then classifies the abnormalities as benign or malignant clusters. A Support Vector Machine is implemented for cluster classification which is trained adopting the Sequential Minimal Optimization technique. The classifier considers one cluster at a time and evaluates several parameters, so that each cluster is fully represented by its own features. The performance of the implemented system is evaluated taking into account the accuracy and the sensitivity in classifying clusters. Obtained results make this method able to operate as a "second opinion" helping radiologists during the routine clinical practice.

Key words: Computer Aided Detection and Diagnosis · Mammography · Microcalcification · Breast · Wavelet Transform · Support Vector Machine

INTRODUCTION

The overall health of people continues to improve in many ways as a consequence of advances in medical technology, research, resources set aside to public health and education [1-6]. At present, medical devices and instruments include a broad range of medical procedures from prevention to screening, diagnosis, treatment and rehabilitation. Since these devices and instruments are very effective in clinical use, their importance as key elements to medical care is increasing more and more [7-13]. In particular, in medical imaging, an accurate diagnosis and/or assessment of a disease depends on not only on the adopted device for image acquisition but also on image interpretation. Therefore, medical image interpretation process can benefit from computer technology [14]. In particular, Computer Aided Detection (CADe) and Computer Aided Diagnosis (CADx) systems are becoming important tools in supporting physicians for neoplastic pathology detection and prevention [15, 16]. As consequence of the spread of nationwide screening programs for early detection of breast cancer, the amount of mammograms to be analyzed by radiologists is much increased. Therefore, the risk that radiologists may miss some subtle abnormalities exists especially because images are often poor in contrast. In cases of dubious diagnosis, the behavior of radiologists tends to be fairly cautious, prescribing further invasive diagnostic procedures such as biopsy to patients. Statistics show that only 15-34% of breast biopsies are proved cancerous and that 10-30% of all cases of breast cancer go undetected by mammography [17]. Diagnosis sensitivity (i.e. accuracy in recognizing all malignant pathologies) may be improved having each mammogram checked by two radiologists, with the consequence of making the process inefficient by reducing the individual productivity of each specialist. An efficient alternative is replacing one of the radiologists by a computer system. The aim of CADx systems is both improvement of physician performance by prompting sites of potential abnormalities and reduction of missed lesion number. Therefore, CADx system normally operates as an automated second opinion that indicates lesion locations and types of possible abnormalities [18].

The high correlation between appearance of microcalcification clusters and breast cancer shows that an automated microcalcification detection and diagnosis is very helpful for cancer control [19].

In this paper, a CADx system is implemented able to classify microcalcification clusters in mammograms of both fatty and dense tissue. The method is composed of two sections each accomplishing different tasks. In particular, the first section detects microcalcification clusters by use of a tool based on wavelet transforms.

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Then a Support Vector Machine (SVM) classifier analyzes clusters previously detected and classifies them into benign and malignant abnormalities.

CADx system performance is evaluated using the MIAS database as procedure testing [20], determining the sensitivity and the accuracy parameters. Results obtained in the cluster diagnosis make this method able to operate as a "second opinion". Therefore, radiologists can use results of this computer analysis in making a diagnosis, but the final diagnostic decision and recommendations for appropriate patient treatment are made by physicians on the basis of their knowledge, experience and authority on the subject.

Previous Researches: Various techniques have been adopted in CADx systems described in literature.

A procedure for microcalcification detection and diagnosis based on combined feature set and SVM is indicated in [21]. Two-dimensional discrete Haar wavelet transform is applied to Region of Interest (ROI) image. The Jacobi moments are calculated for ROI image and Ant Colony Optimization is used to reduce the Jacobi feature set for the classification phase. Two phases characterize the classification process: first an SVM classifier analyzes and distinguishes mammograms between normal (without microcalcifications) or abnormal (with microcalcifications) ones, then abnormal mammograms are classified by another SVM into malignant or benign lesions.

The feasibility of using texture features extracted from mammograms to predict whether the presence of microcalcifications is associated with malignant or benign pathology is investigated in [22]. Microcalcifications are first detected in ROIs by using a morphological filter and wavelet transform. Spatial grey level dependence (SGLD) matrices at one pixel distance in different directions were constructed from the background ROI. Twelve texture measures were extracted from each SGLD matrix and a KNN classifier with Euclidean distance is considered for the task of classifying regions as malignant or benign microcalcifications.

In [23] the fuzzy-logic based genetic algorithm (GA-Fuzzy) is adopted to classify mammographic microcalcifications. Four microcalcification feature values (i.e. number, area, circularity and minimum distance) are calculated for the classification phase. In the GA-Fuzzy process, Gaussian-distributed membership functions are determined from the mean and the standard deviation of the feature values calculated from training images and subsequently, the genetic algorithm optimizes the membership functions.

In [24], a comparison among three classifiers based on ANN is performed. In particular, the first classifier is a conventional feed-forwarded ANN having three inputs, one hidden layer with seven units and one output. The second classifier adopts genetic algorithms for searching the ANN optimal set of weights while the last procedure uses a genetic algorithm for initial weight set definition and applies the back-propagation training method. The transfer function of every neuron in all the methods is the sigmoid hyperbolic tangent function and the error is measured with the mean square error function.

To generate a likelihood map of each mammogram, Radial Basis Function Neural Network (RBFNN) classifier is implemented in [25] having in input image features extracted using Gabor filters. Pixel value in the likelihood map shows the possibility of that pixel being classified as a microcalcification pixel. 2160 Gabor features represent RBFNN inputs for the training phase. The desired output is the cluster classification in malignant or benign.

A two stage texture-based method is presented in [26]. In the first stage microcalcification clusters are characterized using texture features from gray-level co-occurrence matrix (GLCM). In the second stage, an embedded feature selection based on particle swarm optimization and a k-nearest neighbor (KNN) classifier is applied to simultaneously determine the most discriminative GLCM features and to find the best k value for the classifier.

Proposed CADx Method: The system architecture is organized in two sections: the first one looks for microcalcification clusters (called Cluster detection section) and the last section classifies clusters as benign and malignant abnormalities (called Diagnosis section). The system is implemented so that outputs from Cluster detection section represent inputs for Diagnosis section (Fig. 1).

Cluster Detection Section: A mammographic image represents an input to cluster detection section whose outputs are detection of microcalcification clusters (Fig. 2).

The procedure implemented in cluster detection section has been already presented by the authors [27]. The algorithm is composed of three steps. The first step is the preprocessing phase whose purpose is the contrast enhancement of suspected mammographic images, removing both background information and non pathological breast tissue. Therefore, the method starts by separating mammary tissue from non-mammary tissue

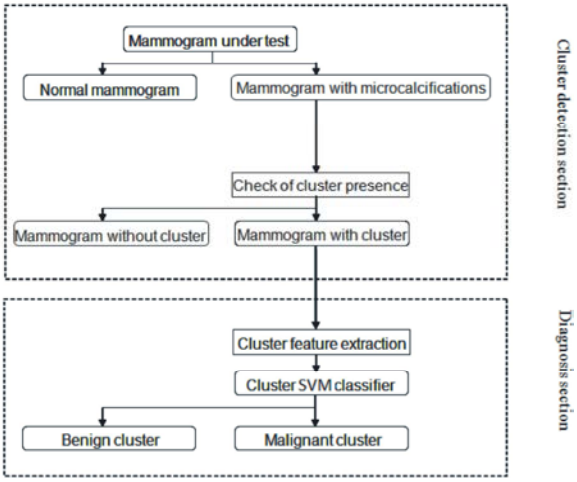

Fig. 1: CADx system architecture

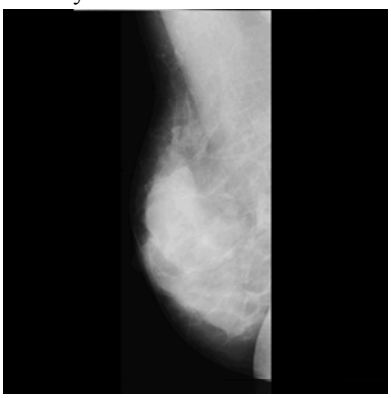

Fig. 2: MIAS database mammogram (image mdb241)

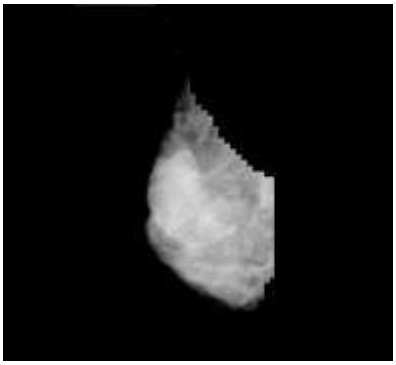

Fig. 3: Resulting image after the preprocessing phase

regions inside the image under test. To reject areas that do not contain tissue pixels, the mammographic image is subdivided into 16 x 16 pixel windows and is segmented. The chosen window dimension is a compromise between the detection rate and processing time parameters. The obtained image is analyzed applying point processing operators such as hard thresholding and full scale histogram stretch (Fig. 3).

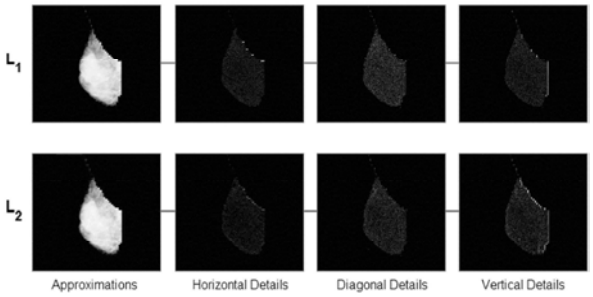

Fig. 4: Obtained image after wavelet decomposition process

In the second step, named microcalcification localization phase, suspicious zones are detected for true microcalcification identification. Mammographic image is generally composed of low frequency features while microcalcifications appear as high frequency details so a wavelet filter has been demonstrated particularly suitable to separate high resolution mammogram components from the low resolution ones. In particular, the Bior 2.6 mother wavelet is used. The chosen wavelet family is biorthogonal so, a perfect reconstruction of the original image is possible.

The aim of the successive step is the detection of suspected zones where microcalcifications can be localized. Since microcalcification tissue has a higher intensity than the surrounding pixels, a wavelet filter can be adopted to analyze the reconstructed image. Indeed, suspect microcalcifications can be detected by discarding the lowest frequency sub-band in the image wavelet decomposition. In the proposed method, mammograms are decomposed into two-level wavelet representations adopting the Haar mother wavelet.

To recognize true microcalcifications, after the adoption of a hard thresholding method, the implemented algorithm employs a 2D nonlinear filtering procedure for each level (Fig. 4). A cluster is identified if more than 3 microcalcifications are detected in a $1cm^2$ square area.

Diagnosis Section: Aim of Diagnosis section is the classification of previously detected microcalcification clusters. Therefore, each cluster, once identified and localized in Cluster detection section (Cluster detection section outputs) is analyzed as a whole to distinguish benign from malignant abnormalities.

During the feature extraction phase, the classifier considers one cluster at a time and evaluates several parameters, so that each cluster is fully represented by its own features. Then the feature set of cluster under test is the classifier input while the output is the class which the

cluster belongs to, either the benign class (simply denoted as "Benign cluster") or the malignant one (simply denoted as "Malignant cluster").

As the classification stage considers the whole cluster instead of single microcalcifications to verify the cluster nature, features describing cluster are to be related to distribution of microcalcifications within it and uniformity of their shape. Therefore, seven features are selected for the classification process, that is: the cluster maximum diameter, the cluster minimum diameter, the number of microcalcifications, the cluster area, the cluster perimeter, the cluster compactness and eccentricity.

The maximum diameter is defined as the maximum distance between two microcalcifications in a microcalcification cluster and the minimum diameter is the maximum distance that exists between two microcalcifications within a microcalcification cluster projected on the perpendicular to the maximum diameter.

Cluster compactness is defined as the ratio of the squared cluster perimeter to the cluster area and it represents the roughness of an object boundary relative to its area.

Cluster eccentricity is related to the ellipsoid hull and it is defined as: $(L_1^2 - L_2^2)^{1/2}/L_1$ where L_1 and L_2 are the major and the minor semiaxis, respectively.

Adopting the SVM formulation, a linear classifier is trained using supervised learning to make the diagnosis of detected clusters in a mammogram.

For extracting training data from the training mammogram set, the seven features are extracted for each detected cluster in the mammogram data set. The vector formed by these seven feature values, denoted by xi, is then treated as an input pattern and is labeled as yi=+1 for the class namely "Benign cluster". “Malignant cluster” samples (yi=-1) are collected similarly.

Together, (xi, yi) forms an input-output pair. These input-output pairs are inherently correlated, because they result from the same case. Therefore, these correlated input-output pairs have been grouped by case such that those from the same case will be used either for training or for testing, but not for both.

Once the training examples are gathered, the classifier construction, that is the SVM decision function determination, is necessary.

The Sigmoid function is adopted as kernel. To achieve the best performance during the training phase, a fine tuning of kernel function associated parameter is necessary. The optimization is obtained adopting a cross-validation method. In this case, the whole training set is divided randomly into equal sized subsets denoted as estimation set and validation set. The basic form of cross-validation is the m-fold cross-validation. In m-fold cross-validation, the training data is randomly divided into m mutually exclusive subsets or folds each of which has equal size. Cross-validation is repeated m times. For each round of cross-validation, one fold is reserved for validating the model and the remaining m-1 subsets are used as estimation sets. Each fold is used exactly once as validation set. Validation result of each round is the number of wrong classifications occurred in that round. All the validation results from each round are then averaged and finally the averaged value is used to measure the classifier accuracy.

In this paper, a 2-folded cross-validation method is adopted. For the SVM classifier training, the Sequential Minimal Optimization technique is implemented. The training phase is carried out adopting eighty clusters; half of which are classified as benign clusters inside the adopted database while the others are considered malignant. Among the selected clusters, twenty clusters annotated as benign and twenty clusters classified inside the database as malignant are adopted for the estimation phase. The remaining clusters (twenty denoted as malignant and twenty as benign) are used for the validation phase.

Data Set and Evaluation Parameters: In order to compare the procedure performance with other algorithms described in literature, well-known public databases are used. In particular the whole MiniMammographic database provided by the MIAS is adopted [20].

The performance of diagnostic systems are measured considering sensitivity and accuracy.

For a CADx system, sensitivity (Se) is defined as the probability of correctly classifying a really existing cluster; specificity (Sp) represents the probability of obtaining a negative mammogram when no malignant microcalcification cluster exists, accuracy (Ac) is defined as the observed agreement between the procedure results and the physicians opinion about the mammogram under test reported inside the MIAS database.

They are computed adopting the following expressions:

$$Se = \frac{TP}{TP + FN} \quad (1)$$

$$Sp = \frac{TN}{TN + FP} \quad (2)$$

$$Ac = \frac{TP + TN}{TP + TN + FP + FN} \quad (3)$$

where:

- TP (number of true positives) is the number of correct identifications of malignant microcalcification clusters inside the mammogram under test
- FN (the number of false negatives) is the number of malignant microcalcification clusters present in the image that the algorithm is not able to correctly classify and, consequently, considers benign
- FP (the number of false positives) is the number of benign microcalcification clusters that the algorithm classify as malignant abnormalities
- TN (the number of true negatives) is the number of microcalcification clusters that the procedure considers benign and that really represent benign abnormalities.

A single pair of numbers representing Se and Sp is not entirely adequate in comparing diagnostic tests because they depend on the particular confidence threshold that the observer or the CADx system use. To overcome this problem Free-response operating characteristic (FROC) curve is usually used [28, 29, 30, 31].

Performance Evaluation: To test the procedure (cluster diagnosis phase), the whole MIAS database has been used (Fig. 5). Because of the MIAS database contains only 22 mammograms with clusters (for a total number of 28 clusters), the DDSM database has been used for the classifier training [32]. The DDSM is a public database that contains approximately 2.500 studies.

The choice of two different databases for the classifier training and the performance evaluation of the whole system, makes the procedure performance independent from the selected database and, therefore, from the image quality (i.e. resolution, medium contrast, signal to noise ratio, etc.). In fact, as database usage is not standardized, it may occur that a CADe/CADx method presenting very satisfactory results with a particular database, provides unsatisfactory performance changing the data set. Nowadays, images composing databases are not homogeneous and they do not show the same accuracy degree: in particular, lesions belonging to the same typology are not annotated in the same manner nor images show lesions in the same way. For these reasons, an algorithm designed using mammograms from one particular database and evaluated using the same mammograms may not perform accurately nor robustly on mammograms from a different database [33]. Therefore, due to the variability present within a database or intra-database, it is difficult the developing of an "optimal algorithm".

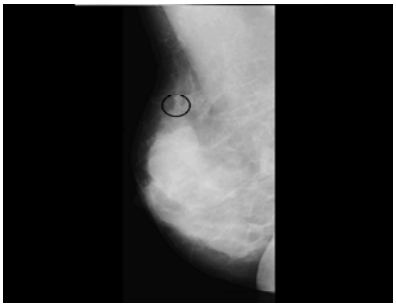

Fig. 5: Visualization of detected microcalcification cluster

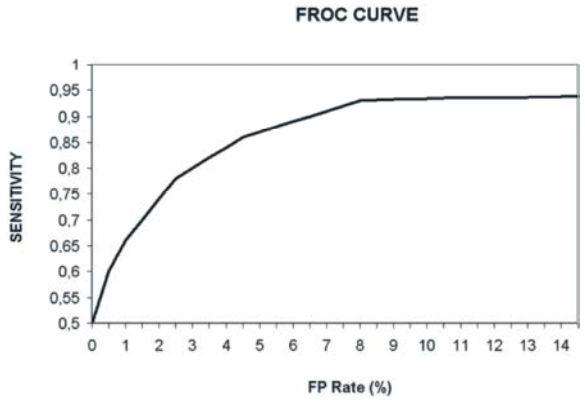

Fig. 6: SVM classifier FROC curve

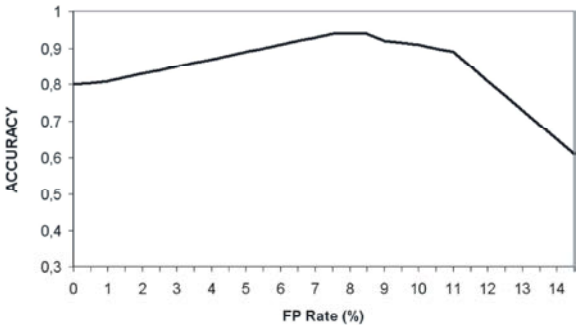

Fig. 7: CADx system accuracy curve

The implemented method, based on the two public databases having different image characteristics in terms of acquisition parameters (i.e. exposure time, energy level), spatial/intensity resolution and artifacts, has a general validity and can be used to classify microcalcification clusters independently from acquisition equipment during the mammographic screening.

Table 1: Comparison among some recent microcalcification cluster diagnosis methods (CADx) adopting the MIAS database as test bench

	Performance		
Paper	Se	Ac	No of MIAS mammograms tested
N. Hamdi, *et al.* [22]	92.31	-	22
Y. Lee *et al.* [23]	85	-	5
J. Dheeba, *et al.* [25]	85.2	-	The whole database
R.R. Hernandez-Cisneros, *et al.* [24]	-	93.88	22
N.V.S. Sree Rathna Lakshmi, *et al.* [21]	-	91.67 for benign, 92.31 for malignant	25
I. Zyout, *et al*. Ref. n. [26]	-	88	20

In Fig. 6 and in Fig. 7, the FROC and the accuracy curves for the diagnosis phase is plotted. The CADx system achieves an Se value of about 93.5% and an accuracy of 94.2% at a FP rate equal to 5%. FP rate is the number of FP occurrences during the diagnosis phase, in comparison with the number of database images having microcalcification clusters. Comparisons of the obtained performance with other method adopting the same database, show the procedure validity (Table 1).

CONCLUSIONS

Mammographic image interpretation by humans is limited due to nonsystematic search patterns of humans and presence of structure noise in image. CADx systems which help radiologists in making a diagnosis and act as a "second opinion", are extremely useful to reduce mortality and morbidity rates.

In this paper, a Support Vector Machine classifier for breast microcalcification cluster diagnosis with an high degree of accuracy, is implemented.

To make the system performance independently from the adopted image quality, the DDSM and the MIAS databases are used for the training phase and the test phase, respectively. Therefore, the implemented CADx system has a general validity and can be adopted for microcalcification cluster classification independently from the diagnostic device adopted during the mammographic screening.

The method achieved a sensitivity parameter of about 93.5% and an accuracy value equal to 94.2%.

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