Accuracy assessment and characterization of x-ray coded aperture coherent scatter spectral imaging for breast cancer classification

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Abstract. Although transmission-based x-ray imaging is the most commonly used imaging approach for breast cancer detection, it exhibits false negative rates higher than 15%. To improve cancer detection accuracy, x-ray coherent scatter computed tomography (CSCT) has been explored to potentially detect cancer with greater consistency. However, the 10-min scan duration of CSCT limits its possible clinical applications. The coded aperture coherent scatter spectral imaging (CACSSI) technique has been shown to reduce scan time through enabling single-angle imaging while providing high detection accuracy. Here, we use Monte Carlo simulations to test analytical optimization studies of the CACSSI technique, specifically for detecting cancer in *ex vivo* breast samples. An anthropomorphic breast tissue phantom was modeled, a CACSSI imaging system was virtually simulated to image the phantom, a diagnostic voxel classification algorithm was applied to all reconstructed voxels in the phantom, and receiver-operator characteristics analysis of the voxel classification was used to evaluate and characterize the imaging system for a range of parameters that have been optimized in a prior analytical study. The results indicate that CACSSI is able to identify the distribution of cancerous and healthy tissues (i.e., fibroglandular, adipose, or a mix of the two) in tissue samples with a cancerous voxel identification area-under-the-curve of 0.94 through a scan lasting less than 10 s per slice. These results show that coded aperture scatter imaging has the potential to provide scatter images that automatically differentiate cancerous and healthy tissue within *ex vivo* samples. Furthermore, the results indicate potential CACSSI imaging system configurations for implementation in subsequent imaging development studies. © 2017 Society of Photo-Optical Instrumentation Engineers (SPIE) [DOI: 10.1117/1.JMI.4.1.013505]

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1 Introduction

Transmission-based x-ray imaging methods, such as mammography, tomosynthesis, and CT, are used widely for breast cancer applications. X-ray-based imaging is considered to be generally more effective than other imaging modalities for breast cancer screening and detection because it is able to visualize microcalcifications more consistently than other methods. For example, microcalcification conspicuity in ultrasound is degraded by speckle noise,¹ and MRI for breast imaging relies on enhancement using contrast agents that do not exhibit uptake by microcalcifications.² However, conventional x-ray imaging is limited by the low contrast of ~3%³ between the x-ray linear attenuation coefficients of healthy and diseased breast tissues at mammography energies (~20 keV). This limited and subtle contrast leads to false negative rates greater than 15% in screening mammography.⁴

As an alternative to relying on the subtle contrast provided by transmission-based x-ray imaging, x-ray coherent scatter imaging⁵ has been proposed as a clinically viable method to detect breast cancers. Instead of the 3% contrast provided by transmission, the x-ray coherent scatter cross sections for healthy and

cancerous tissues exhibit a 19% contrast.³ Coherent scattering is dependent on the spatial configuration of electrons (i.e., the molecular structure of the sample) rather than the density, and the onset of cancer is believed to cause greater changes in tissue molecular structure than in density. As a result, coherent scatter techniques show greater contrast in differentiating cancerous and healthy tissue compared to x-ray transmission techniques (see Fig. 5 in Appendix A). A number of studies have demonstrated the improved contrast that coherent scatter computed tomography (CSCT) is able to provide for breast cancer imaging^{6–8} and for imaging urinary stones.⁹ However, a concerning shortcoming of CSCT is the prohibitively long scan times (>10 min) that are required in raster scanning a pencil beam of x-rays across the sample at every projection angle. Thus, innovations are needed in the area of x-ray coherent scatter imaging to reduce its scan time so that it can offer clinical value.

Methods for reducing the scan time that have been implemented in prior studies include fan-beam CSCT,^{10–12} selected volume tomography (SVT),¹³ kinetic depth effect x-ray diffraction¹⁴ (KDEXRD), coded aperture x-ray scatter imaging (CAXSI),¹⁵ structured illumination coherent scatter imaging

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(SICSI),¹⁶ and coded aperture coherent scatter spectral imaging (CACSSI).¹⁷ Of these techniques, those that employ a coded aperture (i.e., CAXSI, SICSI, and CACSSI) are the only techniques that have shown potential for real-time volumetric imaging through a single snapshot. The other techniques (i.e., fan-beam CSCT, SVT, and KDEXRD) require the acquisition of multiple measurements. Investigating and comparing a coded aperture technique with respect to CSCT for reduced scan time can guide the development of a clinical coherent scatter system with high levels of accuracy and short scan times.

Among the three coded aperture techniques, CACSSI may be the best suited for clinical development due to a number of reasons. CACSSI exhibits a superior momentum transfer [i.e., the spectral parameter in scatter imaging, defined as $q \equiv (E/hc) \sin(\theta/2)$] resolution compared to CAXSI,¹⁷ which is a critical system strength for the task of differentiating cancerous and healthy breast tissue with a high level of accuracy. The SICSI technique requires the sample to be translated once across the sample field of view at a fixed velocity, which provides additional constraints to the imaging system design, constraints that are more suited to large targets, such as luggage moving across a conveyor belt rather than for clinical applications.¹⁶ The flexibility in the CACSSI design makes it better suited for application in a clinical system than SICSI. In this work, we will investigate CACSSI as the snapshot imaging technique of choice for breast cancer imaging.

In CACSSI, a coded aperture mask is placed between the sample and the detector to modulate the scatter signal coming from the sample. The modulation is performed in a way that introduces angular sensitivity in the measured signal at the detector face. This angular sensitivity is achieved by observing the magnification of the coded aperture pattern when it is projected onto the detector. The pattern of the coded aperture is magnified uniquely for each point of scatter along the primary x-ray beam path. Therefore, by deconvolving and analyzing the multiple coded aperture patterns projected onto the detector, the angular information from the scatter signal can be back-projected to the point of origin of scatter in the sample. This approach provides depth resolution without the need for multi-angle tomography. A maximum a posteriori (MAP) estimation method with total-variation (TV) regularization can be applied to reconstruct the depth-resolved object signal. Greenberg et al.¹⁷ showed that CACSSI could be used for depth-resolved molecular imaging with a linear array of energy-sensitive detector pixels as well as with a single energy-sensitive pixel.¹⁸ When using a linear array of pixels, they were able to achieve lateral, depth, and momentum transfer resolutions of 1 mm, 5 mm, and 0.2 nm^{-1} , respectively.

CACSSI has thus far been applied to provide depth resolution along a pencil beam of incident x-rays illuminating a sample. To reconstruct a three-dimensional (3-D) image, the pencil beam must be raster scanned once across the sample to image a slice and repeated at a different height for each additional slice to be imaged. (Note that the coherent scatter imaging techniques that do not employ coded apertures require multiple raster scan acquisitions, as well as multiple angular acquisitions.) In this work, we present the design and evaluation of a CACSSI system for clinical breast cancer imaging and assess the total scan time required for 3-D imaging.

Specifically, we aim to demonstrate CACSSI imaging for cancerous breast tissue samples similar to those resected during lumpectomy procedures. Lumpectomy is the type of therapy

used to treat 59% of women diagnosed with early stage breast cancers, where the surgeon aims to remove the breast tumor along with a minimal margin of healthy tissue.¹⁹ Mapping out the spatial distribution of cancer in the surgically resected tissue sample is one of the most important tasks in determining the success of the lumpectomy procedure because information about the margins is used to conclude whether the entire tumor volume was successfully removed within the resected specimen.²⁰

In prior work,²¹ we demonstrated CACSSI's ability to detect cancerous tumors in *ex vivo* breast samples. We also described a Monte Carlo simulation of a CACSSI system and demonstrated its ability to accurately map out the distribution of cancer in a breast sample. Here, we utilize the Monte Carlo simulation to characterize the various parameters in the CACSSI setup to achieve maximum accuracy for cancerous voxel detection in *ex vivo* breast cancer samples.

2 Methods

In this section, we describe (a) the Monte Carlo modeling of the breast tissue phantom and the imaging system, (b) the data acquisition and coded aperture image reconstruction algorithm that was used, (c) how receiver-operator characteristics (ROC) analysis was used as a diagnostic accuracy metric, and (d) the imaging parameter characterization strategy that was used.

2.1 Monte Carlo Modeling

The Monte Carlo simulations in this work employed the GEANT4²² physics toolkit, which has been validated²³ and previously used to accurately simulate coherent scatter based on molecular structure²⁴ and the various sources of noise and artifacts in our coherent scatter imaging system (e.g., Compton scatter, self-attenuation, etc.).²⁵ The two major components of the GEANT4 simulations were the realistic breast tissue phantom and the coherent scatter imaging system in GEANT4, discussed below.

2.1.1 Breast tissue phantom modeling

The breast tissue phantom used in this work was first described in Ref. 21. It was developed as follows. First, the distribution of healthy breast tissue was taken from an extended cardiac-torso (XCAT) phantom developed in Ref. 26 through segmenting adipose tissue, fibroglandular tissue, and mixtures of the two from high-resolution breast CT images; the breast phantoms were validated for realism through ray tracing x-ray imaging simulations.²⁷ Second, the distribution or shape of the tumor was taken from the work in Ref. 28, which is based on a mathematical tumor model fitted to tumors from tomosynthesis images and validated for resemblance to real tumors by radiologist observers. The tumor size was chosen to be 1.92 cm, which is the average tumor size based on a sample of over 24,000 cases.²⁹ To form a breast tissue phantom for use in the simulations that resembled a tissue sample removed during a breast lumpectomy procedure, a 2.5-cm region of healthy tissue was cropped out of the XCAT phantom and then the tumor shape was inserted into that cropped healthy tissue.

The material properties of the adipose, fibroglandular, and cancerous tissues (see Fig. 1) were modeled based on the atomic or elemental compositions determined through neutron activation analysis for 46 breast tumor samples in Ref. 30. The density of the tumor mass was modeled based on measurements on

Fig. 1 Volume rendering of the four tissue components within the breast tissue phantom.

tumors from eight patients in Ref. 31, and the density of the adipose and fibroglandular tissue-types were modeled based on measurements in Ref. 32. The final breast tissue phantom is shown in Fig. 4(a), where black represents cancerous tissue, blue represents adipose, magenta represents fibroglandular, and red represents mixtures of adipose and fibroglandular.

2.1.2 Imaging system setup

The imaging system modeled in the Monte Carlo simulations was based on a modified version of the experiments presented in Ref. 33. The system consisted of an x-ray source (125 kVp, W-Rh anode), one or more coded aperture masks, and a virtual energy-sensitive planar detector. A schematic of the imaging system is shown in Fig. 2. From right to left the components of the imaging system are the x-ray source, the breast tissue phantom, the coded aperture mask, a lead attenuator, and the detector.

Instead of modeling an x-ray source in GEANT4, we instead directly modeled a collimated pencil beam of x-rays with energy spectrum or energy distribution resembling that from a specific x-ray tube anode and tube electric potential calculated using the XSPECT software.³⁴ The x-ray tube current product (i.e., the mAs), the beam width, the x-ray tube anode, and tube electric potential are variable parameters to be characterized.

The coded aperture mask was modeled as a series of bars made of bismuth-tin and repeating with specific periodicity or spatial frequency (another variable for characterization). The bar pattern has its variations or spatial frequency along the x -axis or perpendicular to the x-ray beam as shown in Fig. 2.

The detector was modeled to resemble the photon counting detector used in our experiment:³⁵ a linear array of 128 cadmium-telluride crystal elements (Multix ME-100 version 2)

Fig. 2 Schematic of the CACSSI imaging system setup in the Monte Carlo simulation in this work. From right to left, the components of the imaging system are the x-ray source, the breast tissue phantom, the coded aperture mask, a lead attenuator, and the detector.

oriented along the x -direction with 780- μ m pixel size and 6.5-keV full-width at half maximum energy resolution. However, instead of directly modeling the crystals, we instead first modeled the detector as a logical volume that reports the position and energies of x-rays intersecting it. Then, in the postprocessing of the detector data from the simulation, the detected x-rays were binned into spatial bins corresponding to the detector pixels and into energy bins corresponding to the energy channels of the Multix detector. Finally, the binned count data were blurred in energy through convolution with a kernel representing the detector response, i.e., a Gaussian with 6.5-keV full-width at half maximum. A lead attenuator was placed in front of the detector pixel exposed to the incident x-ray beam to prevent pileup, i.e., to prevent the detector from being saturated by the high flux of x-rays coming directly from the tube.

2.2 Imaging Data Acquisition and Image Reconstruction

Imaging was performed by raster scanning one slice of the breast tissue phantom, acquiring data at 0.7-mm incremental steps. The sample was stepped in the x -direction 44 times through the beam so that the beam covered a 3-cm field of view. A computational cluster of 300 processors was used to simulate the scan. To optimize simulation time, a job distribution process developed in Ref. 36 was applied. The computational cluster required 3 h to simulate a 0.75-mm width pencil beam of x-rays from a mammography tube (molybdenum at 40 kV) run for 100 mAs.

The data from the detector at each of the 44 raster scan positions were in the form of counts binned into 128 spatial bins by 64 energy bins. For each raster scan position, the coherent scatter intensity as a function of q (momentum transfer) and z position was reconstructed from the 128×64 histogram of count data using a MAP iterative reconstruction algorithm developed in Ref. 37. The reconstruction algorithm inversely solves a matrix equation that analytically models the imaging system by projecting the sample into the detector-measurement space (see Appendix B for a more detailed description of the image reconstruction technique used). After all 44 raster scan positions were individually reconstructed, they were combined to provide an image of the sample in x - z - q space.

2.3 Cancer Identification and Receive-Operator Characteristics Analysis

Once the image of the sample in x - z - q space has been acquired, the next step is to determine which regions or pixels in the sample are cancerous. Similar to the technique that we used for identifying cancer for CSCT imaging³⁸ and the accompanying ROC

analysis, here for CACSSI, we analyzed each pixel of the sample in x - z space individually and diagnosed it as cancerous based on its Euclidean proximity in q -space to the expected behavior for cancerous tissue. The expected behavior for cancer was taken from the scatter intensity for cancerous tissue as a function of q that was measured in Ref. 3.

More precisely, the binary decision of whether a pixel in x - z space should be diagnosed as cancerous was made if its Euclidean distance from the expected behavior for cancer in q -space was greater than a threshold value. The selection of this threshold value was arbitrary, and therefore we chose to treat it as a variable decision criterion in an ROC analysis framework to quantify the accuracy of the pixel-diagnosis independently of the selection of the threshold value.

In the ROC analysis framework, for each value of the variable decision criterion or Euclidean threshold, the pixels in x - z space that are classified as cancerous are compared to the ground truth phantom, which is known in the case of a Monte Carlo simulation. Specifically, the sensitivity (i.e., the fraction of pixels correctly diagnosed as cancerous), specificity (i.e., the fraction of pixels correctly not diagnosed as cancerous), and accuracy were calculated as a function of the Euclidean threshold value. The ROC curve was formed by plotting the sensitivity versus the quantity (1-specificity). Finally, the area-under-the-curve (AUC)—which is a single- or scalar-value measure of the overall accuracy of the ROC curve—can be calculated by integrating the area under the obtained ROC curve. In this work, we used the AUC as an overall accuracy metric for the imaging system, specifically reflecting its accuracy for cancer detection within a sample. In this framework, a characterization study of the imaging system can be performed with the goal of improving the imaging system AUC.

2.4 Characterization of Imaging Parameters

The parameters we seek to characterize for the CACSSI imaging system are the pencil beam diameter, the spatial frequency of the coded aperture mask, the mask location, the detector location, the applied potential across x-ray tube (i.e., kVp), and the x-ray tube current product (i.e., the tube mAs).

The generalized analytic theory for CACSSI spatial resolution and momentum transfer resolution developed in Ref. 17 shows that imaging performance—in terms of spatial and momentum transfer (i.e., q) resolution—improves with higher frequency mask features, smaller beam widths, and with greater separation between the mask and the detector. Based on that analytic theory, we hypothesize (developed in detail in Appendix C) the imaging system that will perform best is one with a $w = 0.5$ mm beam diameter, 1.33 mm^{-1} mask feature size or period, $z_m = 750$ mm mask location, $z_d = 1200$ mm detector location, and our 125 kVp WRe x-ray tube used in our experiments.³⁹ From this proposed best case, we perturb each of the parameters to observe its effect on the overall imaging performance. The final set of imaging parameters that were tested are shown in Table 1.

3 Results

The resulting AUC values we obtain for the various imaging systems are shown in Table 1. The first row represents our hypothesized optimal imaging system based on the analytical optimization from Ref. 17, and in the following rows we indicate the parameters that were perturbed from the first row using bold-face font. The concluded best case imaging system (row 3) based on maximum AUC is indicated in italics.

Table 1 AUC values for various CACSSI imaging systems. As a short-hand, we only indicate the anode material in the “tube” column. The tube “WRe” represents the tungsten-rhenium anode tube used in our prior experimental work, whereas “Mo” represents the molybdenum mammography tube that has been used in prior CSCT simulations. These AUC results were obtained from images acquired using an x-ray tube current product of 50 mAs per pencil beam (although the improvement in AUC for increasing mAs for the top four performing systems here is shown in Fig. 3). Row 1 was our expected best case imaging system based on analytic theory for best spatial and spectral resolution.

#	w (mm)	u (mm^{-1})	z_m (mm)	z_d (mm)	Tube	AUC
1	0.5	1.33	750	1200	WRe	0.81
2	2.0	1.33	750	1200	WRe	0.84
3	0.5	0.50	750	1200	WRe	0.92
4	0.5	1.33	1000	1200	WRe	0.67
5	0.5	1.33	750	900	WRe	0.81
6	0.5	1.33	750	1200	Mo	0.59
7	0.5	0.50	1000	1200	WRe	0.60

Note: Perturbations from row 1 are indicated using bold-face font. The best imaging system (i.e., the one with maximum AUC) is indicated using italic font.

Fig. 3 AUC versus x-ray tube current product for the top four performing imaging setups from Table 1. We can see that the top performing system only has an ~3% improvement in AUC when the tube current product is increased from 50 to 500 mAs. Therefore, 50 mAs should be used for general CACSSI scans to minimize scan time.

To understand how much signal is needed in the imaging system, we also show the AUC as a function of the x-ray tube current product for the top four performing imaging systems in Fig. 3. Finally, we show images of the cancer-classification results in Fig. 4 to demonstrate the imaging accuracy that is obtainable and that corresponds to the AUC values in Table 1.

4 Discussion

4.1 Comparison to Transmission Computed Tomography and Coherent Scatter Computed Tomography

To put it into context, the CACSSI imaging and the cancer-classification results presented here can be compared to the previously used x-ray imaging techniques of conventional transmission

Fig. 4 Cancer-classification results and imaging results from the top three performing imaging systems from Table 1. (a) The ground truth phantom that was modeled in the simulation, where black represents cancerous tissue, blue represents adipose, magenta represents fibroglandular, and red represents mixtures of adipose and fibroglandular. (b), (c), and (d) show cancer-classification images (where black represents pixels diagnosed as cancer) for imaging systems corresponding to different rows from Table 1. Qualitatively, we can see that the resulting classification image in (b) that came from the imaging system represented by row 3 in Table 1 provides the most accurate cancer classification, in agreement with the relative AUC values in Table 1. Also, we see that imaging systems from rows 3 and 1 provide cancer-classification results that are sufficient to detect the edges of the tumor. Whereas the imaging system from row 2, although able to detect the edges along the x -direction, is not able to do so along the z -direction. (f)–(h) show the corresponding grayscale CACSSI images at $q = 1.1 \text{ nm}^{-1}$, which is the momentum transfer value at which cancerous tissue has the greatest contrast from fibroglandular and adipose healthy tissues. The cancer-classification images [(b)–(d)] were obtained from the grayscale CACSSI images [(f)–(h)] based on the Euclidean distance of the reconstructed pixel intensity across q -space from the expected behavior for cancerous tissue as described in Sec. 2.3.

x-ray CT and CSCT. Transmission-based x-ray imaging provides very little (3%) direct contrast in pixel intensity between cancerous and healthy breast tissue, leaving a greater degree of the diseased-tissue identification task to be performed by a trained human reader (i.e., a radiologist). Specifically in mammography, radiologists identify suspicious regions in the breast based on the appearance in the image of the morphology of a potential breast tumor mass (e.g., the shapes and sizes breast tumors tend to take), the presence of microcalcifications, architectural distortions in normal breast tissue patterns, and asymmetries between the left and right breast.^{40,41} We showed in this work that coherent scatter imaging could potentially identify the presence and spatial extent of breast tumors and classify them as malignant.

Qualitatively in Fig. 4(b), we can see that the resulting classification image in subfigure (b) corresponding to the imaging system represented by row 3 in Table 1 provides the most accurate cancer classification, in agreement with the relative AUC values in Table 1. Also, we see that imaging systems from rows 3 [Fig. 4(b)] and 1 [Fig. 4(c)] provide cancer-classification results that are sufficient to detect the edges of the tumor. However, the imaging system from row 2 [Fig. 4(d)], although able to detect the edges along the x -direction, is not able to do so along the z -direction.

When comparing CACSSI to CSCT, the maximum AUC we observed for CACSSI was ~ 0.94 (Fig. 3), whereas we showed⁴²

that CSCT could obtain an AUC of 0.97. The reduced AUC for CACSSI is likely due to its poorer spatial resolution compared to CSCT. The spatial resolution along the beam direction for CACSSI determined in Ref. 17 was $\sim 2.5 \text{ mm}$ (whereas the spatial resolution along the x - and y -directions is the beam width, just as in CSCT).

Greenberg et al.¹⁷ showed that spatial frequency in z could be improved by using higher frequency coded aperture masks. However, in this study, we found that the lower frequency coded aperture masks gave better AUC (Table 1). The worse imaging results when using the higher frequency coded aperture masks is likely caused by the noise in the system. When the reconstruction algorithm does not model the noise in the system accurately, the noise results in artifacts in the reconstructed image. These artifacts are considerably more prevalent when using a higher frequency coded aperture mask. In that case, the target signal is higher frequency due to the modulation from the coded aperture mask. The target signal therefore becomes more difficult to separate or filter from the noise as both target and noise have similar frequency characteristics.

Finally, the necessary scan time for CACSSI is much shorter than that required for CSCT. For example, the results shown in Fig. 3 show that the top performing imaging system (row 3), has only an $\sim 3\%$ improvement in AUC performance accompanying an increase in mAs from 50 to 500 mAs. Experimentally, a 50-mAs scan would result in a scan time of 8 s to acquire the

entire slice shown in Fig. 4(b) using an x-ray tube operating at 50 mA, corresponding to 80 s for a 10-slice scan. On the other hand, CSCT would require 5 min to perform a 10-slice scan when using a two-dimensional (2-D) 512×384 detector array rather than the linear-detector array of 128 pixels used here. Therefore, when using the same detector array, CACSSI would be at least an order of magnitude faster than CSCT.

4.2 Future Work

4.2.1 Spatial resolution

The most important future step for CACSSI for *ex vivo* breast tumor imaging is to improve its spatial resolution in z by optimizing coded aperture masks and modifying the reconstruction algorithm to better model noise in the system. This approach will allow more robust reconstruction of the signal from high-frequency coded aperture masks, thereby bringing the resolution of the CACSSI system closer to that of CSCT. Investigating the application of regularization and smoothing algorithms, such as TV,⁴³ would allow us to improve these reconstructions of extended objects when using higher frequency masks to improve the overall performance of CACSSI for breast cancer detection.

Alternatively, instead of focusing on improving the resolution of CACSSI, an alternative imaging approach could be developed that is a hybrid of CACSSI and CSCT, i.e., acquiring CACSSI data at two or even three angles and using the additional data to improve the reconstructed image resolution and signal. Such a hybrid approach would allow us to exploit the accuracy previously demonstrated for CSCT and the reduced scan time of CACSSI.

A third strategy to improve the spatial resolution for CACSSI is to use coded aperture masks with unique patterns in two dimensions, instead of having only a pattern along one dimension as in this work. A 2-D coded aperture mask would allow us to more precisely modulate the scatter signal and therefore better resolve the sample simultaneously in two dimensions. The biggest challenge with implementing 2-D coded apertures is acquiring a 2-D photon counting detector to measure the modulations in both dimensions.

4.2.2 Potential applications in vivo

Strong potential exists for CACSSI breast imaging applications *in vivo*, such as in routine breast cancer screening and diagnosis, and postsurgery follow up. Two substantial challenges for translating CACSSI to *in vivo* imaging are (1) management of radiation dose and (2) the increased scatter noise and complexity due the larger size of the whole breast.

The radiation dose for CACSSI in breast cancer applications was explored using Monte Carlo simulations of compressed whole breasts *in vivo*.⁴⁴ The results of the study showed that when using a 5-cm compressed breast—the median compressed breast thickness is 5.2 cm and the median breast diameter is 11 cm⁴⁵—a CACSSI exposure would deliver a dose of ~ 17 nGy/mAs. Assuming a 500-mAs exposure, the dose for a CACSSI scan would therefore be 8.5 mGy. (The 500-mAs exposure assumption is higher than typical exposures in mammography where the x-ray tubes operate at ~ 100 mA.) Therefore, the overall dose value from CACSSI is similar to the dose in mammography (~ 8 mGy with 5-cm compression), and it is an order of magnitude less than the dose in breast CT (~ 17 mGy

dose per 100 mAs at 120 kVp without compression).⁴⁵ This comparable dose performance for CACSSI relative to mammography and breast CT is encouraging. There is considerable potential to reduce CACSSI dose further using dose reduction methods.

For larger sample sizes, the increase in the x-ray path-length through the sample leads to an increase in the probability of scatter. Therefore, the number of scattered x-rays measured at the detector also increases. While some of these events are single-scatter interactions, a majority of the events arise from multiple-scatter interactions. These multiple-scatter x-rays cannot be used to reconstruct information about the sample because the sequence of scatter events they undergo is stochastic; and therefore these measured counts contribute noise that degrades the measured signal. Furthermore, the current imaging system design is not able to differentiate x-rays that have undergone multiple-scatter events from those that have undergone a single-scatter event.

Theoretical analysis of image formation in x-ray coherent scatter imaging reveals that the noise originating from multiple scatter cannot be neglected when the object size becomes greater than three half-value layers,⁴⁶ which for human tissue at diagnostic x-ray energies is ~ 10 cm. Consequently, multiple-scatter noise would considerably degrade the accuracy of CACSSI for the case of imaging pendant, uncompressed breasts, which have a median diameter of 11 cm.⁴⁵ On the other hand, for the case of breasts that are compressed for mammography, which have a median thickness of 5.2 cm,⁴⁵ multiple-scatter noise can be neglected and therefore CACSSI can provide a similar level of accuracy for cancer classification as demonstrated in this work.

5 Conclusion

In this work, we described the characterization of the various parameters in a CACSSI system for the task of *ex vivo* breast imaging. We found that the best combination of CACSSI imaging parameters provided an order of magnitude shorter scan times than CSCT, with an AUC of 0.94 in detecting the cancerous tumor edges in the sample. Additional development is needed to improve CACSSI's spatial resolution along the beam direction.

Disclosures

Dr. Lakshmanan has nothing to disclose. Dr. Greenberg has nothing to disclose. Dr. Samei has nothing to disclose. Dr. Kapadia has nothing to disclose.

Appendix A: Contrast Mechanism

Reconstructions of voxel scatter intensity as a function of momentum transfer (q) can be used to distinguish cancerous and healthy breast tissue because the x-ray coherent scatter patterns for adipose, fibroglandular, mixtures of adipose and fibroglandular, and cancerous tissues as shown in Fig. 5 are significantly different. Consequently, the degree to which the intensity variation in momentum transfer-space of a given voxel resembles the literature behavior for one of the four classes of breast tissue shown in Fig. 5 can be used to classify the tissue in that voxel as healthy or cancerous.

Appendix B: Image Reconstruction

For a given incident pencil beam to which the sample is exposed, the number of scatter counts N_s coming off the sample is modeled as being Poisson distributed with mean value equal

Fig. 5 Scatter intensity in momentum transfer (q) space for adipose, fibroglandular, mixtures of adipose and fibroglandular, and cancerous breast tissues. Data acquired from Ref. 3.

described by the matrix transformation $H\vec{f}$, where $\vec{f}$ is a vector containing the scatter intensities of the ground truth object for different spatial voxels (z) and for different momentum transfer values (q) and H is the forward operator that was developed from the physical modeling of the CACSSI system in Ref. 17. Using knowledge of the matrix H based on the physical parameters of the imaging system and using the assumption that any unmodeled signal is Poisson distributed, an image of the object can be reconstructed from the measured N_s using the MAP estimation method. The iterative image estimate can be regularized using TV based on the assumption that the ground truth object is piecewise smooth⁴⁷ in z - and q -space.

Appendix C: Analytic Theory for Optimal Imaging System

Greenberg et al.¹⁷ showed using their analytical impulse response analysis that the spatial resolution of a CACSSI imaging system is (using the variables defined in this work)

$$\Delta z = \frac{(z_d - z)E_{\max}E_{\min}}{2hcqu(z_d - z_m)(E_{\max} - E_{\min})}, \quad (1)$$

where $(E_{\min}, E_{\max})$ is the incident x-ray spectrum range. According to this expression, the best spatial resolution is obtained when using in the imaging system (1) a higher spatial frequency mask (i.e., greater u), (2) a broader energy x-ray spectrum (i.e., greater $E_{\max} - E_{\min}$), and (3) greater separation between the mask and detector (i.e., greater $z_d - z_m$).

Furthermore, in that work,¹⁷ the momentum transfer (i.e., spectral) resolution for a CACSSI imaging system is shown to be

$$\Delta q = q \left[\left(\frac{\Delta z}{z_d - z} \right)^2 + \frac{\Delta E \sqrt{\Delta x^2 + w^2}}{chqz} \right]^{1/2}, \quad (2)$$

where Δx is the detector pixel size and ΔE is the detector energy resolution. As a result, in addition to the parameters that improve spatial resolution, the best momentum transfer resolution is obtained when the imaging system also has a smaller beam radius (smaller w).

To maintain sufficient x-ray scatter signal without considerable degradation in spatial resolution, a pencil beam diameter of $w = 0.5$ mm was hypothesized to be optimal. Machining coded

aperture masks with greater than 1 mm^{-1} spatial frequency has been shown to be technically challenging.⁴⁸ Therefore, as an upper limit of coded aperture mask spatial frequency, we choose to use $u = 1.33 \text{ mm}^{-1}$ as the hypothesized optimal mask frequency. Because a greater energy range is found to improve spatial resolution, we hypothesize that a body CT x-ray tube (125 kVp WRe) will provide better performance than a mammography tube that is lower kVp. Finally, based on its feasibility for implementation in Ref. 17 and the desire to increase the distance between mask and detector for improved spatial resolution, we hypothesize optimal mask and detector locations $z_m = 750$ mm and $z_d = 1200$ mm, respectively.

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