Hyperspectral Imaging for Diffuse Optical Tomography

Thesis

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by

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Dedication

To my parents. They have taught me everything that I know about being a respectable person and a researcher. And more.

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Abstract

Diffuse optical tomography (DOT) has emerged in the last decade as a new and exciting tool for functional medical imaging with applications in a range of areas including breast cancer detection and diagnosis. DOT employs observations of near infrared (NIR) light that has propagated through tissue to reconstruct the spatial distribution of various chromophores present in the region of interest. In the case of breast cancer, oxygenated and de-oxygenated hemoglobin are of particular interest in identifying and characterizing tumors. It is well known that the DOT reconstruction process can be quite sensitive to noise and other un-modeled effects due to the diffusive nature of the underlying physics as well as the limited aperture over which data can be acquired in many practical systems. While there exist a wide array of mathematical techniques for stabilizing the reconstruction, ideally one would like a richer data set. Most DOT instruments employ no more than five NIR wavelengths to probe the tissue; however recent work in the diffuse optical imaging group in the Biomedical department has led to the development of a hyperspectral system in which hundreds of wavelengths can be acquired. With the increase in data however comes an associated rise in the complexity of the image formation process. In this thesis, we explore the development and performance of algorithms for hyperspectral DOT. We detail an efficient method for forming the images based on the use of iterative algorithms applied to a linearized measurement model. Simulation and experimental results will be provided which show the advantages of hyperspectral imaging.

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Chapter 1

Introduction

In the past 10 years there has been increased research into the use of near-infrared light to image inside the human body. One of the techniques of interest is diffuse optical tomography(DOT) [GBD+00]. DOT is sensitive to the functional state of tissue such as the consumption of oxygen which is relevant to processes such as the growth of tumors as well as the state of brain activity. Specifically, the DOT method uses near-infrared light at multiple wavelengths, which allows for reconstruction of the space and time varying profiles of chromophore concentrations (oxy- and deoxyhemoglobin, water and lipids etc.) The latter of which convey functional information about the body [LBZ⁺05]. Although many applications have been shown for the DOT method the most promising ones are for breast imaging or brain imaging [FHP⁺05, SA99]. This thesis will focus on breast imaging but discussion on brain imaging and other applications can be found in Chapter 2.2.

Breast imaging researchers have for a long time been dependent on information from 3D imaging modalities, such as X-ray computed tomography (CT) and magnetic resonance imaging (MRI). Still, there are some drawbacks that plague these imaging methods. MRI remains a large and fairly expensive system and can entail a considerable maintenance cost. CT on the other hand exposes the patient to considerable amount of ionizing radiation which can be harmful. Recently the idea of detecting breast cancer has shifted from anatomical information, obtained from CT and MRI, and towards functional imaging modalities.

DOT represents a very strong candidate for providing this type of information specifically in the context of breast imaging. As was mentioned above, DOT uses near-infrared light, which in essence is electro-magnetic radiation but is at a significantly lower energy level than CT. Operating in the infrared spectrum, 650-900nm, gives us a range which is sometime called the window of transparency [SGA03]. In this window light propagates relatively far into the tissue (on the order of centimeters) before being absorbed thereby allowing us to probe quite deeply. Additionally, light is also scattered within the tissue where it interacts with subsurface inhomogeneities. This process is illustrated in Figure 1.1. Within the window, light is absorbed and scattered differently at different wavelengths depending on the spacevarying oxygenation state of the tissue. This relation gives us a way to using multiple wavelengths when estimating chromophore concentrations which is the basis of this thesis. Using different wavelengths, performing multi- or hyperspectral measurements, more information is added to the system by using more complete spectral information to improve the ability to determine the concentrations of chromophores. With this method it is possible to increase the effectiveness and accuracy of the DOT method.

Light propagating through tissue is highly scattered but significant advances have been made in recent years to solve the problem efficiently, both in terms of theoretically modeling the physics and developing useful codes for simulating the process and thereby setting the DOT method up as the prime candidate for future breast cancer detection systems. X-ray radiation in CT travels generally in a straight line, excluding Compton and Rayleigh scattering, resulting in a much simpler problem than DOT. In the case of diffuse optical tomography the photon's mean free path of travel between two scattering events is very short, most often only a fraction of a millimeter. Because of this, any photon traveling through a human breast undergoes numerous scattering events. Thus, unlike CT where the physics of the problem is basically straight line propagation and yields a linear relationship between the quantity of interest tissue density and the observed data, for DOT a far more complex model is required [SGA03]. More specifically, the physics of light interaction with the tissue is well modeled using a diffusion equation and, as we discuss in Section 2.3, yield a complicated, nonlinear relationship between the chromophore concentrations and the observations of scattered light [SGA03]. This model works well when scattering is stronger than absorption, which is frequently the case for biological tissue and is certainty justified for the breast imaging problem. Diffuse light propagation complicates the image reconstruction, an efficient way to model the propagation is to use the diffusion equation as the model. The diffusion equation expresses the photon density as a function of absorption coefficient and scattering coefficient and solving it will always provide the forward model needed to solve the inverse problem $[GBD^+00, BBM^+01].$

In the case of DOT, the goal is to estimate the concentrations of different chromophores based on the measured photons scattering and absorbing in the tissue. Depending on the wavelength observed by the detectors different scattering and absorption can be calculated from the measured data. This dependence of wavelength encourages the use of hyperspectral information.



Figure 1.1: The process of photons passing through tissue [BBM⁺01].

The DOT method is a nonlinear ill-posed inverse scattering problem due to the physics of the diffusion process just described $[BBM^+01]$. In this thesis, our primary objective is to explore the utility of hyperspectral data on the DOT problem. Thus, we simplify the inverse problem by linearizing the physics using a procedure known as the Born approximation $[GBD^+00]$. The ill-posedness poses a more substantive problem than the non-linearity. Ill-posedness means large changes in parameters yield fairly small changes in the data. In some sense this is a physics-based phenomenon, which means there is a lack of sensitivity in the data to the parameters. It also means that in the image formation process(if you do it naively), small changes in the data from noise and unmodeled effects can cause very large changes to the estimated profiles. In other words the reconstruction process is highly sensitive to small perturbations in the data. Adding to these difficulties is the fact that in many cases one seeks to recover more degrees of freedom (voxel values times number of chromophores) than one has data points $[BBM^+01]$. For the linear problem we consider, even without noise, the resulting inverse problem has no unique solution which again is a major problem $[LBZ^+05, BBM^+01]$. Taken together, the physics-based ill-posedness coupled with the inherent underdetermined nature of the problem severely complicates our ability to stably recover useful information about the state of the tissue from DOT data.

These issues are addressed in two ways. First, regularization techniques are employed to stabilize the reconstructions. When introducing regularization to the system, we take advantage of a priori information that we know is true for the physical system. By choosing the right regularization this a priori information is added to the system, i.e. the smoothness of the system or that the chromophore concentrations are small and slowly changing. Therefore, if we have some information on the true chromophore concentrations, the regularization can be constructed in such a way that the solution is drawn towards the known distribution by the regularization. The other method used to reduce the ill-posedness is to add information to the system. In this thesis this is done by using hyperspectral information. By recovering concentrations using multiple wavelengths we take advantage of as much information as is available to us. Exploring the advantage of adding data to the system in this way is the aim of thesis. By employing the fact that near-infrared light scatters and absorbs depending on wavelengths and the chromophores that it is travelling through it will be possible to create accurate concentration images for multiple chromophores simultaneously. Efforts have been made in multispectral DOT imaging, using only 3-5 wavelengths. Here we will examine the effects of including more complete spectral information in the reconstructions. By including hyperspectral data we will use tens to hundreds of wavelengths in order to deal with the ill-posedness of the DOT problem. We will also examine how hyperspectral data gives way to distinguishing between different chromophores. A forward model will be constructed and inversion techniques will be discussed and employed to solve for chromophore concentrations.

In Chapter 2 we review the history and many applications where DOT can be employed. In that chapter we also define the forward model for the problem. In Chapter 3 we discuss the inverse problem and what methods are traditionally used to solve it along with discussing regularization techniques. In Chapters 4 and 5 we discuss results from simulations and experiments, respectively.

Chapter 2

Diffuse Optical Tomography

Throughout history, researchers have devoted significant efforts to the application of visible and near-infrared light for the detection of breast cancer as well as other applications. In this chapter we start by reviewing the applications as well as the early development for DOT, and then move on to introducing the forward model for the problem.

2.1 Early Development

Research on optical imaging started early as 1920 and a pioneering article from Max Cutler on optical transillumination images of the breast was released in 1929 [Cut29, LCY⁺07]. Specifically, light has been used to detect certain information such as the blood oxygenation level using pulse oximeters since the 1930's. While this is not really optical imaging, it illustrates one way where light carries information about the material through which it travels. Cutler proposed using continuous light to detect breast lesions but this idea was quickly dropped since the intensity of light required caused the patient's skin to overheat. In the 1970's and the early 1980's

significant developments were made that led to commercially available equipment for optical mammography. [GQH72] introduced a concept named diaphanography, in which the breast was positioned between a visible or near-infrared light source and the physician. From this setup the doctor perceived images using his eyes alone. These advances led to the development of pulse oximetry, laser Doppler bloodflowmetry and near infrared spectroscopy(NIRS) which then led to progress in the areas of continuous-wave time-domain, and frequency domain optical mammography [LCY⁺07].

2.1.1 Pulse oximetry

Pulse oximetry was originated in the 1930s and is widely used to monitor patient well being. Pulse oximeters provide accurate information on arterial blood oxygen saturation. The advantage of optical oximeters over oxygen tension monitors, which need to be a part of the circulation or have a blood sample, is that they provide a rapid response to changes in blood oxygenation and yet are non-invasive [BBM⁺01]. The first oximeter was an ear oximeter which only used a lamp and a photocell [Pet86]. It measured average hemoglobin oxygen saturation across vascular compartments. Later it evolved into the more robust pulse oximeter, whose mathematical model is based on an arterial pulse-triggered measurement of the intensity of the light passing through the tissue. After each heartbeat the arteries expand, increasing the volume of blood flowing through them. This causes an increase in the absorption of light in the tissue and therefore the light attenuated by the blood varies as function of the pumping of the heart. Comparing the maximum and minimum absorption the difference can be put into a mathematical model which gives the arterial oxygen saturation [BBM⁺01].

2.1.2 Doppler Blood-Flowmetry

The invention of the laser quickly gave rise to its use in medical applications. As early as the 1970s the laser was being used for laser Doppler studies of blood flow [BBM⁺01]. When a beam of laser light with uniform intensity is incident on a rough surface, the reflection of the beam will not be completely uniform but will include some dark and light spots [TRBS74]. These dark spots, called speckles, are caused by light reflected many different times which causes interference at the detector. This is exactly what occurs when light travels though a highly scattering sample. Additionally, if the scattering particles, red blood cells in the DOT case, are moving the speckle pattern will fluctuate with a time scale which depends on the motion. This was the basis for Laser Doppler Blood Flowmetry in the 1960s.

2.1.3 NIRS

Attempts at applying pulse oximetry and laser Doppler blood flowmetry to measure hemodynamics in the brain were hindered by the photodetector bandwidth limits and photon limits. In the 1970s NIRS was developed to monitor baseline changes in total oxygenation in the brain, as revealed by the average intensity of diffusely reflected light [CD88, Job77, Cop91]. Briefly, NIRS quantifies changes in chromophore concentration within highly scattering tissue by measuring the change in the photon density of light which is diffusely transported through it. The concentration change of each chromophore is then computed by relating them to the measured change in photon density. The measured change in photon density is directly related to the concentration change by the extinction coefficient of the chromophores and the effective pathlength of the tissue. The extinction coefficient is an intrinsic property of each chromophore, but the effective pathlength must be estimated for each measurement as it is heavily dependent upon the measurement setup and the optical properties of the tissue [BBM⁺01]. The 1980s brought continuing research into using NIRS for monitoring cerebral oximetry. It became apparent that the major limitations of NIRS was it could not measure concentrations of deoxy-hemoglobin and hemoglobin without calibration of the optical pathlength through tissue. To measure this path length picosecond pulsed lasers and time-resolved measurements were used in the late 1980s and with that the absorption coefficient and related hemoglobin parameters could be obtained. Instrumentation and complexity became burdensome and more expensive, and thus investigators introduced the use of inexpensive and simple radio frequency modulated laser and measurements of the phase delay of the amplitude modulated light. This provided a measure of the mean tissue optical pathlength and subsequently of the hemoglobin parameters.

In the late 1980s and early 1990s it was soon realized that photon migration spectroscopy measurements could be extended to imaging by solving the inverse problem as is done with X-Ray computed tomography. Research investigating this possibility began in the late 1980s and was reviewed by other investigators [Arr93, BGW⁺93]. The time domain systems produce illumination by picosecond pulses of light. This short pulse allows detection of the temporal distribution of photons as they leave the tissue. The shape obtained from this distribution provides information about the optical properties of tissue. CW systems emit light at a constant amplitude or are modulated at a certain frequency. These systems measure the amplitude decay of the incident light. For frequency domain systems the light is on constantly but is amplitude-modulated at frequencies on the order of tens to hundreds of megahertz. This allows the absorption and scattering properties of tissue to be obtained by recording amplitude decay and phase delay of the detected signal [BBM⁺01].

2.2 Application of DOT

Currently the main applications for diffuse optical tomography are breast, brain, limb, joint and fluorescence/bioluminescence imaging. As discussed in Chapter 1 the application investigated in this thesis is the imaging of the breast. To demonstrate the wide array of possibilities for near-infrared imaging this section will review each applications in addition to discuss the use of DOT with other modalities in the context of breast imaging.

2.2.1 Breast Imaging

Research on this topic started very early as mentioned in Section 2.1. After efforts made in the early 20^{th} century, 1980's investigators for the breast cancer application, started using video cameras as detectors and explored methods to use something other than just the eye as detectors. In 1982 Carlsen published a seminal paper that included a real-time live viewing but more importantly included spectral information [BBM⁺01]. These developments led to a number of pilot clinical studies later in the decade. Some of these studies reported promising data and projected a positive attitude about the potential of optical mammography, although some researchers raised questions about its clinical viability [LCY⁺07]. In the late 1980's a multi-center clinical study on a population of 2,658 women concluded that optical mammography was inferior to standard mammography, obviously showing that significant advancements were needed before optical imaging of he breast could play a clinical role [LCY⁺07].

Around 1990 a Swedish study found that light scanning was inferior to other modalities, the probability of actual detection was low and the probability of false alarm was almost three times higher than in breast imaging methods such as CT or MRI. This caused a significant departure from research concerning optical mammography and it was basically abandoned in the early nineties. Some of the factors that gave rise to optical mammography after this fall were more quantitative approaches to describing light propagation inside biological tissue together with the development of time-resolved experimental techniques[LCY⁺07]. After pulse oximetry, Doppler blood-flowmetry and NIRS were established, as discussed in Section 2.1, significant efforts have been made to develop DOT for breast cancer.

When reconstructing images for concentrations of chromophores in DOT there generally two ways of using spectral information. In this project these two methods will be referred to as the direct method and the indirect method. The indirect method has three steps to obtain the concentration images. First, measurements are taken at two or more wavelengths. Second, images of the absorption and reduced scattering coefficients at the different wavelengths are reconstructed separately and finally the concentration of the separate hemoglobin are derived from the optical properties. On the other hand the direct method skips the step of constructing the spectral absorption images and directly reconstructs the images for hemoglobin $[LZC^+04]$. For this project we will examine the direct method.

In DOT three measurement schemes are used for measuring the light transmitted through tissue. They are time domain, frequency domain and continuous wave, which is essentially zero frequency [FFG⁺96, BBM⁺01]. For a case like breast cancer, detection transmission is measured but for a case of brain imaging reflection is measured [CCD⁺05]. In some cases measuring both transmission and reflection could be useful. Out of these schemes the CW method is the simplest, least expensive, and provides the fastest data collection.

The advantage of functional information obtained from DOT is especially

encouraging when comparing it to common modalities like X-ray mammography. Unlike X-ray mammography, which detects microcalcification characteristic of malignant lesions, optical mammography senses changes in blood perfusion of the tissue surrounding the tumor. These changes occur early in a tumor's growth and can affect a relatively large area [SGA03]. Researchers have developed several instrumentation types for optical mammography, some are similar to X-ray by compressing the breast but others use an unconstrained mesh of detectors where sources and detectors are arranged in planes on the surface [CvdMH⁺99, LCY⁺07, ZJ05]. When the compression technique is used a laser source scans across one plate, which is transparent while a detector on the opposite plate scans over several measurement locations for each source position [SGA03]. This arrangement reduces the thickness of the transilluminated tissue. This technique has of course been used for several years in X-ray mammography and has been proven to improve the detectability of deeply embedded objects. One down side of the compression method is that it can cause blood to drain from the breast, thereby unpredictably altering the optical properties.

The other method, with sources and detectors situated in a plane around an uncompressed breast, has the patient lying prone on a table with the unsupported breast suspended in a cavity. The data acquisition might consist of a set of fixed sources and detectors or a rotating system that scans the breast's surface. This setup can provide a more complete sampling data over the boundary, but makes defining the problem's geometry more difficult. This also has the advantage that this should be much more comfortable since numerous patients have felt the compression method to be uncomfortable and sometimes painful.

Creating a system that makes use of the benefits of DOT with other imaging modalities could be very useful in the future. To enhance DOT performances, researchers have proposed fusing optical techniques with other medical imaging modalities. The high contrast benefits of the DOT method can be used with the high resolution image of and X-ray or MRI image. The high contrast advantages of using the DOT method sparks interest to use the DOT method with other imaging techniques because it offers unique functional information(such as tissue, oxy- and deoxy-hemoglobin concentrations) while high resolution anatomical imaging modalities provide complementary information for disease diagnosis and understanding with superior localization and spatial resolution. Another factor that stimulates the use of multi-modality system is that the contrast elements provided by high resolution imaging modalities correlate with the optical properties.

Use with X-ray

Presently X-rays are widely used for breast cancer detection so pairing them with the DOT modality should be a promising opportunity. [LMK⁺03] propose that the contrast seen in X-ray images should be assumed to be proportional to the DOT contrast. A linear least-squares type of DOT image formation problem was then posed to use the information from the X-ray measurements. The image reconstruction was regularized using the Tikhonov method which is similar to what is tested in this paper. The regularization in general was based on regions of interest, mainly the tumor regions and background regions. Additionally, through simulation they were able to show that their method improved the contrast-to-noise ration and resolution in the reconstructed image.

[ZBL⁺05] published the first pilot study of co-registered tomographic X-ray and optical breast imaging. They used a frequency domain optical imaging system at 70 MHz RF modulation and homodyne detection for its data collection. That was integrated with a prototype 3-D digital mammography system, and both optical and X-ray measurements were collected for the same subject. Similar to [LMK⁺03] they used a Tikhonov regularization with an L-curve regularization parameter selection technique for the reconstruction[ZBL⁺05]. Performing clinical tests they determined that without the help of the co-registered X-ray image, it would have not been possible to determine which optical contrast derived from breast lesions or if it was due other tissue structures or an image artifact. The optical contrast might appear outside the region were X-ray image indicated a lesion. In their system, the image contrast-to-noise ration was limited by modeling error and measurement noise. They were also only taking measurements at two wavelengths, where taking multispectral or even hyperspectral measurements could have benefited their results.

Use with MRI

MRI has achieved high spatial resolution with excellent tissue discrimination, but has shown poor characterization of functional parameters such as hemoglobin dynamics [BDPP03]. Since MRI and NIR signals are independent, a natural medical imaging development would be to capitalize on the positive aspects of each with a combined MRI-NIR imaging device. Using MRI systems concurrently with the DOT method has been examined to some extent. [NYSC00] used a contrast agent, indocyanine green(ICG), to improve the DOT measurement. The ICG is an absorber and fluorophore in the NIR spectral window. They were investigating its applications for using DOT to search for breast cancer. Concurrently MRI images, where gadolinium (Gd) was used as a contrast agent, were acquired. This study showed that comparing the two modalities helped significantly in determining the location of breast cancer. Testing for three different cases, infiltrating ductal carcinoma, fibroadenoma and healthy tissue they showed that both the MRI and DOT detected the carcinoma and fibroadenoma although showing different shapes and intensities. They also proposed using ICG, although not developed as a cancer targeting dye, as a promising addition to the DOT method. This is definitely a possibility but this also carries some drawbacks. This makes the DOT method invasive, compromising one of its biggest pros, being non-invasive. Adding a targeting dye could also complicate things if DOT aims to be a quick, bedside imaging modality.

Another group in 2002, [IYYC02], developed multi-channel/multi-wavelength photon counting instrument that combined DOT with a MR scanner. This was also a co-registration setup. Considering the heterogeneous diffusion equation for the DOT reconstruction they achieved good results when comparing the MRI images with DOT. One thing to take note of in this study is the use of six different wavelengths, showing the benefit of multispectral data. This is especially evident in the fact that they announce the ability of their instrument to recover properly two intrinsic chromophores that were targeted. This encourages our investigation in this thesis.

There have been numerous attempts to use MRI to provide prior information to the DOT reconstruction process. Some groups, have demonstrated that incorporation of a correct first estimate of optical properties, determined from MRI data, can significantly enhance quantitative reconstruction of localized perturbations in the absorption and scattering coefficients for a complex, multilayered neonatal brain model. Making the initial guess more accurate has been shown to improve the stability and speed of convergence of the imaging process [SA99].

The incorporation of high-resolution structural data to assist image reconstruction for ill-posed inverse problems has also been considered [BDPP03]. They examined an algorithm that would take advantage of the data available from such a composite system. They exploited regional segmentation and the benefits of an accurate initial estimate. They stressed that the initial MRI structure that guides the regionization provides a practical approach to starting the problem. In the end the aim is always to improve the resolution and quantitative accuracy of reconstructed images of heterogeneous absorption and scattering within complex, layered distributions. The Brooksby group reported that an exploitation of an MRI a priori information could provide much more than an initial guess. An optimized reconstruction algorithm should consider: i) proper spatially variant regularization and ii) applications of various a priori matrices in the iterative process [BDPP03].

 $[IMG^+04]$ proposed that MRI is the perfect candidate for optical co-registration. They wrote that MRI provided high spatial resolution maps of the breast optical structure that are relevant to the water and lipid distribution. Moreover, MRI can provide a means to estimate the concentration of the two structural chromophores, water and lipids as proposed by $[MGC^+03]$.

In order to incorporate prior information into the solution of the inverse problem Intes studied the Bayesian approach. He based his studies on work done by Guven et al who proposed an algorithm based on the Bayesian framework with a spatially varying a priori probability density function extracted from MRI anatomical maps [GYI⁺04].

The high resolution image obtained from MRI data is segmented into subimages that represent three major types of tissue; parenchyma, glandular and tumor. In order to implement this prior information probability density function of the image is formulated in such a way that each sub-image is assigned a mean value and a confidence level is defined in the form of an image variance formulation to allow local variations within sub-images. The consequence of this is that the overall formulation of the prior information becomes spatially varying, which is specific to the image of interest. Maximum a posteriori (MAP) estimate of the image is formed based on the formulation of the image's probability density function. Using this method resulted in more accurate functional maps, especially better maps of the blood volume and the relative saturation which are the functional parameters $[IMG^+04]$.

Use with Ultrasound

Ultrasonic imaging is a non-invasive, easily portable, and relatively inexpensive diagnostic modality. Operating typically at frequencies between 1 and 10 MHz, it produces images via the backscattering of mechanical energy from boundaries between tissues and from small structures within tissue [Web03]. The choice of frequency is a trade-off between spatial resolution of the image and imaging depth. Lower frequencies produce less resolution but image deeper into the body. US is used to visualize muscles and internal organs. It can image the size and the structure of the organs and possible pathologies and lesions. US is most known for its use during pregnancy (obstetric sonography) to monitor fetal growth. US is frequently used as an adjunct tool to mammography in differentiating simple cysts from solid lesions and also plays an important role in guiding interventional procedures such as needle aspiration, core needle biopsy and pre biopsy needle localization. However, ultrasound features that occur in solid breast masses are not reliable enough to determine whether invasive evaluation is needed or non-invasive follow up is indicated. The lack of specificity of US has prompted radiologists to recommend biopsies on most solid nodules.

Because the US technique is mainly based on reflectance of audio waves, the NIR methods for co-registration with US discussed in this chapter are also based



Figure 2.1: An example of the "banana path" encountered in Ultrasound imaging [ZTK07].

on reflectance similar to that of brain imaging. In the context of US and NIR coregistration a "banana path" is often discussed. Photons that are injected into breast tissue are then scattered in the breast. Scattered photons that reach the detectors have travelled the banana path and carry with them the background tissue and the lesion optical absorption and scattering information [ZTK07]. An example of the banana path travelled is shown in Figure 2.1.

[ZCK03] reported on using two-step image reconstruction scheme that used a combined approach and demonstrated its utility in imaging tumor absorption and hemoglobin distribution. Before [ZDH⁺99] and [CGY⁺01] had examined coregistration of NIR images and US images, in practice similar to the co-registration of MIR and NIR images discussed above. The device that was designed consisted of a probe that had a commercial ultrasound one-dimensional array located at the center of the probe and optical source and detector fibers distributed at the periphery and connected to an NIR image. The NIR imager consisted of 12 dual-wavelength source channels and 8 parallel receiving channels. They only took measurements at two wavelengths, 780 and 830 nm. Their method was the indirect method discussed a the beginning of this chapter. The two-step image reconstruction was designed so that they first segmented the volume of the tissue being imaged into two regions, Land B. Region L contained a lesion, as measured from co-registered ultrasound images and the B region was background tissue. Then the scattered field U_i measured at source-detector pair i to absorption variations in each volume element of two regions within the sample. The discretization was performed for the whole volume but smaller voxel sizes were used for the lesion volume than the background volume. The second step was then to reconstruct total absorption distribution and then divide the total by different voxel sizes of lesion and background tissue to obtain absorption variations. This indirect method has some drawbacks as mentioned, but the a priori use of US is still intriguing. The US probe used acquired two-dimensional images (as most commonly used US devices) but the NIR probe provided three-dimensional images, so the co-registration for their research was limited to an interception plane. They solved this problem by approximating the lesion as being ellipsoid. That way its center and radii could be estimated from two orthogonal US images and then derive the lesion volume.

In 2007 [ZTK07] reported on an hand-held probe consisting of a commercial US transducer and near infrared optical imaging sensors of multiple wavelengths that was used to simultaneously acquire US images and optical measurements. To overcome the problem of intense light scattering caused by breast tissue they devised image scheme to map the US-visible lesions for optical imaging reconstruction. Similar to the study in 2003 the system takes measurements at two or three wavelengths. Also building on the previous research, the optical tomographic reconstruction takes advantages of US localization of lesions and segments the imaging volume into a finer grid for possible larger angiogenesis extension of US identified lesions. As a result the inverse tomographic mapping is well-defined, and since the lesion absorption coefficient is higher than that of background tissue in general, the total absorption of the lesion over a small voxel is of the same scale as the total absorption of the background over a bigger voxel. Using these methods they were able to improve the inverse tomographic mapping.

Use with PET

Positron emission tomography (PET) is a fast growing imaging modality in modern clinical diagnosis. Similar to DOT it is a tomographic technique that is used to measure physiology and function instead of gross anatomy. PET is used clinically in oncology, cardiology and neurology [Web03]. Research has been in co-registration of DOT and PET images showing positive correlations can be found between total hemoglobin concentration and tissue scattering using both modalities. [KCC⁺08] showed that similarities between acquisitions from DOT and PET allowed to coregister images from the two modalities by deforming the DOT image with a volume warping algorithm. This allowed them to compare images at specific locations.

Although PET seem to be a good modality for co-registration it has some significant drawbacks. The biggest disadvantages is that it is very expensive, around \$1.5-2.5 million for a system, and the need to have a cyclotron on-site to produce positron-emitting nuclides. This is needed because the half-lives of these nuclides are very short. Currently there are fewer than 200 PET scanners in the United States. PET is also an invasive modality since it requires injected, or in some cases inhaled, radiopharmaceuticals.

2.2.2 Optical Based Brain Imaging

The early application of optical methods for brain imaging concentrated on the detection of hemorrhages and hematomas in the brain. This area of brain imaging is exactly what DOT can be used for, because hematomas are a localized mass of extravasated blood, therefore subcranial hematomas can be detected with DOT relatively easily. Since the early 1990s, various groups have reported on the development of instrumentation to detect these hematomas [FHF⁺99, TAM⁺03, FFG⁺96]. With computer technology taking leaps forward allowing advanced instrumentation and image-reconstruction algorithms the focus for DOT in brain imaging has moved to a significantly challenging problems. These problems are functional imaging and stroke imaging.

In the area of functional imaging, several investigators have reported on changes in the optical signals as subjects perform a variety of tasks. As an example $[BHV^+00]$ have studied physiological changes in brain oxygenation in male adults during mixed motor and sensory cortex activation. $[HOW^+00]$ obtained quantitative images of hemoglobin concentration changes associated with neuronal activation in the human brain. Both of these efforts are based on multi-wavelength measurements that allow for calculation of changes in optical properties. By using the method of assuming that the primary influences on the changes in the absorption coefficients at each wavelength are a linear combination of oxyhemoglobin and deoxyhemoglobin it has been established that near-infrared light can be used to probe the brain for changes in blood oxygenation and blood volume. Although it is unchallenged that changes in hemodynamic responses to stimuli can be detected, conflicting results have been reported concerning the detectability of scattering changes due to neural activity [HBA+02].
Research has also been done in the field of optical stroke monitoring. NIR optical systems promise several advantages over current brain-imaging modalities such as MRI and CT when applied to critically ill stroke patients. Unlike MRI, CT, or PET, optical systems are portable and can be brought to the bedside to monitor critically ill patients. Stroke patients frequently are unstable and unable to tolerate transport to CT or MRI scanner facilities and do not tolerate the repeated scanning necessary to follow an ongoing or evolving condition. In addition, most established imaging techniques require the patient to be exposed to harmful agents such as intravenous contrast, radiation or radioactive emitters. For the case of the critically ill stroke patient, in whom cerebral blood flow, blood volume and brain oxygenation constantly are changing, a continuous imaging technology is highly desirable. Promising research has been published on this subject as early as 1993 [Hir93]. In 1996 [WLO⁺96] reported on the use of NIR spectroscopy for non-invasive on-line detection of cortical spreading depression in a pentobarbital treated rat. In 1999, [VRP⁺99] reported on a study that involved the effects of hypercapnia on the near-infrared signal in two patients who had suffered strokes three and four months earlier. Later, in 2000, [CLL⁺00] performed optical studies using an intracranial infraction model in rats. Hielscher et. al published a thorough overview of these studies and others pertaining to this field $[HBA^+02]$. Since most of the work for optical stroke imaging mentioned here above only provides topographic maps the focus has now shifted to the development of 3D image-reconstruction schemes that provide better depth resolution to localize areas of interest inside the brain.

2.2.3 Optical Based Joint Imaging

Although near-infrared imaging is useful for measuring hemodynamics and changes in various blood-related parameters, optical techniques are also quite sensitive to scattering changes in tissue. DOT has been shown to be useful in imaging and monitoring the progression of rheumatoid arthritis (RA) [GHA04]. RA is an inflammatory and chronic disease that primarily attacks peripheral joints, surrounding tendons and ligaments. Visualization of early stages of the disease has not been successful and imaging of the joint so far has played a role only in later stages of the disease. It has long been recognized that radiography is insensitive to the early manifestation of RA. The application of optical techniques become very promising in this context and provide a new tool for the early detection of RA. Changes in the optical properties of the synovium and in the synovial fluid can be observed even in very early stages of the disease [HBA⁺02].

In the case for RA DOT is employed to monitor the optical properties of the synovial fluid and the synovium. Here RA results in changes in the scattering properties of these quantities as opposed to the absorption profiles. [HBA⁺02] developed a device that permits high-accuracy measurement of transmission profiles. Their results showed that although the spatial resolution was poor, the decrease in value of the optical properties around the location of the joint, which is filled with the low-scattering and low-absorbing synovial fluid, is clearly visible. In reconstructions of the joint affected with RA, this decrease is much less pronounced. The results illustrated how near-infrared imaging can be useful in diagnosing RA in its early stages.

[ZJ05] showed, performing direct in vitro and ex vivo measurements, that DOT was a useful modality image joints. They were able to demonstrate the optical contrast between normal and diseased joint tissue using the DOT method. Along with $[XIJ^+02]$ they showed that a full three dimensional image reconstruction approach is needed for joint imaging due to the strong 3D scattering nature of light in the joints. To be able to obtain this full 3D volumetric image reconstruction of joint tissue they developed a 64x64 channel photodiodes-based DOT imaging system capable of providing tomographic data for the reconstruction. These laser diodes take measurements at eight wavelengths ranging from 634 to 974 nm. They also proposed that one of the key factors in obtaining high quality image reconstruction was to have a coupling medium between the detector and the medium. The reconstruction algorithm used a regularized Newton method to update the initial optical property distribution iteratively in order to minimize the object function. Performing phantom experiments the results obtained suggested that the system performed well and importantly showed that there exists optimum absorption and scattering coefficients for the coupling medium for good image reconstruction. This proposition of a coupling medium could also be researched to be used in the breast cancer application [ZJ05].

2.2.4 Fluorescence Imaging

The non-invasive mapping of molecular events in intact tissues using fluorescence is of significant interest in biomedical imaging. The basis of the development of the discovery of bio-compatible, specific fluorescent probes and proteins and the development of highly sensitive imaging technologies for in vivo fluorescent detection. Near-infrared imaging comes into play when fluorochromes that emit in the near infrared window are of interest [NBW03]. As mentioned in previous sections the reason of interest in NIR for this application is its ability to penetrate several centimeters of tissue. Some investigators have combined the DOT method and fluorescent optical tomography, but it should be noted that the reconstruction problem for fluorescent tomography is linear with respect to the source distribution. Since DOT is the main focus of this paper fluorescent imaging is a bit out of scope but important to realize that NIR imaging could have possibilities in that field.

2.2.5 Hyperspectral and Multispectral

Research on the DOT has shown that including multiple wavelengths in measurements can increase the accuracy of the measurement. Multispectral measurements made it possible for $[BFC^+07]$ to obtain hemoglobin images of the concentration and the hemoglobin oxygen saturation. $[CCD^+05]$ showed that using multiple wavelengths are the key for obtaining physiologically relevant tissue parameters with CW light. Indeed, a factor in detecting breast cancer is the discrimination of actual cancer and benign lesions or normal tissue inhomogeneities in the breast. Multi-wavelength information has been shown to be useful to make this distinction $[FHP^+05]$. This is due to the fact that determining the level of blood oxygenation in the breast can show the local supply and demand of oxygen. Since cancer tumors have low-oxygen levels this information can be extremely useful in making the difference between harmful objects and benign artifacts $[FHP^+05]$. Because multi-wavelength data can be used to obtain this kind of information it shows that DOT can be used not only for anatomic imaging but also functional imaging which distinguishes it from x-ray mammography and ultrasonography $[ZGT^+05]$.

Additionally, it has been shown that using multispectral measurements can be successfully used along with x-ray tomosynthesis [BFC $^+07$]. This method and others that combine DOT with other imaging techniques are discussed further in

Chapter 2.2.1 [CDB+05].

Considering the fact that multiple wavelengths increase the accuracy it is imperative to discuss how many wavelengths should be included in the measurement. This is where hyperspectral measurements come into play. Hyperspectral imaging is the method of using a great number of wavelengths for measurement, but there is no set number of wavelengths that defines hyperspectral imaging from multispectral imaging. To give some definition it is stated that hyperspectral imaging resolves the spectrum of the emitted light into ~ 100 spectral bins while multispectral resolves the spectrum into less than 10 spectral bins $[CDB^+05]$. Hyperspectral imaging has been used extensively in the fields of remote sensing and geology of natural and manmade materials that are indistinguishable using standard colour imagery [Lan02, SM02]. The fundamental basis for space-based remote sensing is that information is potentially available from the electromagnetic energy field arising from the Earth's surface and, in particular, from the spatial, spectral and temporal variations in that field. Some problems can occur when focusing on spatial variations so researchers have moved on to look at how the spectral variations might be used. This concept is not new and has been researched extensively for the past 20 years. In the case of CW measurements, it has been shown that different sets of absorption and scattering parameters can yield identical data. Also, inversions can have cross-talk between absorption and scattering [AL98]. Cross-talk happens when a reconstructed image of a chromophore shows traces of concentrations from other chromophores. These "ghost" images greatly reduce accuracy of the overall reconstruction. [CCD⁺05] showed how this nonuniqueness problem could be solved by using multispectral data, provided that it is used with the correct wavelengths. In this thesis, we will explore the value of hyperspectral data for addressing the many issues associated with illposedness encountered with DOT. It will be examined how hyperspectral data can increase resolution and reduce cross-talk. In other words, the ability to localize small perturbations from individual species and ability to separate multiple species. A special note will be taken to when a sufficient number of wavelengths has been reached. That is, should there be an upper limit on how many wavelengths to be used.

2.3 DOT forward model

2.3.1 Discrete model and use of Green's function

A model of light propagation in a highly scattering medium is necessary both to compute the simulated fluence at the detectors and to map the fluence back to the chromophore concentrations.

One useful and commonly employed model for the photon fluence in a highly scattering medium is the Helmholtz frequency domain diffusion equation

$$\left(\nabla^2 + \frac{j\omega - v\mu_a^0(r,\lambda)}{D(\lambda)}\right)\phi(r,\lambda) = \frac{-v}{D(\lambda)}S(r)$$
(2.1)

This is the homogeneous version of the Helmholtz equation where $\phi(r, \lambda)$ is the photon fluence at position r, v is the electromagnetic propagation velocity in the medium, $\mu_a^0(r, \lambda)$ is the spatially varying absorption coefficient, ω is the modulation frequency in rad/s, λ is the wavelength and S(r) is the source function. For the aim of this thesis the sources are considered to be delta sources $S(r) = \delta(r)$. For the continuous wave case $\omega = 0$. Lastly $D(\lambda)$ is the diffusion coefficient, given by

$$D(\lambda) = \frac{v}{3\mu'_s(\lambda)} \tag{2.2}$$

where μ'_s is the reduced scattering coefficient.

2.3.2 Born Approximation

Using perturbation approach the spatially varying absorption coefficient, $\mu_a^0(r, \lambda)$, is written as the sum of a constant background absorption, $\mu_a(\lambda)$, and a spatially varying perturbation $\Delta \mu_a(r, \lambda)$. Then (2.1) takes the form

$$\left(\nabla^2 + \frac{j\omega - v\mu_a(\lambda)}{D(\lambda)} - \frac{v\Delta\mu_a(r,\lambda)}{D(\lambda)}\right)(\phi_i(r,\lambda) + \phi_s(r,\lambda)) = \frac{-v}{D(\lambda)}S(r).$$
(2.3)

In (2.3) the fluence is written as the sum of the incident field $\phi_i(r, \lambda)$, due to the source acting on the background medium and a scattered fluence, $\phi_s(r, \lambda)$ due to the imhogeneties. To obtain an equation for the scattered fluence, (2.1) is subtracted from (2.3) giving

$$[\nabla^2 + k_0^2(\lambda)]\phi_s(r,\lambda) = -\Delta k^2(r,\lambda)(\phi_i(r,\lambda) + \phi_s(r,\lambda))$$
(2.4)

where $k_0^2(\lambda) = (j\omega - v\mu_a(\lambda))/D(\lambda)$ and $\Delta k^2(r, \lambda) = (v/D(\lambda))\Delta\mu_a(r, \lambda)$. To obtain a linear relationship we use a Green's function approach and the assumption that $\phi_i(r, \lambda) \gg \phi_s(r, \lambda)$. This linearization, which is based on ignoring the contribution of the scattered field is known as the first Born approximation. Physically it amounts to treating each point in an inhomogeneity as if it existed in isolation form the rest of the inhomogeneity ignoring the contributions of perturbations of the scattered field from one part of an inhomogeneity on the field incident on another part [GBD+00]. Thus, for each delta function source we calculate the incident field everywhere in the domain using Green's function and then the scattered field present at each detector by the integral equation

$$\phi_s(r_d,\lambda) \approx \int_V G(r_d,r',\lambda)\phi_i(r',r_s,\lambda)\Delta k^2(r',\lambda)dr'$$
(2.5)

providing a linear relationship between the scattered fluence and the absorption perturbation. Here r_d is the location of detector and r_s is the location of the source. This equation can be discretized by considering only voxel points in the medium. Then the value r_i is defined as the position vector, denoting location in the medium with r_i denoting the location of the i^{th} such point. More formally, we expand $\Delta k^2(r', \lambda)$ using Dirac delta functions

$$\Delta k^2(r',\lambda) = \sum_{r_i} \Delta k^2(r_i,\lambda)\delta(r'-r_i)$$
(2.6)

The kernel of (2.5) is simplified by writing

$$H(r_d, r_s, r', \lambda) = G(r_d, r', \lambda)\phi_i(r', r_s, \lambda).$$
(2.7)

Inserting (2.6) into equation (2.5) allows for discretization, by

$$\phi_s(r,\lambda) \approx \int_V H(r_d, r_s, r', \lambda) \sum_{r_i} \Delta k^2(r_i, \lambda) \delta(x - r_i) dr'$$
 (2.8)

$$= \sum_{i} \Delta k^{2}(r_{i},\lambda) \int_{V} H(r_{d},r_{s},r',\lambda) \Delta(x-r_{i}) dr'$$
(2.9)

$$= \sum_{i} \Delta k^2(r_i, \lambda) H(r_d, r_s, r_i, \lambda)$$
(2.10)

$$= \sum_{i} G(r_d, r', \lambda) \phi_i(r', r_s, \lambda) \Delta k^2(r_i, \lambda)$$
(2.11)

In this thesis we consider only the free-space problem for which the Green's function is [GBD⁺00]

$$G(r, r', \lambda) = \frac{-1}{4\pi |r - r'|} e^{jk_0(\lambda)|r - r'|}$$
(2.12)

This form of (2.12) is put into (2.5) to obtain a model, so

$$\phi_s(r,\lambda) \cong \sum_{r_i} G(r_d, r_i, \lambda) G(r_i, r_s, \lambda) \Delta k^2(r_i, \lambda)$$
(2.13)

Using these equations with (2.13) the following relation is derived

$$\phi_{s}(r_{d}, r_{s}, r_{i}, \lambda) = \sum_{r_{i}} \frac{-e^{jk_{0}(\lambda)|r_{d} - r_{i}|}}{4\pi |r_{d} - r_{i}|} \frac{-e^{jk_{0}(\lambda)|r_{i} - r_{s}|}}{4\pi |r_{i} - r_{s}|} \frac{v}{D(\lambda)} \Delta \mu_{a}(r_{i}, \lambda)$$

$$= \frac{v}{16\pi^{2}D(\lambda)} \sum_{r_{i}} \frac{e^{jk_{0}(\lambda)(|r_{d} - r_{i}| + |r_{i} - r_{s}|)}}{|r_{d} - r_{i}||r_{i} - r_{s}|} \Delta \mu_{a}(r_{i}, \lambda)$$
(2.14)

Now as mentioned in Chapter 1, DOT is often used to image the concentration of oxyhemoglobin and deoxy-hemoglobin in tissue. The technique exploits the fact that oxyhemoglobin, Hb0₂, and deoxy-hemoglobin, HbR, are dominant absorbers in the infrared region [LBZ⁺05]. It can be assumed that the absorption coefficient is dominated by the hemoglobin [LBZ⁺05], then for these two chromophores absorption coefficient would be written as

$$\Delta \mu_a(r_i, \lambda) = \varepsilon_{\text{HbO}_2}(\lambda) \delta[\text{HbO}_2] + \varepsilon_{\text{HbR}}(\lambda) \delta[\text{HbR}].$$
(2.15)

where $\varepsilon_{\rm X}$ are the extinction coefficient of chromophore X and [X] represents the concentration of X. The dependence of r_i in (2.15) comes from the concentration of each chromophore. Even though the DOT method benefits from the reactions of hemoglobin to infrared light, it can be extended to image other chromophores, like

water or lipids for example. For the case of n chromophores (2.15) would become,

$$\Delta \mu_a(r_i, \lambda) = \varepsilon_{\rm CP_1}(\lambda) \delta[{\rm CP_1}] + \varepsilon_{\rm CP_2}(\lambda) \delta[{\rm CP_2}] + \dots + \varepsilon_{\rm CP_n}(\lambda) \delta[{\rm CP_n}].$$
(2.16)

Where CP_n represents the n^{th} chromophore. Using (2.16), (2.14) is written as

$$\phi_s(r_d, r_s, r_i, \lambda) = \frac{v}{16\pi^2 D(\lambda)} \sum_{r_i} \frac{e^{jk_0(\lambda)(|r_d - r_i| + |r_i - r_s|)}}{|r_d - r_i||r_i - r_s|} (\varepsilon_{\mathrm{CP}_1}(\lambda)\delta[\mathrm{CP}_1] + \dots + \varepsilon_{\mathrm{CP}_n}(\lambda)\delta[\mathrm{CP}_n]).$$
(2.17)

The terms $|r_d - r_i|$ and $|r_i - r_s|$ represent the distance from the detector to a certain point, r_i , in the medium. In the continuous wave case where w = 0, $k_0^2 = v\mu_a/D(\lambda)$ so (2.17) becomes

$$\phi_s(r_d, r_s, r_i, \lambda) = \frac{v}{16\pi^2 D(\lambda)} \sum_{r_i} \frac{e^{-k_0(\lambda)(|r_d - r_i| + |r_i - r_s|)}}{|r_d - r_i||r_i - r_s|} (\varepsilon_{\mathrm{CP}_1}(\lambda)\delta[\mathrm{CP}_1] + \dots + \varepsilon_{\mathrm{CP}_n}(\lambda)\delta[\mathrm{CP}_n])$$
(2.18)

Because (2.18) provides a linear relationship between chromophore concentrations and measurement data we can rewrite it as

$$\begin{bmatrix} \phi_s(\lambda_1) \\ \phi_s(\lambda_2) \\ \vdots \end{bmatrix} = \begin{bmatrix} \varepsilon_{\mathrm{CP}_1}(\lambda_1)\mathbf{A}(\lambda_1) & \dots & \varepsilon_{\mathrm{CP}_n}(\lambda_1)\mathbf{A}(\lambda_1) \\ \varepsilon_{\mathrm{CP}_1}(\lambda_2)\mathbf{A}(\lambda_2) & \dots & \varepsilon_{\mathrm{CP}_n}(\lambda_2)\mathbf{A}(\lambda_2) \\ \vdots & \vdots & \vdots \end{bmatrix} \begin{bmatrix} \delta[\mathrm{CP}_1] \\ \vdots \\ \delta[\mathrm{CP}_n] \end{bmatrix}. \quad (2.19)$$

Where the column vectors in $\phi_s(\lambda_i)$ represent the measurement at wavelengths λ_i , each element in those vectors represent a source/detector pairs. As for the dimensions of the weight matrix, $\mathbf{A}(\lambda_l)$ the number of rows is equal to the number of source/detectors pairs in the experimental setup and the number of the columns in the $\mathbf{A}(\lambda_i)$ is given by the number of pixels in the image. Then each element of the weight matrix there is the l^{th} wavelength, the m^{th} source/detector pair and the i^{th} pixel or image point, which gives

$$\mathbf{A}(\lambda_l)_{m,i} = \frac{v}{16\pi^2 D(\lambda)} \frac{e^{jk_0(\lambda_l)(|r_d^m - r_i| + |r_i - r_s^m|)}}{|r_d^m - r_i||r_i - r_s^m|}.$$

To simplify notation, (2.19) is written in matrix notation

$$\mathbf{g} = \mathbf{K}' \mathbf{f}',\tag{2.20}$$

where \mathbf{K}' has been defined as an expanded weight matrix, a measurement vector \mathbf{g} and concentration vector \mathbf{f}' is written as

$$\mathbf{K}' = \mathbf{E}\mathbf{\Lambda} \qquad \mathbf{g} = \begin{bmatrix} \phi_s(\lambda_1) \\ \phi_s(\lambda_2) \\ \vdots \end{bmatrix} \qquad \mathbf{f}' = \begin{bmatrix} \delta[\mathrm{CP}_1] \\ \vdots \\ \delta[\mathrm{CP}_n] \end{bmatrix}$$

where $\boldsymbol{\varepsilon}$ and $\boldsymbol{\Lambda}$ is defined as

$$\mathbf{\Lambda} = \begin{bmatrix} \mathbf{A}(\lambda_1) & 0 & \dots & 0 \\ 0 & \mathbf{A}(\lambda_2) & \dots & 0 \\ \vdots & \vdots & \ddots & \vdots \\ 0 & 0 & 0 & \mathbf{A}(\lambda_l) \end{bmatrix} \qquad \boldsymbol{\varepsilon} = \begin{bmatrix} \varepsilon_{\mathrm{CP}_1}(\lambda_1) & \dots & \varepsilon_{\mathrm{CP}_n}(\lambda_1) \\ \varepsilon_{\mathrm{CP}_1}(\lambda_2) & \dots & \varepsilon_{\mathrm{CP}_n}(\lambda_2) \\ \vdots & \vdots & \vdots \\ \varepsilon_{\mathrm{CP}_1}(\lambda_l) & \dots & \varepsilon_{\mathrm{CP}_n}(\lambda_l) \end{bmatrix}.$$

The Kronecker product is used to define

$$\mathbf{E} = \boldsymbol{\varepsilon} \otimes \mathbf{I}.$$

2.3.3 3D computation

For the case of this thesis the light sources are considered as 3D point sources. A medium is defined which has a defect which is, for all practical purposes, infinite along the z-axis. Therefore only a 2D representation of the components of the vector \mathbf{f}' are really needed for the work in this thesis, thereby greatly lowering the computational burden.

As an example to illustrate how this simplifies computations, consider three different 3x3 planes at different locations on the z-axis.

$$\mathbf{z}_{1} = \begin{bmatrix} \mathbf{f}'1 & \mathbf{f}'(2) & \mathbf{f}'(3) \\ \mathbf{f}'(4) & \mathbf{f}'(5) & \mathbf{f}'(6) \\ \mathbf{f}'(7) & \mathbf{f}'(8) & \mathbf{f}'(9) \end{bmatrix}$$
$$\mathbf{z}_{2} = \begin{bmatrix} \mathbf{f}'(10) & \mathbf{f}'(11) & \mathbf{f}'(12) \\ \mathbf{f}'(13) & \mathbf{f}'(14) & \mathbf{f}'(15) \\ \mathbf{f}'(16) & \mathbf{f}'(17) & \mathbf{f}'(18) \end{bmatrix}$$
$$\mathbf{z}_{3} = \begin{bmatrix} \mathbf{f}'(19) & \mathbf{f}'(20) & \mathbf{f}'(21) \\ \mathbf{f}'(22) & \mathbf{f}'(23) & \mathbf{f}'(24) \\ \mathbf{f}'(25) & \mathbf{f}'(26) & \mathbf{f}'(27) \end{bmatrix}$$

The ordering of the planes along the axis can be seen in Figure 2.2. Because the problem and defect is defined as invariant along the z-axis we can state that the reconstruction for each z-plane should be the same. Mathematically this would



Figure 2.2: Different z-planes along the z axis.

mean

$$\mathbf{f}'(1) = \mathbf{f}'(10) = \mathbf{f}'(19)$$

 \vdots
 $\mathbf{f}'(9) = \mathbf{f}'(18) = \mathbf{f}'(27).$

Because of this statement a base matrix can be defined that combines the reconstruction from the different planes into a solution for a single plane. The location of that imaging plane is arbitrary since the z-axis is invariant.

Therefore we can write the 3D collection of voxels in terms of the 2D values on any

plane as

$$\begin{bmatrix} \mathbf{f}'(1) \\ \mathbf{f}'(2) \\ \vdots \\ \mathbf{f}'(9) \\ \mathbf{f}'(10) \\ \mathbf{f}'(11) \\ \vdots \\ \mathbf{f}'(27) \end{bmatrix} = \begin{bmatrix} 1 & 0 & \dots & 0 \\ 0 & 1 & \dots & 0 \\ 0 & 0 & \dots & 1 \\ 1 & 0 & \dots & 0 \\ 0 & 1 & \dots & 0 \\ \vdots \\ 0 & 0 & \dots & 1 \end{bmatrix} \begin{bmatrix} \mathbf{f}(1) \\ \mathbf{f}(2) \\ \vdots \\ \mathbf{f}(9) \end{bmatrix}$$
(2.21)

or simply

$$\mathbf{f}' = \mathbf{B}\mathbf{f} \tag{2.22}$$

In (2.21) the sparse matrix is the base matrix **B** and the vector **f** is the solution to the inverse problem. Using this, (2.20) is rewritten as

$$\mathbf{g} = \mathbf{K}' \mathbf{B} \mathbf{f} = \mathbf{K} \mathbf{f},\tag{2.23}$$

Choosing the number of z-planes to use in the reconstruction is important. Using a higher number of planes increases the number of variables in the problem and additionally slows down the process of computing the \mathbf{K} matrices. For each problem the number of z-planes used in the reconstruction are chosen so that a balance is obtained between the computational intensity and a number of z-planes that give the best reconstruction. For simulations this decision is made by examining the reconstructed images and calculating the mean squared error. For measured data this decision is made only by examining the reconstructed images.

Chapter 3

The Inverse problem

As discussed in Chapter 1 a number of challenges need to be dealt with when solving the inverse problem. This chapter shows methods used to solve inverse problems and regularization techniques that are used to optimize the problem.

3.1 Inversion Methods

When dealing with inverse problems pseudoinverse methods are often employed. Here we will discuss some of the methods that can be used when calculating the pseudoinverse.

3.1.1 SVD and TSVD methods

Considering a matrix **K**, as in (2.20), which is a $m \times p$ rectangular matrix with m > pthen the SVD is a factorization takes the form

$$\mathbf{K} = \mathbf{U} \mathbf{\Sigma} \mathbf{V}^T = \sum_{i=1}^p u_i \sigma_i v_i^T$$
(3.1)

where **U** is an $m \times m$ unitary matrix, the matrix Σ is $m \times p$ diagonal matrix with nonnegative real numbers on the diagonal, and **V** is an $p \times p$ unitary matrix.

The common convention is to order the diagonal entries $\Sigma_{i,j}$ in non-increasing fashion. The diagonal entries of Σ are known as the singular values of \mathbf{K} . The number of singular values r is the rank of \mathbf{K} . Then Σ is written as:

$$\Sigma = diag(\sigma_1, \sigma_2, \dots, \sigma_r) \tag{3.2}$$

The pseudo inverse of \mathbf{K}, \mathbf{K}^+ , is defined as

$$\mathbf{K}^+ = \mathbf{V} \mathbf{\Sigma}^+ \mathbf{U}^T \tag{3.3}$$

where Σ^+ is formed by

$$\Sigma^{+} = diag(\sigma_{1}^{-1}, \sigma_{2}^{-1}, \dots, \sigma_{r}^{-1})$$
(3.4)

This pseudo inverse is then used to obtain $\mathbf{f} = \mathbf{K}^+ \mathbf{g}$

$$\mathbf{f} = \sum_{i=1}^{r} \frac{1}{\sigma_i} v_i \langle u_i, g \rangle = \mathbf{V} \mathbf{\Sigma}^+ \mathbf{U}^T \mathbf{g}$$
(3.5)

When dealing with a matrix, \mathbf{K} , where the singular values decay over many orders of magnitude towards zero, like in the DOT case, the problem becomes more complicated.

To see how the SVD gives insight into the ill-conditioning of \mathbf{K} , consider the

following relations [Han97]:

$$\mathbf{K}\mathbf{v}_{i} = \sigma_{i}\mathbf{u}_{i}, \quad \|\mathbf{K}v_{i}\|_{2} = \sigma_{i}$$

$$\mathbf{K}^{T}\mathbf{u}_{i} = \sigma_{i}\mathbf{v}_{i}, \quad \|\mathbf{K}^{T}\mathbf{u}_{i}\|_{2} = \sigma_{i}$$
(3.6)

where \mathbf{u}_i , \mathbf{v}_i are the i^{th} elements in the \mathbf{V} and \mathbf{U} matrices. It can be seen that a small singular value σ_i , relative to $\sigma_1 = \|\mathbf{K}\|_2$, means that there exists a certain linear combination of the columns of \mathbf{K} , characterized by the elements of the right singular vector v_i , such that $\|\mathbf{K}v_i\|_2 = \sigma_i$ is small. The same holds for u_i and the rows of \mathbf{K} . In other words, a situation with one or more small σ_i implies that \mathbf{K} is nearly rank deficient, and the vectors \mathbf{u}_i and \mathbf{v}_i associated with the small σ_i are the numerical null vectors of \mathbf{K}^T and \mathbf{K} respectively. From this property it can be concluded that the matrix corresponding to a discrete ill-posed problem is always highly ill conditioned.

The SVD is an invaluable tool for analysis of problems with ill-conditioned matrices and the truncated SVD (described below) has been used successfully to solve a variety of ill-posed problems of the form (2.20). When \mathbf{g} in (2.20) is perturbed by errors then the solution to the perturbed problem is very likely to be dominated by large amplitude, high frequency errors with structure of singular vectors correlated to small singular values [Han90]. It is therefore necessary to use some sort of regularization to compute a solution that is less sensitive to the perturbations. The Tikhonov method is commonly used in this respect and will be discussed in detail in Section 3.1.2. An alternative method for regularization of (2.20) is the Truncated SVD. TSVD uses a reduced rank approximation to \mathbf{K} that is obtained by setting all but the first l largest singular values equal to zero and using only the

first columns of **U** and **V**. Thus the TSVD solution, \mathbf{f}_l , is defined by

$$\begin{aligned} \mathbf{f}_l &\approx \sum_{i=1}^l v_i \langle u_i, g \rangle = \mathbf{V} \mathbf{\Sigma}_l^+ \mathbf{U}^T \mathbf{g} \quad \text{where} \\ \mathbf{\Sigma}_l^+ &= diag(\sigma_1^{-1}, \sigma_2^{-1}, \dots, \sigma_l^{-1}, 0, \dots, 0) \end{aligned}$$

The integer l is called the truncation parameter. The TSVD becomes especially useful when dealing with ill-posed problems such as the forward model matrices for the DOT problem which are often poorly conditioned with a very wide range of singular values. The singular value spectrum can have a range of seven orders of magnitude in the singular values[GBD+00].

3.1.2 Iterative Methods

When solving problems in an optimization, like DOT, iterative methods are commonly employed. In Chapter 2 a discretization of the forward model was obtained with (2.20). Solving this system using a least squares approach amounts to solving the following error minimization problem:

$$\widehat{\mathbf{f}} = \operatorname*{argmin}_{\mathbf{f}} \|\mathbf{g} - \mathbf{K}\mathbf{f}\|_2^2 \tag{3.7}$$

where $||X||_2$ is the norm 2 of the matrix X. Using (3.7) and assuming that $(\mathbf{K}^T \mathbf{K})$ gives a solution of

$$\widehat{\mathbf{f}} = (\mathbf{K}^T \mathbf{K})^{-1} \mathbf{K}^T \mathbf{g}.$$
(3.8)

In (3.8) $(\mathbf{K}^T \mathbf{K})^{-1} \mathbf{K}^T$ is the pseudo inverse of \mathbf{K} thereby connecting the least squares problem to SVD-based inverse methods. In any event, the issues associated with illposedness remain since no regularization has been employed. To overcome these, in this thesis we employ a Tikhonov-type regularization method in which (3.7) is replaced with

$$\widehat{\mathbf{f}} = \underset{\boldsymbol{f}}{\operatorname{argmin}} \|\mathbf{R}^{-1/2}(\mathbf{g} - \mathbf{K}\mathbf{f})\|_{2}^{2} + \alpha \|\mathbf{L}\mathbf{f}\|_{2}^{2}.$$
(3.9)

The addition of the second term in the minimization problem constrains the solution, depending on how the regularization matrix \mathbf{L} , and corresponding α are chosen. Using this regularization method and assumming that $(\mathbf{K}^T \mathbf{R}^{-1} \mathbf{K} + \alpha \mathbf{L}^T \mathbf{L})$ is invertible, the solution to (3.9) becomes,

$$\hat{\mathbf{f}} = (\mathbf{K}^T \mathbf{R}^{-1} \mathbf{K} + \alpha \mathbf{L}^T \mathbf{L})^{-1} \mathbf{K}^T \mathbf{R}^{-1} \mathbf{g}.$$
(3.10)

The noise covariance matrix, \mathbf{R} , is included in the solution to take in the effect of the noise that is added into the simulated data. When adding the noise the standard deviation of the noise is defined, the \mathbf{R} matrix is then defined as a diagonal matrix with the standard deviation on the diagonal elements,

The regularization matrix, \mathbf{L} , serves the purpose of regularizing the solution to increase the quality of the reconstructed image. Different configurations for \mathbf{L} were tested, for example when \mathbf{L} is set as the identity matrix the regularization is purely controlled by the regularization parameter α . Choosing the regularization matrix to be the identity matrix allows us to take into account prior information about the quantities being reconstructed. The implicit prior assumptions when the identity matrix is used is that the concentrations are small, for sufficiently large α . This reduces non-physical artifacts in the reconstructed images. To take advantage other types of prior beliefs, such as that the chromophore distributions are spatially smooth it is reasonable to choose \mathbf{L} to be a derivative-like term [KS05]. The gradient matrix is constructed so that it takes the gradient both along the x-axis and the yaxis. Then the regularization matrix is written as follows

$$\mathbf{L} = \begin{bmatrix} \begin{bmatrix} \nabla_x \\ \nabla_y \end{bmatrix} & 0 \\ 0 & \begin{bmatrix} \nabla_x \\ \nabla_y \end{bmatrix} \end{bmatrix}$$

where ∇_x and ∇_y take the gradient in x and y directions, respectively making the gradient matrix is a first difference operator [GW02].

The challenge lies in how to choose the α parameter. There exist formal methods for choosing the parameter, such as generalized cross-validation (GCV) or the L-curve, but it is not necessary to use them in all cases [Hyd02]. The appropriate value may be selected by trial and error and visual inspection. Larger α makes the system better conditioned, but this new system is farther away from the original system, the system without regularization. Under the no noise condition, any sufficiently small value of α will produce almost the same result. When noise is encountered, however, α may need to be made much larger. Furthermore the effect of having two separate regularization parameters α_1 and α_2 is explored. It is shown how the mean square error behaves for reconstruction of two chromophores and how having separate parameters for each hemoglobin increases the quality of the reconstruction. For that case the regularization parameters are incorporated into the matrix and then L takes the form

$$\mathbf{L} = \begin{bmatrix} \alpha_1 \begin{bmatrix} \nabla_x \\ \nabla_y \end{bmatrix} & 0 \\ 0 & & \\ 0 & & \alpha_2 \begin{bmatrix} \nabla_x \\ \nabla_y \end{bmatrix} \end{bmatrix}$$
(3.11)

To generalize this to *n* chromophores, one might want to have different regularization parameters for each chromophore. Then we define a matrix, Π_{xy} , for both directions of the gradients and a parameter matrix, Υ , for every regularization parameter.

$$\mathbf{L} = diag(\Upsilon \otimes \Pi_{xy})$$

$$\Pi_{xy} = \begin{bmatrix} \nabla_x \\ \nabla_y \end{bmatrix} \qquad \Upsilon = \begin{bmatrix} \alpha_1 \\ \vdots \\ \alpha_n \end{bmatrix}$$

In this thesis the α parameters are chosen by trial and error. A set of parameters is selected, and reconstructions done for each pair, then in the case of simulations, each solution is evaluated by the mean square error and visually. When selecting regularization parameters for experiment a broad range of pairs is tested and the best result is chosen visually. The parameters are selected to be as low as possible to maintain the regularized system closed as close as possible to the original system, but high enough to counter the ill-posedness of the problem.

3.1.3 Computational issues

Assembly of normal equations and the use of direct methods (SVD, QR, Gaussian elimination etc.) for their solution is infeasible for 3D problems with hyperspectral data, especially when one needs to perform these calculation many times in the evaluation of regularization parameters.

To reduce these computational issues we use iterative methods, specifically LSQR [JXS⁺08]. For the case of LSQR, the problem is solved through a method similar to the conjugate gradient method [PS82]. An interesting feature of this algorithm is that it interacts with the matrix \mathbf{K} only through the matrix vector products \mathbf{Kf} and $\mathbf{K}^T \mathbf{v}$, for various vectors \mathbf{f} and \mathbf{v} . For the case of DOT LSQR becomes highly attractive for its computational efficiency when compared to a direct solution of traditional least squares. This is due in part to the fact that computing $\mathbf{K}^T \mathbf{K}$ can require large amounts of computational overhead. The number of voxels in a given solution becomes somewhat limited by the necessity of solving the system defined by $\mathbf{K}^T \mathbf{K}$ or some regularized version thereof. Because of the design of \mathbf{K} , as mentioned in Chapter 2, when the voxels increases, the size of $\mathbf{K}^T \mathbf{K}$ and the computation required for elimination both increase much more rapidly than with LSQR [PS82].

Solving the regularized version of the system in (3.9) is equivalent to a least squares solution to the system:

$$\begin{bmatrix} \mathbf{K} \\ \alpha \mathbf{L} \end{bmatrix} \mathbf{f} = \begin{bmatrix} \mathbf{g} \\ 0 \end{bmatrix}.$$

We define the augmented weight matrix and data vector as

$$\overline{\mathbf{K}} = \begin{bmatrix} \mathbf{K} \\ \alpha \mathbf{L} \end{bmatrix} \qquad \overline{\mathbf{g}} = \begin{bmatrix} \mathbf{g} \\ \mathbf{0} \end{bmatrix}.$$

Using this formulation we can write the problem up as

$$\widehat{\mathbf{f}} = \operatorname{argmin}_{\mathbf{f}} \|\overline{\mathbf{g}} - \overline{\mathbf{K}}\mathbf{f}\|_2^2.$$
(3.12)

This setup is very attractive for the purpose of this thesis. In this formulation it is only needed to store one **K** matrix for each wavelength. This solves the problem of when using hyperspectral information, the **K** matrix for all wavelengths would be too big for computations. The LSQR method allows for using hyperspectral information meanwhile keeping computations efficient by storing only one **K** at a time. This reduces the number of computations immensely. Utilizing the fact that the iterations compute the matrix vector products $\mathbf{K}^T \mathbf{f}$ and $\mathbf{K} \mathbf{f}$ allows us to construct and store only the **K** matrix needed for a single wavelength. When the computations have been done for all wavelengths within each iterations the **f** vector is updated when the **Kf** product is compared to the data vector. This results in working with very small **K** matrices at each time compared to if a **K** matrix would be constructed for all of the wavelengths wanted in the reconstruction. In the case of hyperspectral information this becomes very important where the complete **K** matrix including all wavelengths would be very big.

Furthermore, sometimes employing a simple LSQR method is not enough. Because the basic LSQR does not consider any bounds it can sometimes result in a negative concentrations which are physically impossible. Therefore the NLLS algorithm is used instead of the LSQR method. This is an algorithm included in the MATLAB library and allows me to impose upper and lower bounds on the reconstruction as well as using a Jacobian in the process. When dealing with measurement data we used the LSQR method to obtain a reasonable initial guess for the concentrations to then put into the NLLS algorithm. This is discussed further in Chapter 5.

Chapter 4

Simulations

Simulations are done to test the effect of hyperspectral information when doing reconstruction of more than one chromophore. To create simulated measurement data (data that would have obtained from detectors) the reconstruction model is used to obtain that data from the simulated images. Normally this would be considered an inverse crime, where numerically produced simulated data is produced by the same model that is used to invert the data [KS05], but in this case that will be ignored.

The reason for ignoring this inverse crime is that it is the general consensus that creating simulated data with the inverse solver is not damaging to results. As mentioned before there have been claims that a forward solver (predictor) is needed to simulate data, i.e. it involves predicting the response of a physical system with the help of some mathematical model incorporating the parameter one wishes to recover [KS05], [CK92]. Some have proposed that a separate inverse solver (estimator) is needed to estimate the response of some physical system with the help of another mathematical model incorporating a variable usually having the same physical and mathematical attributes as the parameter one wishes to recover. It has been shown that it this separation of predictor and estimator is not necessary to avoid trivial inversion, in fact it has been derived that might be impossible to obtain a solution, whose relative error lies below some prescribed threshold, when employing an estimator that is separate to the predictor [Wir08]

4.1 Simulated Images

When creating simulated images of two chromophores, images of boxes are created, a simple one shown in Figure 4.2, to simulate concentration of chromophores. More complex chromophore images are shown in Figures 4.3 and 4.4.

Information for the background from is taken literature. It is assumed that the μ'_s follows Mie Scattering theory. A scattering prefactor Ψ depends primarily on the number and size of scatterers, and a scattering exponent *b* depends on the size of scatterers [KCC⁺08]. This is combined as:

$$\mu'_s = \Psi \lambda^{-b} \tag{4.1}$$

Values for Ψ and b are obtained from [TPT+03] for the breast. Values for μ_a are obtained from [SB81], which are values in the 600-900 nm range in 10 nm intervals. For wavelengths between those intervals we interpolate between values from the article.

For the concentration defined in the simulated images it is defined units of molarity or mol per liter, M. The extinction coefficients for each chromophore are in the units cm^{-1}/M and are obtained from Scott Prahl of the Oregon Medical Laser



Figure 4.1: Molar extinction coefficients used in simulations plotted as a function of wavelength.

Center [Pra]. The extinction coefficients are shown in Figure 4.1.

Three different sets of images are created to test the reconstruction. The first set is a simple image with only a concentration for HbO₂ and none for HbR. Reconstruction is done for these images to explore effects of adding hyperspectral information to the problem, i.e. the reduction of crosstalk where a concentration of one chromophore creates a false concentration in an image for another chromophore. The second set is a little more complex with concentrations of HbR in different areas than HbO₂. The third set is more complicated with concentrations for HbO₂ and HbR in the same areas. In the third set the intensity of the concentrations are not the same for the two chromophores. These images are shown in Figures 4.2-4.4. The alignment of sources and detectors with the respect of the simulated images is displayed in Figure 4.5.

In simulations the forward model is used to create data from the images. This is done by doing the following process,

$$\mathbf{g} = \mathbf{K} \begin{bmatrix} \mathbf{f}_{\mathrm{CP}_1} \\ \mathbf{f}_{\mathrm{CP}_2} \end{bmatrix} + n \tag{4.2}$$



Figure 4.2: Simple concentration images for a single chromophore. Left image is for HbO_2 and right image is for HbR.



Figure 4.3: Images with concentrations for two chromophores. Left image is for HbO_2 and right image is for HbR.



Figure 4.4: Images with concentrations for two chromophores with different intensities. Left image is for HbO_2 and right image is for HbR.



Figure 4.5: The setup of sources and detectors.

where \mathbf{f}_{CP_1} and \mathbf{f}_{CP_2} are the simulated concentration images for each chromophore. After this, data vector is created and noise is added to it in the range of 60-120 dB. The SNR of adding this noise will be calculated by using the following equation

$$SNR = 10\log_{10} \frac{\|\mathbf{g}\|^2}{N\sigma^2} \tag{4.3}$$

where N is the number of data points and \mathbf{g} is the signal with out additive noise. Because phantoms are assumed to be infinite in the z-direction, 50 z-planes are used when creating the simulated data. The images are created to test the inverse solution with respect to spectral information, regularization, cross-talk and accuracy. To estimate the effectiveness of the reconstruction in simulations, for the n^{th} chromophore the mean square error is computed by using the following equation

$$MSE_{CP_n} = \frac{\|\mathbf{f}_{CP_n} - \widehat{\mathbf{f}}_{CP_n}\|_2}{\|\mathbf{f}_{CP_n}\|_2},\tag{4.4}$$

Another metric used in evaluating reconstructions is the symmetric difference. This evaluates how many pixels are correctly identified as a chromophore concentration in the reconstructed images. This is done by computing for the n^{th} chromophore

$$\Xi_{CP_n} = \frac{1}{M} (\mathbf{f}_{CP_n} \oplus \widehat{\mathbf{f}}_{CP_n})$$
(4.5)

where M is the number of pixels in the reconstructed image and \oplus is the XOR operator. The reconstructed images are thresholded relative to the peak value in each image, which gives a 'logical' map of the concentrations. This is compared to the original images to determine how many pixels are correctly determined as chromophore concentrations. The reconstructed images are then judged on the basis of the MSE values, symmetric distance and also by judging them visually. The results are not only judged on how well they locate the chromophore concentrations but also it is important that the intensities of each concentration is close to the target value. All simulations were performed in MATLAB and tested in both Linux and Windows operating systems. All programs were written from scratch specifically for this thesis.

4.2 Using gradient matrix and two parameters

For reconstructions shown here the L matrix was chosen to be a gradient matrix, shown in (3.11). Using an identity matrix was also tested but the gradient matrix resulted in far better results. By using the gradient matrix and using separate regularization parameters for each chromophore allows the reconstruction to, in a way, separate the reconstruction for HbO₂ and HbR. In order two examine the effectiveness of having two parameters the mean square error is plotted as a function of α_1 and α_2 . Plotting this produces a three dimensional surface which shows the optimal parameters, where the mean square error is minimized. The MSE is the then computed using (4.4). Plots for the mean square error for the first set is shown in Figure 4.6. From these plots it is possible to determine an optimal value for α_1 and α_2 . For a simple chromophore concentrations like in the first set, choosing the regularization parameters is an easy problem. The reason for separating the regularization parameters in this case is that the MSE for HbR reaches a lower value for a higher α_1 than HbO₂ and as mentioned in Chapter 3 the best choice for the parameters is the lowest choice possible. Although keeping the parameters separate is useful for multiple chromophore, it could be seen from the plot in Figure 4.6 that α_1 could be equal to α_2 . This is because in this case only one chromophore is being reconstructed, so it is much easier to find an optimal value for the parameter regularizing the "missing" chromophore. Examining the results visually shows that separating them gives better results. The importance of separating the regularization parameters becomes even more visible when regularizing more complex concentration sets. In Figure 4.7 it shows that the lowest MSE values for HbO_2 and HbR occur at two very different values. For this set the separation of the regularization parameters is very important. Using only one regularization parameter in this set and more complicated ones, would result in a trade off between reconstructions of chromophores. To reduce that trade off the separation of the chromophores becomes very important. This separation becomes even more important when dealing with data sets with low SNR values such as true measurement data.



Figure 4.6: Mean square error as function of regularization parameters for the first set. Left image is HbO_2 and right image is HbR.



Figure 4.7: Mean square error as function of regularization parameters for the second set. Left image is HbO_2 and right image is HbR.

4.3 Reconstruction

The main goal is to show the advantage of hyperspectral information. The increased number of wavelengths should make the inverse problem less ill-posed and reduce cross-talk between chromophores. First we will display simple images to show these advantages and then show examples for more complicated images. Although crosstalk can in most cases be eliminated completely it is greatly reduced by using a very high number of wavelengths.

4.3.1 First set

In reconstructions done for the images in Figure 4.8, noticeable crosstalk is present when few wavelengths are used. Using few wavelengths results in a diffuse reconstruction of the HbO₂ concentration. This result also shows evidence of HbR, which is a result of cross-talk. Increasing the number of wavelengths to 26 wavelengths gives somewhat better results. The jump from 6 wavelengths to 26 wavelengths is not significant but some reduction in cross-talk is evident and better definition of the HbO₂ concentration is obtained.

In Figure 4.9 results are shown for 126 wavelengths and 251 wavelengths. This shows a significant improvement in reconstructions for both chromophores. In the 126 wavelengths case the cross-talk is almost vanished and the HbO₂ concentrations is better defined and approaching the correct intensity values. Moving to 251 wavelengths shows a very good reconstruction with a good approximation of HbO₂ and negligible crosstalk.

In Figure 4.10 the MSE is plotted as a function wavelengths to show how hyperspectral information results in better reconstructions. The MSE values show that the accuracy increases greatly when wavelengths are added. The trend for HbR shows small changes as there is no chromophore to reconstruct, but crosstalk is shown to be reduced.

Examining the symmetric difference in Figure 4.11 the HbR reconstructions

are well described. The improvement is not much, no chromophore present, but the difference decreases a little bit when the cross-talk is eliminated more and more. As with the MSE the improvement for HbO_2 is clear.

4.3.2 Second set

Examining reconstructions at few wavelengths are shown in Figure 4.12. A good approximation is obtained for HbR but HbO₂ results in a blurry reconstruction. It is noticeable for both the 6 and 26 wavelength cases that noticeable cross-talk is evident in the HbR images. The effects of the HbO₂ concentrations are appearing in the HbR images, same as what happened in the first set. Increasing the wavelengths to 26 wavelengths gives a better results for HbO₂ but remains blurry.

Using 126 and 251 wavelengths, shown in Figure 4.13, the cross-talk in the HbR image is reduced. As in the first set the reconstruction for HbO₂ is greatly improved. A very good approximation of both chromophores is shown for 251 wavelengths. Even using 126 wavelengths the localization of HbO₂ is better and approaching the correct intensity.

The improvement in using hyperspectral information is shown in the MSE values, Figure 4.14. The localization of HbR remains good with all wavelengths resulting in a small increase of the symmetric difference, Figure 4.15, for the HbR. The decrease in that case is due to the reduction of cross talk. The symmetric difference significantly decreases when more wavelengths are added as expected when the images become more accurate.



Figure 4.8: Reconstruction for first set, low complexity. Middle images is done with 6 wavelengths and rightmost images is done with 26 wavelengths. Upper row is for the HbO_2 chromophore and the lower for HbR. SNR is 64.9 dB.



Figure 4.9: Reconstruction for first set, low complexity. Middle images is done with 126 wavelengths and rightmost images is done with 251 wavelengths. Upper row is for the HbO_2 chromophore and the lower for HbR. SNR is 63.9 dB.



Figure 4.10: MSE plotted as a function of the number of wavelengths for the first set.



Figure 4.11: Symmetric difference plotted as a function of the number of wavelengths for the first set.

4.3.3 Third set

In Figure 4.16 the reconstruction for the HbO_2 fails almost completely. Although the reconstruction show good results for HbR the HbO_2 concentrations are far off the true values. When increasing number of wavelengths to 26 the localization HbO_2 are somewhat better but the intensities are far off.

Using hyperspectral information, Figure 4.17, results in much better reconstructions. For 126 wavelengths the separation of the two concentrations in the HbO₂ case becomes better defined. In the 251 wavelength case a good approximation for


Figure 4.12: Reconstruction for second set, medium complexity. Middle images is done with 6 wavelengths and rightmost images is done with 26 wavelengths. Upper row is for the HbO_2 chromophore and the lower for HbR. SNR is 83.6 dB.



Figure 4.13: Reconstruction for second set, medium complexity. Middle images is done with 126 wavelengths and rightmost images is done with 251 wavelengths. Upper row is for the HbO_2 chromophore and the lower for HbR. SNR is 90.6 dB.



Figure 4.14: MSE plotted as a function of the number of wavelengths for the second set.



Figure 4.15: Symmetric difference plotted as a function of the number of wavelengths for the second set.

both chromophore is reached.

This improvement in reconstruction is shown for both chromophores in Figure 4.18 and the improvement of the localization of HbO_2 is evident in Figure 4.19. As in the second set the localization of the HbR is acceptable for all wavelength cases.



Figure 4.16: Reconstruction for third set, high complexity. Middle images is done with 6 wavelengths and rightmost images is done with 26 wavelengths. Upper row is for the HbO_2 chromophore and the lower for HbR. SNR is 80.7 dB.



Figure 4.17: Reconstruction for third set, high complexity. Middle images is done with 126 wavelengths and rightmost images is done with 251 wavelengths. Upper row is for the HbO_2 chromophore and the lower for HbR. SNR is 85.5 dB



Figure 4.18: MSE plotted as a function of the number of wavelengths for the third set.



Figure 4.19: Symmetric difference plotted as a function of the number of wavelengths for the third set.

Chapter 5

Physical Measurements

In order to test the simulation results, physical measurements were performed. The goal of the measurement were to show how hyperspectral information gives way to the imaging of two different chromophores by using the direct method.

5.1 Measurement Process

The process can be divided into four parts.

- 1. Construction and measurement of the actual phantoms,
- 2. Construction of the medium
- 3. Measurement of the background
- 4. Measurement of the phantoms in the medium

Each process will be discussed in this section along with measurement results compared to simulations.

5.1.1 Phantoms

To simulate two different chromophores black india ink and blue food dye were used. Two different sets of phantoms were measured for this thesis, each with different concentration of ink and dye. The first had only one phantom, ink, but the second two each had two different phantoms. Detailed listing of the concentrations and configuration of the phantom sets are provided in Table. 5.1.

Set #	Concentration	Length [cm]	Diameter [cm]
1	80 mL medium + 1 μ L india ink	19	1
	$80 \text{mL} \text{ medium} + 1 \ \mu \text{L} \text{ blue dye}$	19	1
2	$80 \text{mL} \text{ medium} + 2 \ \mu \text{L}$ india ink	19	1
	$80 \mathrm{mL} \mathrm{medium} + 2 \ \mu \mathrm{L} \mathrm{blue} \mathrm{dye}$	19	1

Table 5.1: Concentrations of the phantoms used in measurements. The medium was made out of 2 parts water and 1 part milk.

Using the first measurement set proved to be difficult since the intensity of the ink and dye was too low. For the results displayed in this chapter only the second set was used.

As was discussed in Section 3 the extinction coefficients of the chromophores are needed in order to do perform the direct method reconstruction. These coefficients are obtained by measuring the phantom solutions in a spectrometer. A measurement in a spectrometer yields the absorption of the solution for multiple wavelengths, shown in Figure 5.1, which can be used to calculate the extinction coefficients using the following relation:

$$\Psi = \epsilon c \tag{5.1}$$

where Ψ is the absorption, ϵ the extinction coefficient and c is the concentration of

the subject at hand. It should be noted that when the solutions are measured in the spectrometer milk is not used. This is due to the fact that absorption cannot be measured with milk in the medium since the light in the spectrometer would be fully absorbed by the milk. Because of the similarities in the spectra of milk and water this does not cause big errors in calculation of the extinction coefficients. In measurements the unit of the extinction coefficients are 1/cm.



Figure 5.1: (a) Absorption spectra for set #1.(b)Absorption spectra for set #2.

It should also be noted that the actual intensity of the ink concentration is relatively small. That is because if too much ink is put into the phantom, it will absorb all the light passing through it and no spectral information will reach the detector. So a fine line has to be tread when creating the phantoms, keeping the intensities low enough so that spectral information can be obtained, but still having them as strong as possible so that they can be seen reconstructed images.

5.1.2 Background

The medium is constructed using milk and water. Milk, with 2% fat, is used due to the similarities of the optical properties to human skin. A tank is filled with 7 liters of milk and 14 liters of water so that the ratio between water and milk is 2:1.

Set #	$\mu_a @ 690 \text{ nm}$	$\mu_a @ 830 \text{ nm}$
Literature[HQ73]	0.0053	0.031
Set from 26^{th} Jan. '09	0.0028	0.046
Set from 28^{th} May '09	0.0088	0.036

Table 5.2: Value of μ_a from measurements compared to the value used from literature.

In order to obtain multi- and hyperspectral reconstruction valued for μ_a , the absorption coefficient, and μ'_s , the reduced scattering coefficient, have to be known. This is somewhat tricky due to the fact that the machine used for measurement on μ_a and μ'_s only performs measurements at two wavelengths. For the μ'_s coefficient values at multiple wavelengths can be approximated through Mie Scattering theory as in (4.1). Using the two measurements from the machine we can solve for the Ψ and b values and from there obtain values for μ'_s at any wavelength.

Getting values for the absorption coefficient is harder. Since μ_a does not follow a law like μ'_s , values from the literature are used. Using data from [HQ73] gives values for μ_a in the 400-1200 nm range in 25 nm intervals. Interpolation is done between these values to obtain values at smaller intervals in that range.

The measurement to obtain values for the μ'_s calculation and to verify that μ_a is close to the values used from literature is performed at two wavelengths, 690 nm and 830 nm. The measurement value for μ_a is compared to literature in Table 5.2. The measurement give AC, DC and phase data for a signal travelling in the medium which can be used to calculated μ'_s and μ_a for the medium. This information is obtained by moving a detector away from a light source inside of the medium. Then the change in both AC amplitude, DC amplitude and phase is plotted as a function of the position. Then S_{φ} , S_{α} and S_{δ} are defined as the slopes when the phase, $ln(DC \cdot r)$ and $ln(AC \cdot r)$ are plotted respectively as a function of position of r the source-detector separation. The absorption coefficient and scattering coefficient can then be calculated from S_{α} by using

$$\mu_a = \frac{\omega}{2\upsilon} \left(\frac{S_{\varphi}}{S_{\alpha}} - \frac{S_{\alpha}}{S_{\varphi}} \right) \qquad \mu'_s = \frac{S_{\alpha}^2 - S_{\varphi}^2}{3\mu_a}$$

where ω is the modulation frequency set at 110 MHz, v is the speed of light divided by the index of refraction [FFFG94]. Using S_{δ} these values can be verified by using these relations

$$\mu_a = -\frac{\omega}{2\upsilon} \left(\frac{S_{\varphi}^2}{S_{\delta}^2} + 1\right)^{-\frac{1}{2}} \qquad \mu'_s = \frac{S_{\delta}^2}{3\mu_a} - \mu_s$$

The values of μ_a are then compared to literature values in Table 5.2 and used to compute μ'_s with (4.1). As can be seen in Table 5.2 the value at 690 nm is not as close as the one for 830 nm. Although this introduces some error in the reconstruction it is the only way to obtain hyperspectral information regarding μ_a since the onsite machine only takes measurement at two values. Constructing weight matrices for different μ_a values showed that the error in μ_a should not be expected to dominate the reconstructions.

5.1.3 Spectrograph

When phantoms have been constructed and all the necessary background measurements have been taken of the medium, the final step is to actually perform the measurement. A single source and a single detector are placed in the medium on opposite sides of the phantoms. Then the detector takes measurements at multiple



Figure 5.2: Target image for the first measurement taken on January 28^{th} 2009. This is using only a single ink phantom from set #2. Upper image is for ink and lower image is for dye.

points for each location of the source. This gives a tomographic data set that can be used for reconstruction and source-detector pairs were used in the range from 30 to around 100.

The results displayed are from two data sets. First set was taken on January 28^{th} 2009. A single phantom was used, from set #1 in Table 5.1. A total of 6 sources and 10 detectors were placed 4 cm apart to result in a 60 source/detector pair tomographic data. The other two sets were taken on May 28^{th} 2009. The second set has two phantoms, one ink and one dye separated by 4 cm. A total of 9 sources and 11 detectors were placed 4.5 cm apart resulting in 99 source/detector pairs. For each measurement set we created target images which show what is expected to get from the reconstructed images. These images are shown for each set in Figures 5.2



Figure 5.3: Target image for the first measurement taken on May 28^{th} 2009. Both ink and dye phantoms from set #2 were used. Upper image is for ink and lower image is for dye.

to 5.3.

5.2 Results

In this section we will show the reconstructed images obtained from experiment data. The results will be judged by using the MSE value and visually as before. Additionally we examine how effective the method is in localizing the concentrations by examining only the boundary of reconstructed concentrations and the symmetric difference between the target image and the reconstructed image.

5.2.1 First set

In this case there is only the ink phantom from set #3, shown in table 5.1. With 2 μ L of ink in 80 mL solutions the target concentrations are $2.5 * 10^{-5}$ %. Initially reconstruction was tried by using zero as an initial guess in the NLLS algorithm. This proved to be unsuccessful resulting in unusable images. After trying many regularization parameters, an initial guess was obtained by running the LSQR algorithm. Images obtained from that resulted in some negative values, which is of course not possible with a physical concentration. This result was then used as an initial guess for the NLLS algorithm by setting negative values to zero which resulted in better reconstructions. The NLLS algorithm allows me to put on upper and lower bounds for the reconstruction since the concentrations should be between zero and 1, since in the measurement the concentrations are a percentages.

Reconstruction for 3 wavelengths is shown in Figure 5.4. This reconstruction resulted with some reconstruction for ink and almost none for the dye chromophore. Although it gives some concentration for the ink, the spread of the ink is considerable and bigger than expected. Additionally to that, there is noticeable interference from the outermost sources and detectors. The singularity of the Green's function, in (2.12), creates these artifacts. Although regularization parameters were set so that these interference were as little as possible it is very hard to get rid of them completely.

Increasing the number of wavelengths results in better reconstructions as shown in Figure 5.5. This reconstruction is done with 6 wavelengths and locates the phantom very well. it is noticeable that increasing the wavelengths further than 6 wavelengths results in very similar results. The reconstruction at 13 wavelengths in Figure 5.6 shows similar results. Increasing the number of wavelengths to 26, Figure



Figure 5.4: Reconstruction done for a single ink phantom. 3 wavelengths and 21 z-planes used. Upper image is for ink and lower image is for dye.



Figure 5.5: Reconstruction done for a single ink phantom. 6 wavelengths and 21 z-planes used. Upper image is for ink and lower image is for dye.



Figure 5.6: Reconstruction done for a single ink phantom. 13 wavelengths and 21 z-planes used. Upper image is for ink and lower image is for dye.



Figure 5.7: Reconstruction done for a single ink phantom. 26 wavelengths and 21 z-planes used. Upper image is for ink and lower image is for dye.

5.7, creates a more accurate image where the concentration of ink is more localized to the expected region. As can be seen the singularities due to the outermost detectors were somewhat reduced. Although the accuracy is not increase greatly by the adding of wavelengths it is noticeable that the reconstruction approaches the target value when the number of wavelengths is increased. This is also reconstruction done for a single chromophore so the issues of cross-talk is not noticeable.



Figure 5.8: MSE displayed for second measurement set for ink at every wavelength.

In Figure 5.8 the mean square error is shown for each reconstruction as a function of wavelength. This gives a good idea how the reconstruction is better when multiple wavelengths are used. Examining the symmetric difference in Figure 5.9 it is evident that it follows the same trend as the MSE in Figure 5.8, that a good result is obtained by using 6 wavelengths. It should be emphasized that this is reconstruction only done for a single chromophore, so there is very little cross-talk to deal with. The localization of the phantom is also emphasized in Figure 5.10 where it is shown how effectively the reconstruction located the phantom by drawing the boundaries of the reconstructed concentrations compared to the target image.



Figure 5.9: The symmetrical difference of reconstructions for the first set plotted as a function wavelength.



Figure 5.10: Localization of reconstruction of the ink for the first set plotted with respect to the target image.

5.2.2 Second set

In this case there is only phantoms from set #3, shown in table 5.1. Like before set #3 With 2 μ L of ink and dye in 80 mL solutions the target concentrations are $2.5 * 10^{-5}$ %. And as before the initial guess was first worked out by trying many regularization parameters using the LSQR algorithm.

In Figure 5.11 concentrations for both ink and dye are visible in the expected locations. Cross-talk between the two chromophores is significant but artifacts due to sources and detectors are minimal. In the ink image the concentration is very spread out and it is clear that the reconstruction is picking up the ink concentration. It is noticeable that in this image where only three wavelengths are used, the location of the dye chromophore is very noticeable in the reconstructed image for the ink. The dye chromophore completely outweighs the ink in this case.

Doubling the number of wavelengths gives right away somewhat better results, shown in Figure 5.11. The intensity of the cross-talk is reduced and a better defined dye concentration is obtained. On the other hand, reconstruction for the ink concentrations fails in the desired region. Although some is noticeable it is still dominated by the cross-talk from the dye chromophore. This case is similar in Figure 5.13. As expected when only three more wavelengths are added a similar result is obtained. The dye cross-talk is prevalent very little accuracy for the ink.



Figure 5.11: Reconstruction done for two ink and dye phantoms. 3 wavelengths and 21 z-planes used. Upper image is for ink and lower image is for dye.

Increasing the number of wavelengths further gives much better results, as shown in Figure 5.14. The ink concentration becomes much better defined and the cross-talk in the right side of the ink image is greatly reduced. As before the dye concentration is well defined, but using this number of wavelengths gives a closer estimate to the intensities expected. Using every wavelength available, shown in Figure 5.15 gives a very good localization of the ink concentration. The cross-talk from the dye is still observable but is greatly reduced. The dye concentration is around the area expected and similar to the reconstructed value from Figure 5.14.

Examining the MSE of the reconstructions in Figure 5.16 shows explicitly how the reconstruction for ink improves as the number of wavelength is increased. As was discussed the reconstruction of dye is relatively steady, but the elimination of cross-talk in the ink reconstruction is greatly reduced by adding wavelengths.



Figure 5.12: Reconstruction done for two ink and dye phantoms. 6 wavelengths and 21 z-planes used. Upper image is for ink and lower image is for dye.



Figure 5.13: Reconstruction done for two ink and dye phantoms. 9 wavelengths and 21 z-planes used. Upper image is for ink and lower image is for dye.



Figure 5.14: Reconstruction done for two ink and dye phantoms. 26 wavelengths and 21 z-planes used. Upper image is for ink and lower image is for dye.



Figure 5.15: Reconstruction done for two ink and dye phantoms. 251 wavelengths and 21 z-planes used. Upper image is for ink and lower image is for dye.

Looking at the symmetric difference shown in Figure 5.17 that the use of hyperspectral information greatly increases the accuracy of the reconstructions. The symmetrical difference corresponds to the MSE values where the more noticeable improvements are in the Ink image. As in the MSE values the dye reconstructions are more consistent but advantage of hyperspectral information is clearly visible. As before the localization of the phantom is emphasized in Figure 5.18 where it is clearly shown how the crosstalk is reduced by increased number of wavelengths.

It is noticeable in all the images that the concentrations never reach the expected intensities. This is expected with the Born Approximation where previous efforts have shown that it usually underestimates chromophore intensities.



Figure 5.16: MSE displayed for second measurement set for ink and dye at every wavelength.



Figure 5.17: The symmetrical difference of reconstructions for the second set plotted as a function wavelength.



Figure 5.18: Localization of reconstruction for the second set plotted with respect to the target image. Upper image is for ink and lower image is for dye.

Chapter 6

Conclusion

We have shown through simulations and measurements that using hyperspectral information for the DOT problem can greatly help in creating concentration images of multiple chromophores. Not only can images can be created simultaneously for many chromophores but including data from multiple wavelengths greatly reduces cross-talk in the images and improves accuracy.

Including information for decades or even hundreds of wavelength information results in significantly increased accuracy in the image and reduces cross-talk. Optimizing the regularization parameter to accent each chromophore are an important element to getting a good reconstruction, effects of changing the regularization constants were examined and chosen to get the best reconstruction. Together these two factors eliminate artifacts in the image and evoke interest in using this kind of technique for physical measurements. Simulated reconstructions showed significant improvements of including hyperspectral data along with the importance of using multiple regularization parameters for each chromophores.

Physical measurements were also performed to prove this for actual mea-

surement data. Although cross-talk was not eliminated in reconstructions done for measured data, it was shown to be reduced and overall accuracy in the image improved. This is especially evident in figures 5.12 and 5.14 where the imaging of two separate chromophores is made more accurate and effective by using hyperspectral information. The improvement of adding hyperspectral data was more evident in the imaging of two chromophores rather than a single ink chromophore. This emphasizes the advantage of hyperspectral information when doing reconstructions for more than one chromophores.

Future work based on this thesis will be focused on obtaining better results from experimental data. This will entail designing different phantoms and testing different source/detector setups in the experiment. Using other chromophores instead of ink and dye is a possibility to obtain a stronger signal in the experiment, resulting in a better reconstructions. Further simulations will also be tested, using simulated data constructed from different forward models, such as Monte Carlo and Padé approximations.

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