RECENT ADVANCES IN
Breast Imaging, Mammography, and Computer-Aided Diagnosis of Breast Cancer
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Jasjit S. Suri
Rangaraj M. Rangayyan
Editors

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Dr. Jasjit S. Suri dedicates this book to his children Harman and Neha, his wife Malvika, and his dear friends and collaborators all around the world who have made this possible.

Dr. Rangaraj M. Rangayyan dedicates this book to his students, fellow researchers, and clinical collaborators.
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Preface

Breast cancer is the most common type of cancer in women worldwide. About ten percent of women are confronted with breast cancer in their lives. Breast cancer can be most efficiently treated if detected at an early stage. This book focuses on the application of computer vision for lesion identification in mammograms and breast imaging volumes called computer-aided diagnosis (CAD) and computer-aided detection (CADx). The book is divided into four parts: Part I presents the anatomic, histopathology, and mammographic views of the breasts, and the physics of different breast imaging modalities. Part II presents the techniques for lesion detection, mass detection through CAD. Part III presents the applications of different computer vision fields in breast-image registration. Finally, Part IV presents the performance evaluation section for breast CAD techniques.

Chapter 1 summarizes 20 years of Dr. Tibor Tot’s experience in routine diagnostics using breast imaging. The group at Uppsala University, the Sweden has more than 5,000 operated breast lesions documented on large 2D histological sections, more than 400 of them are also examined in thick 3D sections. Their statistical work-up was carried out during the period of 1996–2003, corresponding to more than 1,700 breast carcinoma cases. This chapter not only aims to describe the morphologic findings in their static state, but attempts to place them in a perspective of the dynamic changes involving pathologically altered breast tissue: an ambition similar to describing a life-long movie with a couple of words and photographs.

Breast MRI has shown great potential as a diagnostic tool and is rapidly becoming part of the standard of care in breast cancer evaluation. The Chapter 2 describes the clinical science of breast MRI from clinical presentation, composition, and scientific first principles. Major technological advances and recent emergent technologies in breast MRI, including anatomically oriented pulse sequences; human factors in imaging; and molecular imaging techniques are discussed. The reader is introduced to concepts, clinical presentations, and manifestations of disease. As such, the goal is to provide a resource for scientists and clinicians to be able to better understand the multitude of decision-making capabilities of breast MRI by understanding established techniques, as well as emerging new technologies for this major women’s health issue.

Computer-aided diagnostic systems are being developed to assist radiologists in the interpretation of ambiguous mammographic features corresponding to possible signs of early breast cancer. Databases of digital mammograms are needed
for testing such systems. Chapter 3 presents an overview of a few such databases. Most databases are limited to single-exam sets of two or four mammograms on which a diagnosis was made, some ground-truth information related to the position of diagnostically significant mammographic features, and the diagnosis. The chapter presents the design of a comprehensive, indexed atlas of digital mammograms. The design of an appropriate indexing scheme facilitates the implementation of content-based retrieval techniques needed for efficient access to and retrieval of relevant cases from the atlas. Finally, the chapter proposes the use of mobile software agents for facilitating remote consultation of the atlas. Mobile agents can move between data sources such as the atlas and hospital repositories, perform computational tasks at each site, and return only relevant data to the user. These features reduce the computational requirements of the local computer system, bandwidth requirements, and overall network traffic. Proposed applications of the atlas include research, remote consultation, teaching, evaluation of CAD systems, and self-evaluation by radiologists.

The Chapter 4 focuses on the application of genetic algorithms (GAs) in computer-aided diagnostics (CAD). An overview of the GAs is supplied, with a special focus on their use as optimization techniques. In particular, the use of GAs for optimizing the choice of the numerous parameters involved in a CAD detection method is described. Major advantages induced by the use of a GA in CAD detection issues are described, both in terms of performance improvement and of the investigation of the importance of the different CAD parameters.

Effective mass detection and analysis are important steps in mammography. Chapter 5 discusses a study showing two aspects: (a) automatic detection of masses surrounded by glandular or dense glandular breast tissues, based on robust image-segmentation techniques that cluster information to ensure that suspicious masses are isolated from background breast tissue and as few false positives (FP) as possible; and (b) mass-pattern analysis to classify the region of interest (ROI) into normal or abnormal, and benign or malignant cases by a semi-automatic analysis approach, where a new classification of vicinal support-vector machine is proposed. Experimental results based on the Mini-MIAS* database demonstrate that the proposed algorithms are effective for mammographic mass detection and analysis.

Chapter 6 presents a procedure for analysis of left–right (bilateral) asymmetry in mammograms. The procedure is based on the detection of linear-directional components using a multiresolution representation based upon Gabor wavelets. A particular wavelet scheme with 2D Gabor filters as elementary functions with a varying tuning frequency and orientation specifically designed to reduce the redundancy in the wavelet-based representation, is applied to the given image. The filter responses for different scales and orientation are analyzed by using the Karhunen–Loève (KL) transform and Otsu’s method of thresholding. The KL transform is applied to select the principal components of the filter responses, preserving only the most relevant directional elements appearing at all scales. The selected principal

*Mammographic Image Analysis Society, London, U.K.
components, thresholded by using Otsu’s method, are used to obtain the magnitude and phase of the directional components of the image. Rose diagrams computed from the phase images and the statistical measures computed thereof are used for quantitative and qualitative analysis of the oriented patterns. A total of 80 images from 20 normal cases, 14 asymmetric cases, and six architectural distortion cases from the Mini-MIAS database were used to evaluate the scheme using the leave-one-out methodology. Average classification accuracy rates of up to 74.4% were achieved.

Chapter 7 focuses on the use of machine-learning techniques such as support vector machines (SVM) in CAD issues. First, an introduction of SVMs is presented, with a particular attention to their use as classifiers. A brief theory preamble and a survey of the advantages of SVMs over other classifiers is provided. Finally, examples of mass and microcalcification detection based on SVMs are described and reviewed. Particular emphasis is given to detection techniques that do not make use of extracted features for isolating the suspect regions.

In Chapter 8, a novel methodology for the unsupervised and supervised segmentation of mammograms for the purpose of detecting masses is proposed using weighted Gaussian mixture models and Markov random fields (MRF), consisting of a total of four image segmentation models. The results of implementing these models on the randomly selected Brodatz composite images and DDSM database are shown and discussed. Then a novel adaptive weighted model for the combination of experts based on different features using one of the four segmentation models, show it to perform significantly better at 5% significance level to the conventional ensemble-combination rules strategy.

Chapter 9 first presents a small review of the most significant existing methods to detect microcalcifications in mammograms. Next, a method developed by the authors for detecting microcalcification is exposed. The method is based on a seed selection procedure, which consists in an analysis of the prediction error obtained after applying a 2D linear-prediction-adaptive filter to the image. Subsequently, a region growing algorithm is performed in order to identify the microcalcifications. The method was tested on 23 mammograms from the Florida DDSM database. Two parameters were calculated to measure the performance of the algorithm: sensitivity (S) and positive predictive value (PPV), obtaining a value of $S = 82.72\%$ and $PPV = 88.39\%$, respectively.

Chapter 10 discusses the application of several computational intelligence paradigms to the classification and diagnosis of breast cancer using mammogram screen-film data sets from several different institutions. Specifically, the theory, application, and results obtained for the following paradigms has been discussed: evolutionary programming, evolutionary programming/adaptive boosting hybrid, probabilistic neural network (PNN), generalized regression neural network (GRNN), support vector machines (SVM) with several different kernels, SVM/GRNN oracle hybrid, differential evolution, partial least squares, and kernel partial least squares. The approach discusses the theories of each of these paradigms followed by a description of their specific application to screen-film
Accurate breast skin-line estimation is an important prerequisite for both enhancement and analysis of mammograms for computer-aided diagnosis of breast cancer. In Chapter 11, the authors proposed a novel system for skin-line estimation. First, an initial estimate of the skin line is first computed using a combination of adaptive thresholding and connected-component analysis. Due to noise, this skin line is susceptible to errors in the top and bottom portion of the breast region. Using the assumption that the Euclidean distance from the edge of the stroma to the actual skin line is usually uniform, the chapter develops a novel dependency approach for estimating the skin-line boundary of the breast. In this dependency approach, first the constraints are developed between the stroma edge and initial skin-line boundary using the Euclidean distance. These constraints are then propagated to estimate the upper and lower skin-line portions. The selection of the constrained region is based on a greedy algorithm, which is also a new component in the system. The authors evaluate the performance of their skin-line estimation algorithm by comparing the estimated boundary with respect to the ground-truth boundary drawn by an expert radiologist. Two different metrics for error measurement are used: the polyline distance measure, and the Hausdorff distance measure. As part of the protocol, the dependency approach methodology is compared with a deformable model strategy (proposed by Ferrari et al.\textsuperscript{1}). On a dataset of 82 images from the MIAS database, the dependency approach yielded a mean error ($\mu$) of 3.28 pixels with a standard deviation ($\sigma$) of 2.17 pixels using the polyline distance measure. In comparison, the deformable model strategy yielded $\mu = 4.92$ pixels with $\sigma = 1.91$ pixels. The improvement is statistically significant. The results are clinically relevant and appealing according to the radiologists who evaluated the results.

Chapter 12 is the application of CAD on 3D digital tomosynthesis data sets. Digital tomosynthesis has recently emerged as a new and promising modality in breast imaging. Digital breast tomosynthesis (DBT) produces a quasi-3D data set that is reconstructed from a small number of projections of the compressed breast. The 3D data set consists of 1-mm thick slices through the breast. As a result, the radiologist is typically required to read 50 images of each breast. Computer-aided detection (CADe) may be useful in helping radiologists read this large image set. The chapter shows two different approaches to detect mass lesions in the DBT. The first is a 3D method to examine the reconstructed image slices. The second is to operate directly on the set of raw projection images. The second technique has several advantages including independence from the exact reconstruction algorithm used. This is important since reconstruction algorithms for this DBT are not yet fully optimized and can produce considerable artifacts in the reconstructed slices.
It is known that a number of breast imaging methods for diagnosis and biopsy of suspicious lesions are available. X-ray mammography, magnet resonance imaging (MRI), and sonography are the methods used most often. Chapter 13 focuses on image registration as an important problem in breast imaging. It is used in a wide variety of applications that include better visualization of lesions on pre- and post-contrast breast MRI images, speckle tracking and image compounding in breast ultrasound images, alignment of positron emission, and standard mammography images on hybrid machines, etc. It is a prerequisite to align images taken at different times, using different imaging modalities, on different breast sections. The inhomogeneous, anisotropic nature of the soft-tissue within the breast, and its inherent nonrigid body behavior, in addition to temporal changes of the breast tissue, breast position, and the imaging conditions, all make breast-image registration a challenging task. This chapter gives an overview of the current state-of-the-art in the breast-image registration techniques. Methods are classified according to the modalities involved in the registration process. For the intramodality registration techniques, x-ray and MRI are the primary focus of interest in the literature. Multimodality techniques cover the combination of x-ray and ultrasound, x-ray and MRI, and more.

Two-dimensional mammography is the most common modality and 3D MRI is second. The Chapter 14 focuses on multilevel framework for 2D and 3D registration of mammographic data, which uses the following distinct steps: (a) extraction of anatomical linear structures, (b) selection of salient linear structures, (c) extraction of local features, and (d) matching the set of feature points. Temporal and contralateral 2D x-ray and temporal 3D MR registration are used as examples.

Chapter 15 describes AMDI – Atlas Indexado de Mamografias Digitais, an indexed atlas of digital mammographic images that includes four views for each case, the patient’s clinical history, global and specific radiological findings, contours of the breast and diagnostic features, and details of features, such as the number of individual calcifications present in each cluster as identified by an authorized specialist. AMDI integrates three systems: a mammogram database registration system, a research system, and a teaching system. AMDI includes concepts related to Web-based medical databases and ontologies for the representation of knowledge in the area of mammography and computer-aided diagnosis of breast cancer. The system facilitates the entry of new cases and related mammograms, radiological information, clinical information, and information related to the health and life style of a patient by a registered and authorized clinical user. The atlas incorporates a teaching system and a research system. The systems are designed to permit computer-aided diagnosis, teleradiology, telemedicine, content-based case or image retrieval, data mining, and distance learning. All the resources of AMDI are available via the Web to authorized users.

Chapter 16 presents the current status of breast screening in Japan and the sophisticated detection, classification, and visualization techniques are described. Breast screening using ultrasound images has started in some regions of Japan for early detection of breast cancer. Although the mammography is also recommended
for screening, the effectiveness of ultrasound testing is recognized for dense breasts of women aged over 40. A CAD scheme for detection of breast masses using a freehand probe and 3D imaging ultrasound devices has been developed. The scheme includes a detection technique for breast lesions based on active contour and balloon models in 2D and 3D spaces, a classification step using statistical approaches using image features, and a fine visualization browser using virtual B- and C-mode images to confirm the shape and the position of the lesion.

In addition to distinguishing cysts from solid breast tumors, ultrasound is a valuable adjunct to mammography in breast imaging. Chapter 17 focuses on 3D ultrasound for distinguishing benign and malignant lesions. Ultrasound criteria for the classification of solid breast masses include lesion shape, orientation, margin, echogenicity, and acoustic transmission. Recently, similar criteria were applied to CAD and promising results were obtained for the classification of breast lesions. The conventional 2D ultrasound of the breast is increasingly used in surgical clinical practice because it offers many benefits compared with other medical imaging techniques. Nevertheless, conventional 2D ultrasound images are not enough to transmit the entire US information of a solid breast lesion, while the 3D ultrasound can offer comprehensive information of all 2D lesion aspects and provide, in addition, simultaneously, the coronal plane. This additional information has been proved to be helpful for both clinical applications and CAD. The 2D CAD and 3D CAD are expected to be a useful CAD tool for classifying benign and malignant tumors in ultrasonograms, and can provide a second reading to help reduce misdiagnosis.

When mammograms are analyzed by computer, the pectoral muscle should be excluded from processing that is intended for the breast tissue. For this and other reasons, it is important to identify and segment out the pectoral muscle. In Chapter 18, a new, adaptive algorithm is proposed to automatically extract the pectoral muscle on digitized mammograms; it uses knowledge about the position and shape of the pectoral muscle on mediolateral oblique (MLO) views. The pectoral edge is first estimated by a straight line, which is validated for correctness of location and orientation. This estimate is then refined using iterative “cliff detection” to delineate the pectoral margin more accurately. Finally, an enclosed region, representing the pectoral muscle, is generated as a segmentation mask. The algorithm was found to be robust to the large variations in appearance of pectoral edges, to dense overlapping glandular tissue, and to artifacts such as tape. The algorithm has been applied to the entire Mammographic Image Analysis Society (MIAS) database. The segmentation results were evaluated by two expert mammographic radiologists, who rated 83.9% of the curve segmentations to be adequate or better.

Image processing algorithms are the foundation for designing systems such as CADe to automatically process mammograms for tasks such as identifying potential abnormalities. A major limitation in the design of image processing algorithms lies in the difficulty of demonstrating that algorithms work to an acceptable measure of performance. Chapter 19 explores some of the issues, successes, and short-
comings related to existing performance evaluation paradigms for image processing algorithms in mammography, particularly in the context of image enhancement, segmentation, and registration. It reviews common algorithms in each category, the role that mammogram databases play in the performance evaluation of algorithms, and some of the challenges of designing image processing for mammograms.

Chapter 20 presents a simple, fast, and accurate method for automatically locating the nipple on digitized mammograms that have been segmented to reveal the skin-air interface. If the average gradient of the intensity is computed in the direction normal to the interface and directed inside the breast, a sudden and distinct change in this parameter close to the nipple is found. A nipple in profile is located between two successive maxima of this parameter; otherwise, it is near the global maximum. Specifically, the nipple is located midway between a successive maximum and minimum of the derivative of the average intensity gradient; these are local turning points for a nipple in profile, but are global otherwise. The method has been tested on 24 images, including both oblique and cranio-caudal views, from two digital mammogram databases. For 23 of the images (96%), the rms error was less than 1 mm at image resolutions of 400 and 420 µm/pixel. Because of its simplicity, and because it is based on both the observed behavior of mammographic tissue intensities and on geometry, this method has the potential to become a generic method for locating the nipple on mammograms.

Automated detection of microcalcifications in mammograms is particularly challenging because microcalcifications are small and have low contrast. Typically, an automated system for detection of microcalcifications includes algorithms for segmentation, feature extraction, and classification that perform separation of candidate objects from the background, representation of candidate objects with informative metrics, and decision making, respectively. In Chapter 21, sequential process segmentation has a seminal role and dictates the performance of the entire system. Candidate objects must be delineated appropriately to allow effective feature extraction and classification. This chapter presents algorithms that specialize in segmentation of small, low-contrast objects, and illustrates their application to segmentation of microcalcifications.

Noninvasive assessment of microcirculatory characteristics of tissues using MRI is one of the emerging technologies as discussed in Chapter 22. Dynamic contrast-enhanced (DCE) breast magnetic resonance imaging (MRI), in which the breast is imaged before, during, and after the administration of a contrast agent, enables a truly 3D examination of breast tissues. This functional angiogenic imaging technique provides a noninvasive assessment of microcirculatory characteristics of tissues in addition to traditional anatomical structure information. The use of DCE breast MRI is increasing, and it is recommended as an adjunctive breast screening modality to mammography. Traditional manual interpretation of DCE breast MRI is time-consuming, tedious, and can lead to oversight errors due to the large size of 4D data sets (three spatial dimensions plus time). Manual interpretation is also subject to inter- and intra-observer variability. There is a great need for computer-aided detection and diagnostic systems capable of increasing the efficiency, accuracy, and
consistency of breast MRI interpretation. In this chapter, the underlying principles of DCE breast MRI are reviewed the challenges of registration, segmentation, and classification in the design of CADe/CADx systems for breast MRI discussed, the progress made in this arena to date explored, and future directions for research suggested.

The pre- and postcontrast Gd-DTPA MR images of any body organ hold diagnostic utility in the area of medicine, particularly for breast lesion characterization. The Chapter 23 reviews state-of-the-art tools and techniques for lesion characterization, such as uptake curve estimation (functional segmentation), image subtraction, and velocity thresholding, differential characteristics of lesions such as maximum derivation of image sequence, steep slope and washout, fuzzy clustering, Markov random fields, and interactive deformable models such as live-wire.

Research has shown that 10 to 30% of cases missed by mammography can be detected using breast MRI (BMRI). And while BMRI has increased sensitivity, it suffers from limited specificity. Chapter 24 discusses BMRI, which is more difficult to interpret than mammography because it generates significantly more data; however, there are fewer people qualified to use it for diagnosis because it is not the standard breast imaging modality. Mammographers appear to be the best qualified, and certainly the most likely to read BMRI, but they are accustomed to reading 4–6 images per patient as compared with the 200–400 images per patient that BMRI generates. Also, some mammographers may be uncomfortable interpreting MR images. A user-friendly computerized system for BMRI presentation and lesion classification may help mammographers overcome their objections and anxieties concerning BMRI. Such a system would reduce the time required to read BMRI, making the technique a more practical clinical tool. Research shows that the diagnostic accuracy of mammography is increased when two radiologists view the same mammogram, or when the same radiologist rereads a mammogram. Using such strategies decreases the number of missed cancers, which leads us to the fundamental reason of using CAD systems—that is, to replace the second pair of human eyes with a set of “electronic eyes.” The development of dependable, low-cost CAD systems for breast lesion detection and classification is of great practical interest. In this chapter, examples of CAD systems are shown that were developed to provide computer assistance for humans reading BMRI data and classifying BMRI lesions.

Before looking at a mammogram in detail, a radiologist scans it globally to ensure that it is adequate and of acceptable quality. Adequacy means that all of the relevant breast tissue has been captured on the mammogram. Image quality covers a multitude of attributes like exposure, sharpness, etc. Adequacy and image quality ensure that a subsequent decision on the presence or absence of an abnormality may reasonably be based on the information presented by the mammogram. With computer-aided diagnosis, it is equally important to discard inadequate, poor quality images before they are analyzed further, because such analysis would be futile. The automatic assessment of mammogram adequacy and quality is thus an important quality assurance step in computer-aided diagnosis of mammograms.
Chapter 25 describes how aspects of image adequacy and quality may be assessed automatically by computer using guidelines established by radiologists themselves. Visual inspection in medical care has always been a tedious and costly task that is prone to errors. Because of these errors, computer imaging systems have been designed to assist the human inspection process in the provision of better health care. Chapter 26 presents the analysis of the economic feasibility of any proposed system: costs associated with equipment operation, human inspection, as well as false positives, and false negatives that must be taken into account. Practical mathematical models based on probability theory can be used effectively to assist the decision-maker in the purchase of a computer-assisted imaging system by predicting its operational and financial performance implications. This chapter describes a mathematical model for the economic analysis of a computer-assisted imaging system for the detection of breast cancer.

Breast imaging is currently limited by inadequate sensitivity and specificity. About one in five breast cancers is missed by mammography screening, and when suspicious lesions are found and referred to biopsy, about 4 in 5 biopsies turn out to be benign and were thus arguably unnecessary. Chapter 27 addresses sensitivity, computer-aided detection has come a long way, with multiple commercial products now available and promising results from large clinical studies. On the other hand, specificity remains a major challenge, and to date there are still no commercially viable options due to medicolegal risks, lack of information explaining the computer diagnoses, and difficulties in clinical trial design. This chapter reviews the considerable research to date in computer-aided characterization in breast imaging, describes those current problems, and proposes some possible new approaches that may lead to eventual clinical translation of this important technology.

In Chapter 28, the book is concluded in contemplation of the future of computer aided detection. The future work that needs to be done to make the system more robust is discussed, as well as what it takes to develop a product, stages for FDA approval, and clinical trials. Finally, the chapter projects this research into the next decade.

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