NON-INVASIVE IMAGING OF BREAST CANCER WITH DIFFUSING NEAR-INFRARED LIGHT

Soren D. Konecky

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Arjun G. Yodh
Supervisor of Dissertation

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Ravi K. Sheth
Graduate Group Chairperson
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Soren D. Konecky
Dedication

To everyone who reads this thesis.
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Abstract

Non-Invasive Imaging of Breast Cancer with Diffusing Near-infrared Light

Soren D. Konecky
Arjun G. Yodh

Diffuse optical tomography (DOT) is a new medical imaging technique that combines biomedical optics with the principles of computed tomography. We use DOT to quantitatively reconstruct images of complex phantoms with millimeter sized features located centimeters deep within a highly-scattering medium. A non-contact instrument is employed to collect large data sets consisting of greater than $10^7$ source-detector pairs. Images are reconstructed using a fast image reconstruction algorithm based on an analytic solution to the inverse scattering problem for diffuse light. We also describe a next generation DOT breast imaging device for frequency domain transmission data acquisition in the parallel plate geometry. Frequency domain heterodyne measurements are made by intensity modulating a continuous wave laser source with an electro-optic modulator (EOM) and detecting the transmitted light with a gain-modulated image intensifier coupled to a CCD. Finally, we acquire and compare three-dimensional tomographic breast images of three females with suspicious masses using DOT and Positron Emission Tomography (PET). Co-registration of DOT and PET images is facilitated by a mutual information maximization algorithm. We also compare DOT and whole-body PET images of 14 patients with breast abnormalities. Positive correlations are found between both total hemoglobin concentration and tissue scattering, and fluorodeoxyglucose ($^{18}$F-FDG) uptake.
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Chapter 1

Introduction

Imaging has become an indispensable tool of modern medicine. It permits physicians to see inside the human body non-invasively (i.e. without having to cut it open). Godfrey Hounsfield revolutionized medical imaging in the early 1970’s by introducing the first X-ray computed tomography (CT) scanner. By shooting X-ray photons through a patient’s head from multiple directions, the device enabled Hounsfield to reconstruct cross-sectional images representing the spatially varying absorption of X-rays by different regions inside the skull and brain. Since then, the field of medical imaging has seen explosive growth, and many new imaging modalities have been developed. Ultrasound imaging probes tissue with high frequency sound waves and detects the sound that is reflected back to the surface. In Magnetic Resonance Imaging (MRI), tissue placed in a strong magnetic field is probed with radio-waves. Single Photon Emission Computed Tomography (SPECT) and Positron Emission Tomography (PET) detect the gamma ray photons emitted from radioactively tagged pharmaceuticals which are injected into or inhaled by the patient. While all of these modalities use different forms of energy, and are sensitive to different types of biological contrast, they all enable experimenters and clinicians to reconstruct maps of the interior properties
of the body. In this thesis, I will describe my research on a relatively new medical imaging modality called Diffuse Optical Tomography (DOT), which uses near-infrared light to form images of the interior of the body.

Like medical imaging, biomedical optics is a rapidly expanding field which is providing biologists and clinicians new ways to detect, diagnose, and study disease. Laser scanning confocal microscopy provides high resolution, depth resolved, three-dimensional images. Techniques such as two-photon fluorescence microscopy and second harmonic generation microscopy, whose dependence on the applied light intensity is non-linear, achieve even higher resolution and deeper penetration into tissues. Optical coherence tomography (OCT) forms cross-sectional images of tissue scattering by detecting the interference between backscattered light from the sample and light from a reference beam. While these techniques are all extremely useful, they have a common limitation. They can only be used to image tissue near the surface. Confocal microscopy penetrates up to depths of about 50 $\mu$m. Two-photon microscopy allows one to look slightly deeper, up to hundreds of micrometers. OCT goes even deeper, but only to depths of at most 2-3 mm in highly scattering tissue.

The two principle obstacles to looking deep into tissue with visible light are the high degree of light absorption and scattering by tissue. There exists however, a spectral region in the near-infrared (NIR) where the absorption of light by tissue is relatively low. As can be seen in Fig. 1.1, the absorption of light by oxy- and deoxy-hemoglobin drops dramatically at around 600 nm. Likewise, the absorption of light by water is very low through wavelengths up to around 900 nm. As a result, there is a window in the NIR from about 650-950 nm where light can penetrate more deeply into tissue. Indeed, much work as been done using NIR light with the techniques mentioned in the previous paragraph in order to maximize their penetration depth. However, the
Figure 1.1: Spectra of the principal absorbers of near-infrared light in tissue.

second obstacle, the high degree of light scattering, prevents the use of any of the above techniques to a few millimeters. The mean free path of visible light in tissue is only about $100 \ \mu m$, and multiple scattering events will cause the direction of the average photon to be randomized after about 1 mm. Thus techniques which rely on ballistic or quasi-ballistic light are inherently limited in depth.

Note, the problem is not that NIR light cannot penetrate deeply into tissue. It does. For example, NIR light transmitted through 10 cm of human breast tissue can be detected. The problem is that beyond a few millimeters deep, almost all of the remaining photons will have been scattered multiple times, and their directions will be random. Thus, in order to acquire information about tissues deep below the surface, a method is needed which permits this information to be extracted from detected photons which have been scattered many times. This is the goal of the diffuse optical method.

The key observation behind diffuse optical methods is that the paths of NIR photons in tissue
can be described as a random walk with a step length equal to the distance over which their directions become randomized. As mentioned above, this distance is about 1 mm in human breast tissue. As a result, if experiments are performed over distances much greater than the step length, the propagation of the NIR photons can be modeled by a diffusion equation (see Chapter 2). With an accurate model of how the light propagates, experimenters can then use the light they detect, to gain information about the tissue through which it has passed, including the concentration of absorbing chromophores such as oxy- and deoxy-hemoglobin, the amount of light scattering, and the concentration and lifetime of exogenous fluorophores.

By adapting the ideas of X-ray CT, one can also use diffusing light to reconstruct images of the spatially varying optical properties of tissue. In X-ray CT, X-rays are shot through the sample along multiple lines. Almost all the X-ray photons will either travel along a straight line to a detector, or be absorbed by the sample. Detectors on the opposite side of the sample detect the X-rays which are not absorbed. If all the lines are parallel, the result will only reveal the total absorption of the sample along one direction. However, by detecting X-rays from multiple directions, a cross sectional image of X-ray absorption can be derived (Fig. 1.2).

Diffuse optical tomography uses this same idea of shooting photons through the sample from multiple directions. However, unlike X-rays, NIR photons do not travel in straight lines through tissue. Instead they diffuse through the tissue. As will be shown in Chapter 2, by using the diffusion model one can determine the most likely volume through which detected photons have traveled. If many measurements are made corresponding to different volumes within the tissue, a three-dimensional image of optical properties can be reconstructed.

A significant portion of DOT research is devoted to the detection and characterization human breast lesions [30,42,43,72,81–83,88]. Unlike X-ray CT, PET and SPECT, DOT uses non-ionizing
Figure 1.2: X-rays are sent through a sample consisting of two X-ray absorbers. If only the vertical direction is used, the measured attenuation will reveal only one absorber. An additional measurement in the horizontal directions will reveal two separate absorbers. By sending X-rays through the sample from many directions, a cross sectional map of X-ray absorption can be reconstructed.

radiation which presents no risk to the patient. DOT is relatively inexpensive (e.g. MRI scanners cost millions of dollars and require expensive maintenance as well), and DOT also acquires information about tissue that is different from other modalities, such as hemoglobin concentrations and light scattering. As will be discussed in Chapter 5, its ability to acquire physiological information non-invasively and inexpensively make DOT well suited for monitoring and predicting the outcome of cancer therapy [24, 51, 119].

While initial studies exploring the use of DOT for breast imaging have shown potential, significant work remains to be done if DOT is to be successfully translated to a clinical setting. More accurate reconstructed images will require new instrumentation and image reconstruction techniques. In addition, clinical work with breast cancer patients must be performed in which the imaging results are compared with histopathology as well as with other imaging modalities such as X-ray mammography, MRI, ultrasound imaging, and PET. In this thesis, I review my work in
the areas of instrumentation, reconstruction algorithms, and clinical measurements.

In Chapter 2, I present the theory of diffuse light propagation and image reconstruction. The image reconstruction problem in optical tomography is much more difficult than in X-ray CT. As previously mentioned, X-ray photons travel along straight lines. When an X-ray photon is detected, one knows the path along which it traveled (i.e. a straight line between source and detector). In the case of near-infrared photons, which diffuse through tissue, one only knows the relative probability that a photon passed through a particular location. In addition, with X-rays, the paths of the photons are determined solely by the geometry of the scanner. With near-infrared light the photon paths also depend on the tissue optical properties we are trying to determine. This makes the reconstruction problem in DOT non-linear. In Chapter 2, I review the major approaches to modeling diffuse light transport in tissue and image reconstruction.

Chapter 3 is concerned with experiments we performed to validate new image reconstruction techniques. Large three-dimensional problems, such as human breast imaging, have a substantial computational burden. Most researchers attempt to solve the image reconstruction problem with a brute force numerical approach (see sections 2.2.3 and 2.2.7). However, as the number of measurements increases, straightforward approaches quickly become intractable. Recently, reconstruction algorithms have been developed [65–67, 89, 90] which take advantage of symmetry in the measurement geometry to reduce the computational burden. We quantitatively reconstruct images of complex phantoms with millimeter sized features located centimeters deep within a highly-scattering medium. A non-contact instrument is employed to collect large data sets consisting of greater than $10^7$ source-detector pairs. The images are reconstructed using these fast image reconstruction algorithms.

In Chapter 4, I give a detailed description of a next generation breast imager which we have
constructed. The new instrument differs from the previous generation instrument in several respects. In the previous instrument, a CCD array is used to detect the continuous-wave (CW) light intensity transmitted through the breast. The addition of a gain modulated image intensifier in the new instrument allows simultaneous detection of CW intensity, RF amplitude, and phase delay of the transmitted light. In the previous instrument, the laser intensity was individually modulated by modulating the current going through each diode laser. In the new instrument stable CW lasers are used, and the light intensity is modulated with an electro-optic modulator. The new instrument is built using a breast biopsy bed, allowing better positioning of the breast in the scanner. Finally, a rotating stage in the new instrument, allow the breast to be imaged in multiple orientations facilitating comparison of the images with other imaging modalities such as MRI.

Chapter 5 is devoted to clinical work. I show the results from our study comparing DOT and PET for human breast cancer. We acquire and compare three-dimensional tomographic breast images of three females with suspicious masses using Diffuse Optical Tomography (DOT) and Positron Emission Tomography (PET). The reconstructed DOT and PET images are co-registered using a mutual information maximization algorithm. We also compare DOT and whole-body PET images of 14 patients with breast abnormalities. Positive correlations are found between both total hemoglobin concentration and tissue scattering, and fluorodeoxyglucose (\(^{18}\)F-FDG) uptake. In light of these observations, we suggest potential benefits of combining both PET and DOT for characterization of breast lesions.

In Chapter 6, I summarize the preceding chapters and suggest new directions for further research.
Chapter 2

Theory

2.1 Light Propagation in Tissue

2.1.1 Diffusion Equation

The propagation of near-infrared light in highly scattering media such as tissue can be modeled by the diffusion approximation to the radiative transport equation [50, 102]. This diffusion equation, which governs the electromagnetic energy density $u(r)$ inside the medium, is written in the frequency domain as follows:

$$
\left[-\nabla \cdot D(r) \nabla + c \mu_a(r) + i\omega\right] u(r, \omega) = S(r, \omega).
$$

Here $D(r)$ is the light diffusion coefficient, $c$ is the speed of light in the medium, $\mu_a(r)$ is the optical absorption coefficient, $\omega$ is the temporal frequency, and $S(r)$ is the electromagnetic power density of the light source. The diffusion coefficient satisfies the equation...
where $\mu_s'$ is the reduced scattering coefficient. The reduced scattering coefficient represents the inverse of the random walk step length, $l'$, for photons in the medium. It is related to the scattering coefficient, $\mu_s$, by the equation

$$\mu_s' = \mu_s(1 - g) = (1 - g)/l,$$

(2.3)

where $l$ is the average distance photons travel between scattering events, and $g$ is the anisotropy factor. The anisotropy factor is the average cosine of the angle through which photons are scattered during a single scattering event. It is defined as

$$g = \langle s \cdot s' \rangle = \int (s \cdot s') A(s \cdot s') d^2 s,$$

(2.4)

where $s$ and $s'$ are unit vectors pointing in the incoming and outgoing photon directions, and the phase function $A(s \cdot s')$ is the probability distribution for photon coming in one direction $s$ to be scattering into another direction $s'$. It is normalized to unity (i.e. $\int A(s \cdot s') d^2 s = 1$). By writing the phase function as a function of the angle between $s$ and $s'$, we are assuming there is no preferred scattering direction. This assumption corresponds to spherically symmetric (or randomly orientated) particles. When the phase function is constant (i.e. isotropic scattering), the anisotropy factor is zero. The anisotropy factor is also zero when the phase function is symmetric about $\pi/2$.

For the case of near-infrared light in tissue, most of the light is scattered in the forward direction, and $g$ is positive (i.e. $\sim 0.9$). When $g$ is negative, most of the light is scattered in the backwards direction.
The diffusion approximation is valid when $\mu_a \ll \mu'_s$ and the distance between sources and detectors is much greater than the random walk step length (i.e. $d \gg l'$). For near-infrared light in human breast $\mu_a \sim 0.05 \text{ cm}^{-1}$, $l \sim 100 \mu\text{m}$, $g \sim 0.9$, $l' \sim 1 \text{ mm}$, and $\mu'_s \sim 10 \text{ cm}^{-1}$. Depending on the experimental geometry, the distances between sources and detectors typically range from 1 to 10 cm. Thus we expect the diffusion equation to be valid in our breast imaging applications.

To derive unique solutions, the diffusion equation (2.1) must be supplemented by a boundary condition. In an infinite medium we only require that the electromagnetic energy density goes to zero as we move far from any sources. However, in all cases of interest (i.e. in tissue), there will be a boundary satisfying the following condition:

$$ u + \ell \nabla u \cdot \hat{n} = 0 \, .$$

(2.5)

Here $\ell$ is the extrapolation distance [4,44,50], and $\hat{n}$ is the outward unit vector normal to the surface of the medium. If there is an index of refraction mismatch at the boundary the extrapolation distance is modeled as $\ell = D/(c \alpha(n))$. Here $\alpha$, which is of order 1, depends on the index of refraction mismatch $n$ on the boundary, and accounts for the internal reflection of diffusing photons at the boundary. (See appendix A of this chapter for a derivation of the boundary condition 2.5 and $\alpha(n)$.)

Once the diffuse equation has been solved, one can combine Fick’s rule with equation (2.5) to predict the electromagnetic energy leaving the medium along the outward normal at a given point on the surface [5].

$$ J(r, \hat{n}) = -D\nabla u(r) \cdot \hat{n} = \frac{D}{\ell} u(r) = c \alpha(n) u(r) \, .$$

(2.6)
Here $J(r, \hat{n})$ is the component of the electromagnetic current density flowing in the direction of the outward normal $\hat{n}$ at a position $r$ on the surface.

### 2.1.2 Analytical Solutions

In a homogeneous medium with an isotropic point source, the diffuse equation can be written as a Helmholtz equation.

$$[\nabla^2 + k_0^2] G(r, r') = -\frac{1}{D} \delta(r - r')$$

where

$$k_0 = \frac{-c \mu_a + i \omega}{D}.$$  \hspace{1cm} (2.8)

When the medium is infinite, the Greens function for this equation is well known.

$$G(r, r') = \frac{e^{ik_0|r-r'|}}{4\pi D|r - r'|}.$$  \hspace{1cm} (2.9)

However, it is instructive to derive this result here (which is also derived in standard mathematical physics texts such as [3]), as we will use a similar approach when solving the diffuse equation in the presence of boundaries. The approach we use is to diagonalize the diffusion operator by decomposing it into plane waves. The Greens function is written as

$$G(r, r') = \frac{1}{(2\pi)^3} \int d^3k \ g(k) \ e^{ik \cdot (r-r')}.$$  \hspace{1cm} (2.10)

Each Fourier component $g(k)$ gives the amplitude and phase of each plane wave. Substituting equation (2.10) into equation (2.7), and taking advantage of the orthogonality of the plane waves, one gets the following algebraic equation for Fourier components (see Appendix B):
\[ g(k) = \frac{-1}{D} \frac{1}{k_0^2 - k^2} \]  \hspace{1cm} (2.11)

For the case of an infinite medium, the integral (2.10) can be solved analytically. Substituting the solution (2.11) back into (2.10) yields the expected result:

\[
G(r, r') = \frac{1}{(2\pi)^3 D} \int \frac{e^{ik \cdot (r-r')}}{k^2 - k_0^2} d^3 k
\]

\[
= e^{ik_0 |r-r'|}
\]

\[
= \frac{1}{4\pi D |r-r'|}. \hspace{1cm} (2.12)
\]

In the presence of boundaries, the diffusion operator can no longer be diagonalized by plane waves. However, similar arguments can be used to make the diffusion operator block diagonal when the boundary conditions allow for symmetries. For the semi-infinite, slab, cylindrical, and spherical geometries, simple formulas can the be derived for the Fourier components of the Greens functions. Here we will derive the solutions for the more experimentally relevant semi-infinite and slab geometries. These results, along with analogous ones for the cylindrical and spherical geometries, can be found in [66]. We define \( r = (\rho, z) \) where the variable \( z \) represent the depth in the medium and \( \rho \) points parallel to the surface(s), and the conjugate Fourier variable \( k = (q, k_z) \) (Fig. 2.1). The Helmholtz equation can be written as:

\[
(\nabla_\rho^2 + \frac{\partial^2}{\partial z^2} + k_0^2)G(r, r') = -\frac{1}{D_0} \delta(r - r'). \hspace{1cm} (2.13)
\]

Since there is no longer translation symmetry in the \( z \) direction, we can only expand the Greens
function in plane waves along $\rho$. This expansion appears as

$$G(\mathbf{r}, \mathbf{r'}) = \frac{1}{(2\pi)^2} \int d^2 q \, g(q, z, z') e^{i\mathbf{q} \cdot (\mathbf{r} - \mathbf{r}')} , \quad (2.14)$$

where $g(q, z, z')$ gives the amplitude and phase of each plane wave. Substituting into the Helmholtz equation and utilizing orthogonality yields a one-dimensional differential equation for each value of the continuous variable $q$.

$$\left( \frac{\partial^2}{\partial z^2} - (q^2 - k_0^2) \right) g(q, z, z') = \frac{-1}{D} \delta(z - z') . \quad (2.15)$$

Equation (2.15) can easily be solved by standard methods as follows. For each value of $q$ the analytic solution will have the form:

$$g_<(q, z, z') = Ae^{-Qz} + Be^{Qz} \quad \text{for } z < z'$$

$$g_>(q, z, z') = Ce^{-Qz} + De^{Qz} \quad \text{for } z > z'$$

(2.16)
where \( Q = q^2 - k_0^2 \). We solve for the four constants by imposing four conditions. First, the solution must obey the boundary conditions of the diffusion equation for the semi-infinite (or slab) geometry. This gives the conditions one and two. In addition, \( g(q, z, z') \) must be continuous at \( z = z' \) so that its second order derivative exists there. This gives condition three. Finally, its first order derivative must be discontinuous at \( z = z' \). This can be seen by integrating equation (2.15) with respect to \( z \) over the small interval \([z' - \epsilon, z' + \epsilon]\) and taking the limit as \( \epsilon \to 0 \). This gives

\[
\lim_{\epsilon \to 0} \int_{z' - \epsilon}^{z' + \epsilon} \left( \frac{\partial^2}{\partial z^2} - (q^2 - k_0^2) \right) g(q, z, z') \, dz = \lim_{\epsilon \to 0} \int_{z' - \epsilon}^{z' + \epsilon} -\frac{1}{D} \delta(z - z') \, dz = -\frac{1}{D} .
\]

(2.17)

Since, \( g(q, z, z') \) is continuous, the zero order term goes to zero. This leaves

\[
\lim_{\epsilon \to 0} \int_{z' - \epsilon}^{z' + \epsilon} \frac{\partial^2}{\partial z^2} g(q, z, z') \, dz = \lim_{\epsilon \to 0} \frac{\partial}{\partial z} g(q, z, z') \bigg|_{z' - \epsilon}^{z' + \epsilon} = -\frac{1}{D} .
\]

(2.18)

where I have integrated by parts. Thus, the four conditions are:

1. \( g_<(q, 0, z') - \ell \frac{\partial}{\partial z} g_<(q, 0, z') = 0 \)
2. \( g_>(q, L, z') + \ell \frac{\partial}{\partial z} g_>(q, L, z') = 0 \) (slab of thickness \( L \))
   \( g_>(q, \infty, z') < \infty \) (semi – infinite)
3. \( g_<(q, z', z') = g_>(q, z', z') \)
4. \( \frac{\partial}{\partial z} g_>(q, z', z') - \frac{\partial}{\partial z} g_<(q, z', z') = -1/D .\)

(2.19)

Solving the algebraic equations for A,B,C, and D gives the solutions for \( g(q, z, z') \) for the
semi-infinite and slab geometries.

\[ g_{\text{semi}}(q; z, z') = \frac{1}{2QD} \left\{ \frac{Q\ell - 1}{Q\ell + 1} e^{-Q|z+z'|} + e^{-Q|z-z'|} \right\} \]  

(2.20)

\[ g_{\text{slab}}(q; z, z') = 
\frac{[1 + (Q\ell)^2] \cosh[Q(L - |z - z'|)] - [1 - (Q\ell)^2] \cosh[Q(L - |z + z'|)]}{2DQ \sinh(QL) + 2Q\ell \cosh(QL) + (Q\ell)^2 \sinh(QL)} \\
+ \frac{2Q\ell \sinh[Q(L - |z - z'|)]}{2DQ \sinh(QL) + 2Q\ell \cosh(QL) + (Q\ell)^2 \sinh(QL)} \]  

(2.21)

For most applications, either \(z\) or \(z'\) is located on the surface of the scattering medium. (It does not matter if its \(z\) or \(z'\) that's on the surface.) In this case equations (2.20) and (2.21) take a somewhat simpler form.

\[ g_{\text{semi}}(q; z, z') = \frac{\ell}{D} \frac{e^{-Q|z|}}{Q\ell + 1} \]  

(2.22)

\[ g_{\text{slab}}(q; z, z') = \frac{\ell}{D} \frac{\sinh[Q(L - |z - z'|)] + Q\ell \cosh[Q(L - |z + z'|)]}{\sinh(QL) + 2Q\ell \cosh(QL) + (Q\ell)^2 \sinh(QL)} \]  

(2.23)

2.1.3 Extrapolated Boundary Solutions

In the preceding section we derived solutions to the diffusion equation with boundaries for simple geometries. These solutions are exact, but appear in the form of an integral, which must be computed numerically to give an answer in real space. They will play a central role in the inversion formulas presented later. It is also possible to compute approximate analytic solutions directly in real space. The most common approach is [4,44] to use an “extrapolated boundary condition.” According to this approach, one starts with the boundary condition (2.5) which specifies the gradient of the electromagnetic energy density at the surface. One then makes the approximation that the
rate at which the electromagnetic energy density decreases remains constant outside of the scattering medium. With this approximation, the electromagnetic energy density \( u(r) \) becomes zero at an extrapolated boundary that is a distance \( \ell \) from the actual boundary of the scattering medium. One can then use the method of images to construct sources and sinks that force the electromagnetic energy density to be zero at the extrapolated boundary. In order to be consistent with the diffusion approximation, the laser source directed at a point on the medium surface, is modeled as an isotropic point source located one random walk step length beneath this point on the surface \( (z_s = 1/\mu_s') \). This requires an isotropic sink of equal magnitude to be placed a distance \( 2\ell + 1/\mu_s' \) outside the surface (Fig. 2.2). For the semi-infinite geometry, this is the only sink required to satisfy the boundary condition. For the the slab geometry, an infinite number of sources and sinks are required to satisfy the boundary conditions at both surfaces. The general solution appear as:

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

\[
r_{+,m} = \sqrt{\left(\rho - \rho_s\right)^2 + \left(z - z_{+,m}\right)^2}
\]

\[
r_{-,m} = \sqrt{\left(\rho - \rho_s\right)^2 + \left(z - z_{-,m}\right)^2}
\]

(2.24)

where \( z_{+,m} = 2m(L + 2\ell) + z_s, z_{-,m} = 2m(L + 2\ell) - 2\ell - z_s, m = 0, \pm 1, \pm 2, \ldots \), and \( L \) is the thickness of the slab. For the semi-infinite geometry, only the \( m = 0 \) term is used.
Figure 2.2: Schematic of the extrapolated boundary condition. The electromagnetic energy density $u(z)$ is plotted as a function of distance from the surface (dotted line). The extrapolated boundary is located half way between a source and sink such that $u(z)=0$ at the extrapolated boundary.

### 2.1.4 Finite Element Solutions

The analytic solutions to the diffusion equation presented in the preceding sections are accurate and can be calculated extremely quickly. However, they are only valid for homogeneous media, with simple boundaries. The Finite Element Method has become popular in the optical tomography community, because it allows one to solve for the solution of the diffusion equation for arbitrary geometries and optical property distributions [9]. While it requires the inversion of a large matrix, and thus is slower than analytical methods, it is significantly faster than Monte Carlo methods. Finite element methods are important when using non-linear model based reconstructions, where the expected electromagnetic energy density must be computed multiple times with heterogeneous optical properties.

In section 2.1.2 the function specifying the electromagnetic energy density was written as a sum of plane waves which were smooth and had infinite support. With finite element methods, the electromagnetic energy density is approximated as a sum of piecewise linear functions with finite
support such that
\[ u(r) \approx \tilde{u}(r) = \sum_{i} u_i \psi_i(r) \] (2.25)

where \( N \) is the number of nodes in the finite element mesh. Our goal is to find the coefficients \( u_i \) such that the difference between \( u(r) \) and \( \tilde{u}(r) \) is minimized. As explained in Arridge et. al. [9], this leads to the matrix equation

\[
[K(D) + C(c\mu_a) + c\alpha(n)A + i\omega B]u = Q
\] (2.26)

where

\[
K_{ij} = \int_{V} D(r) \nabla \psi_i(r) \nabla \psi_j(r) dV
\] (2.27)

\[
C_{ij} = \int_{V} c\mu_a(r) \psi_i(r) \psi_j(r) dV
\] (2.28)

\[
A_{ij} = \int_{S} \psi_i(r) \psi_j(r) dS
\] (2.29)

\[
B_{ij} = \int_{V} \psi_i(r) \psi_j(r) dV
\] (2.30)

\[
Q_j = \int_{V} \psi_i(r) S(r) dV
\] (2.31)

(See appendix C for a derivation of this matrix equation.) For large 3D problems this matrix equation becomes very large, and is difficult to solve with direct matrix inversion methods. However, the matrices are sparse, and can be efficiently inverted with iterative matrix solvers. In our work we have used linear conjugate gradients (for CW problems), and biconjugate gradients (in the frequency domain) to solve this matrix equation.
2.2 Image Reconstruction

2.2.1 Spectroscopy

For all the image reconstruction methods that will be described in this section, it is crucial to begin with an estimate of the average optical properties of either the medium being imaged, a homogeneous reference medium with similar average optical properties, or both. For an experiment in which the laser sources are intensity modulated in time, three types of data can be collected for each source detector pair per wavelength: the continuous wave light intensity, the frequency domain amplitude of the diffusing photon wave, and the phase delay of the diffusing wave at the detector after passing through the medium. In order to extract the average optical properties of the medium, the data is compared to the predictions of one of the models described in the previous section. The optical properties used in the model are modified until the sum squared difference between measured and predicted data is minimized. As will be described in section 1.2.8, one can make measurements at several different wavelengths. When this is done, one can use the spectral features of absorbing chromophores to fit for their concentrations. In general, the following function must be minimized.

\[
\chi^2(x, \alpha, \beta, \gamma) = \sum_{i}^{N} \left\{ \left( \frac{I_i^{(m)} - \alpha I_i^{(c)}(x)}{\sigma_I} \right)^2 + \left( \frac{A_i^{(m)} - \beta A_i^{(c)}(x)}{\sigma_A} \right)^2 + \left( \frac{\phi_i^{(m)} - \gamma - \phi_i^{(c)}(x)}{\sigma_\phi} \right)^2 \right\} .
\]

Here \( x \) represents the quantities we are solving for (i.e. \( \mu_a, \mu'_a \), and chromophore concentrations). The variables \( \alpha \) and \( \beta \) are scaling factors for the continuous wave intensity and frequency domain amplitude. We must fit for \( \alpha \) and \( \beta \). Likewise \( \gamma \) is a phase offset which we must also fit for. \( N \) is the total number of measurements (i.e. source/detector pairs \( \times \) wavelengths). \( I, A, \) and \( \phi \)
are continuous wave intensity, frequency domain amplitude, and phase delay of the measured and
calculated data. In our next generation breast scanner (see chapter IV) multiple measurements are
made for each source/detector separation distance. The mean values for each separation distance
are used for $I^{(m)}$, $A^{(m)}$, and $\phi^{(m)}$. The standard deviations are used for $\sigma_I$, $\sigma_A$, and $\sigma_\phi$. We
minimize this function using a Newton based minimization algorithm as implemented in the Matlab
function “lsqnonlin.”

2.2.2 Scattering Theory

Given that the average optical properties of a medium are known, we can then attempt to image
spatially dependent perturbations to these properties. In our breast imaging experiments a refer-
cence scan of a homogeneous medium is always performed in addition to the breast scan. As will
be shown below, it is the change in data between these two scans that is used for image recon-
struction. It is also possible to do imaging without a reference scan, in which case the breast scan
is compared directly with simulated data. However, we have found that the use of an experimen-
tally obtained reference scan reduces the effects of systematic errors such as boundary effects and
variable strengths and sensitivities of sources and detectors.

We use perturbation theory to relate the changes in the data to the spatially varying optical
properties. The absorption coefficient $\mu_a(r)$ is decomposed as $\mu_a(r) = \mu_a^{(0)} + \delta \mu_a(r)$. where $\mu_a^{(0)}$ is
the constant value of the absorption coefficient in the reference, while $\delta \mu_a(r)$ represents the spatial
fluctuations. Likewise the diffusion coefficient $D(r)$ is decomposed as $D(r) = D^{(0)} + \delta D(r)$. We
then substitute into the diffusion equation (2.1) with a point source, and pull the $\delta \mu_a$ and $\delta D$ terms
to the right hand side giving:

\[ -D^{(0)} \nabla^2 + c\mu_a^{(0)} - i\omega \] \( G(r_s, r) = \delta(r - r_s) - [c\delta\mu_a(r) - \nabla \cdot \delta D(r) \nabla] G(r_s, r) . \] (2.33)

Equation 2.33 is the diffusion equation for homogeneous media with an additional source term. This extra term can be thought of as the additional source distribution caused by the interaction of the diffusing wave with the perturbations in optical properties. Convolving with the Greens function for homogeneous media results in

\[ G(r_s, r_d) = G_0(r_s, r_d) - \int_V G_0(r, r_d) [c\delta\mu_a(r) - \nabla \cdot \delta D(r) \nabla] G(r_s, r) \, d^3r , \] (2.34)

where the integral is taken over the volume of the sample and \( G_0 \) is the Green’s function in the reference medium with \( \mu_a(r) = \mu_a^{(0)} \) and \( D(r) = D^{(0)} \). \( G_0 \) satisfies Eq. (2.1) with the substitutions \( \mu_a(r) \rightarrow \mu_a^{(0)} \), \( D(r) \rightarrow D^{(0)} \), and \( S(r) \rightarrow \delta(r - r_s) \). It can be calculated using the any of the methods described in section 1.1. The left-hand side of Eq. (2.34) is directly measurable but \( G(r_s, r) \), which appears in the right-hand side, cannot be measured since the point \( r \) lies inside the medium. Since \( G(r_s, r) \) depends on the optical properties for which we are solving (i.e. \( \delta\mu_a \) and \( \delta D \)), equation (2.34) is nonlinear. The non-linearity can also be seen by expanding equation (2.34) to higher order in \( [c\delta\mu_a(r) - \nabla \cdot \delta D(r) \nabla] \). This is done by substituting equation (2.34) for \( G(r_s, r) \) on the right-hand side of equation (2.34), and then iterating this process.

One can then use the first Born approximation to transform Eq. (2.34) to an equation which is linear in \( \delta\mu_a \) and \( \delta D \). In the first Born approximation we set \( G(r_s, r) = G_0(r_s, r) + \phi_{sc}(r_s, r) \) where \( \phi_{sc} \) is the scattered field due to the changes in the optical properties. We then assume that \( \phi_{sc} \ll G_0 \) and let \( G(r_s, r) \rightarrow G_0(r_s, r) \) in equation (2.34). Another approximate linear
equation for $\delta \mu_a$ and $\delta D$ is the first Rytov approximation. In the Rytov approximation we let

$$G(r_s, r) = \exp(\psi_0(r_s, r) + \psi_{sc}(r_s, r)).$$

One must then make the assumption that $\nabla \psi_{sc}(r_s, r)$ is small compared to the perturbations in the optical properties (i.e. the scattered field must change slowly). The first Rytov approximation appears as

$$\ln \left( \frac{G(r_s, r_d)}{G_0(r_s, r_d)} \right) = \frac{1}{G_0(r_s, r_d)} \int_V G_0(r, r_d) \left[ c\delta \mu_a(r) - \nabla \cdot \delta D(r) \nabla \right] G_0(r, r) \, d^3r. \quad (2.35)$$

(For a derivation of equation (2.35), see appendix D.) Let us define the data function as

$$\phi(r_s, r_d) = -G_0(r_s, r_d) \ln \left[ T(r_s, r_d) \right], \quad (2.36)$$

where $T(r_s, r_d) \equiv \Phi(r_s, r_d)/\Phi_0(r_s, r_d)$ is the experimentally measurable transmission function. For a continuous-wave measurement, $\Phi$ and $\Phi_0$ are just the measured light intensities for the breast and reference measurements. They are related to the Greens function by $\Phi = C_s C_d G$ where $C_s$ and $C_d$ are coupling coefficients that account for the relative strengths of the sources and sensitivities of the detectors. For frequency domain measurements $C_s$ and $C_d$ are in general complex to account for phase offsets in addition to coupling efficiencies. Note that

$$T(r_s, r_d) = \frac{\Phi(r_s, r_d)}{\Phi_0(r_s, r_d)} = \frac{(C_s C_d) G(r_s, r_d)}{(C_s C_d) G_0(r_s, r_d)} = \frac{G(r_s, r_d)}{G_0(r_s, r_d)}, \quad (2.37)$$

so that we do not need to know the coupling coefficients as long as a proper reference measurement is made. For purely notational convenience we define:

$$V(r) = c\delta \mu_a(r) - \nabla \delta D(r) \nabla \quad (2.38)$$
By substituting equations (2.36), (2.37), and (2.38) into equation (2.35) we obtain the following linear integral equation:

$$\phi(r_s, r_d) = \int_V G_0(r, r_d) V(r) G_0(r_s, r) \, d^3 r .$$

(2.39)

The kernel on the right-hand side is known analytically, and the left-hand side $\phi(r_s, r_d)$ is measured experimentally. Equations (2.36) and (2.39) are the main equations of linearized DOT.

### 2.2.3 Numerical Solutions

The most straightforward approach to inverting integral equation (2.39) is to simply discretize the volume into small cubes of volume $h^3$. Equation (2.39) then becomes the matrix equation $Ax = b$ where $A$ is composed of two blocks such that $A = (A^\mu | A^D)$. Letting the $i$’s index source/detector pairs numbered 1 to N, and the $j$’s index volume elements numbered 1 to M, results in [79]:

$$A^\mu_{i,j} = G_0(r_{si}, r_j) G_0(r_j, r_{di}) \, c \, h^3$$

(2.40)

$$A^D_{i,j} = \nabla G_0(r_{si}, r_j) \nabla G_0(r_j, r_{di}) \, c \, h^3$$

(2.41)

$$x_j = \begin{cases} 
\delta \mu_a(r_j) & j = 1 : M \\
\delta D(r_j-M) & j = M + 1 : 2M 
\end{cases}$$

(2.42)

$$b_i = \phi(r_{si}, r_{di}) .$$

(2.43)
This matrix can be inverted by a number of methods including singular value decomposition and the algebraic reconstruction technique [77]. However, for three dimensional problems, this matrix becomes quite large. The number of rows is equal to the number of measurements \( N \). As will be shown in chapter 3, using a lens coupled CCD and galvanometer mirrors it is easy to collect data sets with \( 10^8 \) source detector pairs. If measurements are made with multiple wavelengths and modulation frequencies, then the number of rows of the matrix \( A \) is \( N = \text{source/detector pairs} \times \text{wavelengths} \times \text{modulation frequencies} \). Likewise, the number of columns of \( A \) is \( M = \text{number of voxels} \times \text{number of parameters} \). In our breast imaging experiments, we reconstruct a volume with typical dimensions of 20 cm \( \times \) 20 cm \( \times \) 6 cm. Dividing this volume into volume elements with dimension of 3 mm results in \( 10^5 \) volume elements. As will be described in section 2.2.8, we are interested in solving for many parameters including the concentrations of oxy-hemoglobin, deoxy-hemoglobin, water, lipids, as well as scattering parameters \( A \) and \( b \). Since the matrix is dense, methods for solving large sets of sparse equations will not be helpful. Thus, it is a major challenge for the brute force method described in this section to solve the fully 3D, multi-spectral, multi-frequency, image reconstruction problem.

### 2.2.4 Block Diagonal Integral Equations

One solution to the computational problem in diffuse optical imaging is to take advantage of symmetry in the measurement geometry. In this section we will show that by making the appropriate change of basis, the integral equation (2.39) can be put into block diagonal form, making it possible to solve problems that could not otherwise be solved due to memory constraints and excessive computing times. We put equation (2.39) into block diagonal form by utilizing the analytic solutions to the diffusion equation presented in section 2.1.2. As stated in section 2.1.2, these analytic
solutions have been derived for simple geometries. Here we will concentrate on the semi-infinite and slab geometries, as they are relevant for our experiments. The results, along with results for the the cylindrical and spherical geometries are given in [63].

We begin by substituting the plane wave decomposition of the Greens functions (2.14) into the kernel of equation (2.39) to get the following equation.

\[
\phi(\mathbf{r}_s, \mathbf{r}_d) = \frac{1}{(2\pi)^n} \int d^2 q_s \int d^2 q_d \int d^3 r \ g(q_d, z, z_d) \exp[i \mathbf{q}_d \cdot (\mathbf{r} - \mathbf{r}_d)] \\
\times V(\mathbf{r}) \ g(q_s, z_s, z) \exp[i \mathbf{q}_s \cdot (\mathbf{r}_s - \mathbf{r})] 
\]

(2.44)

We now take the Fourier transform of (2.39) with respect to the source and detector locations on the surface(s). Since we are taking the Fourier transform with respect to discrete source and detector locations, the Fourier transform is defined as:

\[
\tilde{\phi}(\mathbf{q}_s, \mathbf{q}_d) = \sum_{\mathbf{\rho}_s, \mathbf{\rho}_d} \phi(\mathbf{\rho}_d, z_d; \mathbf{\rho}_s, z_s) \exp[i (\mathbf{\rho}_d \cdot \mathbf{q}_d + \mathbf{\rho}_s \cdot \mathbf{q}_s)] . 
\]

(2.45)

Taking advantage of the orthogonality of the plane waves we arrive at a set of one dimensional integral equations (see appendix E)

\[
\tilde{\phi}(\mathbf{q}_s, \mathbf{q}_d) = \int^{z_d}_{z_s} \left[ \kappa_A(\mathbf{q}_s, \mathbf{q}_d; z) \ c \ \delta_{\mu_a}(\mathbf{q}_s + \mathbf{q}_d) + \kappa_D(\mathbf{q}_s, \mathbf{q}_d; z) \ \delta \tilde{D}(\mathbf{q}_s + \mathbf{q}_d) \right] dz 
\]

(2.46)
where

\[
\kappa_A(q_s, q_d; z) = g(q_s; z_s, z)g(q_d; z, z_d) \tag{2.47}
\]

\[
\kappa_D(q_s, q_d; z) = \frac{\partial g(q_s; z_s, z)}{\partial z} \frac{\partial g(q_d; z, z_d)}{\partial z} - q_s \cdot q_d \, g(q_s; z_s, z)g(q_d; z, z_d) \tag{2.48}
\]

\[
\delta \tilde{\mu}_a(q_s + q_d, z) = \int \delta \mu_a(\rho, z) \exp \left[ i \rho \cdot (q_s + q_d) \right] d^2 \rho \tag{2.49}
\]

\[
\delta \tilde{D}(q_s + q_d, z) = \int \delta D(\rho, z) \exp \left[ i \rho \cdot (q_s + q_d) \right] d^2 \rho . \tag{2.50}
\]

Equation 2.46 can be put in a more convenient form by making the change of variables \( q = q_s + q_d \) and \( p = -q_s \). This substitution yields:

\[
\tilde{\phi}(q, p) = \int_{z_s}^{z_d} \left[ \kappa_A(q, p; z) e \, \delta \tilde{\mu}_a(q) + \kappa_D(q, p; z) \, \delta \tilde{D}(q) \right] dz \tag{2.51}
\]

where

\[
\kappa_A(q, p; z) = g(-p; z_s, z)g(q + p; z, z_d) \tag{2.52}
\]

\[
\kappa_D(q, p; z) = \frac{\partial g(-p; z_s, z)}{\partial z} \frac{\partial g(q + p; z, z_d)}{\partial z} + p \cdot (q + p) \, g(-p; z_s, z)g(q + p; z, z_d) \tag{2.53}
\]

\[
\delta \tilde{\mu}_a(q, z) = \int \delta \mu_a(\rho, z) \exp \left[ i \rho \cdot q \right] d^2 \rho \tag{2.54}
\]

\[
\delta \tilde{D}(q, z) = \int \delta D(\rho, z) \exp \left[ i \rho \cdot q \right] d^2 \rho . \tag{2.55}
\]

There is a separate integral equation for each value of \( q \) which corresponds to a block of the main integral equation (2.39). Each block can be inverted independently of all other blocks to find \( \delta \mu_a(q, z) \) and \( \delta D(q, z) \) for all values of \( q \). It is possible at this point to solve each block
numerically. For each block, a finite number of data points can be selected corresponding to
different values of $p$. Each integral equation can then be discretized in the $z$ direction, and solved
numerically in a similar fashion to what was shown in section 2.2.3. Then for each discrete value
of $z$ one can readily perform an inverse Fourier transform on the solutions $\delta \mu_\alpha(q, z)$ and $\delta D(q, z)$
to get solutions in real space. However, as will be shown in the following sections, the integral
equations can also be inverted analytically, without any need to discretize in space at all. The result
will be inversion formulas that give the change in optical properties at specified points in space.

2.2.5 Singular Value Decomposition

Before describing inversion formulas in the next section, it is necessary to give a quick review of
singular value decomposition as it applies to solve sets of one-dimensional integral equations. Let
us assume for a moment that either $\delta \mu_\alpha(r) = 0$ or $\delta D(r) = 0$. Then equation 2.51 takes the form:

$$\phi_p = \int dz K_p(z) f(z) , \quad (2.56)$$

where $p$ indexes the (discrete) measurements and $z$ is a continuous variable. This can be written
using the bra-ket notation as:

$$|\phi \rangle = K |f \rangle . \quad (2.57)$$
Let’s assume we can expand $|\phi >$ and $|f >$ in two orthonormal basis $|m >$ and $|n >$ such that $K$ is diagonal when expanded in terms of these two bases. That is, we write:

$$|\phi > = \sum_i |m_i > < m_i |\phi >$$  \hspace{1cm} (2.58)

$$|f > = \sum_i |n_i > < n_i |f >$$  \hspace{1cm} (2.59)

$$K = \sum_i \sigma_i |m_i > < n_i |$$  \hspace{1cm} (2.60)

This decomposition of the operator $K$ is called a singular value decomposition, and the $\sigma_i$’s are called the singular values. By direct substitution we see that

$$KK^* = \sum_i \sigma_i^2 |m_i > < m_i |.$$  \hspace{1cm} (2.61)

Thus $KK^*$ is diagonal in the $|m >$ basis with real eigenvalues $\sigma_i^2$. Its inverse is:

$$(KK^*)^{-1} = \sum_i \frac{1}{\sigma_i^2} |m_i > < m_i |.$$  \hspace{1cm} (2.62)

Furthermore:

$$K^*(KK^*)^{-1} = \sum_i \frac{1}{\sigma_i} |n_i > < m_i | \equiv K^+,$$  \hspace{1cm} (2.63)

where we have defined the pseudoinverse operator $K^+$. Note that

$$K^+ K = \sum_i |n_i > < n_i | = \sum_i |m_i > < m_i | = KK^+ = I$$  \hspace{1cm} (2.64)
is the identity matrix. The solution

\[ |f> = K^*(KK^*)^{-1}|\phi> \]  \hspace{1cm} (2.65)

is called the pseudoinverse solution and can be shown to be the minimizer of difference between \( K|f> \) and \( |\phi> \) (i.e. \( \|K|f>-|\phi>|^2/2 \)) with the smallest norm [70]. Going back to the original (p,z) basis we have

\[ f(z) = \sum_{r,p} K_r^*(z) (KK^*)^{-1}_{r,p} \phi_p . \] \hspace{1cm} (2.66)

Thus, we can solve integral equation (2.56) by solving the eigenvalue problem of \( KK^* \). The matrix elements of \( KK^* \) are easily calculated analytically. They are:

\[ KK^*_{r,p} = <r|KK^*|p> \]
\[ = \int dz <r|K|z><z|K^*|p> \]
\[ = \int dz K_r(z)K_p^*(z) \] \hspace{1cm} (2.67)

For image reconstruction in optical tomography the function \( K_p(z) \) is either \( \kappa_A \) or \( \kappa_D \) from equations (2.52) and (2.53). These functions are just weighted sums of exponentials, and can be integrated analytically.

If there is more than one unknown function (e.g. \( \mu_a \) and \( D \)), then equation (2.56) becomes:

\[ \phi_p = \int dz \sum_{j=1}^{N} [K_p^{(j)}(z)f^{(j)}(z)] , \] \hspace{1cm} (2.68)

where \( N \) is the number of unknown functions (e.g. \( N = 2 \) if we are solving for both \( \mu_a \) and \( \mu'_a \)).
The pseudoinverse solutions are,

\[ f^{(j)}(z) = \sum_{r,p} K_r^{(j)*}(z) (KK^*)^{-1}_{rp} \phi_p, \quad (2.69) \]

and the matrix elements are,

\[ KK^*_{rp} = \int dz \sum_{j} N K_r^{(j)}(z)K_p^{(j)*}(z). \quad (2.70) \]

Three final observations are in order. First, the formulas (2.66) and (2.69) are analytic in the \( z \) variable. Integration in \( z \) is done analytically when computing the matrix elements of \( KK^* \). It is never necessary to discretize along the \( z \) direction, and the value of \( f^{(j)}(z) \) can be determined at as many points as one chooses without an additional computational burden. Second, although there is a separate formula for each unknown function \( f^{(j)}(z) \), the matrix \( KK^* \) is the same in all of them and its eigenvalue problem needs to be computed only once. Finally, some of the eigenvalues \( \sigma_i^2 \) of \( KK^* \) will be small. Since these small eigenvalues appear in the denominator of \((KK^*)^{-1}\), they will amplify noise in the data function \( \phi \). We ameliorate this problem by discarding the small eigenvalues of \( KK^* \) such that its inverse (equation (2.62)) becomes

\[ (KK^*)^{-1} = \sum_i \Theta(\sigma_i^2 - \epsilon) \frac{1}{\sigma_i^2} |m_i| < m_i. \quad (2.71) \]

where

\[ \Theta(x) = \begin{cases} 1 & x > 0 \\ 0 & x \leq 0 \end{cases} \quad (2.72) \]

and \( \epsilon \) is a small number called the regularization parameter.
2.2.6 Inversion Formulas

We are now in a position to write down a relationship between the Fourier transform of our data, and the perturbation in optical properties. The procedure is simple. Fourier transform the data with respect to the source and detector positions on the surface according to equation (2.45) to make the integral equation (2.39) block diagonal. Solve for $\delta \mu_a(q, z)$ and $\delta D(q, z)$ using singular value decomposition. Take a 2D inverse Fourier transform for each value of $z$ to get the optical properties at that depth. The inversion formulas appear as:

$$\delta \mu_a(r) = \frac{1}{(2\pi)^2} \int d^2q \exp(-i q \cdot \rho) \sum_{r,p} \kappa_A^*(q, r; z) \left[ \kappa \kappa^* \right]^{-1}(q, r, p) \tilde{\phi}(q, p)$$  \hspace{1cm} (2.73)

$$\delta D(r) = \frac{1}{(2\pi)^2} \int d^2q \exp(-i q \cdot \rho) \sum_{r,p} \kappa_D^*(q, r; z) \left[ \kappa \kappa^* \right]^{-1}(q, r, p) \tilde{\phi}(q, p)$$  \hspace{1cm} (2.74)

The computational complexity of the image reconstruction algorithm described in this section is $O(N_q N_p^3)$, where $N_q$ is the number of discrete values of the vector $q$, while $N_p$ is the number of discrete values of $p$ used to invert each one-dimensional equation (2.51). This is the computational cost of inverting the integral operator only. To this one should add the cost of Fourier-transforming the real-space data function and computing $\tilde{\phi}(q, p)$. With the use of the fast Fourier transform, the latter scales as $O(N_q^2 \ln N_q)$. If the same amount of data and the same grid of voxels is used with a purely algebraic image reconstruction method, the computational cost of matrix inversion scales as $O((N_q N_p)^3)$. In the above estimate, we have assumed that the number of measurements is equal to the number of voxels. We thus see that the fast image reconstruction methods exploit the block
structure of the linear operator that couples the data to the unknown function. Instead of inverting a large matrix of size $N_q N_p$, these methods require inversion of $N_q$ matrices of the size $N_p$ each, thus gaining a factor of $N_p^2$ in computation time. We note that reconstructions which utilized data sets of up to $10^7$ source-detector pairs required less than one minute of CPU time on a 1.3GHz workstation.

2.2.7 Model Based Reconstructions

While the inversion formulas presented in the previous section are fast and allow for large data sets, they have several limitations. Most notably they cannot be performed in arbitrary geometries, and the data function is assumed to have finite support when its Fourier transform is taken. In this section I will give a general description of model based reconstructions in which experimental data is compared to data predicted by the diffusion model calculated with the finite element method. The optical properties of the medium are then adjusted in order to minimize a function representing the difference between predicted and measured data. This process is iterated until some criterion is met. This section is organized as follows. I start with a description of non-linear optimization methods. Then I show how these methods can be applied to least-square type problems. Finally, I show how they are implemented in optical tomography. For a more thorough treatment of non-linear optimization I recommend Refs. [36, 71].

Non-linear optimization

Let’s say we are trying to minimize the function $f(x)$, and we have already evaluated $f$ at the point $x^{(k)}$. We want to find a search direction $\delta$ such that $f(x^{(k)} + \delta)$ is minimized. Expanding $f$ to second order gives
$$f(x^{(k)} + \delta) \approx f(x^{(k)}) + \delta^T \nabla f + \frac{1}{2} \delta^T (\nabla^2 f) \delta .$$

(2.75)

Here $\nabla f$ and $\nabla^2 f$ are the gradient and Hessian (matrix of second order partial derivatives) of $f$ evaluated at $x^{(k)}$. The function $f$ is minimized when its gradient is equal to zero. To second order, this occurs when

$$\nabla f + (\nabla^2 f) \delta = 0 .$$

(2.76)

In Newton’s method, one solves matrix equation (2.76) for $\delta$, and updates the parameter $x$ as $x^{(k+1)} = x^{(k)} + \delta$ in order to find $f(x^{(k+1)})$. This process is iterated until (hopefully) the minimum of $f$ is reached. Newton’s method can be modified by adding a line search along the $\delta^{(k)}$ direction at every iteration to find the minimum value of $f$ along that line. In this case, $\delta^{(k)}$ specifies only the update direction, but not its magnitude. In either case, for an arbitrary non-linear function there is no guarantee that $f$ will be smaller at $x^{(k+1)}$ than it was at $x^{(k)}$.

One way to guarantee that we make $f$ smaller is by moving in the opposite direction as the gradient. The search direction is now

$$\delta = -\nabla f .$$

(2.77)

As with Newton’s method, a line search can then be added to find the minimum of $f$ along the $\delta$ direction. When this process is iterated it is known as the Steepest descent method. Unfortunately the steepest descent method is extremely inefficient and slow. Ultimately, we want an optimization algorithm that is both efficient (like Newton’s method) and robust (like Steepest descent). Conjugate gradient methods are known to speed up convergence of steepest descent for many problems.
In conjugate gradient methods, the search direction on the first iteration is simply the steepest descent direction. On all subsequent iterations the new search direction is a linear combination of the steepest descent direction and the old search direction from the previous iteration. That is

\[ \delta^{(k+1)} = -\nabla f^{(k+1)} + \beta^{(k+1)} \delta^{(k)} . \]  

(2.78)

For a positive definite quadratic function, \( \beta^{(k+1)} \) can be chosen to guarantee converge to the minimum in \( N \) steps, where \( N \) is the number of unknowns. For non-linear problems such as found in DOT, there is no such guarantee. Several choices for \( \beta \) are available for non-linear problems. In our work we use the one proposed by Polack and Ribiere [84] according to which

\[ \beta^{(k+1)} = \frac{\nabla f^T (k+1) (\nabla f^{(k+1)} - \nabla f^{(k)})}{\| \nabla f^{(k)} \|^2} . \]  

(2.79)

The clinical breast reconstructions that are shown in chapter 5 were reconstructed using the non-linear conjugate gradient method. Gradient methods are well suited to solving large problems, since there is no need to compute and invert the Hessian as there is in Newton type methods. The Hessian is a \( N \times N \) matrix where \( N \) is the number of unknowns. In our 3D multi-spectral breast reconstructions there are typically \( \sim 10^5 \) unknowns. While it may be possible to reconstruct images by inverting such large matrices implicitly using iterative methods that can be parallelized on large computer clusters [93], we have not been successful in doing so. On the other hand, the non-linear conjugate gradient method only requires the construction of a vector of length \( N \) at each iteration, and there is no matrix to invert.
Least Squares Problems

In model based image reconstruction, the function we seek to minimize is the sum squared difference between measured and predicted data, plus a regularization term (to be discussed later). Such a function can be written as

$$\chi^2(x) = \frac{1}{2} \sum_{i}^{N} \left( \frac{r_{i}^{(m)} - r_{i}^{(c)}(x)}{\sigma_i} \right)^2 + \frac{1}{2} \sum_{i,j}^{M} (L^TL)_{i,j}(x_i - x_i^{(0)})(x_j - x_j^{(0)})$$

$$= \frac{1}{2} r^T r + \frac{1}{2} \| L(x - x^{(0)}) \|^2 . \quad (2.80)$$

Here $r_{i}^{(m)}$ and $r_{i}^{(c)}$ are the measured and calculated data for the $i$'th measurement, $\sigma_i$ is the uncertainty for that measurement, $x$ is the vector of unknowns, and $x^{(0)}$ is a vector representing a priori information about $x$, and $L$ is a regularization matrix. The simplest choice for $L$, called Tikhonov regularization, is to make $L$ a multiple of the identity matrix. In our clinical breast reconstructions, $x^{(0)}$ is chosen to represent the measured average optical properties of the breast.

The Gradient and Hessian of $\chi^2$ are (see appendix F):

$$\nabla \chi^2 = J^T r + L^T L(x - x^{(0)}) \quad (2.81)$$

$$\nabla^2 \chi^2 \approx J^T J + L^T L . \quad (2.82)$$

Here the Jacobian $J$ is the matrix of first order partial derivatives. Equation (2.81) gives the steepest descent direction needed in the non-linear conjugate gradient method. Substituting equations (2.81) and (2.82) into equation (2.76) gives a Newton-like equation.
\[
\begin{align*}
[J^T J + L^T L] \delta &= -[J^T r + L^T L(x - x^{(0)})].
\end{align*}
\] (2.83)

When equation (2.83) is used in conjunction with a “line search” to find the minimum value of \( \chi^2 \) along the \( \delta \) direction on every iteration, it is called a Gauss-Newton method.

**Optimization in DOT**

In order to apply these methods to diffuse optical tomography, all that is left now is to find an efficient way to calculate all the partial derivatives for the Jacobian or Gradient. The most direct way would be to perturb each unknown at each voxel separately, and solve the diffusion equation to determine the change in the data. This would require numerically solving the diffusion equation at least \( N = \text{number of voxels} \times \text{number sources} \sim 10^7 \) times at each iteration for a 3D problem!

The method applied by most researchers in the field is to think of the kernels of the Rytov/Born approximations (equations 2.39 and 2.35) as signifying the change in the data for a given source detector pair with respect to a small change in the optical properties at each location \( \mathbf{r} \). Non-linear optimization in DOT amounts to iteratively solving the Rytov/Born approximation, and updating their kernels at every step.

Let \( P_{i,j} = \log(\Phi_{i,j}^{(c)}) \) and \( M_{i,j} = \log(\Phi_{i,j}^{(m)}) \) be the logarithm of the predicted and calculated data corresponding to source \( i \) and detector \( j \). The partial derivatives with respect to a small change in absorption or scattering in the \( k \)'th voxel appear as

\[
\frac{\partial P_{i,j}}{\partial \mu_a(k)} = -\frac{1}{\Phi(r_i, r_j) G^+(r_j, r_k) \Phi(r_i, r_k)}
\] (2.84)
\[
\frac{\partial P_{i,j}}{\partial \mu_{s(k)}^{i'}} = -3D^2 \frac{1}{\Phi(r_i, r_j)} \nabla G^+(r_j, r_k) \cdot \nabla \Phi(r_i, r_k)
\] (2.85)

Here we have taken advantage of the reciprocity of the Greens functions (i.e. \( G(r_1, r_2) = G^*(r_2, r_1) \)) to define the adjoint Greens function \( G^+(r_2, r_1, \omega) \equiv G(r_1, r_2, \omega) \) as the solution to the adjoint diffusion equation (i.e. equation (2.1) with \( i\omega \rightarrow -i\omega \)) with a delta function source term located at the detector location [7]. In order to compute the entire Jacobian it is now only necessary to compute the forward problem \( N_s + N_d \) times where \( N_s \) and \( N_d \) are the number of sources and detectors respectively. The gradient can actually be calculated by solving the forward problem \( 2N_s \) times [8]. This presents an advantage for situations where there are many more detectors than sources. This situation is common in optical tomography when a lens coupled CCD is used for detection.

In our model based reconstructions, we make the assumption that the uncertainty in each measurement \( \Phi^{(m)} \) is proportional to its magnitude (i.e. \( \sigma_{i,j} \propto \Phi^{(m)}_{i,j} \)). Accordingly, the uncertainty in the logarithm of all measurements \( M_{i,j} \) is equal because \( \sigma_M = \Delta(\log \Phi) \approx \Delta \Phi/\Phi = \text{constant} \). As a result, all terms in our \( \chi^2 \) are weighted equally, and \( \sigma \) can be removed from equation (2.80).

### 2.2.8 Multi-spectral Multi-frequency Reconstructions

Our ultimate goal is not to know merely the optical properties of the tissue we are imaging, but to derive the underlying composition of the tissue which determines these optical properties. To this end, we use multiple wavelengths of light to determine the concentrations of different chromophores in the tissue. We model the total optical absorption of tissue as a weighted sum of the contributions to absorption from different chromophores such as oxy-hemoglobin, deoxy-hemoglobin, water, and lipids. The absorption coefficient is written as:
\[ \mu_a(\lambda) = \sum_l c_l \epsilon_l(\lambda). \]  \hfill (2.86)

Here each \( c_l \) is the concentration of the \( l \)’th chromophore, and \( \epsilon_l(\lambda) \) is the corresponding wavelength dependent extinction coefficient.

We model the wavelength dependence of the reduced scattering coefficient using simplified Mie scattering theory [16, 69]. A scattering prefactor \( A \) depends primarily on the number and size of scatterers, and a scattering exponent \( b \), depends on the size of the scatterers. They are combined as follows:

\[ \mu'_a = A\lambda^{-b}. \]  \hfill (2.87)

In addition to using multiple wavelengths of light, it is also possible to use multiple modulation frequencies. While the optical properties of the medium do not depend on modulation frequency, the diffusive wave number \( k \) (Eqn. 2.8) does. It can be shown that with two modulation frequencies, the inversion formulas present in section 1.2.6 can be used to solve for both the absorption and diffusion coefficients simultaneously [64].

The modifications needed to make any of the above reconstructions formulas multi-spectral and multi-frequency are straightforward. For the model based reconstructions, the Jacobian takes on a block structure, where each block corresponds to a single wavelength, modulation frequency, chromophore combination. Extra columns correspond to the additional unknowns (i.e. the chromophore concentrations, \( A \), and \( b \)). Extra rows correspond to additional measurements at different wavelengths and modulation frequencies. The partial derivatives of the expanded Jacobian can be obtained from equations (2.84,2.86) and (2.85,2.87) by application of the chain rule for partial derivatives. Following Corlu et al. [28] we have
\[
\frac{\partial P_{i,j}(\lambda, \omega)}{\partial c_{l,k}} = \epsilon_l(\lambda) \frac{\partial P_{i,j}(\lambda, \omega)}{\partial \mu_{a(k)}(\lambda)} 
\]
(2.88)

\[
\frac{\partial P_{i,j}(\lambda, \omega)}{\partial A_k} = \lambda^{-b_k} \frac{\partial P_{i,j}(\lambda, \omega)}{\partial \mu'_{s(k)}(\lambda)} 
\]
(2.89)

\[
\frac{\partial P_{i,j}(\lambda, \omega)}{\partial b_k} = -A_k \lambda^{-b_k} \ln(\lambda) \frac{\partial P_{i,j}(\lambda, \omega)}{\partial \mu'_{s(k)}(\lambda)} 
\]
(2.90)

The inversion formulas of section 1.2.6 are also easily modified to solve directly for chromophore concentrations using multi-spectral, multi-frequency data. The integral operator in equation (2.51) is modified almost exactly as the Jacobian is for the model based reconstructions. For notational convenience, I make the substitution \( A \rightarrow 1/\alpha \) in equation 2.87 such that \( D = \alpha \lambda^b/3 \).

I also assume that the scattering amplitude \( b \) is constant. Equation (2.51) is now

\[
\tilde{\phi}(\mathbf{q}, \mathbf{p}) = \int_{z_a}^{z_d} \left[ \sum_l^N \kappa_{c_l}(\mathbf{q}, \mathbf{p}; z) \delta \tilde{c}_l(\mathbf{q}) + \kappa_\alpha(\mathbf{q}, \mathbf{p}; z) \delta \tilde{\alpha}(\mathbf{q}) \right] dz 
\]
(2.91)

where

\[
\kappa_{c_l}(\mathbf{q}, \mathbf{p}; z) = \epsilon_l(\lambda) g(-\mathbf{p}; z, z) g(\mathbf{q} + \mathbf{p}; z, z_d) 
\]
(2.92)

\[
\kappa_\alpha(\mathbf{q}, \mathbf{p}; z) = \frac{\lambda^b}{3} \left[ \frac{\partial g(-\mathbf{p}; z, z)}{\partial z} \frac{\partial g(\mathbf{q} + \mathbf{p}; z, z_d)}{\partial z} + \mathbf{p} \cdot (\mathbf{q} + \mathbf{p}) g(-\mathbf{p}; z, z) g(\mathbf{q} + \mathbf{p}; z, z_d) \right] 
\]
(2.93)

\[
\delta \tilde{c}_l(\mathbf{q}, z) = \int \delta c_l(\mathbf{\rho}, z) \exp[i \mathbf{\rho} \cdot \mathbf{q}] d^2 \mathbf{\rho} 
\]
(2.94)

\[
\delta \tilde{\alpha}(\mathbf{q}, z) = \int \delta \alpha(\mathbf{\rho}, z) \exp[i \mathbf{\rho} \cdot \mathbf{q}] d^2 \mathbf{\rho} 
\]
(2.95)

Equation 2.70 can be used to calculate the matrix elements of \( \kappa \kappa^* \). The summation with the index \( j \) is now over the new unknowns (i.e. the chromophore concentrations and \( \alpha \) instead of \( \mu_a \) and \( \mu'_s \)).
The matrix now has a block structure where each block is labeled by a wavelength/modulation frequency pair.

### 2.3 APPENDIX A: Derivation of boundary conditions

Here we follow the approach of Ref. [44]. The specific intensity, \( I(r, s) \), gives the electromagnetic energy density (number of photons) at the position \( r \) and traveling in the direction \( s \). The electromagnetic energy density, \( u(r) \) is simply the integral of the specific intensity over all possible directions. That is:

\[
u(r) = \int_{4\pi} d^2s \ I(r, s) .
\] (2.96)

Within the diffusion approximation the specific intensity is approximated as the sum of an energy density term and the component of the energy current density in the \( s \) direction such that

\[
I(r, s) = \frac{1}{4\pi} \left[ u(r) + 3 \frac{\mathbf{j}(r) \cdot s}{c} \right].
\] (2.97)

At the boundary of the scattering medium, there will be an index of refraction mismatch. For example, \( n=1 \) for air, \( n=1.33 \) for water, and \( n \) is slightly higher (about 1.4) for tissue. This means that some of the outward going electromagnetic energy will be reflected back into the medium when it reaches the boundary. Let \( \mathbf{n} \) be the outward normal from the tissue, \( \theta \) be the angle between \( \mathbf{n} \) and the direction \( s \), and \( R(\theta) \) be the Fresnel reflection coefficient for unpolarized light. For any outward facing direction \( s \), the amount of light hitting the boundary at point \( r \) is \( (s \cdot \mathbf{n})I(r, s) \). Multiplying this by \( R(\theta) \) and integrating over all outward facing directions gives the total electromagnetic energy density being reflected back into the medium at that point. The energy traveling inwards is \( (s \cdot -\mathbf{n})I(r, s) \) integrated over all inward pointing directions. Assuming that there is no
external light source directed at a particular point on the surface, the number of inward traveling photons must be equal to the number of outward photons being reflected back into the medium at that point. This gives the boundary condition

$$\int_{s \cdot n > 0} R(s) I(s)(s \cdot n) d^2 s = \int_{s \cdot n < 0} I(s)(s \cdot -n) d^2 s. \quad (2.98)$$

Taking $n$ as pointing in the $-z$ direction, substituting equation 2.97 into equation 2.98 and performing the angular integrals gives:

$$R_u \frac{u}{4} - R_j \frac{J_z}{2c} = \frac{u}{4} + \frac{J_z}{2c}, \quad (2.99)$$

where

$$R_j = \int_{0}^{\pi/2} 3 \sin \theta \cos^2 \theta R(\theta) \, d\theta \quad (2.100)$$

and

$$R_u = \int_{0}^{\pi/2} 2 \sin \theta \cos \theta R(\theta) \, d\theta. \quad (2.101)$$

It is common to define an effective reflection coefficient as:

$$R_{eff} = \frac{R_u + R_j}{2 - R_u + R_f}. \quad (2.102)$$

Then boundary condition (2.99) now appears as:

$$R_{eff} \left( \frac{u}{4} - \frac{J_z}{2c} \right) = \frac{u}{4} + \frac{J_z}{2c}. \quad (2.103)$$

$R_{eff}$ gives the fraction of outgoing light that is reflected back into the medium at the boundary.

We use Fick’s rule, according to which the current density in proportional to the gradient such
that

\[ j_z = -D \nabla u \cdot z, \quad (2.104) \]

to arrive at the boundary condition

\[ u + \left[ \frac{2D}{c} \frac{1 + R_{eff}}{1 - R_{eff}} \right] \nabla u \cdot n = 0. \quad (2.105) \]

Defining the extrapolation distance \( \ell \) as the term in brackets, gives the boundary condition of equation (2.5).

### 2.4 APPENDIX B: Calculation of Fourier coefficients

Start with equation (2.7) with the plane wave decomposition of the Greens function.

\[ [\nabla^2 + k_0^2] \frac{1}{(2\pi)^3} \int d^3 k \ g(k) \ e^{ik \cdot \left( r - r' \right)} = -\frac{1}{D} \delta (r - r'). \quad (2.106) \]

Bring the integral out front such that

\[ \frac{1}{(2\pi)^3} \int d^3 k \left[ k_0^2 - k^2 \right] g(k) \ e^{ik \cdot \left( r - r' \right)} = -\frac{1}{D} \delta (r - r'). \quad (2.107) \]

Now act on both sides with

\[ \int d^3 r \ e^{-i k' \cdot \left( r - r' \right)} \]

keeping in mind that the plane waves are orthogonal such that

\[ \frac{1}{(2\pi)^3} \int d^3 r \ e^{i \left( k - k' \right) \cdot r} = \delta (k - k'). \quad (2.109) \]
The integral over $d^3r$ gives:

$$
\int d^3k [k_0^2 - k^2] g(k) \delta(k - k') = -\frac{1}{D}
$$

such that

$$
g(k) = -\frac{1}{D} \frac{1}{k_0^2 - k^2}.
$$

2.5 **APPENDIX C: Finite element method**

Here I derive the matrix equation (2.26) which must be inverted to find the electromagnetic energy density. I use the finite element method (FEM) with the Galerkin formulation of the method of weighted residual and linear basis functions. We begin with the diffusion equation according to which

$$
[-\nabla \cdot D(r) \nabla + c \mu_a(r) - i\omega] u(r, \omega) = Q(r, \omega).
$$

with boundary condition

$$
u + \frac{D}{c \alpha(n)} \nabla u \cdot \hat{n} = 0.
$$

Next we approximate the electromagnetic energy density as a sum of known basis functions ($\psi_j$) and unknown coefficients ($u_j$) as

$$
u(r) \approx \tilde{u}(r) = \sum_j u_j \psi_j(r)
$$
where $N$ is the finite number basis functions. Our goal is to find the coefficients $u_i$ such that the difference between $u(r)$ and $\tilde{u}(r)$ is minimized. That is, we want to minimize a residual such that

$$R(\tilde{u}) = -\nabla \cdot D\nabla \tilde{u} + c\mu_0 \tilde{u} - i\omega \tilde{u} - Q = 0 .$$

(2.115)

(To make the formulas easier to read I am suppressing the spatial dependence on $r$.) In the Galerkin formulation of the method of weighted residuals the idea is to make $R = 0$ by choosing the $u_j$’s such that $R$ is orthogonal to the complete set of basis function $\psi_i$. That is we require

$$R_i = \int_V \psi_i [-\nabla \cdot D\nabla \tilde{u} + c\mu_0 \tilde{u} - i\omega \tilde{u} - Q] dV = 0 .$$

(2.116)

for all the basis functions. We now observe, using the product rule, that

$$\nabla \cdot (\psi D\nabla \tilde{u}) = \psi \nabla \cdot D\nabla \tilde{u} + D\nabla \psi \cdot \nabla \tilde{u} .$$

(2.117)

This allows us to integrate by parts such that

$$R_i = \int_V D\nabla \psi_i \cdot \nabla \tilde{u} + c\mu_0 \psi_i \tilde{u} - i\omega \psi_i \tilde{u} - \psi_i Q] dV - \int_S D\psi_i \nabla \tilde{u} dS = 0 .$$

(2.118)

Finally we substitute equation (2.114) into this equation to get the matrix equation

$$\sum_{j}^{N} \left[ \int_V (D\nabla \psi_i \cdot \nabla \psi_j + c\mu_0 \psi_i \psi_j - i\omega \psi_i \psi_j) dV - c\alpha(n) \int_S \psi_i \psi_j dS \right] u_j = \int_V \psi_i Q dV .$$

(2.119)
Note, we have used boundary condition (2.113) in the surface integral. This can be written more compactly as

\[
[K(D) + C(c\mu_a) + c\alpha(n)A + i\omega B]U = Q, \tag{2.120}
\]

where

\[
K_{ij} = \int_V D(r)\nabla \psi_i(r)\nabla \psi_j(r)dV \tag{2.121}
\]
\[
C_{ij} = \int_V c\mu_a(r)\psi_i(r)\psi_j(r)dV \tag{2.122}
\]
\[
A_{ij} = \int_S \psi_i(r)\psi_j(r)dS \tag{2.123}
\]
\[
B_{ij} = \int_V \psi_i(r)\psi_j(r)dV \tag{2.124}
\]
\[
Q_j = \int_V \psi_i(r)S(r)dV \tag{2.125}
\]

If the basis functions have limited support, then almost all of the matrix elements will equal zero.

The simplest approach is build a mesh using tetrahedral elements with a node at each vertex. Each basis function is one a each node, and decreases linearly to zero at all its neighboring nodes.

### 2.6 APPENDIX D: Rytov approximation

Derivations of the Rytov approximation can be found in Refs. [23,52,79]. Here I consider the case of an inhomogeneous absorption coefficient. We begin with equation 2.33. We use the notation

\[V(r) = c\delta\mu_a(r), \text{ and } k_0^2 = \frac{c\mu_0 + i\omega}{D_0}\]

such that this equation appear as

\[
[\nabla^2 + k_0^2]G(r_s, r) = \frac{1}{D_0}\delta(r - r_s) - \frac{1}{D_0}V(r)G(r_s, r). \tag{2.126}
\]
We now let $G(r_s, r)$ be the product of a homogeneous and a scattering part.

$$G(r_s, r) = G_0(r_s, r) \exp[\psi_{sc}(r_s, r)]$$
$$= \exp[\psi_0(r_s, r) + \psi_{sc}(r_s, r)]$$
$$= \exp[\psi(r_s, r)].$$  \hspace{1cm} (2.127)

In order to make the equations easier to read, for the remainder of the derivation the dependence on position will be implicit, except where it is necessary to show it. The following two facts will be used later on:

$$\nabla G = G \nabla \psi$$  \hspace{1cm} (2.128)

$$\nabla^2 G = [\nabla^2 \psi + (\nabla \psi)^2] G$$  \hspace{1cm} (2.129)

We now substitute equation (2.129) into equation (2.126) such that

$$[\nabla^2 \psi + (\nabla \psi)^2 + \kappa_0^2] G = \frac{1}{D_0} [\delta(r - r_s) - V G]$$  \hspace{1cm} (2.130)

Using the relation $\psi = \psi_0 + \psi_{sc}$ (see equation 2.127), and dividing through by $G$, results in

$$\nabla^2 \psi_0 + \nabla^2 \psi_{sc} + (\nabla \psi_0)^2 + (\nabla \psi_{sc})^2 + 2 \nabla \psi_0 \cdot \psi_{sc} + \kappa_0^2 = \frac{\delta(r - r_s)}{D_0 G} - V$$  \hspace{1cm} (2.131)

We also know from equation (2.129) and the definition of the Greens function $G_0$ that

$$\nabla^2 \psi_0 + (\nabla \psi_0)^2 + \kappa_0^2 = \frac{\delta(r - r_s)}{D_0 G_0}.$$  \hspace{1cm} (2.132)
Subtracting equation (2.132) from equation (2.131) and keeping in mind that near the source \( r_s \) the scattered field is much smaller than the unperturbed field (i.e. \( \psi_{sc} \ll \psi_0 \)) yields

\[
\nabla^2 \psi_{sc} + (\nabla \psi)^2 + 2\nabla \psi_0 \cdot \nabla \psi_{sc} = -V .
\]

(2.133)

We now multiply both sides of this equation by \( G_0 \) and take advantage of equation (2.128) to get

\[
G_0 \nabla^2 \psi_{sc} + 2\nabla G_0 \cdot \nabla \psi_{sc} = -[(\nabla \psi_{sc})^2 + V] G_0 .
\]

(2.134)

By using the product rule the left-hand side can be changed so that

\[
\nabla^2 (G_0 \psi_{sc}) - (\nabla^2 G_0) \psi_{sc} = -[(\nabla \psi_{sc})^2 + V] G_0 .
\]

(2.135)

Now everywhere but where the source is we have \( \nabla^2 G_0 = -k_0^2 G_0 \) so that

\[
[\nabla^2 + k_0^2](G_0 \psi_{sc}) = -[(\nabla \psi_{sc})^2 + V] G_0 .
\]

(2.136)

We now convolve this equation with its Greens function to get

\[
\psi_{sc} G_0(r_s, r_d) = \int_V G_0(r, r_d) [(\nabla \psi_{sc}(r_s, r))^2 + V(r)] G_0(r_s, r) \, d^3r .
\]

(2.137)

In the Rytov approximation we assume that scattered field is changing slowly (i.e. \( (\nabla \psi_{sc})^2 \ll V \)). The final result is:

\[
\psi_{sc} = \frac{1}{G_0(r_s, r_d)} \int_V G_0(r, r_d) V(r) G_0(r_s, r) \, d^3r .
\]

(2.138)
2.7 APPENDIX E: One dimensional integral equations

We want to make integral equation (2.39) block diagonal. For convenience this equation is repeated here:

\[
\phi(r_s, r_d) = \int_V G_0(r_s, r) \delta \mu_a(r) - \nabla \delta D(r) \nabla |G_0(r, r_d) d^3r. \tag{2.139}
\]

The first step is to split the integral into absorption and scattering parts such that

\[
\phi(r_s, r_d) = \int_V G_0(r_s, r)G_0(r, r_d) c \delta \mu_a(r) + \nabla G_0(r_s, r) \cdot \nabla G_0(r, r_d) \delta D(r) d^3r. \tag{2.140}
\]

This result is derived in chapter 5 of [79]. As I have nothing to add to the derivation, the interested reader is referred there for more information. We now use the plane wave expansions of the Greens functions from equation (2.14).

\[
G(r, r') = \frac{1}{(2\pi)^2} \int d^2q g(q, z, z') e^{iq \cdot (r - r')}. \tag{2.141}
\]

The gradient of the Greens function is found by straight forward differentiation.

\[
\nabla G(r, r') = \frac{1}{(2\pi)^2} \int d^2q \left[ i q g(q, z, z') \hat{\rho} + \frac{\partial}{\partial z} g(q, z, z') \hat{z} \right] e^{iq \cdot (r - r')}. \tag{2.142}
\]

The kernels of the integral of equation (2.140) can now be written as

\[
G_0(r_s, r)G_0(r, r_d) = \frac{1}{(2\pi)^4} \int d^2q_s \int d^2q_d \kappa_A(q_s, q_d; z) \exp[i(q_d - q_s) \cdot \rho + i(q_s \cdot \rho_s - q_d \cdot \rho_d)]. \tag{2.143}
\]
\[ \nabla G_0(r_s, r) \cdot \nabla G_0(r, r_d) = \]
\[
\frac{1}{(2\pi)^4} \int d^2 q_s \int d^2 q_d \kappa_D(q_s, q_d; z) \exp[i(q_d - q_s) \cdot \rho + i(q_s \cdot \rho_s - q_d \cdot \rho_d)], \quad (2.144)
\]

where we have defined
\[
\kappa_A(q_s, q_d; z) = g(q_s; z_s, z) g(q_d; z, z_d) \quad (2.145)
\]
\[
\kappa_D(q_s, q_d; z) = \frac{\partial g(q_s; z_s, z) \partial g(q_d; z, z_d)}{\partial z \partial z} - q_s \cdot q_d g(q_s; z_s, z) g(q_d; z, z_d). \quad (2.146)
\]

We now substitute these formulas for the kernels into equation (2.140) and take a 4D Fourier transform with respect to the source and detector locations. The result is
\[
\phi(q_1, q_2) = \frac{1}{(2\pi)^4} \int d^3 r \int d^2 q_s \int d^2 q_d \int d^2 \rho_s \exp[(q_1 + q_s) \cdot \rho_s] \int d^2 \rho_d \exp[(q_2 - q_d) \cdot \rho_d]
\]
\[
\times [\kappa_A(q_s, q_d; z) \delta \mu + \kappa_D(q_s, q_d; z) \delta D(r)] \exp[(q_d - q_s) \cdot \rho] \quad (2.147)
\]

Now recall that the Dirac delta function can be written as a sum of plane waves.
\[
\frac{1}{(2\pi)^2} \int d^2 \rho \exp[i(q_1 - q_2) \cdot \rho] = \delta(q_1 - q_2). \quad (2.148)
\]

This allows us to get rid of the integrals over source and detector positions.
\[
\phi(q_1, q_2) = \frac{1}{(2\pi)^4} \int d^3 r \int d^2 q_s \int d^2 q_d \delta(q_1 + q_s) \delta(q_2 - q_d)
\]
\[
\times [\kappa_A(q_s, q_d; z) \delta \mu + \kappa_D(q_s, q_d; z) \delta D(r)] \exp[(q_d - q_s) \cdot \rho] \quad (2.149)
\]
Integrating again results in:

\[
\phi(q_1, q_2) = \frac{1}{(2\pi)^4} \int d^3r [\kappa_A(q_s, q_d; z)\delta \mu_a + \kappa_D(q_s, q_d; z)\delta D(r)] \exp[(q_d + q_s) \cdot \rho] \quad (2.150)
\]

Note that \( \kappa_A \) and \( \kappa_D \) are even in \( q_s \) and \( q_d \) so that we can always makes these arguments positive. Also note that \( \kappa_A \) and \( \kappa_D \) do not depend on \( \rho \) so that the integral over \( d^2\rho \) can be moved to the right. The final result is

\[
\tilde{\phi}(q_s, q_d) = \int_{z_s}^{z_d} \left[ \kappa_A(q_s, q_d; z) \epsilon \delta \tilde{\mu}_a(q_s + q_d) + \kappa_D(q_s, q_d; z) \delta \tilde{D}(q_s + q_d) \right] dz \quad (2.151)
\]

where

\[
\delta \tilde{\mu}_a(q_s + q_d, z) = \int \delta \mu_a(\rho, z) \exp[i \rho \cdot (q_s + q_d)] d^2\rho \quad (2.152)
\]

\[
\delta \tilde{D}(q_s + q_d, z) = \int \delta D(\rho, z) \exp[i \rho \cdot (q_s + q_d)] d^2\rho \quad (2.153)
\]

\section{2.8 APPENDIX F: Gradient and Hessian}

In this appendix I derive expressions for the Gradient and the Hessian of \( \chi^2 \) in terms of the Jacobian and the Residual. Recall that the Jacobian is a matrix of first order partial derivatives. In DOT the partial derivatives give the change in the each measurement with respect to a change in the optical properties of a voxel of tissue in the sample. The Jacobian is defined as:

\[
J_{i,j} = \frac{\partial r_i^{(c)}}{\partial x_j} \quad (2.154)
\]
The residual is a vector. Each of its components gives the difference between a measurement and the value of that measurement predicted by the diffusion model. For notational simplicity, I normalize each component by the measurement uncertainty for that measurement. The i’th component of the residual is:

\[ R_i = \frac{r_i^{(m)} - r_i^{(c)}(\mathbf{x})}{\sigma_i} \]  

(2.155)

Recall from equation (2.80) that if there are N measurements and M unknowns then \( \chi^2 \) is

\[
\chi^2(\mathbf{x}) = \frac{1}{2} \sum_i^N \left( \frac{r_i^{(m)} - r_i^{(c)}(\mathbf{x})}{\sigma_i} \right)^2 + \frac{1}{2} \sum_{i,j}^M (L^T L)_{i,j}(x_i - x_i^{(0)})(x_j - x_j^{(0)}) = \frac{1}{2} \mathbf{R}^T \mathbf{R} + \frac{1}{2} \| \mathbf{L}(\mathbf{x} - \mathbf{x}^{(0)}) \|^2 .
\]

(2.156)

The k’th component of the gradient is simply the partial derivative of \( \chi^2 \) with respect to \( x_k \). Taking some derivatives it is easy to show that the first term is the dot product of the k’th column of the Jacobian with the residual. That is

\[
\nabla \chi^2_k = \sum_i^N \frac{\partial r_i^{(c)}}{\partial x_k} \left( \frac{r_i^{(m)} - r_i^{(c)}(\mathbf{x})}{\sigma_i} \right) + \sum_i^M (L^T L)_{k,i}(x_i - x_i^{(0)}) = \sum_i^N J_{i,k} R_i + \sum_i^M (L^T L)_{k,i}(x_i - x_i^{(0)}) .
\]

(2.157)

In matrix notation this appears as equation (2.81):

\[
\nabla \chi^2 = \mathbf{J}^T \mathbf{r} + \mathbf{L}^T \mathbf{L}(\mathbf{x} - \mathbf{x}^{(0)}) .
\]

(2.158)
In order to get each component of the Hessian we take one more partial derivative and get

\[
\frac{\partial^2 \chi^2}{\partial x_k \partial x_l} = \sum_i^N \left[ \frac{\partial^2 r_i^{(c)}}{\partial x_k \partial x_l} \left( \frac{r_i^{(m)} - r_i^{(c)}(x)}{\sigma_i} \right) + \frac{\partial r_i^{(c)}}{\partial x_k} \frac{\partial r_i^{(c)}}{\partial x_l} \right] + L^T L_{k,l} .
\] (2.159)

In matrix notation this appears as equation (2.82):

\[
\nabla^2 \chi^2 = \sum_i^N \left[ \nabla^2 r_i^{(c)} R_i \right] + J^T J + L^T L
\]

\[\approx J^T J + L^T L .
\] (2.160)

Note that we have omitted the first term of the Hessian in the last step. This approximation is more accurate when forward problem is almost linear (i.e. \( \nabla^2 r^{(c)} \) is small), or the difference between measured and predicted data is small (i.e. R is small).
Chapter 3

Experimental Validation

3.1 Introduction

In an optically-thick medium such as the human breast, multiple scattering of light creates a fundamental obstruction to the direct formation of images. As described in the previous chapter, DOT overcomes this problem to some extent by solving an appropriate inverse problem, usually based on the diffusion equation, wherein the optical properties of a highly-scattering medium are reconstructed from boundary measurements. Unfortunately, such inverse scattering problems are severely ill-posed [5], and the resultant image quality in DOT is expected to be poor. Typical DOT images resemble structureless ‘blobs’. As a result many accept that anatomically accurate DOT images cannot be reconstructed. Accordingly, the emphasis in DOT has been on functional imaging, and on multi-modality imaging, in which simultaneously acquired MRI or CT images are used to provide anatomical detail [41].

It has been suggested that the relatively low quality of images in DOT can be improved by the use of large data sets [65–67, 89, 90]. Moreover, data sets of approximately $10^8$ measurements
may be readily acquired with non-contact DOT systems [91, 101, 106]. For example, Turner et al. have shown that simple shapes can be imaged in an experiment using an optically-thin sample by employing time gating of early-arriving photons [101]. However, this approach uses photons that travel ballistically through the sample and is therefore not useful in optically thick tissues such as breast and brain.

Utilizing these large data sets requires the use of the fast image inversion formulas described in section 2.2.6. The fast inversion formulas have been applied previously to DOT imaging with large data sets. [106]. However, in that work a sample with very strong absorption and a simple geometrical structure (i.e. two perfectly absorbing balls) was imaged. This choice did not allow the full potential of large data sets to be explored and is of limited relevance to conditions encountered in tissue. The experimental reconstructions obtained in Ref. [106] appeared as spherical inhomogeneities correctly positioned in space, but slightly larger than the actual balls. Thus the detection and localization of targets was shown, but neither the ability to reconstruct the shapes of spatially extended objects nor the ability to image objects with more biologically realistic absorption contrast was demonstrated.

To overcome these limitations, I will present reconstructed images of objects that have complex structure and have optical properties comparable to those of tissue. Experiments with these objects immersed in an optically-thick medium reveal that DOT is capable of producing quantitative images of complex structures with spatially-resolved features on the sub-centimeter scale. The reconstructed images exhibit spatially-resolved features that are much smaller than the overall size of the sample. This level of detail and the spatial resolution achieved in our experiment are expected to significantly enhance the practical utility of DOT, especially for localization and demarcation of breast tumors.
This chapter is organized as follows. I start by describing the instrumentation and experimental samples used in the experiments. I then show reconstructed images using varying numbers of measurements, which show both qualitatively and quantitatively the advantages and limitations of using large data sets. I conclude with an analysis of measurement noise which suggests that shot noise is the most important factor limiting experimental image resolution.

3.2 Instrumentation

A schematic of the experimental apparatus used for these experiments appears in Fig. 3.1. It consisted of a continuous-wave diode laser (Model TC40, SDL Inc., San Jose, CA) operating at 785 nm and coupled via a 100 µm multi-mode fiber to a pair of galvanometer-controlled mirrors (Innovations in Optics, Woburn, MA). The mirrors raster scanned the beam (on a 35 × 35 rectangular grid with 4 mm step size) over a 13.6 × 13.6 cm² square on one side of an imaging tank containing a target. For each laser beam position, the light transmitted through the tank was collected by a f=25 mm F/0.95 lens and focused on a front-illuminated thermoelectric-cooled 16-bit CCD array (DV887ECS-UV, Andor Technology, Belfast, Ireland). A 20 × 20 cm² square area of the opposite surface was mapped onto a square grid of 512 × 512 CCD pixels; this corresponds to a grid of detectors with 0.4 mm step. The signal recorded by each CCD pixel for a given source beam position defined an independent measurement. The total size of the data set recorded in a single experiment was (35 × 512)² ≈ 3 × 10⁸. Somewhat smaller subsets of the data were used for image reconstruction.

The imaging tank had an inner thickness \( L = 6 \) cm, and was filled with a mixture of water, a highly scattering fat emulsion (Liposyn III, 30%, Abbott Laboratories, Chicago, IL), and India ink (Black India 4415, Sanford, Bellwood, IL). The absorption and the reduced scattering coefficients
Figure 3.1: Schematic of the experimental setup used in the experiments. Continuous-wave laser light at 785 nm is collimated after exiting a 100 μm multimode optical fiber. The beam is raster scanned across the imaging tank by a pair of galvanometer controlled mirrors. The transmitted light is collected by a lens coupled CCD array.

of the mixture at 786 nm were $\mu_a = 0.05 \text{ cm}^{-1}$ and $\mu_s' = 7.5 \text{ cm}^{-1}$, respectively. The transport mean free path was $\ell^* = 1/(\mu_a + \mu_s') \approx 1.3 \text{ mm}$. The diffuse wave number (i.e. the inverse characteristic length over which the diffuse waves decay exponentially) was $k_d \approx \sqrt{3\mu_a/\ell^*} \approx 1.1 \text{ cm}^{-1}$. The tank thickness was therefore much larger than $\ell^*$, and thus the experiments were carried out in the diffusion regime. In addition $k_dL \approx 6.6$, and thus the transmitted light was substantially attenuated. These parameters are typical of human breast tissues in the NIR spectral region.

### 3.3 Experimental Samples

Experimental samples used in this chapter were designed to test our ability to measure changes in the absorption coefficient $\mu_a$ only. For all samples, we attempted to make the scattering coefficient $\mu_s'$ similar to that of the scattering fluid contained in the imaging tank. Two types of samples were constructed: solid targets used to test the resolution and image quality of the experiment, and
hollow targets used to test our ability to quantify changes in absorption.

The solid targets (Fig. 3.2) were made of a mixture of silicone rubber (RTV-12, General Electric, Waterford, NY), titanium dioxide (T-8141, Sigma-Aldrich, St. Louis, MO), and carbon black (Raven 5000 Ultra Powder II, Columbian Chemicals Co., Marietta, GA) [26]. The ingredients were mixed in a proportion such that the reduced scattering coefficient of the targets was approximately matched to that in the surrounding fluid while the absorption coefficient $\mu_a$ was four times larger. Targets were made in the shape of letters (3 cm tall, 2 cm wide, 5 mm thick with individual components 3 mm in width), and bars (6 cm tall, 5 mm thick, with widths of 7-9 mm).

Hollow targets were used to perform titration experiments. These targets consisted of an 18 mm tall clear plastic cylinder with a diameter of 17 mm and 1 mm thick walls. The cylinder was positioned in the center of the tank. Laboratory tubing (outer diameter 2 mm) was used to flow fluid through the cylinder. During the first scan, the cylinder contained matching fluid identical to the fluid in the tank. Twelve titrations were then performed in which the ratio of ink concentration in the cylinder to that in the tank gave an expected absorption contrast ranging from 2:1 to 64:1.
3.4 Experimental results

3.4.1 Reconstructed Images

For the reconstructions shown in Fig. 3.3, the target was constructed of silicone rubber and shaped in the form of the letters “DOT” and “PENN”. In the first experiment, we placed the letters “DOT” one centimeter from the source plane and the letters “PENN” one centimeter from the detector plane, directly behind the “DOT” letters. The reconstruction is shown in Fig. 3.3(b). The letters are clearly visible. Note that the central slice from the middle of the tank is empty, as expected.

In a second experiment we placed the letters “DOT” in the center of the tank (the letters “PENN” were not present) three centimeters from source and detector planes. The reconstruction is shown in Fig. 3.3(c). The letters are clearly reconstructed.

In Fig. 3.4 we show the data used to reconstruct the images. Only data corresponding to a single source beam position is shown. For each reconstruction we show, from left to right, the reference intensity $I_0$ when the target is not present (scattering fluid only), the intensity $I$ when the target is present, and the Rytov data, $\phi = -\log(I/I_0)$, which is used in the reconstruction algorithm (see Chapter 2). Note that the letters cannot be identified by simply inspecting images of the transmitted light. Structure is visible in the Rytov data when the letters “PENN” are close to the detector plane (Fig. 3.4(a)). However, when the letters “DOT” are in the center of the tank (Fig. 3.4(b)) their shape is completely blurred.

In order to quantify the transverse resolution of the reconstructed images, we prepared several bar targets from the same material as the letters. The bars were 7 mm to 9 mm thick and placed consecutively (one at a time) in the center of the slab. Fig. 3.5(a) shows the corresponding reconstructions. As the bar widths decrease, the modulation depth between bars decreases. As can be
Figure 3.3: Slices from three dimensional image reconstructions of the relative absorption coefficient ($\delta \mu_a / \mu_a^{(0)}$) for targets suspended in a 6 cm thick slab filled with highly scattering fluid. The three slices shown for each reconstruction correspond to depths of 1 cm (left), 3 cm (middle), and 5 cm (right) from the source plane. The field of view in each slice is 16 cm $\times$ 16 cm. The quantity plotted is $\delta \mu_a / \mu_a^{(0)}$ (a) Schematics of the positions of the letters during the experiments. Left: The target consists of letters “DOT” and “PENN”, suspended 1 cm and 5 cm from the source plane, respectively. Right: The target consists only of the letters “DOT” suspended 3 cm from the source plane, i.e., in the center of the slab. (b) Reconstructed image of the letters “DOT” and “PENN” (c) Reconstructed image of the letters “DOT”.
Figure 3.4: Representative CCD data for the image reconstructions shown in Fig. 3.3. Each image corresponds to the measured light intensity for a single source beam position. The left column shows the reference intensity $I_0$ when the target is not present (scattering fluid only). The middle column shows the intensity $I$ when the target is present. The right column shows the Rytov data, $\phi = -\log(I/I_0)$, which is used in the reconstruction algorithm. (a) The target consists of the letters “DOT” and “PENN” (b) The target consists of the letters “DOT” only

seen, all but the 7 mm bar target are well resolved. Fig. 3.5(b) shows reconstructions for two experiments in which the 7 mm bar target was positioned 1 cm from the source and detector planes, respectively. The bars in this figure are well resolved and the images are smoother and have fewer artifacts. As can be expected, the image is better resolved when the target is closer to the detector plane. This is because the detectors are sampled on a finer grid than the sources. Experiments were also performed with bar targets having an absorption contrast of 2:1. The resulting images were very similar to those acquired with a 4:1 absorption contrast bar targets, but they contained less contrast and more noise.

The images in Fig. 3.5 were reconstructed using approximately $10^7$ measurements. The effect of changing the size of the data set was investigated by sampling the detectors on a grid with a step size of 2 mm, five times larger than the minimum experimentally available detector spacing. We found that increasing the number of detectors up to the experimentally available maximum did not improve image quality. That is, reconstructions performed using 2 mm source separations or with
Figure 3.5: Reconstructed images of bar targets. Only slices drawn at the depth of the actual target are shown. (a) 7 mm to 9 mm bar targets located in the center of the tank. Here d denotes the width of the individual bars in the targets. (b) The 7 mm bar target located 1 cm from the source (left) and detector (right) planes.

A denser sampling of CCD pixels were visually indistinguishable from those in Fig. 3.5. However, decreasing the number of data points does result in poorer image quality, as is illustrated in Fig. 3.6. From left to right, three separate reconstructions of the 8 mm bar target are shown. The data for these reconstructions were taken from a single experiment with the target positioned in the center of the tank. All reconstruction parameters are kept constant, except for the number of measurements used. The reconstruction on the left uses $8 \times 10^6$ measurements with sources and detectors sampled with 4 mm and 2 mm steps, respectively. In the center reconstruction, we use 4 mm spacing for both the sources and detectors, which corresponds to $2 \times 10^6$ data points. In the reconstruction on the right, the sampling is 8 mm for sources and 4 mm for detectors, or, approximately, $5 \times 10^5$ data points. It can be seen that as the number of measurements decreases, image artifacts become more prominent and resolution is lost. We note that the optimal number measurements for a given experiment will vary depending on factors such as experimental geometry and noise level. For example, smaller/larger data sets would be optimal if the reconstruction field of view was smaller/larger.
3.4.2 Titration Experiments

To investigate the capability for quantitative reconstruction of the absorption coefficient, we have performed a titration experiment. A clear plastic cylinder was positioned in the center of the tank, and laboratory tubing was used to flow fluid through the cylinder. During the first scan, the cylinder contained scattering fluid identical to the fluid in the tank. Twelve titrations were then performed in which the ratio of ink concentration in the cylinder, to that in the tank, gave an expected absorption contrast ranging from 2:1 to 64:1. The absorption contrast, i.e., the ratio of the absorption coefficient in the cylinder to that in the surrounding fluid, was taken from the corresponding reconstructed value for a single voxel located inside the cylinder. This voxel was chosen to be the voxel with the maximum reconstructed value of the absorption coefficient for the tenth titration. In Fig. 3.7, the reconstructed contrast $\mu_a / \mu_a^{(0)}$ is plotted against the expected contrast. It can be seen that the absorption is quantitatively reconstructed with a linear dependence on ink concentration over nearly a decade in absorption contrast. Deviation from linearity occurs at higher concentrations, as expected.

The saturation effect seen in Fig. 3.7 can be explained as follows. When the absorption of the target is very high, most of the light is absorbed as soon as it enters the target and almost no light reaches its interior; the absorption coefficient of the interior can be arbitrarily changed with no
Figure 3.7: Reconstructed contrast of the absorption coefficient $\frac{\mu_a}{\mu_a^{(0)}}$ between the cylinder and the tank vs. the expected contrast.

significant effect on the measured signal. This is a manifestation of the nonlinearity of the inverse problem of DOT. Given that the optical properties remain constant, nonlinearity is stronger when the absorbing target becomes larger, as less and less light can penetrate the interior.

An important observation to make is that saturation effect cannot be fully removed by using a non-linear reconstruction method, as opposed to the linear one used here. The experimental data has limited sensitivity and contains noise. As explained above, as the target becomes larger and darker, its optical properties can be changed without changing the measured signal by a measurable amount. However, no reconstruction method will be able to distinguish to set of optical properties that result in the same measured data. Fortunately, the onset of nonlinearity in Fig. 3.7 occurs at absorber concentrations which are well beyond the range of contrast encountered in biological tissues.
3.5 Transverse resolution

3.5.1 Theoretical Analysis

Factors that may limit the ability to achieve even greater spatial resolution include the finite size of the source and detector grids, the shot noise in the measured light, the noise in the CCD array (a combination of dark current and read noise), and systematic errors. The latter are errors of the model. In particular, the light transmitted through the tank is described by the diffusion equation only approximately. There are also systematic errors associated with non-ideal optics (diffraction, multiple reflections on the lens and tank surfaces). Finally, there are systematic errors associated with the nonlinearity of the inverse problem of DOT.

To better understand the dependence of transverse spatial resolution on the factors listed above, we performed the following analysis. Let all inhomogeneities be confined in a thin slice of the medium parallel to the slab, \( z_0 - h/2 < z < z_0 + h/2 \), where \( h \) is small. We seek to reconstruct the deviation of the absorption coefficient in this slice, \( \delta \mu_a(\rho, z_0) \), from the respective value in the surrounding fluid, as a function of the transverse variable \( \rho = (x, y) \). The formula (2.51) derived in the Chapter 2 Section becomes in this case

\[
\phi(q, p) = h \kappa(q, p) \delta \bar{\mu}_a(q, z_0).
\]

Here \( \phi(q, p) \) is the measurable data function, \( \kappa(q, p) \) is known analytically (see Chapter 2 for precise definitions of \( \phi \) and \( \kappa \)), and \( \delta \mu_a(q, z_0) \) is the transverse Fourier transform of \( \delta \mu_a(\rho, z_0) \) with respect to \( \rho \). The real-space function \( \delta \mu_a(\rho, z_0) \) is obtained by inverse Fourier transformation, namely,
\[
\delta \mu_\alpha(\rho, z_0) = \frac{1}{\hbar} \int \exp(i\mathbf{q} \cdot \rho) \frac{\phi(\mathbf{q}, \mathbf{p})}{\kappa(\mathbf{q}, \mathbf{p})} \frac{d^2 q}{(2\pi)^2}.
\]

The choice of \( \mathbf{p} \) in the above formula is arbitrary since the problem is overdetermined (we use four-dimensional data to reconstruct a two-dimensional function); it is sufficient to choose \( \mathbf{p} = 0 \). We then use the data function \( \phi(\mathbf{q}, 0) \) for reconstruction. The latter is taken from experiment and contains noise. It is important to note that the “ideal” data function is rapidly (exponentially) decreasing with \(|\mathbf{q}|\). However, the experimental noise is approximately white, i.e., the amplitude of its Fourier transform is approximately constant in the range of \(|\mathbf{q}|\) which is of interest. In image reconstruction, integration in the above formula is over a disc \(|\mathbf{q}| < q_{\text{max}}\) such that outside of this disc, the signal-to-noise ratio in \( \phi(\mathbf{q}, 0) \) becomes smaller than unity. It then follows that the minimum spatial feature that can be resolved has a characteristic transverse dimension of \( \Delta x \sim \frac{\pi}{q_{\text{max}}} \).

A few comments on the above analysis are necessary. First, if the target is not confined to a thin slice, the transverse resolution can only be lower than the estimate \( \pi / q_{\text{max}} \). Second, one can attempt to use additional degrees of freedom (i.e., \( N \) distinct values of \( \mathbf{p} \)) to improve the resolution. This approach, however, is not expected to yield a significant improvement since the noise amplitude decreases no faster than \( 1/\sqrt{N} \), while the function \( \phi(\mathbf{q}, \mathbf{p}) \) decreases exponentially with \(|\mathbf{q}|\).

### 3.5.2 Simulations and Experiments

To illustrate the above resolution estimate, we performed simulations and experiments for small dark absorber located in the center of the tank. Simulated data functions for a point absorber were
generated within the linear approximation by representing $\delta \mu_d(r)$ as a delta-function in equation (2.39). Data for infinite lattices of sources and detectors was computed directly in the Fourier domain using (2.51). For finite lattices we computed $G_0$ numerically using (2.14) and substituted the result into (2.45); in the latter formula, summation over real space variables was truncated.

We then added noise to the data function generated for the finite lattice as follows. We expect the standard deviation due to shot noise for repeated measurements of a single source detector pair to be equal to the square root of the mean number of detected photo-electrons ($\sigma_I(r_s, r_d) = \sqrt{I(r_s, r_d)}$). Propagating the error to the data function defined in equation (2.36) we get to first order $\sigma_{data}(r_s, r_d) = \sqrt{2I_0(r_s, r_d) - \phi(r_s, r_d)}$. We scaled both the simulated data function and the simulated reference intensity $I_0$ to have the same maximum values as were experimentally measured. The resulting data function with shot noise was then

$$\phi_{\text{noise}}(r_s, r_d) = \phi(r_s, r_d) + \sigma_{\text{data}}(r_s, r_d) R.$$  \hspace{1cm} (3.1)

Here $R$ is a random variable with a Gaussian distribution and a variance of one. We note that since $I_0 \gg \phi$, the shot noise depends primarily on the reference intensity, not on the data function itself. In order to simulate the effect of read noise and dark current, we determined the standard deviation $\sigma_{bg}$ of a background image taken with the light source blocked. This error was propagated as $\sigma_{data} = \sqrt{2\sigma_{bg}^2}$, and the resulting data function was calculated according to (3.1).

In Fig. 3.8 we plot the power spectrum of the data for a point absorber located in the center of the tank. The data function $\phi(q, 0)$ is in this case cylindrically symmetric and we can write $\phi(q, 0) = \Psi(q)$, where $q = |q|$. The five curves shown in Fig. 3.8 contain (i) simulated ideal data corresponding to infinitely large and dense grids of noiseless sources and detectors, (ii) simulated data (without noise) for the finite grids of sources and detectors that were used in the experiments,
Figure 3.8: Power spectra of the data function $|\Psi(q)|^2$ (defined in the text) for a small absorber located in the center of the tank. The different curves correspond to simulated ideal data, simulated data from finite grids of sources and detectors, simulated data with background noise, simulated data with shot noise, and to experimental data, as indicated.

(iii) simulated data for the finite grids with background noise added (i.e. Gaussian distributed noise with a variance equal to the variance of the detected signal when the laser is off), (iv) simulated data for the finite grid with shot noise added (i.e. Gaussian distributed noise with a variance equal to the number of photo-electrons detected experimentally), and (v) data from an experiment with a small (4 mm) highly absorbing target in the tank. The early onset of noise in the simulated data with shot noise, suggests the latter is the limiting factor in our experiments. We thus conclude that the other errors discussed above (e.g. the finite numbers of sources and detectors, CCD noise, errors in the diffusion model, non-ideal optics, and non-linearity) do not play a significant role in limiting image resolution. We see that noise begins to dominate the data at $q_{\text{max}}/\pi \approx 0.1 \text{ mm}^{-1}$. This corresponds to a spatial resolution of $\lesssim 1 \text{ cm}$. For objects closer to the surface, the power spectrum decays more slowly. For example, for a point absorber located 1 cm from the surface, shot noise begins to dominate the data at $q_{\text{max}}/\pi \approx 0.25 \text{ mm}^{-1}$, which corresponds to a spatial resolution of $\lesssim 4 \text{ mm}$. 
3.6 Conclusion

It is possible to obtain high quality, quantitatively accurate, reconstructed images of complex structures deeply embedded in highly-scattering media. We were able to produce such images, by using both a non-contact scanner capable of collecting large amounts of data and a fast image reconstruction algorithm capable of utilizing this data. The addition of extra measurements results in images that have less noise and artifacts. It also allows for higher resolution, especially near the surface. However, for any given set of optical properties and depth below the surface, there is a hard resolution limit that cannot be substantially improved by adding more measurements.
Chapter 4

Next Generation Breast Scanner

4.1 Introduction

As part of our ongoing breast imaging program, we have built a next-generation breast imager to replace our current clinical device. While the current clinical device has been successfully used in several studies [25,27,31,55], the new instrument builds on this success by adding new capabilities. These new features include simultaneous frequency domain and continuous-wave detection using a gain modulated image intensifier, laser light intensity modulation with an electro-optic modulator (EOM), a 209 channel galvanometer source position switch, a rotating arm for imaging at multiple orientations, and an improved patient interface for better breast coverage. In this chapter, I motivate and describe the new features, and present initial test results. The chapter is organized as follows. I begin with a brief description of our previous generation breast imager. I then describe how the new features of the next generation instrument overcome weaknesses of the older instrument. This is followed by preliminary data and image reconstructions.
4.2 Previous Generation Breast Scanner

The previous imaging device is a hybrid system (Figure 4.1). The instrument takes both continuous-wave transmission and frequency-domain remission measurements at six near-infrared wavelengths in the parallel-plate soft-compression geometry. The patient lies in a prone position with her breasts inside a box with an anti-reflection coated glass window on the detector side. A compression plate holds the breast in place against the viewing window by mildly compressing the breast to a thickness between 5.5 and 7.5 cm. The box is then filled with a matching fluid with optical properties similar to human breast. The matching fluid consists of water, India ink for absorption, and a fat emulsion for scattering.

The device contains six diode lasers (650, 690, 750, 786, 830, 905 nm). Four of these lasers (690, 750, 786, 830 nm) are intensity modulated at 70MHz. The lasers are connected via optical fibers and series of optical switches (DiCon Fiber Optics, Richmond, CA) to 45 source positions located on the compression plate. The source positions form a $9 \times 5$ grid with a separation of 1.6 cm between nearest neighbors. The breast is scanned by serially guiding the light from each laser to each source position.
For remission detection, nine homodyne frequency domain detector units [114] are connected to the compression plate by a 3×3 grid of 3 mm detector fibers with a spacing 1.6 cm. The light collected by each fiber is detected by an avalanche photodiode (APD). A homodyne technique is used to derive the RF amplitude \( A_\omega \) and phase shift \( \phi \) of the detected signal. This is accomplished as follows. The 70MHz signal used to modulate the diode laser also serves as a reference signal for the detector unit. The reference signal \( R(t) = A_r \sin(\omega t) \) is split into two branches. The phase of one branch is shifted by \( \pi/2 \) radians. The two branches are separately multiplied by the detected signal \( D(t) = A_0 + A_\omega \sin(\omega t + \phi) \) to give the signals

\[
I(t) = \frac{1}{2} A_r A_\omega \cos(\phi) + \omega \text{ and } 2\omega \text{ terms}.
\]

\[
Q(t) = \frac{1}{2} A_r A_\omega \sin(\phi) + \omega \text{ and } 2\omega \text{ terms}.
\]

These signals are then low pass filtered so that only their DC component remains. The amplitude and phase are then calculated as

\[
A_\omega \propto \sqrt{I_{DC}^2 + Q_{DC}^2},
\]

\[
\phi = \tan^{-1} \frac{Q_{DC}}{I_{DC}}.
\]

The offsets of \( I_{DC} \) and \( Q_{DC} \) can be measured by blocking the light source. The offsets are subtracted before calculating the amplitude and phase with equations (4.3) and (4.4). Note, this technique does not give the measured DC signal \( A_0 \).
For transmission detection, a CCD camera (Roper Scientific, Trenton, NJ, VersArray:1300F) is focused on the viewing window. It acquires an image for each source-position/laser combination with a typical exposure time of 500 ms for breast imaging. A $24 \times 41$ grid of 984 measurements is selected from the CCD chip. Each measurement consists of a $2 \times 2$ hardware binned array of $20 \times 20 \, \mu m$ pixels on the CCD. The measurements correspond to the continuous wave light intensity at locations on the viewing window with a spacing of $\sim 3 \, mm$.

### 4.3 Next Generation Breast Scanner

#### 4.3.1 Frequency Domain CCD Detection

As described above, our clinical devise detects transmitted light using a lens coupled CCD. This is a simple and affordable method to acquire large amounts of data in optical tomography. The advantages of collecting large amounts of data were explored in Chapter 3. Unfortunately, the slow temporal resolution of the CCD prevents the measurement of the phase delay of the diffusing photon density wave. While the current clinical device does have nine frequency domain remission detectors, the data from this small number of detectors is only used to acquire bulk property estimates of the entire breast. In general, it is difficult to separate the contributions of absorption and scattering in a CW measurement. For example, imagine two experiments in which diffusing light is detected after transmission through a highly scattering medium. In the first, scattering coefficient of the medium is large, but the absorption coefficient is small. There will still be significant attenuation of the light even though the absorption coefficient is small. This is because the high degree of scattering causes the photons to travel longer random walk pathlengths, increasing their
probability to be absorbed. In the second experiment absorption coefficient is larger, but scattering coefficient is lower. The larger absorption coefficient does not necessarily mean that more photons will be absorbed than in the first experiment. If the scattering is sufficiently small, the photon pathlengths will become sufficiently shorter, decreasing the probability of a given photon to be absorbed. Thus, both media may attenuate the light by the same amount. In fact it has been shown that within the diffusion approximation, it is virtually impossible to simultaneously reconstruct images of both scattering and absorption using continuous-wave measurements at a single optical wavelength [6]. We have had some success separating absorption from scatter in images reconstructed from multi-spectral CW data [28,29]. However, there still remains some uncertainty about the amount of scatter/absorption crosstalk in the reconstructed images.

The data from the two experiments described above will differ, however, if in addition to making intensity measurements, one also makes temporal measurements as well. This is because the time it takes photons to travel through the medium is related to the pathlengths that the photons traveled. There are two basic ways to make the temporal measurement. In a time domain measurement, a pulsed laser deposits short bursts of light into the medium. Both the amount and average time of flight of the photons can be measured. (Some researchers also measure the temporal dispersion of the collected light.) One can also make frequency domain measurements. In this case, the laser source is intensity modulated, and one attempts to measure the decreased amplitude and phase delay of the resulting diffusing photon density wave after it passes through the medium.

In order to combine the advantages of CCD and frequency domain detection we have mounted a gain modulated image intensifier (Lambert Instruments, II 18MD GENIII) in front of a CCD array (Andor Technology, iXon DV887-ECS-UV). A pair of phase-locked frequency generators (Rhode and Scwhartz, SMB100) produce signals at frequencies $\omega$ and $\omega + \delta$. In our current protocol
Figure 4.2: Schematic of the heterodyne detection set-up using to phase-locked frequency generators, an electro-optic modulator, and CCD detection with a gain modulated image intensifier.

\( \omega = 70 \text{ Mhz} \) and \( \delta = 1 \text{ Hz} \). The 70 Mhz signal is used to intensity modulate the laser light as described below in section 4.3.2. The 70 Mhz + 1 Hz signal is used to modulate the gain of the image intensifier. As a result, a signal with a slow cross correlation frequency of 1 Hz is produced (see Figure 4.2). This can be seen as follows. The intensity of the light source is described as

\[
S(t) = I_s + M_s \cos(\omega t).
\]

(4.5)

The transmitted light has the form

\[
T(t) = I_s A_0(r) + M_s A_\omega(r) \cos(\omega t + \phi(r)).
\]

(4.6)

Here \( A_0, A_\omega \) and \( \phi \) are the spatially varying DC intensity, RF amplitude, and phase delay we are trying to measure at the surface of the scattering medium. The sensitivity of the image intensifier varies as
\[ D(t) = I_d + M_d \cos (\omega t + \delta) . \] (4.7)

The CCD records the light intensity coming from the image intensifier with a frame rate of 10 Hz and a 40 ms exposure time. Thus all high temporal frequencies are filtered out (the phosphor screen which generates the light at the photoanode of the image intensifier has a response time of about a millisecond and also acts as a low pass filter) and the light intensity recorded by each pixel of the CCD array is

\[ \Gamma(t) = I_s I_d A_0(r) + M_s M_d A_\omega(r) \cos(\delta t + \phi(r)) . \] (4.8)

In figure 4.3 the time traces for 5 locations on the sample surface are shown. At every detector location, we fit the time trace of intensity values to equation 4.8 to obtain the DC intensity \(A_0\), RF amplitude \(A_\omega\), and phase delay \(\phi\) of the diffusing photon wave.

In our current protocol, we spend two seconds on each source position. Fifteen exposures are captured at a frame rate of 10 Hz for each source position. The remaining 500 ms are used to save the acquired images to the hard drive. Our CCD array consists of a 512 \(\times\) 512 array of pixels. We use 2 \(\times\) 2 hardware binning. This has two advantages. First, it speeds up the CCD readout. Second, it causes the CCD to saturate sooner, reducing the risk of damaging the image intensifier. Unlike the image intensifier, the CCD array can be saturated without causing an damage. By using CCD settings that cause the CCD to saturate at relatively modest light levels that will not harm the image intensifier, we reduce the chance of unknowingly damaging the image intensifier.

In order to maximize the modulation depth of the detector sensitivity (see equation (4.7)), the DC photocathode is kept at -1 V, and the amplitude of RF modulation is set to be 1 V. Thus the
Figure 4.3: Time traces for five pixels on the CCD array for increasing source detector separations. Dots correspond to measured data points. Lines are the sinusoidal fits to the data.

voltage of the photocathode oscillates from 0 to -2 V. When the voltage is greater than zero, the electrons are not accelerated from the photocathode, and no signal is detected. In addition to maximizing the modulation depth, this choice of DC offset also allows the maximum amplitude of gain of the device. This is because the change in gain per change in voltage is much higher for low voltages than high ones. Figure 4.4 shows a plot of measured light intensity over a region of interest as a function of photocathode voltage, with all other parameters kept constant. One concern when using this approach results from the fact that the change in gain of the image intensifier to a change in the photocathode voltage does not become linear until voltages of less than -10 V. This means that the gain of the image intensifier is not modulated as a perfect sinusoid. However, this is not critical. As long as the gain modulation is perfectly periodic, then all other frequencies will be at least 2\(\omega\), and they will be averaged due to the low pass filtering of the detection scheme.
We do observe however, that images at modest voltages (e.g. -1 V) are noisier than images taken at lower voltages (e.g. -50 V). Although this results in additional noise for each exposure, it has been the only way in which we have been able to measure RF amplitude and phase. In addition, 15 exposures are used for each measurement so that the fitted DC signal has less noise than the individual exposures. As will be shown below, the measured DC signal suffers from less noise than RF amplitude and phase, even with these settings.

We also note that the RF power that must be given to the image intensifier control unit in order to achieve a particular voltage amplitude at the photocathode varies depending on frequency. Although the device is designed to have as close to possible a 50 Ω input impedance, the impedance of the photocathode changes with frequency, causing standing waves between the frequency generator and image intensifier. The RF amplitude at the photocathode can be measured by evenly...
illuminating the image intensifier. If the voltage of the photocathode is being modulated, light will be detected even when the DC offset is slightly greater than zero. However, when the DC offset becomes greater than the RF amplitude, no signal will be detected. Thus by gradually increasing the DC offset until no signal is detected, one can measure the RF amplitude of the photocathode. For our device we find that a signal power of -19 dBm corresponds to an amplitude of ~1 V at the photocathode.

After being emitted from the photocathode, electrons pass through a multichannel plate (MCP). Most of the amplification of the image intensifier occurs at this stage. The MCP contains approximately 10 million parallel channels through which electrons can travel. The potential of the input side of the plate is kept fixed at 0 V. A positive voltage is maintained at the output of the MCP, causing an electric field to exist in the channels. (We currently use a setting of approximately 700 V when imaging through 6 cm of scattering medium.) As the electrons are accelerated by the electric field, they repeatedly collide with the channel walls resulting in the emission of additional electrons. Upon leaving the MCP, electrons are further accelerated as they travel toward the photoanode, whose voltage is fixed by the manufacturer at 6 kV. A phosphor screen at the photoanode emits green light when bombarded by these electrons. It is this green light that is detected by the CCD array.

4.3.2 Electro-optic Modulator

The previous device uses six diode lasers at 650, 690, 750, 785, 830, and 905 nm. Out of these, four (690, 750, 785, and 830 nm) are intensity modulated. Unfortunately, many commercially available diode lasers do not support RF modulation at 70 MHz. For this reason the 650 and 905 nm laser were not modulated. We have also found from previous work that stability is difficult to
Figure 4.5: Schematic of the electro-optic modulator. Light enters at the left, passes through a wire-grid polarizer orientated at 45 degrees, passes through two crystals whose axes are orientated at 0 and 90 degrees, and a final wire-grid polarizer orientated at 45 degrees. The birefringence of the crystals is modulated using capacitors.

achieve with intensity modulation.

In the next generation instrument, the lasers are operated in continuous-wave mode, allowing their power stability to be maintained to \(~0.1\%\). Currently five diode lasers (670, 785, 808, 850, 915 nm) have been incorporated. Light from the lasers is selected in series by a 9x1 optical switch (Piezosystem Jena, F-109-95). Then a single electro-optic modulator (EOM) (Nova Phase Inc., EO-AM-R70-C1) is used to intensity modulate the light intensity at 70 MHz. Moving to an EOM-based system allows us to use CW lasers which have a wider selection of power and wavelengths. Using a single EOM for all our wavelengths also reduces the amount of electronics required.

An electro-optic (amplitude) modulator consists of a pair of linear polarizers, and one or more crystals whose birefringence is linearly dependent on the electric field applied to it (see Figure 4.5). Typically the first polarizer is positioned to transmit light polarized at an angle of \(\pi/4\) with respect to the crystal axes. The light entering the crystal can then be represented as a Jones vector with electric field components along these crystal axes according to

\[
\mathbf{E}_{in} = E_0e^{i\phi_0} \frac{1}{\sqrt{2}} \begin{bmatrix} 1 \\ 1 \end{bmatrix}.
\]

The speed at which light travels through the crystal depends on its orientation with respect to the
crystal axes. As a result, after traveling through the crystal there will be a phase shift between the two components of the electric field due to the different indices of refraction experienced by the two components. This change can be represented by the Jones matrix

\[
M_{\text{crystal}} = \begin{bmatrix} e^{i\phi} & 0 \\ 0 & 1 \end{bmatrix}.
\]

If the polarizer on the output side is parallel to the input polarizer, it will act on the electric field according to the matrix

\[
M_{\text{polarizer}} = \frac{1}{2} \begin{bmatrix} 1 & 1 \\ 1 & 1 \end{bmatrix}.
\]

Thus the electric field exiting the device will be

\[
E_{\text{out}} = M_{\text{polarizer}} M_{\text{crystal}} E_{\text{in}} = E_0 e^{i\phi_0} \frac{e^{i\phi/2}}{\sqrt{2}} \cos(\phi/2) \begin{bmatrix} 1 \\ 1 \end{bmatrix}.
\]

resulting in the light intensity

\[
I = \frac{I_0}{2} (1 + \cos(\phi)) \quad (4.9)
\]

If the light entering the input polarizer in unpolarized, the output intensity will be decreased by an additional factor of two.

In an EOM, a crystal is used in which the phase shift \(\phi\) is proportional to the applied electric field. The electric field across the crystal is generated by applying an electric potential across a capacitor. The field induces a change in both the ordinary and extraordinary indices of refraction.
of the crystal. It is common to refer to the necessary voltage need to cause a phase shift of π radians as the half-wave voltage. It is denoted as \( V_\pi \). It corresponds to rotating the linearly polarized input light by \( \pi/2 \) radians. If the potential across the crystal is modulated sinusoidally, the phase change will be

\[
\phi(t) = \frac{\pi}{V_\pi} [V_{DC} + V_{AC} \sin(\omega t)] + \phi_{static} \tag{4.10}
\]

Here \( \phi_{static} \) is the phase shift due to the natural birefringence that exists when there is no applied electric field. In order for the EOM to function optimally, the RF amplitude \( V_{AC} \) should equal approximately \( V_\pi/2 \), and the DC bias should be such that \( \phi \) oscillates about \( \pi/2 \). If the crystal has no birefringence when the voltage is zero (i.e. \( \phi_{static} = 0 \)), then \( V_{DC} \) should equal \( V_\pi/2 \). Figure 4.6 shows the expected light intensity for different choices of \( V_{AC} \) and \( V_{DC} \) in which (a) \( V_{AC} = 0.45V_\pi \) and \( V_{DC} \) is optimal, (b) \( V_{AC} = 0.45V_\pi \) and \( V_{DC} \) is too small, and (c) \( V_{DC} \) is optimal but \( V_{AC} \) is too large. Notice the decrease in modulation depth in case (b), as well as the appearance of higher frequencies in both (b) and (c). The modulation depth of the EOM is also sensitive to proper alignment of the polarizers. For an arbitrary orientation \( \theta_1 \) of the first polarizer, the light entering the crystal (equation (4.3.2)) will now be

\[
E_{in} = E_0 e^{i\phi_0} \frac{1}{\sqrt{2}} \begin{bmatrix} \cos \theta_1 \\ \sin \theta_1 \end{bmatrix}.
\]

The matrix representing the action of the second polarizer with orientation \( \theta_2 \) is

\[
M_{polarizer} = \begin{bmatrix} \cos^2 \theta_2 & \cos \theta_2 \sin \theta_2 \\ \sin \theta_2 \cos \theta_2 & \sin^2 \theta_2 \end{bmatrix}.
\]
Figure 4.6: Expected light intensity for different choices of $V_{AC}$ and $V_{DC}$ in which (a) $V_{AC} = 0.45V_\pi$ and $V_{DC}$ is optimal, (b) $V_{AC} = 0.45V_\pi$ and $V_{DC}$ is too small, and (c) $V_{DC}$ is optimal but $V_{AC}$ is too large. Notice the decrease in modulation depth in case (b), as well as the appearance of higher frequencies in both (b) and (c)
Following the procedure demonstrated above, the light intensity exiting the EOM is

\[ I = I_0 [A + B\cos(\phi)] \]  

(4.11)

where \( A = \cos^2\theta_1\cos^2\theta_2 + \sin^2\theta_1\sin^2\theta_2 \) and \( B = 2\cos\theta_1\sin\theta_1\cos\theta_2\sin\theta_2 \). Notice, when \( \theta_1 \) and \( \theta_2 \) are both equal to \( \pi/4 + n\pi/2 \) where \( n \) can be any integer, this equation reduces to equation (4.9). However, when the polarizers are not aligned at 45° to the crystal axis, the modulation depth decreases. At \( \theta_{1,2} = \pi/2 + n\pi/2 \) there will be no modulation. In addition, the electric field across the crystal is not entirely constant, and misalignment of the input beam can also cause a decrease in modulation depth.

In our EOM, the light beam passes through two lithium niobate crystals, whose axes are orientated at \( \pi/2 \) radians relative to each other. Lithium niobate is birefringent even without an applied electric field. Furthermore, this static birefringence is temperature dependent. By having two matched crystals, oriented at \( \pi/2 \) degrees from each other, the temperature dependent phase change caused by the first crystal, is canceled by the second crystal, and the EOM is almost temperature independent (1 mrad per °C).

4.3.3  Source Position Switch

The number of source fibers has also been increased from 45 to 209. A 209 channel conventional fiber-optic switch using mechanical or prism switching would be extremely costly, slow, and have high losses. For this reason, our system uses a custom designed galvanometer mirror based optical switch (Innovations in Optics, Woburn, MA). Light from an 100 um input fiber is collimated by a lens and directed to a pair of galvanometer controlled mirrors. Light from the mirrors passes through a telecentric lens, which focuses the light onto a bundle of 600 um fibers (see Figure 4.7).
The fibers terminate on a connect plate where they are connected to individual fibers. These fibers go to the source plate, where they are arrange in a 11x19 lattice with 8 mm separation between nearest neighbors (as opposed to 16 mm in the old system). The use of a connector plate and an additional stage of fibers is intended to protect the fiber bundle, which is costly and difficult to replace. The additional fibers allow the arrangement of the source plate to be changed without having to touch, and risk damage to, any of the fibers in the bundle. In addition, the source plate rotates, (see section 4.3.4 below), and this introduces some risk to the source fibers as well. The transmission of light across the switch is a little less than 50 percent and the switch time between any two channels is less than 1 ms.

4.3.4 Patient Bed

The new system also has an improved patient interface. In both systems the patient lies prone with her breast gently compressed in an imaging tank filled with an intralipid solution. However, the new device incorporates modified biopsy bed which allow more of the breast to enter the tank. In addition to giving better breast coverage, this improved patient positioning minimizes gaps between the patient’s chest and the intralipid in the tank. This is crucial, because light from source positions near an air-intralipid boundary reflects back into the tank saturating the CCD image. Finally, in the new instrument, the imaging tank and the CCD are mounted on a rotatable arm allows for breast imaging in the axial and sagital orientations (see Figure 4.8). This feature will allow better comparison of our results with MRI acquired with a sagital orientation.
Figure 4.7: Photographs of the parts of the galvanometer based source position switch. (a) Light enters through a collimating lens (top), reflects of a pair of galvanometer positioned mirrors, and is focused on a fiber bundle using a telecentric lens. (b) Photograph of the front end of the fiber bundle.
Figure 4.8: Photographs of the next generation breast scanner. (a) Photograph with the rotating arm at 0 degrees. (b) Photograph with the rotating arm positioned at 90 degrees.
4.4 Initial Results

4.4.1 Measurement Noise

The imaging tank was filled with a mixture consisting of 12 liters of water and 500 ml of an intravenous fat emulsion (Lyposin III 20%, Hospira Inc., Lake Forest, IL). According to the manufacturer, the ‘20%’ means that the Lyposin contains 20 g of soybean oil per 100 ml. As a ballpark estimate, from previous work in our lab, we expect at 1% mixture (1 g per 100 ml) to have a reduced scattering coefficient of approximately 10 cm$^{-1}$. Thus, the 0.8% mixture in the tank was expected to have a reduced scattering coefficient of about 8 cm$^{-1}$. We used 785 nm light. Absorption from the soybean oil is expected to be negligible. Water has an absorption coefficient of 0.21 cm$^{-1}$ at 785 nm. No ink was added for additional absorption, so that we could compare our results for absorption with the known value for water. The separation between source and detector planes was kept fixed at 6 cm, as this is the most common separation we have used for breast imaging.

In a first experiment, repeated measurements were made using a single source position. Each measurement consisted of 15 camera exposures at 10 Hz with an exposure time of 40 ms. For each individual pixel, we fitted the measured data for the 15 exposures to equation (4.8) to determine the DC light intensity, RF amplitude, and phase shift at the measurement plane. This was done for 209 measurements. For each pixel we then determined the mean and standard deviation of the fitted values over the 209 measurements. In figure 4.9, depicts the measurement noise for a row of pixels corresponding to a line on the detector window directly across from the source position. In figure 4.9(a-b) the percent error (i.e. standard deviation divided by mean value) for each pixel is plotted as a function of position for the DC and amplitude signals. The phase uncertainty in degrees (i.e. standard deviation) is plotted in figure 4.9(c). The best signal to noise occurs directly
Figure 4.9: Plots of measurement uncertainty vs. position on the detector window for a row of pixels on the CCD array. The three plots correspond to (A) DC intensity, (B) RF amplitude, and (C) RF phase delay across from the source where the source/detector separation is 6 cm. The minimum values are 0.3% for DC, 0.9% for amplitude, and 0.5° for phase. However, as we move laterally across the detector plane, the measurement uncertainty increases. For a lateral distance of 6 cm from the closest detector position, the uncertainties are 0.7% for DC, 3% for amplitude, and 1.8° for phase. This corresponds to a source/detector separation of 8.5 cm.

Note, each measurement was filtered by one pass of a 3 × 3 square top filter. This step is important, if the data is going to be used in a model based reconstruction (see section 2.2.7) because not all the data points can be used in the model based reconstruction. Without some form of
smoothing or binning, the majority of collected photons will be thrown away, leading to additional measurement uncertainty. For example, in the current experiment, the minimum uncertainties without smoothing the data were 0.4% for DC, 1.6% for amplitude, and 1° for phase. If the fast inversion formulas of section 2.2.6 are used, then all the data points can be utilized.

### 4.4.2 Spectroscopy Results

As discussed in Chapter 2, reconstructed images can be viewed as spatially varying maps of perturbations from average values in the optical properties of the sample. When reconstructing an image using the Born/Rytov approximations, a homogeneous sample is measured first. Then one measures the change in the data caused by introducing the sample being imaged. In model based reconstructions, the optical properties are updated from an initial guess based determined by a measurement of the bulk optical properties of either the sample or a homogeneous sample with similar optical properties. Regardless of the type of reconstruction used, it is critical to have accurate knowledge of the bulk properties of the sample. In this section, results from measurements on homogeneous samples are presented. The average optical properties of the samples are determined using the method described in section 2.2.1.

In figure 4.10 the DC, amplitude, and phase from one of the measurements from the previous section are plotted as a function of distance between source and detector. We expect that the plots of \( \log(\text{distance} \times \text{DC}) \), \( \log(\text{distance} \times \text{amplitude}) \), and phase to be approximately linear with respect to distance. In order to speed up the computation of the average optical properties, we calculate the mean and standard deviation of all data points corresponding the same source/detector separation. The mean values and standard deviations are used to construct a \( \chi^2 \) which is minimized to find the absorption and reduced scattering coefficients. In figure 4.11, plots of the mean values are shown.
Figure 4.10: Fitted DC, amplitude, and phase data for each individual CCD pixel as a function of source detector separation. (A) semi-log plot of distance $\times$ intensity. (B) semi-log plot of distance $\times$ amplitude. (C) plot of phase delay.

Note that the phase plots begin to bend over at a distance of about 8.5 cm. Data from source detector separations where the measured phase is non-linear are not used in subsequent analysis.

For the 209 measurements of the sample described in the previous section the mean values for absorption and reduced scattering were $\mu_a = 0.0205 \pm 0.0002 \text{ cm}^{-1}$ and $\mu'_s = 6.7588 \pm 0.05 \text{ cm}^{-1}$.

We also performed titration experiments in which the absorption and scattering of the mixture was increased by adding india ink for absorption or additional Lyposin for scattering. Figure 4.12 shows the results of the ink titration experiment. Expected values for $\mu_a$ were determined by
Figure 4.11: Fitted DC, amplitude, and phase data for mean values of all CCD pixels with the same source detector separation as a function of source detector separation. (A) semi-log plot of distance $\times$ intensity. (B) semi-log plot of distance $\times$ amplitude. (C) plot of phase delay.
measuring the (diluted) ink with a spectrophotometer. A least squared fit to the measured results gives a 0.64 increase in measured $\mu_a$ per expected change in $\mu_a$. Reduced scattering coefficient changes by 0.15 cm$^{-1}$ ($\sim 2\%$) per 0.01 cm change in expected $\mu_a$. Figure 4.13 shows the result of the $\mu_s'$ titration experiment. Here, the x-axis represents the percent Lyposin concentration (i.e. grams of soybean oil per 100 ml). Least squared fits to the measured values give 0.9 cm$^{-1}$ change in measured $\mu_s'$ and a 0.002 cm$^{-1}$ change in measured $\mu_a$ per 1% change in Lyposin concentration.
4.4.3 Phantom Images

We have also performed imaging experiments to demonstrate our ability to simultaneously reconstruct spatially varying maps of both absorption and scattering. Two cylinders with heights and diameters of 1.5 cm were positioned halfway between source and detector planes. The slab thickness was 6 cm. The imaging tank was filled with a 0.8% mixture of Lyposin III. No ink was added to the fluid in the tank so that the background absorption was equal to that of water (i.e., 0.021 cm$^{-1}$ for 785 nm light). The two cylinders were initially filled with the same fluid that was in the tank. Then the left cylinder was titrated with Lyposin eight times, while the right cylinder was simultaneously titrated with additional ink. The expected contrasts for both absorption and reduced scattering coefficients ranged from 2:1 to 9:1. The reconstructed images are shown in Fig. 4.14 (top). Only the center slice (which contained the cylinders) is shown for each three-dimensional reconstructed image. Plots of the ratio between the maximum value in the target and the background are shown for both reduced scattering (left) and absorption (right). The scattering contrast has little crosstalk and the measured values are close to the expected ones. In contrast, the absorption contrast is significantly smaller, although it does follow the correct trend. This is due to the fact that more regularization was used to reconstruct the absorption images than was used to reconstruct the reduced scattering images. Unfortunately, the noise in the measured data prevented the use of the optimal regularization needed to reconstruct the expected absorption values. When less regularization was used in the absorption reconstruction, the images were dominated by noise, and the absorbing blob was not visible. This was not a problem for the scattering reconstructions. Apparently, the absorption reconstruction is more sensitive to noise in the data.
Figure 4.14: Images of absorption and reduced scattering coefficients for an experiment with an absorbing and a scattering inhomogeneity. Top row: absorption reconstructions for the 8 titrations. Second row: scattering reconstructions for the 8 titrations. Bottom left: measured scattering contrast in the two inhomogeneities as a function of expected scattering contrast in the left inhomogeneity. Bottom right: measured absorption contrast in the two inhomogeneities as a function of expected absorption contrast in the right inhomogeneity. Bottom center: photo of the two cylinder in the imaging tank before the scattering fluid was added.

### 4.4.4 Human Subject

Finally, a healthy human subject has been measured in the new breast imager. We note here that there is a black box connecting the detector window to the image intensifier which shields stray light. A small door is machined in this box which allows the technician to view the placement of the breast in the imaging tank. One should always check that the breast is centered in the field of view. Since the breast is mildly pressed against the detector window, one can determine its location, even when the tank is filled with the highly scattering matching fluid. One should also check by looking through the detector window, that enough matching fluid is in the tank such that there is no air gap between the fluid and the subject’s chest. The presence of an air gap near the chest or axilla, will allow light from the top source positions to arrive at the image intensifier without having traversed all the way through the entire scattering volume (i.e. the breast and surrounding fluid). First, this makes the experiment incompatible with our model of diffuse photon propagation. Second, and
Figure 4.15: Reconstruction images of absorption and reduced scattering coefficient for the right breast of a healthy human volunteer.

more urgent, there is the potential to over saturate the (60K) image intensifier and damage it.

The reconstructed images of absorption and scattering of the subject appear in Fig. 4.15. Note the breast is easily distinguished from the matching fluid. Higher absorption (and scattering) appears in the center of the breast and towards the chest wall. This is expected because the glandular region in the center of human breast is denser and contains more blood than the outer fatty region.
Chapter 5

Comparison with Positron Emission Tomography

5.1 Introduction

Recently, diffuse optical experimenters have begun to compare and incorporate traditional medical diagnostics such as Magnetic Resonance Imaging (MRI) [18, 47, 73], ultrasound [120], and X-ray mammography [61] with the optical measurement. Typically, the goal of this work is to combine higher resolution imaging modalities with low resolution diffuse optical imaging in order to use structural information from the former to improve upon the functional potential of DOT. In particular, the structural details acquired using MRI and X-ray imaging are used as a priori information to aid the optical reconstructions [18, 47, 120]. The goal of the research described in this chapter is different. DOT images of human breast are co-registered with positron emission tomography (PET). PET is a clinically useful imaging modality that employs the uptake of radio-pharmaceuticals to measure physiological processes. In PET, the increased metabolic rate
of most tumors compared to normal tissue provides a basis for their detectability via the radiopharmaceutical $^{18}$F-fluorodeoxyglucose ($^{18}$F-FDG). Like PET, DOT also primarily measures the physiological characteristics of tissue. DOT is sensitive to changes in the absorption of near-infrared light due to variation of the concentrations of endogenous chromophores such as oxygen and deoxy-hemoglobin, water, and lipid. Using exogenous fluorescence probes, DOT also has the potential to measure other physiological characteristics of tissue such as pH [56], intracellular calcium concentration [58], and tumor specific receptors [2, 14, 37, 53, 57, 74, 85]. Thus, the combined use of DOT, fluorescence DOT (FDOT) [27, 32, 48, 49, 75, 76, 78, 113], and PET holds potential to expand the toolbox for researchers who study cancer in vivo. The goal of this chapter is to compare PET and DOT for breast tumor imaging, to demonstrate how these comparisons can be accomplished, and to suggest ways that the co-registration of these functional imaging techniques may be beneficial.

We begin by reviewing some research in both the PET and DOT literature. Clearly, the ability to detect physiological change is important for measuring and predicting tumor responses to cancer treatment. To date clinicians primarily use tumor size to evaluate the response of tumors to therapy. Unfortunately, however, this approach requires that clinicians must wait weeks-to-months for anatomical changes to occur, even though some physiological changes surely occur on shorter timescales. In addition, some of the newest therapies (e.g. hormone therapies for breast cancer) are potentially ‘cytostatic.’ These therapies may stop cancer growth without destroying the cancer, and may be successful even when no significant reduction in tumor size occurs [35]. PET scans taken after the first round of chemotherapy are demonstrably strong indicators of treatment efficacy in breast cancer patients [40, 62, 87, 92, 96, 104]. Likewise, several case studies using optical methods to monitor neoadjuvant chemotherapy of locally advanced breast cancers have shown
promise [24, 51, 119]. Unlike PET, continuous or repetitive treatment monitoring is feasible with optics due to its low cost and non-invasive nature. In all of these studies, the long term clinical goal is to predict the outcome of treatment early on, while there remains enough time to modify treatment. This is especially important for breast cancer where many treatment options can exist even if the initial chemotherapy fails.

DOT and PET may be able to identify resistance factors to cancer treatments. For example, hypoxic tumors (i.e. those having a low partial pressure of oxygen (pO$_2$)) are often more resistant to radiation and chemotherapy [19, 34, 103, 107]. Several studies report that the determination of the oxygenation status of a tumor might afford improved disease management [17,33,45,68]. DOT detects tumor hypoxia by measuring decreases of tissue blood oxygenation (StO$_2$), and high/low values of StO$_2$ in a lesion with respect to the surrounding tissue, imply high/low relative values of pO$_2$ in the lesion. Likewise, increased $^{18}$F-FDG uptake measured with PET is associated with hypoxia. A lack of oxygen can lead to the anaerobic metabolism of glucose, which is inefficient, and requires that cells increase glucose consumption.

There are further potential benefits to be derived by combining DOT and PET. DOT data may facilitate more accurate determination of the tumor hypoxic state by PET. Some non-hypoxic tumors have high rates of glucose metabolism, and chronic hypoxia can lead to decreases in glucose metabolism. $^{18}$F-FDG PET alone is therefore not always a reliable measure of tissue hypoxia. Indeed, this observation has lead to recent research using nitroimidazole PET tracers such as $^{18}$F-fluoromisonidazole to measure tumor hypoxia in variety of cancers including breast cancer [80,86]. Diffuse optical methods measure tissue oxygenation using endogenous contrast. Thus they are not subject to variations in tracer uptake due to physiological factors such as poor perfusion [99], nor
do they require the subject to return to the hospital on another day for injection and scan of a second tracer. In addition, simple models of the relative rate of oxygen metabolism in tumors can be employed by diffuse optical methods [117] and might in the future provide a means to study the relationship between FDG kinetics and oxygen metabolism. A high rate of glucose consumption that is not accompanied by a high rate of oxygen metabolism, for example, would imply that some glucose is being metabolized inefficiently, presumably due to an insufficient supply of oxygen.

Finally, PET techniques are well suited to validate DOT. This validation is important because, unlike PET, DOT is still in its initial research phase and has not as yet been fully translated to the clinic. It is reasonable to expect that increases in glucose metabolism require more blood for glucose and oxygen delivery and therefore should be accompanied by increases in total hemoglobin concentration. In fact, $^{18}$F-FDG uptake has already been shown to correlate well with the uptake of a tumor blood-flow-specific tracer in breast cancer [100, 115]. If a strong correlation between hemoglobin concentration and glucose consumption exists, PET could be very well suited to validate DOT results.

The remainder of this chapter is organized as follows. I begin with an introduction to PET imaging. This is followed by a section on DOT, which specifies the particular methods used in this work. Next, I will motivate and describe the methods used to co-register the DOT and PET images. Finally, I show results from recent clinical research. Comparisons between DOT and PET imaging for breast cancer suggests correlations between $^{18}$F-FDG uptake and optically measured parameters such as total hemoglobin concentration and scattering [55].
5.2 Positron Emission Tomography (PET)

5.2.1 PET Fundamentals

Positron Emission Tomography (PET) is a clinically accepted imaging modality that images the uptake of a pharmaceutical of physiological interest by tagging it with a positron-emitting radioisotope. The tagged pharmaceutical, called a radio-pharmaceutical, is injected or inhaled. It then distributes in the body in accordance with the biokinetics of the pharmaceutical, which are similar to those of its non-radioactively labeled analog. When a proton in the nucleus of the radioisotope decays into a neutron, it emits a positron and an anti-neutrino. The positron travels a short distance (~1 mm for $^{18}$F) in the tissue losing energy through Coulomb interactions, and eventually annihilates with an electron. The annihilation produces a pair of 511 keV photons traveling in (nearly) opposite directions (Fig. 5.1(a)). Assuming neither photon is absorbed by tissue, the two photons will exit the body at almost the exact same time. PET tomographs are designed to detect these coincident photon pairs along all possible projection lines through the body. (Fig. 5.1(b)). By measuring the number of photon pairs emitted along each projection line, one can reconstruct quantitative maps of the tracer distribution. The resulting image of tracer distribution thus serves as an indication of a physiologic process, which is interpreted by the physician.

The tracer used for most clinical studies is $^{18}$F-fluorodeoxyglucose ($^{18}$F-FDG). With a half-life of 109.8 minutes, a relatively large fraction of the $^{18}$F decays may be detected during a typical 30-minute scan. In addition, the half-life is long enough so that the radioactive flourine can be produced in a regional facility and flown to nearby hospitals. An analog of glucose, $^{18}$F-FDG enters the cell and is phosphorylated in parallel to glucose to form $^{18}$F-fluorodeoxyglucose-6-phosphate ($^{18}$F-FDG-6-P). However once phosphorylated, it cannot be further broken down by
Figure 5.1: (a) Schematic of positron decay and annihilation. A proton in the unstable nucleus decays to neutron giving off a positron and anti-neutrino. The positron travels a few millimeters in tissue before annihilating with an electron to give off a pair of 511 keV photons traveling in opposite directions. (b) An annihilation event produces two 511 keV photons which are detected by a ring of detectors.

the cell. Furthermore, the $^{18}$F-FDG-6-P is not readily dephosphorylated and cannot cross the cell membrane. As a result the $^{18}$F containing molecule is metabolically trapped in the cell. Over time, cells metabolising larger amounts of glucose, will accumulate more $^{18}$F. An image of the $^{18}$F distribution in the body taken about an hour after injection offers a quantitative mapping of $^{18}$F-FDG uptake. It therefore is a good measure of glucose metabolism.

5.2.2 PET Image Reconstruction

Image reconstruction methods in PET can be divided into two general categories: analytic and iterative (see Ref. [110], chapters 21 and 22, for a more in-depth treatment). In the analytic approaches, the data for each pair of detectors (corrected for attenuation) is treated as the Radon transform (line integral) of the tracer concentration across the line connecting the two detectors.
The tracer concentration is determined by inverting the Radon transform using filtered backprojection or a related algorithm. Analytic methods are computationally fast, however they do not permit all effects of the measurement process to be modelled.

Iterative methods require a large amount of computation, but permit more accurate modelling of the measurement process. These methods involve the inversion of a system matrix (similar to the weight matrix from section 2.2.3) which gives the sensitivity of each measurement to each voxel in the image. Unlike the weight matrix in DOT, however, the system matrix for PET is linear (i.e. the values of its elements do not depend on the tracer distribution for which we are solving). Also, in contrast to optical tomography, where the weight matrix is nearly singular, for most detector configurations the PET system matrix is well posed and easily inverted. Each row corresponds to one detector pair and consists primarily of ones for voxels in a narrow volume connecting the pair of detectors, and zeroes for other voxels, with adjustments that take into account the attenuation and scattering of the 511 keV photons, random coincidence events, and detector characteristics.

The principle difficulty in PET reconstructions is that only a small number of photons are collected. As a result, the data is noisy, and it is desirable to take into account the photon statistics of the measurement. For this reason the system matrix is inverted using iterative algorithms which attempt to find the tracer distribution that has the highest probability for producing the measured data. The maximum likelihood expectation maximization (ML-EM) algorithm, first used in emission tomography in the 1980’s, is the best known [59, 95]. Several other algorithms have been developed to speed up the slow convergence of the ML-EM algorithm when reconstructing large 3D volumes. One of these, the three-dimensional row-action maximum likelihood algorithm (3D RAMLA) was used to generate the PET reconstructions for the work presented in this chapter [20].
5.2.3 PET Instrumentation

In this chapter I compare 3D DOT reconstructed breast images with PET images of the same breast acquired by two different PET scanners: a dedicated breast-only PET scanner (BPET) developed at the University of Pennsylvania and a commercially available whole-body PET scanner (Allegro - Philips Medical Systems). We briefly describe the scanners here. For a thorough discussion of PET system design, the reader is referred to the review by Lewellen and Karp (Ref. [110], chapter 10).

Commercially available whole-body PET tomographs achieve high sensitivity to 511 KeV annihilation photon pairs using a cylindrical configuration of detectors surrounding the patient. The imaging instrument used for acquisition of wholebody PET images in this chapter was an Allegro scanner (Philips Medical Systems), with an axial field of view (FOV) of 18 cm, a trans-axial FOV of 56 cm, and a ring diameter of 86.4 cm at the surface of the detectors. The scanner exhibits 5 mm spatial resolution (i.e. FWHM of a point source), and a sensitivity of 4.4 cps/kBq [98].

In our study, patients fasted for at least 4 hours prior to the scan. Each scan was initiated 60 minutes after intravenous administration of $^{18}$F-FDG with a dose of 5.2 MBq/kg. Sequential overlapping scans were acquired to cover the body from neck to pelvis, as the patient lay supine on the gantry. Transmission scans obtained with a $^{137}$Cs point source were interleaved between the multiple emission scans to correct for non-uniform attenuation of the 511 KeV photons by the patients body and the gantry.

The ability to image breast cancer with $^{18}$F-FDG PET has led to the development of a dedicated breast imaging PET scanner, BPET [38, 39]. In a whole-body scanner, the 511 KeV photons emitted from the breast are attenuated by the body, reducing the scanners sensitivity to breast lesions. In contrast, a dedicated breast scanner permits the breast to be imaged with significant
reduction in attenuation, i.e. about a factor of 10 reduction. The subject lies prone on a table with an opening to allow the breast to drop between two detectors whose separation distance can be adjusted to accommodate different sized breasts (Fig. 5.2(a)). This geometry is very similar to the geometry of the DOT scanners (Fig. 5.2(b)). The main difference is that the breast hangs freely in the PET scanner, while in the DOT scanner the breast is mildly compressed.

Breast-only PET Scanner

Figure 5.2: (a) Breast-only PET scanner. The breast hangs freely between the two movable detector units. (b) DOT breast scanner. The breast is mildly compressed to 5.5 - 7.5 cm.

The scanner is composed of two curved plate NaI(Tl) detectors of 1.9 cm thickness each with an active area of 28 x 21 cm². By positioning the detectors close to the breast, a large solid angle
can be covered, thus optimizing the systems sensitivity for a split ring configuration. However, this configuration leads to the loss of data from the 511 KeV photons arriving at angles not covered by the detector plates. In fact, for a typical separation of 20 cm the angular coverage of 180° corresponds to one half of complete angular acceptance. This geometry requires the use of a limited angle reconstruction which we perform using a modified version of 3D RAMLA that compensates for the missing data.

The spatial resolution of the system varies from 3.8 mm (radially at center) to 4.5 mm (radially at r = 5 cm). The Allegro whole-body scanner has a uniform spatial resolution of 5 mm. Phantom measurements have demonstrated superior contrast recovery for BPET compared to the Allegro instrument as a result of the improved spatial resolution, even with the loss of data due to the limited angle geometry. A pilot study of 20 patients imaged with both Allegro and BPET demonstrated good correlation in lesion detectability, but better detail in the breast lesions was achieved in the BPET images [97].

5.3 DOT Protocol

While DOT image reconstruction and instrumentation have already been discussed generally in chapters 2 and 4, in this section I briefly describe the details of the DOT data collection and image reconstruction used for the DOT/PET comparison.

All measurements in this study were made with the previous generation breast scanner described in section 4.2. Two scans were made for each breast: a reference scan in which the tank was filled with matching fluid only and a scan with the breast immersed in matching fluid. We fitted data from the frequency domain remission measurements of the breast to an extrapolated boundary solution of the diffusion equation for a homogeneous medium in the slab geometry (section 2.1.3)
in order to obtain estimates of the average chromophore concentrations, scattering prefactor $A$, and scattering power $b$ inside the breast. The absorption due to volume concentrations of water (31%) and lipid (57%) in the breast was held fixed, based on values from the literature [60,111,112]. The optical properties of the matching fluid were determined independently by fitting to the frequency domain measurements of the reference scan.

To reconstruct images of the breast, we used the model based reconstruction method described in section 2.2.7. We used a multi-spectral approach (section 2.2.8) to solve directly for oxy- and deoxy-hemoglobin concentrations via decomposition of the absorption coefficient into contributions from individual chromophores, assuming a simple Mie-scattering approximation for the reduced scattering coefficient. We implemented this approach by modifying the software TOAST (Time-resolved Optical Absorption and Scattering Tomography) in order to utilize multi-spectral continuous wave data [1]. The method is described in detail in Corlu et. al [28].

A photograph of the compressed breast was taken just before each scan. It allowed us to segment the imaging volume into breast and matching fluid regions. Using average results for the breast as an initial guess, we then employed a nonlinear conjugate gradient algorithm (section 2.2.7) to solve directly for 3D tomographic maps of the chromophore concentrations and scattering prefactor $A$ inside the breast. The scattering amplitude $b$ was held fixed at its bulk value, as were the optical properties of the matching fluid region. At each iteration, a finite element solver (section 2.1.4) predicted the detected continuous-wave light intensity based on the current maps of chromophore concentrations, and these maps were then updated in order to minimize a $\chi^2$, which represented the difference between measured and predicted values of light exiting the breast. Finally, the resulting maps were combined to form images of total hemoglobin concentration $[THC(r) =$
\[ C_{Hb}(r) + C_{HbO_2}(r) \], blood oxygen saturation \[ StO_2(r) = C_{HbO_2}(r)/THC(r) \], reduced scattering coefficient \[ \mu'_s(r) = A(r)\lambda^{-b} \], overall optical attenuation \[ \mu_{eff}(r) = \sqrt{\mu_a(r)/D(r)} \], and an empirical optical index \[ OI(r) = rTHC(r) \times r\mu'_s(r)/rStO_2(r) \].

5.3.1 Subject Protocol

Informed consent was given by all DOT and BPET patients in accordance with the University of Pennsylvania Institutional Review Board. Out of the 30 patients who received both DOT and whole-body PET scans, we selected the 14 who had not received a biopsy or any form of treatment between the dates of the DOT and PET scans. For 12 of these patients, the two scans were on the same day. For the other 2, the scans were separated by 4 and 13 days.

To date, 3 of the 30 patients have also been successfully scanned with our prototype BPET instrument in addition to receiving the whole-body PET scan. The geometries of the DOT and BPET instruments are similar, with the patient lying prone with sources/detectors towards the head and feet, allowing us to coregister the images using a deformation algorithm (see below). Unfortunately, two of these patients received core-biopsies between the DOT and BPET measurements. Nevertheless, given the potential advantages of coregistering the images, we include results for all three BPET patients.

5.4 Image Co-registration

There are two basic approaches for combining diffuse optical measurements with measurements from other medical imaging modalities. In one approach the DOT device is incorporated into the other device [18, 47, 61, 75]. The advantage of such a system is that measurements from the two
modalities can be made concurrently in the same geometry, facilitating co-registration of the resulting images. However, integration of the DOT system into another instrument places restrictions on both instrumentation types. In the second approach, measurements are taken on separate stand-alone devices. Parameters are derived optimally from the respective images (taken separately) and compared. In addition to allowing the optimal instrumentation to be used, this approach readily permits DOT measurements to be combined with more than one other modality. In this section I describe the methods we used to co-register the images for a more detailed comparison [13].

Co-registration of DOT and BPET images makes possible comparison of specific regions of the BPET images with their corresponding regions in DOT images. Co-registration also enables one to determine to what extent lesions appear in the same spatial locations for the two modalities. Although the images were acquired with separate stand-alone scanners, the similar geometries of the scanners made co-registration possible, though the problem was made more challenging because the breast hangs freely in the BPET scanner, while in the DOT scanner, the breast is mildly compressed (to a thickness between 5.5 and 7.5 cm).

3D-DOT/3D-PET image registration presents new challenges and there is no standard of co-registration today to validate against. We have conducted initial patient and phantom validation studies [10–13] for 3D-DOT/3D-MR image registration which confirm the accuracy of our algorithm. The method is automatic with little prior user interaction required. It is robust enough to handle a majority of patient cases and computationally efficient for practical applicability. I briefly review the major features of the registration algorithm below.

Since the DOT images are low resolution, without well defined features, we cannot use a registration process dependent on aligning specific feature in the two images. Instead, we align the DOT and PET images by an iterative process, in which the DOT image is modified until a function
measuring the “similarity” between the DOT and PET images is maximized. Nine parameters in the DOT image are optimized in order to maximize the “similarity” function. They are translation in three directions, rotation in three directions, and linear scaling in three directions.

We proceed by thinking of the DOT and PET images lists of discrete numbers. Each number correspondes to the intensity of some voxel in that image. For each image we make a histogram of the different intensity values. We define the entropy of image $A$ with $N$ discrete intensity values $x$ as

$$H(A) = - \sum_i^N p(x_i) \log(p(x_i)) ,$$

(5.1)

where $p(x)$ is the probability that a voxel picked at random will have intensity value $x$ (i.e. the number of voxel with intensity $x$ divided by the total number of voxels). If there are two images $A$ and $B$, they will have a joint histogram, and we can define their joint entropy as

$$H(A, B) = - \sum_i^N \sum_j^N p(x_i, y_j) \log(p(x_i, y_j)) .$$

(5.2)

Here $p(x, y)$ is the probability that the values of images $A$ and $B$ corresdonding to voxels located at a point picked at random will have the intensity values $x$ and $y$ respectively. The function we choose to maximize is called the mutual information, and was original used for medical image registration by Wells et. al. [109]. It is defined as

$$I(A, B) = H(A) + H(B) - H(A, B) .$$

(5.3)

In our application, the PET image is image $A$. It is held fixed, and its entropy does not change. We then adjust the DOT image. As the two images become aligned, voxels with similar values will
be located in the same areas, and the joint histogram of the two images will become sharply peaked. As a result the joint entropy $H(A, B)$ will decrease, and the mutual information will increase. The presence of the entropy of the DOT image $H(B)$ in Eq. 5.3 assures that the DOT image will not be translated such that none of its features are in the field of view.

In order to speed up the registration process, we do not maximize the mutual information of the 3D images directly. Instead, for each image, we compute its maximum intensity projection (MIP) [21, 22]. The MIP is the projection of a 3D image onto a plane, such that the value for each point on the plane is equal to the maximum intensity of the 3D image on the line perpendicular to the plane which intersects the plane at that point [105]. The DOT MIP is then adjusted so that its mutual information with respect to the PET MIP is maximized. The DOT MIP can be translated and scaled in two directions, and rotated in one. After this has been done, the mutual information between DOT and PET MIP’s is maximized for the two other orthogonal directions. The whole process of maximizing the mutual information for three orthogonal directions is then iterated. We further optimize the performance of projection and 2D-2D registration similarity computation using graphics processing units (GPU’s). A general validation of our approach can be found in [54].

Figure 5.3 shows cross-sections of a 3D reconstructed breast image before and after coregistration. The reconstructed image shown in the left column corresponds to the actual DOT measurement geometry in which the breast is compressed axially. The right column shows the the same reconstructed image after being coregistered by the volume warping algorithm. Once the coregistration was completed, the location of the lesion was determined by looking at the BPET image. An ellipsoidal volume corresponding to the lesion was chosen as the region of interest (ROI), and this exact same ROI was selected in the DOT images.
The situation with whole-body PET is different. During whole-body PET scans, the patient lies in a supine position, as opposed the prone position of the DOT and BPET scanners. In the supine position, the breast is compressed against the chest, and deforms unpredictably. Generally, rigid body motion and linear scaling cannot account for all of these deformations. As a result, when comparing DOT images to those from whole-body PET scans we are unable to coregister the images.
5.5 Clinical Observations

5.5.1 Whole-body PET and DOT

The simplest way to compare images from two different modalities is to use stand-alone scanners, analyse the images from each modality separately, and then compare the results. Several studies have used this approach to compare the results of diffuse optical measurements of human breast with other modalities including, MRI [24, 75, 94], x-ray mammography [43, 82, 83], and ultrasound [43, 118].

We compared DOT and whole-body PET images from 14 subjects with breast lesions [55]. Contrast was visible in both DOT and PET images for 9 subjects, neither DOT or PET for 2 subjects, and PET only for 3 subjects. When contrast was seen in the DOT images it always appeared in THC, $\mu'_s$, $\mu_{eff}$, and optical index. Significant contrast was never observed in StO$_2$. Representative images from a patient with invasive ductal carcinoma are shown in Figure 5.4.

These results were compared with the pathology reports from biopsies taken after imaging. A summary of the results is found in Table 5.5.1. Of the 9 subjects who showed both DOT and PET contrast, histopathology confirmed invasive ductal carcinoma (IDC) with ductal carcinoma in situ (DCIS) in 7 subjects, DCIS only in one subject, and normal breast tissue in one subject. In one of the subjects with IDC, two distinct lesions were visible with PET, but only the larger one was visible with DOT. For the subject with normal breast tissue, the increase in FDG uptake was located at a previous surgical site, and was due to a post-excisional inflammation. This inflammation was visible in the DOT images as well. Of the two subjects who showed neither DOT or PET contrast, one had a possible lipoma (benign), and the other had a cyst. Of the 3 subjects who showed contrast in PET but not in DOT, one had IDC and DCIS, one had a cyst (superficial and probably infected),
Figure 5.4: Axial, sagittal, and coronal slices from the PET (FDG) and DOT ($\mu_{eff}$) reconstructed images of subject 4. The orientation for the PET and DOT images is the same. However, the DOT images are of the left breast only, whereas the entire torso is shown in the PET images. Rectangular boxes denote the breast region in the wholebody PET images.

and one did not receive a biopsy after negative findings from both ultrasound and MRI. For this subject, the uptake of FDG was diffuse, i.e. no clear focus of FDG uptake was visible.

A quantitative comparison of tumor-to-background ratios between the DOT and whole-body PET images showed positive correlations (p value < 0.05) between FDG uptake and THC, $\mu'_n$, $\mu_{eff}$, and optical index. However, correlation coefficients for these parameters were not particularly high (R=0.67 - 0.76). These results are summarized in Figure 5.5. Using the mean and maximum standardized uptake values for the PET scans, as opposed to tumor-to-background ratios, had little effect on the correlations with DOT parameters. Comparison of tumor-to-background ratios for both PET and DOT did not show significant correlations with age, tumor grade, or tumor size.
<table>
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<th>Age</th>
<th>Days between DOT and PET examination</th>
<th>Visible in PET</th>
<th>Visible in DOT</th>
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</tr>
<tr>
<td>6</td>
<td>51</td>
<td>0</td>
<td>Yes</td>
<td>No</td>
<td>none (superficial cyst)</td>
</tr>
<tr>
<td>7</td>
<td>64</td>
<td>0</td>
<td>Yes</td>
<td>Yes</td>
<td>DCIS, 0.9cm</td>
</tr>
<tr>
<td>8</td>
<td>43</td>
<td>0</td>
<td>Yes</td>
<td>No</td>
<td>none (MRI &amp; US negative results)</td>
</tr>
<tr>
<td>9</td>
<td>53</td>
<td>0</td>
<td>No</td>
<td>No</td>
<td>cyst</td>
</tr>
<tr>
<td>10</td>
<td>59</td>
<td>0</td>
<td>Yes</td>
<td>Yes</td>
<td>normal tissue (surgical inflammation)</td>
</tr>
<tr>
<td>11</td>
<td>44</td>
<td>0</td>
<td>Yes</td>
<td>Yes</td>
<td>IDC &amp; DCIS, 3+3+3=9, 1.5cm</td>
</tr>
<tr>
<td>12</td>
<td>50</td>
<td>13</td>
<td>No</td>
<td>No</td>
<td>mature adipose tissue (possible lipoma)</td>
</tr>
<tr>
<td>13</td>
<td>61</td>
<td>0</td>
<td>Yes</td>
<td>No</td>
<td>IDC &amp; DCIS, 1+2+1=4, 0.8cm</td>
</tr>
<tr>
<td>14</td>
<td>37</td>
<td>0</td>
<td>Yes</td>
<td>Yes</td>
<td>IDC &amp; DCIS, 3+3+3=9, 2.3cm</td>
</tr>
</tbody>
</table>

Table 5.1: Visibility of lesions to DOT and wholebody PET compared with histopathology after imaging. The following abbreviations are used. IDC: invasive ductal carcinoma. DCIS: ductal carcinoma in situ. mBR grade: (modified) Bloom-Richardson grade.

5.5.2 Breast-only PET & DOT

Reconstructed DOT images have been co-registered with MRI [13, 18, 47], ultrasound [46, 120], X-ray mammography [61, 116]. In this section I present results from three subjects with breast abnormalities from our study comparing DOT and PET [55] in which we were able to coregister the DOT and PET images. PET images were acquired on the dedicated breast-only PET scanner (BPET) described in section 5.2.3. As described in section 4.2, our DOT device is a stand-alone breast imager. Thus PET and DOT images were not acquired concurrently. Instead they were acquired at different times and in slightly different geometries. Fortunately, the similar geometries of the scanners made co-registration possible, though the problem was made more challenging because the breast hangs freely in the BPET scanner, while in the DOT scanner, the breast is mildly compressed (to a thickness between 5.5 and 7.5 cm). We used the methods presented in section 5.4 [13] to deform the DOT breast images, and align them with the BPET breast images.

Axial slices from the coregistered images of the three patients receiving both DOT and BPET scans appear in Figure 5.6. Regions of interest determined from the PET images are denoted by
Subject A had a suspicious mass in her right breast. A core biopsy performed five weeks before DOT and BPET imaging revealed a ductal carcinoma in situ, with some evidence of invasive carcinoma as well. Biopsy marks were still visible the day imaging was performed. Digital mammography and MRI (performed the same day as DOT and BPET) saw some enhancement, while ultrasound (also the same day) had no suspicious findings. The BPET image shows increased FDG uptake above the nipple. The DOT images show an increase in THC, $\mu'_s$, $\mu_{eff}$, and optical index in this same location. A subsequent biopsy indicated that ductal carcinoma in situ was still present on the day the imaging was performed.

Subject B had a palpable mass in the subareolar region of the left breast. The mass (~3 cm
across) was visible to both X-ray CT and ultrasound. DOT images indicate an increase in THC, $\mu'_s$, $\mu_{eff}$, and optical index at the location of the mass, as well as a decrease in StO$_2$ slightly above this region. An excisional biopsy of the mass (performed later during the same day as the DOT exam) revealed a hemorrhage in its center, consistent with the increase in THC seen by DOT. The lesion was diagnosed as a partially organized abscess with no carcinoma present. BPET was performed 11 days later. The increase in FDG uptake was due to a post-surgical seroma. This collection of serous fluid was located in the same position as the mass which was removed.

Subject C had multiple masses of concern. A core biopsy revealed invasive ductal carcinoma. BPET was performed about a month before the biopsy. FDG uptake is clearly visible. Unfortunately, DOT was not performed until one month after the biopsy (i.e. two months after BPET). Most notable in the DOT image, is an increase in THC, $\mu'_s$, $\mu_{eff}$, and optical index along with a decrease in StO$_2$ in the region above the nipple. A subsequent excisional biopsy showed that invasive ductal carcinoma was still present at the location of the original biopsy at the time of the DOT measurement.

The co-registered images in Figure 5.6 show qualitatively that DOT parameters (with the exception of StO$_2$) are above average in the ROI’s determined from BPET. To confirm this observation, we performed the following analysis. For each DOT image, we calculated the average value of particular image parameters for all voxels in the entire breast and for all voxels in the ROI. The tumor-to-background ratio (TBR) is defined as the ratio of these two parameters (i.e. TBR=<$\text{ROI}$>/<$\text{Breast}$$>). The optical index parameter shows the greatest contrast (TBR=1.5-1.7). THC, $\mu'_s$, and $\mu_{eff}$ exhibit somewhat less contrast (TBR=1.1-1.4), while very little variation in StO$_2$ is observed (TBR$\geq$1.0). These results are summarized in table 5.5.2.
5.6 Summary

PET and DOT are functional imaging techniques that interrogate cancer physiology in deep tissue 
\textit{in vivo}. Combined they have the potential to measure a large number of functional parameters. 
Among these parameters, glucose metabolism, hypoxia, tissue hemoglobin concentration and sat-
uration, and tissue scattering were explored in this chapter. This work, the first to explore the 
potential of PET and DOT multi-modal imaging, will likely stimulate further investigation along 
these lines for cancer response characterization.
<table>
<thead>
<tr>
<th>Subject</th>
<th>Average (Breast)</th>
<th>Average (ROI)</th>
<th>TBR</th>
</tr>
</thead>
<tbody>
<tr>
<td>THC ($\mu$M)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A</td>
<td>20.3</td>
<td>23.7</td>
<td>1.2</td>
</tr>
<tr>
<td>B</td>
<td>18.7</td>
<td>26.0</td>
<td>1.4</td>
</tr>
<tr>
<td>C</td>
<td>21.3</td>
<td>23.0</td>
<td>1.1</td>
</tr>
<tr>
<td>$StO_2$ (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A</td>
<td>92.2</td>
<td>93.0</td>
<td>1.0</td>
</tr>
<tr>
<td>B</td>
<td>87.5</td>
<td>91.3</td>
<td>1.0</td>
</tr>
<tr>
<td>C</td>
<td>73.7</td>
<td>72.0</td>
<td>1.0</td>
</tr>
<tr>
<td>$\mu'_s$ (cm$^{-1}$)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A</td>
<td>7.9</td>
<td>10.5</td>
<td>1.3</td>
</tr>
<tr>
<td>B</td>
<td>17.6</td>
<td>23.8</td>
<td>1.4</td>
</tr>
<tr>
<td>C</td>
<td>8.9</td>
<td>11.0</td>
<td>1.2</td>
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<tr>
<td>$\mu_{eff}$ (cm$^{-1}$)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A</td>
<td>0.99</td>
<td>1.23</td>
<td>1.2</td>
</tr>
<tr>
<td>B</td>
<td>1.41</td>
<td>1.92</td>
<td>1.3</td>
</tr>
<tr>
<td>C</td>
<td>1.10</td>
<td>1.29</td>
<td>1.2</td>
</tr>
<tr>
<td>Optical Index</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A</td>
<td>1.03</td>
<td>1.47</td>
<td>1.5</td>
</tr>
<tr>
<td>B</td>
<td>1.09</td>
<td>1.89</td>
<td>1.7</td>
</tr>
<tr>
<td>C</td>
<td>1.04</td>
<td>1.51</td>
<td>1.5</td>
</tr>
</tbody>
</table>

Table 5.2: Results from co-registered DOT/BPET images. Regions of interest (ROI’s) are selected based on BPET images. Tumor to background ratios (TBR’s) are calculated by dividing the average value in the ROI by the average value for the entire breast.
Chapter 6

Summary

Diffuse Optical Tomography (DOT) is a new imaging modality which combines biomedical optics with the principles of computed tomography. It is sensitive to concentrations of absorbers such as oxy- and deoxy-hemoglobin, water, and lipids. In addition, it can detect differences in the scattering properties of tissue. In this thesis I have focused on breast imaging. As was explored in Chapter 5, DOT holds great promise for monitoring and predicting cancer treatment. Its sensitivity to physiological parameters such as blood volume and oxygenation, which can change over short timescales, may in the future provide a means to predict the outcome of a particular therapy while there is still time to switch to an alternate treatment. For this reason it will most probably occupy a niche similar to that of PET in diagnosing breast cancer. Combined, the two modalities may be better able to guide treatment decisions than either modality alone. Furthermore, DOT’s low cost and use of non-ionizing radiation also make it ideal for treatment monitoring.

In this thesis, I demonstrated new instrumentation, algorithms, and clinical comparisons. A free space instrument, which did not use optical fibers, was developed. The instrument allowed us to collect large amounts of data. In order to analyze this data, we implemented new reconstruction
algorithms capable of utilizing large data sets. In this way we were able reconstructed images in which the sub-centimeter features of extended objects with realistic contrast were clearly resolved. I showed initial results from our next generation breast scanner. The new scanner also collected large data sets. However, the addition of a gain modulated image intensifier allowed us to collect data in the frequency domain, facilitating the simultaneous reconstruction of both absorption and scattering images. Finally, I presented results from the first study ever to compare DOT with PET. The reconstructed images were co-registered using newly developed software. We used correlations with PET to validate DOT results. In addition, we explored the use of the complimentary information provided by the two modalities.

Significant work remains to improve DOT’s ability to give reliable spectroscopic information and images. The fundamental obstacle to more detailed imaging and more accurate spectroscopy is the high degree of scattering of near-infrared light in tissue. As was explored in Chapter 3, the scattering manifests itself in two major ways. First, by randomizing the paths of photons, the scattering causes measured data to be smooth, even when the spatially varying optical properties of the tissue are not. As was shown in Chapter 3, this can be seen mathematically by the rapid decay of the Fourier components of the Greens functions for the diffusion equation, and consequently by the data generated by a point absorber. Second, scattering also decreases the change in the data due to small objects such as tumors simply because a great deal of the detected light never goes near the object even when it is located directly between a source and a detector. Thus, even though a large number of photons are detected, the scattered field is small. Unfortunately, the shot noise is determined by the number of collected photons, resulting in a modest signal to noise ratio.

In order to improve the situation one must either increase the signal-to-noise ratio or decrease the rate at which the Fourier components decrease. To some extent, the signal-to-noise ratio can
be improved by detecting more photons using more sources and detectors. This idea was explored in Chapter 3. Certainly no measured photons should be thrown away. For example, when using CCD detection, either all the pixels on the CCD array should be used as independent measurements (necessitating the inversion formulas of Chapter 2), or some type of binning or averaging of the data should be utilized. However, as explained in Chapter 3, the Fourier components decrease exponentially, whereas the SNR only increases with the square root of the number of measurements. Another approach would be to increase the contrast of the tumor by using an exogenous contrast agent, or a fluorophore with a high quantum yield. At this time, the only contrast agent approved for human use is indocyanine green (ICG) which is not specifically targeted to tumors and has a fluorescence quantum yield of only about 1%. However, this may change, as there is a significant amount of current research devoted to developing optical contrast agents which are sensitive to specific molecular targets [15, 108].

Another feasible approach may be to look at thinner tissues. Everything is expected to get better near the surface. The Fourier components of the Green’s functions decay more slowly as the depth decreases. Likewise, an object near a source or detector will cause a large change in the measurements corresponding to that source or detector, since most photons will have to pass through the object in order to be detected. One could use an instrument similar to the ones described in chapters 3 and 4. The dense grids of sources and detectors used in these instruments would allow one to detect the higher spatial frequencies present in the light transmitted through a thinner slab. Fortunately, the breast is a highly deformable organ, and clinicians already compress the breast during X-ray mammography. Such an approach would require however that the measurement be very short (i.e. tens of seconds) in order to minimize patient discomfort. This might entail (at least at first) performing a continuous-wave measurement at a single wavelength. In this case, one would
not be able to determine the concentrations of different chromophores, or separate the contributions
of absorption and scatter. Instead this approach would facilitate the reconstruction of images that
have less noise, better resolution, are more sensitive to small objects, and more accurately reflect
the size, shape, and contrast of breast lesions. This approach could also be used with fluorophores
with high quantum yields. In this way, one could retain the advantages of compressing the breast,
while also gaining knowledge of the specific molecular environments of breast tumors.
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