Compact tomographic X-ray phase-contrast imaging of breast cancer
by
Ling Xu
B.S., University of California San Diego (2011)
Submitted to the Harvard-MIT Division of Health Sciences and Technology
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Signature redacted

Author .................
Harvard-MIT Division of Health Sciences and Technology
Signature redacted
May 26, 2017
Certified by......
George Barbastathis, Ph.D.
Professor of Mechanical Engineering, MIT
Thesis Supervisor
Signature redacted

Accepted by ....................
Emery N. Brown, M.D. Ph.D.
Professor of Health Sciences and Technology and Professor of Computational Neuroscience, MIT
Director, Harvard-MIT Program in Health Sciences and Technology
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Abstract

Non-invasive imaging plays an important role throughout the clinical diagnosis and management process of breast cancer. Unfortunately, existing imaging methods lack the combination of spatial resolution and soft-tissue contrast necessary to visualize pathological changes in the breast. X-ray phase-contrast imaging (XPCI) has emerged as a promising modality for providing enhanced soft tissue differentiation due to its inherent source of contrast being derived from diffraction effects rather than absorption. Studies using synchrotron sources have demonstrated the potential of XPCI in revealing structural details of the breast undetectable via existing modalities. However, the reliance on high-brilliance synchrotron sources significantly limits the use of XPCI in medical applications. In this thesis, we address this challenge by developing a compact XPCI system compatible with low-brilliance laboratory sources that retrieves phase from free-space propagation. We further combine quantitative phase imaging with computed tomography (CT) which enables us to investigate internal structures in 3D. Existing techniques for phase retrieval either require images to be acquired at multiple defocus planes, or assumptions to be made that do not hold true for many objects of interest. To address these limitations, we developed an iterative algorithm for phase retrieval using images acquired at two different energies. Our results show that this algorithm retrieves phase more accurately than existing methods. Finally, we illustrate the potential utility of our compact XPCI system in visualizing pathological features by imaging transgenic mouse models of breast cancer. These pre-clinical results show that phase CT is able to clearly distinguish tumor masses whereas the same features imaged using commercial microCT are obscured by noise. Overall, the methods developed in this thesis provide a proof of concept for conducting tomographic XPCI outside of synchrotron facilities, thus paving the way towards future clinical implementation.

Thesis Supervisor: George Barbastathis, Ph.D.
Title: Professor of Mechanical Engineering, MIT
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List of Abbreviations

2D ............ 2-dimensional
3D ............ 3-dimensional
CNR ............ contrast to noise ratio
CT ............ computed tomography
FBP ............ filtered backprojection
FFT ............ fast Fourier transform
HA ............ hydroxyapatite
HU ............ Hounsfield unit
MRI ............ magnetic resonance imaging
RMSE ............ root mean squared error
ROI ............ region of interest
SIRT ............ simultaneous iterative reconstruction technique
STD ............ standard deviation
TIE ............ transport of intensity equation
XPCI ............ X-ray phase-contrast imaging
List of Symbols

E .............. photon energy

$\lambda$ ............. wavelength

$\phi$ ............. phase

$A$ ............. amplitude

$Z$ ............. atomic number

$n$ ............. complex index of refraction

$\mu$ ............. attenuation coefficient
Chapter 1

Motivation

1.1 Breast cancer and its clinical management

Breast cancer is the most common cancer among women. Globally, there are an estimated 1.6 million new cases per year, accounting for 25% of total cancer cases [21]. It is also the most common cause of cancer death in women in developing countries and the second most common cause of cancer death in developed countries such as the United States. Worldwide, breast cancer leads to an estimated 522,000 deaths each year, accounting for 14% of all cancer deaths in women [21]. A number of risk factors have been found to be associated with breast cancer including female gender, age, lifestyle, and exposure to ionizing radiation [70, 14]. Reproductive factors such as increasing age of first pregnancy, early menarche and late menopause are also associated with higher risk of breast cancer [67, 17]. A small subset (5-10%) of breast cancers are due to inherited mutations in susceptibility genes such as BRCA1, BRCA1, PTEN, and p53 [5]. Most breast cancers arise from epithelial cells and are categorized as carcinomas. Less than 1% of breast cancers arise from stromal cells and are classified as sarcomas [48].

Imaging plays an important role throughout the clinical diagnosis and management process for breast cancer. The most common initial presentations are presence of palpable lump or abnormal image screening results. Annual breast cancer imaging screen in women over 50 in the general population has been shown to reduce the
incidence of advanced cancer by 38% [53]. The benefits of screening for women under 50 is still widely debated. Additional high-risk screens are performed for women of all ages with a strong family history of breast cancer, a known BRCA mutation, or a history of chest irradiation such as those that have previously undergone radiation therapy. Following the initial presentation, a combination of physical exam and diagnostic imaging are performed to determine if a biopsy is necessary. Among diseases without lymph-node involvement, tumor size at time of diagnosis is the most important prognostic factor. A study of 13,464 women showed that patients with tumor size < 0.5cm had a five year relative survival rate of 99.2% while those with tumor size > 5.0cm exhibited a five year survival rate of 82.2%. We rely on accurate diagnostic imaging to identify these small tumors while avoiding unnecessary biopsy procedures. Final diagnosis is made upon histological evaluation of the biopsy specimen.

Imaging is further used to assess the extent of the disease. Assessment of tumor size is a major component of disease staging alongside lymph node status and presence of metastasis. Accurate staging is important for determining prognosis and guiding treatment decisions. In addition to tumor size, characterization of the disease as focal, multi-focal, or multi-centric is used to determine eligibility for breast-conserving surgery. Prior to breast conserving surgery, neoadjuvant therapy may be administered to reduce tumor size and minimize resection size. Imaging is used to evaluate response to neoadjuvant therapy, and aids in subsequent surgical planning. After surgical resection, imaging is used to detect residual tumor in the lumpectomy cavity. Imaging continues to play a role post-treatment in monitoring tumor recurrence.

1.2 Current imaging technologies

1.2.1 Mammography

Mammography is the mainstay of breast imaging and is widely used throughout the clinical process. In mammography, the breast is compressed between two plates and exposed to X-ray. As photons travel through the breast, they are attenuated based on
compositions of the breast tissue. Routinely, two standard views are obtained in the craniocaudal and mediolateral directions. Mammogram interpretation is summarized into a BI-RAD (Breast Imaging Reporting and Data System) score according to: 0=inconclusive, 1=negative, 2=benign, 3=probably benign, 4=suspicious, 5=highly suggestive of malignancy, 6=proven malignancy. Classical mammography findings include the presence of tissue mass and clustered microcalcifications.

Sensitivity of screening mammography has been reported between 70–92% and specificity between 83–99% [41, 63, 38]. Mammography performance is significantly decreased in women with dense breasts with sensitivity of 38–48% [41, 63]. Mammography screening is associated with 15–20% reduction in relative risk of breast cancer mortality [55]. The benefits of reducing cancer mortality, however, is outweighed by the high burden of overdiagnosis and overtreatment. Estimates suggest that about 18–45% of patients are overdiagnosed, and undergo unnecessary treatment [55, 29]. Even if a false-positive mammogram is dispelled upon biopsy, patients may sustain considerable psychological distress and anxiety. The 10 year cumulative risk of having at least 1 false-positive result is 50–61% [36, 9].

The limitations of mammography derive from two main factors. The first is the 2D nature of mammography, which projects 3D structures onto a 2D plane. This causes tissue layers to overlap, making it difficult to distinguish overlapping structures from true abnormalities. Breast compression aims to ameliorate some of these issues by reducing and evening out the thickness of the breast. High degrees of compression, however, can be painful and intolerable for patients, and the level of achievable compression can significantly influence mammogram quality. The lack of 3D information about the tumor presents further difficulties in surgical planning, where accurate knowledge about a tumor’s location and extent is important to achieving complete resections and avoiding re-excisions. The second major limitation of mammography is the lack of soft tissue contrast. While mammography is effective in identifying microcalcifications, it is much less effective in distinguishing small changes in soft tissue composition. This is due to the fact that these modalities derive contrast from differences in attenuation by components of breast tissue. In weakly absorbing tissues such
as the breast, these differences are difficult to discern and easily obfuscated by noise. Approximately 9–22% of palpable breast cancers are mammographically occult, as a result of insufficient contrast between the tumor and surrounding tissue [68, 83]. This inability to visualize the tumor impedes diagnosis and characterization of the tumor for clinical decision making.

1.2.2 Ultrasound

Ultrasonography is a modality frequently used to complement mammography. In ultrasonography, a piezoelectric transducer emits short pulses at a frequency of 7 to 14 Megahertz. The sound wave is focused to a specific desired depth in the tissue. Ultrasound waves are refracted and reflected at the interfaces between mediums of different acoustic impedance. Reflected waves are measured by the transducer and interpreted to produce an image. Sonographic features associated with malignancy include presence of spiculation, angular margins, hypoechogenicity, microlobulation, and shadowing [71]. Ultrasound is often used as a follow-up to an abnormal screening mammogram, and is especially useful in characterizing palpable lesions that are occult or inconclusive on mammogram. A study of 2020 patients found that the use of ultrasound in conjunction with diagnostic mammography led to an increase in sensitivity from 91.5% with mammography alone, to 96.9% with mammography plus ultrasound [24]. Furthermore, specificity was improved from 87.0% with mammography alone, to 94.8% with both mammography and ultrasound [24]. Ultrasound benefits from low cost, portability, and lack of ionizing radiation. However, its low spatial resolution and inter-operator variability limits its clinical value when used independent of other imaging modalities.

1.2.3 Magnetic Resonance Imaging (MRI)

Magnetic resonance imaging is an emerging modality in the breast imaging space, and there has been increasing interest in its clinical use for breast cancer. MRI measures characteristic frequency emitted by hydrogen atoms in response to the application of
magnetic field. Breast MRI is performed with administration of intravenous gadolinium for contrast enhancement. Increased permeability of tumor-associated blood vessels leads to preferential uptake of contrast agent, which helps distinguish malignant lesions from those that are benign. MRI has very high sensitivity (94–100%) due to nearly all invasive breast cancers being enhanced by gadolinium [52, 54]. However, its specificity is much lower ranging from 67-77% [60]. MRI findings are not definitive and does not obviate the need for biopsy. MRI also has poorer resolution compared to mammography. Using MRI for assessment of response to neoadjuvant therapy has been shown to overestimate the amount of residual tumor [47]. As such, pre-operative MRI is only indicated when the tumor extent cannot be sufficiently visualized on mammography. Although MRI benefits from the increased contrast afforded by gadolinium, use of contrast agent makes the procedure much more time consuming, and is not compatible with patients with renal failure. MRI itself is contraindicated in patients with ferromagnetic implants such as pacemakers and insulin pumps. Furthermore, the cost of MRI is 10-15 times that of mammography and ultrasound. Due to these limitations, MRI is predominantly reserved for patients with known BRCA gene mutations and others that have highly elevated risk profiles.

1.3 X-ray phase contrast imaging

X-ray phase contrast imaging (XPCI) is emerging as a modality that may be especially suitable for visualizing soft tissue. This imaging modality is based on a fundamentally unique mode of contrast generation. Whereas conventional mammography and CT achieve contrast based on the absorption of X-ray through matter, XPCI derives contrast from the refraction of X-ray through matter. As such, XPCI enables visualization of materials that have similar attenuation characteristics, such as soft tissue, which are poorly distinguished in conventional attenuation-based X-ray imaging, but generate distinct phase signatures. Furthermore, phase imaging can produce quality images at higher, more penetrating X-ray energies since phase contrast diminishes much more slowly with increased energy ($\propto 1/E^2$) compared to attenuation
Imaging at higher energies would improve diagnostic performance in dense breasts, as well as enable the use of lower currents to reduce radiation dose to the patient.

Because to these advantages, there has been growing interest in applying XPCI to breast cancer imaging. However, XPCI studies have largely been limited to synchrotron X-ray facilities due to the strict coherence requirement of existing techniques. Nevertheless, a number of proof-of-concept studies point to XPCI's potential for improving diagnosis and characterization. In projection mode analogous to mammography, phase contrast imaging has been shown to be able to visualize fine collagen strands and collagen remodeling due to cancer growth [22, 39]. Another study showed, in highly dense breast, visualization of microlobulated contours and surrounding fine fibrous structures, which could not be seen on conventional mammogram [51]. A recent clinical trial in 47 patients showed that XPCI mammography achieved a sensitivity of 81% and specificity of 94%, an increase compared to a clinical mammography unit which achieved sensitivity and specificity of 69% and 52% respectively in the study [15]. Though, in these results, it is difficult to untangle the benefits of phase from simply the use of a more powerful and spatially coherent source.

In addition to mammographic projection mode, a number of studies have also looked at phase contrast imaging in the context of computed tomography (CT). Phase CT studies of isolated breast tumor samples using synchrotron revealed strong correlation between features in phase CT and histological features [10, 23]. Another group showed in excised specimens that phase CT can resolve fine breast tumor structures such as dilated ductules in DCIS, while absorption CT was not able to distinguish these structures [73]. Further feasibility experiments suggested that phase CT can be acquired at clinically compatible doses [59]. Due to phase imaging being confined to synchrotron facilities, the techniques used in these studies could not be implemented in a rotating gantry, and therefore phase CT studies have been limited to excised specimen.

Research so far has provided mounting evidence to the potential value of XPCI in breast cancer imaging. The clinical usefulness of this technology relies on the
successful translation to a clinical non-synchrotron setting. Development of effective
techniques for XPCI in clinical settings, and the evaluation of their performance on
in vivo tumors rather than excised specimens, is key to determining whether XPCI
will remain a scientific curiosity or become a clinically impactful innovation.

1.4 Thesis Overview

The objective of this thesis is to demonstrate the feasibility of a bench-top X-ray phase
contrast tomographic imaging system and its application to breast cancer imaging.
We seek to explore performance optimization strategies and develop new computa-
tional imaging algorithms to improve accuracy of phase retrieval and reconstruction.
We do so with significant consideration for the design limitations of clinical imple-
mentation. We aim to move past existing studies in excised tissue to imaging whole
animal disease models that more accurately mimic in situ imaging conditions.

The proceeding chapters are structured as follows. In Chapter 2, we present an
overview on the interactions of X-ray with matter. The concept of the complex index
of refraction is introduced in terms of its relationship to the absorption and phase
properties of a wave. The physical basis and mathematical formalism for image for-
modation is established. In Chapter 3, we describe the development of an X-ray phase
contrast tomography system which is implemented using a micro-focus X-ray source
in a laboratory setting. We describe the instrumentation and the phase retrieval
process that is used, and we demonstrate the system’s performance in imaging two
different types of specimen. In Chapter 4, we give consideration to optimization of
the tomographic acquisition scheme in terms of distributing dose between acquiring
less noisy projection images and sampling more projection angles. In Chapter 5, we
introduce a novel technique for phase retrieval using images acquired at two differ-
ent incident X-ray energies. Simulation and experimental results are presented. The
new algorithm is compared to existing algorithms in terms of their phase retrieval
accuracy. In Chapter 6, we demonstrate the first of its kind imaging of breast tu-
mors in whole transgenic mouse models of breast cancer. We present comparisons
to commercial microCT and pre-clinical MRI. We also examine correlations between the phase reconstruction of a tumor and its histological features. Finally, in Chapter 7, we suggest future research directions, and remaining steps to bringing X-ray phase contrast tomography to achieving its clinical potential.
Chapter 2

Theory

2.1 X-ray Fundamentals

X-rays are electromagnetic radiation with wavelengths ranging from approximately 10 pm to 1 nm. Like all electromagnetic radiation, X-rays can be viewed as a particle or as a wave. In the particle model, an X-ray photon’s energy $E$ is given by

$$E = \frac{hc}{\lambda}$$

where $h = 6.62607004 \times 10^{-34}$ J·s is Planck’s constant, $c = 2.99792458 \times 10^8$ m/s is the speed of light in vacuum, and $\lambda$ is the wavelength. X-ray energy is often represented in electron volts (eV), which is equal to $1.602 \times 10^{-19}$ J. An electron volt is the amount of energy gained by an electron when it moves through 1 volt of electric potential difference.

As a monochromatic wave, X-rays can be represented as a scalar electromagnetic field under the paraxial approximation

$$U(\vec{r}, z) = A(\vec{r}, z) \exp[i\phi(\vec{r}, z)]$$

where $\vec{r}$ is the position $(x, y)$ transverse to the optical axis, $U(\vec{r}, z)$ is the complex field, $A(\vec{r}, z)$ is the amplitude, $\phi(\vec{r}, z)$ is the phase, and $k = 2\pi/\lambda$ is the wave number.
2.2 X-ray Interaction with Matter

2.2.1 Types of Atomic Interactions

When X-ray passes through a material, the wave undergoes an amplitude change due to absorption, and it also experiences a phase shift due to scattering. These changes arise from interactions of X-ray photons with atoms in the material. In the X-ray regime, there are three main mechanisms of interaction between X-ray photons and matter. Figure 2-1 shows the contribution of each of these interaction effects to the total attenuation coefficient for soft tissue, and how their relative contributions vary with energy.

Photoelectric Effect

In photoelectric effect, a photon interacts with a tightly bound electron from the inner shells. If the energy of the incident photon is higher than or equal to the binding
energy of the electron, all of the photon’s energy is transferred to the electron causing the electron to be expelled from the atom in an ionization event. In this process, the X-ray photon is absorbed, therefore the mechanism is often referred to as photoelectric absorption. The probability of this interaction can be described by the interaction cross-section, which is approximately proportional to $Z^4/E^3$, where $Z$ is the atomic number and $E$ is the photon energy. From this, it is evident that photoelectric effect dominates absorption for materials with high atomic number, and the probability drops off sharply with increasing energy.

Compton Scattering

In Compton scattering, also known as incoherent scattering, the incident photon interacts with an electron from the outer shell. In this inelastic process, the X-ray photon partially transfers its energy to the electron causing the electron to be ejected from the atom. The photon, now at a lower energy, is scattered at an angle determined by the amount of energy that was transferred. The energy dependence of the Compton scattering cross section is defined by the Klein-Nishina formula [40]. The probability of Compton scattering is mainly dependent on the electron density of the material, and the effect dominates absorption at higher X-ray energies.

Coherent Scattering

Coherent scattering, also known as Rayleigh scattering, is an elastic process in which the incident X-ray is scattered in a random direction without losing any energy. In the diagnostic X-ray energy range, the contribution of coherent scattering to absorption is negligible. On the other hand, coherent scatter is the dominant process by which X-rays incur phase shift when traveling through a material.
Figure 2-2: Phase shift and attenuation of a wave passing through a material of complex index of refraction $n = 1 - \delta + i\beta$.

Figure 2-3: Ratio $\delta/\beta$ of different materials in the diagnostic energy range. This plot shows that $\delta$ which is associated with the phase property of the material, is many orders of magnitude larger than $\beta$ which is associated with the absorption property of the material.
2.2.2 Complex Index of Refraction

The combined effects of absorption and refraction by a material can be described by the complex index of refraction, given by

\[ n = 1 - \delta + i\beta \]  

(2.3)

where the imaginary component \( \beta \) relates to absorption while the real component \( \delta \) relates to phase shift. The refractive index \( n(x, y, z) \) is a spatially varying property of the material. For materials of medical interest, \( \delta \) can be \( 3 - 4 \) orders of magnitude greater than \( \beta \). Figure 2-3 shows the ratio of \( \delta \) to \( \beta \) for four different materials in the clinical X-ray energy range.

At wavelengths away from absorption edges, \( \delta \) and \( \beta \) can be expressed as

\[ \delta = \frac{r_e \lambda^2}{2\pi \rho_e} \]  

(2.4)

\[ \beta = \frac{\lambda \rho}{4\pi \mu} \]  

(2.5)

where \( r_e = 2.81794032 \times 10^{-15} \) is the classical electron radius, \( \rho_e \) is the electron density, \( \rho \) is the mass density, and \( \mu \) is the mass attenuation coefficient.

An electromagnetic wave passing through a material with refractive index \( n \) can be described as

\[ U(\mathbf{r}) = e^{ik \int n(s) \, ds} = U_0(\mathbf{r}) \, e^{ik \int -\delta(s)+i\beta(s) \, ds} \]  

(2.6)

where \( U_0(\mathbf{r}) \) is the incident field, \( k = 2\pi/\lambda \) is the wave number and the line integral is taken along the length of the ray \( s \). We see that this corresponds with the general formalism for an electric field (Eq. 2.2), such that

\[ \phi(\mathbf{r}) = k \int \delta(s) \, ds \]  

(2.7)

\[ A(\mathbf{r}) = A_0(\mathbf{r}) \, e^{-k \int \beta(s) \, ds} \]  

(2.8)

This allows us to relate the index of refraction to the phase \( \phi(\mathbf{r}) \) and amplitude \( A(\mathbf{r}) \)

33
properties of the wave.

### 2.2.3 Projection approximation

For an object of sufficiently small thickness, the projection approximation allows us to model interactions between the wave and the object by the two-dimensional transmission function \( T(x, y) \)

\[
T(x, y) = A(x, y)e^{i\phi(x, y)}
\]  
(2.9)

where

\[
A(x, y) = e^{-\frac{2\pi}{\lambda} \int \beta(x, y, z) dz}
\]  
(2.10)

and

\[
\phi(x, y) = -\frac{2\pi}{\lambda} \int \delta(x, y, z) dz
\]  
(2.11)

The field emerging from an object modeled by the transmission function \( T(x, y) \) can then be written as

\[
U(\vec{r}) = U_0(\vec{r}) \cdot T(\vec{r})
\]  
(2.12)

where \( \vec{r} \) is the spatial coordinate \((x, y)\) in the plane transverse to the optical axis, and \( U_0 \) is the incident field.

This approximation assumes that phase and amplitude changes imparted on the wave field are accumulated along the ray path of the unscattered beam. For a wave emerging from the exit plane \( z = z_0 \), changes to the wave field are accumulated along the line \((x, y, 0)\) to \((x, y, z_0)\). This approximation is valid if Fresnel diffraction inside the object is small compared to the size of the smallest feature. For an object of thickness \( \Delta t \), the thickness is considered sufficiently small if

\[
\Delta t < \frac{\Delta r_\perp^2}{\lambda}
\]  
(2.13)

where \( \Delta r_\perp^2 \) is the smallest feature in the lateral direction [56]. If we consider an X-ray system of resolution \( \Delta r_\perp^2 = 10 \mu m \) operating at 20 keV, the maximum thickness
for which the projection approximation is valid is $\sim 1.6 \text{ m}$. This is larger than the thickness of most objects of interest in medical imaging, including the breast.

From Eq 2.12, we can take the square modulus of the complex field such that $I(\vec{r}) = |U(\vec{r})|^2$ to arrive at Beer-Lambert's law relating the intensity at the output plane to the absorption properties of the object

$$ I(\vec{r}, z_0) = I(\vec{r}, 0) \exp \left[ \int -\mu(\vec{r}, z) dz \right] $$

(2.14)

where $\mu = 2\beta k$ is the linear attenuation coefficient.

### 2.3 Coherence

In order to understand phase, we must first consider the concept of coherence. Coherence is a property which is rarely fully achieved in reality. However, understanding the degree to which experimental conditions deviate from these ideals is important to the design of phase imaging systems.

#### 2.3.1 Spatial Coherence

Spatial or transverse coherence refers to the cross-correlation between the field at two different points in space transverse to the direction of propagation, as in between $\psi(x)$ and $\psi(x + \Delta x)$. It characterizes the ability of the field at spatially separated points to form interference fringes. The degree of spatial coherence between two plane waves is quantified by the coherence width

$$ W_c = \frac{\lambda L}{2D} $$

(2.15)

where $L$ is the propagation distance, and $D$ is the distance between two point sources from which different waves originate [3]. This coherence width is the distance over which two points on the wavefront will be coherent with each other, therefore longer coherence width corresponds to higher degree of spatial coherence. From Eq. 2.15,
we can see that coherence width increases as the distance between the wave sources decrease. If we consider an X-ray source of a finite size as many point sources that are spread over some distance $D$, it is evident that spatial coherence is inversely proportional to the source size. Additionally, the coherence width is directly proportional to the propagation distance. Therefore, in an extended source, for which $D$ is large, the source could have high spatial coherence if considered from a sufficiently far away distance.

2.3.2 Temporal Coherence

Temporal or longitudinal coherence is the cross-correlation between the field at different points in time, as in between $\psi(t)$ and $\psi(t+\Delta t)$. For two paraxial plane waves, the degree of temporal coherence is characterized by the coherence length

$$L_c = \frac{\lambda^2}{2\Delta\lambda} \quad (2.16)$$

where $\lambda$ and $\lambda - \Delta\lambda$ are different wavelengths of two waves [3]. The coherence length is the longitudinal distance that the waves can travel while maintaining their temporal coherence. Temporal coherence is determined by the bandwidth of the X-ray source. A broadband X-ray source can be considered as producing waves at multiple wavelengths. In this case, the bandwidth can be characterized as $\Delta\lambda$, and is inversely proportional to the coherence length.

2.4 Phase Imaging Techniques

Phase imaging aims to measure the phase shift that occurs when X-ray passes through an object, and in doing so measure the real component of the refractive index $\delta$. Since phase cannot be directly measured by a detector, a number of techniques have been developed to measure phase indirectly. These techniques can be classified into three main categories: 1) analyzer-based, 2) grating-based, and 3) propagation-based techniques.
2.4.1 Analyzer-Based Imaging

In analyzer-based imaging, a collimated X-ray beam is monochromatized through a crystal monochromator before passing through the object [16, 19, 37]. The beam emerging from the object then passes through an analyzer crystal which selectively filters the X-rays such that only those arriving at a specific angle reach the detector. The analyzer is rotated through a range of angles to acquire signal of different refraction angles. This yields images that separate non-deviated, refracted, and scattered rays. From this set of images, various algorithms can be used to extract the phase and absorption components. Analyzer-based methods are capable of imaging large fields of view and with high sensitivity to small changes in refractive index. However, it is also highly sensitive to vibrations and environmental disturbances. The use of the analyzer crystal also significantly reduces the dose efficiency of the technique, since it filters out much of the radiation that emerges from the patient. Furthermore, the reliance on monochromatic collimated high brilliance sources limits its application outside of synchrotron facilities.

2.4.2 Grating-Based Imaging

Grating-based imaging utilizes a series of high-frequency gratings to detect deviations in the ray orientation due to the object [84, 62, 49]. When implemented using a spatially coherent synchrotron source, a phase grating is placed immediately after the object, which introduces a periodic phase shift. Due to what is known as the Talbot effect, these phase shifts manifest as intensity modulations at a specific distance from the phase grating. Interactions of the X-ray with the object alters this interference pattern. These changes are measured by phase stepping an absorption grating placed in front of the detector. Through this process, three types of images are acquired: absorption, differential phase, and dark-field, which correspond to attenuation, refraction, and scattering effects respectively. These measurements can be analyzed to retrieve the complex index of refraction of the object. Grating interferometry can also be implemented with an extended laboratory X-ray source by placing
an additional absorption grating in front of the source such that the beam is split into an array of small sources. The compatibility of this technique with conventional X-ray sources has made it attractive for translating into clinical settings. However, its spatial resolution is limited by the ability to produce gratings of sufficiently small periods. Another limitation of this method is phase stepping, which requires at least three images to be acquired per projection, and demands highly precise movement and instrument stability.

2.4.3 Propagation-Based Imaging

Propagation-based imaging involves the simplest experimental setup of the three phase imaging methods, requiring only a spatially coherent radiation source and a detector placed a sufficient distance away from the sample. While phase modulations induced by the object cannot be measured at the plane immediately after the object, the phase modulations transform into intensity modulations after free-space propagation. Neglecting dissipation, the measured signal is proportional to the second derivative of the phase, from which phase can in turn be retrieved. This method relies on a high resolution detector to be able to resolve the high frequency fringes. It is compatible with polychromatic laboratory sources of a sufficiently small spot size. The lack of optical elements required for this technique enables an implementation that is robust to mechanical errors and disturbances while also optimizing dose efficiency. The experimental simplicity also makes this technique the most compatible with tomography for 3D phase imaging. For these reasons, in this thesis, we have chosen to develop a propagation-based phase imaging system in a bench-top setting. In the follow sections, we discuss the theoretical basis of propagation-based imaging.

2.5 X-ray Propagation

X-ray imaging is carried out in transmission mode in which waves travel through an object and is measured on the other side. In conventional absorption imaging, the detector captures the intensity of the field immediately after the object such
that only field changes incurred within the material contribute to image formation. However, phase cannot be captured in this way because taking the intensity captures the absolute value of the field. On the other hand, if the wave-field is propagated in free-space, refracted rays will interfere with unrefracted rays to form interference patterns that can be measured by the detector. This propagation of the wave-field through space can be modeled using wave optics. In this section, we will establish the theoretical basis for image formation in propagation-based phase imaging.

2.5.1 Fresnel Diffraction

The propagation of a paraxial wave field is described by the Fresnel diffraction integral

\[
U(x', y'; z) = \frac{e^{ikz}}{i\lambda z} \int \int U(x, y; 0) \exp \left\{ \frac{ik}{2z} \left[ (x' - x)^2 + (y' - y)^2 \right] \right\} dxdy
\]

(2.17)

where \( U(x', y'; z) \) is the field \( U(x, y; 0) \) propagated by a distance \( z \). The Fresnel integral can be cast as a convolution between the field and a function \( h(x, y) \) such that

\[
U(x, y; z) = U(x, y; 0) * h(x, y)
\]

(2.18)

where

\[
h(x, y) = \frac{e^{ikz}}{i\lambda z} e^{\frac{ik}{2z}(x^2+y^2)}
\]

(2.19)

where \(*\) denotes convolution in 2D.

The regime in which Fresnel diffraction applies is determined by the Fresnel number

\[
F = \frac{a^2}{\lambda L}
\]

(2.20)

where \( a \) is the characteristic aperture size and \( L \) is the propagation distance. Propagation can be modeled by Fresnel diffraction when \( F \gg 1 \). For an X-ray beam at 20 keV that propagates 0.5m to a detector of pixel size 50\( \mu m \), the Fresnel number is 80, therefore the system falls in the near-field Fresnel regime. Most propagation-based X-ray imaging systems fall within the Fresnel regime.

The Fresnel integral in Eq. 2.17 is formulated for a parallel wave field. However,
compact laboratory sources originate from a point and are divergent. Propagation of a divergent wave field can be described with the Fresnel scaling theorem, which provides a simple mapping between Fresnel diffraction from a plane wave and Fresnel diffraction from a divergent wave, such that

\[ U(x, y, z_2) = \frac{1}{M^2} U^{(P)}(\frac{x}{M}, \frac{y}{M}, z_{\text{eff}}) \] (2.21)

where \( U \) is the propagated wave field for point illumination, \( U^{(P)} \) is the propagated wave field for parallel illumination, \( z_1 \) and \( z_2 \) are the source-to-object and object-to-detector distances respectively, \( z_{\text{eff}} = z_2 / M \) is the effective propagation distance, and \( M = (z_1 + z_2) / z_2 \) is the geometric magnification factor. The Fresnel scaling theorem establishes that the amplitude of the divergent field propagated by \( z_2 \) is equal to the amplitude of the planar field propagated by a distance \( z_{\text{eff}} \) and multiplied by a factor \( 1/M \).

### 2.5.2 Transport of Intensity Equation

Wave propagation in the Fresnel regime can alternatively be described in terms of the real-valued quantities of intensity and phase. From the paraxial wave equation, a relationship can be derived between the axial derivative of the intensity \( I(\mathbf{r}) \) and the Laplacian of the phase \( \phi(\mathbf{r}) \), known as the transport of intensity equation (TIE) [74]

\[-k \frac{\partial I(\mathbf{r})}{\partial z} = \nabla_{\perp} \cdot \left( I(\mathbf{r}) \nabla_{\perp} \phi(\mathbf{r}) \right) \] (2.22)

where

\[ \nabla_{\perp} = (\frac{\partial}{\partial x} + \frac{\partial}{\partial y}) \] (2.23)

is the 2D Laplacian operator in the lateral direction and \( k = 2\pi/\lambda \) is the wave number.

If the transverse gradient for either \( I \) or \( \phi \) is small, the right hand side of the TIE
can be approximated as

\[ \nabla_\perp \cdot \left( I(\vec{r}) \nabla_\perp \phi(\vec{r}) \right) = I(\vec{r}) \nabla^2 \phi(\vec{r}) + \nabla_\perp I(\vec{r}) \nabla_\perp \phi(\vec{r}) \]

\[ \approx I(\vec{r}) \nabla^2 \phi(\vec{r}) \]  

(2.24)

(2.25)

For sufficiently short propagation distances, the partial derivative \( \partial I(\vec{r})/\partial z \) on the left hand side of the TIE can be approximated by the finite difference

\[ k \frac{\partial I(\vec{r}, z)}{\partial z} \approx k \frac{I(\vec{r}, z + \Delta z) - I(\vec{r}, z)}{\Delta z} \]

(2.26)

For polychromatic illumination, the TIE can be approximated by replacing \( k \) with a spectrally weighted mean wavelength [78, 64]. The TIE provides a useful basis for phase recovery from intensity measurements.

2.6 Tomography - Phase Contrast Imaging in 3D

Amplitude and phase represent projections of an object's material properties along one direction, the optical axis. Computed tomography (CT) enables us to obtain the 3D distribution of an object's index of refraction from a set of 2D projections acquired at different angles around the object. Consider a function \( f(x, y) \) which represents the distribution of a material property \( \delta(x, y) \) or \( \beta(x, y) \). The process of acquiring projections from multiple angles is embodied by the Radon transform

\[ p(r, \theta) = \mathcal{R}\{f(x, y)\} = \int_{-\infty}^{\infty} \int_{-\infty}^{\infty} f(x, y) \delta(x \cos \theta + y \sin \theta - r) dx dy \]

(2.27)

where \( \delta \) is the Dirac delta function, and the coordinates \( x, y, r, \theta \) are defined in Fig.2-4. The Radon transform of a function is known as the sinogram. The goal of tomographic reconstruction is to reconstruct \( f(x, y) \) from a set of projections \( p(r, \theta) \). The Fourier slice theorem allows us to relate a function \( f(x, y) \) to its sinogram \( p(r, \theta) \) through the
Fourier transform. The Fourier slice theorem states that

$$\mathcal{F}_1{\{p_\theta(r)\}} = \mathcal{F}_2{\{f(r \cos \theta, r \sin \theta)\}}$$

(2.28)

where $\mathcal{F}_1$ and $\mathcal{F}_2$ are the Fourier transforms in 1D and 2D respectively, and $p_\theta(r)$ is the projection along angle $\theta$. Otherwise put, the 1D Fourier transform of a 1D projection $p_\theta(r)$ is equivalent to a line through the origin at an angle $\theta$ in the 2D Fourier transform of $f(x, y)$. Given this, information about the 2D Fourier space of $f(x, y)$ can be filled by acquiring a set of projection images at rotation angles ranging from 0 to $\pi$. Theoretically, for a continuous function, the 2D slice $f(x, y)$ could be reconstructed by taking the inverse Fourier transform of the fully sampled Fourier space. However, in the discrete case, the Fast Fourier Transform (FFT) and its inverse are implemented on a Cartesian grid, whereas the Fourier space sampling through the Fourier slice theorem occurs on a polar grid. The necessary interpolation between these two coordinates in the Fourier domain leads to artifacts in the reconstruction.

Alternatively, a procedure called backprojection can be used. In backprojection,
the value \( p(r, \theta) \) is assigned to all points \((x, y)\) along the path of the projection, essentially 'smearing' the sinogram back into the volume. The function \( f(x, y) \) can then be obtained by integrating the projection values associated with projection lines going through the point \((x, y)\). In this case, the interpolation is carried out in the space domain as opposed to the Fourier domain. Because projections sample the Fourier space on a polar grid, low spatial frequencies are more densely sampled than high spatial frequencies. To compensate for this uneven sampling, a Fourier domain filter can be used in conjunction with backprojection in a reconstruction process called filtered backprojection (FBP)

\[
f(x, y) = \int_0^\pi \int_{-\infty}^\infty F(k, \theta) |k| e^{i2\pi k(x \cos \theta + y \sin \theta)} dk d\theta
\]  

where \( F(k, \theta) = \mathcal{F}_{2D}\{f(x, y)\} \), and \(|k|\) is a ramp filter. In experimental implementations, a number of alternative filters which were designed to optimize noise performance, can be used in place of the ramp filter. Some commonly used filters include Ram-Lak filter, Shepp-Logan filter, Hanning filter, and Hamming window.

In absorption CT, the distribution of \( \mu(x, y) \) is directly reconstructed from the log of the intensity measurements. For phase CT, the distribution of \( \delta(x, y) \) can be reconstructed by first carrying out phase-retrieval on individual projections to obtain a phase sinogram \( \phi(r, \theta) \), then performing CT reconstruction on the phase sinogram.
Chapter 3

Implementation of a bench-top X-ray phase contrast tomography system

To date, much of the work on X-ray phase imaging has been conducted in synchrotron facilities. In order to investigate the feasibility of phase-contrast tomography in a laboratory setting, we built a bench-top system to retrieve phase from field propagation using a compact laboratory X-ray source.

3.1 Instrumentation

The primary hardware components of propagation-based phase imaging are the X-ray source, the motion-control stage, and the detector.

3.1.1 X-ray Source

Compact sources produce X-ray via electron impact with a metal anode. Electrons are emitted by the cathode and accelerated by an electric field toward the anode. Magnetic lenses focus the electron beam to a small focus on the anode. The anode is typically made of a solid metal. When accelerated electrons impinge on the anode, the
nuclei of the anode material decelerates the electrons to produce a broad spectrum of photons called Bremsstrahlung. Additionally, the incident electrons may dislodge a bound electron in the anode material. When an outer-shell electron fills this vacancy, photons of a wavelength specific to the element are emitted, in a process known as characteristic emission. The resultant spectrum contains a combination of these two emission types.

For phase imaging, the X-ray beam must be highly spatially coherent. Microfocus X-ray sources satisfy this requirement by focusing the electron beam to a small spot on the anode such that the X-ray photons all originate from very close to each other. To accommodate this small spot size, microfocus sources must operate at a current much lower than conventional X-ray sources to prevent the anode from melting. As such, microfocus sources produce a lower X-ray flux. In these flux-limited conditions, the lack of optical elements in propagation-based phase imaging is especially advantageous.

Our experimental system uses a tungsten anode microfocus source (Hamamatsu L8121-03) with a minimum spot size of 5μm. The source operates at an energy range of 40-150 kVp and at a current of up to 0.5mA. For a propagation distance of 1 m, the illumination would have a spatial coherence width of $W_c \sim 10\mu m$, based on Eq. 2.15.
Table 3.1: Detector specifications

<table>
<thead>
<tr>
<th>Detector</th>
<th>Shad-O-Box 4K</th>
<th>Shad-O-Box 6K HS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(Teledyne DALSA Inc)</td>
<td>(Teledyne DALSA Inc)</td>
</tr>
<tr>
<td>Resolution</td>
<td>48 μm</td>
<td>49 μm</td>
</tr>
<tr>
<td>Number of pixels</td>
<td>2000 × 2048</td>
<td>2940 × 2304</td>
</tr>
<tr>
<td>Dynamic range</td>
<td>4000 : 1</td>
<td>4000 : 1</td>
</tr>
<tr>
<td>Bit depth</td>
<td>12 bit</td>
<td>14 bit</td>
</tr>
</tbody>
</table>

This provides sufficient spatial resolution since the coherence width is small relative to the detector's pixel size.

### 3.1.2 X-ray Detector

Propagation-based phase imaging relies on a high resolution detector to resolve the Fresnel fringes in the intensity images. In our system, we use scintillator-coupled flat-panel digital detectors. The scintillator converts X-ray photons to visible light photons via a scintillating crystal (Gd₂O₂S). The visible light photons are then detected by a CMOS (complementary metal oxide semiconductor) sensor. The imaging system's resolution, field of view, sensitivity, and dynamic range are influenced by the detector's pixel size, pixel number, bit depth, and dynamic range respectively. The specifications of detectors used in our system are summarized in Table 3.1.

X-ray detectors often have variations in sensor response between different pixels on the sensor or between different regions on the detector. Correcting for these variations is important to achieving optimal image quality. We perform flat field correction by acquiring a flat field image and a dark field image. The flat field image is taken with the source on and no object in the field of view, while the dark field image is taken with the source turned off. Using these measurements, flat field correction was carried out using the ShadoCam Imaging Software.

Another common problem in X-ray detectors is the presence of defective pixels in the detector. Some defective pixels manifest as ultra-bright signals independent
of the image and often leads to reconstruction artifacts. Since the signals from these pixels are abnormally high, we can identify them by setting a threshold well outside of the normal range of signal distribution. We then apply a $3 \times 3$ median filter to remove the pixel.

### 3.1.3 Stage

To enable precise alignment of the imaging system and tomographic acquisitions, we built an integrated multi-axis motion control system on which samples can be mounted. The system has two linear stages (Zaber Technologies) in the directions parallel to and horizontally transverse to the optical axis. The linear stage along the optical axis allows adjustment of the source-to-object and object-to-detector distances. The transverse stage enables translation of the object in and out of the field of view such that flat field images can be obtained for calibration. A rotation stage is incorporated into the system, which allows tomography acquisition. The rotation stage (Thorlabs, Inc.) provides 360° rotation at angular resolution of up to 2.19 arcsec. We also integrated two goniometer stages (Thorlabs, Inc.) which enable adjustment of in-plane and out-of-plane tilt. The tilt stages allow precise alignment of the rotation axis, which is essential to achieving artifact-free tomographic reconstructions.

To align the stage’s axis of rotation to the that of the imaging system, we use a needle mounted vertically on the multi-axis stage. To adjust the in-plane tilt, we image the needle at 0° and 180°, and tune the goniometer such that the two images match. To adjust for out-of-plane tilt, we raise the stage such that the top surface is at the center of the detector. We then adjust the second goniometer such that the curvature of the stage surface on the image is minimized.

### 3.2 Tomographic phase retrieval

The process of phase retrieval involves computing the phase from measured intensity images, while the process of tomography involves reconstructing an object’s internal 3D material properties from images acquired at multiple angles around the object.
Tomographic phase retrieval relies on combining these two processes to retrieve the 3D distribution of $\delta$. This is carried out by first retrieving the projected phase at each projection angle $\phi(x, y, \theta)$ from the corresponding intensity images $I(x, y, \theta)$, then solving for $\delta(x, y, z)$ by tomographic reconstruction.

The transport of intensity equation (TIE) allows us to relate the measured intensity to the phase via Eq 2.22. Traditionally, solving the TIE requires two or more measurements of the intensity taken at different propagation distances to estimate the derivative of the intensity. However, taking images at multiple propagation distances either by translating the detector or the object is highly impractical for tomographic implementation. X-ray waves evolve much more slowly with propagation distance than optical waves due to the much small refractive index. Therefore, the translation distance necessary to achieve a measurable change in the Fresnel fringes is on the order of 10 - 100 cm for X-rays. The Fresnel fringes we seek to measure, however, are on the order of 10 - 100 $\mu$m. Minuscule angular misalignments between the translational axis and the optical axis are easily magnified after the large translation distance to lateral displacements greater than 10 $\mu$m. In our initial attempts to implement multi-shot phase imaging, we found that it is extremely difficult to align the system so precisely as to avoid this problem.

Instead, we turned to a phase retrieval method that enables phase retrieval from a single propagated intensity image by assuming the object's attenuation are dominated by Compton scattering [80]. This assumption generally holds true for objects of low atomic number materials such as soft tissue. Under this assumption, the real and complex components of the refractive index are characterized by a proportionality constant known as the phase-attenuation duality

$$\gamma = \frac{\delta}{\beta} = \frac{2\lambda r_e}{\sigma_{KN}}$$

where $r_e = 2.81794 \times 10^{-15}$ is the classical electron radius, $\sigma_{KN}$ is the Klein Nishina function [40], and $\lambda$ is the wavelength. For polychromatic illumination, such as in the case of the microfocus source, $\lambda$ can be approximated by the spectrally-weighted
mean wavelength [78, 64]. Incorporating the duality relationship into Eq 2.22 and applying the Fresnel scaling theorem (Eq. 2.21) gives the phase-attenuation duality form of the TIE for a divergent wave [80]

\[
\frac{I(Mx, My)}{I_0} = \frac{1}{M^2} \left(1 + \frac{z_{\text{eff}} \lambda \gamma}{4 \pi} \nabla^2 \right) \exp \left(\frac{2\phi(x, y)}{\gamma}\right)
\]

where \( M = (z_1 + z_2)/z_2 \) is the geometric magnification factor, \( z_{\text{eff}} = z_2/M \) is the effective propagation distance, \( I_0 \) is the incident field intensity, and \( \nabla^2 \) is the 2D Laplacian operator in the lateral direction. We solve for the phase \( \phi(x, y) \) using the Fourier domain solution to Poisson’s equation as [80]

\[
\phi(\mathbf{r}) = \frac{\gamma}{2} \ln \mathcal{F}^{-1} \left\{ \frac{\mathcal{F}\{M^2 I(M\mathbf{r})/I_0\}}{\pi z_{\text{eff}} \lambda \gamma |w|^2 + 1} \right\}
\]

where \( \mathbf{r} = (x, y) \) is the spatial coordinate, \( w = (u, v) \) is the spatial frequency, and \( \mathcal{F} \) and \( \mathcal{F}^{-1} \) are the discrete 2D and inverse 2D Fourier transforms respectively.

By adopting a phase retrieval technique that requires only a single propagated intensity image, we can incorporate tomography to achieve 3D reconstruction of the complex refractive index. To do so, we reconstruct \( \delta(x, y, z) \) from the retrieved phase at multiple projection angles \( \phi(x, y, \theta) \) using the Fourier slice theorem implementation of filtered back projection (FBP) as

\[
\delta(x, y, z) = \mathcal{F}^{-1}_{1D} \left\{ |w| \mathcal{F}_{1D}\{\phi(x, y, \theta)\} \right\}
\]

where \( w \) is the spatial frequency variable.

### 3.3 Experimental performance

#### 3.3.1 Liquid sample

To validate the phase imaging system’s performance, we imaged two Eppendorf tubes containing liquids of similar density: water and hydrogen peroxide. The microfocus
source was operated at a peak voltage of 100 kVp and a current of 100μA. The source-to-object and object-to-detector distances were 0.7 m and 1.42 m respectively. For tomographic reconstruction, we acquired 72 projection images over 360°. The real component δ of the refractive index was reconstructed as outlined in the previous section by first retrieving the projected phase at each angle then reconstructing δ via FBP. The complex component β of the refractive index corresponding to attenuation is reconstructed from the log of the intensity projection images using FBP.

Figure 3-2 a) shows an intensity image of the liquid samples, and Figure 3-2 b) shows the corresponding phase projection retrieved from the intensity image. Figure 3-2 c) and d) show axial reconstructions of β and δ respectively. In these reconstruction images, the tube on the left contains water while the tube on the right contains hydrogen peroxide. On visual inspection, it is evident that phase imaging affords improved contrast between the two liquids compared to absorption imaging, which is laden with noise. Further quantitative analyses found that phase imaging provided an accurate H₂O₂/H₂O ratio with an error of 1.40% while the estimate obtained via absorption imaging was less accurate with an error of 20.13%. Contrast to noise ratio (CNR) between the two liquids was calculated as

<table>
<thead>
<tr>
<th></th>
<th>β</th>
<th>δ</th>
</tr>
</thead>
<tbody>
<tr>
<td>Water (H₂O)</td>
<td>-8.70 × 10⁻¹¹ ± 8.20 × 10⁻¹¹</td>
<td>-1.14 × 10⁻⁷ ± 1.11 × 10⁻⁸</td>
</tr>
<tr>
<td>Hydrogen peroxide (H₂O₂)</td>
<td>-7.86 × 10⁻¹¹ ± 7.63 × 10⁻¹¹</td>
<td>-1.29 × 10⁻⁷ ± 1.15 × 10⁻⁸</td>
</tr>
<tr>
<td>Measured ratio (H₂O₂/H₂O)</td>
<td>0.904</td>
<td>1.13</td>
</tr>
<tr>
<td>Expected ratio (H₂O₂/H₂O)</td>
<td>1.1322</td>
<td>1.1114</td>
</tr>
<tr>
<td>Error</td>
<td>20.13%</td>
<td>1.40%</td>
</tr>
<tr>
<td>Contrast to noise ratio</td>
<td>0.101</td>
<td>1.3</td>
</tr>
</tbody>
</table>
Figure 3-2: Experimental imaging results of liquid-filled tubes a) Image of projected intensity image from direct detector measurement, b) The corresponding phase projection image retrieved from the projected intensity image, c) Axial slice of $\beta$ reconstructed from intensity images, d) Axial slice of $\delta$ reconstructed from phase images. In all images, Eppendorf tube on the left contains H$_2$O and the one on the right contains H$_2$O$_2$.
CNR = (H₂O_{signal} - H₂O_{2signal})/H₂O_{noise}, where the signal was measured as the mean value within the respective regions, and noise was estimated as the standard deviation in the region of interest. Phase CT displayed a 10 fold increase in CNR compared to absorption CT, from 0.101 in absorption CT to 1.3 in phase CT. Numerical results for the two imaging methods are summarized in Table 3.2. These results show that phase CT of chemically similar specimens is able to provide more accurate and sensitive information compared to absorption CT. Since breast tissue also consists mainly of water, these results provide relevant support to the capabilities of phase CT in breast imaging. We note that the reconstruction artifact surrounding the water sample are due to misalignment of the rotational axis with the optical axis. We were able to reduce these artifacts in subsequent experiments by implementing a rigorous rotational alignment process.

3.3.2 Biological specimen

To further evaluate the system’s performance for objects with more intricate structural components, we imaged a lime specimen. We acquired 500 projections over 360°. The source was operated at 60 kVp energy and 500 μA current and exposed for 6.7s per projection. The source-to-object and object-to-detector distances were 1.04 m and 1.14 m respectively. Figure 3-3 shows axial slice of reconstructions from absorption CT (left) and phase CT (right). In the phase reconstruction, the fibrous structures of the mesocarp, the white spongy material surrounding the fruit, can be made out clearly, whereas the same structures are poorly distinguished in the absorption image. The exocarp, the outermost layer of the lime also known as the zest, contains oil glands which can also be clearly visualized in the phase reconstruction. Additionally, the individual juice-filled vesicles in the endocarp of the lime, corresponding to the pulp, are faintly delineated in the phase image, whereas they are not at all visible in the absorption image. These structural components of the lime are composed of low atomic number elements such as hydrogen, oxygen, carbon, and nitrogen, and are therefore of similar chemical composition to soft tissue. These results demonstrate the ability of phase CT in distinguishing biological structures at a high resolution.
Figure 3-3: Absorption CT (left) and phase CT (right) reconstructions of a lime specimen shows phase imaging provides superior visualization of fine biological structures compared to absorption CT.
Figure 3-4: Histograms of the axial reconstruction of absorption (top) and phase (bottom) shown in Fig 3-3.
Chapter 4

Optimization of tomographic phase contrast imaging system

In X-ray phase contrast CT, as in conventional absorption CT, the effective use of dose is important to minimizing radiation exposure to the patient. Dose can be distributed between obtaining less noisy projection images and acquiring more projection angles. Unlike absorption CT, which is directly reconstructed from the measured intensity, phase CT involves an additional step of retrieving the phase from each intensity projection prior to tomographic reconstruction. Acquiring less noisy projection images at the expense of fewer projection angles may lead to undersampling artifacts; while, on the other hand, collecting more numerous projections sacrifices the quality of phase retrieval at each projection. Simulations shown in Figure 4-1 demonstrates the effect of increasing noise on phase retrieval and Figure 4-2 shows the effect of number of projections on tomographic reconstruction.

In this chapter, we investigate how the distribution of dose between these two parameters influences the resulting phase CT reconstructions. We examine these relationships through simulations of a digital phantom and experimentally in a tissue-equivalent experimental phantom. These insights will help inform dose-efficient acquisition techniques for phase CT.
4.1 Simulations

4.1.1 Methods

We start with a 3D Shepp-Logan type digital phantom of 256×256×256 pixels, with known complex index of refraction \( n = 1 - \delta + i\beta \). We apply the forward radon transform to simulate a set of 2D projections taken across 360° of rotation at evenly-spaced projection angles. This produces a transmission function for each projection angle, which represents the wave-field immediately after the object. This wave field is propagated to the detector plane \((z = z_d)\) using the Fresnel integral

\[
U(x, y, z_d) = \mathcal{F}^{-1}\{\mathcal{F}\{T(x, y)\} \times H(u, v)\}
\]  

(4.1)

where

\[
T(x, y) = A(x, y)e^{i\phi(x, y)}
\]

(4.2)
is the object transmission function, and

\[ H(u, v) = \mathcal{F}\left\{ \frac{e^{ikz}}{i\lambda z}e^{\frac{i}{2\lambda}(x^2+y^2)} \right\} \]  \hspace{1cm} (4.3)

is the impulse response function. Subsequently, the intensity image is taken as

\[ I(x, y, z_d) = |U(x, y, z_d)|^2 \]  \hspace{1cm} (4.4)

Photon noise is modeled as a Poisson process, where, for an average detector photon count \( N_0 \), the probability mass function is

\[ Pr(N = k) = \frac{e^{-N_0}N_0^k}{k!} \]  \hspace{1cm} (4.5)

We add varying levels of Poisson noise based on the expected photon count to the propagated intensity images. We simulated seven dose-equivalent imaging schemes varying the distribution of dose between number of projections and exposure time which corresponds to level of Poisson noise. The various simulated imaging conditions are summarized in Fig. 4-4. Tomographic phase reconstruction was carried out by first solving the TIE at each projection angle then reconstructing \( \delta \) using FBP as outlined in Section 3.2. Since the object being imaged remains the same under each imaging condition, we use current \( \times \) exposure time (mA \( \cdot \) s) as the metric for dose.

4.1.2 Results

Axial reconstruction slices from the seven simulated dose-equivalent imaging schemes are shown in Fig. 4-4. Artifacts due to undersampling are apparent in the reconstruction where only 64 projections were taken. The artifacts are visibly reduced when dose is distributed across more projections with less dose per projection, hence higher noise. Root mean squared error was calculated for each reconstruction and plotted against the log2 of the number of projections and Poisson noise level (Fig. 4-3). The plot shows that error is initially reduced by distributing the dose across more projections due to suppression of undersampling artifacts. However, the error increases
again when the number of projections are increased to over 4000. This arises from the increasing error in the phase retrieval step due to the elevated noise in the intensity images. Phase retrieval relies on the Fresnel fringes in the intensity images generated by free-space propagation. When the noise level is so high as to obscure the phase signal in the intensity images, the phase retrieval will become increasingly erroneous.

4.2 Experiments

4.2.1 Methods

We acquired tomographies of a mouse phantom (CIRS Inc, Virginia, USA) consisting of 7 rods that mimic medically relevant materials in their electron density. The rods are contained within a polycarbonate cylindrical casing, which is filled with water. Fig. 4-5 shows a diagram of the experimental phantom and the materials represented. The source was operated at 60 kVp and 500 μA. Source-to-object and source-to-detector distances were 535 mm and 1505 mm respectively. We performed
<table>
<thead>
<tr>
<th># of projections</th>
<th>poisson mean</th>
<th>RMSE</th>
</tr>
</thead>
<tbody>
<tr>
<td>64</td>
<td>1e5</td>
<td>5.103e-07</td>
</tr>
<tr>
<td>128</td>
<td>5e4</td>
<td>4.395e-07</td>
</tr>
<tr>
<td>256</td>
<td>2.5e4</td>
<td>4.394e-07</td>
</tr>
<tr>
<td>512</td>
<td>1.25e4</td>
<td>4.565e-07</td>
</tr>
<tr>
<td>1024</td>
<td>6.25e3</td>
<td>4.476e-07</td>
</tr>
<tr>
<td>2048</td>
<td>3.125e3</td>
<td>4.454e-07</td>
</tr>
<tr>
<td>4096</td>
<td>1.563e3</td>
<td>4.777e-07</td>
</tr>
</tbody>
</table>

Figure 4-4: Phase reconstruction of Shepp-Logan phantom simulated at constant dose with 7 different dose distribution schemes.
five different dose distribution schemes with a fixed total dose of 450 mA\cdot s, which is calculated as number of projections $\times$ current $\times$ exposure time. The different dose distribution schemes are shown in Fig. 4-7. Phase retrieval and reconstructions were carried out in the same way as the simulations.

### 4.2.2 Results

Phase reconstructions from the five different dose-equivalent imaging schemes are shown in Fig.4-6. Contrast to noise ratio (CNR) was calculated for each material in the phantom relative to the surrounding water. Noise was estimated as the standard deviation of the water region. CNR for each material was plotted against the $\log_2$ of the number of projections and exposed dose (in mA\cdot s). These experimental results mirror the simulations in that undersampling artifacts are reduced when dose
is distributed to a sufficient number of projections. In this case, Fig.4-6 shows that contrast to noise ratio is increased by distributing dose to up to 300 projections, past which no further benefits to CNR is gained by distributing to even more projections and reducing mA·s per projection. We also see that this trend holds for all 7 materials represented in the phantom. Unlike in the simulations, we did not see the CNR decrease again at higher numbers of projections and correspondingly higher noise per projection. This may be due to the fact that we did not push the noise limit to the degree that was simulated. It is possible that if the number of projections is further increased past 1200, and the exposed dose per projection is thus further decreased, we may see a similar decline in image quality as we saw in the simulation results.
Figure 4-7: Axial slice of phase reconstruction of the experimental phantom at 5 different dose distribution schemes at a fixed total dose
4.3 Conclusion

Through simulations and experiments, we examined the effect of dose distribution on the reconstruction quality in phase-contrast tomography. Our results suggest that there is significant benefit to image quality in terms of RMSE and CNR in distributing dose to collecting more projections in order to overcome undersampling artifacts. However, once sufficient sampling is reached, further distributing dose to more projections may negatively impact the ability to retrieve phase from intensity images. These results suggest that for a fixed exposure dose, there is an optimal distribution scheme which can minimize error in the reconstruction, and maximize the image quality.
Chapter 5

Iterative algorithm for multi-energy tomographic phase retrieval

5.1 Introduction

In propagation-based phase imaging, quantitative phase is obtained by solving the transport of intensity equation (TIE), relating intensity at the detector to the Laplacian of the projected phase under paraxial and small-wavelength approximations [75]. This method presents two significant limitations. Solving the TIE requires multiple axially displaced intensity measurements [33]. However, taking even just two-images at two different distances for each rotation angle is impractical for implementing tomography, due to the challenges of physical alignment and motion artifacts. The divergent nature of beams from laboratory sources adds further alignment challenges due to changes in magnification when propagation distances are altered. Furthermore, the ill-posed nature of TIE causes solutions to be highly susceptible to low-frequency noise. There exists a number of single-shot methods which are more suitable for tomography as they require only a single intensity image to be collected at each projection angle [65, 57, 44, 32, 11]. These single-shot methods rely on assumptions
that the absorption is constant or negligible, or that the absorption and phase coefficients are proportional to each other [45, 12]. In the previous chapters, we have used the phase-attenuation duality method which makes this latter assumption. However, most objects of interest contain variations in both absorption and phase properties, and neglecting the absorption leads to significant errors. The assumption of constant proportionality between absorption and phase only holds up for low Z (atomic number) materials, whose attenuation is limited to contributions from Compton scattering. This assumption fails to hold in the context of materials containing high atomic number elements, such calcium in bone.

In this chapter, we present a novel approach to achieve accurate and quantitative phase retrieval of multi-material objects using two images collected at a single distance without making broad assumptions about the object. Despite using two images per projection, the single distance nature of our approach allows us to avoid misalignment errors and makes the method compatible with tomography. We build on the previously developed attenuation-partition concept and adapt it to retrieve phase from a single defocus distance using images acquired at two different energies [82]. We implement the algorithm in simulation, and experimentally using a tunable table-top microfocus source.

5.2 Theory

In Section 2.2, we introduced the three mechanisms by which X-ray interacts with matter: photoelectric effect, coherent scattering, and Compton scattering. In the diagnostic X-ray energy range, Compton scattering and photoelectric effect are the main contributing effects to the attenuation coefficient μ. The attenuation coefficient can be parsed in terms of these two effects as [4]

$$\mu = \mu_{cs} + \mu_{pe}$$  \hspace{1cm} (5.1)
Existing single-shot phase retrieval methods rely on the assumption that \( \mu \approx 0 \) or that \( \mu_{cs} \gg \mu_{pe} \) [13]. In the X-ray energy range of 10–100 keV used in medical imaging, few objects of interest satisfy these assumptions as most objects incur significant absorption, and contain high Z materials that contribute to photoelectric effect.

The energy dependence of each attenuation coefficient component is well known, and allows us to write the attenuation coefficient in terms of their separate energy-dependent and spatially-dependent components.

\[
\int \frac{\mu}{2} dl = \sigma_{KN}(\lambda) f(\vec{r}) + \lambda^3 g(\vec{r})
\]  

(5.2)

where \( \int \frac{\mu_{cs}}{2} dl = \sigma_{KN}(\lambda) f(\vec{r}) \) corresponds to Compton scattering effects and \( \int \frac{\mu_{pe}}{2} dl = \lambda^3 g(\vec{r}) \) corresponds to photoelectric effects. Regardless of the energy at which the image is captured, the functions \( f(\vec{r}) \) and \( g(\vec{r}) \) are wavelength-independent properties of the material itself. Additionally, we know that

\[
\int \mu_{cs} dl = \sigma_{KN}\rho_{e,p} \text{ therefore } f(\vec{r}) = \frac{\rho_{e,p}}{2}
\]  

(5.3)

where \( \sigma_{KN} \) is the Klein-Nishina function, and \( \rho_{e,p} \) is the projected electron density. The phase can then also be written in terms of its energy-dependent and -independent components as

\[
\phi = \lambda r_e \rho_{e,p} = 2\lambda r_e f(\vec{r})
\]  

(5.4)

where \( r_e = 2.81794032 \times 10^{-15} \) is the classical electron radius.

If an object’s attenuation were dominated by Compton scattering such that \( \mu \approx \mu_{cs} \), then the phase can be retrieved from a single propagated intensity image \( I_{cs}(\vec{r}, z_1) \) via the phase-attenuation duality form of the transport of intensity equation (TIE) [80]:

\[
\phi(\vec{r}) = \gamma \ln \mathcal{F}^{-1} \left\{ \mathcal{F} \left( \frac{I_{cs}(\vec{r}, z_1)/I_0}{\pi d \lambda \gamma |\mathbf{w}|^2 + 1} \right) \right\}
\]  

(5.5)

where \( \gamma = \frac{2\lambda r_e}{\sigma_{KN}} \) is the proportionality constant between \( \delta \) and \( \beta \), \( d \) is the propagation
distance, $I_0$ is the incident intensity, $w = (u, v)$ is the spatial frequency, and $\mathcal{F}$ and $\mathcal{F}^{-1}$ are the discrete 2D and inverse 2D Fourier transforms respectively. This phase-attenuation duality form of the TIE has been shown to be more robust to noise compared to the ill-posed two-shot TIE solution [81]. However, the assumption that Compton scattering is the only contributor to attenuation does not hold for objects that contain significant amounts of high Z elements, such as bone. And even in soft tissue, this assumption can lead to various degrees of inaccuracies depending on the imaging condition.

In order to take advantage of the robust noise performance of the duality-based phase retrieval, while still accounting for the photoelectric effect component of the attenuation coefficient, we build on a previously established concept of partitioning the attenuation in the form of [82]

$$A(\vec{r}) = A_{cs}(\vec{r}) - \delta A(\vec{r})$$

(5.6)

where $A_{cs}$ is the attenuation due to Compton scattering, and $\delta A(\vec{r}) = A_{cs}(\vec{r}) \cdot (1 - A_{pe})$ is the remainder term. It has also been shown that the corresponding propagated intensities at the detector plane $z_1$ can be similarly partitioned such that [82]

$$\sqrt{I(\vec{r}, z_1)} \approx \sqrt{I_{cs}(\vec{r}, z_1)} - \sqrt{\delta I(\vec{r}, z_1)}$$

(5.7)

Using these concepts, we developed an iterative algorithm to retrieve phase using images taken at two different wavelengths at a single propagation distance: $I(\vec{r}, z_1, \lambda_j), \ j = 1, 2$. With each iteration, we use the current estimate of $\delta I(\vec{r}, z_1, \lambda_j)$ and the intensity measurement $I(\vec{r}, z_1, \lambda_j)$ to calculate $I_{cs}(\vec{r}, z_1, \lambda_j)$. We can then justly retrieve phase from $I_{cs}(\vec{r}, z_1, \lambda_j)$ using the phase-attenuation duality method. We update the estimate for $\delta I(\vec{r}, z_1, \lambda_j)$ by enforcing consistency in the wavelength-independent functions $f(\vec{r})$ and $g(\vec{r})$ between phase retrieval results from the two intensity images. Detailed steps of the algorithm is described in the next section, and flowchart of the algorithm is shown in Fig 5-1.
Figure 5-1: Flowchart of multi-energy iterative phase retrieval algorithm
5.3 Algorithm

Start with initial guess for $\delta I_n(\vec{r}, z_1, \lambda_j)$ and measurements $I(\vec{r}, z_1, \lambda_j), j = 1, 2$. At each iteration $n$, perform the following:

1. Calculate Compton scattering component of the intensity

\[
I_{cs,n}(\vec{r}, z_1, \lambda_j) = \left( \sqrt{I(\vec{r}, z_1, \lambda_j)} + \sqrt{\delta I_n(\vec{r}, z_1, \lambda_j)} \right)^2 \quad (5.8)
\]

2. Retrieve phase $\phi_n(\vec{r}, \lambda_j)$ from $I_{cs,n}(\vec{r}, z_1, \lambda_j)$ using the analytical solution to the phase-attenuation duality TIE Eq. 5.5. (An optional noise suppression step can be taken here by tomographically reconstructing the phase volume, using SIRT, then forward-projecting the volume back into the original projections).

3. Using the finite difference form of the transport of intensity equation, find the intensity at the contact plane $I_n(\vec{r}, z_0, \lambda_j)$

\[
I_n(\vec{r}, z_0, \lambda_j) = I(\vec{r}, z_1, \lambda_j) - \frac{d}{k} \nabla_\perp \cdot (I_{n-1}(\vec{r}, z_0, \lambda_j) \nabla_\perp \phi_n(\vec{r}, \lambda_j)) \quad (5.9)
\]

where $d = z_1 - z_0$ and $k = 2\pi/\lambda_j$. (An optional noise suppression step can again be taken here by tomographically reconstructing the attenuation volume, using SIRT, then forward-projecting the volume back into the original projections).

4. Calculate $f_j(\vec{r}), j = 1, 2$

\[
f_j(\vec{r}) = \frac{\phi_n(\vec{r}, \lambda_j)}{2r_e \lambda_j} \quad (5.10)
\]

5. Calculate $g_j(\vec{r}), j = 1, 2$

\[
g_j(\vec{r}) = \frac{\log \sqrt{I_n(\vec{r}, z_0, \lambda_j)} - \sigma_{KN} f_j(\vec{r})}{\lambda_j^3} \quad (5.11)
\]
6. Compute the consistency function \( b(f_j, g_j) \)

\[
b(f, g) = \sqrt{\sum_{\bar{x}} \left( \frac{f_1(\bar{x}) - f_2(\bar{x})}{f_1} \right)^2} + \sqrt{\sum_{\bar{x}} \left( \frac{g_1(\bar{x}) - g_2(\bar{x})}{g_1} \right)^2} \tag{5.12}
\]

7. Check convergence: if \( b_{n-1} - b_n < L \), where \( L \) is the convergence criterion, exit iterations.

8. Calculate the correction term at the contact plane \( \delta I_n(\bar{x}, z_0, \lambda_j) \)

\[
\delta I_{n+1}(\bar{x}, z_0, \lambda_j) = e^{\sigma_{KN}(\lambda_j)f_2(\bar{x})} \left( 1 - e^{\lambda_j \gamma_1(\bar{x})} \right) \tag{5.13}
\]

9. Update estimate for the correction term at the detector plane \( \delta I_{n+1}(\bar{x}, z_1, \lambda_j) \)

\[
\delta I_{n+1}(\bar{x}, z_1, \lambda_j) = \left| \mathcal{F} \left( \sqrt{\delta I_{n+1}(\bar{x}, z_0, \lambda_j) \cdot e^{i\phi_n(\bar{x}, \lambda_j)}} \right) \right|^2 \tag{5.14}
\]

where \( \mathcal{F} \) denotes convolution with the Fresnel propagation kernel.

5.4 Simulation

5.4.1 Methods

We created a customized 3D Shepp-Logan type digital phantom of size \( 128 \times 128 \times 128 \) pixels using material constants from physiologically relevant materials including muscle, adipose tissue, soft tissue, cortical bone, water, and air. Empirical electron density values were obtained from the International Commission on Radiation Units [2] to determine the real component \( \delta \) of the refractive index. Individual mass attenuation coefficient components (Compton scatter and photoelectric effect) were calculated with WinXcom software [25] using material composition data from [1]. The total mass attenuation coefficient is used to determine the imaginary component \( \beta \) of refractive index.
The 3D volume phantom was forward-projected according to the projection approximation to simulate a set of 2D projections across 256 angles spread evenly through 360 degrees of rotation. Forward and back projection operations were performed with the help of the ASTRA toolbox in conjunction with the SPOT toolbox, to enable GPU-accelerated projection operations [8, 18]. Each projected field at the object plane was subsequently propagated using the Fresnel integral to simulate images captured at the detector plane at a propagation distance of 0.5 m from the object. Poisson noise corresponding to a detector photon count of $N = 10^6$ was added. The simulation was carried out for two X-ray energies 26 and 68 keV to generate propagated intensity images at two different wavelengths.

At each projection angle, the previously described algorithm was applied to the two corresponding simulated intensity images to retrieve the projected phase image. The initial guess for $\delta I_n(F, z_1, \lambda_j)$ was set to a $128 \times 128$ matrix of zeros. In this way, phase retrieval was carried out for all 256 projection angles. The 3D complex refractive index was reconstructed from the set of retrieved phase projections using the simultaneous iterative reconstruction technique (SIRT) [26].

In the phase retrieval algorithm, we initialized $\delta I_n(F, z_1, \lambda_j)$ as a matrix of zeros and $I(F, z_1, \lambda_j)$ as a matrix of ones. Additionally, we found that an initialization is require in the first iteration ($n=1$) at step 5 of the algorithm to set $g(F)$ to be a sufficiently large negative value such that in Eq. 5.13, $\delta I_{n+1}(F, z_0, \lambda_j)$ does not give a negative value. In order for the algorithm to converge, this initialization value should be more negative than the true value of $g(F)$. As long as this is satisfied, the exact value of the initialization value does not affect the convergence of the algorithm, nor does it significantly influence the rate of convergence. In our simulation, for example, the expected value of $g(F)$ was on the order of $-1 \times 10^{11}$. Setting the initialization for $g(F)$ to a uniform matrix where every element is equal to $-1 \times 10^{12}$ resulted in the algorithm converging after $\sim 160$ iterations. When we set the initial value to $-1 \times 10^{22}$, which is 10 orders of magnitude beyond the expected value, the algorithm converged to the same result after 180 iterations, under the same convergence criterion. Due to the forgiving nature of this initialization criteria, a satisfactory value can be determined.
5.4.2 Results

Fig 5-2b shows the reconstructed electron density result from the multi-energy algorithm compared to the ground truth Fig 5-2a and an existing single-shot method Fig 5-2c [34]. The multi-energy algorithm produced accurate results with a normalized RMSE of 0.15, which was over an order of magnitude smaller than that achieved through the Fourier method [34], which had a normalized RMSE of 2.04. We see that in the solution obtained using the Fourier method, the electron density is vastly over-estimated especially in the region consisting of cortical bone. This is due to the assumption of proportionality between $\delta$ and $\beta$ being violated. Comparison of the phase projection profiles shown in Fig 5-3 further demonstrates that our multi-energy algorithm faithfully retrieved the phase, and is significantly more accurate than two existing prominent single-shot phase retrieval methods: the Bronnikov method and the Fourier method with Rytov approximation [31, 34].

We plotted the RMSE for absorption and phase retrieval at each iteration. This is shown in Fig 5-4. The plots show the convergence of the algorithm after 161 iterations. The consistency function (Eq. 5.12) for each iteration is also plotted in Fig 5-4, and captures the consistency between the phase retrieval solutions at the
Figure 5-3: Profile of phase retrieved projections using iterative multi-energy method, and comparison to other single-distance phase-retrieval methods.

Figure 5-4: Plot of normalized root mean squared error of absorption and phase at each iteration, and plot of the consistency function at each iteration.

two wavelengths. From these plots, we see that the accuracy of the phase retrieval correlates with the consistency function, and by enforcing this consistency with each iteration, the algorithm increases accuracy of the phase reconstruction.

5.5 Experiment

5.5.1 Methods

We validated our approach experimentally in a benchtop phase contrast tomography system. We acquired propagated intensity images of a mouse phantom (CIRS Inc, Virginia, USA) containing 7 rods with material compositions that simulate lung, muscle, adipose tissue, and four different bone densities. Images were acquired at
40 and 150 kVp using a tunable microfocus source (Hamamatsu Photonics, Hamamatsu, Japan). For the 150 kVp tomography, a 0.005" Sn filter was placed at the source to reduce the bandwidth of the emerging beam. This filter acts as a high pass energy filter to remove lower energy component of the beam. Since 150 kVp is the upper energy limited of the microfocus source, this method allows us to increase the mean-weighted energy to create a greater energy separation between the pairs of images. A current of 0.5 mA was used for both energies. At each X-ray energy, we acquired 250 projections over 360°, with an exposure time of 6.7 s per projection. The source-to-object and object-to-detector distances were 56.5 cm and 106 cm respectively. Images were acquired using a CMOS detector with a 48μm pixel size (Teledyne DALSA Inc. Ontario, Canada). Acquisition is carried out by collecting a full set of projection images at 40 kVp over the 360° rotation range, then tuning the X-ray to 150 kVp to acquire a second set of projection images. We use a high precision rotation stage (Thorlabs, Inc.) with angular resolution of up to 2.19 arcsec to ensure precise registration between the image pairs.

Phase was retrieved using the multi-energy algorithm from the two corresponding intensity images at each projection angle. Additionally, phase retrieval was carried out using two existing single-distance methods: 1) TIE method with weak attenuation assumption [76], and 2) Fourier method with Rytov approximation [34]. For the case of polychromatic illumination, $\lambda$ in the algorithm is approximated by the spectrally-weighted mean wavelength [78, 61]. Mean wavelengths are calculated based on X-ray spectrums simulated using SpekCalc [66]. The mean weighted wavelengths for the tube voltages 40 kVp and 150 kVp (with Sn filter) were calculated to be 26 keV and 68 keV respectively. This corresponds to the energies used in the simulation. Tomographic reconstruction was carried out using SIRT. Tomographic reconstruction results are represented in phase Hounsfield units (pHU), defined as [20]: 

$$pHU = \frac{(\delta - \delta_{\text{water}}) \times 1000}{\delta_{\text{water}} - \delta_{\text{air}}}.$$ 

The algorithm was initialized as in the simulation. We initialized $g(\bar{r})$ at $-1 \times 10^{14}$, which was sufficient for convergence. In the phase retrieval process for the experimental case, we carried out the optional step indicated in step 2 and step 3 of the
algorithm. In this step, the respective phase and attenuation volumes are reconstructed from the sinograms $\phi(\vec{r}, \theta, \lambda)$ and $I(\vec{r}, z_0, \theta, \lambda)$ respectively using SIRT. The volume is then immediately propagated back into their original form. This process effectively acts as a regularizer to suppress the noise which accumulates with progressive iterations. We find that without this step, the noise overtakes the algorithm, and convergence cannot be reached. For images acquired at lower noise levels, this additional step may not be necessary.

5.5.2 Results

Sinograms of the intensity images are shown in Fig 5-5 at the two X-ray energies. The vertical axis corresponds to the projection angles while the horizontal axis corresponds to space in the horizontal direction. Phase contrast fringes are evident in the propagated intensity images at the boundaries between materials. These measured intensity images were the input measurements to the algorithm. Figure 5-6 shows sinograms of the retrieval results from the multi-energy algorithm. The algorithm retrieved the total projected absorption and phase (Fig 5-6 a and b). Additionally, the individual components of the attenuation coefficient (Compton scatter and photoelectric effect) are recovered (Fig 5-6 c and d).

We compared the results of our multi-energy algorithm to the manufacturer provided ground truth data by computing the mean and standard deviation of 8 ROIs defined by the location of the homogeneous rods and the surrounding water. Fig 5-7 shows the tomographic reconstruction of the multi-energy phase retrieval result with
Figure 5-6: Retrieved sinograms of a) total attenuation, $A$; b) phase, $\phi$; c) attenuation due to Compton scatter, $A_{cs}$; d) attenuation due to photoelectric effect, $A_{pe}$.

Figure 5-7: Axial slice of phase reconstruction. Dashed lines define regions of interest for which material composition is known.

1) 750 mg/cc HA  2) 250 mg/cc HA  
3) 50 mg/cc HA  4) 0 mg/cc HA  5) Muscle  
6) Adipose  7) Lung  8) Water
Figure 5-8: Quantitative phase Hounsfield units reconstructed using the multi-energy iterative algorithm (black), compared to two existing single-distance methods: direct inversion of the TIE assuming weak absorption (brown) and Rytov-approximation-based direct retrieval method (blue). The ground truth pHU values for each material are indicated by asterisks.
dashed lines defining the ROI's. Fig 5-8a shows a box plot comparing results from the multi-energy algorithm, the existing methods, and the ground truth, for each material corresponding to an ROI. From these results, we see that the multi-energy algorithm produced the most accurate and precise recovery of the pHU compared to the other methods. This improvement in accuracy is especially prominent for materials that contain high amounts of calcium in the form of hydroxyapatite (HA). This is expected as the assumptions of weak attenuation and $\delta/\beta$ proportionality, fail to hold for these materials. Improvements in accuracy is also evident in non-calcified materials such as muscle, adipose, and 0 mg/cc HA which is a general soft-tissue equivalent material. We note that although application of additional regularization technique to the weak-absorption TIE and Rytov approximation-based TIE may improve the precision of their results, the measurements' accuracy will remain poor due to violation of the underlying assumptions on which these methods are based.

5.6 Conclusions

We presented a novel iterative algorithm for phase retrieval, which uses propagated intensity images with the same defocus distance, acquired using two different X-ray energies. This is achieved by enforcing consistency in the wavelength-independent functions between solutions from the two intensity measurements. Our method overcomes the noise susceptibility and mechanical challenges of solving TIE from multiple propagation distances, without making overreaching assumptions that existing single-shot methods rely on, which fail to hold up for many objects of interest. We show in simulation and experimentally that the algorithm accurately retrieves phase from objects containing both low and high Z materials. We also demonstrate significant improvement in accuracy compared to existing single-distance phase retrieval methods. We note that in our definition of the consistency function (Eq.5.12), we weigh equally the consistency of $f(\vec{r})$ and $g(\vec{r})$. It would be of interest in future studies to examine different weighing of these two components based on their relative contributions. Future studies may also investigate optimal energy pairs.
<table>
<thead>
<tr>
<th>Materials</th>
<th>Weak-absorption (Mean ± STD)</th>
<th>Weak-absorption (RMSE)</th>
<th>Rytov approx. (Mean ± STD)</th>
<th>Rytov approx. (RMSE)</th>
<th>Multi-energy (Mean ± STD)</th>
<th>Multi-energy (RMSE)</th>
</tr>
</thead>
<tbody>
<tr>
<td>750 mg/cc HA</td>
<td>4413.38 ± 782.94</td>
<td>4009.1</td>
<td>3033.56 ± 197.63</td>
<td>2559.7</td>
<td>695.76 ± 80.51</td>
<td>228.9</td>
</tr>
<tr>
<td>250 mg/cc HA</td>
<td>836.23 ± 276.74</td>
<td>689.4</td>
<td>1116.00 ± 77.85</td>
<td>914.5</td>
<td>302.70 ± 27.24</td>
<td>101.6</td>
</tr>
<tr>
<td>50 mg/cc HA</td>
<td>286.53 ± 67.84</td>
<td>203.8</td>
<td>83.82 ± 20.37</td>
<td>22.9</td>
<td>59.16 ± 8.36</td>
<td>36.1</td>
</tr>
<tr>
<td>0 mg/cc HA</td>
<td>-149.39 ± 69.71</td>
<td>162.9</td>
<td>-169.34 ± 23.48</td>
<td>168.8</td>
<td>-14.65 ± 5.51</td>
<td>13.7</td>
</tr>
<tr>
<td>Muscle</td>
<td>162.05 ± 72.13</td>
<td>139.3</td>
<td>40.75 ± 19.26</td>
<td>19.3</td>
<td>31.33 ± 5.95</td>
<td>12.9</td>
</tr>
<tr>
<td>Adipose</td>
<td>-210.95 ± 72.27</td>
<td>175.9</td>
<td>-198.07 ± 27.29</td>
<td>150.0</td>
<td>-63.13 ± 8.34</td>
<td>15.06</td>
</tr>
<tr>
<td>Lung</td>
<td>-239.97 ± 156.43</td>
<td>577.7</td>
<td>-653.50 ± 46.31</td>
<td>149.9</td>
<td>-598.37 ± 77.72</td>
<td>212.4</td>
</tr>
</tbody>
</table>

Table 5.1: Numerical results corresponding to the boxplot shown in Fig 5-8.
Chapter 6

Tomographic phase imaging of breast tumor in small animal model

6.1 Introduction

As we outlined in Section 1.2, mammography, the current gold standard for breast cancer diagnosis, suffers from poor sensitivity and limited specificity. These limitations stem from the lack of soft tissue contrast in absorption-based X-ray imaging. Conventional mammography and CT derive contrast from differences in attenuation by various components of breast tissue. In weakly absorbing tissues such as the breast, these differences are difficult to discern and easily obfuscated by noise. On the other hand, differences in phase signal imparted by breast tissue are significantly greater than attenuation, and therefore provide substantially enhanced contrast.

Phase imaging studies of the breast to date have primarily been restricted to synchrotron sources due to the strict coherence requirement of existing XPCI techniques [77, 50, 69, 85]. However, the reliance on high-brilliance sources significantly limits the use of XPCI in medical applications. Existing studies of XPCI for breast cancer have also been limited to imaging of excised and fixed tissue specimens [30, 85, 6].
However, these excised specimens do not accurately represent the *in vivo* conditions in which breast cancers must be diagnosed. Recently, significant advances have been made in the development of transgenic mouse models of breast cancer [27]. In these transgenic models, tumors arise spontaneously within a normal mammary gland architecture, and are therefore more clinically representative than previous xenograph models.

In order to investigate the capabilities of XPCI to visualize breast tumor in a laboratory setting, first we imaged excised mouse breast tumor specimens using the propagation-based benchtop XPCI system we have developed, and correlated the results with histopathological findings. Then, we performed whole animal X-ray phase contrast tomography on transgenic mouse models of breast cancer. We compared these results to those obtained using a commercial microCT and a preclinical MRI system.

### 6.2 Materials and Methods

#### 6.2.1 Excised Tissue Preparation

Female CD2F1 mice at 6 weeks of age were implanted with subcutaneous 40 mg/90 day release medroxyprogesterone hormone pellets then treated with intragastric DMBA (7,12-dimethylbenz(a)anthracene) at weeks 9, 10, 12 and 13. Tumors were harvested at 1.5 cm or 32 wks, then preserved in 70% ethanol and embedded in paraffin. Formalin fixation does not degrade or artificially enhance image contrast in XPCI, and is therefore suitable for biomedical phase-contrast investigations [79]. Histopathology sections 5 μm in thickness were obtained and stained using hematoxylin and eosin.

#### 6.2.2 Whole Animal Preparation

MMTV-rtTA/tetO-HER2 transgenic mouse models of mammary carcinoma were created as previously described [27]. The model expresses a wild-type human ERBB2 transgene in the mammary epithelium, under the control of a reverse tetracycline
Figure 6-1: a) Diagram of experimental setup where $R_1$ and $R_2$ are the source-to-object and source-to-detector distances respectively. b) Photograph of experimental setup with source on the left, sample stage in the middle, and detector on the right.

controlled transactivator. As such, the mice undergo normal mammary gland development. A total of three animals were used for the study. At 7–8 weeks of age, transgene expression was induced in 2 of 3 animals with administration of a 2500 ppm doxycycline diet. One animal was kept uninduced for control. All animals were sacrificed by $CO_2$ inhalation at 8.5 weeks after commencement of doxycycline.

All animal husbandry and experiments were performed in accordance with protocols approved by the Institutional Animal Care and Use Committees of Dana-Farber Cancer Institute.


6.2.3 Experimental Imaging Setup

X-ray phase contrast tomography scans were performed using a microfocus source (Hamamatsu Photonics) operated at 60 kVp and 0.5 mA producing a focal spot size of 20 μm. Images were acquired using a 2904×2304 pixel CMOS detector with 49.5 μm pixel size (Teledyne DALSA Inc). Specimens were mounted on a motorized rotation stage, and tomography was acquired by taking 500 projection images spaced evenly over 360°. The experimental setup is depicted in Fig 6-1, and the experimental parameters are summarized in Table 6.1. Images of excised specimens were acquired with an exposure time of 4.0 s per projection at a source-to-object distance of 415 mm and source-to-detector distance of 1700 mm. Imaging of whole animal specimens were performed immediately after sacrifice. Tomography was acquired with an exposure time of 5.0 s per projection, at a source-to-object distance of 555 mm and source-to-detector distance of 1700 mm.

Table 6.1: Imaging parameters

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Phase CT</th>
<th>Micro CT (GE)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tube voltage</td>
<td>60 kVp</td>
<td>70 kVp</td>
</tr>
<tr>
<td>Current</td>
<td>0.5 mA</td>
<td>50 mA</td>
</tr>
<tr>
<td>Tomography range</td>
<td>360°</td>
<td>360°</td>
</tr>
<tr>
<td>Step size</td>
<td>0.72°</td>
<td>0.5°</td>
</tr>
<tr>
<td>Number of projections</td>
<td>500</td>
<td>720</td>
</tr>
<tr>
<td>Exposure time</td>
<td>5 s</td>
<td>0.032 s</td>
</tr>
<tr>
<td>Dose</td>
<td>1250 mA·s</td>
<td>1152 mA·s</td>
</tr>
<tr>
<td>Detector type</td>
<td>CCD</td>
<td>CCD</td>
</tr>
<tr>
<td>Detector size</td>
<td>2940×2304 pixels</td>
<td>3500×2300 pixels</td>
</tr>
<tr>
<td>Detector pixel size</td>
<td>49.5 μm</td>
<td>32 μm</td>
</tr>
</tbody>
</table>

6.2.4 Phase Retrieval and Tomographic Reconstruction

Tomographic phase reconstruction was carried out as outlined in Section 3.2 by first solving the phase-attenuation TIE at each projection angle then reconstructing δ using FBP with a Hanning filter. Tomographic reconstructions of β(x, y, z) are similarly
obtained from the intensity projections. Absorption and phase reconstruction images are represented in Hounsfield units (HU) and its analog for phase signal (pHU), which are defined as [20]

\[ HU = \frac{\beta - \beta_{\text{water}}}{\beta_{\text{water}} - \beta_{\text{air}}} \times 1000, \quad \text{pHU} = \frac{\delta - \delta_{\text{water}}}{\delta_{\text{water}} - \delta_{\text{air}}} \times 1000 \] (6.1)

Compressive phase reconstruction is performed by modeling the system as

\[ \mathbf{g} = \mathbf{A} \mathbf{n} \] (6.2)

where \( \mathbf{g} \) is a vector containing phase at all projections, and \( \mathbf{n} \) is a vector of the 3D refractive index [76, 58]. We solve for \( \mathbf{n} \) using the total variation (TV) sparsity basis

\[ \hat{\mathbf{n}} = \arg \min_{\mathbf{n}} ||\mathbf{n}||_{TV} \quad \text{such that} \quad \mathbf{g} = \mathbf{A} \mathbf{n} \] (6.3)

where \( ||\mathbf{n}||_{TV} = \sum \sqrt{(\nabla_z \mathbf{n})^2 + (\nabla_y \mathbf{n})^2 + (\nabla_z \mathbf{n})^2} \) is the TV norm. The regularization parameter was chosen on inspection by trial and error. The minimization problem is solved using FASTA (Fast Adaptive Shrinkage/Thresholding Algorithm [28]). Forward- and back-projection operations were performed with the help of the ASTRA toolbox in conjunction with the SPOT toolbox, to enable GPU-accelerated operations [8].

### 6.2.5 Comparative microCT and MRI

The transgenic mice were subsequently imaged using two commercial systems for comparison. MicroCT volumes were acquired using eXplore CT120 whole mouse MicroCT (GE Healthcare) operated at 70 kVp and 50 mA. Volumes were reconstructed using the system's associated reconstruction software. MicroCT parameters are summarized in Table 6.1. Magnetic resonance imaging of whole animal specimens were obtained using Varian 7T/310/ASR-whole mouse MRI system (Varian/Agilent).
6.3 Results

6.3.1 Excised tissue imaging

Reconstructed sections of an excised paraffin embedded tumor tissue are shown in Fig 6-2. The absorption reconstructed from propagated intensity images is shown in Fig 6-2a) while the compressive phase reconstruction result is shown in Fig 6-2b). The corresponding histopathological section is shown in Fig 6-2 c). The histology slice reveals that the specimen contains a mass composed of high grade invasive ductal carcinoma with extensive necrosis. The tumor cells show glandular, trabecular and solid pattern arrangement with hyperchromasia and extensive necrosis consistent with high grade malignancy. This central malignant mass can be delineated in both the absorption and phase reconstructions, however, the compressive phase reconstruction displays superior contrast between the tumor and surrounding fat tissue. Because the absorption is reconstructed from propagated intensity images, it also benefits from edge enhancements at boundaries due to the phase contrast signal attained from free-space propagation.

The increase in contrast conferred by phase can be even better appreciated by zooming in to a lesion to the left of the main mass (Fig 6-2 d-f). Histology shows that the lesion corresponds to malignant tumor cells invading a ductule with surrounding lymphoplasmicytic inflammatory infiltration (Fig 6-2-f). In the absorption reconstruction, the legion is obscured by noise (Fig 6-2-d). However, the legion can be clearly distinguished in the compressive phase reconstruction (Fig 6-2-d).

6.3.2 Whole animal imaging

Phase-contrast tomography reconstructions revealed multiple masses in the thoracic and abdominal mammary glands of the two doxycycline-induced animals. We verified that these features were pathological rather than normal anatomical features by comparing the results to those obtained from the non-induced control animal. The mammary glands of the control animal were patent and did not contain any masses.
Figure 6-2: Orthogonal cross-sections of paraffin-embedded mouse tumor. a) Absorption reconstruction from propagated intensity images. b) Phase reconstruction obtained from compressive tomographic phase retrieval. c) Histology section corresponding to the tomographic cross-sections shown in b) and c). d), e), and f) correspond to the boxed regions in a), b), and c) respectively.
Figure 6-3: Axial slice through thoracic mammary gland of animal model specimen are shown in a) and c), with a) being the absorption reconstruction from propagated intensity images, and b) being the phase reconstruction. b) and d) correspond to the boxed region in a) and c) respectively, containing a tumor mass. Profiles along the blue lines are shown Fig. 6-4.
Figure 6-4: a) Absorption profile along the dotted blue line indicated in Fig.6-3; b) Phase profile along the same line.
Fig 6-3 shows an axial slice through the thoracic mammary gland of one of the induced animals. We see that overall, soft tissue features are enhanced in the phase reconstruction (Fig 6-3c) compared to the absorption reconstruction (Fig 6-3a) with the former containing less noise in these regions. Close up of a region containing an abnormal mass shows enhanced contrast between the tumor and surrounding tissue in the phase reconstruction (Fig 6-3d) compared to the absorption reconstruction (Fig 6-3b). A comparison of the profile taken across the tumor structure further shows that in absorption (Fig 6-4a) the structure is obscured by noise, while the phase reconstruction (Fig 6-4b) shows clear distinction between the tumor and surrounding tissue. Effectively, tomographic phase retrieval increases contrast by reducing noise without sacrificing resolution or causing blurring, as a low-pass filter would. Streaking artifacts are evident in both absorption and phase reconstructions. These are due to beam hardening caused by dense calcification structures. We note that the dense bone structures within the mouse violate the phase attenuation duality since they contain high amounts of calcium, a high atomic number element. Thus in these regions, $\delta$ is over estimated and the phase reconstruction of bony features display a slightly dilated effect. However, since the soft tissue structures of the mammary gland in which we are interested do not significantly violate the phase-attenuation duality, the phase reconstruction of these regions remain qualitatively valid.

We compared results from our phase CT system to those obtained using two commercially available modalities: microCT and preclinical MRI. An axial phase reconstruction slice through the thoracic mammary gland of a second induced animal is shown in Fig 6-5a alongside the corresponding cross sections in microCT (Fig 6-5b) and MRI (Fig 6-5c). The microCT volume was acquired such that the total exposed dose of the scan (1152 mA·s) is comparable to that of the phase CT acquisition (1250 mA·s). The phase CT shows significant contrast enhancement of the tumor masses compared to the commercial microCT, where the mass is barely distinguishable. Streaking artifacts present in the phase CT are not present in the microCT, because the microCT was acquired using more projections than the phase CT (720 projections compared to 500 projections). Pre-clinical MRI imaging provided
Figure 6-5: Axial slice of mouse model imaged using three different modalities: a)-b) Phase CT, c)-d) commercial microCT, e)-f) preclinical MRI.
some contrast between the tumor masses and the surrounding tissue. We note that in MRI, some tissue types will appear drastically different post-mortem compared to \textit{in vivo}. Therefore, these MRI results may not be representative of living tissue. Nevertheless, these MRI results allowed us to further verify the presence of abnormal masses in the mammary glands.

6.4 Discussion

We demonstrated the application of our bench-top X-ray phase contrast tomography system for visualizing breast cancer. We showed that the phase reconstruction results obtained from this system correlate with pathologically significant features, and that these features are more clearly distinguished in phase compared to absorption. We further demonstrated phase CT imaging of breast cancer in whole animals using a clinically relevant transgenic mouse model. Our results showed improved contrast and visualization of tumor masses in phase CT compared to the corresponding absorption CT as well as commercial microCT under comparable dose and system parameters. In humans, CT of the breast usually reveals more dense lobular structures, which were not seen in the mouse model. Further \textit{in situ} studies in human breast are needed to determine the capabilities of phase-contrast imaging in distinguishing tumor tissue in the context of lobular architectures. Nevertheless, our results support the feasibility and potential value of XPCI in diagnostic breast cancer imaging.
Chapter 7

Perspectives and Future Directions

We have demonstrated a bench-top X-ray phase contrast tomography system which provides a proof-of-concept for the translation of X-ray phase imaging from the narrow setting of synchrotron facilities toward a broadly accessible clinical implementation. We developed a new phase retrieval algorithm which provides significant improvements in accuracy. We further showed pre-clinical results that point to the considerable potential of phase CT in breast cancer diagnosis.

Clinical realization of XPCI of the breast will require further developments in both hardware technology and computational techniques. Currently, one of the major bottlenecks is the limited flux from compact high spatial coherence X-ray sources. This leads to unacceptably long acquisition times. An emerging technology which has made headway in producing compact high brilliance X-ray beams is the liquid-metal-jet source. Whereas traditional electron-impact sources use a stationary solid metal target anode, the anode in the liquid-metal-jet source is a stream of liquid metal. This technology has been demonstrated with a number of room temperature liquid metal alloys such as Galinstan [46]. The main factor limiting flux in traditional electron-impact sources is the overheating of the solid metal anode. Liquid-metal-jet sources, however, are able to dissipate heat more quickly than a solid metal target by cycling the liquid metal [35]. In this way, liquid-metal-jet anodes can withstand a higher density of impinging electron-beam and consequently produce more X-ray photons from a similar sized anode area. A traditional microfocus X-ray source with
a spot size of $\sim 10\mu m$ is able to produce a beam of $\sim 30$ W power. On the other hand, liquid-metal-jet sources can produce $\sim 300$ W beams at a similar $10 \mu m$ spot size, increasing the flux by an order of magnitude [42].

In addition to advancements in X-ray source technology, creative computational imaging techniques can help address the flux limitation. We have conceptualized a method for phase-contrast imaging using a coded X-ray source, consisting of multiple elements, each of which generates a spatially-coherent X-ray beam. This multitude of coherent X-rays are simultaneously incident on the object to produce a spatially-multiplexed image at the detector. The system could be formulated as a linear inverse problem and solved compressively. The use of compressed sensing in conjunction with a coded source can enable higher flux while maintaining the necessary spatial coherence for XPCI. We demonstrated the theoretical feasibility of this approach in numerical simulations and showed that $\sim 40 \times$ increase in photon flux can be achieved using this method [72]. In these simulations, individual elements of the coded sources are considered to be similar to standard microfocus X-ray sources. As such, we show that this level of flux increase can be achieved independent of advancements in X-ray generation technology. The promising results presented in this thesis contributes to motivating these necessary technical developments.

If a clinically compatible acquisition time can be achieved, phase CT imaging of the breast can be implemented in the form of a dedicated breast CT gantry. In a dedicated breast CT system, the patient lies on a table in the prone position. The table has a cutout from which the breast hangs in the field of view. The X-ray tube and detector would rotate around the breast. This geometry is especially desirable because it limits dose to the rest of body, and requires lower flux since the X-rays only travel through an individual breast as opposed to the full thickness of the torso. Dedicated breast CT prototypes have been demonstrated for absorption CT and could be adapted for phase CT by increasing the propagation distance [43].

As the technology continues to progress toward clinical implementation, it will be increasingly important to identify the specific clinical role that XPCI would fulfill. XPCI will not likely replace mammography as a screening modality, since the
cost effectiveness and low dose of mammography are highly desirable features for wide-spread screening program. However, phase CT can be a useful complementary modality for diagnostic characterization in cases where mammography alone is insufficient. An area of potential impact is the imaging of breasts with dense parenchyma, in which mammography has been shown to have poor diagnostic performance. By imaging at higher, more penetrating energies, phase CT would be able to distinguish diagnostically important features amongst the dense tissue. Another application area is the imaging of mammographically occult legions, in which patients present with a palpable lump which cannot be seen on mammogram. Phase CT may be useful in this case in either ruling out a positive diagnosis to avoid unnecessary biopsy, or in providing spatial guidance for a biopsy procedure. Correlation studies comparing phase CT images to existing imaging modalities and histology should be conducted in a broad range of disease sub-types and other benign conditions to determine how phase image should be interpreted clinically. Finally, controlled randomized prospective trials will need to be carried out to assess the impact of phase CT on clinical outcomes.
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