Multi-Contrast X-Ray Breast Imaging Prototype System

Ke Li, PhD

Assistant Professor
Department of Medical Physics and Department of Radiology
University of Wisconsin-Madison

Medical Physics & Radiology

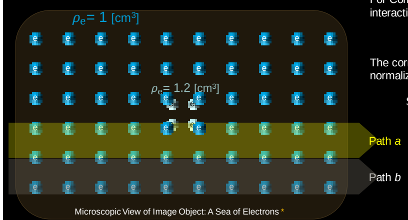
Acknowledgements

- Department of Medical Physics
  - Ran Zhang, PhD
  - John Garrett, PhD
  - Guang-Hong Chen, PhD
- Department of Radiology
  - Amy Fowler, MD, PhD
  - Frederick Kelcz, MD, PHD
- Department of Surgery
  - Lee G Wilke, MD
- Department of Pathology
  - Andreas Friedl, PhD
- Hologic, Inc.
  - Zhenxue Jin, PhD
  - Baorui Ren, PhD
- Funding Supports
  - DOD Breakthrough Award W81XWH-16-1-0031
  - NIH R01EB020521

Outline

- Motivation of developing the prototype multi-contrast breast imaging system
- Challenges and technical considerations in system design
  - Compact geometry
  - Limited spatial coverage of gratings
  - Radiation dose and patient safety
- Technical solutions to these challenges; construction of the prototype system
- Performance of the prototype system
  - Phantom results
  - Fresh mastectomy specimen results
- Summary

Dependence of Image Contrast on X-Ray Interaction Mechanism: Compton Scattering



For Compton Scattering (CS), its interaction cross-section σ_{CS} is *

$$\sigma_{CS}(\vec{x}) = \sigma_{CS}^{e}\rho_e(\vec{x})$$

The corresponding signal in a log-normalized x-ray projection measurement is

$$\text{Signal}_{CS} = \sigma_{CS}^{e}\int_{\text{Path}} \rho_e(\vec{x})d\vec{x}$$

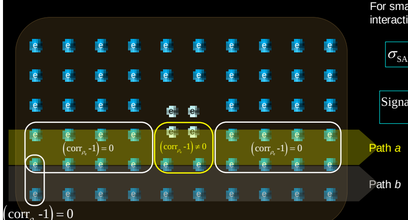
Path *a*

Path *b*

$$\frac{\text{Signal}_{CS}^{a} - \text{Signal}_{CS}^{b}}{\text{Signal}_{CS}^{b}} = \frac{\sigma_{CS}^{e}}{\sigma_{CS}^{e}}\frac{(8\times1+2\times1.1)-10\times1}{10\times1} = 2\%$$

* G.-H. Chen, *Lecture Notes on Radiation Physics and Dosimetry*

Dependence of Image Contrast on X-Ray Interaction Mechanism: Small Angle Scattering (SAS)



For small angle scattering (SAS), its interaction cross-section σ_{SAS} is [1-4]

$$\sigma_{SAS}(\vec{x}) = \text{corr}_{\rho_e}(\vec{x}, \vec{x}+\vec{\eta}_{\perp}) - 1$$

$$\text{Signal}_{SAS} = \int_{\text{path}} \left[\text{corr}_{\rho_e}(\vec{x}, \vec{x}+\vec{\eta}_{\perp}) - 1\right]d\vec{x}$$

Path *a*

Path *b*

$$\frac{\text{Signal}_{SAS}^{a} - \text{Signal}_{SAS}^{b}}{\text{Signal}_{SAS}^{b}} \rightarrow \infty$$

[1] Wang et al., APL (2009) [2] Chen et al., Optics Express (2010) [3] Yashiro et al., Optics Express (2010) [4] Bech et al., PMB (2010)

Potential Application of X-Ray Dark Field Imaging in Breast Cancer Imaging

- Reveal micron-sized calcifications that were invisible in clinical mammography [1]
- Selective imaging of calcifications and heterogeneous tissues with significantly reduced anatomical noise [2]
- Noninvasive classifications of microcalcifications in the breast [3]
  - Discrimination of calcium oxalates vs. calcium phosphates
- Potentially enables new exogenous contrast media (e.g. microbubbles) without nephrotoxicity [4]

Dark field

Absorption

Differential phase

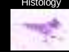
[1] Michel et al., Phys. Med. Biol. (2013)
[2] Garrett et al., Med. Phys. (2014)
[3] Wang et al., Nature Communications (2014)
[4] Zhang et al., Proc. SPIE (2016)

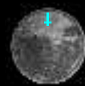
Potential Application of X-Ray Phase Contrast Imaging in Breast Cancer Imaging

- Refined visualization of tumor boundaries
- Provide advanced insight into tumor morphology or collagen architecture [1-3]
- Improve the visualization of subtle density variations, spiculation, or abnormal fibrous structures in highly dense breasts [4-5]
- Synchrotron-based study resulted in specificity and sensitivity values of 94% and 81% for breast cancer diagnosis, compared with 52% and 69% for conventional mammography [6]

[1] Bravin et al., PMB 52, 2197 (2007)
[2] Friedler et al., PMB 49, 175 (2004)
[3] Stampanoni et al., Invest. Radiol. 46, 801 (2011)
[4] Morita et al., Lect Notes Comput Sci 5116, 228 (2008)
[5] Hauser et al., Invest. Radiol. 49, 131 (2014)
[6] Castelli et al., Radiology 259, 684 (2011)

Histology





Phase contrast

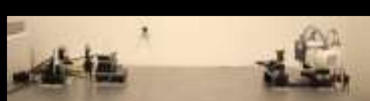
Absorption

J. Zambelli, PhD Thesis, UW-Madison (2010)

Synchrotron- and Benchtop-based Multi-Contrast Imaging Systems

Synchrotron-based

Lab bench-based



Motivation of Developing the Prototype System

- Limitations of synchrotron- and benchtop-based studies
  - Improved image quality can be partially attributed to improved x-ray beam characteristics at the synchrotron, such as monochromaticity and finite beam size, rather than the phase contrast mechanism itself [1]
  - Studies that suggest added clinical value have so far largely been performed at dose levels and data acquisition time far exceeding those deemed clinically acceptable [2,3]

[1] Auweter et al., Br. J. Radiol. 87, 1034 (2014)
[2] Grandl et al., Z. Med. Phys. 23, 212 (2013)
[3] Stampatoni et al., Invest. Radiol. 46, 801 (2011)

Motivation of Developing the Prototype System

- Limitations of synchrotron- and benchtop-based studies
  - Did not consider the compactness requirement of clinical systems
    - For these noncompact systems:
      - Longer wave propagation length → better spatial coherence
      - Higher Talbot order → higher phase contrast sensitivity
      - Quasi-parallel geometry → negligible beam divergence
  - Did not include mechanical vibration
  - Did not include gravitational sag
  - Incompatible with in vivo human subject studies

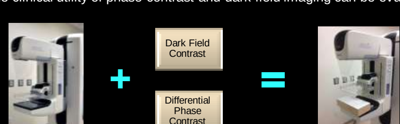
Motivation of Developing a Prototype System

- Majority of previous works used formalin-fixed tissue specimens
  - Formalin fixation preserves cellular morphology but may modify other tissue properties[1-3]
    - Dehydration
    - Change of tissue density
    - Loss of x-ray opacity
    - Demineralization (a particular problem for microcalcification imaging)
    - Content and Integrity of nucleic acids
    - Change of acidity and basicity
- True clinical utility of multi-contrast imaging should be evaluated *in vivo* or using fresh breast tissues

[1] M. Srinivasan et al., *Am J Pathol*. 161, 1961 (2002) [2] R. Thavarajah et al., *J Oral Maxillofac Pathol*. 16, 400 (2012)
[3] A. Fonseca et al., *Dentomaxillofac Radiol*. 37, 137 (2008)

Overall Goal of the Project

- The purpose of this work was to develop a multi-contrast breast imaging prototype system based on a clinical FFDM system:
  - Compatible with clinical requirements and conditions
  - Compatible with in vivo human subject imaging
  - True clinical utility of phase contrast and dark field imaging can be evaluated



Conventional FFDM (Absorption Contrast)

Multi-Contrast X-Ray Breast Imaging Prototype System

Outline

- Motivation of developing the prototype multi-contrast breast imaging system
- Challenges and technical considerations in system design
  - Compact geometry
  - Limited spatial coverage of gratings
  - Radiation dose and patient safety
- Technical solutions to these challenges; construction of the prototype system
- Performance of the prototype system
  - Phantom results
  - Fresh mastectomy specimen results
- Summary

Compact Geometry of Mammographic Imaging Systems

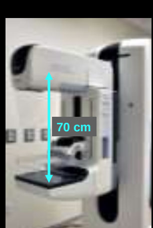
GE Senographe 2000D

vs.

Hologic Selenia Dimensions

	Senographe 2000D
SDD	66 cm
Tube	Rotating anode, dual track (Mo/Rh)
Tube Rating	5 kW max
kV Range	22-49
mAs Range	4-500
Detector type	CsI indirect conversion
Pixel size	100 µm

Challenges Introduced by Compact Geometry: I. Grating Fabrication



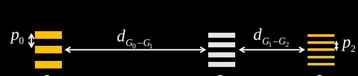
Hologic Selenia Dimensions™

- The periods of the three gratings (p_0, p_1, p_2) are directly related to the source-to-detector distance (SDD) as follows:

$$d_{G_1-G_2} = \frac{p_1^2}{8\lambda^2} \frac{d_{G_0-G_1} + d_{G_1-G_2}}{d_{G_0-G_1}}$$

$$\frac{p_0}{d_{G_0-G_1}} = \frac{p_2}{d_{G_1-G_2}} \qquad p_2 = \frac{d_{G_0-G_1} + d_{G_1-G_2}}{d_{G_0-G_1}} \frac{p_1}{2}$$

$$d_{spot-G_0} + d_{G_0-G_1} + d_{G_1-G_2} = 65 \text{ cm}$$

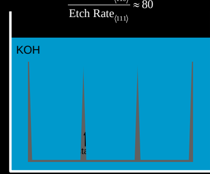


Challenges Introduced by Compact Geometry: I. Grating Fabrication

		Noncompact (benchtop) system
SDD		188
G0	Pitch (p_0)	37 um
	Height	60 um
	Aspect Ratio	3:1
G1	Pitch (p_1)	8 um
	Height	40 um
	Aspect Ratio	10:1
G2	Pitch (p_2)	4.5 um
	Height	50 um
	Aspect Ratio	22:1

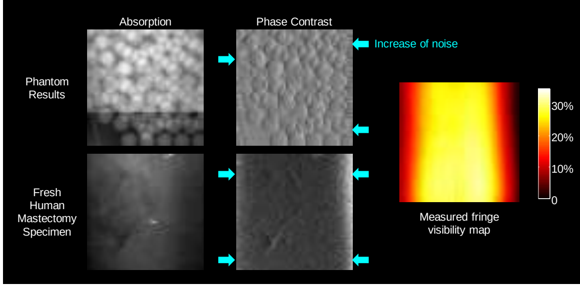
- Challenges introduced by high grating aspect ratio

$$\frac{\text{Etch Rate}_{(110)}}{\text{Etch Rate}_{(111)}} \approx 80$$

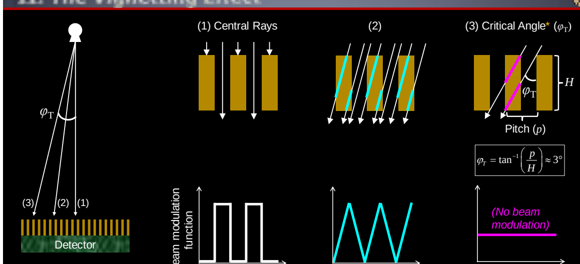


Loss of structural integrity

Challenges Introduced by Compact Geometry: II. The Vignetting Effect

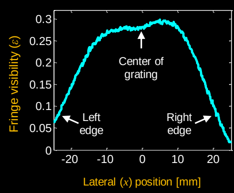


Challenges Introduced by Compact Geometry: II. The Vignetting Effect



* V. Revol et al., *Nucl. Instrum. Methods Phys. Res*, 648, S302 (2011)

Challenges Introduced by Compact Geometry: II. The Vignetting Effect



The noise variance (σ^2) of differential phase contrast (DPC) image is related to the fringe visibility (ε) by*

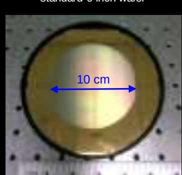
$$\sigma^2_{\mathrm{DPC}} \propto \frac{1}{\varepsilon^2}$$

Therefore, the rapid reduction in fringe visibility towards the edges of the grating leads to the undesirable vignetting effect

* G. H. Chen, et al., *Med. Phys.* 38, 584 (2011)

Challenge III: Limited Spatial Coverage of Single Grating

Grating fabricated on standard 6 inch wafer



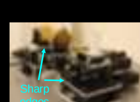
GE Senographene 2000D™

Hologic Selenia Dimensions™

Other Consideration: Patient Safety

- System should withstand compression force up to 200 N (45 lbs)*
- Potential safety hazard: sharp components of the grating interferometer that may contact the patient
- Radiation dose consideration
  - e.g., MGD of the “Standard Breast” ≤ 3 mGy*

(Compression of an udder specimen for illustration purpose)



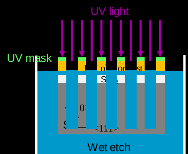
* *The Mammography Quality Standards Act Final Regulations: Preparing for MQSA Inspections; Final Guidance for Industry and FDA*, November 2001

Outline

- Motivation of developing the prototype multi-contrast breast imaging system
- Challenges and technical considerations in system design
  - Compact geometry
  - Limited spatial coverage of gratings
  - Radiation dose and patient safety
- Technical solutions to these challenges; construction of the prototype system
- Performance of the prototype system
  - Phantom results
  - Fresh mastectomy specimen results
- Summary

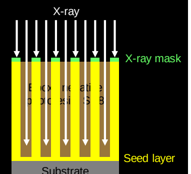
High Aspect Ratio Grating Fabrication using X-Ray Lithography

Conventional "Top Down" approach*
using UV lithography



Limitations:
- Undesirable etch along the lateral dimension
- Relatively long wave length ($\lambda_{UV} \approx 200$ nm)
  - → greater diffraction effect and limited lateral resolution

"Bottom Up" approach†,‡
using soft x-ray lithography



* C. David et al., Microelectron. Eng. 84, 1172 (2007)

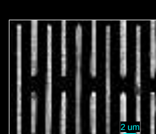
† E. Reznikova et al., Microsyst Technol. 14, 1683 (2008)
‡ D. Noda et al., J. Electrochem. Soc., 150, H299 (2009)

High Aspect Ratio Grating Fabrication using X-Ray Lithography

- Advantages of the bottom-up approach
  - Bypass wet etching
  - Finer feature resolution Δx

$$\frac{\Delta x_{\text{x-ray}}}{\Delta x_{\text{uv}}} = \frac{\lambda_{\text{x-ray}}}{\lambda_{\text{uv}}} = \frac{0.4\ \text{nm}}{200\ \text{nm}} = 2\times 10^{-3}$$

- Lateral dimension routinely achievable: 1 um
- Accuracy: within ±0.1 um from the designed lateral dimension
- Feature height routinely achievable: 80 µm
- Aspect ratio achievable: > 50



http://www.micro-works.de

Parameters of the Grating Interferometer System

Grating Specifications

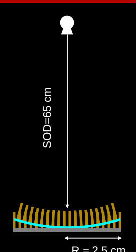
	Gratings		
	G0	G1	G2
Pitch (um)	20.7	4.3	2.4
Duty cycle (%)	58	50	50
Feature width (µm)	12	2.15	1.2
Feature height (µm)	60	11.2	50
Aspect ratio	5	5	42
Material	Au	Ni	Au
Diameter (cm)	3	10	5

Geometric Parameters

	Distance
Source to G0	5 cm
Source to object	62 cm
G0 to G1	60 cm
G1 to G2	5 cm
Object to detector	8 cm
Source to detector	70 cm

The feature size and aspect ratio are within the achievable range of the x-ray lithography technology

FOV Enlargement using Curved Grating



- To machine or 3D-print the curved grating frame, the required z resolution (Δz) is related to the inplane resolution (Δx) by

$$\Delta z < \left(\frac{R}{\mathrm{SOD}}\right)\Delta x = 0.04\Delta x$$

- For a 3D printer with 50 µm inplane resolution, the required z resolution is 2 µm
- Our solution:

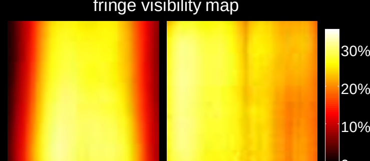
Wood softening

Drying and shaping

Wooden frame for bending the G2 grating (side view)

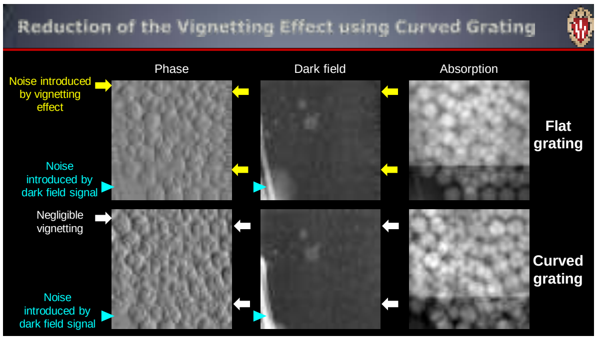
Reduction of the Vignetting Effect using Curved Grating

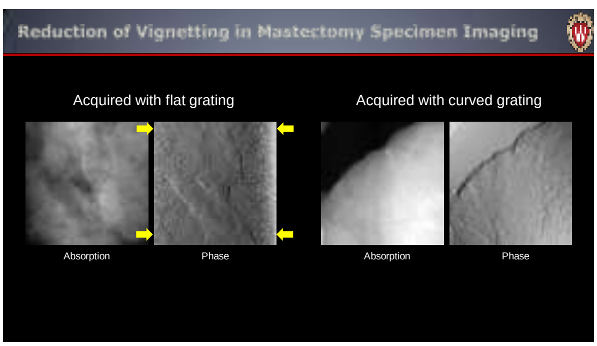
Experimentally measured fringe visibility map

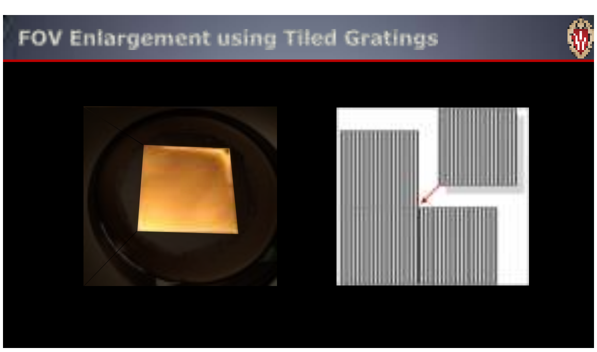


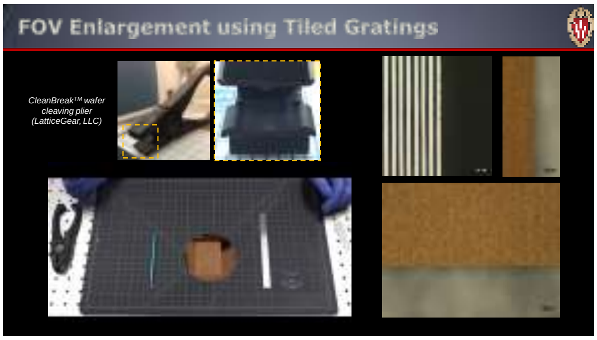
With flat grating *With curved grating*

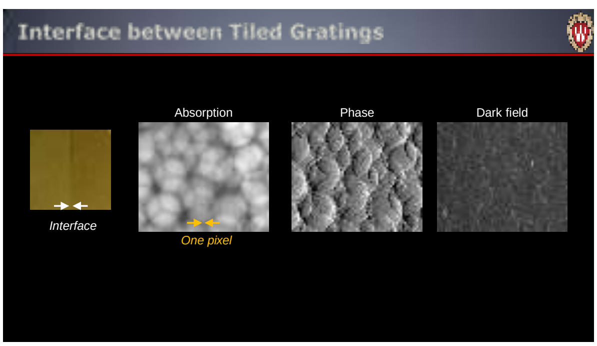
R. Zhang et al. to-be-submitted

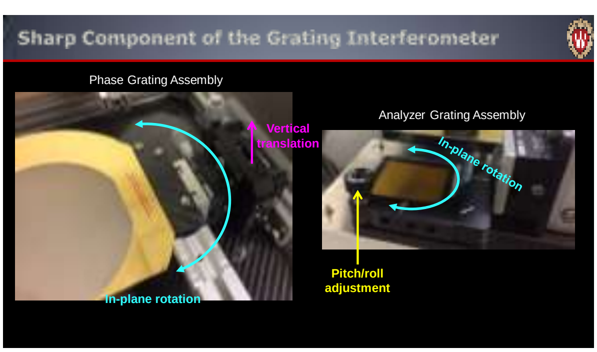

Reduction of the Vignetting Effect using Curved Grating
Phase
Dark field
Absorption
Noise introduced by vignetting effect
Noise introduced by dark field signal
Flat grating
Negligible vignetting
Noise introduced by dark field signal
Curved grating

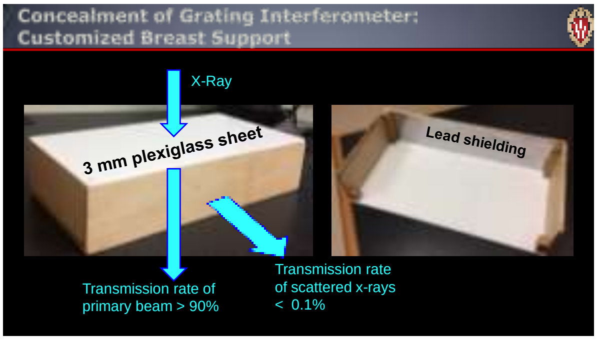

Reduction of Vignetting in Mastectomy Specimen Imaging
Acquired with flat grating
Acquired with curved grating
Absorption
Phase
Absorption
Phase


FOV Enlargement using Tiled Gratings

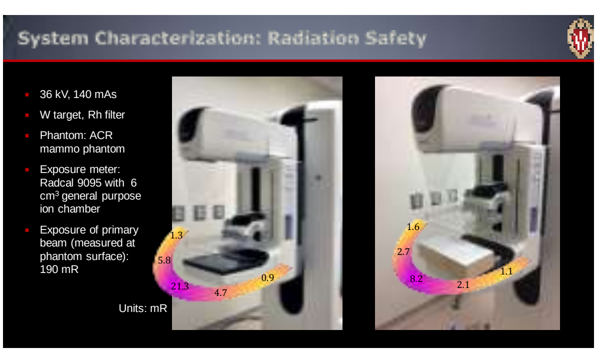

FOV Enlargement using Tiled Gratings
CleanBreak™ wafer cleaving plier (LatticeGear, LLC)


Interface between Tiled Gratings
Absorption
Phase
Dark field
Interface
One pixel


Sharp Component of the Grating Interferometer
Phase Grating Assembly
Vertical translation
In-plane rotation
Analyzer Grating Assembly
In-plane rotation
Pitch/roll adjustment


Concealment of Grating Interferometer:
Customized Breast Support
X-Ray
3 mm plexiglass sheet
Lead shielding
Transmission rate of
primary beam > 90%
Transmission rate
of scattered x-rays
< 0.1%


Construction of the Prototype System:
Step-by-Step Illustration


System Characterization: Radiation Safety
36 kV, 140 mAs
W target, Rh filter
Phantom: ACR mammo phantom
Exposure meter: Radcal 9095 with 6 cm³ general purpose ion chamber
Exposure of primary beam (measured at phantom surface): 190 mR
1.3
5.8
21.3
4.7
0.9
Units: mR
1.6
2.7
8.2
2.1
1.1

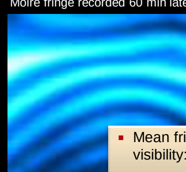
Outline

- Motivation of developing the prototype multi-contrast breast imaging system
- Challenges and technical considerations in system design
  - Compact geometry
  - Limited spatial coverage of gratings
  - Radiation dose and patient safety
- Technical solutions to these challenges; construction of the prototype system
- Performance of the prototype system
  - Phantom results
  - Fresh mastectomy specimen results
- Summary

Fringe Visibility and System Reproducibility

Initial moiré fringe

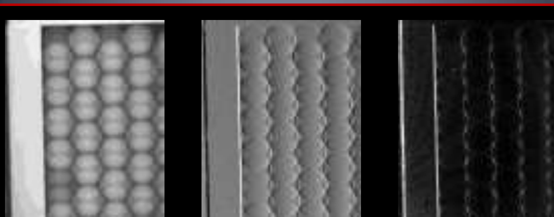
Moiré fringe recorded 60 min later



rRMSE = 3.2%

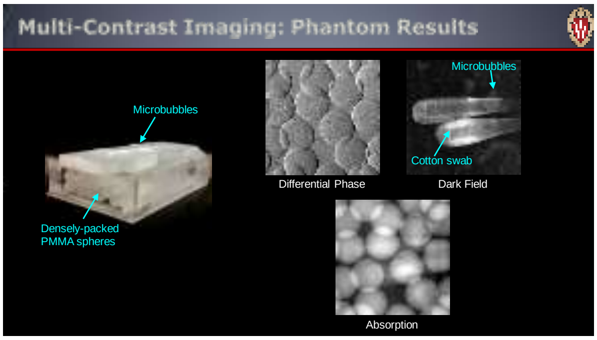
- Mean fringe visibility: 28%
- Standard deviation: 4%

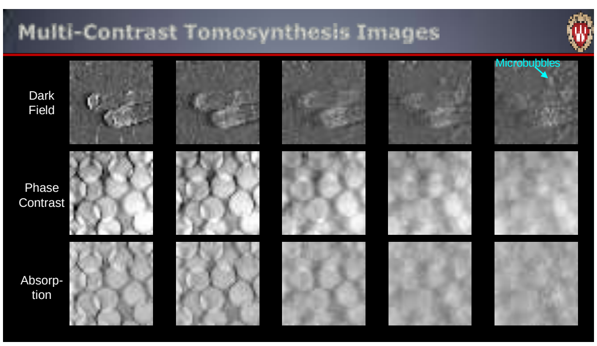
Multi-Contrast Imaging: Phantom Results



Absorption | Differential Phase | Dark Field

36 kVp; Exposure time: 4 s; Entrance exposure 565 mR; estimated MGD: 2.35 mGy





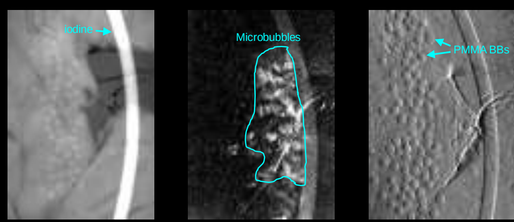
Multi-Contrast Imaging: Bovine Tissue Specimen


Fresh bovine specimen

- Image object: fresh bovine specimen
  - The specimen is mostly composed of the longissimus dorsi muscle
  - Also contains complexus and spinalis muscles
  - Thickness: 4 cm
- Contrast agents
  - Agent A: iodine (for absorption contrast)
  - Agent B: microbubbles (for dark field contrast)*
  - Agent C: PMMA spheres (for differential phase contrast)

* R. Zhang et al., Proc SPIE, 9783, 97830N (2016)

Multi-Contrast Imaging: Bovine Tissue Specimen

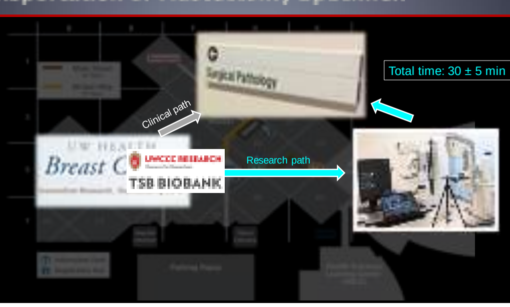


Absorption Contrast | Dark Field Contrast | Differential Phase Contrast

Protocol of Multi-Contrast Imaging Fresh Mastectomy Specimen

- UW Health Science IRB #2016-0814
- Eligibility
  - Female patients of all races and ethnic backgrounds
  - At least 18 years of age
  - Undergoing unilateral or bilateral mastectomy
  - With known biopsy-proven breast cancer
  - Amendment #CT014: include high-risk patients that are undergoing prophylactic mastectomy
- The fresh mastectomy specimen must arrive to Surgical Pathology no later than 40 minutes post-resection

Transportation of Mastectomy Specimen



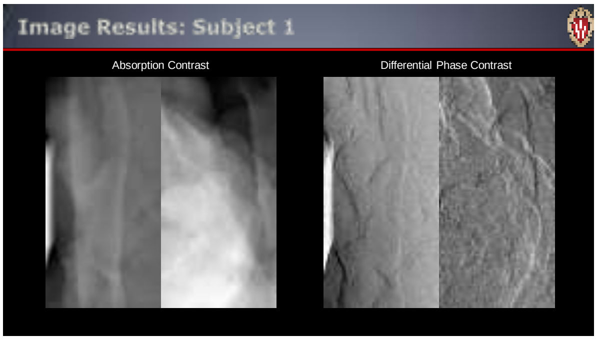


Image Results: Subject 1
Absorption Contrast
Differential Phase Contrast

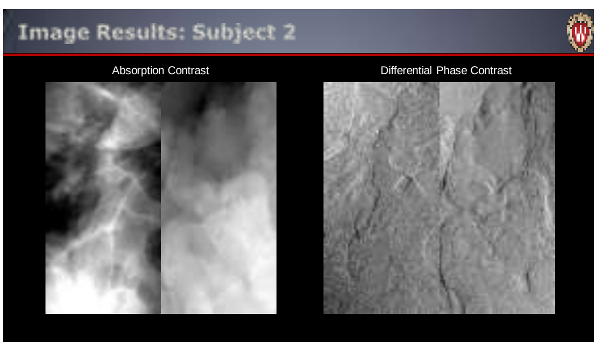


Image Results: Subject 2
Absorption Contrast
Differential Phase Contrast

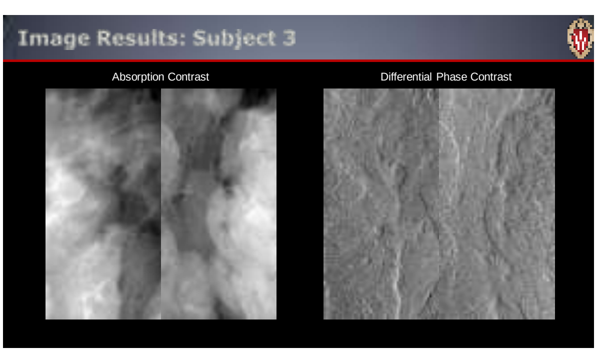
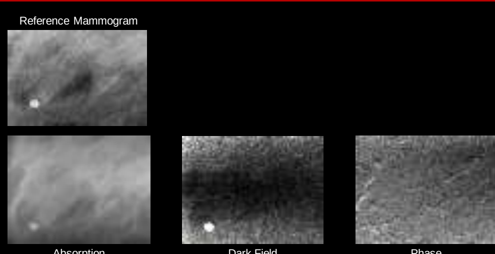


Image Results: Subject 3
Absorption Contrast
Differential Phase Contrast

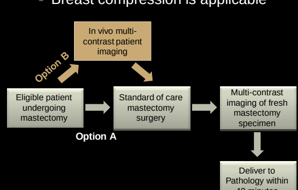
Image Results: Subject 4

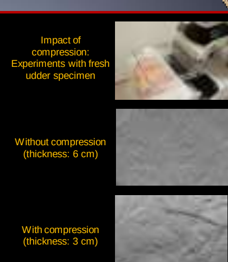
Calcification Imaging



Ongoing Work

- In vivo human subject study
  - Breast compression is applicable

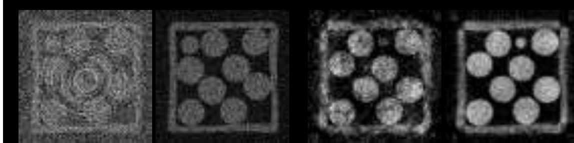




UW IRB #2016-0814

Ongoing Work

- Incorporation of the photon counting detector (PCD) technology



Absorption Contrast | Phase Contrast

Summary

- The quest for understanding the true medical utility of multi-contrast breast imaging under clinically-relevant conditions motivated the development of the prototype system
- The prototype was built upon clinical full field digital mammography system with minimal modification to the data acquisition hardware. Therefore, it automatically meets the following clinical requirements and conditions:
  - Geometric compactness
  - Tube power and image acquisition speed
  - Vertical geometry
  - System and building vibrations

Summary

- Major technical challenges in developing the prototype system and corresponding solutions
  - Smaller grating pitch introduced by compact geometry
    - The "bottom-up" approach with x-ray lithography and electroplating
  - Limited FOV introduced by finite grating area and beam divergence
    - Grating bending + tiling
  - Scatter radiation and sharp devices introduced by grating interferometer
    - Concealment of all interferometer components with lead-shielded and customized breast support
- Phantom results
  - Multi-contrast imaging capability with satisfactory fringe visibility and repeatability
- Initial fresh mastectomy specimen results
  - Compatibility with clinical mastectomy workflow
  - Supplementary information to absorption mammography; further image interpretation by breast radiologists is needed

Thank You