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Quantification of breast density with spectral mammography based on a scanned multi-slit photon-counting detector: A feasibility study

Huanjun Ding and Sabee Molloy

Department of Radiological Sciences, University of California, Irvine, California 92697

Abstract

Purpose—A simple and accurate measurement of breast density is crucial for the understanding of its impact in breast cancer risk models. The feasibility to quantify volumetric breast density with a photon-counting spectral mammography system has been investigated using both computer simulations and physical phantom studies.

Methods—A computer simulation model involved polyenergetic spectra from a tungsten anode x-ray tube and a Si-based photon-counting detector has been evaluated for breast density quantification. The figure-of-merit (FOM), which was defined as the signal-to-noise ratio (SNR) of the dual energy image with respect to the square root of mean glandular dose (MGD), was chosen to optimize the imaging protocols, in terms of tube voltage and splitting energy. A scanning multi-slit photon-counting spectral mammography system has been employed in the experimental study to quantitatively measure breast density using dual energy decomposition with glandular and adipose equivalent phantoms of uniform thickness. Four different phantom studies were designed to evaluate the accuracy of the technique, each of which addressed one specific variable in the phantom configurations, including thickness, density, area and shape. In addition to the standard calibration fitting function used for dual energy decomposition, a modified fitting function has been proposed, which brought the tube voltages used in the imaging tasks as the third variable in dual energy decomposition.

Results—For an average sized breast of 4.5 cm thick, the FOM was maximized with a tube voltage of 46kVp and a splitting energy of 24 keV. To be consistent with the tube voltage used in current clinical screening exam (~ 32 kVp), the optimal splitting energy was proposed to be 22 keV, which offered a FOM greater than 90% of the optimal value. In the experimental investigation, the root-mean-square (RMS) error in breast density quantification for all four phantom studies was estimated to be approximately 1.54% using standard calibration function. The results from the modified fitting function, which integrated the tube voltage as a variable in the calibration, indicated a RMS error of approximately 1.35% for all four studies.

Conclusions—The results of the current study suggest that photon-counting spectral mammography systems may potentially be implemented for an accurate quantification of volumetric breast density, with an RMS error of less than 2%, using the proposed dual energy imaging technique.

Keywords

breast imaging; breast density; mammography; photon counting detector

I. Introduction

Mammographic breast density is quantified as the percentage of the stroma and epithelial tissue, which is usually collectively referred to as fibroglandular tissue, over the whole breast, as the x-ray attenuation coefficient of those tissue is different from that of the fatty tissue present in breast. In 1976, Wolfe first reported the positive association between a qualitative classification of mammographic breast density and breast cancer risk (Wolfe, 1976a, b). Such a relationship has been substantially confirmed by more recent studies (Saftlas and Szklo, 1987; Heine and Malhotra, 2002a, b; Goodwin and Boyd, 1988; Boyd *et al.*, 2007; Boyd *et al.*, 1995; Byrne *et al.*, 1995; Byrne *et al.*, 2001; Harvey and Bovbjerg, 2004; McCormack and Silva, 2006). It has been suggested that women with a mammographic breast density higher than 75% have a four- to sixfold higher risk of developing breast cancer than women with little or no dense tissue (Boyd *et al.*, 2007). Despite its significant relationship with breast cancer development, breast density is perhaps the most undervalued and underexamined risk factor (Byrne, 1997). This is partly due to the relatively poor inter- and intra-observer agreement in qualitative classification (Oza and Boyd, 1993). It has been suggested that qualitative assessments are less reproducible and tend to overestimate the degree of density, in comparison with quantitative classifications (Byng *et al.*, 1994; Warner *et al.*, 1992). The advantage of using a precise assessment of breast density has been suggested by Boyd *et al.*, who have reported that for every 1% increase of mammographic breast density, there is a 2% increase of the relative risk for breast cancer (Boyd *et al.*, 1997). In addition, unlike most other breast cancer risk factors, breast density can be affected by hormonal agents, alcohol usage, diet and many other factors. Studies have suggested that mammographic breast density, and thus the breast cancer risk, can be altered by hormonal therapies (Stomper *et al.*, 1990; Son and Oh, 1999). For example, tamoxifen, a hormonal cancer risk reducing therapy, may decrease the mammographic breast density by 4.3% to 5.3% annually (Chow *et al.*, 2000). Therefore, if a simple and accurate method can be implemented to measure breast density, it is potentially possible to monitor changes in individuals' breast cancer risk over time.

Attempts to accurately measure mammographic breast density can be dated back to 1980s (Boyd *et al.*, 1982). Many of those measurements were obtained by simple segmentation of the areas with different x-ray attenuation properties directly from the 2D projection image of the compressed breast (Byng *et al.*, 1994; Sivaramakrishna *et al.*, 2001; Zwiggelaar and Denton, 2006). However, the accuracy of the area method is limited by the fact that the pixels are segmented into a binary classification of either pure adipose or pure fibroglandular tissue. In addition, the area method ignores the physical 3D character of a real breast. Breasts of different fibroglandular percentages can potentially all yield the same measurement of the areal breast density, due to the lack of the knowledge about the compressed breast thickness.

In order to measure volumetric breast density it is necessary to measure the glandular and adipose tissue thicknesses in each pixel. This is not possible using only a standard mammogram. One possible solution is to use the total estimated compressed breast thickness between the compression and the support plates along with a system calibration to estimate glandular and adipose tissue thicknesses. Several techniques have been proposed to segment the fibroglandular tissue in the column above each pixel, so that a measurement of the volumetric breast density can be acquired from mammograms. Highnam and colleagues use the standard mammogram form (SMF), which is a standardized, quantitative representation of the breast, to estimate the volume of non-fat tissue and breast density (Highnam *et al.*, 2006; Highnam *et al.*, 2007). Kaufhold *et al.* (Kaufhold *et al.*, 2002) and Pawluczyk *et al.* (Pawluczyk *et al.*, 2003) have developed volumetric method to measure breast density using calibrations from breast tissue-equivalent materials of known thicknesses and compositions.

However, these techniques depend critically on knowledge about breast thickness, which is difficult to obtain in practice. This is particularly true in the periphery of the breast where the breast is not in contact with the compression plate. In this region of the breast, a good shape model is necessary to estimate the breast thickness. Uncertainties in thickness estimation, induced by the shape model and the mechanical precision of the compression paddle, can lead to a two- to three- fold increase in measurement error for volumetric breast density (Alonzo-Proulx *et al.*, 2008). The limited accuracy in breast density estimation can reduce the predictive power in breast cancer risk evaluation (Ding *et al.*, 2008; McCormack *et al.*, 2007). Dedicated breast computed tomography (CT) based on cone beam geometry has recently been proposed for breast imaging (Benitez *et al.*, 2009; Chen and Ning, 2002; Lindfors *et al.*, 2008; Shaw *et al.*, 2005; Glick, 2007; Schmidt, 2010). Since CT provides 3D information of the volumetric breast tissue composition, it can potentially be used to quantify the volumetric breast density. However, the potential of using breast CT in screening exams for the general population is still under investigation, as several important questions has to be addressed, such as detection of microcalcification, breast anatomy coverage, finite resolution and data management (Glick, 2007; Schmidt, 2010).

An accurate measurement of the volumetric breast density with current mammography technique can be achieved by quantitative decomposition of the two primary tissues using dual energy imaging. We have recently reported simulation and phantom studies to quantify the volumetric breast density using a dual kVp technique, which uses the standard screening mammogram as the low-energy image and an additional exposure at a higher kVp with modified filtration from a tungsten target x-ray tube (Ducote and Molloy, 2008, 2010a). The results of these studies indicate that dual energy mammography can be used to accurately measure breast density. Although these studies show the feasibility of dual energy imaging in breast density measurement, this approach requires the acquisition of an additional high energy image. This slightly increases the mean glandular dose (MGD) in addition to the potential misregistration artifacts due to patient motion between the acquisitions of low- and high-energy images.

Another solution to this problem is to use energy sensitive detectors, which can sort photons into low- and high-energy bins according to their energy. With the recent developments in detector technology, the advantage of using photon-counting x-ray detectors in medical imaging has been extensively studied (Toyokawa *et al.*, 2011; Takahashi *et al.*, 2005; Shikhaliev and Fritz, 2011; Shikhaliev, 2008; Le and Molloy, 2011b, a; Le *et al.*, 2010; Aslund *et al.*, 2007; Aslund *et al.*, 2010; Bornefalk and Danielsson, 2010; Bornefalk *et al.*, 2007; Bornefalk *et al.*, 2006; Fredenberg *et al.*, 2010a; Ding *et al.*, 2012). Recently, a photon-counting spectral mammography system based on scanning multi-slit Si-strip detectors has been reported (Fredenberg *et al.*, 2010b; Fredenberg *et al.*, 2010a; Bornefalk *et al.*, 2007; Aslund *et al.*, 2007; Bornefalk *et al.*, 2006), which has the potential to accurately measure breast density with a standard screening mammogram without any additional exposures. Traditionally, the application of Si in x-ray detectors has been limited due to its low atomic number ($Z=14$). However, the reported system is designed in edge-on geometry, where the Si wafers are placed with their long axis parallel to the x-ray beam direction, thereby providing a long attenuation path with high quantum efficiency for the full energy spectrum. Dual-energy data acquisitions can be completed simultaneously with a single exposure and are realized by means of multiple energy thresholds. The energy-resolving capability not only avoids any potential spectra overlap in dual-energy decomposition, but also eliminates the motion artifacts, resulting from patient movement during the delay time between the two exposures in the dual kVp technique. Furthermore, the electronic readout noise can be effectively eliminated by proper selection of the background threshold, which dramatically improves detection efficiency, especially for low-dose applications. Fredenberg *et al.* suggest the desirability of a six-fold increase in detectability for dense breast with high

anatomical noise (Fredenberg *et al.*, 2010a). In addition, the scanning multi-slit technique also helps to eliminate scattered radiation, which remains a major limitation for charge-integrating flat panel detectors that are widely used in clinical mammography systems.

In the present study, we investigate the feasibility of quantification of volumetric breast density with the spectral mammography system based on a scanning multi-slit Si strip photon-counting detector. Simulation studies were carried out to predict the optimized the imaging protocol for the specific system, by maximizing the dual energy SNR with respect to mean glandular dose (MGD). A comprehensive phantom study was also performed to characterize the accuracy in breast density measurement with the specific system. Four phantom configurations were designed to represent the various combinations of different thicknesses, densities, sizes and shapes. Errors in the breast density and thickness measurements were reported for each configuration.

II. Methods

II.A. Analytic simulation model

A previously reported analytical model was modified for the breast density analysis with mammography systems (Ding *et al.*, 2012; Ducote and Molloy, 2008). The simulation traces the emission of photons from the x-ray source, their attenuation through the patient and subsequent absorption in the detector. From this ray tracing, the x-ray attenuation coefficients of the low- and high-energy bins for each material in the study were calculated as were the recorded detector signals and their uncertainties due to statistical x-ray noise. These quantities were used to further calculate quantities relevant to dual energy imaging, namely the dual energy signal and uncertainty for each basis material (i.e. fibroglandular and adipose tissues) image.

Polyenergetic x-ray beams were simulated for a tungsten anode x-ray tube, with tube voltage varying from 20 to 150 kVp in intervals of 1 kVp. Spectra were provided by the TASMIP code (Boone and Seibert, 1997). The aluminum pre-filtration was set at 0.75 mm, which agrees with the equivalent pre-filtration for the experimental setup.

The breast was modeled as a mixture of the adipose and mammary gland tissues with a breast density of 30%, which is close to the most recent estimates of clinical breast density (Nelson *et al.*, 2008). Various sample thicknesses were used, including 2.0, 3.1, 4.5, 6.0, 7.5, and 8.8 cm, which cover the clinical range for compressed breasts.

The simulated detector was a Si-based photon counting detector. The detector response function was assumed to be ideal. The quantum detection efficiency (QDE) of the detector was estimated from the x-ray attenuation property of a 3.6 mm thick Si crystal, which is consistent with the effective thickness of the Si strip detector used in the experimental studies. The first energy threshold was determined by the noise floor of the detector, which is set at 8.7 keV. The second threshold, which we used as the splitting energy that sorts the photons into the low- and high-energy bins, was tested in range of 10 ~ 150 keV in increments of 1 keV for each tube voltage used in the simulation. No additive electronic noise was included in the simulation, due to the nature of photon-counting detectors. Effects from x-ray scatter were not included in the simulation.

For each imaging protocol, i.e. the combination of tube voltage and splitting energy, the dual energy signal-to-noise ratio (SNR) was calculated. The simulated SNR was determined by the uncertainty in the thickness measurement of the dual energy decomposition image of a given type of tissue. Since adipose tissue accounts for the largest fraction of breast mass, the standard deviation (σ_{tA}) of the adipose image derived from dual energy decomposition was

used as the quantitative metric for the optimization. The analytical derivation of σ_{t_A} has been previously reported (Ducote and Molloy, 2008) and can be written as:

$$\sigma_{t_A}^2 = \frac{\frac{(\overline{\mu}_G^H)^2}{SNR_{S_L}^2} + \frac{(\overline{\mu}_G^L)^2}{SNR_{S_H}^2}}{(\mu_A^L \mu_G^H - \mu_A^H \mu_G^L)^2} \quad \text{Eq. 1}$$

where $\overline{\mu}_i^j$ is the mean attenuation coefficient, with the subscript i referring to either fibroglandular (G) or adipose (A) tissues, and the superscript j referring to either the low- (L) or high- (H) energy bins, respectively. $SNR_{S_i}^2$ is the squared SNR with the subscript i referring to the low- (L) or high- (H) energy detector signal.

Mean glandular dose (MGD) was taken as the measurement of radiation risk and was calculated using previously reported data generated from the Monte Carlo simulations (Boone, 1999, 2002). Dose data were available for breast thickness of 2 to 10 cm and energies of 5 to 150 keV.

Finally, a figure-of-merit (FOM) was calculated to optimize the dual energy SNR with respect to patient dose, and was defined as:

$$FOM = \frac{SNR_{t_A}}{\sqrt{MGD}} \quad \text{Eq. 2}$$

This definition permits an easy comparison of the image qualities of the different configurations. The optimal image protocols, in terms of the combination of the tube voltage and splitting energy, were determined by maximizing the FOM for breast with different thicknesses.

II.B. Photon-counting spectral mammography system

The system consists of a photon-counting detector based on silicon strip detectors and pulse-counting application specific integrated circuits (ASICs) in a scanned multi-slit geometry. A tungsten-anode x-ray tube, an Al-filter, a pre- and a post-collimator and the detector unit are mounted on a common arm, which can rotate around the center of the source, so that the collimators and the photon counting detector can scan relative to the compressed breast. A sketch of the spectral mammography system is shown in Fig. 1. Within the detector unit, the silicon strip detectors are placed in an edge-on geometry, where the long-axis is placed in the x-ray beam direction, providing approximately 3.6 mm of effective thickness, and thereby offering a high quantum efficiency. The 500 μm thick wafers are configured with p-doped strips with a pitch size of 50 μm , forming linear arrays of fully depleted channels. Scatter shields are used between the detector modules to eliminate detector to detector cross-talk (Fredenberg *et al.*, 2010a). An anti-coincidence logic is implemented in the ASICs, so that double counting induced by charge sharing events can be eliminated, which improves the detective quantum efficiency (DQE). A detailed description of the system has previously been reported (Fredenberg *et al.*, 2010b).

II.C. Phantom composition and geometry

In the phantom study, glandular and adipose equivalent phantoms of uniform thickness (CIRS, Norfolk, VA) were used for dual energy calibration and measurements. All phantoms have the same dimension of $10.0 \times 12.5 \text{ cm}^2$ in size. Three thicknesses (0.5, 1.0, and 2.0 cm) were available. The maximum possible thickness for each phantom material

was 8.5 cm. The known breast densities were determined by the thickness percentages of the glandular phantom. The change in breast density was achieved by varying the combination of glandular and adipose phantoms.

II.C.1 Calibration—The proposed dual energy imaging technique for breast density measurement requires a careful calibration process to determine the system parameters for tissue decomposition. The calibration points were selected to cover the full range of clinically relevant breast thicknesses and densities. As listed in Table I, 15 calibration points were used, which include glandular phantom up to 8.5 cm in thickness, adipose phantom up to 8.5 cm in thickness and an equal combination of the two up to 8.0 cm in thickness. Such selection provided three possible breast densities (0%, 50% and 100%). The 15-point calibration was carried out individually for each of the four tube voltages used in the phantom study, yielding a total of 60 calibration points. In addition, open field images at each tube voltage were also acquired during the calibration.

II.C.2 Phantom study—After calibration, four phantom studies were designed to evaluate the performance of the photon-counting spectral mammography system in measuring breast density. Each study focused on one variable of the breast, including thickness, density, area and shape. The first study investigated the accuracy of breast density quantification for phantoms of different thicknesses. 14 data points were selected in this study. The total thickness of the phantoms varied from 2.0 to 8.5 cm in 0.5 cm steps, while the known breast densities ranged from 22% to 40%. The second study fixed the phantom's total thickness at 4.0 cm, which is approximately the average thickness of the compressed breast from clinical data. (Boone *et al.*, 2005) However, the breast densities of the 9 data points were changed from 0% to 100% in increments of 12.5%. The third study was designed to image phantoms of fixed thickness (4.0 cm) but different areal sizes (62.5, 125.0 and 250.0 cm²). Three representative breast densities (25%, 50%, and 75%) were selected in this study. Finally, in the fourth study, phantoms were constructed to form steps on one dimension to more closely mimic the shape of a female breast. Thus, the five data point investigated in this study consists of majority area that has a uniform thickness and a sharp taper at the periphery. The maximal thicknesses were 3.0 ~ 7.0 cm in increments of 1.0 cm, and the density was fixed at 50%. The specific combination of the glandular and adipose phantoms and the corresponding known breast densities for the four studies are listed in Tables III to VI.

II.D. Image acquisition and processing

During image acquisition, the tube voltage and the splitting energy were varied depending on the total thickness of the phantoms. The imaging parameters are shown in the “Experiment” section in Table II. The low-energy threshold was set at 8.7 keV to ensure that electronic noise can be effectively eliminated from the image. Phantoms were imaged with the compression paddle in place. The equivalent filtration was approximately 0.75 mm of Al. During data acquisition, all photons whose energies are above the noise floor were recorded in the total image. At the same time, photons whose energies are higher than the splitting energy were recorded in the high-energy image. Subsequently, the low-energy image was obtained by subtracting the high-energy image from the total image.

All images were processed with an open source image processing software package. (Sheffield, 2007) Both the calibration and the phantom study images were normalized by the open field images at the corresponding tube voltages. Attenuation information was obtained using log transformed image. The low- and high-energy signals were measured within regions of interest (ROI), which is defined using the following steps: First, a small sample ROI of 4.5 cm² centered at the center-of-mass of a phantom was selected. The mean and the standard deviation within the ROI were measured. Then, a threshold was determined by

subtracting three standard deviations from the mean, and was used to select the pixels in the measurement ROI. The final signals were determined by the mean values within the measurement ROI. Such procedure minimizes the uncertainties from the edge of the phantom. However, it can only be used for images with a uniform phantom thickness. In the fourth phantom study, user-defined thresholds were used to draw the ROIs, so that the entire phantom can be covered. In either case, the measurement ROIs were determined using high energy images, and the same ROIs were used on the low-energy images for signal measurement without modification.

II.E. Dual energy decomposition

For breast density evaluation, the thickness of the fibroglandular and adipose tissues (t_G and t_A) can be used as two basis materials for the dual energy decomposition (Ducote and Molloy, 2008). The low- and high-energy signals of each pixel (S_L and S_H) can be written as functions of the fibroglandular and adipose tissue thicknesses (Ducote and Molloy, 2008; Alvarez and Macovski, 1976):

$$\begin{pmatrix} \mu_G^L & \mu_A^L \\ \mu_G^H & \mu_A^H \end{pmatrix} \begin{pmatrix} t_G \\ t_A \end{pmatrix} = \begin{pmatrix} S_L \\ S_H \end{pmatrix} \quad \text{Eq. 3}$$

where μ_G^i and μ_A^i are the linear attenuation coefficients of fibroglandular and adipose tissues, with i denoting for either low- (L) or high- (H) energy bins, respectively. The thickness of the two primary tissues in the column above each pixel can then be derived by linear numerical matrix inversion. And the mammographic breast density percentage (D) can be determined as:

$$D = \frac{\sum t_G}{\sum(t_G + t_A)} \times 100 \quad \text{Eq. 4}$$

where $\sum t_G$ and $\sum(t_G + t_A)$ denote for the total thickness of the fibroglandular tissue and the whole breast, respectively.

Although the exact analytical solutions for Eq. 3 are not available, the unknown coefficients can be determined from a set of calibration data point with known thicknesses of glandular and adipose phantoms, using a least-squares curve fitting procedure. The method has been widely used in a practical system for dual energy decomposition (Alvarez and Macovski, 1976). A proper general fitting function with undetermined system parameters can be used to recover material thickness values (t_i) from the measured dual energy log signals (S_L and S_H). Due to the presence of non-linear effects, a non-linear rational fitting function, which was suggested to have high fitting accuracy, was chosen in this study for dual energy calibration (Cardinal and Fenster, 1990):

$$t_i = \frac{a_0 + a_1 S_L + a_2 S_H + a_3 S_L^2 + a_4 S_L S_H + a_5 S_H^2 + a_6 S_L^3 + a_7 S_H^3}{1 + b_1 S_L + b_2 S_H + b_3 S_L^2 + b_4 S_H^2} \quad \text{Eq. 5}$$

Higher order terms were introduced in Eq. 5 to improve the fitting accuracy and minimize the uncertainties induced by non-linear artifacts of the detector. The cross terms of the 3rd orders were removed to reduce the number of fitting parameters.

During the calibration process, the known thickness values, t_p for either glandular or adipose phantom, and the corresponding dual energy attenuation measurement S_L and S_H were substituted into Eq. 5. Subsequently, the system calibration parameters ($a_0, a_1 \dots$) for each

material were determined separately from a non-linear least-squares minimization algorithm (Levenberg, 1944). In the following decomposition process, the two sets of parameters were used to estimate the unknown thickness values of the corresponding phantoms, with the measured dual energy signals.

In the phantom study, multiple tube voltages were used, depending on the total thickness of the phantoms. Therefore, the calibration based on Eq. 5 has to be carried out for each tube voltage separately. A total of 60 calibration points with phantom configurations listed in Table I was used in this procedure. For each material, four sets of system calibration parameters were obtained from the least-squares fitting for tube voltage of 29, 32, 35 and 38 kVp, respectively. In the phantom studies, the corresponding parameter set was selected according to the tube voltage used for a given data point.

Since tube voltage turns out to be an additional variable in the calibration procedure, we used a modified fitting function, which include the alternative tube voltage (V) as the third variable:

$$t_i = \frac{a_0 + a_1 S_L + a_2 S_H + a_3 V + a_4 S_L^2 + a_5 S_L S_H + a_6 S_H^2 + a_7 S_L V + a_8 S_H V + a_9 V^2 + a_{10} S_L^3 + a_{11} S_H^3 + a_{12} V^3}{1 + b_1 S_L + b_2 S_H + b_3 V + b_4 S_L^2 + b_5 S_H^2 + b_6 V^2} \quad \text{Eq. 6}$$

Similar calibration procedures can be used for Eq. 6 to determine the 19 system calibration parameters. However, since the tube voltage has been included in the fitting, only one set of parameters is needed for each material in the dual energy decomposition process. A selection of 32 out of the total 60 calibration data points were used for the curve fitting. Both Eq. 5 and 6 (referred to as fixed kVp and alternative kVp fitting, respectively, in the following text) were used to evaluate the accuracy of breast density measurement with the photon-counting spectral mammography system. The root-mean-square (RMS) errors in the thickness and density measurement using both methods were compared for the four phantom studies.

III. Results

III.A. Simulation results

The 2D contour plot of the simulated FOM as a function of the tube voltage and the splitting energy for the investigated Si-based (a) and an ideal (b) photon-counting detector are presented in Fig. 2. The simulation was carried out for a 4.5 cm thick breast with breast density of 30%. In Fig. 2(a), the QDE of the photon counting detector was estimated from the x-ray attenuation property of a Si crystal with the known specification of the investigated spectral mammography system, while in Fig. 2(b), the QDE was simply set to one for an ideal photon-counting detector which stops all incident x-ray photons. The simulated FOM values in both plots were shown in a contour plot and normalized to the maximum values obtained for an ideal detector. The optimal imaging protocol, which leads to the highest FOM, for Si-based photon-counting detector can be found at a tube voltage of 46 kVp with a splitting energy at 24 keV. Accordingly, the optimal imaging protocol for an ideal photon-counting detector is at a tube voltage of 66 kVp with a splitting energy at 27 keV. The lower tube voltage required by the Si-based detector can be attributed to the smaller stopping power due to limited detector thickness. Detailed analysis also suggests that under the optimal imaging conditions, in terms of the tube voltage and the splitting energy, the simulated FOM of the Si-based detector is about 80% of that of an ideal detector.

A more detailed analysis of the simulated FOM for the investigated spectral mammography system is shown in Fig. 3, where the FOM is plotted as a function of the splitting energy for

certain tube voltages that were more closely related to clinical applications. The simulation was also carried out for 4.5 cm breast with breast density of 30%. Here, the simulated FOM values were normalized with respect to the maximum values found at the splitting energy of 24 keV for the 46 kVp tube voltage curve. It can be seen that the simulated FOM values depend strongly on the selection of the splitting energy for all tube voltages. The FOM stays above 90% of the peak value for a given tube voltage, if the splitting energy is chosen within an approximately 5 keV window around the optimal values. Beyond that, it drops fairly fast. Another observation is that the peak values of the FOM increases as the tube voltage goes up. It is thus suggested that high tube voltage may be preferred for the investigated photon-counting spectral mammography system, in the aspect of improving the accuracy of breast density quantification. However, the simulated FOM started to drop when the tube voltage went beyond 46 kVp, due to the dose penalty and the reduced contrast of the fibroglandular and the adipose tissues at high energies.

The FOM simulations were performed for breast of different thicknesses with a fixed breast density at 30%. The results were similar to what is shown in Fig. 2 for the 4.5 cm breast. The optimal imaging protocols, in terms of the tube voltage and the splitting energy, are summarized in Table II for various thickness values. The imaging protocols used in the phantom studies are also listed, along with the simulated FOM expected with the corresponding imaging protocols. All FOM values were normalized to the optimal values at the corresponding thickness. Finally, a list of the proposed imaging protocols for the investigated photon-counting spectral mammography system was provided, which consists of tube voltages that are commonly used in the current clinical application. The optimal splitting energy is presented here for each of the tube voltages, along with the corresponding FOM values from the simulation studies for various breast thicknesses. Thus, the imaging protocol summarized in the last section of Table II serves as the guideline for better quantification of breast density with the investigated system. In spite of the fact that the clinically relevant tube voltages are much less than the optimal values suggested by the simulation for the corresponding breast thickness, they can still be used for dual energy imaging with a careful selection of the splitting energy. The expected FOM in this case can be higher than 90% of the optimal values.

III.B. experimental phantom study results

Eq. 5 was first used to fit the calibration data for each material at each tube voltage separately. The fitting errors in thickness and density from all 60 calibration data points are shown in Fig. 4(a) and (b), respectively. The errors were derived from the difference between the know values and the fitted values calculated with Eq. 5. Therefore, it indicates the accuracy of the fitting function over the full calibration data set. The RMS errors in the thickness estimation of the glandular and adipose phantoms were approximately the same (0.08 mm). And the RMS error in density estimation was derived to be 0.19%.

The dual-energy decomposition images of a phantom configuration investigated in the fourth phantom study are shown in Fig. 5. The glandular and adipose phantoms were constructed into a step wedge, which comprised of 1 cm adipose phantom at the bottom, 1 cm glandular phantom in the middle, and a combination of two 0.5 cm adipose and glandular phantoms on the top. The total image, which is the sum of the low- and high-energy images, is shown in Fig. 5(a) with a description of the phantom configuration. Dual-energy decomposition images of the glandular and adipose phantoms derived from Eq. 5 are shown in Fig. 5(c) and (d), respectively. A good segmentation of the two kinds of phantoms can be clearly observed from the step regions. A total thickness image is also shown in Fig. 5(b), where the color scale represents the phantom thickness estimated by the proposed dual-energy technique. There is a good agreement between the measured thickness and the known values.

The total thickness and breast density measurements of the four phantom studies are summarized in Table III ~ VI, along with the known values of the phantom configurations and the tube voltage used for imaging. The results of dual energy decomposition using Eq. 5 are shown in the middle section of each table, referred to as the fixed kVp fitting. In this case, calibrations were carried out separately for each of the four tube voltages used in the phantom studies. The measured thickness of each phantom configuration was compared to the known value in the first three studies. For the fourth study with a step configuration, only the maximum thickness (step 3) was used for comparison. The RMS errors in thickness estimation using fixed kVp fitting were 0.32, 0.23, 0.71 and 0.50 mm for the four phantom studies, respectively. The measured breast densities were derived from Eq. 4 using thickness of the glandular and adipose phantoms estimated from Eq. 5. The RMS errors in density estimation using fixed kVp fitting were 1.69%, 0.91%, 1.75% and 1.58% for the four phantom studies, respectively. The largest single error in density estimation was 3.44% and was part of the third study. The measured values of all four phantom studies as a function of the known values for the thickness (a) and the breast density (b) are shown in Fig. 6. Linear regressions were performed for the thickness and density estimations, and are shown as the straight lines in the figure. In both cases, a nice linear correlation can be observed with a R^2 higher than 0.99. The slope and the intercept of the linear fitting for thickness estimation were 1.00 and -0.03 , respectively, and those values for density estimation were 0.99 and 1.56, respectively. The RMS error in density estimation using Eq. 5 for all four phantom studies was determined to be approximately 1.54%.

The thickness and density quantification using Eq. 6, where alternative tube voltages were introduced as the third variable in the fitting function, are also summarized in the last section of Table III ~ VI. In this approach, tube voltages used in the exposure for phantoms with various thicknesses were employed in dual energy decomposition, and only one set of fitting parameters was obtained from the calibration to estimate the thickness of each material. A similar error analysis was conducted as discussed in the previous paragraph. The RMS errors in thickness estimation using alternative kVp fitting were 0.50, 0.61, 1.04 and 0.54 for the four phantom studies, respectively. The RMS errors in density estimation were 1.30%, 0.95%, 1.80% and 1.18% for the four studies, respectively. The largest single error in density estimation was 3.56% and was also found in the third study with largest phantom area. The linear correlation of the measured values with respect to the known values of all four studies is presented in Fig. 7 for the thickness (a) and the breast density (b) estimations derived from Eq. 6. The slope and the intercept of the linear fitting for thickness estimation were 1.00 and -0.06 , respectively, and those values for density estimation were 0.99 and 1.32, respectively. Introducing the tube voltage as the additional fitting variable in the dual energy calibration (Eq. 6) led to a RMS error of approximately 1.35% in breast density estimation for all four studies.

IV. Discussions

The estimation of the volumetric breast density requires measurements of two independent variables (thickness and density). Most of the current approaches derive the breast density based on an assumption of the thickness that is generated from the compression paddle thickness and a breast shape model for the periphery of the breast (Highnam *et al.*, 2006; Pawluczyk *et al.*, 2003; Kaufhold *et al.*, 2002; Highnam *et al.*, 2007). However, it is very difficult to obtain the knowledge of breast thickness above each pixel that is covered by the compressed breast due to various reasons (Ducote and Molloy, 2010a). The accuracy of the volumetric breast density measurement is thus greatly limited. The proposed spectral mammography technique solves this problem by directly measuring the thickness and density through dual energy decomposition. The results from the phantom studies indicate that breast density can be accurately measured by photon-counting spectral mammography

with a single exposure. Although the optimal tube voltages suggested by the simulation model are generally higher than the standard values for screening mammography, the simulation results also suggest that the accuracy of breast density quantification can still be reasonably good at the reduced tube voltages, if the splitting energies can be properly selected. In this context, the proposed imaging parameters for various breast thicknesses in Table II provide a guideline for breast imaging using the investigated photon-counting spectral mammography system. The combination of the energy sensitive photon-counting detector and the multi-slit geometry make this system nearly ideal for dual energy material decomposition. Breast density measurement is one of many potential applications of spectral mammography. The development of an accurate volumetric breast density measurement technique can potentially have a high impact in the assessment of breast cancer risk.

Recent progresses in dedicated breast CT have shown promising potential for 3D breast imaging with good contrast resolution at dose levels comparable to a standard two view mammography screening (Glick, 2007; Shaw *et al.*, 2005; Lindfors *et al.*, 2008; Ning *et al.*, 2010). However, volumetric breast density measurement using breast CT data requires manual or semi-automatic image segmentation algorithm to distinguish between glandular and adipose tissues (Benitez *et al.*, 2009). Therefore, intra- and inter-observer variations cannot be completely eliminated. On the other hand, breast density measurement with the proposed spectral mammography technique is based on physical principles and does not require tissue segmentation. Dual energy breast CT can potentially be used for more reliable breast density quantification. However, it will be challenging to minimize the dose level in this case. More importantly, despite the substantial progress in the field of breast CT, the implementation of current breast CT technique in the clinical environment requires further studies. More sophisticated gantry designs have to be developed to image the entire breast including the chest wall and axillary tail. Improved image visualization and automatic detection algorithms are also necessary. On the other hand, the proposed spectral mammography technique can be readily implemented in current clinical applications, providing important information, such as volumetric breast density, with the standard screening mammography images.

For the proposed dual energy decomposition technique, it is crucial to perform a careful calibration that covers the full range of expected values for all imaging parameters, including thickness, density and tube voltage. The lack of enough calibration points or the selection of an improper imaging configuration may limit the accuracy in breast density quantification. In addition, the selection of the fitting function used in the least-squares curve fitting also plays an important role that determines the errors in dual energy decomposition. A fitting function, employed up to the 2nd order terms, has been successfully used for breast density quantifications for a mammography system based on a charge-integrating flat panel detector (Ducote and Molloy, 2010a). Higher order terms were introduced in Eq. 5 to accommodate the non-linear effects observed with the investigated photon-counting mammography system. A similar approach has been suggested by a previous report to improve the accuracy in dual energy decomposition (Cardinal and Fenster, 1990). Although it is possible to include all the 3rd order terms in Eq. 5, it will require additional calibration points and more complicated curve fitting procedures. However, the improvement in accuracy is negligible. The fitting errors in the calibration data set were less than 0.1 mm in thickness and 0.2% in density estimation. The small errors in thickness and density quantifications suggest the effectiveness of Eq. 5 in dual energy imaging (Ducote and Molloy, 2010a).

However, Eq. 5 does not contain information about the tube voltage used for dual energy imaging. Therefore, the calibration using Eq. 5 requires a large amount of data points and leads to multiple sets of system parameters which are needed in the dual energy

decomposition according to the tube voltages involved in the imaging tasks. The effort to employ the tube voltage as the third variable in the fitting function, as suggested in Eq. 6, significantly simplified the calibration process. In this study, only 32 data points were used for the calibration procedure based on Eq. 6, while a total of 60 points were required for the use of Eq. 5. Subsequently, a unique set of system parameters was obtained for each material, which can be applied for dual energy decomposition with the knowledge of the corresponding tube voltages used for the imaging tasks. Therefore, using Eq. 6 in dual energy calibration removes the limitation for tube voltage selection in imaging. One can freely select the tube voltages, even for the values that are not included in the initial calibration. In all four phantom studies reported here, the RMS errors in the density estimations derived from the alternative kVp fitting (Eq. 6) were in good agreement with that from Eq. 5. The results indicate that the accuracy of the fixed kVp fitting is slightly better than that of the alternative kVp fitting for phantoms with fixed thickness, thus unique tube voltage (study 2 and 3). However, the alternative kVp fitting performs better than the fixed kVp fitting in studies 1 and 4, where significant changes in the phantom thickness requires the usage of a wide range of tube voltages. Therefore, we suggest that Eq. 6 may be used in place of Eq. 5 for quantification of breast density in tasks where tube voltage varies significantly, which is more relevant to the clinical situations.

In flat panel based digital mammography systems, scatter radiation remains a major limitation. Anti-scatter grids have been widely used to address this issue, however, it is a fairly inefficient approach. Scatter correction algorithm has also been proposed (Ducote and Molloy, 2010b). In a previous study, the error in breast density estimation was reduced from approximately 5.04% to 2.87% after scatter correction (Ducote and Molloy, 2010b). Although scatter correction works well for uniform thickness phantoms, the effectiveness is significantly reduced for more complicated shapes. As a result, the errors in density estimation increase approximately eight times higher when a step phantom configuration, as described in the fourth phantom study, is investigated (Ducote and Molloy, 2010b). In the current study, the employment of the scanning multi-slit detector geometry minimizes the detection of scatter radiation. The scatter to primary ratio (SPR) for this geometry has been investigated for different phantom thicknesses at various tube voltages (Aslund *et al.*, 2006). The SPRs were measured below 6% for phantom thickness ranged from 3 to 7 cm. Therefore, the effect of scatter radiation on the current breast density measurement is expected to be minimal. The results from the phantom studies corroborate the above assumption. In the fourth study, where the affect of scatter radiation is expected to be the most significant due to the irregular shape of the phantoms, the errors in density estimation were comparable to those from other uniform thickness phantoms. This is an indication of the absence of scatter artifacts in the investigated system. On the other hand, the highest error in density estimation for this study was from the phantoms with large area. It is expected that the observed errors in phantom study can be, at least, partially attributed to the imperfect detector flat field correction. Errors induced by the imperfect flat field correction have been reported in many studies based on photon-counting detectors (Wang *et al.*, 2011; Shikhaliev and Fritz, 2011; Ding *et al.*, 2012). Improvement in the flat field calibration of the photon-counting system may further increase the accuracy of breast density quantification.

In conclusion, the results of the current study suggest that photon-counting spectral mammography systems can provide an accurate quantification of the volumetric breast density using the proposed dual energy decomposition technique. Optimal imaging parameters for the investigated spectral mammography system have been proposed for various thicknesses of the compressed breast. The phantoms studies, which were designed to test the accuracy of dual energy decomposition for various thicknesses, densities, areas and shapes of the phantoms, indicate that the photon-counting spectral mammography can be

used to measure breast density with an RMS error of less than 2%. Furthermore, a calibration fitting function that includes the information about the tube voltage used in the imaging task has been evaluated. This approach increases the freedom for tube voltage selection in clinical imaging.

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Fig. 1.
A sketch of the scanned multi-slit photon-counting spectral mammography system based on Si-strip detectors

Fig. 2. 2D contour plot of the simulated FOM as a function of the tube voltage and the splitting energy for the investigated (a) and an ideal (b) photon-counting detector. The DQE was determined by the physical dimensions of the Si strip detector used in the investigated spectral mammography system in (a), and was set to one for ideal detector in (b).

Fig. 3.
The simulated FOM as a function of the splitting energy for various tube voltages for a 4.5 cm thick breast.

Fig. 4. Fitting errors in thickness (a) and density (b) from all 60 calibration data points from dual energy decomposition using Eq. 5.

Fig. 5. An illustration of dual-energy decomposition for a step wedge phantom configuration: (a) total image; (b) total phantom height measured with dual-energy imaging technique; (c) glandular and (d) adipose phantom height images. The color scale shows the phantom thickness in mm for (b) to (d).

Fig. 6.

The results of thickness (a) and density (b) measurements for all four phantom studies using fixed kVp fitting based on Eq. 5 in the calibration procedure. The measured (M) and known (K) densities were related by $M = 0.99 K + 1.56$.

Fig. 7.

The results of thickness (a) and density (b) measurements for all four phantom studies using alternative kVp fitting based on Eq. 6 in the calibration procedure. The measured (M) and known (K) densities were related by $M = 0.99 K + 1.32$.

Table I

Thickness and density of the phantom combinations used in calibration for each of the four tube voltages.

Calibration points	Thickness (cm)	Density (%)
1	1.0	100
2	2.0	100
3	4.0	100
4	6.0	100
5	8.5	100
6	1.0	0
7	2.0	0
8	4.0	0
9	6.0	0
10	8.5	0
11	3.0	50
12	4.0	50
13	5.0	50
14	7.0	50
15	8.0	50

Table II

Simulated FOM values for the optimal, experimental and the proposed imaging techniques. FOM values were normalized with respect to the optimal configurations for each breast thickness.

Thickness (cm)	Optimal			Experiment			Proposed		
	Tube Voltage (kVp)	E _{split} (keV)	FOM	Tube Voltage (kVp)	E _{split} (keV)	FOM	Tube Voltage (kVp)	E _{split} (keV)	FOM
2.0	41	21	1	29	18.5	0.926	29	19	0.926
3.1	42	22	1	32	19.9	0.935	32	21	0.938
4.5	46	24	1	32	19.9	0.863	32	22	0.907
6	48	25	1	35	21.0	0.852	35	24	0.923
7.5	53	27	1	38	21.6	0.851	38	25	0.943
8.8	55	28	1	38	21.6	0.786	38	25	0.922

Table III

Errors in thickness and density estimations for the first phantom study. The results from dual energy decomposition based on Eq. 5 and 6 are listed as fixed kVp fitting and alternative kVp fitting, respectively. The RMS errors in each case are summarized in the last row.

Thickness (cm)	Known values			Fixed kVp fitting			Alternative kVp fitting		
	Density (%)	Tube Voltage (kVp)	Thickness (cm)	ΔT (cm)	Density (%)	ΔD (%)	Thickness (cm)	ΔT (cm)	Density (%)
2.0	25.00	29	1.97	-0.03	28.07	3.07	2.06	0.06	26.35
2.5	40.00	29	2.46	-0.04	42.03	2.03	2.52	0.02	43.16
3.0	33.33	32	2.98	-0.02	35.32	1.98	2.96	-0.04	33.79
3.5	28.57	32	3.47	-0.03	30.06	1.49	3.43	-0.07	29.64
4.0	25.00	32	3.97	-0.03	26.28	1.28	3.92	-0.08	26.40
4.5	22.22	32	4.46	-0.04	23.06	0.83	4.43	-0.07	23.28
5.0	30.00	32	4.96	-0.04	30.90	0.90	4.99	-0.01	30.50
5.5	27.27	35	5.47	-0.03	29.50	2.23	5.45	-0.05	28.00
6.0	25.00	35	5.95	-0.05	27.57	2.57	5.95	-0.05	26.21
6.5	30.77	38	6.48	-0.02	31.54	0.77	6.48	-0.02	32.12
7.0	28.57	38	6.99	-0.01	28.99	0.42	6.99	-0.01	29.34
7.5	26.67	38	7.46	-0.04	27.79	1.12	7.46	-0.04	27.85
8.0	25.00	38	7.98	-0.02	25.96	0.96	7.98	-0.02	25.65
8.5	29.41	38	8.46	-0.04	30.98	1.57	8.43	-0.07	30.34
RMS error				0.03		1.69		0.05	
									1.30

Errors in thickness and density estimations for the second phantom study. The results from dual energy decomposition based on Eq. 5 and 6 are listed as fixed kVp fitting and alternative kVp fitting, respectively. The RMS errors in each case are summarized in the last row.

Table IV

Known values			Fixed kVp fitting				Alternative kVp fitting			
Thickness (cm)	Density (%)	Tube Voltage (kVp)	Thickness (cm)	ΔT (cm)	Density (%)	ΔD (%)	Thickness (cm)	ΔT (cm)	Density (%)	ΔD (%)
4.0	0.00	32	3.96	-0.04	1.82	1.82	3.91	-0.09	2.09	2.09
4.0	12.50	32	3.98	-0.02	12.78	0.28	3.93	-0.07	12.99	0.49
4.0	25.00	32	3.98	-0.02	25.31	0.31	3.93	-0.07	25.43	0.43
4.0	37.50	32	3.97	-0.03	37.91	0.41	3.93	-0.07	37.97	0.47
4.0	50.00	32	4.00	0.00	51.09	1.09	3.96	-0.04	51.07	1.07
4.0	62.50	32	3.99	-0.01	63.45	0.95	3.95	-0.05	63.38	0.88
4.0	75.00	32	3.97	-0.03	76.07	1.07	3.94	-0.06	75.98	0.98
4.0	87.50	32	3.98	-0.02	87.81	0.31	3.95	-0.05	87.66	0.16
4.0	100.00	32	4.00	0.00	100.74	0.74	3.99	-0.01	100.44	0.44
RMS error				0.02		0.91		0.06		0.95

Table V

Errors in thickness and density estimations for the third phantom study. The results from dual energy decomposition based on Eq. 5 and 6 are listed as fixed kVp fitting and alternative kVp fitting, respectively. The RMS errors in each case are summarized in the last row.

Known values				Fixed kVp fitting			Alternative kVp fitting		
Thickness (cm)	Density (%)	Tube Voltage (kVp)	Area (cm ²)	Thickness (cm)	ΔT (cm)	Density (%)	ΔT (cm)	Density (%)	ΔD (%)
4.0	25.00	29	62.5	3.98	-0.02	25.01	0.01	25.13	0.13
4.0	50.00	29	62.5	4.01	0.01	50.26	0.26	50.24	0.24
4.0	75.00	32	62.5	3.98	-0.02	75.08	0.08	74.97	-0.03
4.0	25.00	32	125	3.97	-0.03	25.79	0.79	25.91	0.91
4.0	50.00	32	125	4.01	0.01	50.98	0.98	50.95	0.95
4.0	75.00	32	125	3.98	-0.02	75.80	0.80	75.69	0.69
4.0	25.00	32	250	3.87	-0.13	28.17	3.17	28.23	3.23
4.0	50.00	35	250	3.86	-0.14	53.44	3.44	53.56	3.56
4.0	75.00	35	250	3.92	-0.08	76.88	1.88	76.95	1.95
RMS error					0.07		1.75	0.10	1.80

Table VI

Errors in thickness and density estimations for the fourth phantom study. The results from dual energy decomposition based on Eq. 5 and 6 are listed as fixed kVp fitting and alternative kVp fitting, respectively. The RMS errors in each case are summarized in the last row.

Known values			Fixed kVp fitting				Alternative kVp fitting					
Step1 (cm)	Step2 (cm)	Step3 (cm)	Density (%)	Tube Voltage (kVp)	Thickness (cm)	ΔT (cm)	Density (%)	ΔD (%)	Thickness (cm)	ΔT (cm)	Density (%)	ΔD (%)
1.0	2.0	3.0	50.00	32	2.98	-0.02	50.75	0.75	2.94	-0.06	50.04	0.04
1.0	3.0	4.0	50.00	32	3.97	-0.03	49.70	-0.30	3.93	-0.07	49.71	-0.29
1.0	3.0	5.0	50.00	32	4.95	-0.05	50.01	0.01	5.01	0.01	48.76	-1.24
1.0	3.0	6.0	50.00	35	5.94	-0.06	53.20	3.20	5.96	-0.04	51.93	1.93
1.0	4.0	7.0	50.00	38	6.93	-0.07	51.24	1.24	6.93	-0.07	51.30	1.30
RMS error						0.05		1.58		0.05		1.18