COMBINED MRI AND NEAR-INFRARED SPECTROSCOPY FOR INCREASED SPECIFICITY OF BREAST CANCER IMAGING

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Abstract

A yearly breast contrast-MR scan is recommended to high-risk women because of MR’s high sensitivity to breast tumors. However, breast contrast-MR yields a high number of false positives that lead to expensive and sometimes unnecessary biopsy procedures. Therefore, there is a growing need for superior biomarkers derived from the lesion during the scan so that MRI’s high sensitivity can be matched by a high specificity. Near-Infrared Spectroscopy (NIRS) has been examined here to augment MR by providing information about blood content, blood oxygen saturation, water, lipid, and scatter components. This functional information is correlated with tumor malignancy; however, the low spatial resolution of NIRS imaging has limited its usefulness as a single system. An instrument that synergistically combines the strengths of MRI and NIRS into one patient exam has been developed to non-invasively image high-contrast intrinsic properties of malignant breast lesions. This work concentrates on the development of instrumentation and methods to optimize a multimodal imaging technology and describes the results of a prospective clinical trial (n=50 subjects). The hypothesis was that NIRS could increase the specificity above MRI alone, to distinguish malignant lesions from benign prior to biopsy. This increased sensitivity was achieved through a customized 9 wavelength NIRS system, developed with an optical fiber interface compatible with most clinical MR breast coils. The study was carried out at Xijing Hospital in Xi’an China. Through this partnership, we showed that MRI/NIRS characterization of MR-identified regions was correlated to the histopathological diagnosis of that same region, as assessed by pathology on the surgically removed tissues. This hybrid imaging technology could aid healthcare decisions, by
adding information to clinical MRI exams, lowering the number of necessary breast biopsies performed, and thereby improving patients’ quality of life.
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Chapter One: Introduction

1.1 Project Overview

A yearly breast contrast-MR scan is recommended to high-risk women because of MR’s good sensitivity to breast tumors. However, breast contrast-MR yields a high number of false positives that lead to expensive and sometimes unnecessary biopsy procedures. Therefore, there is a growing need for superior biomarkers derived from the lesion during the scan so that MRI’s high sensitivity might eventually be matched by a high specificity. Near-Infrared Spectroscopy (NIRS) has been examined here to augment MRI by providing information about blood content, blood oxygen saturation, water & lipid concentrations, and scatter components. This functional information is correlated with tumor malignancy; however, the low spatial resolution of diffuse NIRS tomography has limited its usefulness as a single diagnostic system. A hybrid instrument that synergistically combines the strengths of MRI and NIRS into one patient exam has been developed to non-invasively image high-contrast intrinsic properties of malignant breast lesions and was systematically developed and tested in this thesis.

This work concentrates on the refinement of the instrumentation and methodology development to optimize it as a true multimodal imaging technology, which culminated in testing within a prospective clinical trial (n=50 subjects). The hypothesis was that NIRS could increase the specificity above MRI alone, to distinguish malignant lesions from benign, prior to biopsy. This increased sensitivity was achieved through a customized 9 wavelength NIRS system, developed with an optical fiber interface
compatible for use with most clinical MR breast coils. The study was carried out at Xijing Hospital in Xi’an China. Through this partnership, we showed that MRI/NIRS characterization of MR-identified regions was correlated to the histo-pathological diagnosis of that same region, as assessed by pathology on the surgically removed tissues. This hybrid imaging technology might eventually aid healthcare decisions during MRI by lowering the number of required breast biopsies preformed in the MRI, resulting in improvements in patients’ quality of life and reduction of processing costs.

1.2 The Current State of Clinical Breast Cancer Imaging

Breast cancer is the most common newly diagnosed cancer among women in the US with an estimated 230,000 new cases in 2013 and over 1 million cases diagnosed worldwide (1). It is the leading cause of female cancer death in women aged 20-59 (2). Based on clinical research, long-term survival odds are greatly increased by early detection and treatment prior to tumor metastasis (3). As a result, there is great motivation for breast cancer screening and most organizations recommend annual screening for women over the age of 50. Some groups such as the American Cancer Society, American Medical Association, and the National Cancer Institute recommend that screening begins at age 40, a debated topic due to the additional cost of screening (4–8). By screening more women, more cancers will be discovered at early stages and can be treated with good success rates. However, administering more screening exams will also lead to more false positive results. False positive results are emotionally difficult for patients and strain the healthcare system with follow up treatments. Therefore, there is great motivation to
develop or improve clinical imaging tools that can reduce false positive rates by identifying lesions with high specificity.

X-ray mammography is the current standard of care for yearly breast cancer screening. As a result, the clinical progression of breast cancer management, shown in Figure 1, often begins with a suspicious mammogram or occasionally a palpable mass (9). These patients are called back for additional mammographic views, ultrasound, or MRI (10). They would then go on to biopsy, where a sample of cells will be taken from the lesion and sent to pathology for diagnosis. Based on the aggressiveness and size of the cancer, the patient would go on to neoadjuvant chemotherapy and then surgery.

Figure 1: Example clinical progression of breast cancer. Patient has a suspicious screening mammogram (a) and is called back for additional views or imaging modalities (b). A biopsy sample (c) would be sent to pathology (d) and the patient would either be enrolled in a neoadjuvant chemotherapy program or go straight to surgery for mastectomy or lumpectomy (e).

Mammography has an overall reported sensitivity and specificity of 77% and 97% in a randomized multi-center trial (11). However, the technique is much less effective in women with radiographically dense breasts, claiming a sensitivity and specificity of 63% and 89% (12). Ultrasound is commonly used alongside mammography because the differing contrast mechanism makes it possible to detect many lesions missed by x-ray imaging. In one study of 9,000 negative mammograms of dense breasts, ultrasound was
able to detect an additional 37 cancers (13). Another study found ultrasound to be useful for screening dense breasts when used with mammography, reaching an AUC of 0.8 compared with 0.78 for mammography and 0.9 when used together (14). Though the combination of ultrasound and mammography has high sensitivity, it is not as good as MRI (15).

1.3 The Role of MRI in Breast Cancer Management

Women with more dense breasts have higher incidence of breast cancer and associated mortality rate. They are also the most difficult group to screen with mammography (16–18) because x-ray contrast diminishes in dense tissue. Therefore, current clinical care includes breast Gadolinium Dynamic Contrast Enhanced MRI (DCE-MRI) for surgical staging and screening of high-risk and/or young patients (19,20). Nearly all malignant lesions can be identified based on DCE-MRI, but many benign lesions also enhance (21,22). The Gd contrast agent collects in areas of abnormal vasculature and is sensitive to increased vessel density, vascular permeability, and interstitial space, all traits of invasive cancers. DCE-MRI is recommended for the screening of women at high risk for the development of breast cancer in combination with mammography because it has greater sensitivity than standard mammography, reported to be 88-100% (15,23–25). Screening specificity is less consistent but is reported to be 72% and generally leads to 3-5x more false-positive findings than mammography (26).

Though MRI is able to identify nearly all cancers, the relatively poor ability to characterize invasive cancers leads to many unnecessary invasive biopsy procedures.
This results in motivation to development new imaging tools to improve MRI specificity (27–29). One such method, NIRS, is a highly specific emerging imaging modality that could help to meet this need by improving MRI specificity to breast cancers.

1.4 NIRS Imaging of Breast Cancer

The contrast mechanism for optical imaging comes from the high vascular density that is present in malignant lesions. High metabolic demands lead to the creation of a dense yet immature vascular network that is unable to supply the tissue with adequate oxygen (30). As a result, several genetic factors such as HER2 (31), VPF, and VEGF (32,33) can become overexpressed and lead to further vascular angiogenesis, which is a hallmark of invasive cancer (34,35). NIRS is a non-invasive technique that measures the absorption of light in tissue and is capable of quantifying hemoglobin content, oxygen saturation, water and lipid content, and scattering parameters. The dense vasculature found in malignant lesions gives optical imaging the potential for high specificity to breast cancers.

Optical imaging is a non-invasive, inexpensive, and safe technique that provides functional information about breast tissue that is unique amongst current clinically available modalities due to its contrast mechanism. Hundreds of patients have undergone standalone NIRS breast studies at multiple academic centers across the USA and in Europe. In addition, several commercial systems have been developed over the years (36,37). The sensitivity and specificity of breast cancer detection with NIRS varies depending on the system geometry but have been reported to be as high as 91-96% and 93-95%, respectively (38,39). Despite differences in system design, many optical
imaging methods seek to assist in clinical decision-making by providing information about the functional status of breast tissue. Diffuse optics has potential clinical application from risk assessment to screening, diagnosis, therapy monitoring, and follow up imaging. To date, NIRS imaging has been most effective in neoadjuvant chemotherapy monitoring as demonstrated in studies by Cerussi et al. and Jiang et al. (40–42). However, NIRS imaging suffers from having relatively poor spatial resolution, on the order of 1cm (43). Because many immature tumors are small, NIRS may not be able to identify lesions during this critical early stage well enough to be adopted clinically as a stand-alone approach. Modern radiology is currently trending towards multimodal imaging because complementary systems can enhance each other to provide more information. Following this trend, NIRS imaging is well suited to add functional information to highly sensitive established clinical modalities such as MRI.

1.5 Combining NIRS with MRI

One of the first widely accepted combinations to image structure and function of tissue was PET/CT, which integrated the structural imaging from x-ray CT with the function of glucose uptake, as measured by PET. PET/CT has become an essential tool for detecting cancer metastases, yet it still provides fairly limited functional information. PET imaging does not have a well-defined role in breast cancer management but has been studied to assessment of axillar lymph nodes. Development of new radiotracers able to measure hormone receptor status and function could eventually influence breast cancer management (44,45). Similarly, the rich functional information derived from NIRS imaging could benefit clinical modalities that are mainly structural.
Ntziachristos et al. and then Brooksby et al. first developed combined MRI-NIRS systems for concurrent MRI and optical imaging (46–49). They are very well suited for quantifying tissue properties in small suspicious areas prior to biopsy as a follow-up to mammographic screening and could potentially increase the specificity of clinical MRI. MRI has high soft tissue resolution (~1mm) but more limited functional use. Optical imaging has the opposite characteristics. Since both are non-ionizing, risk of their repeated use on patients is minimal. Their combination has been successful in increasing the information available from clinical MRI exams, showing distinctions between malignant and benign lesions in several case studies (47,50). Incorporating the strengths of each modality into one system can create a synergistic combination that outperforms either separate technique and ultimately leads to the best patient care.

1.6 Organization of this Thesis

The core instrumentation used in this thesis was developed by Brooksby et al. (48,51). Methodology for reconstruction, patient interfaces, 3D imaging, and patient studies were introduced and developed by Brooksby et al. (49,52,53), Srinivasan et al. (54–56), and Carpenter et al. (50,57,58). Chapter 2 summarizes the important hardware aspects of the imaging system and emphasizes developments made as part of this thesis. Light delivery and collection, coupling with MRI, and detector calibration are discussed in detail. Chapter 3 further develops the critical aspect of coupling optics with the MRI. The design and evaluation of two major iterations of the patient interface are presented with phantom results and in-vivo results from cancer patients. Discussion comparing these two patient interfaces and others with respect to patient imaging is presented.
Chapter 4 describes the physics of light-tissue interaction to explain optical imaging from a mathematical point of view. Methods are presented for NIRS image reconstruction using several wavelengths of light and both continuous wave and frequency domain optical data. This chapter also details the process of using prior information derived from MRI to improve optical reconstruction through synergies between the two imaging modalities. In Chapter 5, extensive phantom results are presented from the development of the system. We detail motivation and methods for the phantom calibration procedure applied to patient data. There are also phantom results pertaining to 3D imaging, nine-wavelength versus six-wavelength imaging, and the new triangular patient imaging geometry. Chapter 6 continues by showing results from healthy volunteers imaged as part of several studies. Most importantly, healthy subjects were used extensively for the development and testing of the triangular imaging geometry.

Chapters 7 and 8 detail the culminating experience completing a prospective clinical trial of 50 surgical patients in Xi’an, China in collaboration with Dr. Junqing Xu. Chapter 7 develops important methodology for processing large data sets in whole breast NIRS focusing on sensitivity to the tumor region, spectrally constrained reconstruction, and regularization parameters within the image reconstruction. Chapter 8 goes on to present the conclusions of the clinical trial comparing clinical pathology, MRI alone, NIRS alone, and MRI/NIRS. Statistical analysis of both the whole patient population and a subset based on the most spatially sensitive lesions was included, using methods developed in Chapter 7. Finally, Chapter 9 discusses conclusions learned from the work presented in this thesis and worthwhile future investigations and improvements.
Chapter Two: Instrumentation for MRI-guided Near-Infrared Spectroscopy

2.1 Imaging the Breast With Diffuse Light

Optical imaging is often used generically to imply the use of either visible wavelengths (400-650 nm) or near infrared (NIR) wavelengths (650-1000 nm) of light. It can be used to image or measure transmittance or reflectance and characterize the absorption and scattering properties of tissue. The main difference between these two wavelength bands is the depth of tissue light can propagate through. Visible light does not penetrate very far due to high absorption and scatter, whereas NIR light is highly scattered but only weakly absorbed. Thus, NIR light can be used for imaging through thicker tissue such as the breast. As a less energetic form of electromagnetic radiation, NIR light has the benefit of being non-ionizing, and thus, poses less of a health risk to patients and medical personnel relative to traditional x-rays.

2.1.1 Imaging types

As tissue malignancy has been correlated with higher light absorption, it is desirable to quantify absorption (42,59). However, absorption and scatter mask each other. A highly scattering medium can appear to a light detector to be a highly absorbing one and vice versa. Therefore, system design should ideally be designed carefully to separate them based upon the signal measured. There are three types of diffuse optical imaging: continuous wave (CW), time domain (TD), and frequency domain (FD). Using a single wavelength of light, CW techniques are able to extract absorption only by assuming an amount of scatter, which is not ideal given the known heterogeneity and
variation in tissue scattering. TD and FD techniques are more expensive and complicated, but are able to be used to quantify absorption and scatter simultaneously, because the effects alter the signals in different ways that can be estimated through model-based fitting of the signal. An overview of these techniques is shown in Figure 2.

Figure 2: CW, TD, and FD imaging techniques are shown. All methods measure a change in amplitude to quantify absorption. CW methods must assume scatter while TD imaging measures it through the spread of light pulses and FD measures it through phase shift of intensity modulated sources. From Delpy and Cope, 1997 (60).

In CW imaging, light is emitted into tissue at a constant amplitude (or with very low frequency amplitude modulation) and detected at another position. It is the simplest, fastest, most compact and least expensive technique. However, as already mentioned, it would require scatter to be assumed based on literature values or other measurements of the tissue. Absorption is then determined based on the difference in amplitude before and after tissue interaction, through fitting to diffusion theory. Even with these assumptions, CW techniques have been used in many successful studies (61–64) and are favored due to their simplicity.

Time domain imaging injects several short light pulses and detects the temporal distribution of photons that pass through the tissue. The detected distribution has a
greater temporal spread than the initial light pulse due to scattering. Some photons travel longer path lengths than others as they scatter between the source and detector. From the shape of the collected distribution, absorption and scattering properties can be determined. The decrease in amplitude of the latter part of the pulse corresponds to exponential attenuation from only absorption while the temporal spread in the peak of the distribution corresponds predominantly to scatter. Through fitting of the data to time-domain diffusion theory it is feasible to separate these parameters. Time domain systems are the most sensitive to low light levels because they can operate in photon counting mode, but are also the most expensive technology since they require pulsed lasers and time-correlated photon counting detectors and electronics (65–68).

In FD imaging, a laser source is intensity modulated at a high frequency, usually in the 100MHz range. Absorption and scatter together affect the signal by a decrease in the modulated amplitude, while scatter is predominantly estimated through a shift in phase of the modulated wave. Precise estimation of these parameters requires fitting the signal to frequency-domain diffusion theory solutions. FD imaging instrumentation is typically more stable than time domain components but has lower signal sensitivity (69,70). Like CW, it is relatively easy to add additional wavelengths to create a spectral system. The lower cost and simplicity makes it a popular choice for breast imaging, and the one this thesis will focus on (41,54,71,72).

Though TD imaging gives the most robust measurements of tissue, FD is still capable of measuring both absorption and phase through many centimeters of tissue with good SNR. The additional cost of FD instrumentation is justified over simply CW measurements by gaining phase measurements, which then allows accurate estimate of
absorption spectra and hence chromophore concentrations. The other important factor in choosing an imaging type is the number of wavelengths that will be employed. FD instrumentation is especially good for using with multiple wavelengths as they can be added at minimal additional cost over CW, and much less than TD techniques, which used short-pulsed lasers.

**2.1.2 Spectroscopic Imaging**

Tissue absorption and scattering varies as a function of wavelength. While the instrumentation employed measures absorption and scatter, the valuable clinical information reported are concentrations of the major absorbers in tissue: hemoglobin, deoxyhemoglobin, water content, and lipid content. Spectroscopy is a technique that uses absorption and scattering coefficients to quantify these tissue chromophores. Quantification of parameters relies on accurate characterization of the absorption coefficient (and thus, scattering) at each wavelength. Therefore, the ideal system would use a large number of wavelengths spread across the whole NIR window to capture all the spectral features of the main absorbers.

In general, more wavelengths give higher spectral accuracy but require a longer time to image and higher instrumentation cost. Using broadband illumination gives the best spectral sensitivity but falters since detectors cannot measure phase or compete with single wavelengths detectors at very low light levels (73,74). Our system compromises on spectral sensitivity by using nine wavelengths to minimize cost and imaging time. These wavelengths are shown in Figure 3. Six wavelengths are modulated and detected in the frequency domain by photomultiplier tubes (PMTs) and three operate in CW mode and are detected by photodiodes (PDs). Two sets of detectors are required because PMT
sensitivity decays rapidly at approximately 850nm. Three CW wavelengths cover the fat/water peaks that occur in the 900s inexpensively without adding excess additional time to the scan.

![Figure 3: NIR window showing tissue absorbers and scattering spectrum. Absorption is low enough for deep tissue imaging with distinct spectral features. Blue and pink shading represent areas covered by PMT and PD detection, respectively. FD wavelengths and CW wavelengths are illustrated.](image)

Though this system is complicated by the need for two separate detector arrays, it is presented in a design that switches automatically between fibers, detectors, and wavelengths. The system is efficient, taking 12 minutes to scan a patient through nine wavelengths. It is portable, with all components fitting inside a single rack. It is also cost-effective, using FD channels to characterize scatter and additional CW channels to
quantify chromophores without adding significant cost. This hybrid system represents a logical way to accurately cover all spectral features of the NIR window, leading to accurate tissue quantification.

2.2 System Design

The MRI/NIRS imaging system used in this thesis was first developed by Brooksby et al. (75) based off of a standalone optical imaging system for human use. This section will focus on its design and operation.

2.2.1 Overview

After being developed by Brooksby et al., this system was later improved by Carpenter et al. (76) for volumetric imaging. El-Ghussein et al. then outfitted the system with three additional wavelengths in CW mode in order to improve water quantification (77). The system, outlined in Figure 4, uses six laser diodes at 661, 735, 785, 808, 826 and 852nm (Thorlabs, Newton, NJ) that are modulated at 100MHz through 16 separate source fibers. These wavelengths operate in the frequency domain and both absorption and scatter are recovered by the array of 15 photomultiplier tube detectors. Three additional wavelengths at 903, 912, and 948nm (Thorlabs, Newton, NJ) are operated in CW mode and amplitude is measured by 15 photodiodes. The breast tissue is scanned sequentially with the nine wavelengths, taking approximately 1.5 minutes per wavelength. The imaging system is housed in the MR console room and 12m fiber bundles are passed through a conduit in the wall to enter the MR scanner room. These fibers are coupled into a custom breast MR coil for simultaneous MR and optical imaging of patients or phantoms and the optical and MRI exams are concurrent.
Figure 4: Overview of MRI/NIRS system. RF signal generators drive six laser diodes at 100MHz and deliver light through 16 sequential source fibers. An array of 15 PMTS measure amplitude and phase of collected light. Optical fibers are housed within an MRI breast coil and the optical and MRI exam are concurrent.

One of the benefits of frequency domain imaging is the relative simplicity of the instrumentation. A diode laser for each wavelength is modulated at 100.0005MHz and a small portion of this is mixed with a 100MHz signal. The resulting 500Hz signal serves as the reference. Meanwhile, the majority of the 100.0005MHz signal is sent through the tissue and mixed with the same 100MHz signal. This results in a second 500Hz signal that has probed the tissue. These 500Hz signals are compared using lock-in detection and amplitude and phase from each detector are measured. The frequency domain imaging requires two signal generators, several amplifiers, and detectors fast enough to record the modulated signals. On the CW side, lasers are modulated with a slow, 50Hz signal that makes detection more robust in the presence of noise. These longer wavelengths were chosen as CW since we already had 6 FD wavelengths to accurately quantify phase. This
kept the cost of a new detector bank low and used much of the existing instrumentation.

A block diagram of these signals is shown in Figure 5.

![Block Diagram](image)

**Figure 5:** A block diagram with signal paths for both FD and CW portions of the system is shown. FD wavelengths are modulated at 100.0005 MHz and mixed with a reference signal for digitization at 500Hz. CW wavelengths are modulated at 50Hz for low frequency noise minimization.

The hybrid imaging system was designed to accommodate both FD and CW measurements. All of the imaging components, data acquisition, and control software are housed inside a single portable rack. Sixteen 12m long, 4mm diameter fiber bundles are stored on top of the rack and the whole assembly can be rolled to the imaging location by a single person. The overall configuration of this system covers the entire NIR window with reasonable spectral sensitivity and can be adapted to clinical MRI machines of different models.

### 2.2.3 Operation

The system is operated by a computer running a custom LabVIEW software program that automates the entire system. A screenshot of this program is shown in
Figure 6. The program allows the user to select the lasers and detectors to be used for imaging, geometry-specific PMT gain finding methods, and advanced settings like laser current. After the exam has been configured, the software will collect the entire exam’s data, calibrating and displaying it in real time. The package also has built-in routines to calibrate the detectors, check the status of the lasers, and a host of advanced manual options for troubleshooting and custom operation of the individual components of the system. Throughout its use on the MRI system, the software has been very robust and user-friendly.

Figure 6: Screenshot of the custom LabVIEW routine used to control the entire system. This routine allows a user to select wavelengths, detectors, and gain finding methods before collecting the entire patient exam’s data automatically. Data is calibrated and displayed as it is collected.

2.2.2 Light Delivery
Light from the FD side is delivered to the tissue from a bank of fiber launch systems (Thorlabs, Newton, NJ) and diode lasers that are modulated at 100.0005MHz using a laser driver (LDX-3220, ILX Lightwave, Bozeman, MT) and signal generator (IFR-2023A, Aeroflex, Wichita, KS). These lasers are chosen to have approximately 100mW possible output power. They are not temperature controlled, so it is important to be able to use 40mW of power without overheating them. Diodes are selected based on a low threshold current and low operation current. The fiber launch system and related optics are shown in Figure 7. The purpose of the launch system is to house the diode and focus into a fiber. Above the threshold current, these lasers emit light in a cone shape that is collected by a collimating lens to create a beam. The beam is focused into a 200µM 6-1 fiber combiner with a focusing lens (Fiberguide, Stirling, New Jersey).

Though the lasers are used sequentially, the fiber combiner prevents the operator from needing to switch fibers. This combiner is then fed into the rotary switch that houses the detectors and interfaces with the 12m patient fiber bundles. The patient fibers are 200µM silica fibers (Z-light, Lativa) packed into 4mm bundles and protected by a PVC jacket. This setup couples the lasers into the large fibers efficiently, going from approximately 40mW at the laser to 20mW at the tissue and staying under the maximum permissible exposure.
Figure 7: A fiber launch system and block diagram showing beam shapes and powers. Light is coupled into a fiber and delivered to the tissue with losses of about 50%.

On the CW side of the system, lasers are modulated at 50Hz and driven by a custom current source. A separate 3-1 fiber combiner is used to couple these wavelengths into the rotary switch automatically.

2.2.4 Light Collection

Sources and detectors are interfaced with the tissue through a custom optical switch, shown in Figure 8. It houses 15 PMTs (H9305-3, Hamamatsu, Japan), 15 PDs (C10439-3, Hamamatsu, Japan), and source fibers. The detector array rotates underneath fixed fiber bundles that go to the tissue. Each fiber is sequentially used as a source and the other fibers then line up with the detectors to collect the emitted light. There is one rotating source position for the FD wavelengths and another for the CW wavelengths. Source/detector locations are programmed into the computer so that no action is needed to move between positions.
Figure 8: Photo of the custom rotary switch used to interface sources and detectors with tissue. 15 detector positions and 1 source position rotate underneath fixed fibers going to tissue. +20dB amplifiers and RF mixers for each PMT are also housed in the rotary stage.

The spectral response range of the PMTs is 185 to 900nm with peak sensitivity at 450nm. Since the PMTs’ sensitivity is very limited above 850, they only detect the FD wavelengths (850nm and below). After detection, the RF signal is amplified using a +20dB RF preamplifier (Minicircuits, Brooklyn, NY) and mixed with the reference channel to create a 500Hz signal. This signal is amplified 100x, filtered, read by the DAQ card (6225, National Instruments, Austin, TX), and detected vs. the reference signal for phase and amplitude.

We have improved the detector array in this system since the last iteration of its design. On the FD side, PMTs are still used but a +20dB preamplifier was added before the RF mixer after every PMT. As a result, the PMTs are more stable at low light levels, displaying approximately an order of magnitude less error than the McBride system (78).
The PMTs display on the order of 1% AC amplitude error and 1 degree phase error vs. 10% and 10 degrees, shown in Figure 9. The preamp results in a 100x gain of the signal before being mixed with the reference. While these signals are more robust and lead to cleaner measurements, the PMTs’ limiting factor is their linearity, characterized during calibration.

Figure 9: Standard deviation of the natural log of AC amplitude and standard deviation of phase. The addition of a +20dB preamplifier reduces the current hybrid system’s noise by an order of magnitude from the previous McBride system.

The spectral response of the PD detectors is 190 to 1100nm. They detect the CW wavelengths (903 and up) but are only modulated at 50Hz for noise cancelation. The PDs operate with either a high or low gain setting, set manually. We operate the detectors closest to the source on low gain and all others at high gain. Since the signal is slower and phase locking is not required, the output of the PDs is connected directly to the DAQ.
The other improvement to the MRI/NIRS system is the added bank of PD detectors. The detectors were characterized at both high and low gain, showing linearity from 1pW to 20nW and 0.1nW to 2μW, respectively. Using these gain settings gives the PDs a dynamic range of 2x10^6, shown in Figure 10. This dynamic range is a little smaller from a practical standpoint, 2x10^4, since the gain cannot be switched automatically during a patient exam. Construction and characterization of the new detector array was lead by El-Ghussein et al. (77)

![PD response as a function of input light at two gain settings. Each gain setting gives more than 4 decades of linear response. Since gain cannot be changed during the exam, this is the effective range.](image)

2.2.5 Coupling to MRI

Perhaps the biggest challenge in MRI/NIRS system development is the restriction on using metals with ferrous content (and nonferrous metals in general which can cause eddy-current related artifacts). Additionally, the space inside the bore of an MR scanner is very limited especially when accounting for the presence of the MR breast coils. These
requirements can be met in a number of ways through the design and implementation of MR-specific hardware. The primary function of the MR portion of the MRI/NIRS system is acquisition of diagnostic quality images of the breast. In this case, NIRS is added to complement MRI, and thus, must not interfere with MR image quality. From the optical imaging perspective, the MR images guide optical image reconstruction and the particulars of the MRI scanner are less critical.

Patients are typically placed in the same prone position used in breast MR during the multi-modality MRI/NIRS breast exam. Both breasts are pendant within the MR coil platform and one side is lightly compressed to accommodate the NIRS fiber positioning. Breast coils best suited to MRI/NIRS integration have large open spaces beneath the patient to allow fiber positioning close to the chest wall. For fiber-based delivery and collection of light, extensions of the fibers with low attenuation losses can be used, although they must be lengthened to 10-15 meters (from 2-3m in standalone systems) in order to deliver and receive light when the optical instrumentation resides outside the scanner bay. The cost of these fibers scales with material use and the large fiber bundles needed for breast imaging (6mm diameter) can quickly become the most expensive component of an MRI/NIRS imaging system. For example, the MRI-guided NIRS imaging systems at Dartmouth use 0.4 mm and 4 mm silica fiber bundles to deliver and collect light with a unit cost of approximately $700 and $4,000 per channel, respectively (75,79). An overview of the NIRS/MRI system coupling to the MRI is shown in Figure 11.
Figure 11: The NIRS/MRI system (a) is housed in the MRI suite and 12m long fiber bundles are piped into the MRI scanner room through a hole in the wall (b). Fibers couple directly into the MRI breast coil (c) for simultaneous imaging. (d) shows the MRI bed before padding for patient comfort is added.

As with standalone NIRS tomography, the most important function of the breast interface is maintenance of fiber contact with the patient’s tissue in order to satisfy the assumptions of diffusion theory. Thus, adjustability and degrees of freedom in positioning the optical fibers in contact with the breast are paramount and an effective interface must not only be reasonably comfortable for the patient, but also enable robust and repeatable fiber positioning relative to the region of interest within the breast. The patient interface is a critical part of the NIRS/MRI system that Chapter 3 discusses in detail.

2.3 Detector Calibration

Every imaging modality requires standardization and packaging before clinical use. For example, x-ray computed tomography systems are calibrated based on standardized
phantoms, standardized to Houndsfield (or CT) units, and QA tested routinely for quality assurance (80–82). The detectors in PET (83–85), mammography (86–88), ultrasound (89–91), and MRI systems (92,93) must be similarly calibrated in their infancy and then tested regularly to normalize out individual detector responsivity variations. Each system has a slightly different procedure depending on the detector type, but the goal remains the same: every pixel, detector, or coil element must produce the same numerical response for equivalent inputs, across as wide a dynamic range as is possible. These calibration procedures are especially important for imaging systems that work on relative measurements since there is no absolute reference for them to compare to (94,95), and care must be taken to ensure their reliability over time.

2.3.1 Individual PMT Characterization

Previously, calibration of these systems has been a difficult and time-consuming process (96–98), which was designed for development, rather than being designed for the day to day user. To improve on this issue, we developed a methodology to automatically characterize and calibrate a large array of optical detectors. This simplifies standardization and quality control between scans and when the system is transported to other sites, and ensures consistent measurements during large-scale trials.

The experimental set up uses the calibration phantom with a central SMA source and 15 detector fibers arranged in circular geometry around the phantom, all with equal path lengths between source and detector. A 785nm frequency modulated laser is maximally attenuated to a source strength of approximately 10µW by a pair of motorized filter wheels with filters ranging from 0 to 4OD. This setup is shown in Figure 12.
Figure 12: Outline of calibration process (a) and calibration imaging geometry with a source fiber in the center of the delivery (b) and motorized OD filter wheels (c) are used to automatically vary the incident laser intensity before going into the phantom and detector array.

The filters are then automatically adjusted such that measurements are collected for each PMTs’ entire dynamic range at all of nine gain settings. The amplitude should scale linearly with input power with a slope of unity, and while gain levels change the offset and slope, the linear regions are the ones which can be calibrated. The phase shift should be constant with input intensity, and so calibration for the phase shift offset and slight slope effects is needed across the different gain levels. To calibrate individual detectors, collected data is sorted by gain setting and detector number and plotted versus relative source strength, as shown in Figure 13. Input laser power is assumed to be 10mW and is adjusted based on the filter configurations. Data outside the range of linearity is thrown away, with the exception of the lowest gain setting, which is only at the very bottom of the linear region. Amplitude data is then collected and a first order trend line is fit to the data using an algorithm that throws out drastic outliers. Amplitude data yields a slope and an offset for each PMT and gain setting, making a total of 15x9 slopes and
15x9 offsets. The data points used in these calculations are also saved for use in phase processing. Phase data typically has a slightly smaller range of linearity than amplitude data (75,99), but within that range, phase response is expected to be flat independent of source strength. These phase data are fit to a 0th order approximation to yield phase offset for each PMT and gain setting. The amplitude slope, amplitude offset, and phase offset are tabulated and subtracting them off the uncalibrated data yields the calibrated data, as shown in Figure 13.

Figure 13: Intra-PMT calibration. (a) Amplitude recorded over a large range of input intensities and a region of linearity is selected. (b) Same as (a) for phase. (c) Calibrated amplitude for each individual detector at every gain setting after slopes and offsets are fit to the data in (a). (d) Same as (c) for phase.

2.3.2 Inter-PMT Calibration
Next, the PMTs should be calibrated to each other so that amplitude and phase offset such that regardless of gain setting, any detector would the same response. This particular optical imaging system uses a custom-made rotary stage optical switch that rotates which optical fibers are paired with each PMT for each measurement. It is possible to rotate the calibration file with the detectors and this method is acceptable when using a circular collection geometry because of the high degree of symmetry. Since this system is built for clinical imaging in the MRI, it is advantageous to use a parallel plate or triangular geometry (76,100), and more accurate to account for each PMT-detector-fiber combination separately. Thus, we use a second step to expand the calibration file for each source position. Figure 14 shows aggregated data collected for each combination before calibration, after intra-PMT calibration, and after inter-PMT calibration. As long as a detector array has good repeatability, these calibration factors remain applicable after movement, using different phantoms, and in arbitrary imaging geometries.

Figure 14: Inter-PMT calibration. (a) Amplitude. (b) Phase. Box plots show the standard deviation of each gain setting at three stages of calibration. Intra-PMT calibration

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reduces the standard deviation significantly, but after inter-PMT calibration each source-detector pair is equivalent.

2.3.3 Performance

The effectiveness of this calibration method is only as good as the repeatability of the imaging system that uses it. We tested the repeatability of the frequency domain imager being used by measuring the same phantom five times over the course of one week and found the standard deviations for amplitude are typically below 0.1 V and below 0.2 degrees for phase. Figure 15 shows data from a highly attenuating 86mm diameter homogeneous circular phantom with properties similar to an optically dense breast. The data recorded here is filtered to be within the detectors’ range of linearity, but it can be seen that data closest to the noise floor exhibits more variation. Also, since this phantom is a different from the calibration phantoms, bias error is introduced and it is seen that even the calibrated data has more variation that is exhibited in the repeatability measurements. Calibration improves this data almost to identical parabolas, one for each source position, but imperfections can still be seen. The phase data especially shows where a detector fiber could have had poor coupling and the signal seems to jump periodically. The use of a reference phantom could help to correct small imperfections and yield a more accurate reconstruction (76,101) when imaging patients.
As multi-detector NIR spectroscopy makes its way into more mainstream clinical use, standardization and calibration will become critical. Image quality and ROI quantification accuracy are largely dependent on detector response, though it is not relevant to clinical workflow. In this work, the design and testing of a novel, automated, calibration system was described, used to calibrate a MR-guided diffuse optical spectroscopy system, and employed image tissue simulating phantoms of varying geometries. The effectiveness of our system was tested for performance and repeatability, and finally used to accurately recover total hemoglobin in tissue-simulating phantoms. Imaging results were similar to other studies, and these methods could be applied to any optical imaging system with a large detector array.

2.4 Conclusions
This chapter focused on the instrumentation of the NIRS/MRI system used in these studies and critical improvements made to the system. A brief description of different optical imaging techniques was presented with rationale for choosing hybrid FD/CW spectroscopy in the design of the current system. The +20dB preamplifiers were added after each PMT to amplify the signal prior to mixing and improved the standard deviation of repeated measurements by an order of magnitude. Using adjustable gains, the PMTs display linearity from 0.002 to 1V for amplitude and 0.02 to 1V for phase. These detectors displayed less than 1% AC noise and 1 degree phase noise even at low light levels. The PDs that were added to the NIRS/MRI system are linear over six decades, from 1pW to 2μW but are limited to four orders by their two gain settings. Though the system must use two separate arrays of detectors to cover the whole NIR window, it does so with a portable, integrated package that does not require manual source switching.

This chapter also describes the calibration process used for calibration of these detectors and shows the development and testing of a system for automatically calibrating the detectors. This method can be useful for phase adjustments, installing new detectors, and after transportation. Finally, it takes an important step towards clinical implementation where push-button calibration is desirable. While the method is not perfect, it automates a very tedious process and promotes regular checking and quality assurance of the detector array.
Chapter Three: NIRS/MRI Breast Interface Design

3.1 Introduction

3.1.1 Coupling Optical Fibers to the Breast

Most fiber-based diffuse optical imaging requires that optical fibers are placed in contact with the breast tissue to satisfy assumptions made in the diffusion approximation to the radiative transport equation. Therefore, the patient interface is the critical connection between the optical instrumentation and the patient that must always be created such that the measured data matches the predicted light transport model. The patient interface is responsible for holding the breast in place while light is delivered and collected during a patient exam. Thus, adjustability and degrees of freedom in positioning the optical fibers in contact with the breast are paramount and an effective interface must not only be reasonably comfortable for the patient, but also enable robust and repeatable fiber positioning relative to the region of interest within the breast. Approaches to optical breast imaging have appeared in the published literature with fiber arrangements sufficient for volumetric imaging and flexible tissue sampling through arrays in planar or circular geometries, as will be reviewed in this chapter.

While this is typically a simple and often overlooked part of an optical imaging system, poor designs can lead to poor fiber contact, patient discomfort, and limited tissue coverage. Normal breast composition, shape, and size varies widely between individuals and intelligent engineering is required to achieve a solution that adapts to most patients. The two most difficult challenges are adapting to different sizes and maintaining full coverage of the breast volume. This problem has been solved in many ways.
3.1.2 Optical Fiber Arrays

A stand alone optical imaging system typically has its own bed with one or two holes in it for the patient to lie prone with her breast or breasts hanging pendant through the opening. Fibers and other equipment are hidden beneath the bed. One planar array produced at UPenn consisted of a 9×5 grid of 45 fibers attached to a plate placed on the breast during an exam(102,103). Schmitz et al created a circular array of up to 25 fibers which were optimized for fast data collection at SUNY Downstate Medical Center(104). A combined optical imaging and x-ray tomosynthesis system was developed at Massachusetts General Hospital with a denser coverage of 40 source fibers arranged in a fixed grid and 9 avalanche photodiode detectors located on the opposite side of the breast(105). Each of these designs exploits NIR’s ability to cover large tissue volumes with arrays of measurement probes connected to dedicated channels of data acquisition hardware.

More recently, measurement geometries have been adapted specifically to each patient through conformal fiber arrays. The SUNY Downstate group designed a dual breast optical tomography system which acquired data through as many as 31 fibers that completely covered each breast within two semispheres having adjustable radii. The associated fiber array could be altered for size, tilt, lift, and pitch during an individual breast exam(106). Similarly, efforts at Dartmouth have used circular rings of fibers to sample three separate anatomically coronal planes through the breast with adjustable radial and coronal positions(107,108). An interface evaluated at University College London (UCL) consisted of interconnected fiber bundle rings mounted to an adjustable
conical frame that allowed construction of shapes customized for each breast to be imaged. An overview of some of these devices is presented in Figure 16.

Figure 16: Stand alone optical imaging system configurations for breast imaging. Upenn uses a large array of fibers arranged in a parallel plate geometry (a). A commercial system developed by Advanced Research Technology has a self contained bed and circular geometry (b). SUNY Downstate developed an adjustable dual breast scanner (c). A circular system at Dartmouth uses three concentric rings of fibers to image multiple planes of breast tissue (d,e). UCL uses a liquid-coupled breast interface (f,g) and a NIRS unit at MGH is coupled into x-ray tomosynthesis (h).

In all of these solutions, patient geometry is adapted to either the natural circular breast shape or alternate imaging geometry such as in the case of combined optical imaging and tomosynthesis. These arrays rely on very few possible adjustments to accommodate different patients and achieve wide coverage through high optical fiber density. Stand-alone interfaces are typically quite successful and do a good job making
sure that the patient is comfortable and that images are obtained. However, they are not always suitable for MRI-guided NIRS due to additional constraints added from MRI.

3.2 Combined NIRS/MRI Instrumentation

3.2.1 Challenges specific to NIRS/MRI patient interfaces

Perhaps the biggest challenge in realizing an MRI-guided NIRS breast imaging system is the restriction on using metals with ferrous content (and nonferrous metals in general which can cause eddy-current related artifacts). As a result, electronic equipment must stay outside of the scanner room and light must be piped in through long fiber optic cables. Additionally, the space inside the bore of an MR scanner is very limited especially when accounting for the presence of the MR breast coils. Finally, rather than using a separate bed or apparatus that is designed for optical imaging, optical fibers must be incorporated directly into MRI breast coils. These requirements present an engineering challenge but can be overcome in a number of ways through the design and implementation of MR-specific hardware.

3.2.2 MR Hardware

The primary function of the MR portion of the MRI/NIRS system is acquisition of diagnostic quality images of the breast. In this case, NIRS is added to complement MRI, and thus, must not interfere with MR image quality. From the optical imaging perspective, the MR images guide optical image reconstruction (discussed in the next section). Chance et al. found the sensitivity and specificity of optical imaging to be excellent in breast (96% and 93% respectively), although its spatial resolution is not sufficient to reliably detect tumors smaller than 1.0 cm (109–111). Pogue et al and Tromberg et al
have suggested that the spatial resolution of NIRS can be increased to nearly 1 mm, if the technique is used synergistically with other imaging modalities (110,112).

Because NIRS is added to clinical MRI, the particulars of the MRI scanner (e.g. vendor) are less critical. Considerations do arise when coupling the optical fibers into a specific MR breast coil, but the NIRS technology is otherwise widely adaptable to any type of scanner. Patients are typically placed in the same prone position used in breast MR during the multi-modality MRI/NIRS breast exam. Both breasts are pendant within the MR coil platform and one side is lightly compressed to accommodate the NIRS fiber positioning. Breast coils best suited to MRI/NIRS integration have large open spaces beneath the patient to allow fiber positioning close to the chest wall. Padding for patient comfort and the thickness of the breast coil platform make positioning of the optical fibers against the chest wall very challenging but is important because many breast lesions are located close to the chest wall or even adjacent to the pectoral muscle.

3.2.3 Optical Hardware

Adapting NIRS to operate in an MR scanner also involves modifications to the optical hardware. A clinical MR scanner is sited within a magnetically shielded room and the hardware components of an optical imaging system cannot be placed next to the exam table as they would be for a standalone system. For fiber-based delivery and collection of light, extensions of the fibers with low attenuation losses can be used, although they must be lengthened to 10-15 meters (from 2-3 m) in order to deliver and receive light when the optical instrumentation resides outside the scanner bay. The cost of these fibers scale with material use and the large fiber bundles needed for breast imaging (6mm diameter) can quickly become the most expensive component of an MRI/NIRS imaging system. For
example, the MRI-guided NIRS imaging systems at Dartmouth use 0.4 mm and 4 mm silica fiber bundles to deliver and collect light with a unit cost of approximately $700 and $4,000 per channel, respectively\(^{(113,114)}\).

Attenuation over the increased fiber length is a concern but is typically much less than the light losses occurring at the fiber junctions with the lasers (light sources) or the detectors, which can be 50%. Transmission losses are maintained below a few percent if high-grade materials such as silica are used as in the fiber optic communications industry. Multiple fiber bundles of this size can be bulky and become cumbersome to manipulate, but many MRI suites are equipped with waveguide conduits for passing cables through the walls. Fibers are easily concealed below the padding on conventional MRI tables and a MRI/NIRS specific patient platform could be incorporated into a dedicated breast scanner.

### 3.2.4 Optical-MRI Breast Coupling

Translating these types of fiber interfaces into an MRI-guided breast exam presents a number of challenges. Since MRI/NIRS systems are coupled into a clinical scanner, the patient is placed in an MR breast coil with limited space for deploying elaborate fiber configurations. Cost is also a factor because every sampling channel requires a long (and expensive) optical fiber. Large numbers of fibers quickly increase costs. The group at UPenn produced the first MRI-guided NIRS system, which consisted of an 8x3 source fiber grid and a 4x2 detector fiber panel arranged in a parallel-plate geometry\(^{(115)}\). Brooksby et al. developed an MRI/NIRS platform with 16 fibers arranged in a circular array inserted in a clinical breast coil\(^{(113)}\). These early fiber interfaces could accommodate different breast sizes but their coverage of breast volume
was limited relative to standalone NIRS systems. Representative breast coils and scanners with integrated NIRS imaging arrays are shown in Figure.

Figure 17: MRI systems and their combined optical MRI breast interfaces at Dartmouth College (a,b) (Brooksby), UPenn (c,d) (Ntziachristos), and Stanford (e,f) (Carpenter) are shown. These arrays use circular (b) and parallel plate geometries (d,f) to hold fibers in contact with the breast. Here (d) requires a custom breast coil, while (b) and (f) use a clinical coil.

3.3 Remote, real-time positioning parallel plate array

3.3.1 Motivation for development

While MR produces a fully three-dimensional (3D) image volume, the optical instrumentation developed by Brooksby et al was limited to data collection from a single plane of fibers. The imaging plane would then need to intersect the region of interest/suspicion in the breast (114). This could be difficult without information
concerning the location of the lesion or when imaging a breast with multiple lesions. Furthermore, many lesions would be squeezed out of the plane of imaging by the optical fiber array. We addressed the single fixed plane limitation by designing a system to reposition the optical fibers in order to move a single or multiple planes of data acquisition to the areas of suspicion while the breast was positioned in the coil and the patient was in the bore of the MR scanner. The goal of this system was to increase sensitivity across the complete breast volume and lead to more accurate quantification of the relevant tissue volumes. Our design aimed to fix the single plane limitation. We also hoped to provide complete coverage of the breast volume without purchasing additional fiber optic cables, position fibers more accurately with respect to the tumor, and to give better access to lesions located the chest wall area of the breast.

3.3.2 Materials and methods

Additional instrumentation was implemented to obtain more highly resolved volumetric images. The redesigned optical fiber holder increases the available degrees of freedom for imaging multiple planes in a single patient exam. Since the device is operated from the MR control room, the imaging plane can be adjusted based on the patient’s MR image to ensure good coverage of regions of interest. Control from inside the MR computer room is especially important since positioning the tissue in the fiber interface each exam can displace the anatomical structures. Thus, it is beneficial to use the MR scan to target optimal planes of tissue before optical data acquisition.

Design models and photographs of this interface can be seen in Figure 3 as well as a schematic of the control system. Two lift bags (Breton Ind., Amsterdam, NY) can be inflated and deflated remotely to raise and lower the imaging plane. These lift bags are
shown in Figure 19. The air control system utilizes medical air at 50psi from inside the MR suite, which is controlled to a lower pressure of 5psi with an adjustable air regulator (Model # R21-03-L00, Wilkerson, Richland, MI). Single-acting air solenoid valves (Model # N2-SCD, Mead Fluid Dynamics, Chicago, IL) allow or prevent airflow to the lift bags to increase height or remain stationary. Each solenoid valve is electrically connected to a solid-state relay (Model # G3NA210BDC524, Omron, Schaumburg, IL) and can be activated by a 5VDC signal from the system’s data acquisition board. A Labview routine controls the height of both of the imaging arrays separately or simultaneously and provides feedback on the current positions.

Figure 18: MR breast coil with MR-optical breast interface integrated (a) and block diagram of control system used to remotely move fibers (b). Photos of interface (c) showing location of the optical fiber-tissue interface (black circles) and (d) in MR breast coil from side with lift bags, optical fibers, and tissue-simulating phantom.
The diffusion light propagation model used for spectral image formation requires that the fiber bundles be in reliable contact with the tissue. Thus, we developed a method for keeping these bundles in contact with the breast tissue after placement in the MR coil. This is accomplished with the use of two fiber optics faceplates (Model # 47A, Schott Lighting and Imaging, Southbridge, MA). This serves as an immobile barrier between the patient and optical fibers. The faceplate acts as a zero-depth window of fused fibers, transferring an undistorted image from one side to the other as shown in Figure 19. The plate’s fiber-based constructions have a numerical aperture of 1.0, and remain in rigid contact with the tissue. The source/detector fibers are free to move vertically up and down against the plates, while collecting light emitted from the tissue.

Figure 19: Fiber optic faceplate samples shown one inch away from text (a) and on top of text (b). The fiber plates transfer an undistorted image only when it is against the plate because of their high numerical aperture. Side views of the lift bags deflated (c) and inflated (d), capable of raising the fiber array 2cm.

This design met our specifications by allowing the optical fibers to be repositioned during the MRI scan without moving the patient. It increased breast volume coverage and was able to interactively target lesions found on MRI.

3.3.3 Parallel plate NIRS/MRI coil performance
The fiber positioning system was tested for positioning accuracy and repeatability using pressures from 0.5 psi to 5.5 psi. Results from the system being repeatedly raised \((n=10)\) are shown in Figure 20 in a graph of height vs. pressure. The array was set up for patient imaging and the computer raised the fibers from bottom to top. A first order fit constrained to go through \((0, 0)\) was applied to the data with the norm of the residuals equal to 0.067. Error bars relating to the standard deviation of each measurement are shown and the average standard deviation of all the measurements is 0.23cm. Due to the system’s limited repeatability, precise fiber locations are found using an MR “scout” image and adjusted if necessary after preliminary positioning. Absolute position is most important clinically and can be determined within the resolution limits of MRI.

![Figure 20: Fiber height vs. system pressure. Height was measured every 0.5 psi from 1.5 psi to 5 psi. Error bars show standard deviation at each pressure and a linear fit was applied to the data.](image)

We tested the linearity of the MR guided NIRS system and multi-planar fiber interface using a resin phantom with dimension of 13.3cm by 5.7 cm with a cylindrical inclusion of radius 1cm. Using an ink solution concentration of 0.5% for calibration, the
phantom was imaged seven times with ink solution concentrations between 1.0% and 4.0%, both with and without the fiber optic plates. 1.0% Intralipid was added to match background scattering. Images were reconstructed on a two-dimensional rectangular finite element mesh with 2577 nodes. Representative single wavelength reconstructions of $\mu_a$ and $\mu_s'$ are shown in Fig. 3a-b, at varying ink concentrations with and without the fiber optic plates. As expected, recovered concentration increased linearly with ink concentration. A 2-region mask with the actual dimensions of the phantom was applied to the image to separate background and inclusion regions. Nodal values within regions were averaged and their ratio defines recovered contrast. The difference between the plates data and the no plates data is minor and can be seen on the graph of image contrast vs. absorber concentration in Figure 21. A line of best fit to the plates data yields an equation of $0.17x + 0.94$ while the no-plates data yields an equation of $0.17x + 0.98$. Linear fits account for the variance in the data well, with the norm of the residuals being 0.067 and 0.054 respectively. The small difference shows that the fiber plates have a negligible effect on system linearity.
Figure 21: Images from a phantom experiment showing system linearity with (a) and without (b) faceplates. The left block of images quantifies $\mu_a$ (mm$^{-1}$) in the domain while the right block shows $\mu_s'$ (mm$^{-1}$). The percentage of ink solution concentration used is written on each image. The graph (c) shows results of linearity over different ink solution concentrations with associated linear regression lines.

Finally, the interface was tested on a cancer patient. Details on patient imaging procedures can be found in Chapters 6 and 7. The purpose of this exam was to target a lesion found on MRI using the patient interface. After patient positioning, lesion targeting was guided by a radiologist experienced in breast MR. This interface was able to successfully target the lesion quickly and accurately, validating the design. Figure 22 shows a representative axial MR image used for segmentation, along with coronal slices from the reconstructed volume. These solutions were overlaid on corresponding coronal MR images. The tumor region was found to have increases in total hemoglobin, water fraction, and decreases in scattering parameters.

Figure 22: Illustrative example of patient exam results using parallel plate breast
Axial MR imaging showing coronal plane of optical imaging (a). (b) shows a 3D representation of combined maximum intensity projection MR image and 3D rendering of optical solution of HbT. Optical solutions for HbT (d), water (e), oxygen saturation (f), scatter amplitude (g), and scatter power (h), are shown overlaid on top of coronal MR (c). In each case the background value is removed.

### 3.3.4 Parallel plate NIRS/MRI coil discussion

Imaging the breast using NIRS can be highly dependent on the coupling between optical fibers and breast tissue(116). The ideal breast coupling interface must be adaptable to many patient sizes, be easily adjustable, and allow for good volumetric sampling - especially close to the chest wall. It must maintain a reliable patient-fiber junction regardless of the position on the breast surface, and be repeatable during different imaging sessions. This current design of the NIRS breast interface is not ideal, but it improves on old iterations in many ways. The most significant improvement is the ability to move vertically with arbitrary slice-selection. Previous designs were most limited by their inability to adjust based on MR scans after patient positioning. If the suspected lesion was outside the plane of the fibers, or was displaced after compression, time constraints of the MR exam prevented readjustments. The adjustable pneumatic interface ensures that the most valuable coronal plane is always imaged. Positioning repeatability is limited to ±2.3mm, though the exact location can be found using MRI and fibers can be repositioned if necessary. The fibers can be positioned as close to the chest wall as the MR breast coil will allow, 1.5cm, and have almost unlimited resolution in step size over an available range of 3.5cm. The interface used in previous studies(117,118) is able to get fibers within 2cm of the chest wall over a range of 4.5cm. The smaller range
of 3.5cm is large enough for almost all cases, and data can be acquired 0.5cm closer to the chest wall. The breast is held rigidly between the two plates and compressed to uniform, flat sides, which simplifies meshing.

There are shortcomings to the interface as well. We see approximately 28% loss in light per plate compared to imaging without the plates due to extra index of refraction changes and cladding between fibers. Since transmission across the breast can produce attenuation of 10 orders of magnitude, the additional loss is not extremely important. The authors attempted to use high quality optical glass instead of fiber face plates but found similar results to Del Bianco et al(119), where transverse light channeling significantly corrupted reflection mode data. The construction of fiber face plates prevents channeling-related artifacts, justifying the higher cost.

Another problem with the design is that immediate feedback on position is not perfectly accurate. The inherent non-repeatability of pneumatic systems and the difficulty of measuring air pressure in the MR prevents the computer from knowing exactly where the fibers are positioned at all times. Our accuracy and repeatability test yielded an average standard deviation in positioning of 0.23 cm. Though this is not a negligible amount of uncertainty, we circumvent the problem by using fast scout scans on the MR and looking for fiducial markers that are attached to the fibers. This gives exact positions, but the delay caused to take the scan (usually around 1 minute) is still not ideal. Future design iterations will try to improve the accuracy of the interface’s position before MR scanning.

We also found that this interface had issues imaging women with small or dense breasts. In the case of A and B cup women, the interface is typically not able to get close
enough to the chest wall to position fibers in contact with the breast. While this design
does get fibers closer to the chest wall than previous iterations, its inability to image A
and B cup women is a major drawback. We have also found that this device has difficulty
with very dense breasts since the faceplates apply compression over a very large area.
Dense breasts do not conform to the parallel plate geometry as easily as fatty breasts.
This is a shortcoming of the device, but we expect the majority of cancer patients to have
larger breasts and less dense breasts because patients typically undergo screening
beginning at age 50 and breasts become less dense during menopause(120,121).

Validation of new imaging systems can be difficult and usually relies on phantom
studies. Though phantoms are not a complete representation of tissue, they are the best
way to validate the performance of hardware. Phantoms were tested using absorption
induced by diluted India ink and scattering from Intralipid, though absolute values of \( \mu_a \)
and \( \mu_s' \) are still only approximately known for these solutions. Several factors, including
batch-to-batch variation, can cause changes in optical properties in phantoms made with
these materials from a set recipe. Though it is possible to measure their optical properties,
we have found that it is typically more reliable to use relative images(122). More
importantly, it is not possible to make a phantom that can tailor all imaging parameters to
known levels(107,123). The best option is to use whole blood and evaluate changes in
HbT. Even so, this approach does not allow for control of water or scattering parameters
exactly. Due to these challenges, we test our instrumentation using linearity over different
ink concentrations and contrast recovery at different 2D planes.

The phantom experiment demonstrates linearity over a range of absorber contrasts
with and without the fiber plates in place. The absolute values of the image sets are
slightly different, possibly exhibiting crosstalk between absorption and scatter. This could be due to lower light levels from signal loss at the plates’ extra index of refraction change. According to these results, the plates do not have a large effect on the recovered image contrast, and large changes from previous patient imaging are not expected.

Design goals of increasing the available degrees of freedom for fiber positioning while being able to hold the breast rigidly and maintain a reliable patient-fiber interface were accomplished. A system was implemented for repositioning optical fibers from the MR computer room during a patient exam to target suspicious lesions with MR scans as reference and collect multiple planes of data. Unfortunately, the utility of this system is maximized when imaging a patient with fatty, D-cup sized breasts. We found this to be a critical limitation for younger populations as well and looked to address this issue for future designs.

3.4 Clinical NIRS/MRI breast coil for full breast coverage

3.4.1 Motivation for development

While the parallel plate design is the clinical standard for MR-guided breast biopsy, it is not the optimal arrangement for NIRS because coverage near the chest wall is difficult to provide, making examination of women with small breasts, dense breasts, or posteriorly located tumors nearly impossible. We have addressed these practical issues by realizing a NIRS-compatible breast coil that is capable of imaging more breast sizes with a more variable range of tissue heterogeneity.

The NIRS interface described here was designed to accommodate multiple breast sizes and composition, while also providing optical coverage of the entire region of
interest including the posterior medial breast and axillary region. Another goal was to
minimize geometrical distortions of the breast being scanned, as well as preserve the
shape of the contralateral breast to maintain MR image quality and house the NIRS
optodes within a clinical MR breast coil. The interface is based on a triangular
arrangement of optical fibers with six degrees of freedom for adjustment. We
demonstrate that robust fiber contact occurs with breasts of all cup sizes during
simultaneous MR and NIRS breast exams involving healthy volunteers and cancer
patients, using a typical V-shaped clinical breast coil. Results are compared to the
previous generation of breast interface design.

3.4.2 Materials and Methods

The development of this system has focused on the fiber interface’s ability to
accommodate variable breast sizes and compositions through a clinical MRI breast coil
(Invivo Corp, Gainesville, FL) retrofitted with the optical fiber array. An adjustable
triangular breast interface was designed using Solidworks (Solidworks Corp, Waltham,
MA) and fabricated using a 3D printer (Stratasys, Inc., Eden Prairie, MN) that deposits
ABS plastic, and white acetal, both MR compatible materials. CAD drawings of the
prototype are shown in Figure 23.

The design is unique to optical tomography and provides patient-specific
adjustments without the need for a custom MR breast coil. The interface is based on 16
fiber-optic bundles divided into one set of eight and two sets of four fibers. The set of
eight fibers, located on the lateral side of the breast, incorporates a slight curvature
(radius 8 inches) to couple to smaller breasts more effectively. These fibers not only slide
in the medial-lateral direction, similarly to a breast biopsy plate, but also in the anterior-posterior direction to adjust for different breast diameters.

The interface consists of two additional sets of four fibers on the medial side of the breast, one of which is offset slightly superiorly while the other is positioned slightly inferiorly. Both sets of fibers are angled towards the center of the breast. They can be adjusted for different breast diameters. At the maximum extent of their range, the medial sets of fibers extend beyond the surface of the breast coil to cover tissue nearest the chest wall.

![Figure 23: CAD drawings of triangular patient interface with semi-transparent MRI breast coil (a) with fiber holder parts shown in blue. (b) shows the completed design with optical fibers and (c) shows an axial MR with locations of fiber rows highlighted.](image)

These fibers are secured using nylon set screws and translate across friction-coupled, dovetailed tracks. They slide easily for adjustment. After being positioned against the subject’s breast, a lock is inserted to prevent further movement. The lock ensures that the fibers remain stationary and are mildly compressed against the breast.
surface during imaging. Breast stabilization is also important to minimize MR image artifact. Since the technique is an adjunct to clinical breast MRI, we were also careful not to interfere with the imaging of the contralateral breast.

This device was tested first by working closely with the MRI coil to ensure a proper fit and functionality. We then imaged phantoms and healthy volunteers with different breast sizes and compositions. First, we imaged an Agarose phantom to ensure that we could accurately recover optical chromophores in this geometry. The phantom is an irregular shape that is fit to the fiber optics within the breast coil and specific to their arrangement. The phantom used was made of Agarose, 15um whole porcine blood background, and 1% Intralipid. A 2cm diameter inclusion with 1.5x hemoglobin contrast was placed near the middle of the phantom. We also added 0.5ml of Gadolinium to the inclusion for recovery on the MRI image. The phantom was imaged using NIRS and MRI simultaneously, reconstructed using Nirfast, and viewed as an overlay with the MR image.

Our imaging protocol for human subject examination was approved by the Committee for the Protection of Human Subjects at Dartmouth-Hitchcock Medical Center and is detailed in Chapter 5. Briefly, written consent was obtained prior to imaging and subjects were imaged simultaneously by MRI and optics in prone position. Because the data collection from the two imaging modalities do not interfere with each other, optical data was typically collected twice per subject as time permitted. We tested the device using several volunteers spanning all cup sizes and breast composition to accurately with emphasis smaller cup sizes (A+B) to simulate a diverse patient population and the weaknesses of previous designs.

3.4.3 Triangular patient interface performance
Preliminary data are presented from phantom experiments where the triangular geometry is used to image a phantom of Agarose and blood in 3D and recover the inclusion to background ratio to within 5% of the true value. Results from this phantom experiment are shown in Figure 24, demonstrating that we are able to reconstruct images in this geometry and that it is a feasible breast imaging geometry for MRI/NIRS. This triangular phantom shows good HbT recovery of 12.9:18.9um or 1.47x versus the correct concentrations of 15:22.5um or 1.5x. Oxygen saturation was consistently high between regions, agreeing with past results and expectations (117,124). Water was found to be 93% in the background but very low in the inclusion. This is likely to crosstalk with scattering parameters, which also vary more than we would expect them to (125).

Figure 24: Phantom study using the triangular geometry. (a) 3D representation of combined maximum intensity projection MR image and 3D rendering of optical solution of HbT. (b) Coronal plane of optical imaging. (c) Quantitative hemoglobin overlaid. (d) Oxygen saturation. (e) Actual phantom cut in half. (f) water fraction, (g)scatter amplitude, (h) scatter power. Color bars reflect the values of the two regions in each case.
We then tested the interface for functionality on a healthy volunteer with an A-cup breast size by positioning the optodes in contact with the tissue and scanning her with MRI/NIRS. The interface was able to adjust to a small diameter and raise the fibers close enough to the chest wall to contact the subject’s breast. In this case, we successfully positioned 15 of 16 optodes in contact with the breast within one centimeter from the chest wall as shown in Figure 23. One fiber was not in contact with tissue because of the curvature of the breast. Our interface covered the medial chest wall and upper outer-quadrant fully. In previous designs (113,124,126), positioning the fibers in contact with an A-cup breast was not possible due to the thickness of the breast coil and padding. Positioning the volunteer took approximately 10 minutes prior to imaging and she reported no discomfort during the procedure.

Figure 25: *Side view of NIRS/MRI breast coil with green arrows representing available degrees of freedom (a). The optodes can accommodate both large (b) and small (c) breast diameters. Axial (d) and coronal (e) MRI images of an A-cup sized breast show fiber locations corresponding to surface projections of the medial (f) and lateral (g) sides.*
3.4.4 Triangular breast interface discussion

The ideal MRI/NIRS breast interface must adapt to patient size, be easily adjustable, and provide adequate volumetric sampling. It must maintain fiber contact with tissue during the breast exam, be repeatable from one exam to the next, and be comfortable for the subject. MR image quality of the contralateral breast should also be unaltered since MRI has a high sensitivity to lesions in that breast (127). Finally, the interface should be adaptable to a range of clinical breast coils rather than be integrated into a single manufacturer’s design coil. While our unit is imperfect, we have addressed all of these issues and find the most significant improvement is its ability to image variable breast sizes provided they are compatible with a standard clinical breast coil platform.

In testing the device in human subjects for functionality, we were very satisfied with the results. In a study with an A-cup sized volunteer, patient positioning was easier and faster than it has been in previous geometries. The fiber optics were able to contact the volunteer’s breast on both the medial and lateral side, contacting 15 out of 16 optodes. We were able to position this volunteer multiple times prior to imaging. MRI image quality was unaffected by the optics on the contralateral side. The imaged breast is notched where the fiber planes contact it, but this is a necessary compromise.

The phantom experiment that we performed was also encouraging, as we were able to recover absolute hemoglobin and hemoglobin contrast within 5% of the expected value. Oxygen saturation in the phantom was found to be nearly 100%, which is consistent with other phantom studies (125) and that the blood should become oxygenated during its exposure to the air. We expect water content in agarose phantoms
to be high since they are water based, and our system recovered water to be 93% in the background. It was very low in the inclusion however. We also saw scatter contrast in the inclusion though the inclusion was made with the same scatter as the background. The false contrast in the scattering and water images was likely due to crosstalk between the water and scattering parameters. These results are consistent with phantom imaging on this system and improvements are being made to improve water and scatter quantification by adding longer wavelengths (124,126,128). As in the other phantoms, water crosstalk also could be amplified in this experiment because Agarose phantoms have approximately double the water content of breast tissue and our ability to recover water is limited by the PMTs’ sensitivity to wavelengths above 850nm. Admittedly these results are not perfect, however they demonstrate basic functionality of the interface.

3.5 Comparison of NIRS/MRI breast coils

3.5.1 Parallel Plate Geometry Versus Triangular Geometry

In comparing the two patient geometries this thesis describes in detail, the most important characteristic is clinical relevance. Both geometries have their strengths and weaknesses, and both are good for NIRS/MRI. In our experience, the triangular interface is a clinically applicable and adaptable geometry, so has therefore been the preferred way to couple optics and MRI in our larger clinical efforts.

The parallel plate geometry (used at DHMC) is housed within a custom MRI breast coil (Phillips Research, Germany). This custom coil is unique as it has a flat top and open design that maximizes empty space beneath where the patient lies. This allows the optical equipment free space to move, rotating 360 degrees and rising to within 2cm of
the chest wall. This system is shown in its clinical setting in Figure 26. The main advantage to this design is the ability to interactively target lesions found on the MR image during the patient exam. However, we found that this was not possible in the majority of cases. This interface is not capable of imaging women with A or B cup sized breasts, and it must be positioned near the top of its effective range to image C cup sized breasts successfully. A D cup sized breast is required for the interface to achieve good fiber contact and have enough range to justify interactive targeting. While this is a large number of patients, the targeting is not a necessity, and we were forced to reject many women with A and B cup sizes breasts from the study due to the interface not fitting. The triangular geometry addresses this issue.

Figure 26: Comparison of parallel plate and triangular MRI coil. The parallel plate bed set up with a Phillips Achiva 3.0T scanner (a) and custom breast coil (b). A side view of the coil (c) shows fibers at their lowest position. The triangular interface set up for patient imaging on a Siemens Tim Trio 3.0T scanner (d) and clinical breast coil (e). A side view shows the fibers in their highest position (f).
The triangular breast interface, designed at DHMC and used in a clinical study in Xi’an, China, can be adapted to multiple MRI machines since it couples directly into a common clinical breast coil. Fibers are arranged around the breast in 3 rows and can be adjusted before the exam to fit cup sizes A through D. The interface is naturally positioned very close to the chest wall (within 1cm) but can be adjusted by adding more padding between the patient and the breast coil if necessary. In moving away from the traditional parallel-plate geometry, we have improved considerably the pre-scan adjustability but at the expense of interactively selecting the slice during the imaging exam (124). There have been some clinical cases where the lesion was missed with the triangular imaging geometry and repositioning would have been useful. However in many of these cases the lesion was located so far to the anterior side of the breast that no interface would actually be able to achieve fiber contact near them anyways. Since fibers are arranged in a triangle rather than parallel plates, considerably less compression is required to achieve fiber contact with the breast tissue. Additionally, the triangular design separates the fibers from the contralateral breast, minimizing any effects on MR image quality.

For direct comparison, we imaged a B-cup breast-sized volunteer using both our previous parallel-plate optical-array geometry placed in a custom MR breast coil, and the new triangular geometry integrated with a standard clinical MR breast coil. Side views of the two geometries are shown in Figure 27. In this subject, the fibers must be raised to be closer to the chest wall than is possible in the parallel plate geometry. The top side of the coil prevented the fibers from reaching closer than 1.5cm from the chest wall before padding was added for patient comfort, leaving contact with this volunteer’s breast in
only 2 of 16 fibers, which was inadequate for imaging. In the triangular geometry, the fibers are angled and they are uninhibited by the top of the coil platform and find contact with the chest-wall directly. The triangular interface was able to easily contact the same breast with 15 of 16 fibers, and produce a successful NIRS image. The V-shape of the clinical coil also provided better access to the upper outer quadrant of the breast.

![Figure 27: Comparison of previous design of NIRS/MRI breast coil. Side view of parallel plate interface (a) and coronal image of a B-cup sized volunteer (b). Green arrows show where fibers are located. A surface projection (c) illustrates acceptable (green) and poor (red) fiber contact. Side view of triangular breast interface (d) and axial image of the same volunteer (e). Green arrows show where fibers are located. A surface projection (f) illustrates significant improvement in fiber contact.](image)

One advantage of the parallel plate design is the relative simplicity of the finite element mesh required for NIRS image reconstruction. Rather than a smooth-sided rectangular shape, breasts imaged in the triangular geometry tend to be more irregular with indentations occurring where fibers contact the skin. This makes mesh generation more time consuming and technically demanding, though algorithms and computational
resources are improving. This concern increases with patient volume because meshes must be customized for every subject. Seemingly, the fiber indentations could be eliminated without compromising functionality, mitigating the drawback in the future, if it proves important.

Smaller breast sizes present the additional challenge to previous MRI/NIRS breast coil designs that they are also likely to be more dense. Density increases breast cancer risk and this subgroup of women must not be ignored (129). The parallel-plate interfaces used in previous studies were able to position fibers within 1.5cm to 2cm of the chest wall (118,126) which is not sufficient for NIRS imaging of smaller cup sizes (A,B) and very dense breasts. An example is shown in Figure 3, where fiber coupling in the parallel plate geometry prevented NIRS imaging of a B-cup sized breast. The triangular interface was able to accommodate this volunteer and many others who were not able to undergo a successful NIRS exam in the past which represents a significant step forward in the clinical acceptance of the technology.

3.5.2 Clinically relevant breast interfaces
After working with several different breast imaging geometries in the MRI we think that the triangular NIRS/MRI coil is by far the best way to arrange the fibers to date. This geometry couples into a clinical breast coil and is adaptable to many different MR systems rather than the parallel plate geometry that requires a custom coil to be most effective. The biggest advantage that the triangular geometry has is its ability to image small breasts in the A and B cup range, not possible with the other geometries. As a result, the triangular geometry also provides excellent coverage to the whole breast volume including the axillar region and the medial posterior breast, both regions that were
previously inaccessible. According to technicians who have positioned patients in both geometries, the triangular geometry is the simplest. After the patient is on the table, there is only one adjustment from the lateral side that is necessary. Data acquisition speed in the triangular geometry is not as fast as in the circular geometry, but the gain finding methods explored in Chapter 2 manage to keep imaging time under 15 minutes, well below the length of the MRI exam. These results are summarized in Figure 28.

![Figure 28](image)

**Figure 28:** *Summary of breast imaging geometries and their clinical relevance. Green circles indicate the best performance, yellow acceptable, red bad. The triangular geometry is very good in almost all categories and is the most clinically relevant imaging geometry to date.*

During our clinical trial in Xi’an, China, the triangular geometry was used to image over 60 women with breast sizes ranging from A to D cup. It was usually possible to place at least 12/16 fibers in contact with each breast. Many cases were able to achieve perfect contact despite the large variation in breast shape, size, and density. The
technicians and doctors involved in the work in Xi’an were able to learn how to operate the interface easily and repeatedly position patients quickly and effectively. The triangle geometry was an effective way to do NIRS/MRI patient imaging in a clinical setting. From a clinical standpoint, future designs of the breast interface should concentrate on sliding more freely and locking in place. It would also be convenient to be able to adjust both the medial and lateral sides of the interface all from the lateral side of the breast. The fiber optics cause deformation of the breast that would be good to eliminate but is acceptable. Major redesigning of the interface would be required to use a new breast coil or incorporate additional fibers.

3.6 Conclusions

While the present design for MRI/NIRS was an improvement, it was not perfect. For example, the fibers translate on friction couplings, which were difficult to use and often required some adjustments to be made from the medial side, whereas, ideally, all adjustments would be made from the lateral side of the patient, where technologist access is much simpler and less intrusive. The access question is challenging given the space constraints within standard breast coil systems, but state-of-the-art breast biopsy coils have already incorporated these types of adjustments and future designs would likely benefit from a triangular array that is coupled directly to the biopsy plates. Some state of the art breast biopsy coils are shown in Figure 29 and demonstrate how effective a fiber interface coupled to the biopsy system could be. These coils have a lot of open space and have tracks and slides installed for the biopsy procedures. Though they cost approximately $100k, major hospitals that perform MR guided biopsy have them.
Figure 29: State of the art breast biopsy coils are shown in side view (a) and top view (b). These coils have lots of open space and come with tracks and slides for biopsy procedures. Future patient interfaces should couple directly into biopsy arrangements and use the coil for adjustment.

The patient interface is often overlooked during system design but must be considered as it is the most important thing about the system after suitable sources and detectors are functioning properly. Source-detector coupling to the breast within the confines of the MR bore influences the breast sizes and densities that can be imaged, and partially determines whether NIRS is a useful addition to MRI. In this chapter, the design and evaluation of both a remotely positioned parallel plate interface and a triangular interface integrated with a standard clinical MRI breast coil were presented. This chapter has documented the ability of the system to target suspicious lesions based on real time feedback from MRI and to improve patient positioning and imaging in MRI/NIRS, especially in terms of simultaneous MRI and NIRS imaging of breast cup sizes A and B as well as C and D. Future chapters in this thesis will focus on the imaging of patients with lesions in many locations to evaluate the potential for MRI/NIRS to add to the sensitivity and specificity of DCE-MRI.
Chapter Four: Image Formation Methods

Optical imaging is often used generically to imply the use of either visible wavelengths (400-650 nm) or near infrared (NIR) wavelengths (650-1000 nm) of light to image or measure transmittance or reflectance in order to characterize the absorption and scattering properties of breast. The main difference between these two wavelength bands is the depth of tissue through which light can propagate. Visible light does not penetrate very far due to high absorption and scatter, whereas NIR light is nearly equal in the amount of scatter but only weakly absorbed (see Figure 30). Thus, NIR light can be used for imaging through thicker tissue such as the breast because of this reduced total attenuation. NIR photons do not have sufficient energy to break molecular bonds, and so the use of NIR in imaging has the benefit of being non-ionizing, and thus, poses less of a health risk to patients and medical personnel relative to traditional x-rays. NIR photons undergo multiple scattering events as they travel through tissue, whereas x-rays and visible light have at least an order of magnitude less scatter. These differences give optical imaging unique sensitivity to soft tissue but come at the cost of being more complicated to model the propagation and tissue interactions. This chapter focuses on the physics of NIR light transport in tissue, how it can be used for image reconstruction, and the finite element methods used for this model-based imaging.
Figure 30: Absorption spectra of chromophores oxy- and deoxy-hemoglobin, water, and fat vary as a function of wavelength. If tissue is probed with multiple wavelengths of near infrared light, these spectra and the measured absorption coefficients can be used to quantify their concentrations (130).

4.1 Light Transport in Tissue

4.1.1 Optical Properties

The intrinsic optical properties of tissue affect how light propagates and changes in these properties can provide information on tissue metabolic status. The transport of optical photons is dominated by high anisotropic scattering, largely coming from index of refraction differences in tissue components such as mitochondria and collagen fibrils, contributing to Mie and Rayleigh scattering of NIR light. The absorption and scattering
coefficients ($\mu_a$ and $\mu_s$) coefficients represent the likelihood of a photon undergoing an absorption or scattering event per unit depth in tissue. The transport mean free path describes the average distance between photon interactions and is usually on the order of 1 mm. The reduced scattering coefficient, $\mu_s'$, is more frequently used when considering the effective scattering coefficient as measured over multiple scattering distances, where directionality is lost. Individual scattering events are highly anisotropic with average cosine of the scattering angle, $g$, being close to 0.9 in most tissues. Whereas multiple scattering can appear effectively isotropic in the far field, it is parameterized through the transport or reduced scattering coefficient defined as $\mu_s' = (1-g)\mu_s$. This characteristic of the multiple scattering transport mechanism limits the attainable spatial resolution of NIR imaging techniques.

Absorption of light can also attenuate the signal, both in the visible wavelengths as well as in the NIR when light is transmitted through thick tissues. In the NIR regime, the absorption coefficient is about two orders of magnitude lower than its scattering counterpart whereas in the visible regime the two are more comparable (see Figure 30). Hence, light can travel through several centimeters of tissue and still have enough intensity to be detected. Thus, its spectrum (which is altered by absorption and scatter) can be used for breast imaging. The absorption coefficient, $\mu_a$, represents the inverse of the mean free distance for exponential attenuation, estimated in the absence of scatter. Since tissue absorption and scattering coefficients vary as a function of wavelength, measurements at multiple wavelengths can be used to gain additional information about the properties of tissue.

Each of the major absorbers has a characteristic molar extinction spectrum in the
NIR, which is its absorption coefficient per unit concentration at each wavelength. If measurements of the absorption coefficient are recorded at different wavelengths, concentrations of absorbers such as hemoglobin, water, beta-carotene, bilirubin and lipids can be determined based on the known extinction coefficients for each contributor at the different wavelengths. At each wavelength, these individual chromophores contribute linearly to the total absorption coefficient, weighted by their respective concentrations and molar extinction coefficients.

Clinical implementation of diffuse optical spectroscopy takes advantage of tissue optical properties to estimate absorption and scatter from transmission measurements, and ultimately describe physiological properties in tissue through the concentration of these chromophores.

4.1.2 Diffusion Modeling and Other Methods

Optical photon transport through tissue can be modeled in several ways. Analytical solutions exist for simple shapes such as circles and rectangles, but are very difficult to adapt to geometries of clinical relevance (131). Numerical techniques such as Monte Carlo and Finite Element Methods (FEM) are generally preferred. Monte Carlo is the most accurate and adaptable approach for modeling light transport, but it can be prohibitively slow computationally (132–134). A modeling domain is established and the paths of individual photons (ballistic particles that can be redirected in this case) are calculated in very small steps based on the probability of absorption and scattering events. After a sufficient number of individual photons are simulated, usually millions, results can be reliably interpreted. Because of the computational costs associated with Monte Carlo calculations, especially in image reconstruction, it is used mostly to validate other
methods, or preferentially used for cases of small source-detector separation where the accuracy is far better than diffusion theory approximations.

The RTE can be simplified under two assumptions: 1) optical radiance is only linearly anisotropic, all higher order terms are insignificant, and 2) the rate of change of photon flux is much lower than the photon collision frequency. The first assumption holds for regions far (>1 mm) from light sources and tissue boundaries, and is readily satisfied in breast imaging because the tissue volume is relatively large. The second assumption is true because scattering occurs much more frequently than absorption in breast tissue in the NIR regime. With these assumptions met, a simplification in the RTE known as the diffusion approximation is possible and is represented mathematically in the frequency domain by

\[-\nabla \cdot D \nabla \Phi(r, \omega) + \left( \mu_a + \frac{i\omega}{c} \right) \Phi(r, \omega) = S(r, \omega)\]

where \( \Phi \) is the photon fluence, \( D = \frac{1}{3(\mu_a + \mu_s')} \) is the diffusion coefficient, \( \mu_a \) is the absorption coefficient, \( c \) is the speed of light and \( S \) is the light source. This equation describes the fluence of light at a certain position, \( r \), at frequency \( \omega \). The four terms represent changes in flux, diffusion, loss due to absorption and gain from a light source and are balanced in the form of a conservation law. A complete derivation of the diffusion equation (from the RTE) can be found in (135). In addition to modeling light as it travels through tissue, whether it is reflected back inside or exits at a tissue surface is accommodated through incorporation of appropriate boundary conditions, as is elaborated on below with numerical modeling.

4.1.3 Finite Element Modeling
Applying diffusion theory to optical breast imaging requires that the breast is modeled in numerical simulations which capture the shape and internal heterogeneity of the tissue optical properties. One effective option has been the Finite Element Method (FEM), where the imaging domain is discretized into a grid, or mesh, as illustrated in Figure 31. The mesh is a collection of shapes, called elements, which are used to create a point cloud within a domain. In 2D problems, squares and triangles are common, and in 3D problems, cubes and tetrahedrons. The diffusion equation is solved for a fluence represented as a piecewise continuous basis function expansion over the mesh. To discretize onto finite elements, the diffusion equation is multiplied by weighting functions at each node, becoming:

$$\langle -\nabla \cdot D \nabla \Phi \phi \rangle + \left( \mu_a + \frac{i \omega}{c} \right) \Phi \phi_i = \langle S \phi \rangle$$

where $\langle x \rangle$ means integration over the solution domain. $\phi_i$ is the weighting function at the $i^{th}$ node, $\phi_i = \sum_{j=1}^{N} \Phi_j \phi_j$, and is solved numerically along with the fluence.
Figure 31: Segmented breast mesh showing adipose (blue), glandular (white), and tumor (red) (a) with outlines of tetrahedrons (b). The same domain is used to show the sensitivity of a measurement (log scale) from one source to a detector on the other side of the breast (c) and with elements (d). Many photons probe areas right near the source and the sensitivity is high.

It makes sense to use tetrahedral elements in breast imaging since the domain is three dimensional and irregularly shaped. More detailed discussion of finite element methods is can be found in extensive published literature on this topic (136,137). Since the diffusion problem is solved discretely on a mesh, the accuracy of the solution is governed by the resolution of the mesh (i.e., spacing between nodes). A finer mesh (more nodes) will have higher accuracy since the solution is obtained at more points but will take longer to compute. In this thesis, patient images are reconstructed in 3D using meshes with between 40,000 and 60,000 nodes. Depending on the breast size, this
translates to between 1.8mm and 2.5mm between nodes, which has been found to be
sufficient for accurate forward modeling of the light diffusion over these distances.

While light gradient generally shows loss with distance from the source
throughout the domain, the diffuse model can have abrupt departures from this near the
boundary as it has the potential to be reflected back into the domain at the air-tissue
interface. We use a type III boundary condition where photons at the edge can leave but
do not return (138,139). The number of photons leaving is equal to the flux in that
direction weighted by a factor that accounts for the internal reflection off of the boundary
back into the medium. This is described by the equation,

$$\Phi(\xi, \omega) + 2A \hat{n} \cdot \kappa(\xi) \nabla \Phi(\xi, \omega) = 0$$

where $\xi$ is a point on the boundary and $\hat{n}$ is a vector pointing outwards, normal to the
surface. $A$ describes the probability of internal reflection at point $\xi$ and can be obtained
from Fresnel’s law,

$$A = \frac{2 / (1 - R_0) - 1 + |\cos \theta_c|}{1 - |\cos \theta_c|^2}$$

where $\theta_c$ is the angle at which internal reflection occurs and $R_0 = (n / n_a - 1)^2 / (n / n_a + 1)^2$.

Breast tissue NIR imaging is modeled well by diffusion theory because the
mathematical solution is nearly isotropic with only a mild anisotropic gradient in the
fluence within the domain. Additionally, the temporal approximation of the change in
flux being much lower than the collision frequency is quite valid for NIR signals of
interest. The diffusion approximation is not valid near boundaries and sources, but this
region is very small compared to the total in breast imaging (135). Using FEM meshes,
we are able to model the diffusion of light with computational efficiency and resolution around 2mm.

4.2 Image Reconstruction

4.2.1 Forward Problem

Accurate modeling of diffuse light propagation in tissues of known optical properties allows computation of the light remittance at external boundaries. This is known as the forward problem, and as stated, the FEM solution to the diffusion approximation on a discretized domain representing the tissue is used to calculate the photon fluence, $\Phi$, at each location in the region. The approach to FEM expresses of the domain mesh elements as piecewise linear basis functions that provide a smooth solution at any point in the mesh (i.e., within the breast).

In the forward problem, the optical properties of a domain are assumed known. Given source locations and strengths, the diffusion equation is solved for boundary data at detector locations. The forward problem is easy to solve on an FEM mesh as long as the resolution is reasonable, though it is only a building block of image reconstruction. In the imaging problem, the tissue optical properties are not known. Therefore, many forward problems are used to reconstruct using sophisticated iterative estimation-type algorithms with an initial guess of the properties.

4.2.2 Inverse Problem

In clinical implementation, NIRS is carried out with measurements being recorded at detectors external to the tissue volume of interest. $\mu_s$ and $\mu_s'$ can be estimated from this data at every node in the mesh by solving the inverse problem. The inverse
problem is non-linear, ill posed, and underdetermined, and thus, challenging to solve.
Underdetermined refers to the fact that there are many more unknowns (i.e. the tissue optical properties at each node) existing as compared to the number of known data values input (i.e. measurements). In an ill-posed problem, small changes in the signal or noise can result in large changes in the solution due to the inversion matrix having large variations in magnitude along the normalized diagonal. The general inverse solution requires an initial estimate of the optical properties of the tissue of interest, coming from the calibration function. Using these values, the forward problem is solved and compared with the collected measurement data. Differences between the model and the data update the approximation of the optical properties based on the sensitivity of the boundary measurements to the internal optical proprieties. The sensitivity matrix is known as the Jacobian, $J$, and is structured as:

$$
J = \begin{bmatrix}
\frac{d\ln I_1}{dD_1} & \frac{d\ln I_1}{dD_1} & \ldots & \frac{d\ln I_1}{dD_{NN}} & \frac{d\ln I_1}{d\mu_1} & \frac{d\ln I_1}{d\mu_2} & \ldots & \frac{d\ln I_1}{d\mu_{NN}} \\
\frac{d\theta_1}{dD_1} & \frac{d\theta_1}{dD_1} & \ldots & \frac{d\theta_1}{dD_{NN}} & \frac{d\theta_1}{d\mu_1} & \frac{d\theta_1}{d\mu_2} & \ldots & \frac{d\theta_1}{d\mu_{NN}} \\
\frac{d\ln I_2}{dD_1} & \frac{d\ln I_2}{dD_1} & \ldots & \frac{d\ln I_2}{dD_{NN}} & \frac{d\ln I_2}{d\mu_1} & \frac{d\ln I_2}{d\mu_2} & \ldots & \frac{d\ln I_2}{d\mu_{NN}} \\
\frac{d\theta_2}{dD_1} & \frac{d\theta_2}{dD_1} & \ldots & \frac{d\theta_2}{dD_{NN}} & \frac{d\theta_2}{d\mu_1} & \frac{d\theta_2}{d\mu_2} & \ldots & \frac{d\theta_2}{d\mu_{NN}} \\
\vdots & \vdots & \vdots & \vdots & \vdots & \vdots & \vdots & \vdots \\
\frac{d\ln I_{NM}}{dD_1} & \frac{d\ln I_{NM}}{dD_1} & \ldots & \frac{d\ln I_{NM}}{dD_{NN}} & \frac{d\ln I_{NM}}{d\mu_1} & \frac{d\ln I_{NM}}{d\mu_2} & \ldots & \frac{d\ln I_{NM}}{d\mu_{NN}} \\
\frac{d\theta_{NM}}{dD_1} & \frac{d\theta_{NM}}{dD_1} & \ldots & \frac{d\theta_{NM}}{dD_{NN}} & \frac{d\theta_{NM}}{d\mu_1} & \frac{d\theta_{NM}}{d\mu_2} & \ldots & \frac{d\theta_{NM}}{d\mu_{NN}}
\end{bmatrix}
$$

5
Here, $NM$ is the number of source-detector measurements, and $NN$ is the number of nodes.

The matrix is structured in blocks by chromophore. In the single-wavelength frequency domain case, they are $D$, the diffusion coefficient, and $\mu_a$, the absorption coefficient with respect of intensity and phase measurements. The Jacobian is calculated at each iteration of the reconstruction based on the adjoint method, computationally efficient because it takes advantage of reciprocity (141). This process is repeated until a stopping criterion is reached. Methods are available for solving inverse problems, which have advantages and disadvantages in NIRS image reconstruction, and a number of research groups are working on optimizing these techniques (62,142–144).

Images in this thesis were reconstructed using Nirfast software (140,145) ([www.nirfast.org](http://www.nirfast.org)) and an outline of the solver is presented. Measured data, $\phi^M$, is compared with calculated data from the forward problem, $\phi^C$ to minimize the objective function, $\chi^2$, until a stopping criteria is reached. In the Levenberg-Marquardt formulation, the objective function is:

$$
\chi^2 = \sum_{i=1}^{NM} (\phi^M_i - \phi^C_i)^2.
$$

To minimize, the first derivative $\frac{d\chi^2}{d\mu}$ can be Taylor expanded about a nearby point $\mu_i$ to form a relationship between the data $\phi$ and the optical properties $\mu$ :

$$
\frac{d\chi^2}{d\mu} = \frac{d\chi^2}{d\mu_i} (\mu_i) + (\mu_{i+1} - \mu_i) \frac{d}{d\mu_i} \left( \frac{d\chi^2}{d\mu} (\mu_i) \right) + ... \quad (7)
$$

Since we are trying to minimize $\chi^2$, we set $\frac{d\chi^2}{d\mu_i} = 0$. Ignoring higher order terms and solving for $\mu_{i+1}$,
\[ \mu_{i+1} = \mu_i - \left( \frac{d}{d\mu} \left( \frac{d\chi^2}{d\mu} (\mu_i) \right) \right)^{-1} \frac{d\chi^2}{d\mu} (\mu_i). \] 

This yields an iterative update for the optical properties. Solving for \( \frac{d\chi^2}{d\mu} \) and \( \frac{d^2\chi^2}{d\mu^2} \) from equation 6, we obtain

\[ \frac{d\chi^2}{d\mu} (\mu_i) = 2 \left( \frac{d\phi^C}{d\mu} \right)^T (\phi^C - \phi^M) \]

and

\[ \frac{d}{dx} \left( \frac{d\chi^2}{d\mu} (\mu_i) \right) = 2 \left( \frac{d\phi^C}{d\mu} \right)^T \frac{d\phi^C}{d\mu} + 2 \frac{d^2\phi^C}{d\mu^2} (\phi^C - \phi^M). \]

The second derivative term in equation 10 is very small compared to the other terms and ignored, leaving

\[ \frac{d}{dx} \left( \frac{d\chi^2}{d\mu} (\mu_i) \right) = 2 \left( \frac{d\phi^C}{d\mu} \right)^T \frac{d\phi^C}{d\mu}. \]

Substituting in equations 9 and 11, equation 8 becomes

\[ \mu_{i+1} = \mu_i - \left[ \left( \frac{d\phi^C}{d\mu} \right)^T \left( \frac{d\phi^C}{d\mu} \right) \right]^{-1} \left( \frac{d\phi^C}{d\mu} \right)^T (\phi^C - \phi^M). \]

Knowing that \( \frac{d\phi^C}{d\mu} \) is the Jacobian Matrix \( J \), the update equation is

\[ \mu_{i+1} = \mu_i - \left[ J^T J \right]^{-1} J^T (\phi^C - \phi^M). \]

Since \( J^T J \) is always, ill-conditioned, the inversion is typically stabilized by adding a regularization term, \( \lambda \), to make it more diagonally dominant, resulting in:

\[ \Delta \mu = \left[ J^T J + \lambda I \right]^{-1} J^T (\phi^C - \phi^M). \]
This equation is iterated on until the change in $\mu$ from one iteration to the next is less than 2%, which is an empirically derived factor. The inversion process is computationally intense because the forward problem must be solved at every iteration.

**4.2.3 Frequency Domain & Continuous Wave Combined Spectral Image Recovery**

The inverse problem can be applied to spectral data as well. Rather than reconstruct each wavelength separately and then solve for chromophore concentrations, it is possible to restructure the problem in terms of the chromophores and solve for them directly. This approach is faster, more accurate, and more robust to noise (146,147). The absorption coefficient at each wavelength is a linear combination of the absorbers at that wavelength. Therefore, with several wavelengths of data, a chromophore concentration $C$ can be determined by:

$$C = \sum_{i=1}^{\#wv} \mu_a(\lambda_i) \varepsilon_i(\lambda_i).$$  \hfill 15

Here, $\mu_a$ is the absorption coefficient at the chosen wavelength, and $\varepsilon_i$ is the molar extinction coefficient as a function of wavelength of $i^{th}$ chromophore. The absorption is measured at several wavelengths and $\varepsilon_i$ is well known in the literature (148,149). In Nirfast, a least squares fit is used to calculate chromophore concentrations from absorption coefficients. Similarly, scattering amplitude $A$ and scattering power $b$ are fit to an empirically derived power law approximation to Mie Theory, shown to be a good approximation (150,151):

$$\mu_s' = a\lambda^{-b}.$$  \hfill 16

To reconstruct directly for tissue chromophores $C$ and scattering parameters, the Jacobian is modified to incorporate the sensitivity of the tissue chromophores, scatter
amplitude, $A$, and scatter power, $b$, (rather than $\mu_a$ and $D$) on the on the boundary data then blocked by wavelength:

$$J(\lambda_i) = \begin{bmatrix}
J_{c1}(\lambda_1) & J_{c2}(\lambda_1) & \cdots & J_{cM}(\lambda_1) & J_A(\lambda_1) & J_b(\lambda_1) \\
J_{c1}(\lambda_2) & J_{c2}(\lambda_2) & \cdots & J_{cM}(\lambda_2) & J_A(\lambda_2) & J_b(\lambda_2) \\
\vdots & \vdots & \ddots & \vdots & \vdots & \vdots \\
J_{c1}(\lambda_N) & J_{c2}(\lambda_N) & \cdots & J_{cM}(\lambda_N) & J_A(\lambda_N) & J_b(\lambda_N)
\end{bmatrix}.$$  

The update equation is also modified slightly,

$$\begin{bmatrix}
\Delta c_1 \\
\vdots \\
\Delta c_1 \\
\Delta a \\
\Delta b
\end{bmatrix} = \left[ J^T J + \lambda I \right]^{-1} J^T \begin{bmatrix}
\phi^{C1} - \phi^{M1} \\
\vdots \\
\phi^{CN} - \phi^{MN}
\end{bmatrix},$$

to account for the fact that $c$ is a vector and there is a $\phi^C - \phi^M$ term for each wavelength. 

Including multiple wavelengths makes the reconstruction less ill-posed since all data is used to estimate all parameters simultaneously and is favorable because spectral constraints can be introduced during the reconstruction. Previous work has shown improvement in chromophore concentration using this method (152).

In the case of this thesis, it was advantageous to be able to reconstruct both continuous wave and frequency domain data since patient data presented is collected at six frequency domain (FD) and three continuous wave (CW) wavelengths. CW wavelengths do not have phase and the Jacobian must be adjusted to incorporate both data types by padding every other row with zeroes where the phase data would be. In this formulation, when $J^T J$ (the Hessian) is evaluated, the matrices are properly sized for multiplication and the zeros do not contribute to the product. Using CW and FD
wavelengths in one reconstruction is more efficient than reconstructing in two steps for scattering parameters and then tissue chromophores. It has also been shown to be more accurate in phantoms in previous work in the lab (153,154).

An example of a combined frequency domain and continuous wave reconstruction is shown Figure 32 from a neoadjuvant chemotherapy patient. A maximum intensity projection of the MRI volume marks the lesion location and reconstructed chromophores are shown as coronal slices from the volume at the location of the optical plane of measurement. This patient displayed the highest total hemoglobin concentration in the tumor region with only slightly lower values in the fibroglandular tissue. As stated, this technique can be used to efficiently recover optical solutions from combined FD/CW datasets.

Figure 32: FD/CW reconstruction from a cancer patient undergoing neoadjuvant chemotherapy. DCE-MRI, shown as a maximum intensity projection (a), is characterized by optical imaging. A 3D volume of total hemoglobin is shown (b) as well as 2D coronal slices from the reconstructed optical volume (c-g).
4.2.4 Inclusion of Anatomical Spatial Priors

Image-guided algorithms have been hypothesized to have value for increasing the accuracy of multimodal instrument recovery of tissue parameters (62, 76). They are attractive for two reasons: computational efficiency and potentially higher accuracy. These techniques require an image of tissue structure be known *a priori* and co-registered with the optical scan. The spatial information is fed into the optical reconstruction in the form of a segmented map where glandular, adipose, and tumor tissue types are identified (see section 4.3). In the *hard priors* formulation, optical properties are allowed to vary between regions, but not within. In *soft priors*, properties are allowed to vary everywhere but are discouraged from significant variation within regions. Images presented in this thesis are all using hard priors. Examples of both types of images are shown in Figure 33.
Figure 33: An example of a 2D soft prior reconstruction of HbT, StO₂, Water, Scatter amplitude and power (a). Properties are deterred from varying within regions, but are allowed to (50). (b) shows cross sections of a 3D hard priors reconstruction where properties are not allowed to vary within regions.

Making these assumptions yields a smaller computational problem because the bulk optical properties of the segmented regions are found rather than the optical properties at each node of the mesh. Since the optical properties only vary over regions, the Jacobian matrix can be region-mapped to provide the sensitivity of the measurements to the regions rather than the nodes. As a result, the Jacobian is reduced to columns sized by the number of regions rather than the number of nodes. The amount of Jacobian storage space required is drastically reduced since the number of regions is typically multiple orders of magnitude less than the number of nodes. The reshaped Jacobian is

$$J = \begin{bmatrix}
\frac{d \ln I_1}{d C_1} & \frac{d \ln I_1}{d C_2} & \cdots & \frac{d \ln I_1}{d C_{NR}} \\
\frac{d \theta_1}{d C_1} & \frac{d \theta_1}{d C_2} & \cdots & \frac{d \theta_1}{d C_{NR}} \\
\frac{d \ln I_2}{d C_1} & \frac{d \ln I_2}{d C_2} & \cdots & \frac{d \ln I_2}{d C_{NR}} \\
\frac{d \theta_2}{d C_1} & \frac{d \theta_2}{d C_2} & \cdots & \frac{d \theta_2}{d C_{NR}} \\
\vdots & \vdots & \ddots & \vdots \\
\frac{d \ln I_{NM}}{d C_1} & \frac{d \ln I_{NM}}{d C_2} & \cdots & \frac{d \ln I_{NM}}{d C_{NR}} \\
\frac{d \theta_{NM}}{d C_1} & \frac{d \theta_{NM}}{d C_2} & \cdots & \frac{d \theta_{NM}}{d C_{NR}}
\end{bmatrix}$$

for one wavelength and one chromophore. On a mesh using 50,000 nodes, 240 measurements, 9 wavelengths, and 6 chromophores, the size of the full spectral Jacobian
becomes \((50,000 \text{nodes} \cdot 9 \text{wv} \cdot 6 \text{chrom}) \cdot (240 \text{meas} \cdot 2) = [2,700,000 \times 480]\). After region mapping (assuming three regions), the Jacobian is resized to
\((3 \text{regions} \cdot 9 \text{wv} \cdot 6 \text{chrom}) \cdot (240 \text{meas} \cdot 2) = [162 \times 480]\), a tremendous savings in computational space.

During reconstruction, a single forward model for a mesh and dataset of this size would take approximately 5 minutes on a powerful computing cluster. Thus, a reconstruction with 10 iterations would take approximately one hour.

The other advantage of these methods is that the optical properties are estimated more accurately on the spatial scale defined by the segmentation of the complimentary imaging modality. Since optical imaging by itself is unable to detect lesions smaller than about 1cm, it is advantageous to use a highly resolved imaging modality to complement the optical imaging. Hard priors algorithms and MR prior information can enable detection of smaller lesions with lower contrasts on a spatial scale approaching 3mm (155). One important distinction to make is that when using hard priors algorithms, optical imaging becomes more like optical spectroscopy or region fitting. If MRI is unable to identify a region of interest, it will not appear on the optical image. MRI sensitivity is very high, and suspicious lesions almost always show up if there is other clinical evidence. Optical imaging systems have been combined with MRI and x-ray tomosynthesis for breast applications and may represent the most promising clinical approaches (50,62) as they merely enhance the clinical modality rather than stand as their own imaging system.

### 4.3 Creating Meshes from MRI Images
Using the available prior information from MR images requires that a mesh is created for every patient. The MR image provides the boundary, internal tissue structures, highlights any regions of interest, and locates optical fibers. By creating a mesh specifically for every patient, we avoid any approximation or generalization about breast sizes or shapes. Prior information can be used to refine mesh resolution within regions of interest and combining available information from multiple modalities yields the most accurate final results.

4.3.1 MRI Image Types

Creating meshes from MR images first requires a review of what different MR images look like. In standard clinical breast MRI, the main images that are taken are T1 weighted, T2 weighted, and dynamic contrast enhanced series. The T1 weighted image gets higher signals from fat than fibroglandular tissue, resulting in images that are bright near the edge of the breast. T2 weighted images emphasize water, resulting in fat appearing dark and glandular tissue appearing brighter. Cysts and lesions with high water content appear very bright on T2. One or both breasts can be scanned as T1W, T2W, or variations that suppress fat signal. DCE images scan both breasts and offer a time series after the injection of a bolus of Gadolinium contrast agent. The post contrast images can be subtracted from the pre contrast image and show the relative uptake of different parts of the breast. Finally, MIP images are made using the highest signal in the $z$-direction for every $x$-$y$ pixel (or $x$ for every $z$-$y$, etc.). These image types can be taken in any orientation, though they are usually acquired in the axial direction. Examples of each image type are shown in Figure 34. Most image sets take between 2 and 4 minutes, and the entire clinical procedure usually takes approximately 30 minutes. Each image type
can be used for image segmentation to create patient specific meshes, but careful use of specific image types yields faster and more effective results.

Figure 34: Standard bilateral clinical images are shown. T1W images (a) make fat appear bright while glandular tissue is dark and are used in DCE series. Pre contrast image series are subtracted from post contrast series to show areas of enhancement (b) and MIP images are 2D projections of the brightest pixels of the entire image stack (c). T2W images get high signal from watery tissue such as the cystic lesion in (d).

4.3.2 Tissue Segmentation

Tissue segmentation is done using the open source software, Nirview, freely available as a part of Nirfast, developed in collaboration with Kitware (Cliffton Park, NY). The software is based on the ITK/VTK platform and has many useful segmentation tools such as thresholding, morphological operations like erosion and dilation, hole filling, and automatic segmentation through k-means clustering. Additionally, it has filters
specific to MRI breast images such as bias field correction for low-frequency gradients, and skin and air separation for misclassification of those tissue types. A screenshot of the Nirview GUI is shown in Figure 35.

![Figure 35: A screenshot of the Nirview GUI is shown. A 3D view and axial, coronal, and sagittal view are available for segmentation and viewing. This software was developed for automatic and manual segmentation, source-detector placement, and mesh creation.](image)

Breast image sets are processed by first segmenting out the lesion and any suspicious tissue defined on MRI. The lesion is segmented using a k-means classification and Markov random field generation with 5 classes on a post contrast subtraction image. K-means classification is an iterative algorithm that groups data points by minimizing their distance to the center value of a cluster. The approach does more than thresholding, since it takes spatial coherence into account when used in coordination with the Markov algorithm and has been widely used in image processing (156). Depending on the enhancement kinetics, the lesion might appear brightest at the beginning or end of the series. The lesion is segmented from the brightest image stack, cleaned up so only the
mass is masked, and then saved. It is favorable to segment the lesion using a k-trans map, which collects information from all of the enhancement kinetics (157), but since not every clinical case gets this image set, this method can’t always be used.

Then, the healthy tissue is separated into adipose and glandular tissues using a k-means classification with 9 classes on the pre-contrast T1W image stack. The pre-contrast images must be used since they are the same size as the post contrast images that were used to segment the tumor. By using 9 classes for the 3 regions (air, fat, glandular), there is gradation at the transition between regions. The extra classes can be combined manually and this method is affected less by image noise. After the glandular and adipose tissues have been segmented, the tumor map is loaded and all the tissue types are saved, ready for mesh creation. An outline of the segmentation process is shown in Figure 36.

Figure 36: Segmentation workflow is shown starting from a subtraction image set (a) to segment the lesion (b,c). Then, a pre-contrast image (d) is used to segment the healthy tissue (e). Finally, the results are cropped and combined (f) and are ready for meshing.
After the segmentation process is complete, care must be taken to ensure that there are no holes in the masks and that there are no extra pixels outside the masks. A mask-based thresholding plugin can be used to remove disconnected pixels and an iterative hole filling algorithm can be used to fill in holes. Both of these issues cause problems when trying to model light propagation in subsequent steps but are easily avoided.

4.3.3 Source-Detector Placement

After tissue segmentation is complete, the sources and detectors must be placed. During set up for the patient exam, fiducial markers (vitamin E tablets) are placed on either side of the fibers arrays. These fiducial markers are easily located on the MR images and used as a landmark for optical fibers. In the parallel plate geometry, fibers slide against the faceplates and prevent any indentation in the skin. Therefore, 8 sources are equally spaced between the two pairs of fidicials. Since the faceplates are rigidly fixed, if the curvature of the breast prevents a fiber from falling onto the line between fiducial markers, the fiber must be dropped.

In the triangular geometry, there are three arrays of fibers. They leave indentations in the skin that can be seen on 3D projections, as shown in Figure 37. The center of each indentation is located in space using a 3D cursor and then on the corresponding coronal MRI slice to be placed. The process is repeated for all 16 fibers. Though the triangular geometry does a very good job of accommodating most breast shapes and sizes, it is possible that some fibers are unable to contact. In that case, there will be no indentation at the correct location and the fiber will be dropped. Nirview vastly improves on the issue of source-detector placement, giving an effective GUI tool for
placement and then streamlined mesh creation, a necessity for patient-specific mesh creation.

Figure 37: A fiber indentation is located using a 3D cursor on a 3D MRI projection (a) and the location is found on the corresponding coronal MRI slice (b). The source is placed at that location (c) and the process is repeated for all fibers.

4.3.4 Meshing

After source-detector placement, a meshing GUI is loaded in Nirfast and can be used to specify tetrahedron size and quality, surface triangle size and quality, sources to be loaded, and which type of mesh to create (145). The GUI, shown in Figure 38, gives the ability to refine certain regions to have higher node density, which can be useful when meshing small tumors. Depending on the tumor size, node spacing of 1mm is usually necessary to get a reasonable number of nodes in the region but that spacing is far too small for the whole breast volume.
Figure 38: The Nirfast mesh creation GUI allows users to load segmented label maps, source locations, specify node density, and create a 3D mesh. The GUI also allows different regions to be refined with smaller node spacing.

When meshing clinical cases for image reconstruction, the optimal number of nodes is somewhere between 40k and 60k nodes, trading off spatial resolution with computation time. While it is possible to reconstruct a mesh of 100k nodes, it does not greatly enhance the results since the glandular tissue structures do not usually require such detail and tumor regions can be refined to the necessary sizing. In one example shown in Figure 39, the same breast was meshed using node spacing of 1.5mm and 3mm, resulting in final meshes of 115k nodes and 16k nodes. These meshes are either too big or too small for effective image reconstruction. When meshed with 2mm node spacing, this breast generated a 52k node mesh, a more ideal size.
Figure 39: The same breast is meshed with node spacing of 1.5mm (a) and 3mm (b). These meshes result in 115k nodes and 16k nodes, too big and too small for optimal image reconstruction. This is an illustration of one of the more subtle issues of creating the proper mesh size for accurate forward modeling of light diffusion.

Mesh creation for FEM modeling of breast tissue is a challenging topic that the latest versions of Nirfast do a very good job addressing. Patient specific meshes require a robust mesh generator that is computationally efficient and produces high quality meshes for irregular shapes. Nirfast has developed into an effective platform for mesh creation from medical images.

4.4 Conclusions

This chapter describes how NIR light propagates through tissue, image reconstruction, and creating meshes from clinical MR images. Though scatter dominates light transport, clinically relevant tissue chromophores such as hemoglobin, oxygen saturation, water and fat content can be derived from absorption properties. Using the diffusion approximation to the radiative transport equation, it is possible to generate boundary data based on the optical properties of an FEM mesh. Comparing simulated
data from forward models allows for iterative solutions of the inverse problem, generating optical properties from boundary data. Using careful formulation of the Jacobian matrix, the sensitivity of the measurements to the optical properties, we are able to reconstruct multiple wavelengths of both frequency domain and continuous wave data simultaneously. This chapter also describes how spatial priors from the MR image stack can be used to guide the image reconstruction and turn the problem into optical spectroscopy where tissue types are defined ahead of time and then characterized based on optical data. This is advantageous because it improves the spatial resolution of the optics to that of MRI, reduces the number of unknowns in the inversion by several orders of magnitude, and simplifies interpretation of the optical image to the point where it might be useful as an adjunct to MRI.

Finally, this chapter reviews the usage of the software, Nirview, a part of Nirfast, developed in collaboration with Kitware. This software streamlines mesh creation from DICOM images through mesh creation and image reconstruction. After MRI images are loaded, tissue can be segmented using semi-automatic algorithms to sort tissue into adipose, glandular, and tumor regions. Sources and detectors are placed after tissue segmentation, co-registering the optical and the MR images. A patient specific mesh is created and data is submitted to a computing cluster for image reconstruction.
Chapter Five: Phantom Imaging

5.1 Introduction

Before an imaging technology can be transitioned into clinical use, packaging and standardization are required. Software must be robust and user-friendly and lead to only basic post processing (112,158). For example, x-ray computed tomography is calibrated based on phantoms and standardized to Houndsfield (or CT) units, then tested routinely for quality assurance (QA) (159–161). Reconstruction algorithms are automatic or push button and happen in nearly real time. Other widespread clinical modalities possess similar qualities. As multi-modality imaging techniques have become more widespread over the recent years with the adoption of PET-CT and PET-MRI, these steps become even more important as the complexity of the systems escalates. Data calibration is perhaps the most important issue for an emerging imaging technique to solve so that experiments are repeatable and consistent. Ideally, it should be based on a known, absolute, measurement and also take advantage of any multimodal synergy that potentially exists. In this study, a method for calibration of MRI-guided NIRS is presented that uses both spectral and spatial prior information to calibrate data versus a reference phantom.

5.1.1 Phantom Uses

Before image reconstruction in MRI-guided NIRS is possible, calibration must account for bias error, differences in coupling between fibers and tissue volume, model-data-mismatch, and differences in virtual source strength in the model and real laser power at the time of imaging. None of these things can be controlled perfectly and will
vary slightly between patient and phantom exams. After calibrating hardware using a previously published method (162), there was motivation to develop a new method for software calibration based on tissue phantoms and absolute measurements, commonly used to calibrate and validate imaging systems (163,164). To this end, we designed an algorithm that calibrates data in NIRS imaging with respect to a known, absolute reference phantom, takes advantage of patient specific geometry from MRI prior information, and generates an initial guess without the need for a large data set. This study contributes towards clinical translation of NIRS/MRI and hopes to eventually increase the specificity of clinical breast MRI. We present methods, characterization, and performance of a data calibration algorithm for a novel imaging system in phantoms and volunteers.

5.1.2 Agarose Phantom Techniques

Tissue phantoms can be easily made to simulate scattering and hemoglobin properties of breast tissue. Phantom properties can be precisely measured to be similar to literature values in breast. As a starting point, water, Agarose, 1% Intralipid, and 1% whole blood can be mixed to create a phantom with optical properties of approximately $\mu_a = 0.006$ and $\mu_s' = 0.9$. These phantoms can be made in a variety of shapes, with or without inclusions, in layers of varying properties, and can vary in absorption or scatter. Figure 40 shows several Agarose phantoms of different shapes and concentrations that can be used for testing system performance and reconstruction techniques.
Agarose phantoms in a variety of shapes and concentrations. Slab phantom (a) with inclusion (a) and cross section (b), triangular phantom (c), two concentrations of homogeneous slab phantoms (d, e), and parallel plate geometry breast phantom (f).

Agarose phantoms have significant advantages over gelatin-based phantoms. Since Intralipid interferes with the gelling process in gelatin phantoms, titanium dioxide must be used to create scattering. However, TiO$_2$ is a solid, and it can settle to the bottom of the phantom and cause uneven scattering distribution. Agarose phantoms use Intralipid and are able to gel with even scatter distribution. Also, Agarose phantoms are much easier to handle, as they are not as fragile as gelatin. These phantoms should be imaged on the same day they are made as they change color within 24 hours and would have unknown optical properties. As a result, they cannot be used to test system performance over time or for daily calibration but are currently the best substitute for hemoglobin concentrations in breast tissues. A more thorough recipe for Agarose tissue phantoms can be found in the appendices.
5.2 Absolute Phantom Calibration

5.2.1 Characterization of Reference Phantom

After data is collected, it is calibrated in two steps. Data is first calibrated to adjust for the difference in detector gain settings and differences between individual detectors as outlined in previous work (162). This step ensures that all data has been adjusted such that each source-detector is equivalent. However, since we require coupling optical fibers with the breast tissue, there is error introduced by differences in fiber coupling. Before iterative reconstruction, a second step of calibration must remove these errors, fit the data to the model, and generate an initial guess. We account for this form of error by imaging a homogeneous reference phantom prior to patient imaging as described previously (164,165). Briefly, these methods fit a first-order approximation to the log of the intensity times the source-detector distance (or simply phase) vs. the source-detector distance (Figure 41). According to both model and experiment, data presented this way are linear (163). The slopes of these lines are equal to the attenuation coefficient (\(\mu_a\)) or the reduced scattering coefficient (\(\mu_s'\)) at a particular wavelength. In a geometry with many source detector distances and data points, this is a robust way to calibrate data to the model and remove the uncertainty between source strengths fiber couplings. Unfortunately, this method can smooth the data, reduce image contrast, and tends to break down when the number of data points is severely limited (122). Therefore, we were motivated to develop a method to calibrate data points absolutely rather than versus their \(\ln(rI)\) vs. pathlength slope.
Figure 41: Amplitude (a) and phase (b) data from a healthy volunteer. The natural log of source-detector distance times intensity is linearly decreasing with source-detector distance with the slope being $\mu_a$ at that wavelength. Similarly, the slope of phase vs. source-detector distance is $\mu_s$.

5.2.2 Direct Calibration of Data

Photon fluence can be calculated as a function of depth analytically for simple shapes but not for the complex ones characteristic of patient-specific breast meshes (166,167). Rather than calculate photon fluence directly, we use a surrogate, the difference between the diffusion model and measured data on a known reference phantom.

The complete method is explained in Figure 42 with three steps: Assigning the optical properties of the homogeneous reference phantom, calibrating the measured data, and generating the initial guess for reconstruction. The properties of the reference phantom must be measured or supplied, and once they are assigned, they can be used in future experiments. Since we must measure the reference phantom during each patient exam, we calculate the properties using the slope-dependent calibration method. In this case, the slope-dependent method is a very good approximation of the true properties.
Figure 42: A flowchart outlines the main parts of the absolute calibration algorithm. Optical properties of the reference phantom are assigned and data is calibrated versus a diffusion model. Bulk estimates of $\mu_a$ and $\mu_s'$ at each measured wavelength are generated and a spectral reconstruction is used to calculate an initial guess.

Patient data ($d_p$) is calibrated absolutely with respect to measured data on the homogeneous reference phantom ($d_r$) and simulated data from a tetrahedral finite element mesh of the phantom with correct optical properties ($f_r$). Amplitude and phase data ($d_c$) are calibrated by

$$d_{c\text{-amp}} = \frac{\log(f_r)}{\log(d_r)} \log(d_m)$$ \hspace{1cm} 20

$$d_{c\text{-phase}} = (f_r - d_r) + d_m.$$ \hspace{1cm} 21

This corrects for errors in fiber coupling that are present in the data acquired from the reference phantom and patient as well as fitting all the data to the model in one step. Maximum image contrast is preserved because there is no averaging for difference over sources. Instead, each data point is calibrated absolutely versus the difference between the reference and the model. More importantly, the absolute method is effective when the number of data points is limited.
5.2.3 Single Wavelength Reconstructions

Next, the initial guess for reconstruction must be generated. Previous studies have found that wavelength-by-wavelength calibration methods are more robust for calibration than multi-wavelength methods (78). Similarly to the slope-calibration method, we obtain $\mu_a$ and $\mu_s'$ at each wavelength and then fit them to the main absorbers’ extinction coefficients. Rather than using the slope of the data, we elect to use single-region reconstructions at each wavelength. This method fits the data to the model iteratively, is independent of source strength, and can be used with only a handful of data points. The drawback is that these reconstructions also require an initial guess. However, since they are only calculating $\mu_a$ and $\mu_s'$ in one region, they are much less sensitive than the initial guess of multi-region spectral problems (97).

The robustness of this calibration method was tested in two separate experiments. The first was designed to test how sensitive the simulated data is with incorrect optical properties assigned to the reference phantom. The initial optical properties of a phantom simulating mesh were set to $\mu_a=0.01$ and $\mu_s'=1.0$ and data was simulated. The mesh’s optical properties were changed from -100% to +100% and data was simulated at each set. This data was used to calibrate a reference case and compared with the calibrated data from the correct optical properties assignment. Error was considered to be the difference between the two data sets. As expected, as the optical properties stray from the true values, the error increases. Perturbing the assigned optical properties by 10% could cause error in simulated data to increase by an order of magnitude or more. These results are presented in Figure 43 and it is extremely important to take care in assignment of reference phantom properties. If incorrect properties are assigned, there is error.
introduced due to the mismatch between the measured reference data and the simulated reference data. Extra care must be taken to ensure that the reference phantom’s optical properties are accurate by calculating properties based on multiple imaging systems.

Figure 43: Error maps of incorrect reference phantom optical property assignment (a) and incorrect initial guess for single wavelength reconstructions (b).

The second test was designed to see how robust the single-wavelength single-region reconstructions are with a changing initial guess. Again, the initial optical properties of a phantom simulating mesh were set to $\mu_a=0.01$ and $\mu_s'=1.0$ and data was simulated. The mesh’s optical properties were changed from -100% to +100% and data was simulated at each set. Then, the error was calculated to be the difference between the two data sets, equivalent to the first step of the reconstruction. Within these bounds the reconstructions all converged to the same results. This test tells us that the single-wavelength reconstructions are largely unaffected by initial guess with regard to calculating a single-region $\mu_a$ and $\mu_s'$ value.
Finally, the data is fed into a single-region, multi-wavelength spectral reconstruction to apply the spectral constraints that are present in the full image reconstruction. This is desirable because it means that the initial guess will be closer to the final values and minimizes the chances of the optimization falling into a local minimum (168).

5.2.4 Phantom Reconstruction Results

We tested the calibration scheme versus the slope-dependent method on a phantom with known optical properties both for initial guess prior to full reconstruction and final reconstructed result. Phantoms were made from Phosphate Buffered Saline (PBS), type I Agarose, 1% Intralipid, and whole porcine blood to match the optical properties of normal breast tissue (169). In addition to a homogeneous reference phantom, an inclusion phantom was made with a cylindrical inclusion with 1.5x hemoglobin contrast and 0.5ml gadolinium MR contrast.
Figure 44. Chromophore concentrations in phantom dataset after hard prior multi-region reconstruction using direct calibration (red) and slope calibration (blue). The two regions are Background and Inclusion. Panels show total hemoglobin, oxygen saturation, water, scatter amplitude, and scatter power. Chromophores and scatter vary between regions but not within.

After reconstruction, it is clear that the direct method does a better job of preserving contrast in the dataset. Images from direct calibration show 1.39x contrast in HbT vs. 0.91x for the slope calibration and 1.5x for the expected contrast. All other chromophore concentrations are comparable between the two methods and are close to what we expected. Figure 44 compares the final results of the two methods while Figure 45 shows quantitative images based on the direct calibration method. The slope calibration gives a more accurate initial guess than the direct calibration in this example, but data contrast is preserved during direct calibration, producing a more accurate image reconstruction. Since this was a phantom image, data from several pathlengths was available with good SNR. In a typical patient case where the pathlengths are larger and the light attenuation is greater, we would expect the direct calibration to perform as well or better than the slope calibration.
Figure 45: Phantom images from direct calibration reconstruction within 10% of actual value and recovered contrast. A maximum intensity projection image and the recovered optical solution of total hemoglobin are fused. Quantitative coronal images taken from the reconstructed 3D phantom volume show total hemoglobin, oxygen saturation, water fraction, scatter amplitude and scatter power.

This method of calibration allows for more accurate quantification of total hemoglobin, oxygen saturation, water content, scattering, and lipid concentration as compared with other, slope-based methods. Direct calibration is advantageous because it is with respect to an absolute reference phantom rather than other data points from the same experiment. This means that small numbers of data points can be accurately calibrated and that the geometry of the imaging domain is taken into account during calibration.
5.3 Multi-Level Phantom Experiment

5.3.1 Experimental Design

After completion of the adjustable, multi-planar fiber array presented in Chapter 3, we performed a phantom experiment to test the device using an Agarose tissue phantom. This phantom was made from Phosphate Buffered Saline (PBS), type 1 Agarose, 1% Intralipid, and whole porcine blood to match the optical properties of normal breast tissue (169). One phantom had a background hemoglobin concentration of 15 µM, and a 20mm diameter cylindrical inclusion with 3x hemoglobin (60µM) contrast and gadolinium MR contrast agent for localization. The phantom’s total height was approximately 50mm with the inclusion descending the top 30mm. The other phantom was homogeneous with the same background concentration for calibration purposes.

The inclusion phantom was measured at four different coronal planes: 18mm, 24mm, 33mm, and 41mm using six FD wavelengths. The exact location of the optical fibers with respect to the inclusion was determined using coronal MR images as a reference. The lowest two levels were not in the plane of the inclusion while the upper two were. Data was processed and reconstructed using each plane individually as well as with all four planes combined. This allowed us to simulate the effect of having additional sources and detectors through the moveable parallel plate interface. We measured the homogeneous phantom at one level to use for data calibration.

5.3.2 Results and Discussion

These data were processed and reconstructed using Nirfast with a three-dimensional finite element mesh consisting of 34211 nodes. Four planes of data were collected and processed using a region-based hard priors approach. Contrast was recorded
from each of the four different imaging levels shown on the axial MR image in Figure 46 as well as all of the data together. Absolute optical images of reconstructed HbT are also shown for data set in Figure 46 and quantified in Table 1. Though recovered contrast does not reach the true value of 3:1, the dataset with all the planes combined yields image contrast of 2.08:1 with nearly correct inclusion values. The lowest plane has an expectedly low contrast of 1.04:1 and all recovered contrasts are near expected values.

Figure 46: Phantoms used (a,b) in experiment showing contrast recovery. Axial MR image of inclusion phantom (c) with locations of 4 imaging planes shown and text reporting imaging plane distance from bottom of phantom. 3D representation (d) of reconstruction using all 4 data sets simultaneously, and slices (e) through the inclusion after being reconstructed by individual data sets.

<table>
<thead>
<tr>
<th></th>
<th>18mm</th>
<th>24mm</th>
<th>33mm</th>
<th>41mm</th>
<th>All Planes</th>
<th>Truth</th>
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<tbody>
<tr>
<td>Background</td>
<td>21.4</td>
<td>22.8</td>
<td>19.8</td>
<td>18.5</td>
<td>22.6</td>
<td>15.0</td>
</tr>
<tr>
<td>Inclusion</td>
<td>22.3</td>
<td>26.8</td>
<td>40.7</td>
<td>27.8</td>
<td>47.0</td>
<td>45.0</td>
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<tr>
<td>Contrast</td>
<td>1.04</td>
<td>1.18</td>
<td>2.05</td>
<td>1.50</td>
<td>2.08</td>
<td>3.0</td>
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</table>
In this experiment, we examined contrast recovery at different planes within a regular volume. As expected, the combined dataset came closest to recovery of the true phantom properties (2.08 vs. 3.00) because the additional data create a less ill-posed problem and allow a more accurate reconstruction. The lowest plane is actually homogeneous. It saw little contrast, as only a small portion of the photon path, which is narrow at the source and detector and spreads to roughly 20% of the path length in the middle (170,171), went through the inclusion. The actual contrast recovered was never perfect, likely because the only parameter that varied was blood concentration. Complete contrast recovery is a known problem in diffuse optical tomography (155) that makes contrast imaging more attractive (122). When looking at HbT values, any crosstalk with other chromophores would decrease the recovered HbT contrast, because it was the only chromophore in the phantom with varying concentration. Water crosstalk also could be an important factor in this experiment because Agarose phantoms have approximately double the water content of breast tissue and our ability to recover water was limited by the PMTs’ sensitivity to wavelengths above 850nm. It has been shown that longer wavelengths can improve water quantification (153,169) and that led to the addition of longer wavelengths in this system. These reconstructed volumes from one plane of data through the moveable breast MR interface are comparable to past results. As predicted in previous studies (76,97,172), the combined dataset yields the most accurate quantification due to the larger size and more complete sampling of the volume.

While these results are encouraging for phantom imaging, they come at a cost that could complicate their use in patient imaging. The extra planes extend the length of the patient exam by approximately 15 minutes per plane. Even by carrying PMT gain settings
from one plane to the next, after moving the device, there may only be time for two planes during a typical MRI exam. Additionally, the main drawback to the parallel plate interface is its inability to image women with small breasts. Imaging at multiple planes is essentially only possible in women with D-cup sized breasts, further limiting its practical use. In our experience with patient imaging, we found it most important to be able to image all breast sizes, thoroughly discussed in Chapter 6.

5.4 Phantom Imaging Above 900nm

5.4.1 Experimental Design

This phantom experiment was to test the system’s ability to recover blood concentration using 6 FD wavelengths versus 6 FD and 3 CW wavelengths. The phantoms were made from Phosphate Buffered Saline (PBS), type 1 Agarose, 1% Intralipid, and whole porcine blood to be on the higher end of normal breast tissue hemoglobin concentration of 25 µM. As with the previous experiment, one phantom had a 20mm diameter cylindrical inclusion. It had 1.5x hemoglobin (37.5µM) contrast to mimic typical malignant tissue contrast (173) and gadolinium MR contrast agent for localization. The other phantom was homogeneous with the same background concentration for calibration purposes.

The inclusion phantom was measured at one plane using six FD wavelengths and 3 CW wavelengths. The optical data and MR images were coregistered using fiducial markers in the plane of the fibers and the MR as a reference. The imaging plane was chosen to intersect the inclusion. After imaging the inclusion phantom, the homogeneous phantom was also imaging using nine wavelengths. Data was processed and
reconstructed using PMT data only and then using PMT/PD combined data. The same homogeneous mesh and anomaly meshes were used for both reconstructions.

5.4.2 Results and Discussion

These data were processed and reconstructed using NIRFAST and a 3D FEM mesh. We used a region-based hard priors method to reconstruct data from 6 FD wavelengths as measured by PMTs. Then, using the same meshes and FD data, we added 3 CW wavelengths above 900nm, measured by the new PD detectors. Image contrast was recorded from each reconstruction type, with the results displayed in Figure 47 along with the true values estimated based on literature and previous results (174,175). In the FD only case, we were able to recover contrast to within 5% of the true value, obtaining 1.47x. The FD/CW case performed equally well, recovering 1.52x, but taking three minutes longer for data collection (15min vs. 12min). The combined approach was more successful in recovering the absolute absorber concentrations than the FD only approach, 2% vs. 16% respectively. The FD/CW dataset also yielded a more accurate estimation of water contrast and scattering parameters then the FD only dataset, as well as recovering lipid concentrations.
Figure 47: Phantom results for 6 FD wavelengths (top row) vs. 6 FD/3CW wavelengths (middle row). The true values are shown (bottom row). Parameters recovered (from left to right) were total hemoglobin, oxygen saturation, water content, scatter amplitude, and scatter power. Lipid content was reconstructed in the 6FD/3CW case but is not shown. In both cases, HbT contrast was recovered within 5%, though the 9-wavelength set was closer to the actual values.

Based on these results, we are confident in the new system’s ability to recover contrast using 9 wavelengths of combined FD and CW data. While the results are comparable from a contrast standpoint, we found that the FD/CW data set and combined reconstruction yielded more accurate absolute values in HbT, water, and lipid concentrations, making it more reliable for patient imaging and worth the extra three minutes of exam time. We see full contrast recovery since the contrast is relatively low compared with the previous experiment. Unfortunately, we don’t expect the system to perform this well in human imaging. Though we used a higher absorbing background
than we expect to see, these phantoms are not nearly as complicated as human tissue. They have contrast in only HbT, are entirely oxygenated, have no lipid content, and no variation in scatter. The regions are regular and continuous, and light levels are high throughout. However, phantom imaging is the best test that an imaging system can undergo before human imaging. In this case, the system is capable of accurate HbT contrast recovery through combined data collection and image reconstruction.

5.5 Triangular Breast Geometry

5.5.1 Experimental Design

The purpose of this phantom experiment was to validate the effectiveness of the triangular geometry and the 9 wavelength combined system over a variety of absorber concentrations. Two Agarose phantoms were made in the triangular geometry with properties mimicking breast tissue. One phantom had a 2 cm cylindrical hollow inclusion that could have varied optical properties and the other was homogeneous. The background of the phantom was measured to be 15μM and had 1% Intralipid. During the experiment, the inclusion was filled with varying concentrations of blood from 0 to 45μM in 5μM increments in order to vary the absorption systematically. After each concentration, the phantom was imaged with all nine wavelengths. We used the 15μM concentration as a homogeneous calibration data set.

Images were reconstructed using hard priors and both FD and CW data simultaneously. Optical data was coregistered into MR image space using fiducial markers and making a phantom specific mesh. The sources and detectors were placed in 3D space in the triangular geometry.
5.5.2 Results and Discussion

After imaging the phantoms with the FD/CW system at concentrations ranging from 0μM to 45μM in 5μM increments, all concentrations were reconstructed using the 15μM as a homogeneous calibration data set. Hemoglobin recovery in the background was 25μM compared to the actual 15μM concentration. The background values were very stable across concentrations, with the norm of the residuals being 0.0054. These results are shown in Figure 48. Recovered HbT values from the inclusion showed a linear increase (norm of the residuals 0.0066) with an average recovery of 71% of the true blood concentration. While the system displayed very good linearity, it was unfortunately not perfect in recovery of absolute concentrations. The background was repeatedly overestimated in each concentration and likely contributed to the underestimation of the inclusion concentration. This could have been caused by an error in making the phantom but is more likely to be crosstalk between absorption and scatter. Even in the case where there is no blood in the inclusion, it is reconstructed to have 0.73x the background concentration.

Figure 48: Reconstruction values on a gelatin phantom with 2 cm inclusion. The
inclusion was filled with varying concentrations of blood. MRI images of the phantom are shown with the 2 cm inclusion overlaid. Graphs show the reconstruction as a function of true total hemoglobin values for total hemoglobin, oxygen saturation, water, lipids, scatter power, and scatter amplitude. Blue circles are for the background, while red circles are for the inclusion. Modified from El-Ghussein et al (77).

The other chromophores are very stable across all concentrations with near perfect agreement between background and inclusion. We also see that these values reconstruct with accurate absolute values. The blood is nearly 100% oxygenated, water content is 75%, lipid content is nearly 0%, and scattering parameters are nearly constant. It is worth noting that scatter amplitude increases slightly with increasing hemoglobin concentrations, taking away from HbT contrast (122,155). The hybrid system was validated using Agarose phantom experiments that were able to track the linear increase of blood inside a 2-cm inclusion in a pentagonal phantom that is specific to our clinical NIR-MRI breast coil. This experiment validates the system’s ability to recover hemoglobin contrast from a local absorber in the triangular geometry.

5.6 Conclusions

Calibration phantoms are used to account for bias error, differences in coupling between fibers and tissue volume, model-data-mismatch, and differences in virtual source strength in the model and real laser power at the time of imaging. This chapter focuses on a method to calibrate NIRS data with respect to a known, absolute reference phantom, takes advantage of patient specific geometry from MRI prior information, and generates an initial guess without the need for a large data set. We present results from three
separate phantom experiments. A parallel plate geometry phantom is measured at four different coronal planes and the phantom volume is reconstructed at all four planes individually as well as with the combination. This experiment showed that imaging accuracy falls off as a function of distance from the target absorber and that more measurements lead to the most accurate sampling of the volume. In second experiment, a parallel plate phantom is used to investigate the effects of an additional three lasers operating in continuous wave mode. Both the 6 wavelength FD and the 9 wavelength FD/CW measurements were able to recover HbT contrast within 5% of the expected value. The FD/CW case was also able to improve the background optical properties within 2% of the expected values. Finally, a concentration phantom in the triangular geometry validated the hybrid FD/CW system in a new patient imaging geometry. Contrast recovery was linear over a wide range of HbT concentrations but absolute recovery and full contrast recovery were hindered by crosstalk with scattering parameters. These studies illustrate many uses of phantom imaging and prepared the researchers with a starting point before patient imaging.
Chapter Six: Healthy Volunteers

6.1 Introduction

Since phantoms can only provide an approximate representation of the optical and material properties of living tissue, it is important for emerging imaging techniques to utilize healthy volunteers for complete performance characteristics. Healthy volunteers can be used to gain understanding of normal tissue properties before imaging abnormal or malignant tissue, and to test imaging systems and algorithms. Phantoms are made with tightly controlled and known properties, shapes, and sizes, making them ideal for testing algorithms and system performance versus a regular standard. The best phantoms today are able to mimic total hemoglobin content and scattering properties of breast tissue but are unrealistic in oxygen saturation, fat, and water contents, as well as material properties. Therefore, to get a complete picture of all imaged chromophores and material properties, it is necessary to image real breast tissue. The main drawback of imaging healthy volunteers that the true optical properties before reconstruction cannot be recovered and results must simply be compared against the literature. However, coupling healthy volunteer studies with phantom imaging studies can give a complete assessment of an imaging technique.

Here, data from healthy volunteers are used for several different purposes. Extensive testing of the parallel plate interface for mobility and in coupling with the spectrometer-based fluorescence tomography system designed by Davis et al. was performed (79). A group of eight healthy volunteers shows improvement in patient positioning and imaging in MRI/NIRS using the triangular optical fiber interface in breast
cup sizes A and B as well as C and D. They demonstrate fiber coupling over all breast cup sizes and normal parenchymal heterogeneity (176). Finally, three healthy volunteers were used to test the NIRS/MRI system after it was shipped to Xi’an, China, assembled, and calibrated. These volunteers confirmed normal operation of the system and gave Dr. Junqing Xu and Dr. Wang Ke time to practice positioning the optical fibers against breast tissue in the MRI. All of the volunteers presented here were used in conjunction with phantom imaging for testing prior to abnormal subject imaging and are organized based on what part of the system they were used to evaluate.

Our imaging protocol for human subject examination was approved by the Committee for the Protection of Human Subjects at Dartmouth-Hitchcock Medical Center and at Xijing Hospital. Written consent was obtained during which the nature of the procedure was fully explained to each volunteer. Subjects were positioned into the triangular breast interface while prone on the MR exam table by bringing the fiber optic cables into contact with the breast. In cases of smaller breast sizes, all fibers were not in contact with the skin surface because of curvature, and data from these channels was not used during image reconstruction. The interface involves mild compression as is standard in MR biopsy plates to maintain patient comfort during the imaging procedure. Co-registration between optical and MR images was accomplished through MR fiducial markers placed in the plane of each set of fibers, and MR images were acquired with the slice-direction in the axial geometry. NIRS and MR data were collected concurrently with data acquisition requiring 15 and 30 minutes, respectively. Because the data collection from the two imaging modalities do not interfere with each other, optical data was typically collected twice per subject as time permitted.
6.2 Nine-Wavelength Spectrometer System

After phantom testing, the parallel plate interface was tested using several healthy volunteers for the ability to move via remote control as well as the ability to couple fibers from both the NIRS/MRI system and the spectrometer system outlined in (79). This system is based on an array of 16 spectrometers and can be used to detect multiple CW wavelengths at once or fluorescence data spanning multiple wavelengths. After collection, spectrometer data must be spectrally unmixed to get each wavelengths’ contribution to the peak (177).

During the testing, the interface was moved through its range with each person but since there were no abnormalities in the breast, we tested the interface only to a functional degree and reserved actually targeting a lesion for the cancer patient reported in Chapter 3.

We also used these healthy volunteers to develop methods for coupling the two MRI guided imaging systems in the parallel plate fiber interface. We used this scheme to image a total of 9 healthy volunteers and collected 6 wavelengths of FD data, 3 wavelengths of CW data, and fluorescence data in emission and excitation mode. Absorption images from three representative healthy subjects are shown in Figure 49. Fibers were positioned near the top of the interface’s range to ensure contact of all fibers and all data was collected in approximately 30 minutes.
Figure 49: Illustrative example of healthy volunteer exam results using parallel plate interface with two sets of fibers. Coronal MR in plane of optical imaging. Optical solutions for HbT, water, oxygen saturation, scatter amplitude, and scatter power are shown based on reconstructions of 9 wavelengths.

Testing the parallel plate interface using these healthy volunteers showed that it was difficult to achieve good fiber contact with small or dense breasts. In the case of small breasts, it was not possible to get the fibers close enough to the chest wall to image. Furthermore, if the breast was dense, it was difficult to compress the tissue against the fiber plates used in the interface. Though nine healthy volunteers were imaged using this scheme, breast density and/or size necessitated that many cases were thrown out. These three cases all displayed similar trends, with higher HbT in the glandular tissue than the adipose, high oxygen saturation in both tissues, and more water and scattering content in
the glandular tissues. The values fall within the range of reported values in the literature and confirmed that this combined system was capable of imaging human breast tissue in the MRI (49,54,178).

Though the ability to reposition fibers remotely to target suspicious lesions is very attractive, it is quite difficult in reality. It requires a large breast that can be compressed against the fiber faceplates. This interface was also used to image two cancer patients successfully, presented in Chapters 3 and 4. Due to the restrictions on breast size and density, future research looked to develop an interface that accommodated a larger size and elasticity range. This group of healthy volunteers was critical in the assessment of the parallel plate interface and eventually led to the development of a new patient interface rather than a clinical trial with potentially disappointing results due to patient exclusion.

### 6.3 Triangular Interface Testing

The triangular NIRS interface was designed to accommodate multiple breast sizes and composition, while also providing optical coverage of the entire region of interest, addressing the needs illustrated in the previous iteration of the design. This version hoped to minimize geometrical distortions of the breast being scanned as well as preserve the shape of the contralateral breast to maintain MR image quality. It demonstrated that robust fiber contact occurs with breasts of all cup sizes during simultaneous MR and NIRS breast exams involving healthy volunteers using a typical V-shaped clinical breast coil.

As far as tissue elasticity goes, the healthy breast is very similar a diseased breast. They give the most realistic physiological chromophore values and are the definitive test
for new instrumentation. This group of healthy volunteers was critical to assess the performance of the triangular breast interface before leaving for Xi’an. Several generations of the interface were tested in one volunteer during its development and the final prototype was used to image eight women in the MRI. The interface was able to recover optical images successfully from each volunteer despite the widely varying breast size, shape, density, and composition. Breast density was characterized based on MRI images by a radiologist experienced in breast MRI and mammography. Imaging procedures on were performed on three A-, two B-, two C-, and one D-cup sized breasts. The distribution of breast sizes and densities is shown in Figure 50. In the smaller and more difficult to access breasts (A,B-cups), the interface was typically extended as high as it can traverse and in as small of a diameter as it can maintain. When imaging the larger breast cup sizes (C,D), fibers were centered on the breast coronally since the curvature was larger and easier to accommodate. Fibers were positioned such that they would likely be sensitive to all but the most posterior or anterior lesions but actual measurement sensitivity needed confirmation from cancer patients in future studies.
Figure 50: Bilateral axial images of all healthy volunteers imaged in this study arranged by cup size. The NIRS/MRI breast coil was able to accommodate all sizes, densities, and compositions in the group.

Figure 51 shows a combined image set from both C-cup volunteers, one of dense composition and the other of fatty composition. In both cases, all 16 fibers were able to contact the breast. Optical images are overlaid on the corresponding axial MRI slice and color-coded specific to the NIRS chromophore being represented. In each case, the adipose region is transparent, but the color bar approximately represents its value.

Figure 51: Images from two C-cup sized volunteers of total hemoglobin, blood oxygenation, water and lipid fraction, scatter amplitude and scatter power along with their current craniocaudal and mediolateral oblique mammograms.

Finally, volunteers were grouped by MR breast density. Figure 52 shows data when subjects were grouped as either dense or not dense, as defined by a radiologist experienced in breast MRI. In both groups, total hemoglobin was higher in the glandular
region compared to adipose with the difference being statistically significant ($p = 0.0412$) in the dense group. No noticeable trends in oxygen saturation were found between tissue types or between groups, each being near 80% oxygenated. The water content was higher in the glandular regions in both groups, and higher in the dense group relative to the not-dense group, but not to a statistically significant level. The lipid content of adipose tissue was higher than glandular tissue in both groups. The dense group had lower lipid content in the adipose tissue than then not-dense group with statistical significance ($p = 0.015$). These results are promising as the fiber interface enabled the acquisition of NIRS images consistently across all breast sizes with physiologically reasonable responses.
Figure 52: Data from all subjects grouped by MR breast density (4 subjects per group).
Glandular tissue shows higher hemoglobin levels than adipose tissue while not-dense breasts show higher lipid levels than dense breasts with statistical significance (p<0.05).

Since the primary benefit of the design was accommodation of variable breast sizes, the interface was tested on women with breasts representing some of the natural heterogeneity, shape, and size that would be expected in clinical practice. Specifically, eight healthy volunteers with cup sizes of A through D and fatty and dense parenchymal compositions were examined successfully. All subjects were quickly positioned (less than 5 minutes) and did not report discomfort due to the procedure. The triangular interface performed extremely well in the small cup sizes, allowing imaging of both A and B cup breasts for the first time with almost all fibers in contact. In larger breasts, the interface performed equally well. It was possible to target the entire breast, which is important for localizing suspicious regions in the diagnostic work-up of a typical MRI patient. Finally, the interface provided unprecedented access to the axillary region and upper outer quadrant of all breast sizes, which is a common lesion location (7). Based on examining this group of healthy volunteers, the triangular interface could provide complete coverage and accurate targeting of lesions in all breast sizes.

When compared to results from studies of other healthy volunteers in both MR and non-MR guided NIRS systems, the chromophore quantification is physiologically reasonable and comparable (126,180–182). In this cohort of eight subjects, oxygen saturation fell between 75% and 95% for all tissue types and categories. The system also estimated average water, lipid, and hemoglobin concentrations to within normal physiological limits for each tissue type, illustrating the capability of the NIRS/MRI
breast coil. In previous work (95, 173), relative hemoglobin concentration has been shown to be an indicator of tissue malignancy and we are optimistic about future patient studies using the new breast imaging interface.

The absolute values of our tissue components occur within physiological limits, but were not as robust as the relative quantification, as is commonly reported for other imaging modalities (122). The variation in our images could stem from factors other than the natural variation between subjects. For example, our current system provides fairly low spectral resolution with only nine wavelengths, making it susceptible to noise in the data from instrumentation or variations in fiber coupling which creates crosstalk between chromophore estimates (116). Furthermore, with only six wavelengths of frequency domain data, co-dependencies in the absorption and scattering information is probable (183). Finally, effects from partial volume averaging are likely to occur in these healthy volunteers, because even with anatomical priors, pure separation of absorption and scattering is difficult due to the blended sensitivity profiles across tissue types. As a result, we may see water and lipid content distorted in the adipose region relative to its glandular counterpart (184).

One of the major challenges in combining NIRS with MRI has been source-detector coupling to the breast within the confines of the MR bore. This influences the breast sizes and densities that can be imaged, and partially determines whether NIRS is a useful addition to MRI. Though volunteers are typically discussed less, they are essential to validation of new techniques and are the most rigorous test before patient imaging. In this work, the design and evaluation of a triangular optical fiber interface integrated with a standard clinical MRI breast coil was shown to improve patient positioning and
imaging in MRI/NIRS, especially in terms of simultaneous MRI and NIRS imaging of breast cup sizes A and B as well as C and D. Fiber coupling was demonstrated over all breast cup sizes and normal parenchymal heterogeneity found in a group of eight healthy volunteers.

6.4 Volunteers in Xi’an

6.4.1 Methods

After arriving in Xi’an and assembling the system, a series of tests on the system were performed to verify that it was working properly after transport. It was calibrated and used to image several phantoms in the MRI. Due to the new arrangements in the hospital, three healthy volunteers were also imaged. These volunteers gave the researchers practice setting up the system in the new location, gave Dr. Xu a chance to practice positioning the fibers against the breast tissue, and give the instrumentation a final, definitive test before imaging cancer patients. This included the optical imaging system, MRI breast coil with integrated optical fibers, and MR image acquisition with fibers in place.

Since there was no lesion, MRI contrast agent was not injected. However all of the MR sequences were used as if there was to simulate realistic imaging time for cancer patients. A complete list of the MR sequences can be found in Chapter 8. During the 30 minutes of MR scan time, two optical scans of 9 wavelengths were acquired. After the exams, volunteers commented on whether there was anything uncomfortable about the procedure or concerns to be aware of before imaging cancer patients.

6.4.2 Results and Discussion
Volunteers first underwent informed written consent process (modified for healthy volunteers) and were typically completed within 10 minutes. The NIRS/MRI system and MR bed were set up with no difficulties during this time. Dr. Xu prepared the patient for imaging while Dr. Jiang ensured that the fibers were positioned correctly. This process took 15 minutes per subject, though as Dr. Xu became more familiar with the NIRS/MRI breast coil, this time could be reduced. Then, optical data and MRI data were collected simultaneously within 30 minutes. Each volunteer took approximately one hour to consent and image with optics and MRI.

After the scans, improvements to the fiber interface that would make it easier for Dr. Xu to position the fibers and any changes in the procedure that needed to be made were discussed. Results from the three volunteers are shown in Figure 53 and confirmed that the system was working properly through volunteers in addition to phantom images. They served as the first in-human test of the combined NIRS/MRI breast coil designed for use in Xi’an and familiarized Dr. Xu with the fiber positioning process.

Figure 53: Healthy volunteer images collected in Xi’an prior to imaging cancer patients.
This group of volunteers (cup sizes B, C, and C) served to test the optical MRI breast coil designed in Xi’an and give the clinical team practice setting up the fibers for imaging.

Fibers were positioned within 15 minutes for these subjects and all three had contact with 16 out of 16 fibers. These subjects had breast cup sizes of B, C, and C. Perfect contact was achieved and we hoped for more efficient positioning in future exams. After data collection, meshes were made specifically for each person based on T1W MRI images (shown in Figure 53). Reconstructions were done using the methods outlined in Chapter 7 with fixed regularization and hard-priors formulation. Since these were healthy volunteers, two regions were used: adipose and fibroglandular. Each volunteer displays higher hemoglobin in the glandular region than the adipose region with oxygen saturation for both regions between 50 and 90%. They displayed higher lipid content in the adipose region than the glandular region except for one case, where they were nearly equal. None of the cases showed any water contrast between regions, but this is likely due to crosstalk between lipids and scattering. The prominent spectral features of the water and lipid absorption spectrum fall onto the highest measured wavelengths and likely mingle. Similarly, those three wavelengths are reconstructed in CW mode and their scatter could be estimated incorrectly at those wavelengths. The scatter values were reconstructed higher in the glandular for scatter amplitude, nearly constant for scatter power, and consistent with the literature. Also, as in the previous study, it is likely that there was partial-volume averaging between regions as is common in diffuse optical imaging.

6.5 Conclusions

This chapter outlines the importance of healthy volunteers and gives examples of
how they were used in three different settings. A cohort of nine volunteers tested the remotely controlled parallel plate fiber interface and found that the interface was able to remotely target breast lesions found on the MRI. However, fiber contact was limited to the largest and least dense breast tissue, potentially outweighing the benefits and prompting the design of a fiber holder that could accommodate more breast cup sizes and tissue compositions. Positioning issues necessitated exclusion of data from all but three cases in cup sizes A and B and in dense breasts that couldn’t be adequately compressed.

Next, results are presented from a more complete study of eight healthy volunteers using the newly developed triangular breast interface. This interface was able to image breasts of every cup size and the full range of natural tissue heterogeneity. Fibers were positioned closer to the chest wall as well as more posterior in the axillary region than in previous fiber arrangements. The data from these volunteers were reconstructed into images that were consistent with the literature and helped to prepare for imaging cancer patients using this geometry. The study concluded that the triangular geometry was an improvement to combined MRI/NIRS imaging in terms of coverage and performance.

Finally, a small group of three volunteers helped prepare for imaging cancer patients at the new site in Xi’an, China. These volunteers verified that instrumentation was functional after transit and that the newly constructed NIRS/MRI breast coil would be able to perform NIRS/MRI imaging. Finally, it gave the clinical team practice using the interface and positioning the fibers against specific locations on the breast tissue before moving forward to cancer patients. Based on these three volunteers (and phantom images), we concluded that the system was working properly after shipment and that we
were ready to scan abnormal subjects as part of the study. Though healthy volunteers are not frequently discussed in the literature, they are critical for the validation of new techniques and are the most realistic test that an imaging system can undergo before trying to scan abnormal tissue.
Chapter Seven: Methods for Whole-Breast MRI-Guided NIRS

7.1 Introduction

Whole-breast MRI-guided NIR spectroscopy is an emerging technique that has been untested in a large patient population. There are many subtle but important issues in the methods specific to human imaging that are related to the non-linear sensitivity of the NIRS methods, which make it unlike most conventional linear projection imaging systems. NIRS studies and existing hardware configurations present today have a distinct lack of sensitivity to 1) deeper lesions, 2) lesions distant from measurement locations, or 3) lesions that are very small in size. As a result of the limited clinical testing, the understanding of when useful data can be obtained is not well established. For example, there are several issues where data exclusion seems essential in image-guided spectroscopy, yet this is not well articulated in the literature simply from a lack of testing in clinical trials. The field of non-linear reconstruction has matured significantly with many different possible techniques, but choices of parameters in the inversion must be tailored to the system hardware and obtainable measurements. In this trial, a large cohort of data was collected and the system measurements were optimized for the logistics of data exclusion, inversion parameter selection, and property reliability.

Whole-breast MRI-guided spectroscopy has been developing for several years (52,76,168), and the system described in these previous chapters was deployed in this clinical trial to evaluate the quality of the data and optimize the methodology for processing the data. Figure 42 shows an outline of the NIRS/MRI process and highlights where processes or methods were evaluated and key decision points chosen in how to
utilize the data.

Figure 54: Flowchart of reconstruction scheme and decision criteria during image creation. Decision points have newly developed methodologies that could greatly enhance clinical results from MRI/NIRS imaging.

As outlined in previous chapters, NIRS/MRI begins with data collection and calibration. This work explores the idea of a quantitative sensitivity calculation on the patient specific mesh to eliminate over interpretation of low sensitivity lesions. After an initial guess is generated, the non-linear reconstruction is computed either with or without spectral constraints. As a part of image reconstruction, a regularization parameter must be selected to reduce image artifacts while enhancing image contrast between regions. Finally, NIRS images are displayed in an intuitive way that enhances MR images rather than complicates them. This chapter seeks to develop methodologies for clinical whole breast MR-guided spectroscopy in the areas of measurement sensitivity, reconstruction
type, regularization parameter, and image display. The methods, results, and discussion on these steps are presented while trying to understand their influence on a large pool of cancer patients (n=44).

7.2 Methods - Sensitivity

7.2.1 Sensitivity Analysis

7.2.1.1 Calculating Whole Breast Sensitivity

Many groups have strived to develop NIRS methods for complete or nearly complete breast coverage. This is important since it is not feasible to image lesions outside the volume of projection of the measurements. Since the Jacobian matrix used in reconstruction stores the spatial sensitivity information of each measurement, it is useful to quantify the overall sensitivity before reconstruction. First, the CW Jacobian matrix, J, was calculated for the breast, outlined in Chapter 4. The Jacobian is then composed of the geometric sensitivity of each measurement at all locations in the finite element mesh. Thus, it is possible to determine the sensitivity of a region identified by MRI, $S_r$, through the equation, $S_r = \text{sum}[\log(J \cdot r)]$, where $r$ is a logical column vector that identifies nodes within the region of interest. If $r$ is given entirely as ones at points within the region of interest and null outside this, then the total sensitivity of the measurements to the domain, $S_r$, is obtained and the relative sensitivity of the region to the total sensitivity can be found by $S_r / S_r$. Regions are identified by MRI during image segmentation and each node of the created mesh is assigned a region number according to its tissue type. Relative tumor sensitivity is an especially important quantity that could predict measurement accuracy. Figure 55 shows a visual example of the Jacobian-calculated sensitivity in relation to the
tumor region location.

Figure 55: The Jacobian field is plotted within the volume of 3 different breasts with lesions shown in blue (found by MRI) with their corresponding MIP images. The overlap between the lesion and the Jacobian yields the sensitivity of the measurements to the lesion. These examples show two cases (a,b) with good sensitivity and one with very poor (c). Note that because lesions can have extensive lateral shape to them, it is not always obvious how well the NIR array interrogates the heterogeneity at the time of imaging.

7.2.1.2 Calculating Measurement Sensitivity

Similarly to finding the sensitivity of each region, it is also possible to calculate the sensitivity of each measurement. This is beneficial to learn which measurements are interrogating which regions. The sensitivity of the $i^{th}$ measurement, $S_i$, to region $r$ can be calculated by $S_i = sum[log(J(i,:)) \cdot r)]$ where $i$ selects the corresponding row of $J$. When this method is applied to all of the measurements in a given dataset, it is possible know exactly how much sensitivity to a lesion there is and in which measurements it lies. Examples of measurements that have good and bad sensitivity to a lesion are shown in
Figure 56: Sensitivity of two measurements from two different breasts are shown. The Jacobian field is shown in 3D across a coronal slice of the breast volume. Measurements demonstrating good sensitivity to the tumor region (a,b) will have an effect on the recovered properties of the tumor while other measurements will not (c,d).

After obtaining relative sensitivity to all regions for all measurements, it is useful to view them versus measurement number to see where the sensitivity to the tumor region is within the data. Viewing data in this manner shows relative sensitivity of all measurements to all regions. Examples from three different cases are shown in Figure 57 where two cases display good sensitivity and one does not.
Figure 57: Percent sensitivity to each region for three different patients. (a) has tumor sensitivity in many sources, concentrated near measurement 100. (b) has tumor sensitivity in fewer sources, concentrated near measurement 160, and (c) has very little sensitivity to the tumor region. Gaps in the plots are caused by excluded measurements below the noise floor.

The examples in Figure 57 show the relative sensitivity to fat, glandular, and tumor regions for each measurement. Viewing the data in this fashion can help inform an operator how much tumor sensitivity there is and which sets of measurements are most sensitive to it. The influence of the adipose and glandular regions can also been seen. Finally, the measurement sensitivity can be applied to the actual data before reconstruction.
7.2.1.3 Encoding Sensitivity to the Data for Visualization

It is common to view NIRS data sets in terms of \( \ln(rI) \) (or degrees for phase data) versus \( r \), where \( r \) is the source detector separation and \( I \) is the measurement intensity. In this form, data is linear and bad data points can be deleted according to their distance from a line of best fit. The calculated sensitivity of each measurement can also be applied to the data, encoding information about what regions an individual data point is most sensitive to. Figure 58 shows single wavelength data sets from three patients before and after exclusion.

Sensitivity can be applied to the data visualization by coloring points based on their relative sensitivity to each region. This quantity is used to calculate the number of data points to be classified to each region. Though tumor sensitivity is sometimes below 2\%, at least 2\% of data are characterized as tumor measurements due to the region’s importance. The number of adipose/glandular points follows volumetric ratio of the two regions. By including this sensitivity visualization step, more information is contained within the dataset during the preprocessing stage.
Figure 58: Sensitivity-encoded data from three patients are shown before (a-c) and after (d-f) exclusion. Data is removed based on distance from a line of best fit. Coloring points based on sensitivity can be used to ensure inclusion of points that are most sensitive to tumor regions.

Encoding sensitivity information into data visualization could become a critical stage of preprocessing in NIRS. Poor fiber contact with the tissue or measurements near the noise floor could cause data points to stray from the line of best fit and necessitate their exclusion. However, a high absorber or natural variation in the imaging domain could also cause data points to stray from the line of best fit. In these latter cases, data points could carry critical information about the region of interest that must be preserved. Encoding this sensitivity information can help during the pre-processing step by identifying falsely noisy data points that are most sensitive to the regions of interest from the MRI scan. It is likely that this kind of data encoding will have an impact on which
Sensitivity-based methodology was applied to a large group of cancer patients to test its influence on reconstructed results in a large patient pool (n=44). The relative sensitivity to each lesion was calculated as described above and patients were sorted from most sensitive to least sensitive. Reconstructed chromophore concentrations were compared versus the gold standard of surgical pathology in patients with high sensitivity, moderate sensitivity, and poor sensitivity to assess the impact of measurement sensitivity on NIRS’ ability to image breast lesions. The Jacobian can be used to calculate a quantitative measure of the sensitivity of data to the tumor region, of each measurement to the tumor region, and applied to influence data inclusion. Though it is possible to do image-guided spectroscopy without these methods, a lack of sensitivity can have a huge influence on the final results that warrants it being considered throughout the whole reconstruction process.

7.2.2 Reconstruction Type

As discussed in Chapter 4, the accepted methods for reconstruction use spectral prior information to enhance reconstruction accuracy. However, it is possible to implement these constraints during different steps of the reconstruction and still recover the same tissue chromophores. The constrained spectral reconstruction method employs spectral priors during reconstruction while the unconstrained spectral reconstruction introduces prior information after data inversion is complete.

It can be helpful to monitor the iterations and the intermediate solution during the reconstruction to fully understand it. In this work, each patient was reconstructed with both constrained and unconstrained spectral reconstruction in order to analyze if there is
value in the constrained approach or not. The model-data mismatch at each iteration, individual wavelength solutions, and initial guess was monitored, as shown below. An example case study to show the process of in a malignant subject is presented in Figure 59.

**Figure 59:** Unconstrained spectral reconstructions from a malignant subject. Projection error vs. iteration number is shown in (a) for single region and three region reconstructions. (b) shows recovered single region $\mu_a$ and $\mu_s'$ vs. wavelength along with simulated literature values. (c) shows recovered $\mu_a$ and $\mu_s'$ vs. wavelength in three regions along with simulated literature values. Simulated tumor contrast is 1.5x HbT. (d) shows the final unconstrained spectral solution.

This figure shows the recovered $\mu_a$ and $\mu_s'$ at each wavelength for both the single (Figure 59b) and multi region case (Figure 59c) as the unconstrained spectral reconstruction is completed (Figure 59d). In both cases, simulated $\mu_a$ and $\mu_s'$ were also plotted versus wavelength for comparison. The simulated values assume normal background breast properties with 1.5x absorber contrast and no scatter contrast (49).
Looking at the reconstructed spectra next to modeled spectra can be useful for identifying bad wavelengths or strange spectral shapes. The model-data mismatch at each iteration for each wavelength typically decays exponentially as convergence is reached. After individual wavelengths are reconstructed, the tissue chromophores were calculated using the known spectral information. The constrained spectral method was used to solve for the tissue chromophores directly, and the prior molar extinction spectra information was used in the reconstruction. Figure 60 shows this process in the same malignant subject for comparison to Figure 59.

![Graph showing projection error vs. iteration number for single and three region reconstructions.](image)

**Figure 60:** Constrained spectral reconstructions from the same malignant subject. Projection error vs. iteration number is shown (left) for single region and three region reconstructions. The right side shows recovered chromophore concentrations for single region reconstruction and three region reconstructions at three separate regularizations.

Like in the unconstrained case, it can be instructive to look at the projection error from constrained reconstruction of the initial guess and final solutions. It is shown here with three regularization factors that affect the convergence rate and contrast recovery. The initial guess and final solutions are shown for each chromophore and can show how
much influence the spectral constraints play on a specific case when unconstrained with the unconstrained solutions.

Monitoring both of these reconstruction methods can help to understand the spatial and spectral influence of the data on the final solution. The influence of including spectral priors during the reconstruction was tested in a large cohort of patients. Patient reconstructions are analyzed versus sensitivity, surgical pathology, and normal physiological conditions in an effort to determine the most effective prior inclusion methods in a large patient study.

7.2.3 Regularization Parameters

Since the matrix to be inverted, $J^T J$, is ill-conditioned, the update equation is stabilized by adding a regularization term, $\lambda$, to make it more diagonally dominant and dampen noise in the data. While there are many theoretically proposed methods to determine this, in practice this regularization parameter must be chosen carefully based on the amount of noise in the measurements. Though noise from the system is consistent, the noise introduced by fiber coupling or high breast density is patient specific. However, measurement noise and contrast caused by highly absorbing regions cannot be distinguished in the data. Therefore, it can be difficult to choose a regularization parameter that is best suited to all cases as a high regularization dampens both contrast and noise.

In this work, a modified Levenberg-Marquardt scheme regularizes amplitude and phase components separately and is scaled by the maximum of the diagonal of the Hessian. The regularization parameter is reduced between iterations as the reconstruction gets closer to convergence but not by a set amount each iteration (185). Because the
regularization is typically higher throughout the reconstruction, the convergence criteria must be extended from previous work to ensure solution convergence. The reconstruction is stopped when the change between successive iterations is less than 0.2%. Since the regularization is not being lowered quickly, the low stopping criteria allows the reconstructions to converge slowly but robustly.

The effects of regularization were tested by applying constrained spectral reconstructions across the group of patients with 3 different regularization settings. Results from each regularization group were compared against relative tumor sensitivity, surgical pathology, and normal tissue properties to investigate the influence of regularization parameters on clinical data.

7.2.4 Image Display

Lastly, results from image-guided spectroscopy are displayed in a new format. Unlike other imaging techniques, NIRS/MRI does not reconstruct an image with spatial variation since the data is fit to a region map provided by MRI. Rather than chromophore concentrations at every point in the imaging domain, each region is given one concentration per chromophore. Therefore, it follows logically that results can be effectively interpreted by viewing MR images, region maps, and quantitative region concentrations instead of images. Case examples are provided using the new format.

7.3 Results

7.3.1 Sensitivity Analysis

The effects of spatial sensitivity were analyzed using a large group of cancer patients (n=44) by first calculating the relative sensitivity to each lesion. The results are
shown in Figure 61 where patients are separated based on their surgical pathology results into either benign or malignant groups.

![Relative tumor sensitivity for malignant (n=28) and benign (n=16) lesions according to surgical pathology. This group of patients yielded an average sensitivity of approximately 3.5% with little difference between malignant and benign groups.](image)

Figure 61: *Relative tumor sensitivity for malignant (n=28) and benign (n=16) lesions according to surgical pathology. This group of patients yielded an average sensitivity of approximately 3.5% with little difference between malignant and benign groups.*

This group of cancer patients yielded an overall average tumor sensitivity of 3.4%. The benign group (n = 16) showed a slightly lower average of 3.1% and the malignant group (n = 28) was 3.6%. There was no statistical difference (p=0.8) between the two groups, meaning that the measurements were not significantly different in their sensitivity to either malignant or benign lesions.

Sensitivity analysis had a large effect on recovery of tumor chromophore concentrations in malignant versus benign lesions. The patient cohort was sorted from most sensitive to least sensitive and reconstructed chromophore concentrations were compared versus surgical pathology in patients with descending sensitivity. Student T-tests were performed with inclusion of the most sensitive 4 patients through the entire group of 44 patients in order of sensitivity. These results are shown in Figure 62.
Figure 62: The p-values of malignant versus benign groups in recovered chromophores are plotted versus relative sensitivity to the tumor (left axes). Also shown is the number of patients included in the analysis (right axes). As more patients are included, p-values decrease until approximately 1% sensitivity.

P-values from TOI were shown be significant ($p<0.05$) when relative sensitivity to the tumor was above 1.2%. TOI was maximally significant above a relative tumor sensitivity of 2.5% ($p=0.00019$). HbT was also a significant indicator when sensitivities above 1.2% were included. Maximum significance occurred including patients above a sensitivity of 2.5% ($p=0.0037$). Scatter amplitude was nearly significant when sensitivity was above 1.2% ($p=0.09$). In this cohort of subjects, a sensitivity of greater than 1% was required for effective imaging.

7.3.2 Reconstruction Type

The effects of spectral prior inclusion on recovery of tumor chromophore concentrations were also investigated. After sorting the patient cohort by sensitivity, it was possible to compare $p$ values between malignant and benign lesions for constrained
and unconstrained spectral reconstructions. Student T-tests were performed with inclusion of the most sensitive 4 patients through the entire group of 44 patients in order of sensitivity. These results are shown in Figure 63.

![Graph showing p-values and patient count](image)

Figure 63: The p-values of malignant versus benign groups in recovered chromophores are plotted versus relative sensitivity to the tumor (left axes) for constrained and unconstrained spectral reconstruction. Also shown is the number of patients included as a function of sensitivity (right axes). Unconstrained reconstructions give more slightly better results in HbT and SA but far worse in water, lipids, and TOI.

In the constrained spectral reconstructions, the p values from TOI had significance ($p<0.05$) when sensitivity was greater than 1.2%. TOI was maximally significant ($p=0.00019$) for sensitivities above 2.5%. HbT was also a significant indicator for sensitivities above 1.2% and maximally significant above 2.5% ($p=0.0037$). In the unconstrained spectral reconstructions, both HbT and SA were significant predictors of malignancy. HbT achieved statistical significance above a sensitivity of 0.5% and SA
was significant through nearly the entire sensitivity range. HbT was maximally significant above 1% sensitivity \((p=0.015)\) and SA was maximally significant above 1.3% sensitivity \((p=0.012)\).

### 7.3.3 Regularization Parameters

Since image reconstruction is a computationally intensive process, regularization parameters were widely varied across two patient case studies (rather than the whole group), one benign and one malignant. Starting \(\lambda\) was varied from 100 down to 0.001 and image contrast was recorded after spectrally constrained reconstructions. The effects of \(\lambda\) on tissue chromophore contrast in these two cases are presented in Figure 64.

![Figure 64: Tumor to adipose chromophore ratios vs. regularization parameter in one benign case and one malignant case (46 and 51 respectively). Very high regularizations smooth image contrast while very low regularizations fail to adequately dampen noise, causing unpredictable results.](image)

When the regularization parameter was set between 100 and 10, both patients
were smoothed to contrast of near 1 in all chromophores. As regularization was lowered, the contrast displayed a region of stability between 10 and 0.1 where change was slow but consistent. Chromophores such as HbT, SA, and lipids were stable down to a regularization of 0.01. Below 0.01, chromophore contrasts were more erratic and trends change. In this region, behavior was unpredictable, the conclusion reached was that a higher regularization parameter should ideally be used in these cases.

Using these results as an indication of the influence of $\lambda$ in two representative patient cases, these methods were then applied to the whole cohort of patients. Constrained spectral reconstructions were performed on all patients with three different regularization parameters (1, 0.1, and 0.01). Malignant and benign lesions were compared as lower tumor sensitivities were included. These results are shown in Figure 65.

Figure 65: The $p$-values of malignant versus benign groups in recovered chromophores HbT and SA are plotted versus relative tumor sensitivity (left axes) for three different regularizations in constrained spectral reconstructions. Also shown is the number of patients included (right axes). A regularization of 0.1 is the most effective for HbT, adequately smoothing noise but allowing image contrast to persist. SA requires a lower
regularization of 0.01 to be most effective but does not reach statistical significance.

The data showed that HbT was able to achieve significance ($p<0.05$) for nearly the whole cohort, when regularization was equal to 0.1. At $\lambda = 1$, significance was achieved from patients with sensitivity above 1.2%, and at $\lambda = 0.01$ significance was achieved in patients with sensitivity above 3%. Regularization of $\lambda = 0.1$ was maximally significant above 5.8% tumor sensitivity ($p=0.03$). SA was not as good an indicator, with no $\lambda$ value yielding significance in any patient group. Above 1% sensitivity, $\lambda =0.01$ was nearly significant ($p=0.068$). As evidenced by the differences in these results, the value of lambda used has a large effect upon the entire patient cohort as well as the individual cases.

### 7.3.4 Case examples

Example case studies from NIRS/MRI are displayed in Figure 66 and Figure 67. This format highlights the combination of NIRS and MRI by showing MRI contrast images, quantitative region-fit optical chromophores, region maps, and recovered contrasts.

![Figure 66: Benign case (pathology confirmed cystic hyperplasia). A post contrast MIP](image)
image (a) and a pre contrast T1W image (b) were used to segment tissue types (c) for NIRS region fitting. Red arrows show the tumor location while green arrows show the optical fiber locations. Optical solutions for each chromophore in each region are shown in rows by absorption, scatter, and TOI/contrast based quantities.

Figure 67: Malignant case (pathology confirmed IDC). A post contrast MIP image (a) and a pre contrast T1W image (b) were used to segment tissue types (c) for NIRS region fitting. Red arrows show the tumor location while green arrows show the optical fiber locations. Optical solutions for each chromophore in each region are shown in rows by absorption, scatter, and TOI/contrast based quantities.

The presented case studies show MRI images, optical region maps, and quantitative recovered chromophores and contrasts between adipose and tumor regions. In the malignant case, elevated HbT (1.29x) and water (1.4x) were seen in the tumor while the benign lesions showed decreases in both (0.89x and 0.98x respectively). Scatter amplitude was also split, with more scatter in the malignant tumor and less in the benign lesion (1.12x and 0.78x respectively). Lastly, the benign lesion shows a decrease in TOI
while the malignant lesion increases (0.74x and 1.41x respectively). The quantitative tissue chromophores obtained from NIRS imaging hope to enhance the MRI images.

7.4 Discussion

7.4.1 Sensitivity Analysis

7.4.1.1 Overall Sensitivity

Based on the results, it can be concluded that the overall sensitivity of the measurements to the region of interest being characterized has a dominant effect on the performance of the NIR quantification. It follows logically that there should be a quantitative measure of tumor sensitivity for each subject prior to interpreting the data, as it has been shown in the literature that imaging performance falls off as a function of distance from the imaging plane (172,186,187). Contrast-detail studies in NIRS imaging have shown that region size plays a large role in minimum recoverable contrast as well (185,188). The method developed here to quantify tumor sensitivity is easy to calculate and gives the user a quantitative metric for determining the likelihood that the NIRS exam is actually interrogating the lesion and could accurately characterize it.

Though the method does not currently differentiate lesion size from location, given that many lesions are approximately spherical with 1 to 3 cm radius, this might indicate that lesion location is more important than lesion size. Changes in approximate tumor radius allows tumor volume to change by a factor of \( r^3 \) while the Jacobian changes by several orders of magnitude over a span of centimeters. Further study is needed to understand the effect of size versus location. This would be very useful information to have that could eventually determine a practical limit for minimum tumor size detectable
by NIRS/MRI.

7.4.1.2 Encoding Sensitivity to the Data for Visualization

After calculating the sensitivity to the tumor, it is extremely helpful to apply the information to the whole dataset. This approach allows the user to view the data prior to reconstruction with more information than was previously possible. Removal of bad data can be very difficult as there are many things that can necessitate a measurement’s removal. Data can be noisy due to being outside the linear range of the detector, an artifact of poor fiber coupling, or due to a high absorber in the tissue. Identifying and removing bad data points is difficult since many of these types of points appear similarly. With tumor sensitivity incorporated into the data, it is possible to tell which measurements will have the most influence over the tumor region during the reconstruction. Relative tumor sensitivity is typically low, 3.4% on average in this dataset, and it is detrimental to accidentally remove measurements that might be the most sensitive to the tumor region. That said, if a measurement must be dropped for any valid reason, it must still be removed even if tumor sensitivity suffers.

7.4.1.3 Mean Sensitivity

The mean tumor sensitivity was 3.4%. The benign group (n = 16) showed a slightly lower average of 3.1% and the malignant group (n = 28) was 3.6%. The study did not have any significant difference in sensitivity towards malignant versus benign lesions, meaning that the technique is equally sensitive towards all regions of interest. Recovered sensitivities are likely higher than one might expect to see in a screening group since all of the patients were surgical patients and had reasonably mature tumors. Tumor sensitivity is dictated by tumor size and the location of the optical fibers with
respect to the lesion. Size cannot be changed, but having complete coverage or the ability to target the lesion with prior knowledge of its location would help to improve sensitivity of the measurements to the lesions. Many of these lesions were targeted based on palpitation but without the assistance of prior imaging. A screening group would likely have smaller lesions but would potentially be able to achieve high tumor sensitivity due to more effective targeting and future work could confirm this.

7.4.1.4 Sensitivity Affects NIRS Effectiveness

Finally, it was possible to investigate the effects of sensitivity on patient imaging. After sorting the patients by their relative tumor sensitivity, the data fell into three categories:

1. Statistical analysis on only a handful of the most sensitive patients does not result in any statistical difference, likely due to a small sample size (n<6).

2. As the sample size increased, the confidence that the two groups come from different distributions increased. Using tumor sensitivities greater than 2.5%, malignant and benign groups could be distinguished with statistical significance in both HbT and TOI ($p=0.0037$ and $p=0.00019$ respectively). Both of these parameters remain significant at the $p=0.05$ level until a relative tumor sensitivity of 1%.

3. When patients with less than 1% sensitivity were included, the groups’ distributions became inseparable due to the fact that the measurements were no longer really probing the region of interest. Any influence that the tumor region might have on the measured data is lost within the normal variation of the measurements and it is not possible to reconstruct any contrast.

These results suggest that prognostically useful data comes from cases where the
lesion is adequately sampled, ideally with greater than 2.5% sensitivity. Tumor sensitivity can be improved by targeting the lesion based on prior knowledge of its position or with more complete coverage of the breast volume during NIRS imaging. The technique produces good results using our planar fiber interface but many additional cases would be included with more complete coverage. Future designs of the NIRS/MRI breast coil should emphasize complete coverage in all breast sizes, but this remains a substantial technical challenge for NIRS/MRI. Still, the sensitivity parameter investigated here can be calculated prospectively on data sets where the tissue-fiber geometry and the suspected lesion geometry are all known from the MRI scan.

7.4.2 Reconstruction Types

The concept of using prior information in image reconstruction has been investigated for several years. First introduced by Li et al, Brooksby et al, and Guven et al, prior information has been shown to improve NIRS image quantification in simulation, phantoms, and among patient populations (146,152,189–191). Studies have used both spectral and spatial prior information in patient populations, as well as smaller case studies with more sophisticated prior information such as water maps from simultaneous MR imaging (72,192–194). While it is fairly well established that prior information is beneficial for NIRS imaging, it remains unclear when prior information is most effectively incorporated (43,142,195). This data was reconstructed using spatial and spectral prior information but applied the spectral priors at two different times.

The unconstrained spectral reconstruction method was able to significantly differentiate the distributions of the benign and malignant groups’ tumor to adipose ratios in HbT and SA. Both chromophores were significant when tumor sensitivity was above
0.5%. They were maximally significant when patients above 1% sensitivity were included (\(p=0.015\), HbT, \(p=0.012\), SA). Though StO\(_2\), water, lipid, and TOI concentrations were obtained, none of the chromophores produced any meaningful results. It is likely that since these chromophores were not constrained during the reconstruction process, they were calculated with a wider and less physiologically valid spread that they would have been with the spectral priors. With only three wavelengths sensitive to the important spectral features of water and lipids in this NIRS/MRI system, it is also possible that there is not enough spectral sensitivity to accurately calculate these chromophores after reconstruction. Similar to previous results, HbT and SA make very good indicators of tumor malignancy and this method would likely be promising in a larger patient study (49,147).

When the constrained spectral reconstruction method was applied, HbT and TOI were the most successful indicators of tissue malignancy. They were maximally significant when tumor sensitivity was above 2.5% (\(p=0.0037\), HbT, \(p=0.00019\), TOI). Scatter amplitude was never significant (minimum \(p=0.09\)). This method required higher tumor sensitivity to achieve significance in HbT and TOI than the unconstrained method (2.5% vs. 1%). Though SA and HbT did not perform as well in the constrained case as the unconstrained case based on tumor sensitivity, they separated the means with more overall confidence when tumor sensitivity was greater than 1%. Since the constrained method yielded considerably more accurate StO\(_2\), water, and lipid concentrations than the unconstrained, it is the more clinically useful algorithm. When the inversion is spectrally constrained, all recovered chromophores are more accurate absolutely. As a result, TOI calculated from the constrained reconstructions was the best overall predictor
(p=0.00019) and will continue to be an important indicator along with HbT (39).

7.4.3 Regularization Parameter

The starting value of $\lambda$ is where the maximum amount of smoothing and noise suppression will occur since $\lambda$ decreases during iterations where the model-data mismatch decreases. Therefore, a very noisy data set will require a higher starting lambda to adequately suppress noise than a clean data set (185,196). If too high a value is chosen, the regularization can overshadow the differences in the data due to the heterogeneity and hinder contrast recovery. As shown in Figure 64, if the regularization is set very high, above 1, the image contrast is significantly dampened and nearly homogeneous solutions are recovered. If the regularization is too low, under 0.01, the reconstructions become unstable as the noise suppression is not sufficient and solutions fail to converge to physiologically valid solutions. Furthermore, small changes in $\lambda$ can cause very large changes in chromophore concentrations. Finally, there is a region of stability in the middle of the range, from 0.01 to 1 where solutions are able to converge to physiologically reasonable values and small changes in regularization produce small, predictable changes in solutions. Ideally, this region of stability would be determined and then lambda could be minimized to recover optimal image contrast. It is possible to guess a starting lambda based on previous reconstructions, but variation between breast density and data quality make it necessary to experiment with values to reach the optimal image contrast (144,197,198). Since it is the last step of the reconstruction process, it is possible to run multiple reconstructions to obtain the optimal starting lambda, influencing the reconstruction process by adding time as opposed to changing the data or the mesh.

While it is ideal to minimize $\lambda$ in the region of stability for individual patient
reconstructions, it was difficult to assign a $\lambda$ value that would work for all patients. The amount of regularization required varies based on breast density, optical fiber placement, noise within the measurements, and other factors. Therefore, regularization must be chosen to adequately suppress noise while still allowing image contrast to be recovered in most patients. Using HbT as an example chromophore, $\lambda = 0.1$ was able to best suppress noise while allowing image contrast. This $\lambda$ achieved statistical significance at all levels of sensitivity. However, we found that this regularization was not best for other chromophores that might need more noise suppression such as water, lipids, and scatter. Those chromophores favored a higher regularization, and $\lambda = 1$ was the best match for all chromophores. While this caused unwanted smoothing in HbT, we still saw significant results above tumor sensitivity of 1% and favorable results in other chromophores that benefited from the increased noise suppression. This value of $\lambda$ works well for the patient study presented here, but chosen values in future prospective trials would ideally be based off of a much larger patient group. Even with that type of data, it is possible that another study with different conditions (fiber geometry, patient population, hardware calibration scheme…) would require its own analysis.

7.4.4 Case Examples

Lastly, two case examples were presented using the new display format. This format shows two of the most important MRI images, pre-contrast T1W and post-contrast subtraction MIP. The optical region map was shown overlaid with an MRI image to show the optical coverage and the optical data was shown in bar graph form for each region. Chromophores were divided based on their contrast mechanism into categories absorption, scattering, and TOI/contrast and all displayed quantitatively.
When compared to results from other NIRS studies in both MR and non-MR guided NIRS systems, the chromophore quantification from these subjects seems physiologically reasonable and comparable (41–44). These examples include one benign case with pathologically confirmed cystic hyperplasia and one malignant case with pathologically confirmed IDC. There was increased hemoglobin concentration in the malignant case and decreased concentration in the benign case. In previous work (95,173), relative hemoglobin concentration, TOI, and SA have been shown to be indicators of tissue malignancy and future patient studies hope to confirm this in NIRS/MRI.

The absolute values of recovered tissue components occurred within physiological limits but were not as robust as the relative quantification, common among other imaging modalities (122). The variation in our images could stem from factors other than the natural variation between subjects. For example, our current system provides fairly low spectral resolution with only nine wavelengths, making it susceptible to noise in the data from instrumentation or variations in fiber coupling which creates crosstalk between chromophore estimates (116). Furthermore, with only six wavelengths of frequency domain data, co-dependencies in the absorption and scattering information is probable, especially between SA and deoxy hemoglobin, leading to distorted StO₂ (183). Finally, effects from partial volume averaging are likely to occur in these subjects, because even with anatomical priors, pure separation of absorption and scattering is difficult due to the blended sensitivity profiles across tissue types. As a result, chromophore concentrations may be distorted in the adipose region relative to its glandular counterpart (184). Larger patient studies should ideally be completed, in order
to better to draw conclusions from larger datasets where smaller differences might be discerned with higher reliability.

7.5 Conclusions

In this study, approaches for whole-breast MRI-guided near infrared spectroscopy were analyzed using the clinically derived data from a group of 44 breast surgery patients (16 benign, 28 malignant). The data indicates that sensitivity, reconstruction type, and regularization parameters are all important aspects of NIRS/MRI that should be considered during image processing. For relative tumor sensitivities above 1%, NIRS/MRI was able to differentiate malignant and benign groups obtained from clinical pathology in both HbT (p=0.0037) and TOI (p=0.00019). Tumor sensitivity was a critical finding as there was no significance when patients with very low sensitivities were included in the analysis. Reconstruction type determined both separation of malignant from benign as well as robustness of images. Spectral constraints were required to obtain clinically useful information from measurements of water, lipids, and TOI. The ideal regularization parameter varies case by case and must be carefully selected to adequately reduce image noise while still allowing maximal image contrast to persist in the entire group.

Results from this study will influence how future NIRS/MRI data is processed from a standpoint of reconstruction, regularization, and sensitivity analysis. Larger clinical studies will benefit from this analysis. Finally, these results confirm the need for future system design to provide full coverage to the breast while still being able to accommodate all breast sizes for the most effective data collection.
Chapter Eight: MRI-Guided NIRS for Increased Diagnostic Specificity

8.1 Introduction

Women with more dense breasts have higher incidence and mortality from breast cancer, and are the most difficult group to screen with mammography (16–18). Therefore, current clinical care includes breast Gadolinium (Gd) Dynamic Contrast Enhanced MRI (DCE-MRI) for surgical staging and screening of high-risk and/or young patients (19,20). Nearly all malignant lesions can be identified based on DCE-MRI but many benign lesions also enhance (21,22), leading to diminished specificity. The Gd contrast agent collects in areas of abnormal vasculature and these images are sensitive to increased vessel density, vascular permeability, and interstitial space, all traits of invasive cancers. DCE-MRI is recommended for the screening of women at high risk for the development of breast cancer in combination with mammography because it has greater sensitivity than standard mammography, reported to be 88-100% (15,23–25). Screening specificity is less consistent but is reported to be 72% and generally leads to 3-5x more false-positive findings than mammography (26). MRI is able to identify nearly all cancers, but the high false positive rate leads to unnecessary MR-guided biopsy procedures that are invasive and stressful for the patients, and expensive to the point where it can diminish the value of breast MRI if not controlled. This high sensitivity paired with the limited ability to characterize invasive cancers has motivated the development of new imaging tools to improve MRI specificity (27–29). In this study, MRI-guided NIRS was examined as a functional adjunct to DCE-MRI, hoping to increase the information content available at the time of imaging in regions defined by contrast enhancement.
With so few functional imaging tools available clinically, the potential for introducing novel optical imaging systems to monitor specific molecules, cellular activity, drug uptake, and tissue physiology is high. MRI-guided NIRS is an emerging imaging approach that could benefit patients after screening (118) by increasing the specificity of DCE-MRI prior to biopsy (112). The technique can be used to non-invasively quantify oxy- and deoxy-hemoglobin, water and lipid content, and scattering parameters in adipose, fibroglandular, and tumor tissues. Combined NIRS and MRI systems have been developed in the US and Germany for human imaging (111,199), but they have been slow to progress due to design challenges and cost. Hundreds of patients have undergone standalone NIRS breast imaging at multiple academic centers in the USA and Europe (200,201) with promising results. The sensitivity and specificity of breast cancer detection with NIRS alone varies depending on the system geometry but has been reported to be as high as 91-96% and 93-95%, respectively (109,202), although studies at Dartmouth have indicated this is clearly size dependent (95). Since MRI information can be used to guide image reconstruction in NIRS/MRI, the technique may improve on the standalone NIRS results, especially when lesions are smaller than 1-2 cm, one of the primary issues of standalone NIRS.

Ntziachristos et al. and then Brooksby et al. demonstrated combined NIRS/MRI systems for concurrent MRI and optical imaging (46–49). Their combination has been successful in increasing the information available from clinical MRI exams. The technology has shown distinctions between malignant and benign lesions in several case studies but has never been tested in a large patient population (47,50). In this study, a pool of 50 breast cancer surgical patients was imaged to define the diagnostic value of
MR-guided NIRS used to characterize abnormalities as defined by DCE-MRI. Abnormalities are characterized relative to the background breast tissue as either malignant or benign and scored versus pathologic diagnosis. Results from these exams are used to generate sensitivity and specificity and Receiver Operating Curves (ROC) for MR-guided NIRS. Individual case studies are presented along with a discussion of the potential for NIRS/MRI imaging as a follow-up to mammographic screening that could potentially increase the specificity of clinical MRI.

8.2 Methods

8.2.1 Patients

Our study protocol for human subject imaging was approved by the Committee for the Protection of Human Subjects at Dartmouth-Hitchcock Medical Center and at Xijing Hospital, in Xi’an China. Because the funding was from the National Institutes of Health, approval was required from this agency as well as the US State Department. This trial became the first NIH-funded radiological imaging study in China, and so the multiple levels of approval were required in this case. All patients provided written consent after the nature of the procedure was fully explained to them by their physician. Patients were recruited for imaging by several breast surgeons at Xijing Hospital and each continued on to surgery following MRI-NIRS as part of their standard of care treatment. Patients were selected based on: being greater than 18 years of age, having breast size and epithelial integrity adequate to allow NIRS imaging, having a palpable mass or confirmed mass from clinical imaging, no prior biopsy within the previous 10 days, the ability to provide informed written consent, and no serious associated
psychiatric illnesses. Recruited patients were excluded prior to imaging based on: complication with MRI such as the presence of an electronic or metal implant, claustrophobia, a history of allergy to iodides, pregnancy, or other contraindication to MRI as determined by the radiologist.

All disease was confirmed by histo-pathological analysis following surgery and a summary of all patients is presented in Table 2. All subjects were female, age ranged 20-81 years old. Within the malignant group, mean age was 49 years with a standard deviation of 11 years, and a total range of 24 to 81 years. Within the benign group, mean age was 37 years old with standard deviation of 10 years, and total range 20 to 51 years. The benign population was significantly younger than the malignant population \( (p<.001) \), as would be expected in this clinically detected population. Patient BMI had a mean of 23.0 with standard deviation of 3.3. Patient breast sizes were distributed as follows: 16 A-cup, 15 B-cup, 7 C-cup, and 6 D-cup. Since many patients did not have mammography imaging as is standard in China, breast density was assessed by an experienced breast radiologist from MRI as follows: 3 fatty, 14 scattered, 13 heterogeneously dense, and 14 extremely dense. 16 subjects were postmenopausal while 28 were premenopausal. Imaging was typically completed the evening before patients’ surgery, though it was based on patient convenience and MRI availability. Finally, care was taken to avoid recruiting patients who had biopsy procedures less than ten days prior due to the likelihood of bruising caused by the biopsy. Of the 50 subjects, 6 were excluded due to a recent biopsy. All of the patient data is summarized in Table 2.
Table 2: Patient clinical information with tumor radiologic and pathology information as recorded.

8.2.2 Instrumentation

The MRI/NIRS system deployed in this study (77,113) is well described in the previous chapters, but a brief recap here describes the salient features. It consisted of six intensity modulated laser diode lasers and three continuous-wave laser diode lasers with wavelengths spanning from 660nm to 850nm, and 900nm to 950nm, respectively. Sixteen sequential source positions illuminated the breast through the custom optical switch. During each individual source illumination, the remaining 15 fibers detected transmitted...
light with photomultiplier tubes (PMTs) (Hamamatsu H9305-03) and large active area photodiodes (Hamamatsu C10439-03). The amplitude and phase (when available) of the detected light were separated by lock-in detection. The NIRS imaging system was always located in the MR console room, and 13m fiber bundles with 4mm working optical diameters were passed through the MR scanner room door. These fibers were coupled into a clinical breast coil for simultaneous MR and NIRS imaging of patients or phantoms. Clinical MRI image quality and acquisition time were not affected by the addition of the NIRS fiber array. All key details on the imaging instrumentation can be found in a previous publication and chapter (113).

The MRI scanner used in this study was a Siemens TIM Trio 3T MRI machine. A clinical MRI breast coil (Invivo Corp, Gainesville, FL) was retrofitted with the optical fiber array that is capable of accommodating variable breast sizes and compositions. The fibers remained stationary and were mildly compressed against the breast surface during imaging, slightly distorting the shape of the imaged breast. There was no degradation of MRI image quality due to the optical fibers. Since the technique was an adjunct to clinical breast MRI, a key goal was to be careful not to interfere with the imaging of the contralateral breast. More details on the patient-fiber coupling within the MRI can be found in a previous publication (176).

8.2.3 Measurement Procedure

Subjects were positioned into the triangular breast interface while prone on the MR exam table by bringing the three fiber optic cable holders into contact with the breast. In some cases of smaller breast sizes, all fibers were not in contact with the skin surface because of curvature, and data from these channels was not used during image
reconstruction. The interface involves mild compression as is standard in MR biopsy plates to maintain patient comfort during the imaging procedure. Co-registration between optical and MR images was accomplished through MR fiducial markers placed in the plane of each set of fibers, and MR images were acquired with the slice-direction in the axial geometry. MRI sequences typically acquired were: unilateral T2W turbo spin echo with fat suppression, bilateral diffusion weighted, bilateral apparent diffusion coefficient, bilateral T1W pre contrast, and 5 series of bilateral T1W post contrast spaced at 90 seconds apart. If there was suspicion of a mass in both breasts, unilateral sequences were repeated for the contralateral breast. NIRS and MR data were collected concurrently with data acquisition requiring 15 and 30 minutes, respectively. Because the data collection from the two imaging modalities does not interfere with each other, optical data was typically collected twice per subject as time permitted. Following patient imaging, a NIRS calibration phantom was imaged and the data reserved for use in image reconstruction.

8.2.4 Data Analysis

8.2.4.1 Clinical Data

After MRI/NIRS imaging and surgery, an experienced breast pathologist performed routine pathological analysis approximately one week after the surgery on the processed specimens, and the pathology report was provided to the clinical trial personnel. The analysis used standard clinical processing including formalin fixed H+E stained sections and frozen sections. Reported for each patient were tumor sizes, diagnosis, margin assessment, and CK5/6, p63, and Ki-67 indices. For the study, photos of the tissue specimens and frozen sections were also obtained.
A radiologist experienced in breast MRI read these images blinded from pathological analysis for each patient. The reports included MRI-based assessment of breast density, lesion dimensions and location, and contrast enhancement patterns. The lesion was assigned a BIRADS category according to the following standard scale:

0 – incomplete, needs further evaluation,

1 – normal dense breasts,

2 – benign,

3 – probably benign, recommend short-interval follow-up,

4a – low suspicion for malignancy, biopsy should be considered,

4b – intermediate suspicion for malignancy,

4c – moderate concern but not classic for malignancy,

5 – highly suggestive of malignancy, appropriate action should be taken (203).

In addition to enhancement characteristics, the lesion location and dimension was recorded by image series and slice number for optical image reconstruction.

8.2.4.2 Optical Image Reconstruction

Data were analyzed using Nirfast, a custom software package written in Matlab (Mathworks, Natick MA) (196). First, a patient-specific finite element mesh was created to accurately model the light transport within the imaging domain. Tissue regions were assigned to the mesh based on segmented MRI images and divided into adipose, fibroglandular, and tumor regions (76,204,205). Data was calibrated based on the homogeneous phantom to correct for small variations in detector response and light delivery. Then, images were reconstructed by minimizing the difference between measured data and a diffusion-based model of light propagation through the medium.
to yield estimates of the optical properties of the tissue of interest. The image formation algorithm is non-linear and solved with a Newton-type minimization method that optimizes the estimation of the physiological parameters, \( c \), which include oxygenated and deoxygenated hemoglobin concentrations, water and lipid fractions, scatter amplitude, and scatter power (30,31). Here is reported total hemoglobin,

\[
HbT = HbO + Hb,
\]

oxygen saturation, \( StO_2 = \frac{HbO}{HbT} \), and a modified tissue optical index \( TOI = \frac{HbT \times \text{Water}}{\text{Lipid}} \) from these parameters.

The three-dimensional reconstruction algorithm was designed to employ a priori information gained from MRI to guide the optical solution as outlined in previous work by Carpenter et al (126). This technique makes the assumption that each of the segmented regions defined from the MR images have similar optical properties throughout. We simplify the inversion problem computationally by completely eliminating variation within regions, and thus, are able to quantify optical properties between regions but not within them (210), transforming the problem from an image reconstruction to one of region-based spectroscopic recovery of the properties. Solutions are displayed using MRI post-contrast MIP images and pre-contrast T1W images, bar graphs to quantify optical solutions, and the region map used to calculate optical solutions.

8.2.4.3 Statistical Analysis

For statistical analysis, patients were divided into malignant (n=33) and benign categories (n=17) based on clinical pathology as outlined in Figure 68. Then, patients were further divided based on optical measurement sensitivity to the tumor region. As outlined in previous work (172,186,206), optical image accuracy is dependent on having
measurements that interrogate the region of interest. Therefore, analysis was performed for two different cohorts. One group included all patients (44 inclusions) and the other group included only cases where measurement sensitivity was greater than 1% (26 inclusions) as this threshold was found to be important for tumor quantification accuracy in the previous chapter (211).

Figure 68: Outline of data analysis procedure and exclusion criteria for 50 subjects. Two statistical analyses were performed: on the whole group results (blue), and on the subset where relative tumor sensitivity was greater than 1% (red). 6 cases were excluded from both sets due to recent biopsy.

Statistical analysis was performed using Matlab. Student t-tests examined correlation between NIRS imaging and clinical pathology for all reconstructed optical parameters for the whole study as well as the >1% subset. ROC analysis was performed for the most promising optical indicators (TOI, HbT, and SA), MRI performance, and combined performance for both groups. The combined evaluation was completed using logistic regression to obtain the optimal coefficient weights for MRI and optical results.
versus clinical pathology. Significance for all statistical tests was assumed at a confidence interval of 95% (p-value<0.05) for a two-tailed distribution.

8.3 Results

8.3.1 MRI Interpretation

The MRI results of the study are presented in Table 3. The mean lesion size was 18x23x25mm with a range of 6x7x9mm to 33x58x46mm. The maximum tumor dimension ranged from 9mm to 87mm with a mean and standard deviation of 31mm and 19mm. T2 appearance and contrast enhancement degree and pattern are reported as well. Every patient was then assessed using The ACR BIRADS scoring system.

<table>
<thead>
<tr>
<th>Patient ID</th>
<th>Pathology</th>
<th>T1 Appearance</th>
<th>T2 Appearance</th>
<th>Degree of Enhancement</th>
<th>Enhancement Pattern</th>
</tr>
</thead>
<tbody>
<tr>
<td>01</td>
<td>OC, high grade</td>
<td>5</td>
<td>3</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>02</td>
<td>OC, low grade</td>
<td>4</td>
<td>3</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>03</td>
<td>OC, anaplastic</td>
<td>5</td>
<td>2</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>04</td>
<td>OC, metastatic</td>
<td>4</td>
<td>2</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
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<td>OC, mixed</td>
<td>5</td>
<td>3</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>06</td>
<td>Other tumors</td>
<td>4</td>
<td>2</td>
<td>3</td>
<td>2</td>
</tr>
</tbody>
</table>

Table 3: MRI image results for each patient as determined from the Radiologist read of the DCE-MRI scans.
Using a BIRADS 4 or 5 as malignant, there was one false negative out of 28 pathologically confirmed malignant lesions. There were 6 false positive results out of 16 benign cases, corresponding to a sensitivity and specificity of 0.96 and 0.65 respectively.

ROC analysis of MRI alone showed an area under the curve of 0.86 (shown in Figure 76).

8.3.2 Optical Results

Optical results are presented in Table 4 and Table 5 for the analyses of only patients with tumor sensitivity greater than 1% and for all subjects. NIRS quantification of normal tissue, tumor tissue, and their ratio (tumor/normal) is reported for HbT, StO2, water, lipids, SA, SP, and TOI. In the 26 patient analyses, malignant lesions showed significant increases in HbT ($p=0.0050$) and TOI ($p=0.0019$), with SA being nearly significant ($p=0.087$). Mean HbT ratio for malignant and benign was 1.15x and 0.94x with standard deviations 0.13 and 0.2. Mean SA was 1.05x and 0.93x with standard deviation 0.14 and 0.16. Mean TOI was 1.12x and 0.92x with standard deviation 0.32 and 0.19. Other chromophores showed separation of means but none were significant.
Table 4: Optical imaging results for patients with greater than 1% tumor sensitivity (n=26). Normal tissue, tumor tissue, and their ratio are tabulated for seven optical chromophores.

In the 44 patient analyses, malignant lesions showed significant increases in HbT (p=0.048). Mean HbT ratio for malignant and benign was 1.60x and 1.11x with standard deviations 0.91 and 0.42.

Table 5: Optical imaging results for all patients (n=44). Normal tissue, tumor tissue, and their ratio are tabulated for seven optical chromophores.

Figure 69 shows boxplots of all NIRS parameters for the 26 patient analysis. The ratio of normal tissue to tumor tissue was calculated for malignant and benign groups as
defined by surgical pathology. When tumor sensitivity is greater than 1%, NIRS quantification of the ratio of tumor to normal tissue is significant in total hemoglobin ($p=0.0050$) and tissue optical index ($p=0.0019$). Scatter amplitude is nearly significant ($p=0.087$) as the medians are separated but outliers are present in the data.

![Boxplots for NIRS parameters HbT, StO2, water and lipid fractions, SA, SP, and TOI for benign (n=9) and malignant groups (n=17). There were significant differences in the means in HbT and TOI.](image)

Figure 69: Boxplots for NIRS parameters HbT, StO2, water and lipid fractions, SA, SP, and TOI for benign (n=9) and malignant groups (n=17). There were significant differences in the means in HbT and TOI.

ROC analysis was performed for all optical parameters for both patient groups, with results shown in Figure 70. When tumor sensitivity was greater than 1%, the HbT, SA, and TOI were all good predictors of malignancy with AUCs of 0.79, 0.8, and 0.82. When all patients were included in the analysis, AUC values declined to 0.68 for HbT, 0.64 for SA, and 0.5 for TOI.
Figure 70: ROC analysis of patients with tumor sensitivity greater than 1% (n=26) (a) and for all patients (n = 44) independent of the lesion sensitivity to measurements (b).

In addition to ROC analysis of the two analyses, we also examined AUC as a function of tumor sensitivity to try to determine the ideal tumor sensitivity for ROC analysis. The results are shown in Figure 71. When tumor sensitivities were greater than 2.5%, the AUCs of HbT and TOI are 0.92 and 0.97 respectively. Lower than 2.5% tumor sensitivity, the AUC of these parameters steadily declined. Conversely, the AUC of SA increases up to tumor sensitivity of 1%, reaching 0.8 before falling off. Below a tumor sensitivity of 1%, the AUC of SA also decreased.
Figure 71: Area under the curve from ROC analysis vs. relative tumor sensitivity is shown (left axes). Also plotted is the number of patients included vs. relative tumor sensitivity (right axes). When tumor sensitivity was above 2.5%, TOI and HbT were both excellent ($AUC > 0.9$) but declined as the sensitivity decreased. A dashed red line shows the cut off used in the sub-analysis just above 1% tumor sensitivity.

8.3.3 Case Examples

The next four figures show four case examples of MRI/NIRS where MRI was a false negative, false positive, or uncertain about a diagnosis. Typically, the normal tissue to tumor tissue ratio of HbT, SA, and TOI appear to be predictive of malignancy. Contrast values greater than 1x in each of these three chromophores, appear in lesions which were ultimately diagnosed as malignant. Values lower than 1x were indicative of benign lesions. In all examples shown here, a post contrast MRI MIP image shows tumor location, along with a bilateral T1W pre contrast MRI for reference. An MRI based region map is color-coded with bar graphs quantifying absorption parameters, scattering parameters, and TOI and contrast. Green arrows show the fiber optics’ locations on the surface of the breast.
Figure 72 shows results from a pathologically confirmed IDC. Her BIRADS score was 2, which is a false negative. NIRS/MRI imaging quantified the HbT contrast at 0.96x, SA contrast at 1.08x, and TOI contrast at 1.31x, suggesting a possibility of malignancy.

Figure 72: MRI/NIRS results for Patient 4 (Tumor size: 25x22x26mm, MRI: BIRADS 2, Path: IDC). SA and TOI suggest that this lesion is malignant based on ROI to normal contrast greater than 1x. A post contrast MRI MIP image shows tumor location (a) along with bilateral T1W pre contrast MRI (b). Absorption parameters, scattering parameters, and TOI and contrast are shown as bar graphs quantifying tumor and normal tissues according to MRI-based region map (c). Green arrows show fiber optics' location.

Figure 73 shows results from a pathologically confirmed adenosis. Her BIRADS score was 4a, which is low suspicion for malignancy but would require a biopsy. MRI/NIRS imaging quantified the HbT contrast at 0.56x, SA contrast at 0.76x, and TOI contrast at 0.65x, strongly suggesting that the lesion was benign.
Figure 73: MRI/NIRS results for Patient 6 (Tumor size: 48x53x22mm, MRI: BIRADs 4a, Path: Adenosis). HbT, SA, and TOI all suggest that this lesion is benign based on ROI to normal contrast less than 1x. A post contrast MRI MIP image shows tumor location (a) along with bilateral TIW pre contrast MRI (b). Absorption parameters, scattering parameters, and TOI and contrast are shown as bar graphs quantifying tumor and normal tissues according to MRI-based region map (c). Green arrows show fiber optics’ location.

Figure 74 shows results from a pathologically confirmed fibroadenoma. Her BIRADS score was 4a, which is low suspicion for malignancy but would require a biopsy. NIRS/MRI imaging quantified the HbT contrast at 0.79x, SA contrast at 0.90x, and TOI contrast at 0.95x, suggesting that the lesion was benign.
Figure 74: MRI/NIRS results for Patient 10 (Tumor size: 10x20x19mm, MRI: BIRADS 4a, Path: Fibroadenoma). HbT, SA, and TOI all suggest that this lesion is benign based on ROI to normal contrast less than 1x. A post contrast MRI MIP image shows tumor location (a) along with bilateral TIW pre contrast MRI (b). Absorption parameters, scattering parameters, and TOI and contrast are shown as bar graphs quantifying tumor and normal tissues according to MRI-based region map (c). Green arrows show fiber optics’ location.

Figure 75 shows results from a pathologically confirmed IDC. Her BIRADS score was 4a, which is low suspicion for malignancy but would have been confirmed by a positive biopsy. MRI/NIRS imaging quantified the HbT contrast at 1.13x, SA contrast at 1.14x, and TOI contrast at 1.05x, increasing the confidence in the MRI diagnosis.
Figure 75: MRI/NIRS results for Patient 21 (Tumor size: 9x16x16mm, MRI: BIRADS 4a, Path: IDC). HbT, SA, and TOI all confirm that this lesion is malignant based on ROI to normal contrast greater than 1x. A post contrast MRI MIP image shows tumor location (a) along with bilateral TIW pre contrast MRI (b). Absorption parameters, scattering parameters, and TOI and contrast are shown as bar graphs quantifying tumor and normal tissues according to MRI-based region map (c). Green arrows show fiber optics’ location.

8.3.4 Combined ROC Analysis

Finally, we examined the combined results of MRI diagnosis, NIRS/MRI imaging, and the combined total as a predictive imaging modality. In each ROC analysis, the most effective optical predictor is plotted in Figure 76. Combined MRI – NIRS/MRI was based on logistic regression to select ideal weighting coefficients for the combined indicators. When tumor sensitivity was greater than 1%, TOI was the best optical indicator with AUC of 0.82. MRI alone had an AUC of 0.81 and the combined AUC was of HbT+MRI was the highest, 0.88. Combined AUC of MRI/SA and MRI/TOI were 0.84 and 0.86, respectively. When all patients were included in the analysis, HbT was the best predictor,
with an AUC of 0.68. MRI had an AUC of 0.86 and the combined AUC was 0.88. Combined AUC of MRI/SA and MRI/TOI were 0.64 and 0.5, respectively. Complete AUC, sensitivity, specificity, PPV, and NPV are summarized for optical and combined indicators from both analyses in Table 6.

**Figure 76:** Combined ROC analysis of patients with tumor sensitivity greater than 1% (n=26) (a) and all patients (n = 44) (b). HbT is plotted along with MRI alone and the combined result.

<table>
<thead>
<tr>
<th>44 Patients</th>
<th>HbT</th>
<th>TOI</th>
<th>SA</th>
<th>MRI</th>
<th>MRI+HbT</th>
<th>MRI+TOI</th>
<th>MRI+SA</th>
<th>MRI+HbT+TOI</th>
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</thead>
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<td>0.50</td>
<td>0.64</td>
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<td>0.85</td>
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</tr>
<tr>
<td>Specificity</td>
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<td>0.50</td>
<td>0.64</td>
<td>0.96</td>
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<tr>
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<td>92.31</td>
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<tr>
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<td>91</td>
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<td>72.22</td>
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<table>
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<th>26 Patients</th>
<th>HbT</th>
<th>TOI</th>
<th>SA</th>
<th>MRI</th>
<th>MRI+HbT</th>
<th>MRI+TOI</th>
<th>MRI+SA</th>
<th>MRI+HbT+TOI</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC</td>
<td>0.79</td>
<td>0.82</td>
<td>0.80</td>
<td>0.81</td>
<td>0.88</td>
<td>0.86</td>
<td>0.84</td>
<td>0.88</td>
</tr>
<tr>
<td>Specificity</td>
<td>0.63</td>
<td>0.75</td>
<td>0.88</td>
<td>0.94</td>
<td>0.88</td>
<td>0.76</td>
<td>0.78</td>
<td>0.75</td>
</tr>
<tr>
<td>Sensitivity</td>
<td>0.89</td>
<td>0.71</td>
<td>0.83</td>
<td>0.97</td>
<td>0.78</td>
<td>0.88</td>
<td>0.88</td>
<td></td>
</tr>
<tr>
<td>PPV</td>
<td>71.43</td>
<td>54.55</td>
<td>70.00</td>
<td>84.00</td>
<td>93.33</td>
<td>92.86</td>
<td>93.33</td>
<td>88.89</td>
</tr>
<tr>
<td>NPV</td>
<td>84.21</td>
<td>85.71</td>
<td>93.75</td>
<td>85.00</td>
<td>63.64</td>
<td>63.64</td>
<td>63.64</td>
<td>85.71</td>
</tr>
</tbody>
</table>

**Table 6:** Statistical analysis for optical and combined indicators for both analyses.

Statistics were omitted for TOI and SA in all patients.
8.4 Discussion

8.4.1 MRI Interpretation

The MRI results of the study are presented in Table 3 and represent the interpretation of an experienced breast radiologist. The mean lesion size was 18x23x25mm, which is fairly large. However since all patients enrolled in the study were surgical patients, one would expect larger and more mature lesions than would be present in a comparable screening study. There is also a skewed ratio of malignant to benign lesions due to the fact that only patients who were going to surgery were enrolled. As a result, there are more malignant lesions in the study but that enhances the data by giving the technique more exposure to malignant lesions.

Every patient was assessed using the guidelines outlined in the ACR BIRADS scoring system for mammography where a BIRADS 4 or 5 is considered malignant. Based on this scoring system, there was one false negative out of 28 pathologically confirmed malignant lesions. There were 6 false positive results out of 16 benign cases, corresponding to a sensitivity and specificity of 0.96 and 0.65 respectively. While this specificity is lower than is typically reported for MRI (0.72), it is likely an artifact of a small sample size (23,24,212). ROC analysis of MRI alone yielded an area under the curve of 0.86 (shown in Figure 76). Again, this is lower than other reported MRI based ROC analysis but could be due to the sample size of the study.

8.4.2 Optical Results

MRI/NIRS imaging was able to quantify HbT, StO2, water and lipid content, SA, SP, and TOI in 44 surgical patients. Histo-pathological analysis after surgery identified 28 cancers and 16 benign lesions. Based on previous results, analysis was performed on
the entire cohort of subjects as well as a subset that had relative optical tumor sensitivity of greater than 1% (213). Previous studies have shown that relative measurements are more effective for accuracy in imaging systems and analyses (95). We found that the ratio of tumor to normal tissue was most predictive of tumor malignancy in these data as well. Like many other studies, HbT was a significant indicator of tumor malignancy ($p=0.048$) when examined in the entire cohort as well as in the most sensitive subset ($p=0.005$). TOI was also significant in the subset with greater than 1% tumor sensitivity ($p=0.0019$) but not in the entire group. Other NIRS breast imaging studies have also shown HbT and TOI be significant (72,214). While this system uses 9 wavelengths of light to image the breast, the chosen wavelengths favor the quantification of HbT over TOI, one possible explanation for why HbT is a more robust predictor than other chromophores. TOI is derived from noisier measurements than HbT in our system, and high tumor sensitivity is required for reliable quantification. In other studies with scanning spectroscopic probes, the tumor region is always probed except for cases with very deep lesions. HbT is the most robust chromophore in our system, but as tumor sensitivity declines, so does quantification accuracy. For this reason, the analysis was split in this study. Future studies should make certain that the tumor is within the imaged volume and could use poor measurement sensitivity as an exclusion criterion.

ROC analysis of the entire MRI/NIRS imaging data set yielded AUCs of 0.68, 0.64, and 0.5 for HbT, SA, and TOI. These numbers are much lower than previous ROC analysis of optical imaging, but again, it is likely due to a lack to measurement sensitivity to the ROI (38,39). HbT was the only significant chromophore in this group and also had the highest AUC of 0.68, similar to Poplack et al. (95). When AUC was examined in the
subset of patients with tumor sensitivity greater than 1% (n=26), the AUCs were 0.79, 0.8, and 0.82 for HbT, SA, and TOI. While these numbers are higher, they are still lower than past results where Chance et al. used NIRS to obtain an AUC of 0.95 in 116 patients (44 cancers). Here, TOI was the most significant indicator and also performs the best in ROC analysis, though SA and HbT were nearly as good.

If the patient group is broken down further, and a subset of only patients with greater than 2.5% tumor sensitivity are included (n=19), HbT and TOI become excellent predictors with AUCs of 0.92 and 0.97 respectively. These numbers are quite promising for MRI/NIRS imaging, and more consistent with previous results, though in a smaller subset of patients. This analysis also strongly supports the theory that good tumor sensitivity is needed to effectively quantify breast lesions (213). Providing full breast coverage is a unique logistical and engineering challenge in MRI/NIRS but efforts are under way to find a solution that economically maximizes coverage and still accommodates all breast sizes (176,186).

8.4.3 Case Examples

All of the case studies presented in this report were chosen because they are incorrectly diagnosed or nearly so on MRI. There was one false negative, two false positives, and one true positive that was not confidently diagnosed. In each case, there was adequate tumor sensitivity for the optical measurements to be reliable, greater than 3%. As illustrated in previous sections, when tumor sensitivity is that high, TOI and HbT are excellent indicators of malignancy, with SA being a moderate indicator. In these three parameters, a tumor to normal ratio greater than one tends towards malignancy and less than one indicates that a lesion may be benign. Previous studies using tomographic NIRS
imaging have found mean HbT contrasts of 1.5x (95) in cancers greater than 6mm, 1.78x (72) and 1.37x (61). Here, we report mean malignant HbT contrast of 1.6x and 1.72x in the subset (or 1.15x when a higher noise smoothing factor is applied). These numbers are highly dependent on system configuration and reconstruction algorithm but are all significant versus the equivalent benign contrasts. These studies are encouraging for clinical NIRS imaging (43) but illustrate the need for standardization in image reconstruction.

Patient 4 was a pathologically confirmed IDC with a BIRADS score of 2. This case was the only false negative. MRI/NIRS imaging quantified the HbT contrast at 0.96x, SA contrast at 1.08x, and TOI contrast at 1.31x. Though the HbT contrast suggests that the lesion is also benign, it is not strongly suggestive, while TOI and SA are suggestive of malignancy. In a clinical setting, this could be a lesion where NIRS imaging prompted at least a second look at MRI.

Patients 6 and 10 were false positive results on MRI. Patient 6 was a pathologically confirmed adenosis with a BIRADS score of 4a. This false positive result would require a biopsy despite the low suspicion for malignancy. MRI/NIRS imaging quantified the HbT contrast at 0.56x, SA contrast at 0.76x, and TOI contrast at 0.65x, strongly suggesting that the lesion was benign as all parameters were well below one. Though this patient would have gone to surgery anyways due to her age (26 years old), NIRS/MRI could have better informed the decision. Patient 10 was a pathologically confirmed fibroadenoma with a BIRADS score was 4a. MRI/NIRS imaging quantified the HbT contrast at 0.79x, SA contrast at 0.90x, and TOI contrast at 0.95x, suggesting that the lesion was benign and could have potentially influenced the diagnosis.
Lastly, patient 21 was a true positive result with pathologically confirmed IDC. Her BIRADS score was 4a, which is low suspicion for malignancy but would have been confirmed by a positive biopsy. MRI/NIRS imaging quantified the HbT contrast at 1.13x, SA contrast at 1.14x, and TOI contrast at 1.05x. Though it wouldn't have changed anything, all contrasts above 1.0 would have likely increased the confidence in the MRI diagnosis. Multimodal imaging systems are designed to provide more information to influence disease management than would be available from a single modality. These four examples show how information from NIRS imaging could improve MRI specificity for breast cancer management.

8.4.4 Combined ROC Analysis

Lastly, the best optical indicators were combined with MRI for ROC analysis to perform the analysis using HbT as the NIRS parameter in the whole group of patients and in the sensitivity subset. When all patients were used, the AUC of MRI alone was 0.86 but was improved to 0.88 with the inclusion of HbT. Though these numbers for MRI are somewhat low compared to literature values, it is a small sample size of surgical patients. The NIRS imaging only slightly improves MRI, but as previously discussed, many of these patients did not have adequate tumor sensitivity for reliable NIRS measurements. When the subset with >1% sensitivity was investigated, AUC values increased substantially from 0.79 and 0.81 for HbT and MRI to 0.88 for the combination. We also saw that the optical measurements’ AUC increased to as high as 0.97 when minimum tumor sensitivity was 2.5%, which would lead to very substantial improvement for the combined modality. While these results show that NIRS imaging does improve MRI specificity (0.63 to 0.8), a combined multimodal imaging system would realize the most
potential with more effective optode coverage, increasing possible tumor sensitivity across the whole breast volume.

8.5 Conclusions

This chapter reports the results of the clinical trial in Xi’an, China where 50 surgical breast lesion patients underwent simultaneous DCE-MRI and NIRS/MRI imaging. NIRS was used to quantify HbT, StO₂, water and lipid content, SA, SP and TOI in MRI-defined regions of interest. In the entire cohort of patients, HbT contrast imaging differentiated malignant subjects from benign with statistical significance \((p=0.048)\) and was able to achieve an AUC of 0.68 (n=44). When measurement sensitivity to the tumor region was restricted to being greater than 1% (n=26), HbT and TOI were both significant indicators \((p=0.0050, p=0.0019)\) respectively, with AUCs of 0.79 and 0.82 respectively. In both cases, combined MRI and NIRS/MRI imaging had the highest AUC and (0.88 and 0.88), and performed better as NIRS tumor sensitivity increased.

In conclusion, whole breast image-guided NIR spectroscopy in combination with clinical MRI performed better than clinical MRI by itself, increasing the area under the curve and significantly improving the differentiation of malignant lesions from benign. The effectiveness of NIRS/MRI imaging is dependent on adequate measurement sensitivity and future technical studies are likely to concentrate on development of an improved NIRS source-detector array that provides full breast coverage with minimal clinical overhead in terms of positioning and use. Despite this, the functional information gained from NIRS/MRI imaging can be used to improve clinical MRI AUC. The eventual adoption of this technique in combination with MRI could help to reduce the number of
false positive results and improve patient quality of life by reducing the number of unnecessary biopsy procedures.
Chapter Nine: Conclusions and Future Directions

9.1 Completed Work

This work concentrated on the development of instrumentation and methods to optimize a multimodal imaging technology and tested the hypothesis that NIRS could increase specificity above MRI alone, to distinguish malignant lesions from benign prior to biopsy. This was achieved through use of the optimized custom 9 wavelength NIRS/MRI system, with an optical fiber interface compatible with most clinical MR breast coils. The study was successfully carried out at Xijing Hospital in Xi’an China, and through this partnership, we showed that MRI/NIRS characterization of MR-identified regions was correlated to the histo-pathological diagnosis of that same region, as assessed by pathology on the surgically removed tissues. Each section of the study results are recapped here with a focus on discussing what was most successful and what directions would be most profitable for future work.

9.1.1 System Instrumentation and Calibration

Chapter 2 summarized the important hardware aspects of the imaging system and emphasized developments made as part of this thesis. This chapter focused on the instrumentation of the NIRS/MRI system used in the clinical study and critical improvements made to the system hardware. A 9 wavelength hybrid FD/CW detector array was implemented to completely cover the spectral features of the NIR window. +20dB preamplifiers were added after each PMT to amplify the signal prior to mixing and lowered the standard deviation of repeated measurements by an order of magnitude. Using adjustable gains, the PMTs display linearity from 0.002 to 1V for amplitude and
0.02 to 1V for phase. These detectors displayed less than 1% AC noise and 1 degree phase noise even at low light levels. The PDs that were added to the NIRS/MRI system are linear over six decades, from 1pW to 2μW input light, but are limited to four orders by their two gain settings. The system uses two separate arrays of detectors to cover the whole NIR window in an integrated package that does not require manual source switching. The results of these contributions were published by El-Ghussein et al. (77).

This chapter also describes the process used for calibration of the detector array and shows the development and testing of a system for automatic calibration. This method can be useful for phase adjustments, installing new detectors, and after moving the system across the world. Finally, it takes an important step towards clinical implementation where push-button calibration is desirable. While the method is not perfect, it automates a very tedious process and promotes regular checking and quality assurance of the detector array. These methods were published by Mastanduno et al. (128).

9.1.2 NIRS/MRI Breast Coils for Combined Imaging

Chapter 3 develops the critical aspect of coupling optics with the MRI. The design and evaluation of two major iterations of the patient interface are presented with phantom results and in-vivo results from cancer patients. Discussion comparing these two patient interfaces and others with respect to patient imaging is presented. The interaction between the patient and the system must be carefully engineered specific to every imaging system to achieve maximal effectiveness. The tight confines of the MR bore make source-detector coupling to the breast even more critical in NIRS/MRI imaging. It
determined the breast sizes and densities that could be imaged, and partially determined whether NIRS was a useful addition to MRI.

In this chapter, the design and evaluation of two patient interfaces was presented. A remotely positioned parallel plate interface allowed the system to target suspicious lesions based on real time feedback from MRI. The interface was developed and tested using phantoms and healthy volunteers before being deployed in cancer patient imaging. The published paper (186) reported on the design and evaluation of the device when compared against previous generations of the interface. This device increased the degrees of freedom available to the patient imaging system and allowed for more unique measurements to be acquired in a single patient exam. However, it suffered from being unable to accommodate all breast sizes and densities, ultimately leading to a new design.

The latest generation of the patient coupling was a triangular interface integrated with a standard clinical MRI breast coil. This work made possible for imaging of breast cup sizes A and B as well as C and D. The device was tested extensively in phantoms and healthy volunteers before being used in cancer patients. The ability of this NIRS/MRI coil to image all breast sizes and compositions makes it the best patient interface to date, relative to previous generations of the technology. Key results on the development and testing of this hardware were published by Mastanduno et al. (176) and presented at the Radiological Society of North America meeting in 2012.

9.1.3 Image Formation

Chapter 4 provided background on the physics of light-tissue interaction and explained NIR spectral region recovery from a mathematical point of view using prior information derived from the MR images to improve optical reconstruction through
synergies between the two imaging modalities. Using careful formulation of the Jacobian matrix, we are able to reconstruct multiple wavelengths of both frequency domain and continuous wave data simultaneously.

Spatial priors from the MR image stack can be used to guide the NIRS estimation and turns the inverse problem into a spectroscopic region fitting rather than diffuse tomography. Tissue types were defined ahead of time and then characterized based on optical data using the custom software package, developed for this project. This process forgoes need for an exact spatial resolution in the optics, rather using that of MRI, and therefore benefits from a reduction in the number of unknowns by several orders of magnitude.

Finally, this chapter reviewed the usage of the software, Nirview, a part of Nirfast software package (www.nirfast.org), developed in collaboration with Kitware Inc. The software streamlines patient-specific mesh creation from DICOM images through image reconstruction. Tissue can be easily segmented using semi-automatic algorithms to sort tissue into adipose, glandular, and tumor regions. Sources and detectors are placed after tissue segmentation, co-registering the optical and the MR images. Originally published by Jermyn et al. (145), methods reviewed in this chapter are critical for patient imaging and represent an integrated and professional implementation of software for image-guided spectroscopy. The continued use and development of this type of software is an essential part of implementation of a hybrid system like this where one image is inherently used in the data interpretation of the other modality. Chapter 7 studied the optimization of this process in more detail for patient data as well.

9.1.4 Phantom Imaging
In Chapter 5, extensive phantom results were presented from the development of
the system. Calibration phantoms were used to account for bias error, differences in
coupling between fibers and tissue volume, model-data-mismatch, and differences in
virtual source strength in the model and real laser power at the time of imaging. This
chapter focused on an algorithm to calibrate NIRS data with respect to a known, absolute
reference phantom, and took advantage of patient specific geometry from MRI prior
information, to generate an initial guess without the need for a large data set (168).

It was shown in the parallel plate geometry phantom that imaging accuracy fell
off as a function of distance from the target absorber and that more measurements lead to
the most accurate sampling of the volume. In the second experiment, the added effects of
three more CW lasers were tested. Using both the 6 wavelength FD and the 9
wavelength FD/CW measurements, it was observed that recovered HbT contrast was
improved to only 5% error and background values to within 2% of the expected values.
Finally, a concentration phantom in the triangular geometry validated the hybrid FD/CW
system in a new patient imaging geometry. Contrast recovery was linear over a wide
range of HbT concentrations but absolute recovery and full contrast recovery were
hindered by crosstalk with scattering parameters.

9.1.5 Imaging Healthy Volunteers

Healthy volunteers were used to gain understanding of normal tissue properties
before imaging abnormal or malignant tissue, and to test imaging systems and algorithms.
Since the best phantoms today are only able to simulate some properties of the living
breast (HbO and scatter), it is necessary to image real breast tissue to get a complete
picture of all imaged chromophores and material properties. Chapter 6 continued this
testing by showing results from healthy volunteers imaged as part of three separate studies. Most importantly, healthy subjects were used extensively for the development and testing of the triangular imaging geometry.

A cohort of nine volunteers tested the remotely controlled parallel plate fiber interface and the interface was able to remotely target breast lesions found on the MRI. However, fiber contact was limited to the largest and least dense breast tissue, potentially outweighing the benefits and prompting the design of a fiber holder that could accommodate more breast cup sizes and tissue compositions. Positioning issues necessitated exclusion of data from all but three cases in cup sizes A and B and in dense breasts that couldn’t be adequately compressed. In part due to this study, accommodation of all breast sizes was found to be a more important specification than adjustability during an exam.

Next, results are presented from a more complete study of eight healthy volunteers using the newly developed triangular breast interface. This interface was able to image breasts of every cup size and the full range of natural tissue heterogeneity. Fibers were positioned closer to the chest wall as well as more posterior in the axillar region than in previous fiber arrangements. The data from these volunteers were reconstructed into images that were consistent with the literature and helped to prepare for imaging cancer patients using this geometry. The study concluded that the triangular geometry was an improvement to combined NIRS/MRI imaging in terms of coverage and performance.

Finally, a small group of three volunteers helped prepare for imaging cancer patients at the new site in Xi’an, China. These volunteers verified that instrumentation
was functional after transit and that the newly made NIRS/MRI breast coil would be able to perform clinical imaging. It gave the clinical team practice using the interface and positioning the fibers against specific locations on the breast tissue before moving forward to cancer patients. Results from these three volunteers (and phantom images) suggested that the system was working properly after shipment and was ready to scan abnormal subjects.

9.1.6 Methods for Whole-Breast MRI-Guided NIRS

After completing a prospective clinical trial of 50 surgical patients in Xi’an, China in partnership with our collaborator radiologist, Dr. Junqing Xu, Chapter 7 discussed important methodology development for processing these large data sets. It was concluded that the spatial sensitivity to the tumor region was a critical determining factor in the accuracy of recovery. Additionally, the approach to spectrally constrain the reconstruction was determined, and the choice of regularization parameter determined for this data set as a whole.

Effective NIRS imaging required greater than 1% relative tumor sensitivity, as defined by the overlap of the Jacobian sensitivity matrix with the lesion to be characterized. Above this threshold value of sensitivity, NIRS/MRI was able to separate the means of malignant and benign groups obtained from clinical pathology in both HbT \( (p=0.005) \) and TOI \( (p=0.0019) \).

Inclusion of spectral prior information affected both separation of malignant from benign as well as robustness of recovered chromophore concentrations. Spectral constraints were required to obtain clinically useful information from measurements of water, lipids, and TOI. Both reconstruction methods can be good predictors. At this point,
the overall accuracy of the constrained method makes it the preferable choice though additional work could be done on the most effective inclusion of prior information.

Though the amount of regularization required to adequately suppress noise varied based on breast density, optical fiber placement, noise within the measurements, and other factors, it was possible to find a regularization parameter that balanced tolerated noise with image contrast recovery in this data set.

9.1.7 MRI-Guided NIRS for Increased Diagnostic Specificity

Lastly, chapter 8 presented the conclusions of the clinical trial comparing clinical pathology, MRI alone, NIRS alone, and MRI/NIRS in 50 surgical breast lesion patients.

In the entire cohort of patients (n=44), HbT contrast imaging differentiated malignant subjects from benign with statistical significance ($p=0.048$) and was able to achieve an AUC of 0.68. When measurement sensitivity to the tumor region was restricted to being greater than 1% (n=26), HbT and TOI were both significant indicators ($p=0.0050$, $p=0.0019$) respectively, with AUCs of 0.79 and 0.82 respectively. In both cases, combined MRI and NIRS/MRI imaging had the highest AUC and (0.88 and 0.88), and performed better as NIRS tumor sensitivity increased.

Whole breast MRI-guided spectroscopy in combination with clinical MRI performed better than clinical MRI by itself as evidenced by ROC analysis. The functional information derived from NIRS imaging increased AUC and significantly differentiated malignant lesions from benign in multiple indicators. The adoption of this technique in combination with MRI could help to reduce the number of false positive results and improve patient quality of life by reducing the number of unnecessary biopsy procedures.
9.2 Future Directions

The work presented in this thesis has provided a great starting point to continue clinical development of NIRS/MRI imaging. The major conclusion is that the technology can be successful. It was implemented in a clinical trial of 50 patients and significantly distinguished malignant cancers from benign lesions and increased the AUC of MRI alone from 0.82 to 0.88. The study illustrated that measurement sensitivity to the tumor is critical for diagnostic value and opened doors to several methodological questions. Therefore, there are a wealth of worthwhile studies in both hardware and software.

9.2.1 Hardware Developments

9.2.1.1 NIRS/MRI Integrated Breast Coils

Throughout the course of this dissertation, two new patient interfaces were developed. The first allowed movement of optical fibers to increase the number of measurements and target regions of interest. While this aspect worked very well, the interface failed to accommodate women with very dense breasts and women with A and B cup sized breasts. The second iteration addressed these issues and accommodated all breast sizes and compositions but remains stationary during the exam. Both interfaces overcome the substantial engineering challenge of fitting optical fibers into an MRI breast coil and have strengths that justify their use. However, neither design was able to deliver the full package of accommodating all sizes while providing complete coverage. The optical fibers that are critical to light delivery and collection are bulky and cumbersome. The next generation of NIRS/MRI breast coil will likely be a complete departure from the current state.
Figure 77 shows newly developed clinical MRI breast coils that are designed to maximize open space for biopsy procedures. These coils have tracks and locking systems in place for moving biopsy equipment and would accommodate optical instrumentation well if it could be integrated intelligently.

![Breast MRI coils](image)

Figure 77: Commercially available breast biopsy MRI coils (a,b) are designed with lots of open space for biopsy procedures. Bulky and expensive optical fibers are a drawback in the current NIRS/MRI system (c).

The current design of the NIRS/MRI system also suffers due to the large, bulky fiber optic cables. They are expensive and cumbersome, making it impractical to add more fibers to collect more measurements. If the fiber diameter is reduced, it would be possible to include more fibers, but collection fibers need to be large to gather lots of light. One possible solution would be to shorten the fibers and bring the detectors closer to the patient, or to eliminate them entirely.

9.2.1.2 MRI Compatible NIRS Detectors

With the recent commercialization of combined PET/MRI, many MRI compatible detectors have become available (215). These detectors are typically photodiodes or silicon photomultiplier (SiPM) detectors and can be used to measure very low light
levels down to individual photons. They are optimized for visible light detection in PET imaging, but often have sensitivity ranges that extend into the NIR (216). Figure 78 shows an example of an SiPM detector and MR phantom images with the detector in the field.

Figure 78: AdvansID silicon photomultiplier (a) is an MRI-compatible detector developed for PET/MRI imaging. Spectral sensitivity (b) is comparable to a PMT above 600nm and MR image artifact is quite minimal (c,d).

This AdvansID (Trento, Italy) SiPM detector has a 3mm square active area and is capable of operating in linear mode or single photo counting. Though it is an MRI compatible detector, it did create artifact on an MR phantom image when it was placed directly against the phantom. When the detector was moved to 3mm away from the phantom, there was no artifact. This experiment confirmed that this detector could be placed nearly in contact with the breast without causing artifact. Light could be collected using a thin piece of inexpensive plastic light pipe.

The potential for this class of detectors to be used in NIRS imaging then comes down to their ability to measure NIR light. The AdvansID SiPM detector was tested in
phantom experiments over a wide range of input light levels, shown in Figure 79. The detectors require an amplifier that does cause MR image artifact but can be separated using a connecting wire. Two tests were done, one using an amplifier that was connected to the SiPM and one that had the amplifier on a 10m cable.

![AdvansID SiPM Dynamic range](image)

**Figure 79:** An AdvansID SiPM detects light linearly from 100pW to 100nW. The amplifier can be located 10m away with no difference in signal.

The AdvansID detector was able to linearly detect light spanning 3 decades from 100pW to 100nW. This is roughly equivalent to many PD-based NIRS systems and is certainly suitable for NIRS imaging. Furthermore, there was no difference in recovered signal when the amplifier was next to the detector or connected with a 10m cable. Therefore, this detector could even be suitable for NIRS/MRI right up against the tissue.

El-Ghussein et al. also tested a Hamamatsu SiPM device, shown in Figure 80. This detector shows similar performance to the AdvansID when tethered to the amplifier.
with a 1m cable. This detector is especially exciting since the dynamic range can be adjusted by changing the bias voltage, similar to a regular PMT.

Figure 80: A Hamamatsu SiPM (a) has spectral sensitivity (b) suitable for NIRS imaging. This detector’s dynamic range can be adjusted with a varying bias voltage (c) (unpublished, El-Ghussein et al).

The SiPM detectors seem promising for NIRS imaging in the MRI, though formal proof of concept studies need to be done. These detectors could be used inside the MRI scanner and would eliminate the need for long fibers. With careful design, these detectors could be incorporated into a breast interface that provides complete coverage. Unfortunately, SiPM detectors are not fast enough to do frequency domain imaging and separate solutions for detection of scatter would be required.

9.2.2 Software Developments

From a software standpoint, there are many questions that could be studied that would eventually lead to methodology development for future NIRS/MRI studies. The large clinical data set presented in Chapter 8 will provide lots of opportunity for data mining and development.
9.2.2.1 3D Cross Sectional Imaging

One obvious question that arises from the work done on sensitivity is that of 3D cross sectional imaging. Figure 81 shows a breast with the relative tumor sensitivity plotted in relation to the breast volume. It is apparent that a large portion of the breast away from the plane of the fibers is outside the region of sensitivity. Therefore, is it worth meshing and performing computations on that part of the breast? It could be possible to use a thick slice of the breast to achieve diagnostically equivalent results to the full 3D reconstruction. This would save drastically on computation time and simplify meshing, making it a potentially worthwhile investigation.

![Image](image.png)

Figure 81: *Measurement sensitivity only extends a few centimeters away from the plane of imaging. It could be possible to reduce computation time by reconstructing only the sensitive region.*

9.2.1.2 Deriving Scatter from MRI

Another area that could be worth investigating is the idea of deriving scattering information from MRI. MRI is exceptionally good at separation of adipose and fibroglandular tissues and previous studies have shown significant correlation between fibroglandular content and NIRS based water and lipid measurements (59). It is possible that the bulk scattering values in breast are largely dependent on the ratio of the two
tissue types and that correlation between the optical scattering parameters and MRI derived ratios exist as shown in Figure 82. If it was possible to assign scatter with a reasonable degree of accuracy based on MRI only, NIRS/MRI imaging would be simplified substantially because continuous wave methods would be sufficient.

![Figure 82: $\mu_s'$ at 785nm versus the ratio of adipose nodes to glandular nodes in 44 NIRS/MRI patients. The data is messy but shows a downward trend.](image)

9.2.1.3 Regularization vs. Sensitivity

As described in Chapters 4 and 7, the amount of regularization required to adequately suppress noise varies based on breast density, optical fiber placement, noise within the measurements, and other factors that vary on a case-by-case basis. Regularization and tumor sensitivity are closely related. Data sets that have relatively good tumor sensitivity are able to handle large amounts of regularization because the tumor has substantial influence on the data set. Noise is smoothed and it is still possible to recover contrast. However when tumor sensitivity is very small, the regularization can smooth the small amount of influence that the tumor has on the data. Reconstructing the same data with many different regularization parameters is not always feasible due to
computation time. An investigation of how to determine starting regularization could prove to be very useful. Since tumor sensitivity is quantifiable and influences regularization, it may be possible to correlate the two to efficiently select the ideal regularization parameter for an individual case.

9.2.2.4 Inclusion of A-Priori Knowledge

Inclusion of spectral prior information affects the results obtained from a patient exam and different methods seem to work better for various situations (217). The results in Chapter 7 suggest that scattering parameters may be more effective when reconstructions are unconstrained but that tissue chromophores require constraints to achieve the highest accuracy. Though the overall accuracy of the spectrally constrained method is higher, it could be possible to combine the two reconstruction schemes to couple the strengths of each. Ultimately, larger patient studies will confirm the most effective methods and the most effective hardware, and the future directions discussed here could be useful contributions to NIRS/MRI.
Appendices

Appendix A: Agarose Phantom Recipe

These instructions can be used to make tissue phantoms of Agarose and whole blood with optical properties of approximately $\mu_s' = 0.9$ and $\mu_a = 0.006$.

Overview:

1. Measure blood levels
2. Microwave agarose/PBS to rolling boil
3. Add intralipid/PBS and stir on stir plate
4. Cool to 38°C
5. Add blood and mix
6. Pour into mold
7. Set in refrigerator 30 minutes

Measure ingredients into containers:

Measure the hematocrit of your blood using the hemocue device, which is next to the sink in a drawer in the breast imaging lab across from the AIC. Fill the glass sample with blood by just touching the corner of a slide to a drop of blood. It will suck up the correct amount. Measure a few different drops and average to get an accurate reading, usually between 5 and 15 g/dL in pig blood.

Container A, 600ml beaker:

240 ml Phosphate buffered saline (PBS)
4.8 g Agarose
The steps below outline the procedure to make 480ml of phantom with a background at normal breast tissue levels (15µM HbT).

Measured hematocrit: 14.8g/dL = 148g/L

\[
148g/L \times \left( \frac{1 \text{ mol}}{64500g} \right) = 2295\mu\text{M blood}
\]

\[
2295\mu\text{M} \times \left( \frac{X}{480\text{ml}} \right) = 15\mu\text{M} \quad X = 3.14\text{ml whole blood}
\]

**Container B**, 600ml beaker:

- 18 ml Intralipid
- 240 ml – (18 ml +X ml) PBS

**Container C**, syringe:

- X ml whole blood

**Mix containers:**

Put container A in the microwave long enough to get it to a rolling boil for 15 or 20 seconds. This usually takes about 2 minutes. If this solution does not get hot enough, then your phantoms will be weak and likely to break. After it’s been boiling, take it out and put it on a stir plate, stirring quickly. The substance should be hot (maybe 60°C) and clear. While it’s still stirring, add container B’s contents into container A. The mixture will now be milky and hot (~50°C). Monitor the temperature of this mixture closely. When it gets to 38°C, add the blood in container C. Adding the blood much hotter than this could cook it and change the optical properties.

The mixture should now be smooth, with the consistency of a heavy cream, pink, and about 38°C. Let the blood stir in for a minute or two, pull the stir bar out, and poor the contents into your mold. The Agarose will start to set at about 35°C. If the mixture is
chunky when you’re pouring it into the mold, it will have air bubbles in the final phantom. Place this in the fridge for at least 30 minutes.

**Inclusions, removal, and expiration date:**

If you want an inclusion in your phantom, prepare the mold by suspending a syringe with the plunger up where you want the inclusion. After the background sets, you can pull the syringe out by depressing the plunger, equalizing the pressure in the bottom of the hole. You can fill it with higher concentration blood/Agarose mixture or liquid.

To remove the phantom from its mold, use a knife to go around the edge and break the seal. Be careful not to cut into the phantom. Turn it upside down and it should slowly slide out of the mold. The phantom should be firm but jiggly, and slimy.

Image as soon as possible, and then discard. As long as it has anti-coagulant in it, opened infrequently, and is stored in a dark place, blood will last (optically) for 2-3 weeks from the time it's drawn. Whole blood can be obtained from the DHMC animal labs or from Lampire Biological.
Figure: Finished phantom with a 2x blood contrast absorbing inclusion.
## Appendix B: Matlab Code

<table>
<thead>
<tr>
<th>Function Name</th>
<th>Description</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Best_dataXX</em></td>
<td>Script to calibrate and reconstruct China patient XX</td>
<td></td>
</tr>
<tr>
<td><em>Calibrate_spectral_initial</em></td>
<td>Uses Nirfast slope based calibration to set the optical properties of a phantom before using direct calibration</td>
<td></td>
</tr>
<tr>
<td><em>Case_report</em></td>
<td>Plots 3 region graphs of China patients given solution structures</td>
<td>Solution structures come from <em>read_bestdata_solutions</em></td>
</tr>
<tr>
<td><em>Case_report_bg</em></td>
<td>Plots 2 region graphs of China patients given solution structures</td>
<td>Solution structures come from <em>read_bestdata_solutions</em></td>
</tr>
<tr>
<td><em>Combine_cursor_data</em></td>
<td>Brushed data from <em>plot_lnri</em> is removed by adding a zero in the correct place in the link field</td>
<td>Used with <em>plot_lnri</em> and <em>remove_cursor_data_func</em></td>
</tr>
<tr>
<td><em>Direct_cal</em></td>
<td>Calibrates data versus an absolute reference phantom using single wavelength, single region reconstruction. A single region spectral reconstruction should be done afterwards.</td>
<td>Other versions: Spectral FD, CW, FDCW Parallel FD, CW, FDCW Standard and parallel standard</td>
</tr>
<tr>
<td><em>Drop_fibers</em></td>
<td>Removes all data from a given fiber</td>
<td></td>
</tr>
<tr>
<td><em>Find_nodes</em></td>
<td>Finds sensitivity to</td>
<td></td>
</tr>
<tr>
<td><em>Load_experiment</em></td>
<td>Loads data from a NIRS/MRI system and removes data points below given voltage threshold</td>
<td></td>
</tr>
<tr>
<td><em>Partest</em></td>
<td>Calculates statistics for patient data (from matlab central)</td>
<td>Used with <em>roc</em></td>
</tr>
<tr>
<td><em>Phantom_calculator</em></td>
<td>Solves concentrations for phantom recipe given desired optical properties</td>
<td></td>
</tr>
<tr>
<td><em>Plot_2_datasets</em></td>
<td>Plots 2 datasets versus data point number on the same graph</td>
<td></td>
</tr>
<tr>
<td>Function</td>
<td>Description</td>
<td>Notes</td>
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</tr>
<tr>
<td>Plot_Lnri</td>
<td>Plots data versus source detector distance</td>
<td></td>
</tr>
<tr>
<td>Plot_Lnri_regions</td>
<td>Plots data versus source detector distance and color codes data points by sensitivity</td>
<td>Uses find_nodes</td>
</tr>
<tr>
<td>Plot_vs_femdata</td>
<td>Plots a dataset versus femdata for a given mesh</td>
<td></td>
</tr>
<tr>
<td>Read_proj_error</td>
<td>Reads through the log file of a reconstruction to find the projection error versus iteration</td>
<td></td>
</tr>
<tr>
<td>Read_solution_pj</td>
<td>Reads a mesh solution at the lowest projection error</td>
<td></td>
</tr>
<tr>
<td>Readmesh</td>
<td>Plots bar graphs of all regions and chromophores in a hard priors mesh (&lt;=4 regions)</td>
<td></td>
</tr>
<tr>
<td>Read_best_data_func</td>
<td>Loads solution data from China patients</td>
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<tr>
<td>Read_best_data_solutions</td>
<td>Creates patient solution structures from China data</td>
<td></td>
</tr>
<tr>
<td>Reconstruct_spectral_region_fdCW</td>
<td>Reconstructs data as in Nirfast but accommodates combined FD and CW data. Regularization can be different for amplitude and phase</td>
<td></td>
</tr>
<tr>
<td>Reconstruct_spectral_region_fdCW_fixedreg</td>
<td>Reconstructs data as in Nirfast but accommodates combined FD and CW data. Regularization is not decreased between iterations. Regularization can be different for amplitude and phase. Stopping criteria is &lt;0.2% change.</td>
<td>Used with combine_cursor_data</td>
</tr>
<tr>
<td>ROC</td>
<td>Calculates ROC analysis for clinical data (from matlab central)</td>
<td>Used with partest</td>
</tr>
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</table>
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