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14. ABSTRACT

This project aims at developing a trimodel x-ray mammography imaging system to improve both sensitivity and specificity in breast cancer screening and diagnosis, particularly for radiologically dense breasts. In the proposed system, three complementary image datasets will be generated from a single data acquisition: the first is the conventional absorption contrast mammography image, the second is a novel phase contrast mammography image with enhanced edges and reduced anatomical background, the major confounding factor in reading mammography; the imaging characteristics suggest that this contrast mechanism would be preferable for cancer mass detection. The third image is the dark-field mammogram, which is sensitive to the local distribution of microcalcifications, calcified vessels, and other small objects in the breast. The proposed system will be constructed, optimized, and evaluated using mastectomy specimens.

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1. INTRODUCTION: Narrative that briefly (one paragraph) describes the subject, purpose and scope of the research.

This project aims at developing a trimodal x-ray mammography imaging system to improve both sensitivity and specificity in breast cancer screening and diagnosis, particularly for radiologically dense breasts. In the proposed system, three complementary image datasets will be generated from a single data acquisition: the first is the conventional absorption contrast mammography image, the second is a novel phase contrast mammography image with enhanced edges and reduced anatomical background, the major confounding factor in reading mammography; the imaging characteristics suggest that this contrast mechanism would be preferable for cancer mass detection. The third image is the dark-field mammogram, which is sensitive to the local distribution of microcalcifications, calcified vessels, and other small objects in the breast. In this project, a prototype imaging system that generate mammographic images of these complementary contrast mechanisms is constructed and evaluated using human mastectomy specimens.

2. KEYWORDS: Provide a brief list of keywords (limit to 20 words).

Early breast cancer detection, dense breast, mammography, x-ray phase contrast imaging, x-ray dark field imaging, Talbot-Lau interferometer, prototype imaging system

3. ACCOMPLISHMENTS: The PI is reminded that the recipient organization is required to obtain prior written approval from the awarding agency Grants Officer whenever there are significant changes in the project or its direction.

What were the major goals of the project?

1. Develop a grating interferometer for a trimodal mammography system;
2. Integrate the grating interferometer into existing digital mammography system;
3. Objective and quantitative performance evaluation of the proposed system;
4. Subjective performance evaluation of the proposed system using mastectomy specimens.

What was accomplished under these goals?

1. Develop a grating interferometer for a trimodal mammography system

1.1 A unified theoretical framework for grating interferometer design

In the past decades, several types of x-ray grating interferometers have been developed and implemented, including Talbot interferometer, Talbot-Lau interferometer, dual phase grating interferometer, far-field interferometer, etc. (**Figure 1**).

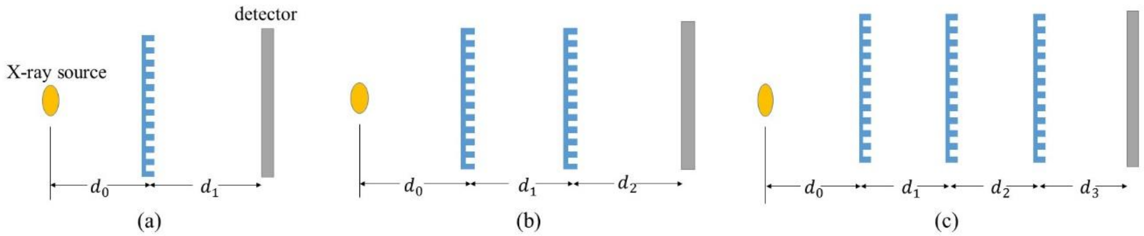


Figure 1: X-ray grating interferometer system with (a) one, (b) two, or (c) three diffraction gratings.

While the requirements on the source, detector, number and type of grating are different for each configuration, the performance characteristics known as the phase sensitivity may also vary a lot. In order to find the best design given the available hardware and the desired imaging task, we developed a unified theory of x-ray grating interferometers that consist of one, two and three gratings with arbitrary amplitude-phase modulations. The fringe visibility and phase sensitivity have been derived for each configuration (**Figure 2**).

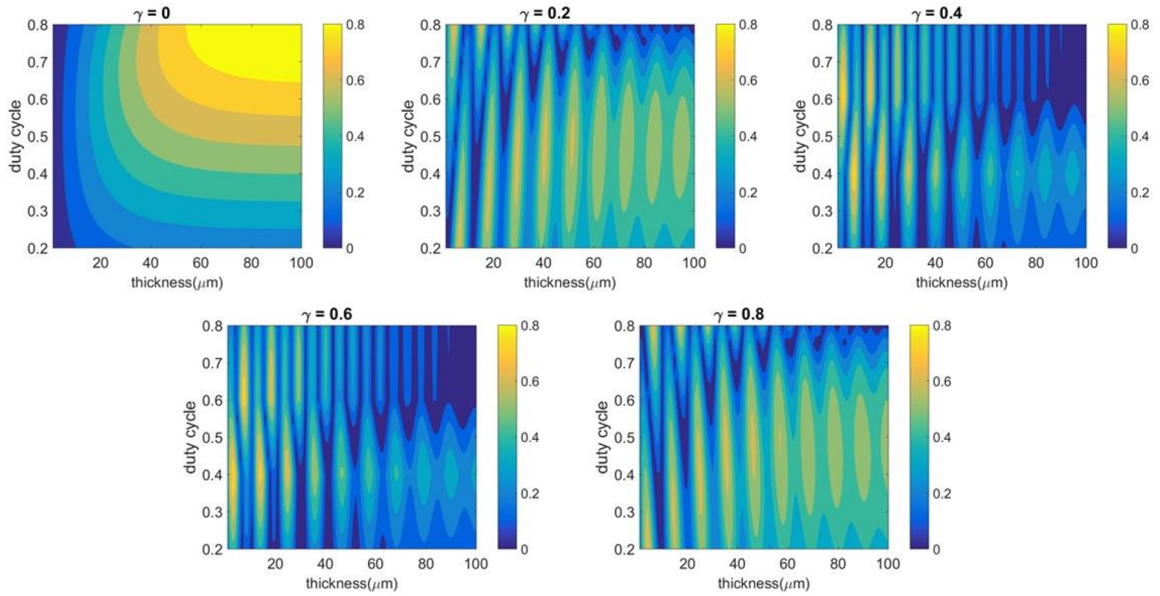


Figure 2: Contour map of the interferometer efficiency as a function of the gold thickness and grating duty cycle.

Based on our developed wave optics simulation framework, the visibility of the interferometer was analytically written as a product of the visibility of each individual grating with three parameters that are determined by the focal spot size, detector pixel pitch, and inter-grating spacing, together with an explicit dependence on the structure height and duty cycle of the gratings. As a result, the overall maximal visibility of the entire grating interferometer can be optimized by selecting the appropriate grating duty cycle and structure height of the gratings.

As shown by the example in **Figure 2**, performance of the interferometer depends on both duty cycle and structure height of the gratings. It also strongly depends on parameter γ, which is given by the multiplication of x-ray wave length (λ), source to grating distance (d_0), divided by the product of source size (p_s) and the period of the grating (p_1). When γ is close to 0, the optimal duty cycle and structure height clustered in the upper right corner of the interferometer efficiency contour map. It means the grating needs to have sufficient x-ray absorption (gold thickness > 40 µm). As γ increases, the grating thickness corresponding to the optimal efficiency can be greatly reduced, which corresponds to the far-field interferometer. For non-zero γ values, the high visibility regions are isolated to some cigar-shaped islands in the contour map. Therefore, the fabrication precision must be high enough for both the duty cycle and structure thickness. As an example, for typical values such as $\lambda = 4.4 \times 10^{-11}$ m, source to the first grating distance $d_0 = 0.5\,m$ and $p_s = 0.0001\,m$, in order to get $\gamma = 0.2$, the period of the grating should be less than a micron.

1.2 Design of Talbot-Lau grating interferometer for the trimodal mammography system

Under the guidance of the unified theoretical framework, parameters of a Talbot-Lau interferometer were determined for a clinical mammography system with a compact system geometry (source to detector distance = 70 cm). Major parameters of these gratings, including their pitch, duty cycle, aspect ratio, and material, are listed in **Table I**.

Table I: Grating Parameters.

Grating	Wafer size	Effective area	Pitch	Duty cycle	Material of x-ray absorber	Depth of x-ray absorber
G0	4 inch	3×3 cm^2	22.96 µm	58%	Gold	100 µm
G1	6 inch	7×7 cm^2	4 µm	50%	Nickle	11 µm
G2	4 inch	5×5 cm^2	2.19 µm	50%	Gold	50 µm

1.3 Grating fabrication and testing

Based on the design given in **Table I**, gratings (G0, G1, and G2) was fabricated by MicroWorks GmbH (Karlsruhe, Germany). After receiving the gratings, their performance was tested in a benchtop system shown in **Figure 3**. The uniformities of the fabricated gratings were characterized by taking their x-ray projection images and measuring the relative variation of the image signal value across different ROIs. As shown in **Figure 4**, the relative variabilities for G0, G1, and G2 are 0.6%, 0.2%, and 5%, respectively.

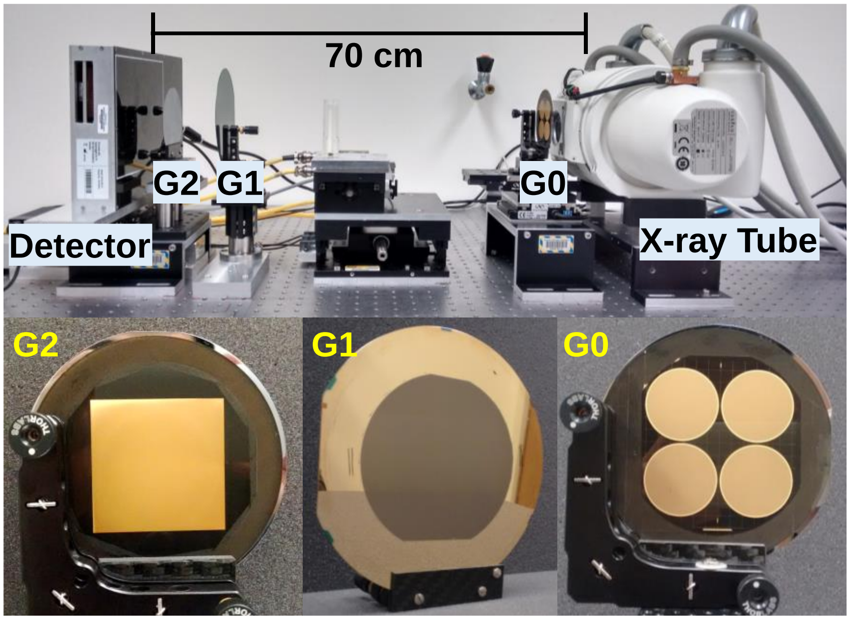


Figure 3: Evaluation of gratings in a benchtop imaging system that simulates the geometry of a clinical digital mammography unit.

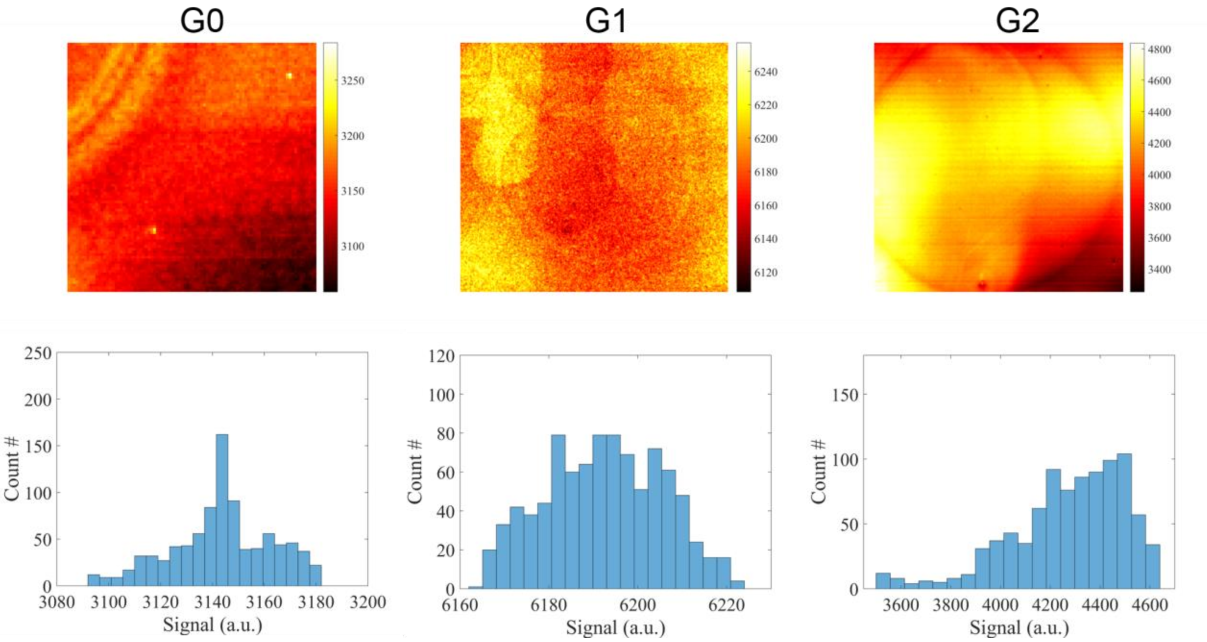


Figure 4: Top row: x-ray projection images of the three gratings. Bottom row: Uniformity of the gratings characterized by the histograms of the mean signal values measured in different ROIs in the gratings.

As shown by the fringe visibility map in Figure 4, the average fringe visibility is 15%±3%.

2. Integrate the grating interferometer with a digital mammography system

2.1 Lab installation of a full field digital mammography unit

At the end of Year 1, a used first-generation full field digital mammography system (Senographe 2000 D, GE Healthcare) found in the storage garage of our hospital was salvaged by us and installed in our laboratory (**Figure 5**).

Figure 5: A full field digital mammography system (Senographe 2000 D, GE Healthcare) was installed in our lab to construct the prototopye trimoal mammography imaging system.

Before modifying this system into the proposed trimodal system, we characterized its physical performance to provide the needed reference for the trimodal system. First, we performed flat field checks of the system. **Figure 6** shows a histogram of the measured pixel values. The system passed the following tests: brightness nonuniformity, high frequency modulation, bad pixel verification uniformity, and bad ROI.

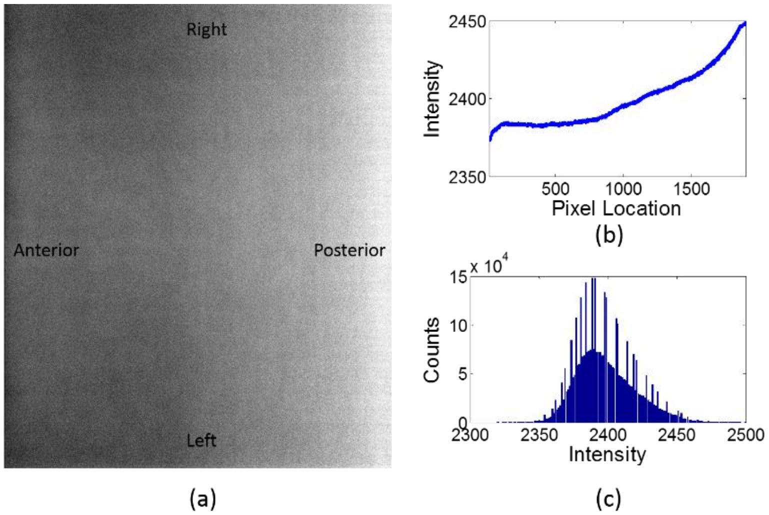


Figure 6: (a) Flat field image. (b) Horizontal line profile of the flat field image. (c) Histogram of the pixel values. The horizontal (anterior-posterior) variation was within 5% and was primarily caused by the heel effect.

Second, we performed phantom image quality (IQ) test using the ACR Mammography Accreditation Phantom. Below is a summary of the test results. The system passed the IQ test.

	No. of Fibers	No. of Speck Groups	No. of Masses
Measured	5.2	5.1	5.0
Required Minimum	4	3	3

Third, we tested the Automatic Optimization of Parameters (AOP) mode of the system using a 40 mm acrylic plate. The system passed the AOP test.

	Track	Filter	kV	mAs	SNR
Measured	Mo	Rh	28	66	75.6
Required	Mo	Rh	28	35-90	> 50

Finally, we measured the beam quality of the system at three representative x-ray energies. The half value layer (HVL) of the system was within the range recommended by MQSA.

Track/Filter	kV	HVL (mm of Al)	Required HVL	Pass?
Rh/Rh	30	0.406	Between 0.33 and 0.52	Yes
Rh/Rh	40	0.516	Between 0.43 and 0.62	Yes
Rh/Rh	49	0.570	Between 0.53 and 0.71	Yes

2.2 Installation of the grating interferometer

Based on the geometric constraints of clinical mammography imaging systems and the optical properties of the grating interferometer, geometric parameters of the interferometer setup have been determined and are summarized in **Table II**.

Table II: Parameters of system geometry

Tube-detector distance	70 cm
Tube-G0 distance	5.1 cm
Tube-G1 distance	59.2 cm
G0-G1 distance	54.1 cm
G1-G2 distance	5.62 cm

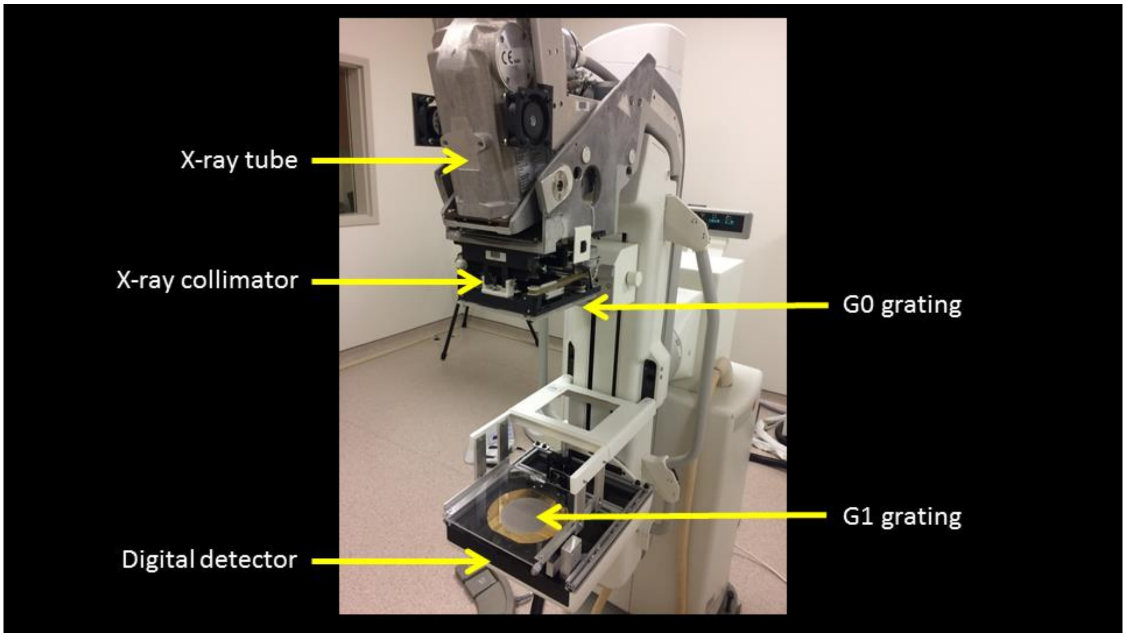


Figure 7: Modified mammography imaging system. Close-ups of the fixtures for the gratings are provided in Figure 6.

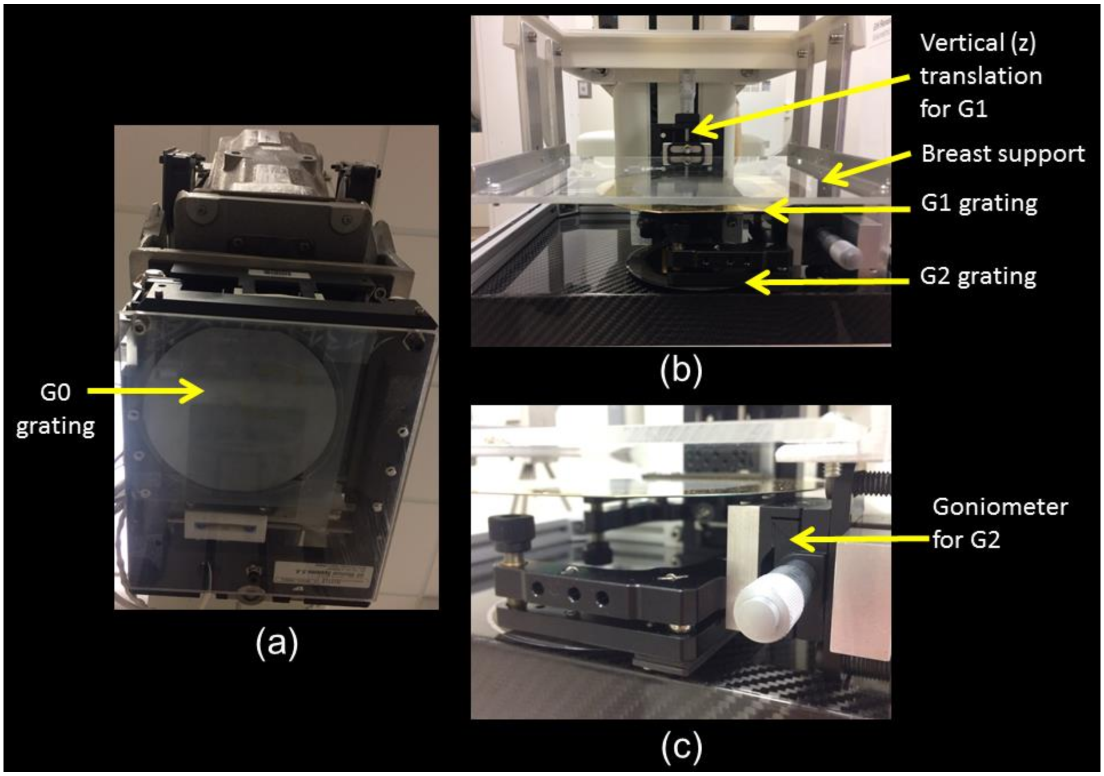


Figure 8: (a) The source grating G0 was attached to the exit window of the x-ray collimator assembly. (b) The phase grating G1 and analyzer grating G2 were installed above the detector surface. (c) A close-up of the optical system.

Photos showing how the gratings were installed in the digital mammography system were provided in **Figures 7 and 8**. The source grating (G0) was directly attached to the exit window of the x-ray collimator assembly. No other optical device was used for this grating. The phase grating (G1) was installed to an optics mount, which was then attached to a goniometer and a vertical translation stage. The optics mount and the goniometer allow the angular position (pitch, yaw, roll) of G1 to be adjusted, while the translation stage helps to adjustment the relative distance between G1 and the analyzer grating (G2). G2 was fixed in a position that is directly above the detector surface. An optics mount and a goniometer provide the needed degrees of freedom in aligning its angular position relative to G0.

2.3 Calibration of the grating interferometer

Calibration of the angular positions of the three gratings is crucial for the imaging performance of the trimodal imaging system. The calibration was performed as follows: Based on a straight line maker etched into the source grating, this grating was oriented to be perpendicular to the chest wall. Next, the other two gratings were aligned to the source grating by adjusting two goniometers, and the fringe visibility of the detected moiré pattern (**Figure 9a**) was used to monitor the coplanarity of the three gratings. Finally, the distance between the phase and analyzer gratings was fine-tuned using a linear translation stage, so that the fringe visibility of the interferometer system is maximized. **Figure 9(b)** shows a visibility map of the calibrated interferometer system, which generated a peak fringe visibility of 24% and a mean fringe visibility of 18% within an area of approximately 50 mm x 30 mm.

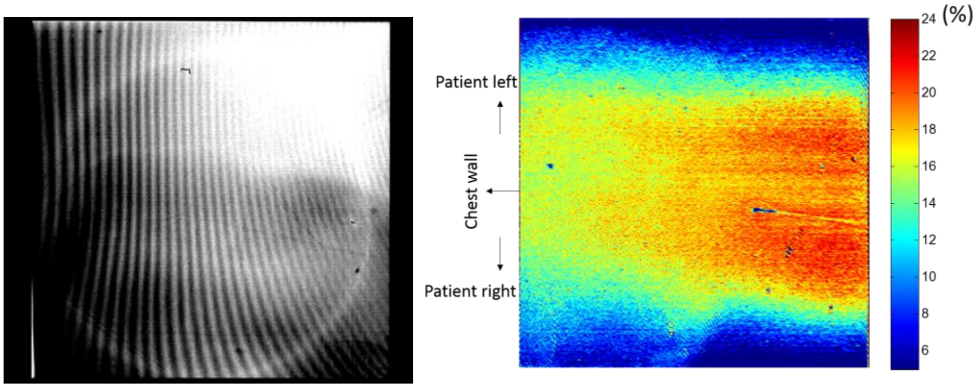


Figure 9: (a) The very first moiré pattern generated by the prototype system; (b) Fringe visibility map of the calibrated interferometer system.

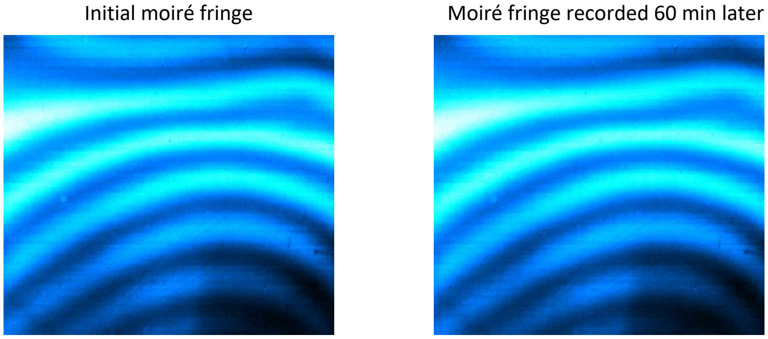


Figure 10: Two consecutive moiré patterns were acquired with a time interval of 60 minute. Compared with the first moiré image, the relative root mean square error of the second image is 3.2%, indicating good system reproducibility and no significant drift of grating response.

3. Objective characterization and optimization of the trimodal mammography system

3.1 Phantom results

Figure 11 shows the very first phantom result generated by the constructed prototype trimodal imaging system. The phantom contains a layer of calcification power overlaid on top of microbubbles. **Figure 12** shows additional images generated from the constructed prototype system. The three contrast mechanisms provided additional material information that was missing in the conventional x-ray absorption contrast image.

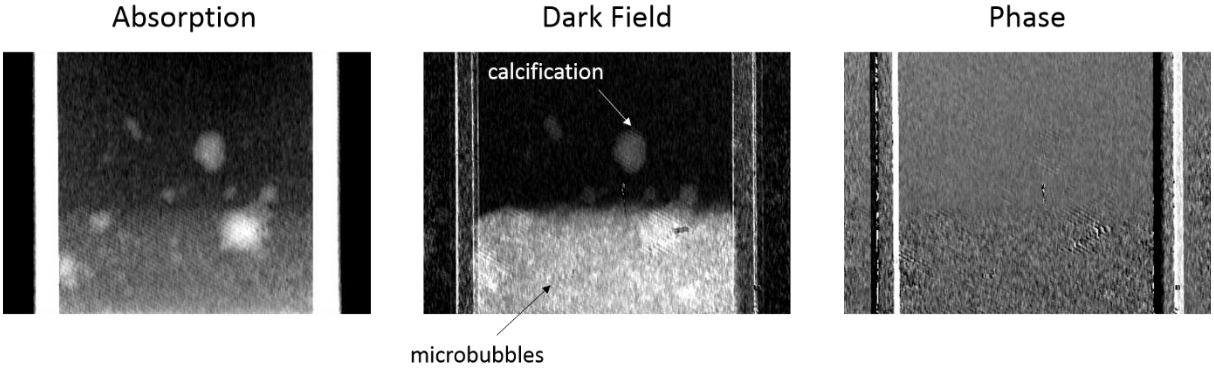


Figure 11: First phantom results generated by the constructed multi-contrast (x-ray absorption, dark field, and differential phase) imaging prototype system. The phantom contains an overlay of calcifications on top of microbubbles.

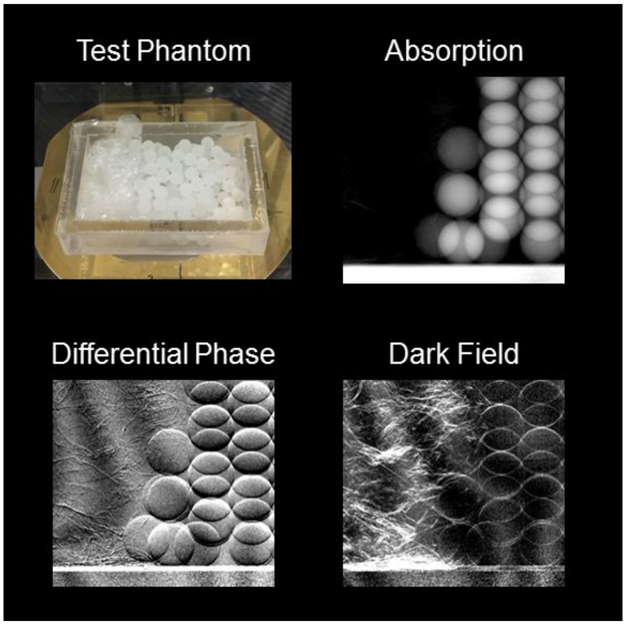


Figure 12: Multi-contrast (absorption, differential phase, dark field) images of another physical phantom generated by the prototype trimodal imaging system.

3.2 Results of biological specimens

Performance of the calibrated prototype trimodal x-ray imaging system was further evaluated using the following biological specimens. **Figure 13** shows multi-contrast images of this specimen acquired from the prototype system. The three contrast mechanisms are mutually supplementary, and in together, provided rich information about the pulmonary parenchyma and vasculature.

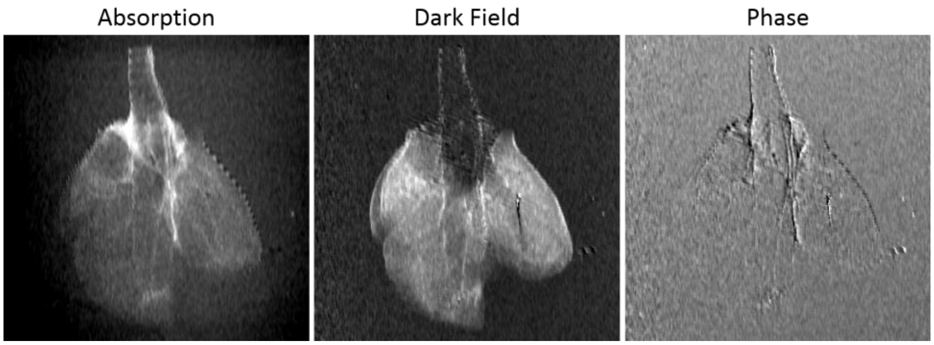


Figure 13: Multi-contrast images of a mouse lung specimen acquired from the prototype system.

To study the potential of using multi-contrast agents for trimodal imaging, a fresh bovine specimen was imaged. This specimen contains three contrast agents, including iodine that can be highlighted by the absorption contrast, microbubbles that can be highlighted by the dark field contrast, and PMMA spheres that can be highlighted by the phase contrast mechanism. As shown in **Figure 14**, the three contrast agents can be clearly differentiated by the three contrast mechanisms, which do not seem to be achievable by the conventional x-ray absorption contrast alone.

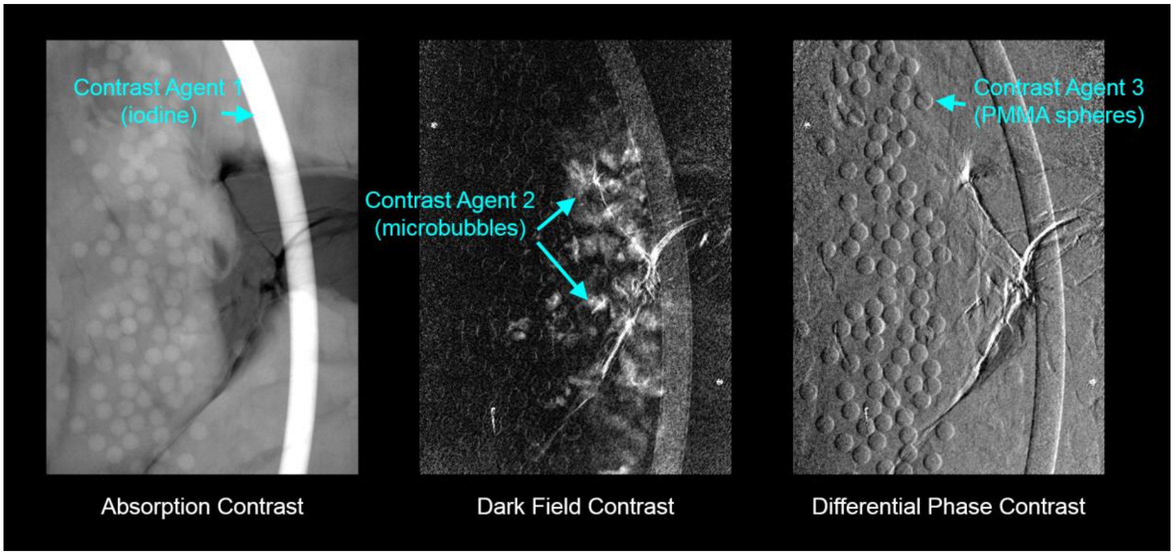


Figure 14: Each of the three contrast mechanisms highlights a unique contrast agent embedded in the bovine specimen.

3.3 Reduction of vignetting effect

Grating-based trimodal x-ray imaging often suffers a so-called vignetting effect. As shown in **Figure 15**, in the far left and right edges of the 5 cm x 5 cm field-of-view (FOV), the image noise increased significantly, which degraded image quality, impaired the detectability of local features, and reduced the effective system FOV almost by 30%. Since the noise magnitude of phase contrast images is inversely proportional to the diffraction fringe visibility, we experimentally measured the visibility for every spatial location in the FOV in order to find out the origin of the vignetting effect. As shown in the right image in **Figure 15**, there is significant reduction in fringe visibility when the location gets closer to the left and right edges of the FOV. We found that the effect was induced by the beam divergence of the prototype system. As shown by the schematic illustration in **Figure 16**, when a flat grating was used in a divergent x-ray beam, except the central ray, most x-rays will impinge the grating from certain oblique angles; in certain extreme cases, the beam modulation effect introduced by an ideal grating setup will be completely lost (e.g., ray 3 in Figure 2), which basically eliminate fringe visibility.

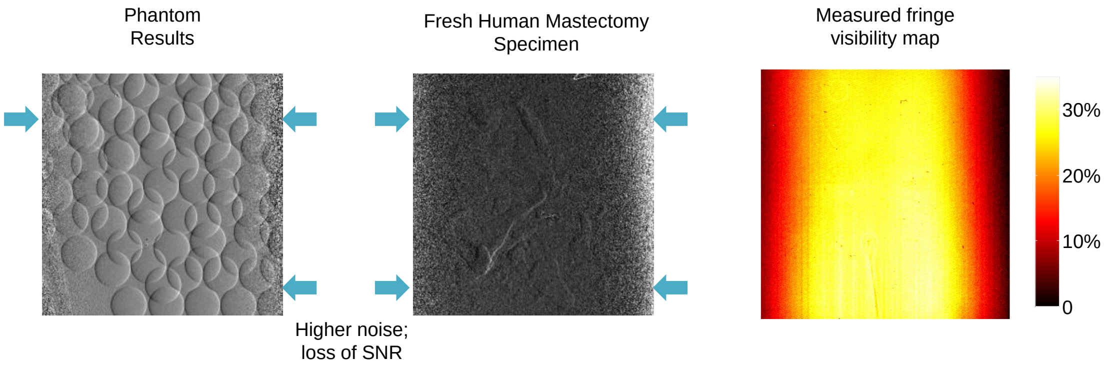


Figure 15: Examples of the vignetting effect. The phase contrast images of the physical phantom and mastectomy specimen acquired from the prototype system demonstrated significant loss of signal-to-noise ratio (SNR) at the left/right peripheral regions of the field-of-view. The experimentally measured fringe visibility map indicates that the loss of visibility contributes to the vignetting effect.

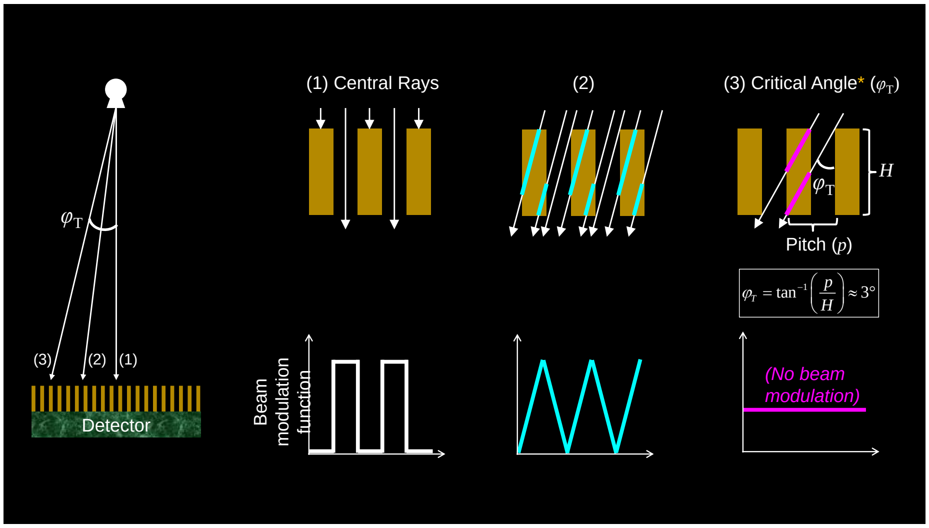


Figure 16: Demonstration of the influence of beam divergence on the wave optical efficiency of the grating interferometer system. Except the central ray (1), x-rays reaching the grating at certain oblique angles experience certain degrees of beam modulation reduction. Beyond a critical angle φ_T, all beam modulation will be lost (ray 3).

This vignetting effect is undesirable since it reduces the effective FOV of the prototype system. To address this technical challenge, we developed a practical method to bend the gratings based on the system geometry and beam divergence of the prototype system. As shown in **Figure 17**, we softened and bent a wood panel, then fixed its shaped based on the desired curvature. Then we fabricated a grating holder using the curved wood panel. The holder sandwiched the grating to force it to bend to the desired curvature. As shown by the visibility map acquired with the curved grating in **Figure 17**, no significant visibility reduction was observed at the edge of the FOV. **Figure 18** shows example mastectomy specimen images acquired without and with the curved grating. The grating bending method reduced the vignetting effect and maximized the utilization of the 5×5 cm^2 grating area.

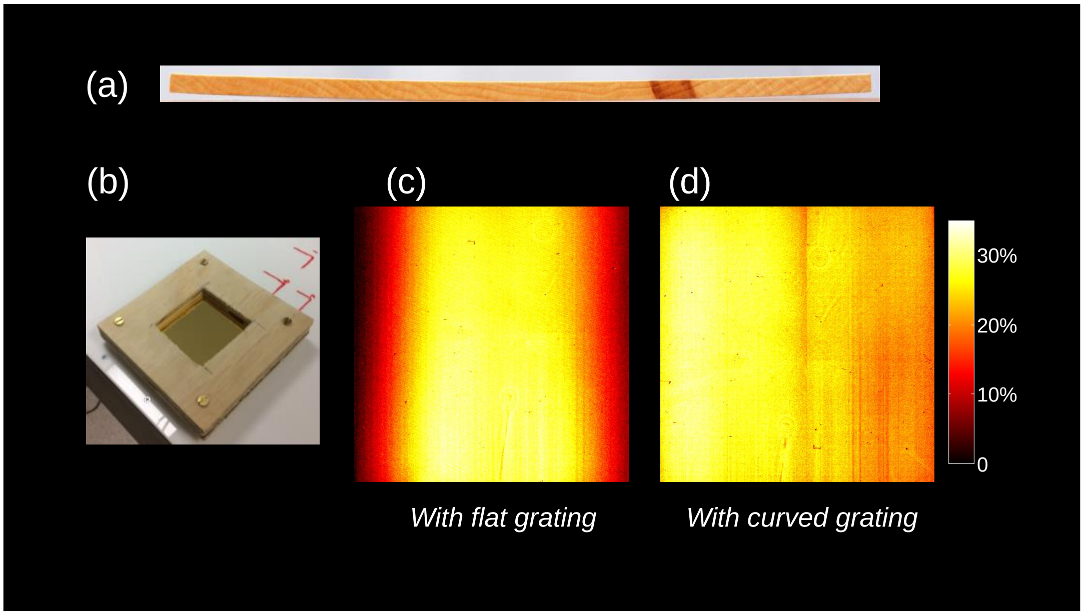


Figure 17: (a) Curved wood panel. (b) Grating holder made of the curved wood panel. (c) Visibility map acquired with the original flat grating. (d) Visibility map acquired using the curved grating.

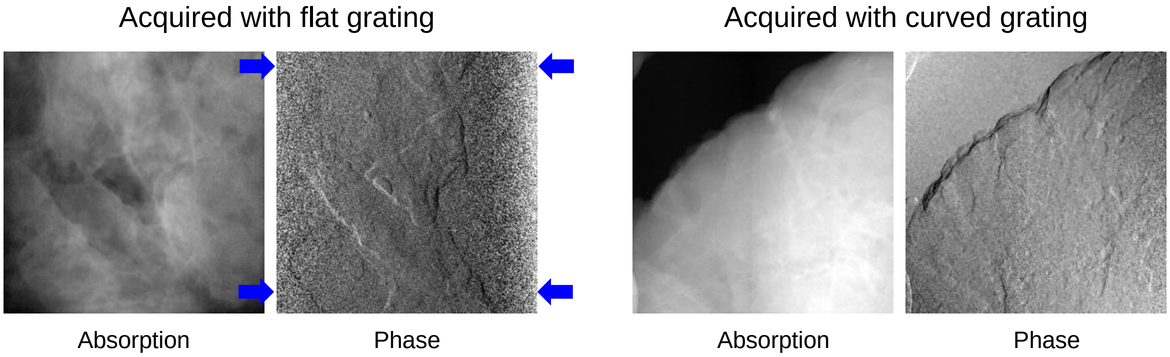
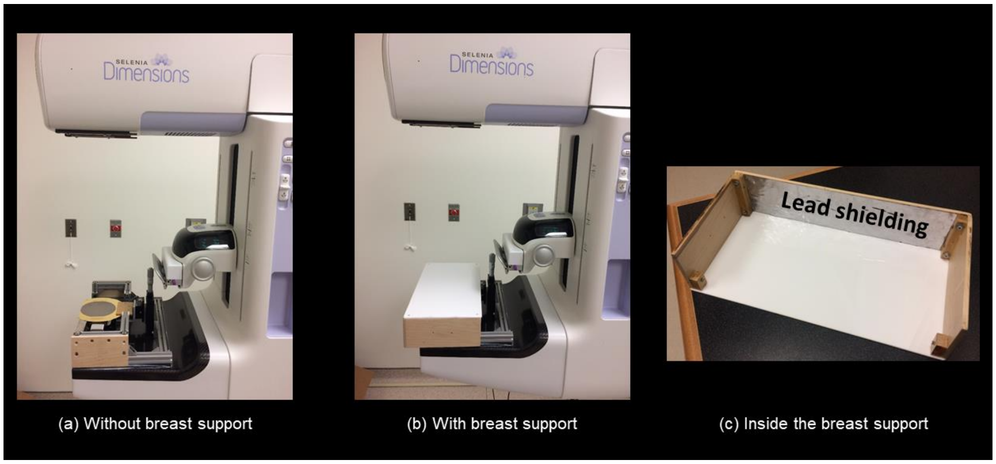


Figure 18: Comparison of multi-contrast images acquired before and after the system upgrade with the curved grating. The previous vignetting problem (pointed by the arrows) is addressed after the system upgrade.

3.4 Reduction of scattered radiation

Based on the experience accumulated during the construction of the first prototype system, an additional trimodal x-ray imaging prototype was developed in Year 2 to provide a version 2.0 system with upgraded functionality. This 2.0 prototype system was built based on a state-of-the-art x-ray breast imaging machine (Hologic Selenia Dimensions) with up-to-date operating systems that greatly facilitates postprocessing and transfer of the acquired multi-contrast images (**Figure 19**).



(a) Without breast support
(b) With breast support
(c) Inside the breast support

Figure 19. Customized breast support for the prototype system.

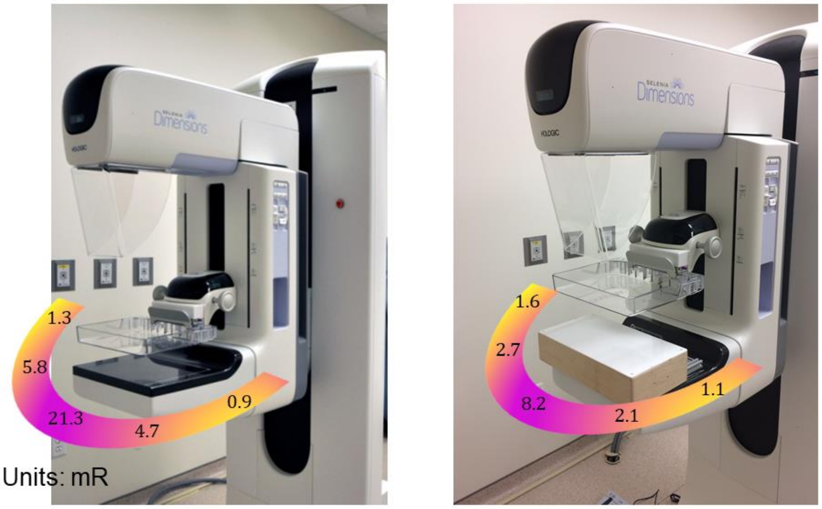


Figure 20: Measured scattered radiation for the conventional digital breast imaging system (left) and the prototype trimodal x-ray breast imaging system (right). Both systems were operated at 36 kV and 140 mAs. The prototype system led to reduced exposure levels at locations corresponding to the patient chest wall.

To eliminate the possible scatter radiation introduced by the grating assembly, a lead shielding was introduced to a side wall of the breast support that faces the patient chest wall (**Figure 20**). Exposure measurements were performed to both the original Hologic system and the constructed trimodal system. At positions that correspond to the patient chest wall, scattered radiation was reduced due to the use of lead shielding. In other words, the prototype system does not introduce additional scattered radiation to patients.

3.5 Potential for further radiation dose reduction using photon counting detectors

Since breast is a radiosensitive organ and there is strict regulation on the amount of ionizing radiation that can be delivered during a mammographic imaging procedure, it is highly desirable to reduce radiation dose of the trimodal image acquisition as much as possible (as long as the desired diagnostic imaging performance can be accomplished). In this project, we leveraged the photon counting detector (PCD) technology to further reduce radiation dose of trimodal imaging. The first strategy is to utilize the energy resolving capability of PCD: Based on the low dimensionality of the phase contrast images generated from different energy bins of an energy-resolving photon counting detector (PCD), we have developed a method to reduce noise of phase contrast images. **Figure 21** compares phase contrast images generated with or without the proposed method. This method can potentially be used to improve the radiation dose efficiency of the proposed trimodal mammography imaging system.

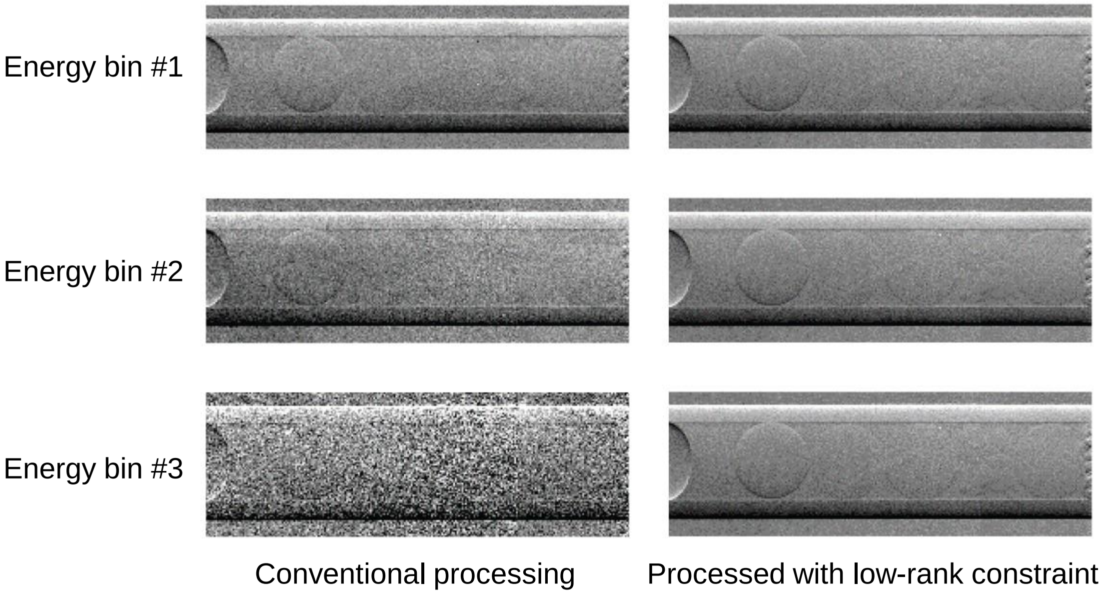


Figure 21: Phase contrast images of a physical phantom. Images in the left row were generated from the three energy bins of the PCD with standard processing. Images in the right row were processed using the proposed rank-one approximation method (adapted from *Optics Express*, Vol. 24, pp.12955, 2016).

The another dose reduction strategy is to utilize the higher detective quantum efficiency of PCD due to its direct conversion x-ray detection mechanism and electronic noise rejection capability. As shown in **Figure 22**, there is potential for radiation dose reduction in trimodel mammography by combing the PCD with the grating interferometer.

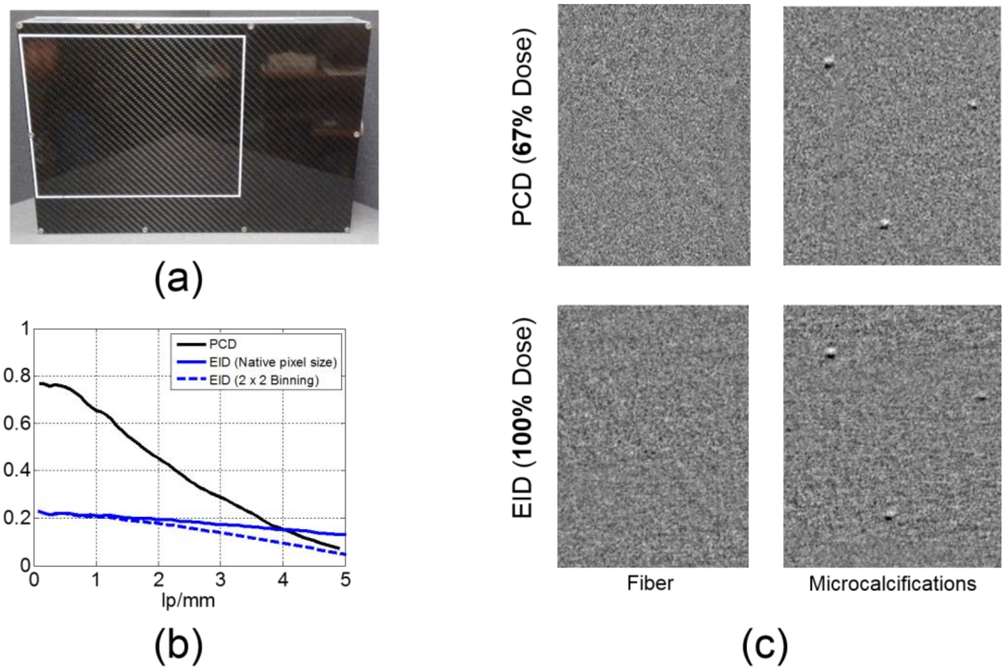


Figure 22: (a) XC-FLITE X1 PCD (XCounter, Sweden) used in this project. (b) Comparison of detective quantum efficiency (DQE) of the PCD and a conventional energy integrating detector (EID) (Shad-o-box 2028, Teledyne DALSA Canada). (c) Phase contrast images of an American College of Radiology (ACR) Mammography Accreditation Phantom shows that the PCD leads to at least 33% reduction in radiation dose.

3.6 Improvement of trimodal image acquisition speed

A major technical obstacle to bringing x-ray multi-contrast (i.e., attenuation, phase, and dark-field) imaging methodology to clinical use is the prolonged data acquisition time caused by a so-called phase stepping procedure. During this project, we developed a Fast Acquisition with Seamless Stage Translation (FASST) technique reduce the trimodal image acquisition time to a clinically acceptable level. During each FASST acquisition process (**Figure 23**), a motorized stage holding a diffraction grating travels continuously with a constant velocity, and a train of 15 short x-ray pulses (35 ms each) was delivered by using the Zero-Degree Tomo mode of the Hologic system. Standard phase retrieval was applied to the 15 sub-images without spatial interpolation to avoid spatial resolution loss.

The FASST method was evaluated using a physical phantom (**Figure 24**), a bovine udder specimen (**Figure 25**), and a freshly resected mastectomy specimen (**Figure 26**). The FASST technique was experimentally compared with single-shot acquisition methods and the standard phase stepping method. Using FASST, the trimodal image acquisition time is 3.7 s. In comparison, conventional phase stepping took 105 s using the same prototype imaging system. The mean glandular dose of both methods was matched at 2.2 mGy. No artifacts or spatial resolution loss was observed in images produced by FASST. In contrast, the single-shot methods led to spatial resolution loss and residual moiré artifacts. Because 3.7 s is identical to one mammographic view of a clinical DBT exam, this imaging time is considered clinically acceptable

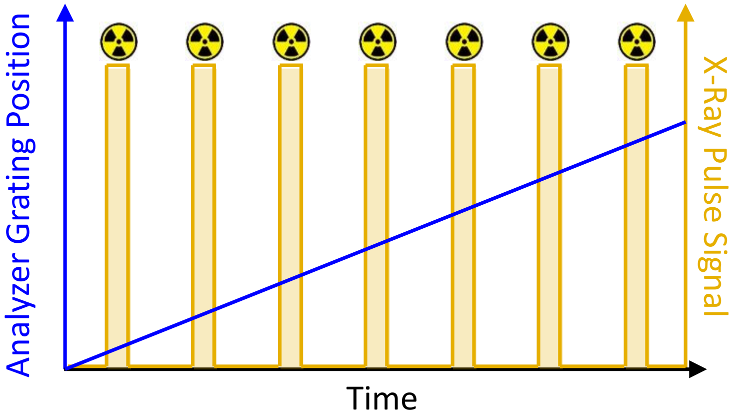


Figure 23: Schematic illustration of the FASST trimodal image acquisition method. The basic idea of the FASST technique is to replace the interleaved grating motion by a continuous translation, during which a rapid train of ultra-short x-ray pulses are fired. The continuous translation eliminates the time spent on accelerating, decelerating, and stabilizing the grating. The speed of the translation stage is fixed at a value such that between the first and last pulses, the stage travels one grating period. Because of the ultra-short pulse width, during each exposure, the grating only travels about 0.02 mum, which makes motion artifact negligible. Moreover, this short pulse also reduces motions from the patient and system vibration. The FASST technique was implemented in System 2.0 using the Zero-Degree Tomo mode provided by the Hologic DBT system. This mode was originally designed by the vendor for DBT quality control: its acquisition parameters and time are identical to those of a typical DBT exam, except that the x-ray tube is kept stationary at the zero-degree projection angle. During each FASST procedure, a zero-degree tomo acquisition is activated once the translation stage goes to a continuous motion. The tube and generator systems fire a total of 15 pulses (35 ms each) over a time span of 3.7 s.

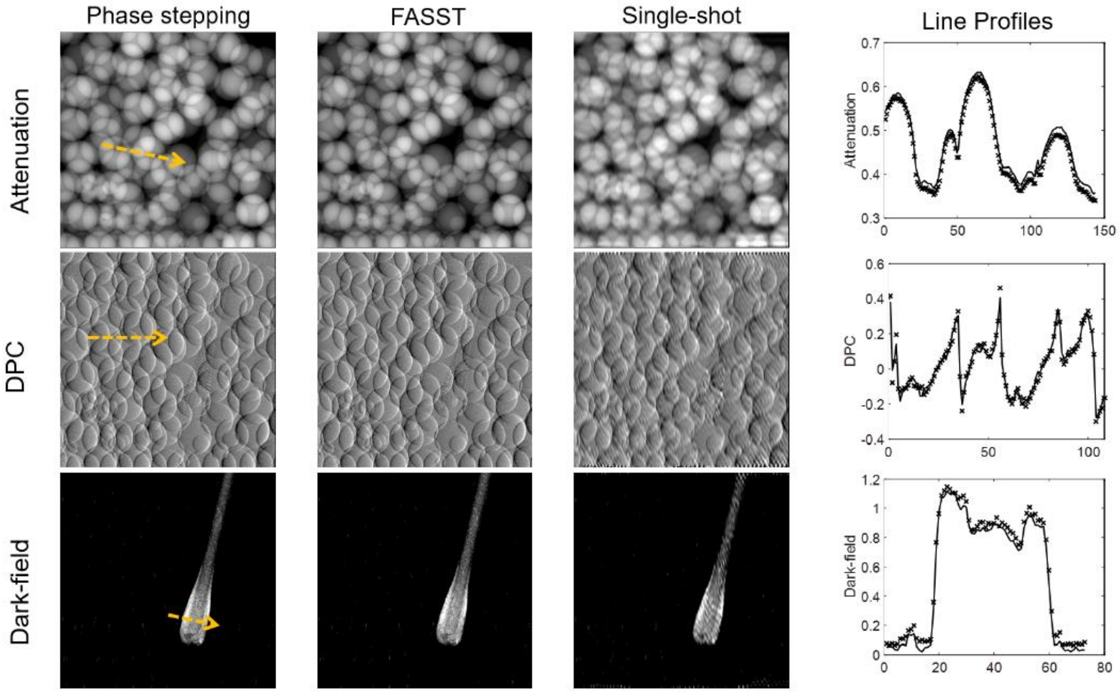


Figure 24 (bottom of the previous page): Trimodal images of a physical phantom that contains PMMA spheres and a cotton swab. Images in the first, second, and third column were acquired using standard phase stepping, FASST, and a single-shot (moire) method, respectively. The arrows in the phase stepping images indicate the pixels for which line profiles were drawn and shown in the last column. Although all three methods were able to produce trimodal images with complementary material information, the single shot method generated images with blurred edges and residual moire artifacts. In comparison, the image quality of FASST images matched that of standard phase stepping images. The line profiles shown in this figure confirmed the absence of spatial resolution loss in the FASST images.

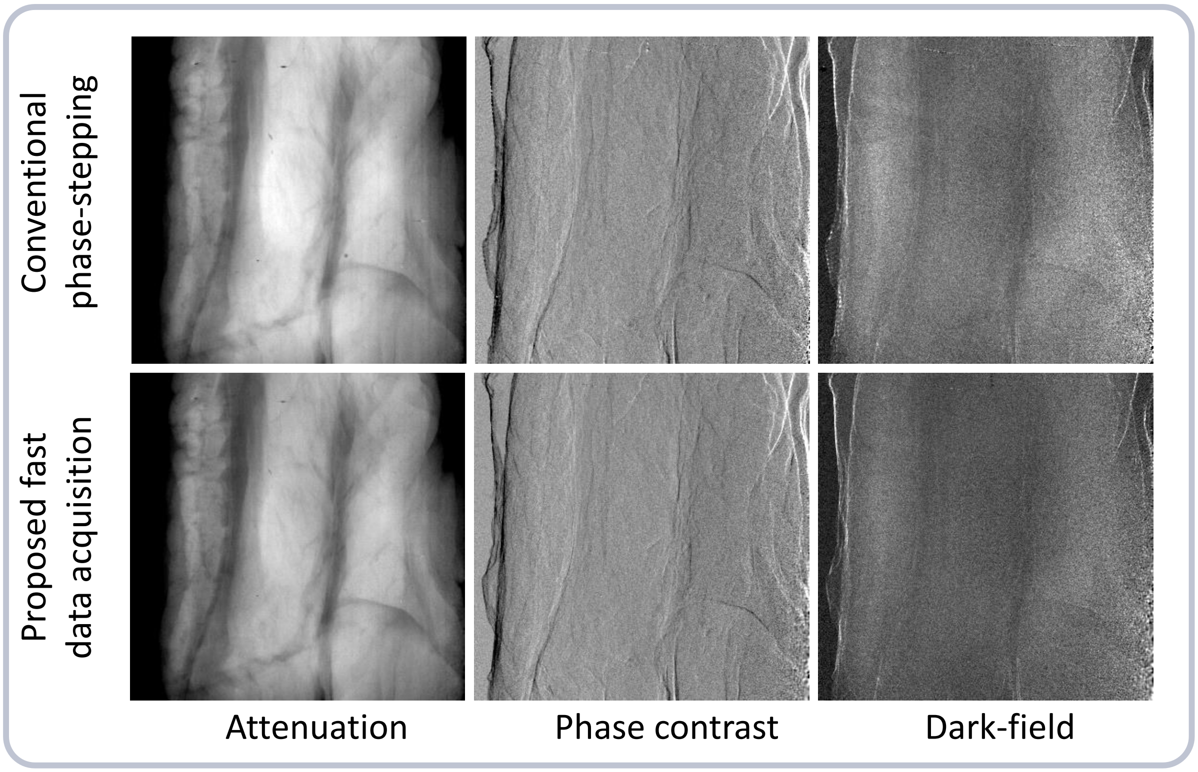


Figure 25: Images of a pork belly specimen purchased from a local grocery store. Imaging time of the proposed FASST technique is only 6% of standard phase stepping procedure. No spatial resolution loss is observed in the FASST images.

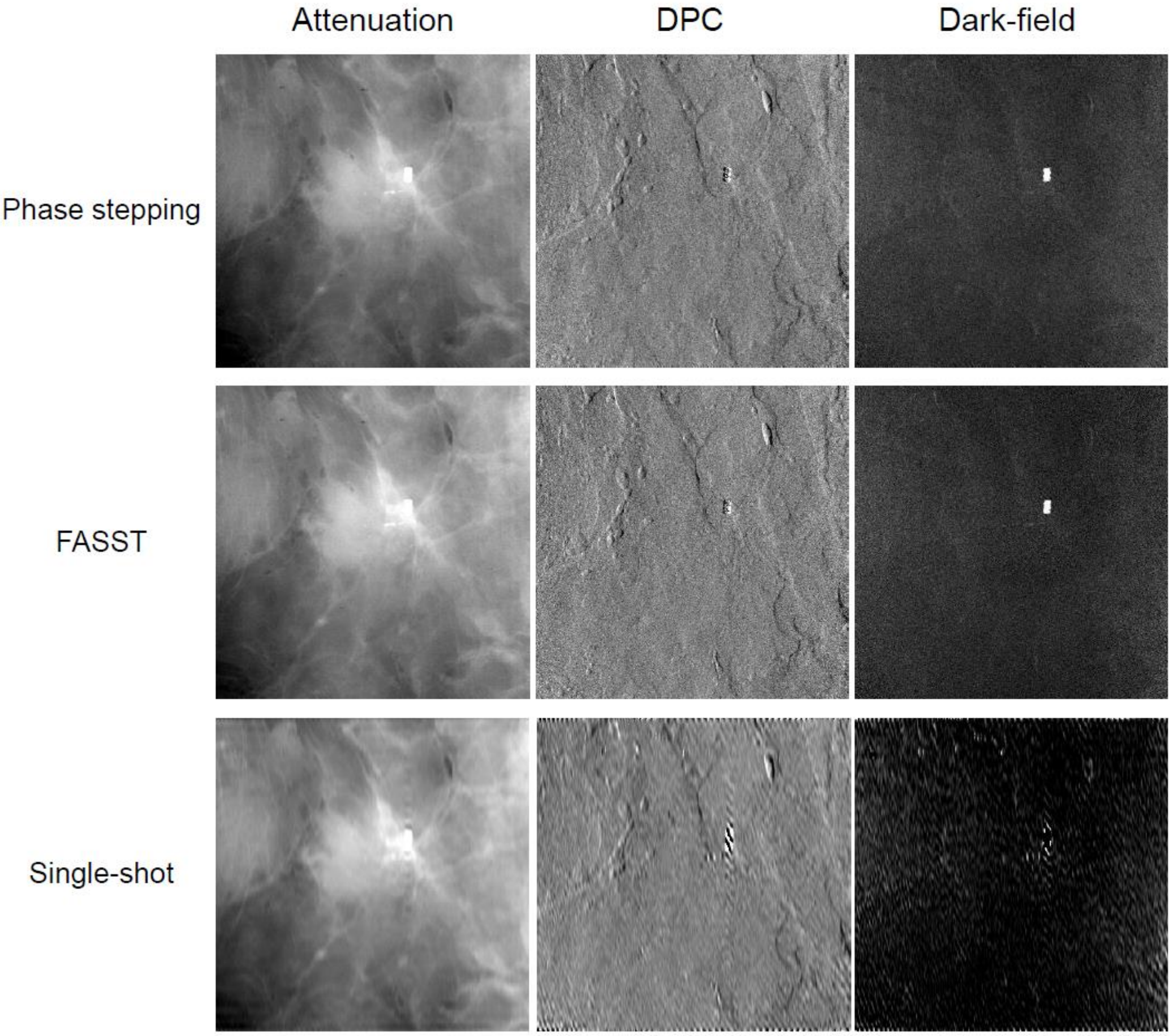


Figure 26: Trimodal images of the human mastectomy specimen. Images in the top row were acquired using conventional phase stepping (105 s). Images in the second and third rows were acquired using FASST (3.7 s) and a single-shot method (moire metrology, 1 s), respectively. Compared with the conventional phase stepping method, the FASST method preserved the sharpness of the metal clips and interfaces between fibroglandular and adipose tissues. In comparison, the single shot method not only degraded spatial resolution but also introduced residual moire artifacts and contrast loss (e.g., for the metal clip in the DPC and dark field images).

4. Performance evaluation of the trimodal mammography imaging system using mastectomy specimens

Performance of the prototype trimodal mammographic imaging systems was also evaluated using freshly resected mastectomy specimens. As shown in Figures 27-28, compared with conventional x-ray absorption contrast images, x-ray phase contrast images of the mastectomy specimens provide complementary soft tissue information and effectively enhanced the boundaries between glandular and adipose tissues.

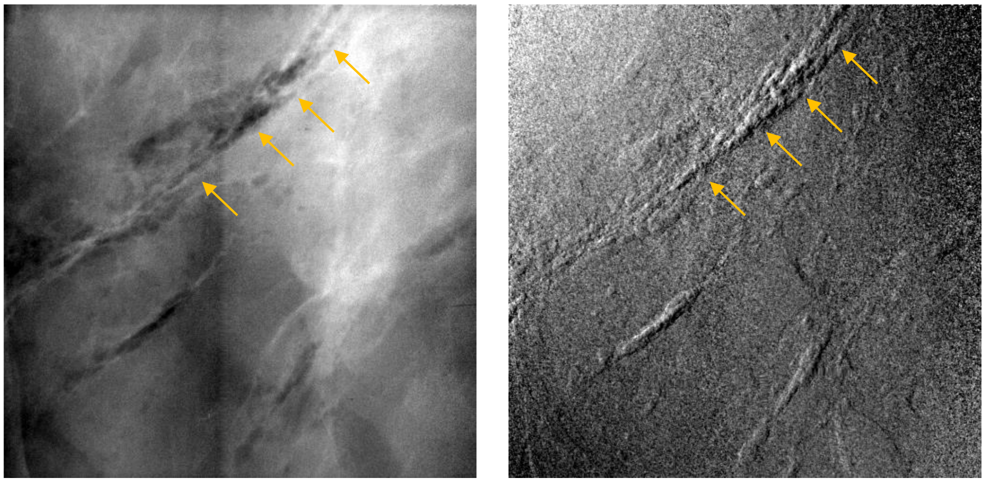
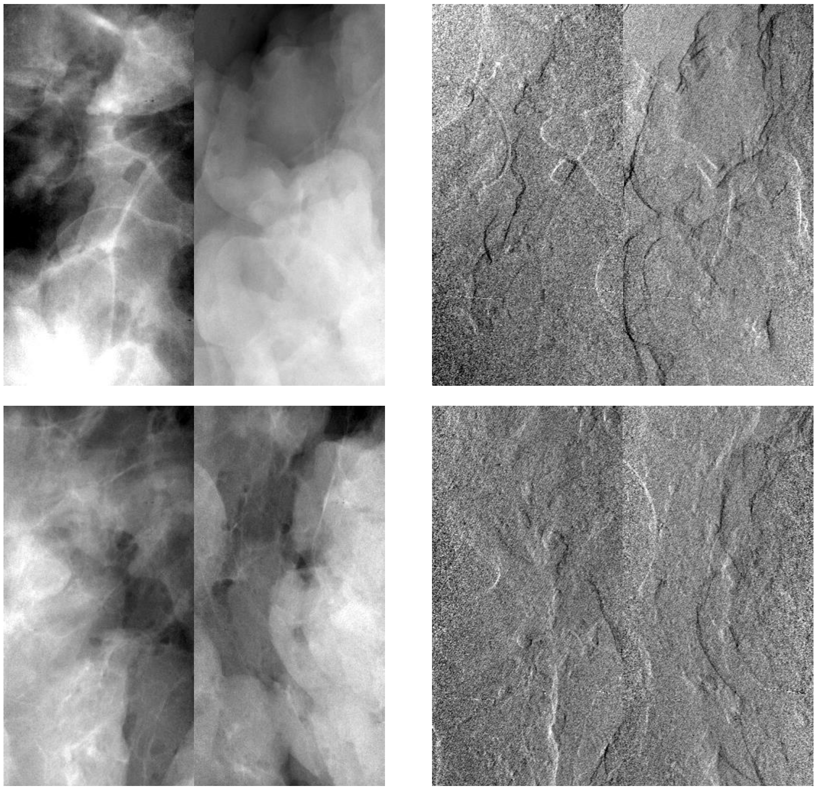


Figure 27: Absorption contrast (left column) and differential phase contrast (right column) images of mastectomy specimens. The arrows point to adipose tissue.



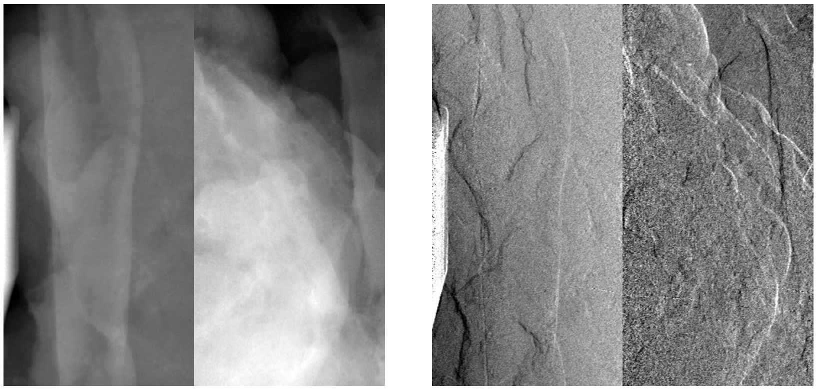
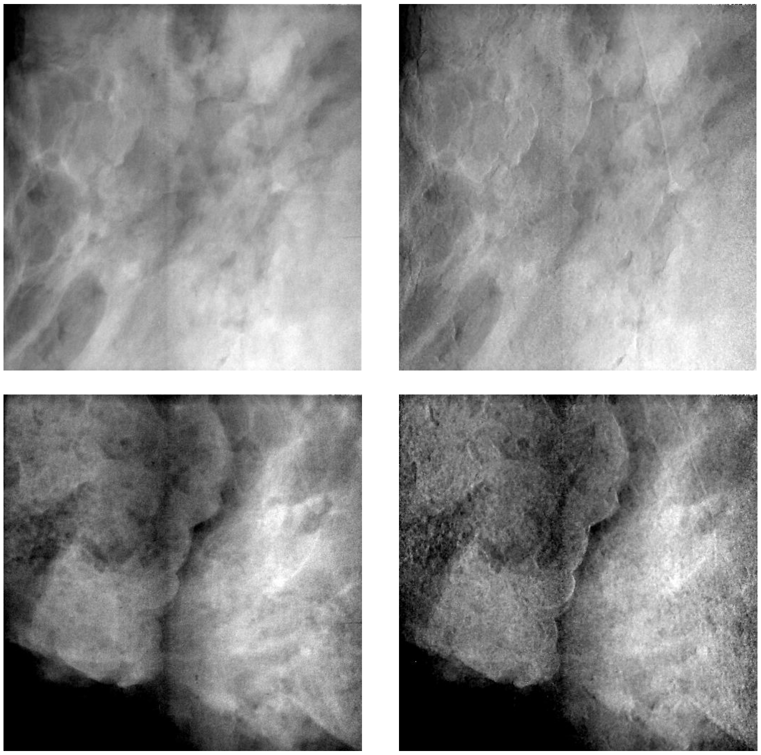


Figure 28: Absorption contrast (left column) and differential phase contrast (right column) images of mastectomy specimens.

Because differential phase contrast image generated from the trimodal mammography system has a unique visual appearance which a breast radiologist may be unfamiliar with, we applied a wavelet transform-based method to fuse the edge enhancement information of the differential phase contrast image with the absorption contrast image with the classical mammographic appearance (**Figure 29 and Figure 30**).



(a) Absorption

(b) Fused image

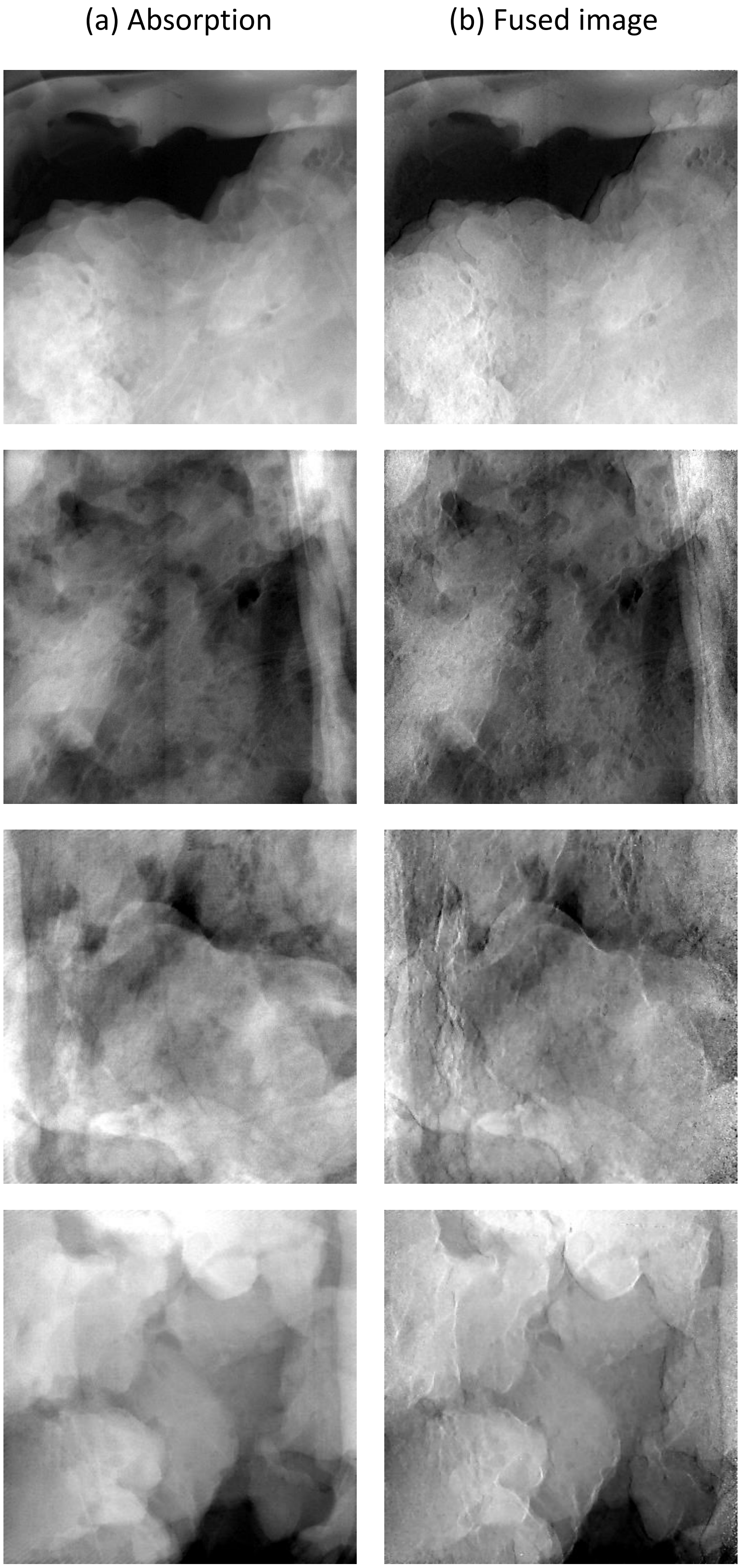
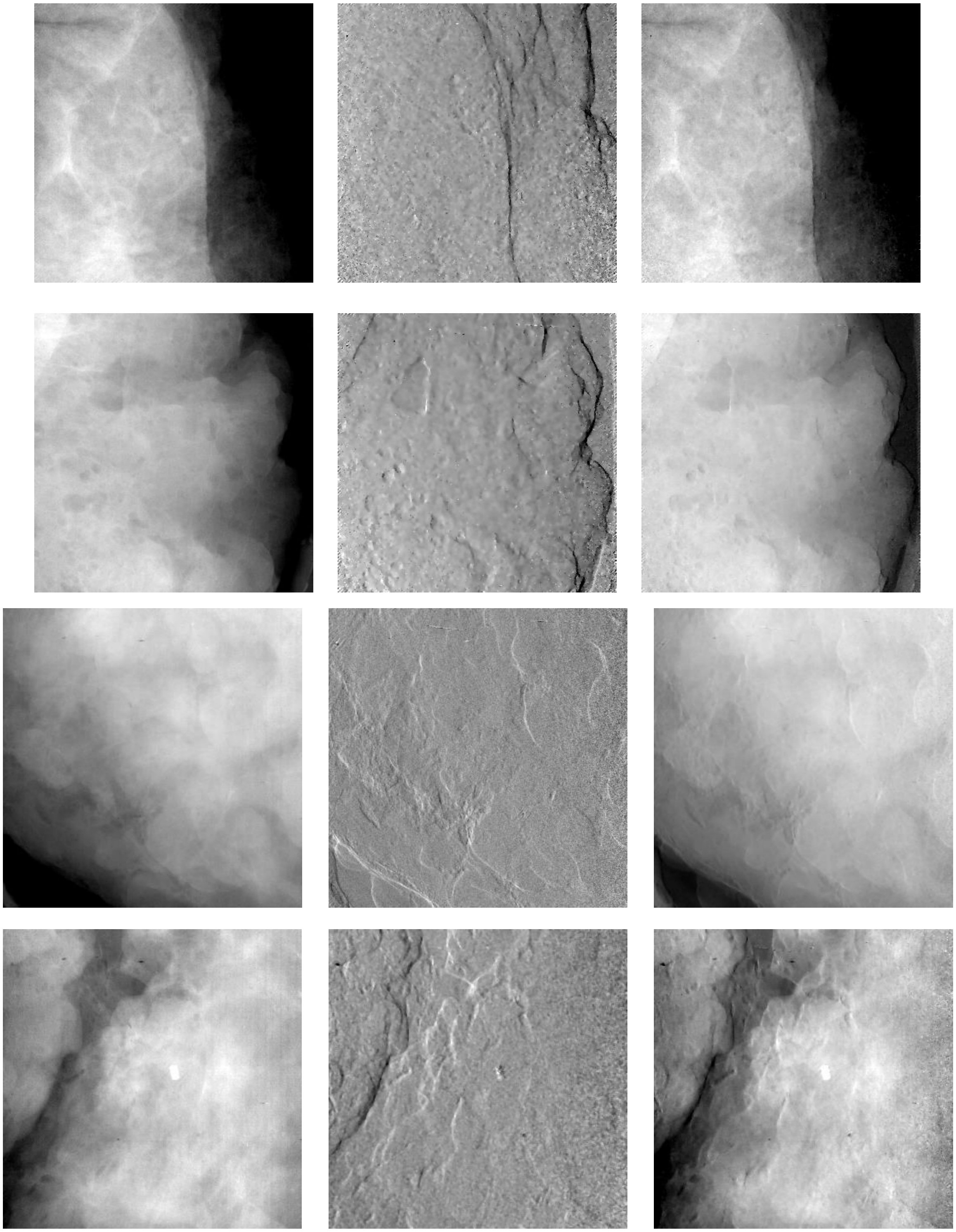

(a) Absorption
(b) Fused image

Figure 29: Absorption contrast (left column) and fused images (absorption + differential phase, right column) of mastectomy specimens.



Absorption contrast image

Differential phase contrast (DPC) image

Absorption + DPC image fusion

Figure 30: Comparison of individual absorption and differential phase contrast images with the fused images for each mastectomy specimens.

What opportunities for training and professional development has the project provided?

The University of Wisconsin-Madison requires that all graduate students and postdoctoral researchers supported by federal funding utilize Individual Development Plans to set academic and career goals and facilitate conversations with their mentors. The university offers a collection of resources and tools to support mentees, mentors, and PIs in implementing IDPs. These include a UW-Madison IDP template, workshops for mentees (both face-to-face and online videos), peer learning groups for mentees, as well as guidelines for mentors.

How were the results disseminated to communities of interest?

We published results in peer reviewed journals such as Physics in Medicine and Biology, Medical Physics, and IEEE Transactions on Medical Imaging. The results were also disseminated to the breast imaging community via our presentations at medical imaging conferences including the AAPM Annual Meeting, the RSNA Annual Meeting, the SPIE Medical Imaging Conference, and the International Conference on X-ray and Neutron Phase Imaging with Gratings.

What do you plan to do during the next reporting period to accomplish the goals?

Nothing to Report

4. IMPACT: Describe distinctive contributions, major accomplishments, innovations, successes, or any change in practice or behavior that has come about as a result of the project relative to:

What was the impact on the development of the principal discipline(s) of the project?

The impact made by research in Year 1 is on how to adapt the trimodal imaging method to the geometry and x-ray spectrum of clinical mammography systems. Research conducted under the support of this project generated new knowledge on how to modify a conventional mammography to enable three x-ray contrast mechanisms to be generated from the same data acquisition. The field of x-ray phase contrast and dark field imaging can benefit from the research developments in this project, which for the first time demonstrated the feasibility of x-ray multi-contrast imaging using a clinical full field digital mammography system.

For the research developments in Year 2: The successful construction of the prototype trimodal mammographic imaging system provides the first experimental demonstration of the compatibility of the trimodal x-ray imaging method with the geometry and hardware of clinical full field digital mammography system. The constructed system would significantly advance the field, since previous studies on multi-contrast x-ray breast imaging were performed using synchrotron- or benchtop-based systems that are usually not directly compatible with the clinical dose constraint, system compactness, and limited x-ray beam quality as seen in clinical mammography systems. Additional knowledge has been gained on how to integrate the gratings with a digital mammography system together with the needed mechanical support for a compressed breast, while not introducing any additional radiation to the patient. Knowledge is also gained on how to calibrate the three gratings to maximize the trimodal imaging performance.

For the research developments in Year 3: This project demonstrates the feasibility of human mastectomy specimens trimodal mammography imaging within 30 minutes after surgical resection using the prototype system developed in this project. Upon further radiologist evaluation, imaging results of these fresh breast specimens will advance knowledge about the bio-signature of breast cancer in x-ray phase contrast and dark field images.

Research performed in Year 4 demonstrated that the both the radiation dose level and data acquisition time of trimodal mammography imaging can be reduced to a clinically acceptable level, which will help translating the trimodal imaging technology to clinical breast imaging.

What was the impact on other disciplines?

If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe how the findings, results, or techniques that were developed or improved, or other products from the project made an impact or are likely to make an impact on other disciplines.

Nothing to Report.

What was the impact on technology transfer?

If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe ways in which the project made an impact, or is likely to make an impact, on commercial technology or public use, including:

- *transfer of results to entities in government or industry;*
- *instances where the research has led to the initiation of a start-up company; or*
- *adoption of new practices.*

Nothing to Report.

What was the impact on society beyond science and technology?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe how results from the project made an impact, or are likely to make an impact, beyond the bounds of science, engineering, and the academic world on areas such as:

- *improving public knowledge, attitudes, skills, and abilities;*
- *changing behavior, practices, decision making, policies (including regulatory policies), or social actions; or*
- *improving social, economic, civic, or environmental conditions.*

Nothing to Report.

5. CHANGES/PROBLEMS: The Project Director/Principal Investigator (PD/PI) is reminded that the recipient organization is required to obtain prior written approval from the awarding agency Grants Officer whenever there are significant changes in the project or its direction. If not previously reported in writing, provide the following additional information or state, "Nothing to Report," if applicable:

Changes in approach and reasons for change
Describe any changes in approach during the reporting period and reasons for these changes. Remember that significant changes in objectives and scope require prior approval of the agency.

Nothing to Report.

Actual or anticipated problems or delays and actions or plans to resolve them
Describe problems or delays encountered during the reporting period and actions or plans to resolve them.

Nothing to Report.

Changes that had a significant impact on expenditures

Describe changes during the reporting period that may have had a significant impact on expenditures, for example, delays in hiring staff or favorable developments that enable meeting objectives at less cost than anticipated.

Nothing to Report.

Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents

Describe significant deviations, unexpected outcomes, or changes in approved protocols for the use or care of human subjects, vertebrate animals, biohazards, and/or select agents during the reporting period. If required, were these changes approved by the applicable institution committee (or equivalent) and reported to the agency? Also specify the applicable Institutional Review Board/Institutional Animal Care and Use Committee approval dates.

Significant changes in use or care of human subjects

Nothing to Report.

Significant changes in use or care of vertebrate animals.

Nothing to Report.

Significant changes in use of biohazards and/or select agents

Nothing to Report.

6. PRODUCTS: List any products resulting from the project during the reporting period. If there is nothing to report under a particular item, state "Nothing to Report."

- **Publications, conference papers, and presentations**
  Report only the major publication(s) resulting from the work under this award.

  Journal publications. *List peer-reviewed articles or papers appearing in scientific, technical, or professional journals. Identify for each publication: Author(s); title; journal; volume: year; page numbers; status of publication (published; accepted, awaiting publication; submitted, under review; other); acknowledgement of federal support (yes/no).*

  - Ge Y., Zhang R, Li, K., Chen GH, "Improving radiation dose efficiency of X-ray differential phase contrast imaging using an energy-resolving grating interferometer and a novel rank constraint." Optics Express, Vol. 24, Issue 12, page 12955-12968 (2016) *Acknowledgement of federal support: Yes*

  - Ge Y., Zhang R, Li, K., Chen GH, "X-ray differential phase contrast imaging using a grating interferometer and a single photon counting detector," Proc. SPIE, Vol. 9783, page 97830M (2016) *Acknowledgement of federal support: Yes*

  - R. Zhang, B. Qin, Y. Ge, B. Whiting, K. Li, F. Villanueva, G.-H. Chen, "Potential use of micorobubles (MBs) as contrast material in x-ray dark field (DF) imaging: How does the DF signal change with the characteristic parameters of the MBs?," Proc. SPIE, Vol. 9783, page 97830N (2016) *Acknowledgement of federal support: Yes*

  - Ji X, Ge Y., Zhang R, Li, K., Chen GH, "Studies of signal estimation bias in grating-based x-ray multi-contrast imaging." Medical Physics, Vol. 44, Issue 6, page 2453-2465 (2017) *Acknowledgement of federal support: Yes*

  - Ge Y., Ji, X., Zhang R, Li, K., Chen GH, "K-edge energy-based calibration method for photon counting detectors." Physics in Medicine and Biology, Vol. 63, Issue 1, page 015022 (2017) *Acknowledgement of federal support: Yes*

  - Ji X, Ge Y., Zhang R, Li, K., Chen GH, "Potential bias in signal estimation for grating-based x-ray multi-contrast imaging." Proc. SPIE, Vol. 10132, page 1013219 (2017) *Acknowledgement of federal support: Yes*

  - Ji X, Ge Y., Zhang R, Li, K., Chen GH, " Weighted singular value decomposition (wSVD) to improve the radiation dose efficiency of grating-based x-ray phase contrast imaging with a photon counting detector." Proc. SPIE, Vol. 10132, page 101325I (2017) *Acknowledgement of federal support: Yes*

- Ji X, Ge Y., Zhang R, Li, K., Chen GH, " Signal and noise characteristics of a CdTe-based photon counting detector: cascaded systems analysis and experimental studies." Proc. SPIE, Vol. 10132, page 1013219 (2017) *Acknowledgement of federal support: Yes*
- Ji X, Zhang R, Chen GH, Li K. "Impact of anti-charge sharing on the zero-frequency detective quantum efficiency of CdTe-based photon counting detector system: cascaded systems analysis and experimental validation." Physics in medicine and biology. Vol. 63, page 095003 (2018) *Acknowledgement of federal support: Yes*
- Li K, Zhang R, Garrett J, Ge Y, Ji X, Chen GH. "Design, Construction, and Initial Results of a Prototype Multi-Contrast X-Ray Breast Imaging System." Proc. SPIE. Vol. 10573, page 105730W (2018) *Acknowledgement of federal support: Yes*
- Zhang R, Li K, Garrett J, Chen GH. "Human-Compatible Multi-Contrast Mammographic Prototype System." Proc. SPIE, Vol. 10948, page 10480X (2019) *Acknowledgement of federal support: Yes*
- Ji X., Feng M, Zhang R, Chen GH, Li K, "An experimental method to correct drift-in." Proc. SPIE, Vol. 10948, page 109480H (2019) *Acknowledgement of federal support: Yes*
- Ji X, Feng M., Zhang R, Chen GH, Li K. "An experimental method to directly measure DQE(k) at k = 0 for 2D x-ray imaging systems." Physics in medicine and biology 64 (7), 075013 (2019) *Acknowledgement of federal support: Yes*
- Ji X, Zhang R, Li K. Chen GH, "Phase contrast CT enabled three-material decomposition in spectral CT imaging." Proc. SPIE, Vol. 11312, page 113121B (2020) *Acknowledgement of federal support: Yes*
- Li K, "Analogous Lubberts effect in photon counting detectors." Proc. SPIE, Vol. 11312, page 113120Z (2020) *Acknowledgement of federal support: Yes*
- Ji X, Zhang R, Li K. Chen GH, "Is high sensitivity always desirable for a phase contrast imaging system?" Medical Physics, 47(3), 1215 (2020) *Acknowledgement of federal support: Yes*
- Ji X, Zhang R, Li K. Chen GH, "Dual Energy Differential Phase Contrast CT (DE-DPC-CT) Imaging." IEEE Transaction on Medical Imaging, early access, DOI: 10.1109/TMI.2020.2990347 (2020) *Acknowledgement of federal support: Yes*
- Zhang R, Fowler A. M, Wilke L. G, Kelcz F., Garrett J W, Chen GH, Li K, "Fast Acquisition with Seamless Stage Translation (FASST) for a human-compatible trimodal x-ray breast imaging system." Medical Physics (under review) *Acknowledgement of federal support: Yes*
- Ji X, Li K, "Anomalous edge response of photon counting detector induced by pulse pileup and charge sharing effects." Medical Physics (under review)

Books or other non-periodical, one-time publications. *Report any book, monograph, dissertation, abstract, or the like published as or in a separate publication, rather than a periodical or series. Include any significant publication in the proceedings of a one-time conference or in the report of a one-time study, commission, or the like. Identify for each one-time publication: Author(s); title; editor; title of collection, if applicable; bibliographic information; year; type of publication (e.g., book, thesis or dissertation); status of publication (published; accepted, awaiting publication; submitted, under review; other); acknowledgement of federal support (yes/no).*

Ke Li and Guang-Hong Chen, "Chapter 52 X-ray Phase Contrast Tomosynthesis Imaging" in "Handbook of X-ray Imaging: Physics and Technology", edited by P. Russo, CRC Press, Boca Raton, FL (2018)

Other publications, conference papers, and presentations. *Identify any other publications, conference papers and/or presentations not reported above. Specify the status of the publication as noted above. List presentations made during the last year (international, national, local societies, military meetings, etc.). Use an asterisk (*) if presentation produced a manuscript.*

- X. Ji, Y. Ge, R. Zhang, K. Li, G.-H. Chen, "Low Dose Performance of a CdTe Single Photon Counting Detector and Its Application in Radiation Dose Reduction for X-ray Differential Phase Contrast Imaging." Radiological Society of North America 2016 Scientific Assembly and Annual Meeting, November 27 - December 2, 2016, Chicago IL (RSNA Student Travel Stipend Award)
- Y. Ge, X. Ji, R. Zhang, K. Li, G.-H. Chen, "Radiation Dose Reduction in X-ray Differential Phase Contrast Breast Imaging using an Energy-resolved Grating Interferometer." Radiological Society of North America 2016 Scientific Assembly and Annual Meeting, November 27 - December 2, 2016, Chicago IL.
- Y. Ge, J. Garrett, R. Zhang, X. Ji, J. P. Cruz Bastida, G.-H. Chen, K. Li., "Initial Experimental Results from the First X-Ray Dark Field Breast Tomosynthesis Prototype System." Radiological Society of North America 2017 Scientific Assembly and Annual Meeting, Chicago, IL, 2017 (RSNA Student Travel Stipend Award)
- Y. Ge , X. Ji, R. Zhang , K. Li , G.-H. Chen. "Energy Calibration of Photon Counting Detectors Based On Measurement of X-Ray Attenuation Curve of K-Edge Materials." AAPM 2017 Annual Meeting, Denver, CO, 2017

- K. Li, Y. Ge, J. Garrett, R. Zhang, X. Ji, J. P. Cruz-Bastida, G.-H. Chen. "First results from an x-ray dark field breast tomosynthesis prototype system." The 4th International Conference on X-ray and Neutron Phase Imaging with Gratings, Zurich, Switzerland, 2017
- X. Ji, Y. Ge, R. Zhang, K. Li, G.-H. Chen. "Is High Sensitivity Always Good for a Grating-based Differential Phase Contrast Imaging System?" The 4th International Conference on X-ray and Neutron Phase Imaging with Gratings, Zurich, Switzerland, 2017
- R. Zhang, K. Li, G.-H. Chen. "Optimization of Grating Interferometer Parameters for a General Three-Grating Interferometer." The 4th International Conference on X-ray and Neutron Phase Imaging with Gratings, Zurich, Switzerland, 2017
- R. Zhang, K. Li, G.-H. Chen. "How many gratings are needed for a high sensitivity differential phase contrast imaging system?" The 4th International Conference on X-ray and Neutron Phase Imaging with Gratings, Zurich, Switzerland, 2017
- Zhang R, Li K, Garrett J, Chen GH, "Initial Evaluation of a Prototype Multi-Contrast X-Ray Breast Imaging System: Radiation Dose Performance." AAPM 2018 Annual Meeting, Nashville, TN
- Ji X., Zhang R, Chen GH, Li K, “How Does Anti-Charge Sharing Impact the Zero-Frequency DQE of Photon Counting Detector Systems? Theoretical Framework and Experimental Validation.” AAPM 2018 Annual Meeting, Nashville, TN
- Li K, Ji X, Zhang R, “Impacts of pulse pileup, charge sharing, and anti-charge sharing on the noise power spectra of photon counting detectors: theoretical analysis and experimental demonstrations.” SPIE Medical Imaging Conference, Houston, TX (2020)
- Zhang R, Garrett JW, Chen GH, Li K, “Multi-contrast x-ray breast imaging prototype system 2.0: fast data acquisition technique without spatial resolution loss.” SPIE Medical Imaging Conference, Houston, TX (2020)
- Zhang R, Li K, Chen GH, “How to design x-ray grating interferometers for grating-based multi-contrast x-ray imaging?” SPIE Medical Imaging Conference, Houston, TX (2020)
- Zhang R, Ji X, Li K, Chen GH, “Single-shot information retrieval in grating-based multi-contrast imaging using deep learning.” SPIE Medical Imaging Conference, Houston, TX (2020)
- Zhang R, Fowler A. M, Wilke L. G, Kelcz F., Garrett J W, Chen GH, Li K, “Fast Data Acquisition for a Human-Compatible Multi-Contrast Breast Imaging System.” RSNA Annual Meeting, Chicago, IL (2019)

- Ji X, Feng M., Zhang R, Chen GH, Li K. "An Experimental Method to Measure Zero-Frequency DQE in the Presence of System Drift." AAPM Annual Meeting, San Antonio, TX (2019)
- Ji X, Feng M., Zhang R, Chen GH, Li K. "A Practical Model for the Energy Response Function of Photon Counting Detector Systems with Anti-Charge Sharing Logic." AAPM Annual Meeting, San Antonio, TX (2019)
- (Invited Talk) Chen GH, "Multi-contrast X-ray breast imaging system: From bench-top physics experimental studies to prototype engineering system construction and final clinical translations." International Conference on X-ray and Neutron Phase Imaging with Gratings, Sendai, Japan (2019)
- Zhang R, Garrett JW, Chen GH, Li K, "Human-compatible phase contrast mammography system with fast image acquisition." International Conference on X-ray and Neutron Phase Imaging with Gratings, Sendai, Japan (2019)

- **Website(s) or other Internet site(s)**
  List the URL for any Internet site(s) that disseminates the results of the research activities. A short description of each site should be provided. It is not necessary to include the publications already specified above in this section.

Nothing to Report.

- **Technologies or techniques**
  Identify technologies or techniques that resulted from the research activities. In addition to a description of the technologies or techniques, describe how they will be shared.

Nothing to Report.

- **Inventions, patent applications, and/or licenses**
  Identify inventions, patent applications with date, and/or licenses that have resulted from the research. State whether an application is provisional or non-provisional and indicate the application number. Submission of this information as part of an interim research

performance progress report is not a substitute for any other invention reporting required under the terms and conditions of an award.

Nothing to Report.

- **Other Products**
  Identify any other reportable outcomes that were developed under this project. Reportable outcomes are defined as a research result that is or relates to a product, scientific advance, or research tool that makes a meaningful contribution toward the understanding, prevention, diagnosis, prognosis, treatment, and/or rehabilitation of a disease, injury or condition, or to improve the quality of life. Examples include:

- *data or databases;*
- *biospecimen collections;*
- *audio or video products;*
- *software;*
- *models;*
- *educational aids or curricula;*
- *instruments or equipment;*
- *research material (e.g., Germplasm; cell lines, DNA probes, animal models);*
- *clinical interventions;*
- *new business creation; and*
- *other.*

- Video record of a SAM Imaging Symposium presentation delivered at the 2018 AAPM Annual Meeting: Link:
  https://vimeo.com/aapm/review/288790203/c73cb8e755
  Title: Multi-Contrast X-Ray Breast Imaging Prototype System

- Video recording of a SAM Imaging Symposium talk delivered at 2017 AAPM Annual Meeting:
  Link: http://www.aapm.org/education/vl/vl.asp?id=12253
  Title: Phase-Contrast Imaging of the Breast with Photon-Counting Detectors

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

What individuals have worked on the project?

Provide the following information for: (1) PDs/PIs; and (2) each person who has worked at least one person month per year on the project during the reporting period, regardless of the source of compensation (a person month equals approximately 160 hours of effort). If information is unchanged from a previous submission, provide the name only and indicate "no change."

Name: Ke Li
Project Role: PI
No change

Name: Guang-Hong Chen
Project Role: Co-Investigator
No change

Name: Ran Zhang
Project Role: Assistant Scientist
No change

Name: Amy Fowler
Project Role: Co-Investigator
No change

Name: Frederick Kelcz
Project Role: Co-Investigator
No change

Name: Andreas Friedl
Project Role: Co-Investigator
No change

Name: John Garrett
Project Role: Assistant Scientist
No change

Name: Kelley Salem
Project Role: Post-doc
No change

Name: Yongshuai Ge
Project Role: Graduate Student
No change

Name: Xu Ji
Project Role: Graduate Student
No change

Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

If the active support has changed for the PD/PI(s) or senior/key personnel, then describe what the change has been. Changes may occur, for example, if a previously active grant has closed and/or if a previously pending grant is now active. Annotate this information so it is clear what has changed from the previous submission. Submission of other support information is not necessary for pending changes or for changes in the level of effort for active support reported previously. The awarding agency may require prior written approval if a change in active other support significantly impacts the effort on the project that is the subject of the project report.

Nothing to report

What other organizations were involved as partners?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe partner organizations – academic institutions, other nonprofits, industrial or commercial firms, state or local governments, schools or school systems, or other organizations (foreign or domestic) – that were involved with the project. Partner organizations may have provided financial or in-kind support, supplied facilities or equipment, collaborated in the research, exchanged personnel, or otherwise contributed.
Provide the following information for each partnership:
Organization Name:
Location of Organization: (if foreign location list country)
Partner's contribution to the project (identify one or more)

- *Financial support;*
- *In-kind support (e.g., partner makes software, computers, equipment, etc., available to project staff);*
- *Facilities (e.g., project staff use the partner's facilities for project activities);*
- *Collaboration (e.g., partner's staff work with project staff on the project);*
- *Personnel exchanges (e.g., project staff and/or partner's staff use each other's facilities, work at each other's site); and*
- *Other.*

Nothing to Report.

8. SPECIAL REPORTING REQUIREMENTS

COLLABORATIVE AWARDS: For collaborative awards, independent reports are required from BOTH the Initiating PI and the Collaborating/Partnering PI. A duplicative report is acceptable; however, tasks shall be clearly marked with the responsible PI and research site. A report shall be submitted to https://ers.amedd.army.mil for each unique award.

QUAD CHARTS: If applicable, the Quad Chart (available on https://www.usamraa.army.mil) should be updated and submitted with attachments.

9. APPENDICES: Attach all appendices that contain information that supplements, clarifies or supports the text. Examples include original copies of journal articles, reprints of manuscripts and abstracts, a curriculum vitae, patent applications, study questionnaires, and surveys, etc.

No appendix to attach.