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Abstract. The potential of dual-energy mammography for microcalcification classification was investigated with simulation and phantom studies. Classification of type I/II calcifications was performed using the tissue attenuation ratio as a performance metric. The simulation and phantom studies were carried out using breast phantoms of 50% fibroglandular and 50% adipose tissue composition and thicknesses ranging from 3 to 6 cm. The phantoms included models of microcalcifications ranging in size between 200 and 900 μm . The simulation study was carried out with fixed MGD of 1.5 mGy using various low- and high-kVp spectra, aluminum filtration thicknesses, and exposure distribution ratios to predict an optimized imaging protocol for the phantom study. Attenuation ratio values were calculated for microcalcification signals of different types at two different voltage settings. ROC analysis showed that classification performance as indicated by the area under the ROC curve was always greater than 0.95 for 1.5 mGy deposited mean glandular dose. This study provides encouraging first results in classifying malignant and benign microcalcifications based solely on dual-energy mammography images. © 2019 Society of Photo-Optical Instrumentation Engineers (SPIE) [DOI: 10.1117/1.JMI.6.1.013502]

Keywords: spectral mammography; breast microcalcifications; energy integrated detector; dual-energy exposure acquisition.

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1 Introduction

Mammography is an effective tool for breast cancer detection and diagnosis and has greatly contributed to the decrease in breast cancer mortality observed since 1990, when widespread mammography screening was introduced.¹

Patients with a suspicious mammographic abnormality or a palpable breast lump will typically undergo breast biopsy to determine if the abnormality is benign or malignant. Between 60% and 80% of breast biopsies^{2,3} are performed on benign cases and are unnecessary, causing undue patient anxiety and increased healthcare costs. Ductal carcinoma *in situ*,⁴ which is thought to be an early form of breast cancer, is typically identified in a mammographic image by the presence of microcalcification depositions grouped into clusters. However, not all calcifications are necessarily associated with cancerous neoplasms. A number of features of such a cluster are analyzed, including the number of calcification specks, the lesion's morphological appearance, calcification size, and spatial distribution.^{5,6} However, these features alone cannot be used to accurately distinguish malignant and benign lesions.⁷

Based on chemical composition, two major types of microcalcifications are found in the breast. Type I calcifications consist of calcium oxalate (CO) crystals dihydrate ($\text{CaC}_2\text{O}_4 \cdot 2\text{H}_2\text{O}$), whereas type II deposits are composed predominantly of calcium phosphates, $[\text{Ca}_5(\text{PO}_4)_3(\text{OH})]$, mainly hydroxyapatite (HA). Type I microcalcifications are sometimes found in benign cysts and are not typically associated with carcinoma, whereas type II microcalcifications can be found in both benign and malignant lesions. It is hypothesized that type I microcalcifications are

a product of secretion, whereas type II microcalcifications are the result of cellular degeneration or necrosis.^{8–10} In one study, it was estimated that lesions with solely type 1 calcifications represented 12% of benign breast biopsies performed¹¹ based on visualization of microcalcifications. Therefore, a noninvasive method to accurately predict type I lesions might help in reducing benign breast biopsies.

X-ray phase contrast with grating interferometer¹² and coherent scatter methods¹³ have shown good potential for differentiation between type I and type II microcalcifications based on their x-ray scattering signatures. Although phase contrast and coherent scatter imaging are very promising imaging modalities, they are not currently available for routine clinical use.

Ghammraoui and Glick¹⁴ have recently shown that photon-counting spectral mammography has the potential to be used for the same purpose. Martini et al.¹⁵ explored simulation and phantom studies using a dual-kVp technique with high-kVp exposures (up to 70 kVp) to characterize calcification minerals, based on determination of the calcium/phosphorus mass ratio. However, photon-counting spectral mammography and dual-energy mammography with these high-kVp settings are not widely available in clinical mammography systems.

Dual-energy x-ray techniques have also shown that they could enhance the detectability of calcifications in mammographic examinations.^{16,17} In this study, we investigated the feasibility of discrimination between type I and type II microcalcifications with a conventional mammography system based on dual-energy exposure acquisition. Simulation studies were carried out to predict an optimized imaging protocol for the specific system, by maximizing the classification performance metric—area under the curve (AUC) with respect to mean

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glandular dose (MGD). A comprehensive phantom study was also performed to characterize the accuracy of the proposed method with the specific system. Four phantom configurations were designed to represent various combinations of different breast phantom thicknesses and calcification sizes.

2 Methods

2.1 Classification Method

In dual-energy imaging, different materials in a sample can be distinguished through their differential attenuation coefficients as a function of photon energy. To detect this distinction, two separate x-ray measurements are made with different x-ray spectra using two different tube voltages and filters.¹⁸

An approach used here for classification of microcalcifications relies on two simplifying assumptions. First, the scatter component can be neglected or substantially reduced by assuming collimation with an antiscatter grid. Second, pixel values within the microcalcification region-of-interest S_{calc} and its nearest neighboring pixels S_{bkg} differ only by attenuation of the microcalcification, as shown in Fig. 1. That is, it is assumed that the estimates of the fibroglandular and adipose composition and thickness are similar along the line integral through the microcalcification and the nearby line integral just outside the microcalcification of interest. Therefore, the expected detector signal in a pixel representing the line integral through a microcalcification can be expressed as

$$S_{\text{calc}} = \int_0^\infty \Phi(E) e^{-[\mu_a(E)l_a + \mu_g(E)l_g + \mu_{\text{calc}}(E)l_{\text{calc}}]} \psi(E) Q_i(E) dE, \quad (1)$$

and the expected detector signal for a pixel nearby (Fig. 1) can be expressed as

Fig. 1 Diagram of the mammographic system that was studied.

$$S_{\text{bkg}} = \int_0^\infty \Phi(E) e^{-[\mu_a(E)l_a + \mu_g(E)l_g]} \psi(E) Q_i(E) dE, \quad (2)$$

where $\Phi(E)$ is the x-ray fluence. Here, μ_a , μ_g , and μ_{calc} represent the linear attenuation coefficients of adipose, glandular tissues, and a calcification (HA or CO), respectively; l_a , l_g , and l_{calc} represent the propagation path lengths through adipose tissue, glandular tissue, and calcification, respectively; $\psi(E)$ represents the mean detector gain [e.g., $\psi(E) \propto E$]; and $Q_i(E)$ represents the energy-dependent detector quantum efficiency.

A quantity referred to as the x-ray density of the calcification, D , can be defined as the natural logarithm of $S_{\text{bkg}}/S_{\text{calc}}$,¹⁹ and used to relate the image signals to attenuation of the calcification in a way that is independent of the intensity variation of incident x rays. Therefore, low and high energy densities D_l and D_h can be expressed as

$$D_l = \ln \left(\frac{S_{\text{bkg}}^l}{S_{\text{calc}}^l} \right),$$

$$D_h = \ln \left(\frac{S_{\text{bkg}}^h}{S_{\text{calc}}^h} \right), \quad (3)$$

where S_{bkg}^l and S_{calc}^l represent the image signals from the low-energy spectrum, and S_{bkg}^h and S_{calc}^h represent the corresponding signals from the high-energy spectrum.

Finally, each calcification pixel was classified as being hydroxyapatite or CO based on the score λ defined as the ratio of their attenuation density D_l over D_h :

$$\lambda = D_l/D_h. \quad (4)$$

2.2 Simulation Methods

Numerical simulations were performed using equation a realistic mammography x-ray spectrum, modeling x-ray attenuation through a virtual compressed breast phantom composed of 50% fibroglandular tissue and 50% adipose tissue of 3, 4, 5, and 6 cm thickness. Small calcification of different sizes was added to the breast phantom. The calcifications sizes were randomly selected from a uniform probability density ranging from 200 to 900 μm ²⁰ with weight density of 2.1 g/mm³ to approximate attenuation properties of real breast calcifications.²¹ X-ray spectra were generated for a tungsten target by using the IPED report 78²² and data from Ref. 23. The tube voltage was varied from 26 to 36 kVp, for the low-energy spectrum, and from 38 to 50 kVp, for the high-energy spectrum, with 2 kVp increments. Aluminum filtration with filter thickness ranging from 0.1 to 1 mm with 0.1 mm increment was tested. For each low- and high-kVp setting, x-ray spectra were scaled to produce a fixed MGD of 1.5 mGy split between the low- and high-kVp spectra with different proportions.

An ideal energy integrating detector with a single pixel of a size of $100 \times 100 \mu\text{m}^2$ was modeled. To simulate measured data, Eqs. (1) and (2) were used with mass attenuation coefficients obtained from the PENELOPE code (Fig. 2).²⁴ Noise realizations were generated assuming a Poisson process. Previously published monoenergetic DgN values were used for calculation of the MGD.²⁵

Fig. 2 (a) Linear attenuation coefficients used in the simulation study for adipose and glandular tissues and (b) for CO and hydroxyapatite estimated from their chemical structure by using the PENELOPE code.

2.3 Experimental Settings

2.3.1 Phantom studies

In the experimental part of the study, we used 50%/50% adipose/glandular mass fraction equivalent phantoms of uniform thickness (CIRS, Norfolk, Virginia). All the phantoms had the same dimensions of $10 \times 12.5 \text{ cm}^2$. Four thicknesses of 3, 4, 5, and 6 cm were used in experiments. To simulate microcalcifications, disks of hydroxyapatite and CO, the major components of type I and type II microcalcifications, of thicknesses between 300 and 900 μm were made from powder (commercially available, Sigma-Aldrich) via mechanical pressing. In brief, a specified amount of either hydroxyapatite or CO

was mixed with 1% w/w polyvinyl pyrrolidone (PVP) K30 in a tumbling mixer (W.A. Bachofen, Basel, Switzerland) for 10 min at 50 rpm. The mixture was then granulated to 1:0.2 weight ratio powder to binder mixture, with 3% w/v PVP alcoholic solution. The obtained substance was vacuum-dried at 30°C for 24 h, followed by compression into flat-faced 8-mm diameter disks using a rotary tableting machine (PICCOLA, Riva S.A., Buenos Aires, Argentina). The weight of disks was varied to yield approximately the same density of 1.8 and 2 g/cm^3 , for HA and CO, respectively, and thicknesses of ≈ 300 , 500, and 900 μm , using 20 kN target compression load for each disk. The disks were attached to the x-ray detector prior to imaging as shown in Fig. 3. To reduce scattered

Fig. 3 (a) Illustration showing the mammographic examination system. (b) Experimental benchtop. The image receptor is an amorphous selenium flat panel with $24 \times 30 \text{ cm}^2$ active area and $85 \times 85 \mu\text{m}^2$ pixel size.

radiation in an x-ray beam reaching the detector, the breast phantom was placed close to the x-ray tube as shown in Fig. 3. With the phantom positioned away from the detector, a larger fraction of scattered x-ray photons misses the detector field of view.

2.3.2 Image acquisition

An amorphous selenium direct conversion detector with $24 \times 30 \text{ cm}^2$ active area and $85 \times 85 \mu\text{m}^2$ pixel size was used with a Varian RAD-70SP (Varian Medical Systems, Salt Lake City, Utah) tungsten anode mammographic x-ray tube with 0.3-mm focal spot. The resulting images were normalized by their corresponding open-field images before log transformation. Open-field images were acquired with 2-mm aluminum filtration. The focal spot-to-detector distance was 60 cm. Based on the simulation results, a group of settings [kVp/filtration and MGD (mGy) at low- and high- exposures] was chosen and used for validation.

To estimate the phantom MGD, we first calculated the polychromatic normalized glandular dose coefficients (pDgN) values using monochromatic normalized glandular dose coefficients:²⁵

$$\text{PDgN} = \frac{\sum_{E=E_{\min}}^{E=E_{\max}} \Phi(E) \xi(E) DgN(E)}{\sum_{E=E_{\min}}^{E=E_{\max}} \Phi(E) \xi(E)}, \quad (5)$$

where $\xi(E)$ (units of mR per photons/ mm^2) is the fluence to exposure conversion factor. We then measured the source air kerma using a Radcal Accu-Pro 9096 (Radcal Corporation, Monrovia, California) radiation monitor with a mammography ionization chamber 10X5-6M located 65 cm from the source. The air kerma value for each exposure technique and x-ray filter combination was averaged over five consecutive measurements and shown to have negligible uncertainty. Finally, the experimental x-ray current (in mAs) corresponding to the simulated MGD is then obtained as

$$I = \frac{\text{MGD}}{\text{PDgN} \times R(\text{mR/mAs})}. \quad (6)$$

2.4 Statistical Analysis

A binary classification task with N type I samples and M type II samples was used for analysis. We denote $x_1, \dots, x_N$ to be the λ scores [Eq. (4)] of type I (CO) samples and $y_1, \dots, y_M$ to be the λ scores of type II (hydroxyapatite) samples. Nonparametrically, the AUC can be estimated using Wilcoxon–Mann–Whitney statistics

$$\text{AUC} = \frac{1}{MN} \sum_{i=1}^M \sum_{j=1}^N H(x_i - y_j), \quad (7)$$

where $H(z) = \{1 \text{ if } z > 0; 1/2 \text{ if } z = 0; 0 \text{ if } z < 0\}$. The maximum variance can be estimated as^{26,27}

$$\sigma_{\max}^2 = \frac{\text{AUC}(1 - \text{AUC})}{\min\{M, N\}}. \quad (8)$$

3 Results

3.1 Simulation Studies

As was mentioned in Sec. 2.2, simulations were performed for breast phantoms of different thicknesses with fixed MGD of 1.5 mGy using various low- and high-kVp spectra, aluminum filtration thicknesses, and exposure distribution ratios. The optimal settings were selected by, first, applying the criterion of AUC [Eq. (7)] maximization. In general, the best performing combinations of kVp and exposure distributions were found to occur when using 26 kVp with a MGD of 0.6 mGy for the low-kVp exposure and 50 kVp with an MGD of 0.9 mGy MGD for the high kVp.

The surface plots shown in Fig. 4 indicate that many combinations of filtration thicknesses show similarly good performance for microcalcification classification. In practical experiments, it is always better to keep the heat load to the tube low; therefore, the second criterion of the chosen setting (for experimental validation) for each breast thickness was selected to be the lower filtration thicknesses of the the settings that gave an AUC score within the highest computed AUC [Eq. (7)] score and its deviation [Eq. (8)].

Some insight into how irradiation conditions can affect performance of microcalcification classification can be gained from the plots in Fig. 5. A search for optimal exposure settings involved varying low- and high-kVp values, thickness of Al filter for both modes, and dose distribution between the two. Shown in Figs. 5(a) and 5(b) is the comparison of distributions of the score λ and corresponding AUC for the optimal dose proportion 0.6 mGy/0.9 mGy and one of the tested proportions 0.3 mGy/1.2 mGy for the breast phantom thickness of 3 cm, respectively. Similarly, Figs. 5(c), and 5(d) demonstrate a comparison between distributions λ and resulting AUC for the optimal x-ray tube high voltage of 50 kVp and for one of the tested values of 44 kVp, respectively. Selected optimal irradiation conditions for the experimental study are summarized in Table 1.

Some limitations in the simulation study should be noted. First, we simulated a slightly different pixel size from the one used in the experimental study, which might have had a minor influence on our optimization study. Unfortunately, the simulation study was performed before it was certain what detector would be used for the experimental study. However, the energy-dependent pixel cross-talk and detector quantum efficiency effects were not included in the simulation and therefore the pixel size effect will only have a small statistical influence. Second, nonuniformities of the background, scatter radiation, pixel cross-talk, and quantum efficiency of the detector were not present in this simulation study. We would expect that making the simulation model more realistic would moderately influence the simulation results.

3.2 Experimental Phantom Study Results

Selected settings obtained from the simulations were tested in the phantom study for validation. First, Eq. (6) was used with measured entrance air kerma R (mR/mAs) to convert MGD from the simulation (Table 1) to experimental x-ray tube current I (mAs). The exposure settings that were used for low- and high-kVp modes are listed in Table 1.

Experimental images of the the breast-mimicking phantoms with microcalcification disks of different thickness are shown in

Fig. 4 AUC scores versus aluminum filter thickness for low- and high-kVp exposures for different breast thicknesses using 26 and 50 kVp tungsten spectra for low and high energies, respectively. The exposure level was set to 0.6 and 0.9 mGy for low and high exposure settings, respectively. Scores were computed from 1000 type I and type II simulated samples of thickness ranging between 200 and 900 μm . Relative error bars corresponding to the square root of the maximum variance were always below 5%.

Fig. 6. As can be seen, it is hard to differentiate between the two types based on visual inspection only. As was previously discussed, the first step in the microcalcification classification process is to estimate the x-ray densities D_l and D_h [Eq. (3)] from the low- and high-energy images, using pixels inside the calcification disks and 10 neighboring pixels outside the microcalcification disk under analysis [for S_{bkg} in Eq. (2)].

The top row of Fig. 7 shows scatter plots with the scores λ [Eq. (4)] and the results of the Wilcoxon–Mann–Whitney test on types I and II microcalcifications for the pixels corresponding to the disks (Fig. 7) of varying thicknesses. The bottom row of Fig. 7 shows the score histogram obtained from the same data points as used in the scatter plots, providing an alternative visual interpretation. As was mentioned earlier, data shown in Figs. 6 and 7 were obtained from measurements with 1.5 mGy of deposited MGD. These results were computed using ~ 800 type I pixels and 800 type II pixels inside the disk for each breast thickness. Expectedly, better performance was achieved with thinner phantoms despite the very little difference in type I and type II histograms observed for 4 and 5 cm breast phantoms. Lower λ scores observed in the experimental results, compared to those obtained from the simulation, can be explained by a reduction in quantum

efficiency of the x-ray detector as kVp was increased. Quantum efficiency was assumed to be 100% in the simulation study.

In the ROC curve analysis, the resulting AUC was always above 0.76. Although this data suggest that classification of calcification type is possible with some accuracy, the AUC observed values are still limited since very high AUC values (e.g., >0.98) would be required for the intended purpose of reducing negative biopsies. However, the data shown in Fig. 7 were computed using a single pixel within one microcalcification. It is well known that calcified breast lesions typically present with clusters of microcalcifications²⁸ over several mm in distance. Park et al.²⁹ reported the mean number of microcalcifications within a 2.5 mm² area to be 16.4 in malignant and 16.7 benign lesions, respectively. As suggested by Winston et al.,³⁰ if only CO is present in a calcification cluster, then it is very likely to be associated with benign epithelium. Thus, the goal would be to predict with high likelihood that all calcifications within a cluster are of CO composition, and thus benign. To decrease the variance on the estimates of calcification type thickness and subsequently increase classification accuracy, multiple calcifications in a cluster can be analyzed together.¹⁴ Figure 8 shows AUC curves for varying breast thickness that

(a) Selected configuration for breast thickness of 3 cm: 26 kVp + 0.2 mm Al and 50 kVp + 0.5 mm Al and dose_{low} = 0.6 mGy + dose_{high} = 0.9 mGy

(b) Random configuration for breast thickness of 3 cm: 26 kVp + 0.2 mm Al and 50 kVp + 0.5 mm Al and dose_{low} = 0.3 mGy + dose_{high} = 1.2 mGy

(c) Selected configuration for breast thickness of 6 cm: 26 kVp + 0.2 mm Al and 50 kVp + 0.8 mm Al and dose_{low} = 0.6 mGy + dose_{high} = 0.9 mGy

(d) Random configuration for breast thickness of 6 cm: 26 kVp + 0.2 mm Al and 44 kVp + 0.8 mm Al and dose_{low} = 0.6 mGy + dose_{high} = 0.9 mGy

Fig. 5 First column: scatter plots showing attenuation density D_l and D_h of 200 independent microcalcification pixels simulated with different breast thicknesses and irradiation conditions. Second column: scatter plots showing scores λ calculated using Eq. (4). Third column: distribution of the scores λ .

Table 1 Selected kVp settings, filtration thickness, and dose distribution proportions that gave highest classification performance AUC with the least heat load to the tube.

0.6 mGy for 26 kVp spectra + 0.9 mGy for 50 kVp spectra

Breast thickness	Selected Al filtration thickness for low kVp	Selected Al filtration thickness for high kVp
3 cm	0.2 mm, 11.6 mAs	0.5 mm, 4.3 mAs
4 cm	0.2 mm, 15.0 mAs	0.6 mm, 5.5 mAs
5 cm	0.5 mm, 29.9 mAs	0.5 mm, 5.87 mAs
6 cm	0.2 mm, 22.5 mAs	0.8 mm, 8.3 mAs

Fig. 6 Experimental images at low- and high-kVp exposures of the breast-mimicking phantoms with microcalcification disks of different thicknesses (randomly ordered). The three disks on top of these images correspond to the hydroxyapatite disks whereas the three on the bottom correspond to the CO disks.

Fig. 7 First row: scatter plots showing the scores λ of ~ 800 microcalcifications pixels calculated from data measured of 3, 4, 5, and 6 cm breast phantom thicknesses and microcalcification disks of thicknesses between 300 and 900 μm . Second row: distribution of the scores λ .

Fig. 8 Scatter plots of the scores λ after averaging (obtained by calculating the score λ separately for each calcification and then averaging over five of them selected randomly). Second row: distribution of the scores λ .

4 Conclusions

In this study, we have tested the use of dual-energy mammography for microcalcification classification. Both theoretical and experimental tests were performed. First, computer simulations were conducted to determine optimal irradiation conditions. Then, experimental measurements were performed on a bench-top breast mammography system to validate simulation results. Disks of hydroxyapatite and CO, the two major components of type I and type II microcalcifications, were combined with a 50%/50% of adipose/glandular mass fraction breast equivalent phantom for testing.

Low- and high-energy attenuation ratios were calculated for microcalcifications of different types and breast thickness values. Classification of type I or II calcifications was carried out by using the attenuation ratio as a discrimination criterion. The results were studied using receiver operating characteristic analysis and showed that classification performance achieved by analyzing a single microcalcification was only moderately accurate; however, inclusion of several calcifications in the cluster allowed for a substantial increase in performance, as expressed by the area under the ROC curve.

This approach has a practical justification since calcified lesions of diagnostic importance typically contain more than five microcalcifications distributed within a cluster, where often there are 10 to 20 microcalcifications per cluster. Future work will investigate classification performance in more clinically relevant conditions including scatter radiation, breast tissue nonuniformity, and microcalcifications detection task and will analyze a broad range of breast tissue samples containing clustered microcalcifications. To reduce radiation to the breast, this approach can be used with magnification mammography, where only a small area of the breast is exposed.

Disclosures

No conflicts of interest, financial or otherwise, are declared by the authors.

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