X-ray Phase Contrast Imaging of Preclinical Atherosclerosis

by

Adam Pan

Submitted to the Department of Health Sciences and Technology in partial fulfillment of the requirements for the degree of Doctor of Philosophy in Medical Engineering and Medical Physics at the MASSACHUSETTS INSTITUTE OF TECHNOLOGY

September 2016

© Massachusetts Institute of Technology 2016. All rights reserved.

Signature redacted

Author .............................................................

Department of Health Sciences and Technology

Signature redacted

Certified by ....

George Barbastathis, PhD
Professor of Mechanical Engineering, MIT
Thesis Supervisor

Signature redacted

Certified by ...

Rajiv Gupta, MD, PhD
Associate Professor of Radiology, Harvard Medical School
Thesis Supervisor

Signature redacted

Accepted by ...

Emery N. Brown, MD, PhD
Director, Harvard-MIT Program in Health Sciences and Technology
Professor of Computational Neuroscience and Health Sciences and Technology
X-ray Phase Contrast Imaging of Preclinical Atherosclerosis

by

Adam Pan

Submitted to the Department of Health Sciences and Technology
on September 1, 2016, in partial fulfillment of the
requirements for the degree of
Doctor of Philosophy in Medical Engineering and Medical Physics

Abstract

Atherosclerosis is the leading cause of mortality and morbidity in the world. While there are a plethora of methods for treating clinical atherosclerosis, the primary cause of mortality is acute coronary syndrome (ACS) following rupture of an atheroma, an event that is poorly predicted and remains the most common first indicator of cardiovascular disease. Current tools for determining atherosclerotic burden rely on assessing a patient’s risk factors, clinical symptoms, and biochemical profile, followed by angiographic imaging. However, patients with subclinical atherosclerotic disease can also be at high risk for ACS. In fact, nearly half of the patients suffer from sudden cardiac death without any prior indication of atherosclerotic disease. For these patients, proper characterization of the plaque burden has been shown to have a strong diagnostic value in guiding preventative treatments. Current noninvasive medical imaging methods lack the combination of resolution and contrast required to characterize atherosclerotic plaque. Recently, a new mode of medical imaging known as X-ray phase contrast imaging (XPCI) has been shown to produce exceptional contrast in soft tissues, and has the potential to noninvasively characterize atherosclerotic disease.

This thesis develops a new experimental XPCI system, as well as novel algorithms for reconstructing the amplitude and phase of X-rays for the purpose of noninvasive imaging of atherosclerotic disease. Our methods extend the transport of intensity equation, which enables the retrieval of phase and amplitude from multi-dimensional intensity distributions. We present a compressive tomographic reconstruction framework for 3-dimensional phase distributions, including algorithms for both single-shot and multi-shot phase retrieval. We introduce a method for compressive phase tomography based on the phase attenuation duality. We further propose a novel regularization scheme for projection imaging called the structural similarity regularizer, which exploits the sparsity of phase edges according to an absorption prior. Finally, we present an algorithm known as simultaneous attenuation phase retrieval, which is capable of combining absorption and phase information to improve reconstruction results. For each algorithm, we present simulation and experimental results from test phantoms and biological specimens.
The results of this thesis show that X-ray phase imaging can successfully characterize atherosclerotic plaques, and lays the groundwork for the use of XPCI as a diagnostic tool for atherosclerosis.

Thesis Supervisor: George Barbastathis, PhD
Title: Professor of Mechanical Engineering, MIT

Thesis Supervisor: Rajiv Gupta, MD, PhD
Title: Associate Professor of Radiology, Harvard Medical School

Thesis Committee Chair: Brett Bouma, PhD
Title: Professor of Health Sciences and Technology and Dermatology, Harvard Medical School

Thesis Reader: Elena Aikawa, MD, PhD
Title: Associate Professor of Medicine, Harvard Medical School
To my grandparents, 史文華 (Wen Hua Shi) and 陳福華 (Fu Hua Chen).
I am incredibly grateful to attend an institution as wonderful and unique as MIT. I can’t think of any place I have felt more welcomed and cared for, both as a student and as an individual. I would first like to thank my advisor, Prof. George Barbastathis, for being the best mentor that I could have hoped for. It is his support and guidance that have made the last few years seem to fly by. His passion for scientific inquiry is second to none, I will cherish our engaging conversations for years to come. I thank my co-advisor, Prof. Rajiv Gupta, who has provided invaluable advice, as well as insight into the clinical aspects of my work. It is with his support that I can claim to be truly multidisciplinary. I thank my thesis readers, Prof. Brett Bouma and Prof. Elena Aikawa, for their insightful suggestions, and for being so supportive of me during my thesis project.

My colleagues at the 3D Optical Systems Group have been extraordinary. I would like to thank all of its current and former members: Nilu Zhao, Shuai Li, A Disi, Prof. Jonathan C. Petruccelli, Dr. Lei Tian, Dr. Yi Liu, Dr. Hyungryul Choi, Dr. Hanhong Gao, Dr. Max Hsieh, Dr. Nader Shaar, Dr. Yongjin Sung, Prof. Yunhui Zhu, Dr. Qin Miao, Prof. Laura Waller, and of course all of our friends in Singapore. I thank you all for being so supportive whenever I had difficulties with research. In particular, I thank the members of my HST cohort: Ling Xu, Justin Lee, and Nikhil Vadhavkar. It has been a wild journey, and I would not have made it without you.

I thank the rest of my classmates in HST, and all the great memories we shared over the years. In particular, I thank Andrew David Warren, Vyas Ramanan, Matthew Li, and Husain Danish, whom have helped me balance my research and my personal life.

I would like to thank Bipin Singh, Haris Kudrolli, and Shane Waterman at Radiation Monitoring Devices, for kindly allowed us to use their lab space to perform our experiments, and for their discussions while the X-ray tubes were humming. I also want to thank Dr. Synho Do at Massachusetts General Hospital, for his support and insightful comments.
I would like to acknowledge funding from the Department of Homeland Security, the Defense Advanced Research Projects Agency, and the Singapore-MIT Alliance for Research and Technology, without which none of my research would have been possible.

Finally, I would like to thank my amazing family and my fantastic girlfriend, Lara Fu, who has been unwaveringly supportive of me since the outset. My parents, Clara and James, who are my role models and showed me the importance of education. I love you all dearly.
## Contents

1 Introduction 21  
1.1 Outline ................................................. 21  
1.2 Atherosclerosis ......................................... 24  
1.3 Current methods for detecting atherosclerosis ........ 25  
\hspace{1em} 1.3.1 Framingham risk score (FRS) .................... 25  
\hspace{1em} 1.3.2 Angiography .................................. 25  
\hspace{1em} 1.3.3 Coronary computed tomographic angiography (CTA) . 25  
\hspace{1em} 1.3.4 Cardiac stress test ............................. 26  
\hspace{1em} 1.3.5 Ultrasonography and intravascular ultrasound (IVUS) . 27  
\hspace{1em} 1.3.6 Optical coherence tomography (OCT) .............. 27  
1.4 X-ray phase imaging .................................... 28  

2 Theoretical Background 31  
2.1 Phase ..................................................... 31  
\hspace{1em} 2.1.1 Coherence ..................................... 32  
2.2 X-ray interaction with matter ........................... 34  
\hspace{1em} 2.2.1 Complex index of refraction ..................... 36  
2.3 Techniques for phase retrieval .......................... 40  
\hspace{1em} 2.3.1 Analyzer based imaging ......................... 41  
\hspace{1em} 2.3.2 Grating interferometry .......................... 41  
\hspace{1em} 2.3.3 Propagation based imaging ...................... 42  
2.4 X-ray propagation ..................................... 43  
\hspace{1em} 2.4.1 Fresnel diffraction ............................. 43
2.4.2 The transport of intensity equation ........................................ 45
2.4.3 Definition of phase for partially coherent illumination .......... 48
2.4.4 Exact solutions for propagation ........................................... 50

2.5 Computed Tomography .......................................................... 51
  2.5.1 The Radon transform ....................................................... 51
  2.5.2 Filtered backprojection (FBP) ........................................ 52
  2.5.3 Cone-beam effects ....................................................... 53
  2.5.4 Iterative reconstruction techniques ................................. 54

3 Experimental System Design .................................................... 59
  3.1 X-ray sources ................................................................. 59
    3.1.1 Anode-based X-ray sources ...................................... 59
    3.1.2 Synchrotron X-ray sources ..................................... 62
  3.2 X-ray detectors .............................................................. 63
  3.3 Optomechanical system .................................................... 63
  3.4 Test phantoms ............................................................... 65
    3.4.1 Microspheres ......................................................... 65
    3.4.2 Liquid phantoms .................................................... 66
    3.4.3 Mouse phantom ...................................................... 67

4 Simulation of X-ray phase images ............................................ 69
  4.1 Effect of temporal coherence .......................................... 69
  4.2 Effect of partial coherence ............................................ 75
  4.3 X-ray phase imaging simulator ........................................ 75
    4.3.1 Scattering approximation using the first Rytov approximation 76
    4.3.2 GPU Acceleration ................................................. 78
    4.3.3 Simulation results ................................................. 79
    4.3.4 Comparison to X-ray DPC imaging of a frog .................. 82

5 Compressive tomography using the phase-attenuation duality ......... 83
  5.1 Reconstruction process .................................................. 85
5.2 Discrimination of liquid samples ........................................ 87
5.3 Verification using a mouse phantom .................................... 89
  5.3.1 Comparison to commercial microCT ............................... 95
  5.3.2 Comparison to MRI .................................................. 96
5.4 Compressive tomography of an artery specimen ................. 97
  5.4.1 Comparison to MRI .................................................. 100
5.5 Preclinical imaging ....................................................... 101
  5.5.1 Comparison to commercial microCT ............................... 104
5.6 Discussion ................................................................. 105

6 Simultaneous retrieval of object phase and attenuation ......... 109
  6.1 Structural-similarity regularization of TIE ......................... 111
  6.2 Simultaneous solutions for absorption and phase ............... 114
  6.3 Noise Power Spectrum of Phase CT ................................. 116
  6.4 Algorithms for Phase-Only Reconstruction ........................ 117
  6.5 Measures for Image Similarity ...................................... 122
  6.6 Joint Sparsity Regularization in Simultaneous Attenuation-Phase Re-
       construction ............................................................ 125
     6.6.1 Guarantees of convergence ...................................... 127
  6.7 Simulation results ..................................................... 129
  6.8 Extension to X-ray dark field imaging .............................. 133

7 Conclusion and future work .............................................. 143

A Derivation of Fresnel diffraction .................................... 147

B NURBS ........................................................................... 149
List of Figures

2-1 Illustrations of temporal and spatial coherence, adapted from [4]. . . 33
2-2 An example showing an X-ray wave passing through free space and through a medium with index of refraction $n$. . . . . . . . . . . . 36
2-3 Atomic scattering factors for carbon. While the real component responsible for phase effects remains roughly constant at all energies, the complex component rapidly decreases with increasing energy. . . 38
2-4 Complex index of refraction values for common biological materials . 39
2-5 Refraction in a wedge shaped object. The beam is perpendicularly incident on the first interface, and hits the second interface at an incident angle $\theta_i$. It exits the second interface at angle $\theta_o$. . . . . . . . . . . . 40
2-6 A graphical example of the Fourier slice theorem: The 1D Fourier transform of a projection of a function along one direction is equivalent to the slice of the Fourier transform of the function through the origin. 51
2-7 Backprojection and filtered backprojection. Without filtering, the backprojection operator overestimates the energy near the center of the rotation axis. . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . 53
2-8 Parallel vs. fan beam projection geometries. . . . . . . . . . . . . 54
2-9 Iterative reconstruction flowchart. . . . . . . . . . . . . . . . . . . . . 55
3-1 Schematic diagram of an X-ray tube source. . . . . . . . . . . . . 59
3-2 Source spectrum of with a Tungsten anode at 140 kVp, simulated using SpekCalc [130]. . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . 60
3-3 For X-ray sources with finite spot size, images of the object are blurred due to a convolution between the source distribution and object transmission functions. This is known as the penumbra effect. 61

3-4 Shift and tilt corrections for (a-b) in-plane shift and tilt and (c-d) out-of-plane tilt 65

3-5 Technical drawing of mouse phantom. Loading configuration is given in table 3.2. 67

4-1 Simulation phantom, source spectrum, and dispersion relation for water at simulated spectrum. 70

4-2 Simulated broadband phase image. 71

4-3 Monochromatic intensity images at sampled energies. 71

4-4 Cross-sectional intensity plots. 73

4-5 TIE propagated intensity image, taken at the spectrally weighted mean wavelength. 74

4-6 Phase retrieval using the TIE. 74

4-7 TIE phase retrieval under partial coherence conditions. 75

4-8 Simulator process. (a) XCAT model of the left anterior descending artery. (b) Schematic diagram of projection onto Ewald sphere and mapping to detector spatial frequency. (c) Magnitude plot of propagated image. (d) Simulated intensity image at 30 keV and $z = 1$ m. (e) Simulated intensity image at $z = 5$ m. (f) Cross sectional intensity along the dotted lines in (d) and (e). 80

4-9 Simulated amplitude and phase at the detector. Scale bars are 5 cm. 80

4-10 DPC images. 81

4-11 in vivo images of a frog. Scale bars are 5mm. 81

5-1 Imaging geometry for TIE tomography. 85

5-2 A projection image of the sample (a), with its profile (b) showing significant white noise at the detector level. 88
<table>
<thead>
<tr>
<th>Page</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-3</td>
<td>Reconstruction results. (a) Filtered backprojection, (b) compressive PAD TIE, (c) plot along line in (a), and (d) plot along line in (b). These reconstructions show cross sections of the Eppendorf tubes containing the liquids taken along the plane coinciding with the line in Section 5.2.</td>
</tr>
<tr>
<td>5-4</td>
<td>Micromouse phantom</td>
</tr>
<tr>
<td>5-5</td>
<td>Reconstruction results using experimental X-ray phase imaging system</td>
</tr>
<tr>
<td>5-6</td>
<td>ROI showing soft-tissue components of the mouse phantom</td>
</tr>
<tr>
<td>5-7</td>
<td>Images showing (a) the path used to measure rod profiles, (b) the ROIs used in to measure quantities in table 5.1, (c) the absorption profile along (a), and (d) the phase profile along (a).</td>
</tr>
<tr>
<td>5-8</td>
<td>MicroCT imaging results of the mouse phantom</td>
</tr>
<tr>
<td>5-9</td>
<td>Axial slice of mouse phantom imaged in a Varian 7T preclinical MRI</td>
</tr>
<tr>
<td>5-10</td>
<td>Reconstruction results for a paraffin-embedded artery specimen</td>
</tr>
<tr>
<td>5-11</td>
<td>Comparison of SIRT reconstruction of projection-domain phase retrieval and our compressive technique for phase retrieval. Images show areas of the artery wall where streaking is evident in the SIRT reconstruction. In the compressive reconstruction, the streak artifacts virtually eliminated.</td>
</tr>
<tr>
<td>5-12</td>
<td>Histopathological correlation. A 5 μm thick slice of the artery sample was stained using hematoxylin and eosin. The corresponding slice in the phase reconstruction is shown, and we observe extremely good correlation between histology and phase imaging.</td>
</tr>
<tr>
<td>5-13</td>
<td>MRI images of a human iliac artery</td>
</tr>
<tr>
<td>5-14</td>
<td>Axial slices of an in vitro mouse, showing (top) thoracic, (middle) mid-abdominal, and (bottom) lower-abdominal views.</td>
</tr>
<tr>
<td>5-15</td>
<td>Coronal slice of an in vitro mouse.</td>
</tr>
<tr>
<td>5-16</td>
<td>Sagittal slice of an in vitro mouse.</td>
</tr>
</tbody>
</table>
5-17 Comparison between absorption and phase CT for the GI tract. The blue arrow indicates the ring artifact, while the red arrow indicates a streak artifact. The white spots around the intestines are due to scattering errors on the absorption image, while they are largely corrected on the phase images.

5-18 Axial views of the heart. Due to the positioning, the orientation of the heart and lungs is more similar to a coronal slice. The blue arrow denotes the left heart, while the red arrow denotes the right heart.

5-19 Axial views of the lungs. Due to the positioning of the mouse, the torso was slightly twisted, resulting in a much more prominent right lung in this view. Certain bronchi and vasculature, such as those indicated by the arrows, are significantly enhanced on the phase reconstruction.

5-20 MicroCT results for in vitro mouse: (left) axial slices of an in vitro mouse, showing (top) thoracic, (middle) mid-abdominal, and (bottom) lower-abdominal views; (top right) coronal and (middle right) sagittal views; (bottom right) Axial slice of heart and lungs.

6-1 Imaging geometry for TIE.

6-2 Raw intensity image of sample. Scale bar denotes 2 mm.

6-3 Magnitude of transfer function for TIE and inversion kernel for TIE.

6-4 Experimental results of a rubber and nylon sphere in a water-filled test tube. Scale bars represent 2 mm.

6-5 Image profiles along the dashed blue line in Figure 6-4.

6-6 Schematic diagram of experimental setup.

6-7 (a) Radial and (b) axial noise power spectrum of attenuation backprojection and phase-retrieving backprojection. Note that this is not a direct comparison of magnitude, since the relative magnitudes of the phase and absorption signals vary based on object and experimental parameters.

6-8 3D Shepp Logan Phantom
Filtered backprojection of attenuation and phase images. ............... 119
SIRT of attenuation and phase images. ........................................ 120
Application of the phase attenuation duality to retrieving phase images.121
L1 minimizing reconstructions of attenuation and phase images. ... 123
Effect of tolerance on L1 regularized reconstruction of the phase-only
solution. Note that a even with an extreme number of iterations, the
solution does not converge due to the ill-posedness of TIE reconstruc-
tion problem. ................................................................. 124
SIRT minimizing reconstructions of attenuation and phase images, us-
ing intensity measured at two distances. .................................. 130
Plots of $\lambda_\mu$ and $\lambda_\delta$, the objective function, and the attenuation and
phase errors of the solver at each iteration. .............................. 131
SAP minimizing reconstructions of attenuation and phase images from
intensity images taken at a single propagation distance. .............. 132
Schematic of X-ray dark field imaging setup. .............................. 133
Rocking curve for Laue crystal. Note that there is a region where the
intensity linearly depends on the rocking curve. .......................... 134
SIRT reconstruction of the measured absorption and phase for the
coronary artery. .................................................................... 135
Reconstructed absorption and phase of the coronary artery using SAPR.135
Comparison between absorption reconstruction techniques around cal-
cification. The calcium image is significantly enhanced and the internal
structure appears sharper on the SAPR. ..................................... 136
Zoomed view of coronary artery reconstruction. ............................ 137
SIRT reconstruction from measured absorption and phase for the coro-
nary artery. ....................................................................... 137
Reconstructed absorption and phase of the coronary artery using SAPR.138
Zoomed view of iliac artery reconstruction. ................................. 138
Zoomed view of iliac artery reconstruction. ................................. 139
6-27 Difference between SIRT phase reconstruction and compressive reconstruction using SAPR phase reconstruction. .......................... 139
List of Tables

3.1 Table of microsphere compositions .......................... 66
3.2 Mouse phantom loading configuration. ......................... 68
5.1 ROI analysis of mouse phantom ............................... 94
5.2 Signal quality metrics ........................................ 94
5.3 MicroCT protocol parameters. ................................. 95
6.1 Simulation parameters. ....................................... 118
Chapter 1

Introduction

X-ray phase contrast imaging is a field of research that has recently seen a flurry of activity. Advances in the construction of increasingly high-resolution and sensitive detectors, realization of new and innovative X-ray sources, as well as a flurry of activity in computational imaging have enabled a whole new dimension of imaging signal from the phase of X-ray waves.

1.1 Outline

The purpose of this thesis is to describe computational imaging approaches to X-ray phase imaging and it’s applications to imaging human atherosclerotic disease. The reader is assumed to have a basic understanding of optics and X-ray physics, but most of the necessary theory is included herein.

This chapter introduces the motivation for developing new methods for imaging of atherosclerotic disease, as well as the historical context of X-ray phase imaging.

Chapter 2 lays the theoretical foundation for the methods discussed in this thesis. The concept of phase is introduced in the context of X-ray imaging. The generation of phase signal from the interaction between X-rays and matter is described. Absorption and refraction are considered from a classical interpretation of the interaction between an electromagnetic field and a medium. Next, we introduce the major techniques for X-ray phase retrieval, discussing the benefits and drawbacks of each
technique, and provide justification the use of a propagation-based imaging system for X-ray phase retrieval. We then develop the theory required for propagation-based imaging: the propagation of X-rays in free space is investigated, and the formalism of Fresnel propagation is derived. From Fresnel diffraction, the transport of intensity equation (TIE) is derived. A short analysis of the quantity retrieved from the TIE in the case of coherent and partially-coherent illumination is given. Next, we introduce the concept of computed tomography (CT), i.e. reconstructing a volume from projected transmission images. The Radon transform is introduced, and the inverse reconstruction problem is discussed. Both analytic and iterative solutions for the computed tomography problem are presented, and a short description of common reconstruction artifacts is given.

In chapter 3, we describe the hardware design of our experimental system. We introduce two types of X-ray sources relevant to X-ray phase imaging, and describe the X-ray sources and detectors used in our phase imaging experiments. Next, optomechanical system for tomographic acquisition is described. We discuss the need for alignment in experimental tomographic systems, and outline our alignment process. Finally, we provide a list of test phantoms used in our imaging experiments.

Simulation methods for X-ray phase imaging are discussed in chapter 4. We investigate the effect of temporal and partial coherence on the phase image, and justify the use of the TIE in the case of a broadband, partially coherent source, expanding on the results of [124]. Next, we introduce the X-ray phase imaging simulator developed in [155]. Unlike other X-ray phase simulation techniques the describe method uses a surface-modeling method known as non-uniform rational b-splines (NURBS) to model the object. The simulation method enables highly accurate simulation of the full X-ray wave at the scale of a human body, something not possible using current methods. We discuss the tradeoffs of using a surface-modeling approach, and the need for computational optimization in the simulator design. We describe the use of GPUs to accelerate the simulation, reducing required computation times by a factor of 300. Finally, we present simulation results of a human thorax using the XCAT human chest phantom, and provide a comparison of our simulation results to thoracic X-ray
phase images obtained from a frog.

In chapter 5, we present the results of our compressive phase contrast algorithm based on the phase-attenuation duality [122, 121], and present new experimental results. We show a new algorithm for single-shot X-ray phase retrieval which utilizes the phase-attenuation duality to relate the quantities of attenuation and phase. We apply concepts from compressed sensing to perform tomographic phase CT using few angles. We present experimental results which show that our algorithm is capable of differentiating from two liquids with similar attenuation characteristics using only a few views. Next, we validate our reconstruction method using a mouse phantom with known material composition, compare our results to images obtained from commercial CT and MRI systems, and demonstrate that our compressive phase CT produces higher quality reconstructions than current CT methods. We perform compressive tomography on a human artery specimen, and demonstrate that phase provides sufficient contrast to visualize artery structures, even when for few angles. We discuss the potential of using X-ray phase imaging for low-dose imaging of atherosclerosis. Finally, we present imaging results from an in-vitro mouse, discuss the potential applications of the method in the larger field of medical imaging.

In chapter 6, we present two methods which utilize the absorption signal in new ways for phase reconstruction. The first method, called structural-similarity regularization, is a novel regularization method for two-shot phase retrieval. By utilizing edge information from the absorption image, the structural-similarity regularizer greatly reduces the effect of low-frequency noise in two-shot phase retrieval. Experimental results are presented for projection imaging of spheres in a microtube [119]. The second method that we have developed is called simultaneous absorption-phase reconstruction (SAPR). Unlike previous algorithms for phase retrieval, which consider absorption and phase as separate signals during the reconstruction process, SAPR links the absorption and phase signals during the reconstruction process. By iterating between the absorption and phase signals, and maximizing a mutual information metric known as the joint sparsity, our algorithm significantly increases the accuracy of phase reconstruction from multiple measurements. We present simulation results
from a 3D numerical phantom, as well as an extension to experimental results from a differential phase contrast system [8].

The thesis is then concluded in chapter 7, with a brief perspective on the future of X-ray phase imaging.

1.2 Atherosclerosis

Atherosclerosis is a systemic disease involving chronic inflammation of arterial walls. Atherosclerotic lesions (atheromata) manifest as thickenings of the innermost layer of the artery: the intima. Atheromata are composed of cells, lipid deposits, and debris. While the bulk of cells in an atheromata are endothelial or smooth muscle cells, inflammatory and immune cells are an important component of the atherosclerotic process [69].

Atherosclerosis is the underlying cause of a majority of cardiovascular disease (CVD) events, and is the leading cause of mortality and morbidity worldwide [54]. While angioplasty and intervention pharmacological therapies do improve patient outcome [93, 6, 89, 30], CAD is a systemic disease and in many cases there are recurrent cardiac events. Retrospective studies have shown that atherosclerotic burden confers significant risk for subsequent ACS, and most atherosclerotic plaques responsible for ACS are asymptomatic (subclinical atherosclerosis) [5, 53]. There exists a need for better methods to detect and quantify subclinical atherosclerosis [123, 165, 92, 159].

However, detection of atherosclerotic disease can be difficult. There is a strong correlation between plaque burden and major adverse cardiac events (MACE), as larger plaque burden is associated with more advanced, complex, and vulnerable atheromas [149]. Measuring a patient’s plaque burden is difficult to do reliably, and conventional cardiac imaging techniques such as angiography do not provide sufficient signal to adequately estimate plaque burden. Instead of direct measurement of atherosclerotic lesions, most estimates depend on patient history and indirect measurements. In this thesis, we propose the use of X-ray phase contrast imaging (XPCI) to characterize atherosclerotic plaques.
1.3 Current methods for detecting atherosclerosis

1.3.1 Framingham risk score (FRS)

The Framingham Risk Score is a risk assessment framework built upon a long-term, ongoing cardiovascular study on residents in Framingham, Massachusetts [40]. The FRS gives an multiple risk score corresponding to an estimate of a patient’s 10-year cardiovascular risk based on several factors: age, sex, cholesterol levels, smoking, and blood pressure. The FRS is used for stratifying patient risk. Patients at a medium (10 to 20%) or high (>20%) risk typically undergo additional diagnostic tests, such as angiography or cardiac stress testing [60, 123]. Although the FRS is reliable for predicting risk in populations, the accuracy in predicting cardiovascular events in individuals varies considerably across populations, and is not conclusive in individual patients [21, 40].

1.3.2 Angiography

X-ray imaging was the first radiographic technique ever developed, and has since remained a staple of medical imaging due to its speed, high spatial resolution, and low cost [139]. Since X-rays are only strongly attenuated by dense materials, contrast agents such as iodine and gadolinium based compounds are required to visualize soft-tissue structures, and discern the arterial lumen [106, 114]. The use of intravenous contrast agents impart a non-negligible risk of complications, and have been shown to be linked to nephropathy [13, 31, 103]. Angiography is a minimally invasive procedure, since a catheter is necessary to inject contrast agent into the blood vessels of interest. Coronary angiography is only capable of evaluating the degree of stenosis, and fails to identify non-stenotic plaques that may still be prone to rupture [105].

1.3.3 Coronary computed tomographic angiography (CTA)

Conventional X-ray CT operates by taking multiple radiographic images at different angles around the subject; the images are then reconstructed into a single 3D im-
An important goal in CT research is the reduction of ionizing radiation dose without compromising in image quality [49, 140]. Conventional X-ray CT forms a robust basis for anatomic imaging, but does not provide sufficient contrast without contrast agents, which introduce confounding factors and toxic risk. Furthermore, contrast agents only enhance visualization of the lumen, i.e. the interior boundary of atheromata, and does not provide enhanced characterization of soft-tissue features such as the necrotic core or fibrous cap. Modern X-ray systems take advantage of a variety of optimizations to improve scan quality and speed, such as cone beam CT, helical scanning, and multiple detector arrays [45, 46, 74, 96, 132, 151, 183]. As CT technology has advanced, CTA has become an increasingly stable method for imaging atherosclerosis [23, 72]. Modern multi-detector ECG-gated CTA is capable of resolving individual coronary arteries in between heartbeats, and provides high-resolution, and has been demonstrated in several promising studies [23, 72, 2, 117, 59, 24, 3, 141]. Recently, CTA has been extended to coronary artery calcium (CAC) scoring as a surrogate for atherosclerotic burden [25, 3, 143, 60]. CAC scoring can be used as a marker for tracking atherosclerotic progression, but like the FRS, provides risk assessment and not conclusive results in individual patients [25, 54].

1.3.4 Cardiac stress test

The cardiac stress test is used to measure the heart’s ability to cope with external stress. The stress response is induced by exercise or pharmacological stimulation [172, 51, 38]. Cardiac stress tests can reveal severe stenosis (which may or may not be due to severe CAD) when the patient experiences stable angina during a stress test, accompanied with ST depression (indicative of ischemia) [47, 144]. Like angiography, the cardiac stress test can only detect stenosis in atherosclerosis, and do not detect the general thickening of the arterial wall present in atherosclerosis. The tests are a popular diagnostic tool due to the low cost in the case of EKG testing, (basic EKG stress tests are $200 [1]) and high specificity in the case of nuclear stress testing.
1.3.5 Ultrasonography and intravascular ultrasound (IVUS)

Medical ultrasonography is capable of delivering real-time structural information as well as functional information. Ultrasonography does not require chemical contrast, there are no known long term side-effects to ultrasound diagnostics, and the equipment is easy to handle. Ultrasonography has been applied to imaging carotid intima-media thickness (CIMT), a possible surrogate for atherosclerosis [129, 19, 61, 94]. While thickening of the intima-media is strongly associated with atherosclerosis [95], moderate increases in CIMT are not conclusive in evaluating atherosclerotic burden. The resolution of ultrasound images is inversely related to attenuation, requiring trade-offs between image quality and penetration depth, and hamstringing any efforts to use ultrasound for deep tissue imaging [12, 116, 84]. Medical ultrasonography is also incapable of imaging inside dense tissue such as bone and traversing gas filled regions. Intravascular ultrasound provides a method for direct ultrasound imaging of vascular anatomy, and has been used to image subclinical atherosclerosis in several studies [163, 104, 131, 115, 43]. IVUS was the first method capable of producing high-quality images of atheromata, and has been crucial to the understanding of the atherosclerotic process, as well as to the development of treatment strategies. However, ultrasonography has a characteristically low SNR, being prone to coherent noise. Catheter techniques are time-consuming and expensive, and IVUS studies are typically reserved for patients with clinical atherosclerosis, either as an imaging procedure prior to angioplasty, or a post-operative checkup to ensure proper location of a stent.

1.3.6 Optical coherence tomography (OCT)

In many ways, OCT is analogous to IVUS, but in the optical regime. OCT utilizes white light interferometry to capture and localize reflections inside tissue, effectively performing optical ultrasound. The advantage of OCT is significant resolution enhancement compared to IVUS. Several studies have demonstrated the utility of OCT in imaging atherosclerosis [79, 180], and there has been much discussion on the rela-
tive merits of OCT and IVUS, as well as combined use of both [78, 66, 88, 77, 145]. Like in ultrasound, multiple scattering results in image artifacts and degraded image quality [176]. However, OCT has lower penetration than IVUS, as blood is nearly opaque to infrared light, and clinicians may find it difficult to obtain clear images of high-flow arteries such as in the aortic ostia [20, 176, 67].

1.4 X-ray phase imaging

X-ray imaging utilizes high-energy electromagnetic waves to image through the human body. Unlike visible light, which does not penetrate much deeper than a few millimeters of skin, X-rays are capable of passing through the human body largely unimpeded. Typical cameras image the light reflected from an object, a mode known as reflective imaging, while X-ray imaging typically images the light after it has passed through the object, a mode of imaging known as transmission imaging. In this way, X-ray imaging systems are more similar to microscopes than the typical point-and-shoot camera.

Like all electromagnetic waves, X-rays possess both amplitude and phase. While the absorption term is certainly serviceable for detecting the difference between bone, metal, and the soft tissue of the body, it does not work as well for differentiating soft-tissues, such as the various components of an atherosclerotic plaque. On the other hand, the phase term often provides significant amounts of contrast between soft tissues, and is often higher in magnitude than the attenuation term.

Unfortunately, modern X-ray cameras are not fast enough to image at the frequencies required to detect phase. Similar to attempting to record the spokes of a rapidly rotating wheel with a video camera, the oscillation of the X-rays is far beyond the resolvable frequency of the camera. This inability to satisfy the Nyquist-Shannon sampling rate prevents us from directly imaging the phase of X-rays. Until recently, we simply haven’t had the technology to measure the phase of an X-ray wave in an imaging sense.

However, in the last 20 years, new methods have been developed to allow the
imaging of the phase of X-rays. These methods have been made possible by the
development of two new fields: X-ray optics, and computational imaging. Pioneering
works were made possible by the invention of synchrotrons, behemoth photon factories
that could produce X-ray beams millions of times more brilliant than laboratory
sources. This quantum leap in source technology enabled the use of X-ray filters that
could produce highly monochromatic, collimated beams.

From these initial experiments [150, 108], it was clear that the phase of X-rays
contained a wealth of untapped information. Since then, several X-ray phase imaging
techniques have been developed. Current X-ray detectors are still limited to only mea-
suring X-ray intensity, so phase imaging techniques must convert phase information
into intensity patterns. The differentiating factor between phase imaging techniques is
the different mechanisms used in achieving this conversion. These techniques are gen-
erally divided into propagation-based techniques, crystal analyzer-based techniques,
and interferometry-based techniques. These methods are further described in chap-
ter 2. In this thesis, the primary technique being investigated is propagation-based
imaging, which uses the free space propagation of X-ray waves after they have passed
through the object to mix phase information into the intensity signal. Due to the
simplicity of the imaging system – no X-ray optics are required – propagation-based
imaging is well suited to being adapted to existing X-ray imaging systems with mini-
mal modifications. Unlike interferometric systems, propagation-based systems do not
require careful alignment of optical elements, resulting in easy adaptation to tomo-
graphic imaging. The lack of X-ray optics also minimizes the loss of X-rays through
absorption during imaging, significantly reducing acquisition times.
Chapter 2

Theoretical Background

This chapter provides the theoretical underpinning of phase contrast image formation in the X-ray regime, and computed tomographic reconstruction from projected phase images. The concept of phase is explained in the context of wave optics, and the interactions between X-rays and matter is explored. We discuss several common methods for retrieving phase, and derive the propagation relationships for X-ray phase imaging. Finally, the chapter is concluded with an introduction to computed tomographic reconstruction.

2.1 Phase

Since Laue's discovery that X-rays could be diffracted by crystalline structures, researchers have applied the wave nature of X-rays to measure structural properties of materials, a field known as crystallography. However, its application to clinical imaging would not see development until the turn of the century, after developments in the research of synchrotron sources and phase retrieval in electron microscopy. X-ray phase imaging arose as an intersection of these developing technologies and techniques.

Phase contrast imaging refers to imaging the differences in refractive index of different materials to determine composition, instead of using material absorption to achieve contrast. In this respect, X-ray phase imaging is a complimentary technique...
to conventional absorption imaging, and it stands to reason that clinical practitioners should have full use of both when making medical diagnoses with the hope that phase information could supplement the radiologist’s toolbox, and lead to better diagnosis with less dose.

Like all waves, X-rays have amplitude, frequency, and phase shift. The amplitude of an X-ray wave is analogous to its brightness, or intensity. The frequency of the wave describes its “color”, while the phase is analogous to the shape of the wavefront. For monochromatic plane waves, that is, a wave with a single frequency that is propagating along a single direction (as is universally assumed for transmission imaging), the properties of the wave are expressed using the following mathematical formalism:

\[ u(\vec{r}) = A(\vec{r})e^{i\phi(\vec{r})} \]  

(2.1)

where \( \vec{r} \) is the position in space, \( u(\vec{r}, t) \) is the complex field of the X-ray wave, \( A(\vec{r}, t) \) is the amplitude of the X-ray wave, and \( \phi(\vec{r}, t) \) is the phase of the X-ray wave. Phase shift, unlike absorption, is a relative term; we can only describe the phase of a wave relative to other waves, or itself. Thus, to describe wavefronts, we often consider surfaces where \( \phi \) is constant, that is, there is no phase shift between parts of a wavefront.

### 2.1.1 Coherence

To understand phase, familiarity with the concept of coherence is needed. As we will discuss in section 2.4.3, the interpretation of phase depends on the coherence properties of illumination. In practical applications, X-rays are not monochromatic plane waves, so the idea of coherence allows us to quantify how an X-ray wave deviates from these assumptions.

When discussing coherence, two abstractions are often used: temporal and spatial coherence. Temporal coherence refers to the cross-correlation between the wave at a two points in space, at different times, while spatial coherence refers to cross-correlation at different points in space, at the same time. Cross-correlation in this
Temporal coherence is quantified through the coherence time and coherence length. The coherence time, $\tau_c$, of a wave describes the amount of time delay after which the amplitude and phase of the wave changes significantly (decreasing correlation), and the coherence length, $L_c$, is the distance that the wave travels over $\tau_c$. The concept of coherence length is illustrated in fig. 2-1a. We see that for two waves with wavelengths $\lambda$ and $\lambda - \Delta \lambda$, the two waves are exactly out of phase at $L_c$. We also observe the following:

$$2L_c = N\lambda = (N + 1)(\lambda - \Delta \lambda)$$  \hspace{1cm} (2.2)

$$N + 1 \Delta \lambda = \lambda$$  \hspace{1cm} (2.3)

Combining the two equations results in an expression for the coherence length

$$L_c = \frac{\lambda^2}{2\Delta \lambda} - \lambda$$  \hspace{1cm} (2.4)

$$\approx \frac{\lambda^2}{2\Delta \lambda}$$  \hspace{1cm} (2.5)

Spatial coherence is quantified by the coherence width, $W_c$, over which two points are considered to still significantly interfere. As shown in fig. 2-1b, when two plane
waves are traveling in slightly different directions, denoted by \( \Delta \theta \), the wavefronts become out of phase at \( W_c \). In the case where \( \Delta \theta \) is small, we can see that

\[
W_c = \frac{\lambda}{2\Delta \theta}
\]

If the two waves originate from two points from the same source, \( \Delta \) apart, and propagate to a distance \( L \), then we see that \( W_c = \frac{L}{2\Delta} \). Thus, the larger the propagation distance, the more spatially coherent a source appears from afar, and even extended sources can be made to appear spatially coherent.

Temporal coherence can also be thought of as the finite bandwidth of the X-ray source, while spatial coherence would be the extent of the source. For synchrotron sources, the X-rays emitted are essentially monochromatic and plane, and have virtually infinite temporal and spatial coherence. On the other hand, microfocus X-ray sources are highly polychromatic, and possess coherence lengths on the order of nanometers. However, the small spot size of the microfocus source, about 5 \( \mu \)m, results in a spatial coherence length on the order of 100 \( \mu \)m, which we will see in later chapters is sufficient to resolve fringe patterns.

### 2.2 X-ray interaction with matter

As X-ray radiation passes through matter, it interacts in several ways, resulting in absorption or scattering of the incoming radiation. Unlike in visible light, the regime of X-ray frequencies results in a different set of dominant absorption and scattering effects unique to X-rays. This is why X-ray easily pass through a human body, while visible light has difficulty penetrating more than millimeters of skin.

X-rays interact with matter through both classical and non-classical mechanisms. In the classical model of scattering, known as Rayleigh scattering, the electric field of the X-rays interact with the dipoles formed by the electrons and nuclei of the atoms, which act as oscillators. The oscillation of the electrons results in a change in momentum of the incoming X-rays, resulting in the elastic and coherent scatter-
ing of the wave. While Rayleigh scattering is a dominant source of scattering in the visible regime, the contribution to overall scattering is relatively low at X-ray wavelengths. The inelastic and incoherent scattering model is known as Compton scattering. In this case, X-ray photons do not behave as an ensemble, but instead exhibit quantum particle behavior. The incoming photons transfer part of their energy into electrons around the atom, resulting in a longer-wavelength photon being emitted while conserving the momentum of a system. Finally, it is also possible for a photon to completely dislodge an electron through a similar transfer of energy, resulting in the annihilation of the photon and ejecting a free electron from the atom. This process is known as the photoelectric effect, and results in absorption edges seen in fig. 2-4. Further more effects such as pair production exist, but for the energy ranges of interest in this thesis, only the effects of the aforementioned phenomena are of relevance.

At photon energies far from absorption edges, the effect of both absorption and scattering decreases with increasing energy. In medical imaging, this phenomenon is used to adjust the amount of image contrast; while lower energy scans may produce more image contrast due to larger absorption values, higher energies are often used when imaging bone, reducing the amount of dose to the patient. Additionally, the absorption edges of most biological materials fall below 20 keV, with the sole exception being calcium. The magnitude of the effect of absorption then depends only on the photon energy, the density of electrons in the material, and the strength with which electrons are bound to the nuclei of the atoms. For scattering, all electrons contribute equally to the scattering cross section of the material, and the magnitude of the scattering effect is directly proportional to the electron density. Thus, absorption imaging detects a combination of the electron density and atomic number of a material, while X-ray phase contrast imaging detects the electron densities.

The primary components of soft tissue are carbon, hydrogen, oxygen, and nitrogen, all of which have similar atomic numbers, while bone contains large amounts of calcium, which has a significantly higher atomic number. This results in excellent contrast between soft tissue and bone on absorption images, but also makes
Figure 2-2: An example showing an X-ray wave passing through free space and through a medium with index of refraction $n$.

distinguishing different kinds of soft tissue difficult. Phase imaging, as this thesis demonstrates, relies only on the electron densities of the materials, where there is a significant diversity in signal, resulting in superior soft tissue contrast.

2.2.1 Complex index of refraction

The aforementioned absorption and scattering quantities are summarized by the complex index of refraction

$$n(\lambda) = 1 - \delta(\lambda) + i\beta(\lambda),$$

where $\delta$ is the phase component, and when the wavelength of incident radiation, $\lambda$, is far from an absorption edge, is given by

$$\delta = \frac{\rho_e \sigma_p(\lambda)}{k} \quad (2.6)$$

where $\rho_e$ is the electron density and $\sigma_p$ is the phase scattering cross section [4]. The imaginary component, $\beta$, is responsible for absorption and given by

$$\beta = \frac{\rho_A \sigma_a(\lambda)}{k} \quad (2.7)$$

where $\rho_A$ is the atomic number density and $\sigma_a$ is the absorption cross section [4].

The complex index of a material can also be described relative to its atomic
scattering factors,

\[ n = 1 - \frac{\rho_a r_e \lambda^2}{2\pi} (f_1 + if_2) \]  \hspace{1cm} (2.8)

where \( \rho_a \) is the atomic density of the medium, \( r_e \) is the classical radius of an electron, and \( f = f_1 + if_2 \) is the atomic scattering factor. We see that the real and imaginary parts of the atomic scattering factors can be directly related to \( \beta \) and \( \delta \):

\[ \delta = \frac{\rho_a r_e \lambda^2}{2\pi} f_1 \]  \hspace{1cm} (2.9)

\[ \beta = \frac{\rho_a r_e \lambda^2}{2\pi} f_2 \]  \hspace{1cm} (2.10)

While the imaginary atomic scattering factor is measured directly, the real component of the atomic scattering factor is computed through the Kramers-Kronig relationship, which can be calculated from the Kramers-Kronig relations [87]:

**Theorem 1 (Kramers-Kronig relations)** Let \( f(\omega) = f_1(\omega) + if_2(\omega) \) be a function that is analytic in the closed upper half complex plane of \( \omega \), and is bounded by \( 1/|\omega| \) at \( \infty \). Then there exists a bidirectional relation between \( f_1 \) and \( f_2 \) such that

\[ f_1(\omega) = \frac{1}{\pi} \mathcal{P} \int_{-\infty}^{\infty} \frac{f_2(\omega')}{\omega' - \omega} d\omega' \]  \hspace{1cm} (2.11)

\[ f_2(\omega) = -\frac{1}{\pi} \mathcal{P} \int_{-\infty}^{\infty} \frac{f_1(\omega')}{\omega' - \omega} d\omega' \]  \hspace{1cm} (2.12)

where \( \mathcal{P} \) denotes the Cauchy principle value of the integral.

Therefore, \( f_2 \) can be calculated from knowledge of \( f_1 \), and vice versa. An example plot of the atomic scattering factors for carbon from [73] is given in fig. 2-3.

When X-rays pass through any medium, the waves are attenuated and delayed, as shown in fig. 2-2. We consider a monochromatic beam, but note that the formalism for a polychromatic beam is simply the monochromatic case integrated across the energies. This interaction can described mathematically as a multiplication of the incident X-ray wavefront by the object transmission function:

\[ u(\hat{r}) = u_0(\hat{r}) \cdot T(\hat{r}) = u_0(\hat{r}) e^{-\int \beta k \hat{r} e^{i(1-\delta)\hat{k} \cdot \hat{r}}} \]  \hspace{1cm} (2.13)
Figure 2-3: Atomic scattering factors for carbon. While the real component responsible for phase effects remains roughly constant at all energies, the complex component rapidly decreases with increasing energy.

where $u$ is the wave field after passing through the medium, $U_0$ is the incident field, $T$ is the transmission function, and $k$ is the wave vector of the incident field. We see that the first and second terms of the transmission function correspond to an attenuation and phase shift of the wave, respectively. The absorption of an object is often related to the intensity of the incident and output fields through Beer-Lambert’s law:

$$\frac{I}{I_0} = \frac{|A|^2}{|A_0|^2} = e^{-\mu ds} \tag{2.14}$$

where $\mu = 2\beta k$ is the linear attenuation coefficient. The phase shift the linear integral of the decrement in the real part of the complex index of refraction:

$$\phi = \int \delta k ds \tag{2.15}$$

We see from the eqs. (2.14) and (2.15) that while absorption signals are multiplicative, phase signals are additive. Figure 2-4 shows the values for $\delta$ and $\beta$ for some common compounds found in X-ray imaging. We see that the phase coefficient of the complex index is several orders of magnitude higher at all X-ray energies, an indication that the phase contrast signal should be significant. We also note a more significant contrast
Figure 2-4: Complex index of refraction values for common biological materials between the $\delta$ values of soft tissue compounds such as glucose and water, suggesting that phase contrast should provide superior soft-tissue discrimination compared to absorption contrast. Indeed, a wealth of literature suggests that phase contrast X-ray imaging achieves a higher contrast from the same radiation dose when compared to absorption based methods [109, 175, 97, 85, 63, 48].

It is helpful to compare the refraction of X-rays to the refraction of light, as to gain a better understanding of the length scales at play in X-ray phase contrast imaging. Therefore, we consider the thought experiment posed in fig. 2-5. Then from Snell’s law we can calculate the exit angle $\theta_o$:

$$\sin(\theta_o) = n_i \sin(\theta_i) \tag{2.16}$$

$$\theta_o \approx n_i \theta_i \tag{2.17}$$

The angle of refraction, which is simply the difference between $\theta_o$ and $\theta_i$, is approximated by $n_i - 1$. In materials that are transparent to visible light, the index of refraction often varies significantly between different materials of interest. For example, while air has an index of refraction of 1 at all wavelengths of light, water has
Figure 2-5: Refraction in a wedge shaped object. The beam is perpendicularly incident on the first interface, and hits the second interface at an incident angle $\theta_i$. It exits the second interface at angle $\theta_o$.

an index of refraction of roughly 1.34 for most visible frequencies, oil has an index of 1.47, and glass has an index of 1.5. This suggests that for visible light, where $n_i > 1$, refraction angles can be on the order of deciradians. On the other hand, in X-ray wavelengths, both absorption and scattering effects are significantly reduced as shown in fig. 2-4, index values are typically on the order of $n_i = 1 - \delta \sim 1 - 10^{-6}$, the angle of refraction will be on the order of microradians. Clearly, refraction in X-rays will be much more challenging to detect than refraction in visible light.

2.3 Techniques for phase retrieval

X-ray phase contrast techniques often rely on mechanisms of phase contrast first demonstrated in the visible domain. However, not all visible light techniques for phase retrieval are suitable for X-ray phase imaging. As shown in the previous section, X-ray phase effects are significantly more difficult to detect than in the visible domain. Therefore, adaptations must be made to achieve the sensitivity required to detect the refractive index of materials at X-ray wavelengths. Phase contrast imaging methods employ a wide variety of modern X-ray equipment, including synchrotron sources, sub-wavelength diffraction gratings, and high resolution X-ray detectors [109, 175, 126, 125, 110, 97, 85, 80, 63, 48, 39, 107]. The use of these equipment follows a
common goal: converting the phase information of a wave into intensity fluctuations measurable with an X-ray detector. Phase information provides better contrast-to-noise ratio (CNR) when the image contrast is small, such as between different types of soft tissue, or micropatterned structures [68]. Tomography is also fairly straightforward to implement for X-ray phase imaging, and we can reconstruct the 3D refractive index structure in a manner analogous to conventional CT. Furthermore, many of the optimizations seen in conventional CT are also readily applicable to phase contrast CT. There are currently three major techniques used to perform XPCI: grating interferometry, analyzer based imaging, and propagation based imaging.

2.3.1 Analyzer based imaging

This imaging method operates by passing monochromatic, parallel X-rays through a sample and onto a perfect analyzer crystal acting as an angular filter for any refraction and radiation caused by the sample. The image is retrieved as data encoded by the angular deviation of the crystal from the Bragg angle, creating high-quality phase imagery [39, 9]. However, major drawbacks of this method include limited field of view, the need for perfect alignment of the analyzer crystals, anisotropic bias between phase changes parallel and perpendicular to the optical path, and the need for a highly collimated, intense X-ray source (only synchrotrons meet such demands). [39, 9, 33].

2.3.2 Grating interferometry

In Talbot interferometry, the phase image is taken as the moiré fringes observed by passing the X-ray image through two gratings spaced a multiple of a Talbot length apart [125, 126]. The Talbot effect is a self-imaging phenomenon that arises from propagating waves from a periodic illumination pattern, and allows for differential interferometry. Since phase contrast is achieved by measuring the distortion relative to a reference grid pattern, Talbot interferometry is highly sensitive to defects and alignment of the gratings, and gratings must be small to maximize the spatial resolution of the technique [110, 125, 126], and requires that the X-ray source must have
high brilliance [109]. Thus, X-ray Talbot interferometry is subject to the same limitations as typical interferometric techniques (such as the phase unwrapping problem [134]), and requires a more complex imaging system, which is non-trivial in the X-ray regime as well as higher radiation doses than propagation based imaging, due to the presence of gratings [181].

2.3.3 Propagation based imaging

Propagation-based techniques rely on free-space propagation as the primary means of signal formation. Unlike ABI or grating interferometry, propagation-based imaging systems do not require X-ray optical elements. Instead the only requirement is that the X-ray source be spatially coherent, and that the detector have sufficient resolution to resolve the phase effects in an image. Phase retrieval achieved using images taken at multiple propagation distances, and there is no need for optical elements or highly conditioned X-ray sources [62, 35]. Even the spatial coherence of the x-ray source becomes less of an issue, since in actuality it is the optical path length (OPL) of the specimen that we seek to recover, not the phase per se, as we will demonstrate in section 2.4.3.

In this method, the phase signal is retrieved by exploiting the effects of free-space propagation on an X-ray wave. Propagation based imaging methods are also sometimes referred to as inline holography, or non-interferometric phase retrieval. Our proposed method uses the transport of intensity equation, which relates the phase of a wave to its multidimensional intensity distribution [135]. By taking the image at multiple focal planes, the phase map can be retrieved. The transport of intensity equation is compatible with Fourier domain solvers, allowing for high performance phase retrieval [170, 167, 168]. The composition for a transport of intensity X-ray imager is simple: a point source, the subject, and a detector, with no intermediate optics. Such a system can be integrated into an existing cone beam X-ray imaging setup as long as the X-ray source has sufficient spatial coherence [175]. A propagation based X-ray imager would be as simple as an absorption based X-ray imager, requiring no additional X-ray optics compared to current modes of X-ray imaging. In the next
section, we will describe the theories that underpin propagation-based imaging.

2.4 X-ray propagation

In section 2.2, we explored the interactions between X-rays and matter, and how the X-ray wavefront is altered by these interactions. But the X-ray wavefront also evolves after the object – during propagation in free space – which we will describe in this section.

To obtain quantitative information of the phase from an X-ray image, we must know the details of how the image is formed. In conventional absorption based imaging, the detector is placed close to or immediately behind the object of interest, forming a contact image. Contact images do not contain phase effects, as there is insufficient distance for propagation-related intensity changes to manifest. However, if the detector is placed further away from the object, phase effects begin to manifest. These effects can be modeled using either ray-tracing methods or wave optics methods. Both models are valid approaches, and are suited to different contexts. In this thesis, we will concern ourselves primarily with the wave optics approach, which is based on a phenomenon known as diffraction.

2.4.1 Fresnel diffraction

To model propagation, we will introduce the wave optics formalism for modeling diffraction. The idea that light could be modeled as a wave was first proposed by Hooke, after observing interference patterns in optical experiments [75]. This was iterated on by Huygens and Fresnel, who extended Hooke’s theories to include interference and diffraction, resulting in the Huygens-Fresnel principle, which states that any arbitrary wavefront can be formulated as the superposition of spherical waves. Then, all we have to do is figure out propagation for a single spherical wave, we can express any wavefront as a superposition of spherical waves.

In wave optics, there are two regimes of propagation to consider: the near-field, or Fresnel domain, and the far-field, or Fraunhofer domain. A common heuristic to
determine which propagation domain we are in is the Fresnel number:

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

(2.18)

where \( a \) is the characteristic size of the aperture, \( \lambda \) is the wavelength of light, and \( L \) is the propagation distance. If \( F \gg 1 \), propagation should be modeled by Fresnel diffraction, and if \( F \ll 1 \) Fraunhofer diffraction is the more appropriate model. In transmission imaging, the features of the object act as the apertures, so the Fresnel number takes on different values for different length-scaled feature sizes. For example, with a 30 kV incident X-ray beam at 1 m of propagation, the Fresnel number for an object with 100 \( \mu \)m feature sizes is \( F = 242 \), while an object with 10 \( \mu \)m feature sizes will have \( F = 2.41 \). The Fresnel number can also be affected by the detector pitch; if our detector has a pixel size \( \Delta x \), then the Fresnel number of the system cannot go below \( \frac{\Delta x^2}{\lambda L} \) with direct measurements. Crystallography is typically performed at low Fresnel numbers, with a combination of large propagation distances and relatively longer wavelengths. X-ray phase imaging, on the other hand, must use larger pixel pitches to increase the field of view, and must operate at shorter distances, to maximize flux. Virtually all X-ray phase imaging performed in this thesis is performed in the Fresnel regime of propagation, which is described by the Fresnel diffraction integral:

\[ u(x, y, z) = \frac{e^{ikz}}{i\lambda z} \int\int u(x_0, y_0) e^{\frac{ik}{2z}[(x-x_0)^2+(y-y_0)^2]} dx_0 dy_0 \]  

(2.19)

The Fresnel-Kirchoff diffraction integral can be thought of as a convolution between the wavefunction \( u_0 \) and the propagator function \( h(x, y) \). For the derivation, please refer to appendix A.

\[ u(x, y, z) = u_0(x, y) * \frac{e^{ikz}}{i\lambda z} e^{\frac{ik}{2z}(x^2+y^2)} \]  

(2.20)

This allows us to implement Fresnel diffraction in a very efficient way through the
convolution theorem:

\[
    u(x, y, z) = \mathcal{F}^{-1} \left\{ \mathcal{F} \left\{ u_0(x, y) \right\} \mathcal{F} \left\{ \frac{e^{ikz}}{i\lambda z} e^{\frac{i\kappa}{2} (x^2 + y^2)} \right\} \right\}
\]  

(2.21)

This means that given an incident wave \( u_0 \), we can model the wavefront at any point \( u(x, y, z) \) through a simple Fourier multiplication. This is particularly useful in numerically simulating wavefront propagation, which will be used in sections 4.1 and 4.2.

2.4.2 The transport of intensity equation

Consider the electric field in the previous section, \( u(x, y, z_d) \), as it falls onto a detector \( z_d \) away from the object. The quantity that the detector measures is the intensity of the electric field, \( I(x, y, z_d) = |u(x, y, z_d)|^2 \). It is useful to think of the field as it exits the object comprising of two parts, an amplitude part and a phase part: \( u_0(x, y) = A(x, y)e^{i\phi(x,y)} \). It is clear that when \( z_d = 0 \), the measured intensity \( I(x, y, 0) = A(x, y)^2 \) does not capture any phase information of the wave. However, if the wave is allowed to propagate, \( I \) instead measures the following:

\[
    I(x, y, z_d) = |u(x, y, z_d)|^2
\]

(2.22)

\[
    = \left| A(x, y)e^{i\phi(x,y)} * \frac{e^{ikz_d}}{i\lambda z} e^{\frac{i\kappa}{2} (x^2 + y^2)} \right|^2
\]

(2.23)

\[
    = \left| A(x, y)e^{i\phi(x,y)} * e^{i\kappa z_d (x^2 + y^2)} \right|^2
\]

(2.24)

This intensity measurement now contains a mixture of both the object absorption and phase information. This is a phenomenon known as “phase mixing”. Consider again the \( +z \) propagating component of the Helmholtz equation in eq. (A.9). If we apply the paraxial approximation directly, we arrive at the paraxial wave equation:

\[
    \left( i \frac{\partial}{\partial z} + \frac{\nabla^2}{2k} \right) u(x, y, z) = 0
\]

(2.25)
By multiplying eq. (2.25) by $u^*$, and the complex conjugate of eq. (2.25) by $u$,

\[
\begin{align*}
\frac{i}{\partial z}u^* + \frac{\nabla^2 u}{2k}u^* &= 0 \tag{2.26} \\
-i\frac{\partial u^*}{\partial z} + \frac{\nabla^2 u^*}{2k}u &= 0 \tag{2.27}
\end{align*}
\]

Subtracting eq. (2.26) and eq. (2.27) results in

\[
\begin{align*}
\frac{i}{\partial z}u^* + \frac{\nabla^2 u}{2k}u^* + \frac{u^*\nabla^2 u - u\nabla^2 u^*}{2k} &= 0 \tag{2.28} \\
i\frac{\partial uu^*}{\partial z} + \frac{\nabla \cdot (u^*\nabla u - u\nabla u^*)}{2k} &= 0 \tag{2.29}
\end{align*}
\]

Finally, we apply the definition that $u(x,y,z) = A(x,y,z)e^{i\phi(x,y,z)}$, and $I(x,y,z) = A(x,y,z)^2$

\[
\begin{align*}
&\frac{i}{\partial z}\frac{\partial A^2}{\partial z} + \frac{1}{2k} \nabla \cdot \left( Ae^{-i\phi} (A\nabla e^{i\phi} + e^{i\phi}\nabla A) - Ae^{i\phi} (A\nabla e^{-i\phi} + e^{-i\phi}\nabla A) \right) = 0 \tag{2.30} \\
&\frac{i}{\partial z}\frac{\partial I}{\partial z} + \frac{1}{2k} \nabla \cdot \left( iA^2\nabla \phi + A\nabla A + iA^2\nabla \phi - A\nabla A \right) = 0 \tag{2.31} \\
&\frac{\partial I}{\partial z} + \frac{1}{k} \nabla \cdot (I\nabla \phi) = 0 \tag{2.32}
\end{align*}
\]

The result of the derivation is a relationship between the intensity, the derivative of intensity along the optical axis, and the phase of the wave. Equation (2.32) is known as the Transport of Intensity Equation (TIE). The transport of intensity equation allows us to determine the phase of a wave, given measurements of its intensity and derivative of intensity. The TIE is a very powerful equation, and is a useful tool both for modeling propagation, as well as the inverse problem of determining phase from multidimensional intensity measurements.
Analogies for the TIE

To better understand the behavior of the TIE, it is helpful to draw analogies to other physical phenomenon which exhibits a similar mathematical behavior.

The TIE can be interpreted as a conservation equation. In this context, the quantity being conserved is energy in the form of intensity. The differential form for a general continuity equation is:

$$\frac{\partial \rho}{\partial t} + \nabla \cdot j = \sigma, \quad (2.33)$$

where $\rho$ is the quantity per unit volume, $j$ is the flux of $\rho$, and $\sigma$ is the generation of $\rho$ per unit volume per unit time. We see that the TIE is readily adapted to the form of eq. (2.33), as a 2D continuity equation, with the distance along the optical axis, $z$ acting as time, $t$:

$$\frac{\partial I}{\partial z} = \nabla_{\perp} \cdot (I \nabla_{\perp} \phi). \quad (2.34)$$

This is a continuity equation for intensity, where the flux of intensity along $z$ is given by the Poynting vector, $I \nabla_{\perp} \phi$. Furthermore, this continuity equation contains no source or sink for intensity, as there is assumed to be no amplification or absorption of intensity in free space.

This continuity behavior of light has previously been described using an analogy to hydrodynamics [160], where the propagation equation can be rewritten as the Euler equation for an inviscid and irrotational flow is described by [161]:

$$k_0 \frac{\partial I}{\partial z} + I \cdot \nabla I = k_0^2 n_0 \nabla_{\perp} (\Delta n), \quad (2.35)$$

where $k_0$ is the free-space wavevector, $n_0$ is the refractive index of the media, and $\Delta n$ is the local variation in refractive index. Here the intensity, $I$, is analogous to the fluid velocity, and the distance along the optical axis, $z$, again replaces time.

This has enabled the study of complex fluid behaviors through analogy, by using an optical system instead of the corresponding fluid system [171, 102, 101].
2.4.3 Definition of phase for partially coherent illumination

As described above, the phase $\phi$ of a wave $U$ is well defined when the illuminating wave is coherent:

$$U = A(x,y)e^{i\phi(x,y)}$$  \hspace{1cm} (2.36)

However, for partially-coherent waves, as in the case of the X-rays emitted by a tube source, the phase cannot be directly related to the above expression. To explain the significance of the quantity obtained from the TIE, we refer to the approach taken in [124].

Consider a quasi-monochromatic wave which is characterized by its cross-spectral density $W(x_1, y_1, x_2, y_2, z) = \langle U^*(x_1, y_1, z)U(x_2, y_2, z) \rangle$, where $x_1, y_1, x_2, y_2, z$ are spatial coordinates, and $\langle \cdot \rangle$ is the ensemble average over all fields $U$ which satisfy the paraxial wave equation ineq. (2.25). We see that if the field is coherent, the spectral density, $S(x, y, z) = W(x, y, x, y, z) = |U|^2 = I$ is the equivalent of the intensity measured upon the detector for a monochromatic coherent field. Unlike $I$, $W$ is a 4D field at each $z$, and the phase of $W$ is the correlation of the field at all pairs of a point in the plane $z$. Therefore, when the TIE is applied to a partially-coherent set of measurements $S$, the recovered value is not the phase of the 4D function $W$. Instead, the transport of intensity equation is interpreted as follows:

$$\frac{\partial}{\partial z} S(x, y, z) + \nabla_\perp F(x, y, z) = 0$$  \hspace{1cm} (2.37)

$$F(x, y, z) = \lim_{(x',y') \to (0,0)} \frac{1}{ik} \nabla_{(x',y')} W \left( \frac{x - x'}{2}, \frac{y - y'}{2}, \frac{x'}{2}, \frac{y'}{2}, z \right)$$  \hspace{1cm} (2.38)

The recovered term $F$ can be interpreted as a flux term necessary for the conservation of spectral density; if spectral density at a point changes between $z$ planes, there must be a flow of spectral density into or out of that point in the transverse direction. Based on this intuition, we represent $F$ as a product of the spectral density and a
flow vector: \( F(x, y, z) = S(x, y, z)\vec{v}(x, y, z) \), assuming \( S(x, y, z) \neq 0 \). The flow vector \( v(x, y, z) \) can be expressed as a composition of curl free and divergence free terms through a Helmholtz decomposition. Since the transport of intensity measures only the curl-free component, the divergence-free term can be neglected, and thus the reconstructed term can be expressed as

\[
v(x, y, z) = \nabla_\perp \phi(x, y, z)
\]

(2.39)

Now we are equipped to interpret the quantity obtained from the TIE. From eqs. (2.37) and (2.38), we see that the gradient of the recovered "phase" is the transverse flux of spectral density, analogous to the transverse Poynting vector for spectral density.

To relate this to the optical properties of the object, consider a thin object \( T(x, y) = e^{-\beta k r} e^{i(1-\delta)k r} = A(x, y)e^{i\phi(x, y)} \) illuminated by a field with cross-spectral density \( W_0 \) and spectral density \( S_0 \). The cross-spectral density immediately after the object is then given by:

\[
W(x_1, y_1, x_2, y_2, z) = T^*(x_1, y_1)T(x_2, y_2)W_0(x_1, y_1, x_2, y_2, z)
\]

(2.40)

and the spectral density is given by

\[
S(x, y, z) = A(x, y)^2 S_0(x, y, z)
\]

(2.41)

The transport of intensity equation can be shown to be

\[
\frac{\partial}{\partial z} S(x, y, z) + \nabla_\perp \left( A(x, y)^2 F(x, y, z) \right) = -\frac{1}{k} \nabla_\perp \cdot \left( S_0(x, y, z)A(x, y)^2 \nabla_\perp \phi(x, y) \right)
\]

(2.42)

When the illumination is symmetric, \( F(x, y, z) = 0 \). This results in a form of eq. (2.42) that is similar to the equation derived under full coherence conditions:

\[
\frac{\partial}{\partial z} S(x, y, z) = -\frac{1}{k} \nabla_\perp \cdot \left( S_0(x, y, z)A(x, y)^2 \nabla_\perp \phi(x, y) \right)
\]

(2.43)
Given that \( S_0 \) is known, the TIE therefore recovers \( A(x, y) \) and \( \phi(x, y) \), i.e. the object’s attenuation and optical path length.

2.4.4 Exact solutions for propagation

While the Fresnel diffraction kernel and the transport of intensity equation provide approximations for propagated waves, there are also exact solutions for certain object geometries, known as Mie solutions [153]. There are known Mie solutions for objects comprised of spheres and cylinders. Mie solutions are formulated as infinite series, in a manner similar to the Taylor expansion. In numerical solutions, the number of terms in the Mie solution can be tuned to the accuracy required. Numerous implementations of Mie scattering code for the case of a single homogeneous sphere and homogeneous cylinder exist and are readily accessible [16, 90, 17].
2.5 Computed Tomography

X-ray computed tomography is a technique that enables the reconstruction of a 3D volume from a series of 2D projections. In conventional X-ray tomography, the projections are arranged such that they capture absorption information from different angles around the object. These measured projections can then be combined back into the original 3D volume, a process known as computed tomography.

2.5.1 The Radon transform

The acquired images at the detector can be thought of line integrals through the object. Mathematically, this process is encapsulated by the Radon transform, denoted as $\mathcal{R}\{\cdot\}$:

$$\mathcal{R}\{f(x, y)\}(r, \theta) = \int \int f(x, y) \delta(r - x \cos \theta - y \sin \theta) dx dy \quad (2.44)$$

where $f(x, y)$ is any analytic function on $\mathbb{R}^2$, and $\delta$ is the dirac delta function. On the other hand, the Fourier transform of a function provides a frequency-space representation

$$\mathcal{F}_{2D}\{f(x, y)\}(u, v) = \int \int f(x, y) e^{-2\pi i (ux + vy)} dx dy \quad (2.45)$$

The Radon transform is intimately related to the Fourier transform through the Fourier slice theorem, which relates the Fourier transform of an object with its Radon
transform. An illustrative example is given in fig. 2-6.

**Theorem 2 (Fourier slice theorem)** For a function \( f(x, y) \), with a corresponding Radon transform \( \mathcal{R} \{ f(x, y) \} (r, \theta) \), and a 2D Fourier transform \( \mathcal{F}_{2D} \{ f(x, y) \} (u, v) \), the following are equivalent:

\[
\mathcal{F}_{1D} \left\{ \mathcal{R} \{ f(x, y) \} \right\} (r, \theta)(r) = \mathcal{F}_{2D} \{ f(x, y) \} (r \cos \theta, r \sin \theta)
\] (2.46)

### 2.5.2 Filtered backprojection (FBP)

It is possible to perfectly reconstruct a function from its Fourier transform provided that the Fourier transform satisfies the Nyquist-Shannon sampling requirements. Therefore, the Fourier slice theorem suggests that a function can be reconstructed from its projections. This operation is called the inverse Radon transform. However, this is a misnomer; in reality, we are only able to acquire a finite set of projection angles and ray paths through the object. This results in a discrete polar sampling of the Fourier transform, which must then be translated into a real-space representation in cartesian coordinates. Therefore, the process is imperfect, and there is no true "inverse Radon transform" in the discrete case. Instead, the we consider the dual of the Radon transform, known as the backprojection:

\[
\mathcal{R}^{-1} \{ \mathcal{R}(r, \theta) \} (x, y) = \int_0^\theta \int_{-\infty}^{\infty} R(r, \theta)e^{2\pi ir(x \cos \theta + y \sin \theta)} dr d\theta
\] (2.47)

Due to the nature of the discrete measurements, pixels near the center of rotation are sampled at a much higher density than pixels at the periphery. If we attempt to invert the radon transform directly through backprojection, the energy of the system is not conserved. Therefore, the projections must be filtered before applying the backprojection operator, compensate for unevenly distributed measurements. We can intuitively reconstruct the reweighting filter. We assume that the measurements are taken using a uniform detector, with uniform angular spacing. Then, the density of measurements in Fourier space is directly proportional to \( \frac{1}{|w|} \), where \(|w|\) is the distance in Fourier space to the origin (the magnitude of spatial frequency). To compensate
for this distribution, we may choose to filter the projected images with the the $|w|$ kernel. However, since our projections can only sample finite spatial frequencies, our use of the $|w|$ filter may result in the Gibb’s phenomenon due to the sharp cutoff at the maximum spatial frequency. Instead of using a ramp filter, several filters have been designed for CT to minimize the apparent noise in backprojections, such as the Shepp-Logan, Hamming, and Hann windows [82]. The effects of performing a filtered and unfiltered backprojection are shown in fig. 2-7.

### 2.5.3 Cone-beam effects

The algorithms described in the section thus far apply only when the rays of projection are parallel. However, this would only be the case for plane wave illumination. In reality, X-ray sources act as point sources, producing a spherical wave. Therefore the rays traced are not parallel, but fan out from the source, as illustrated in fig. 2-8b. If enough projections are acquired in the tomogram, it is possible to reassign rays such that an equivalent set of parallel projections can be synthesized. This is a process known as rebinning.

However, in cone beam geometries, the rays of projection diverge not only in the plane of reconstruction, but through axial slices of the object as well. When the cone angle is small, this effect is minimized. However, when the cone angle is large, rays can interact with several slices at once. Therefore, the filtered backprojection, which assumes that each slice of the reconstruction is independent, cannot provide accurate results. Feldkamp, Davis, and Kress proposed a synonymous method (FDK)
that produces an approximate solution to the problem through a three-dimensional backprojection [50]. The FDK algorithm imposes an additional weight onto the backprojection, which is proportional to the distance from the central plane of the illumination.

2.5.4 Iterative reconstruction techniques

As outlined in the preceding section, while the implementation of the FBP is simple and computationally efficient, it does not allow for regularization of the solution. Iterative techniques provide a means to improve on the results obtained from FBP at the cost of increased computational complexity. Instead of directly inverting the Radon transform, iterative techniques iterate between a current estimate of the object function and the measurements obtained. Typically, iterative techniques employ the forward Radon transform and its dual, or adjoint. As noted above, the adjoint of the Radon transform is the backprojection operator. By projecting from the estimated object to the measurements, accounting for the differences, and backprojecting, a new estimate can be obtained. Regularization methods are often used to improve the performance of iterative techniques. A simple example would be to restrict all attenuation values to be positive real numbers at each iteration. Iterative reconstruction typically proceeds as describe in fig. 2-9.

Unlike filtered backprojection, iterative techniques can also account for many phys-
ical factors such as source spot size, cone-beam geometry, noise statistics, and X-ray beam spectrum. Iterative techniques can also account for artifacts such as beam hardening, ringing, and nonlinearities in the detector.

In this thesis, we make extensive use of the iterative reconstruction framework for CT reconstruction, and demonstrate several novel methods for iterative phase computed tomography.

A common form of iterative reconstruction is the class of algebraic reconstruction techniques. These techniques solve the following problem:

\[ Ax = b \]  \hspace{1cm} (2.48)

where \( x \) is a vector containing the voxel representation of the volume of interest, \( A \) is the a matrix which performs tomographic projection, and \( b \) is a vector containing the sinogram measurements.

Several different methods exist to solve this problem, the most popular being the algebraic reconstruction technique (ART) and simultaneous iterative reconstruction technique (SIRT). Both ART and SIRT can be applied to 2D and 3D reconstructions.
Algebraic reconstruction technique

Originally known as the Kaczmarz method for solving linear systems [81], the algebraic reconstruction technique was rediscovered by Gordon, Bender, and Herman as a method for image reconstruction [58]. The ART is a simple algorithm. To solve the overall system $Ax = b$, we iterate over every row of $A$, solving the $i^{th}$ row as follows:

$$x^{k+1} = x^k + \lambda_k \frac{b_i - \langle a_i, x^k \rangle}{\|a_i\|^2} a_i$$

(2.49)

If the linear system is consistent, $x^k$ is guaranteed to converge to the least-squares solution. Priors can easily be incorporated into ART, by performing regularization steps on $x^k$ after each iteration. Recently, a randomized version of ART where each row is chosen at random [112]. The randomized Kaczmarz algorithm has been shown to be superior to the ordered method in certain cases.

Simultaneous iterative reconstruction technique

Unlike ART, the simultaneous iterative reconstruction technique solves the entire projection problem at once, as its name suggests. In SIRT, a similar scheme is followed to ART, but operating over all rows at the same time. The successive iterates are obtained using the following equation:

$$x^{k+1} = x^k + CA^TR \left( b - Ax^k \right)$$

(2.50)

$$c_{ij} = \begin{cases} 
    i = j, & \left( \sum_i a_{ij} \right)^{-1} \\
    i \neq j, & 0 
\end{cases}$$

(2.51)

$$r_{ij} = \begin{cases} 
    i = j, & \left( \sum_j a_{ij} \right)^{-1} \\
    i \neq j, & 0 
\end{cases}$$

(2.52)

(2.53)
The matrices $C$ and $R$ are normalization matrices which account for the number of rays traversing each pixel and number of pixels traversed by each ray, respectively. Equation (2.50) is essentially a gradient descent algorithm which minimizes the least-squares norm of $Ax - b$. 
Chapter 3

Experimental System Design

3.1 X-ray sources

So far, we have reviewed the fundamental properties of X-rays and their interaction with matter. In this section, we will review the generation of X-rays. Two categories of sources are of particular interest, anode-based sources, and synchrotron radiation sources.

3.1.1 Anode-based X-ray sources

![Figure 3-1: Schematic diagram of an X-ray tube source.](image-url)
In anode-based sources, electrons are emitted from a cathode, and accelerated to an anode under a high voltage (typically in the kilovolt range). A schematic diagram of an anode-based source is presented in fig. 3-1. When the accelerated electrons collide with the anode, they are rapidly decelerated, releasing X-ray photons in a broad spectrum. This phenomenon is known as Bremsstrahlung radiation. The maximum energy of the spectrum is bounded by the maximum energy in the electrons, so for electrons accelerated at 30 kVp, the Bremsstrahlung spectrum cannot exceed 30 kVp. Additionally, electrons striking the anode may excite electrons in the atoms of the anode to a higher energy orbital. The subsequent fluorescent relaxation of the electron results in a narrow spectrum of radiation called characteristic radiation. Thus, in all anode-based sources, the resulting X-ray spectrum is a superposition of the Bremsstrahlung spectrum with the characteristic spectrum of the anode material. An example of such a spectrum is presented in fig. 3-2. It is clear from this example that these sources are typically not temporally coherent. The cross-sectional area of the anode that emits X-rays is known as the spot size, and governs the apparent size of the X-ray source. Typical X-ray sources have spot sizes on the order of millimeters.

Source intensity is primarily limited by two properties of the source: the rate
Figure 3-3: For X-ray sources with finite spot size, images of the object are blurred due to a convolution between the source distribution and object transmission functions. This is known as the penumbra effect.

at which the cathode supplies electrons (the “tube current”), and the rate at which the anode must dissipate heat (“heat load”). For a vast majority of tube sources, electrons are generated at the cathode through the thermionic effect. In these sources the cathode is a length of tungsten filament. By passing a large current through the filament, heating it up, and electrons are released from the cathode. Thermionic cathodes are capable of supplying large amounts of electrons, and thus in thermionic source design the heat load to the anode is the major limiting factor. While increasing the surface area of the anode would decrease the amount of heat load, doing so would increase the spot size of the source. Smaller spot sizes are desired even in conventional X-ray imaging, as the finite spot size of the tube results in a penumbra effect, shown in fig. 3-3, reducing the quality of the image. In modern sources, the anode is rotated while the source is emitting, distributing the heat load over a larger anode surface while maintaining a small spot size.

**Microfocus X-ray sources**

A microfocus X-ray source is used extensively throughout this thesis as the primary means of producing coherent X-ray illumination. While conventional X-ray tubes do not have the spatial coherence required for phase imaging, microfocus X-ray sources can easily satisfy the spatial coherence requirement for X-ray phase imaging. Conventional X-ray tubes typically have focal spot sizes on the order of 0.5 mm. As seen
in fig. 3-1, the electrons emitted from the cathode are accelerated towards the anode by the potential difference between the anode and cathode. By adding a magnetic lens between the anode and cathode, the electron beam can be focused to region on the anode as small as 5 μm in diameter. However, focusing the electron beam also significantly increases the heat load onto the anode. To prevent the anode from melting due to heat load, microfocus sources must operate at lower tube currents than normal X-ray sources. Recently, researchers have shown that by replacing the rotating metal anode with a liquid metal jet, the output flux of a microfocus source can be increased by over an order of magnitude [71, 162].

Most of the experiments were conducted at Radiation Monitoring Devices (Watertown, MA). The microfocus source used was a Hamamatsu L8121–03 with a tungsten target. The source operates at a range of 40 kV to 150 kV, and produces a minimum focal spot size of 5 μm. This produces sufficient spatial coherence for phase contrast imaging: at a distance of 2 meters the transverse coherence length is on the order of 10 μm, which is sufficient to produce X-ray phase contrast.

### 3.1.2 Synchrotron X-ray sources

In this thesis, we will use images taken at synchrotron facilities to demonstrate the full potential of X-ray phase contrast imaging. Unlike anode-based sources, synchrotrons produce radiation through the cyclic acceleration of charged particles. Synchrotrons are capable of producing extremely brilliant and spatially coherent X-ray beams, which make them perfect for experimental X-ray phase imaging. However, there are only a few synchrotron facilities in the world, and access to them is highly limited; synchrotron facilities are multimillion dollar endeavors, and thus are only feasible for experimental imaging studies. For widespread use, our methods must be adaptable to more compact and affordable X-ray sources. In addition to limited accessibility, synchrotron sources are only capable of providing beams that are centimeters in diameter. This significantly limits the field of view, and restricts our synchrotron experiments to small samples.

Synchrotron images were obtained from beam-line 14C on the 2.5 GeV storage
ring at the KEK Photon Factory (Tsukuba, Japan) and beam-line 6C on the 3.0 GeV storage ring at the Pohang Light Source (Pohang, Korea). At either synchrotron facility, the incident illumination beam was conditioned by first passing through a monochromator system, resulting in a coherent X-ray beam with a mean energy of 35 keV. The beam diameter was 60 mm at both synchrotron facilities.

3.2 X-ray detectors

All imaging experiments were conducted using scintillator-coupled digital X-ray detectors. Alternative detection methods such as film and digital radiography plates were considered, but only direct digital detectors were able to achieve both the high resolution and high throughput required for X-ray computed tomography. For propagation based imaging, high resolution detectors are required to resolve the diffraction fringes required for phase retrieval.

For imaging with the microfocus system at Radiation Monitoring devices, we used two detectors. The first is an Andor iXon electron-multiplying CCD that was coupled with a fiber optic taper to a cesium iodide (CsI) scintillator. The resulting effective pixel size of the EMCCD was 48 µm x 48 µm, with a field of view of 24.6 mm. The second camera was a Radicon Shad-o-box 4K, which was a CMOS detector directly coupled to a gadolinium oxysulfide (Gd₂O₂S) scintillator. The Shad-o-box also had an effective pixel pitch of 48 µm.

At both synchrotron facilities, a Photonic Sciences X-FDI camera with a pixel size of 7.4 µm was used. The camera was coupled to a Gd₂O₂S scintillator with a 1:1 fibre optic taper.

3.3 Optomechanical system

To perform tomographic acquisitions, either the sample or the imaging system must be rotated during imaging. Precise rotation of the subject is crucial to the quality of tomographic reconstruction, and it is common for the rotational mechanics (i.e.
gantry) of a commercial CT system to account for half of it’s manufacturing cost. Additionally, calibration of the rotational axis and sample positioning are much more difficult to achieve using manual stages, as the X-ray beam must be interrupted during each adjustment. Therefore we have developed a 6 axis motion control system for sample positioning and rotation for tomographic phase retrieval. The system consists of 2 linear stages which enable movement in the horizontal directions, a z-stage for adjusting sample height, two tilt stages for aligning the axis of rotation, and a high-resolution rotation stage. The motion control system has a programmable interface, which we use in conjunction with detector software to perform automated tomographic acquisition.

The two linear stages (Zaber Technologies) and z-stage (Thorlabs Inc.), not only allow us to align the system with respect to the rotational axis, but also enable adjustment of the propagation distances. This gives the system the ability to perform intensity measurements at multiple propagation distances, and to synthesize larger fields of view by translating the object. The linear stages can be used to remove the object from the field of view to obtain calibration images, and precisely placed back into its original position, enabling calibration images to be taken during various points in the tomographic acquisition. For the Shad-o-box detector, this capability is extremely important, as there is significant pixel drift during acquisition.

The optically encoded rotation stage (Thorlabs Inc.) enables tomographic acquisition at a resolution of up to 2°, allowing for highly precise angular registration. To align the rotational axis of the stage, it is mounted upon a two-axis motorized goniometer, which is used to correct for both in-plane and out-of-plane tilt.

Calibration is performed first by correcting for in-plane tilt by imaging a needle phantom. The needle phantom is imaged at 0° to 180° of rotation, as shown in figs. 3-4a and 3-4b. The resulting 0° image is registered to the y-axis mirrored 180° image to obtain a translation and rotation correction factor, \( \Delta x_r \) and \( \theta_r \). The goniometer is adjusted to \( \theta_r/2 \), and the x-axis stage is translated by \( \Delta x_r/2 \). To

To correct for out-of-plane tilt, the stage is raised such that the upper surface of the rotation stage is at the midpoint of the detector, as seen in fig. 3-4c. The curvature
Figure 3-4: Shift and tilt corrections for (a-b) in-plane shift and tilt and (c-d) out-of-plane tilt

of the stage silhouette is measured, and an approximate corrective adjustment is applied to the goniometer. The measurement-correction process is repeated until the curvature of the stage silhouette is maximized.

### 3.4 Test phantoms

Test phantoms were used to calibrate and validate our experimental X-ray phase contrast system. Phantoms were chosen to test both the resolution and linearity of the system.

#### 3.4.1 Microspheres

Microspheres provide an excellent phantom for initial phase imaging tests. Due to their symmetry, the total material thickness at any point is easy to calculate. In
<table>
<thead>
<tr>
<th>Material</th>
<th>Diameter</th>
<th>Composition</th>
<th>Density</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetal resin</td>
<td>4.763 mm</td>
<td>(CH₂O)ₙ</td>
<td>1.41 g cm⁻³</td>
</tr>
<tr>
<td>Nylon 6-6</td>
<td>4.763 mm</td>
<td>(C₁₂O₂N₂H₂₂)ₙ</td>
<td>1.16 g cm⁻³</td>
</tr>
<tr>
<td>Neoprene</td>
<td>4.763 mm</td>
<td>(C₄H₅Cl)ₙ</td>
<td>0.96 g cm⁻³</td>
</tr>
<tr>
<td>Polypropylene</td>
<td>4.763 mm</td>
<td>(C₃H₆)ₙ</td>
<td>0.855 g cm⁻³</td>
</tr>
<tr>
<td>Polycarbonate</td>
<td>4.763 mm</td>
<td>(C₁₅H₁₆O₂)ₙ</td>
<td>1.22 g cm⁻³</td>
</tr>
<tr>
<td>Styrene</td>
<td>700 µm</td>
<td>C₈H₈</td>
<td>0.909 g cm⁻³</td>
</tr>
</tbody>
</table>

Table 3.1: Table of microsphere compositions

addition, the exact solution for phase effects of a sphere can be obtained from the Mie scattering solutions to Maxwell’s equations, which provide a theoretically predicted response with which we can compare our experimental results.

In our imaging experiments, we make use of microspheres from McMaster-Carr and Cospheric. Table 3.1 presents a detailed list of the microspheres used as imaging phantoms.

### 3.4.2 Liquid phantoms

Liquid phantoms were used to evaluate the ability of our system to detect small changes in refractive index. Liquid phantoms by nature are homogeneous, and lend themselves readily to simple analysis after computed tomography. By diluting and mixing liquid phantoms, smaller gradations in refractive index are possible. In our liquid phantom experiments, we use water, acetone, and hydrogen peroxide as imaging targets. Water and hydrogen peroxide are very similar in atomic composition, and the refractive index of peroxide in the visible domain is the same as the refractive index of water. However, the density of hydrogen peroxide is higher than that of water. Therefore, telling hydrogen peroxide apart from water is difficult to do in the visible domain or with direct X-ray imaging, it is possible to measure this difference using X-ray phase imaging. Acetone, on the other hand, is significantly less dense than water, and has an X-ray signature similar to adipose tissue.
3.4.3 Mouse phantom

In both clinical and preclinical CT systems, the use of a calibration phantom is used for quality assurance purposes. The typical reference phantoms used in these systems are designed to mimic the range of materials encountered in everyday imaging studies.

A water-filled MicroMouse phantom (CIRS, USA) was used to evaluate the effectiveness of the system for imaging of common biological substrates. The mouse phantom consists of a polycarbonate container containing 11 rods of varying material compositions and diameters which simulate both soft and bony tissue. The rods are comprised materials with equivalent absorption and electron density to lung, muscle, adipose tissue, as well as calcium hydroxyapatite (HA) loaded rods to simulate various bone densities. The HA rods are titrated with a tissue equivalent material to achieve the desired bone densities. The dimensions and arrangement of the mouse phantom is given in fig. 3-5 and table 3.2.
<table>
<thead>
<tr>
<th>Rod #</th>
<th>Material</th>
<th>Material density $\text{g cm}^{-3}$</th>
<th>Electron density $1 \times 10^{23} \text{ cm}^{-3}$</th>
<th>Relative electron Density to water</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 &amp; 6</td>
<td>750 mg/cc HA</td>
<td>1.571</td>
<td>4.948</td>
<td>1.481</td>
</tr>
<tr>
<td>2 &amp; 11</td>
<td>250 mg/cc HA</td>
<td>1.245</td>
<td>4.024</td>
<td>1.205</td>
</tr>
<tr>
<td>3 &amp; 7</td>
<td>50 mg/cc HA</td>
<td>1.115</td>
<td>3.655</td>
<td>1.094</td>
</tr>
<tr>
<td>4 &amp; 8</td>
<td>0 mg/cc HA</td>
<td>1.083</td>
<td>3.562</td>
<td>1.066</td>
</tr>
<tr>
<td>5</td>
<td>Adipose</td>
<td>0.960</td>
<td>3.171</td>
<td>0.949</td>
</tr>
<tr>
<td>9</td>
<td>Muscle</td>
<td>1.063</td>
<td>3.483</td>
<td>1.043</td>
</tr>
<tr>
<td>10</td>
<td>Lung</td>
<td>0.205</td>
<td>0.681</td>
<td>0.204</td>
</tr>
<tr>
<td>Fill</td>
<td>Water</td>
<td>1.00</td>
<td>3.340</td>
<td>1.00</td>
</tr>
</tbody>
</table>

Table 3.2: Mouse phantom loading configuration.

With known attenuation and phase values, the mouse phantom allows us to verify the results of new reconstruction algorithms. The HA rods enable controlled testing of compensating algorithms for calcium artifacts in phase reconstructions, and the soft-tissue rods enable us to quantify the improvement in soft-tissue contrast of our algorithms.
Chapter 4

Simulation of X-ray phase images

The ability to simulate image formation is a crucial aspect in the design and evaluation of new X-ray phase imaging systems. Simulations can provide realistic predictions for propagated phase images without experimental artifacts such as detector variations. By modeling the imaging process, we are able to test our algorithms in situations where the exact anatomy of the phantom is known, i.e. the "ground truth".

We have developed a set of tools which can be used to simulate the performance of X-ray phase imaging. These simulations are focused at modeling the observed image contrast in experimental X-ray phase imaging systems.

4.1 Effect of temporal coherence

While most phase retrieval techniques assume quasi-monochromatic illumination, X-ray tube sources generally do not produce highly coherent illumination. In fact, most X-ray sources produce broadband illumination, as shown in section 3.1.1.

We simulated a source with a broadband spectrum as shown in fig. 4-1b. The simulation phantom was a 1 mm sphere of water suspended in air shown in fig. 4-1a. The propagation distance is set to 1 m.

As shown in section 2.4.1, for a particular wavelength the Fresnel propagated
(a) Simulation phantom: a 1 mm sphere of water suspended in air.

(b) Simulated X-ray spectrum

(c) Complex refractive index of water at simulated energies

Figure 4-1: Simulation phantom, source spectrum, and dispersion relation for water at simulated spectrum.
Figure 4-2: Simulated broadband phase image

Figure 4-3: Monochromatic intensity images at sampled energies.
image at distance is given as

\[ u(x, y, z; k) = \mathcal{F}^{-1} \left\{ \mathcal{F} \left\{ u_0(x, y) \right\} \mathcal{F} \left\{ e^{ikz} e^{ikz} (x^2 + y^2) \right\} \right\} \]  \hspace{1cm} (4.1)

To generate final propagated phase image, we performed a weighted incoherent sum over Fresnel propagated images at equally sampled wavelengths along the source spectrum:

\[ I_{\text{sum}} = \sum_k w_k |u(x, y, z; k)|^2 \]  \hspace{1cm} (4.2)

where \( w_k \) are the spectral weights, and \( \sum_k w_k = 1 \).

The final propagated image is shown in fig. 4-2, and a selection of quasi-monochromatic images are presented in fig. 4-3. Intensity plots along the cross-section of the sphere are presented in fig. 4-4. We see that for second and higher-order fringes, there is a large amount of interference between different energies. However, the first fringe constructively interferes at all energies.

To correlate the measured intensity with the value reconstructed by TIE, we simulated both forward propagation and phase retrieval using the transport of intensity equation. Instead of using Fresnel propagation, we use the TIE as a model for propagation, and assume quasi-monochromatic illumination at the spectrally weighted mean wavelength, resulting in the image shown in fig. 4-5. Next, we apply TIE as a phase retrieval method, and apply TIE retrieval to both the Fresnel propagated and TIE propagated images. The results are shown in fig. 4-6. We see that there is a good agreement between TIE and Fresnel propagation at the propagation distances chosen. In addition, the TIE model successfully retrieves phase when Fresnel propagation is used. The resultant low error rates (RMSE = 0.00128) show that the TIE provides an accurate estimation of the phase effects in this near-field regime.
(a) Mean intensity image

(b) Fringe pattern at edge of sphere

(c) Individual spectral components

(d) Fringe pattern of spectral components. Note the constructive interference of the first fringe

Figure 4-4: Cross-sectional intensity plots
Figure 4-5: TIE propagated intensity image, taken at the spectrally weighted mean wavelength.

Figure 4-6: Phase retrieval using the TIE
4.2 Effect of partial coherence

We have shown in section 2.4.3 that for partially coherent illumination, the TIE retrieves the optical path length the sample of interest. In this section we demonstrate this empirically. We model a microfocus source with a gaussian beam profile and a 5 μm spot size. As shown in fig. 4-7, the partial coherence manifests as a blurring of the propagated intensity image, and upon retrieval, acts as a blurring of the retrieved image.

4.3 X-ray phase imaging simulator

While Fourier implementations of Fresnel diffraction are relatively fast, they require a minimum spatial sampling to prevent aliasing of the Fresnel kernel. This sampling
limit is determined by the imaging parameters as well as phase boundaries within the object. If the Fresnel kernel is aliased, the fringes that we rely on for phase imaging may be incorrectly generated. Voxelized phantoms, which are the norm for reconstruction, require careful discretization to avoid strong phase artifacts. At X-ray energies, the spatial resolution required is typically on the order of 1 μm. Therefore, to simulate a body-scale object, which may be on the order of 20 cm × 20 cm × 20 cm, a voxel grid of 200,000^2 = 4 × 10^{10} voxels are required to prevent aliasing of the Fresnel kernel.

Current methods for X-ray simulation include ray-tracing [26, 174] and Monte Carlo methods [148]. While these methods are the current gold standards for computing dose and attenuation signal, these methods do not account for the coherent scatter and diffraction effects which give rise to phase signal.

To create a scalable simulation system, we propose a surface-based X-ray simulation platform. Instead of representing the object in a voxelized manner, we represent the object as a collection of non-uniform rational B-splines (NURBS). The NURBS formalism is presented in appendix B. Since the majority of phase signal comes from interfaces between different refractive indices, the NURBS model is a suitable model for representing the signal.

As described in 2.3, X-ray phase imaging techniques can image the phase, the gradient of phase, or the laplacian of phase. Therefore, in designing our simulator, we emphasized the ability to compute all three.

4.3.1 Scattering approximation using the first Rytov approximation

We utilize the Rytov solution the wave equation, which is valid when the object satisfies the slowly varying phase approximation, that is:

$$|\nabla \phi(x, y, z)|^2 \ll Q(x, y, z)$$

(4.3)

Then, the first Rytov approximation provides a simple relationship between object
phase and scattering potential:

\[
\mathcal{F} \{ \phi \} (k_x, k_y, k_z) = \frac{\exp(2\pi i k_z z) \mathcal{F} \{ Q \} (k_x, k_y, k_z)}{4\pi i (k_z + k)} \quad (4.4)
\]

\[
Q(x, y, z) = k^2 (1 - n(x, y, z))^2 \quad (4.5)
\]

where \( Q \) is the scattering potential, \( \phi \) is the phase map at the detector, \( k = \lambda^{-1} \) is the wavenumber, \( k_x \) and \( k_y \) are spatial frequencies at the detector coordinate, and \( k_z \) is a projection onto the Ewald sphere, as shown in [42]: 

\[
k_z = \sqrt{k^2 - k_x^2 - k_y^2 - k^2}.
\]

To adapt this description to NURBS, we consider the case where \( Q \) is given by a superposition of homogeneous nested volumes with nonintersecting surfaces.

\[
Q(x, y, z) = \sum Q_i \chi_i(x, y, z) \quad (4.6)
\]

where \( Q_i \) is the homogeneous scattering potential, and \( \chi_i \) is the support function of the sub-volume.

The Fourier transform of \( Q \) is then the superposition of the Fourier transforms of each sub-volume, each given by:

\[
\mathcal{F} \{ \chi_i(x, y, z) \} (k_x, k_y, k_z) = \iiint e^{-2\pi i (k_x x + k_y y + k_z z)} dx dy dz \quad (4.7)
\]

This is equivalent to integrating the function \( e^{-2\pi i (k_x x + k_y y + k_z z)} \) over the volume, so we can apply the divergence theorem to express eq. (4.7) as a surface integral:

\[
\mathcal{F} \{ \chi_i(x, y, z) \} (k_x, k_y, k_z) = \int_S F \cdot dS \quad (4.8)
\]

\[
F = \frac{1}{3} e^{2\pi i (k_x x + k_y y + k_z z)} \begin{bmatrix}
x \sin(k_x x) \exp(i\pi k_x x) \\
y \sin(k_y y) \exp(i\pi k_y y) \\
z \sin(k_z z) \exp(i\pi k_z z)
\end{bmatrix}
\quad (4.9)
\]

Now consider that each \( Q_i \) can be defined using a NURBS surface as described in eq. (B.8). To easily evaluate eq. (4.8), we rewrite it over the knot vectors \((u, v, \text{which} \)
traverse the surface:

$$\mathcal{F} \{ \chi_i(x, y, z) \} = \iint F(u, v) \cdot \left( \frac{\partial S_n(u, v)}{\partial u} \times \frac{\partial S_n(u, v)}{\partial v} \right) dudv$$

The surface normal $S_n(u, v)$ can be evaluated using methods described in [127] and the integral can be numerically evaluated using methods described in [133]. For a NURBS surface of order 3, Simpson’s 3/8 rule can be used to compute the exact value of eq. (4.8).

### 4.3.2 GPU Acceleration

While our simulator is very memory-efficient compared to current the Fresnel-diffraction method (the entire NURBS model only occupies a hundred megabytes of memory), it is very computationally intensive. Using a single Intel i7 CPU, each simulation would take months to complete.

In the past 6 years, graphics processing units (GPUs) have garnered considerable in high performance computing research as a cheap alternative to clusters for scalable, computationally intensive tasks. A modern server-grade CPU may be able to perform 300 billion floating-point operations per second (GFLOPS), while the current batch of consumer GPUs can 9000 GFLOPS of computing power per chip, at less than half the price. In addition, most PCs can support 4-8 GPUs at a time, while only costly server motherboards can accommodate more than a single CPU.

To increase the speed of the algorithm, the NURBS model code was implemented on a system with four NVIDIA Tesla C2050 GPUs. While GPUs are capable of very high computational throughput, algorithms must be properly designed to take advantage of the architecture while mitigating weaknesses.

The computation of $\phi$ can be parallelized for each pixel on the detector, and can be further subdivided into tasks for each NURBS surface composing the model. This form of computation is also known as MapReduce [41], and is extremely efficient to perform on GPUs [154, 70]. A weakness of GPU architecture is memory bandwidth and latency. While CPU computation enjoys the benefit of rapid access to memory...
resources in the form of L1, L2, and L3 cache, GPU computation must be carefully memory managed to maximize precious shared memory resources. By pooling multiple pixels into a grouped process, we maximized shared memory resources between adjacent pixels. By streaming the NURBS surfaces into the GPU during computation, our model is capable of simulating objects of arbitrary complexity.

As a result of our GPU implementation, the computational time required for each computation was decreased by about 300 times, over 2 orders of magnitude. In practice, the complete simulation of a human chest took about 2 weeks to complete.

4.3.3 Simulation results

Figure 4-8 shows the simulation pathway for creating X-ray phase images. The scattering potential is encoded using material properties and object geometry. The scattering potential is then projected onto points on the Ewald sphere corresponding to the spatial frequency sampling of the detector.

To simulate our object, we use the 4-D extended cardiac torso (XCAT) phantom [147], which is a NURBS-based phantom that represents a parametric, time-varying human torso. The XCAT phantom is composed of approximately 2000 NURBS surfaces, which can be fed into our simulation model.

We simulated attenuation and phase contrast images for a whole human chest. To achieve this, we utilized roughly 600 NURBS surfaces which represented the gross anatomy of a human chest, and assigned suitable refractive index values to each surface based on material composition. For each NURBS surface, the contribution to amplitude and phase at the detector plane are calculated, and the final image is the taken as the coherent sum of the contribution of each surface. The simulation was performed assuming monochromatic illumination at 70 keV, with a detector pixel pitch of 125 µm, and a propagation distance of 1 m. The resulting amplitude and phase images are presented in fig. 4-9. Note that due to the propagation distance, the intensity images captured at the detector also include diffraction fringes due to free-space propagation.

For grating and analyzer crystal based methods, the gradient of phase is mea-
Figure 4-8: Simulator process. (a) XCAT model of the left anterior descending artery. (b) Schematic diagram of projection onto Ewald sphere and mapping to detector spatial frequency. (c) Magnitude plot of propagated image. (d) Simulated intensity image at 30 keV and $z = 1\text{ m}$. (e) Simulated intensity image at $z = 5\text{ m}$. (f) Cross sectional intensity along the dotted lines in (d) and (e).

Figure 4-9: Simulated amplitude and phase at the detector. Scale bars are 5 cm.
sured instead of the absolute value. Therefore, we also simulate the differential phase contrast (DPC) images, which are shown in fig. 4-10.

In the attenuation images, gross structures such as the cardiac shadow and spine are easily visible, but fine details such as the respiratory tract and coronary vasculature are difficult to visualize. However, in the DPC images, the fine structures in the thoracic cavity are greatly enhanced. However, detailed tissue structures such as muscle fiber and intrapulmonary lobules are not included in the XCAT model, and thus there is some degree of missing texture.
4.3.4 Comparison to X-ray DPC imaging of a frog

While there is currently no way of generating human scale X-ray phase images, we attempt to provide a basis for comparison by imaging an animal analogue. We use an analyzer crystal based imaging method known as X-ray dark-field imaging (XDFI) [9] to retrieve differential phase contrast images of an *in vitro* frog specimen. XDFI, like other analyzer crystal based methods, utilizes a finely cut crystal to filter refracted x-rays from the un-refracted beam. XDFI is capable of providing high-quality DPC imaging, but requires synchrotron radiation to produce the coherence required for the technique to be successful. The results from the DPC study are shown in fig. 4-11. Only a horizontal DPC was taken. We see that like the simulation images, while large structures such as the spine and skull exhibit good contrast on the absorption image, the bronchi and air spaces in the thorax are much better visualized on the DPC image compared to the absorption image. Soft tissue structures such as the tympanic drums and the dorsolateral folds are also significantly enhanced on the DPC.
Chapter 5

Compressive tomography using the phase-attenuation duality

The primary contributions of this thesis are the development of new computational imaging methods for performing projection and tomographic phase retrieval at X-ray wavelengths. Current methods for phase retrieval rely on algorithms which were originally tailored for absorption-based contrast mechanisms. However, in phase retrieval poses it’s own unique challenges and conditions, which must be satisfied to achieve high-quality reconstructions. In this chapter and the following, we will describe our proposed algorithms, which apply computational imaging approaches to the phase retrieval problem.

In this chapter, we adopt the transport of intensity equation (TIE) described in section 2.4.2, which relates the measured intensity to the phase [136]:

$$k \frac{\partial I(x, y, z)}{\partial z} = \nabla \cdot \left[ I(x, y, z) \nabla \phi(x, y) \right], \quad \nabla \perp = \left( \frac{\partial}{\partial x}, \frac{\partial}{\partial y} \right), \quad (5.1)$$

where $I(x, y, z)$ is the intensity image at the propagation distance $z$, $\phi(x, y)$ is the phase map (equivalently, OPL) of the object, and $k$ is the wavenumber. By solving the TIE at multiple angles of exposure, the refractive index distribution of an object can be obtained through tomographic reconstruction. In this way, TIE tomographic reconstruction can be thought of as a two-step problem.
Direct inversion of the TIE tomographic reconstruction problem is ill-posed for two reasons: (1) due to the existence of a zero in the TIE transfer function (the projection component); and (2) undersampling of the object index of refraction distribution in radon space in cases where only a small number of projections are acquired (the tomographic component).

For TIE, the traditional choice of regularizer to relieve the ill-posedness is Tikhonov [22, 27, 65]. However, this type of regularization also strongly deteriorates the low-frequency signal in the phase image. Myers et al. propose inversion of the TIE using prior knowledge that the sample consists of a single material of known refractive index [111]. For tomography, the traditional regularized solution is the filtered backprojection (FBP), which utilizes the ramp filtered dual of the Radon transform. The drawback to this technique is that the quality of FBP reconstructions depends on having a large number of projection angles. Recently, iterative solvers have been shown to relax these requirements, specifically the solvers which exploit the sparsity of the expected tomographic reconstruction [29, 55].

We have previously demonstrated the effectiveness of a single-step TIE based method for compressive X-ray phase tomography of weakly attenuating samples, wherein the TIE and tomographic reconstruction steps are computed in a combined transfer function, and solved using iterative methods [158]. However, this method places a severe restriction on the class of objects suitable for imaging.

We extended this method to account for samples which consist of only light materials, based on the phase-attenuation duality for light materials [177]. The formulation of the TIE solver exploiting the duality is shown in section 5.1. We also demonstrate experimentally in section 5.2 the use of duality to resolve the refractive index of water from that of chemically similar (in terms of Z number) but potentially hazardous materials, such as hydrogen peroxide and acetone; this particular application is potentially significant for security in airports and other controlled spaces.
5.1 Reconstruction process

A schematic diagram of the imaging geometry is presented in fig. 5-1. A microfocus source with a spectrally weighted mean wavelength $\lambda$ is located at the plane $z = -z_0$, and a detector is located at the plane $z = d$. The sample, centered at $z = 0$, is characterized by a complex refractive index $n(x, y, z; \lambda) = 1 - \delta(x, y, z; \lambda) + i\beta(x, y, z; \lambda)$, where $1 - \delta(x, y, z; \lambda)$ and $\beta(x, y, z; \lambda)$ are the real and imaginary parts of the refractive index, respectively. We assume that the geometry of our experiment is such that the beam passing through the object is approximated by a plane wave oriented along the optical axis, and that the interaction between the sample and the field follows the projection approximation.

While TIE is typically formulated using two intensity measurements at different positions along the optical axis [64], the phase-attenuation duality (PAD) approximation allows us to reformulate the TIE such that only one intensity measurement is necessary. We assume that electron interactions are the primary source of x-ray attenuation and phase delay, thus the real and complex components of the complex index are correlated such that $\delta(x, y, z; \lambda)/\beta(x, y, z; \lambda) = \gamma(\lambda)$ [177]. Under paraxial and small-wavelength approximations, the TIE gives the following relationship between the projected phase map of the object, $\phi(x, y)$, and the image of the object at time
the detector, \( I(x', y') \),

\[
g(x, y) = \frac{I(Mx, My)}{I_0} = \left[ 1 + \frac{d' \lambda \gamma(\lambda)}{4\pi} \right] \exp \left[ \frac{2\phi(x, y)}{\gamma(\lambda)} \right],
\]

(5.2)

where \( M = (z_0 + d)/z_0 \) is the magnification at the detector plane, \( d' = d/M \) is the effective propagation distance given by the Fresnel scaling theorem. Equation (5.2) is the discretized form of PAD TIE which uses a single image to retrieve phase. In a tomographic measurement, the sample is rotated about the \( x \) axis such that the projected phase \( \phi \) at a certain angle \( \theta \) is

\[
\phi(x, y; \theta) = \int \int \delta(x, y_s, z_s; \lambda) D(y - y_s \cos \theta + z_s \sin \theta) dy_s dz_s,
\]

(5.3)

where we use \( D(\cdot) \) to denote the Dirac delta function to avoid confusion with the real component of the refractive index. Equation (5.2) along with the forward Radon transform (5.3) provide us with a forward model for describing the image generated on our X-ray detector by our object, and implementation of these operators in the Fourier domain is computationally efficient [100]. To perform direct reconstruction, eq. (5.2) can be inverted using the Fourier domain solution to Poisson’s equation, and (5.3) can be inverted using the Fourier slice theorem implementation of FBP as

\[
\phi(x, y) = \frac{\gamma(\lambda)}{2} \ln \mathcal{F}_\text{2D}^{-1} \left\{ \mathcal{F}_\text{2D} \left\{ \frac{I(x, y)}{I_0} \right\} \frac{1}{1 + \pi z \lambda \gamma(\lambda) |u^2 + v^2|} \right\},
\]

(5.4)

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

(5.5)

where \( u, v, \) and \( w \) are spatial frequency variables, and \( \mathcal{F}_\text{1D} \) and \( \mathcal{F}_\text{2D} \) both denote Fourier transforms but in two different domains: the former is for applying the Fourier slice theorem in tomography and, hence, it operates along the projection coordinate variable; whereas the latter applies to the lateral plane \( (x, y) \). The superscript \( \mathcal{F}^{-1} \) denotes the inverse Fourier transform correspondingly in the two cases.

To perform iterative reconstruction, we utilize a modified form of our approach
in [158], which we will summarize here. The detector is assumed to consist of an $N \times N$ grid of square pixels of side length $M \Delta$. Let $\Theta$ denote the number of angular projections. Then the measured projections $g$ at all angles may be arranged into a real-valued vector $g$ of length $N^2 \Theta$. The refractive index of the object will also be discretized into a $N \times N \times N$ cube width side length $\Delta$, packed into a complex valued vector $n$. Then let $P$ and $R$ denote operators corresponding to the discretized forms of eqs. (5.2) and (5.3), respectively, such that

$$g = P R n \equiv A n$$  (5.6)

where the operator $A$ is the cascade of the linear operators $P$ and $R$. If $n$ is sparse in some basis, as it often is the case in tomography, then eq. (5.6) can be solved using compressive reconstruction [29, 55, 14]. Specifically, total variation (TV) minimization has been shown to be an effective sparsity basis for tomographic reconstruction:

$$\hat{n} = \arg \min_n ||n||_{TV} \text{ such that } g = A n$$  (5.7)

where the TV norm is defined as $||n||_{TV} = \sum_n \sqrt{ (\nabla_x n)^2 + (\nabla_y n)^2 + (\nabla_z n)^2 }$, and $\nabla_x$, $\nabla_y$, and $\nabla_z$ are the finite difference operators in Cartesian coordinates [142]. We use the two-step iterative shrinkage/thresholding algorithm (TwIST) to solve the minimization [14].

### 5.2 Discrimination of liquid samples

To investigate tomography and identification of liquids with similar density profiles but differing chemical compositions, we imaged four Eppendorf tubes containing water, hydrogen peroxide, acetone, and air. Water and hydrogen peroxide are chemically similar to one another, and therefore their absorption signatures are also essentially indistinguishable. Acetone and hydrogen peroxide are both common components used in explosive synthesis. The air filled tube was added as a control.
Figure 5-2: A projection image of the sample (a), with its profile (b) showing significant white noise at the detector level.

A total of 72 projections were taken, with source-to-detector distance 2.159 m and source-to-object distance 0.635 m. The X-ray microfocus source (Hamamatsu L8121-03) was set to 7µm spot size, 100 kVp, and 100µA. The spectrally weighted mean energy of 46 keV was used to determine k in phase reconstruction.

These experiments showed that X-ray phase imaging allows for far higher sensitivity than standard absorption contrast (figs. 5-2 and 5-3). In fig. 5-3, we see that absorption based tomography is heavily noise-corrupted, and does not provide sufficient visual information to distinguish between water and hydrogen peroxide, while compressive phase reconstruction can clearly distinguish between the two samples. To quantify this difference, we measured a peak signal-to-noise ratio (PSNR) of 3 dB in a conventional CT, while obtaining a PSNR of 38 dB in our phase CT, with all other experimental parameters constant, a SNR gain of 35 dB.

In a Student’s T-test comparison between phase and attenuation based imaging, both methods were able to achieve discrimination with the full CT data, though phase was able to provide much higher certainty in the signal region (P < 0.010 for absorption, P < 6.79 × 10⁻⁷ for phase). Taking only 100 randomly sampled voxels from each CT (after segmentation), intensity based CT could only distinguish water and peroxide in 26% of tests, meaning rejection of the null hypothesis at the 5% significance level, while phase based CT could distinguish the two liquids in 100% of tests.
Figure 5-3: Reconstruction results. (a) Filtered backprojection, (b) compressive PAD TIE, (c) plot along line in (a), and (d) plot along line in (b). These reconstructions show cross sections of the Eppendorf tubes containing the liquids taken along the plane coinciding with the line in Section 5.2.

5.3 Verification using a mouse phantom

To confirm the appropriateness of our method for medical imaging, we imaged the CIRS micromouse phantom described in section 3.4.3. The mouse phantom was imaged using a much longer acquisition protocol than the liquid samples to mimic current standards for medical CT. A total of 300 projection angles were taken, with a source-to-detector distance of 1.5 m and a source-to-object distance of 0.56 m. The resultant effective propagation distance was 35.14 cm, and the effective pixel size was 18 μm. The X-ray microfocus source was operated at a spot size of 20 μm, at 60 kVp and 500 μA. The exposure time at each angle was 3 s, resulting in an overall
acquisition time of 15 min. The resultant exposure is 1.5 mA s at each angle, and 450 mA s over the entire tomography. Based on experimental values for patient dose in cone beam CT [76], the dose to the phantom was on the order of 40 mGy, which is similar to current in vivo protocols for preclinical CT.

Reconstruction results for conventional absorption and compressive phase CT are shown in figs. 5-5 to 5-7. To reconstruct the absorption image, a standard iterative reconstruction is performed using SIRT, with the constraint that absorption values cannot fall below that of $-1000 \text{HU}$, i.e. air. To reconstruct the phase image, we utilize our compressive tomographic algorithm. In absorption tomography, we were able to successfully identify all rods except for muscle. In phase contrast, all rods were visualized, as seen in fig. 5-6. We see that the compressive phase reconstruction exhibits significantly lower artifacts and noise than conventional absorption reconstruction. To quantify this difference, we computed the statistics of the ROIs shown in section 5.3, which are compiled in table 5.1.

Since each rod can be assumed to be a homogeneous material, the standard deviation in each ROI provides an estimate of the noise present in the reconstruction. We see that on average, the compressive phase reconstruction increases the SNR by a factor of $\sim 5$ for soft tissues and $\sim 2$ for bone. Furthermore, we see that for
Absorption reconstruction

Phase reconstruction

(a) Reconstructed absorption image using SIRT
(b) Reconstructed phase image using compressive phase-attenuation duality tomography

Figure 5-5: Reconstruction results using experimental X-ray phase imaging system

soft tissues, including muscle, adipose, and 0 mg/cc HA, while there is ambiguity between the absorption measurements (i.e. muscle is difficult to distinguish from water (43 ± 59 HU vs. 0 ± 61 HU) and adipose is difficult to distinguish from 0 mg/cc HA (196 ± 61 HU vs. 134 ± 51 HU), this SNR increase is sufficient to fully differentiate all three tissues using just visual inspection. To quantify the detection capability of each imaging method, we use two metrics for determining visibility: the contrast-to-noise ratio (CNR), and the Kolmogorov-Smirnov test. The CNR is widely used in medical imaging as a means to evaluate the visibility of objects by relating the apparent contrast between two regions and the pure image noise\(173, 166\). The CNR for two signals \(S_A\) and \(S_B\) is defined as:

\[
CNR_{AB} = \frac{S_A - S_B}{\sigma_0}
\]  

(5.8)

where \(\sigma_0\) is the pure image noise. The CNR can be thought of as the difference between the SNRs of the two signals \(S_A\) and \(S_B\). In general, humans have difficulty distinguishing signals with a CNR of lower than 1. The Kolmogorov-Smirnov test, or KS test, is a well-known test for whether or not two samples belong to the same or different distributions. The two-sample KS test statistic quantifies the distance
between the empirical distribution functions of the two samples. For two samples $S_A$ and $S_B$, the KS test statistic is defined as:

$$D_{AB} = \sup \left| \frac{1}{n_A} \sum I_{[-\infty,x]}(S_A) - \frac{1}{n_B} \sum I_{[-\infty,x]}(S_B) \right|$$

(5.9)

where $I_{[-\infty,x]}(X)$ is the indicator function equal to 1 if $X_i \leq x$ and 0 otherwise. The KS test is particularly useful in image analysis because it does not make any assumptions about the distributions that the two samples originate from; the test only checks whether or not the two samples originated from the same distribution. The null hypothesis can be checked at different confidence intervals by testing the following inequality:

$$D_{AB} > c(\alpha) \sqrt{\frac{n_A + n_B}{n_A n_B}}$$

(5.10)

where $c(\alpha)$ is a parameter at each confidence interval $1 - \alpha$. For $\alpha = 0.01$, this value is 1.63, and for $\alpha = 0.001$, this value is 1.95. The statistical results are summarized in table 5.2.

Based on these statistics, the advantage of phase imaging is clear. For CNR, there is a uniform gain of a factor of 2 for water vs. any of the sample materials, but the
Figure 5-7: Images showing (a) the path used to measure rod profiles, (b) the ROIs used in to measure quantities in table 5.1, (c) the absorption profile along (a), and (d) the phase profile along (a).
<table>
<thead>
<tr>
<th>Material</th>
<th>Absorption (HU)</th>
<th>Phase (HU)</th>
<th>Relative nuclear density (H₂O)</th>
<th>Relative electron density (H₂O)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Air</td>
<td>−1000 ± 16</td>
<td>−1000 ± 9</td>
<td>0.000</td>
<td>0.000</td>
</tr>
<tr>
<td>Water</td>
<td>0 ± 61</td>
<td>0 ± 29</td>
<td>1.000</td>
<td>1.000</td>
</tr>
<tr>
<td>750 mg/cc HA</td>
<td>2731 ± 107</td>
<td>2802 ± 42</td>
<td>3.731</td>
<td>1.481</td>
</tr>
<tr>
<td>250 mg/cc HA</td>
<td>1014 ± 76</td>
<td>1008 ± 51</td>
<td>2.014</td>
<td>1.205</td>
</tr>
<tr>
<td>50 mg/cc HA</td>
<td>92 ± 56</td>
<td>91 ± 10</td>
<td>1.092</td>
<td>1.094</td>
</tr>
<tr>
<td>0 mg/cc HA</td>
<td>−134 ± 51</td>
<td>−143 ± 11</td>
<td>0.866</td>
<td>1.066</td>
</tr>
<tr>
<td>Muscle</td>
<td>43 ± 59</td>
<td>39 ± 15</td>
<td>1.043</td>
<td>1.043</td>
</tr>
<tr>
<td>Adipose</td>
<td>−196 ± 61</td>
<td>−195 ± 11</td>
<td>0.804</td>
<td>0.949</td>
</tr>
<tr>
<td>Lung</td>
<td>−668 ± 61</td>
<td>−667 ± 19</td>
<td>0.332</td>
<td>0.204</td>
</tr>
</tbody>
</table>

Table 5.1: ROI analysis of mouse phantom

<table>
<thead>
<tr>
<th>ROI 1</th>
<th>ROI 2</th>
<th>CNR</th>
<th>KS statistic</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Absorption</td>
<td>Phase</td>
</tr>
<tr>
<td>Water</td>
<td>Water</td>
<td>45.04</td>
<td>96.27</td>
</tr>
<tr>
<td>Water</td>
<td>250 mg/cc HA</td>
<td>16.73</td>
<td>34.62</td>
</tr>
<tr>
<td>Water</td>
<td>50 mg/cc HA</td>
<td>1.52</td>
<td>3.12</td>
</tr>
<tr>
<td>Water</td>
<td>0 mg/cc HA</td>
<td>2.22</td>
<td>4.90</td>
</tr>
<tr>
<td>Water</td>
<td>Muscle</td>
<td>0.70</td>
<td>1.35</td>
</tr>
<tr>
<td>Water</td>
<td>Adipose</td>
<td>3.24</td>
<td>6.71</td>
</tr>
<tr>
<td>Water</td>
<td>Lung</td>
<td>11.02</td>
<td>22.91</td>
</tr>
<tr>
<td>Adipose</td>
<td>Muscle</td>
<td>4.08</td>
<td>16.01</td>
</tr>
<tr>
<td>Adipose</td>
<td>0 mg/cc HA</td>
<td>1.01</td>
<td>4.91</td>
</tr>
<tr>
<td>Muscle</td>
<td>50 mg/cc HA</td>
<td>0.84</td>
<td>4.97</td>
</tr>
</tbody>
</table>

Table 5.2: Signal quality metrics

real benefit is the increase in contrast between different soft-tissues. We see that in particular, for adipose-muscle, adipose-0 mg/cc HA, and muscle-50 mg/cc HA, there is a CNR increase of a factor of 4-6. This is expected, as the benefits of phase imaging lie primarily in increasing soft-tissue contrast.

In terms of the KS test statistic, we see that phase imaging only provides a non-unity KS statistic in one case, water-muscle, while absorption imaging only provides KS statistics of unity for high concentration HA and water-lung. The KS statistic provides some insight into the similarity between two ROIs. Under the KS statistic, the criteria for rejection the null hypothesis (i.e. differentiating two ROIs as being different materials) depends on the sample size, with larger sample sizes being required for lower KS statistics. This is a direct consequence of eq. (5.10). In other words,
more pixels are required to differentiate between materials when the KS statistic is lower. Therefore we conclude that phase imaging should produce better soft-tissue discrimination for thin or fine features, such as the fibrous cap of an atheroma.

5.3.1 Comparison to commercial microCT

To correlate our results current standards of imaging, we then imaged the mouse phantom using a GE CT 120 preclinical MicroCT (fig. 5-8). The images were captured using the soft-tissue imaging protocol, for which the parameters are summarized in table 5.3. The resulting dose is 1.6 mA s at each angle and 352 mA s overall exposure. While this is a lower quantity than our experimental system, the detector in the GE CT 120 is also most likely a higher performance detector than the Shad-o-box 4K, which somewhat offsets the difference in exposure time. Furthermore, the center of rotation of the GE system is significantly closer than in our experimental system,
Figure 5-9: Axial slice of mouse phantom imaged in a Varian 7T preclinical MRI

further reducing the relative dose gap. Since the differences in source construction, filtering, and detector collimation are difficult to reconcile between the two systems, we consider this a qualitative comparison rather than a quantitative one.

As seen in fig. 5-8, the microCT produces similar results to attenuation-based tomography. The lack of beam-hardening artifact can be accounted for by the use of filters for the microCT source (our system does not use any filters) as well as proprietary beam hardening correction algorithms that may be used in the GE reconstruction software. As expected, the HA rods and lung insert are clearly visualized, and adipose is marginally visualized. However, muscle and 0 mg/cc HA demonstrate extremely reduced contrast-to-noise, and are virtually impossible to see on the resulting reconstruction. We conclude that the results obtained from our system far outperform this commercial microCT system.

5.3.2 Comparison to MRI

We have attempted to compare the results from our experimental system to MRI, but due to the lack of water content in the phantom, individual rods are not visualized at all by MRI systems. In particular, while the mouse phantom uses a tissue-equivalent material that mimics the atomic density and electron density of tissues, the rods themselves do not have a sufficient proton density to produce comparable MRI signals to their tissue equivalents. In MRI, the imaging signal depends on the oscillation
of protons, usually hydrogen atoms in water. However, since the resins used in the micromouse phantom have a low hydrogen content, no significant signal enhancement occurs.

Imaging results using a 7T Varian preclinical MRI are presenting in fig. 5-9. We see that there is exceptionally low proton density in each rod of the mouse phantom, making them essentially indistinguishable from air.

5.4 Compressive tomography of an artery specimen

To evaluate the performance of our algorithm in visualizing atherosclerotic plaque from few views, we obtained and imaged in vitro samples of a human common iliac artery with extensive atherosclerosis. The artery sample was obtained from MGH after IRB approval, and was harvested from discarded tissue from a routine autopsy. The sample was fixed and embedded in paraffin wax for stability. For this experiment, the source was operated at 100 keV and 100 μA. Tomographic images were taken at an angular step size of 2.5 s, resulting in 72 images over a 180° arc. The exposure time at each angle was 6.7 s, with an overall exposure of 42 mA s.

The results of both conventional X-ray CT and compressive X-ray phase CT
Figure 5-11: Comparison of SIRT reconstruction of projection-domain phase retrieval and our compressive technique for phase retrieval. Images show areas of the artery wall where streaking is evident in the SIRT reconstruction. In the compressive reconstruction, the streak artifacts virtually eliminated.

are presented in fig. 5-10. While the calcification is readily visible on absorption reconstruction, the remainder of the artery specimen is difficult to visualize. On the other hand, the artery specimen is easily seen on phase reconstruction, and the full structure of the atherosclerotic plaque can be readily appreciated. A comparison between our compressive technique and standard tomographic phase imaging is also given in fig. 5-11. We observed a significant reduction in both streak and ringing artifacts in our reconstruction, as well as better delineation of the artery structure.

We note that the calcification appears larger in the phase image compared to the absorption image. This artifact is caused by a violation of the phase attenuation duality assumption, as calcium is not a light material, and thus, the assumed ratio of $\gamma$ is incorrect for this region of the object. In reality, elements with higher atomic numbers will have much higher absorption than their electron density would suggest and, as a result, PAD ascribes a much higher value of phase than usual. This results in a “phase sink” phenomenon in the reconstructed image, as the phase retrieval algorithm attempts to compensate for the model mismatch. However, since absorption imaging adequately retrieves the attenuation of calcified regions, the absorption image can be used in conjunction with the phase image to provide visualization of dense structures.
Figure 5-12: Histopathological correlation. A 5 μm thick slice of the artery sample was stained using hematoxylin and eosin. The corresponding slice in the phase reconstruction is shown, and we observe extremely good correlation between histology and phase imaging.

We have verified our results by correlating phase imaging results to histopathology. A 5 μm thick section of the artery was stained using hematoxylin and eosin, and microscopy results were compared against our phase imaging results in fig. 5-12. We observed extremely good correlation between our phase imaging results and microscopy images, indicating that the signal measured was not spurious, but a reflection of the anatomy.

Qualitatively, phase CT provided significantly better visualization of the artery structure than the absorption. The fibrous cap and lipid core (along with artifacts due to fixation) were visible in both histology and phase imaging, but not absorption imaging. Even the delamination of the artery wall near the top of fig. 5-12 is visualized.

One potential concern is the use of paraffin to encase the artery. If paraffin has a significantly different electron density from soft tissue, contrast may be artificially enhanced. Paraffin is primarily composed of hydrocarbons of the form \( C_nH_{n+2} \), with the most common form being \( C_{31}H_{64} \), which has an electron density of \( 3.13 \times 10^{23} \text{ cm}^{-3} \), or a relative electron density to water of roughly 0.94, which is similar to the electron density of adipose tissue, which is 0.95. Smooth muscle cells typically have a relative
electron density of roughly 1.04. Therefore, our imaging experiment accurately captures the contrast between adipose tissue and muscle. In the case of atherosclerotic disease, the primary concern is the ability to image the atheroma, which is comprised of a necrotic core which is largely lipid-based. We believe that these results demonstrate that phase imaging can adequately image the necrotic core, given that paraffin is similar in electron density to adipose tissue.

5.4.1 Comparison to MRI

While most MRI systems lack the resolution to visualize atheromas, 7T MRI systems are capable of providing resolutions on the order of 100 μm. Therefore we imaged a separate set of iliac arteries to provide a qualitative point of comparison for our X-ray phase imaging system. The arteries were obtained from discarded tissue from routine autopsy at MGH, and fixed in a 10% formalin bath before being sealed in microtubes. MRI results are presented in fig. 5-13. We see that while tissue enhancement on T1 is relatively poor, T2 weighted imaging produces good contrast between tissue components. However, tissue contrast in MRI often changes drastically [146], so the contrast in living tissue may differ. For the microMRI system, 2 minutes of imaging time was required to obtain the T1 weighted images, and 15 minutes was required to obtain the T2 weighted images. The final reconstructions
had a resolution of $128 \times 128 \times 10$, with a voxel size of $117, \times 117, \times 500$, far lower than the $2048 \times 2048 \times 2048$ resolution and $17 \times 17 \times 17$ voxel size produced by the X-ray phase imaging system.

### 5.5 Preclinical imaging

While the primary focus of this thesis is the study of human-scale imaging, X-ray phase imaging is also relevant to the field of pre-clinical imaging. To investigate the usefulness of our system for preclinical imaging experiments, we imaged a C57BL/6 mouse immediately after sacrifice.

For this imaging study, the microfocus source was operated at 100 kVp, with a tube current of 500 μA. The tomography was taken over 500 angles of exposure, with an exposure time of 6.7 s at each angle. The overall current budget was was 1675 mA s. The size of this dataset was particularly large, with a sinogram dimension of $2048 \times 2048 \times 500$ and a reconstruction volume of $2048^3$. The source-to-object distance was 313.4 mm and the source-to-detector distance was 882.0 mm. The magnification was 2.81, resulting in an effective field of view of 4 cm and an effective pixel size of 17 μm.

Reconstruction results are presented in figs. 5-14 to 5-16. We see that again, phase provides a significant enhancement of soft-tissue features, and our compressive reconstruction method is able to greatly reduce the streaking artifacts caused by calcifications, as well as ring artifacts. For example, in fig. 5-17, we can see that while the absorption image has significant streak and ringing artifact, the compressive phase reconstruction significantly reduces reconstruction artifacts while preserving detail in the fine tissue structures. Furthermore, due to the abundance of air interfaces in the intestines, there is a large amount of uncorrected scatter in the absorption reconstruction. In the phase reconstruction, which accounts for diffraction effects, these artifacts are significantly reduced. The next view of interest is the heart, which is shown in fig. 5-18. Again, the streaking artifact due to the presence of the spine makes the absorption image significantly more difficult to interpret, while the phase image
(a) Absorption reconstruction using (b) Phase reconstruction using our compressive algorithm.

Figure 5-14: Axial slices of an in vitro mouse, showing (top) thoracic, (middle) mid-abdominal, and (bottom) lower-abdominal views.
provides a clear view of both the left and right ventricles, as well as the surrounding pulmonary vasculature. A lung window is shown in Fig. 5-19, where we see that phase imaging provides improved visualization of finer vasculature and airways. Note that similar to the case of the intestinal tract, there is a significant amount of scatter signal that remains uncorrected in the absorption images. Typically this effect is reduced through the use of anti-scatter grids. However, the use of these grids results in a significant amount of attenuation of the X-ray beam. This attenuation is quantified by the Bucky factor of the grid, which is the reciprocal value of the transmittance of the grid [137, 152]. Typical Bucky factors range from 4–16, resulting in an increase in quantum noise by a factor of 2–4 times. Here, we see that we are able to correct for scattered signal (which is largely due to propagation effects) using phase retrieval.

These results show that X-ray phase contrast tomography has significant potential
in the medical imaging applications. Radiologists can use X-ray phase CT as part of pulmonary exams, to differentiate between a variety of possible causes of dyspnea (e.g. asthma, pneumonia, cardiac ischemia, interstitial lung disease, congestive heart failure, or chronic obstructive pulmonary disease, to name a few) some of which may look similar on a chest X-ray, but may be easily distinguished on X-ray phase CT.

5.5.1 Comparison to commercial microCT

After phase imaging, the mouse was imaged using the same GE CT 120 scanner used in section 5.3. We used the in vivo imaging protocol, which is summarized in table 5.3.

Images are presented in fig. 5-20. As in section 5.3, we see that while the absorption reconstruction results from our system exhibit similar amounts of noise to the absorption results of the microCT scanner, our phase reconstruction are of significantly higher quality. The liver and heart are noisy in the microCT results, and while large airspaces such as gas within in intestines are well resolved, the airways and vasculature of the lungs are very poorly resolved on microCT, with only the larger airways being visible. Contrast this to fig. 5-19, where a substantial amount of the parenchymal structure of the lungs is visible.
5.6 Discussion

We have demonstrated a technique for quantitative phase contrast tomographic reconstruction, and our results show a significant gain in contrast enhancement compared to its conventional counterpart. Our system produces results that are comparable to current standards of preclinical imaging in the absorption case. Based on this, we conclude that our phase imaging system produces superior results to which are not attributable to hardware differences, but due to the manner in which signal is retrieved by our system.

Furthermore, the compressive nature of our reconstruction greatly reduces the number of images required for reconstruction, requiring only a fraction of the number of images required for a conventional absorption scan. To that end, we have applied our technique to detect small differences in phase content between two radiographically similar objects, showing a clear distinction between water and hydrogen peroxide. While absorption imaging was still able to distinguish hydrogen peroxide from water given a full CT reconstruction, phase imaging is able to produce the same confidence in measurement in a much smaller sample, such as in the case of an incomplete CT reconstruction, and has significant potential applications in the radiographic detection of hazardous materials.
Figure 5-19: Axial views of the lungs. Due to the positioning of the mouse, the torso was slightly twisted, resulting in a much more prominent right lung in this view. Certain bronchi and vasculature, such as those indicated by the arrows, are significantly enhanced on the phase reconstruction.

We next applied our system to a medical imaging phantom to demonstrate the capabilities for soft-tissue contrast. The phase imaging mode of the system was shown to produce significantly increased soft-tissue contrast, and was able to successfully distinguish all components of the phantom. We then compared our system to a commercial-grade microCT, and demonstrated that with comparable dose, we were able to achieve significantly higher performance.

After verification of our system, we show experimental results for compressive tomography of a human artery specimen with atherosclerosis. These results demonstrate that while conventional absorption contrast is only capable of identifying calcifications in an artery, our compressive phase contrast algorithm is able to delineate the atheroma from surrounding tissue, and correlate our results with histology.

Finally, we demonstrate the utility of phase in preclinical imaging, and image an in-vitro mouse. We show how phase enhances the signal in several physiologically relevant organs, including the gastrointestinal tract, the lungs, and the heart.
Figure 5-20: MicroCT results for *in vitro* mouse: (left) axial slices of an *in vitro* mouse, showing (top) thoracic, (middle) mid-abdominal, and (bottom) lower-abdominal views; (top right) coronal and (middle right) sagittal views; (bottom right) Axial slice of heart and lungs.
Chapter 6

Simultaneous retrieval of object phase and attenuation

In the previous chapter, we demonstrated techniques which in essence, reconstructed only the phase signal. Our reconstructions were augmented by priors about the object, but the phase retrieval component consists of a treatment of a single signal vector. However, both the attenuation and phase signal have value. The work in this chapter is based on the intuition that the absorption and phase signal are intimately linked, and by considering the relationship between the absorption and phase signature, a better reconstruction for both can be obtained.

As we have discussed in previous chapters, a vast majority of propagation-based X-ray phase imaging methods use a single propagated image, and rely on assumptions of homogeneity and pure phase, or priors such as phase-attenuation duality [28]. These constraints, however, limit the ability to image more complex samples. In the original formulation of the TIE, the derivative term is estimated through the finite difference

![Image](image.png)

Figure 6-1: Imaging geometry for TIE.
of two intensity images at different propagation distances [156]:

$$\frac{I_2(M_2x, M_2y) - I_1(M_1x, M_1y)}{d'_2 - d'_1} = \frac{\lambda}{2\pi} \nabla_{\perp} \cdot (I_1(x, y)\nabla_{\perp} \phi_d(x, y)), \quad (6.1)$$

where $\nabla_{\perp}$ is the gradient operator in the $(x, y)$ plane, $\phi_d$ is the phase at the detector plane, $I_1$ and $I_2$ are the two normalized intensity images, $d'_1$ and $d'_2$ are their effective propagation distances given by the Fresnel scaling theorem, and $M_1$ and $M_2$ are their respective magnification factors. Note that the retrieved phase image is not at the sample plane, but at the detector plane. However, since both intensity and phase are known after reconstruction, direct propagation can be used to determine the phase at the sample plane, as we have described in section 2.4.1. By using multiple images obtained at different propagation distances, we can explicitly decouple attenuation and phase without restrictive assumptions.

By solving the TIE at multiple angles of exposure, the refractive index distribution of an object can be obtained through tomographic reconstruction. In this way, TIE tomographic reconstruction can be thought of as a two-step problem.

Direct inversion of the TIE, however, is ill-posed and highly susceptible to noise. We propose two iterative compressive methods for solving the TIE for retrieval of non-pure phase objects; first in the projection domain by applying a smoothness constraint regularizer based on the spatial gradient of the intensity image, then in the tomographic domain by an iterative method that seeks to retrieve both the absorption and phase images using a mutual-information maximizing regularizer.
6.1 Structural-similarity regularization of TIE

We formulate the forward linear problem as

\[ b = Ax, \] (6.2)

where \( b \) and \( x \) are the left hand side of eq. (6.1) and phase image \( \phi \), respectively, arranged as vectors, and \( A \) is the discretized TIE operator in eq. (6.1).

The Fourier implementation of the TIE has the following form:

\[
\mathcal{F} \left\{ \frac{\partial I(x, y)}{\partial z} \right\} = 2\pi \lambda \left| u^2 + v^2 \right| \mathcal{F} \{ \phi(x, y, 0) \}\]

(6.3)

where \( \frac{\partial I(x, y)}{\partial z} = [I(x, y, d_z) - I(x, y, 0)]/d_z \) is the axial derivative of the intensity approximated by finite differencing is the propagation distance, \( \lambda \) is the wavelength, \( d_z \) is the effective propagation distance, \( (u, v) \) are spatial frequencies in the \( x \) and \( y \) directions, respectively, and \( \phi(x, y, 0) \) is the phase map at the object plane.

A plot of the magnitude of the transfer function \( \frac{\mathcal{F} \left\{ \frac{\partial I}{\partial z} \right\}}{\mathcal{F} \{ \phi \}} \) is given in fig. 6-3. We see that while propagation significantly amplifies high-frequency signals in the projection images, low-frequency components are largely attenuated. Therefore, in a set of projection images, the phase signal will have strong high-frequency components and weak low-frequency components. During retrieval, low-frequency components must be amplified. Because of this, TIE phase retrieval is susceptible to low-frequency noise in the propagated images.

However, an effective approach to invert the transport of intensity equation and solve for the phase image is possible when we assume that the phase map can be expressed as sparse, i.e. it only contains a small number of nonzero coefficients in some basis [29]. In principle, the change in imaging signal, be it amplitude or phase, arises from an underlying change in sample material composition and projection thickness. Thus, edges which exist in the phase image but not in the intensity image are sparsified.
by solving the weighted TV norm minimization problem

\[
\arg\min_x \frac{1}{2} \| b - Ax \|_2^2 + \alpha \| W G x \|_1,
\]

where \( \alpha \) is a regularization parameter, \( G \) is the 2-D spatial gradient operator, and \( W \) is a diagonal weighting matrix. The weighting matrix represents our prior of edge information present in the intensity image. The gradient of the intensity image is thresholded so that the strongest 10\% of all pixels are considered to contain edge information. In a typical image, only 20\% of the diagonal elements of \( W \) take on a value between 0 and 1. We adapt the two-step iterative shrinkage/thresholding algorithm (TwIST) to solve the minimization [14].

A schematic diagram of the experiment is provided in fig. 6-1. A microfocus source (Hamamatsu L8121-03) located at \( z = 0 \) m was operated at 150 kVp and 66 mA to produce a circular focal spot 7 \( \mu \)m in diameter. The resulting X-ray beam has a central wavelength of \( \lambda = 0.0210 \) nm. Intensity images were taken with a CMOS photodiode image sensor (Rad-icon, Shad-o-Box 4K, 2000 \( \times \) 2048 pixels, 48 \( \mu \)m pixel size). The scintillator was placed at \( d = 2.00 \) m. The intensity of the incident beam
Figure 6-4: Experimental results of a rubber and nylon sphere in a water-filled test tube. Scale bars represent 2 mm.

(a) Tikhonov-regularized TIE inversion [22]
(b) Single-shot reconstruction of phase image using the phase-attenuation duality [178]
(c) Iterative reconstruction using the structural similarity promoting regularizer

Figure 6-5: Image profiles along the dashed blue line in Figure 6-4.

I₀ was calibrated by taking a single background image without the sample in place. Intensity images were obtained with the sample placed at two different positions along the optical axis ($z₁ = 0.50 \, \text{m}; \, z₂ = 1.30 \, \text{m}$), resulting in two different magnifications and effective pixel sizes ($M₁ = 4, \, \Delta₁ = 12 \, \mu\text{m}; \, M₂ = 1.54, \, \Delta₂ = 31.2 \, \mu\text{m}$). I₂ was registered using a mutual-information maximizing method built into MATLAB and scaled to I₁ to allow for finite differencing.

The imaging phantom consists of a rubber and a nylon sphere inside a water-filled test tube. A projection at the first propagation distance, I₁, shown in Figure 6-2, demonstrates the range of attenuation throughout the sample. Note that while the rubber sphere is clearly visible in this image, the nylon sphere is index-matched, and
produces a very weak intensity signal. Figure 6-4 shows reconstruction results from direct two-shot retrieval, single-shot retrieval, as well as the regularized two-shot retrieval. From Figure 6-5, we see that the structural similarity-promoting regularizer significantly enhances the profile of the nylon sphere, without sacrificing edge information, producing better imagery than direct phase reconstruction as well as Wiener filtering.

6.2 Simultaneous solutions for absorption and phase

We have previously proposed several methods to improve the low-frequency response of TIE [182, 157, 169]. However, these techniques often require strong prior knowledge of the object, or impose restrictions on the class of object imaged, in addition to being designed primarily for projection imaging. Methods for reducing low-frequency noise in TIE are often implemented as an intermediate step between phase retrieval and tomographic reconstruction. In tomographic imaging, multiple projections are taken of the same object, yielding significantly more information than projection imaging. Numerous algorithms exist to reconstruct an object based on prior information about the object, ranging from assumptions about the structure of the object, to detailed prior knowledge of the object [34].

A weakness of the application of discrete measurements such as those performed in CT to the tomographic reconstruction problem is that only finite samples of the
object’s projection into Radon space are possible [83]. As predicted by the Fourier slice theorem, the density of measurements in Fourier space is inversely proportional with the spatial frequency being measured; that is, conventional tomographic imaging performs better sampling of the object’s low spatial frequency signal compared to its high spatial frequency signal. To compensate for this uneven sampling of Radon space, backprojection models such as the Feldkamp Davis Kress (FDK) algorithm re-weight the sinogram using a ramp-like filter, such as the Ram-Lak filter. For direct backprojection methods, this results in a sensitivity of the technique to high-frequency noise, which is amplified by the presence of the correction filter [138]. In this chapter, we demonstrate that tomographic reconstruction from propagation based imaging provides a complementary signal to that of tomographic reconstruction from attenuation measurements. This arises as a consequence of edge-enhancement in propagation based imaging, where high spatial frequencies of the object can be more reliably retrieved. We show that phase retrieval provides complimentary information to absorption data.

We demonstrate this complementary property by considering the noise power spectrum of free space propagation and projection. The combined effect of TIE projection and CT projection results in an operator with a new spectral response that can supplement the information obtained from only performing CT projection.

The observations above lead to the intuition that by combining information from attenuation and phase, the reconstruction accuracy of both can be improved. We have previously applied compressed sensing methods to improve the quality of phase reconstructions. In particular, we have proposed a method that maximizes the structural similarity between the phase and attenuation signal [120]. In our previous work, this was restricted to propagation imaging, and relied on an edge sparsifying transform known as the total variation (TV) norm. In this section, we extend the concept of structural similarity, and demonstrate that this concept is equivalent to the concept of joint sparsity in the field of compressed sensing.
Figure 6-7: (a) Radial and (b) axial noise power spectrum of attenuation backprojection and phase-retrieving backprojection. Note that this is not a direct comparison of magnitude, since the relative magnitudes of the phase and absorption signals vary based on object and experimental parameters.

### 6.3 Noise Power Spectrum of Phase CT

With a slight modification to the results of Riederer et. al. [138], the power spectrum of the backprojection operator is given by

\[
S_k(k_x, k_y, \theta) = \frac{\pi}{mN} \frac{|G_k(k_x, k_y)|^2}{|k_y|},
\]

where \(k_x, k_y\) are the spatial frequencies corresponding to the projective system given in fig. 6-6, \(\theta\) is the angle of rotation on the rotational axis \(\hat{x}\), \(m\) is the number of projections, \(\tilde{N}\) is the number of incident photons, assumed to be uniform for every pixel in each projection, and \(G_k(\cdot)\) is the corrective filter applied to each projection. We deviate from Riederer et. al. in the design of our corrective filter, which must also perform phase retrieval. As shown in other works [122, 158], for pure-phase objects, phase retrieval can be implemented as a deconvolution by a parabolic kernel, so we design our phase CT filter as follows:

\[
G_{k,pCT}(k_x, k_y) = \frac{\Delta z \lambda}{2\pi} \frac{|k_y|}{|k_x^2 + k_y^2|},
\]

where \(\Delta z\) is the propagation distance and \(\lambda\) is the spectrally-weighted mean wavelength. The application of our modified corrective filter leads to the following noise
power spectrum:

\[ S_{k, pCT}(k_x, k_y, \theta) = \frac{\Delta z^2 \lambda^2}{4\pi m \bar{N}} \frac{|k_y|}{|k_x^2 + k_y^2|^2} \]  \hspace{1cm} (6.7)

Compared to attenuation CT, where \( S_{k, aCT}(k_x, k_y, \theta) = \frac{\pi}{4m\bar{N}}|k_y| \) for a ramp-filtered backprojection, we see that the combined phase-retrieval backprojection operator exhibits amplification of low-frequency noise, but suppression of high frequency noise. The shapes of \( S_{k, aCT} \) and \( S_{k, pCT} \) are shown in fig. 6-7. Unlike the noise power spectrum of the absorption CT reconstruction, the noise power spectrum of the phase CT reconstruction varies with \( k_x \). From fig. 6-7, it is clear that the power spectra of the absorption and phase CT reconstructions are complimentary, with the absorption reconstruction suppressing noise in low spatial frequencies while the phase reconstruction suppresses high-frequency noise. Therefore, the accuracy of the phase and attenuation reconstructions can be improved if information is shared between reconstructions.

### 6.4 Algorithms for Phase-Only Reconstruction

We demonstrate several methods for propagation-based phase reconstruction from the TIE: direct inversion of the TIE, inversion using the phase attenuation duality, as well as an iterative solver using sparse wavelet regularization. The simulation phantom was a modified complex-valued 3-dimensional Shepp-Logan object (fig. 6-8). The absorption values are typical for X-ray imaging, while the phase values are chosen so that methods relying on direct proportionality fail, while maintaining the maximum amount of mutual information between the attenuation and phase values. A histogram of the phantom absorption and phase values is given in section 6.4. Reconstruction was performed using physical parameters typical of in-line X-ray phase imaging, listed in table 6.1. Simulations were performed using 4 noise levels: no noise, low noise, average noise, and high noise, corresponding to detector photon counts of \( N = 10^6 \), \( N = 10^5 \), and \( N = 10^6 \), respectively. The noise was assumed to be Poisson.
These noise levels are chosen to represent the range of photon counts seen during X-ray imaging.

To perform direct inversion, the TIE is first solved for each angle using methods proposed by Teague [156], and the resultant phase maps are input into a filtered backprojection (FBP) operator. Reconstruction using simultaneous iterative reconstruction technique (SIRT), a common iterative CT method is also performed [52]. The results for direct phase reconstruction, as well as the attenuation image for comparison, are presented in figs. 6-9 and 6-10.

Another common method for reducing the noise as well as measurement effort associated with phase retrieval is to assume a proportionality between the absorption and phase images, and several methods exist to exploit this simplification of measurement [27, 177, 65]. We demonstrate the application of the phase-attenuation duality [177] to retrieve the phase maps at each angle, followed by SIRT to reconstruct the
Figure 6-9: Filtered backprojection of attenuation and phase images.
Figure 6-10: SIRT of attenuation and phase images.
Figure 6-11: Application of the phase attenuation duality to retrieving phase images.

Finally, we have implemented an iterative method for phase retrieval, similar to one we have applied in the pure-phase case [158], with a modification to the type of regularizer used. Instead of applying a TV regularization scheme, we chose an analysis/synthesis framework. This enabled us to express the image in a sparse basis, which will be important in later sections, when we will want to apply similarity metrics to our sparse representations.

In this section, we use a wavelet operator as our sparsifying transform. Wavelet transforms have long been known to be sparsifying basis for many image classes [99]. Unlike the gradient operator commonly used in total-variation denoising methods, which tends to amplify noise, the wavelet transform has been found to have easily accessible denoising characteristics, and wavelet shrinkage and thresholding are popular methods for denoising and compressing signals [99, 32]. Thus, the wavelet basis is a natural choice for reconstructing a sparse signal in the presence of noise.

The phase CT problem is reformulated as the following minimization, which is solved assuming perfect knowledge of $\mu$:

$$\arg \min_\delta \frac{1}{2} || A_{CT,TIE}(\mu, \delta) + A_{CT}(\mu) - I_m ||_2^2 + \lambda || W \delta ||_1.$$  \hspace{1cm} (6.8)

where $A_{CT,TIE}$ is an operator combining the CT projection operator with the TIE propagation operator. Since both operators are linear, this is usually implemented as
a composition of the CT and TIE projection functions. This problem is commonly known as the L1 sparse analysis problem, where $W$, the wavelet transform, projects $\delta$ onto a sparsifying basis. We chose $W$ to be a stationary Haar wavelet transform of $\text{floor}(\log_2(n))$ levels, where $n$ is the longest dimension of the image, in pixels. The minimization is solved using FASTA [56, 57]. The results for reconstruction using a L1 regularizer are presented in fig. 6-12. An analysis of the sensitivity to tolerance is presented in fig. 6-13.

### 6.5 Measures for Image Similarity

The idea of maximizing image similarity is motivated by a prior that can be assumed for a large class of imaged objects: that object phase and attenuation is linked to its underlying material composition, and as a consequence, spatial variations in attenuation are likely to be correlated to spatial variations in phase, and vice versa.

There are many measures of the similarity between two images, most of which can be formulated as a distance between the images. The most basic similarity measurement is the root mean squared error (RMSE) between two images. For two images $I_A(x, y)$ and $I_B(x, y)$, the RMSE is:

$$\Delta_{\text{RMSE}} = \sqrt{\sum_x \sum_y (I_1(x, y) - I_2(x, y))^2}. \quad (6.9)$$

The RMSE is often used in mono-modal image registration, where two images taken under similar conditions must be registered. For images corrupted with additive gaussian white noise, minimization of the RMSE produces the same result as the maximum-likelihood solution. However, when images are not taken under the same conditions, the RMSE does not provide a suitable metric for the similarity between two images.

A popular measure of the similarity between two images is the mutual information
Figure 6-12: L1 minimizing reconstructions of attenuation and phase images.
<table>
<thead>
<tr>
<th>Tolerance</th>
<th>Iterations</th>
<th>RMSE</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.001</td>
<td>499</td>
<td>3.6823</td>
</tr>
<tr>
<td>0.0001</td>
<td>5889</td>
<td>2.67593</td>
</tr>
<tr>
<td>1e-05</td>
<td>23996</td>
<td>2.15315</td>
</tr>
<tr>
<td>1e-06</td>
<td>1e+06</td>
<td>2.10712</td>
</tr>
</tbody>
</table>

Figure 6-13: Effect of tolerance on L1 regularized reconstruction of the phase-only solution. Note that even with an extreme number of iterations, the solution does not converge due to the ill-posedness of TIE reconstruction problem.

\[(MI)\] which for two images \(I_A\) and \(I_B\) is expressed as

\[
MI(I_A, I_B) = \sum_a p_A(a) \log p_B(b) + \sum_b p_B(b) \log p_B(b) - \sum_{a,b} p_{AB}(a, b) \log p_{AB}(a, b),
\]

where \(p_A(a)\) and \(p_B(b)\) represent the estimated probabilities determined from binned histogram values of \(I_A\) and \(I_B\), respectively, and \(p_{AB}(a, b)\) represents the estimated probabilities obtained from the joint histogram between \(I_A\) and \(I_B\). Maximization of the mutual information is often used in multi-modal image registration, where the intensity values of two images may be correlated, but not equivalent. However, in the problem case of image retrieval, the mutual information is difficult to maximize. Whereas in image registration, the dimensionality of the problem is limited to the dimensions of an affine transform (4 in 2D, 6 in 3D), in image retrieval the dimensionality of the problem is the number of pixels to be retrieved. Therefore image retrieval through maximization of the mutual information quickly becomes a computationally intensive problem with increasing image dimensions.

Another concept in image matching, which we have applied in our previous work, is the idea of similarity through matching the gradient of the image [120]. The general class of edge-matching algorithms is commonly used in CT reconstruction, where it’s expected that the reconstructed object has a sparsity in edges. However, it is often the case that the phase and attenuation of an object are not directly proportional...
to one another, and thus there is not a 1-to-1 correlation between the gradients of the amplitude and phase image. While the gradient is an acceptable measure of similarity between images in the absence of noise, it is prone to give spurious results in the presence of high frequency noise.

For sparse signals, determining similarity between two images is useful in the multiple measurement vector (MMV) problem. The MMV problem arises when instead of retrieval of a single signal from a sparse system from a single measurement, many signals must be retrieved from the same system from many measurements. For these systems, the plurality of signals often share a common support on the sparse basis. A means of expressing this common support between two signals is known as the joint sparsity, which is a class of metrics for expressing the common support in sparse matrices. A useful expression of joint sparsity is the $L_{(2,1)}$ norm, which has been applied to robust data analysis [113] and sparse coding [91]. Given two sparse signals $I_A$ and $I_B$, the joint sparsity of the two signals can be quantified through the $L_{(2,1)}$ norm, which is the sum of the two-norms between the pixels of $I_A$ and $I_B$:

$$||I_A, I_B||_{2,1} = \sum_x \sum_y \sqrt{I_A(x,y)^2 + I_B(x,y)^2}.$$  \hspace{1cm} (6.11)

Note that the $L_{(2,1)}$ norm is minimized when $I_A$ and $I_B$ share the same support. This norm has the benefit of having a well known proximal operator, which is analogous to the shrinkage operator in compressive sensing.

### 6.6 Joint Sparsity Regularization in Simultaneous Attenuation-Phase Reconstruction

Using the $L_{(2,1)}$ norm definition for joint sparsity, we can consider the following unconstrained minimization:

$$\arg\min_{\mu, \delta} \frac{1}{2}||A_{CT, TIE}(\mu, \delta) - I_m||_2^2 + \lambda||W\mu, W\delta||_{2,1},$$  \hspace{1cm} (6.12)
where \( \mu \) and \( \delta \) are the object attenuation and phase distributions, \( A_{CT,TIE} \) is the combined CT and TIE operator, \( I_m \) is the measured phase contrast sinogram, \( \lambda \) is a regularization parameter, and \( W \) is the sparsifying wavelet transform.

However, this minimization problem is nonlinear, and highly ill-posed due to the TIE, making direct solution of the minimization exceedingly difficult. To enable numerical solution of this problem, we propose a relaxation to the nonlinear problem by iteratively solving the following two linearized subproblems:

\[
\begin{align*}
\arg \min_{\mu} & \frac{1}{2} \| A_{CT}(\mu) - \log(\hat{I}) \|_2^2 + \| \lambda_{\mu} W \mu, \lambda_{\delta} W \delta \|_{2,1} \\
\arg \min_{\delta} & \frac{1}{2} \| A_{CT,TIE}(\hat{\mu}, \delta) + A_{CT}(\mu) - I_m \|_2^2 + \| \lambda_{\mu} W \hat{\mu}, \lambda_{\delta} W \delta \|_{2,1}
\end{align*}
\]  

(6.13)  

(6.14)

where \( \hat{I} \) represents the current estimate for intensity with no propagation distance, and can either be measured, as in the case of multi-shot phase retrieval methods, or estimated based on estimates for \( \mu \), resulting in single-shot phase retrieval.

We define the forward operator \( A_{CT} \) as the CT projection operator mapping a \( N \times N \times M \) volume to a \( N \times M \times \Theta \) sinogram. The forward operator \( A_{CT,TIE} \) is an operator mapping two \( N \times N \times M \) volumes to a single \( N \times M \times \Theta \) sinogram, and is defined as the projection operation on each volume followed by an application of the TIE:

\[
A_{CT,TIE}(\mu(x,y,z), \delta(x,y,z)) = \frac{2\pi \Delta z}{\lambda} \nabla_1 \cdot \left[ \exp \left( -A_{CT}(\mu(x,y,z)) \right) \nabla_1 A_{CT}\delta(x,y,z) \right]
\]

(6.15)

We see that \( A_{CT} \) is a linear operator with respect to \( \mu \), and \( A_{CT,TIE} \) is nonlinear with respect to \( \mu \) but linear with respect to \( \delta \). Additionally, \( A_{CT} \) is widely known to be an orthogonal projector, while \( A_{CT,TIE} \) can also be shown to be an orthogonal projector for \( \delta \). The regularization term \( \| \cdot \|_{2,1} \) can be efficiently solved using a proximal operator. Thus, the minimization problems in eqs. (6.13) and (6.14) can be solved using L1 minimization techniques commonly used in compressed sensing, resulting in orders of magnitude reductions in the time required to solve the overall optimization.
Therefore, we propose the following iteration scheme to solve the minimization:

**Algorithm 1** SAPR iteration step

1: Initialize $\hat{\mu}_0 = \hat{\delta}_0 = 0$
2: for $k \rightarrow 0, 2, 1, \ldots$ do
3: $\mu_{k+1} = \arg \min_{\mu} \frac{1}{2} || A_{CT}(\mu) - \log(\hat{I}_k) ||_2^2 + \lambda_\mu || W_\mu, W \hat{\delta}_k ||_{2,1}$
4: $\delta_{k+1} = \arg \min_\delta \frac{1}{2} || A_{CT,TIE}(\hat{\mu}_k, \delta) + A_{CT}(\hat{\mu}_{k+1}) - I_m ||_2^2 + || \lambda_\mu W_\mu \hat{\mu}_{k+1}, \lambda_\delta W \delta ||_{2,1}$
5: $f(\mu_{k+1}, \delta_{k+1}) = \frac{1}{2} || A_{CT,TIE}(\hat{\mu}_{k+1}, \delta_{k+1}) - I_m ||_2^2 + || \lambda_\mu W \hat{\mu}_{k+1}, \lambda_\delta W \hat{\delta}_{k+1} ||_{2,1}$
6: if $f(\mu_k, \delta_k) - f(\mu_{k+1}, \delta_{k+1}) < \text{tol}$ then return

To implement the CT projection operator, we leveraged the ASTRA toolbox [164, 118] and SPOT toolbox [15], which allowed us to easily incorporate GPU-accelerated projection/backprojection routines to achieve order of magnitude gains in processing speed compared to CPU-bound code.

To accelerate our propagation projection operators, we have implemented the TIE operator as a Fourier domain operator, as in previous papers [158], which are now implemented as GPU operators for further speed enhancements.

For smaller reconstruction volumes ($N \times N \times M \leq 64^3$), it is possible to implement $A_{CT}$ and $A_{CT,TIE}$ as matrix operations, greatly reducing the use computational complexity. However, for problems of larger dimensions, the size of the matrix operators prevents a GPU implementation. To solve the minimization problems, we utilize FASTA [56, 57].

### 6.6.1 Guarantees of convergence

As discussed in the previous section, the linearized subproblems are convergent. The objective function for each subproblem is given by eqs. (6.13) and (6.14). We see that for each subproblem, the contribution from the other component remains constant during minimization. Then eqs. (6.13) and (6.14) can be expressed as

\[
\begin{align*}
\arg \min_{\mu} & \frac{1}{2} || A_1 \mu - b_1 || + || \lambda_\mu W \mu, \lambda_\delta W \hat{\delta} ||_{2,1} \quad (6.16) \\
\arg \min_{\delta} & \frac{1}{2} || A_2 \delta - b_2 || + || \lambda_\delta W \mu, \lambda_\delta W \hat{\delta} ||_{2,1} \quad (6.17)
\end{align*}
\]
More simply, this is now a minimization of the form:

\[
\arg \min_{\mu} F_1(\mu) + \Psi(\mu, \delta)
\]

\[
\arg \min_{\delta} F_2(\delta) + \Psi(\mu, \delta)
\]

which is attempting to minimize the overall problem objective of

\[
\arg \min_{\mu, \delta} F_0(\mu, \delta) + \Psi(\mu, \delta)
\]

where \(F_0(\mu, \delta)\) is minimized by minimizing \(F_1(\mu) + F_2(\delta)\). This successive minimization scheme is known as Alternating Minimization Method (AMM) [36].

Given that eq. (6.13) and eq. (6.14) have well known minimizers, the successive minimization of eqs. (6.18) and (6.19) causes \(F_0(\mu, \delta) + \Psi(\mu, \delta)\) to monotonically decrease. Furthermore, minimizing \(\Psi(\mu, \delta)\) with respect to either \(\mu\) or \(\delta\) is convex, with a well known proximal operator known as the shrinkage operator:

\[
shrink_\mu(||\lambda_\mu W\mu, \lambda_\delta W\delta||_{2,1}, \tau) = \max \left(1 - \frac{\tau}{\sqrt{(\lambda_\mu W\mu)^2 + (\lambda_\delta W\delta)^2}}, 0\right) \cdot \mu
\]

\[
shrink_\delta(||\lambda_\mu W\mu, \lambda_\delta W\delta||_{2,1}, \tau) = \max \left(1 - \frac{\tau}{\sqrt{(\lambda_\mu W\mu)^2 + (\lambda_\delta W\delta)^2}}, 0\right) \cdot \delta
\]

where \(shrink_\mu\) and \(shrink_\delta\) are the shrinkage operators onto the subspaces \(\mu\) and \(\delta\), respectively.

Given that \(\Psi(\mu, \delta)\) is convex, then if \(F_1(\mu)\) and \(F_2(\delta)\) are convex, then the overall minimization must also be convex, and result in a global minima, as shown in [11]. However, if either \(F_1(\mu)\) or \(F_2(\delta)\) are non-convex, convergence can still be guaranteed if \(F_0(\mu, \delta) + \Psi(\mu, \delta)\) satisfies the Kurdyka-Łojasiewicz property described in [10]. If the objective function is considered is tame, then it satisfies the K-L property. For a description of tame functions, we refer the reader to [10].

In the case of the TIE, \(F_1(\mu)\) and \(F_2(\delta)\) are convex, smooth functions. Therefore the overall minimization is guaranteed to converge to a global minima.
6.7 Simulation results

The results of the SAPR in multi-shot reconstruction are presented in fig. 6-14, and convergence results are given in fig. 6-15. Results for single-shot retrieval are presented in fig. 6-16.

We see in fig. 6-9 that as expected, direct reconstructions of the phase image from TIE is highly sensitive to low-frequency noise. While the attenuation image degrades gradually, the direct phase retrieval rapidly degrades in the presence of noise. Further, it is clear from fig. 6-10 that the nature of the signal is not well suited to SIRT when the noise is high, and direct phase retrieval results in significant inconsistencies that SIRT cannot resolve.

Iteratively solving for attenuation, as expected, provides results in agreement with the literature, namely that with careful selection of the regularization parameter, signal recovery can occur in the presence of significant noise. On the other hand, phase retrieval using L1 minimization techniques is extremely time-consuming. This is due to the ill-posedness of eq. (6.8), which results in a vanishing low-frequency gradient, causing the FASTA algorithm to stall. The results shown in fig. 6-12 required on average 50,000 iterations to complete. Even with such a large number of iterations, the L1 regularized solution is actually inferior to the direct back-propagated solution. This is primarily a deficiency of the solver, rather than the formulation of the problem. This is demonstrated in fig. 6-13. Here we see that even with an extreme number of iterations, the error cannot be reduced to levels superior to the filtered backprojection.

In contrast, SAPR produces solutions for both attenuation and phase that exhibit overall lower errors than any of the previous methods. In line with the expectations set in section 6.3, by combining information from both attenuation and phase reconstructions, we are able to surpass the performance of methods which only retrieve absorption and phase separately. In addition to providing superior results, our algorithm also converges significantly faster than other L1 techniques; as seen in fig. 6-15, our algorithm converges at <100 iterations of the outer loop. Each outer loop iteration is equivalent to roughly 50 iterations of the phase-only L1 solver. The exception
Figure 6-14: SAP minimizing reconstructions of attenuation and phase images, using intensity measured at two distances.
Figure 6-15: Plots of $\lambda_{\mu}$ and $\lambda_{\phi}$, the objective function, and the attenuation and phase errors of the solver at each iteration.

is the noise-free case, where the solver requires a fairly long time to converge, but produces a errors many orders of magnitude lower than other methods.

Our algorithm is also flexible with respect to measurement schemes. Due to the splitting of the absorption and phase estimation steps, it is possible to perform phase retrieval from a single propagation distance, enabling the use of existing microCT systems. While other methods exist for phase retrieval from a single propagation distance, they rely on proportionality between the absorption and phase of the object [27]. As shown fig. 6-11, these methods are incapable of retrieving phase from objects do not possess phase-attenuation proportionality. However, our method is capable of reconstructing the object attenuation and phase even from images at a single propagation distance. In fig. 6-16, we see that while performance decreases significantly compared to the multi-shot case, phase retrieval is still relatively accurate even in the presence of moderate noise. We believe that this is the first algorithm that enables phase retrieval from Fresnel regime propagated images in the case where attenuation and phase are not strongly proportional to each other.
Figure 6-16: SAP minimizing reconstructions of attenuation and phase images from intensity images taken at a single propagation distance.
6.8 Extension to X-ray dark field imaging

Part of the flexibility of SAPR is the ability to apply it to any phase imaging setup that has a suitable forward model. In this section, we extend our reconstruction algorithm to retrieving phase from an analyzer based crystal system, and demonstrate phase retrieval of artery specimens using a crystal-based system.

X-ray dark field imaging (XDFI) is an extension of the analyzer-based crystal method described in section 2.3.1. In typical analyzer-based imaging (ABI), an analyzer crystal is used in reflection mode (also known as Bragg mode) in a setup referred to as DEI (diffraction enhanced imaging). The angular sensitivity of DEI can be increased by adopting multiple crystals to increase the sharpness of the rocking curve [179]. However, this gain trades off spatial resolution for angular sensitivity. XDFI is a technique which instead uses a thin crystal in the transmission, or Laue, mode, and is known to produce both higher angular sensitivity and spatial resolution than conventional Bragg mode imaging systems [7, 8].

An schematic of the Laue mode XDFI system is shown in fig. 6-17. The optical path of the XDFI system consists of a synchrotron radiation source, an asymmetrically cut monochromator-collimator crystal system operating in Bragg mode, an asymmetrically cut crystal operating in Laue mode, and two CCD cameras. The monochromator system ensures that the incident X-ray beam is quasi-monochromatic.
Figure 6-18: Rocking curve for Laue crystal. Note that there is a region where the intensity linearly depends on the rocking curve.

\((\delta \lambda/\lambda = 2.9 \times 10^{-4})\) and extremely low divergence on the order of 0.05\(^\circ\). Unlike typical analyzer crystal systems, the asymmetrically cut crystals enable significant expansion of the beam width by a factor of up to 50 times, resulting in significantly increased field of view. At the experimental system used in this section, the effective FOV was 60 mm \(\times\) 60 mm.

The contrast mechanism of XDFI is based on the crystal rocking curve. When a coherent beam of X-rays hits the crystal at the Laue angle, the entire beam is reflected according to the crystal condition \([86]\). In fig. 6-17, this corresponds to the bright-field image. When the angle of the beam deviates from the Laue angle, only a portion of the beam is diffracted, and the remainder continues through the crystal. This angular dependence is often summarized by a plot known as the rocking curve. An example is given in fig. 6-18. By slightly tilting the analyzer crystal, the point corresponding to the angle of coherent beams can be shifted from the peak to the point denoted \(A\), which rests on the linear portion of the rocking curve. By rotating the Laue crystal far from the Laue angle, to point \(B\), intensity images can be measured. When X-rays are refracted by the sample, the small deviations can
Figure 6-19: SIRT reconstruction of the measured absorption and phase for the coronary artery.

Figure 6-20: Reconstructed absorption and phase of the coronary artery using SAPR.

be directly measured by correlating the beam brightness to the refracted angle. The refraction angle in the plane of diffraction $\theta(x)$ is defined as the angle by which X-rays deviate from the original direction they would travel without the presence of the sample, and is related to the intensity measurement without the sample $I_0(x)$ and with the sample $I_s(x)$:

$$\theta(x) = \frac{I_0(x) - I_s(x)}{dI/d\theta}$$  \hspace{1cm} (6.23)

where $dI/d\theta$ is the slope of the rocking curve [44].

For small diffraction angles, this quantity is also proportional to the gradient of
Figure 6-21: Comparison between absorption reconstruction techniques around calcification. The calcium image is significantly enhanced and the internal structure appears sharper on the SAPR.

the optical path length. Consider a wavefront passing through a phase object which imparts a phase $\phi(x)$. When the phase is small, the resulting refraction angle follows the relationship:

$$\theta(x) = \frac{1}{k} \frac{\partial \phi(x)}{\partial x}$$  \hspace{1cm} (6.24)

Therefore, the refracted angle is directly proportional to the differential optical path length, or phase:

$$\int \frac{\partial n(x, y)}{\partial dx} dz = \theta(x)$$  \hspace{1cm} (6.25)

where $z$ is is the optical axis. Therefore XDFI is sensitive to the unidirectional derivative of phase. Note that in the presence of severe deflections, the intensity may no longer track the linear part of the rocking curve. The new nonlinearity may result in an over- or under-estimation of the differential phase component. This can potentially result in significant artifacts around calcifications.

In XDFI, tomography is achieved by setting the axis of rotation perpendicular to the direction of the phase derivative. We see that unlike TIE, which retrieves the laplacian of the phase, XDFI retrieves the first derivative of phase. Remembering
that the noise power spectrum is given by:

\[ S_k(k_x, k_y, \theta) = \frac{\pi}{mN} \frac{|G_k(k_x, k_y)|^2}{|k_y|}, \quad (6.26) \]

and substituting the Fourier space integration filter combined with the ramp filter as 
\[ G_k(k_x, k_y) = |k_x| \cdot \frac{1}{|k_z|} = 1, \]
we see that the noise power spectrum of XDFI retrieval is

\[ \frac{\chi^2}{4\pi mN |k_y|}, \quad (6.27) \]

which again suggests a complimentary nature between the noise power spectrum of
the retrieved absorption and phase.

To implement our algorithm for differential phase retrieval, we consider the following minimization problem:

$$\arg\min_{\mu, \delta} \frac{1}{2} \left\| A_{CT}(\mu) - \log(I_{BF}) \right\|^2_2 + \frac{1}{2} \left\| \frac{d}{dx} A_{CT}(\delta) - \frac{I_{DFI}}{I_{BF}} \right\|^2_2 + \left\| \lambda_\mu W_\mu, \lambda_\delta W_\delta \right\|^2_2$$

(6.28)

Note that unlike the TIE case, the XDFI imaging system measures absorption and phase separately, resulting in two fidelity terms. However, the form of eq. (6.28)
clearly follows that of

\[ \arg\min_{\mu, \delta} F_1(\mu) + F_2(\delta) + \Psi(\mu, \delta) \]  

(6.29)

and therefore is a case of AMM. We see that in this case, \( F_1 \) and \( F_2 \) are again smooth, convex functions. Therefore our algorithm is guaranteed to converge to a global minimum.

We have applied our algorithm to experimental XDFI data taken at KEK photon factory (Japan) [8]. The monochromator system was set to produce a beam with
a mean energy of 31 keV. In this study, we present reconstruction results from a human coronary artery and iliac artery, both with extensive atherosclerotic disease. The specimens were fixed using 20% formalin prior to scanning. Samples were obtained from MGH following IRB approval from discarded human tissue during routine autopsy.

For the coronary artery, 600 projections were obtained, with an angular step size of 0.3°. The exposure time was 6 s at each angle, the total imaging time was roughly 2 hours.

For the iliac artery, 720 projections were obtained with an angular step size of 0.5°. The exposure time was 5 s at each angle. The total imaging time was roughly 1 hour.

Reconstruction results for the coronary artery are presented in figs. 6-19 to 6-21 and results for the iliac artery are given in figs. 6-23 and 6-24. While the artery is virtually invisible in the absorption reconstruction, the phase reconstruction provides extremely good contrast for the artery structure. The fibrous cap and necrotic core are clearly delineated in both the ordinary and compressive reconstructions. Overall, we observed improved reconstruction results around calcifications, where nonlinearities in the rocking curve tend to cause incorrect values for the gradient. SAPR corrects for these inconsistent values using information from the absorption reconstruction. Again, we see that SAPR corrects for low-frequency noise in the differential signal. Either one or two integration steps are required for phase retrieval from differential phase contrast measurements, these techniques have the same low-frequency noise sensitivity that TIE suffers from. Therefore, small drifts in the phase signal are likely to occur. However, these do not manifest in the absorption reconstruction, since the absorption signal component is a conventional tomographic reconstruction. Figure 6-27 illustrates the corrections that SAPR makes to each phase reconstruction. In the coronary reconstruction, the primary source of noise is a calcium artifact, which is corrected in the SAPR reconstruction, as seen in fig. 6-21. For the iliac artery reconstruction, a constellation of artifacts are observed. In fig. 6-25 we see that there are significant ringing artifacts in the SIRT reconstruction in and around the
artery, even after a standard de-ringing procedure. In fig. 6-26, an artifact can be seen traversing the plastic rod in the container, which should have a perfectly uniform refractive index. The section of artery near the rod is also artificially darkened, similar to the behaviour seen in streaking artifacts. In the SAPR reconstruction, we see that these artifacts are largely eliminated, save for some slight ringing present in fig. 6-25.
Chapter 7

Conclusion and future work

Atherosclerotic disease is one of the leading causes of death worldwide. Among those with arterial disease, patients who have yet to experience clinical symptoms are at a high risk of being under-monitored. While current CT and MRI systems are routinely used in the diagnosis of atherosclerotic disease with clinical symptoms, identification of plaque in subclinical atherosclerotic disease is limited to research efforts, and most plaques in this patient population are assessed using invasive catheterization techniques. X-ray phase imaging is proving to be a promising technology in enabling the noninvasive visualization of atherosclerotic plaque. However, until recently, X-ray phase imaging experiments have been limited by their steep requirements, namely the lack of low-cost X-ray optics, and the need for synchrotron radiation sources.

The rise of computational imaging has given researchers a much-needed remedy for these long-standing problems in X-ray imaging. The development of computational X-ray imaging has followed a similar trajectory to the field of computational photography, where there has been a movement towards simplified optical setups and – in many cases – bare detector arrangements. Our primary contributions show that computation can supplant the need for expensive gratings and highly conditioned sources, distilling the canonical X-ray phase imaging system to only a source and detector. To this end, we have demonstrated a proof-of-concept X-ray phase imaging system capable of tomographic measurements, and developed new methods of computational imaging suitable for X-ray phase retrieval.
Our system was validated using numerical simulation and experimental test phantoms, and has been shown to be suitable for imaging animal-scale objects, with the potential to image at the human scale provided sufficient hardware upgrades. To simulate X-ray images at the human scale, we have implemented a surface-modeling based method capable of realistically modeling the signals expected in phase imaging. We have implemented this simulator on a cluster-scale using GPU hardware, and demonstrated simulated phase images for a computational human phantom.

We have developed compressive algorithms for phase retrieval based on the TIE from a single intensity image at each angle using the phase attenuation duality. merits of phase imaging are explored in a series of experiments on test phantoms and biological specimens, and with correlations to microCT and microMRI. Phase retrieval is shown to significantly increase image quality in terms of minimizing noise and scattering effects. Imaging of atherosclerotic disease is demonstrated, with results are correlated to histology, and preliminary results from preclinical imaging are shown.

Lastly, we have introduced novel methods, where the phase retrieval problem is recast as a multimodal signal retrieval problem. We present a new algorithm, called structural similarity regularization for phase retrieval in projection imaging, and provide experimental validation. Next, we introduce a new algorithm, called SAPR, which can be applied to multiple signal retrieval. We develop a minimization algorithm for the joint-sparsity between the absorption and phase signal, which seeks to maximize the mutual information. Comparisons to current methods for phase retrieval are given, and we demonstrate significantly improved convergence and noise-robustness properties compared to previous algorithms. Finally, we extend the algorithm beyond propagation based imaging, and demonstrate SAPR with experimental results from a XDFI system.

There still remains a significant amount of research effort necessary before X-ray phase imaging will see clinical use. Flux limitations prevent us from imaging at human-scale. However, there are several promising technologies which can provide a high-flux, high spatial coherence system that is necessary for propagation-based
X-ray phase imaging. The first such technology is the liquid metal jet source [71]. By using a flowing anode target, these sources can dissipate significantly larger thermal loads than static anodes, while maintaining a much smaller spot size than rotating anode sources. Another promising avenue is the development of distributed sources for X-ray imaging. Assembled from a multitude of sources which provide low flux individually, but a very high aggregate flux, distributed sources can implement coded illumination schemes which are compatible with phase imaging [37].

There are still many unexplored avenues of research in computational X-ray phase imaging. Integration of phase retrieval with computed tomography can greatly enhanced the retrieved images. However, in this thesis we have only explored methods which follow the standard pattern of circular or helical scanning trajectories during tomography. More exotic scanning geometries may be better suited to exposing the phase information of a human body. For example, a spiral scanning geometry enables a diversity of projection distances to be captured around the region of interest, and could enable the use of multi-distance phase retrieval algorithms, such as polynomial fitting or Kalman estimation [168, 169]. In another example a beam path tracing out a sphere could provide samples in the high spatial frequencies along the axis of rotation, something that is absent from circularly scanned data, as seen in section 6.3.

While the need for better sources is a pressing concern, the future of X-ray phase imaging is bright. This thesis and its contemporary works show that computational phase imaging is possible with technologies that already exist in modern CT systems, without the need for specialized equipment. A computational imaging system can acquire both absorption and phase data, and at a higher contrast-to-noise ratio than a conventional X-ray CT system.
Appendix A

Derivation of Fresnel diffraction

The derivation begins from Maxwell’s equations:

\[ \nabla \cdot \mathbf{E} = \frac{\rho}{\varepsilon_0} \]  
\[ \nabla \cdot \mathbf{B} = 0 \]  
\[ \nabla \times \mathbf{E} = -\frac{\partial \mathbf{B}}{\partial t} \]  
\[ \nabla \times \mathbf{B} = \mu_0 \left( \mathbf{J} + \varepsilon_0 \frac{\partial \mathbf{E}}{\partial t} \right) \]

where \( \mathbf{E} \) and \( \mathbf{B} \) are the electric and magnetic fields, respectively, \( \varepsilon_0 \) and \( \mu_0 \) are the permittivity and permeability of free space, \( \mathbf{J} \) is the current, and \( \rho \) is the charge density.

Given that we are modeling propagation in free space, we can assume that there are no free charges (\( \rho = 0 \)) and no currents (\( \mathbf{J} = 0 \)). Then, Maxwell’s equations can be simplified to the wave equations:

\[ \frac{1}{c^2} \frac{\partial^2 \mathbf{E}}{\partial t^2} - \nabla^2 \mathbf{E} = 0 \]  
\[ \frac{1}{c^2} \frac{\partial^2 \mathbf{B}}{\partial t^2} - \nabla^2 \mathbf{B} = 0 \]

where \( c \) is the speed of light in free space.

The wave equation is separable with respect to the spatial and temporal compo-
The spatial component is also known as the Helmholtz equation:

\[
\left( \nabla^2 + k^2 \right) u(x, y, z) = 0 \quad (A.7)
\]

where \( u \) is the spatially-varying component of the solution to the electric field. We consider the case where \( u \) is a scalar field, i.e. \( k_x^2 + k_y^2 \ll k_z, k = k_z \), as is true when refraction angles are small, such as in the X-ray case. This is known as the paraxial approximation. By a quick rearrangement to the Helmholtz equation,

\[
\left( \frac{\partial^2}{\partial z^2} + \nabla^2_{\perp} + k^2 \right) u(x, y, z) = 0 \quad (A.8)
\]

\[
\left( \frac{\partial}{\partial z} - i k \sqrt{1 + \frac{\nabla^2_{\perp}}{k^2}} \right) \left( \frac{\partial}{\partial z} + i k \sqrt{1 + \frac{\nabla^2_{\perp}}{k^2}} \right) u(x, y, z) = 0 \quad (A.9)
\]

where \( \nabla_{\perp} = (\frac{\partial}{\partial x}, \frac{\partial}{\partial y}) \), we see that the Helmholtz equation can be factorized into two solutions propagating in the \( +z \) and \( -z \) directions. A solution to the forward propagating component can be written as:

\[
u_+(x, y, z) = -\frac{1}{2\pi} \frac{\partial}{\partial z} \left( \int \int u_0(x_0, y_0) \frac{e^{ik\sqrt{x^2+(x-x_0)^2+(y-y_0)^2}}}{\sqrt{x^2+(x-x_0)^2+(y-y_0)^2}} dx_0 dy_0 \right) \quad (A.10)
\]

where \( u_0 \) is an arbitrary field at at the plane of origin, i.e. \( z = 0 \). This is the Rayleigh-Sommerfield diffraction integral. However, it is not very useful for our purposes due to the need to differentiate along the \( z \) direction. To simplify it to a more useable form, we apply the paraxial approximation again, where \( \lambda \ll \sqrt{x^2+y^2} \ll z \).

This results in the formulation of the Fresnel-Kirchoff diffraction integral [18]

\[
u(x, y, z) = \frac{e^{ikz}}{i\lambda z} \int \int u(x_0, y_0) e^{ikz\frac{[(x-x_0)^2+(y-y_0)^2]}{2z}} dx_0 dy_0 \quad (A.11)
\]
Appendix B

NURBS

Non-uniform rational B-splines are a mathematical model for representing curves and surfaces. Unlike other surface modeling approaches, such as polygon meshes and point cloud models, NURBS models offer increased flexibility and precision for analytic shapes. NURBS models enable us to model a continuous surface as an analytic, smooth function, and therefore sidestep issues with vertex discontinuities and mesh density.

NURBS curves are constructed from NURBS basis function, which are defined for at the $i$ control points and order $n$. NURBS basis functions of order $n$ are an interpolated blending of lower order basis functions, with $N_{i,0}$ being the piecewise constant functions:

\begin{align}
N_{i,n} &= f_{i,n} N_{i,n-1} + g_{i+1,n} N_{i+1,n-1} \tag{B.1} \\
f_{i,n}(u) &= \frac{u - k_i}{k_{i+n} - k_i} \tag{B.2} \\
g_{i,n}(u) &= \frac{k_{i+n} - u}{k_{i+n} - k_i} \tag{B.3}
\end{align}

$k_i$ denote the knot spans, i.e. the boundaries between where control points become active.

A NURBS curve is defined by its order, a set of weighted control points, and its
knot vector:

\[ C(u) = \sum_{i=1}^{k} R_{i,n}(u)P_i \quad \text{(B.4)} \]

\[ = \sum_{i=1}^{k} \frac{N_{i,n}(u)w_iP_i}{\sum_{j=1}^{k} N_{j,n}(u)w_j} \quad \text{(B.5)} \]

\[ (B.6) \]

where \( P_i \) are the control points, and \( w_i \) are their weights.

A NURBS surface is the tensor product of two NURBS curves:

\[ S(u,v) = \sum_{i=1}^{k} \sum_{j=1}^{l} R_{i,j}(u,v)P_{i,j} \quad \text{(B.7)} \]

\[ = \sum_{i=1}^{k} \sum_{j=1}^{l} \frac{N_{i,n}(u)N_{j,m}(v)w_{i,j}}{\sum_{p=1}^{k} \sum_{q=1}^{l} N_{p,n}(u)N_{q,m}(v)w_{p,q}} P_{i,j} \quad \text{(B.8)} \]

The spatial coordinates and surface normals for a NURBS surface are well defined and can be computed to arbitrary accuracy, as described in [127].
Bibliography


[115] Steven E Nissen and Paul Yock. Intravascular ultrasound novel pathophysio-


[117] Matthew P Ostrom, Ambarish Gopal, Naser Ahmadi, Khurram Nasir, Eric
Yang, Ioannis Kakadiaris, Ferdinand Flores, Song S Mao, and Matthew J Bud-
off. Mortality incidence and the severity of coronary atherosclerosis assessed
by computed tomography angiography. *Journal of the American College of

iterative electron tomography reconstruction using graphics processing units

[119] Adam Pan, Justin W Lee, Laura Waller, and George Barbastathis. Transport
of intensity imaging with wavelet intensity derivative estimation. In *Digital
Holography and Three-Dimensional Imaging*. Optical Society of America, 2013.

[120] Adam Pan, Ling Xu, Justin W Lee, Rajiv Gupta, and George Barbastathis.
Structural similarity regularization of x-ray transport of intensity phase re-
Society of America, 2014.

[121] Adam Pan, Ling Xu, Jon C Petruccelli, Rajiv Gupta, and George Barbastathis.
Contrast enhancement of propagation based x-ray phase contrast imaging. In *
SPIE Optical Engineering+ Applications*, pages 92090R–92090R. International
Society for Optics and Photonics, 2014.

[122] Adam Pan, Ling Xu, Jon C Petruccelli, Rajiv Gupta, Bipin Singh, and George
Barbastathis. Contrast enhancement in x-ray phase contrast tomography. *Op-

Improvements in risk stratification for the occurrence of cardiovascular disease
by imaging subclinical atherosclerosis: a systematic review. *Heart*, 98(3):177–
184, 2012.

of intensity equation for optical path length recovery using partially coherent

[125] Franz Pfeiffer, Martin Bech, Oliver Bunk, Philipp Kraft, Eric F Eikenberry,
Ch Brönnimann, Christian Grünzweig, and Christian David. Hard-x-ray dark-
field imaging using a grating interferometer. *Nature materials*, 7(2):134–137,
2008.


