Diffuse Optical Tomography: Breast Imager Studies

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# Table of contents

1 Background ................................................. 4
   1.1 Medical physics ....................................... 4
   1.2 Medical imaging ...................................... 4
      1.2.1 Existing technology ............................... 4
      1.2.2 Diffuse optical imaging ......................... 5
      1.2.3 Breast imaging .................................. 6
      1.2.4 DOT breast imager ................................. 7

2 Diffuse optics theory ........................................ 8
   2.1 Background ............................................ 8
      2.1.1 Introduction ..................................... 8
   2.2 Photon diffusion equation ............................... 9
      2.2.1 Radiative transport equation ....................... 9
      2.2.2 Diffusion approximation .......................... 10
      2.2.3 Photon diffusion equation ......................... 12
   2.3 Frequency-domain DOT .................................. 13
      2.3.1 Introduction ...................................... 13
      2.3.2 Photon diffusion equation ......................... 13
   2.4 Solving the diffusion equation .......................... 15
      2.4.1 Boundary conditions ............................... 20
   2.5 Reconstruction theory .................................. 22
      2.5.1 Introduction ...................................... 22
      2.5.2 Perturbation methods ............................. 22
      2.5.3 Linearization .................................... 24
      2.5.4 Solving the inverse problem ....................... 25

3 DOT experiment ............................................. 28
   3.1 Background ............................................ 28
      3.1.1 Introduction ..................................... 28
   3.2 Instrumentation ........................................ 28
      3.2.1 G3 overview ..................................... 28
      3.2.2 Light source and imaging chamber ................. 28
      3.2.3 Imaging system .................................. 29
      3.2.4 Patient interface ................................ 31
      3.2.5 Freespace setup .................................. 31
   3.3 Analysis ................................................. 32
      3.3.1 Heterodyne detection .............................. 32
      3.3.2 Signal processing ................................ 36
      3.3.3 Optical parameters ............................... 38
   3.4 Experiments ............................................. 39
      3.4.1 Optimization experiments ........................ 39
      3.4.2 Transillumination ................................ 43
4 Results and discussion

4.1 Optimization results .............................. 46
  4.1.1 Imaging system ............................... 46
4.2 Transillumination results .......................... 46
  4.2.1 Slab solution results .......................... 47
4.3 Reconstruction results ............................ 48
4.4 Conclusion ......................................... 49
Chapter 1

Background

1.1 Medical physics

Introduction

Beginning with Röntgen’s discovery of X-rays in the late nineteenth century, advances in physics have often led to new technologies in the field of medicine. Familiar tools, from endoscopes to ultrasound, all rely on principles whose origins could be traced back to the physics laboratory. Even magnetic resonance imaging, a more recent invention, has at its foundation insights first experimentally discovered by E. M. Purcell with his “great heaps of protons quietly precessing in the earth’s magnetic field” [1].

Today, with the advent of increasingly versatile electronics and greater computational power, medical physics research has become a burgeoning and interdisciplinary field. Advances in medical physics in areas such as radiation therapy and diagnostic imaging offer solutions to previously intractable problems. Medical imaging, in particular, has grown far beyond its humble beginnings with X-ray radiographs and now include novel technologies with greater flexibility and resolution than ever before.

1.2 Medical imaging

1.2.1 Existing technology

X-ray imaging

Even with the tremendous advances in modern medicine, medical imaging remains instrumental for reliable diagnosis and effective treatment of disease. The aforementioned X-ray radiograph, though simple in principle, remains a reliable and prevalent technology today. According to Kane, 70% of U.S. citizens receive at least one X-ray per year [2]. However, despite its ubiquity, images from traditional radiographs have poor contrast and no depth information since the images are essentially shadows from ballistic photons. These shortcomings were circumvented with the arrival of computed tomography (CT) in 1972 [3]. CT is an innovative use of traditional X-ray imaging in which multiple scans of the subject at different angles are aggregated for tomographic reconstruction of interior structures [4]. Such improvements allow X-ray technology to remain relevant in modern medical imaging.

Magnetic resonance imaging

Magnetic resonance imaging (MRI) is based fundamentally on the principle of nuclear magnetic resonance (NMR). While NMR has a long history beginning with its discovery by I. I. Rabi in 1938 and pioneering work led by E. M. Purcell in 1945, the implementation of NMR for MRI took place decades later. MRI imaging was first realized by P. Lauterbur in 1972, the same year that CT was introduced [3]. As described by Kozłowski, MRI, though more time-consuming than CT, far surpasses other imaging modalities in terms of its flexibility with image contrast [3]. Contrast in MRI can be achieved by measuring proton densities, $T_1$ and $T_2$ relaxation times from NMR, or by introducing strongly paramagnetic atoms such as gadolinium.
into the body [2]. More recently developed contrast methods include “blood oxygenation level dependent” (BOLD) contrast, which examines blood hemoglobin oxygenation and provides the basis for functional MRI (fMRI). MRI has provided some of the most dramatic demonstrations of the versatility of MRI by mapping brain activation from measurements of hemodynamic response [3]. Modern MRI technology allows virtually any part of the body to be imaged in tomographic detail.

**Nuclear medicine**

As the name implies, the field of nuclear medicine includes diagnostic and therapeutic procedures using radioactive material. For imaging, typical methods include positron emission tomography (PET) and single-photon emission computed tomography (SPECT) [3]. Both methods require the imaged subject to ingest or receive chemical compounds labeled with radionuclides [2]. Some types of these compounds go through the same metabolic pathways as normal glucose, which allows PET to measure metabolism. The radiation from the ingested radionuclides is then measured using an array of detectors. Various configurations for the array measure different projections of the source of emissions, which are combined, similar in fashion to CT, to create tomographic images of the observed region. This is the basic principle behind SPECT, which, like MRI, is superior to radiography in terms of contrast [2]. PET is a similar imaging technique whereby the ingested radionuclides decay by emitting positrons that emit 511 keV photons from an annihilation event [3]. Though less effective in terms of resolution when compared to MRI, both PET and SPECT excel in terms of providing functional information such as hemodynamics and metabolism of a cancer tumor [2].

**Ultrasound**

Another prevalent medical imaging technology is ultrasound, known commonly for its use in obstetrics with imaging the fetus within the womb [4]. Such devices use a transducer which emit and measure sound waves at frequencies between 2 and 15 MHz. Through this pulse-echo technique, information from the echoes of the emitted source is used to image the interior of the body. Differences in acoustic impedances provide soft tissue contrast which is encoded in the multiple echoes [2]. Because of its non-ionizing radiation, ultrasound has many diverse applications including echocardiography, which employs the Doppler effect to measure blood flow. Ongoing research seek to improve the resolution and contrast of ultrasound imaging as well as to explore the possibility of tomographic reconstructions from multiple measurements [2].

**1.2.2 Diffuse optical imaging**

**Limitations of current technology**

As demonstrated earlier, modern medical imaging include myriad technologies that address many diagnostic and therapeutic needs. However, despite their prevalence, existing techniques have various shortcomings in terms of safety, image contrast, ability to record functional information, or expense. Many existing imaging modalities such as radiography, CT, and radionuclide imaging expose the patient to ionizing radiation, which must be carefully monitored and limit the frequency with which the imaging procedure could be carried out. This becomes problematic when frequent diagnostic procedures are needed, for instance, in tracking cancer treatment. Other drawbacks for X-ray imaging are low image contrast and the lack of functional information since external, ballistic photons are used in the imaging process [5].

Other imaging methods such as radionuclide imaging, despite their reliance also on ionizing radiation, do provide excellent contrast and functional information. However, such methods often require a source of very specific radioisotopes [2]. This dramatically increases the costs for a device, making it unfeasible for smaller clinics. Ultrasound, though non-ionizing and relatively inexpensive, lags behind MRI in terms of contrast and CT in resolution [5]. Finally, MRI, which seems the most flexible and safe, with great image contrast, ability to record functional information, and non-ionizing radiation, suffers from prohibitive costs and size [5]. These limitations for current imaging technologies has lead to research in other imaging modalities, including optical imaging.
Optical imaging

Returning to Röntgen’s discovery of the X-ray, the first image that he took with the newly invented technology was of his wife’s hand. Such a feat would have been impossible with visible light since typical tissue in the body is highly absorbing in those wavelengths. However, if one were to cup one’s hand around a flashlight at night, it is possible to see light shining through the edges of one’s fingers [2]. In certain cases, biological tissue is not entirely opaque to visible light. This is the basis for “transillumination” studies conducted in the early 19th century to study fluid buildup in a child’s head. These studies were possible since the cerebrospinal fluid in the head was somewhat transparent, and more importantly, not highly scattering [6].

In recent decades, transillumination has been applied to mammography, sometimes coupled with infrared photography [4]. However, such methods were inferior in resolution to X-ray mammography. Beyond simple transillumination, optical imaging was found to be effective in measuring blood oxygenation based on the different absorption spectra of oxygenated (oxy-) and deoxygenated (deoxy-) hemoglobin. A major advance for optical imaging came from Jóbsis’ use of the “near-infrared window” (~650-950 nm) for what later became near infrared spectroscopy (NIRS) to study the oxygenation of hemoglobin [6, 16]. In 1995, Gratton aggregated multiple NIRS measurements for the first imaging application of NIRS [6]. Today, optical imaging includes various modalities, including high resolution, low scattering and more superficial imaging (< 1 mm in depth), or lower resolution, high scattering, diffuse optical imaging (DOI) [6]. DOI includes what Gibson terms optical topography, where short source-detector separations (< 4 cm) are used to image brain hemodynamics. It also includes diffuse optical tomography (DOT), where the light penetrates the entire imaged object, and reconstruction methods are used to recover tomographic information [6].

1.2.3 Breast imaging

Existing methods

In the U.S., breast cancer is the second most common and deadly cancer (to skin and lung cancer respectively) for women [7]. In recent years, although the mortality rate of breast cancer has decreased significantly, early diagnosis and treatment remain critical toward improving a patient’s prognosis [2].

Currently, X-ray mammography is the most widely adopted method for breast cancer screening and involves X-ray imaging of the breast under compression. Current devices allow for imaging at multiple angles and are estimated to be able to detect at least 80% of all breast cancers [2]. The resulting images are sent to radiologists who screen for cancer indicators such as tumors or microcalcifications (calcium deposits ~0.1 mm in size). In order to image such fine detail, many constraints are placed on the specific sources and detectors of X-rays [2]. As mentioned earlier, since X-rays do not provide good soft tissue contrast, it is difficult to effectively image denser breast tissue (found in younger women), or complex tissue structures (e.g. those following surgery) [2, 8]. Though generally effective, X-ray mammography has several shortcomings that may be mitigated by other imaging modalities.

Following a positive result from an X-ray mammogram, additional tests can include a more detailed mammogram or tests using high resolution ultrasound to distinguish between benign cysts and malignant tumors. Another method currently under study is breast magnetic resonance (MR) imaging. Breast MR is not susceptible to challenges posed by overlapping tissue or very dense breasts. Also, as Kane points out, breast MR has very high sensitivity (low number of false negatives) and have been shown to have a 94 to 100% probability to detect all tumors in the breast [2]. However, MR has lower spatial resolution than X-ray mammography and low specificity (high number of false positives) compared to the 97% specificity for X-ray mammography [2, 6]. In practice, the main shortcoming of breast MR is its high cost of operation [2].

DOT breast imaging

The main advantages of DOT breast imaging are that the method is non-invasive and non-ionizing, unlike X-ray mammography or CT, scalable, and relatively inexpensive, especially when compared to MR methods. The main benefit of DOT is its unique capability for functional imaging (i.e. providing physiological rather than anatomical information). Because breast tumors are often associated with the formation of blood vessels (angiogenesis) and other blood metabolic indicators, DOT’s ability to measure blood volume and oxygenation provides functional contrast. DOT applied to mammography can be accomplished with or without breast
compression. Even with compression, DOT breast imaging is gentler than X-ray mammography. Recent experimental tests of DOT devices have shown that they are able to resolve 80 to 85% of all confirmed tumors [6]. Additionally, studies with compression have demonstrated potential ability to provide additional, dynamic, physiological information. Emerging technologies employing DOT for breast imaging have already begun providing information that augments existing methods [6].

However, DOT imaging has difficulty identifying small malignant tumors (< 1 cm in size) as well as benign tumors (e.g. fibroadenomas). Therefore, as Gibson points out, DOT imaging is appropriate for niche areas such as neoadjuvant therapy or monitoring cancer treatments. There, since the lesions have already been identified, requirements for spatial resolution are relaxed and the functional contrast provided by DOT is most effectively utilized [6]. Additionally, DOT, in conjunction with other imaging modalities such as X-ray mammography, have been an area of ongoing research [9]. Therefore, as Gibson observes, while DOT imaging is unlikely to replace traditional breast cancer screening procedures such as X-ray mammography, it does present unique benefits to particular subsets of the population and is an useful auxiliary tool when used in conjunction with other imaging techniques [6].

1.2.4 DOT breast imager

Development

As mentioned earlier, the applications of DOT are manifold, one of which includes diagnostic breast imaging. The studies described below were conducted on the Generation-III breast imaging device at the Yodh Biomedical Optics Group at the University of Pennsylvania. The current system is non-invasive, non-ionizing, and includes a higher density source plate and other improvements over the previous device.

The previous (Generation-II) DOT breast imager included 45 laser source positions (16 mm spacing), with four lasers at wavelengths of 690, 750, 786, and 830 nm, and operated under the frequency domain (FD) configuration [10]. Two additional lasers (wavelengths 650, 905 nm) were added for operation in the continuous-wave (cw) mode. The detector consisted of a 400 x 560 pixel 16-bit charge-coupled device (CCD) camera which operates in both the cw and FD (with heterodyne detection) configurations. The device used an Intralipid box to match the background to the optical properties of breast tissue, required soft compression and an acquisition time of 8 minutes for imaging [11].

Generation-III imaging device

The new, Generation-III breast imaging device (G3) uses a denser source plate with 209 source positions (8 mm spacing) with up to 9 laser wavelengths in the FD configuration. The detectors use a 512 x 512 pixel CCD camera and gain-modulated image intensifier for heterodyne detection. The new device allows imaging from multiple angles (axial and sagittal view), also uses Intralipid as the matching fluid, soft compression, and requires an acquisition time of 20 minutes. Although the mechanical source switching time of the G3 device improved from ~100 ms to less than 10 ms per source, the total acquisition time is longer (20 minutes) due to the large number of source-detector pairings [12]. Additional design changes were also made to improve patient comfort for clinical tests of the device.

The main improvement of the new device is the increased number and density of source positions. This is expected to dramatically improve the resolution of the image reconstructions of the G3 device. In order to calibrate and optimize the device for clinical use, we conducted a series of imaging experiments using breast phantoms (synthetic material with the same optical properties as biological tissue) and different targets (optically transparent enclosures) through which synthetic dyes were circulated to simulate tumors. The following thesis will discuss the requisite DOT theory, describe the experiments for the imaging studies, and evaluate their resulting image reconstructions to demonstrate the capabilities of the G3 device.
Chapter 2

Diffuse optics theory

2.1 Background

2.1.1 Introduction

While the effects of the interaction of light with matter in biological tissue are diverse and manifold, diffuse optics relies primarily on the absorption and scattering properties of tissue. Suitable media are highly scattering, meaning that incident photons quickly lose their directionality after multiple scattering events with the particles in suspension. Examples of such media include turbid liquids such as the solutions of Intralipid (a soy fat emulsion) used in this study, or more commonly, the colloidal air on a foggy day. Additionally, such materials exhibit comparatively low absorption, which facilitates the large number of scattering events before a photon is absorbed. Photon transport in biological tissue is governed by the radiative transfer equation, which, in highly scattering media, is approximated by the photon diffusion equation. Before examining these models for light interaction, it is helpful first to examine photon absorption and scattering in greater detail.

Absorption

Absorption in tissue is characterized by $l_a$, the mean absorption length (mean free path before an absorption event, $\sim$10 cm) [5]. The absorption coefficient, $\mu_a$, defined where $\mu_a = 1/l_a$ gives the probability that a photon is absorbed per infinitesimal path length. Absorption in tissue arises primarily from oxy- and deoxyhemoglobin, melanin, and water [5]. The molar extinction coefficient is defined as the probability of photon interaction with a medium per unit path length. For hemoglobin, the molar extinction coefficient is approximately equal to the molar absorptivity since absorption dominates scattering [5]. Moreover, in the 600-800 nm wavelength range, the molar absorptivity for oxy- and deoxy-hemoglobin are pronouncedly different. This is the basis of one of the applications of diffuse optical imaging in the near-infrared ($\sim$650-950 nm wavelength) regime [5, 6]. For instance, as given in [5], the absorption coefficients can be used to estimate the concentrations of the two forms of hemoglobin:

$$\mu_a(\lambda_1) = \ln(10)\epsilon_{ox}(\lambda_1)C_{ox} + \ln(10)\epsilon_{de}(\lambda_1)C_{de}$$
$$\mu_a(\lambda_2) = \ln(10)\epsilon_{ox}(\lambda_2)C_{ox} + \ln(10)\epsilon_{de}(\lambda_2)C_{de}$$

(2.1)
(2.2)

where $\lambda_1, \lambda_2$ denote different wavelengths; $\epsilon_{ox}, \epsilon_{de}$ the molar extinction coefficients; and $C_{ox}, C_{de}$ the molar concentrations of oxy- and deoxyhemoglobin, respectively. This then allows for the calculation of the oxygen saturation $\left\langle \text{StO}_2 = C_{ox}(C_{ox} + C_{de})^{-1} \right\rangle$ and total hemoglobin concentration ($C_{Hb} = C_{ox} + C_{de}$) in the blood. These provide functional markers for potential tumors since angiogenesis can increase $C_{Hb}$ and tumor hypermetabolism tends to decrease StO$_2$ [5].
Scattering

Optical scattering in tissue arises from light interaction with cellular structures, particularly those with sizes comparable to the wavelength of the impinging light and have refractive index mismatches with the medium. Cell nuclei and mitochondria are the best scatterers, with indices of refraction of 1.38-1.41 [5]. Analogous to absorption, scattering in tissue is described by $l_s$, the scattering mean free path. In highly scattering media, we assume that the distance between particles is much greater than the scatterer size and the optical wavelength. Therefore, the multiple scattering events described earlier are independent and hence simpler to model. Additionally, $\mu_s$, the scattering coefficient, gives the probability of photon scattering per infinitesimal path length (~0.01 cm in typical tissue) [5]. This also gives the total scattering cross section per unit volume:

$$\mu_s = N_s \sigma_s$$

(2.3)

where $\sigma_s$ denotes the scattering cross section of a single scatterer and $N_s$ denotes the number density of scatterers per unit volume. The sum of the absorption and scattering coefficients give the extinction coefficient, $\mu_t$ [5]:

$$\mu_t = \mu_a + \mu_s$$

(2.4)

Figure 2.1: A He-Ne laser beam in solutions of Intralipid at different concentrations illustrates the behavior of light in low, moderate, and highly scattering media (right) (Images courtesy of H. Ban and R. Mesquita).

2.2 Photon diffusion equation

2.2.1 Radiative transport equation

Notation

As Wang describes in [5], photon transport in tissue may be modeled by a numerical Monte Carlo method which is computationally intensive. The radiative transfer equation (RTE), though slightly less accurate, is used instead as an equivalent model since it is more computationally tractable. In the following, we adopt the notation conventions in [5] for the physical quantities in the RTE.

The radiance, $L$, is given by the spectral radiance, $L_\nu$, integrated over narrow frequency range $[\nu, \nu + \Delta \nu]$:

$$L(r, \hat{s}, t) = L_\nu(r, \hat{s}, t) \Delta \nu$$

(2.5)

[$\text{W}m^{-2}\text{sr}^{-1}$], where $L_\nu$ is defined as the energy flow per unit area per unit solid angle per unit time per unit temporal frequency and $r$ denotes the position, $\hat{s}$ the unit direction vector, and $t$ time, with physical units included in brackets above and in the following.

The radiant energy, $dE$, transported across a differential area element $dA$ within the differential solid angle $d\Omega$ during a short time interval $dt$ is then given by:

$$dE = L(r, \hat{s}, t)(\hat{s} \cdot \hat{n})dA d\Omega dt$$

(2.6)
where \( \hat{n} \) denotes the outward normal for \( dA \). Other quantities may then be derived from \( L \), including the photon fluence rate (or intensity), \( \Phi \), which represents the energy flow per unit area per unit time over all flow directions:

\[
\Phi(r, t) = \int_{4\pi} L(r, \hat{s}, t) d\Omega \tag{2.7}
\]

\([\text{Wm}^{-2}]\), and the fluence, \( F \), the time-integrated fluence rate:

\[
F(r) = \int_{-\infty}^{\infty} \Phi(r, t) dt, \tag{2.8}
\]

as well as the current density \( \mathbf{J} \), the energy flux per unit time:

\[
\mathbf{J}(r, t) = \int_{4\pi} L(r, \hat{s}, t) \hat{s} d\Omega \tag{2.9}
\]

\([\text{Wm}^{-2}]\), which is the vector version of \( \Phi \).

**Radiative transport equation**

Radiative transport applies linear transport theory to model radiation in matter. It has applications in astrophysics, such as the study of radiative transport in stars [13], or atmospheric science, such as the temperature structure of the Earth’s atmosphere [14]. Using the notation defined earlier, the RTE, or Boltzmann equation, is given by:

\[
\frac{1}{v} \frac{d}{dt} L(r, \hat{s}, t) + \hat{s} \cdot \nabla L(r, \hat{s}, t) = -\mu_t L(r, \hat{s}, t) + \mu_s \int_{4\pi} L(r, \hat{s}, t) P(\hat{s} \cdot \hat{s}) d\Omega' + S(r, \hat{s}, t) \tag{2.10}
\]

where \( v = c/n \) denotes the speed of light in the medium, \( P(\hat{s}' \cdot \hat{s}) \) the normalized differential scattering cross section for light propagating in the \( \hat{s}' \) direction scattered into some solid angle \( d\Omega \) around \( \hat{s} \), and \( S(r, \hat{s}, t) \) the source term for the radiation [15]. In the continuous wave (cw) configuration, the responses are time independent so that \( L = 0 \), which requires a time-invariant light source [5].

**2.2.2 Diffusion approximation**

**Diffusion expansion in spherical harmonics**

The RTE is dependent on vector quantities \( r, \hat{s} \), as well as \( t \) and is difficult to solve. However, it may be simplified using an diffusion approximation, which assumes isotropic radiance in highly-scattering media \( (\mu_s \gg \mu_t) \). The following derivation closely follows the one given in [5, 15].

First, the radiance, \( L \), can be expanded to first order in terms of spherical harmonics, \( Y_{n,m}(\hat{s}) \):

\[
L(r, \hat{s}, t) \approx \sum_{n=0}^{1} \sum_{m=-n}^{n} L_{n,m}(r, t) Y_{n,m}(\hat{s}) \tag{2.11}
\]

where \( L_{n,m} \) denotes the expansion coefficients. The diffusion approximation is hence also known as the \( P_1 \) approximation where the series is truncated at \( n = 1 \) [5]. For anisotropic tissue structures, additional terms are required in the series for the \( P_N \) approximation where \( N > 1 \) [16]. We can substitute 2.11 into 2.7 and have:

\[
\Phi(r, t) = \sum_{n=0}^{N} \int_{4\pi} L_{n,m}(r, t) Y_{n,m}(\hat{s}) d\Omega \tag{2.12}
\]

\[
= 4\pi L_{0,0}(r, t) Y_{0,0}(\hat{s}) \tag{2.13}
\]

so that the isotropic term for \( L \) is homogenous over all solid angles and given by: \( \Phi(r, t)/4\pi \).
For the anisotropic component of $L$, denoted $L_a$, we first re-express $\hat{s}$, the unit direction vector, in terms of spherical harmonics:

$$\hat{s} = (\sin \theta \cos \phi, \sin \theta \sin \phi, \cos \theta)$$

$$= \sqrt{\frac{2\pi}{3}} \left( Y_{1,-1}(\hat{s}) - Y_{1,1}(\hat{s}), i (Y_{1,-1}(\hat{s}) + Y_{1,1}(\hat{s})), \sqrt{2} Y_{1,0}(\hat{s}) \right)$$

We then employ Eq. 2.14, Eq. 2.11, and Eq. 2.9 to expand for $J$, the current density:

$$J(r,t) = \sqrt{\frac{2\pi}{3}} \left( -L_{1,1} + L_{1,-1}, -i (L_{1,1} + L_{1,-1}), \sqrt{2} L_{1,0} \right)$$

which required the following symmetry and orthonormality conditions for the spherical harmonics:

$$Y_{n,-m}(\theta,\phi) = (-1)^m Y_{n,m}^*(\theta,\phi)$$

$$\int_{4\pi} Y_{n,m}(\hat{s}) Y_{n',m'}^*(\hat{s}) d\Omega = \delta_{nn',mm'}$$

where $\delta_{nn',mm'}$ denotes the Kronecker delta. We then have:

$$J(r,t) \cdot \hat{s} = \int_{4\pi} \hat{s} \cdot (\hat{s} L'(\hat{r},\hat{s},t)) d\Omega$$

$$= \frac{4\pi}{3} \sum_{m=-1}^{1} L_{1,m}(r,t) Y_{1,m}(\hat{s})$$

$$= \frac{4\pi}{3} L_a$$

so that

$$L_a = \frac{3}{4\pi} J(r,t) \cdot \hat{s}$$

We then have both parts of $L$:

$$L(r,\hat{s},t) = \frac{1}{4\pi} (\Phi(r,t) + 3J(r,t) \cdot \hat{s})$$

Additionally, the source, $S$, is assumed to be isotropic and hence independent of $\hat{s}$:

$$S(r,\hat{s},t) = \frac{1}{4\pi} S(r,t).$$

**Scalar and vector equations**

Given the diffusion expansion of $L$ (Eq. 2.23), we can substitute it back in the RTE (Eq. 2.10). Integrating over the entire solid angle gives the following scalar differential equation [5]:

$$\frac{1}{v} \frac{d}{dt} \Phi(r,t) + \mu_a \Phi(r,t) + \nabla \cdot J(r,t) = S(r,t)$$

Similarly, after substituting the diffusion expansion of $L$ into the RTE, we can multiply both sides by $\hat{s}$ then integrate over the all solid angles to obtain the following vector differential equation [5]:

$$\frac{1}{v} \frac{d}{dt} J(r,t) + (\mu_a + \mu_s') J(r,t) + \frac{1}{3} \nabla \Phi(r,t) = 0$$

where $\mu_s'$ denotes the transport (or reduced) scattering coefficient:

$$\mu_s' = \mu_s (1 - g)$$
where $g$ is the scattering anisotropy, the average cosine of the scattering angle [15]:

$$g = \int_{4\pi} (\hat{s}' \cdot \hat{s}) P(\hat{s}' \cdot \hat{s}) d\Omega$$  \hspace{1cm} (2.28)

For typical biological tissue, $g$ ranges approximately between 0.7 and 0.99 [17]. The transport (or reduced) interaction coefficient, $\mu'_t$ is then given by:

$$\mu'_t = \mu_a + \mu'_s$$  \hspace{1cm} (2.29)

whose reciprocal gives the transport mean free path, $l'_t$:

$$l'_t = \frac{1}{\mu'_t}.$$ \hspace{1cm} (2.30)

The diffusion expansion using spherical harmonics effectively eliminates the $\hat{s}$ dependence from the RTE [5]. We may then find an equation dependent only on $\Phi(\mathbf{r}, t)$.

### 2.2.3 Photon diffusion equation

**Diffusion equation**

Continuing with the derivations outlined in [5], we make the assumption that the fractional change in $J(\mathbf{r}, t)$ across $l'_t$ is small:

$$\frac{l'_t}{v} \left( \frac{1}{|J(\mathbf{r}, t)|} \left| \frac{d}{dt} J(\mathbf{r}, t) \right| \right) \ll 1$$  \hspace{1cm} (2.31)

where the first term enclosed in the parentheses gives the time needed for photons to traverse $l'_t$, known as the transport mean free time, and the second enclosed term gives the fractional change in $J$ per unit time. By definition of $l'_t$, we have from [5]:

$$\left| \frac{1}{v} \frac{d}{dt} J(\mathbf{r}, t) \right| \ll (\mu_a + \mu'_s) |J(\mathbf{r}, t)|,$$ \hspace{1cm} (2.32)

which implies that we may ignore the time-dependent term in Eq. 2.26, which gives:

$$J(\mathbf{r}, t) = -D \nabla \Phi(\mathbf{r}, t)$$  \hspace{1cm} (2.33)

which is known as Fick’s law [15] where the diffusion coefficient, $D$ is given by:

$$D = \frac{1}{3(\mu_a + \mu'_s)}.$$ \hspace{1cm} (2.34)

We may now substitute Eq. 2.33 into Eq. 2.23 and find:

$$L(\mathbf{r}, \hat{s}, t) = \frac{1}{4\pi} \left( \Phi(\mathbf{r}, t) - 3D(\mathbf{r}) \nabla \Phi(\mathbf{r}, t) \cdot \hat{s} \right)$$  \hspace{1cm} (2.35)

which eliminates the $J$ dependence. Substituting this equation into Eq. 2.25 then gives:

$$\frac{1}{v} \frac{d}{dt} \Phi(\mathbf{r}, t) + \mu_a \Phi(\mathbf{r}, t) - \nabla \cdot (D(\mathbf{r}) \nabla \Phi(\mathbf{r}, t)) = S(\mathbf{r}, t)$$  \hspace{1cm} (2.36)

the diffusion equation in terms of $\Phi$, as desired. For homogeneous media, the diffusion coefficient is independent of $\mathbf{r}$, which further simplifies the equation to:

$$\frac{1}{v} \frac{d}{dt} \Phi(\mathbf{r}, t) + \mu_a \Phi(\mathbf{r}, t) = D \nabla^2 \Phi(\mathbf{r}, t) + S(\mathbf{r}, t)$$  \hspace{1cm} (2.37)
As mentioned in [5], two approximations were necessary for the derivation of the diffusion equation: the first-order expansion in spherical harmonics, and the negligible fractional change in $J$ in $l_a'$. The first approximation is valid since radiance is nearly isotropic from directional broadening [5]. The second is reasonable in biological tissue for source frequencies less than $\sim 1$ GHz [15]. The broadening in both cases result from multiple scattering events, so they could be subsumed into the single condition: $\mu'_a \gg \mu_a$ where all diffuse photons have undergone a sufficient number of scattering events before being absorbed. However, a limitation of the diffusion equation is that the observation point must be sufficiently far from sources and boundaries [5]. However, the judicious application of boundary conditions can improve the accuracy of the diffusion approximation for realistic experimental configurations [5, 15].

## 2.3 Frequency-domain DOT

### 2.3.1 Introduction

Diffuse optical tomography (DOT) allows non-invasive imaging of biological tissue under the diffusion approximation for photon transport. Physically, this involves various geometries for the locations of sources and detectors [5]. The DOT breast imager described in the following sections uses a planar transmission geometry, whereby a planar set of laser sources provide the input light. In general, DOT is characterized by two main modalities: the time domain or frequency domain (FD). Time domain systems have a pulsed light source (\(\sim\)ps in length) and measures the broadening of the reemitted signal. Frequency domain systems use an amplitude-modulated light source (\(\sim\)MHz in frequency) and measures the changes in the reemitted light. Though both modalities are equivalent via the Fourier transform, the FD system is less expensive to implement and have been more thoroughly researched [5]. The DOT breast imager operates in the frequency domain and contains a DC component, which, when used alone, is termed the continuous-wave (cw) configuration.

### 2.3.2 Photon diffusion equation

#### Solutions to the photon diffusion equation

From earlier, the photon diffusion equation is given by:

$$\frac{1}{v} \frac{d}{dt} \Phi(r, t) + \left[ \mu_a(r) - \nabla \cdot D(r) \nabla \right] \Phi(r, t) = S(r, t)$$  \(2.38\)

where $D(r)$ denotes the diffusion coefficient as a function of $r$, approximated for $\mu'_a \gg \mu_a$:

$$D(r) = \frac{1}{3\mu'_a(r)}.$$  \(2.39\)

Similar to the derivation given in [5], Eq. 2.38 can be rewritten as follows:

$$\frac{d}{dt} \Phi(r, t) + \left[ v\mu_a(r) - v \nabla \cdot D(r) \nabla \right] \Phi(r, t) = v S(r, t)$$  \(2.40\)

In the frequency domain, the point light source (modeled as a $\delta$-function) is modulated at frequency $\omega$:

$$S(r, t) = (S_{DC} + S_{AC} e^{-i\omega t}) \delta(r)$$  \(2.41\)

where $S_{DC}$ and $|S_{AC}|$ denote the magnitude of the DC and AC amplitudes, respectively. $S_{AC}$ may be attributed a phase so that [5]:

$$S_{AC} e^{-i\omega t} = |S_{AC}| \exp(-i(\omega t - \phi_{AC}))$$  \(2.42\)

We may then assume fluence of the form:

$$\Phi(r, t) = u_{DC}(r) + u_{AC}(r) e^{-i\omega t}$$  \(2.43\)
where $u_{AC}$ is complex. For a homogeneous medium, $D(r) = D$, a constant. Eq. 2.37 then gives for the DC component:

$$ (\mu_a - D \nabla^2) u_{DC}(r) = S_{DC} \delta(r) $$

which can be rewritten as a Helmholtz equation and has the solution:

$$ u_{DC}(r) = \frac{S_{DC} e^{-k_{DC}r}}{4\pi D r} $$

where $k_{DC}^2 = \frac{\mu_a}{D}$.

For the AC component, substituting Eq. 2.41 and 2.43 into Eq. 2.38 gives:

$$ [-i\omega + v\mu_a(r) - v\nabla \cdot D(r) \nabla] u_{AC}(r, t) = v S_{AC} \delta(r) $$

which is soluble analytically in the infinite, semi-infinite, and finite (or “slab”) geometries. The solutions given below are derived in the next section. Similarly, for homogeneous media, we have the following solution:

$$ U_{AC}(r) = \frac{S_{AC} e^{i k_0 r}}{4\pi D r}, $$

which represents a damped spherical photon density wave [5], where:

$$ k_0^2 = \frac{-v\mu_a + i\omega}{vD}. $$

**Applications of the diffusion equation**

Combining Eq. 2.45 and 2.47 then gives for the full solution in the infinite geometry [5]:

$$ U(r, t) = \frac{S_{DC} e^{-k_{DC}r} + S_{AC} e^{i(k_0 r - \omega t)}}{4\pi D r} $$

The propagation constant $k_0$ may be separated into real and imaginary parts as given in [5]:

$$ k_r \equiv \Re(k_0) = \sqrt{\frac{v^2 \mu_a^2 + \omega^2}{\omega^2 D^2}} \sin \left( \frac{1}{2} \tan^{-1} \left( \frac{\omega}{v\mu_a} \right) \right) $$

$$ k_i \equiv \Im(k_0) = \sqrt{\frac{v^2 \mu_a^2 + \omega^2}{\omega^2 D^2}} \cos \left( \frac{1}{2} \tan^{-1} \left( \frac{\omega}{v\mu_a} \right) \right) $$

so that $k_0 = k_r + ik_i$ and Eq. 2.47 gives:

$$ u_{AC}(r) = S_{AC} e^{-k_r r} e^{i k_i r} \frac{e^{i k_0 r}}{4\pi D r} $$

where the $e^{ik_0 r}$ term gives the phase delay of the photon density wave, which gives information about the effective path lengths of the diffuse photons [5]. Wang also points out that the $e^{-k_r r}$ term represents the attenuation of the photon density wave due to diffusion and absorption [5]. Even without absorption, the photon density wave is strongly damped from diffusion [15].

Durduran presents in [16] an equivalent form of the real and imaginary parts of $k_0$:

$$ k_r = \sqrt{\frac{\mu_a}{2D}} \left[ \sqrt{1 + \left( \frac{\omega}{v\mu_a} \right)^2} + 1 \right]^{1/2} $$

$$ k_i = -\sqrt{\frac{\mu_a}{2D}} \left[ \sqrt{1 + \left( \frac{\omega}{v\mu_a} \right)^2} - 1 \right]^{1/2} $$
These characteristics of photon density waves allow the measurement of optical properties. As given in [5], we can compute $\mu_a$ and $D$ from $k_0$ using Eqs. 2.50, 2.52:

$$\mu_a = -\frac{\omega \text{Re}(k_0^3)}{v \text{Im}(k_0^3)}$$  \hspace{1cm} (2.57)

$$D = \frac{\sqrt{v^2\mu_a^2 + \omega^2}}{v|k_0^3|}$$  \hspace{1cm} (2.58)

Moreover, as Wang explains in [5], photon density waves, though physically different from electromagnetic waves, possess many classical wave characteristics. Since resolution in near-field imaging is dependent on the SNR, photon density waves are typically used to image in this regime because of their long wavelengths. However, resolution in far-field imaging can also be improved by a factor dependent on the SNR. Therefore, as explained in [5], the SNR is what limits the spatial resolution in most optical imaging devices.

### 2.4 Solving the diffusion equation

#### Infinite geometry

Following an example from [18], we give the the solution for the Helmholtz equation for the photon diffusion equation in the infinite geometry. For homogeneous media where $D(r) = D$, a constant, Eq. 2.46 can be written as a Helmholtz equation:

$$(\nabla^2 + k_0^2)u_{AC}(r) = -\frac{S_{AC}}{D} \delta(r)$$  \hspace{1cm} (2.59)

where again, $k_0^2 = -\frac{\omega \mu_a + \omega}{vD}$ and $r$ denotes the position from the source. We then find that $u_{AC}(r)$ is the Green’s function, $G(r)$, for the Helmholtz equation:

$$(\nabla^2 + k_0^2)G(r) = -\frac{S_{AC}}{D} \delta(r)$$  \hspace{1cm} (2.60)

In the infinite medium, there are no boundary surfaces and $G(r)$ is radially symmetric. So, in spherical coordinates, we have

$$\frac{1}{r^2} \frac{d}{dr} r^2 \frac{d}{dr} G(r) + k_0^2 G(r) = -\frac{S_{AC}}{D} \delta(r)$$  \hspace{1cm} (2.61)

For all $r$ except $r = 0$, the equation above becomes:

$$\frac{d}{dr} r^2 \frac{d}{dr} G(r) + k_0^2 r^2 G(r) = 0$$  \hspace{1cm} (2.62)

which has the solution:

$$G(r) = \frac{1}{r} (A e^{ik_0 r} + B e^{-ik_0 r})$$  \hspace{1cm} (2.63)

As $r \to 0$, $G(r)$ must converge so that $B = 0$ (since $k_0$ is complex). To solve for $A$, we return to Eq. 2.60 and take a volume integral in the limit where $r \to 0$:

$$\lim_{r \to 0} \int_V (\nabla^2 + k_0^2)G(r)dV = -\frac{S_{AC}}{D} \int_V \delta(r)dV$$  \hspace{1cm} (2.64)

$$= -\frac{S_{AC}}{D}$$  \hspace{1cm} (2.65)

Evaluating the integral, we find that $k_0 \to 0$:

$$\lim_{r \to 0} \int_V k_0^2 G(r)dV = \lim_{r \to 0} \int_0^{4\pi} \int_0^r A e^{ik_0 r} r dr d\Omega$$  \hspace{1cm} (2.66)

$$= 0$$  \hspace{1cm} (2.67)
For the laplacian term, using the divergence theorem, we have:

$$\lim_{r \to 0} \int_V \nabla^2 G(r) dV = \lim_{r \to 0} \oint_S \nabla G(r) \cdot dS$$

$$= \lim_{r \to 0} \oint_S A e^{i k_0 r} \left( \frac{i k_0}{r} - \frac{1}{r^2} \right) dS$$

$$= \lim_{r \to 0} \int_0^{2\pi} A e^{i k_0 r} (i k_0 r - 1) d\Omega$$

$$= -4\pi A$$

which gives $$A = \frac{S_{AC}}{4\pi D}$$ and:

$$G(r) = \frac{S_{AC}}{4\pi D} \frac{e^{i k_0 r}}{r}$$

the solution for a photon density wave [15].

Griffiths presents an alternative way to solve the Helmholtz equation in [19], given below. Beginning with Eq. 2.60:

$$(\nabla^2 + k_0^2)G(r) = -\frac{S_{AC}}{D} \delta(r)$$

we first take the Fourier transform of the Green’s function, $$G(r)$$:

$$G(r) = \frac{1}{(2\pi)^3/2} \int g(k) e^{ikr} d^3k$$

so that the LHS of the diffusion equation becomes:

$$(\nabla^2 + k_0^2)G(r) = \frac{1}{(2\pi)^3/2} \int (\nabla^2 + k_0^2)e^{ikr} g(k)d^3k$$

$$= \frac{1}{(2\pi)^3/2} \int (k_0^2 - k^2)e^{ikr} g(k)d^3k$$

For the RHS, the $$\delta$$-function becomes

$$\delta(r) = \frac{1}{(2\pi)^3} \int e^{ikr} d^3k$$

since $$\delta(r) = (2\pi)^n$$ where $$n$$ is the dimension. We then have for Eq. 2.60:

$$\frac{1}{(2\pi)^3/2} \int (k_0^2 - k^2)e^{ikr} g(k)d^3k = -\frac{S_{AC}}{(2\pi)^3D} \int e^{ikr} d^3k$$

which gives:

$$g(k) = -\frac{S_{AC}}{(2\pi)^3/2D(k_0^2 - k^2)}$$

which we substitute into the Green’s function in Eq. 2.74 and find:

$$G(r) = \frac{S_{AC}}{(2\pi)^3D} \int \frac{e^{ikr}}{k^2 - k_0^2} d^3k$$

As described in [19], this integral can be evaluated in spherical coordinates in $$k$$-space. The polar axis is defined along $$r$$ so that $$k \cdot r = kr \cos \theta$$. The $$\phi$$ integral evaluates to $$2\pi$$ and we have for the $$\theta$$ integral:

$$\int_0^\theta e^{ikr \cos \theta} \sin \theta d\theta = \frac{2 \sin(kr)}{kr}$$
which gives for the Green’s function:

\[ G(r) = \frac{S_{AC}}{2\pi^2 Dr} \int_0^\infty \frac{k \sin(kr)}{k^2 - k_0^2} dk \]

\[ = \frac{S_{AC}}{(2\pi)^2 Dr} \int_0^\infty \frac{k \sin(kr)}{k^2 - k_0^2} dk. \]  

(2.82)

(2.83)

The integral is more tractable returning to exponential notation and factoring the denominator [19]:

\[ = \frac{S_{AC}}{(2\pi)^2 Dr} \left( \int_{-\infty}^{\infty} \frac{ke^{ikr}}{k^2 - k_0^2} dk - \int_{-\infty}^{\infty} \frac{ke^{-ikr}}{k^2 - k_0^2} dk \right) \]

\[ = -\frac{iS_{AC}}{8\pi^2 Dr} (I_1 - I_2). \]  

(2.84)

(2.85)

The integrals \( I_1 \) and \( I_2 \) may be evaluated by taking contour integrals with Cauchy’s integral formula:

\[ \oint \frac{f(z)}{z - z_0} dz = 2\pi if(z_0) \]

(2.86)

if \( z_0 \) lies within the contour and 0 otherwise.

For \( I_1 \) we enclose the pole at \( k_0 \) and close the integral on the positive imaginary side so that \( e^{ikr} \) goes to zero as the imaginary part of \( k \) goes to infinity:

\[ I_1 = \oint \left( \frac{ke^{ikr}}{k + k_0} \right) \left( \frac{1}{k - k_0} \right) dk \]

\[ = 2\pi i \left( \frac{ke^{ikr}}{k + k_0} \right)_{k=k_0} \]

\[ = i\pi e^{ik_0r}. \]  

(2.87)

(2.88)

(2.89)

Similarly, for the second integral, we enclose the pole at \( -k_0 \) and close the contour on the negative imaginary side and traverse the line integral in a clockwise direction [19]:

\[ I_2 = -\oint \left( \frac{ke^{-ikr}}{k - k_0} \right) \frac{1}{k + k_0} dk \]

\[ = -2\pi i \left( \frac{ke^{-ikr}}{k - k_0} \right)_{k=-k_0} \]

\[ = -i\pi e^{ik_0r}. \]  

(2.90)

(2.91)

(2.92)

Finally, substituting back into Eq. 2.84, we have:

\[ G(r) = \frac{S_{AC}}{4\pi D} \frac{e^{ik_0r}}{r} \]

(2.93)

as desired.

**Semi-infinite geometry**

The semi-infinite geometry describes the situation where air and the diffusive medium are separated by a planar boundary but are otherwise infinite. Its solution for the diffusion equation is straightforward given the previous results for the infinite geometry. However, we do need to introduce an extrapolated zero boundary, located a distance \( l \) from the air-diffusive media interface, where the fluence rate, \( \Phi = 0 \). The physical boundary is then defined by the location where \( z = 0 \). The derivation of the location of the extrapolated zero boundary is included in a later section on boundary conditions.

For the solution in the semi-infinite geometry, we employ the method of images. Given a source located some distance \( l + z_s \) away from the zero boundary, we can place an image term (or sink) diametrically
opposite so that the net fluence is zero at the boundary (Fig. 2.2). The solution is then given by a sum of Green’s functions from the infinite geometry for the source and sink:

\[ G(\rho_s, z_s; \rho, z) = \frac{S_{AC}}{4\pi D} \left( \frac{\exp(ikr_+)}{r_+} - \frac{\exp(ikr_-)}{r_-} \right) \]  

(2.94)

for

\[ r_\pm = \sqrt{(\rho - \rho_s)^2 + (z - z_\pm)^2} \]  

(2.95)

where \( \rho - \rho_s \) denotes the lateral radius from the source fiber, \( r_\pm \) the distances to the sources and sinks, respectively, \( z_+ = z_s \) the position of the source, and \( z_- = -2l - z_s \) is the position of the sink. Also, let \( k \equiv k_0 \) henceforth for notational convenience.

While the tip of the optical fiber is often placed at the fiber-media interface during experiments, the location of the source, \( S(\mathbf{r}, t) \) is not at such a physical boundary. The probability distribution that an incoming photon undergoes its first scattering event in terms of distance traversed is modeled by an exponential distribution, \( p(z) \):

\[ p(z) \propto e^{-(\mu'_s + \mu_a)z} \]

(2.96)

\[ \approx e^{-\mu'_s z} \]  

(2.97)

since \( \mu'_s \gg \mu_a \). The mean penetration depth, \( z_+ \), for the photons is then given by \( \langle z \rangle = 1/\mu'_s \), the isotropic scattering mean free path, \( l'_s \). We use this distance to approximate the location of the isotropic source term inside the medium [15].

![Figure 2.2: Semi-infinite geometry for the photon diffusion equation. Air and the Intralipid solution form the two regions separated by the physical boundary at \( z = 0 \). The extrapolated zero boundary is located at a distance \( l \) away from the physical boundary.](image)

**Slab geometry**

Expanding on the solution for the semi-infinite case, we again use the method of images for the finite (or “slab”) geometry. Here, the diffusive media is infinite in the planar direction as before but finite in the azimuthal direction with two extrapolated zero boundaries, located at a distance \( l \) from the two air-diffusive media interfaces. The top boundary defines the location \( z = 0 \) and separates the top and diffusive media regions while the second, bottom boundary, located at \( z = L \), separates the region with media and the bottom region (Fig. 2.3).

The source is located at \( z = z_{+,0} \). Since \( \Phi = 0 \) at the boundaries, we must place a sink in the top region at \( z = z_{-,0} \). Similarly in the bottom region, there is another sink at \( z = z_{-,1} \). Now, for this sink, we must place an image source located at \( z = z_{+,2} \) in the top region to satisfy the top boundary condition. Analogously, for the sink in the top region, we must place another image source in the bottom region, located at \( z = z_{+,1} \). This process repeats for an infinite number of source-sink image pairs (Fig. 2.3).
Figure 2.3: The slab geometry for the photon diffusion equation. The first three terms of the infinite series of sources and sinks are shown. Arrows indicate source-sink pairs for the method of images.

To compute the locations of the sources and sinks, let $u_{\pm}, v_{\pm}$ denote the distances for sources (+) or sinks (−) from the top and bottom zero boundaries, respectively. The series of images beyond the initial two obey the following recursion relation:

$$u_{\pm,m+1} = v_{\mp,m} + L + 2l$$  \hspace{1cm} (2.98)

$$v_{\pm,n+1} = u_{\mp,n} + L + 2l$$  \hspace{1cm} (2.99)

where $m$ are odd positive integers and $n$ are even nonnegative integers. The top and bottom extrapolated zero boundaries are located at $z = -l$ and $z = L + l$, respectively. Let the distance to the source be $z_s \equiv z_{+,0}$, its image is then located at $z_{-,0} = -z_s - 2l$. Rather than solving this recursion relation, it is useful to note that the distance between the source itself and its first image (across the top boundary) remains constant for all of the subsequent pairwise reflections. So the problem reduces to one where the “center of radiance” (CR) and its images are reflected multiple times across two parallel axes of symmetry, which gives a simpler relation:

$$u_{m+1} = v_m + L + 2l$$  \hspace{1cm} (2.100)

$$v_{n+1} = u_n + L + 2l$$  \hspace{1cm} (2.101)

where $u_j, v_j$ denote the distances of the CR from the top and bottom media boundaries, respectively. Let $z_c$ denote the coordinates of the CR, we then solve the recursion relations for $z_{c,j}$:

$$z_{c,m} = 2m(L + 2l) - l$$  \hspace{1cm} (2.102)

$$z_{c,n} = -2n(L + 2l) - l$$  \hspace{1cm} (2.103)

From the definition of the CR, we also have: $z_{\pm,j} = z_{c,j} \pm (z_s + l)$. This then gives the locations for all of the image charges:
\[ z_{+j} = (-1)^j + 12j(L + 2l) + z_s \]  
(2.104)  
\[ z_{-j} = (-1)^j + 12j(L + 2l) - z_s - 2l \]  
(2.105)

which is used again, for the sum of Green’s functions for the series of image terms:

\[
G(\rho_s; z_s; \rho, z) = \frac{S_{AC}}{4\pi D} \sum_{j=1}^{\infty} \left( \frac{\exp(ikr_{+,j})}{r_{+,j}} - \frac{\exp(ikr_{-,j})}{r_{-,j}} \right)
\]

(2.106)

where \( r_{\pm,j} = \sqrt{(\rho - \rho_s)^2 + (z - z_{\pm,j})^2} \) as before.

### 2.4.1 Boundary conditions

The extrapolated zero boundary used earlier is essential for applying the method of images for solving the photon diffusion equation in realistic geometries. However, more than a problem-solving convenience, the extrapolated zero boundary accurately models the behavior of diffuse light at physical boundaries. In the following, we summarize the detailed study by Haskell in [15] by deriving the extrapolated zero boundary and discuss how it approximates other boundary conditions such as the partial current boundary condition.

#### Partial-current boundary condition

As Wang mentions in [5], boundary conditions are often needed to improve the accuracy of the diffusion approximation. Haskell also exhorts in [15] that failure to account for boundary conditions can give erroneous results for values of optical properties by 50\% or more. In the semi-infinite geometry, noninvasive measurements require sources and detectors to be placed on the tissue [15]. Depending on the changes in the index of refraction at the media boundary, different boundary conditions apply.

When the scattering medium and the surrounding, non-scattering material have the same index of refraction, we have a refractive-index-matched boundary where no light propagates into the scattering medium in the direction from the outside [5]:

\[
\int_{\hat{s} \cdot \hat{n} > 0} L(r, \hat{s}, t) \hat{s} \cdot \hat{n} d\Omega = 0
\]

(2.107)

where \( \hat{s} \) denotes the unit direction vector and \( \hat{n} \) denotes the unit vector pointing into the medium [5]. This creates a discontinuity as \( \hat{s} \) varies from pointing out to into the medium which violates the nearly-isotropic assumption for the radiance [15]. With the diffusion approximation and Eq. 2.33 for \( \mathbf{J} \), Eq. 2.107 becomes:

\[
\Phi(r, t) - 2D\nabla \Phi(r, t) \cdot \hat{n} = 0
\]

(2.108)

Let positive \( z \) be defined along \( \hat{n} \), we then have

\[
\Phi(z, t) - 2D \frac{d\Phi(z,t)}{dz} = 0
\]

(2.109)

which is a homogeneous Cauchy boundary condition [5]. We can Taylor expand for \( \Phi \) to first order about \( z = 0 \) and find:

\[
\Phi(z = -2D, t) = \Phi(z = 0, t) - 2D \frac{d\Phi(r, t)}{dz} \bigg|_{z=0}
\]

(2.110)

\[
= 0
\]

(2.111)

using Eq. 2.109. So, \( \Phi \approx 0 \) at \( z = -2D \), the extrapolated zero boundary [5].

The model is slightly more complicated for the case where the index of refraction of the scattering medium differs from that of the surrounding medium. Such refractive-index-mismatched boundaries circumvent the
discontinuity for index-matched boundaries since total internal reflection for certain angles allow $\hat{s}$ to change direction as before and $L(r, \hat{s}, t)$ to vary smoothly [15]. We then have the following equation for the boundary:

$$\Phi(r, t) - 2C_R L \frac{d}{dz} \Phi(r, t) = 0$$

where

$$C_R = \frac{1 + R_{\text{eff}}}{1 - R_{\text{eff}}}$$

and $R_{\text{eff}}$, the effective reflection coefficient, gives the fraction of outgoing radiance that is reflected and becomes incoming radiance [5, 15]:

$$R_{\text{eff}} = \frac{R_\Phi + R_J}{2 - R_\Phi + R_J}$$

where:

$$R_\Phi = \int_{-\pi/2}^{\pi/2} 2 \sin \theta \cos \theta R_F(\cos \theta) d\theta$$

$$R_J = \int_{-\pi/2}^{\pi/2} 3 \sin \theta \cos^2 \theta R_F(\cos \theta) d\theta$$

and $R_F$ denotes the Fresnel reflection coefficient for light from a direction $\hat{s}$ from within the medium [15]. For $0 \leq \theta < \theta_c$:

$$R_F(\cos \theta) = \frac{1}{2} \left( \frac{n_{\text{rel}} \cos \theta' - \cos \theta}{n_{\text{rel}} \cos \theta' + \cos \theta} \right)^2 + \frac{1}{2} \left( \frac{n_{\text{rel}} \cos \theta - \cos \theta'}{n_{\text{rel}} \cos \theta + \cos \theta'} \right)^2$$

and for $\theta_c \leq \theta \leq \pi/2$, $R_F(\cos \theta) = 1$. The angle of incidence, $\theta$, is given by:

$$\theta = \cos^{-1}(\hat{s} \cdot \hat{n})$$

and $\theta'$ denotes the angle of refraction where:

$$\theta' = \sin^{-1}(n_{\text{rel}} \sin \theta)$$

where $n_{\text{rel}} = n_{\text{scattering}}/n_{\text{outside}}$ [5]. The critical angle for total internal reflection, $\theta_c$, is given by:

$$\theta_c = \sin^{-1} \frac{1}{n_{\text{rel}}}$$

Both results follow from Snell’s law. The extrapolated zero boundary, $z_b$, given in [5], otherwise follows the same form:

$$z_b = -2C_RD$$

As [15] points out, this is a mixed Dirichlet-Neumann boundary condition, which has been widely applied for diffusion approximations for the RTE.

**Other boundary conditions**

At first glance, a simpler boundary condition would be to choose $\Phi(r, t) = 0$ at the physical boundary. However, as Haskell discusses in [15], such a boundary is unphysical, violates the diffusion approximation, and cannot model index-mismatches. The extrapolated boundary condition presented above approximates the partial current boundary condition, whose solution involves an infinite series of sinks for the source term. It is a good approximation because the extrapolated boundary solution differs from that for the partial current boundary condition only in octupole and higher moments [15]. A detailed analysis of both boundary conditions, including experimental and simulation results, can be found in [15].
2.5 Reconstruction theory

2.5.1 Introduction

The ultimate goal of DOT is to reconstruct chromophore concentrations or optical properties of the interior of a volume of tissue using measurements of the fluence rate on its surface. This represents an inverse problem, which, unlike examples of the forward problem given earlier, is often ill-posed and challenging also because it is inherently nonlinear [16]. Another complication for implementing DOT is that biological tissue often include non-diffusing domains, where higher order $P_N$ approximations to the RTE or hybrid models that include both types of regions are necessary [16]. However, for studies conducted using the G3 device, the diffusion equation from the $P_1$ approximation usually sufficient. Additionally, prior information, such as anatomical information from MRI’s, are useful for constraining reconstructions [16], which is also very important for obtaining reasonable reconstruction results. Furthermore, though the inverse problem for DOT is nonlinear, for slight inhomogeneities from the background, the problem may be linearized. In the following, we present a simple introduction to the process of DOT reconstruction based on current literature [16]. The full details of the algorithms involved for reconstructions using the G3 device are beyond the scope of this thesis and may be found in the literature given in §2.5.4.

2.5.2 Perturbation methods

As shown earlier, the solution of the diffusion equation in the frequency domain allows us to solve for $\mu_a$ and $D$. The following procedure for simple reconstructions follows the one given in [20]. For a volume with slight inhomogeneities, we begin with small perturbations for $\mu_a$ and $D$:

$$\mu_a(r) = \mu_a^{(0)} + \delta \mu_a(r) \quad (2.122)$$

$$D(r) = D^{(0)} + \delta D(r) \quad (2.123)$$

where the superscript $(0)$ denotes the optical properties of a homogeneous background. The photon diffusion equation for the AC component (Eq. 2.46) then gives:

$$(vD^{(0)} + v \nabla \cdot \delta D(r) \nabla + i\omega - v\mu_a^{(0)} - v\delta \mu_a(r))\phi = -vS_{AC}\delta(r) \quad (2.124)$$

Let $|S_{AC}| = 1$ for notational convenience. Rearranging, we have:

$$(vD^{(0)}\nabla^2 + i\omega - v\mu_a^{(0)})\phi = -v\delta(r) + [v\delta \mu_a(r) - v\nabla \cdot \delta D(r) \nabla]\phi \quad (2.125)$$

**Born series**

For the Born series, we assume a solution of the type $\phi = \phi_0 + \phi_S$. Substituting this solution and subtracting the equation for the homogeneous background (Eq. 2.59) then gives:

$$(vD^{(0)}\nabla^2 + i\omega - v\mu_a^{(0)})\phi_S = [v\delta \mu_a(r) - v\nabla \cdot \delta D(r) \nabla]\phi \quad (2.126)$$

We then have:

$$(\nabla^2 + k_0^2)\phi_S = -V\phi \quad (2.127)$$

where, as before:

$$k_0^2 = -\frac{v\mu_a^{(0)} + i\omega}{vD^{(0)}} \quad (2.128)$$

and

$$V = v(\nabla \cdot \delta D(r) \nabla - \delta \mu_a(r)) \quad (2.129)$$
As given in Eq. 2.60, $\phi_0$ is the Green’s function for Eq. 2.59. So the convolution of the inhomogeneous term with the Green’s function gives the solution for $\phi_S$:

$$\phi_S(r, r_s) = \int_{\Omega} G(r - r')V(r')\phi(r', r_s)d^3r'$$

(2.130)

where the subscript $(\Omega)$ denotes a volume integral over all space for the Green’s function and $r_s$ denotes the position of the photon density source [5]. We then have:

$$\phi(r, r_s) = \phi_0(r, r_s) + \int_{\Omega} G(r - r')V(r')\phi_0(r', r_s)d^3r'$$

(2.131)

We may then expand for the Born series as follows (where the differentials are omitted for clarity):

$$\phi = \phi_0 + \int GV\phi$$

(2.132)

$$= \phi_0 + \int GV\left(\phi_0 + \int GV\phi\right)$$

(2.133)

$$= \phi_0 + \int GV\phi_0 + \int \int GVGV\phi_0 + \int \int \int GVGVGV\phi_0 + ...$$

(2.134)

or, more concisely:

$$\phi_i \equiv \int r^{(i)}(GV)^i\phi_0$$

(2.135)

$$\phi = \sum_{i=0}^{n} \phi_i$$

(2.136)

which physically represents the photons’ multiple scattering events from an initial position $r_s$ [5].

**Rytov series**

Another approximation uses the Rytov series, which is defined as follows:

$$\phi = \exp\left(\sum_{i=0}^{\infty} \psi_i\right)$$

(2.137)

For the zeroth order approximation, we have: $\phi_0 = e^{\psi_0}$ so that $\psi_0 = \ln \phi_0$. For higher order approximations, we use terms from the Born series [20]. For the first order approximation, we may Taylor expand for the $e^{\psi_1}$ term in the Rytov series:

$$\phi_0 + \phi_1 = e^{\psi_0 + \psi_1}$$

$$\approx \phi_0(1 + \psi_1)$$

(2.138)

(2.139)

which gives:

$$\psi_1 = \frac{\phi_1}{\phi_0}$$

(2.140)

in terms of the Green’s functions:

$$\psi_1(r, r_s) = \frac{1}{\phi_0(r, r_s)} \int_{\Omega} d^3r'G(r - r')V(r')\phi_0(r', r_s).$$

(2.141)

Using this approach, the higher order terms of the Rytov series are given in terms of the Born series in [20] by:

$$\psi_2 = \frac{\phi_2}{\phi_0} - \frac{1}{2} \left(\frac{\phi_1}{\phi_0}\right)^2$$

(2.142)

$$\psi_3 = \frac{\phi_3}{\phi_0} - \frac{\phi_2\phi_1}{\phi_0^2} + \frac{\phi_1^2}{3}$$

(2.143)
2.5.3 Linearization

There are many methods for linearizing the problem for image reconstruction using the Born or Rytov series [16]. The following derivation, which retain both series only to first order, follows the one given in [20]. For the Born series:

\[ \phi = \phi_0 + \phi_1. \]  

(2.144)

We let the \( \phi \) on the LHS be the measured value and rearrange to find:

\[ \phi^m - \phi_0^m = \int GV \phi_0 \]

(2.145)

where the superscript \((m)\) denotes an experimentally measured value (differentials for the integral are again omitted for brevity). Note that this suggests that the method requires a calibration measurement or computation using a forward solver for the fluence from a homogeneous volume [16].

Similarly, for the Rytov series, we have:

\[ \phi = e^{\psi_0 + \psi_1} \]

(2.146)

\[ \phi_0^m \ln \left( \frac{\phi^m}{\phi_0^m} \right) = \int GV \phi_0 \]

(2.147)

However, as noted in [20], the Rytov approximation has more terms than the linearized form of the Born series:

\[ \phi = e^{\psi_0 + \psi_1} \]

(2.148)

\[ = \phi_0 \left( 1 + \psi_1 + \frac{\psi_1^2}{2} + \ldots \right) \]

(2.149)

\[ = \phi_0 \left( 1 + \frac{\psi_1^2}{2} + \ldots \right) + \phi_1 \]

(2.150)

Discretization

To illustrate the inverse problem, we discretize Eq. 2.130 and assume as in [5, 20] that the imaged object has absorption contrast only:

\[ \int_\Omega GV \phi_0 \rightarrow \sum_l h^3 G(r_j - r'_l) V(r_l) \phi_0(r'_l, r_s, i) \]

(2.151)

where, following the notation convention in [5], let \( i \) and \( j \) be the indices for the sources and detectors, respectively, \( h^3 \) be the volume of the voxel chosen for the discretization, \( k = (i, j) \) be the composite coordinate for the source-detector pairings, \( l = (m, n) \) be the composite coordinate for the perturbations. More concisely, we have:

\[ \int_\Omega GV \phi_0 \rightarrow \sum_l h^3 G_{j,l} V_l \phi_0; l, i, t, \]

(2.152)

so that the linearization becomes, as given in [20]:

\[ Ax = d \]

(2.153)

whose entries are given by:

\[ A_{k,l} = h^3 G_{j,l} \phi_0; i, t \]

(2.154)

\[ x_l = \frac{\delta \mu_{i,l}}{D^{(0)}} \]

(2.155)

\[ d_k = \begin{cases} \phi^m_k - \phi^m_{0,k} & \text{Born series} \\ \phi^m_{0,k} \ln \left( \frac{\phi^m_k}{\phi^m_{0,k}} \right) & \text{Rytov series} \end{cases} \]

(2.156)
To obtain the desired measurements of the absorption, we then invert the Jacobian, or sensitivity matrix, \( A \), for \( x \):

\[
x = A^{-1}d
\]  

(2.157)

However, the Jacobian is often ill-posed so that methods such as singular value decomposition (SVD) or iterative methods such as algebraic reconstruction technique (ART), and simultaneous iterative reconstruction technique (SIRT) is used [5, 16]. A brief overview of these methods will be included in the next section.

Although for simplicity, only absorption contrast was included in the derivation given above, it is possible to discretize simultaneously for small perturbations in \( \mu_a \) and \( D \) using the linearized Born or Rytov series. The details of such a discretization, which involves with a more complicated Jacobian matrix, especially for the Rytov expansion, may be found in [16].

Moreover, though the derivation above involved the infinite geometry, this technique is easily generalized to more complex geometries (e.g. semi-infinite, slab, infinite cylindrical [16]) with the inclusion of the correct Green’s function solutions that accurately reflect boundary conditions. However, as Wang mentions in [5], for geometries that do not have analytical solutions for the Green’s functions, numerical techniques must be used.

### 2.5.4 Solving the inverse problem

#### Direct methods

As mentioned earlier, the Jacobian in Eq. 2.153 is often ill-posed, and require methods such as SVD, ART, or SIRT for inversion. SVD is a standard method whereby \( A \) is decomposed as follows:

\[
A = U\Sigma V^T
\]  

(2.158)

\[
x = V\Sigma^{-1}U^T
\]  

(2.159)

where \( U \) is formed by the eigenvectors of \( AA^T \), \( V \) the eigenvectors of \( A^T A \), and \( \Sigma \) is a diagonal matrix composed of the square roots of the nonzero eigenvalues of \( AA^T \) and \( A^T A \) [21].

Though SVD boasts computational stability, iterative methods such as ART and SIRT have the advantage of including constraints in the inversion. As Wang points out in [5], such constraints could include the fact that \( \mu_a > 0 \), so that any negative value computed for \( \mu_a \) may be set to 0 before the next step. A more detailed discussion of the applications and limitations of the direct inversion method may be found in [16].

#### Iterative methods

One limitation of the perturbation-based approach is that the inhomogeneities for scattering and absorption must be small compared to the background. For instance, the underlying assumption of the Born series was that \( \delta \mu_a \ll \mu_a^{(0)} \) and \( \delta D \ll D^{(0)} \). This assumption is violated for measurements of tissue inhomogeneities that differ significantly in terms of optical parameters. In those cases, alternative methods must be used to solve the inverse problem. As explained in [16], the Born iterative method (BIM) and distorted Born iterative method (DBIM) are two such methods. After the problem has been successfully discretized according to Eq. 2.152, the BIM follows the following algorithm given in [16, 20]:

1. Initialize optical parameters: \( \mu_a(r) = \mu_a^{(0)}(r), D(r) = D^{(0)}(r) \)
2. Solve for \( G_{jl} \) and \( \phi_{0,i,l}, \phi_{0,k} \) using homogeneous optical parameters
3. Forward solve for \( \phi_k \) by finite element (FEM) or finite difference methods (FDM)
4. Check for convergence: \( \phi_k - \phi_k^m \leq \epsilon \) (STOP if true; GO otherwise)
5. Update \( \phi_{i,l} \) in the Jacobian
6. Solve for \( \delta \mu_a \) and \( \delta D \) via SVD, ART, SIRT, or conjugate gradient (CG) methods
7. Update optical properties and return to (2)
This is the basic algorithm for both BIM and DBIM. As described in [16, 20], DBIM differs from BIM in that the Green’s function $G$ is updated at each iteration, which makes the algorithm faster but less robust against noise. Equivalent methods using the Rytov series also exist for both methods [16]. Another, often less computationally intensive approach, uses gradient based methods [16]. As Durduran outlined in [16], such methods do not compute the Jacobian at each step but instead calculate the gradient of some objective function, $\chi^2$:

$$\chi^2 = \sum_k \frac{(\phi_k^{(m)} - \phi_k)^2}{\sigma_k^2}$$

(2.160)

with respect to the optical parameters ($\nabla = [\partial_{\mu_0}, \partial_D]$) and uses it to perform a line search to directly minimize $\chi^2$. This is accomplished iteratively until $\chi^2 < \epsilon$, which also provides a criterion for the desired level of convergence in step (4) of the BIM algorithm. Additionally, for nonlinear methods, as suggested in [20], it may be ill-advised to use nonlinear inverse solvers in an algorithm that uses linear methods for the forward solver (e.g. truncated Born series). In those instances, convergence may be very difficult when solving the inverse problem.

**TOAST**

It is important to note that the examples above give only a simple introduction to the inverse problem in DOT. In order to reconstruct images using data from the G3 device, the software package Time Resolved Optical Absorption and Scattering Tomography (TOAST) is used [22]. TOAST uses a finite element method (FEM) based forward solver and a gradient-based inverse solver for image reconstruction [23, 24]. The details of the numerical methods implemented in TOAST are beyond the scope of this thesis. However, initial results from the image reconstructions, using data collected in the experiments conducted on the G3 device, will be included in § 4.3.
Chapter 3

DOT experiment

3.1 Background

3.1.1 Introduction

In order to optimize the device and to demonstrate its imaging capabilities, a series of experiments were carried out on the G3 breast imager. They involved breast phantoms (synthetic material with the same optical properties as breast tissue) and imaging targets (optically transparent enclosures used to simulate tumors). Studies were done using synthetic dyes with the same optical properties (absorption and scattering) as that of hemoglobin. An alternate experimental setup, termed freespace (FS), is analogous to the G3 system in instrumentation but includes greater flexibility in the setup of the sources and unconstrained by the physical limitations of the clinical device. The FS system was used to test the new experimental setup and examine several theoretical results from DOT theory.

3.2 Instrumentation

3.2.1 G3 overview

The G3 breast imager includes a laser light source, from which lasers of various wavelengths may be selected, modulated, and emitted through one of 209 optical fibers that emerge at the source plate. The source plate is placed on one transparent wall of the breast imaging chamber (or breast tank). In the clinical setting, a single breast is placed in a rectilinear breast tank, submerged in an Intralipid solution in order to match the background optical properties of the slab, and compressed (Fig. 3.1).

The imaging system for the G3 device consists of an image intensifier, CCD camera, and computer system to control the device and to record images (Fig. 3.1). The gain of the image intensifier may be modulated using radio-frequency (RF) signal generators. This facilitates the heterodyne detection of the transmitted light, which is necessary due to the finite write speed of the CCD camera. Details of the instrumentation and implementation of the components of the G3 device are given in the following sections.

3.2.2 Light source and imaging chamber

Laser system

The G3 light source uses fiber-coupled continuous-wave (cw) laser diodes mounted in a custom-fitted laser box (Fig. 3.2) The system is designed to support lasers of up to nine different wavelengths for near-infrared (NIR) light sources. Lasers in five wavelengths (660, 785, 808, 830, 980 nm) have been installed and have power in the ranges of 100 to 500 mW. Four additional wavelengths (685, 750, 850, 905 nm) are planned to be installed in the final version of the device.

For switching between the wavelengths, a 9-by-1 multimode fiber switch (Piezosystem Jena FSM 1×9) is used. The intensity of the light at the selected wavelength is then deeply modulated (> 90%) at 70 MHz
by modulating the input voltage. Then, for scanning between the 209 source positions, we use a custom-designed galvanometer-based optical switch (Innovations in Optics). In this switch, light from an 100 μm input fiber is collimated and directed to a pair of galvanometer controlled mirrors. The reflected light then passes through a telecentric lens, which focuses the light onto a bundle of 209 optical fibers of diameter 600 μm (Fig. 3.3) [25]. This rapid switching method is employed to shorten the image acquisition time.

After traversing ~3 m of the optical fibers (Fig. 3.4), the overall throughput of the light is ≈50%. The polished ends of the fiber optics are mounted on a black plastic (DuPont Delrin) source plate in a square lattice with 11 rows and 19 columns, with 8 mm spacing (Fig. 3.5). The source plate is mounted outside the anti-reflective coated Plexiglas enclosure for the breast imaging tank, described in the following section.

**Imaging chamber**

The imaging chamber (or breast tank) is an adjustable, rectilinear enclosure with dimensions 27.5 cm by 43.5 cm by a variable width depending on the amount of compression required. During experiments and in planned clinical use, the tank is filled with an Intralipid-water solution to create a volume that approximates the slab geometry (§2.4) whose optical properties match that of healthy breast tissue.

New imaging targets were implemented for experiments on the G3 imager. They are made of white plastic (DuPont Delrin) whose optical properties (μ= 7 cm⁻¹) and negligible absorption closely match that of the Intralipid background. These cylindrical containers (1 cm in length and diameter with 0.5 cm tapered ends) have maximum thickness of 1 mm for the walls so as to be optically “transparent.” Furthermore, the imaging targets are attached to tubing (radius 2 mm, thickness 0.5 mm) that allow them to be continuously titrated with synthetic dyes (Fig. 3.6).

In addition to liquid breast phantoms, a solid breast phantom was also used in a series of characterization studies. The solid phantom is made of resin, TiO₂, carbon black, and has optical properties similar to those of typical, healthy breast tissue (Fig. 3.7).

### 3.2.3 Imaging system

**Camera system**

For detecting and recording the transmitted laser light, a charge-coupled device (CCD) camera (ANDOR iXon3 897) is used (Fig. 3.8). The camera has a resolution of 512 x 512 pixels (pixel size: 16 x 16 μm²) and is thermo-cooled to −75°C during experiments. It has a full-resolution frame rate of 35 fps and maximum readout rate of 10 MHz. The CCD sensor (BV) used is back-illuminated and optimized for visible wavelengths.
Figure 3.2: Photo of interior of laser box showing five lasers currently installed and their associated power supplies and controllers.

Figure 3.3: Schematic and photo of the components of the light source, including the galvanometer-controlled optical switch (left) and fiber bundle (right) used to send light via optical fibers to the source plate.

with the highest available quantum efficiency for visible and NIR wavelengths. Images captured on the camera are transferred to the computer and saved in the FITS file format.

Image intensifier

A proximity-focused type image intensifier (Lambert Systems II18MD) is mounted on the CCD camera (Fig. 3.8). The gain of the device, controlled with a microchannel plate (MCP) may be modulated at high frequencies (~100 MHz). The time resolution of the device depends on the modulating frequency but the decay time of the phosphor is ~1 ms. The gain of the image intensifier is modulated for the heterodyne detection used in the study whose theoretical details are included in the §3.3.1.

System control

The instruments used in the study were controlled by programs written in LabVIEW (National Instruments, NI) software using the NI DAQ interface (NI USB-6210). Other controls, such as those for operating the CCD camera, uses proprietary software and programming languages (e.g. ANDOR Basic). Signal generation for modulating both the laser electro-optic modulator and the image intensifier gain used radio-frequency (RF) signal generators (Rhode & Schwarz SMB100A). All other controls and implementation were manual, using the associated instruments or software.
Figure 3.4: Photo of the 209 optical fibers from the 9-by-1 switch mounted on a bulkhead and connected to the source plate of the imaging chamber.

3.2.4 Patient interface

Clinical configuration

The breast tank, galvanometer switch, and imaging system are housed under the a hydraulic-controlled, elevated, modified biopsy bed (Fig. 3.9) A patient, lying prone on the bed, places her breast through an opening in the center of the bed into the breast tank. The tank is filled with the background Intralipid solution and compressed during imaging. This configuration is designed to maximize breast coverage for imaging and minimize the width of the gap between the patient’s chest and the background solution in the breast tank. This is important since, as discussed in section on boundary conditions of the photon diffusion equation (§2.4), light from sources near an air-Intralipid interface will reflect back into the tank and saturate the CCD image [25]. Lastly, the breast tank and imaging system are mounted on a rotatable arm to facilitate imaging in the axial and sagittal orientations.

All other instruments, including the power supply, laser source box, signal generators, computer, and other control systems are mounted in an upright instrument rack. The two components, the instruments mounted in the bed, and those in the instrument rack, are connected through a fiber optic cable, shielded coaxial cables, and power cords. Care has been taken to ensure that the entire system is portable but robust in a clinical setting.

3.2.5 Freespace setup

The freespace (FS) experimental setup is conceptually identical to the G3 breast imager. However, it is set up on an optical table and free from the physical constraints of the G3 device. Since it is designed only for experimental purposes, the FS system uses a laser at a single wavelength and has a breast tank with fixed dimensions (length 44.5 cm, width 44.5 cm, depth 6.15 cm). Same as that of the G3 device, the walls of the FS breast tank are made of Plexiglass. Furthermore, the FS system uses the identical imaging system implemented on the G3 device. However, the FS laser “source plate” differs from that of the G3 imager, as explained below (Fig. 3.10).

The FS system also has a galvanometer controlled mirror system system (ThorLabs Scanning Galvo GVS012 ) that allows precise deflections of an input laser beam. The beam may be programmed to raster scan a grid of points with arbitrary distance and number of lattice points. This allows the system to be programmed to mimic a source plate with an arbitrary pattern. Though the distances that the laser light travels differs from position to position, the point source approximation under the diffusion approximation
Figure 3.5: Photo of the source plate which houses the 209 fiber optics from the light source. A single source is illuminated to illustrate the scanning process.

Figure 3.6: Photo of the white Delrin imaging targets and tubing which allow changes to the optical properties of the targets during experiments.

is obeyed. Because of the flexibility and ease of set up of the FS system, it was used to carry out several diagnostic experiments, such as those comparing the experimental data with theoretical results for the slab solution (§2.4). Details of that experiment and several others are included in the following.

3.3 Analysis

3.3.1 Heterodyne detection

As mentioned earlier, since the camera has a limited write speed, heterodyne detection is implemented for the imaging system. In this setup, the laser light is modulated at 70 MHz and the image intensifier is modulated at 70 MHz + 1 Hz. With this detection scheme, the laser modulation is coupled to the gain modulation for the image intensifier at a slightly different frequency. Heuristically, the signals can be considered to combine and form a “beat” frequency that is more tractable for the camera to record. The following analysis provides a detailed model for the heterodyne detection used in the experiment.

Image intensifier model

As discussed in §3.2, the laser source signal and the gain of the image intensifier are both modulated using an RF signal generator. In the following model, let the frequency of the signal at the source be denoted $f_C$, the
frequency for the image intensifier (modeled ideally as a Dirac Comb, Fig. 3.11) be $f_i$, and their difference $f' = f_i - f_C$. Experimentally, the frequencies are $f_C = 70$ MHz, $f_i = 70$ MHz + 1 Hz, and $f' = 1$ Hz.

The Dirac Comb

The Dirac Comb is a series of δ-functions, separated by a period $T$:

$$C_T(t) = \sum_{n=-\infty}^{\infty} \delta(t - nT)$$  \hspace{1cm} (3.1)

which may be rewritten through a Fourier transform:

$$C_{1/T}(f) = \mathcal{F}[C_T(t)]$$

$$= \frac{1}{T} \sum_{n=-\infty}^{\infty} \delta \left( f - \frac{n}{T} \right)$$  \hspace{1cm} (3.2)

where $f$ is the frequency.
Signal derivation

The source intensity, $g(t)$, is modeled with an DC component $A_0$ and an AC amplitude $A$ with frequency $f_i$ (Fig. 3.12):

$$g(t) = A_0 + A \cos(2\pi f_i t) \quad (3.4)$$

The sampled signal (the images captured by the camera), $s(t)$, is then given by $g(t)$ multiplied by a Dirac Comb, $C_{T_C}(t)$:

$$s(t) = g(t)C_{T_C}(t) \quad (3.5)$$

$$s(t) = (A_0 + A \cos(2\pi f_i t)) \left( \sum_{n=-\infty}^{\infty} \delta(t - nT_C) \right) \quad (3.6)$$
Figure 3.11: Illustration of an approximate Dirac comb with experimental parameters for the frequency. $C_T(t)$ denotes the Dirac comb as a function of time, $t$, in seconds.

Figure 3.12: The source intensity, with $A_0 = A = 1$ with the frequency used in the experiment, $f_i = 70$ MHz + 1Hz.

We can perform a Fourier transform of the source intensity:

$$G(f) = \mathcal{F}[g(t)] = \int_{-\infty}^{\infty} g(t) e^{-2\pi i ft} dt$$

$$= \int_{-\infty}^{\infty} (A_0 + A \cos(2\pi f_i t)) e^{-2\pi i ft} dt$$

$$= A_0 \int_{-\infty}^{\infty} e^{-2\pi i ft} dt + A \int_{-\infty}^{\infty} (e^{2\pi i ft} + e^{-2\pi i ft}) e^{-2\pi i ft} dt$$

$$= A_0 \delta(f) + A \int_{-\infty}^{\infty} (e^{-2\pi i(f-f_i)t} + e^{-2\pi i(f+f_i)t}) dt$$

$$= A_0 \delta(f) + A \left(\delta(f-f_i) + \delta(f+f_i)\right)$$

From the Convolution Theorem, multiplication in the time domain is equivalent to a convolution in the frequency domain.

$$S(f) = G \ast C_{1/T_c}$$

$$= \int_{-\infty}^{\infty} \left[ A_0 \delta(f') + A \left(\delta(f'-f_i) + \delta(f'+f_i)\right) \right] C_{1/T_c}(f-f') df'$$

$$= A_0 \int_{-\infty}^{\infty} \delta(f') C_{1/T_c}(f-f') df' + A \int_{-\infty}^{\infty} \delta(f'-f_i) + \delta(f'+f_i) C_{1/T_c}(f-f') df'$$

$$= A_0 C_{1/T_c}(f) + A \left(C_{1/T_c}(f-f_i) + C_{1/T_c}(f+f_i)\right)$$
Using the definition of the Dirac Comb:

\[
S(f) = \frac{A_0}{T_C} \sum_{n=-\infty}^{\infty} \left[ \delta \left( f - \frac{n}{T_C} \right) + \frac{A}{2} \left( \delta \left( f - f_i - \frac{n}{T_C} \right) + \delta \left( f + f_i - \frac{n}{T_C} \right) \right) \right]
\]

(3.16)

We now expand term by term. For \( n = 0 \)

\[
S_{n=0}(f) = \frac{1}{T_C} \left[ A_0 \delta(f) + \frac{A}{2} (\delta(f - f_i) + \delta(f + f_i)) \right]
\]

(3.17)

\[
s_{n=0}(t) = \mathcal{F}^{-1} [S(f)] = \frac{1}{T_C} (A_0 + A \cos(2\pi f_i t)).
\]

(3.18)

Similarly, for \( n = 1 \)

\[
S_{n=1}(f) = \frac{1}{T_C} \left[ A_0 \delta \left( f - \frac{1}{T_C} \right) + \frac{A}{2} \left( \delta \left( f - f_i - \frac{1}{T_C} \right) + \delta \left( f + f_i - \frac{1}{T_C} \right) \right) \right]
\]

(3.20)

\[
= \frac{1}{T_C} \left[ A_0 \delta(f - f_i) + \frac{A}{2} (\delta(f - f_i - f_C) + \delta(f + f_i - f_C)) \right]
\]

(3.21)

\[
= \frac{1}{T_C} \left[ A_0 \delta(f - f_i) + \frac{A}{2} (\delta(f - f') + \delta(f + f')) \right]
\]

(3.22)

For the signal, we perform an inverse Fourier transform:

\[
s_{n=1}(t) = \mathcal{F}^{-1} [S(f)]
\]

(3.23)

\[
= \frac{1}{T_C} \int_{-\infty}^{\infty} \left[ A_0 \delta(f - f_i) + \frac{A}{2} (\delta(f - f') + \delta(f + f')) \right] e^{2\pi if t} df
\]

(3.24)

\[
= \frac{1}{T_C} \left( A_0 e^{2\pi if_i t} + A \cos(2\pi f' t) \right)
\]

(3.25)

Including the \( n = -1 \) term then gives:

\[
s_{n=-1,0,1}(t) = \frac{1}{T_C} \left[ A_0 (1 + 2 \cos(2\pi f_i t)) + A (\cos(2\pi f_i t) + 2 \cos(2\pi f' t)) \right]
\]

(3.26)

The full series for \( s(t) \) is given by:

\[
s(t) = s_{n=-1,0,1}(t) + \sum_{n=2}^{\infty} \left[ 2A_0 \cos(2\pi nf_i t) + A (\cos(2\pi (f_i - nf_i t) + \cos(2\pi (f_i + nf_i t))) \right]
\]

(3.27)

However, the response time for the image intensifier is limited by the decay time of the phosphor (\( \sim 1 \) ms), so the signals at higher frequencies (\( f \gg f' \)) time average to 0, which gives:

\[
s(t) \approx \frac{1}{T_C} (A_0 + 2A \cos(2\pi f' t))
\]

(3.28)

the form of the experimentally-observed signal. This equation is then used to extract the information from the images for reconstructions.

### 3.3.2 Signal processing

Because the image reconstructions are computationally intensive, the data must first be preprocessed. The preprocessing pipeline begins with the FITS files saved from the camera and uses a fast Fourier transform (FFT) to obtain the information relevant for the reconstruction algorithms.
Fast Fourier transform

A FFT is performed on each pixel of every image and extracts the AC, DC amplitude, and phase for the sampled signal. This procedure was developed during this study to replace a previous method using a nonlinear least-squares (LS) fit to harmonic functions using the data. It was shown that the FFT and LS methods give equal results for the preprocessing pipeline, with the former method computationally much faster (Fig. 3.13).

![Graph](image)

**Figure 3.13:** Example of a non-linear least-squares (LS) fit to harmonics (dashed) and the fit using the FFT (solid). Note that the FFT obtains an essentially identical fit to the LS method, with small differences in the phase. The data shown were collected on the G3 device using the 785 nm wavelength laser.

Data quality

The main measure of data quality is the signal-to-noise ratio (SNR) of the data. Estimates of the SNR in the frequency domain is obtained through FFT methods. First, the SNR is defined by [26]:

$$\text{SNR} = \frac{\text{Signal power}}{\text{Noise power}}$$

(3.29)

The traditional procedure for estimating the SNR in the frequency domain is given by [26]:

$$\text{SNR} = \frac{\sum_f A^2(f) > A_t^2}{\sum_f A^2(f) < A_t^2}$$

(3.30)

where $A^2(f)$ denotes the sampled power at frequency $f$ and $A_t^2$ denotes a particular threshold power (Fig. 3.14). For this experiment, since the width of the power spectrum is very narrow, we may use a modified definition for the SNR:

$$\text{SNR} = \frac{A_t^2}{\sum_f A^2(f) \neq A_t^2}$$

(3.31)

where $A_t$ denotes the amplitude of the signal at the “beat” frequency, $f' = 1$ Hz, from the heterodyne detection scheme excluding the $f = 0$, or DC component. Since the ratio $A_t^2/A_{\text{other}} f > 10$ for every experiment, this definition is adopted for the diagnostic trials (Fig. 3.15).
Figure 3.14: Illustration of thresholding used to calculate SNR (simulated data). The frequency of interest is 1 Hz and the threshold is $10^9$ for the power. The SNR is then given by the sum of power at the four frequencies where the power exceeds the threshold, divided by the sum of the power for all the other frequencies below the threshold.

### 3.3.3 Optical parameters

#### Spectroscopic parameters

As mentioned earlier, the NIR window defines the spectroscopic region where different biological chromophores differ in absorption. This is essential for the unique imaging capabilities of DOT, whereby different compounds such as oxy- and deoxyhemoglobin (HbO₂, Hb) may be used as the chromophores that provide functional contrast for diagnostic imaging.

#### Effective reflection coefficient

Though the effective reflection coefficient was derived analytically in the DOT theory (§2.3.2), it can also be determined experimentally. Beginning with the definition of reflectance and transmission coefficients, $R$ and $T$, respectively:

$$R + T = 1$$

In diffuse media, Snell’s law and the conservation of energy gives for the external and internal transmission, ($T_{\text{ext}}$ and $T_{\text{int}}$, respectively) [27]:

$$T_{\text{int}} = \frac{T_{\text{ext}}}{n_{\text{rel}}^2}$$

where $n_{\text{rel}} = n_{\text{medium}}/n_{\text{air}}$ is the relative refractive index. We then have:

$$R_{\text{int}} = 1 - (1 - R_{\text{ext}})n_{\text{rel}}^{-2}.$$  \hspace{1cm} (3.34)

Egan used a power series curve fit in [28] for data collected by Orchard in [27] and found:

$$R_{\text{ext}} = 0.440 + 0.710n_{\text{rel}} - 0.332n_{\text{rel}}^2 + 0.0636n_{\text{rel}}^3$$

which gives for Eq. 3.34:

$$R_{\text{eff}} = R_{\text{int}}$$

$$= -1.440n_{\text{rel}}^{-2} + 0.710n_{\text{rel}}^{-1} + 0.668 + 0.0636n_{\text{rel}}$$

which provides an experimental method to compute $R_{\text{eff}}$.  

38
Figure 3.15: Power spectrum of G3 data using the 785 nm laser and the 500 MCP setting on the image intensifier. Since the width of the peak for the heterodyne frequency of 1 Hz is so narrow, any reasonable threshold would lead to the single power at 1 Hz to appear in the numerator for the SNR calculation.

3.4 Experiments

3.4.1 Optimization experiments

Though the setup for the instruments in the G3 imaging device is straightforward, the settings for each component must be optimized to quickly and accurately obtain data for reconstructions. A series of experiments, described below, were conducted to find the optimal settings for the modulation for the gain on the image intensifier.

Image intensifier gain

Though we had modeled the image intensifier as a Dirac comb in the analysis (§3.3.1), experimentally, the spikes of the comb have a finite width. These approximate δ-functions are generated by modulating the photocathode voltage from positive to negative voltages at 70 MHz + 1 Hz on the image intensifier. To model the δ-functions thus obtained, we first examine the gain intensities as functions of the photocathode voltage (Fig. 3.18).

Gain optimization

The photocathode voltage, $V_C$, can be modulated with an DC and AC component:

$$V_C = V_{DC} + V_{AC} \sin \omega t$$

(3.38)

where the possible values for $V_{DC}$ are between $-1$ and $2$ V, for $V_{AC}$, the range is 0 to 1.8 V and $\omega = 2\pi (70 \text{ MHz} + 1 \text{ Hz})$. Given the fitted gain curves and the model for the system in deriving the obtained signal (§3.3.1), we have a range of possible results for the approximated Dirac Comb (Fig. 3.19-3.21). The analysis for the 800 MCP setting for the image intensifier is similar with modeled results for the best approximate Dirac comb (Fig. 3.22).

Guided by these qualitative results, we performed a scan of the cathode DC and AC voltages ($V_{DC}, V_{AC}$) on the image intensifier. Using a liquid slab phantom with standard optical properties ($\mu_a = 0.041 \text{ cm}^{-1}$ and $\mu'_a = 7.5 \text{ cm}^{-1}$), we examined the SNR for a range of the voltage values. The results of these experiments may be found in §4.1.1.
Figure 3.16: Plot of the absorption coefficient, $\mu_a$, as a function of wavelength of the impinging light for several tissue chromophores. This shows the range of wavelengths for the NIR window (650-950 nm). (Figure courtesy of H. Ban)

Figure 3.17: Detailed plot of absorption coefficient, $\mu_a$, as a function of wavelength within the NIR window. This illustrates the different spectra for tissue chromophores such as HbO$_2$, Hb, and water. The green dashed vertical lines indicate available wavelengths on the G3 breast imager. (Figure courtesy of H. Ban)

Modulation frequencies

Using these models for the gain of the image intensifier, we found that the experimental implementation of the Dirac comb has a finite width. Since changing the modulation frequency changes the spacing between the approximate $\delta$-functions, the performance of the image intensifier may also depend on the modulation frequency. To examine this effect, we performed a series of experiments using different RF modulation frequencies for the image intensifier. With the same heterodyne detection setup (1 Hz frequency difference), we examined the SNR for the preprocessed data for a range of $V_{DC}$ values. The results for the SNR may also be found in §4.1.1.

Optical dyes

Two water-soluble dyes, nigrosin and Epolight (Epolight 2735, Epolin Inc.), were used to titrate the solutions that filled the imaging targets. These dyes were chosen because their absorbance spectra were similar to those of Hb and HbO$_2$ (Fig. 3.23). Furthermore, these dyes were used instead of blood in the phantom targets because it is much more challenging to prepare and maintain oxygenated and deoxygenated blood samples during an experiment. However, studies using blood phantoms are possible with the current experimental setup and may be conducted before clinical trials of the G3 device.
Figure 3.18: The experimentally-determined gain curves for the image intensifier for the 500 and 800 MCP settings (left and right, respectively). Since the gain for the 800 MCP setting decreases more quickly over a small voltage difference, it is expected to produce signals that better approximate δ-functions for the Dirac comb. Also, the gain intensity is zero for positive photocathode voltages, which allows the spacing between the spikes of the Dirac comb.

Figure 3.19: Modeled Dirac combs for the 500 MCP setting where \( V_{DC} = -1 \) V and \( V_{AC} = 0, 0.5, 1, 1.8 \) V, (left to right, respectively, beginning at top). The gain modulation is zero for \( V_{AC} = 0 \) and increases in intensity as \( V_{AC} \) increases.
Figure 3.20: Modeled Dirac combs for the 500 MCP setting where $V_{DC} = 0$ V and $V_{AC} = 0.5, 1, 1.5, 1.8$ V (left to right, respectively, beginning at top). The higher value of $V_{DC}$ allows larger spacings to be generated, better approaching the form for the ideal Dirac comb.

Figure 3.21: Modeled output at the 500 MCP setting where $V_{DC} = 1$ V and $V_{AC} = 1.25, 1.5, 1.75, 1.8$ V (left to right, respectively, beginning at top). Qualitatively, the setting where $V_{AC} = 1.8$ V generates the best approximate Dirac comb.
Figure 3.22: Modeled output at the 800 MCP setting where $V_{DC} = 1$ V and $V_{AC} = 1.25, 1.5, 1.75, 1.8$ V (left to right, respectively, beginning at top). Just as for the 500 MCP setting, the setting where $V_{AC} = 1.8$ V gives qualitatively the best approximation to the ideal Dirac comb.

3.4.2 Transillumination

As mentioned previously in §1.2.2, transillumination, or diaphonography, was used as an imaging technique in the early development of optical imaging. Although the G3 device is designed for tomographic imaging, it can also perform transillumination studies. A number of diagnostic studies were performed under this imaging mode to evaluate the validity of the phantom imaging experiments.

Unlike other devices that employ traditional transillumination techniques, the G3 imager and FS experimental setup include a large number of sources and detectors. One method for transillumination with this setup is to scan through the sources and record the image for each step. Then, using the preprocessing infrastructure, we obtain the AC, DC amplitudes and phase per pixel. Because of the high density of the laser sources, the resulting data may be viewed on a computer as a “movie” which resembles footage of the imaged targets backlit with a movable source. For qualitative evaluations, the recorded amplitudes per pixel may also be averaged over all of the sources. The latter method was used to evaluate the performance of the imaging targets and both methods were used to evaluate the absorption and scattering contrast for these targets. Results from these evaluations are given in §4.2.

New targets

First, a series of experiments were conducted using the FS setup to test the newly-designed target chambers (or targets) described in §3.2. To begin, the targets were titrated with the same Intralipid solution used in the background for the liquid phantom. This Intralipid-nigrosin solution, henceforth referred to as the “standard solution,” has optical properties: $\mu_a = 0.041$ cm$^{-1}$ and $\mu'_s = 7.5$ cm$^{-1}$. The targets where mounted in opposing quadrants of the FS tank, as shown in Fig. 3.24.

After examining their optical transparency, these targets were used in absorption and scattering studies with solutions that differed from the standard solution in the slab background. Results for the optical transparency experiments may be found in §4.2.

Single-source transillumination

It is useful also to examine “single-source” transillumination whereby the images are not averaged, but analyzed for the single pixel closest to the location of the light source as it is scanned across the source plate.
The data for each of the 209 sources may then be combined to give a low-resolution image of the scattered light at each source. This experiment was conducted in the G3 breast tank with a liquid slab phantom created with the standard solution (or baseline slab). An image target was then filled with a solution with three times the scattering as the background ($\mu_s' = 22.5 \text{ cm}^{-1}$) and the same absorption. The target was mounted in the top right of the viewing rectangle formed by the source plate and the preprocessing analysis was performed on the images obtained. This then gave the single-source transillumination images for the difference in AC amplitude from the two experiments. The target could be identified in all three laser wavelengths tested (785, 808, and 830 nm). The images are included also in §4.2.

### Absorption and scattering contrast

After examining the efficacy of the new imaging targets, we carried out a series of experiments in the FS setting using different absorption and scattering contrast. The positions of the targets were similar to those in the experiments for testing the new imaging targets (Fig. 3.10).

For one such experiment, the target on the lower left (when viewed along the impinging laser beam) was filled with Intralipid solution with twice the absorption ($\mu_a = 0.082 \text{ cm}^{-1}$) than that of the standard solution and otherwise the same scattering ($\mu_s' = 7.5 \text{ cm}^{-1}$). The target on the upper right was filled with a solution that has twice the scattering ($\mu_s' = 15 \text{ cm}^{-1}$) and otherwise the same absorption as the standard solution ($\mu_a = 0.041 \text{ cm}^{-1}$). These targets, mounted side-by-side, were studied using “multi-source” transillumination whereby the data from each scanned source were averaged to provide an aggregated image. The images produced are included in §4.2.

### 3.4.3 Other experiments

#### Slab solution

Another experiment using the FS configuration examines the validity of the solution to the photon diffusion equation for the slab geometry (§2.4). In this experiment, the FS tank was filled with the standard solution ($\mu_a = 0.041 \text{ cm}^{-1}$ and $\mu_s' = 7.5 \text{ cm}^{-1}$) to create a homogeneous slab. Data for a cw laser source was then obtained on the CCD (without an image intensifier in this mode). The resulting image may then be normalized and compared to the modeled data for the analytical solution with the same physical parameters (e.g. dimensions, optical parameters for the slab). Such analysis gave the results in §4.2.1.
Another application of the slab solution is to use it to experimentally determine the optical parameters of the slab. Given the analytical solution in §2.3.2, we may fit for $\mu_a$ while supplying the known value for $\mu'_a$. This was implemented in MATLAB using the iterative nonlinear least-squares fitting function. The details and results for this analysis is included also in §4.2.1.
Chapter 4

Results and discussion

In this study, we carried out a series of experiments to examine the imaging capabilities of the G3 device. We began with tests imaging various breast phantoms and image targets, then optimized the components of the imaging system. Since tomographic reconstructions are very computationally intensive, we developed a method using the fast Fourier transform (FFT) to obtain the AC, DC amplitudes and phase from the data using a heterodyne imaging technique (§3.3.1). We also carried out several other imaging studies studying absorption and scattering contrast in the newly-implemented imaging targets (§3.4.2). Lastly, we examined the experimental results for the homogeneous slab geometry and compared them with those predicted by theory. Data from the experiments with absorption and scattering contrast were used for image reconstructions using TOAST (§2.5.4). Ongoing studies aim to improve the accuracy and efficiency of the image reconstructions. Human imaging studies are planned in order to test the device in a clinical setting.

4.1 Optimization results

4.1.1 Imaging system

The calibration experiments were focused on optimizing the components of the heterodyne detection system in the G3 device. We began with signal generation for the Dirac comb in the heterodyning process, which depended on the gain for the image intensifier. We first obtained the gain curves for the image intensifier at the 500 and 800 MCP settings with a series of calibration trials. These were then used to model the signals obtained using different combinations of the cathode AC and DC voltages ($V_{AC}$, $V_{DC}$, respectively) on the image intensifier (§3.4.1). Based on these modeled Dirac combs, we also performed a scan of the parameter space attainable with the electronics of the imaging system.

Due to issues with image noise for the 800 MCP setting on the image intensifier, the 500 MCP setting was chosen for the imaging studies. Using a scan of the cathode DC voltage, we found that the SNR is maximized for the values of $V_{DC} = 0.75 \pm 0.25$ V and $V_{AC}$ corresponding to $-13$ dBm on the instrument (Fig. 4.1). The analytical models for the approximate Dirac combs suggested that changing the modulation frequency for $V_{AC}$ could also affect the SNR of the obtained signal. We performed a study scanning $V_{DC}$ and modulation frequencies from 60 to 85 MHz. However, the results from this study showed that changing the modulation frequency had little effect toward improving the SNR of the obtained data and that the $V_{DC}$ which maximized SNR in the earlier study remained optimal for all available modulation frequencies (Fig. 4.2).

4.2 Transillumination results

New target results

The first goal of the transillumination studies was to validate the use of a new imaging target made of custom-machined Delrin plastic. This replaced the previous image targets that were made of a different and much thicker type of plastic. Using the FS device setup, we imaged the new and old targets simultaneously.
as described in §3.4.2. Using the updated FFT preprocessing method, we obtained the AC, DC amplitudes, and phase information for each source. This data was then averaged for the 209 sources to obtain an aggregate image. The new image target was shown to give much smaller perturbations in AC amplitude and phase (Figs. 4.3, 4.4). Though these results employing transillumination give only a qualitative measure of the effectiveness of the new targets, they were sufficient to validate the use of these targets in subsequent experiments.

**Single-source transillumination results**

The “single-source” transillumination studies on the G3 device allowed us to ensure that the laser, galvanometer-controlled switching system, and imaging system were all operating properly. Following the steps outlined in §3.4.2, the aggregated image gives a very low resolution mosaic of the target image (Fig. 4.5). Despite the very low resolution, the image target was clearly identifiable for lasers at all three wavelengths.

**Multi-source transillumination results**

After optimizing the instruments and testing the new targets, we used multi-source transillumination (averaging method) to check the scattering and absorption contrast available for the G3 device. For these experiments, we mounted two new targets, each filled with solution that contained Intralipid titrated to twice the absorption and scattering, respectively, of the standard solution for the slab background (§3.4.2). The aggregated transillumination images obtained through the FFT preprocessing (Fig. 4.6) showed that the device has sufficient spatial resolution, even in transillumination using AC amplitude, to identify the imaging targets that are 1 cm² in cross-sectional area. Additionally, through examining the phase information from the preprocessed data (Fig. 4.7), we were also able to distinguish between the more highly absorbing or scattering target.

4.2.1 Slab solution results

**Modeled slab solution**

Following the optimization and transillumination studies, we also performed experiments in the FS setup to examine the validity of the slab solution from DOT theory (§2.4). Using known optical parameters of
the standard solution, we modeled the expected transmitted signal for a homogeneous slab with accurate physical parameters for Eq. 2.106 (Fig. 4.8).

Using data collected from the procedure given in §3.4.3, we averaged radial slices of the measured signal and compared it to the modeled slab solution (Fig. 4.9). An interesting feature in Fig. 4.9 is the larger variance for the more intense regions of the obtained image. This result is possible with Poisson statistics and may be due to the photon counting mechanism used in the CCD. Both results show excellent agreement between the observed data for the slab geometry and the modeled solution based on DOT theory.

Optical parameters

For fitting for optical parameters using the slab solution, we first set a threshold for the data at 2% of the maximum intensity (lower data values were comparable in magnitude to the amplitude of the signal noise on the CCD). The fitting routine used the log transformed data (for better convergence). Beginning with the initial guess of $\mu_a = 0.01 \text{ cm}^{-1}$, the iterative fitting function implemented in MATLAB gave the fitted value of $\mu_a, \text{fitted} = 0.0498 \text{ cm}^{-1}$, which is approximately 22% different from the known value for $\mu_a$, ($\mu_a = 0.041 \text{ cm}^{-1}$) in the standard solution (Fig. 4.10). An identical result was obtained using a different initial guess for $\mu_a = 0.1 \text{ cm}^{-1}$ (Fig. 4.11).

4.3 Reconstruction results

Using the experimental methods developed earlier in the study, we obtained computed reconstructions for a single image target immersed in standard solution for the slab geometry (Fig. 4.12). The target is mounted near the middle ($x \equiv 0$) of the midplane ($y = 30 \text{ mm from the source plate}$) and the upper region of the imaging window ($z \equiv 0$). The volume of the slab was reconstructed using methods outlined in §2.5.4 for the concentrations of both nigrosin and Epolight, the experimental analogs of tissue chromophores Hb and HbO2, respectively. From a slice of the reconstructed volume at $y = 30 \text{ mm}$, we can clearly identify the location of the image target using the computed distribution of the concentration of nigrosin (Fig. 4.13). Using the reconstruction for the distribution of Epolight, we may infer the size of the image target along the $y$-direction with the slices at various distances from the source plate (Fig. 4.14). Also for that dye, we may measure the height of the image target using the computed slice in $z$ for the slab. Though these are only

![Figure 4.2: Plot of the SNR for a scan of $V_{DC}$ at different RF modulation frequencies for the image intensifier. $V_{DC} \approx 0.75 \text{ V}$ appears to be the optimal voltage for all 4 frequency settings. The trends of the SNR appear to be similar for the different modulation frequencies.](image-url)
Figure 4.3: Photo of the mounted targets taken through the image intensifier before immersion in the background fluid (left) and the map of the AC amplitude from the aggregated transillumination image (right). The older target is mounted on the upper right and the new target is mounted on the lower left. The new target shows a smaller perturbation in AC amplitude than that of the old target.

preliminary reconstructions, the image target can be clearly identified.

Note also that unlike the results from the transillumination studies (§4.2), which provided only two-dimensional images from the transmission of light, these results are truly tomographic. The images in Fig. 4.14 are slices of a three-dimensional reconstructed volume. However, there are issues facing these reconstructions which concern the computed concentrations and image artifacts. The known concentrations of Epolight and nigrosin are 0.02 and 0.0023 mM/L, respectively, inside the image target. So the computed peak concentrations of 0.0078 and 0.0008 mM/L are approximately one-third of the true concentrations. Current work is underway to resolve these discrepancies in the reconstructed values for the concentrations of the dyes. Another issue being tackled is reducing the amount of image artifacts, which were faintly visible in both Figs. 4.13 and 4.14 and more apparent for a slice in the yz-plane (Fig. 4.15).

4.4 Conclusion

In this study, we set out to optimize and examine the capabilities of the G3 breast imaging device. First, through simple transillumination studies, we examined the performance of the components of the imaging system and newly-designed image targets. Also, using existing data, we made several improvements to the data preprocessing pipeline for image reconstruction. A fast Fourier transform was implemented to improve the preprocessing efficiency, replacing an earlier method using a nonlinear least-squares fit to harmonics. The newly fitted values for the AC and DC amplitude were identical to those from the previous method. The FFT method also provided the power spectrum for the heterodyned signal, which allowed the SNR to be calculated for different experimental settings and facilitated instrument optimization.

Following these calibration studies, we moved on to imaging studies using liquid phantoms and image targets. Using frequency-domain DOT theory, we accurately modeled a homogeneous slab using known optical parameters such as absorption, scattering, and other physical parameters such as the extrapolated zero boundaries. Comparing the results from this model to the preprocessed data for an actual slab, we found that the simulated data agreed, within error, to the experimental values obtained through the FFT. After observing this agreement, we went on to fit for $\mu_a$ for a slab with known optical parameters: $\mu_a = 0.041$ cm$^{-1}$ and $\mu_s' = 7.5$ cm$^{-1}$. Using a nonlinear least-squares fitting routine, we were able to calculate a fitted value of $\mu_a,\text{fitted} = 0.0498$ cm$^{-1}$, which differs by more than 20% from the actual value. This illustrates only a rudimentary method to compute optical properties using theoretical models such as the slab solution. We
also carried out absorption and scattering studies with solutions of synthetic dyes nigrosin and Epolight. Through additional transillumination studies, we found that the device provides adequate resolution to identify image targets \( \sim 1 \text{ cm}^2 \) in cross-sectional area.

Once the system was fully optimized and new image targets successfully implemented, we collected data for tomographic image reconstructions. We successfully obtained initial tomographic reconstructions for the concentrations of the optical dyes nigrosin and Epolight used to simulate tissue chromophores Hb and HbO\(_2\), respectively. The images demonstrated excellent spatial resolution in the dimensions perpendicular to the axis pointing from the source plate to the detector plane. However, the computed values for the concentrations of dyes are smaller than the known values for the solution in the image target. Moreover, the resolution is poorer in the direction parallel to the source-detector axis and some regions of the reconstruction volume contain artifacts. Work is underway to investigate the difference in the computed concentrations and to reduce the amount of computational artifacts in the reconstructed images.

In this study, we successfully calibrated the G3 device, established several experimental techniques for creating and imaging liquid breast phantoms, and obtained preliminary reconstruction results. Imaging studies with human subjects are planned to prepare the device for use in a clinical setting. Though still under development, the G3 device appears to be a promising implementation of DOT for breast imaging.
Figure 4.5: Transillumination images showing ratios of the AC amplitudes for the $3\mu_o$ target vs. that of a homogeneous background. Lasers at three wavelengths (785, 808, 830 nm) gave the results at the top, middle, and bottom, respectively. The titrated target is clearly identifiable in all three images.
Figure 4.6: Image of the mounted targets taken through the image intensifier before immersion in Intralipid solution (left). Aggregated transillumination image of the AC amplitude of the two targets from FFT preprocessing (right). The AC amplitude has been normalized to unity.

Figure 4.7: Image of the mounted targets taken through the image intensifier before immersion in Intralipid solution (left). Aggregated transillumination image of the phase difference, $\phi$, of the two targets through FFT preprocessing (right). This illustrates how the phase information allows targets otherwise identical in AC amplitude to be distinguished. The more absorbing target shows a smaller $\phi$ (given in degrees in the colormap) while the scattering target shows a greater value for $\phi$, as expected from DOT theory.
Figure 4.8: Normalized plots of simulated data from the homogeneous slab solution (using 10 terms in the series in Eq. 2.106; left) and the observed data for a homogenous liquid slab phantom (right) with $\mu_a = 0.041 \text{ cm}^{-1}$ and $\mu'_s = 7.5 \text{ cm}^{-1}$. Since the results are radially symmetric, we may take axial slices to further evaluate the validity of the data (Fig. 4.9).

Figure 4.9: Cross section of the analytical solution for the slab geometry (denoted $|G|$ in legend) and the observed data averaged over four slices (in different perpendicular directions) from the center. The data agrees, within experimental error, with the analytical solution.
Figure 4.10: Plot of log transformed data (blue) and iterative solutions (dashed) obtained by the fitting function. Fitting for $\mu_a$, the lower and upper bounds for its estimate were set to 0 and 0.1 cm$^{-1}$, respectively. The initial guess for the algorithm was $\mu_{a,0} = 0.01$ cm$^{-1}$, which gave the values of $\mu_{a, \text{fitted}} = 0.01, 0.0321, 0.0451, 0.0493, 0.0498$ cm$^{-1}$ after each iteration (plotted, beginning at the top), terminating at the last fitted value where the step size exceeded the tolerance value from the fitting algorithm.

Figure 4.11: Plot of log transformed data (blue) and iterative solutions (dashed) obtained by the fitting function. Fitting for $\mu_a$, the lower and upper bounds for its estimate were set to 0 and 0.1 cm$^{-1}$, respectively. A different initial guess for the algorithm of $\mu_{a,0} = 0.100$ cm$^{-1}$ gave the values of $\mu_{a, \text{fitted}} = 0.100, 0.0633, 0.0517, 0.0498$ cm$^{-1}$ after each iteration (plotted, beginning at the bottom), terminating at the last fitted value, same as the result shown in Fig. 4.10.
Figure 4.12: Photo of the image target mounted in the breast tank used for reconstructions. The tank is filled only halfway with the standard solution here to show the location of the target.

Figure 4.13: Reconstruction image showing the concentration of nigrosin at distance of $y = 30$ mm from the source plate. The vertical distance from the known location of the image target is given by $z$ while $x$ denotes the horizontal distance from the center of the slab. The target is clearly distinguishable in this image where the concentration of nigrosin peaks at 0.0078 mM/L.
Figure 4.14: Reconstructed slices showing the concentration of Epolight at distances of $y = 30.0$, 41.6, 49.4, and 55.2 mm from the source plate, respectively, beginning at the top. The target is easily located for the slice in the midplane (30 mm in the slab) by the high concentration of Epolight, which peaks at $\approx 0.0008$ mM/L. The shape of image target may be inferred by the decreasing concentrations of the Epolight at greater distances from the source plate. Note also the appearance of several image artifacts from the reconstruction distributed in the homogeneous portions of the slab.
Figure 4.15: Slice (yz-plane) of the reconstructed slab at the $x = 21.8$ mm position. The image target is clearly identifiable at the $(y = 30, z = 0)$ position. Also noticeable in this slice of the reconstructed voxels are artifacts in the upper left and middle right.
Bibliography


