IMAGING WITH DIFFUSE PHOTON DENSITY WAVES
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DEDICATION

This work is dedicated to
Mom, Dad,
Terry, Stephen, Kathleen,
and Surge.
ACKNOWLEDGEMENTS

Because my project has straddled the mutually exclusive worlds of Penn physics and Penn biophysics, it has been my privilege to have had the guidance of two advisors, Dr. Britton Chance from the Biochemistry and Biophysics Department, and Dr. Arjun Yodh from the Physics department.

Arjun Yodh provided me with many of the ideas and helped me learn the physics I needed to solve some difficult problems. I thank him for the many nights and weekends he spent helping me with papers and presentations. In the physics department I took my courses, and exams, and defended this thesis. Dr. Ralf Amado has been a constant support throughout this process. Tony Dinsmore, Peter Kaplan and especially Xingde Li, have been valuable coworkers from the physics department.

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Acknowledgements

without David’s support.
Diffusing photons can be used to probe and characterize optically thick turbid samples such as paints, foams and human tissue. In this work, we present experiments which illustrate the properties of diffuse photon density waves. Our observations demonstrate the manipulation of these waves by adjustment of the photon diffusion coefficients of adjacent media. The waves are imaged, and are shown to obey simple relations such as Snell's Law.

Next we present images of heterogeneous turbid media derived from measurements of diffuse photon density waves. These images are the first experimental reconstructions based on frequency-domain optical tomography. We demonstrate images of both absorbing and scattering homogeneities, and show that this method is sensitive to the optical properties of a heterogeneity. The algorithm employs a differential measurement scheme which reduces the effect of errors resulting from incorrect estimations of the background optical properties.

In addition to imaging absorption and scattering changes, we are also able to image the lifetime and concentration profile of heterogeneous fluorescent media.
## Contents

1 Introduction

1.1 Historical Perspective .................................. 2
1.2 Photon Diffusion Equation ................................. 5
1.3 Introduction to Optical Imaging ............................ 6
  1.3.1 Forward Models .................................... 6
  1.3.2 The Inverse Problem ................................. 10
1.4 Resolution .................................................. 11
1.5 Contrast .................................................... 13

2 Optics for Diffuse Photon Density Waves .................. 17

3 Hardware Specifications ................................. 33

3.1 Photon Detection - Photomultiplier tubes ................ 34
3.2 Photon Detection - Avalanche Photodiodes ................ 39
3.3 Laser diodes .............................................. 42
3.4 Amplitude-phase detector ................................ 44
3.5 Signal Generators ......................................... 46
3.6 Filters ..................................................... 47
3.7 Mixers ..................................................... 51
3.8 Summary ................................................... 51

4 Imaging the Absorption Coefficient ......................... 55

4.1 The Heterogeneous Diffusion Equation .................... 56
4.2 Born Approximation ........................................ 56
4.3 Rylov Approximation ....................................... 58
4.4 Breakdown of the Born and Rylov Approximations ........... 59
4.5 Inverting the Solutions to the Heterogeneous Diffusion Equation ...... 60
4.6 Singular Value Decomposition ............................. 64
4.7 Algebraic Reconstruction Techniques ....................... 69
4.8 Data Analysis .................................................. 72
4.9 Experimental and Computational Results ...................... 79
4.10 Updating the Weight Functions ............................. 80
4.11 Resolving Multiple Objects ................................. 83
4.12 DPDW Imaging Combined With Other Imaging Modalities ........... 84
4.13 Finite Systems .................................................. 92

5 Imaging the Scattering coefficient ................................. 95
5.1 Born Expansion .................................................. 96
5.2 Rylov Expansion ................................................ 97
5.3 Matrix Equations ............................................... 101

6 Absorption and Scattering ........................................... 105
6.1 Simulation Results .............................................. 106

7 Imaging Fluorescence ................................................. 111
7.1 Fluorescent Diffuse Photon Density Wave Theory ............. 112
7.2 Localizing Fluorescent Objects ............................... 116
7.3 Tomographic Imaging of Fluorescent Objects .................. 123

8 Summary ............................................................ 133

A Singular Matrices ................................................... 135

B Time Resolved Spectroscopy ...................................... 137
C Time Domain Fluorescent DPDW Derivation 141

D Back Projection 143

E The Photon Migration Imaging Software Package 147
  E.1 Sample PMI scripts 149
  E.2 PMI Command Summary 152

F Parallel Processing 177
List of Figures

1.1 Absorption spectra of major tissue chromophores. 3
1.2 A simplified schematic of the RunMan\textsuperscript{TM} instrument. 4
1.3 A typical RunMan\textsuperscript{TM} oxygenation trace 4
1.4 A reconstruction of two absorbing objects 7
1.5 Sample weight distributions for CAT and diffuse photon imaging. 8
1.6 Sample weight distributions for a pulsed source on the surface of a semi-infinite medium. 9
2.1 Experimental DPDW phase contours. 24
2.2 Refraction of DPDW’s. 27
2.3 Refraction by a spherical surface 28
2.4 The amplitude and phase of a simulated phased array 29
2.5 The amplitude and phase of scanned phased array 30
2.6 Three possible configurations for the phased array measurements. 31
3.1 A schematic of the frequency domain instrument. 34
3.2 The spectral sensitivity and quantum efficiency of the R928 PMT. 36
3.3 Experimental setup for testing the amplitude-phase cross-talk of the PMT. 37
3.4 The dynode structure and position sensitivity of the R928 PMT. 38
3.5 Holding the DC current from the PMT constant reduces the amplitude-phase cross-talk. 39
3.6 The current versus voltage curve of an ideal zener diode. 39
3.7 A Zener diode is used to reduce the space-charge effect on the phase. 40
3.8 Schematic of a silicon photo-diode. .................................. 42
3.9 The spectral sensitivity and quantum efficiency of the photodiode in
an APD. ................................................................. 43
3.10 An AC signal is capacitor coupled to the laser diode driving current. . 44
3.11 A schematic of the lock-in amplifier .................................... 45
3.12 Amplitude-phase cross-talk of the SRS530. .............................. 47
3.13 Twin-T bandpass filter ............................................... 48
3.14 The response of the twin-T band-pass filter at several different Q. . 49
3.15 Amplitude-phase cross-talk of the twin-T filter ......................... 49
3.16 RLC bandpass filter ................................................. 50
3.17 Amplitude-phase cross-talk of the RLC filter .......................... 50
3.18 Schematics of sample mixers ......................................... 52

4.1 Schematic of the Born solution to the heterogeneous diffusion equation. 58
4.2 A comparison of the Born and Rytov approximations .................. 60
4.3 A typical scanning geometry and volume digitization .................. 62
4.4 Linear algebra definitions for SVD ..................................... 66
4.5 Eigenvalue smoothing algorithm for singular value decomposition .... 68
4.6 Algebraic reconstruction .............................................. 70
4.7 Algebraic reconstruction using noisy or incomplete data ............... 71
4.8 Reconstructed absorption images as a function of SIRT iteration .... 72
4.9 Geometry of the reference measurements ................................ 74
4.10 Reconstructions of absorption when the background absorption is mis-
estimated - no SIRT constraints ....................................... 77
4.11 Reconstructions of absorption when the background absorption is mis-
estimated - with SIRT constraints .................................. 78
4.12 Reconstruction of a single perfect absorber ............................ 80
4.13 Reconstruction of a series of absorbing spheres ........................ 81
4.14 Resolution of two absorbing spheres .................................. 85
4.15 An overly simplified breast model .................................... 86
4.16 1st and 2nd iteration of reconstructed absorption versus the true value, for a single spherical inhomogeneity. .......................... 89
4.17 Simulation with six absorbing inhomogeneities. ................. 89
4.18 A tissue phantom simulating a human breast ................... 91
4.19 A schematic of the image sources and image objects needed to model a semi-infinite boundary condition. ......................... 93

5.1 The reconstruction of a highly scattering sphere. .............. 102
5.2 Reconstructed scattering images as a function of SIRT iteration ... 103

6.1 Simultaneous reconstructions of absorption and scattering. ..... 108
6.2 Effect of absorption versus scattering variation on amplitude and phase. 109
6.3 Reconstruction of absorption and scattering using amplitude and/or phase data ................................................. 110

7.1 A schematic of fluorescent DPDW generation. ................. 115
7.2 Experimental measurements of fluorescent diffuse photon density waves. 118
7.3 Experimental measurements of fluorescent diffuse photon density waves from a cylindrical object. ......................... 118
7.4 A device for localizing the center of a fluorescent object. .... 120
7.5 The estimated position of a reradiator using the fitting algorithm. . . 121
7.6 Localization of a fluorescent object using a phased array. ........ 122
7.7 Images proportional to fluorophore concentration show spurious voxels with unphysical optical properties. ....................... 126
7.8 A plot of $\tan^{-1}(\omega \tau)$ versus $\omega \tau$ shows the saturation effect for $\omega \tau$ greater than 1. .............................. 127
7.9 Reconstruction of fluorophore lifetime and concentration in a system with no background fluorophore. ...................... 128
7.10 A cartoon describing the breakdown of the background fluorescence problem. ................................................. 129
7.11 Reconstruction of fluorophore lifetime and concentration in a system with background fluorophore. .............................. 131

B.1 A schematic of the TRS system ................................. 138
B.2 Signal processing by the constant fraction discriminator (CFD) .... 138
B.3 Equivalent circuit for the time amplitude converter (TAC). ........ 138

D.1 The measurement geometry for the NIM back-projection imaging project. 145
D.2 Sample back-projection images for a solid block sample with an embedded heterogeneity. ........................................... 145

F.1 An overview of the PMI software ............................ 178
F.2 A block diagram of the flow of the parallel code. .......... 179
F.3 The CPU times for various homogeneous and heterogeneous systems. 181
List of Tables

1.1 Popular forward models for photon diffusion imaging. 10
1.2 Popular inverse models for photon diffusion imaging. 12
2.1 The optical properties of human tissues. 18
3.1 Specifications of the Hamamatsu R928 photomultiplier tube. 35
3.2 Specifications of the Hamamatsu C5658 Avalanche photodiode. 41
3.3 Specifications of the Sharp LT022MD laser diode. 43
3.4 Specifications of the SRS530 46
4.1 Reconstruction results for multiple absorbing inhomogeneities. 90
F.1 The clock and CPU times for 1, 2, 4 and 8 node trials. 182
Chapter 1

Introduction

In this work, we will explore how light travels through highly scattering media. Although we are primarily concerned with light diffusion through tissue for medical diagnostic purposes, there are many applications of interest. For example, clouds, paint and foams are all highly scattering media. We model the transport of light through the media as a diffusion process. The analysis used here can be applied to other diffusional processes such as heat diffusion, neutron diffusion, or chemical diffusion.

In this chapter we will briefly review some uses of light in medical diagnostics. Next we will give an overview of diffuse photon imaging. As in most imaging techniques, creation of an image requires an understanding of the interaction between the probe and the media (i.e. the forward model). The forward model relates a measurement to the optical properties of the medium. When the forward problem is well understood, a series of measurements are made, and finally, the measurements and the forward model are used together to derive a map of the properties of the medium (i.e. the inverse problem). We will outline some popular forward models and inversion methods, and discuss the resolution of diffusive wave based optical imaging and the types of contrasts measurable using optical probes.
1.1 Historical Perspective

As early as 1929, researchers investigated passing bright light through the body to create shadow images [1]. These transillumination images were of poor quality because light is multiply scattered as it passes through tissue, and it is difficult to separate scattering effects from absorption effects. In the past 20 years, a better understanding of how photons travel through tissue has enabled researchers to correlate internal physiological changes to optical changes. We and other investigators have begun to image these optical changes using a variety of methods.

As the diagnostic power of optical measurements is improved, optical measurements are expected to gain wider acceptance within the medical community. Recent technological developments afford the possibility of compact, low cost medical optical instruments. In low power (less than 100 mW peak power) near infra-red studies, the developments include light emitting diodes and laser diodes, which replace table top laser systems used in research laboratories, and solid state detectors such as the avalanche photodiode which have a fast response time and broad spectral sensitivity.

Most medical optical instruments use single scattering to probe tissue at or near its surface. Laser Doppler flow-meters and angiograms are examples of near surface measurements. In this work we are interested in developing instruments which probe more deeply (3 - 10 cm) into the tissue.

An example of an instrument which uses multiply scattered light is the finger pulse meter. Here the amount of light which passes through a patient’s finger changes as blood pressure causes vessels to expand and contract. As the finger fills with blood and expands, the amount of transmitted light decreases. This change in transmission is currently used to continuously, and non-invasively monitor the pulse rate of many intensive care patients.

An improvement to the pulse meter introduces the use of spectral filters to compare light transmission at different wavelengths. If we examine the water absorption spectra of the major tissue chromophores (figure 1.1), we see that in the near infra-
red, the absorption is low, and there is a crossover point between oxygenated and de-oxygenated hemoglobin. In simple devices such as the RunMan\textsuperscript{TM} [2] shown in figure 1.2, two wavelengths are used to measure qualitative trends in blood oxygenation (see figure 1.3). The optical probe consists of a pair of small tungsten light bulbs which give brief flashes of light every second (The peak power is less than 1 W, the average power is less than 0.5W.) The white light migrates through the tissue and is collected by silicon diode detectors at wavelengths selected by gelatin optical filters at the surface of the detector. Typically one detector uses a 760 nm filter, and the other a 850 nm filter. It is assumed that the blood is the prominent absorber at these wavelengths, so the absorption at 760 nm is predominately from de-oxygenated hemoglobin.
Figure 1.2: A simplified schematic of the RunMan$^TM$ instrument.

Figure 1.3: A typical RunMan$^TM$ oxygenation trace. Courtesy of B. Chance, University of Pennsylvania. Note that as the exercise begins, the muscle contracts and the blood volume decreases. This results in a decreased absorbence in both 760 nm and 850 nm light. At the same time, the muscle begins to use oxygen resulting in a decrease in oxygenated blood concentration (850 nm) and an increase in de-oxygenated blood concentration.
and the absorption at 850 nm is predominately from oxygenated hemoglobin. The sum of the two signals is an indicator of blood volume changes, and the difference is an indicator of a change in oxygenation. These qualitative trends are used in exercise studies for professional athletes, analysis of myoglobin disorders, and the detection of hematomas.

1.2 Photon Diffusion Equation

In 1988 Patterson et al. [3] experimentally demonstrated that the propagation of light through tissue is well described by a diffusion equation. Thus analogies between light transport in tissues and the theories of heat diffusion and neutron diffusion were possible. This idea allowed researchers to quantify the average absorption and scattering of a region of tissue by fitting the diffusion solution to their measurements. These early experiments were performed with a pulsed laser source and a time resolved measurement of the response. Researchers quickly realized that similar experiments could be done in the frequency domain using amplitude modulated light sources, and measuring the amplitude and phase of the diffusing photon density waves [4]. For amplitude modulated sources in homogeneous media, the diffusion equation for the oscillating part of the light energy density reduces to a Helmholtz equation with simple spherical wave solutions. Microscopically, the waves are composed of random walking photons with a random walk step on the order of 1 mm, but macroscopically, the photons add to form a damped, scalar wave of photon density with a wavelength on the order of 10 cm in biological tissue. We will refer to this wave as the diffuse photon density wave (DPDW).

The wave analysis allows us to draw analogies from the field of electromagnetic radiation, providing valuable insight, as well as computational ease. These waves have been shown to diffract around an edge [5], refract and obey Snell’s Law [6], diffract or scatter from localized heterogeneities [7], and exhibit well defined dispersion characteristics [8]. The properties of DPDW’s have been verified in both biological models [5] and human breast studies [9]. We have shown that DPDW’s scatter from large
spherical inhomogeneities in a way that is similar to, but simpler than, Mie scattering [10]; and that DPDW’s in a fluorescent medium are absorbed and then re-radiated creating fluorescent DPDW’s whose wavelengths are governed by the optical properties of the medium at the Stoke-shifted optical wavelength [7, 11, 12].

1.3 Introduction to Optical Imaging

Since the advent of the photon diffusion equation, researchers have struggled to accurately measure the optical properties of biological systems. For example, the head is made up of blood, white matter, grey matter, bone, skin, etc. Each of these types of tissues has different optical properties. If one assumes a homogeneous model to calculate the average optical properties, one cannot obtain accurate values for the absorption and the scattering. Instead, an average value of the tissue optical properties is derived. Thus, there has been a great deal of interest in creating a quantitative map or “image” of the optical properties. In particular, physicians are interested in functional imaging and the localization and characterization of tumors and hematomas.

A sample optical image is shown in figure 1.4. The sources and detector are scanned around the region of interest as shown in (a), and the measurements are used to reconstruct a map of the absorption.

The methods and algorithms one uses to image with diffuse photons are similar in many ways to x-ray tomography. A source and detector are scanned around the surface of the tissue volume of interest, and the measurements are inverted to reconstruct the optical properties within the tissue volume as a function of position. Although most of the images created to date are of tissue phantoms, preliminary images have been generated of breast [13] and neonatal brain [14].

1.3.1 Forward Models

Nearly all imaging algorithms can be divided into two stages. First, an algorithm must have a model of the forward problem. The forward model describes the passage of photons through the heterogeneous medium. For the image reconstruction, the
Introduction

Figure 1.4: A reconstruction of two absorbing objects. (a) The scanning geometry. The sources and detector scan around the edges of a 5 x 5 x 1 cm region while two absorbing spheres are hidden in the region (b). (c) The reconstructed absorption map. (Born approximation, 3000 SIRT iterations)

region of interest is divided into a set of volume elements (voxels). Generally, the forward algorithm provides a weight (or importance) to each voxel within the sample volume, and the measured signal is a function of these weights. One can think of the weights as being proportional to the probability of photons from a source reaching a particular voxel, and then continuing on to reach the detector position. We will derive precise definitions of the weights in chapter 4.

In x-ray tomography, it is assumed that the intensity signal decays exponentially as it passes in a straight line from source to detector. In this case the log of the measured intensity ($I$) divided by the initial intensity ($I_0$) is

$$ln(I/I_0) = \int_0^L \alpha(l) dl$$

where $L$ is the source-detector separation, and $\alpha(l)$ is the absorption coefficient as a function of position, $l$ along the line connecting the source and detector. The unknowns are the position dependent x-ray absorption coefficients. This equation may be digitized into $N$ pieces of length $h$,

$$ln(I/I_0) = -\sum_{j=0}^{N} \alpha_j h$$

Measurement $= \sum$ unknown $\times$ weight.  

$$\sum$$
Now we have a relation between the transmission measurement and the unknown, $\alpha_j$. The relation is a function of a calculable quantity called the weight. In this case the weights along the line are all -h.

Traditional imaging techniques such as x-ray tomography typically give equal, non-zero weights along the source-detector line of sight, and zero weights elsewhere. This is a good approximation because detected x-rays do not scatter very much as they move through the tissue, so detected x-rays rarely sample tissue outside of this line. In diffuse photon imaging, the diffusive waves emanate spherically outward from a source, and thus sample tissue well outside the straight line of sight. The weights are usually non-zero over most of the region of interest as shown in Figure 1.5.

In our lab, we developed a forward model which is an approximate solution to the heterogeneous diffusion equation. (In particular we use either a Born or Rytov approximation.) These solutions give us explicit forms for the weights which are functions of the properties of the medium, the modulation frequency, and the position of the source and detector.

Other investigators have chosen to use empirical weights based on measurements made in model systems. For example, investigators have placed a small point-like absorbing object in an otherwise homogeneous medium and determined its effect on the measured signal [15]. By moving this object to each voxel, one can generate a set
Introduction

Figure 1.6: Sample weight distributions for a pulsed source on the surface of a semi-infinite medium.

of weights for a particular source detector geometry. These weights have been verified in simple geometries using a three point Green function approach [15]. Studies such as these have shown that the weights in a semi-infinite medium may be roughly described by the so called “banana function” (see figure 1.6). Nioka et al. have developed a model in which the weights are generated by hand based on this banana pattern [2].

A numerical solution to the heterogeneous diffusion equation using finite difference, finite element or Monte Carlo simulation are other robust but time consuming methods of generating the weights. The advantage of these calculations is that they can accurately model irregular boundary conditions and heterogenous media. The analytic solution for a homogeneous system with an embedded spherical or cylindrical object can also be used to generate the weights. As a rule, the more approximate models such as the straight line approximation, and the empirical functions are quick to calculate. The most precise models such as the finite difference and Monte Carlo can take days to calculate. Table 1.1 lists some of the popular forward models with a rough estimate of the calculation time for each.
Table 1.1: Popular forward models for photon diffusion imaging. These times are rough estimates for a system with about 100 source-detector pairs and 500 voxels covering a 6 cm x 6 cm x 2 cm area.

### 1.3.2 The Inverse Problem

The object of tomographic imaging is to use some set of measurements to solve for the properties of the medium. We will see in chapter 4 that for forward model may be written in the following form;

\[
\text{measurement} = \int_V \text{weight} \times \text{unknown}. \quad (1.4)
\]

Using Fourier transform methods, it may be possible to invert this integral equation to solve for the unknowns. These methods are currently under investigation in our laboratory and in other laboratories [23, 24]. This equation can be approximated as a discrete matrix equation;

\[
\text{measurement}_i = \sum_j \text{weight}_{ij} \times \text{unknown}_j. \quad (1.5)
\]

Where \(i\) enumerates the measurements, and \(j\) enumerates the voxels. After specifying the forward model which describes the passage of photons through heterogeneous
Introduction

media, the investigator must then invert the problem to solve for the unknown optical properties in each voxel.

Table 1.2 lists some of the popular inversion methods. One set of methods is to directly invert the forward equations to solve for the unknowns. Theoretically, the direct matrix inversion should yield the unknowns in equation 1.5. But the inversion of a large matrix is a time consuming calculation, and due to the nature of the problem, the solutions are not unique. We will use regularization techniques to control the uniqueness problem. In addition, the inverse matrix can be pre-calculated and stored before the experiment.

There are many error minimization routines which find the unknowns by fitting the forward model to the measured data. The error minimization routines mainly differ in the way that they move from an initial guess toward the correct solution. Some error minimization methods, such as the algebraic reconstruction techniques (ART), are only valid for linear equations. In our lab we use both ART and a direct matrix inversion to create images. The relative merits of these techniques are discussed in chapter 4.

Back-projection algorithms, often used in creating x-ray images, are gaining popularity in photon imaging, especially for two dimensional projection images. Generally, a back-projection algorithm will give a fast, rough image. In some cases we have used a modified back projection method which is briefly described in appendix D.

1.4 Resolution

The resolution of images with diffuse photons is ultimately limited by the underlying length scale of the diffusion theory, the random walk step of the photon (typically about 1 mm in tissue). In our experiments, we have resolved two 1.2 cm diameter spheres separated by a center-to-center distance of 2 cm. The resolution is dependent on the wavelength of the DPDW. The shorter the wavelength, the better the resolution. However, the positive effect of shortening the wavelength is offset by the fact that the amplitude of the wave decays exponentially at a spatial rate inversely
<table>
<thead>
<tr>
<th>Method</th>
<th>Typical CPU Time</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Direct Inversion</td>
<td></td>
<td></td>
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<tr>
<td>matrix inversion</td>
<td>hours</td>
<td>[19],[25],[18]</td>
</tr>
<tr>
<td>Fourier transform</td>
<td>seconds</td>
<td>[23],[26],[24]</td>
</tr>
<tr>
<td>Error Minimization</td>
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<td>algebraic reconstruction - ART</td>
<td>minutes</td>
<td>[17],[18],[19]</td>
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<tr>
<td>conjugate gradient</td>
<td>minutes</td>
<td>[17]</td>
</tr>
<tr>
<td>projection onto convex sets - POCS</td>
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<td>[17]</td>
</tr>
<tr>
<td>least squares fitting</td>
<td>minutes</td>
<td>[20],[22]</td>
</tr>
<tr>
<td>Back-Projection</td>
<td>seconds</td>
<td>[15],[14],[2]</td>
</tr>
</tbody>
</table>

Table 1.2: Popular inverse models for photon diffusion imaging. These times are rough estimates for a system with about 100 source-detector pairs and 500 voxels covering a 6 cm x 6 cm x 2 cm area.
proportional to the wavelength ($e^{kr}$). The shorter the wavelength, the smaller the measured signal. The wavelength can be shortened by increasing the modulation frequency or increasing the background absorption or scattering.

Boas et al. have used a noise analysis to study the limits of object detection and characterization [22]. The authors found that using a simulation based on realistic positional uncertainties and shot noise, objects whose optical properties are approximately twice the background levels and are 3 mm or larger can be detected and localized; and objects 5 mm or larger can be characterized. The authors studied a system designed to model a lightly compressed breast with an embedded tumor [27].

1.5 Contrast

Optical imaging provides fundamentally different information than MRI, x-ray or ultrasound imaging. Although we generate low resolution images, the contrasts are optical properties, and this opens the door to a host of new physiologic mechanisms. In our lab we have imaged absorption [28], the mean photon scattering length [18] (reduced scattering coefficient) and fluorophore lifetime and concentration [12]. In this thesis, we will concentrate on these studies. Other work in our lab has demonstrated imaging of the dynamic properties of scatterers, such as Brownian motion and flow in model systems [29].

It important to note that by varying the incident optical wavelength it becomes possible to perform spectroscopy in each of these contrasts. Researchers are just beginning to investigate and quantify the optical changes which accompany physiologic changes in the body. There is considerable evidence that mitochondria are the dominant light scatterers in most tissues [30]. This corroborates studies which show that a rapidly growing tumor, which has an increased concentration of mitochondria, is generally more highly scattering than the surrounding tissue [31]. A tumor also has an increased vascularity, and thus a higher absorption due to the high volume fraction of blood [31].

In the past two years, there has been a great deal of interest in the non-invasive
detection of glucose changes in the body [32, 15]. Since scattering depends on a mis-
mismatch in the index of refraction, the presence of solutes such as glucose or potassium,
which change the index of refraction of the intra- or extra-cellular fluid change the
scattering properties of the system.

In addition to natural optical changes, a wide range of optical dyes have been
developed for medical purposes. For example, the lifetime of some fluorescent dyes
has been shown to vary with the amount of oxygen in its environment [33]. Some
dyes have already been approved by the FDA for other uses, but happen to be quite
useful for near infra-red imaging. Indocyanine green (ICG) has been used in liver
studies for over 20 years. Usually the dye is injected into the blood stream, and small
volumes of blood are taken every minute. The rapid decrease of ICG in the blood
indicates a that a healthy liver is removing the ICG.

It is possible that ICG will prove to be a useful contrast agent for optical tumor
detection. ICG has a strong absorption peak in the near infra-red (at 780 nm),
and fluoresces at 830 nm making it an excellent candidate for optical studies. ICG’s
molecular size is roughly the same as gadolinium chelate. Gadolinium chelate has been
shown to leak from the blood vessels in a rapidly growing tumor, and is currently
used as a MRI contrast agent for tumor detection.

The remainder of this thesis will follow the outline below. After a discussion of
diffuse photon density waves (chapter 2), the experimental apparatus we use to mea-
sure the amplitude and phase of the waves will be discussed (chapter 3). Then we
move on to imaging. In chapter 4 we discuss the forward model and inverse algo-
rithms used to image inhomogeneous absorption. Computer simulated experiment
and experimental results are shown. Next we describe a parallel analysis for inho-
mogeneous scattering (chapter 5). Finally, we examine systems with both absorption
and scattering changes (chapter 6). In chapter 7 we discuss diffuse photons in a
fluorescent media. We develop the theory which describes fluorescent diffuse photon
density waves, show how these fluorescent waves can be used to locate the center of
a fluorescent object, and finally we show that the lifetime and concentration of fluo-
ropohore can be tomographically imaged in a manner similar to the absorption case. Additional background information on singular matrices, time resolved spectroscopy and the time-domain fluorescent DPDW derivation is given in appendices A, B, and C respectively. The results of some preliminary back-projection imaging work are shown in appendix D. Appendix E gives an overview of the PMI software program developed in our lab, and appendix F demonstrates a increase in PMI processing speed using parallel processing.
Chapter 2

Optics for Diffuse Photon Density Waves

In order to develop models for the forward and inverse problems, we must first understand how photons travel through homogeneous media. In this section we begin by describing the passage of photons through homogeneous media, and later incorporate heterogeneous media using planar and curved boundaries. In this work we treat the photons as particles, ignoring polarization and interference effects. This approach is valid when the mean free path for photon scattering \((1/\mu_s')\) is much smaller than the absorption length \((1/\mu_a)\) and much smaller than the sample size. The optical properties of some human tissues (table 2.1) demonstrate that this approximation is good for systems such as the brain or breast, and source detector separations of a few random walk steps.

As light enters such a medium, the photons undergo a random walk. When the source-detector separation is much greater than the random walk mean free path, the photon propagation can be modeled by the diffusion approximation to the Boltzmann transport equation [3].

\[
\frac{\partial U(r, t)}{\partial t} + v \mu_s U(r, t) + \nabla \cdot J(r, t) = q_o(r, t), \tag{2.1}
\]
\[
\nabla U(r, t) + \frac{3\partial J(r, t)}{v^2} + \frac{J(r, t)}{D} = 0 \tag{2.2}
\]

where \(U\) is the photon density (number of photons per unit volume), \(J\) is the photon current density (number of photons per unit area per unit time), \(q_o\) is the isotropic source term (number of photons per unit volume per unit time), \(v\) is the speed of
<table>
<thead>
<tr>
<th>Tissue Type</th>
<th>Optical Wavelength (nm)</th>
<th>$\mu_a$ (cm$^{-1}$)</th>
<th>$\mu'_s$ (cm$^{-1}$)</th>
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<td>811</td>
<td>0.09</td>
<td>10.5</td>
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<td>9.5</td>
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<td>Breast, ductal carcinoma</td>
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<td>Grey Matter</td>
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<td>Whole Blood, partially oxygenated</td>
<td>630</td>
<td>14.3</td>
<td>8.9</td>
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</table>

Test descriptions

(1) In vivo, frequency scanning device. See [34] (2) Frozen sections, thawed; 1 mm slabs for (R,T) single integrating sphere with monochromator for R and T; 2-polarizers to filter scattered axial light for direct T. (3) Freshly resected slabs, integrating sphere. (4) diluted, heparinized, in cuvettes; absorbence+goniometry. (5) Freshly drawn, heparinized (anti-clotting agent added), oxygenated at atmospheric equilibrium; semi-infinite slab (Rd); thin cuvettes diffuse R of whole blood; direct T of diluted blood, hemolyzed RBC’s, and centrifuge-isolated plasma.

Table 2.1: The optical properties of human tissues.
Downloaded from ftp://laser.mda.uth.tmc.edu/pub/
light in the medium, \( \mu_a \) is the absorption coefficient, \( D \) is the diffusion coefficient,

\[
D = \frac{v}{3\mu_s},
\]

and \( \mu'_s \) is the reduced scattering coefficient. The scattering coefficient \( \mu_s \) is the reciprocal of the scattering length. The reduced scattering coefficient is the reciprocal of the random walk step, i.e. the average length it takes for a photon’s direction to become random. The scattering coefficient and the reduced scattering coefficient are related by the single-scattering anisotropy factor, \( g \), a measure of how much of the incident light is scattered in the forward direction. Specifically, it is the average of the cosine of the single-scattering scattering angle.

\[
\mu'_s = \mu_s (1 - g) = \mu_s (1 - < \cos \theta >)
\]

In typical biological tissues, the scattering is predominately in the forward direction \( (g = 0.9) \). For example, in breast tissue, the scattering length is about 0.1 mm, but the random walk step is 1 mm, that is it takes about 10 scattering events for the photon direction to become random with respect to its incident direction.

If the source is an amplitude modulated point source of the form,

\[
q_\nu(r, t) = \delta(r)\{A + Be^{-i\omega t}\},
\]

then our solutions \( U \) and \( J \) will have ac and dc parts i.e.

\[
U(r, t) = U_{dc}(r) + U_{ac}(r)e^{-i\omega t},
\]

\[
J(r, t) = J_{dc}(r) + J_{ac}(r)e^{-i\omega t}.
\]

The differential equations for the dc parts are:

\[
v \mu_a U_{dc}(r) + \nabla \cdot J_{dc}(r) = A\delta(r),
\]

\[
\nabla U_{dc}(r) + \frac{J_{dc}(r)}{D} = 0
\]

so

\[
v \mu_a U_{dc}(r) - \nabla \cdot (D\nabla U_{dc}(r)) = A\delta(r)
\]

\[
v \mu_a U_{dc}(r) - D\nabla^2 U_{dc}(r) = A\delta(r).
\]
Here we have used the fact the $D$ is homogeneous so $\nabla D = 0$. The general solution for $U$ is a superposition of the two spherical wave solutions,

$$U_{dc} = C_1 \frac{e^{-kr}}{4\pi Dr} + C_2 \frac{e^{kr}}{4\pi Dr}, \quad (2.12)$$

$$k = \sqrt{\frac{v\mu_a}{D}}, \quad (2.13)$$

The constant $C_2$ must be zero to satisfy the boundary condition that $U_{dc} = 0$ at infinity. When we plug the particular solution into the Helmholtz equation we see that $C_1 = A/D$.

In this work we are generally most interested in the ac components of equation 2.1 and 2.2:

$$-i\omega U_{ac}(r) + v\mu_a U_{ac}(r) + \nabla \cdot \mathbf{J}_{ac}(r) = B\delta(r), \quad (2.14)$$

$$\nabla U_{ac}(r) + \frac{-3i\omega \mathbf{J}_{ac}(r)}{v^2} + \frac{\mathbf{J}_{ac}(r)}{D} = 0 \quad (2.15)$$

Thus,

$$\mathbf{J}_{ac}(r) = \frac{-D}{1 - 3i\omega D/v^2} \nabla U_{ac}(r). \quad (2.16)$$

For most biological tissues of interest,

$$1 >> 3\omega D/v^2. \quad (2.17)$$

For example, for breast tissue, $D \approx 10^9$ m$^2$/s, and we typically use $\omega \approx 5 \times 10^8$ s$^{-1}$ so $3\omega D/v^2 \approx 0.002$. So

$$\mathbf{J}_{ac}(r) \approx -D\nabla U_{ac}(r). \quad (2.18)$$

We now plug equation 2.18 into 2.14,

$$-D\nabla^2 U_{ac}(r) + (-i\omega + v\mu_a)U(r) = B\delta(r), \quad (2.19)$$

$$(\nabla^2 + k^2)U(r) = -B\delta(r)/D. \quad (2.20)$$

Again, we have used the fact that $D$ is homogeneous. The particular ac solution to this Helmholtz Equation in an infinite medium is

$$U(r) \equiv U_{ac}(r) = \frac{B e^{ikr}}{D 4\pi r} \quad (2.21)$$
where

\[ k^2 = (-v \mu_a + i \omega)/D, \]  \quad (2.22)

\[ k = \Re(k) + i \Im(k) \] \quad (2.23)

**Real part**: \[ \Re(k) = \left(\frac{v^2 \mu_a^2 + \omega^2}{D}\right)^{1/4} \sin \left(\frac{1}{2} \tan^{-1} \left(\frac{\omega}{v \mu_a}\right)\right) \] \quad (2.24)

**Imaginary part**: \[ \Im(k) = \left(\frac{v^2 \mu_a^2 + \omega^2}{D}\right)^{1/4} \cos \left(\frac{1}{2} \tan^{-1} \left(\frac{\omega}{v \mu_a}\right)\right). \] \quad (2.25)

Thus, a damped, scalar, spherical wave of light energy density is generated by the source at the origin. The wave has a well-defined amplitude and phase at each position, \( r \).

In this section we will experimentally demonstrate that a great deal of traditional optics can be applied to DPDW’s - albeit in the near field. For example, we will show that these waves interfere and refract. Other work from our lab has demonstrated that DPDW’s diffract and scatter from heterogeneities [7]. The mathematics is slightly different from electromagnetic optics, because the disturbance is a scalar wave, i.e.

\[ EM \ \text{wave}: \ \vec{E} = \vec{E}_0 \frac{e^{i k \vec{r}}}{4\pi |\vec{r}|} \quad \text{DPDW:} \ U = A_0 \frac{e^{i k |\vec{r}|}}{4\pi |\vec{r}|}. \] \quad (2.26)

The fact that we have a scalar wave implies fewer degrees of freedom for the wave, and less complex boundary conditions. This generally simplifies the calculations. It is interesting that because the wavelength is on the order of 10 cm, and we make measurements with typical source-detector separations of 6 cm, we are making near field measurements. This means that the conventional ideas about resolution, which were derived from the far-field approximation, do not apply. For instance, the Rayleigh criteria for fundamental resolution limits states that two objects cannot be resolved if they are within \( \lambda/2 \) of each other. This is not true for diffusive imaging. In fact, we have shown through experiment that one can clearly resolve two objects which are separated by a distance of less than \( \lambda/4 \) (see figure 4.14). In diffusive imaging the fundamental resolution limit is the graininess of the theory, the random walk step governing diffusion theory. In practice, the resolution and characterization limits are determined by signal to noise considerations [22].
We begin by demonstrating that these waves exist in a homogeneous, infinite medium. Our experimental setup consisted of a large fish tank (30 x 30 x 60 cm) filled with a model biological material called Intralipid [35]. Intralipid is a turbid, polydisperse suspension of soy lipid. The particle diameter ranges from about 0.1μm to 1.1μm with an average of about 0.4μm. By changing the solution concentration one can vary the light diffusion constant over a wide range. We typically use concentrations varying from 0.1% (\(D = 7.5 \times 10^9 m^2/s\)) to 1.5% (\(D = 5.0 \times 10^9 m^2/s\)). We can also add inks (such as india ink) and dyes (such as any water soluble laser dye) to vary the absorption coefficient. The absorption of the inks and dyes can be calibrated in a standard spectrophotometer. A laser diode was fiber coupled to the medium using a 0.3 cm diameter fiber bundle, and a similar optical fiber was used to detect diffuse photons. A translation stage enabled measurements of amplitude and phase as a function of position within the tank.

The experimental setup is described in detail in chapter 3. Briefly, source and detector optical fibers (≈3 mm in diameter) were immersed in the solution at the same height above the tank floor (see figure 2.1). The source light was derived from a 3 mW diode laser operating at 780 nm. The diode laser was amplitude modulated at 200 MHz. The detector fiber could be positioned anywhere in the plane, and was connected to a photomultiplier tube on its other end. In order to facilitate the phase and amplitude measurements, both the reference signal from the source and the detected signal were down-converted to 25 kHz by heterodyning with a second oscillator at 200,025 MHz. The low frequency signals were then measured using a lock-in amplifier. The phase shift and AC amplitude of the detected light were measured with respect to the source at each point on a 0.5 cm square planar grid throughout the sample. Constant phase contours were easily determined by linear interpolation of the grid data. Since the signal amplitude decays by a factor of \(e^{2\pi/r}\) in one wavelength, the range of our experiments is limited to slightly more than one wavelength. Nevertheless it is possible to clearly distinguish the essential physical phenomena in the experiments.
Throughout this work, we assume that we have an isotropic point source and a point detector. In reality, we have a finite detector area (usually about 3 mm diameter) and a nearly collimated source fiber with a finite size (usually 1-3 mm diameter). In a collimated source, the light will travel ballistically for approximately one random walk step. After 1 random walk step, a significant portion of the light has been scattered, and the isotropic source approximation is a good approximation. Some researchers place an effective source one random walk step away from the true source to correct for this effect. In this work we have not investigated or used a correction method. This will contribute small errors in the experimental measurements.

Figure 2.1 shows the measured constant phase contours of the disturbance produced by a fiber source located at the origin. First we note that the phase contours are spherical and centered about the source position. Second, both the phase and the log of the amplitude times the source-detector separation are linear with the source-detection separation as shown in the inset of figure 2.1. We can calculate the absorption and scattering coefficients of the medium from the measurements of amplitude and phase. Typically, we characterize a medium by measuring the amplitude and phase as a function of distance. The slopes of these lines give us the real and imaginary parts of the wavenumber \( k \):

\[
\ln(r|U(r)|) = -\Im(k)r + \ln(B) - \ln(4\pi D), \quad (2.27)
\]

\[
\text{phase}(U(r)) = \Re(k)r. \quad (2.28)
\]

Once we know \( k \), we can easily calculate the absorption and and reduced scattering of the medium,

\[
1/\mu_a = \frac{\nu}{\omega} \tan \left( 2 \tan^{-1} \left( \frac{\Re(k)}{\Im(k)} \right) \right), \quad (2.29)
\]

\[
1/D = \frac{\Re(k)^2 + \Im(k)^2}{(\nu^2 \mu_a^2 + \omega^2)^{1/2}}. \quad (2.30)
\]

From these measurements we deduced the wavelength of the diffuse photon density wave (11.2 cm), as well as the photon transport mean free path (0.1 cm), and the
Figure 2.1: Constant phase contours shown as a function of position for homogeneous, 0.5% Intralipid solution. The contours are shown in 20 degree intervals. Inset: The measured phase shift (circles), and $\ln(rU_{ac}(r))$ (squares) are plotted as a function of radial distance from the source $S_o$. 
photon absorption length (52.4 cm) in 0.5% Intralipid at room temperature. The photon absorption can be attributed almost entirely to water [36] at 780 nm.

In figure 2.2 we demonstrate the refraction of these waves in three ways. Figure 2.2 shows constant phase contours (every 20°). This time however, a plane boundary was introduced, separating the lower medium with concentration \([l] = 1.0\%\) and light diffusion coefficient \(D_l\), from the upper medium with concentration \([u] = 0.25\%\) and light diffusion coefficient \(D_u\). The contours below the boundary are just the homogeneous media contours (without reflection); they were obtained before the partition was introduced into the sample. The contours above the boundary were derived from the diffuse photon density waves transmitted into the less concentrated medium. As a result of our detector geometry, our closest approach to the partition was about 1 cm. We expect a number of general results. First, the wavelength in the less dense medium \(\lambda_u = 14.8\ \text{cm}\) should be greater than the wavelength of the diffuse photon density wave in the incident medium \(\lambda_l = 8.17\ \text{cm}\). This was observed. The ratio of the two wavelengths should equal the ratio of the diffusive indices of refraction of the two media. Specifically we found, as expected, that

\[
\lambda_u = \lambda_l \sqrt{\frac{D_l}{D_u}} \approx \lambda_l \sqrt{\frac{l}{u}}.
\]  

We would expect that the apparent source position \(S_i\), as viewed from within the upper medium, should be shifted from the real source position \(S_o = 4.0 \pm 0.2\ \text{cm}\) by the factor \(\lambda_l / \lambda_u = 0.55\). Using the the radii from the full contour plots, we see that the apparent source position is shifted from \(4.0 \pm 0.2\ \text{cm}\) to \(2.0 \pm 0.25\ \text{cm}\).

Finally in figure 2.2 we explicitly demonstrate Snell’s law for diffuse photon density waves. This can be seen by following the ray from \(S_o\) to the point A at the boundary, and then into the upper medium. The ray in the lower medium makes an angle \(\theta_l = 14^\circ\) with respect to the surface normal. The upper ray is constructed in the standard way between the apparent source position \(S_i\), through the point A on the boundary, and into the medium above the boundary [37]. It is perpendicular to the circular wavefronts in the less dense medium, and makes an angle \(\theta_l = 26.6^\circ\) with respect to
the boundary normal. Within the accuracy of the experiment we see that
\[
\frac{\sin(\theta_i)}{\sin(\theta_t)} = 0.54 \approx \frac{\lambda_t}{\lambda_u},
\]
Thus Snell's law accurately describes the propagation of diffuse photon density waves across the boundary. It is interesting to note that the wavefronts become quite distorted when the source ray angle exceeds 30°. These irregularities are a consequence of total internal reflection, diffraction, and some spurious boundary effects.

A third important observation is presented in figure 2.3. We used a circular boundary separating two turbid media to demonstrate that we can alter the curvature of the diffuse photon density wavefronts in analogy with a simple lens in optics. The constant phase contours on the left occur in 20° intervals, and the constant phase contours on the right occur in 40° intervals. The constant phase contours of the transmitted wave exhibit a shorter wavelength, and are clearly converging toward some image point to the right of the boundary. The medium on the left \((l_l)\) has an Intralipid concentration of \([l]\approx 0.1\%\), and the medium on the right \((l_r)\) has a concentration of \([r]\approx 1.6\%\). The wavelength ratio was measured to be \(l_r/l_l = 3.8 \pm 0.3\). The curved surface has a radius \(R = 9.0 \pm 0.4\) cm. The object position (the source) is \(S_o = 9.4 \pm 0.3\) cm, and the image position \(S_i = 10.9\) cm is predicted from the well known paraxial result from geometrical optics for imaging by a spherical refracting surface [37];
\[
\frac{1/|l|}{S_o} + \frac{1/|r|}{S_i} = \frac{1/|r| - 1/|l|}{R}
\]
The image position was measured to be \(S_i = 12 \pm 2\) cm, which is close to the predicted value, 10.9 cm. The image position was found by using a compass to determine the center of the four wavefronts. Although the error in this measurement is large, the central point remains, that is, the curvature of the wavefronts is reversed after traversing the circular boundary.

DPDW's have also been shown to interfere. In much of our work, we will exploit the destructive interference of two DPDW's to increase our sensitivity to heterogeneities [9] and reduce our sensitivity to the background properties. In a typical
Figure 2.2: Constant phase contours (in 20 degree intervals) as a function of position showing the propagation of a diffuse photon density wave across a planar boundary. The solid lines are obtained directly from data. The dot-dashed lines are obtained by interpolation over large distances, and are drawn to show the irregularities at large angles.
Figure 2.3: Refraction by a spherical surface. The reversal of wavefront curvature is evident.

configuration, we use two spatially separated sources, 180° out of phase with each other. The amplitude and phase of such a superposition are shown in figure 2.4. Note that at points equidistant from the two sources, the waves interfere destructively causing an amplitude null and a sharp 180° phase shift in the DPDW. If a detector is scanned along a line parallel to the line connecting the two sources as shown in figure 2.5a, we see more clearly the deep amplitude null, and 180° phase shift. Similarly, if a detector is placed equidistant from the two spatially separated sources, and an object is scanned as shown in figure 2.5b, we see a similar amplitude null and 180° phase shift. One of the exciting effects of the phased array is that when the detector is on the null line, there is no signal from the homogeneous medium. This means that any detected signal is solely due to the presence of a heterogeneity. Such a device is a simple detector for heterogeneities, such as tumors, in highly scattering media such as the breast. We will use this phenomenon to eliminate the background signal when we image heterogeneous media (chapter 4).
Figure 2.4: The amplitude and phase of a simulated phased array
Figure 2.5: The left set of figures shows the measured amplitude and phase as the detector is scanned across the null line and the sources are held still. The right drawings demonstrate the effect of an object which is scanned across the null line. This is equivalent to holding the object fixed and scanning the sources and detector in tandem.
Figure 2.6: Three possible configurations for the phased array measurements.

There are several ways to achieve this superposition of two waves. In the previous discussion, we used two sources, on simultaneously, $180^\circ$ out of phase (figure 2.6a). We also could use one source, make two separate measurements in the two positions, and subtract the two measurements (figure 2.6b). Similarly, we could use one source and two detectors. There are subtle differences between subtracting two measurements and making one simultaneous measurement of two interfering sources. In the two source simultaneous measurement, the sources must be carefully balanced in amplitude and exactly $180^\circ$ out of phase. This balance is difficult given variations in individual laser diodes, and the difficulty increases as the modulation frequency increases. In the second configuration (b), the source strength and phase can be calibrated and then incorporated into the subtraction. However, this method will not work if the system changes in the time between obtaining the left and right measurements. The setup shown in panel (c) allows simultaneous dual measurements. The disadvantage of this system is that two parallel detection systems must be built. In our studies we have generally used the configuration shown in (b).

The experiments depicted in this section indicate that it is possible to exert substantial control over the transport of diffuse light in dense random media. We have clearly demonstrated that the index of refraction of these waves depends on the photon diffusion coefficient or random walk step in these media.
Chapter 3

Hardware Specifications

A schematic of the phase modulation device is shown in figure 3.1. The driving current of a laser diode is modulated at a high (radio) frequency, $\omega = 2\pi f$, causing the output of the diode to be intensity modulated. The modulated light passes through the sample medium, and the intensity is monitored using a photomultiplier tube (PMT). A second radio frequency source with an angular frequency of $\omega + \delta \omega = 2\pi (f + \delta f)$ is used to modulate the gain of the detector. 3 mm diameter multimode fiber bundles deliver the modulated light from the laser source to the medium, and from the medium to the PMT.

The current output of the PMT is proportional to the modulated intensity and the modulated gain (as described in more detail below). By modulating the gain, a “mixed” current composed of sum and difference frequencies is generated. The sum and difference frequency signals are passed through a band pass filter centered around the difference frequency, $\delta \omega$. A reference signal is generated in a similar manner by electronically mixing a portion of the two RF signals and then passing the output reference signal through a similar band pass filter centered at $\delta \omega$. The phase and amplitude of the DPDW are measured with respect to the reference signal using traditional lock-in techniques. In our system we typically use a frequency of around $f = 200$ MHz, and an intermediate frequency of $\delta f = 26.6$ KHz.

A great deal of care must be taken when measuring the phase shift. Many electronic devices will measure phase accurately as long as the amplitude of the signal is approximately constant. Since we have an exponentially damped signal, we expect to
amplitude to vary by more than two orders of magnitude. Each component must be individually tested for amplitude-phase cross-talk. We now discuss each component in more detail.

### 3.1 Photon Detection - Photomultiplier tubes

For photon detection we typically use a Hamamatsu R928 photomultiplier tube (see specifications in table 3.1). This tube has a spectral sensitivity which extends from 250 nm to 800 nm (see figure 3.2), and a rise time of 2.2 ns. Based on the 2.2 ns rise time, the maximum frequency which can be transmitted is about 72 MHz. In general, as the frequency increases, we see an attenuation of the output of the PMT due to this finite rise time. For this reason we modulate the voltage across the second dynode and pass the lower, intermediate frequency along the dynode chain. Although the choice of which dynode to modulate is somewhat arbitrary, we chose the second dynode so that the input signal is slightly amplified before the modulation. The dc voltage across the second dynode is approximately 100V. To modulate this high voltage we need a 50 Volt sine wave. Using a 50 Ohm source, a 50 Volt modulation
### Hardware Specifications

<table>
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<th>Specification</th>
<th>Value</th>
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<tr>
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</tr>
<tr>
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<tr>
<td>Anode dark Current (after 30 Minutes)</td>
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</tr>
<tr>
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<td>2.2 ns</td>
</tr>
<tr>
<td>Transit time</td>
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</table>

Table 3.1: Specifications of the Hamamatsu R928 photomultiplier tube.

requires 1 Ampere of current. To avoid this high current requirement we use a circuit which acts like a transformer to increase the voltage by a factor of 50. To reduce the noise, the circuit is a resonant circuit is designed to pass only the frequency of interest. The specifics of the resonant circuit used for the dynode is beyond the scope of this discussion, and is discussed elsewhere [38].

In a typical PMT configuration, photons strike the photocathode causing electrons to be emitted and subsequently accelerated down the dynode chain [39]. The number of electrons released is proportional to the number of photons striking the photocathode. At each dynode the number of electrons is multiplied, resulting in a total gain of about $10^6$. Thus the current output from the PMT is proportional to the incident light intensity ($A \sin(\phi + \omega t)$) and the gain. In our case, both the light intensity and the gain are modulated. So the current output, $i(t)$ is

$$i(t) = K * \text{Light Intensity} * \text{Gain}$$

$$i(t) = KA \sin(\phi + \omega t) * \sin(\phi_o + \omega t + \delta \omega t)$$
Figure 3.2: The spectral sensitivity and quantum efficiency of the R928 PMT.

\[
\text{PhotoSensitivity (mA/W)}
\]

\[
\text{Quantum Efficiency (%)}
\]

\[
\frac{\text{PhotoSensitivity (mA/W)}}{\text{Wavelength (nm)}}
\]

\[
\frac{\text{Quantum Efficiency (%)}}{\text{Wavelength (nm)}}
\]

\[
K \text{ and } \phi_0 \text{ are constants which depend on the gain, losses, lengths of cables, etc.} [40]. \text{ They are both independent of the sample being measured. Here we have used the identity}
\]

\[
sin(A) * sin(B) = \frac{1}{2} \{cos(A - B) - cos(A + B)\} \quad (3.4)
\]

This output is passed through a band pass filter and the phase, \(\phi\), is measured at the intermediate frequency, \(\delta \omega\) using traditional lock-in techniques.

\[
\text{Measurement} \xrightarrow{\text{filter}} \frac{AK}{2} \sin(\phi - \phi_0 - \delta \omega t)
\]

\[
(3.5)
\]

In a typical experiment we use a medium with a reduced scattering coefficient of 6-10 cm\(^{-1}\) and an absorption of 0.02 cm\(^{-1}\). In this medium, a detector 6 cm from the source with a collection area of 0.1 cm\(^2\), and an efficiency of 1\%, we will detect about 10\(^8\) photons/second. Using a 3 mW laser diode at 800 nm, this corresponds to 3 pW. With a photosensitivity of 20 mA/W and a gain of 10\(^6\), the output current is about 60 \(\times 10^{-9}\) A. We use a load resistor of 10k\(\Omega\), so the output voltage from the
The photon detection system is 0.6 mV. The band-pass filter has a gain of about 100, so the input to the lock-in is on average 60 mV.

Most electronic circuits suffer from the characteristic that the phase of the wave shifts if the amplitude changes (amplitude-phase cross-talk). To test the amplitude-phase cross-talk of the PMT, neutral density filters are placed between the source and detector to change the amplitude and phase in a manner similar to experiment (see figure 3.3). We have experimented with different types of PMT's, with and without gain modulation, and in all of these systems, there is serious amplitude-phase cross-talk in the PMT. Later experiments showed that there are at least two effects contributing to the amplitude-phase cross-talk.

In the course of investigating the amplitude-phase cross-talk in the PMT, we discovered that the phase measurement changes considerably depending on where the photons hit the photocathode. The dynode structure of the R928 is shown in figure 3.4, left panel. The distance which the photoelectrons travel from the photocathode to the first dynode varies a few millimeters depending on where the photon strikes the photocathode. The photoelectrons are in a 100V potential and therefore travel at a speed of about $2 \times 10^7$ m/s. With a 200MHz signal, this gives a photoelectron wave a wavelength of about 2 cm. A 2 mm change in pathlength then corresponds
to a $36^\circ$ change in phase. This phase shift is evident in figure 3.4 (right panel) where the amplitude-phase cross-talk has been observed when the optical fiber is placed near two different locations on the photocathode. We can minimize this effect by focusing the light from our fiber bundle onto the PMT. We found that focusing the light slightly reduces the noise, but does not eliminate the amplitude-phase cross-talk in the PMT.

We also discovered that we were encountering an effect called space-charge coupling. (Basically, as the charge passes down the dynode chain, each electron adds to the effective electric field. This affects the total electric field that each electron feels.) To demonstrate this effect, we did the following experiment. Again, the source and detector were separated by neutral density filters. A small tungsten lamp was attached near the source. As we changed the current driving the lamp, we detected an increase in the DC current from the PMT, and a change in phase of the AC signal (see figure 3.5). In a perfect system, without the problem of a space-charge coupling, the DC light would not have affected the phase. Next we investigated two methods to stabilize the dynode currents. First we tried to use the lamp to stabilize the DC signal from the PMT. As we added neutral density filters, we monitored the DC output from the PMT, and altered the lamp current to stabilize this DC output. This feedback mechanism decreased the amplitude-phase cross talk. (See figure 3.5).

We also investigated stabilizing the dynode voltages by inserting 150V Zener
Figure 3.5: Holding the DC current from the PMT constant reduces the amplitude-phase cross-talk.

Figure 3.6: The current versus voltage curve of an ideal zener diode.

diodes into the dynode chain (see figure 3.7). Zener diodes have a dynamic resistance and are used to create a constant voltage in a circuit (see figure 3.6). This also decreased the amplitude-phase cross-talk. But neither the DC feedback nor the Zener diode solution were adopted in practice. Instead, we changed detectors from a PMT to an avalanche photodiode (APD).

### 3.2 Photon Detection - Avalanche Photodiodes

The following discussion of avalanche photodiodes was adapted from the Hamamatsu Photodiode catalog [41].
Photodiodes are semiconductor light sensors that generate a current or voltage when the P-N junction of the semiconductor is illuminated by light. Figure 3.8 shows a cross section of an avalanche photodiode. The P-layer material at the active surface and the N material at the substrate form a P-N junction which operates as a photoelectric converter. The usual P-layer for a silicon photodiode is formed by selective diffusion of boron, to a thickness of approximately 1 \( \mu \)m or less and the neutral region at the junction between P- and N- layers is known as the depletion layer. By varying and controlling the thickness of the various layers and doping concentrations, the spectral response and frequency range can be controlled.

When light strikes a photodiode, electrons within the crystal structure become stimulated. If the photon energy is greater than the band gap, the electrons are pulled up into the conduction band, leaving holes in their place in the valence band. This results in a positive charge in the P-layer and a negative charge in the N-layer. In an external circuit is connected between the P- and N-layers, electrons will flow away from the N-layer, and holes will flow away from the P-layer towards the opposite respective electrodes.

When a reverse voltage is applied to a PN junction, electrons generated by the
Hardware Specifications

<table>
<thead>
<tr>
<th>Specification</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Active area</td>
<td>0.19 mm²</td>
</tr>
<tr>
<td>Window material</td>
<td>borosilicate glass</td>
</tr>
<tr>
<td>Peak Wavelength</td>
<td>800nm</td>
</tr>
<tr>
<td>Anode to Cathode Voltage (max)</td>
<td>200 V</td>
</tr>
<tr>
<td>Current amplification (without external amplifier)</td>
<td>$1 \times 10^2$</td>
</tr>
<tr>
<td>Dark current</td>
<td>0.1 nA</td>
</tr>
<tr>
<td>Frequency range (equivalent to rise time)</td>
<td>1MHz - 1GHz</td>
</tr>
</tbody>
</table>

Table 3.2: Specifications of the Hamamatsu C5658 Avalanche photodiode.

incident light collide with atoms in the field and produce secondary electrons. This process occurs repeatedly. This is known as the avalanche effect, and since it results in the signal being amplified, this type of device is ideally suited for detection of low light levels.

The APD we used was a Hamamatsu C5658, and the specifications are given in table 3.2. This particular APD has a built-in bias supply, current to voltage converter and a low noise, broad band amplifier.

Because the APD is compact, there are virtually no path length variations as in the photomultiplier tube. We were not able to detect any amplitude-phase cross-talk using the APD, although Yokoyama et al. [42] have detected a small amplitude-phase cross-talk in the APD at 1 GHz. In addition, the sensitivity range of the APD extends much further into the infra-red (400 nm - 1000 nm for the APD, (figure 3.9) 400 nm - 800 nm for the PMT). The disadvantages of the APD are its small active area (0.5 mm) and low gain (with a built in low noise amplifier the ADP module gain is $10^5$ compared to the PMT gain of $10^6$). Finally, the response of the APD is fast enough
that we do not need to modulate the gain, instead we mix the output with the second frequency in an external mixer.

3.3 Laser diodes

The laser diodes we employed are standard 5 mW diodes, mainly used in laser printers and bar code readers (Sharp LT022DC). We modulate the DC driving current to oscillate between the lasing threshold and the maximum current using a standard capacitor coupling (see figure 3.10). The DC driving circuit is a standard chip which may be purchased from Sharp (Sharp IR3C01). A home-made driving circuit is described elsewhere [38]. We have also investigated using light emitting diodes (LED’s) as light sources, but LED’s are difficult to modulate at high (above 20 MHZ) frequencies.
Figure 3.9: The spectral sensitivity and quantum efficiency of the photodiode in an APD. Note that because the APD has an internal gain (x100), the sensitivity and efficiency should be multiplied by a factor of 100.

<table>
<thead>
<tr>
<th>Specification</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>High speed response</td>
<td>greater than 1 GHz</td>
</tr>
<tr>
<td>Optical Power Output</td>
<td>5 mW</td>
</tr>
<tr>
<td>Operating Temperature</td>
<td>-10 to +60°C</td>
</tr>
<tr>
<td>Threshold Current</td>
<td>50 mA</td>
</tr>
<tr>
<td>Operating Current</td>
<td>65 mA</td>
</tr>
<tr>
<td>Operating Voltage</td>
<td>0.9 V</td>
</tr>
<tr>
<td>Wavelength</td>
<td>780 nm</td>
</tr>
</tbody>
</table>

Table 3.3: Specifications of the Sharp LT022MD laser diode.
Figure 3.10: An AC signal is capacitor coupled to the laser diode driving current.

3.4 Amplitude-phase detector

In our studies we have employed a Stanford Research Systems (SRS530) Lock-In Amplifier for our phase detector. The SRS530 is a dual phase detector, which means that it detects both amplitude and phase. A schematic of the lock-in amplifier is shown in figure 3.11. A signal, $A \sin(\omega t + \phi)$, and a reference wave, $\sin(\omega t)$, are input and the reference is split internally into two channels. One channel is shifted by $90^\circ$. Each of these channels multiplies the signal, and the products are sent through band pass filters,

\[
X = A \sin(\omega t + \phi) \ast \sin(\omega t) \tag{3.7}
\]

\[
X = \frac{A}{2} \left\{ - \cos(2\omega t + \phi) + \cos(\phi) \right\} \tag{3.8}
\]

\[
\text{band pass filter } \frac{A}{2} \cos(\phi) \tag{3.9}
\]

\[
Y = A \sin(\omega t + \phi) \ast \cos(\omega t) \tag{3.10}
\]

\[
Y = \frac{A}{2} (\sin(2\omega t + \phi) + \sin(\phi)) \tag{3.11}
\]

\[
\text{band pass filter } \frac{A}{2} \sin(\phi) \tag{3.12}
\]
Here we have used the identities

\[ \sin(A) \cdot \sin(B) = \frac{1}{2} \{ \cos(A - B) - \cos(A + B) \} \]  
\[ \sin(A) \cdot \cos(B) = \frac{1}{2} \{ \sin(A - B) + \sin(A + B) \} . \]

The lock-in will provide either these XY components, or internal circuitry will return the amplitude and phase,

\[ \text{amplitude} = \sqrt{X^2 + Y^2} \]
\[ \text{phase} = \tan^{-1}(Y/X) \]
A GPIB or RS232 interface allows direct data input from, and control of the SRS530. Some additional specifications are shown in Table 3.4.

To make sure that the SRS530 records the phase and amplitude correctly over a wide range of amplitudes, we split the output from a standard low frequency function generator as shown in Figure 3.12. One side is used as the reference signal, and the other is passed through a variable attenuator (Kay brand, model 839) before being input into the measurement channel. The results shown in Figure 3.12 show the lock-in is capable of measuring the phase to within $0.2^\circ$ when the amplitude changes from 1 mV to 500 mV.

### Table 3.4: Specifications of the SRS530

<table>
<thead>
<tr>
<th>Sensitivity</th>
<th>100 nV to 500 mV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Signal Filters</td>
<td>60 Hz notch</td>
</tr>
<tr>
<td></td>
<td>120 Hz notch</td>
</tr>
<tr>
<td></td>
<td>bandpass ($Q = 5$)</td>
</tr>
<tr>
<td>Frequency</td>
<td>0.5 Hz to 100 kHz</td>
</tr>
</tbody>
</table>

#### 3.5 Signal Generators

There are a variety of choices for the signal generators. In our lab, we used either home-made resonant circuits designed from crystal oscillators [38] or 220 MHz radio transceivers (Kenwood TM-321A) which happened to be in the lab. The phase stability of the radio transceivers (about 0.2 KHz/hour frequency drift) is much better than the home-made generators (about 2 KHz/hour frequency drift). But the frequency of each radio transceiver is still apt to drift, especially with changes in temperature. Although this drift is small compared to the RF frequency, it is critical when we try to measure at an intermediate frequency. For example, a 0.002% frequency shift of...
Figure 3.12: Amplitude-phase cross-talk of the SRS530. The error in the SRS530 phase measurement in this configuration is +/- 0.1°.

One of the signal generators at 200 MHz results in a 4 kHz shift in the intermediate frequency. Since our band pass filters are set at a particular frequency with a full width half max of about 5 kHz, a 4 kHz drift is unacceptable. Recently, we have purchased variable signal generators (9 kHz - 2 GHz, Rhode & Schwartz SMY02). These signal generators use a few lower frequency crystal oscillators, and the frequencies are multiplied and combined appropriately to create the desired frequency. These generators have a major advantage over the radio transceivers in that two generators can be phase locked, that is, the crystal from one generator can be used to drive the second generator. On the Rhode & Schwartz, this is done using a single cable to connect the 10 MHz reference on one signal generator to the 10 MHz reference on the other and turning on the 'external reference' switch. Using the same crystal to drive both generators ensures the stability of δω (less than 0.1 kHz/hour drift [43]). The only disadvantage to the Rhode & Schwartz is the cost (about $7,000) and the physical size of the device.

3.6 Filters
Our initial experiments used the twin-T bandpass filter shown in figure 3.13. In the twin-T bandpass filter, the signal is first amplified, and then split. One part of the signal passes through a second, variable amplifier, and the second part passes through the twin-T notch filter. The two signals are then recombined in a differential amplifier. In this way, we have used the sharp attenuation properties of the twin-T notch filter to create a sharp spike filter. The Q of a filter is defined as the central frequency divided by the full width at half max. In this filter the Q is adjustable, by changing the variable 5k resistor in the second amplifier. The capacitors are to eliminate any DC signal. The performance of this filter is demonstrated for several Q in figure 3.14. Typically we use a Q of about 5.

The twin-T notch filter works by combining two signals that are 180° out of phase. The top path is a high pass filter with a characteristic frequency \( \omega_c = 1/RC \), and the bottom path is a low pass filter with the same characteristic frequency. Because the top path has passed through two capacitors, the phase is shifted 180°. Thus at \( \omega_c \) the two signals interfere destructively giving a deep amplitude null. Theoretically,
When we tested the amplitude-phase cross-talk of the twin-T, it did not perform well (see figure 3.15). Basically, as we decreased Q, the amplitude-phase cross-talk was less critical, but the noise was too large.

Next we tried the passive filter shown in figure 3.16. This filter is actually two separate RLC filters, (center frequency, $\omega^2 = 1/LC$) isolated from each other by a small capacitor. This capacitor also acts to further reduce the DC signal. The Q of this filter is about 5. Figure 3.17 demonstrates that the amplitude-phase cross-talk is negligible.
Figure 3.16: A passive bandpass filter. Designed and constructed by Ken Simmons, Philadelphia, Pennsylvania.

Figure 3.17: Amplitude-phase cross-talk of the RLC filter. Both signals have been shifted to 0° for comparison purposes.
3.7 Mixers

The following discussion of mixers was adapted from the Mini-Circuits RF designers handbook [44].

A mixer is a circuit which accepts a radio frequency (RF) signal and a local oscillator (LO) and then multiplies them to form the sum and difference frequencies (intermediate frequencies (IF)).

\[
\cos(\omega_{RF}t) \cos(\omega_{LO}t) = \frac{1}{2} \cos(\omega_{RF}t + \omega_{LO}t) + \frac{1}{2} \cos(\omega_{RF}t - \omega_{LO}t)
\]  

(3.17)

Although any non-linear component will mix two frequencies (for example a diode, as shown in figure 3.18a), a double-balanced mixer as shown in figure 3.18b, will reduce the amount leakage between the RF, IF and LO signals.

The symmetry of the double-balanced mixer’s configuration provides the isolation between the RF and LO and IF ports. Although the full description of how the isolation is achieved is beyond the scope of this discussion, we will review the concepts by examining a simpler circuit. Figure 3.18c is a single balanced mixer. A single-balanced mixer offers good isolation between the LO and RF ports, but does not isolate the RF and the IF ports. Figure 3.18d is an equivalent description of the circuit. If the two diodes are equivalent, then the currents drawn, \(i_{lo1}\) and \(i_{lo2}\) will be equal in amplitude and phase. Therefore at the IF port, the LO signal will exactly cancel, isolating the LO from the IF.

The mixers we use were purchased from MiniCircuits (ZFM-4). Our mixers have a RF frequency range from 5 - 1250 MHz and an intermediate frequency range from DC to 1250 MHz.

3.8 Summary

The phase modulation device which we used evolved over the years. The components that changed during the experiments in this work were the signal generators and the band-pass filters. Although we tested various photon detectors, all of the experiments performed here used a photomultiplier tube.
Figure 3.18: (a) A simple mixer (b) A double balanced mixer designed to isolate the local oscillator (LO), the radio frequency oscillator (RF) and the intermediate frequency (IF). (c) A single balance mixer provides isolation between the LO and RF ports. (d) An equivalent circuit for the single balanced mixer.
The initial experiments demonstrating the existence and properties of DPDW (presented in chapter 2) used a system composed of the twin-T band-pass filter and the home-made radio oscillators. Most of the absorption and scattering images were created using the radio transceivers and the twin-T band-pass filters. The absorption calibration curve was created using the radio transceivers and the LC band-pass filters.
Chapter 4

Imaging the Absorption Coefficient

Near infrared diffusing light probes offer new possibilities for medical imaging. Applications include non-invasive measurement of tissue oxygenation, and tumor detection and characterization [45]. Although investigators have determined the bulk optical properties based on a homogeneous model, direct imaging of the optical properties of heterogeneous tissue is an important potential improvement that has only recently been considered [46, 47]. It is expected that these images will lead to a more accurate representation of the optical properties for tissue characterization and functional imaging.

In this chapter we will assume that only the absorption coefficient varies with position. The other optical properties, such as the scattering coefficient, are assumed to be constant. To investigate the passage of photons through heterogeneous media we first write down the heterogeneous diffusion equation, and then generate solutions to this equation using two methods. The first involves a linear or Born expansion of the light energy density changes, and the second is an exponential or Rylov expansion of the light energy density changes.

We next discuss methods for inverting these solutions to obtain images of the medium. Again, we have investigated two different methods: the first is a matrix inversion, singular value decomposition (SVD), and the second is an algebraic reconstruction technique (SIRT). We present experimental results which demonstrate the feasibility of image reconstruction and characterization of the optical properties. Finally, we suggest an algorithm which exploits a high resolution imaging modality
such as MRI, x-ray tomography or ultra-sound to improve tissue characterization.

4.1 The Heterogeneous Diffusion Equation

The systems we are concerned with in this chapter have an absorption coefficient, \( \mu_a(\mathbf{r}) \) which may be divided into two components, the background, or homogeneous component, \( \mu_a^0 \), and the spatially varying part \( \delta \mu_a(\mathbf{r}) \);

\[
\mu_a(\mathbf{r}) = \mu_a^0 + \delta \mu_a(\mathbf{r}).
\]  

(4.1)

When we substitute equation 4.1 into the diffusion equation or its related Helmholtz equation:

\[
-D \nabla^2 U_{a;}(\mathbf{r}) + (-i \omega + v \mu_a) U(\mathbf{r}) = -A \delta(\mathbf{r}_s),
\]

(4.2)

\[
(\nabla^2 + k^2) U(\mathbf{r}) = A \delta(\mathbf{r}_s)/D.
\]

(4.3)

we arrive at the heterogeneous equation for the light energy density at \( \mathbf{r} \) from a source at \( \mathbf{r}_s \), \( A \delta(\mathbf{r}_s) \);

\[
\left[ \nabla^2 + k^2 + O(\mathbf{r}) \right] U(\mathbf{r}, \mathbf{r}_s) = A \delta(\mathbf{r}_s)/D,
\]

(4.4)

\[
O(\mathbf{r}) = v \delta \mu_a(\mathbf{r})/D.
\]

(4.5)

To solve this heterogeneous diffusion equation, we will explore both the Born and the Rytov formulations. The following discussion is an adaptation of the discussion by Kak et al. [48].

4.2 Born Approximation

In the Born expansion we divide the photon density from a source at \( \mathbf{r}_s \), measured at a position \( \mathbf{r} \), into a linear superposition of its incident (homogeneous) and scattered (heterogeneous) parts;

\[
U(\mathbf{r}, \mathbf{r}_s) = U_o(\mathbf{r}, \mathbf{r}_s) + U_{sc}(\mathbf{r}, \mathbf{r}_s).
\]

(4.6)
The heterogeneous diffusion equation (equation 4.4) becomes

\[
[\nabla^2 + k^2 + O(\mathbf{r})] [U_o(\mathbf{r}, \mathbf{r}_s) + U_{sc}(\mathbf{r}, \mathbf{r}_s)] = -A\delta(\mathbf{r}_s)/D,
\]

If we subtract off the homogeneous Helmholtz equation,

\[
(\nabla^2 + k^2)U_o(\mathbf{r}, \mathbf{r}_s) = -A\delta(\mathbf{r}_s)/D
\]

then we are left with the following heterogeneous Helmholtz equation for \( U_{sc} \).

\[
(\nabla^2 + k^2)U_{sc}(\mathbf{r}, \mathbf{r}_s) = -O(\mathbf{r}) [U_o(\mathbf{r}, \mathbf{r}_s) + U_{sc}(\mathbf{r}, \mathbf{r}_s)]
\]

We next convolve this differential equation with the appropriate Green function solution to the Helmholtz equation, to arrive at the following integral solution for \( U_{sc} \);

\[
U_{sc}(\mathbf{r}_d, \mathbf{r}_s) = -\int G(\mathbf{r} - \mathbf{r}_d) O(\mathbf{r}) [U_o(\mathbf{r}, \mathbf{r}_s) + U_{sc}(\mathbf{r}, \mathbf{r}_s)] d^3r,
\]

\[
G(\mathbf{r} - \mathbf{r}_d) = \exp(ik|\mathbf{r} - \mathbf{r}_d|)/4\pi|\mathbf{r} - \mathbf{r}_d|.
\]

The integral is over the entire sample volume. We now make the Born approximation, i.e. we assume that

\[
U_{sc}(\mathbf{r}) \ll U_o(\mathbf{r}),
\]

and we can write down an explicit solution for the scattered DPDW in a heterogeneous medium,

\[
U_{sc}(\mathbf{r}_d, \mathbf{r}_s) = -\int G(\mathbf{r} - \mathbf{r}_d) O(\mathbf{r}) U_o(\mathbf{r}, \mathbf{r}_s) d^3r
\]

with

\[
U(\mathbf{r}_d, \mathbf{r}_s) = U_o(\mathbf{r}_d, \mathbf{r}_s) + U_{sc}(\mathbf{r}_d, \mathbf{r}_s)
\]

We will refer to this solution (equation 4.13) as the Born solution. Figure 4.1 demonstrates the components of the Born solution. One can think of this solution for \( U_{sc} \) as the number of photons which pass from the source (\( \mathbf{r}_s \)) to some position \( \mathbf{r} \), scatter with an amplitude proportional to \( \delta\mu_a \), and then travel from the position \( \mathbf{r} \) to a detector at \( \mathbf{r}_d \).
4.3 Rytov Approximation

In the Rytov expansion we again divide the photon density into its incident (homogeneous) and scattered (heterogeneous) parts;

\begin{align*}
U(r, r_s) &= \exp(\phi_o(r, r_s) + \phi_{sc}(r, r_s)), \\
U_o(r, r_s) &= \exp(\phi_o(r, r_s)).
\end{align*}

When we plug this into the diffusion equation we obtain,

\begin{align*}
(\nabla^2 + k^2 + O(r)) \exp(\phi_o(r, r_s) + \phi_{sc}(r, r_s)) &= -A\delta(r_s)/D, \\
\nabla^2 \phi_o(r, r_s) + \nabla^2 \phi_{sc}(r, r_s) + (\nabla\phi_o(r, r_s))^2 + (\nabla\phi_{sc}(r, r_s))^2 + k_o^2 + O(r) \\
+2\nabla\phi_o(r, r_s) \cdot \nabla\phi_{sc}(r, r_s) &= (\exp(-\phi_o(r, r_s) - \phi_{sc}(r, r_s))^2)A\delta(r_s)/D. 
\end{align*}

It is clear that at the source position, the scattered signal is negligible compared to the delta function source signal, so we can write the right hand side of this equation as \(\exp(-\phi_o(r))A\delta(r_s)/D\). We then rewrite the homogeneous equation as,

\begin{align*}
(\nabla^2 + k^2) \exp(\phi_o(r, r_s)) &= A\delta(r_s)/D, \\
\nabla^2 \phi_o(r, r_s) + (\nabla\phi_o(r, r_s))^2 + k^2 &= \exp(-\phi_o(r, r_s))A\delta(r_s)/D.
\end{align*}
When we subtract the homogeneous equation \(4.20\) from equation \(4.18\) we are left with
\[
2\nabla \phi_o(r, r_s) \phi_{sc}(r, r_s) + \nabla^2 \phi_{sc}(r, r_s) = - (\nabla \phi_{sc}(r, r_s))^2 - O(r). \tag{4.21}
\]

We then linearize this equation by noticing that
\[
\nabla^2(U_o(r, r_s) \phi_{sc}(r, r_s)) = \nabla \cdot (\nabla U_o(r, r_s) \phi_{sc}(r, r_s) + U_o(r, r_s) \nabla \phi_{sc}(r, r_s)) \tag{4.22}
\]
\[
= \nabla^2 U_o(r, r_s) \phi_{sc}(r, r_s) + 2 \nabla U_o(r, r_s) \cdot \nabla \phi_{sc}(r, r_s) + U_o(r, r_s) \nabla^2 \phi_{sc}(r, r_s)
\]
and using the fact that \(\nabla^2 U_o(r) = -k^2 U_o(r)\) \([49]\) we can rewrite equation \(4.23\) as
\[
2 \nabla U_o(r, r_s) \cdot \nabla \phi_{sc}(r, r_s) + U_o(r, r_s) \nabla^2 \phi_{sc}(r, r_s) = \tag{4.23}
\]
\[
\nabla^2(U_o(r, r_s) \phi_{sc}(r, r_s)) + k^2 U_o(r, r_s) \phi_{sc}(r, r_s).
\]

Finally, we can plug this result into equation \(4.21\) to obtain
\[
(\nabla^2 + k^2) U_o(r, r_s) \phi_{sc}(r, r_s) = -U_o(r, r_s) ((\nabla \phi_{sc}(r, r_s))^2 + O(r)). \tag{4.24}
\]

Just as we did with the Born approximation, we convert this differential equation into an integral equation by convoluting with the Green function solution.
\[
U_o(r_d, r_s) \phi_{sc}(r_d, r_s) = - \int G(r - r_d) U_o(r, r_s) ((\nabla \phi_{sc}(r, r_s))^2 + O(r)) d^3 r. \tag{4.25}
\]

We now make the Rylov approximation, \((\nabla \phi_{sc}(r, r_s))^2 \ll O(r)\), and write the solution for the scattered phase as
\[
\phi_{sc}(r_d, r_s) = - \frac{1}{U_o(r_d, r_s)} \int G(r - r_d) (v \delta \mu_o(r)/D) U_o(r, r_s) d^3 r. \tag{4.26}
\]

\(\phi_{sc}\) will be referred to as the Rylov solution.

### 4.4 Breakdown of the Born and Rylov Approximations

Although the structure of the Born and Rylov solutions look very similar, there are some fundamental differences in their validity and use. We immediately see that the Born approximation makes the assumption that the scattered wave is small, and
absorption varies

\[ \frac{1}{l^*} = 10.0 \text{ cm}^{-1} \]

absorption = 0.05 \text{ cm}^{-1}

\[ \frac{1}{l^*} = 10.0 \text{ cm}^{-1} \]

Figure 4.2: A comparison of the Born and Ryrov approximations. A 1.0 cm diameter sphere is embedded in a medium with an absorption of 0.03 cm\(^{-1}\) and a reduced scattering coefficient of 10.0 cm\(^{-1}\). Although a cylindrical region was reconstructed, an infinite model was used for both the forward and inverse problems.

the scattered wave scales approximately linearly with the absorption. In biological tissue we are interested in imaging absorption values which vary from about 0.02 cm\(^{-1}\) to 0.30 cm\(^{-1}\). In fact, this linear assumption will break down for absorption differences greater than about 0.10 cm\(^{-1}\), well within our region of interest. The Ryrov approximation does not place a restriction on the magnitude of the scattered wave change, but rather assumes that the scattered field is slowly varying. Figure 4.2 demonstrates the breakdown of each approximation in the context of an isolated spherical heterogeneity. We see that the Ryrov approximation is much more suitable for most biological situations. These and other differences will be discussed in section 4.8 and chapter 6.

4.5 Inverting the Solutions to the Heterogeneous Diffusion Equation

Our goal is to use either the Born or Ryrov equations to solve for the absorption as a function of position within the medium. Thus we must invert the integral equations
(4.13, 4.26). There are many methods available to find the best solution to the inverse problem. But care must be taken since the integral equation is a Fredholm integral of the first kind (FI) and is highly susceptible to high frequency noise. A FI is an equation of the form

\[ u(x) = \int_a^b k(x, s) \alpha(s) ds. \]  

(4.27)

The difficulty in solving a FI for \( \alpha \) arises from the instability of the inverse operator. Certain high frequency oscillatory noise in a solution may be screened out by the integral operator, giving a result which is very close to the left hand side. For example, if the correct solution to our problem is \( \alpha(s) \), consider the residual of another solution \( \alpha(s) + \delta \alpha(s) \) where

\[ \delta \alpha(s) = \exp(i \omega s) \]  

(4.28)

The residual, \( \delta u(x) \) that this alternate solution adds to the measurements is

\[ \delta u(x) = \int_a^b k(x, s) \delta \alpha(s) ds \]  

(4.29)

\[ = \int_a^b k(x, s) \exp(i \omega s) ds. \]  

(4.30)

If we integrate by parts,

\[ \delta u(x) = \frac{1}{i \omega} k(x, s) \delta \alpha(s) \bigg|_a^b - \frac{1}{i \omega} \int_a^b \frac{\partial k(x, s)}{\partial s} \exp(i \omega s) ds \]  

(4.31)

we see that the residual is of order \( 1/\omega \). Thus high frequency solutions for \( \alpha \) will contribute little to the measurement, but can contribute significantly to the image.

There are regularization schemes, such as Tikhonov regularization, which reduce the effect of high frequency noise on the reconstructed image. To invert the following equation;

\[ \tilde{u} = \tilde{A} \tilde{x} \]  

(4.32)

we would minimize the norm

\[ ||\tilde{u} - \tilde{A} \tilde{x}||. \]  

(4.33)
To use Tikhonov regularization, we minimize the equation

\[ ||\vec{v} - \hat{A}\vec{x}|| + \beta ||\vec{x}|| \]  

(4.34)

where \( \beta \) is a free parameter which controls the level of regularization. Each time we try a different value of \( \beta \), we create a new matrix to invert. Since inverting a matrix is computationally intensive, choosing the best value for \( \beta \) can be a time consuming process.

To invert our problem, we break up the region of interest into discrete volume elements and likewise digitize the integral equation to create a series of linear equations. A typical digitized volume and scattering geometry is shown in figure 4.3. We next solve these equations using two different techniques: (1) a regularized matrix inversion using singular value decomposition (SVD) and analysis and (2) an algebraic technique called simultaneous iterative technique (SIRT) with constraints.

In this work we have chosen to break the region into rectangular volume elements (voxels), but other geometries have also been investigated [17]. When choosing the voxel size, we must balance computation time with the desired resolution. Since our resolution is generally limited to about 0.5 cm [22], we typically choose to use voxels with approximately 0.2 cm edges. Once the space has been digitized into \( N \) voxels, the integral equation is similarly digitized,
Imaging Absorption

Born:

\[ U_{sc}(r_{si}, r_{di}) = \sum_{j=1}^{N} G(r_j - r_{di})O(r_j)U_o(r_{si}, r_j)h^3, \]  

(4.35)

Rytov:

\[ \phi_{sc}(r_{si}, r_{di}) = -\sum_{j=1}^{N} G(r_j - r_{di})O(r_j)U_o(r_{si}, r_j)h^3/U_o(r_{si}, r_{di}). \]  

(4.36)

Here \( r_{si} \) (\( r_{di} \)) is the \( i \)th source (detector), and \( h^3 \) is the volume of the voxel. The effect of this digitization has been studied by Patterson and Pogue [50]. A series of measurements of the amplitude and phase of the DPDW for different source-detector configurations yields a set of coupled, linear equations which relate the real and imaginary parts of the measurements to the values of \( \delta \mu_a \) in the various voxels within the sample.

Born:

\[
\begin{pmatrix}
U_{sc}(r_{s1}, r_{d1}) \\
\vdots \\
U_{sc}(r_{sm}, r_{dm})
\end{pmatrix} =
\begin{pmatrix}
W_{11}^B & \cdots & W_{1n}^B \\
\vdots & \ddots & \vdots \\
W_{m1}^B & \cdots & W_{mn}^B
\end{pmatrix}
\begin{pmatrix}
\delta \mu_a(r_1) \\
\vdots \\
\delta \mu_a(r_n)
\end{pmatrix}
\]

\[ W_{ij}^B = G(r_{di}, r_{j})U_o(r_{si}, r_j)vh^3/D \]  

(4.37)

Rytov:

\[
\begin{pmatrix}
\phi_{sc}(r_{s1}, r_{d1}) \\
\vdots \\
\phi_{sc}(r_{sm}, r_{dm})
\end{pmatrix} =
\begin{pmatrix}
W_{11}^R & \cdots & W_{1n}^R \\
\vdots & \ddots & \vdots \\
W_{m1}^R & \cdots & W_{mn}^R
\end{pmatrix}
\begin{pmatrix}
\delta \mu_a(r_1) \\
\vdots \\
\delta \mu_a(r_n)
\end{pmatrix}
\]

\[ W_{ij}^R = G(r_{di}, r_{j})U_o(r_{j}, r_{si})vh^3/(U_o(r_{di}, r_{si})D) \]  

(4.38)

\( W^B \) and \( W^R \) are referred to as the weights. The weights are a description of the relative importance of each voxel to a particular measurement. Recall that the measurements and weights are complex. Before we try to invert the problem, we rewrite the matrix as a real matrix;


Born:

$$
\begin{bmatrix}
\Re[U_s(r_{s1}, r_{d1})] \\
\vdots \\
\Re[U_s(r_{sm}, r_{dm})] \\
\Im[U_s(r_{s1}, r_{d1})] \\
\vdots \\
\Im[U_s(r_{sm}, r_{dm})]
\end{bmatrix}
= 
\begin{bmatrix}
\Re[W_{11}^B] & \ldots & \Re[W_{1n}^B] \\
\vdots & \ddots & \vdots \\
\Re[W_{m1}^B] & \ldots & \Re[W_{mn}^B] \\
\Im[W_{11}^B] & \ldots & \Im[W_{1n}^B] \\
\vdots & \ddots & \vdots \\
\Im[W_{m1}^B] & \ldots & \Im[W_{mn}^B]
\end{bmatrix}
\begin{bmatrix}
\delta\mu_a(r_1) \\
\vdots \\
\delta\mu_a(r_n)
\end{bmatrix}
$$

$$
W_{ij}^B = G(r_{di}, r_j)U_o(r_{ai}, r_j)v kh^3 / D 
$$

Rytov:

$$
\begin{bmatrix}
\Re[\phi_s(r_{s1}, r_{ai})] \\
\vdots \\
\Re[\phi_s(r_{sm}, r_{dm})] \\
\Im[\phi_s(r_{s1}, r_{ai})] \\
\vdots \\
\Im[\phi_s(r_{sm}, r_{dm})]
\end{bmatrix}
= 
\begin{bmatrix}
\Re[W_{11}^R] & \ldots & \Re[W_{1n}^R] \\
\vdots & \ddots & \vdots \\
\Re[W_{m1}^R] & \ldots & \Re[W_{mn}^R] \\
\Im[W_{11}^R] & \ldots & \Im[W_{1n}^R] \\
\vdots & \ddots & \vdots \\
\Im[W_{m1}^R] & \ldots & \Im[W_{mn}^R]
\end{bmatrix}
\begin{bmatrix}
\delta\mu_a(r_1) \\
\vdots \\
\delta\mu_a(r_n)
\end{bmatrix}
$$

$$
W_{ij}^R = G(r_{di}, r_j)U_o(r_{ai}, r_j)v kh^3 / (U_o(r_{di}, r_{ai}) D 
$$

4.6 Singular Value Decomposition

We used two different methods to solve the inverse problem. The first is a direct matrix inversion method called singular value decomposition (SVD). This discussion of SVD has been adapted from *Numerical Recipes* [51].
Singular value decomposition is a powerful technique for solving singular, or nearly singular matrices. (See appendix A for a brief review of singular matrices.) It is based on a theorem of linear algebra which states:

Any $M \times N$ matrix $A$, whose number of rows $M$, is greater than or equal to its number of columns $N$, can be written as the product of an $M \times N$ column-orthogonal matrix $U$, an $N \times N$ diagonal matrix $W$, with positive or zero elements, and the transpose of an $N \times N$ orthogonal matrix $V$.

\[
\begin{pmatrix} \vdots \\ A \end{pmatrix} = \begin{pmatrix} \vdots \\ U \end{pmatrix} \begin{pmatrix} w_1 & & \\ & \ddots & \\ & & w_N \end{pmatrix} \begin{pmatrix} \vdots \\ V^T \end{pmatrix}
\]

\[
(M \times N) (M \times N) \cdot (N \times N) \cdot (N \times N)
\]

The matrices $U$ and $V$ are orthogonal in the sense that their columns are orthonormal,

\[
U^T \cdot U = V^T \cdot V = I.
\]

and since $V$ is square,

\[
V \cdot V^T = I.
\]

We will not go into the details of how this matrix decomposition is achieved, but rather refer to reader to Forsythe et al. [52] for a complete description. If $A$ is a square matrix, then $U$ is a $N \times N$ matrix, and $U^{-1} = U^T$. In this case, the inverse of $A$ is

\[
A = U \cdot \text{diag}(w_j) \cdot V^T
\]

\[
A^{-1} = (V^T)^{-1} \cdot \text{diag}(w_j)^{-1} \cdot U^{-1}
\]

\[
A^{-1} = V \cdot \text{diag}(1/w_j) \cdot U^T
\]
If the matrix $A$ is non-singular, then calculation of the inverse is straightforward. However, if $A$ is singular, or nearly singular, then the inverse is not well defined. However SVD can still give a solution. To understand the meaning of the SVD solution in this case, we must review some linear algebra definitions. Recall we are trying to solve the following matrix equation,

$$ A \cdot x = b. \quad (4.47) $$

$A$ is a linear mapping from the vector space $x$ to the vector space $b$ as shown in figure 4.4. The subspace of $b$ which can be reached by $x$ is called the range. If $A$ is singular, then there is some part of $x$ that maps to zero, i.e.

$$ A \cdot x = 0 \quad (4.48) $$

This subspace of $x$ is called the null space.

If the matrix $A$ is non-singular, then there is no null space, and we will obtain a unique solution for $A^{-1}$. If the matrix is singular the solution is not unique, but rather some combination of a general solution with linear combinations of the null space. Mathematically, each singularity corresponds to an eigenvalue $(w_j)$ equal to zero. This creates a problem in the inverse when we try to compute $1/w_j$. We can
however, generate the solution with the smallest absorption by setting $1/w_j$ equal to zero when $w_j$ equals zero. This is equivalent to throwing out all null space solutions. This altering of the eigenvalues is called singular value analysis (SVA). One of the powerful advantages of SVD is that the columns of $V$ with zero eigenvalues form a basis set for the null space. Thus we can easily check the solutions that we are discarding for physical relevance.

The condition number of a matrix is the ratio of the smallest eigenvalue to the largest. The closer to unity the condition number, the more robust the inversion. A condition number of $10^{-6}$ for floating point precision of $10^{-12}$ for double precision will result in eigenvalues which are dominated by round off error. So SVA is also needed when the range of the eigenvalues is larger that the numerical precision of the computer. In the photon diffusion problem the condition number of the matrix is typically $10^{-12}$. In this case we could zero the inverse of the small eigenvalues to generate the solution. We have found the that reconstructed images are improved when we use a simple smoothing algorithm [53] instead of eliminating the small eigenvalues;

$$w_j \rightarrow w_j + \sigma/w_j \quad (4.49)$$
$$1/w_j \rightarrow 1/w_j + \sigma/w_j \quad (4.50)$$

Figure 4.5 demonstrates how the eigenvalues are effected by such an algorithm. $\sigma$ is an arbitrary free parameter. If $\sigma$ is much larger than the square of the maximum eigenvalue, then the eigenvalues are dramatically reduced, and we obtain a solution composed of only a few of the largest eigenfunctions. If $\sigma$ is small compared to the square of the smallest eigenvalue, then there is effectively no smoothing, and we obtain a solution dominated by noise. Although the norm of the solution is reduced as we increase the smoothing, this is not the same as Tikhonov regularization where we minimize the norm of the residual plus the norm of the solution. The advantage of using the smoothing method over Tikhonov regularization is that we only have to perform the time consuming matrix decomposition once.

We can now write down an explicit solution for the absorption as a function of
Figure 4.5: A singular or numerically singular matrix will have eigenvalues $w_j$ which are zero or below the numerical precision of the calculation. In this case, we apply an eigenvalue smoothing procedure to minimize the effect of the small eigenvalues. The left panel shows how the eigenvalues are altered when $w_j \rightarrow w_j + \sigma/w_j$ for a series of different values of $\sigma$. The right panel shows how the inverse eigenvalue is affected.

position;

$$ (\delta \mu_a) = [(V) \cdot (\text{diag}( \frac{1}{w_j+\sigma/w_j}) \cdot (U^T)) \cdot (\text{data})] $$ \hspace{1cm} (4.51)

As we increase $\sigma$, the image becomes less noisy and the image appears smoother. Since the smoothing algorithm always decreases the inverse of $w_j$, the reconstructed absorption will also decrease as the smoothing factor is increased.

There are many other regularization algorithms. In particular, Arridge et al. [19] have tested discussed Tikhonov regulation and SVA within the framework of diffusion imaging.

We have presented SVD for a square matrix. In our case, we often have many more voxels of unknown absorption than we do measurements. This means that we have more unknowns than equations. In this situation, we simply pad the matrix $A$ with rows of zeros, and likewise pad the measurement vector with zeros. We can then invert the square matrix. The solution that we obtain will have a zero eigenvalue for each row of padding, and the solution we get is approximately the minimum
absorption solution as discussed above.

4.7 Algebraic Reconstruction Techniques

The second method we used to solve the linear system of equations is an algebraic reconstruction technique called SIRT - simultaneous iterative reconstruction technique. SIRT is a slight modification to an algebraic reconstruction technique (ART). In this section we will describe ART, and then SIRT. This discussion is based on the discussion in Kak et al. [48].

The ART algorithm is best demonstrated pictorially using a simple example. Suppose we have a system with two linear equations and two unknowns,

\[ \mathbf{A} \cdot \mathbf{x} = \mathbf{b} \]

\[ A_{11}x_1 + A_{12}x_2 = b_1 \]
\[ A_{21}x_1 + A_{22}x_2 = b_2. \]

Here \( b_1 \) and \( b_2 \) are measurements, \( x_1 \) and \( x_2 \) are unknowns, and the \( A \)'s are calculable. The solution space is a 2 dimensional space, i.e. a plane spanned by \( x_1 \) and \( x_2 \). The measurements are lines in that plane with slopes \(-A_{11}/A_{12}, -A_{21}/A_{22}\) and intercepts \( b_1/A_{12}, b_2/A_{22}\) as shown in figure 4.6a. The solution we are searching for is the intersection of these two lines. To find the intersection using ART, we first start from any point in space. (Typically we choose the origin as the initial guess.) We then move from the origin to the closest point on line first line as shown in figure 4.6. The mathematical equation for the move is

\[ \mathbf{x}_{\text{new}} = \mathbf{x} - \frac{\mathbf{x} \cdot \mathbf{A} - b_j}{\mathbf{A} \cdot \mathbf{A}} \]

Here \( \mathbf{A} = (A_{j1}, A_{j2}, \ldots, A_{jN}) \) and \( \mathbf{x} = (x_1, x_2) \) is the the initial guess. We next make a similar move from the first line to the second line. These two moves constitute one iteration. This process, called the Kaczmarz method, is repeated until convergence is achieved. Tanabe [54] has shown that the algorithm will always converge on the correct solution if a unique solution exists.
Figure 4.6: A graphical description of the algebraic reconstruction technique. In the left panel, the solid lines show the equations to be solved. In the right panel the thick arrows show the path that the algorithm takes as it moves from the initial guess, the origin, towards the correct solution. One iteration is shown.

Now suppose we add noise to the data. For the system of two equations and two unknowns, ART converges on the noisy solution as shown in figure 4.7a. If there are more equations than unknowns as shown in figure 4.7b, then no unique solution exists and the final solution oscillates in the neighborhood of the correct solution. If there are fewer equations than unknowns, then the process converges to a space (in this case a line) which contains the correct solution.

We have employed a slight modification to ART, called the simultaneous iterative reconstruction technique (SIRT). In SIRT we choose a starting point, and move from that starting point to the first line to find a new solution. We then move from the starting point to the second line. The two solutions are then averaged. SIRT is believed to produce better images than ART, at the expense of slightly slower convergence [48].

One of the major advantages of using the algebraic techniques instead of the matrix inversion is that the algebraic techniques allow the use of hard constraints. For example, we know that the reconstructed absorption should always be greater than zero. Thus at the end of each SIRT iteration, we zero any voxel which has a
Figure 4.7: (A) ART with two noisy equations and two unknowns. (B) ART with more equations than unknowns. (C) ART with fewer equations than unknowns.

negative absorption. Unless otherwise noted, we use this positivity constraint in all of our SIRT reconstructions.

When ART or SIRT is applied to photon diffusion imaging, we are searching for a solution in a N dimensional space, where N is the number of voxels. We are typically working in the case where the data is noisy, and we have fewer equations that unknowns. In our reconstructions we choose the smallest absorption solution by beginning our search at the origin. However in the cases where we have some \textit{a priori} information, we can speed up the convergence, and arrive at a better solution by using this information to construct a good initial guess. Just as in SVD we had to choose a good smoothing parameter, in ART or SIRT, we have to decide when to stop the iterations. Ideally, the iterations should be stopped when the theoretical prediction coincides with the measured data within the experimental error. However, our situation is slightly more complicated than this.

In all of our simulations we have found that as we continue to iterate, the image of a sphere gets gradually smaller and more absorbing. Boas \textit{et al.} [22] have demonstrated that even in a best case scenario, the difference between a small, highly absorbing
Figure 4.8: Left: The reconstructed images of an object at the center. Images are shown for 5, 10, 15 and 20 thousand SIRT iterations. Right: The reconstructed absorption (maximum value) as a function of iteration.

Object and a larger, less absorbing object is practically immeasurable for objects with a diameter of less than 1 cm [22]. The authors demonstrated that there is a family of degenerate solutions which all conserve the quantity $\delta \mu_n v$ where $v$ in the volume of the sphere. Thus, in the SIRT reconstructions, the consecutive iterations move the reconstruction through this family of solutions. Because we always start from the same initial guess (a homogeneous system) the reconstruction always moves through the family of solutions in the same way. Figure 4.8 demonstrates a series of reconstructions for different numbers of iterations. Note that as the number of iterations increases, the absorption of the object increases, and the size decreases. We have left the iteration number as a free parameter in our reconstructions.

4.8 Data Analysis

At this point, we must consider the measured data. In the Born approximation, we measure a voltage proportional to the total diffuse photon density at a particular position,

$$Voltage = C(U_o + U_{sc}),$$

(4.56)

In order to use the inverse solution (which was for a source of unit amplitude) we must eliminate the constant, $C$, and the homogeneous DPDW, $U_o$. $C$ is a complex
number which includes such factors as the signal amplification, the efficiency of the light detection and the initial amplitude and phase of the source. In our experiments we measure the amplitude and phase of $C$ by making measurements in a homogeneous infinite medium.

After calculating $C$, we have to subtract off the homogeneous part of the signal. This may be done using an analytic solution if the background properties are known. Alternatively, researchers have measured the signal with and without the presence on an inhomogeneity to eliminate the background. However, since both of these measurements are impractical in a clinical situation, we have instead chosen to make a reference measurement which does not rely on finding a homogeneous portion of the sample. In such a scheme we make two measurements with the same source and detector separations as shown in figure 4.9. We then subtract the two measurements, eliminating the homogeneous signal, and are left with only the difference of the heterogeneous signals.

$$ Voltage_1 - Voltage_2 = C(U_o + U_{sc}^1) - C(U_o + U_{sc}^2) $$

$$ = C(U_{sc}^1 - U_{sc}^2) $$

Of course using pairs of measurements changes the form of the weights;

$$ W_{ij}^B = [G(r_j - r_{d1})U_o(r_{si1}, r_j) - G(r_j - r_{d2})U_o(r_{si2}, r_j)] v h^3 / D. $$

For the Rytov approximation, the situation is slightly simpler. In this case we measure

$$ Voltage = C U_o \exp(\phi_{sc}) $$

Again, we could measure or calculate $C$ and $U_o$. However, if we use the reference scheme discussed above, and this time divide the two measurements,

$$ \ln \left( \frac{Voltage_1}{Voltage_2} \right) = \ln \left( \frac{C U_o \exp(\phi_{sc1})}{C U_o \exp(\phi_{sc2})} \right) = \phi_{sc1} - \phi_{sc2}, $$
Figure 4.9: Sample geometries for the reference measurements. See text for discussion.

we have eliminated the need to calibrate the machine to find $C$. The weights for this measurement pair are

$$W_{ij}^R = \left( \frac{G(r_j - r_{d1})U_o(r_{s1}, r_j)}{U_o(r_{s1}, r_{d1})} - \frac{G(r_j - r_{d2})U_o(r_{s2}, r_j)}{U_o(r_{s2}, r_{d2})} \right) \nu h^3 / D. \quad (4.62)$$

Although we have eliminated the need to explicitly remove the background signal, we still need to know the background optical properties to calculate the weights. Specifically, $U_o$ and $G$ are functions of the background optical properties. If we incorrectly guess the background properties, then we introduce and error in $G$ and $U_o$. For example, if we incorrectly guess the background absorption,

$$G(r) \rightarrow G(r) + \frac{\partial G(r)}{\partial \mu_a} \Delta \mu_a + \ldots \rightarrow \left( 1 + \frac{i |r|}{2kD} \Delta \mu_a \right) G(r) \quad (4.63)$$

$$U_o(r) \rightarrow U_o(r) + \frac{\partial U_o(r)}{\partial \mu_a} \Delta \mu_a + \ldots \rightarrow \left( 1 + \frac{i |r|}{2kD} \Delta \mu_a \right) U_o(r) \quad (4.64)$$

These errors show up in the weights for both the single source and double source weight functions, i.e. for a single source

$$U_{sc}(r_d, r_s) = \int d^3r (1 + \gamma(r_d - r) + \gamma(r - r_s) + O(\Delta \mu_a^2)) G(r_d - r)U_o(r, r_s)h^3 / D,$$

$$\gamma(r) = \frac{i |r| \Delta \mu_a}{2kD} \quad (4.65)$$

and for the source pair,

$$U_{sc}(r_d, r_{s1}) - U_{sc}(r_d, r_{s2}) = \quad (4.66)$$
We can see that the same systematic error is introduced in each equation for incorrect estimates of $\mu_a$. If we now look at the calculation of $U_{sc}$ from the measured data, we see the difference between the one source and two source measurements. When we measure the amplitude and phase, we measure the total wave,

$$U_{total} = U_0 + U_{sc} \rightarrow U_{sc} = U_{total} - U_0.$$ (4.67)

In the one source Born approximation we must subtract off the calculated value of $U_o$. Since we use a guess for the background properties to calculate $U_0$, we introduce some error here, i.e.

$$U_{sc}(\mathbf{r}_s, \mathbf{r}_d) = U_{total}(\mathbf{r}_s, \mathbf{r}_d) - (1 + \gamma(\mathbf{r}_s, \mathbf{r}_d))U_o(\mathbf{r}_s, \mathbf{r}_d).$$ (4.68)

But when we use the two source referencing method, since $|\mathbf{r}_d - \mathbf{r}_{s1}| = |\mathbf{r}_d - \mathbf{r}_{s2}|$ this error is eliminated,

$$U_{sc}(\mathbf{r}_{s1}, \mathbf{r}_d) - U_{sc}(\mathbf{r}_{s2}, \mathbf{r}_d) = [U_{total}(\mathbf{r}_{s1}, \mathbf{r}_d) - (1 + \gamma(\mathbf{r}_{s1}, \mathbf{r}_d))U_o(\mathbf{r}_{s1}, \mathbf{r}_d)] - [U_{total}(\mathbf{r}_{s2}, \mathbf{r}_d) - (1 + \gamma(\mathbf{r}_{s2}, \mathbf{r}_d))U_o(\mathbf{r}_{s2}, \mathbf{r}_d)]$$ (4.69)

$$= U_{total}(\mathbf{r}_{s1}, \mathbf{r}_d) - U_{total}(\mathbf{r}_{s2}, \mathbf{r}_d)$$ (4.70)

There is no systematic error introduced in the measurement of $U_{sc}$ when using the referencing scheme. Note that if there is random measurement noise, then the subtraction of the two source measurements will effectively double the random noise.

Only the error in the processed data is reduced by the referencing scheme, the error in the weights is not reduced. Nevertheless, we have found that the procedure gives superior reconstruction as shown in figure 4.10. In these simulations, the background medium has an absorption coefficient of $\mu_a = 0.03 \text{ cm}^{-1}$ and a reduced
scattering coefficient of $\mu'_s = 10.0 \text{ cm}^{-1}$. A 1 cm diameter sphere with the same reduced scattering coefficient as the background and an absorption coefficient of 0.05 cm$^{-1}$ is embedded in the medium. The source (or sources) are scanned around the edges of a 7 cm square, and 26 measurements of amplitude and phase are simulated at a source modulation frequency of 500 MHz. We use the analytic solution for a sphere [10] to simulate the data. No noise was added to the data. We obtained data for two different configurations, first, a single source directly across from a single detector, and second, a source pair separated by 1 cm, directly across from a single detector.

Before we began reconstructing the image, we took a guess at the background absorption, (we assume that we know the correct reduced scattering coefficient). For the single source measurements, we use this guess to calculate the weights. We also use the guess to analytically subtract off the background signal from the total measurement. When the guess for the background was too low, (top left images in figure 4.10) a noisy image with a large positive absorption region in the center, and negative absorption region at the edges. When the background absorption is guessed correctly, we obtain a good image (center left image in figure 4.10), and when the background absorption guess is too high, we obtain the opposite image we saw when we underestimated the background absorption (lower left images in figure 4.10).

When we use the source pair, and underestimate the background absorption, this error cancels in the measured data, and the error is propagated only through the weights. In this situation, we can still see the outline of the solution in each case (see figure 4.11, right column). Although the error in the weights has effected the image quality, but it has not totally degraded the image.

When a positivity constraint is placed on the absorption solution (i.e. we set all voxels with negative absorption equal to zero in the reconstruction algorithm), the quality of the two source reconstructions is improved. The single source reconstruction only works when have the correct guess for the background (see figure 4.11).

If the geometry of the system does not allow these symmetric measurements, this algorithm for background subtraction cannot be used. Instead, the background
Figure 4.10: Reconstructions of absorption when the background absorption is mis-estimated. The left column of reconstruction use a single source and detector, the right uses the two source referencing method. 1000 SIRT iterations were performed with no constraints on the reconstructed absorption.
Figure 4.11: Reconstructions of absorption when the background absorption is mis-estimated. The left column of reconstruction use a single source and detector, the right uses the two source referencing method. 1000 SIRT iterations were performed with a positivity constraint on the reconstructed absorption.
must be subtracted using a theoretical model. Alternatively, investigators attempt to make measurements before and after the addition of the heterogeneity. This allows an explicit measurement of the background signal.

4.9 Experimental and Computational Results

The following experiments were performed in an effectively infinite medium using the equipment described in Chapter 3. Since at this point, we were only using the Born approximation, the initial amplitude and phase of the sources were measured for calibration purposes. A perfectly absorbing sphere was submerged, and moved in a manner to simulate the source pair scanning along the sides of 6.0 cm square as shown in figure 4.12. In each measurement the detector remained opposite the source pair, at a separation of greater than 35 transport mean free paths. 120 measurements of amplitude and phase were made around the square. The volume of the imaged region was $5 \times 5 \times 1 \text{ cm}^3$.

Figure 4.12 demonstrates the reconstruction of a single perfectly absorbing spherical object (1.2 cm in diameter) from experimental data. The background media has $\mu_s = 0.023 \text{ cm}^{-1}$ and $\mu'_s = 6.0 \text{ cm}^{-1}$. In this reconstruction, 1000 SIRT iterations were performed. As we start the reconstruction, the image shows a large object with a low absorption. The position is correct. Had we continued to iterate, the object would rapidly become smaller and more absorbing. We have chosen to stop iterating when the percent error between the forward model and the measured data is less than 1%.

To confirm that we are sensitive to the optical properties of the medium, a series of experiments were undertaken in which spheres of varying absorption were imaged separately using matrix inversion (SVD). The spheres were made of casting resin with titanium oxide ($\text{TiO}_2$) for scatterers and a near infrared absorbing dye for absorption [55]. The reconstructed images are shown in figure 4.13. The reconstructed $\delta \mu_a(\mathbf{r})$ for this series of experimental data is also shown in figure 4.13. Note that the reconstructed absorption (solid circles) qualitatively follows the actual object ab-
absorption, but saturates at large absorption where Born approximation is expected to break down. The theoretical data created from the exact solution (solid line) show the same trend. In calculation of the forward model, we assumed that the index of refraction was homogeneous. In fact the index of refraction of the resin is 1.56 and the index of refraction of water is 1.33. This index mismatch will increase the reconstructed value of $\mu_a$, and begins to explain the discrepancy between the true $\mu_a$ and the reconstructed value.

### 4.10 Upgrading the Weight Functions

We have seen that the inverse problem saturates for highly absorbing objects. This saturation is due to a breakdown of the Born and Rylov approximations. We can reduce this saturation effect by correcting our forward model. For example, in the Born expansion we had the equation,

$$U_{sc}(r_d, r_s) = -\int O(r)G(r - r_d)(U_o(r, r_s) + U_{sc}(r, r_s)), \quad (4.71)$$

and we made the approximation

$$U_o(r, r_s) \gg U_{sc}(r, r_s). \quad (4.72)$$
Figure 4.13: Top: In this experiment, resin spheres (1.2 cm diameter) made with a mixture of scatterer and a known concentration of ink were imaged using matrix inversion (SVD). Bottom: The reconstructed absorption from both the experimental data (circles) and the simulated data (line) are plotted vs the actual absorption. See text for further discussion. Error bars are derived from estimated the calibration errors which we believe to be most significant.
Recall that $U_{sc}$ is the part of the DPDW which has been scattered from the heterogeneity. If we approximate $U_{sc}$ instead of dropping it, we can improve our reconstructions. We need a heterogeneous model to approximate $U_{sc}$. Such models include Monte-Carlo simulations, finite difference calculations, and analytic solutions for specific geometries.

To demonstrate the procedure for improving the weights, we first look at the integral equation. Instead of approximating

$$U_{sc}(r_d, r_s) = -\int O(\mathbf{r}) G(\mathbf{r} - \mathbf{r}_d)(U_o(\mathbf{r}, r_s) + U_{sc}(\mathbf{r}, r_s)) d^3r,$$

as

$$U_{sc}(r_d, r_s) = -\int O(\mathbf{r}) G(\mathbf{r} - \mathbf{r}_d) U_o(\mathbf{r}, r_s) d^3r,$$

we use and iterative procedure,

$$U_{sc}^{n+1}(r_d, r_s) = -\int O(\mathbf{r}) G(\mathbf{r} - \mathbf{r}_d)(U_o(\mathbf{r}, r_s) + U_{sc}^n(\mathbf{r}, r_s)) d^3r.$$  \hspace{1cm} (4.75)

This procedure updates the weights in the matrix equation. We start by making a guess that there is only the homogeneous background absorption ($0^{th}$ order). In this case there is not heterogeneity and $U_{sc}^0 = 0$. The weights in the Born approximation are

$$W_{ij}^B \propto G(r_j - r_{d}) U_o(r_j, r_{s_j}).$$  \hspace{1cm} (4.76)

We then use the measured data to reconstruct the object. We use the results of this $0^{th}$ order reconstruction, and use a heterogeneous forward model to calculate $U_o + U_{sc}^1$. Next we use $U_{sc}^1$ as an approximation to generate a new set of weights, i.e.,

$$W_{ij}^{B'} \propto G(r_j - r_{d})(U_o(r_j, r_{s_j}) + U_{sc}^1(r_j, r_{s_j})).$$  \hspace{1cm} (4.77)

We will show the results of this weight updating routine in section 4.12 using an analytic solution for a spherical inhomogeneity.

We have updated the weights using a heterogeneous model for photon propagation. One could use the Born or Rytov formulations for the scattered wave in the
heterogeneous forward model. This is certainly possible, but there is a small subtlety. To calculate the scattered wave at a particular voxel $k$, from a source $i$, one must calculate the sum (in the Born approximation),

$$U_{sc}(r_k, r_{si}) = \sum_j U_{sc}(r_j, r_{si})G(r_k - r_j)h^3/D.$$  \hspace{1cm} (4.78)

We cannot calculate this when $j = k$. This is the so called 'self-interaction term'. Jacques et al. [56] have calculated the value of the self interaction term and incorporated into a forward model called the 'system of virtual sources' (SVS). The SVS model has been incorporated into the PMI code (see chapter E) and will be released in a future version.

We have assumed throughout this discussion that we were using a good value for the background properties of absorption and scattering. If the system is totally unknown, one would like to update the background values to improve the image.

### 4.11 Resolving Multiple Objects

Figure 4.14 demonstrates that we are able to resolve multiple absorbing objects. The left panels (a-b) show the reconstruction of two 1.0 cm diameter perfectly absorbing spheres from experimental data. The top (a) is the reconstruction using singular value decomposition and analysis, and the bottom (b) panel is a reconstruction using 3000 iterations of SIRT.

We have also investigated the effect of modulation frequency on resolution of multiple objects using simulated data derived from the analytic solution to the diffusion equation for a sphere embedded in an otherwise homogeneous medium [10]. Panels (c-f) are images of two perfectly absorbing spheres from simulated data using a different sphere configuration. In panels (c-d) (background $\mu_a = 0.1$ cm$^{-1}$, inside the spheres $\mu_a = 0.4$ cm$^{-1}$), we see an increase in image quality as the modulation frequency is increased from 50 MHz (c) to 1 GHz (d). However, when the background
absorption is high (background $\mu_n = 1.0 \text{ cm}^{-1}$, inside the spheres $\mu_n = 4.0 \text{ cm}^{-1}$), the image quality does not noticeably improve as the modulation frequency is increased from 50 MHz (e) to 1 GHz (f). This may be understood qualitatively by noting that the wavenumber of a DPDW,

$$k = \sqrt{(-v\mu_n + i\omega)/\lambda},$$

is nearly independent of $\omega$ when $v\mu_n \gg \omega$. This result suggests that sources at low modulation frequencies and sources with high frequency components will yield roughly equivalent images in media characterized by a high average absorption such as the brain. On the other hand, when imaging within bodies with low average absorption, such as the breast, high modulation frequency images will give better resolution.

### 4.12 DPDW Imaging Combined With Other Imaging Modalities

An important contribution of the optical method is its ability to quantify the concentrations of physiologically important pigments, such as oxygenated and de-oxygenated hemoglobin, by providing absolute spatial quantification of scattering and absorption coefficients in the near infra-red region. Anatomical details derived from a conventional medical image, as in the case of X-ray tomography or MRI, can be taken into account in order to improve the quantitative accuracy of the optical image. The feasibility of simultaneously combining optical with other imaging modalities promises to increase the diagnostic certainty of the acquired images. Other researchers have used a priori structural information to improve the formulation of the forward problem [57, 58]. In this section we describe an algorithm which uses structural information to reduce the number of unknowns in the inverse problem, from the number of voxels in the image, to the number of tissue types. This reduces both the complexity of the inverse problem and the number of measurements necessary for an accurate reconstruction. We present simulations which confirm the efficiency of the algorithm, and experimental measurements on a tissue phantom which demonstrate the feasibility of
Figure 4.14: The left panels (a-b) show the reconstruction of two 1.0 cm diameter perfectly absorbing spheres from experimental data. The top (a) is the reconstruction using singular value decomposition and analysis, and the bottom (b) panel is a reconstruction using 3000 iterations of SIRT. Panels (c-f) are images of two perfectly spheres from simulated data using a different sphere configuration. In panels (c-d) (background $\mu_a = 0.1$ cm$^{-1}$, inside the spheres $\mu_a = 0.4$ cm$^{-1}$), we see an increase in image quality as the modulation frequency is increased from 50 MHz (c) to 1 GHz (d). However, when the background absorption is high (background $\mu_a = 1.0$ cm$^{-1}$, inside the spheres $\mu_a = 4.0$ cm$^{-1}$) the image quality does not noticeably improve as the modulation frequency is increased from 50 MHz (e) to 1 GHz (f).
Let us consider an absorbing inhomogeneity embedded in a region broken into $n$ voxels. For simplicity we assume $n=9$ as depicted in figure 4.15.

Thus we have one unknown value of $\delta \mu_a$ in each of the nine voxels. We make one measurement of the amplitude and phase of the diffuse photon density wave, from which we can calculate the real and imaginary part of the scattered phase ($\phi_{sc}$) using the Rylov solution. The scattered phase will obey the following matrix equation:

$$
\begin{pmatrix}
\Re[\phi_{sc}(r_s, r_d)] \\
\Im[\phi_{sc}(r_s, r_d)]
\end{pmatrix} =
\begin{pmatrix}
\Re[W_{11}] & \cdots & \Re[W_{19}] \\
\Im[W_{11}] & \cdots & \Im[W_{19}]
\end{pmatrix}
\begin{pmatrix}
\delta \mu_a^1 \\
\vdots \\
\delta \mu_a^9
\end{pmatrix}
$$

(4.81)

Here $\delta \mu_a^i$ is the absorption in the $i$th voxel. If the structural information is known and we assume that each component in the structure has uniform optical properties, then the problem dramatically simplifies. We need only to solve for the absorption coefficients of each type of inhomogeneity. For example, if the sample is composed of fat (background), vein and tumor, then we only have two actual unknowns, (since
the perturbation to the background, fat, is zero). We may then rewrite:

\[
\begin{pmatrix}
\Re[\phi_{az}(r_s, r_d)] \\
\Im[\phi_{az}(r_s, r_d)]
\end{pmatrix} = \begin{pmatrix}
\Re[W_{11}] & \Re[W_{19}] \\
\Im[W_{11}] & \Im[W_{19}]
\end{pmatrix} \cdot \begin{pmatrix}
\delta \mu_{az}^{fat1} \\
\delta \mu_{az}^{fat2} \\
\delta \mu_{az}^{fat3} \\
\delta \mu_{az}^{fat4} \\
\delta \mu_{az}^{fat5} \\
\delta \mu_{az}^{fat6} \\
\delta \mu_{az}^{vein7} \\
\delta \mu_{az}^{tumor8} \\
\delta \mu_{az}^{tumor9}
\end{pmatrix}
\]

as

\[
\begin{pmatrix}
\Re[\phi_{az}(r_s, r_d)] \\
\Im[\phi_{az}(r_s, r_d)]
\end{pmatrix} = \begin{pmatrix}
\Re[W_{17}] & \Re[\sum_{j=8}^{9} W_{ij}] \\
\Im[W_{17}] & \Im[\sum_{j=8}^{9} W_{19}]
\end{pmatrix} \cdot \begin{pmatrix}
\delta \mu_{az}^{vein} \\
\delta \mu_{az}^{tumor}
\end{pmatrix}
\]

In this way we have reduced the number of linear equations to be solved, from nine to two. This algorithm is easily extended for multiple measurements. It is interesting to note that the sum of the weights in the above matrix represent our sensitivity of each measurement to each tissue type. These sums can be used to design the experimental setup and maximize sensitivity to the tissue type of interest.

Simulations were performed using PMI software [12]. A matrix inversion technique (SVD) was employed to solve for the absorption coefficient of inhomogeneities in a background medium. Because the problem has been dramatically simplified, there was no need for any regularization or singular value analysis. 1% amplitude and 0.5 degree phase noise was added to all simulated data. In all of the following simulations the optical properties of the background were \( \delta \mu_a = 0.03 \text{ cm}^{-1} \) and \( \mu'_s = 10.0 \text{ cm}^{-1} \) and the source-detector separation was 6 cm.
We first tested this algorithm on a series of simple one object systems. The 1 cm
diameter spheres had the same scattering properties as the surrounding medium, but
the absorption varied from 0.035 to 0.355 cm\(^{-1}\). The area of interest, a 6 cm x 6
cm x 1 cm region, was divided into 120 x 120 x 20 = 288,000 voxels. Using a single
source-detector pair and making measurements of amplitude and phase at 4 different
source modulation frequencies (50, 200, 350, 500 Mhz), we had a 8 x 288,000 matrix
to invert. But using the a priori structural information we were able to compress the
8 x 288,000 matrix down to a 8 x 1 matrix. In this reconstruction the computation
time was totally dominated by the time it takes to calculate the weights, and the
matrix inversion time was negligible. In figure 4.16 the reconstructed value of the
object absorption is plotted versus the true value for each sphere simulation (labeled
1st iteration). Note that the reconstructed values agree well at low absorption, but
show saturation effects at higher absorption.

As we mentioned earlier, these saturation effects are a result of the breakdown of
the Rytov approximation. Basically, we have used a homogeneous model to calculate
the weight functions. To improve the reconstructions, we must take into account that
there is a heterogeneity present. When we updated the weight functions using the
1st iteration results, as suggested by Pogue et al. [20], we were able to overcome the
saturation effects. The imaging process now consists of several steps;

1. Create the weights using a homogeneous model.
2. Calculate the inverse using SVD.
3. Use this solution to calculate the weights using a heterogeneous model.
4. Calculate the inverse using SVD.

We have used the exact solution for a sphere to calculate the heterogeneous
weights. The results of this iterative process are also shown in 4.16, labeled 2nd
iteration.

The next simulation used six objects in the medium (background) as shown in
Fig. 3. Objects a,b,c,d had \(\mu_a = 0.036\) cm\(^{-1}\), object e had \(\mu_a = 0.042\) cm\(^{-1}\) and object
f had \(\mu_a = 0.050\) cm\(^{-1}\). A single source and detector were scanned along the sides of
Figure 4.16: 1st and 2nd iteration of reconstructed absorption versus the true value, for a single spherical inhomogeneity.

Figure 4.17: Simulation with six absorbing inhomogeneities. Since the size and position of the spheres are known, the 'reconstructed' image will look just like the original image.

the square. Measurements were simulated at three modulation frequencies (0, 250, 500 Mhz) and 14 source-detector positions. When given the position of the objects the algorithm reconstructs accurately the absorption coefficients as shown in Table 4.1.

Finally, a tissue phantom was built, with a geometry resembling a compressed breast as shown in figure 4.18. The phantom was made from clear polyester resin, in which titanium oxide particles were suspended to create a highly scattering medium (as described by Firbank et al. [55]). Quantities of the scatterer and India ink were added to give an absorption coefficient $\mu_a=0.028 \, \text{cm}^{-1}$ and a reduced scattering coefficient $6.5 \, \text{cm}^{-1}$ (780 nm), values which are close to the values measured for the human breast tissue [22]. The optical properties of the model were verified by inde-
pendent time-resolved spectroscopy (TRS) measurements (see appendix B for a brief overview of the TRS device). A two source one detector configuration was used as depicted in Fig. 5b. The sources were multiplexed (DiCon Fiber Optics multichannel fiber optic switch). In all measurements a 780 nm laser source was employed. In order to create an inhomogeneity, a 12 mm diameter, 35 mm long cylinder was drilled in the phantom. The volume was filled sequentially with twelve different solutes of intralipid and india ink. The concentration of dye was altered in precalculated steps to give absorption values in the range 0.02 - 0.2 cm\(^{-1}\). A TRS system based on the time-correlated single photon counting was used for the measurements.

As we discussed in section 4.8, we must divide out the homogeneous signal to solve for the scattered phase. In the previous computer simulations, we were able to divide out the homogeneous signal using an analytic solution. However in the experimental system, we were not able to obtain such a measurement. To eliminate the homogeneous signal, we used the referencing scheme discussed previously. Briefly, this scheme involves comparing two measurements with equal source-detector separations to eliminate the background contribution. For each intralipid-dye solution a single pair of measurements was acquired. The time resolved data were transformed into the frequency domain using the FFT, and six frequencies, all below 500MHz, were selected. The algorithm reduced a 6 x 144,000 matrix down to a 6 x 1 matrix. (Since only one absorbing inhomogeneity was present to the phantom, the algorithm had to solve only for one unknown value). Figure 4.18 shows the reconstructed absorption

<table>
<thead>
<tr>
<th>Sphere</th>
<th>Real $\mu_a$ (cm(^{-1}))</th>
<th>Recon. $\mu_a$ (cm(^{-1}))</th>
</tr>
</thead>
<tbody>
<tr>
<td>a, b, c, d</td>
<td>0.036</td>
<td>0.037</td>
</tr>
<tr>
<td>e</td>
<td>0.042</td>
<td>0.045</td>
</tr>
<tr>
<td>f</td>
<td>0.050</td>
<td>0.056</td>
</tr>
</tbody>
</table>

Table 4.1: Reconstruction results for multiple absorbing inhomogeneities.
Figure 4.18: A tissue phantom simulating a human breast with one heterogeneity. D denotes the detector and S the sources. (a) Side view, (b) top view. (c) The results from the inversion. See text for more discussion.

values, after one iteration, in comparison with the theoretically calculated ones.

The algorithm we present here simplifies the calculation load by reducing the number of unknowns to the number of regions with different optical properties. These results clearly demonstrate that given the geometry we can accurately reconstruct the absorption of the different regions of the various models. In the case of MRI-guided optical tomography of the human breast, boundary conditions and inhomogeneous background regions are expected to affect the accuracy of the reconstruction. Still we believe that such a method will eventually prove to be of clinical value.
4.13 Finite Systems

In our lab, we have inverted an approximate solution to the infinite, heterogeneous diffusion equation. We realize that in clinical situations, we will not have an infinite system, but rather a system with irregular boundaries. Although we have not investigated finite systems in this work, many investigators have studied how to handle boundary conditions for homogeneous, finite media [59]. In this section we examine the general problem, and then consider the simple, yet clinically relevant geometry of the semi-infinite system.

The most general goal is to write down a solution for the photon density in a homogeneous volume enclosed by a surface, \( S \). We will use the same formalism as the solution of the electrostatic boundary-value problem using Green functions. Using Green’s theorem, for a source distribution \( A(r) \),

\[
U(r) = \int_V A(r') G(r, r') d^3r' + \frac{1}{4\pi} \int_S \left[ G(r, r') \frac{\partial U}{\partial n'} - U(r') \frac{\partial G}{\partial n'} \right] d^2r'.
\]  

(4.84)

In the heterogeneous absorption case \( A(r) = U_o(r, r_s) u \delta \mu_o(r) / D \).

Investigators have used Monte Carlo simulations and experimental results to show that the true boundary conditions for the case of finite media are well modeled by the extrapolated zero boundary condition [60, 61, 62, 63]. The extrapolated zero boundary condition asserts that the photon density is zero a distance of \( 0.704 l^* \) from the actual (planar) boundary [64]. Thus, we re-draw the boundaries at the extrapolated position, and use the condition that \( U = 0 \) on the extrapolated surface. Equation 4.84 becomes,

\[
U(r) = \int_V A(r') G(r, r') d^3r' + \frac{1}{4\pi} \int_S G(r, r') \frac{\partial U}{\partial n'} d^2r'.
\]

(4.85)

This general equation may be simplified by choosing a Green function that satisfies Dirichlet boundary conditions (i.e. \( G = 0 \) on the extrapolated surface). Then

\[
U(r) = \int_V A(r') G(r, r') d^3r'.
\]

(4.86)
Figure 4.19: An extrapolated zero boundary is a good approximation for the photon density boundary conditions in the semi-infinite case. Here we see how a source on the boundary is transformed using a true source position and an image source centered about the extrapolated boundary.
Arridge et al. [59] have worked out the Green function solutions for Dirichlet boundary conditions for a variety of different homogeneous finite systems such as semi-infinite, slab, spherical and cylindrical geometries. It is also possible to use other methods such as Monte-Carlo and Finite Element to derive the Green function solutions.

For the semi-infinite case, we can use the method of images to find the Green function which obeys the Dirichlet boundary conditions (see figure 4.19). In this case

\[
G(r, r') = \frac{\exp(ik|r-r'|)}{4\pi|r-r'|} - \frac{\exp(ik|r-r_i|)}{4\pi|r-r_i|} \tag{4.87}
\]

where \( r' \) is the position of the source in the sample volume, and \( r_i \) is the position of the image source located on the other side of the extrapolated boundary. Using this Green function we can now calculate the incident DPDW,

\[
U(r, r_s) = \frac{B\exp(ik|r-r_s|)}{D} - \frac{B\exp(ik|r-r_i|)}{D} \tag{4.88}
\]

\[
= U_o(r, r_s) - U_o(r, r_i). \tag{4.89}
\]

where \( r_s \) is the position of the source in the sample volume, and \( r_i \) is the image of \( r_s \).

We now plug the incident DPDW solution and the Green Function solution for the finite system into the weights (equation 4.13, 4.26). For example, in the Born approximation, for a detector at \( r_d \), equation 4.13 becomes

\[
U_{sc}(r_d, r_s, r_i) = -\int d^3r \, \frac{G(r_d - r)}{\text{semi-infinite}} \, O(r) \, \frac{U_o(r, r_s)}{\text{semi-infinite}} \tag{4.90}
\]

\[
= -\int d^3r \, [G(r_d, r) - G(r_d, r')] \tag{4.91}
\]

\[
\times O(r) \, [U_o(r, r_s) - U_o(r, r_i)]
\]

where \( r' \) is the image voxel position.

Multiple image sources can be used to solve for the scattered wave in the case of the slab, the cube and other planar geometries. For curved geometries one has to take more care in defining the extrapolated surface.
Chapter 5

Imaging the Scattering coefficient

In the human body there are localized absorption changes and changes in the reduced scattering coefficient. Scattering is caused by a mismatch in the index of refraction and depends on the size and shape of the scattering object. The reduced scattering coefficient also depends on the density of scatterers. The presence of certain solutes such as glucose or potassium can change the index of refraction of the intra- or extracellular fluid, changing the reduced scattering coefficient. Imaging the scattering coefficient is important not only because large scattering changes can easily corrupt an absorption image, but also because scattering is an additional form of contrast. We will use the same expansions (Born, Rylov) that we used for the absorption case and the same inversion techniques (SVD, SIRT) to image the reduced scattering coefficient.

To solve the diffusion equation for an infinite, heterogeneously scattering medium we expand the diffusion coefficient, $D = 1/3\mu'_s$, into spatially dependent, $\delta D(r)$, and independent (background), $D_0$, pieces, i.e.

$$D(r) \Rightarrow \delta D(r) + D_0. \quad (5.1)$$

These terms are then incorporated into the diffusion equation (equation 2.18),

$$J_{ac}(r) \approx -D \nabla U_{ac}(r) \quad (5.2)$$

to obtain

$$-i\omega U(r, r_s) + v_{\mu_s} U(r, r_s) + \nabla \cdot J(r, r_s) = B\delta(r_s), \quad (5.3)$$
\[ J(r, r_s) = -(\delta D(r) + D_o) \nabla U(r, r_s). \] (5.4)

When we insert equation 5.4 into 5.3, we obtain
\[-i\omega U(r, r_s) + \nu \mu U(r, r_s) - \nabla \cdot ((\delta D(r) + D_o) \nabla U(r, r_s)) = B\delta(r_s). \] (5.5)

Then divide through by \(-D_o\) we have
\[ (\nabla^2 + k^2)U(r, r_s) + \nabla F(r) \cdot \nabla U(r, r_s) + F(r) \nabla^2 U(r, r_s) = -B\delta(r_s)/D_o. \] (5.6)
\[ F(r) = \delta D(r)/D_o. \] (5.7)

### 5.1 Born Expansion

To solve this heterogeneous diffusion equation, we will use the same approaches as we described in Chapter 4. We will assume that we have a homogeneous system. A finite system can be handled using image sources, just as we discussed in the absorption case. First, using the Born approximation,
\[ U(r, r_s) = U_o(r, r_s) + U_{sc}(r, r_s) \] (5.8)

so
\[ \underbrace{(\nabla^2 + k^2)U_o(r, r_s)}_{\text{homogeneous}} + \underbrace{(\nabla^2 + k^2)U_{sc}(r, r_s)}_{\text{homogeneous}} \]
\[ + \nabla F(r) \cdot \nabla (U_o(r, r_s) + U_{sc}(r, r_s)) + F(r) \nabla^2 (U_o(r, r_s) + U_{sc}(r, r_s)) \]
\[ = -B\delta(r_s)/D_o. \] (5.10)

If we subtract off the homogeneous diffusion equation (marked \textit{homogeneous}) and assume that \(U_{sc} \ll U_o\), we again arrive at a Helmholtz equation for \(U_{sc}\),
\[ (\nabla^2 + k^2)U_{sc}(r, r_s) = -\nabla F(r) \cdot \nabla U_o(r, r_s) - F(r) \nabla^2 U_o(r, r_s) \] (5.11)
which can be solved using the Green function method,
\[ U_{sc}(r, r_s) = -\int d^3r \ G(r - r_d) \left( \nabla F(r) \cdot \nabla U_o(r, r_s) + F(r) \nabla^2 (U_o(r, r_s)) \right) \] (5.12)
\[ G(r - r_d) = \frac{\exp(|r - r_d|)}{4\pi |r - r_d|}. \] (5.13)
Using Green’s first identity \[65\],
\[
\int_V d^3 x \ \phi \nabla^2 \psi = \int_S d^2 x \ \phi \mathbf{n} \cdot \nabla \psi - \int_V d^3 x \ \nabla \phi \cdot \nabla \psi,
\]
equation 5.12 becomes,
\[
U_{sc}(r_d, r_s) = - \frac{1}{V} \int dr \ G(r - r_d) \nabla F(r) \cdot \nabla U_o(r, r_s) \tag{5.15}
- \frac{1}{S} \int da \ U_o(r, r_s) \mathbf{n} \cdot \nabla (G(r - r_d) F(r))
+ \frac{1}{V} \int dr \ \nabla U_o(r, r_s) \cdot \nabla (G(r - r_d) F(r)).
\]
The integral marked II is equal to zero, since we can take this surface to be at infinity, and both \(U_o\) and \(G\) exponentially decay to zero at infinity. The third integral can be expanded,
\[
\int_V dr \ \nabla U_o(r, r_s) \cdot \nabla (G(r - r_d) F(r)) = \int_V dr \ \nabla U_o(r, r_s) \cdot \nabla G(r - r_d) F(r)
+ \int_V dr \ \nabla U_o(r, r_s) \cdot \nabla F(r) G(r - r_d). \tag{5.16}
\]
Note that the second term in the expansion cancels with the term marked I in equation 5.15 and finally
\[
U_{sc}(r_d, r_s) = \int_V dr \ \nabla U_o(r, r_s) \cdot \nabla G(r - r_d) \frac{\delta D(r)}{D_o}. \tag{5.17}
\]

5.2 Rytov Expansion

Just as we did in the absorption case, we can also make a Rytov approximation,
\[
U(r, r_s) = U_o(r, r_s) U_{sc}(r, r_{sc}) = \exp(\phi_o(r, r_s) + \phi_{sc}(r, r_s)), \tag{5.18}
\]
\[
U_o(r, r_s) = \exp(\phi_o(r, r_s)). \tag{5.19}
\]

For notational ease we will define,
\[
U_o \equiv U_o(r, r_s); \phi_o \equiv \phi_o(r, r_s) \tag{5.20}
\]
\[
U_{sc} \equiv U_{sc}(r, r_s); \phi_{sc} \equiv \phi_{sc}(r, r_s). \tag{5.21}
\]
When we plug these terms into the diffusion equation (5.6) we arrive at,

\[ (\nabla^2 + k^2)(U_oU_{sc}) + \nabla F \cdot \nabla(U_oU_{sc}) + F\nabla^2(U_oU_{sc}) = -B\delta(r) / D_o \]  
(5.22)

\[ F = \delta D(r) / D_o. \]  
(5.23)

We can expand the gradients of products,

\[ \nabla^2 U_o U_{sc} + \nabla^2 U_{sc} U_o + 2\nabla U_o \cdot \nabla U_{sc} + k^2 U_o U_{sc} + \nabla F \cdot \nabla U_o U_{sc} \]  
(5.24)

\[ + \nabla F \cdot \nabla U_o U_{sc} + F \nabla^2 U_o U_{sc} + F \nabla^2 U_{sc} U_o + 2F \nabla U_o \cdot \nabla U_{sc} = -B\delta(r) / D_o \]

Note that

\[ \nabla U_{sc} = \nabla \phi_{sc} U_{sc}. \]  
(5.25)

Using these identities and dividing through by \( U_{sc} \), Equation 5.24 becomes

\[ \underbrace{\nabla^2 U_o}_{\text{homogeneous}} + \underbrace{\nabla^2 \phi_{sc} U_o}_{\text{homogeneous}} + (\nabla \phi_{sc})^2 U_o + 2\nabla U_o \cdot \nabla \phi_{sc} + \underbrace{k^2 U_o}_{\text{homogeneous}} \]

\[ + \nabla F \cdot \nabla U_o + \nabla F \cdot \nabla \phi_{sc} U_o + F \nabla^2 U_o + F \nabla^2 \phi_{sc} U_o \]

\[ + F(\nabla \phi_{sc})^2 U_o + 2F \nabla U_o \cdot \nabla \phi_{sc} = -B\delta(r) / D_o \]  
(5.26)

As in the absorption case we have assumed that \( U_{sc} \) is negligible at the source position.

Next we subtract the homogeneous diffusion equation (marked \textit{homogeneous}) and note that

\[ \nabla^2 (U_o \phi_{sc}) = \nabla^2 U_o \phi_{sc} + \nabla^2 \phi_{sc} U_o + 2\nabla \phi_{sc} \cdot \nabla U_o \]  
(5.27)

\[ = -k^2 U_o \phi_{sc} + \nabla^2 \phi_{sc} U_o + 2\nabla \phi_{sc} \cdot \nabla U_o \]  
(5.28)

We use this equation to replace \( 2\nabla \phi_{sc} \cdot \nabla U_o \) in equation 5.26

\[ \underbrace{\nabla^2 \phi_{sc} U_o}_{\text{Helmholtz-like}} + (\nabla \phi_{sc})^2 U_o + \underbrace{\nabla^2 (U_o \phi_{sc})}_{\text{Helmholtz-like}} + k^2 U_o \phi_{sc} \]

\[ - \nabla^2 \phi_{sc} U_o + \nabla F \cdot \nabla U_o + \nabla F \cdot \nabla \phi_{sc} U_o + F \nabla^2 U_o \]

\[ + F\nabla^2 \phi_{sc} U_o + F(\nabla \phi_{sc})^2 U_o + 2F \nabla U_o \cdot \nabla \phi_{sc} = 0. \]  
(5.31)
This equation can be rearranged to form another Helmholtz equation. This Helmholtz equation is solved by convolving with the appropriate Green function,

\[
U_o(r_d, r_s) \phi_{sc}(r_d, r_s) = -\int_V d^3r \ G \left\{ (\nabla\phi_{sc})^2 U_o + \frac{\nabla F \cdot \nabla U_o + F \nabla^2 U_o}{A} \right\} + \frac{\nabla F \cdot \nabla \phi_{sc} U_o + F \nabla^2 \phi_{sc} U_o + F (\nabla \phi_{sc})^2 U_o + 2F \nabla U_o \cdot \nabla \phi_{sc}}{B}, \tag{5.32}
\]

where

\[
G \equiv G(r_d - r) \tag{5.33}
\]

If we again use Green’s first identity \text{5.14} then the term marked I becomes

\[
\int_V d^3x \ G \nabla^2 U_o = \int_S \left[ d^2x (FG) \mathbf{n} \cdot \nabla U_o - \int_V d^3x \ \nabla (FG) \cdot \nabla U_o \right] = 0 \tag{5.34}
\]

and the resulting term marked A cancels with the term marked A in equation 5.32.

Similarly, the term marked II becomes

\[
\int_V d^3x \ G U_o \nabla^2 \phi_{sc} = \int_S \left[ d^2x \ G U_o \mathbf{n} \cdot \nabla \phi_{sc} - \int_V d^3x \ \nabla (GU_o) \cdot \nabla \phi_{sc} \right] = 0 \tag{5.36}
\]

and the resulting term marked A cancels with the term marked A in equation 5.32.

Likewise with C. This leaves us with

\[
U_o(r_d, r_s) \phi_{sc}(r_d, r_s) = -\int_V d\mathbf{r} \ G(\nabla \phi_{sc})^2 U_o - F \nabla G \cdot \nabla U_o - F U_o \nabla G \cdot \nabla \phi_{sc} + FG(\nabla \phi_{sc})^2 U_o + FG \nabla U_o \cdot \nabla \phi_{sc}. \tag{5.37}
\]

Note that because our system is totally symmetric with respect to the source and detector,

\[
\int d\mathbf{r} \ F U_o(r, r_s) \nabla G(r_d - r) \cdot \nabla \phi_{sc} = \int d\mathbf{r} \ F U_o(r, r_s) \nabla G(r_d - r) \cdot \nabla \phi_{sc} \tag{5.40}
\]
\[
\begin{align*}
\int d\mathbf{r} & \quad F \frac{\exp(ik|\mathbf{r} - \mathbf{r}_s|)}{4\pi D_0 |\mathbf{r} - \mathbf{r}_s|} \cdot \nabla \phi_{sc} 
\end{align*}
\]
\[
\begin{align*}
\int d\mathbf{r} & \quad F \frac{\exp(ik|\mathbf{r}_d - \mathbf{r}|)}{4\pi |\mathbf{r}_d - \mathbf{r}|} \cdot \nabla \phi_{sc} 
\end{align*}
\]
\[
\begin{align*}
\int d\mathbf{r} & \quad FG(r_d - \mathbf{r}) \nabla U_o(\mathbf{r}, \mathbf{r}_s) \cdot \nabla \phi_{sc}.
\end{align*}
\]
If we assume that
\[
(\nabla \phi_{sc})^2 \ll \nabla G \cdot \nabla U_o
\]
and \( F \) less than or on the order of 1, we can now write equation 5.32 as
\[
U_o(\mathbf{r}_d, \mathbf{r}_s) \phi_{sc}(\mathbf{r}_d, \mathbf{r}_s) = \int_V d\mathbf{r} \quad F \nabla G \cdot \nabla U_o.
\]
Note that in most systems of particular interest in the body, the reduced scattering coefficient is not expected to vary more than 100%. So our assumption that \( F \) is less than or on the order of 1 is a good assumption.

\[
F = \delta D / D
\]
\[
= (D - D_0) / D
\]
\[
= 1 - (\mu'_s + \delta \mu'_s) / \mu'_s
\]
\[
= \delta \mu'_s / \mu'_s
\]

As in the absorption case, the structure of the Born and Rytov solutions look very similar. Again, we see that the Born approximation makes the assumption that the scattered wave is small, and the scattered wave scales linearly with the absorption. The Rytov approximation does not place a restriction on the magnitude of the scattered wave change, but rather assumes that the scattered field is slowly varying. In the absorption case, a calibration plot of reconstructed absorption versus true absorption showed that the Rytov solution procured an better reconstruction of the absorption. In the scattering case, the Rytov solution does not improve the calibration plot. Virmont and Ledanois [66] have studied this effect, and have suggested an adjustment to the Rytov solution that improves the scattering images.
5.3 Matrix Equations

We now have an expression which relates the scattered wave to the heterogeneous optical properties. From here the analysis is the same as in the absorption case; we will digitize the integral, and make a series of measurements to generate a matrix.

**Born:**

\[
\begin{pmatrix}
  U_{sc}(r_{s1}, r_{d1}) \\
  \vdots \\
  U_{sc}(r_{sm}, r_{dm})
\end{pmatrix} =
\begin{pmatrix}
  W_{11}^B & \ldots & W_{1n}^B \\
  \vdots & \ddots & \vdots \\
  W_{m1}^B & \ldots & W_{mn}^B
\end{pmatrix}
\begin{pmatrix}
  \delta D(r_1) \\
  \vdots \\
  \delta D(r_n)
\end{pmatrix}
\]

\[
W_{ij}^B = \nabla U_o(r_j, r_{si}) \cdot \nabla G(r_{di} - r_j) v h^3 / D_o
\] (5.50)

**Rytov:**

\[
\begin{pmatrix}
  \phi_{sc}(r_{s1}, r_{d1}) \\
  \vdots \\
  \phi_{sc}(r_{sm}, r_{dm})
\end{pmatrix} =
\begin{pmatrix}
  W_{11}^R & \ldots & W_{1n}^R \\
  \vdots & \ddots & \vdots \\
  W_{m1}^R & \ldots & W_{mn}^R
\end{pmatrix}
\begin{pmatrix}
  \delta D(r_1) \\
  \vdots \\
  \delta D(r_n)
\end{pmatrix}
\]

\[
W_{ij}^R = \frac{\nabla U_o(r_j, r_{si}) \cdot \nabla G(r_{di} - r_j) v h^3}{U_o(r_{di}, r_{si}) D_o}
\] (5.51)

The matrix is inverted using the same algorithms; SVD or SIRT to obtain \(\delta D\).

Figure 5.1 demonstrates the reconstruction of a single spherical object (1.2 cm in diameter) from experimental data. The background media has \(\mu_o^a = 0.023 \text{ cm}^{-1}\) and \(\mu_o^s = 6.0 \text{ cm}^{-1}\). A single, resin sphere having the same absorption coefficient as the surrounding medium, but a higher scattering coefficient (\(\mu_s' \approx 15.0 \text{ cm}^{-1}\)), is imaged using 120 measurements of amplitude and phase. In this reconstruction, we have made use of *a priori* knowledge that the object is either absorbing or scattering, that is we have assumed that the absorption coefficient is homogeneous throughout
the medium. In chapter 6 we discuss solving for both absorption and scattering simultaneously.

Just as in the absorption case, we have found that as we continue to iterate, the image of a sphere gets gradually smaller and more highly scattering. Boas et al. [22] have demonstrated that even in a best case scenario, the difference between a small, highly scattering object and a larger, less scattering object is practically immeasurable for objects with a diameter of less than 1 cm [22]. The authors demonstrate that there is a family of degenerate solutions which all conserve the quantity $\delta \mu_a v$ where $v$ is the volume of the sphere. Thus, in the SIRT reconstructions, the consecutive iterations move the solution through this family of solutions. Because we always start from the same initial guess (a homogeneous system) the reconstruction always moves through the family of solutions in the same way. Figure 5.2 demonstrates a series of reconstructions for different numbers of iterations. Note that as the number of iterations increases, the reduces scattering coefficient of the object increases, and the size decreases. We have left the iteration number as a free parameter in our reconstructions.

If we use a finite medium, we must adjust the weights in our calculation to reflect the new boundary conditions. In particular, we would use the same methodology as we did in section 4.13; replace $U_o$ and $G$ using the appropriate Green function solutions for the given boundary condition.
Figure 5.2: The reconstructed reduced scattering coefficient (maximum value) as a function of iteration. A 1 cm diameter sphere with $\mu'_s = 12 \text{ cm}^{-1}$, $\mu_s = 0.03 \text{ cm}^{-1}$ is embedded with a medium with $\mu'_s = 10 \text{ cm}^{-1}$, $\mu_s = 0.03 \text{ cm}^{-1}$. The sources scan the sides of a 7 cm square with a source modulation frequency of 200 MHz.
Chapter 6

Absorption and Scattering

When we have both variations in both absorption and scattering, the solution to the heterogeneous diffusion equation is a superposition of our previous solutions. The Born Solution is

$$U_{sc}(r_d, r_s) = - \int_V dV \nabla U_o(r, r_s) \cdot \nabla G(r - r_d) \frac{\delta D(r)}{D_o}$$

$$+ \int_V U_o(r, r_s) G(r - r_d) v^{\delta \mu_a(r)} \frac{\delta D(r)}{D_o},$$

and the Rytov is

$$\phi_{sc}(r_d, r_s) = - \frac{1}{U_o(r_d, r_s)} \int_V dV \nabla U_o(r, r_s) \cdot \nabla G(r - r_d) \frac{\delta D(r)}{D_o}$$

$$+ \frac{1}{U_o(r_d, r_s)} \int_V U_o(r, r_s) G(r - r_d) v^{\delta \mu_a(r)} \frac{\delta D(r)}{D_o}.$$

This leads us to the following matrices to invert,

$$\begin{pmatrix} U_{sc}(r_{s1}, r_{d1}) \\ \vdots \\ U_{sc}(r_{sm}, r_{dm}) \end{pmatrix} = \begin{pmatrix} W^{BA}_{11} & \cdots & W^{BA}_{1n} & \cdots & W^{BS}_{11} & \cdots & W^{BS}_{1n} \\ \vdots & \ddots & \vdots & \ddots & \vdots & \ddots & \vdots \\ W^{BA}_{m1} & \cdots & W^{BA}_{mn} & W^{BS}_{m1} & \cdots & W^{BS}_{mn} \end{pmatrix} \begin{pmatrix} \delta \mu_a(r_1) \\ \vdots \\ \delta \mu_a(r_n) \\ \delta D(r_1) \\ \vdots \\ \delta D(r_n) \end{pmatrix}$$
\[
W_{ij}^{RA} = -U_o(r_j, r_{si}) \cdot G(r_{dj} - r_j) v h^3 / D_o
\]  \hspace{1cm} (6.5)
\[
W_{ij}^{RS} = \nabla U_o(r_j, r_{si}) \cdot \nabla G(r_{dj} - r_j) v h^3 / D_o
\]  \hspace{1cm} (6.6)

We use these matrices, and the save inversion techniques (SIRT, SVD) to create separate images of absorption and scattering.

### 6.1 Simulation Results

For the following simulations the forward data were generated using the exact solution for one or more spheres embedded in an otherwise homogeneous infinite medium \[10\]. Random noise (0.5\% amplitude and 0.5\% phase) was added to all simulated data. Unless otherwise stated, the background optical properties of the medium were \(\mu_s = 0.05 \text{ cm}^{-1}\), \(\mu_s' = 10.0 \text{ cm}^{-1}\), and the source modulation frequency is 500MHz. The sources and detectors rotate around a 6.0 cm diameter cylindrical region making a measurement every 20 degrees. The reconstructed area is broken up into 0.25 cm by 0.25 cm pixels and 2000 SIRT iterations were performed. The two-source subtraction technique was not used here. For simplicity, the analytic solution for the incident wave was subtracted as part of the simulation.
Absorption and Scattering

We have reconstructed images of scattering and absorption simultaneously using the Rytov approximation. The results of such a reconstruction are shown in figure 6.1, where 4 samples are considered.

In the first sample, there is only an absorbing inhomogeneity as verified by the reconstruction. In the second sample there is only a scattering inhomogeneity, however the reconstruction produced some noise in the absorption map. We see that an absorbing and a scattering object can be individually imaged. The third sample demonstrates that we can simultaneously image two objects, one absorbing object and one scattering object. Note in the fourth panel a single sphere with different absorption and scattering factor is imaged. We have displaced the scattering and absorption features in the figure to emphasize this point.

An important practical advantage of the Rytov approximation is its natural separation of the amplitude and phase. As stated in equation 5.45, the scattered phase is the logarithm of the ratio of the measured signals; written

\[ \phi_s = \ln \left( \frac{U}{U_0} \right) = \ln \left[ \frac{A \exp(i\phi)}{A_0 \exp(i\phi_0)} \right] = \ln \left( \frac{A}{A_0} \right) + i(\phi - \phi_0). \] (6.9)

Thus the amplitude decay corresponds to the real part of the integral, and the phase shift to the imaginary. Figure 6.2 shows that at 500 MHz, the amplitude ratio (i.e. amplitude with inhomogeneity relative to amplitude without inhomogeneity) and phase change for various objects with either a pure scattering change or absorption change. We see that scattering and absorption changes affect the amplitude to the same degree. However, scattering changes affect the phase a great deal more than an absorption change.

This suggests that the scattering (absorption) reconstructions might be done independently using just the phase (amplitude) of the measured wave. The results of this procedure are presented in figure 6.3. This simulation suggests that while the scattering reconstruction using only phase data is quite successful, the absorption reconstruction using only amplitude data is quite noisy.
Figure 6.1: Simultaneous reconstructions of absorption and scattering.
Figure 6.2: Effect of absorption versus scattering variation on amplitude and phase. At 500 MHz, the amplitude ratio (i.e. amplitude with inhomogeneity relative to amplitude without inhomogeneity) and phase change for various objects with either a pure scattering change or absorption change. Scattering changes affect the phase a great deal more than an absorption change.
Figure 6.3: Using the Rylov expansion, the amplitude and phase can be used separately to reconstruct the absorption and scattering. When both amplitude and phase are used (top) the reconstructions give the correct positions of the object. When the amplitude data alone is used (middle), both objects are seen at slightly offset positions. However, the phase information alone (bottom) gives a very good reconstruction of the scattering for this high modulation frequency (500 MHz).
Chapter 7

Imaging Fluorescence

We have discussed schemes designed to detect and image heterogeneities in biological tissues with diffusing near-infrared (NIR) light. These studies have centered on the detection of variations in the absorption and scattering coefficients in tissue and tissue phantoms. Recently however, fluorescent contrast agents have also been considered as a means to enhance the specificity and sensitivity in tumor detection [7, 11, 67, 68, 69, 70, 71, 33]. Fluorescent lifetime-based quantitation of different biological parameters such as tissue oxygenation \( \text{pO}_2 \) [72], pH value [73] and intracellular calcium concentration \([\text{Ca}^{2+}]\) [74] have been proposed by several investigators. Localized fluorophore concentration

may signal an increased number of small blood vessels associated with rapid tumor growth [75]. The altered concentration of a fluorophore quencher (such as oxygen) which affects the fluorophore lifetime may signal the high oxygen uptake in a rapidly growing tumor [76]. Thus functional imaging of the variations of fluorophore concentration and lifetime may provide useful clinical information.

Much effort has been devoted to formulate the forward problem of fluorescent light in turbid media. An integral form in the time domain has been given by Huthcinson \textit{et al.} for the migration of fluorescent light in turbid media; these investigators have also numerically solved this integral equation in specific two-dimensional homogeneous and heterogeneous systems [21, 77]. A mathematical model for frequency domain fluorescent light propagation in semi-infinite homogeneous turbid media has been obtained by Patterson \textit{et al.} using zero boundary conditions and assuming that
the reduced scattering coefficients are the same for the excitation and emission light [68]. A useful algorithm has been developed by Wu et al. to deconvolve fluorescent emission spectra from tissue reflectance measurements [78]. Finally, in our lab, Li et al. [79] have presented analytic solutions for fluorescent diffuse photon density waves in homogeneous and heterogeneous turbid media with planar boundaries. The frequency domain analysis can easily be applied to time domain experiments by Fourier transformation of the time domain data.

In this chapter we will first discuss the equations which describe the passage of photons through a fluorescent medium. Next we examine the limited case in which we wish to detect and localize the center of a fluorescent object. Finally, we turn our attention to the more complicated problem of tomographic image reconstruction techniques for fluorescence lifetime imaging in turbid media [12].

Identifying and localizing a tumor becomes a simple procedure if we can turn a tumor into a source using exogenous fluorescent contrast agents. Although there are currently no FDA approved fluorescent contrast agents which specifically bind to tumor sites, the rapid growth of a tumor results in increased vascularity in the region and an abundance of leaky blood vessels. Certain molecules, such as the popular MRI contrast agent gadolinium chelate, are known to leak from blood vessels and accumulate in the intravascular space. Other contrast agents of the same molecular size, such as indo cyanine green (ICG) are expected to similarly accumulate at the tumor site. Preliminary studies show a three fold increase in the amount of ICG in rat tumor compared to normal tissue [70]. ICG is an excellent choice for NIR imaging since it has an absorption peak at 780 nm, fluoresces at 830 nm, and is currently used in humans to test hepatic and cardiac function [80].

7.1 Fluorescent Diffuse Photon Density Wave Theory

In this section we will develop the theory of diffusive waves propagating through fluorescent media. In this analysis, the fluorescent radiation is assumed to be well separated in energy from that of incident photons so that we safely ignore the possi-
bility of the excitation of fluorophores by the fluorescent re-emission. We also assume that the excited fluorophores have a single lifetime. We will treat fluorophore and chromophore absorptions separately, and we assume the change of scattering coefficient due to the fluorophore is negligible for the notational simplicity (however the fluorophore scattering effect is easily incorporated). Absorption due to fluorophores concentration is characterized by an additional absorption coefficient over the background, $\sigma N_t$, where $N_t$ is the concentration of fluorophore and $\sigma$ is the fluorophore absorption cross-section. Thus in the presence of fluorophores, the total absorption coefficient is the sum of the chromophore absorption coefficient plus the fluorophore absorption coefficient.

Suppose an intensity-modulated point source is at position $r_s$ in a homogeneous system. A fluorophore in the medium will be excited by the incident DPDW. The excited fluorophore then acts as a secondary point source of fluorescent diffusive waves (Fig.1a). Treating fluorophores as a two level quantum system and ignoring saturation effects, we find that the number of excited fluorophores, $N$ obeys the following linear diffusion equation [70],

$$\frac{\partial N(r,t)}{\partial t} = -\Gamma N(r,t) + \sigma vU(r, r_s)e^{-i\omega t} N_t(r)$$  \hspace{1cm} (7.1)

where $\Gamma$ is the excited dye decay rate, $N_t$ is the number of dye molecules per unit volume at a position $r$, $\sigma$ is the absorption cross section of the dye, and $vU(r, r_s)e^{i\omega t}$ is the incident photon fluence at a position $r$ from a source at $r_s$. For the case of an amplitude modulated source, $N(r, t) = N(r)e^{-i\omega t}$ so 7.1 can be used to obtain

$$-i\omega N(r) = -\Gamma N(r) + \sigma vU(r, r_s)N_t(r)$$  \hspace{1cm} (7.2)

$$N(r) = \frac{\sigma vU(r, r_s)N_t(r)}{\Gamma - i\omega}$$  \hspace{1cm} (7.3)

and the rate of production of fluorescent photons is

$$\Gamma N(r) = \frac{\sigma vU(r, r_s)N_t(r)}{1 - i\omega\tau}$$  \hspace{1cm} (7.4)

where $\tau = 1/\Gamma$ is the fluorescent lifetime.
The term $\Gamma N(r)$ is now a source of fluorescent diffuse photon density waves. These photons will propagate to the detector position $r_d$, so the detected fluorescent signal is

$$u_{fi} = \Gamma N(r)U'(r_d, r) = \Gamma N(r)\frac{\exp(i k'/|r_d - r|)}{4\pi|r_d - r|}$$

(7.5)

where we have written $U'(k')$ instead of $U(k)$ as a reminder that the properties of the fluorescent DPDW are governed by the optical properties of the medium at the fluorescent wavelength. To calculate the total fluorescent signal from a homogeneous distribution of fluorophore, we integrate over all fluorophores,

$$U_{fi} = \int dr \Gamma N(r)U'(r_d, r)$$

(7.6)

$$= \int dr U(r, r_s) \frac{N_t(r)\sigma_v}{1 - i\omega\tau} U'(r_d, r)$$

(7.7)

For notational simplicity, we assume excited fluorophores decay only through the radiation channel, i.e. the fluorescent yield is 100%. A fluorescent yield of less than 100% will result in an overall attenuation factor. The factor $N_t(r)\sigma_v$ will be written as $\eta$.

This process is diagramed in figure 7.1. Excitation photons pass from the source to a position within the sample. The DPDW is demodulated by a factor of $\eta/(1 - i\omega\tau)$ due to the absorption factor and lifetime of the fluorophore, and finally the fluorophore acts as a source of fluorescent DPDW’s which propagate to the detector at position $r$. The detected fluorescent DPDW is found by integrating over all fluorescent sources.

The same solution can be derived using a time domain approach and then taking the Fourier transform of the solution (see appendix C).

In this formulation we have assumed that the emission spectra is at a single optical wavelength. In fact, a fluorophore will usually emit light over a distribution of wavelengths. In our work we have to chosen to approximate the excitation and fluorescent signal as monochromatic. To properly incorporate the broad absorption and reradiation of the fluorescent dyes, we need to integrate over the wavelengths;

$$U_{fi}(r_s, r_d, \tau, \omega) = \int_{\lambda_1 \text{min}}^{\lambda_1 \text{max}} d\lambda_1 \int_{\lambda_2 \text{min}}^{\lambda_2 \text{max}} d\lambda_2 \int_{-\infty}^{\infty} dr U_{\lambda_1}(r_s, r, \omega) \frac{\eta_{\lambda_1}}{1 - i\omega\tau} U'_{\lambda_2}(r_d, r, \omega).$$
Figure 7.1: A schematic of fluorescent DPDW generation. A DPDW travels from the source to a fluorophore, and is demodulated due to the absorption and finite lifetime of the fluorophore. The fluorophore then acts as a source of fluorescent DPDW’s.
7.2 Localizing Fluorescent Objects

In our first set of experiments we have observed the conversion or transduction of a diffuse photon density wave from one optical and diffusive wavelength to another [7, 11]. This was accomplished by illuminating an obstacle filled with ICG with a diffuse photon density wave. Because ICG has a lifetime of less than 1 ns compared to the 5 ns period of the source, the re-radiated energy was also in the form of a diffuse photon density wave that was readily detected at the Stoke-shifted energy. To localize the object we determine the source center from the re-radiated wavefronts.

Light is delivered into the sample through a source fiber, and is collected by a movable detector fiber. The primary results of our re-radiation experiments are shown in figure 7.2. Here the source laser is located at the origin and a 1.8 cm diameter transparent spherical shell filled with a 0.1% solution of Intralipid is located a distance of 4.5 cm from the source. The surrounding Intralipid has the same concentration, giving a photon diffusion constant, \( D = 6.0 \times 10^5 \text{ cm}^2/\text{sec} \). ICG was dissolved in the spherical shell at a concentration of 0.41 mg/cc. The ICG absorbed light from the incident diffuse photon density wave at 780 nm, and then emitted photons at 830 nm. The absorption and emission characteristics of ICG are shown in figure 7.2a. Since the lifetime of the dye is relatively short ( \(<1 \text{ ns})\), the re-radiated signal was also in the form of a diffuse photon density wave. Using spectral filters (2 back-to-back Schott glass filters, 3mm width, RG380, each with a transmittance of 0.003 at 780 nm and 0.46 at 830 nm) we separately measured the incident wave at 780 nm in the presence of the obstacle, and the re-radiated wave at 830 nm.

In 7.2b the constant amplitude contours of the diffuse photon density wave at 780 nm are presented in intervals that decrease by a factor of 0.3 with increasing distance from the source. We see that these contours are reasonably circular and can be extrapolated back to the laser source. The small deviations observed are primarily a result of absorption by the obstacle. A similar contour plot of the phase was also measured, and could also be extrapolated back to the laser source. The measured wavelength of the diffuse photon density wave in the homogeneous Intralipid was \( \approx 18 \) cm.
cm.

In figure 7.2c we exhibit the constant amplitude contours of the wave at 830 nm, and thus demonstrate the diffuse photon density wave character of the re-radiated waves. We see clearly that the re-radiated wave originates from within the absorbing obstacle. From the contours we deduce a source origin which is within 1 mm of the center of the object. Similar conclusions could be drawn from the phase contours although the phase data was more sensitive to the small light leakages at 780 nm, and was therefore considerably noisier. This noise led to a diffuse photon density wavelength at 830 nm which was measured to be ≈27 cm, much larger than the wave at 780 nm. In subsequent experiments using the same system, we were able to decrease the leakage of 780 nm light by adding an additional filter and averaging longer. In these experiments we measured a wavelength which was about ≈18 cm as expected.

We have also compared re-radiated waves from spherical and cylindrical objects (see figure 7.3). The measurements clearly show that the contours in the case of the cylinder are more elliptical than those of the sphere, thereby demonstrating that the re-radiation technique can be sensitive to the shape of the obstacle.

A primary goal of our work is to develop an imaging device and algorithms for use in human subjects. In this section we discuss two imaging devices that we have developed, and localization in one or two dimensions is demonstrated [11].

The first device, shown in figure 7.4, uses multiple sources and a single detector to determine the center of a 1 cm diameter fluorescent sphere. We irradiate a fluorescent sphere with multiple time-shared sources of DPDW’s, and then measure the amplitude and phase of the re-radiated light from each source. The partial amplitude resulting solely from source $i$ is dependent on the $i$th source-detector separation, the efficiency of the dye, $\eta$, and the object-detector separation according to equation 7.7

$$U(\mathbf{r}_s, \mathbf{r}, \mathbf{r}_d, \tau, \omega) = U(\mathbf{r}_s, \mathbf{r}, \omega) \frac{\eta}{1 - i\omega \tau} U^\prime(\mathbf{r}, \mathbf{r}_d, \omega)$$

(7.8)

where $\mathbf{r}_i$ is the position of the $i$th source, $\mathbf{r}$ is the position of the object center, and $\mathbf{r}_d$ is the detector position. The individual sources are separately turned on and off,
Figure 7.2: (a) Indocyanine green absorption (solid line) and emission (dashed line) spectra. (b) Constant amplitude contours of the incident diffuse photon density wave. (c) Constant amplitude contours at the fluorescent wavelength (solid lines) clearly exhibiting the re-radiated nature of the wave. The dashed lines are the incident amplitude contours, and the center of the radiator is located by finding the intersection of the lines normal to the re-radiated contours.

Figure 7.3: left: Constant amplitude contours of the fluorescent DPDW re-radiated from a cylindrical fluorescent object. The source is at the origin. The contours are drawn every 0.3 dBm. right: The contours of constant phase, drawn every $10^2$. The dashed lines are interpolated data.
and the re-radiated amplitude for each source-obstacle separation is measured. Since
the source positions and the detector positions are known, we estimate the object
position by finding the value or r that gives the best agreement with the measured
ratio |U_i|/|U_j|.

\[
\frac{U(r_{si}, r, r_d, \tau, \omega)}{U(r_{sj}, r, r_d, \tau, \omega)} = \frac{|U_{si}|}{|U_{sj}|} \exp\left(i k|r_{si} - r|\right) \exp\left(i k|r_{sj} - r|\right).
\]

(7.9)

Three sources are necessary to locate the object in two dimensions, we use four to
improve the signal to noise of the localization. The results are shown in figure 7.5;
the grey circle represents the actual position of the re-radiator, while the black dot
is the computer estimated position. Using four sources we were able to localize the
center of this 1 cm sphere to within 0.4 cm. This two dimensional localization is
easily extended to three dimensions.

A second, qualitatively different imaging device is shown in figure 7.6. It uses a
scanning phased-array and a single detector as discussed in section 2. The phased-
array consists of two sources, 180° out of phase with respect to each other that
interfere destructively to produce an amplitude null and a sharp 180° phase shift at
the null line (broken line in insets of figure 7.6). If we place a detector on the null
line, and then move an absorbing object from one side of the detector to the other, we
find that the object preferentially absorbs light from the nearest source, and therefore
distorts the null line. When the object is also a re-radiator, the complimentary effect
is seen, that is, the object re-radiates more light derived from the closest source. In
both measurements the phase of the detected DPDW will undergo a 180° shift as
the object crosses the original, undisturbed position of the null line. These effects
are demonstrated in figure 7.6a. Note that the re-radiated wave phase exhibits a
complimentary phase change as discussed above. In our experiments we have scanned
the object, but in the clinic it will be necessary to scan the pair and the detector
simultaneously.

Interestingly, in the situation depicted in figure 7.6a, the location of the phase shift
with respect to the null line of the re-radiated light is always the same, independent
of the detector position. Thus we can detect essentially the same change by fixing
Figure 7.4: A device for localizing the center of a fluorescent object. The individual sources are separately turned on and off, and the re-radiated amplitude for each source-obstacle separation is measured. Since the source positions and the detector positions are known, we estimate the object position by finding the position that gives the best agreement with the theory.
Localization of Absorber/Reradiator

Figure 7.5: The actual size and position of the reradiator are shown by the shaded circles, and the estimated position using the fitting algorithm is shown by the black dot. Note that the algorithm has difficulty localizing an object which is far from the detection plane.
Figure 7.6: These experiments were performed with a 50 MHz oscillation frequency in a 0.4% Intralipid, with a source separation of 2.2 cm. The reradiator was located 2.0 cm, and the detector 4.0 cm in front of two anti-phased sources. (a) As shown in the inset, the detector was placed on the null line (dashed line) and the reradiator was scanned. In the main figure, both the incident and the reradiated light show a 180° phase shift, but the shift is sharper from the reradiated light. (b) Here, the source pair, and consequently the null line, was scanned as shown in the inset. Note that the sharp phase shift from the reradiated (incident) light occurs as the null line crosses the reradiator (detector) position.
the object and the detector, and scanning only the source pair. This configuration is
more clinically realizable than the absorption case which requires scanning both the
source pair and the detector. Figure 7.6b demonstrates this effect for the re-radiated
light. In the left panel, we detect a sharp phase shift for the location of the re-radiator
as we scan the null line. The phase shift of the incident light occurs near the position
of the detector. If we know the position of the null line as a function of time, we
achieve a one dimensional localization of the re-radiator. By performing three scans
down three perpendicular axis, we can achieve three dimensional localization.

7.3 Tomographic Imaging of Fluorescent Objects

So far, we have discussed using diffuse fluorescence in deep tissues as a means of
tumor detection and localization by imaging the center of fluorescing objects. In this
section we demonstrate a more general method whereby one can simultaneously derive
a spatial map of the concentration and lifetime of a fluorophore, using variations in
the amplitude and phase of fluorescent diffuse photon density waves.

For a weakly absorbing spatial distribution of fluorophores, the fluorescent photon
density wave is determined by integrating over the contributions from all fluorophores
as in equation 7.7.

\[
U_{fl}(r_s, r_d, \tau, \omega) = \int d^3r \ U(r_s, r, \omega) \frac{\eta(r)}{1 - i\omega \tau(r)} U^\dagger(r, r_d, \omega).
\]

(7.10)

Note that we have allowed \(\eta\) and \(\tau\) to vary with position.

Hereafter we refer to \(U_{fl}\) as the fluorescent diffuse photon density wave. In a
heterogeneous medium this model is an approximation in the sense that the homoge-
neous solution neglects the effects of heterogeneities on photon propagation from
source to fluorophore and from fluorophore to detector. The model also assumes that
there are no saturation or photon quenching effects.

The fluorescence model in equation 7.10 is of the same form as the first order Born
approximation solution for a scattering medium with inhomogeneous absorption, i.e.
equation 4.13,
\[ U_{sc}(r_s, r_{di}, \omega) = - \int U(r_s, r, \omega)O(r)U'(r, r_{di}, \omega) \, d^3r. \] (7.11)

Thus we are able to generate images for \( \eta(r) \) and \( \tau(r) \) using standard imaging algorithms. The reconstruction differs from the pure absorption case in that the reconstructed quantity is now complex, and is a function of the modulation frequency. Again, the reconstruction algorithm involves digitizing the integral in equation 7.10
\( (\eta(r), \tau(r), r \Rightarrow \eta_j, \tau_j, r_j) \), and for a series of measurements made at source-detector positions \( r_{si}, r_{di} \), we generate the following matrix equation:
\[ U_{jli}(r_{si}, r_{di}, \omega) = \sum_{j=1}^{N_{voxels}} U(r_j, r_{si}, \omega) \frac{\eta_j}{1 - i\omega\tau_j} U'(r_{di}, r_j, \omega) h^3. \] (7.12)

This complex matrix is can be written as a real matrix;
\[
\begin{pmatrix}
\Re[U_{jli}^{11}] & \ldots & \Re[U_{jli}^{1n}] & -\Im[U_{jli}^{11}] & \ldots & \Im[U_{jli}^{1n}] \\
\vdots & \ddots & \vdots & \vdots & \ddots & \vdots \\
\Re[U_{jli}^{n1}] & \ldots & \Re[U_{jli}^{nn}] & -\Im[U_{jli}^{n1}] & \ldots & \Im[U_{jli}^{nn}] \\
\Im[U_{jli}^{11}] & \ldots & \Im[U_{jli}^{1n}] & \Re[U_{jli}^{11}] & \ldots & \Re[U_{jli}^{1n}] \\
\vdots & \ddots & \vdots & \vdots & \ddots & \vdots \\
\Im[U_{jli}^{n1}] & \ldots & \Im[U_{jli}^{nn}] & \Re[U_{jli}^{n1}] & \ldots & \Re[U_{jli}^{nn}]
\end{pmatrix}
\begin{pmatrix}
\alpha(r_1) \\
\vdots \\
\alpha(r_n)
\end{pmatrix}
\]

\[ W_{ij}^{fi} = U(r_j, r_{si}, \omega)U'(r_{di}, r_j, \omega) h^3 \] (7.13)
\[ \alpha(r_j) = \Re[\eta_j / (1 - i\omega\tau_j)] \] (7.14)
\[ \beta(r_j) = \Im[\eta_j / (1 - i\omega\tau_j)] \] (7.15)

This matrix equation can be inverted or solved using many techniques. We have used an algebraic reconstruction method (SIRT) to solve for the real (\( \alpha \)) and imaginary (\( \beta \)) parts of the unknown, \( \eta_j / (1 - i\omega\tau_j) \) [48]. The ratio of the imaginary to the
real parts of the solution yields $\tau$, and then $\eta$ may be calculated.

$$\tau_j = \frac{\beta}{\alpha \omega} \quad (7.16)$$

$$\eta_j = \alpha + \omega \tau \beta \quad (7.17)$$

Computer generated data are obtained from exact solutions to the fluorescence diffusion equation for the case of a fluorescent sphere (1.0 cm diameter) in a uniform background [79]. Using forward amplitude and phase data from this solution (with added 1% amplitude and 0.1° phase noise), we have reconstructed images of $\eta$ and $\tau$. The measurement geometry used is described in figure 7.9a. The scanning geometry consists of a source and detector scanning every 0.2 cm around the four sides of a 7.0 cm x 7.0 cm square in an infinite medium. The reconstruction area is a slab of area 5.0 cm x 5.0 cm and height 1.0 cm. The optical properties of the media are: $\mu_s' = 10$ cm$^{-1}$ everywhere, $\mu_a$ (chromophore) = 0.03 cm$^{-1}$ everywhere for both the excitation and the emission wavelength, and $\mu_a$ (fluorophore - inside the sphere) = 0.02 cm$^{-1}$ at the excitation wavelength, and 0.01 cm$^{-1}$ at the emission wavelength. The source modulation frequency is 50 MHz. In the first set of reconstructions all fluorophores are located in the object and there is no background fluorescence.

In figure 7.9b we demonstrate a reconstruction proportional to the fluorophore concentration. The lifetime inside the 1.0 cm diameter sphere is 0.6 ns. The grey scale ranges from 0 cm$^{-1}$ (grey) to 0.007 cm$^{-1}$ (black). 2500 SIRT iterations were performed with a constraint on both concentration (0.0 $\leq \eta \leq 0.1$ cm$^{-1}$) and lifetime (0 $\leq \tau \leq 10$ ns).

Note that the reconstructed value of $\eta$ is much less than the correct value. This is due to the fact that we have only performed 2500 SIRT iterations to produce this image. This relatively small number of SIRT iterations results in an image of a larger object with a lower concentration of fluorophores. This is exactly analogous to the absorption case where we discovered that as we increase the number of iterations, the reconstructed object becomes smaller and more absorbing. In the course of implementing these reconstructions we found that some isolated voxels had unphysically
Figure 7.7: The top two images show the SIRT reconstructions at 500 and 1000 iterations using a 50 MHz source modulation. The bottom two images show the same reconstruction using a 150 MHz source modulation. Note that at the high modulation frequency, spurious voxels appear which have unphysically high values of $\eta$ and $\tau$. High values for both $\eta$ and $\tau$. (These images look like a single voxel in a homogeneous background.) As we continue to iterate, our image becomes dominated by these voxels (see figure 7.7). However, these voxels do not contribute significantly to the total measured signal since the quantity $\eta/\omega\tau$ is comparable to or smaller than that of the neighboring voxels. As part of our image analysis, we identified these voxels and replaced $\eta$ and $\tau$ with the nearest neighbor averages. Generally, we found that the lifetime reconstructions are more accurate at low source modulation frequencies where the occurrence of these spurious voxels is less frequent (see figure 7.7), and the phase shift due to the lifetime of the fluorophore ($\phi = \tan^{-1}(\omega\tau)$) is far from its saturation value ($\pi/2$) (see figure 7.8).

Using the same setup as in figure 7.9a, the actual lifetime of the fluorophore was varied from 0.5 ns to 1.5 ns, and the average reconstructed lifetime was calculated.
Figure 7.8: A plot of $\tan^{-1}(\omega \tau)$ versus $\omega \tau$ shows the saturation effect for $\omega \tau$ greater than 1.

Figure 7.9c (squares) shows a good agreement between the average reconstructed value of the lifetime and the known value. The reconstructed lifetime is calculated by taking the average value over the area of the object. The area is taken to be any voxel with a fluorophore concentration greater than 50% of the maximum concentration.

The image quality is much improved if some a priori information is given. For example, if the fluorophore distribution is known, then we may focus solely on the lifetime inversion. Possible ways of determining the fluorophore distribution include using the excitation wave at a high modulation frequency, or using the zero modulation frequency fluorescence data. If we choose to use a zero modulation frequency (DC) source, then the equation describing the fluorescent DPDW is

$$U_{fl}(r_s, r_d, \tau, \omega = 0) = \int d^3 r U(r_s, r, \omega = 0) \eta(r) U'(r, r_d, \omega = 0). \quad (7.18)$$

So using this equation we can reconstruct the quantity $\eta(r)$. However DC images traditionally result in low resolution maps, and it is unclear how well this approach will work in practice.

The results of the lifetime-only reconstruction for a 50 MHz source modulation are shown in figure 7.9c (circles). There is a slight improvement over the reconstructed values from the concentration and lifetime inversion.

Panels (d) and (e) are the same as (b) and (c), except the source modulation
Figure 7.9: Reconstruction of fluorophore lifetime and concentration in a system with no background fluorophore. (a) Tee scanning geometry. (b) A sample concentration image. (c) The reconstructed lifetime for a series of reconstruction where the lifetime inside the sphere varied. The open squares are average lifetimes from a reconstruction of both concentration and lifetime, the solid circle are reconstructions in which the concentration was known, and only the lifetime was reconstructed. (b) and (c) are reconstruction using a 50 MHz source modulation, (d) and (e) are the same reconstructions using a 150 MHz source modulation.

frequency has been increased to $f = 150$ MHz. The grey scale in panel (d) ranges from 0 cm$^{-1}$ (grey) to 0.009 cm$^{-1}$ (black).

Thus far our images have consisted of a region of fluorophore embedded in a non-fluorescent background medium. In typical clinical situations, there will also be a background concentration of fluorophore. In this case we separate the contributions from the uniform fluorescent background and the heterogeneous region as shown in figure 7.10, i.e.

$$U_{fl}(r_s, r_d, \tau, \omega) = \int_{all\ space} d^3r \ U(r_s, r, \omega) \frac{\eta_o}{1 - i\omega\tau_o} U'(r, r_d, \omega)$$

$$+ \int_{heterogeneity} d^3r \ U(r_s, r, \omega) \left[ \frac{\eta(r)}{1 - i\omega\tau(r)} - \frac{\eta_o}{1 - i\omega\tau_o} \right] U'(r, r_d, \omega). \quad (7.19)$$

$\eta_o$ and $\tau_o$ are the background fluorescence properties (which exist only outside the heterogeneity) and $\eta$ and $\tau$ are the heterogeneity fluorescence properties. Hereafter we will refer to the first term on the right hand side of eq. 7.19 as $U_{bg}$. If the object contrast is high, i.e. $\eta(r)/(1 - i\omega\tau(r)) \gg \eta_o/(1 - i\omega\tau_o)$, then the fluorescent signal
Figure 7.10: A cartoon describing the breakdown of the background fluorescence problem.
due to the heterogeneity, \( \Delta U_{fl} = U_{fl} - U_{bg} \), is given by

\[
\Delta U_{fl} = \int d^3r ~ U(r_s, r, \omega) \frac{\eta(r)}{1 - i\omega \tau(r)} U'(r, r_d - r, \omega). \tag{7.20}
\]

To accomplish this subtraction, one may use analytic solutions for \( U_{bg} \) [79]. However, this method requires knowledge of the background lifetime and concentration, which may not be possible in clinical situations. Another option is to eliminate the background signal by subtracting two measurements having the same source-detector separation, as shown in fig. 7.11a. In these difference measurements, the background (homogeneous) fluorescent contribution will cancel, and only the inhomogeneous part will remain. This is the same method we employed in absorption reconstructions to reduce the importance of accurate knowledge of the background optical properties [18]. Note that in these images the fluorescent properties of the heterogeneities have been reconstructed; no information about the background fluorescence lifetime is derived. We have however used the background fluorophore concentration in our calculation of the weights. If we incorrectly estimate the background fluorophore concentration, the reconstructed image will be degraded. One could envision an iterative routine to obtain the background fluorophore concentration in which the initial guess for the background fluorophore concentration is updated based on previous images until the clearest image is achieved. This approach, while extremely time consuming, could offer a more exact solution than our approach.

Figure 7.11d depicts the scanning geometry used for a system with fluorophore both inside and outside of the sphere (diameter = 1.5 cm). The setup is the same as in figure 7.9a with the addition of the background fluorophore and a second source 0.6 cm from the first, as shown in figure 7.11. \( \mu_a \) of the background fluorophore = 0.001 cm\(^{-1}\) at the excitation wavelength, and 0.0005 cm\(^{-1}\) at the emission wavelength and the lifetime is 1.0 ns. The reconstruction of the heterogeneous fluorophore distribution is shown in figure 7.11b for a system where the lifetime inside the 1.5 cm diameter sphere is 0.6 ns. The grey scale ranges from 0 cm\(^{-1}\) (grey) to 0.017 cm\(^{-1}\) (black). 2500 SIRT iterations were performed with a constraint on both concentration (0.0 \( \leq \eta \leq 0.1 \) cm\(^{-1}\)) and lifetime (0 \( \leq \tau \leq 10 \) ns).
Figure 7.11: Reconstruction of fluorophore lifetime and concentration in a system with background fluorophore. (a) The scanning geometry. (b) A sample concentration image. (c) The reconstructed lifetime for a series of reconstruction where the lifetime inside the sphere varied. The open squares are average lifetimes from a reconstruction of both concentration and lifetime, the solid circle are reconstructions in which the concentration was known, and only the lifetime was reconstructed. (b) and (c) are reconstruction using a 50 MHz source modulation, (d) and (e) are the same reconstructions using a 150 MHz source modulation.

The average reconstructed lifetime for a series of reconstructions is shown in figure 7.11a. The squares are derived from a reconstruction of both fluorophore concentration and lifetime. The circles are derived from the lifetime reconstruction only. Panels (d) and (e) are the same as (b) and (c) except the source modulation frequency has been increased to $f = 150$ MHz. The grey scale in panel (D) ranges from 0 cm$^{-1}$ (grey) to 0.020 cm$^{-1}$ (black).

We have presented and demonstrated an algorithm by which the heterogeneous fluorophore distribution and lifetime in a turbid medium may be obtained from tomographic measurements of near infra-red diffusing photon distributions. Although these reconstructions were carried out from data in the frequency domain, the results can also be obtained using Fourier transformed time domain data. The solution for finite systems may be obtained by applying the appropriate boundary conditions. Such solutions are readily available for a variety of geometries [59].
Chapter 8

Summary

We have demonstrated that diffusive light can be used to image absorption, scattering and fluorescence lifetime and concentration in thick, turbid media. We hope we have convinced the reader that this work has important medical applications.

There is a great deal of work to be done if DPDW imaging is to become an accepted medical tool. First and foremost, we need many more studies which accurately measure the optical changes which accompany changes in the physiological state of tissues. The intrinsic heterogeneity of the body makes it difficult to measure in vivo the absorption and scattering coefficients. When tissue samples are studied in vitro, the blood and oxygen supply is cut off, thus changing the tissue environment. It is not clear whether or not in vitro measurements accurately reflect the optical properties of the sample in vivo.

We believe that DPDW imaging should be used to complement other imaging modalities. For example, a DPDW probe could be easily attached to an ultrasound, x-ray, or MRI imaging device as we saw in section 4.12. When the data from these two probes are used simultaneously, we can derive accurate structural information as well as quantitative measurements of the optical properties.

DPDW imaging can also be used for low resolution breast tumor screening. There are several academic and industrial research groups performing clinical evaluations of optical mammography systems [13, 81, 82]. These studies are particularly exciting because optical mammography is inexpensive, and has no known adverse side effects. The preliminary results of these studies are encouraging, but a great deal of work still
needs to be done.
Appendix A

Singular Matrices

A singular matrix is one which maps a vector, (other than the zero vector) to the zero vector. For example, the matrix

\[
A = \begin{pmatrix}
1 & -1 \\
-1 & 1
\end{pmatrix}
\]  

maps any vector of the form \( \vec{a} = (\alpha, \alpha) \) to the zero vector. This has very important implications for the inverse solution. Suppose we are trying to invert the following equation,

\[
A \vec{x} = \vec{b}
\]

It is clear that for any solution \( \vec{x} \), \( \vec{x} + \vec{\alpha} \) is also a solution, i.e. if

\[
A \vec{x} = \vec{b}
\]

and

\[
A \vec{\alpha} = \vec{0}
\]

then

\[
A \left( \vec{b} + \vec{\alpha} \right) = A \vec{b} + A \vec{\alpha} \]

\[
= A \vec{b} + \vec{0} = A \vec{b}
\]

Thus for a singular matrix, there is not a unique solution. Mathematically, a singular matrix expresses itself as having a zero eigenvalue. In numerical calculations, an
eigenvalue is rarely exactly equal to zero, but is numerically zero. Numerically zero means that the value of the number is below the numerical precision of the computer.
Appendix B

Time Resolved Spectroscopy

A schematic of the time resolved spectroscopy system (TRS) is shown in figure B.1. The TRS is a single photon counting device built by Hamamatsu Corporation, Japan. A pulsed laser diode with a full-width half-max of about 50 ps and 5 MHz repetition rate is coupled to a 200 \( \mu \)m multi-mode optical fiber. The fiber delivers the light to the sample, and a 3 mm optical fiber bundle is used to collect the light from the sample. This second fiber delivers the collected light to a microchannel plate photomultiplier tube (MCP-PMT).

When a photon strikes the photomultiplier tube, a current is generated, and passed into a constant fraction discriminator (CFD). The CFD converts a irregularly shaped pulse into a clean (TTL) step voltage (figure B.2). This step voltage is passed to the time amplitude converter (TAC). The TAC is a simple timing device which is triggered by the same trigger which pulses the laser source. The timing is stopped when the TAC receives a signal from the CFD. An equivalent circuit is shown in figure B.3. A voltage which is proportional to the amount of time between the trigger and the pulse from the CFD is output from the TAC, to an analog to digital (A/D) converter. Note that only the first photon per pulse will be counted in this system. For this reason, the source light is attenuated so that no more than one photon per pulse is detected.

The A/D converter passes a digital number corresponding to the voltage from the TAC to a multichannel analyzer (MCA). The MCA collects the digital voltage signals and collects them into corresponding time bins which are stored in the computer. The
Figure B.1: A schematic of the TRS system

Figure B.2: Signal processing by the constant fraction discriminator (CFD)

Figure B.3: Equivalent circuit for the time amplitude converter (TAC).
time per bin is calibrated by measuring two signals displaced by a known time delay.

For each pulse, we collect a single photon, and add a count to one bin. This process is repeated for millions of pulses (typically we use a 30 second integration time and a 5 MHz pulse rate) and a histogram of number of photons per time bin is generated. For examples of TRS data and algorithms for fitting the optical properties of unknown media, see Patterson et al. [3].
Appendix C

Time Domain Fluorescent DPDW Derivation

We will follow a time domain discussion similar to that of Sevick et al. [21, 67] and take the Fourier transform of the results to obtain the frequency domain results.

If we inject a pulse of photons at a time, \( t_0 \) at a position \( \mathbf{r}_s \), into a highly scattering medium, then according to the diffusion equation the number of photons per unit volume, \( u \), reaching a position \( \mathbf{r} \) at a time \( t' \) is [3]

\[
u(\mathbf{r}_s, \mathbf{r}, t') = \frac{\exp(-\frac{\mathbf{r}-\mathbf{r}_s \cdot \mathbf{r}}{4Dv t'} - \mu_a(\mathbf{r} \cdot t'))}{(4\pi Dv t')^{3/2}}.
\] (C.1)

A fluorophore at \( \mathbf{r} \) will absorb and re-radiate the light at a time \( t^* \) with some efficiency \( \eta \), and at the rate described by the characteristic lifetime \( \tau \),

\[
\frac{\eta}{\tau} \int_0^{t^*} dt' u(\mathbf{r}_s, \mathbf{r}, t')e^{(t^*-t^*)/\tau}.
\] (C.2)

This is now our fluorescent source term. Photons from this source will propagate from the fluorophore, to the detector and arrive at some time \( t \). So the detected signal is

\[
u_f(\mathbf{r}_s, \mathbf{r}, \mathbf{r}_d, \tau, t) = \frac{\eta}{\tau} \int_0^\infty dt' \int_0^{t^*} dl' u(\mathbf{r}_s, \mathbf{r}, t') \exp\left(\frac{t' - t^*}{\tau}\right)u'(\mathbf{r}_d, \mathbf{r}, t - t^*) .
\] (C.3)

We have used the symbol \( u' \) instead of \( u \) as a reminder that the propagation from the fluorophore to the detector is a function of the optical properties of the medium at the fluorescent wavelength.

To convert from the time domain equation to the frequency domain equation, we first change the limits of the integrals

\[
u_{f1}(\mathbf{r}_s, \mathbf{r}, \mathbf{r}_d, \tau, t) = \frac{\eta}{\tau} \int_0^\infty dt' \int_{-\infty}^{t^*} dl' u(\mathbf{r}_s, \mathbf{r}, t') \exp\left(\frac{t' - t^*}{\tau}\right)u'(\mathbf{r}_d, \mathbf{r}, t - t^*)
\] (C.4)
since \( u(\mathbf{r}, \mathbf{r}, t') = 0 \) when \( t' < 0 \) and \( u'(\mathbf{r}_d, \mathbf{r}, t - t^*) = 0 \) when \( t - t^* < 0 \). Next, we replace \( u \) and \( u' \) with their Fourier transforms,

\[
u(\mathbf{r}, \mathbf{r}, t') = \frac{1}{2\pi} \int_{-\infty}^{\infty} d\omega U(\mathbf{r}, \mathbf{r}, \omega) e^{-i\omega t'} = \frac{e^{ikr}}{4\pi Dr}, \quad (C.5)
\]

\[
u_{fl} = \frac{\eta}{4\pi^2} \int_0^\infty dt' \int_{-\infty}^{\infty} dt'' \int_{-\infty}^{\infty} d\omega \int_{-\infty}^\infty d\omega' \{ U(\mathbf{r}, \mathbf{r}, \omega) e^{-i\omega t'} \\
\times e^{i\omega' t''} U'(\mathbf{r}_d, \mathbf{r}, \omega') e^{-i\omega' t''(t'' - t')} \}. \quad (C.6)
\]

Now we do the integral over \( dt' \)

\[
u_{fl} = \frac{\eta}{4\pi^2} \int_0^\infty dt' \int_{-\infty}^{\infty} d\omega \int_{-\infty}^{\infty} d\omega' U(\mathbf{r}, \mathbf{r}, \omega) \frac{e^{-i\omega' t''}}{1 - i\omega' \tau} U'(\mathbf{r}_d, \mathbf{r}, \omega') e^{-i\omega' t''}, \quad (C.7)
\]

and then over \( dt'' \),

\[
u_{fl}(\mathbf{r}, \mathbf{r}_d, \tau, t) = \frac{\eta}{2\pi} \int_{-\infty}^{\infty} d\omega \int_{-\infty}^{\infty} d\omega' U(\mathbf{r}, \mathbf{r}, \omega) \frac{\delta(\omega - \omega')}{1 - i\omega \tau} U'(\mathbf{r}_d, \mathbf{r}, \omega') e^{-i\omega t}. \quad (C.8)
\]

Finally, integrating over \( \omega' \) we arrive at

\[
u_{fl}(\mathbf{r}, \mathbf{r}_d, \tau, t) = \frac{\eta}{2\pi} \int_{-\infty}^{\infty} d\omega U(\mathbf{r}, \mathbf{r}, \omega) \frac{1}{1 - i\omega \tau} U'(\mathbf{r}_d, \mathbf{r}, \omega) e^{-i\omega t}. \quad (C.9)
\]

If we now Fourier transform both sides of this equation, we see that

\[
U_{fl}(\mathbf{r}, \mathbf{r}_d, \tau, \omega) = U(\mathbf{r}, \mathbf{r}, \omega) \frac{\eta}{1 - i\omega \tau} U'(\mathbf{r}_d, \mathbf{r}, \omega). \quad (C.10)
\]

This formula is for a point fluorophore. We must integration over all fluorophores to model a distribution,

\[
U_{fl}(\mathbf{r}, \mathbf{r}_d, \tau, \omega) = \int_{-\infty}^{\infty} d\mathbf{r} U(\mathbf{r}, \mathbf{r}, \omega) \frac{\eta}{1 - i\omega \tau} U'(\mathbf{r}_d, \mathbf{r}, \omega). \quad (C.11)
\]

This solution agrees with formulations put forth by other researchers [68, 83]. It is clear that the Fourier domain equation is much less computationally intensive than the double convolution in the time domain equation.
Appendix D

Back Projection

We have begun to investigate a simple back projection routine in conjunction with NIM Inc., Philadelphia, PA. At NIM, Robert Danen, Yung Weng and William Thayer are currently building a frequency domain instrument which is capable of the following:

- The source modulation is variable from 10 MHz to 500 MHz.
- APD detection.
- Source fiber multiplexor allows up to 16 source position without repositioning the source fibers.

The goal of the project is to build a device capable of creating a real-time spectroscopic image of a baby brain using a hand-held optical probe. The probe, which houses 9 source fibers and 4 detector fibers, is shown in figure D.1.

Using this instrument, we measure the amplitude and phase for each source-detector pair on a sample with known optical properties. We use these measurements and the theory of DPDW’s in homogeneous, semi-infinite media to calibrate the amplitude and phase of each source-detector pair. Using a single pad, with 9 sources and 4 detectors, this provides 36 measurements of amplitude and phase.

Next the pad is moved to the sample we wish to image. Again we measure the amplitude and phase for each source-detector pair. Using the calibration measurements and the homogeneous diffusion equation, we can easily solve for the absorption and scattering coefficient of the medium. As we discussed earlier, the values we obtain for the absorption and scattering coefficient represent average values.
In this work we have concentrated solely on absorption imaging. To obtain an image from the average absorption values, we must back project the calculated absorption values into the medium. This means that we have a measurement, and we are trying to guess how much of this measurement can be attributed to each volume element in the medium. For example, a particular measurement is unlikely to be affected by a volume element far away from the source and detector. It is most likely to be affected by the volume elements closest to the source or detector.

To figure out the importance of each voxel, we use a simple probability analysis. Consider a volume element, v, centered at a position r. We assume that the amplitude of the DPDW which reaches r is proportional to the probability that a photon from the source would reach r. Based on the theory of DPDW’s in a semi-infinite medium, we can calculate the amplitude of the DPDW. Similarly we can calculate the amplitude of the DPDW which travels from a source at position r to the detector. We use the product of these two amplitudes for our weights (W), and using the weights, be back project the calculated average absorption as such:

$$\mu_j = \frac{\sum_i W_{ij} \mu_{ai}}{\sum_i W_{ij}}$$

where j enumerates the voxels and i enumerates the various measurements. Using this algorithm, we were able to create the images shown in figure D.2. The sample contains a single perfectly absorbing heterogeneity. 36 measurements of amplitude and phase at 190 MHz were used to generate the image. Note that the image does not obtain the correct object position. This is partially because the sample we measured has multiple boundaries which we have not taken into account.
Figure D.1: The measurement geometry for the NIM back-projection imaging project.

Figure D.2: Sample back-projection images for a solid block sample with an embedded heterogeneity.
Appendix E

The Photon Migration Imaging Software Package

PMI is a general purpose program (developed by David Boas, Maureen O’Leary, and Xingde Li at the University of Pennsylvania, and Martin Ostermeyer at the University of Texas/ M.D. Anderson Cancer Center) for solving various forward and inverse problems related to photon migration. The purpose of the program is to enable researchers to explore the propagation of diffusing photons through general heterogeneous, turbid media and to derive information about such turbid media from measurements of the diffusing photons. PMI has a modular design to facilitate the addition of new algorithms as they become available. The following modules are currently available:

- **EXACT**: Various analytic solutions to the diffusion equation are used for calculating the scattering of Diffuse Photon Density Waves (DPDW’s) from spherical and cylindrical objects embedded in infinite or semi-infinite media as well as the propagation of DPDW’s in homogeneous media.

- **TIME DOMAIN**: This module enables calculations to generate data in the time domain and enables time domain data to be used for the inverse problem. The forward problem is done by doing the calculations in the frequency domain and FFT’ed to the time domain. Experimental data in the time domain can be loaded. It is then FFT’ed to the frequency domain for analysis.

- **LAYERED**: This module provides an analytic solution for a two layered, semi-infinite system. The source and detector are assumed to be on the air-top layer interface. The bottom layer is displaced a user definable distance from the air-top
layer interface.

- **FLUORESCENCE:** This module contains analytic solutions for the generation and propagation of fluorescent DPDW’s in media with spatially uniform and spatially varying optical properties.

- **FIT:** This is a chi-squared squares fitting algorithm for analyzing experimental or simulated data to find the optical properties of the background media, optical properties of any spherical or cylindrical objects, and/or the position of any spherical or cylindrical objects.

- **RECONSTRUCTION:** This program uses an iterative routine (SIRT) to solve for the optical properties of an inhomogeneous medium. The inversion will reconstruct absorption and/or scattering, fluorescence lifetime, Brownian diffusion, or shear flow. The theory is based on the First Born or First Rylov approximation and forward data may be generated using these algorithms.

- **MIE:** This module provides commands for calculating the scattering coefficient and anisotropy factor of spherical dielectrics using Mie Theory. The wavelength dependent index of refraction for water and polystyrene is included in this module.

The input is line oriented and can come either from an input file or from the standard input (keyboard). Normally the input file is specified in the command line when the program is started:

```
unixprompt> pmi [inputfilename]
```

The program will execute the commands in the input file and return to the Unix prompt. If no input file is specified, the program switches to the interactive mode and waits at its prompt for input. Now command after command can be typed in, or an inputfile can be specified with the Include command:

```
|PMI> Include [input file name]
```

After the commands in the inputfile are executed, the program will return to its prompt and wait for more commands. Any text after a # sign is taken to be a comment.
Sample input files (scripts) are shown below. Note that the imaging script uses the main shell to set up the medium, etc., the exact module to calculate the forward data, and the reconstruction module to invert the data.

### E.1 Sample PMI scripts

Sample scripts to run with PMI VERSION 2.0

List of sample scripts:

* exact1.pmi - Calculates the DPDW distorted by a spherical absorber.

* fit1.pmi - Fits data for a distorted DPDW for the position and radius of the spherical absorber.

* image1.pmi - Creates an image of the absorption using a reconstruction technique.

------------------------ EXACT1.PMI ------------------------

Following is a sample script to calculate the DPDW distorted by a spherical absorber. A 200 MHz source is positioned at the origin with an initial amplitude of 1 and phase of 0. The absorber has a radius of 0.5 cm and is centered at x=0, y=2, and z=0. The detector is scanned from x=-4 cm to x=4 cm at y=4 cm and z=0 cm.

```plaintext
# The following script will using the analytic solution for the scattering of DPDW’s from spherical objects to calculate the amplitude and phase of the distorted DPDW.

# Define the medium used for the background
# [name] [mua] [mus] [g] [n] [zeros]
Medium Tissue .1 10 0 1.333 0 0 0
Background Tissue

# Define the medium for the spherical inhomogeneity
# [name] [mua] [mus] [g] [n] [zeros]
Medium Tumor .5 10 0 1.333 0 0 0
```

PMI Software
# Define the sphere
#
# [obj_name] [medium_name] [x] [y] [z] [r]
ObjectSphere Tumor Tumor 0 2 0 .5

# Create the source-detector list
CreateSDList grid 1 0 0 0 1 0 200 200 1 0 0 1 -4.1 1 4 4 1 0 0 1

# RUN EXACT
Exact

# Save the source-detector list
# [filename]
SaveSDList foo

# Save the data list
# [FormatType] [DataType] [filename]
SaveDataList NORMAL NORMAL foo

------------------------ fit1.pmi ------------------------

Fits the data created with exact1.pmi for the x position and radius of the absorbing sphere.

# This script includes the script exact1.pmi to calculate the # distorted DPDW and then uses the FIT module to fit for the x # position and radius of the sphere.

# include the exact1.pmi script
Include exact1.pmi

# set the unknown parameters
SetFitParam xo .1 .5
SetFitParam a 1 .5

# Fit for the unknown parameters
Fit

# Save the result
SaveFitResult foo DATA PARAM NOAPPEND

------------------------ image1.pmi ------------------------
PMI Software

Defines a set of measurements, an spherical inhomogeneity, and the data that would be measured. Then inverts this data to solve for the absorption as a function of position.

# this script should produce a nice image of a sphere with a max absorption of .00303

# mua mus g n db
DefineMedium back .03 10. 0. 1.333
DefineMedium obj .04 10. 0. 1.333

# SET UP THE GEOMETRY
background back
gometry infinite
RegionBox entire back -3.0 -3.0 -.0 3.0 3.0 .0

# for reconstruction: solve for absorption, use both amp & phase data, use the born approx, 1000 SIRT iterations, use the homogeneous Green functions
SetReconParams ABSORPTION BOTH BORN 1000 DPDW

# constrain the absorption change to be positive
SirtConstraints 0 50 0 50 0 50

# place a sphere in the medium
objectsphere test/1 obj .5 -.5 0. .5

# scan around the sides of a box
CreateSDList tandem 1 3 0 0 1 0 200 200 5 0 0 .5 -3 3 .5 0 0 .5 -3 0 0
CreateSDList tandem 1 0 3 0 1 0 200 200 5 -3 3 .5 0 0 .5 0 0 .5 0 -3 0

# use the exact module to create the forward data
Exact

# subtracts the incident from the total wave - no noise added
BornData 0. 0.

# free the object list to start with a guess of zero
freeobjectlist

# set up the region to reconstruct
Initimage -4.0 4.0 .25 -4.0 4.0 .25 -.0 .0 .58
# create the weights
createweights

# do the first order reconstruction
runsirt
saveimage filenm

E.2 PMI Command Summary

PMI Online Help from 10 July 96

Version 2.1

PMI Command Groups
* General: General commands
* Programming: Script programming commands
* Sources, Detectors, and Data: Commands for manipulating sets of sources, detectors, and data.
* Medium: Commands for defining the properties of different turbid media.
* Boundaries: Commands for defining the boundaries of a system and the boundary condition.
* Objects: Commands for defining inhomogeneities
* Images: Commands for manipulating Images of the optical properties and the fluence.

Commands associated with different modules

* Exact Module: Commands related to the EXACT module. A description of the EXACT module is found here.
* Time Domain Module: Commands related to performing calculations in the time domain.
* Layered Media Module: Commands related to the layered media module.
* Fluorescence Module: Commands related to the Fluorescence module.
* Fit Module: Commands related to running the FIT module.
* Reconstruction Module: Commands for reconstructing optical properties from measurements of the fluence. A description of the RECONSTRUCTION module is found here. Refer to the sample script imagel.pmi for an example.
* MIE Module: Commands for calculation of the scattering coefficient and anisotropy factor of spherical dielectrics based on Mie Theory. The wavelength dependent index of refraction for water and polystyrene is included in this module.

PMI Command Summary

* General: General commands
  o Include, Prompt, Interactive, System, Bell, Echo, Exit, Quit, Help, SetHTMLhelp, SetPMIdir, Pipes
* Programming: Script programming commands
  o For...Next Loops, Variables, Operations, While Blocks, If Blocks, Functions, SetVariableFormat, Input, PassedArguments, StringCompare
* Sources, Detectors, and Data: Commands for manipulating sets of sources, detectors, and data.
  o For automatic creation of whole SDLLists: CreateSDLList, SaveSDLList, SaveDataList LoadSDLList, LoadSDLList, FreeSourceList, AddNoise, AddConstantNoise Seed
  o For manual creation of SDDSets: OpenNewSDDSet, CloseNewSDDSet, AddSingleSource, AddDetectorLine, AddDetectorPlane, AddDetectorVolume, PrintDetector
* Medium: Commands for defining the properties of different turbid media.
  o Medium, DefineMedium, DefineMediumDynamics, DefineMediumFlourescence, PhotonDiffusion, Background, ShowMedium, FreeMedium, RegionSphere, RegionCylinder, RegionBox
* Boundaries: Commands for defining the boundaries of a system and the boundary condition.
  o Plane, BoxPlanes, FreePlane, BoundaryCondition, Geometry
* Objects: Commands for defining inhomogeneities
  o ObjectSphere, ObjectCylinder, ObjectBox, ObjectGauss, ApplyObjects, ShowObject, FreeObjectList
* Images: Commands for manipulating Images of the optical properties and the fluence.
  o InitImage, SaveImage, SaveDynamicImage LoadImage,
of the EXACT module is found here.
  o Exact, Moments, Smallest

* Time Domain Module: Commands related to performing calculations in the time domain.
  o Freq2Time, SaveTimeData, SaveTimeData_WWWStandard, TRS2TDD, LoadTimeData

* Layered Media Module: Commands related to the layered media module.
  o Layered

* Fluorescence Module: Commands related to the Fluorescence module.
  o FLR_Exact

* Fit Module: Commands related to running the FIT module.
  o Fit, SaveFitResult, SetFitParam, SetFitTolerance, SetFitMaxIter

* Reconstruction Module: Commands for reconstructing optical properties from measurements of the fluence. A description of the RECONSTRUCTION module is found here. Refer to the sample script imagel.pmi for an example.
  o SetReconParams, NoSirtConstraints, PertData RytovData, BornData, CreateWeights, SaveWeights, RunSirt, SirtConstraints, NoSirtConstraints

* MIE Module: Commands for calculation of the scattering coefficient and anisotropy factor of spherical dielectrics based on Mie Theory. The wavelength dependent index of refraction for water and polystyrene is included in this module.
  o Lambda, Mie, MiePoly

Examples can be found in the sample scripts. Check also the PMI homepage.

----------------------------------------

PMI Command Index

* AddConstantNoise
* AddDetectorLine
* AddDetectorPlane
* AddDetectorVolume
* AddNoise
* AddSingleSource
* ApplyObjects
* Background
* Bell
* BornData
* BoundaryCondition
* BoxPlanes
* CloseNewSDDSet
* CreateSDLList
* CreateWeights
* DefineMedium
* DefineMediumDynamics
* DefineMediumFlourescence
* Echo
* Exact
* Exit
* Fit
* SetFitTolerance
* FLR_Exact
* For...Next Loops
* FreeMedium
* FreeObjectList
* FreePlane
* FreeSourceList
* Freq2Time
* Functions
* Geometry
* Help
* If Blocks
* Include
* InitImage
* Input
* Interactive
* Lambda
* Layered
* LoadSDDList
* LoadSDLList
* LoadTimeData
* Medium
* Mie
* MiePoly
* Moments
* NoSirtConstraints
* ObjectBox
* ObjectCylinder
* ObjectGauss
* ObjectSphere
* OpenNewSDDSet
* Operations
* PassedArguments
* PertData
* PhotonDiffusion
* Pipes
* Plane
* PrintDetector
* Prompt
* Quit
* RegionBox
* RegionCylinder
* RegionSphere
* RunSirt
* RytovData
* SaveDataList
* SaveDynamicImage
* SaveFitResult
* SaveImage
* SaveSDLList
* SaveTimeData
* SaveTimeData_WWWstandard
* SaveWeights
* Seed
* SetFitMaxIter
* SetFitParam
* SetHTMLhelp
* SetPMIdir
* SetReconParams
* SetVariableFormat
* ShowMedium
* ShowObject
* SirtConstraints
* Smallest
* StringCompare
* System
* TRS2TDD
* Variables
* While Blocks
* LoadImage

------------------------------------------------------------------
Command Descriptions

-----------------------------------------------------

General Commands

Following is a list of miscellaneous commands for PMI:

* Quit or Exit - to exit PMI.
* Include [filename] - Used to execute the commands in the script
given by [filename]. Included files may in turn use the Include
command. If [filename] could not be found it is searched for in
the PMI directory.
* Interactive - switches the program to the interactive mode. This
makes only sense as a command in an input file. A single point in
a line or "d (Control d) terminates the interactive mode, the
control of the program returns to the superior file from which
the Interactive command was invoked. If the interactive mode was
already the top control level, the program terminates.
* System [unix command] or: ! [unix command] - launches a unix shell
command.
* Help [command] or ? [command]- gives help for the specified
[command] or general help if [command] is missing. Gives
HTML-help if a browser and the help file have been specified
properly with the command SetHTMLhelp, or plain text help at the
PMI-prompt otherwise.
* SetPMIDir [pmi_dir] - Sets [pmi_dir] as the PMI directory. It is
convenient to use this command in the initialization file
".pmi_init" that is executed at startup.
* SetHTMLhelp [browser] [file] - Sets the paths for a HTML-browser
(i.e. Mosaic or Netscape) which is used to display the
HTML-help-file (normally "[pmi_dir]/Help/PMI_HELP.html"). It is
convenient to use this command in the initialization file
".pmi_init" that is executed at startup.
* Bell - Rings a bell.
* Echo [text] - writes text on the screen and to the log file
* Prompt - The program waits for a "RETURN". If one types "i"
"RETURN", the program executes the Interactive command.
* Pipes - Pipes are used to control command driven external
programs i.e. plot programs like gnuplot.
  o OpenPipe [id] [prog_name] - Start
    + [id] - Identifies the pipe
    + [prog_name] - Name (with path) of the program to be
executed
- ToPipe [id] [command] - Sends [command] to pipe [id]
- ClosePipe [id] - Closes pipe [id]
- CloseAllPipes - Closes all pipes. Normally obsolete since all pipes are closed automatically when the program terminates.

---

### Programming Commands

Following is a list of programming commands for use in scripts:

* **For... Next Loops** - For Next loops can be employed in scripts to repeat a block of commands with an incrementing variable. Up to 9 nested loops can be used.
  - For [Variable Name] = [min] to [max] step [step] - Start of the For Next loop
  - [Variable Name] - Float variable to increment.
  - [min] - Start the loop with a value of [min]
  - [max] - End the loop with the value of [max]
  - [step] - increment the value by [step]
  - Next - marks the end of the For Next loop

* **Variables** There are two types of variables: float variables and string variables. The name of a float variable is preceded by an `&` and the name of a string variable is preceded by an `$`. Following are examples of assignments:
  - `&musp = 10` Which gives the float variable `&musp` the value of 10.
  - `&$filename = foobar` Which gives the string variable `$filename` the value of `foobar`.

The values of these variables are used in other commands as follows:
  - `DefineMedium tumor 0.1 &musp 0 1.333`
  - `SaveDataList Normal Normal &$filename NoAppend`

The format used for printing the values of these variables is set using the `SetVariableFormat` command.

* **Operations** Mathematical operations are available. They are addition(+), subtraction(-), multiplication(*), and division(/). Also available are trigonometric functions (sin, cos, tan, asin, acos, atan) and exponentials (exp). These
operations are used in variable assignments. For example:
  o &musp = &musp + 5
  o &D = 2.25e10 / 3 / &mutr
  o &x = 3. * Cos 30 + 1.
  o $filename = data_ + &omega + .dat

NOTE that operations are performed from left to right. For string variables, only the addition operation is available. Arguments for (sin, cos, tan) are in degrees. Arguments returned by (asin, acos, atan) are in degrees.

* While Blocks - While blocks are used as conditional loops in scripts. There can be 9 nested while blocks.
  o While [value1] [condition] [value2] - Start of the While Block.
    + [value1] and [value2] are the values being compared.
    + [condition] - Six conditions are supported: less than (<), less than or equal to (<=), greater than (>), greater than or equal to (>=), equal to (=), and not equal to (!=).
  o Wend - End the While Block.

* IF Blocks - If blocks are used to execute a set of commands depending on the result of a condition. There is no limit to the number of nested If Blocks.
  o If [value1] [condition] [value2] - Start of the If Block.
    + [value1] and [value2] are the values being compared.
    + [condition] - Five conditions are supported: less than (<), less than or equal to (<=), greater than (>), greater than or equal to (>=), equal to (=), and not equal to (!=).
  o IfEnd - End the If Block.

* Functions - Certain commands are capable of returning values to variables in the script, e.g. FIT. The usage is:
  o COMMAND [parameters] -> &1 &2... The -> indicates that the COMMAND will return values to the variables &1 &2.... The number of values returned depends on the COMMAND.

* SetVariableFormat [name] [format] - Used to set the format for printing string and float variables.
  o [name] is the name of a string or float variable. Remember to precede the string (float) variable with a $ (&).
  o [format] is the format string. Standard-C format strings are used. Therefore, string variables must have a string format and float variables must have a float format. %s and %f are the default formats for string and float variables respectively.
* Input [variable_name] [text string] - Used to get input from the user and place the result in a variable. For example,
  - input &musp What is the reduced scattering coeff.?  
* PassedArguments [var1] [var2]... - Used if arguments are passed to an included file. There are two ways to pass arguments to an include file: from the unix prompt you follow the format
  - unixprompt> pmi [include_file] [var1] [var2] ... or from the PMI interactive mode
    - PMI> Include [include_file] [var1] [var2] ... The arguments are then passed to variables in the include file by using this command in the include file. PassedArguments can be used anywhere in the include file and can be used any number of times. For example, if you have an include file that expects musp and mua to be passed as arguments, then include the following line at the top of the include file:
      - PassedArguments &musp &mua The float variable &argc is set equal to the number of passed arguments when a new script is included.
* StringCompare [var1] = [var2] - This FUNCTION does a string compare. It returns 0 if the strings are equal and 1 if they are not equal. The compare is not case sensitive. Example:
  - StringCompare $$FitWhat = MUSP -> &result

-----------------------------------------------

Object Commands

The following commands are used for defining different inhomogeneities:

* ObjectSphere [name] [medium] [x] [y] [z] [r] - Used to define a spherical inhomogeneity.
  - [name] - is the name of the sphere. The name may be exploited in future versions of PMI.
  - [medium] - is the name of the medium which fills the sphere, e.g. tumor or hematoma. The medium must be defined prior to execution of ObjectSphere using the command DefineMedium
  - [x] [y] [z] - define the position of the center of the sphere with units of cm.
  - [r] - is the radius of the sphere in units of cm.
* ObjectCylinder [name] [medium] [x1] [y1] [z1] [x2] [y2] [z2] [r] - Used to define a cylindrical inhomogeneity.
  - [name] - is the name of the cylinder. The name may be
exploited in future versions of PMI.
  o [medium] - is the name of the medium, see in ObjectSphere.
  o [x1] [y1] [z1] - defines the position of the center of the
    bottom of the cylinder (units of cm).
  o [x2] [y2] [z2] - defines the position of the center of the
    top of the cylinder (units of cm). Note that EXACT can only
    work with infinite cylinders and thus only uses these
    positions to define the axis of the cylinder. Presently,
    EXACT can only work with cylinders which have an axis
    parallel to the z-axis.
  o [r] - is the radius of the cylinder (units of cm).

  * ObjectBox [name] [medium] [xlo] [ylo] [zlo] [xhi] [yhi] [zhi] -
    Used to define a rectangular inhomogeneity with sides parallel to
    the coordinate axes.
  o [name] - is the name of the box. The name may be exploited
    in future versions of PMI.
  o [medium] - is the name of the medium, see in ObjectSphere.
  o [xlo] [ylo] [zlo] - define the lower x, y, z values (units
    of cm).
  o [xhi] [yhi] [zhi] - define the upper x, y, z values (units
    of cm).

-----------------------------------------------

Medium Commands

The following commands are used to define the properties of different
media:

  * Medium - THIS COMMAND IS OBSOLETE. Use DefineMedium instead.
  * DefineMedium [name] [mua] [mus] [g] [n] - Used to define or
    change the properties of a medium.
    o [name] - is the name of the medium which is used by other
      parts of the program to reference a particular medium.
    o [mua] - is the absorption coefficient of the medium.
    o [mus] - is the scattering coefficient of the medium.
    o [g] - is the average cosine of the scattering angle.
    o [n] - is the index of refraction.
  * DefineMediumDynamics [name] [Brownian] [Shear] - Used to define
    or change the DYNAMICAL properties of a medium.
    o [name] - is the name of the medium which is used by other
      parts of the program to reference a particular medium.
    o [Brownian] - is the Brownian diffusion coefficient of the
      scattering particles in units of cm^-2/s.
o [Shear] - is the rate of shear for the scattering particles in units of 1/s.

* DefineMediumFluorescence [name] [tau] [mua_f] [musp_f] [fmua] [fmusp] [fmua_f] [fmusp_f] - Used to define or change the FLUORESCENT properties of a medium.
  o [name] - is the name of the medium which is used by other parts of the program to reference a particular medium.
  o [tau] - is the fluorescence lifetime.
  o [mua_f] - is the absorption coefficient of the chromophore at the fluorescence wavelength.
  o [musp_f] - is the reduced scattering coefficient of the chromophore at the fluorescence wavelength.
  o [fmua] - is the absorption coefficient of the fluorophore at the excitation wavelength.
  o [fmusp] - is the reduced scattering coefficient of the fluorophore at the excitation wavelength.
  o [fmua_f] - is the absorption coefficient of the fluorophore at the fluorescence wavelength.
  o [fmusp_f] - is the reduced scattering coefficient of the fluorophore at the fluorescence wavelength.

* Background [medium_name] - Used to set the background medium.
  o [medium_name] - is the name of the medium defined using the DefineMedium command.

Sources and detectors
Several sources, each with its own amplitude and phase, and several detectors, also with amplitude and phase, are organized in a Source-Detector-Data-Set (SDDS). The modulation frequency and the correlation time are the same for a SDDS and all sources are ‘on’ at the same time. The forward algorithms (Exact and PertData) can operate on one SDDS at a time. If one wants to calculate situations with several modulation frequencies or correlation times or with changed source or detector positions, one has to create several SDDSets. All the SDDSets are stored in a list, the SDList.

Because inverse algorithms work with the SDList there is a group of commands for creating, saving, and loading a whole SDList as well as saving and loading the corresponding data in one step. For pure forward calculations it can be more convenient to set a SDDS ‘by hand’, which is done by the second group of commands.

Commands for SDLists
* CreateSDList [format] [parameter...] - Used to create a source-detector set.
  o [format]=GRID This format is used to create a set of detectors for a spatially fixed source group. The modulation frequency and correlation time of the source can be scanned as well as the X, Y, and Z coordinates of the detector.
    + [parameters...] =
    + [number of Sources in Source Group]
    + [Xs] [Ys] [Zs] [Amp] [Ph] ... Position and initial amplitude and phase of each source in the source group.
    + [Omega Min] [Omega Max] [Omega Step] Frequency given in Mhz
    + [Tau Min] [Tau Max] [Tau Step] Correlation time in seconds
    + [X Min] [X Max] [X Step] X coordinates of the detector
    + [Y Min] [Y Max] [Y Step] Y coordinates of the detector
    + [Z Min] [Z Max] [Z Step] Z coordinates of the detector
  o [format]=TANDEM This format is used to scan a source group and detector in tandem. A grid is defined and the position of the source group and detector are given relative to the grid points.
    + [parameters...] =
    + [number of Sources in Source Group]
    + [Xs] [Ys] [Zs] [Amp] [Ph] ... Position and initial amplitude and phase of each source in the source group. The position is given relative to the grid points defined below.
    + [Omega Min] [Omega Max] [Omega Step] Frequency given in Mhz
    + [X Min] [X Max] [X Step] X coordinates of the grid points
    + [Y Min] [Y Max] [Y Step] Y coordinates of the grid points
    + [Z Min] [Z Max] [Z Step] Z coordinates of the grid points
    + [X det] [Y det] [Z det] Position of the detector relative to the grid points
  o [format]=CYLINDER2 This format is used to scan a source and scan a detector around a cylinder. A grid is defined and the position of the source group is given relative to the grid points. Next a detector grid is defined relative to the source grid points. Thus, for each source there are a grid of detectors.
* [parameters...] =
  * [Zmin] [Zmax] [Zstep] The z positions for the source grid.
  * [Phis_Min] [Phis_Max] [Phis_Step] The phi positions for the source grid.
  * [rho] This is the radius of the cylindrical scan.
  * [omega] Modulation frequency
  * [tau] Correlation time
  * [Num_Srcs] number of sources in the source group
  * [Zsrc] [Phi_src] [Amp] [Ph] ... Position and initial amplitude and phase of each source in the source group. The position is given relative to the source grid points.
  * [Z_det] [Phi_Min_Det] [Phi_Max_Det] [Phi_Step_Det] Definition of the detector grid relative to the source grid.

o [format]=TDTANDEM This format is used to define a pulsed source. The source and detector are scanned in tandem on a grid. The source and detector positions are defined relative to the grid.
  * [parameters...] =
    * [xmin] - define the x part of the grid
    * [xmax]
    * [xstep]
    * [ymin] - define the y part of the grid
    * [ymax]
    * [ystep]
    * [zmin] - define the z part of the grid
    * [zmax]
    * [zstep]
    * [xsource] - Separation between grid point and source
    * [ysource]
    * [zsource]
    * [amp] - Initial amplitude of source
    * [ph] - Initial phase of source
    * [xdetector] - Separation between grid point and detector
    * [ydetector]
    * [zdetector]
    * [tmax] - Amount of time to watch the response to a pulse at time = 0. Units of seconds. This sets the frequency step, i.e. freq. step = 1/[tmax].
    * [number bins] - Number of bins to divide [tmax] in
to. Must be a power of 2.
+ [freq max] - Maximum frequency for calculations. Units of MHz. If this is too small then oscillations will appear in the time domain data as artifacts.

* SaveSDList [filename] - Used to save a list of source-detector sets
  o [filename] - is the filename for the output file. Note that .sd is appended to the filename

* SaveDataList [FormatType] [DataType] [filename] [append] - Used to save a list of data.
  o [FormatType] One of the following:
    + Normal - creates a data file with the standard PMI code format. [DataType] can have the following values:
      + Normal - saves the incident and total amplitude and phase.
      + Total/Incident - saves the ratio of the total to the incident.
    + WWWstandard - uses the format designed for sharing data over the WWW. [DataType] can have the following values:
      + Normal - saves the incident and total amplitude and phase.
  o [DataType] - determines what type of data is saved, e.g. save the total amplitude and phase or relative to the incident amplitude and phase. The value of this parameter depends on the chosen [FormatType].
  o [filename] - is the filename for the output file. Note that .dat is appended to the filename
  o [append] - if this equals APPEND then the output is appended to [filename]

* AddNoise [shot noise] [position uncertainty] - Used to add noise to a set of data.
  o [shot noise] - When this is not equal to zero then shot noise is added to the data. The noise is determined by taking the square-root of the fluence multiplied by [shot noise]. [shot noise] is thus the product of the source amplitude in units of photons per second, the signal integration time in units of seconds, the detector area in units of cm^-2, and the quantum efficiency of the detector.
  o [position uncertainty] - When this is not equal to zero then random noise is added to the data as given by the uncertainty of the position of the source and/or detector relative to each other and/or relative to the sample. [position uncertainty] is given in units of cm.
* AddConstantNoise [amp error] [phase error] - Used to add CONSTANT noise to a set of data. [amp error] is given as a percentage. [phase error] is given in degrees.
* Seed [integer] - Used to seed the random number generator. Use large negative integers.

Commands for individual SDDSets

* OpenNewSDDSet [name] [f] [tau] - Used to create a new SDDSet with the identification [name], the modulation frequency [f] in Hz, and the correlation time [tau] in seconds. After this command sources and detectors can be added until the SDDSet is closed with CloseNewSDDSet.
* CloseNewSDDSet [name] - Used to close the SDDSet with the name [name].
* AddSingleSource [amplitude] [phase] [x] [y] [z] - Adds a source to the currently open SDDSet.
  o [amplitude] in W
  o [phase] in degree
  o [x] [y] [z] position in cm
* AddDetectorLine [name] [amp] [ph] [x] [y] [z] [e1x] [e1y] [e1z] [lo1] [hi1] [step1] - Adds a line of detectors with arbitrary orientation to the currently open SDDSet.
  o [amp] [ph] amplitude and phase for the whole line.
  o [x] [y] [z] position
  o [e1x] [e1y] [e1z] vector that specifies the direction of the line, starting from (x,y,z).
  o [lo1] [hi1] [step1] specifies distribution of detectors along the line. The zero of the coordinate system is at (x,y,z), the direction is specified by the vector e1.
* AddDetectorPlane [name] [amp] [ph] [x] [y] [z] [e1x] [e1y] [e1z] [lo1] [hi1] [step1] [e2x] [e2y] [e2z] [lo2] [hi2] [step2] - Adds a plane of detectors with arbitrary orientation to the currently open SDDSet.
  o [amp] [ph] amplitude and phase for the whole plane.
  o [x] [y] [z] position of the origin of the new coordinate system.
  o [e1x] [e1y] [e1z] and [e2x] [e2y] [e2z] are two vectors e1 and e2 that specify the axes of the new coordinate system. The zero of the new coordinate system is at (x,y,z).
  o [lo1] [hi1] [step1] and [lo2] [hi2] [step2] specify the sampling along the axes of the coordinate system. The zero of the coordinate system .
* AddDetectorVolume [name] [amp] [ph] [x] [y] [z] [e1x] [e1y] [e1z] [lo1] [hi1] [step1] [e2x] [e2y] [e2z] [lo2] [hi2] [step2] [e3x]
[e3y] [e3z] [lo3] [hi3] [step3] - Adds a rectangular volume of detectors with arbitrary orientation to the currently open SDDSet. Syntax similar to AddDetectorPlane but with an additional vector e3.

* PrintDetector [name] [printwhat] [style] [filename] - Writes values at detectors.
  o [name] name of a detector that was defined with AddDetectorLine or AddDetectorPlane.
  o [printwhat] ... sorry, no complete description yet, some of many choices are:
    + AM_P - amplitude of perturbation fluence
    + PH_P - phase of perturbation fluence
    + AM_F - amplitude of total fluence
    + PH_F - phase of total fluence
    + AM_B - amplitude of background fluence
    + PH_B - phase of background fluence
    + PH_DIF - phase difference between total and background fluence
    + AM_RAT - amplitude ratio between total and background fluence
  o [style] can be one of the following:
    + GNU - file can be plotted directly with gnuplot.
    + MATH - file can be plotted directly with Mathematica. In Mathematica type: <<filename
  o [filename] specifies the file. If no filename is given, PrintDetector writes on the screen.

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**IMAGE module commands**

The following commands are used for defining the image matrix of a finite system. Each voxel in the image contains the optical properties defined by the user by setting the background medium and the object list.

* InitImage [X min] [X max] [X step] [Y min] [Y max] [Y step] [Z min] [Z max] [Z step] - sets area to be considered. The area to be reconstructed should be a subset of this large cube. The corners on the cube and the step define the region. When InitImage is called, then optical properties of any objects which have been defined are inserted (voxel by voxel) into the image.

* SaveImage [filename] [parameters] - save an image to the file filename. The format of the image file is as follows:
  o [number of x] [number of y] [number of z]
BOUNDARY module commands

The following commands are used for defining the boundaries of a finite system and the boundary condition to be used in the calculations.

* Plane [a] [b] [c] [d] [n out] - Used to define a planar boundary.
  o [a] [b] [c] [d] - The plane is defined by the equation [a] X + [b] Y + [c] Z + [d] = 0. Note that [a] [b] [c] is the normal vector to the plane and must point towards the turbid medium.
  o [n out] - is the index of refraction on the free-space side of the planar boundary.

* BoxPlanes [x1] [y1] [x2] [y2] - Used to define a BOX geometry. The sides of the box are assumed parallel to the XZ and YZ planes. Opposite corners of the box in the XY plane are given by [x1] [y1] and [x2] [y2]. Note that [x1] [y1] must be less than [x2] [y2]. The geometry type is automatically set to BOX.

* BoundaryCondition [parameter] - Used to define the boundary condition. [parameter] is one of the following:
  o Zero - uses the zero boundary condition in calculations.
  o Extrapolated - uses the extrapolated boundary condition in calculations.

* Geometry [parameter] - Used to set the geometry type as given by [parameter]. [parameter] is one of the following:
  o Infinite - Calculations are performed for an INFINITE
medium.
- Planar - for a medium with PLANAR boundaries.
- Box - for a medium with BOX boundaries.

EXACT module commands

These commands will calculate the incident, scattered, and total fluence for the system defined using object, medium, and boundary commands.

* Exact - Used to calculate the analytic solution of the diffusion equation for the defined system.
* Moments [file name] [number of moments] - Used to tell EXACT how many moments to save to file name [file name] during the calculation of the scattered wave. If [number of moments] is negative then the moments are appended to the file.

TIME-DOMAIN module commands

These commands are used to perform calculations in the time-domain. It is necessary to prepare the program for time-domain calculations either by creating pulsed sources with CreateSDList or by loading a time-domain set of data with LoadTimeDomain.

* Freq2Time - All calculations are done in the frequency-domain. After the calculations, it is necessary to tell the program to Fourier transform the results into the time-domain. This is done with Freq2Time. There are no parameters. This will only work if a pulsed source has been defined with CreateSDList or a time-domain data set was loaded with LoadTimeDomain.
* SaveTimeData [Format Type] [Data Type] [File name] [Append] - Used to save time-domain data to file [File name].
  - [FormatType] One of the following:
    + Standard - Creates a data file with the standard PMI code format. [DataType] is not used.
    + Time - Saves the data in two column format. The first column is the time in nanoseconds and the second column is the fluence. [DataType] is not used.
* SaveTimeData_WWWStandard - Don’t use.

* TRS2TDD [File TRS] [File TDD] [nbins] [fbin] [tmax] [fmax] [xs] [ys] [zs] [xd] [yd] [zd] - Reads in one column time-domain data and saves it in the standard time-domain format. The first row of the one column data file must be the number of data points that follow in the subsequent rows.

  o [File TRS] - This is name of the one column time-domain data file. A .trs is appended to the file name. The first row must be the number of data points that follow in the subsequent rows.

  o [File TDD] - This is file name used to save the data in the standard .tdd format. A .tdd is appended to the file name.

  o [nbins] - This is the number of data points to take from the .trs file and save in the .tdd file.

  o [fbin] - This is the first data point to take from the .trs file. The next [nbins]-1 data points are saved as well. This option allows initial zeros or other data sets to be skipped.

  o [tmax] - Since time information is not contained in the .trs file it is necessary to indicate the time range spanned by the [nbins] data points.

  o [fmax] - This is the maximum modulation frequency calculated when the Fourier transform of this data set is taken.

  o [xs] [ys] [zs] - Position of the source.

  o [xd] [yd] [zd] - Position of the detector.

* LoadTimeData [TDD file] [reverse] [Instrument function] - This command will load time-domain data that is in the standard format and deconvolute the data if an instrument function is given.

  o [TDD file] - This is the .tdd file. A .tdd is appended to [TDD file].

  o [reverse] - The .tdd file must have the data in an increasing time sequence. That is the first data point is at time=0 and the last data point is at time=[tmax]. Some data files are saved in the reverse format. This is indicated by typing REVERSE here. If the data is in the proper sequence then type NORMAL.

  o [Instrument function] - This is the file containing the
instrument function. A .inst is appended to the file name. The format is single column with the first row containing the number of data points following in the subsequent rows. The deconvolution of the data only works if the [TDD file] and [Instrument function] have the same number of data points. The time scale of the instrument function is assumed to be the same as the data.

Layered module commands

These commands are used to calculate diffuse back reflection from a layered, turbid system. Analytic solutions of the diffusion equation are used.

* Layered [Medium 1] [Medium 2] [d] - This is the command to start the calculation. The source-detector geometry must be defined before calling this command. The layered medium is semi-infinite with the free-space interface at z=0 in the xy-plane. NOTE that the z coordinates of the sources and detectors are assumed to be zero. It does not matter if you defined them as something other than zero. The index of refraction outside of the turbid media is assumed to be 1.0.
  o [Medium 1] is the medium for the top layer.
  o [Medium 2] is the medium for the bottom layer.
  o [d] - The top layer has a thickness of [d] cm.

FLUORESCENCE module commands

These commands will calculate the incident, scattered, and total FLUORESCENT fluence for the system defined using object, medium, and boundary commands.

* FLR_Exact - Used to calculate the analytic solution of the diffusion equation for the defined FLUORESCENT system.

FIT module commands

Commands for fitting analytic solutions to experimental or simulated data follow:
* Fit [FitWhat] - Used to initiate the fit. The source-detector list and data must already be defined as well as all parameters which are known. Refer to the sample scripts for an example. This command is a function. It returns the chi-squared value for the fit followed by the best fit for the fit parameters. The ordering for the returned fit parameters is given by the list in SetFitParam.
  o [FitWhat] - determines whether to fit the amplitude data (AMP), the phase data (PHASE), or both amplitude and phase (BOTH). For Example, Fit AMP or Fit PHASE or Fit BOTH

* SaveFitResult [filename] [DataFlag] [ParamFlag] [AppendFlag] - Saves the results from the Fit command. Typically, the results of the fit are written as the first line of the output file followed by a comparison of the "experimental" and simulated data. Each line of the data corresponds to a single source-detector pair.
  o [filename] is the filename. An extension is added to [filename] indicating what parameters were fitted.
  o [DataFlag] determines what type of data is saved if any. [DataFlag] can have the following parameters:
    + NODATA - no data is saved.
    + FREQ - each line of the data begins with the modulation freq. in MHz of the source for that measurement.
  o [ParamFlag] determines if the fitted parameters are saved to the file. If [ParamFlag]=NOPARAM then no parameters are saved.
  o [AppendFlag] determines if the new data starts a new file or is appended to the end of an existing file. If [AppendFlag]=APPEND then the data is appended to the existing file.

* SetFitParam [parameter] [value] [uncertainty] - Used to set the initial guess and uncertainty of an unknown parameter. If you wish to make an unknown parameter known then set the [uncertainty] equal to zero.
  o [parameter] - is one of the following
    + Xo - x position of the object center
    + Yo - y position of the object center
    + Zo - z position of the object center
    + a - radius of the object
    + musp_obj - scattering coefficient of the object
    + mua_obj - absorption coefficient of the object
    + db_obj - Brownian diffusion coefficient of the object
    + musp_back - scattering coefficient of the background
    + mua_back - absorption coefficient of the background
+ db_back - Brownian diffusion coefficient of the background
+ musp_f_back - scattering coefficient at emission wavelength due to chromophore
+ mua_f_back - absorption coefficient at emission wavelength due to chromophore
+ fmusp_f_back - scattering coefficient at emission wavelength due to fluorophore
+ fmua_f_back - absorption coefficient at emission wavelength due to fluorophore
+ fmusp_back - scattering coefficient at excitation wavelength due to fluorophore
+ fmua_back - absorption coefficient at excitation wavelength due to fluorophore
+ tau_f_back - lifetime of fluorophore

- [value] - is the initial guess for the unknown parameter
- [uncertainty] - is an estimate of the uncertainty in the initial guess

* SetFitTolerance [tolerance] - Used to set the tolerance that must be met when using the FIT module to determine unknown parameters.
* SetFitMaxIter [max] - Used to set the maximum number of iterations for the AMOEBA fit.

Reconstruction module commands

The reconstruction module inverts the first order solution to the integral equation using either the Born or Rytov Expansion (see Kak and Slaney for descriptions of the Born and Rytov expansions for diffracting sources). The user must define the quantities to be inverted (i.e. absorption, scattering), the grid to reconstruct on, and the measurement geometry. The only inversion available here is the SIRT algorithm. Refer to the sample script image1.pmi for an example.

* SetReconParams [Quantity] [Data Type] [Inverse Method] [Iterations] [Forward Method] - sets up the reconstruction.
  - [Quantity] - can be Absorption or Scattering or Both or Brownian or Shear.
  - [Data Type] - can be Amplitude or Phase or Both.
  - [Inverse Method] - can be Born or Rytov.
  - [Iterations] - the number of SIRT iterations.
  - [Forward Method] - can be DPDW to calculate the green’s
function for a homogeneous medium, or exact to use the exact
calculation for a sphere or cylinder. Note: exact uses the
current object list to determine what homogeneities are
present.
* RytovData [shot noise] [positional error] - divides the total
measured wave by the incident and takes the log of the
results. This is for the Rytov-type inversion. Shot noise and
positional error are added to the measurement before the
division.
* BornData [shot noise] [positional error] - subtracts the incident
wave from the total measured wave. This is for the Born-type
inversion. Shot noise and positional error are added to the
measurement before the subtraction.
* CreateWeights - uses either the Born or the Rytov approximation
to calculate the weights (also called photon hitting densities,
or three point green's functions) to necessary for the inversion
routines. WARNING: You must have a source-detector list and an
image matrix to create the weights.
* SaveWeights [filename] - saves the weights to a file. This
routine is only recommended for debugging purposes as the weight
matrix is generally quite large.
* PertData [filename] - Multiplies the weights by the image to
calculate first order forward data. The data is written to
filename.pert.dat. If filename = none, then the data is saved in
the internal source-detector-data list for further use. WARNING:
the weights and the image matrix have to have been created before
PertData is called.
* RunSirt [flag] - starts the iterative reconstruction routine. See
Kak and Slaney for details on SIRT. If the flag is set to be
CALC_WEIGHTS, then the weights are created before SIRT is
started.
* SirtConstraints [abs. min] [abs. max] [scat min] [scat. max]
[lifetime min] [lifetime max] [Brownian min] [Brownian max]
[shearmin] [shear max] - constrains the SIRT solutions for each
voxel to be between some minimum and maximum values. The
reconstruction quantities that may be constrained are absorption,
scattering, fluorescence lifetime, Brownian diffusion, and shear
flow.
* NoSirtConstraints - removes any/all constraints on reconstruction
quantities.
MIE module Commands

This command will calculate the $l^*$ (random walk step), which is in another word the reciprocal of the scattering coefficient $\mu_s'$ for polystyrene spheres based on Mie Theory. It requires to get the wavelength Lambda first in the units of cm. Then either one of the following commands can be chosen depending upon the situation. A sample script can be found script mie.pmi.

* Lambda [wavelength] - Set the wavelength of light where [wavelength] is in units of cm.
* Mie [param] - Used to calculate the $l^*$ (cm) given the indices of refraction of the polystyrene spheres and the solvent, the diameter of the polystyrene sphere (um), and the volume fraction of polystyrene spheres in the solvent.
* MiePoly [param] - Used to calculate the $l^*$ (cm) if the solvent is water, given the temperature (K), the diameter of the polystyrene sphere (um), and the volume fraction of polystyrene spheres in the solvent.

Incorporating with other PMI commands, you can use the returned value ($l^*$) and take advantage of the For...Next command. For details, please see Functions for the usage of returned values and For...Next for the loops.

REFERENCES

Appendix F

Parallel Processing

There are two very different methods of creating parallel code. The traditional method, employed by Cray computers, created parallel operations (addition, multiplication, etc.). Parallel operations are extremely useful in large matrix calculations. Instead of making these small operations parallel, we could make large routines parallel. In this type of parallel processing, we break up a problem into large, independent jobs, and run them each on a separate processor.

In our code we often simulate the measurements that would result from particular source and detector. Whenever we make more than one measurement, we end up with a set of source-detector pairs. These sets are stored internally as a list of simulations to do. Traditionally, the code would cycle through the list, and return a corresponding list of simulated measurements. In the new parallel code, the source-detector list is broken up, and sections of the list are sent to multiple parallel processors.

The computer system we use for parallel processing is an IBM SP2 (Scalable POWER Parallel2) system. POWER stands for performance optimized with enhanced RISC; RISC stands for reduced instruction set computer. A SP2 consists of a series of racks of nodes. Each node is a separate RISC 6000 superscalar processor. Nodes come in two flavors. The thin nodes have a 64kB cache, and the thick nodes have a 256kB cache. A rack consists of either 8 thick or 16 thin nodes. The system we used had one rack consisting of 16 thin nodes.

In order to communicate between the different nodes, we need a common language. For this work we used the IBM message passing library (MPL). Since there is no
shared memory between the nodes, the MPL was used to pass all of the relevant source-detector lists, medium properties, etc.

All of the computer code used in this dissertation has been incorporated into a central package called Photon Migration Imaging (PMI). PMI is broken up into several modules as pictured in figure F.1. The routine to calculate the forward problem is called not only when we create simulated data, but also to calculate the weight for every source-voxel-detector set. (Recall that the weights are functions of the photon density at particular positions). Thus it is clear that we can greatly speed up the calculation time by making the calculation of the forward problem run in parallel.

The algorithm for parallel calculation of the forward problem is quite simple. First the code is loaded into each node. We define the 0th node as the master. The master node begins loading the medium, source and detector information as usual. The other nodes jump right to the forward calculation and wait. When the master program is given a list of source-detector pairs to calculate, it looks for a waiting node.

Suppose we have 8 nodes (7 slaves plus a master) and 8 source-detector pairs. The master node reaches a point where it is ready to calculate the forward problem. It
Figure F.2: A block diagram of the flow of the parallel code.
now has a list of 8 source-detector pairs. First the master node sends the first source-detector pair to node 1. The next to node 2, until all 7 available nodes are working. The master node now waits for a result to come back. When a result is returned from any of the 7 working nodes, the result is stored, and the last source-detector pair is sent to that node. When all of the source-detector pairs have been sent, the master node waits until all nodes are finished, and stores their results (see figure F.2).

Because we do not have a common, shared memory between processors, a lot of information must be passed between the master and the slave nodes. In particular, we must pass the properties of the medium, the geometry of the sample, the object information, and the source and detector information. If the calculation of the forward problem is simple, as in the case of a homogeneous, infinite medium, then this passing time is significant compared to the calculation time, and we do not expect a substantial savings from the parallel processing. However, if the forward problem is more complicated, for example a slab geometry or a heterogeneous medium, then the passing time is less important. To demonstrate this, we have run a calculation for each of the 4 sample geometries shown in the top panels of figure F.3. In each simulation, the forward problem was calculated 500 times. The results, also shown in figure F.3, clearly indicate that the parallel processing is more efficient for the more complicated system.

Finally, using a heterogeneous slab geometry (F.3d) we demonstrate the effect of adding more nodes. Table F.1 gives both the clock time and the CPU time for the same calculation done using 1, 2, 4 and 8 nodes. Using the 8 nodes, we are able to decrease the calculation time by a factor of 5.
Figure F.3: The CPU times for various homogeneous and heterogeneous systems.
<table>
<thead>
<tr>
<th>computer</th>
<th>number of nodes</th>
<th>Clock time (s)</th>
<th>CPU time (s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SP2</td>
<td>1</td>
<td>91</td>
<td>44</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>104</td>
<td>51</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>38</td>
<td>18</td>
</tr>
<tr>
<td></td>
<td>8</td>
<td>20</td>
<td>9</td>
</tr>
</tbody>
</table>

Table F.1: The clock and CPU times for 1, 2, 4 and 8 node trials.
Bibliography


[27] A 3 mW, 780 nm source is modulated at 200 MHz. The turbid medium is 6.0 cm thick with a reduced scattering coefficient, $\mu'_{s}$, of 10.0 cm$^{-1}$ and $\mu_{a} = 0.05$ cm$^{-1}$. An spherical object is embedded in the middle of the slab. Light is collected and delivered to a photo-multiplier tube via an optical fiber with a diameter of 0.4 cm. For the simulations, the source and detector are scanned together along the boundary or the source is held fixed close to the object and the detector is scanned. Two different objects are studied; an absorbing object with $\mu'_{s,\text{in}} = 10.0$ cm$^{-1}$ and $\mu_{a,\text{in}} = 0.15$ cm$^{-1}$ and a scattering object with $\mu'_{s,\text{in}} = 15.0$ cm$^{-1}$ and $\mu_{a,\text{in}} = 0.05$ cm$^{-1}$. For a positional uncertainty of 10 μm in either the source or the detector, the fractional error in the amplitude is $2 \times 10^{-3}$ and the phase noise is 0.03°.


[35] The Intralipid used here can be obtained from The Hospital of the University of Pennsylvania, Philadelphia, Pennsylvania.


[39] As 780 nm light fields with an optical frequency $\omega \approx 10^{16} Hz$ impinge on a photocathode, the emission of photoelectrons is proportional to the square of the field. The square of the field has a part oscillating at $2\omega$ and a dc part. In our case the detector speed is much slower than $1/2\omega$, so oscillations average to zero, and we only measure the dc part. For this reason we are able to ignore the optical frequency in our calculation of the measured intensity.

[40] There are factors such as the quantum efficiency of the photocathode, the actual gain of the dynode chain, etc. which we do not attempt to measure. Instead we either calibrate the device on a known model system or make relative measurements. In addition, there are phase shifts induced as the modulated light passes through an optical fiber, and as electric signals pass through capacitors and lengths of cable.


[43] The frequency drift of the phase locked Rhode & Schwartz generators drift is less than we are capable of measuring. The upper limit on the phase locked generators (measured with the SRS530) is 0.1 kHz/hour drift.


[49] This is not true at the source position. Thus we have assumed here that we will not be reconstructing the region containing the source.


[80] Cardio-Green is a water soluble, tricarbocyanine dye. We obtained the dye from Hynson, Wescott Dunning, Inc., Baltimore, Md. 21201, USA.


[82] Clinical breast imaging data are expected to be published soon by S. B. Colak, Philips Research Labs, Netherlands.