Computer-Aided Detection and Diagnosis of Breast Cancer With Mammography: Recent Advances

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***Abstract*—Breast cancer is the second-most common and leading cause of cancer death among women. It has become a major health issue in the world over the past 50 years, and its incidence has increased in recent years. Early detection is an effective way to diagnose and manage breast cancer. Computer-aided detection or diagnosis (CAD) systems can play a key role in the early detection of breast cancer and can reduce the death rate among women with breast cancer. The purpose of this paper is to provide an overview of recent advances in the development of CAD systems and related techniques. We begin with a brief introduction to some basic concepts related to breast cancer detection and diagnosis. We then focus on key CAD techniques developed recently for breast cancer, including detection of calcifications, detection of masses, detection of architectural distortion, detection of bilateral asymmetry, image enhancement, and image retrieval.**

***Index Terms*—Breast cancer, computer-aided detection or diagnosis (CAD), key CAD techniques, mammography.**

I. Introduction

FOR YEARS, cancer has been one of the biggest threats to human life; it is expected to become the leading cause of death over the next few decades [1]. Based on statistics from the World Health Organization (WHO) [1], cancer accounted for 13% of all deaths in the world in 2004; deaths caused by cancer are expected to increase in the future, with an estimated 12 million people dying from cancer in 2030 [1].

Of all the known cancers, breast cancer is a major concern among women. It is the second-most common and leading cause of cancer deaths among women [2]. According to published statistics, breast cancer has become a major health problem in both developed and developing countries over the past 50 years, and its incidence has increased in recent years. In the United States, in 2007, there were an estimated 178,480 new cases of breast cancer diagnosed and 40,460 deaths from this disease among women [3]. At present, there are no effective ways to prevent breast cancer, because its cause remains unknown. However, efficient diagnosis of breast cancer in its early stages can give a woman a better chance of full recovery. Therefore, early detection of breast cancer can play an important role in reducing the associated morbidity and mortality rates.

Computer-aided detection or diagnosis (CAD) systems, which use computer technologies to detect abnormalities in mammograms such as calcifications, masses, and architectural distortion, and the use of these results by radiologists for diagnosis [4], can play a key role in the early detection of breast cancer and help to reduce the death rate among women with breast cancer. Thus, in the past several years, CAD systems and related techniques have attracted the attention of both research scientists and radiologists. For research scientists, there are several interesting research topics in cancer detection and diagnosis systems, such as high-efficiency, high-accuracy lesion detection algorithms, including the detection of masses, detection of architectural distortion, and the detection of bilateral asymmetry. Radiologists, on the other hand, are attracted by the effectiveness of clinical applications of CAD systems.

The aim of this paper is to provide an overview of CAD systems and related techniques developed in recent years. It is also intended to draw the attention of more research scientists to the research field of CAD for breast cancer, and advance research on the detection and diagnosis of breast cancer and related techniques, such as image processing, computer technology, and radiological imaging.

The rest of this paper is organized as follows. In Section II, we introduce some basic concepts in breast cancer diagnosis using mammography, including the principles of breast imaging and two types of mammography. We also discuss the relationship between double reading and CAD. In Section III, we review some existing types of CAD systems. In Section IV, we review in details some key techniques used in CAD systems for breast cancer, including many recently developed algorithms for detection of calcifications, masses, architectural distortion, and bilateral asymmetry. We also review several other associated techniques such as image enhancement and image retrieval for CAD. In Section V, we discuss some issues concerning the future of CAD systems for breast cancer. In Section VI, we conclude the paper.

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II. Detection and Diagnosis of Breast Cancer Using Mammography

There are several imaging techniques for examination of the breast, including magnetic resonance imaging, ultrasound imaging, and X-ray imaging. Mammography is a specific type of imaging that uses a low-dose X-ray system to examine the breast, and is currently the most effective method for detection of breast cancer before it becomes clinically palpable [5]. Mammography offers high-quality images at a low radiation dose, and is currently the only widely accepted imaging method used for routine breast cancer screening. Current guidelines of the American Cancer Society (ACS) recommend that women aged 40–49 years have a routine mammogram every one to two years, with the first beginning at age 40 [6].

Currently, there are two types of mammography [7]–[9]: one is film mammography and the other is digital mammography. In film mammography, the image is created directly on film, whereas digital mammography takes an electronic image of the breast and stores it directly on a computer [7]. Although both types of mammography have their advantages and disadvantages, digital mammography has some potential advantages over film mammography. Compared to digital mammography, screen-film mammography has some limitations, which include [10]: 1) limited range of X-ray exposure; 2) image contrast cannot be altered after the image is obtained; 3) the film acts as the detector, display, and archival medium; and 4) film processing is slow and introduces artifacts. All of these limitations have pushed researchers further to develop advanced techniques for digital mammography. Digital mammography is overcoming and will continue to overcome the limitations of film mammography described before, and will have the following potential advantages [10]: 1) wider dynamic range and lower noise; 2) improved image contrast; 3) enhanced image quality; and 4) lower X-ray dose.

Although digital mammography has many potential advantages over traditional film mammography, clinical trials show that [11] the overall diagnostic accuracy levels of current digital and film mammography are similar when used in breast cancer screening. However, digital mammography may be more effective than screen-film mammography for certain women [12], [13]. For example, Spurgeon [12] showed that digital mammography depicts more tumors than screen-film mammography, especially lesions seen as microcalcifications (MCs). Pisano *et al.* [11] showed that digital mammography is more accurate in women under the age of 50, women with radiographically dense breasts, and premenopausal women.

There are two types of examinations performed using mammography: screening mammography and diagnostic mammography. Screening mammography is performed to detect breast cancer in an asymptomatic population [14]. Screening mammography generally consists of four views, with two views of each breast: the craniocaudal (CC) view and the mediolateral oblique (MLO) view. The aim of diagnostic mammography is to examine a patient who has already demonstrated abnormal clinical findings, such as a breast lump [14]. Similar to screening mammography, each breast examined using diagnostic mammography may also have two views. Additional diagnostic mammography may offer an in-depth look at suspicious areas. Diagnostic mammography is often performed as a follow-up examination of an abnormal screening mammography in order to determine whether the area of concern on the screening examination needs additional breast imaging or a biopsy to determine whether the woman has breast cancer [14]. The adoption of mammographic examinations, especially screening mammography, has been proven to increase the rate of detection of cancer and reduce the rates of morbidity and mortality [5].

One of the difficulties with mammography [15] is that mammograms generally have low contrast. This makes it difficult for radiologists to interpret the results. Studies [16], [17] have shown that mammography is susceptible to a high rate of false positives as well as false negatives, causing a high proportion of women without cancer to undergo further clinical evaluation or breast biopsy, or miss the best time interval for the treatment of cancer. Several solutions have been proposed to increase the accuracy, specificity, and sensitivity of mammography and reduce unnecessary biopsies.

Double reading of mammograms [18], [19] has been advocated to reduce the proportion of missed cancers. The basic idea of double reading is to have two radiologists read the same mammograms. According to Warren and Duffy [19], double reading can contribute significantly to high sensitivity and effective screening. However, the workload and cost associated with double reading are high. Instead of double reading, CAD, which is referred to as the "second pair of eyes of the radiologists," is aimed to be used to aid radiologists in their interpretation of mammograms. With a CAD system, only one radiologist is needed to read each mammogram rather than two. The adoption of a CAD system could reduce the experts' workload. It has been proven that CAD systems can improve the detection rate of cancer in its early stages. For example, research by Morton *et al.* [20] indicates that the use of CAD improved the detection of breast cancer with a 7.62% increase in the number of breast cancers detected, with a small but acceptable increase of 0.93% in the recall rate, and a minimal increase in the number of biopsies with benign or negative results. Brem *et al.* [21] reported that use of a CAD system significantly improved the detection of breast cancer by increasing the radiologist's sensitivity by 21.2%.

III. Computer-Aided Detection and Diagnosis of Breast Cancer

CAD, which integrates diagnostic imaging with computer science, image processing, pattern recognition, and artificial intelligence technologies [22], can be defined as a diagnosis [23] that is made by a radiologist who uses the output from computerized analysis of medical images as a "second opinion" in detecting lesions and making diagnostic decisions. In the past several years, CAD systems have drawn much attention from both research scientists and radiologists because of the associated challenging research topics and potential clinical applications.

There are two types of CAD systems based on mammographic technologies: one is based on the conventional screen-film

mammographic technology and the other is based on digital mammographic technology. In the first type of CAD systems, the films are scanned, digitized, and saved on the computer for further examination. The second type of systems use full-field digital mammographic (FFDM) technology, which is expected to provide a higher signal-to-noise ratio, a higher detection quantum efficiency, a wider dynamic range, and a higher contrast sensitivity than digitized film mammograms [24]. Although FFDM technology is expected to be superior to the conventional film-based mammographic technology, the results obtained in a recent study show, with reasonable certainty, that there is no difference in the accuracy between FFDM and screen-film mammography, in particular, for asymptomatic women [25]. Commercial CAD systems based on these two types of mammographic technology have been reported to have similar performance [24].

Research on CAD systems and related techniques has attracted great attention. There are several papers published [4], [22], [26] and at least three commercial CAD systems available on the market in the United States, including the R2 system, the iCAD system, and Kodak's system. There is, however, still a long way to go before CAD systems become widely used in clinics and screening centers. The most important need is to demonstrate clearly that the accuracy of interpretation of screening mammograms with CAD systems is better than the accuracy without CAD. Research [27]–[29] has shown that CAD represents a useful tool for the detection of breast cancer; however, other research [11] has shown that CAD may, instead, make readings less accurate. Such comparisons may be unreliable, however, given the uncertainty associated with the adjustment for the differences in several variables [30]. Regardless, the results from a few recent studies [11], [30] show that the performance of the current commercial CAD systems still needs to be improved so that they can meet the requirements of clinics and screening centers. Thus, improving the performance of CAD systems remains to be a key issue for future research and development.

IV. Key Techniques for CAD Systems

The techniques used in CAD systems have a major impact on their performance. Although many techniques have been proposed so far, the development of new algorithms for CAD of breast cancer is still an active research field, particularly in regard to the detection of subtle abnormalities in mammograms [4]. In the following, we review many techniques for the detection of calcifications, masses, architectural distortion, and bilateral asymmetry, as well as for image enhancement and retrieval. We focus on the methods that have been reported recently in the literature.

A. Image Processing Methods for Detection of MC Clusters

MCs are tiny deposits of calcium that appear as small bright spots in mammograms. Clustered MCs can be an important indicator of breast cancer. They appear in 30%–50% of cases diagnosed by mammographic screenings [31]. In the past two decades, there has been extensive research conducted on the development of computerized methods for automatic detection of MCs in mammograms. Several review paper have been written on this subject [32]–[36]. As described by El Naqa and Yang [36], MC detection methods could be broadly divided into the following four categories: 1) basic image enhancement methods; 2) stochastic modeling methods; 3) multiscale decomposition methods; and 4) machine learning methods. The previous categorization is based on the underlying image processing techniques employed in the different methods. Some of the techniques can easily be placed in more than one category. For example, a neural network approach may use wavelet-based features as input. Nevertheless, we find such categorization to be pedagogically convenient for the presentation of the different methods and adopt it in the following review.

1) Basic Image Enhancement Methods: Methods in this category are motivated by the fact that MCs tend to be brighter than their surroundings. The basic idea here is to employ image enhancement methods to improve the contrast of MCs, and then apply a threshold to separate them from their surroundings. An example of image enhancement methods is the filtering approach developed by Nishikawa *et al.* [37]. This method is based on a difference image technique followed by morphological erosion to reduce false positives. The difference image is produced using two filters, one for enhancing the MCs and the other for suppressing them. More recently, a noise equalization scheme was proposed by McLoughlin *et al.* [38]. In this method, it is assumed that the dominant source of noise in digital mammograms is due to limited quanta of X-rays. The quantum noise is modeled using a simple square-root law of gray levels. The local contrast is improved by removing the noise dependency on the gray level [38]. Qian *et al.* applied a region grouping approach for MC detection based on cluster analysis [39]. A visual model, in conjunction with anisotropic diffusion filtering, was proposed by Linguraru *et al.* [40]. A common theme among these different methods is to apply standard image processing techniques for pre- or post-processing of the images for detection. An apparent advantage of this is its simplicity, ease of implementation, and efficiency, which is very desirable for real-time clinical applications. However, this also comes at the expense of reduced effectiveness in many cases. For instance, the difference image approach can be viewed as a bandpass filter, which can be sensitive to noise. To alleviate this, morphological operators were applied to reduce false positives in a postprocessing step.

2) Stochastic Modeling Methods: In stochastic modeling methods, the basic idea is to utilize statistical differences between MCs and their surroundings. For instance, Gurcan *et al.* [41] used differences in higher order statistics [e.g., the third moment (skewness) and the fourth moment (kurtosis)], where it was conjectured that areas with no MCs would have a Gaussian-like distribution and areas with MCs would be non-Gaussian (nonzero skewness and kurtosis). However, this approach can be prone to errors in background (non-MC) regions that are spatially variant and inadequate to be described by second-order Gaussian statistics. More recently, Caputo *et al.* [42] investigated a Markov random field (MRF) based approach for MC detection. The MRF model is based on using "spin glass" energy functions (generalized Gaussian

kernels) [42]. Casaseca-de-la-Higuera *et al.* compared different approaches based on Gaussian mixture models [43]. The use of MRF models for image segmentation is advantageous over some other statistical methods due to its ability to characterize the spatial intensity distribution of an image. However, estimating a proper prior distribution remains a challenging task in these probabilistic approaches.

3) Multiscale Decomposition Methods: Methods in this category aim to exploit the differences in frequency content between MC spots and their surrounding background. In particular, wavelet transforms have been widely investigated for MC detection. For instance, Strickland and Hahn [44] used undecimated biorthognal wavelet transforms in which MCs were represented by circular Gaussian shapes with varying widths along the different scales. The undecimated wavelet transform has the advantage of being translation invariant. Optimal subband weighting using a Fisher discriminant function was applied prior to reconstruction from subbands 2 and 3 for improved detection and segmentation of clustered MCs. More recently, Lemaur *et al.* studied wavelet regularities and demonstrated that wavelets with higher regularity, such as Matzinger wavelets, yield improved performance compared to the classical Daubechies wavelets for MC detection [45]. Multiplexed wavelets were explored by Mini *et al.*, with mammograms treated as oscillatory signals [46]. Nakayama *et al.* combined filter bank decomposition with a Bayes classifier to detect MCs [47]. Regentova *et al.* combined wavelet transforms with hidden Markov trees in a maximum-likelihood framework for MC detection [48]. Although we have made a separate category for these decomposition methods because of their importance and prevalence in the literature, these methods are often used as feature extraction techniques that are used in conjunction with other approaches (e.g., as input to classifiers).

4) Machine Learning Methods: Machine learning methods aim to decipher dependencies from data. In the context of MC detection, the problem is typically treated as a binary classification process, where the goal is to determine whether an MC is present or not at a pixel location. As an example, Yu and Guan [49] proposed a two-stage neural network approach, where wavelet components, gray-level statistics, and shape features were used to train a two-stage network. The first stage identifies potential MC pixels in the mammograms and the second stage detects individual MC objects. Machine learning methods have received the largest share of research in recent developments. Methods based on evolutionary genetic algorithms were proposed by Jiang *et al.* [50] and Peng *et al.*. [51], where genetic algorithms were used to search for optimal bright spots in mammographic images that could be classified as MCs. A main challenge in evolutionary methods is that numerical instability could occur when no proper initialization is provided. Neural networks have been investigated for MC detection [52]–[55]. However, the high nonlinearity associated with these methods may result in trapping in local minima, and thus limiting their discrimination power.

A more recent development in machine learning is a class of learning algorithms known as support vector machines (SVMs). Conceptually, an SVM utilizes an implicit nonlinear kernel mapping to a higher dimensional space, where an optimal hyperplane classifier (which maximizes the separation margin between two classes) is applied. SVMs were recently reported to achieve high accuracy in MC detection in the literature [56]–[58]. El Naqa *et al.* [56] demonstrated that the prediction power could be further improved by applying a successive enhancement learning (SEL) procedure, where SVM training is adjusted iteratively by reincorporating misclassified samples. More recently, Wei *et al.* [58] demonstrated that the computational efficiency could be improved significantly while maintaining the best prediction power using a Bayesian learning approach known as a relevance vector machine (RVM). This is an important issue for real-time processing of mammograms in a clinical setup.

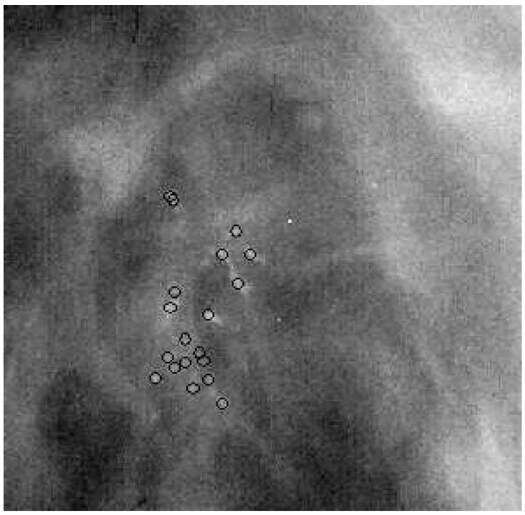
Machine learning methods have been demonstrated to generate powerful classifiers. However, in many instances, there could be a risk of overfitting the data if these methods were not properly validated on independent datasets or tested using statistical resampling methods.

In Fig. 1, we show an example of applying an SVM classifier [56] to a mammographic image, where the MCs are highlighted in the SVM classifier's output. In Fig. 2, we show the detection performance, summarized using free-response receiver operating characteristic (FROC) curves, achieved by different representative methods in an evaluation study based on a clinical mammographic database [56]; machine-learning-based methods seemed to have achieved the best performance.

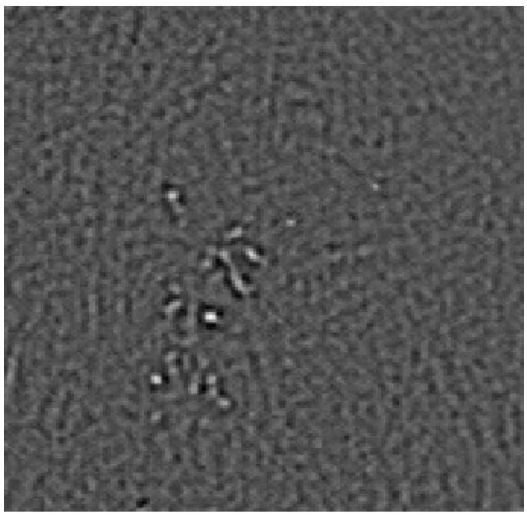
B. Detection of Masses in Mammograms

A mass is defined as a space-occupying lesion seen in more than one projection [60]. A mass is usually characterized by its shape and margin (see Fig. 3) [4], [61]. Generally speaking, a mass with a regular shape has a higher probability of being benign, whereas a mass with an irregular shape has a higher probability of being malignant. Most of the mass detection algorithms are composed of two stages [4], [61]: 1) detection of suspicious regions on the mammogram and 2) classification of suspicious regions as mass or normal tissue. The algorithms for the first stage in mass detection are generally pixel-based or region-based [4], [61], [62].

In the pixel-based approaches, features are extracted for each pixel and classified as suspicious or normal [4]. There have been many published pixel-based approaches. Kegelmeyer *et al.* [63] presented a pixel-based approach in which Laws' texture features and local oriented edge characteristics were extracted from regions of interest (ROIs) and a binary decision tree classifier was employed to classify spiculated lesions from normal tissues. The authors reported 100% sensitivity with a specificity of 82% in experiments with 85 four-view clinical cases containing 36 cancer and 36 normal cases. Liu *et al.* [64] proposed a multiresolution scheme to detect spiculated lesions. The image was decomposed into a multiresolution representation and four features were extracted for every pixel at each resolution. In their experiments, the authors selected 19 mammograms containing spiculated lesions from the Mammographic Image Analysis Society (MIAS) database. The authors reported 84.2% true positive detection at less than 1 false positive per image, and 100% true positive detection at 2.2 false positives per image. Sampat and



(a)



(b)

Fig. 1. (a) Mammographic ROI, where MCs are marked out by circles. (b) SVM classifier output, in which the MCs are highlighted by the classifier.

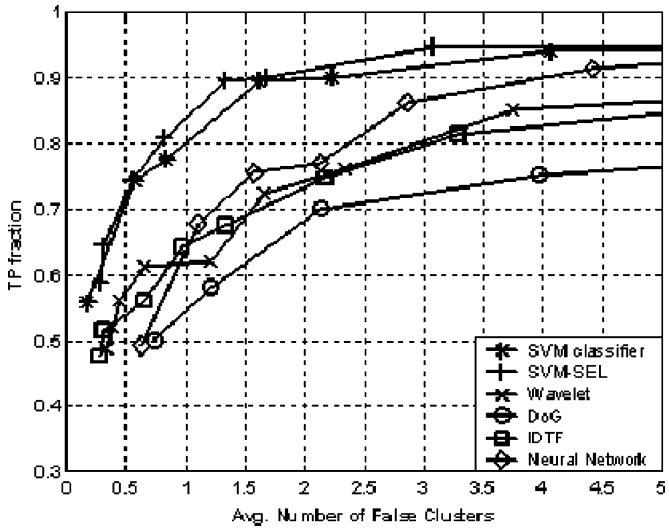
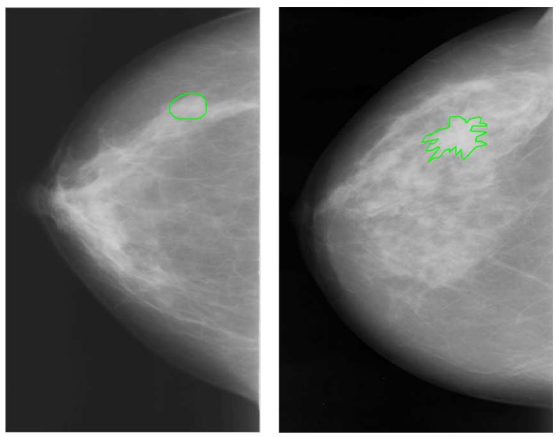


Fig. 2. FROC comparison of different methods for the detection of MCs. The methods include the following: 1) the image difference technique (IDTF) [37] and the difference of Gaussians (DoGs) [59]; 2) multiscale decomposition by wavelets [44]; and 3) machine learning methods using neural networks [49] and SVM [56]. The best performance was obtained by the SVM with SEL (SVM-SEL).



(a) (b)

Fig. 3. Different shapes and margins of masses. (a) Mass shape with oval well-circumscribed margins, having a high probability of being benign. (b) Mass shape with irregular and spiculated margins, having a high probability of being malignant. The images are from the DDSM database (http://marathon.csee.usf.edu/Mammography/Database.html).

Bovik [65] presented an approach to detect spiculated masses in digitized mammograms. The approach consisted of two steps. In the first step, a filter algorithm was used to enhance certain features. In the second step, a radial spiculation filter was used to detect the spatial location with the enhanced features. The algorithm was tested with the Digital Database for Screening Mammography (DDSM). The results showed that mass regions on the mammograms could be correctly located by the proposed algorithm. Campanini *et al.* [66] presented an SVM-based featureless approach for mass detection in digital mammograms. Instead of extracting features from ROIs, the authors used a multiresolution, overcomplete wavelet representation to codify the image with redundancy of information. Two SVM classifiers were used in this approach. The first SVM classifier was used to find the mass candidates and the second SVM classifier was used to reduce the number of false positives. Experiments were conducted with 512 images containing 312 malignant tumors and 200 normal images from the DDSM database. The authors reported that the algorithm achieved nearly 80% true positive detection with a false positive rate of 1.1 marks per image for mammograms containing malignant tumors. Kom *et al.* [67] proposed a breast mass detection algorithm that first used a linear transformation filter algorithm to enhance the image; the enhanced image was subtracted from the original image to obtain a difference image. A local adaptive thresholding technique was developed to detect the mass in the difference image. In their experiment, a database of 61 mammograms on which masses had been marked by expert radiologists was used. The authors reported that the area under the ROC curve ($A_z = 0.94$ and $A_z = 0.938$) corresponded to a sensitivity of 95.91% and 93.87%, respectively, when the preprocessing step was or was not applied. Recently, Eltonsy *et al.* [68] proposed a

multiple-concentric-layers-based algorithm to detect masses in mammograms. The algorithm consisted of three steps. First, the breast regions of screening mammograms were preprocessed by segmentation and granulation techniques. Then, the suspicious focal areas were detected using knowledge-based reasoning. Finally, two different criteria were applied to eliminate the false positives. In their experiment, 270 CC views of mammographic cases with biopsy-proven malignant masses from the DDSM database were selected. One-half of the cases were used for training and the other half were used for testing. The authors reported that the test detection rates were 92%, 88%, and 81% sensitivity at 5.4, 2.4, and 0.2 false positive marks per image, respectively.

The second approach for mass detection is region-based [4]. In the region-based approach, ROIs are segmented, and then, features are extracted from each region, which are subsequently used to classify the regions as suspicious or not suspicious. Many region-based approaches have been proposed. Chan *et al.* [69] presented a region-based algorithm in which eight texture features were calculated from spatial gray-level dependence (SGLD) matrices, and stepwise linear discrimination was used to determine the importance of each feature in distinguishing masses from normal tissue. In the experiment, one-half of a dataset of 168 ROIs containing biopsy-proven masses and 504 ROIs containing normal breast tissue was used for training; the other half was used for testing. The authors reported that the area under the ROC curve was $A_z = 0.84$ for the training set and $A_z = 0.82$ for the testing set. In the work of Sahiner *et al.* [70], four gray-level difference statistics (GLDS) texture features and three SGLD texture features were used for mass detection. A convolution neural network was employed as the classifier to distinguish between the mass and normal breast tissue. The dataset for the experiment, consisting of 168 ROIs containing biopsy-proven masses and 504 ROIs containing normal breast tissue, was extracted from 168 mammograms. The authors reported that the area under the ROC curve was A_z = 0.87, which corresponded to a true positive fraction of 90% at a false positive fraction of 31%. Mudigonda *et al.* [71] proposed a method using both gradient-based and texture-based features to differentiate benign masses from malignant tumors. The gradient-based features were directional gradient strength and the coefficient of variation of gradient strength that represented the sharpness of mass boundaries. The 20 texture features that were based on gray-level co-occurrence matrices (GCMs) represented the texture information possessed by the mass regions. After combining the gradient-based and texture-based features, a posterior probability computed using the Mahalanobis distance was employed to classify breast masses as benign or malignant. The area under the ROC curve of $A_z = 0.84$ was reported with 38 MIAS cases, compared with $A_z = 0.6$ with only gradient-based features. A CAD system for mass detection in FFDM images was developed by Wei *et al.* [24]. First, raw FFDM images were enhanced using multiscale methods. Then, a two-stage segmentation method, which combined gradient field information and gray-level information, was used to detect suspicious masses on FFDM images. In the third step, morphological and SGLD texture features were extracted for each suspicious mass. Stepwise linear discriminant analysis (LDA) with Simplex optimization was employed to select the most useful features. The trained LDA classifier with the most useful feature set was employed to differentiate masses from normal tissues. In their experiment, a mass dataset containing 110 cases with 220 images and a no-mass set containing 90 cases with 180 images were used. The authors reported case-based sensitivity of 70%, 80%, and 90% at 0.72, 1.08, and 1.82 false positive per image with the mass dataset, and at 0.85, 1.31, and 2.14 false positives per image with the no-mass dataset, respectively. Bellotti *et al.* [72] proposed a completely automated CAD system for mass detection. The system included the following three steps. First, an edge-based segmentation algorithm was implemented to select the suspicious regions. Then, eight gray-tone independent texture features of the ROIs were derived from the GLCM at four angles $\theta = k\pi/4$ ($k = 0, 1, 2, 3$). Finally, a supervised two-layered feedforward neural network, which was trained with the gradient-descent learning rule, was employed to classify masses from normal tissues. In their experiment, a database of 3369 mammographic images, which included 2307 negative cases and 1062 positive cases with at least one confirmed mass that had been diagnosed by expert radiologists, was used. The authors reported that the area under the ROC curve was $A_z = 0.783 \pm 0.008$ for the ROI-based classification. For mammographic images diagnosed by expert radiologists, 4.23 false positives per image were found at 80% sensitivity of mass detection.

More recently, an automated mass detection method was presented by Timp *et al.* [73] to detect temporal changes in mammographic masses between two consecutive screening rounds. Two kinds of temporal features, difference features and similarity features, were designed to realize the interval change analysis. An SVM was employed as a classifier to detect the temporal changes in mammographic masses. The classification performance was evaluated with and without the use of temporal features. In their experiment, the database consisted of 465 temporal mammogram pairs containing 238 benign and 227 malignant cases. The authors reported the area under the ROC curve was $A_z = 0.74$ without temporal features and 0.77 with the use of temporal features.

A few other papers published on this topic [74]–[80] are reviewed in the following. Different from feature-based CAD schemes, the template matching scheme uses prior information to segment possible masses from the background [75]. Tourassi and Vargas-Voracek [76] proposed a template matching method based on mutual information. The algorithm utilized the mutual information to measure the similarity between a query mammographic region and a template ROI stored in the knowledge databank. In the work of Lai *et al.* [77], a tumor-like template was first used in the template matching step. Then, the similarity between a suspicious area and the template was measured to detect masses in mammograms.

A support-vector-based fuzzy neural network classifier was proposed by Moayedi *et al.* [78] for the classification of masses. In the work of Tourassi *et al.* [79], by testing two different datasets that were digitized using two different digitizers, a knowledge-based CAD system was studied for mass detection. The authors evaluated the system on the datasets by

performing three experiments: evaluating the system on the datasets independently, evaluating the system on each dataset with the other being used as the knowledge database, and assessing the system's performance when the knowledge database contained mixed cases. An automated breast mass detection system using the Watson filter model was studied by Swatee *et al.* [80]. The authors reported that the Watson filter model outperformed the Laguerre–Gauss channelized Hotelling observer.

C. Detection of Architectural Distortion in Mammograms

Architectural distortion is defined in the Breast Imaging Reporting and Data System (BI-RADS) [81] as follows: "The normal architecture (of the breast) is distorted with no definite mass visible. This includes spiculations radiating from a point and focal retraction or distortion at the edge of the parenchyma. Architectural distortion can also be an associated finding." Architectural distortion is the third most common mammographic sign of nonpalpable breast cancer [22], [82], but due to its subtlety and variable presentation, it is often missed during screening. Architectural distortion accounts for 12%–45% of breast cancers overlooked or misinterpreted in screening mammography [83], [84]. Broeders *et al.* [85] suggested that improvement in the detection of architectural distortion could lead to an effective improvement in the prognosis of breast cancer patients. Whereas many publications have been directed toward the detection and analysis of calcifications and masses, relatively few have been published on the detection of architectural distortion in mammograms [22], [86].

Ayres and Rangayyan [87], [88] and Rangayyan and Ayres [89] applied Gabor filters and phase portrait maps to characterize oriented texture patterns in mammograms to detect architectural distortion. The methods were tested with one set of 19 cases of architectural distortion and 41 normal mammograms, and another set of 37 cases with architectural distortion. The resulting FROC curve gave the sensitivity rates of 84% at 4.5 false positives per image and 81% at 10 false positives per image for the two sets of images [88].

Guo *et al.* [90] investigated the characterization of architectural distortion using the Hausdorff fractal dimension and an SVM classifier to distinguish between ROIs exhibiting architectural distortion and those with normal mammographic patterns. A classification accuracy of 72.5% was obtained with a set of 40 ROIs, of which 19 had architectural distortion and 21 had normal tissue patterns. Tourassi *et al.* [91] studied the use of fractal dimension to differentiate between normal and architectural distortion patterns in mammographic ROIs. The area A_z under the ROC curve achieved was 0.89, with a dataset of 1500 ROIs including 112 with architectural distortion and 1388 with normal tissue patterns.

Matsubara *et al.* [92] used mathematical morphology to detect architectural distortion around the skin line and a concentration index to detect architectural distortion within the mammary gland; sensitivity rates of 94% with 2.3 false positives per image and 84% with 2.4 false positives per image, respectively, were obtained. Ichikawa *et al.* [93] developed an automatic method to detect areas of architectural distortion with spiculations by means of a concentration index of linear structures extracted using the mean curvature of the image; a sensitivity of 68% with 3.4 false positives per image was obtained.

Sampat *et al.* [94] proposed a technique for the enhancement of spiculations, in which a linear filter is applied to the Radon transform of the image. The enhanced image is filtered with radial spiculation filters to detect spiculated masses and architectural distortion. A sensitivity of 80% at 14 false positives per image was achieved with a set of 45 images with architectural distortion; a sensitivity of 91% at 12 false positives per image was obtained with a set of 45 images with spiculated masses. Eltonsy *et al.* [95] developed a method to detect masses and architectural distortion by locating points surrounded by concentric layers of image activity. A sensitivity of 91.3% with 9.1 false positives per image was obtained with a set of 80 images, including 13 with masses, 38 with masses possessing architectural distortion, and 29 images with architectural distortion only; a sensitivity of 93.1% was obtained in the detection of architectural distortion at the same rate of false positives.

Prajna *et al.* [96] and Rangayyan *et al.* [97] extended the method of Ayres and Rangayyan [88] described earlier for the detection of architectural distortion in screening mammograms obtained in the visit prior to that when breast cancer was detected (known as "prior mammograms"). A method based on Gabor filters and phase portrait analysis was used to detect initial candidates for sites of architectural distortion. An example with a prior mammogram is illustrated in Fig. 4. The rectangle shows the area of architectural distortion identified by a radiologist. The node map obtained via phase portrait analysis has provided a high response at the site of architectural distortion, along with several other stronger and weaker responses. Fig. 4(c) shows the ROIs obtained from the mammogram. A set of 386 ROIs was automatically obtained from 14 prior mammograms with 21 ROIs related to architectural distortion. The fractal dimension of each ROI was estimated using the circular average power spectrum technique. FROC analysis with a set of four features, including fractal dimension and three texture features known as entropy, sum entropy, and inverse difference moment [98], provided a sensitivity of 0.79 at 8.4 false positives per image in the detection of sites of architectural distortion in prior mammograms. Due to its potential for the detection of early breast cancer at the premass-formation stage, more recent works have been directed toward the detection of architectural distortion [99]–[102].

D. Detection of Bilateral Asymmetry in Mammograms

Asymmetry between the left and right mammograms of a given subject is an important sign used by radiologists to diagnose breast cancer [103]. The BI-RADS [81] definition of asymmetry indicates the presence of a greater volume or density of breast tissue without a distinct mass, or more prominent ducts, in one breast as compared to the corresponding area in the other breast. Analysis of asymmetry can provide clues about the early signs of breast cancer, such as developing densities, parenchymal distortion, and small asymmetric dense regions. Unlike for the detection and analysis of calcifications and masses, there are only a few publications on the detection of bilateral asymmetry in mammograms [22], [104], [105].

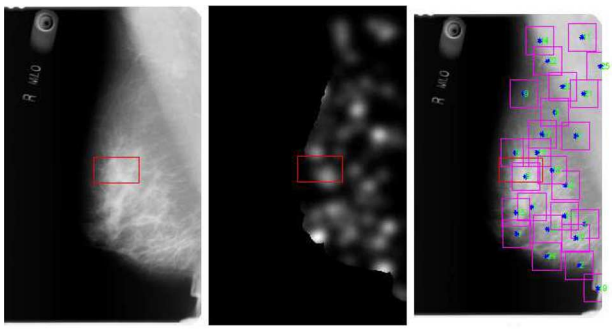


Fig. 4. (a) Example of a prior mammogram (image c52_95ro) acquired 24.2 months before the breast cancer was detected. The rectangle indicates the region of architectural distortion identified by a radiologist. The image size is 1377×850 pixels at 200 μm/pixel. (b) Node map. Each asterisk mark ($*$) corresponds to a peak position detected automatically in the node map. The numbers next to the asterisk marks indicate the peaks in descending order of magnitude. (c) 25 ROIs obtained from the mammogram using the peaks detected in the node map. The size of each ROI is 128×128 pixels (except at the edges of the image).

Scutt *et al.* [106] compared measures of bilateral breast asymmetry among women in a study group that included 252 asymptomatic women who had normal mammography but developed breast cancer later, with those of 252 age-matched women in a control group whose mammograms were normal and free of cancer during the study period. The breast volume was calculated from CC mammograms, and the relationships between asymmetry, established risk factors, and the presence or absence of breast cancer were studied. With the age at menopause included in the model for the subgroup of postmenopausal women, asymmetry was found to be a significant predictor of breast cancer.

A few studies have been presented in the literature on digital image processing techniques addressing bilateral asymmetry, with most of them applying some type of alignment of the left and right breast images before performing asymmetry analysis [107]–[112]. Lau and Bischof [108] and Miller and Astley [110] proposed procedures to compare the corresponding anatomical regions between the left and right breast images in terms of shape, texture, and density. Lau and Bischof [108] also proposed a directional feature to quantify oriented patterns. However, alignment procedures encounter problems, such as the natural asymmetry of the breasts of a given subject, the lack of good corresponding points between the left and right breast images to perform matching, and distortions inherent to mammographic imaging.

Miller and Astley [113] proposed a technique for the detection of bilateral asymmetry that includes a semiautomated texture-based procedure for the segmentation of the glandular tissue and measures of shape and registration cost between views for the detection of asymmetry. An accuracy of 86.7% was reported with a test dataset of 30 screening mammogram pairs. In another report, Miller and Astley [114] presented a method for the detection of bilateral asymmetry based on measures of shape, topology, and distribution of brightness in the fibroglandular disk. The method was tested on 104 mammogram pairs and a classification accuracy of 74% was obtained. Lau and Bischof [108] devised a method for the detection of breast tumors, using a localized definition of asymmetry that encompassed measures of brightness, roughness, and directionality. The method was evaluated using ten pairs of mammograms where asymmetry was a significant factor in the radiologist's diagnosis. A sensitivity of 92% was obtained with 4.9 false positives per mammogram.

Ferrari *et al.* [105] developed a method for the analysis of asymmetry in mammograms using directional filtering with Gabor wavelets. In their method, which was applied to MLO views, the breast boundary is detected first and all artifacts outside the breast are removed [115]. Then, the pectoral muscle is detected and removed [116]. The fibroglandular disk is segmented [117] and the resulting image is decomposed using a bank of Gabor filters at 12 orientations and four scales. The Karhunen–Loève transform is employed to select the principal components of the filters' responses. Rose diagrams are computed from the phase images and subsequently analyzed to detect the presence of asymmetry as characterized by variations in oriented textural patterns. A database of 80 images containing 20 normal cases, 14 asymmetric cases, and six architectural distortion cases was used to evaluate the algorithm. The authors reported classification accuracy rates of up to 74.4%. The Gabor-filter-based method gives quantitative measures of the differences in the directional distribution of the fibroglandular tissue (pattern asymmetry). Rangayyan *et al.* [104] extended the method of Ferrari *et al.* [105] by including morphological measures to quantify differences in fibroglandular-tissue-covered areas in the left and right breasts, which relate to size and shape; in addition, the directional data were aligned with reference to the edge of the pectoral muscle (in MLO views). Fig. 5 illustrates a pair of mammograms of a subject with asymmetry and the resulting rose diagrams [104]. A sensitivity of 82.6% and a specificity of 86.4% were obtained in the detection of bilateral asymmetry with a set of 88 mammograms.

E. Image Enhancement for Diagnosis of Breast Cancer

Image enhancement techniques have been proposed to improve the quality and readability of mammograms or to detect abnormalities because mammographic images generally have poor contrast and visibility of details. The goal of image enhancement is to improve the image quality so that the processed image is better than the original image for a specific application or a set of objectives [119]. Enhancement methods can be classified into two types: direct and indirect contrast enhancements.

In direct contrast enhancement, a contrast measure is first defined and enhancement is performed by directly manipulating the contrast [120], [121]. A direct contrast enhancement technique for mammographic images was developed by Dhawan *et al.* [122], in which a neighborhood consisting of a square region of pixels centered on a given pixel, called the "center" of the neighborhood, and a larger square annulus called the "surround" were extracted around each pixel [122]. A local contrast for each pixel using the average intensities of the center and the surround regions was defined. The contrast value for each pixel was transformed to a new enhanced contrast value using a specific contrast enhancement function, and then, the obtained enhanced contrast value was combined with the original image value to produce a

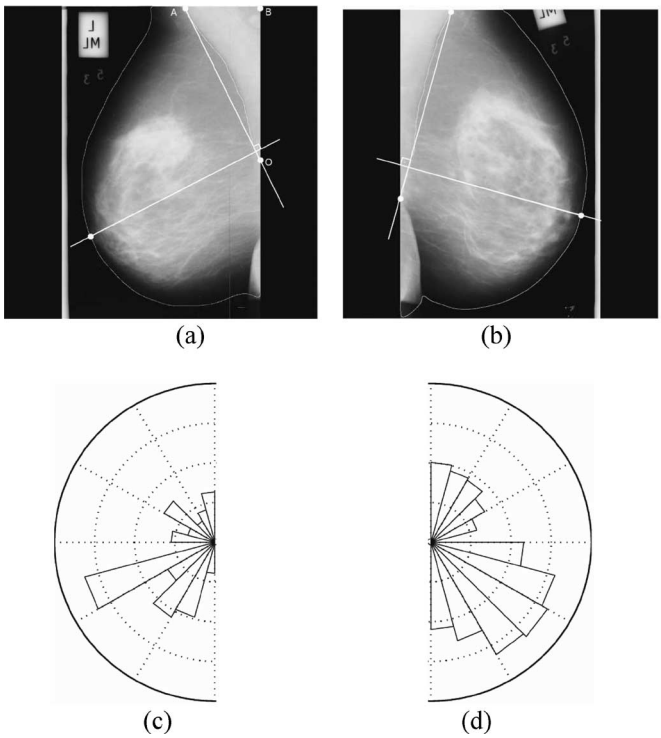


Fig. 5. (a) and (b) Images mdb111 and mdb112 representing a case with bilateral asymmetry [118]. The linear estimate of the pectoral muscle edge detected using the Hough transform and the line perpendicular to the same used in the alignment procedure are shown. (c) and (d) Rose diagrams of the mammograms after alignment. Reproduced with permission from [104]. Copyright SPIE.

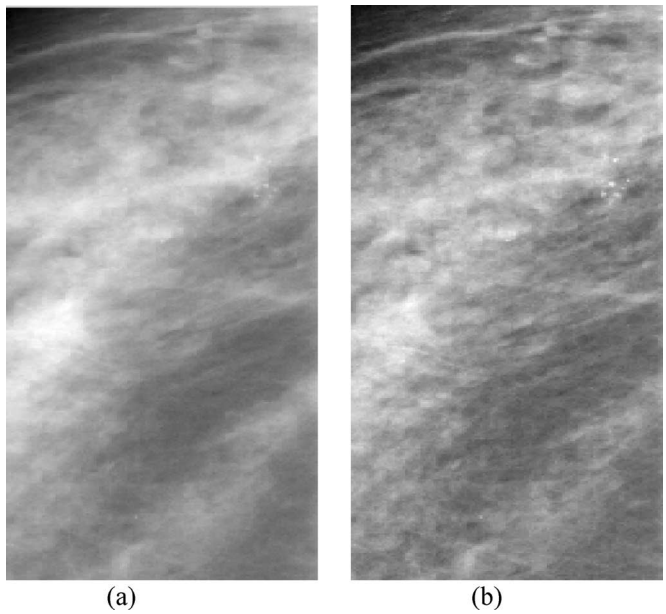


Fig. 6. Direct contrast enhancement of a part of a mammogram using a multiscale local contrast measure defined in the wavelet domain [128]. (a) Original image. (b) Enhanced image.

new pixel value of the enhanced image. Several related papers have been published on direct-contrast-based image enhancement, including region-based methods [123]–[125].

Recently, direct contrast enhancement has been further developed. Cheng and Xu [126] presented an adaptive fuzzy logic contrast enhancement method for mammographic images. The method was based on the maximum fuzzy entropy principle. It transformed the image to a fuzzy domain, and then, a local measure of contrast, called fuzzy entropy in the fuzzy domain, was computed. The contrast was enhanced using both global and local information. Finally, the enhanced image was obtained using defuzzification, by which the enhanced mammogram was transformed back to the spatial domain from the fuzzy domain. The work of Jiang *et al.* [127] developed further the fuzzy method by Cheng and Xu [126], in which a combined approach with fuzzy logic and structure tensor was proposed for the enhancement of potential MCs in digital mammograms. In the proposed method, a structure tensor operator was produced, and then applied to each pixel of the mammographic image, which resulted in an eigenimage. The eigenimage was combined with a fuzzy image, which was obtained by a fuzzy transform from the original image to enhance the contrast. This method can suppress non-MC regions while enhancing the MC regions. Tang *et al.* [128] presented a method for direct contrast enhancement, in which a multiscale local contrast measure was defined in the wavelet domain. The enhancement method was applied in the wavelet domain by manipulating the contrast values computed using the high-frequency and low-frequency information. The advantages of the proposed image enhancement technology lie in [128]: 1) ease of adjustment by end users (for example, adjusting a single parameter); 2) the image enhancement technology can be applied to JPEG2000 compressed images in the decompression stage to reduce the time required for image enhancement, which modifies the wavelet coefficients obtained in the decompression stage; and 3) the proposed image enhancement technology modifies a multiscale measure that matches the human visual system, resulting in the enhanced images having a better visual quality. Fig. 6 shows an example of image enhancement using the method proposed by Tang *et al.* [128].

Different from direct contrast enhancement, an indirect contrast enhancement approach is not designed to manipulate the image contrast directly. Indirect contrast enhancement methods include unsharp masking, histogram equalization, and multiscale/wavelet enhancement. Among them, multiscale/wavelet enhancement methods have been studied extensively. The advantages of multiscale/wavelet enhancement methods relate to the observation that mammograms contain features with varying scale characteristics [9]; subtle features, such as calcifications, are mostly contained at small scales, whereas larger objects with smooth borders, such as masses, are mostly contained in coarse scales [129]. Thus, different features can be selected and enhanced at different scales.

The first work using multiscale/wavelet enhancement for mammographic image enhancement was that of Laine *et al.* [130] in which the authors investigated mammographic image enhancement by overcomplete multiscale representation. An image needed to be enhanced was decomposed into a multiscale representation, and the coefficients in each subband of the multiscale representation were modified using a nonlinear mapping. Three multiscale representations were investigated,

including the dyadic wavelet transform, the φ-transform, and the hexagonal transform. The results suggested that wavelet-based image processing algorithms could play an important role in improving the performance of digital mammography [130]. The drawback of this method was that the parameters in the nonlinear mapping at each scale were global, which was not optimal [129]. Sakellaropoulos *et al.* [129] proposed improvements to the method of Laine *et al.* [130]. The method of Sakellaropoulos *et al.* [129] was based on a spatially adaptive transform of the wavelet coefficients, aimed at overcoming the drawbacks of the method of Laine *et al.* [130]. It included two steps: the first step was to perform noise reduction and the second step was to enhance the contrast of the mammographic images. Experimental results using 22 images from DDSM showed that the method offered significantly improved performance over previously reported methods for global wavelet contrast enhancement [129]. Both Laine *et al.* [130] and Sakellaropoulos *et al.* [129] used dyadic wavelet transforms, which do not allow flexibility in the choice of discrete scales [131]. Heinlein *et al.* [131] proposed an algorithm for feature enhancement in mammograms using discrete wavelet decompositions called integrated wavelets. The integrated wavelet transform allows more flexible and adaptive discretization of scales than the dyadic wavelet transform, leading to better contrast enhancement.

Noise and artifacts are generally introduced when images are enhanced [129]. Thus, many image enhancement methods also include steps to suppress noise and artifacts while enhancing the features of mammographic images [131]–[133]. Kim *et al.*. [132] proposed an adaptive image enhancement method based on the first derivative and local statistics. In this method, film artifacts that could be misread as MCs were removed, and the important features of the mammographic image were enhanced by adding the adaptively weighted gradient images. Scharcanski and Jung [133] presented a wavelet-based method to perform noise reduction and image enhancement, which combined noise equalization, wavelet shrinkage, and scale-space analysis. Different from other wavelet-based methods, this method only used two detail images (horizontal and vertical) instead of three detail images (horizontal, vertical, and diagonal). The wavelet shrinkage step was mainly used to preserve edges that were persistent over several scales and to remove residual noise. An adaptive piecewise linear enhancement function was applied to the denoised wavelet coefficients [133]. In addition to the methods mentioned earlier, several other image enhancement technologies for screening mammograms and cancer detection have been published [134]–[139].

F. Content-Based Image Retrieval (CBIR) in Mammography

CBIR may potentially provide new and exciting opportunities in the analysis and interpretation of mammographic images. The underlying principle in CBIR is analogous to textual search engines (e.g., Google), in which a search engine is used to retrieve information that is relevant (or similar) to the user's query. Instead of textual description, however, in CBIR, the query information is presented in the form of an image or its extracted features. CBIR could serve as a diagnostic tool to aid radiologists by comparing current cases with previously diagnosed cases in a medical archive.

Among the early investigations on CBIR for mammography was the work by Qi and Snyder [140], where simple metrics based on shape, size, and brightness were used to characterize images. The intent was to demonstrate the potential use of CBIR in a picture archival and communication system (PACS). The user would supply a query image and the system would respond by finding images with similar characteristics from the archive and returning them along with their corresponding ancillary data. Despite its simplicity, this approach is one of the earliest attempts to move from textual description of complicated radiological information into using features extracted from the images themselves for representation. A similar approach was investigated recently by Hassan *et al.*, where a grid-based approach for indexing mammographic images for CBIR analysis was applied [141].

Sklansky *et al.* developed a visual neural classifier approach [142], in which a trained classifier is used to reduce the high-dimensional data into a 2-D feature space. Images that are close to each other in the 2-D space are selected for purposes of visualizing relationships in the data. Four radiologists evaluating the system showed significant reduction in the number of benign biopsies and misdiagnosed cancers. El Naqa *et al.* [143] proposed a hierarchical learning approach, which consisted of a cascade of a binary classifier and a regression module to optimize retrieval effectiveness and efficiency. This approach was based on using supervised machine learning algorithms to model radiologists' perception of similarity in their interpretation of clustered MCs. Methods based on neural networks and SVMs were evaluated. A similar approach was further studied and validated using similarity data collected from expert observer studies [144]. Zheng *et al.* [145] applied visual similarity based on a k-nearest neighbor (KNN) algorithm to retrieve mammograms with similar masses. A set of 14 features representing a wide range of morphological- and intensity-related characteristics was selected to optimize the performance of the KNN algorithm. This approach was further improved through optimizing the reference library by identifying and removing less effective ROIs [146].

Burnside *et al.* [147] investigated an inductive logic programming (ILP) approach for CBIR. The idea is to use an ILP algorithm to learn a set of hypotheses, which can discriminate effectively between positive and negative examples. This approach makes use of a standardized descriptive lexicon of mammographic abnormalities defined in BI-RADS. Information-theoretic measures (such as mutual information) were used by Tourassi *et al.* [148] for retrieval of masses in mammograms. An unsupervised learning approach based on Kohonen self-organizing map (SOM) was proposed by Kinoshita *et al.* [149]. The SOM was trained using visual features related to breast density patterns. A set of 88 features was computed for each mammogram, which include shape factors, texture, and moment features, as well as angular projections and morphological features that were derived from segmented fibroglandular tissues. Alto *et al.* [150] proposed a database indexing scheme for

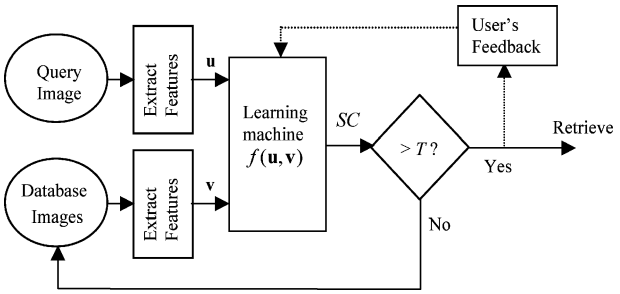


Fig. 7. CBIR framework with relevance feedback. The system consists of two modes of operation: 1) learning the similarity metric and 2) retrieval of relevant images. In the learning mode, feature vectors extracted from pairs of images are presented to the learning machine along with the user's similarity coefficient for each image pair. In the retrieval mode, the learning machine predicts the user's similarity coefficient and uses this value to retrieve the most relevant images from the database with a chosen threshold value T. The user's feedback is incorporated to improve the learning process.

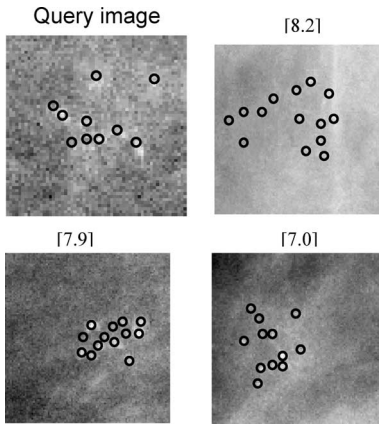


Fig. 8. Example of a query with clustered MCs (left) and retrieved images by a hierarchal two-stage SVM-based CBIR system in descending order of similarity (from left to right). Numbers in brackets on top of each cluster are user's similarity scores.

retrieval of mammograms with masses based on their diagnostic features related to shape, edge definition, and texture.

As reviewed before, most of the methods proposed for CBIR attempt to mimic human visual similarity by extracting some "relevant" imaging features and feeding them into a "learner." The methods differ in the type of features used and the similarity metrics employed, which range from simplistic distance metrics to more sophisticated machine learning algorithms (supervised and unsupervised).

In Fig. 7, we show a functional diagram of a similarity-learning-based approach for CBIR in mammography [143]. Image similarity is modeled by mapping the extracted image features into experts' responses using machine learning. This similarity model can be further adapted online by incorporating the user's feedback. A retrieval example using this model is shown in Fig. 8 [143].

V. Discussion

Future work on computer-aided breast cancer detection should focus on improving the performance of CAD systems. Although current CAD systems have not been fully successful, we believe that further studies on CAD systems and related techniques should help improve their performance, and thereby enable them to gain more widespread adoption in breast care clinics.

For MC detection, the last two decades have witnessed a large number of MC detection algorithms developed for mammograms. In recent years, several CAD systems that support MC detection have been deployed for clinical use. However, literature reports show mixed results on the role of current CAD systems in practice, with some showing improvement [151] and others showing no improvement [152]. Some of these systems may tend to overemphasize the sensitivity in their detection ability at the expense of specificity. This, in many cases, may result in increased unnecessary biopsies when using such CAD systems. Nevertheless, we feel that the problem of MC detection should not be simply treated as looking for "blobs" in an inhomogeneous image background; better understanding of MC characteristics as perceived by experts should be considered. In addition, different conditions of mammographic characteristics associated with X-ray exposure and breast tissue density should be studied across different institutions. Having more public datasets for evaluating the different detection techniques could help better understand the current status of the field. Besides mammography, other imaging modalities such as magnetic resonance imaging and 3-D ultrasonography are currently being investigated in the literature. Information from these imaging modalities could be useful for validating the ground truth used for current and new methods.

Masses are more difficult to detect than MCs because the features of a mass may be obscured by or be similar to those of normal breast parenchyma. Thus, mass detection remains to be a significant topic in breast cancer detection. Besides mass detection, other important topics are the detection of architectural distortion and the detection of bilateral asymmetry in mammograms. Currently, both the detection of architectural distortion and the detection of bilateral asymmetry in mammograms are important research topics, and efficient solutions to these two issues could improve the performance of CAD systems.

As mentioned before, digital mammography has some potential advantages over traditional screen-film mammography. In recent years, there is a tendency for mammography to migrate from screen film to direct digital acquisition because of significant progress in digital mammography [153]. This development is convenient for increasing the use of computers to present, access, and process images; furthermore, the integration of CAD systems and PACS based on high-bandwidth computer networks facilitates rapid electronic transfer of images between different sites [154]. The network-based PACS makes it possible to transmit of digital images from one place to another, which is convenient for healthcare experts at different hospitals or industries, radiologists, and informatics specialists to cooperate with one another. Networked CAD systems and PACS could also address the problems associated with the lack of expert radiologists in remote or rural areas.

VI. Conclusion

CAD is an important tool for early detection of breast cancer. A significant amount of work has been done in this area over the past 20 years. Compared with double reading, CAD can reduce the workload of radiologists. However, the performance of current CAD systems still needs improvements to fully meet the requirements for routine clinical applications.

In the move toward an effective CAD system for breast cancer detection, many techniques have been developed. This paper provided an overview of the recent advances in CAD systems and related techniques. We described some basic concepts related to breast cancer detection and diagnosis, and reviewed many key CAD techniques for breast cancer: detection of calcifications, masses, architectural distortion, and bilateral asymmetry, as well as image enhancement and image retrieval.

Although significant progress has been made over the last 20 years, much work still needs to be done to develop more effective CAD systems. Effective and efficient CAD systems should lead to early detection of breast cancer and improved prognosis for those affected by the disease.

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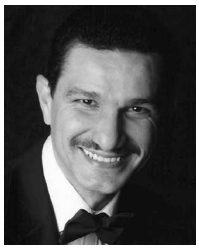

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