Dynamic Digital Optical Tomography for Cancer Imaging and Therapy Monitoring

Molly Flexman

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ABSTRACT

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Diffuse optical tomography is a non-invasive imaging technique that uses near-infrared light to create three-dimensional images of tissue. This dissertation presents the design and validation of an instrument for rapid optical imaging using digital detection techniques. In addition to a detailed description of the instrument, three studies are presented: a clinical study detecting breast cancer using dynamic optical imaging; a pre-clinical study monitoring early tumor response to anti-angiogenic therapy; and a clinical study monitoring individual patient response to neoadjuvant chemotherapy. These studies show that diffuse optical tomography is a valuable imaging modality that can play an important role in cancer detection and treatment.
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<td>MPE</td>
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<td>UART</td>
<td>Universal Asynchronous Receiver/Transmitter</td>
</tr>
<tr>
<td>U</td>
<td>Eurocard Rack Unit (1 U = 1.75 inches)</td>
</tr>
<tr>
<td>US</td>
<td>Ultrasound</td>
</tr>
<tr>
<td>VEGF</td>
<td>Vascular Endothelial Growth Factor</td>
</tr>
</tbody>
</table>
Publications Resulting from This Work

**PATENTS**

**JOURNAL PAPERS**


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**CONFERENCE PROCEEDINGS**


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How could one furry white 40 pound dog called Jack have made an impact on this thesis you might ask? Well, with eager tail wags, licks, and performing tricks every time I come home from a difficult day at the lab. I encourage every PhD student to get a pet.

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Dedication

For Mom and Dad.
Chapter 1 : Introduction

Breast cancer affects approximately 1 in 8 women in the United States and the incidence throughout the world is increasing [1]. While mammography is still the current standard of care, its shortcomings have led to the exploration of novel imaging modalities to improve the sensitivity and specificity and to provide screening alternatives for young women, women at high risk, and women with dense breast tissue. Over the past ten years, research in the field of diffuse optical tomography (DOT) for breast cancer has grown substantially. DOT shows significant promise in both detecting tumors and predicting their responsiveness to treatment due to its strong sensitivity to physiologically relevant parameters such as hemoglobin, fat, and water [2].

1.1 General goals and specific aims

The goal of this thesis is to develop and validate a new DOT system that can perform simultaneous measurements of both breasts at fast imaging speeds for use in dynamic imaging studies. The instrument is built upon digital detection techniques that leverage a digital-signal-processor (DSP) design to acquire and process large amounts of data quickly, with high sensitivity, and a large dynamic range. This system opens up a new realm of breast imaging studies focusing on the hemodynamic signature of the breast in response to an external stimulus. Clinically, there are two main areas where DOT could make an impact in the current state of breast cancer management. Firstly, in breast cancer screening, the non-ionizing, low-cost, and more comfortable imaging geometry makes DOT an ideal tool for use in primary
screening, secondary screening, or the more frequent imaging required for high-risk groups. Secondly, there is a growing need for real-time feedback during chemotherapy treatments to adjust the timing and treatment type according to the individual patient’s response. In investigating the role that DOT may play in breast cancer management we will pursue the following specific aims:

**Aim 1: Develop and characterize a DOT breast imaging system that uses digital detection techniques**

*Challenge:* To capture enough data to image both breasts simultaneously and fast enough to capture dynamic features.

*Approach:* We will employ digital detection techniques including multiple digital signal processor (DSP) chips for processing data. Configured in a master-slave architecture these DSP chips can streamline data collection while minimizing cost, improving scalability, and maintaining low noise levels.

*Impact:* This will be the fastest DOT system to simultaneously image both breasts in a 3D geometry. This will enable studies focused on detecting breast cancer based on the hemodynamic response to a stimulus.

**Aim 2: Test the new DOT system in a pilot study using a breath hold to identify breast tumors**
**Challenge:** To identify dynamic features that can be used to detect breast tumors in response to a breath hold.

**Approach:** We will identify optimal time points during the imaging sequence for separation of tumor/non-tumor regions. We will also explore differences in the transient response of tumor regions as compared to healthy tissue.

**Impact:** This pilot study will provide a basis for further studies looking at the dynamic signature of breast cancer.

**Aim 3: Explore the use of DOT for imaging early vascular response to drug therapy in a pre-clinical tumor model**

**Challenge:** To determine if DOT can distinguish responsive from non-responsive tumors within a few days of beginning therapy.

**Approach:** Two tumor types will be studied: a responsive Ewing Sarcoma and a non-responsive Neuroblastoma. We will aim to differentiate between the two tumor types using DOT imaging performed at baseline and 1, 3, and 5 days following treatment.

**Impact:** Anticipating tumor response to therapy can enable more tailored treatment schedules that reduce toxicity and lower cost, thereby improving patient outcomes. This pre-clinical model will provide a basis for Specific Aim 4.

**Aim 4: Investigate the use of DOT in monitoring and predicting chemotherapy response in breast cancer patients**
**Challenge:** To use DOT to predict if a breast tumor will respond to neoadjuvant chemotherapy treatment.

**Approach:** We will image each patient at scheduled intervals over several months of chemotherapy. We will correlate the response seen in DOT imaging to actual tumor response.

**Impact:** DOT can help inform clinical decisions about treatment schedules and drug effectiveness on a patient-specific basis. Ultimately this could reduce toxicity, lower costs, and improve patient outcomes.

Exploring these specific aims will introduce new state-of-the-art technology to the field of DOT that will facilitate future studies using dynamic changes to detect breast tumors. This technology will be used for studies that could help enhance traditional breast cancer screening and improve the quality of care for patients undergoing chemotherapy treatments.

**1.2 Breast Cancer**

*Breast Cancer Management*

Breast cancer affects approximately 1 in 8 women in the United States and the incidence of breast cancer throughout the world is increasing [1]. Breast cancer currently accounts for 28% of all new cancers diagnosed in women, with almost 40,000 deaths caused by breast cancer each year [3]. However, from 1975 to 2000 there was a 24% reduction in breast cancer deaths due to screening mammography and adjuvant therapy [1, 4]. It is clear that breast cancer screening, diagnosis, and therapy is a critical issue to women's health. In assessing
opportunities for improving breast cancer care and outcomes, there are a number of steps during the screening, diagnosis, and treatment where one can look to improve upon the current techniques. An overview of the steps involved in breast cancer management is shown in Fig. 1-1.

Figure 1-1. Overview of breast cancer management.
Following an abnormal screening mammogram, or a palpable mass detected by a self or clinical breast exam, the patient typically undergoes secondary screening. Secondary screening includes diagnostic mammography, ultrasound (US) or magnetic resonance imaging (MRI). US and MRI are less sensitive to breast density and can provide additional information to differentiate between benign and malignant masses. In cases where the MRI and US imaging is inconclusive, the patient may be referred for nuclear imaging, which includes positron emission mammography (PEM, also known as positron emission tomography PET) or breast-specific gamma imaging (BSGI). Both of these imaging modalities are based on the same technology, but use different radiotracers to identify cancer cells based on their increased uptake of the tracer.

If secondary imaging indicates that there is a possible malignancy in the breast, then a biopsy is performed for a pathological assessment of the cells of the suspicious region. The biopsy needle must be guided into the correct region of the breast and this is usually accomplished by either ultrasound-guided biopsy, stereotactic biopsy (x-ray guided), or MRI-guided biopsy, depending on which modality has the best visualization of the tumor. The imaging and biopsy results combine to form the diagnosis. In cases of locally advanced breast cancer, involving a large tumor that has not metastasized to any other region in the body, the patient may be referred for neoadjuvant therapy prior to surgery. Surgery may include a lumpectomy or mastectomy. Following surgery the patient may undergo a number of adjuvant therapies including radiation, hormone therapy, treatment with monoclonal antibodies, and chemotherapy. Breast reconstruction may also occur following surgery.
Breast cancer management combines a large amount of information from a variety of sources in order to improve patient outcomes. New technologies must consider how they can best fit into and improve the entire process.

Breast Cancer Pathology

Breast cancer is a generic term that covers a wide range of pathologies. Understanding the various types of breast cancer is important in preparing new imaging strategies. Breast cancer typically begins with a mutation to an epithelial cell lining the ducts and/or the lobules. Ductal carcinomas make up the majority of detected breast cancers, but lobular carcinomas, which make up 5-15% of breast cancers, are significantly harder to detect with traditional screening methods due to the fact that they often create single cell strand-like growths as opposed to masses and tend to be multifocal in the breast [5].

Ductal Carcinoma in situ (DCIS) is characterized by the proliferation of large, cohesive malignant cells from the epithelial lining of the duct or lobule, but where there is no evidence of invasion. Approximately 20% of diagnosed breast cancers are caught prior to invasion [5], and mammography is the primary imaging modality for diagnosis of DCIS by identifying microcalcifications. However, mammography is not very sensitive to DCIS and is unable to evaluate the extent of the DCIS. MRI imaging has shown promise in visualizing DCIS, but has variable sensitivity to DCIS, with published studies showing sensitivities ranging from 16-73% [5]. This may be partially attributed to the fact that DCIS is highly heterogeneous and can exist in both mass and non-mass form. DCIS also ranges from low-grade to high-grade classification. High grade is associated with a poorer prognosis, and means that there are malignant nuclear
features as well as necrosis. Low grade DCIS is characterized by uniform cells without necrosis and in its mildest form is identified as Atypical Ductal Hyperplasia (ADH). Lobular Carcinoma in situ (LCIS) and Atypical Lobular Hyperplasia (ALH) are pre-invasive lobular carcinomas and are rarely detected by screening as they do not form masses. LCIS is rarely associated with calcifications, is almost always multifocal, and is more frequently bilateral than DCIS. Invasive Ductal Carcinoma (IDC) and Invasive Lobular Carcinoma (ILC) are cancers where the malignant cells have invaded out of the ducts or lobules into the surrounding normal tissue. Breast cancer spreads three ways: direct invasion, through the lymphatic system, or via the blood vessels. Primary tumors are ultimately responsible for only 10% of deaths from cancer, making metastatic tumors in remote sites in the body the primary cause of death [6]. In breast cancer the most likely locations of metastases are bone marrow, lungs, liver, and brain.

Growing tumors require increased access to nutrients and oxygen, which they obtain by creating new vasculature via a process known as angiogenesis. Angiogenesis is evident even in preinvasive cancers; high-grade DCIS is associated with a rim of microvessels around the ducts to supply the proliferating tumor cells [7]. As the tumor continues to grow and invade, it increases the amount of surrounding vasculature. Studies have shown that the vascular density of a tumor correlates with disease-free-survival [6]. In addition, due to the fact that the pro-angiogenic factors are continuous and abundant in the tumor region, the vasculature fails to create an efficient and mature network. As a result, tumor vasculature is typically irregular, leaky, and tangled with no clear progression from arteries to capillaries to veins. Understanding
and visualizing the vascular features of tumors can help differentiate benign from malignant masses, predict outcomes, and provide additional information about the tumor physiology.

**Breast Cancer Imaging**

The most commonly applied modality for breast cancer screening is x-ray mammography. This screening technique is widely used due to its ease of administration and relatively good sensitivity and specificity given its low cost. However, its use of ionizing radiation limits the frequency with which this modality can be employed. Furthermore, mammography has shown to be less reliable for young women and women with dense breasts, to cause patient discomfort, and its high false positive rate means that after 10 years of screening 1 in 2 women will have had at least one false positive mammogram [8, 9].

As an alternative to x-ray mammography, magnetic resonance imaging (MRI) has proven to be a powerful tool in secondary imaging and in monitoring high-risk women, but its high cost and low specificity hinders its use as a screening modality [8]. In addition, breast MRI typically uses an injected contrast agent and has some contraindications (pacemakers, claustrophobia). Dynamic contrast-enhanced MRI (DCE-MRI) uses the kinetic uptake curves of the suspicious region to differentiate between benign and malignant lesions based on the vascular perfusion, vessel density, and leakiness. MRI can also be used to assess the extent of disease in already detected cancers, and is being investigated for monitoring chemotherapy treatment.

Ultrasound imaging (US) is commonly used as a second-line diagnostic tool to differentiate masses detected with x-ray mammography, but operator variability and low specificity make it unsuitable for front-line screening [8]. Ultrasound imaging can distinguish
cysts from tumors, can be used to estimate tumor size, and is commonly used to guide biopsies. Recently, automated whole breast ultrasound (AWBU) has been explored as a way to standardize breast ultrasound imaging for use in screening applications. This technique is still in early stages of research.

Diffuse optical tomography (DOT) is a non-ionizing modality that is sensitive to physiologic changes and may be able to address some of the shortcomings of other breast imaging modalities [2, 10]. Nuclear imaging techniques including PEM and BSGI have gained attention for their ability to detect small tumors, their high sensitivity, and the ability to visualize ductal and lobular carcinomas. A comparison of some of the available breast imaging modalities is presented in Table 1-1 [11], below. This table is by no means comprehensive, as there is also ongoing research into a variety of imaging techniques including diffusion-weighted MRI, ultrasound elastography, thermography, electrical impedance imaging, and more. The extensive effort that is currently committed to finding new breast imaging modalities to improve breast cancer management is indicative of the importance of this field, and the impact that these new technologies can have on a large population of patients.
### Table 1-1. Comparison of various breast imaging modalities.

<table>
<thead>
<tr>
<th>Modality</th>
<th>Cost</th>
<th>Sensitivity, Specificity</th>
<th>Contrast Mechanism</th>
<th>Current Uses</th>
<th>Radiation</th>
<th>Pros/Cons</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mammography - Digital [8]</td>
<td>$85 $134</td>
<td>65-90%, 30%</td>
<td>Microcalcifications and increased tumor density.</td>
<td>-Primary Screening -Biopsy</td>
<td>Y</td>
<td>+easy to administer +good sensitivity -painful compression -less sensitive for dense breasts -high false positive rate</td>
</tr>
<tr>
<td>MRI (&amp; DCE-MRI) [12]</td>
<td>$1000</td>
<td>79-100%, 37-97%</td>
<td>Gadolinium uptake in the tumor region due to leaky vasculature.</td>
<td>-Secondary Imaging -Biopsy -High Risk Screening -Therapy Monitoring</td>
<td>N</td>
<td>+high resolution +good for dense breasts -requires injection (DCE-MRI) -high false positive rate -~60 minutes/exam -high cost</td>
</tr>
<tr>
<td>Ultrasound - Sonography</td>
<td>$83</td>
<td>13-65%, 45%</td>
<td>Sound waves are reflected due to changes in density.</td>
<td>-Secondary Imaging -Biopsy</td>
<td>N</td>
<td>+good for assessing tumor size +differentiates cysts from tumors +good for dense breasts -low sensitivity -operator-dependent</td>
</tr>
<tr>
<td>Diffuse Optical Tomography</td>
<td>$80*</td>
<td>80%, 70-80%</td>
<td>Increased light absorption in tumor region due to angiogenesis.</td>
<td>-Under Investigation</td>
<td>N</td>
<td>+non-ionizing, non-compressive +sensitive to physiology +endogenous contrast -poorly resolved</td>
</tr>
<tr>
<td>Positron Emission Tomography [13]</td>
<td>$1000</td>
<td>93%, 83%</td>
<td>$^{18}$F-FDG radiotracer has increased uptake in tumor cells.</td>
<td>-Secondary Imaging</td>
<td>Y</td>
<td>+good resolution +good sensitivity for DCIS, ILC -less sensitive for dense breasts -injection of radiotracer</td>
</tr>
<tr>
<td>Breast-Specific Gamma Imaging [14]</td>
<td>$1000*</td>
<td>96.4%, 59.5%</td>
<td>Increased uptake of Tc99M by tumor cells.</td>
<td>-Secondary Imaging</td>
<td>Y</td>
<td>+good at identifying small tumors +good sensitivity for DCIS, ILC -~40 minutes/exam -high false positive rate -injection of radiotracer</td>
</tr>
</tbody>
</table>

*Approximate cost based on similar techniques.

### 1.3 Diffuse Optical Tomography (DOT)

Over the last decade, DOT has emerged as a novel biomedical imaging modality that may be able to address some of the shortcomings of other breast imaging modalities [2, 10]. DOT uses low-intensity light in the red to near-infrared wavelength range to probe and characterize...
breast tissue. By illuminating the tissue from various spatially distributed source positions and measuring the transmitted and reflected light at a number of detector positions surrounding the sample, DOT generates 3D spatial maps of the absorption ($\mu_a$, typically 0.01-1 cm$^{-1}$) and scattering ($\mu_s'$, typically 10-100 cm$^{-1}$) of tissue. The reduced scattering coefficient ($\mu_s'$) is commonly used to characterize both the scattering ($\mu_s$) and the anisotropy ($g$) of the tissue as shown in Eq. 1.1. Anisotropy is a measure of the directionality of the scattering (in isotropic scattering the light is deflected to all angles equally, whereas anisotropic scattering favors a specific angular range).

$$\mu_s' = \mu_s(1 - g)$$  

(1.1)

By illuminating the sample with multiple wavelengths of light and using the known absorption spectra of optically-relevant tissue chromophores, we can extract the concentration of those chromophores. Fig. 1-2 shows the absorption spectra of the four primary optical absorbers in the breast: oxygenated (HbO$_2$) and deoxygenated hemoglobin (Hb), fat, and water [15-17]. Fig. 1-2 illustrates why the near-infrared (NIR) wavelength window from 650-900 nm is ideal for tomographic imaging of tissue: the absorption of blood is significantly lower than at the lower visible wavelengths, but the absorption of water and fat is still quite low (it increases dramatically above 1000 nm).
Figure 1-2. Optical absorption of oxy-hemoglobin (HbO₂), deoxy-hemoglobin (Hb), water (H₂O), and fat plotted versus wavelength, showing the 650-900 nm NIR window ideal for optical imaging of tissue.

For a tissue comprised of $N_c$ absorbing chromophores the total absorption of the tissue at a given wavelength, $\mu_a(\lambda)$, can be described by Eq. 1.2, where $C_i$ is the concentration of the $i$-th chromophore and $\varepsilon_i$ is the molar extinction coefficient of the $i$-th chromophore at that wavelength. $C_i$ is the only unknown in Eq. 1.2, since $\mu_a(\lambda)$ is measured experimentally and $\varepsilon_i$ is known (see Fig. 1-2). By measuring the absorption coefficient at $N_c$ wavelengths, Eq. 1.2 produces four equations with four unknowns, allowing us to solve for the concentrations of the optically absorbing chromophores ($C_i$).

$$\mu_a(\lambda) = \sum_{i=1}^{N_c} \varepsilon_i(\lambda)C_i$$  \hspace{1cm} (1.2)

DOT differs from x-ray imaging in a number of important ways. Firstly, x-ray imaging uses shorter, higher energy wavelengths of electromagnetic radiation whereas DOT uses longer, lower energy wavelengths. This means that optical imaging is a safer method of
imaging than x-ray mammography as it doesn’t expose the tissue to harmful high-energy radiation. However, the use of safer, lower energy electromagnetic radiation (light) comes at a cost. Electromagnetic waves are subject to scattering by structures of a similar size to the wavelength. This means that near-infrared light is subject to scattering by cellular and subcellular structures (such as mitochondria). As a result, unlike high-energy x-rays that pass through the tissue in relatively straight lines with little scattering, near-infrared light will pass through the tissue in a scattered, more diffuse distribution. The propagation of some initial x-ray intensity ($I_0$) through tissue can be modeled by the Beer-Lambert law, Eq. (1.3), and the absorption ($\mu_a$) within the tissue can be reconstructed using the inverse radon transform.

$$I(x) = I_0 e^{-\mu_a dx} \tag{1.3}$$

The Beer-Lambert law requires a known path length ($dx$) for the electromagnetic wave passing through the tissue. In optical imaging, the path length depends heavily on the number of scattering events and will vary for each photon exiting the tissue (Fig. 1-3). As a result, modeling the propagation of light in tissue is significantly more complicated and prevents the use of a direct inversion scheme to solve for the absorption and scattering coefficients of the tissue. Reconstructing optical properties (namely absorption and scattering) is a mathematically ill-posed problem that is computationally expensive and is the subject of significant research effort [18-20].
A second significant difference between DOT and x-ray imaging is the source of contrast. X-ray imaging relies predominantly on the photoelectric absorption of energy by atoms with a high atomic number. In tissue, this means that calcium (atomic number of 20) is a primary x-ray absorber, which is why microcalcifications are a source of contrast in detecting breast tumors using mammography. In DOT, contrast is derived from the primary absorbers and scatterers of light at a given wavelength. In the red to near-infrared wavelength range the primary absorbers of the breast are blood (oxy- and deoxy-hemoglobin), water, and fat. All four of these chromophores have been shown to be valuable in detecting and characterizing breast tumors [21]. Increased blood is a hallmark of growing tumors that require increased vascularization to continue to receive adequate nutrient supply and remove waste products [6]. Growing tumors also push away the surrounding adipose tissue, resulting in decreased lipid. The water content may be related to the cellularity and corresponding aggressiveness of the tumor. Water and lipid are also correlated to breast density, a known breast cancer risk factor. Furthermore, light is sensitive to scattering changes in tissue. Researchers have shown that differences in the scattering properties of tissue, due to cellular changes such as enlarged and
denser nuclei, can be used to detect breast cancer [22, 23]. Specifically, increases in scattering power and scattering amplitude can differentiate certain types of cancer from healthy tissue [24]. Overall, diffuse optical tomography is rich in contrast that is not readily available to any other imaging modality.

1.4 Instrumentation for Diffuse Optical Tomography

DOT is a relatively young technology that has yet to be commercialized on a large scale. Instrumentation for DOT is typically designed by investigators for use in specific applications. Many research groups have made significant advances in the field of DOT breast imaging, focusing on a variety of designs for instrumentation [24-39]. These designs fall into three broad categories based on the type of light illumination: time-domain (TD), frequency-domain (FD), and continuous-wave (CW).

TD systems inject a short light pulse (full-width-half-maximum typically less than 0.1 ns) into the breast and measure the time-dependent transmitted intensities. These systems provide a wealth of information about the optical properties of the tissue, however, data acquisition typically takes 3-5 minutes and the systems are comparably expensive. Taroni et al. have shown an 80% sensitivity in detecting breast lesions with a 5-7 wavelength time TD system in a retrospective study of 194 patients [29]. In particular, they showed that while strong absorption of blood at the short wavelengths is a hallmark of tumors, it is low scattering across wavelengths, and low absorption around the lipid peak (905-916 nm) that allows for the differentiation of cysts. Rinneberg et al. also showed sensitivity and specificity between 80% and 85% for tumor detection in a study of 154 patients using a 2-wavelength TD system [30].
Another type of instrumentation, known as frequency-domain (FD), uses amplitude-modulated light instead of a short light pulse to probe the breast tissue. These systems operate at one or more source-modulation frequencies and gather data on both the amplitude and phase of the light that passes through the tissue. FD instrumentation is typically less expensive than TD instrumentation and allows for faster data acquisition than TD systems. Using this technology Choe et al. showed the ability to differentiate between benign and malignant tumors in 47 subjects with a sensitivity and specificity of 98% and 90% [26]. Analyzing data from 60 healthy patients, Srinivasan et al. conducted one of the most comprehensive studies on the properties of normal breast tissue using a 6-wavelength FD system [32], and have shown promising results in small populations of breast cancer patients [24].

The third category of DOT instrumentation does not rely on a time-varying light source, and instead injects a steady-state beam of light into the breast. Known as continuous-wave (CW) systems, the instrumentation measures the change in the amplitude of the light as it passes through the breast, which results in simpler, more affordable technology. While no phase information is acquired, this approach allows for faster data acquisition than in FD or TD systems, which makes it possible to study intrinsic time-varying dynamic signals. Several groups have made successful use of CW instrumentation for breast cancer detection including Liang et al. who showed sensitivity and specificity of 82% and 71% in 33 patients [33] and van de Ven et al. who showed detection rates of 60 to 80% in 17 patients [40].
In addition to these three classes of optical tomography imaging systems (TD, FD, and CW), a number of promising hybrid systems have been developed that combine DOT with other imaging modalities such as x-ray mammography [27], ultrasound [35, 36], and MRI [25, 38].

1.5 Dynamic Optical Imaging

Regardless of the type of instrumentation, all categories of DOT systems rely on endogenous contrast generated by the physiology of the tissue. Most studies have focused on the steady-state changes that can be observed in malignant tissue, notably, increase blood due to tumor angiogenesis, increased scattering due to tumor cellularity, or decreased oxygen saturation due to tumor hypoxia. However, there are also transient features that can be used to identify malignant tissue.

Tumor vasculature is known to be tortuous and disorganized, hyperpermeable, and lack proper vasomotor function [41]. Tumor cells consume large amounts of oxygen which, coupled with poor oxygen delivery, leads to tumor hypoxia. These changes not only affect the steady state appearance of the malignant tissue, but also affect the hemodynamic response of the cancerous tissue, providing additional information that can assist with the diagnosis. Some common sources of dynamic contrast used to evoke a hemodynamic response include a respiratory maneuver [42], the application of pressure to the breast [27, 39, 43], the respiration of carbogen [44], and the injection of indocyanine green (ICG) [38, 45, 46].

The existing systems used in dynamic imaging studies are limited in three-dimensional spatial resolution, temporal resolution, or dynamic range. Almost all of the systems image only one breast at a time, and therefore are without a reference, or use a reference acquired under
a different stimulus. Further, the clinical application of dynamic imaging is still relatively recent, and hence most published work focuses on case studies and small patient populations.

1.6 Optical Imaging of Neoadjuvant Chemotherapy

Neoadjuvant chemotherapy (NACT), chemotherapy given prior to surgery, is the standard of care for locally advanced breast cancers that have not metastasized to other regions of the body. It can reduce tumor size, thereby allowing for breast conserving surgery in patients who would have otherwise have required a mastectomy [47]. It also provides clinicians with valuable information on the tumor responsiveness to treatment. Following NACT the patient undergoes surgery, at which point the pathological effect of the treatment can be assessed. A complete pathological response (pCR) occurs when no residual tumor cells are observed in the pathological specimen obtained during surgery. Studies have shown that pCR correlates with the more traditional cancer endpoints of 5-year and 10-year disease-free-survival [48, 49]. However, only 3-27% of women achieve a pCR after months of NACT [50]. Developing a way to monitor the progress of the therapy would make it possible to detect non-responders early in treatment and then adjust the therapy to improve response and overall survival.

The low pCR rate for NACT has been the impetus for studies looking to predict individual patient response to neoadjuvant chemotherapy. There is currently no modality that is ideal for assessing the tumor response to NACT. Physical exam, mammogram, ultrasound, and magnetic resonance imaging (MRI) are based on measuring tumor size changes and are insensitive to early response. In a retrospective study of 141 women, Chagpar et al., found that size estimates by palpation, US, and mammography were only moderately correlated with residual
tumor size after NACT (correlation coefficients of 0.42, 0.42, and 0.41 respectively) [51]. PET-CT has shown promise in predicting response to NACT; however, in addition to high cost ($1000 per study) [52], the disadvantage of successive PET-CT imaging is the exposure of patients to radioactive isotopes and ionizing radiation (30 mSv for a CT scan compared to 0.1 mSv for a chest x-ray).

DOT has the potential to make an impact in NACT monitoring due to its low cost, lack of ionizing radiation or isotopes, and fast imaging speeds. In addition, it is sensitive to hemoglobin and the corresponding vascular changes, which occur early on during treatment and could be a more reliable way of predicting the tumor response. Preliminary work by groups using handheld diffuse optical spectroscopy systems [53, 54], ultrasound guided tomography [55], and 3D diffuse optical spectroscopy [56, 57] has shown that DOT may be a promising technique, but further investigation is needed. In particular, there is a need for studies using full 3D DOT implementations and larger patient groups with better controlled drug types and schedules.

1.7 Overview of this Thesis

This work aims to improve the understanding of dynamic imaging by developing novel instrumentation for use in cancer imaging studies. Here, we present a new CW optical tomographic breast imaging system designed for dynamic optical breast imaging. This new system uses digital detection techniques with multiple digital-signal-processor (DSP) chips arranged in a master-slave configuration to maximize the processing throughput, reduce noise, and provide a system design that can be scaled to accommodate a variable number of detectors and wavelengths.
The clinical use of the new optical tomography system is demonstrated in two breast cancer studies. The first study uses dynamic DOT to identify breast tumors by their hemodynamic response to a breath hold. The second study uses DOT to monitor the response of breast tumors to neoadjuvant chemotherapy over the course of 5 months. The neoadjuvant chemotherapy monitoring study is complemented by a pre-clinical study looking at the early vascular response (<5 days) to anti-angiogenic therapy in a mouse tumor model. And finally, the design of a wireless, handheld version of the digital imaging instrument is presented.
Chapter 2: Instrument Design

This chapter introduces a novel CW optical tomographic breast imaging system designed for dynamic optical breast imaging. To overcome the inherent difficulty in obtaining high frame rates while collecting large amounts of data, we expand upon the concept of digital-based detection previously introduced by our group [58]. This new system extends the digital detection performance by using multiple digital signal processing (DSP) chips arranged in a master-slave setup to maximize the processing throughput, reduce noise, and provide a system design that can be scaled to accommodate a variable number of detectors and wavelengths.

2.1 System Requirements

A number of requirements were important in designing the dual-breast dynamic optical tomography system. These requirements are listed in order of importance:

A. **Speed**: To perform dynamic imaging of vascular changes the temporal resolution of the system should be on the order of 1 Hz.

B. **Channels**: A large number of source-detector channels are necessary to provide 3D spatial coverage of both breasts.

C. **Sensitivity and Dynamic Range**: The system must be sensitive enough to detect light that has been attenuated by up to 10 cm of tissue. However, it must also be able to detect light that has only passed through 1 cm of tissue. A large dynamic range allows for both small and large source-detector separations.

D. **Linearity**: The system must maintain a linear response over the complete dynamic range for accurate measurements.
E. Stability: As dynamic experiments will take place over an interval of time, the system should have a stable response over that time.

F. Size: The system should be compact for use in a clinical setting.

G. Scalability: The system should be able to scale with the number of detector channels, wavelengths, and sources to facilitate future design.

2.2 Benefits of Digital Design

To accomplish these design requirements, we implemented a system that uses digital techniques for the optical detection. Digital signals rely on a sequence of high and low voltages to encode a binary number. Analog signals use a voltage level to indicate the number. Digital signals are much less sensitive to fluctuations in the voltage level (due to changes in temperature, power supply) and to noise introduced on the signal (due to external interference, power line noise). Fig. 2-1, below, outlines the advantage of digital signals.
Figure 2-1. Example of an analog and digital representation of the value 5.
(a) The digital signal transmits high-low-high as 10V-0V-10V to encode the number 5 in binary format, while the analog signal is transmitted as a level 5 volts.
(b) In the case of ±10% noise the digital high-low-high signal becomes at worst 9V-1V-9V which, if we assume that anything above 7V triggers a ‘high’ and anything below 3V triggers a ‘low’ signal then the digital signal will be unchanged and interpreted as high-low-high, encoding the value 5. However, in the analog domain, the ±10% noise directly affects the level of the signal, resulting in a range of results from 4.5 to 5.5.
(c) In the case of 10% droop in the driving voltage, the binary signal changes to 9V-0V-9V, still resulting in high-low-high, or 5. However, the analog signal will decrease due to the droop in the driving voltage, resulting in a value of 4.5.

By bringing the detected signal into the digital domain close to the point of detection, the amount of noise introduced onto the signal as it is transmitted back to the host computer is reduced. Moving into the digital domain also facilitates the use of increasingly sophisticated digital hardware including integrated circuits (ICs), digital-signal-processors (DSPs) and microcontrollers. DSPs can be dynamically updated, scale with increased channels, and can
achieve the same or similar performance to the equivalent analog hardware with a significantly smaller footprint. The design described here incorporates multiple DSP chips in a master-slave configuration to streamline the signal detection and reduce noise.

2.3 Instrument Overview

The system uses four near-infrared wavelengths to illuminate the tissue through 32 source fibers on each breast and simultaneously collects the transmitted and reflected light from 64 detector fibers on each breast. The instrument is made up of four main components, as shown in Fig. 2-2. The following chapters will discuss each of these components in further detail.

![Schematic of the dynamic optical tomography breast instrument.](image)

Figure 2-2. Schematic of the dynamic optical tomography breast instrument.

The Input Unit is responsible for generating the light used to illuminate the tissue. The system uses four wavelengths of near-infrared light that are generated by laser diodes (LD) and modulated at two different radio frequencies. The four wavelengths are combined into two streams of light that are sequentially switched between various optical fiber positions on the target tissue. The design of the input unit is discussed in Chapter 3.
The Breast-Fiber Interface is the physical component that brings the optical fibers in contact with the tissue. The configuration varies depending on the type of tissue being imaged and the experimental design. Two fiber-tissue interface designs are discussed in Chapter 8.

The Detection Unit measures and conditions the transmitted and reflected light from the tissue before passing it onto the Host Computer. As each source fiber sequentially illuminates the tissue, all detectors surrounding the tissue measure the light intensity. The signal is detected with a photodiode (PD) prior to amplification by a trans-impedance amplifier (TIA) and programmable gain amplifier (PGA), low-pass filtered (LPF), and then digitized with an analog-to-digital converter (ADC). The signal is then processed in the digital domain by a master DSP (mDSP) and three slave DSPs (sDSP). To coordinate the system timing and data throughput the mDSP relies on a master complex programmable logic device (mCPLD) and slave CPLD (sCPLD). The final signal is deposited into data buffers that coordinate with data acquisition cards (DAQ) to transmit the data to the Host Computer. In addition, the Detection Unit, via the mCPLD, communicates directly with the Input Unit to coordinate the timing of the system. The detection unit is discussed in detail in Chapters 4 and 5.

The Host Computer communicates with the instrument hardware and provides a graphical user interface (GUI) through LabVIEW to control the instrument and collect data. The software control of the system is described in Chapter 6.

An overview of the system, along with the characterization of the system performance, is presented in Chapter 7.
Chapter 3: Input Unit Design

3.1 Multi-wavelength Illumination

The input unit is responsible for generating the light that illuminates the target. The system uses four wavelengths of near-infrared light at 765 nm, 808 nm, 827 nm, and 905 nm generated by continuous-wave laser diodes controlled by laser drivers. The intensity of each laser is modulated at either 5 kHz or 7 kHz. The four wavelengths are passed through two optical combiners to create two streams of light, with each stream containing two colors of light modulated at different frequencies. The two light streams are input to a 2x32 optical switch that is responsible for sequentially switching the light into the 32 optical fibers that surround the tissue. Optical fibers bifurcate to simultaneously illuminate the left and right breast with the same input light. An overview of the generation of the input light is shown in Fig. 3-1.

Figure 3-1. Schematic of the light input unit.
The light is generated at two different modulation frequencies by four laser diodes (LD). Two optical combiners bring the four wavelengths into two streams of light that are input to the 2x32 optical switch (OS). The optical switch sequentially redirects the light to each of the 32 output fibers that simultaneously illuminate the left and right breast.
Modulating the laser light intensity is an important feature of the input unit as it allows for simultaneous illumination of the target with multiple wavelengths at the same time, and also improves the rejection of ambient light. Due to the fact that each stream must be detected with the same hardware, the same amount of gain must be applied to all wavelengths of the stream. In cases where the attenuation through the tissue is significantly different at the various wavelengths it can be difficult to find one gain setting to accommodate all four wavelengths, thus our design uses two streams of light with two wavelengths in each stream as opposed to combining all four wavelengths into a single stream.

3.2 DDS Modulation

Each modulation frequency is generated by a direct digital synthesis (DDS) chip (AD9854, Analog Devices Inc.) and passed through a series of filters as well as offset and amplitude adjustment stages prior to being input to the laser driver controller. A DDS chip is an inexpensive solution that is compact and can generate a more stable frequency than other commercial laser drivers. In this system we use a pre-programmed fixed reference signal on the detection side of the system. This makes it essential to have a highly stable illumination modulation frequency.
Fig. 3-2 shows a circuit diagram of the components responsible for generating the modulated current that is used to modulate the intensity of the laser driver. The DDS chip generates a sinusoidal waveform (IOUT1), that develops a 10 mA 0.5 V peak-to-peak signal with 12 bits of resolution across an LC filtering stage (as specified in the application notes for AD9854 [59]). This digital signal cannot fully capture the smoothly varying sinusoid, and instead approximates the sinusoid with a staircase-like waveform with \(2^m\) available levels where \(m\) is the number of bits of resolution. This effect is exemplified in Fig. 3-3. This approximation introduces white noise onto the signal. IOUT1 must be amplified to a suitable level, filtered to reduce the white noise, and offset and amplified to control the output intensity of the laser.
Figure 3-3. Graph demonstrating the effect of quantization on an analog signal.
Here we show a sinusoid quantized with $2^3$ bits of digital resolution. Note the staircase effect that the quantization produces – resulting in white noise that is present along with the sinusoidal frequency.

The first amplification stage (AMP1) uses an operational amplifier (EL5203IS, Elantec) whose R2/R1 ratio determines the amount of gain applied (in this case R1=3.3 kΩ, R2=15 kΩ, and ~4.5x gain is applied). AMP1 amplifies the signal in preparation for the filtering stage.

The low-pass filtering consists of two 4th order Butterworth filters (LTC1563, Linear Technology) whose cutoff frequency and filter characteristics are determined by a number of resistors, as specified in the application notes [60]. The purpose of the filtering stage is to remove some of the white noise introduced onto the modulation signal through quantization. Specifically, the filtering must improve the signal-quantization-to-noise-ratio (SQNR) of the modulation signal so that it is not the limiting factor in our system. The detection electronics make use of 16 bits of resolution, but our input DDS synthesizer only uses 12 bits of resolution. To compensate for this difference, we must reduce the white noise present on the IOUT1 signal.
by low-pass filtering the signal to remove the noise contained in the high-frequency spectrum of the signal. The cutoff frequency of the low-pass filter is selected as 12.5 kHz, well above our 5 kHz and 7 kHz modulation frequencies, and exactly matches the anti-aliasing filter used in the detection unit. For a detailed discussion of the SQNR considerations please refer to [56].

Following the filtering stage, the signal must be amplified to control the laser intensity. A laser driver regulates the laser output power according to the driving input voltage to the driver. Therefore the voltage offset and amplitude of the modulated signal must be considered, since they will set the output power and the lowest part of the signal must stay above a 1.5 volt threshold that will keep the laser driver “on”. Operating in a constant current mode, the laser driver modulates the input current to the laser with a coefficient of 200 mA/V. The amplitude of the input signal to the driver is primarily controlled by the final amplification stage (AMP2) according to ratio of R4/R3. The offset, originally derived from the DDS, is also amplified according to the AMP2 gain. In this design, it is not explicitly controlled. This feature could be introduced by replacing the ground connection at the positive input to AMP2 with a voltage divider circuit that would precisely set the offset of the signal.

The modulation signal synthesis and conditioning is all performed on a printed circuit board (PCB) of a standard 3U height and 16 cm length for ease of use with commercial enclosures. Each board contains the circuitry to generate two distinct modulation frequencies, and the system uses two of such boards to drive the four laser drivers. The four-layer PCB has a top and bottom copper layer for part placement and routing, one dedicated inner ground layer, and one inner layer for power planes. The board is powered by a 12 V supply voltage and uses
on-board voltage regulators to generate +3.3 V and ±5 V power lines. The board connects to a backplane via a standard 96-pin connector (650473-5, Tyco Electronics).

A photograph of the board is shown in Fig. 3-4. The detailed schematic, board layout, and bill of materials (BOM) for the DDS board are included in Appendix A.

Figure 3-4. Photograph of the DDS board with the key functional components outlined in white.

### 3.3 Microcontroller Design

The output frequency and operating settings of the DDS chips are controlled by a programmable microcontroller (AT89S8252, Atmel) that sits on the backplane of the Input Unit. The microcontroller receives a 3.3 V power supply and an input 10 MHz clock (M_CLK) generated by a crystal oscillator (SG8002, Epson). There is a master reset (M_RST) that is controlled by a push button located on the backplane that will reset the microcontroller. This is
principally used for debugging purposes. The key microcontroller inputs and outputs and their connection to the DDS chips is outlined in Fig. 3-5.

Figure 3-5. Outline of the connections between the microcontroller (µCTLR) and the direct digital synthesis (DDS) chips.

With an 8-bit Atmel 8501 architecture the microcontroller also has 12 Kbytes of In-System Programmable Flash memory and 2 Kbytes of EEPROM data memory. The program for the device is written in C++ through Keil µVision and programmed directly onto the microcontroller using an EEPROM programmer (in our case a BK Precision 864). The microcontroller connects to the backplane using a socket. This allows the microcontroller to be
reprogrammed at any time by removing it from the socket, programming it, and then returning it to the socket. The microcontroller program is included in Appendix B.

The microcontroller has 32 bidirectional digital input/output lines configured into 4 ports (P0-P3) with 8 bits each. In our configuration, P0 is unused, P1 is configured for write (WR/) and update clock (UCLK/) active low signals (as indicated by the “/” following the signal name), P2 is configured for the address lines and the reset (RST) active high signal, and P3 is configured as data lines. All four DDS chips share the address, data, and RST lines, but have individual WR/ and UCLK/ lines that allow for individual programming of each DDS chip. A summary of this configuration is in Table 3-1.

<table>
<thead>
<tr>
<th>Port</th>
<th>Bits</th>
<th>Configuration</th>
</tr>
</thead>
<tbody>
<tr>
<td>P0</td>
<td>0.0-0.7</td>
<td>Unused</td>
</tr>
<tr>
<td>P1</td>
<td>1.0</td>
<td>WR1/</td>
</tr>
<tr>
<td></td>
<td>1.1</td>
<td>UCLK1/</td>
</tr>
<tr>
<td></td>
<td>1.2</td>
<td>WR2/</td>
</tr>
<tr>
<td></td>
<td>1.3</td>
<td>UCLK2/</td>
</tr>
<tr>
<td></td>
<td>1.4</td>
<td>WR3/</td>
</tr>
<tr>
<td></td>
<td>1.5</td>
<td>UCLK3/</td>
</tr>
<tr>
<td></td>
<td>1.6</td>
<td>WR4/</td>
</tr>
<tr>
<td></td>
<td>1.7</td>
<td>UCLK4/</td>
</tr>
<tr>
<td>P2</td>
<td>P2.0-P2.7</td>
<td>DATA[0:7]</td>
</tr>
<tr>
<td>P3</td>
<td>P3.0-P3.5</td>
<td>ADDR[0:5]</td>
</tr>
<tr>
<td></td>
<td>P3.6</td>
<td>Unused</td>
</tr>
<tr>
<td></td>
<td>P3.7</td>
<td>RST</td>
</tr>
</tbody>
</table>

The microcontroller program consists of two parts: initialization and frequency programming. The initialization sets the mapping of the pins as shown in Table 3-1, and then initializes the DDS registers for the correct mode of operation. Specifically, this involves setting the mode of operation to single mode (as opposed to chirp or frequency shift keying) and an external update clock (the UCLK/ set by the microcontroller determines when registers are
updated as opposed to a periodic update pulse internally generated by the DDS chip). Both of these settings are updated by writing 0x00 to address 0x1F. By default, the DDS implements a feature known as the inverse sinc function to compensate for amplitude roll-off in high bandwidth signals, something that is not relevant for our low-bandwidth, single-tone frequency. This feature uses a lot of power, and so we disable it by writing 0x40 to address 0x20. There are many other features that can be enabled by writing to the respective registers, as outlined in the DDS AD9854 datasheet [59], but those features exceed our design requirements. Once the initialization is complete, the modulation frequency is programmed to the appropriate registers. The modulation frequency is specified as a 48-bit frequency tuning work (FTW) that is defined according to Eq. 3.2.

\[
FTW = \frac{\text{Desired output frequency} \times 2^{48}}{M_{\text{CLK}}} \tag{3.2}
\]

The FTW number is typically a decimal number that must be rounded to the nearest integer and then converted to a binary number. For our modulation frequencies of 5 kHz and 7 kHz the FTWs are 0x20C49BA5E3 and 0x2DE00D1B71 respectively. The FTWs are programmed as 6 sequential 8-bit writes to 6 DDS registers (0x04 to 0x09). The phase offset of the signal is not important to our application and thus is left at the default of 0. Upon a low pulse of the UCLK/ signal, the DDS begins outputting the sinusoid at the programmed frequency. Prior to the UCLK/ pulse the DDS output consists of a default DC (0 Hz) signal of approximately 0.5 V. Fig. 3-6 shows a timing diagram for the microcontroller initialization and programming of the DDS registers.
The microcontroller sits on the backplane of the input unit. The backplane is the anchor of the input unit and is comprised of a two-layer PCB that routes all of the signals between the DDS cards and the laser controllers. The backplane is designed for use with standard enclosures. The input unit is powered by a two 12 V switching power supplies (GLM75-12, Condor) configured to provide a +12 V and -12 V line. Switching power supplies are known to be noisy, with background noise of up to 120 mV, however, as originally implemented by Lasker et al. [56] and reproduced here, we use a capacitive and balun choke filter on the power lines entering the backplane to reduce the noise to around 5 mV. The schematic, board layout, and BOM for the input unit backplane are included in Appendix C.
3.4 Light Generation

Light at four wavelengths (765, 808, 827, and 905 nm) is generated by continuous-wave high power laser diodes (HPD-1010-HHLF-TEC, High Power Devices, Inc). Each laser diode is controlled by a laser driver controller (ITC110, Thorlabs Inc.) and intensity modulated at either 5 kHz (765 nm and 808 nm) or 7 kHz (827 nm and 905 nm). Two wave division multiplexers (Oz Optics Ltd.) combine the four colors of light into two separate streams: one stream that combines 765 nm modulated at 5 kHz and 827 nm modulated at 7 kHz, and one stream that combines 808 nm modulated at 5 kHz and 905 nm modulated at 7 kHz. Each light stream is fed into a 2x32 optical switch to control the sequential illumination of various positions around the tissue.

The specifications for each laser diode, including the maximum input current, the maximum power, the maximum voltage, and the spectral response of the diode are included in Appendix D. It is important that the driver for each laser diode is adjusted according to these specifications. This should be done with the use of the ITC1xx Operation Manual. With the help of the display module (ITC100D, ThorLabs Inc.) potentiometers P1-P7 can be adjusted for each laser driver and corresponding laser diode. Specifically P1 should be set to the laser diode limit current, P2 can set the laser current, and P3 and P4 can be used to set the thermo-electric cooler (TEC) properties.

Fig. 3-7, shows a photograph of the input unit, as seen from above. The power supply, DDS synthesis boards, laser drivers, laser diodes, and optical combiners are all visible.
3.5 Optical Switching

The optical switching is performed by a 2x32 Sercalo Rack System Solution (RS-FSPA-2x1x32-62FCPC) optomechanical switch. The switch begins by illuminating the target at one source position with the first wavelength set (765 nm & 827 nm) and then the second wavelength set (808 nm & 905 nm) before moving onto the next source position. It continues this source switching until all programmed source positions (up to 32 per breast) have illuminated the target. The switching is customizable so that the system can run with only two wavelengths twice as quickly since it doesn't need to repeat the measurements at each source position a second time for the additional wavelength set.
The optical switch accepts wavelengths from 700 to 1650 nm and takes less than 7ms to settle when switching between positions. Control of the switch position is accomplished through a 36 pin Centronics connector. The timing to control the switch, specified by the Sercalo Operating Manual, is outlined in Fig. 3-8, along with the pin positions for the connector. In our design we implemented a set-up time 16 µs and a hold-time of 26 µs to match the values observed by probing the Sercalo control software, as opposed to the > 10 µs set-up time and > 1 ms hold time specified in the manual.

Figure 3-8. Optical switch details.
Shown are (a) the connector pinout and (b) pin descriptions along with (c) the digital programming timing.

An optical switch, which relies on a MEMS based switch network that uses micro-machined silicon mirrors to redirect light between the selected output fibers, is preferred to a mechanical switch in this case (often involving a rotating mirror that reflects the incoming light into the sequential output fibers) for a couple reasons. Optical switches are quieter and more compact than mechanical switches, and there are a number of commercially available optical
switches that can be digitally controlled and that have good temporal response for fast switching between source positions.

3.6 Optical Fibers

32 optical fibers (Fiberoptic Systems Inc.) connect to the optical switch by fixed connection (FC) connectors. The fibers bifurcate to simultaneously illuminate both the left and right breast. Each source fiber converges with a detector fiber, so that a single fiber tip can perform both illumination and detection. This accounts for 32 of the fibers per breast. The other 32 fibers are solely used for detection. The 64 total detection fibers return back to the detection module.

3.7 Light Intensity

The intensity of light that is used to irradiate tissue is limited by the American National Standard Institute (ANSI) and recommended by the Occupational Safety and Health Administration (OSHA) of the US Department of Labor. According to these standards (ANSI Z136.12000 pg 48, Table 7) the maximum permissible exposure (MPE) before tissue damage occurs is given by Eq. 3.3 where \( \lambda \) is the light wavelength in nm.

\[
MPE = 200 \times 10^{0.002(\lambda - 700)} \text{ [mW/cm}^2]\]  
(3.3)

In this system, the light intensity is well below the ANSI standards and is essentially limited by the input power to the switch. Sercalo recommends limiting the input intensity of light into the switch to 100 mW. As such, the output power from the laser diodes is currently optimized to give 100 mW of light out of the optical combiners (and into the switch). Loss through the switch and connectors amounts to 50%, followed by a 50% loss due to the
bifurcation of light to the left and right breast, and accompanied by a 50% loss through the optical fibers, bringing the output power from the optical fiber to approximately 12.5 mW shared between the two wavelengths in that light stream. This means each wavelength of light inserts just over 5 mW of power into the breast, well below the ANSI standards.
Chapter 4: Digital Detection Techniques

4.1 Detection Unit Overview

The role of the detection unit is to quantitatively measure the amplitude of the light that is emitted from the tissue surface. As described in the previous chapter, the light is radio-frequency modulated, and so the detection unit must extract the amplitude from the modulated detected signal. There are three factors that make the design of this unit challenging.

1. Sensitivity: There is considerable attenuation as light passes through the tissue, making it essential that the detection electronics be very sensitive to low light intensity.

2. Dynamic Range: While many of the signals will be very small, detectors located in close proximity to the source will be exposed to a high light intensity. The detection unit must be able to accommodate both these low and high intensities.

3. Speed: For dynamic imaging the system must collect data very quickly, while still accommodating the large number of sources and detectors needed to cover 3D breast geometries.

The detection electronics are specifically designed to address these challenges. The detection unit begins by converting the incident light into an electric current using a photodetector. It then amplifies and converts that current to a voltage, filters the signal, quantizes the analog signal into a digital signal, and finally performs the lock-in detection and
filtering in the digital domain. All of these stages, outlined in Fig 4-1, will be described in detail in the following sections.

Figure 4-1. Block diagram of the detector board electronics.

The light is detected with a silicon photodiode (SiPD), amplified in two gain stages: the trans-impedance amplifier (TIA) and the programmable gain amplifier (PGA), filtered to remove the DC offset (RC-HP) and filtered to prevent aliasing prior to quantization of the signal using an analog-to-digital converter (ADC).

4.2 Analog Detection, Amplification, and Filtering

The detection unit begins with the optical fibers that bring light from the surface of the tissue back to the detection electronics. A custom connector uses a set screw to hold the fiber in alignment with a silicon photodiode (SiPD) (S1337-33BR, Hamamatsu) that converts the incoming photons into electrons (and a corresponding electrical current). The S1337-33BR SiPD provides a response of 0.5-0.6 A/W in the 750-900 nm range with a fast response time (0.2 µs). We chose to use a photodiode due to the highly linear response it provides across a large range of incident light intensities. In addition, other optical detection devices such as avalanche photodiodes and photomultipliers require very large supply or bias voltages, which is undesirable in a clinical device.

A photocurrent is induced across the device when an incident photon dislodges an electron in the SiPD. The next step is to convert this photocurrent into a voltage, while also applying some gain. This is achieved through a trans-impedance amplifier (TIA). The TIA,
shown in Fig. 4-2a, produces a voltage that is equal to $V_{out} = -I_{in} \cdot R_f$. By changing the value of $R_f$, it is possible to change the amplification of the incoming signal, thus providing a way to increase the dynamic range so that both very small and very large signals are accommodated. However, $R_f$ cannot be increased without consideration of the frequency response of the filter. In this design we want to insure that any signals modulated in the 3-9 kHz range can be detected with less than 1% of ripple in the pass-band. As such, we must insure that the frequency response of the TIA adheres to this requirement. The TIA will pass all frequencies up until a cutoff frequency $f_c = 1/(2\pi R_f C_f)$. To insure a flat pass band for our core frequency range we choose $f_c$ to be greater than 60 kHz (this is to insure minimal dropout at our upper core frequency of 9 kHz – see Appendix E for bode plots of the magnitude, phase, and transient response of this RC filter). As the feedback resistance $R_f$ increases, the corresponding feedback capacitor $C_f$ must similarly decrease in order to maintain the same $f_c$. This introduces a problem at high values of $R_f$ because parasitic board capacitance is typically around 1-2 pF and the smallest capacitors available are similarly ~1pF. To overcome this issue, we use a bandwidth extension technique originally demonstrated by Michel et al. [61] and first applied to optical detection techniques by Lasker et al. [58]. The circuit diagram for a bandwidth-extended TIA is shown in Fig. 4-2b. With this modified design, $V_{out} = -I_{in} R_1$ and the cutoff frequency is $f_c = 1/(2\pi R_2 C_2)$ where $R_2 << R_1$ and $R_1 C_1 = R_2 C_3$ and brings the capacitor values into a more reasonable range.
Figure 4-2. Trans-impedance amplifier (TIA) schematic.
Shown are two configurations: (a) a typical trans-impedance amplifier (TIA) with a feedback resistor and capacitor and (b) a TIA with a bandwidth-extension feedback circuit.

In our design we use three different feedback resistors across the TIA: 10 kΩ, 10 MΩ, and 100 MΩ. Each of the gain settings used in the TIA amplification stage are outlined in Table 4-1 along with the resistor and capacitor values selected for the circuit design.

Table 4-1. Description of gain settings and corresponding resistor and capacitor values for the TIA.

<table>
<thead>
<tr>
<th>Gain</th>
<th>Bandwidth Extension</th>
<th>RC values</th>
</tr>
</thead>
<tbody>
<tr>
<td>10 kV/A</td>
<td>No</td>
<td>$R_f = 10 , \text{kΩ}$</td>
</tr>
<tr>
<td></td>
<td></td>
<td>$C_f = 220 , \text{pF}$</td>
</tr>
<tr>
<td>10 MV/A</td>
<td>Yes</td>
<td>$R_1 = 10 , \text{MΩ}$</td>
</tr>
<tr>
<td></td>
<td></td>
<td>$R_2 = 10 , \text{kΩ}$</td>
</tr>
<tr>
<td></td>
<td></td>
<td>$C_1 = 15 , \text{pF}$</td>
</tr>
<tr>
<td></td>
<td></td>
<td>$C_2 = 220 , \text{pF}$</td>
</tr>
<tr>
<td></td>
<td></td>
<td>$C_3 = 15 , \text{nF}$</td>
</tr>
<tr>
<td>100 MV/A</td>
<td>Yes</td>
<td>$R_1 = 100 , \text{MΩ}$</td>
</tr>
<tr>
<td></td>
<td></td>
<td>$R_2 = 10 , \text{kΩ}$</td>
</tr>
<tr>
<td></td>
<td></td>
<td>$C_1 = 1.5 , \text{pF}$</td>
</tr>
<tr>
<td></td>
<td></td>
<td>$C_2 = 220 , \text{pF}$</td>
</tr>
<tr>
<td></td>
<td></td>
<td>$C_3 = 15 , \text{nF}$</td>
</tr>
</tbody>
</table>
The operational amplifier (op-amp) used for the TIA (AD8610A, Analog Devices) is specifically chosen for this application due to its low bias current and noise. The bias current of this device is ~2 pA which allows us to measure photodiode currents in the tens of picoamps. In addition, the AD8610A has excellent voltage noise performance of 6 nV/Hz$^{-1/2}$ and 5 fA/Hz$^{-1/2}$ which means that with a 100 MΩ resistor the noise generated from the op-amp is:

$$V_{op-amp, noise} = I_{noise}R = \left(\frac{6 \text{nV}}{\sqrt{\text{Hz}}}\right)(\sqrt{12.5 \text{kHz}})(100 \text{ MΩ}) = 56 \mu\text{V} \quad (4.1)$$

Whereas the thermal noise of the 100 MΩ resistor is:

$$V_{thermal} = \sqrt{4kTRf} \quad (4.2)$$

$$= \sqrt{4(1.38 * 10^{-23} m^2 kgs^{-2} K^{-1})(298 K)(100 MΩ)(12.5 kHz)}$$

$$= 143 \mu\text{V}$$

The noise generated by the op-amp is still well below the thermal noise of the resistor. In both Eq. 4.1 and 4.2 the frequency used is 12.5 kHz which is the bandwidth of our acquired signal, as specified by the cutoff frequency of the low-pass anti-aliasing filter. Notice that in Eq. 4.2 it is important that temperature be controlled as it can lead to an unwanted increase in the thermal noise.

The output signal from the TIA is high-pass RC filtered to remove any DC offset. As we are solely interested in the amplitude of the modulated signal, the DC offset is not important, and can limit the amount of gain that can be applied to the signal in the PGA gain stage. In addition, the high-pass filter reduces low-frequency noise including power-line noise (at 60 Hz). We choose a cutoff frequency of ~500 Hz which provides a flat passband for our 3-9 kHz core frequency range while also removing the DC offset and providing about 20 dB of power line
noise suppression. The RC high-pass filter also determines the settling time of the output of the TIA stage – an important factor for the timing of our detection unit. The settling time for this filter is approximately 3 ms for the signal to settle to within 99.9% accuracy. See Appendix E for the amplitude, phase, and transient response of the passive RC high-pass filter. Increasing the cutoff frequency of this filter would decrease the settling time and improve the low-frequency noise rejection, but would cause the passband to be less flat in our core frequency range, likely resulting in rolloff and subsequent loss of signal amplitude at lower frequencies.

Following the TIA and high-pass filter the signal is passed through a second amplification stage, the programmable gain amplifier (PGA) that is used to increase the peak-to-peak amplitude of the signal so that it best occupies the full 5V range of the analog-to-digital converter (ADC). In addition, the PGA provides for more gain settings beyond the three levels provided by the TIA. The PGA uses an instrumentation amplifier (INA128U, Texas Instruments) where the gain across the amplifier is determined according to \( G=1+50k\Omega/R_G \) where \( R_G \) is the resistance between pins 1 and 8 of the amplifier. This amplifier has low input bias current (5 nA max, which means that even at a gain of 100 with \( R_{in} \) of 4.7 kΩ the offset is only a couple mV, thus not causing any risk of saturation of the PGA). With a gain-bandwidth product of 20 MHz the PGA has cutoff frequency of 200 kHz at a gain of 100, which corresponds to only 0.1% signal loss at 9 kHz (the upper limit of our core frequency range). For the PGA stage we use resistor values of 47 Ω, 487 Ω, 5.6 kΩ, 10 MΩ to accomplish gain of approximately 1000, 100, 10, and 1, respectively. Although we provide the option to apply 1000 times PGA gain, in reality the noise levels at the gain setting are prohibitively high and it is not typically used.
By providing options for the amount of gain applied at each amplification stage, we enable a broad range of signals that can be detected – from very small signals that require a lot of amplification to large signals that require very little amplification. In order to select which feedback resistors will be used to set the amplification for a given channel, we use a combination of multiplexers and switches. When switching the feedback resistance across the TIA, care must be taken with regards to switching and settling time of the detected signal. For this reason we use two reed relays (Coto Technologies) that have fast settling times and moderate current across them (10 mA @ 5V supply). Both the TIA and PGA have 8:1 multiplexers (MUXs) (ADG608BRZ, Analog Devices) whose output is selected based on 3 bits, referred to in our design as the ‘gain bits’ that can be controlled by the user. Table 4-2 shows the gain bit control of the amplification settings available in our design.

<table>
<thead>
<tr>
<th>Gain Setting</th>
<th>Gain Bits</th>
<th>TIA Gain (V/A)</th>
<th>PGA Gain (V/V)</th>
<th>Overall Gain (V/A)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0 0 1</td>
<td>10 k</td>
<td>10</td>
<td>10 k</td>
</tr>
<tr>
<td>2</td>
<td>0 0 1</td>
<td>10 k</td>
<td>10</td>
<td>100 k</td>
</tr>
<tr>
<td>3</td>
<td>0 1 0</td>
<td>10 k</td>
<td>100</td>
<td>1 M</td>
</tr>
<tr>
<td>4</td>
<td>0 1 1</td>
<td>10 M</td>
<td>1</td>
<td>10 M</td>
</tr>
<tr>
<td>5</td>
<td>1 0 0</td>
<td>10 M</td>
<td>10</td>
<td>100 M</td>
</tr>
<tr>
<td>6</td>
<td>1 0 1</td>
<td>10 M</td>
<td>100</td>
<td>1 G</td>
</tr>
<tr>
<td>7</td>
<td>1 1 0</td>
<td>100 M</td>
<td>100</td>
<td>10 G</td>
</tr>
<tr>
<td>8</td>
<td>1 1 1</td>
<td>100 M</td>
<td>1000</td>
<td>100 G</td>
</tr>
</tbody>
</table>

The gain bits are stored on the detector board in first-in-first-out (FIFO) (IDT72V02, Integrated Device Technology) storage registers and when the source position is changed the corresponding gain bits are updated across the TIA and PGA via a read from the FIFO. After each imaging frame the retransmit feature of the FIFO brings the read pointer back to the
bottom of the FIFO in preparation for the next imaging sequence. The optimal gain bits can be determined prior to the image acquisition and loaded into the FIFOs for optimal timing of the system. The programming of the gain bit FIFOs is discussed in more detail in Section 5.2.

Following the TIA and PGA gain stages, the signal is filtered with an 8th order Butterworth anti-aliasing filter that removes high frequency components and whose primary purpose is to ensure there are no frequencies present above the Nyquist frequency prior to digitization. The signal is sampled by the ADC at 75 ksamples/s which establishes a Nyquist frequency of 37.5 kHz. As a result, we choose a cutoff frequency of 12.5 kHz and a Butterworth filter that has a flat passband for the 5 and 7 kHz signals, while also providing strong attenuation of any higher frequency noise at risk of aliasing into the passband. The 8\textsuperscript{th} order Butterworth filter is implemented using two filter chips (LTC1563-2IGN, Linear Technologies). These filters, in combination with a number of resistors, form an 8\textsuperscript{th} order low-pass Butterworth filter with a 12.5 kHz cutoff frequency that has <0.1% attenuation at our upper core frequency of 9 kHz, but still offers over 100 dB of noise suppression in our first aliasing range of 67 to 72 kHz. The design and analysis of this filter can be performed through LTSpiceIV and FilterCAD software provided by Linear Technologies. The optimal layout for the filter components, as used in our design, is specified in the LTC1563 application notes [60]. The magnitude and phase response of the filter are shown in Fig. 4-3.
Figure 4-3. Magnitude and phase response of the 8th order Butterworth low-pass anti-aliasing filter.

Following the filter, the final analog component of the detection board is the offset buffer that centers the signal around 2.5 V for optimal detection by the 0 to 5 V input range of the ADC. The offset amplifier also buffers the signal according to the ADC specifications. These specifications are outlined in the ADC AD7655 Datasheet and include the following requirements for the amplifier: low noise, low total harmonic distortion (THD), and a fast settling time [62]. Based on these requirements we selected an amplifier (AD8028, Analog Devices) with -100 dBc THD, settles to 0.1% in 35 ns, and has good noise performance. The amplifier is configured according to Fig. 4-4, below.
Eq. 4.3 describes the relationship between $V_{\text{out}}$ and $V_{\text{in}}$. In our case we do not desire any additional amplification, which is accomplished by selecting $R_1=R_2=R_3=R_4=R_5=20$ kΩ. This gives a relationship $V_{\text{out}} = V_{\text{ref}} - V_{\text{in}}$. By setting $V_{\text{ref}}=2.5$ V we convert $V_{\text{in}}$ from a zero-bias signal with 5 V peak-to-peak amplitude to $V_{\text{out}}$, a 2.5 V biased signal (the center point of the ADC) with a 5 V peak-to-peak amplitude. This allows $V_{\text{out}}$ to span the full 0 to 5 V input range of the ADC.

$$V_{\text{out}} = \frac{R_5 R_2}{R_3 R_1} V_{\text{ref}} - \frac{R_5}{R_4} V_{\text{in}} \quad (4.3)$$

### 4.3. Analog-to-Digital Converter (ADC)

Following the offset buffer we are ready to transition from the analog domain to the digital domain. To do this we must convert a continuous, smoothly varying signal, into a finite number of samples that adequately capture the shape of the signal. Resolution in both $x$ (time) and $y$ (amplitude) are both important. Resolution in time is determined by the sampling rate of the ADC, $f_s$ (or inversely, the sampling period $T_s=1/f_s$), while the resolution of the amplitude is
determined by the number of bits that the ADC can capture in its digital sample. More bits allows for more resolution in approximating the analog signal.

Figure 4-5. Diagram outlining the challenge of digitally sampling an analog signal. Here the sin(2x) analog signal is shown in solid grey, the digital samples are shown as black x markers, and the reconstructed waveform using the digital samples is shown in dashed black for (a) a sampling period of π/4 and m=3 (8 quantization levels); (b) a sampling period of π/16 and m=3 (8 quantization levels); (c) a sampling period of π/16 and m=4 (16 quantization levels).
The 16-bit ADC used in our design provides $2^{16} = 65536$ levels of quantization, and given that we have a supply range of 5V, the ADC provides a resolution of 76 µV (~0.0015%). Fig. 4-5 illustrates how both sampling frequency and resolution both play a role in adequately describing the analog signal in the digital domain. As the sampling period decreases and the number of bits (and corresponding levels of quantization) increase, the digital representation of the signal gets closer to the true analog equivalent.

In our design we use a four channel, 16-bit, successive approximation register ADC (AD7655, Analog Devices) that samples at a maximum rate of 1 Msps. Fig. 4-6, below, is a functional diagram for the ADC showing the significant pins.

![Functional block diagram of the ADC7655](image)

Figure 4-6. Functional block diagram of the ADC7655 [62].

The ADC has four inputs and can quantize two inputs at a time (INA1 and INB1 or INA2 and INB2). Selection of the input channels is performed using the A0/ pin. To acquire a digital sample of the analog input, the CNVST/ signal must be held low for at least 5 ns, following which the BUSY signal will go high and 2 µs later the digital sample will be available. We choose to operate the ADC in serial mode by pulling the SER/PAR pin high. This means that the data
can be read (controlled by CS/, RD/, and CLK) from the serial data line (SDOUT) with the data from Channel B followed by the data from Channel A (this order is determined by the A/B pin which is pulled low in our design). Outputting the data serially allows for significantly less data lines to be routed from the ADC to the other boards for processing of the digital signal. The timing diagram for converting and reading the data from the ADC is shown in detail in Fig. 4-7.

Figure 4-7. Timing diagram for converting and sampling the digital signal from the ADC.

In our system the ADC samples the data from each detector channel at 75 kHz. The ADC timing is synchronized with the rest of the digital electronics through the master CPLD and DSP. This is described in more detail in the following chapter.

4.4 Detector Board Design

There are 16 detector boards used to capture the 128 detector channels in the system. Each board houses 8 channels that have their own analog circuitry feeding into two 4-channel ADCs. The four-layer PCB has a top and bottom copper layer for part placement and routing, one dedicated inner ground layer, and one inner layer for power planes. Each detector board is provided with a +5V, +12V, and -12V line which is then adjusted through voltage regulators to
the necessary 3.3 V, 2.5 V, +8 V, -8 V, +5 V, and -5 V lines that are used by the ICs on the board. The initial gain stages are covered by custom-made copper shields to reduce noise. The shields attached directly to the board by screws and are soldered to the ground plane. The board connects to a solid 6U/4HP front panel (Vero Technologies) that holds the optical fiber connectors. The boards connect to the backplane of the detection unit via two 96-pin connectors (650473-5, Tyco Electronics). Fig. 4-8 shows a photograph of a detector board. The detector board BOM, schematic, and layout are included in Appendix F.

Figure 4-8. Photograph of the detector board with the key functional components outlined in white.

Key components include the power regulation, gain bit FIFOs, the ADCs, and the components of each of the 8 detector channels: the location for the silicon photodiode (SiPD) and fiber connector (not shown in this photo), the TIA and PGA amplification stages, the multiplexers (MUXs), the anti-aliasing filter, and the offset buffer.
Chapter 5 : Master-Slave Digital Signal Processor Architecture

5.1 Master-Slave Architecture

One of the key challenges in fast optical tomography for breast imaging involves designing a system that obtains measurements from a large number of sources and detectors without sacrificing the imaging speed. In our design, this is accomplished by implementing a master-slave DSP architecture that involves multiple DSP chips for fast simultaneous processing of all 128 detectors. The master DSP (mDSP) chip is the single DSP that coordinates the behavior of the system, including the other slave DSP (sDSP) chips. It handles all of the handshaking with the host computer and works with the master CPLD (mCPLD) to control the timing of the optical switch, gain bits, and acquisition of the signals from the ADCs. The mDSP relies heavily on the mCPLD to control the timing of all of the signals related to shifting and setting the gain bits, controlling the conversion and sampling from the ADCs, and sending out the address signals to control the source position of the optical switch.

The mDSP also relies on a slave CPLD (sCPLD) whose job is to multiplex the incoming data from the 32 detector ADC chips (each ADC is responsible for digitizing 4 detector channels) and routing it to the DSP chips for processing. This multiplexing is controlled through a chip select (CS) signal that keeps the CPLDs, ADCs, and DSPs in sync. Each DSP acquires two simultaneous serial streams of data through the A and B serial ports. The mDSP is referred to as the master because it controls the operation of all the components in the system. The other three DSP chips (sDSP1, sDSP2, sDSP3) are referred to as “slave chips” because they can only respond to one signal (IMAGING Start) that tells them to either acquire data or sit idly. The
master-slave configuration helps simplify the control of the system and keeps the data acquisition for all DSP chips in unison. This configuration also allows for easy scaling of the system for a larger number of sources, wavelengths, or detectors which is achieved either by reprogramming the existing DSPs or by adding additional slave DSP chips.

Each pair of DSP chips share an output data buffer. Following demodulation of the detected signal, the amplitude is written to the data buffer, where it is held until the host computer performs a read of the data buffer, via a data acquisition card (DAQ). An overview of the detection unit, including the way in which the master and slave DSPs and CPLDs combine to rapidly process large amounts of detected data, as shown in Fig. 5-1, below.

Figure 5-1. Overview of the detection unit.

The interaction between the Detection Board, the DSP Master Board, the DSP Slave board, and the Host Computer is outlined.
5.2 Digital Signal Processor (DSP) States

The behavior of the DSP chips is controlled through Visual DSP++ code written according to the Analog Devices standard. This code is compiled and programmed onto one Electrically Erasable Programmable Read-Only Memory (EEPROM) (M29W040B90K1E, ST Microelectronics) per DSP. The DSP code is included in Appendix G. The master and slave code is compiled from the same source, with a global define (#DEFINE MASTER_DSP) to distinguish the master DSP-specific portions of the code. As the DSP is powering up or coming out of reset, it loads the programming code from the EEPROM into its internal memory (via 8-bit reads over the external address and data lines). After the EEPROM program is loaded into memory, the mDSP begins executing the program, starting with an initialization sequence that allocates memory, configures registers and interrupts, and allocates I/O ports (Appendix G: initializeDSP.c, myIRQ.c). Interrupt signals play an important role in alerting the DSP program to important inputs or outputs. Table 5-1 contains a summary of the interrupts used in the mDSP program, along with their function. Note that the sDSP chips are only concerned with input from the ADC and output to the output buffer, thus they only use SPORT0 and DMACh10 interrupts.

<table>
<thead>
<tr>
<th>Interrupt</th>
<th>Triggered By:</th>
<th>Cause DSP to:</th>
</tr>
</thead>
<tbody>
<tr>
<td>RST</td>
<td>A low signal on Pin E2, RESET/</td>
<td>Return to start of main program</td>
</tr>
<tr>
<td>IRQ0</td>
<td>A low signal on Pin H2, IRQ0/</td>
<td>Wake up from Standby and read the command from the host PC encoded on DIO_PC0 and DIO_PC1</td>
</tr>
<tr>
<td>SPORT0</td>
<td>Serial Port 0 has received all of the data from the ADCs.</td>
<td>Disable SPORT0. Proceed to next source position in Imaging State</td>
</tr>
<tr>
<td>SPORT1</td>
<td>Serial Port 1 has finished sending gain bits.</td>
<td>Disable SPORT1. Proceed to next source in Gainbit state.</td>
</tr>
<tr>
<td>EP0I</td>
<td>DMA Channel 10 has finished writing the demodulated data to the output buffer.</td>
<td>Disable DMACH10. Proceed to next operation in Imaging Bits State.</td>
</tr>
<tr>
<td>EP1I</td>
<td>DMA Channel 11 has received all of the gain bits from the host PC.</td>
<td>Disable DMACH11 operation. Proceed to next operation in Gain Bits State.</td>
</tr>
</tbody>
</table>
TIMEXP | 7 ms timer has expired. | Disable the timer. Alert mCPLD and mDSP that 7 ms timer has elapsed by outputting TIMEXP.

The DSPs communicate with the outside world through a number of channels: input/output flags, Serial Port 0 (SPORT0), Serial Port 1 (SPORT1), External Port 0 (DMACH10), and External Port 1 (DMACH11). Flags are the simplest interface, consisting of 9 digital pins that can be configured as either inputs or outputs. The flags used by the mDSP and sDSP are shown in Table 5-2.

<table>
<thead>
<tr>
<th>Flag</th>
<th>Input/Output</th>
<th>Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flag0</td>
<td>Input</td>
<td>DIO_PC0: Instruction from the host PC.</td>
</tr>
<tr>
<td>Flag1</td>
<td>Input</td>
<td>DIO_PC1: Instruction from the host PC.</td>
</tr>
<tr>
<td>Flag2</td>
<td>Input</td>
<td>DIO_PLD0: High when the mCPLD is in Standby. Important for ensuring mDSP and mCPLD are synchronized.</td>
</tr>
<tr>
<td>Flag3</td>
<td>Input</td>
<td>DIO_PLD1: Used by the mCPLD to acknowledge instructions from the mDSP.</td>
</tr>
<tr>
<td>Flag5</td>
<td>Output</td>
<td>DIO_IMST/: Instructs the mCPLD and sDSPs to go into Imaging State.</td>
</tr>
<tr>
<td>Flag9</td>
<td>Output</td>
<td>DIO_LED/: Turns on the Idle LED whenever the mDSP is in Standby.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Flag</th>
<th>Input/Output</th>
<th>Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flag2</td>
<td>Input</td>
<td>DIO_PLD0: High when the mCPLD is in Standby. Tells sDSP to leave Imaging and return to Standby State.</td>
</tr>
<tr>
<td>Flag3</td>
<td>Input</td>
<td>DIO_PLD1: Currently unused by the sDSP.</td>
</tr>
<tr>
<td>Flag5</td>
<td>Input</td>
<td>DIO_IMST/: Instructs the sDSP to go into Imaging State.</td>
</tr>
</tbody>
</table>

There are two types of interfaces used for data transfer: serial ports (SPORT0 and SPORT1) and external, parallel ports (DMACH10 and DMACH11). SPORT0 receives the serial data from the ADCs, SPORT1 sends the gain bits to the mCPLD, DMACH10 sends the demodulated data to the output buffer, and DMACH11, receives the imaging parameters and gain bits from the host computer. The operation of four ports is very similar:
1. Instruct the port where to store the data (for incoming data) or where to begin reading the data to send out (for outgoing data).

2. Tell the port how many words of data to send or receive.

3. Enable the port.

Once the port is initialized and enabled it conducts the data transfer independently and will trigger an interrupt (see Table 5-1) upon completion of the transfer. The serial ports have two data lines that use the same clock (A and B). The word size for each port is determined as part of the DSP initialization: SPORT0 uses 16-bit words, SPORT1 uses 32-bit words, DMACh10 uses 8-bit external words with 32-bit internal words, and DMACh11 uses 16-bit internal words with 32-bit external words (Appendix G: Initialize_DSP.c). The word count written to the register specified in Table 5-3 must match the word size of the port. Each port is initialized as either an input or output port. Table 5-3 outlines the registers that are updated for data transfers on each of the data ports. A full description of the registers and functionality of the ports can be found in [63].

<table>
<thead>
<tr>
<th>Port</th>
<th>Function</th>
<th>Rx/Tx Address</th>
<th>Word Count Address</th>
<th>Word Size</th>
<th>Enable</th>
</tr>
</thead>
<tbody>
<tr>
<td>SPORT0</td>
<td>Receive data from ADCs.</td>
<td>I10A</td>
<td>C0A</td>
<td>32-bit</td>
<td>SPORT0[0]=1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>I10B</td>
<td>C0B</td>
<td>32-bit</td>
<td>SPORT0[24]=1</td>
</tr>
<tr>
<td>SPORT1</td>
<td>Send gain bits to mCPLD.</td>
<td>I11A</td>
<td>C1A</td>
<td>16-bit</td>
<td>SPORT1[0]=1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>I11B</td>
<td>C1B</td>
<td>16-bit</td>
<td>SPORT1[24]=1</td>
</tr>
<tr>
<td>DMACh10</td>
<td>Send demodulated data to output buffer.</td>
<td>IIEPO</td>
<td>CEP0 (Internal)</td>
<td>8-bit</td>
<td>DMAC10[0]=1</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>ECEP0 (External)</td>
<td>32-bit</td>
<td></td>
</tr>
<tr>
<td>DMACh11</td>
<td>Receive Imaging parameters and gain bits from host computer.</td>
<td>IIEP1</td>
<td>CEP1 (Internal)</td>
<td>16-bit</td>
<td>DMAC11[0]=1</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>CEP0 (External)</td>
<td>32-bit</td>
<td></td>
</tr>
</tbody>
</table>
The state machine for the mDSP is comprised of four states: Standby, Imaging Parameters, Gain Bits, and Imaging. After initialization the DSP sits idle in Standby waiting for a command (encoded by DIO_PC0 and DIO_PC1) to arrive from the host computer. Following the completion of each state the mDSP returns to Standby. In the Imaging Parameters State the host PC sends the mDSP the number of sources, detectors, and wavelengths to be used in the current experiment. In the Gain Bits state the mDSP receives the gain bits from the host PC and transmits them via the mcPLD to the detector boards. In the Imaging state the mDSP coordinates the acquisition of data from the ADCs on the detector boards, demodulates the data, and sends the result to the host PC via an output buffer. Unlike the mDSP, the sDSPs have only two states: Standby and Imaging. The sDSP sits idle in the Standby State until it receives a signal (DIO_IMST/) from the mDSP to begin processing incoming data from the ADCs. The sDSP then returns back to Standby when DIO_IMST/ has returned high, and the mcPLD has returned to Standby (indicated by DIO_PLD0=1). Fig. 5-2 shows a state machine diagram detailing how the (a) mDSP and (b) sDSPs transition between the various states.

![State machine diagram](image)

Figure 5-2. State machine for the (a) mDSP and (b) sDSP.
Also shown are the transitions between the four main states: Standby, Imaging Parameters, Gain Bits, and Imaging. Transitions out of the Standby state are controlled by the values of DIO_PC1 and DIO_PC0 from the host computer.
**Standby State**

This is a low-power state where the DSPs sit idle waiting for an interrupt (IRQ0) in the case of the mDSP, or a flag (Flag5: DIO_IMST/) in the case of the sDSPs. When the mDSP receives the IRQ0 interrupt it checks DIO_PC0 and DIO_PC1 to determine which state it should enter. When the sDSP sees DIO_IMST/ go low, it enters the Imaging State and begins processing data. When the DSPs are in the Standby State the IDLE LED is on (Appendix G: LED.c).

**Imaging Parameters State**

The first state that must be entered following reset is Imaging Parameters (Appendix G: ImParameters.c). In this state, the host computer sends the mDSP the global parameters for the current experiment. These global parameters are `src`, the number of sources (in binary representation from 1 to 32); `det`, the number of detectors per breast (in binary representation from 1 to 64); and `wl_set`, the number of wavelength sets (`wl_bit=0` corresponds to one wavelength set and `wl_set=1`, `wl_bit=1` to two wavelength sets and `wl_set=2`). These parameters are all encoded into a single 32-bit data transfer on DMACh11, as illustrated in Fig. 5-3.

![Figure 5-3. Encoding of the imaging parameters into a single 32-bit DMA transfer.](image)

To send the imaging parameters to the DSP, the host PC initiates a data write through the DAQ, sending both the DATA and a REQ signal. The data is latched by a flip flop
(SN74LVC574ADBR, Texas Instruments) onto the DATA[16:32] lines of the mDSP. The latch clock is a delayed version of REQ. The mDSP reads the data on DATA[16:32] on the falling edge of DMAR1/. DMAR1/ is a 50 ns delayed version of REQ to allow time for the data to arrive at the mDSP DATA[16:32] lines. This timing is outlined in Fig. 5-4, where $t_p$ is the delay from REQ to DMAR1/ (50 ns), $t_{latch}$ is the time it takes for the latched data to appear on the DATA[16:32] lines (<8 ns), $t_{pw}$ is the pulse width of the REQ signal and $t_{period}$ is the interval between REQ data transfers. The 32-bit transfer is comprised of two 16-bit words. The Imaging Parameters state sets up DMACh11 to expect a 2 word write (see Table 5-3). Once DMACh11 receives 2 words it triggers an interrupt EP1I that informs the program that the data has been received and can be read from the address specified in register IIEP1. Following the completion of the Imaging Parameters state the mDSP returns to the Standby state.

![Figure 5-4. Timing diagram for DMACH11 data transfer from the host PC to the mDSP.](image)

**Gain Bits State**

As described in Chapter 4, there are 3 gain bits for each detector channel that encode the amount of amplification to apply across the TIA and PGA gain stages. The gain bits are unique
to each detector channel, source position, and wavelength set. As such there are 
3*128*32*2=24,576 bits that must be correctly transferred from the software interface onto 
the detection boards. The software interface allows the gain bits to be set manually, or to be 
automatically detected through an iterative routine, described in Section 6.3. Determining the 
gain bits prior to imaging and storing the values locally on the detector boards speeds up 
switching the gain bits with each source position.

In the Gain Bits State three main operations occur: the gain bits are received from the 
host computer via DMACh11, the imaging parameters are passed to the mCPLD via SPORT1, 
and the gain bits are streamed from mDSP to the mCPLD via SPORT1 and from the CPLD onto 
the Detector Boards (Appendix G: Gain_Bit.c). The first part of this transfer occurs from the 
host computer to the DSP. This transfer occurs over DMACh11 as described in the Imaging 
Parameters State (see Fig. 5-4). DMACh11 is programmed to expect 3*src*wl_set*128/16 
words of data. The factor of 128 is due to the fact that in our design, regardless of the number of 
detectors used in the experiment, the full set of gain bits must be transmitted.

Once the mDSP receives the gain bits from the host PC it must coordinate with the 
mCPLD to arrange for the transfer of the gain bits to the Detector Boards. The first step is to 
put the mCPLD into the Gain Bits state. This is accomplished by performing a write on SPORT1. 
The one-word write of zeros causes the frame sync signal (FS) to pulse high, instructing the 
CPLD to go into the Gain Bits state. Once the mCPLD is in its Gain Bits state it indicates this by 
setting DIO_PLD1 high for two clock cycles. The mDSP waits until it sees this flag pulse high 
before it proceeds. The CPLD Gain Bits state machine is shown below.
Once both the \textit{mDSP} and \textit{mCPLD} are in the Gain Bits State the \textit{mDSP} must tell the \textit{mCPLD} how many sources and wavelength sets to use in this experiment. Note that the \textit{mCPLD} is oblivious to the number of detectors. The \textit{src} and \textit{wl\_set} values are transmitted to the \textit{mCPLD} via a one-word SPORT write similar to the lower 16-bits of the DMA encoding shown in Fig. 5-3. When the \textit{mCPLD} sees the FS go high it moves from the Init sub-state into the GetSource sub-state and receives the number of sources and wavelength sets from the \textit{mDSP}. The \textit{mCPLD} knows it is finished receiving the data when the FS signal goes low, and then proceeds to the ShiftGB sub-state. As the \textit{mCPLD} moves into the ShiftGB sub-state it pulses DIO\_PLD1 high to confirm to the \textit{mDSP} that it has received the number of sources and wavelength sets.

Next, the \textit{mDSP} loops through each source position and wavelength set and sends the gain bits for all left breast detectors out on SPORT1A and the gain bits for the right breast
detectors on SPORT1B. As long as the frame sync (FS) signal is high, the mCPLD passes the incoming bits from SPORT1A onto GBL and from SPORT1B onto GBR, which are the data lines that connect from the mCPLD to the detection boards. Synchronized with the data bits is a sync clock (SCL) that shifts the gain bits through a series of shift registers (TC74VHC595, Toshiba) located on the detector boards. Each of the 8 detector boards containing 8 channels that require 3 gain bits to encode their amplification, resulting in 192 gain bits per breast that must be programmed for each source position. These gain bits arrive from the mDSP and are output to the detector boards via the mCPLD along with a synchronized shift register input clock (SCK). With each input clock (SCK) the shift register reads in the value present on its serial input (SI). The shift register output clock (RCK) causes the values stored in the register to be latched onto the output ports (QA through QH). Fig. 5-6 shows the timing diagram for the gain bit shift register as well as the logic diagram detailing the operation of the chip. Since the timing of RCK and SCK must be carefully synchronized with the long series of gain bits that must be shifted through the registers, the Master DSP Board provides the ability to introduce from 0 to 40 ns of delay onto each clock through the use of jumpers (SCK: J3,J4, RCK: J5,J6). Each jumper position adds an additional 4 ns of delay onto the signal (SCK is a 30 MHz clock).
Figure 5-6. Shift register timing and operation.

Shown are (a) the timing diagram and (b) the logic diagram [64] for the operation of the shift register responsible for daisy-chaining the gain bits through the detector boards. The timing diagram shows the tail end of the gainbit shifting of 192 gain bits.

There are three shift registers on each board that continue passing the gain bits along for 192 pulses of SCK. The input to the first shift register on a given Detector Board comes from the Detector Board before it (or from the mCPLD for the first board) and the output of the last shift register is connected to the input of the next board (with the exception of the last of the 8 boards). This means that the last gain bits to be sent out from the mDSP and mCPLD are the gain bits for the first board. Fig. 5-7 shows how the gain bits are daisy chained through the detector boards.
Figure 5-7. Diagram showing the gain bits shifting through the detector boards for the left and right breast.

Once the gain bits have been shifted through the registers they are latched onto the shift register outputs by RCK in preparation for writing the values into three 1k x 9-bit FIFOs (IDT72V02, Integrated Device Technologies) on each detector board. RCK is triggered each time the mCPLD passes from the ShiftGB sub-state into the UpdateFIFO sub-state. Each time the mCPLD enters the Gain Bit state it resets the FIFOs to clear their contents and to prepare to write the new set of Gain Bits. During the UpdateFIFO sub-state the gain bits are written into the FIFOs from the shift registers using a write (W) command from the mCPLD and the values are stored in the FIFO for use during the imaging sequence. Each row of the FIFO contains the gain bits for a different source and wavelength set, therefore, by the time the gain bit storage is
complete, there should be src*wl_set entries in the gain bit FIFO. The connections between the shift registers and the FIFOs for each detector board are shown in Fig. 5-8.

![Diagram of FIFO and shift registers](image)

**Figure 5-8.** Shift register and gain bit FIFO connections on the detector board.

The mCPLD progresses from the UpdateFIFO sub-state into the Loop sub-state. In the Loop sub-state it checks if all of the sources and wavelength sets have been programmed with gain bits. If it still has more sources and wavelength sets to cover it returns to the GetSource sub-state. Otherwise it returns to the Init sub-state and leaves the Gain Bit state and returns to the Standby state. After returning to Standby the DIO_PLD0 flag goes high, informing the mDSP that it, too, can return to Standby state.

**Imaging State**

The Imaging State is where the mDSP acquires the data from the Detection Boards and performs the digital lock-in detection to extract the amplitude of the waveform, which is then passed to the host PC through an output buffer (Appendix G: Imaging.c). The Imaging state begins with the mDSP telling the mCPLD and sDSPs to go to the Imaging State by setting
DIO_IMST/ low. The mDSP will loop through each source for both wavelength sets and perform the following sequence:

1. Switch the source position.
2. Wait for the 7 ms timer to expire.
3. Acquire 150 samples from the detector channels.

To optimize the timing, the mDSP performs the demodulation of data from the previous source position and sends the result to the output buffer, while waiting for the source to settle.

The mCPLD plays a central role in the imaging state, and its behavior is governed by the state machine shown in Fig. 5-9, shown below.

![Figure 5-9. mCPLD Imaging State Machine.](image)

The mCPLD enters the Imaging state by the active low signal DIO_IMST/ and immediately progresses from the Init sub-state to the Switch sub-state. Once in the Switch sub-state, the optical switch is programmed to illuminate the correct source position via 7 bits (PS0-
PS6) that behave according to Fig. 3-8. The mcPLD then progresses to the Wait sub-state to allow the optical switch time to settle at its new position. Upon entering Wait the mcPLD triggers a read from the Detector Board FIFOs to apply the gain bits for the current source position across the TIA and PGA amplification stages. While in Wait, the mcPDL outputs DIO_PLD1 to tell the mDSP to start the 7 ms timer. The mDSP initializes the timer to 0xAAE60, which is hexadecimal representation for 700,000 cycles of the 100 MHz internal DSP clock to give 7 ms. When the timer expires it asserts TIMEXP, which alerts the mcPLD that it can move out of Imaging.Wait, pass through the Update sub-state (where it updates the source position counter, but doesn’t use it until the next time it enters the Switch sub-state), and into the Convert sub-state. In the Convert sub-state the mcPLD waits for 2.4 µs. During the entire Imaging.Convert State the CVST/ signal to the ADCs is held low, causing the ADCs to convert the analog input into a digital value. Once the 2.4 µs has elapsed, the F_CNVT signal goes high, pushing the state machine into the SendData sub-state.

While in SendData, the mcPLD samples the data from all of the ADCs and works with the sCPLD to route the data from the ADCs to the correct DSP for processing. The read port of the ADC is held low, which allows the chip select (CS/) to act as the read enable. The data from the 32 ADCs in the system is collected through the careful data multiplexing controlled through four chip select signals CS1/, CS2/, CS3/, and CS4/. In the SendData sub-state each chip select signal pulses low for 32 clock cycles, thereby reading the 32-bit value from the ADC.
Figure 5-10. Routing of chip selects and data for the 16 detector boards.
The chip select also coordinates the correct routing of the incoming data from the ADCs to the correct DSP for processing, via the sCPLD. The routing of the chip selects and sampled data from the 16 boards (Right Breast: Boards 1-8, Left Breast: Board 9-16) is shown in Fig. 5-10. Only one chip select is held low at any given time, which means that the inverted value (!CS/) will only ever be high for one CS/ and corresponding data line at a time. The data is routed by the sDSP as follows:

**Right Side**
- \( m_{DSP\_D0A} = \{ICS1/ \text{and} \ IND1c \} \text{ or } \{ICS2/ \text{and} \ IND3c \} \text{ or } \{ICS3/ \text{and} \ IND5c \} \text{ or } \{ICS4/ \text{and} \ IND7c \} \)
- \( m_{DSP\_D0B} = \{ICS1/ \text{and} \ IND2c \} \text{ or } \{ICS2/ \text{and} \ IND4c \} \text{ or } \{ICS3/ \text{and} \ IND6c \} \text{ or } \{ICS4/ \text{and} \ IND8c \} \)
- \( s_{DSP1\_D0A} = \{ICS1/ \text{and} \ IND1d \} \text{ or } \{ICS2/ \text{and} \ IND3d \} \text{ or } \{ICS3/ \text{and} \ IND5d \} \text{ or } \{ICS4/ \text{and} \ IND7d \} \)
- \( s_{DSP1\_D0B} = \{ICS1/ \text{and} \ IND2d \} \text{ or } \{ICS2/ \text{and} \ IND4d \} \text{ or } \{ICS3/ \text{and} \ IND6d \} \text{ or } \{ICS4/ \text{and} \ IND8d \} \)

**Left Side**
- \( s_{DSP2\_D0A} = \{ICS1/ \text{and} \ IND1a \} \text{ or } \{ICS2/ \text{and} \ IND3a \} \text{ or } \{ICS3/ \text{and} \ IND5a \} \text{ or } \{ICS4/ \text{and} \ IND7a \} \)
- \( s_{DSP2\_D0B} = \{ICS1/ \text{and} \ IND2a \} \text{ or } \{ICS2/ \text{and} \ IND4a \} \text{ or } \{ICS3/ \text{and} \ IND6a \} \text{ or } \{ICS4/ \text{and} \ IND8a \} \)
- \( s_{DSP3\_D0A} = \{ICS1/ \text{and} \ IND2b \} \text{ or } \{ICS2/ \text{and} \ IND3b \} \text{ or } \{ICS3/ \text{and} \ IND5b \} \text{ or } \{ICS4/ \text{and} \ IND7b \} \)
- \( s_{DSP3\_D0B} = \{ICS1/ \text{and} \ IND2b \} \text{ or } \{ICS2/ \text{and} \ IND4b \} \text{ or } \{ICS3/ \text{and} \ IND6b \} \text{ or } \{ICS4/ \text{and} \ IND8b \} \)

Once the data from all of the ADCs has been transmitted to the DSPs (indicated by F_SD=1 in the mCPLD), the mCPLD must return to the Imaging.Convert State to take the next sample. This time it will sample the other two ADC ports (the A1 and B1 ports). The mCPLD will continue cycling between the Convert and SendData sub-states until 150 samples have been acquired from both the A0&B0 and A1&B1 ports of the ADCs (300 samples total). Once all 300 samples are acquired (indicated by F_SMPL) the mCPLD is ready to go back to the Switch sub-state to cause the switch to move to the next source position. And the cycle continues until data for all sources and wavelength sets has been acquired (F_IMG=1).

When 150 samples have been acquired from all detector channels for the last source and wavelength set, the mCPLD progresses from the SendData to Init sub-state. The Imaging
state will also transition to Standby, triggering the DIO_PLD0 to indicate to the mDSP that the imaging frame is complete and it has returned to Standby. In addition, as the mCPLD exits the Imaging state, it pulses the FIFO retransmit signal (FIFO_RT/) to the gain bit FIFOs on the Detector Boards. This causes the read pointer to return to the first entry (the gain bits for source 0, wavelength set 1) in preparation for the next imaging frame (which will start back at source 0, wavelength set 1 and must read the corresponding gain bits from the FIFOs).

The DSP chips are unaware of the intricacies of the data acquisition from the ADCs. They program the SPORT0 register to expect 150 16-bit words of data from 16 detector channels on each D0A and D0B port. Once this data is received the SPORT0 interrupt is triggered, alerting the Imaging state that it can proceed. However, it doesn’t immediately use the newly sampled data. First, it confirms that the mCPLD is not inStandby (it shouldn’t be, but if for some reason it is, the mCPLD leaves the Imaging state and returns to Standby) and then waits to see the DIO_PLD1=1, indicating that the mCPLD is in Wait state and needs the mDSP to start the timer.

While the mDSP is waiting for the timer to expire, it has 7 ms during which it can demodulate the data it just received for the previous source. The details of the digital demodulation are discussed in Section 5.5. The digital demodulation takes in 150 samples for each channel and computes the amplitude as a 32-bit floating point number. Once all channels have been demodulated, the mDSP programs the DMACH10 to write the data to the output buffer. Two DSPs share one dual 9-bit output buffer. As a result, the DMACH10 outputs each 32-bit value as 4 8-bit writes. It takes approximately 2 ms to perform the digital demodulation
and write the values to the demodulation buffer. This means that the 7 ms settling time of the optical switch is the delay most critical to the system timing.

Once the data has been acquired for all sources and wavelength sets the mDSP must still send the data for the final source and wavelength set. Once that is complete, the mDSP waits for the mcPLD to transmit DIO_PLLD0 which indicates that it is in Standby before returning to its own idle state Standby to await the next instruction from the host computer. In the case of the sDSPs, which are oblivious to the number of sources and wavelength sets, they continue iterating in Imaging until they see the mcPLD return to Standby, as indicated by DIO_PLLD0, at which point they transition back to Standby.

The DSPs acquire 150 samples from each of the 128 detectors over a period of 2 ms which results in each detector being sampled at 75 ksamples/s. To collect a complete sample on one serial input port, the DSP must wait for the ADCs to convert the sample for A0&B0 and will then read the two 16-bit values from 4 ADCs (one for each chip select). Next, the DSP must wait for the ADCs to convert the sample for A1&B1 and then read the two 16-bit values from the 4 ADCs. This means that the sampling time is \(2 \times (t_{\text{cnvst}} + 16 \times 2 \times 4 \times t_{\text{read clk}})\), where \(t_{\text{cnvst}}\) must be at least 1.75 µs and \(t_{\text{read clk}}\) is dictated by the CPLD clock, which is 30 MHz, so in this case \(t_{\text{read clk}}=33.33\) ns. By this calculation, the fastest sampling rate possible is \(~83\) kHz. To allow for ample conversion time, while also obeying the constraints for digital lock-in detection outlined in 5.5, we choose a sampling rate of 75 kHz. To maintain this sampling rate we lengthen \(t_{\text{cnvst}}\) to 2.4 µs. The detailed digital logic signals and timing to acquire data for a single source and wavelength set are shown in Fig. 5-11.
Figure 5-11. Digital signals for acquiring image data for a source and wavelength set.

The overall sequencing and timing to acquire a complete frame in the imaging state is illustrated in Fig. 5-12.
### 5.3 DSP-CLP Coordination

The mDSP and mCPLD work closely together to synchronize the timing of the events in the system and to control the other chips. The mCPLD is used to communicate the control logic to the detection boards, but the mDSP closely controls the mCPLD and is responsible for the timer that counts the 7ms required for the optical switch settling. The intricate way in which the mDSP and mCPLD work together to progress through the various states of setup and data acquisition is shown in Table 5-4.

![Figure 5-12. Timing sequence for the acquisition of a complete image.](image-url)

<table>
<thead>
<tr>
<th>SRC1, WL162</th>
<th>SRC1, WL162</th>
<th>SRC1, WL162</th>
<th>SRC1, WL162</th>
<th>SRC1, WL162</th>
<th>SRC1, WL162</th>
<th>SRC1, WL162</th>
<th>SRC1, WL162</th>
<th>SRC1, WL162</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adjust Optical Switch and Update Gain Settings for:</td>
<td>Illuminate Sample With:</td>
<td>Convert Sample:</td>
<td>Send Data for ADC Channels:</td>
<td>mDSP</td>
<td>DSP1</td>
<td>DSP2</td>
<td>DSP3</td>
<td>DSPs Demodulate &amp; Send Data to PC for:</td>
</tr>
<tr>
<td>SRC1, WL162</td>
<td>Sample 1</td>
<td>Channel 1 &amp; 3</td>
<td>ADC16 &amp; ADC9 &amp; ADC10</td>
<td>ADC17 &amp; ADC8</td>
<td>ADC25 &amp; ADC26</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Sample 1</td>
<td>Channel 2 &amp; 4</td>
<td>ADC18 &amp; ADC9 &amp; ADC10</td>
<td>ADC17 &amp; ADC8</td>
<td>ADC25 &amp; ADC26</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Sample 2</td>
<td>Channel 1 &amp; 3</td>
<td>ADC19 &amp; ADC10</td>
<td>ADC17 &amp; ADC8</td>
<td>ADC25 &amp; ADC26</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Sample 150</td>
<td>Channel 2 &amp; 4</td>
<td>ADC7 &amp; ADC18</td>
<td>ADC15 &amp; ADC16</td>
<td>ADC23 &amp; ADC24</td>
<td>ADC31 &amp; ADC32</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Table 5-4. State by State Description of the PC, mCPLD, and mDSP Interaction

<table>
<thead>
<tr>
<th>State</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Standby</strong></td>
<td><em>mDSP</em> is idle waiting for a signal from the host computer.</td>
</tr>
<tr>
<td></td>
<td><em>mCPLD</em> is idle waiting for a signal from the <em>mDSP</em>.</td>
</tr>
<tr>
<td><strong>Imaging</strong></td>
<td>1. <em>mDSP</em> receives CMD:01 from the host computer telling it to go into the Imaging Parameters state.</td>
</tr>
<tr>
<td></td>
<td>2. The host computer sends the number of sources, detectors, and wavelengths to the <em>mDSP</em> via DMACh11.</td>
</tr>
<tr>
<td></td>
<td>3. <em>mDSP</em> returns to <strong>Standby</strong>.</td>
</tr>
<tr>
<td></td>
<td><em>mCPLD</em> remains in <strong>Standby</strong>.</td>
</tr>
<tr>
<td><strong>Gain Bits</strong></td>
<td>1. <em>mDSP</em> receives CMD:10 from the host computer telling it to go into the Gain Bit download state.</td>
</tr>
<tr>
<td></td>
<td>2. PC sends the gain bits for each source-detector pair to the <em>mDSP</em> on DMA Ch11.</td>
</tr>
<tr>
<td></td>
<td>3. <em>mDSP</em> tells the mCPLD to go into Gain Bit state by transmitting an empty word on SPORT1A.</td>
</tr>
<tr>
<td></td>
<td>4. <em>mDSP</em> sends the mCPLD the # of sources and wavelengths as a word on SPORT1A.</td>
</tr>
<tr>
<td></td>
<td>5. <em>mDSP</em> sends the gain bits to the mCPLD via SPORT1A (Left Breast) and SPORT1B (Right Breast). mCPLD passes them directly onto the detection boards along with the control signals for the shift registers and FIFOs.</td>
</tr>
<tr>
<td></td>
<td>6. mCPLD returns to <strong>Standby</strong> and sets DIO_PLD0=1.</td>
</tr>
<tr>
<td></td>
<td>7. <em>mDSP</em> returns to <strong>Standby</strong>.</td>
</tr>
<tr>
<td><strong>Imaging</strong></td>
<td>1. <em>mDSP</em> receives CMD:11 from the host computer telling it to acquire one frame.</td>
</tr>
<tr>
<td></td>
<td>2. <em>mDSP</em> tells mCPLD to go into Imaging State by setting DIO_IMST=0.</td>
</tr>
<tr>
<td></td>
<td>3. mCPLD tells the optical switch to move to the next position. Updates the gain bits by triggering a read from the detection board FIFOs. Waits for the TIMEXP signal from <em>mDSP</em>. Outputs DIO_PLD0=1 while waiting for TIMEXP=1.</td>
</tr>
<tr>
<td></td>
<td>4. <em>mDSP</em> waits to see DIO_PLD0=1 to start the 7ms timer. While waiting for the timer to expire it runs the lock-in detection and sends data from previous source back to the PC via DMA Ch10. When the 7 ms has elapsed it sets TIMEXP=1.</td>
</tr>
<tr>
<td></td>
<td>5. mCPLD acquires 150 samples from all detectors.</td>
</tr>
<tr>
<td></td>
<td>6. <em>mDSP</em> receives 150 samples from 16 detectors on SPORT0A and from 16 detectors on SPORT0B.</td>
</tr>
<tr>
<td></td>
<td>7. mCPLD asserts DIO_PLD0=1 to show it has finished acquiring data.</td>
</tr>
<tr>
<td></td>
<td>8. <em>mDSP</em> returns to step 3 until all sources and wavelength sets are acquired.</td>
</tr>
<tr>
<td></td>
<td>9. mCPLD returns to <strong>Standby</strong> and sets DIO_PLD1=1.</td>
</tr>
<tr>
<td></td>
<td>10. <em>mDSP</em> returns to <strong>Standby</strong>.</td>
</tr>
</tbody>
</table>

5.4 Data Sample Reordering

The 150 data samples are received in a time-multiplexed fashion from the ADCs according to the chip selects (CS1-CS4/) and the ADC Channel select (A0/). Table 5-5 shows the order in which the samples are acquired. Each DSP is responsible for 32 detector channels (housed on 4 Detector Boards). The chip select (CS1/-CS4/) identifies the board from which to read, while
the ADC Channel Select (A0/) chooses which pair of channels to read from the four-channel ADC. Each read from the ADC samples two channels that are output serially to the DSP. The ordering of the data samples captured in the DSP memory following the acquisition of one source position measurement is shown in Table 5-5.

<table>
<thead>
<tr>
<th>Sample #</th>
<th>Sampling From:</th>
<th>IDA</th>
<th>IDB</th>
<th>Chip Select</th>
<th>ADC Channel Select</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Board 1</td>
<td>3</td>
<td>7</td>
<td>CS1/=0</td>
<td>A0/=0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1</td>
<td>5</td>
<td>CS1/=0</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Board 2</td>
<td>11</td>
<td>15</td>
<td>CS2/=0</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>9</td>
<td>13</td>
<td>CS2/=0</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Board 3</td>
<td>19</td>
<td>23</td>
<td>CS3/=0</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>17</td>
<td>21</td>
<td>CS3/=0</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Board 4</td>
<td>27</td>
<td>31</td>
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<td>8</td>
<td>CS1/=0</td>
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<td>CS1/=0</td>
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<td>Board 3</td>
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<td>23</td>
<td>CS3/=0</td>
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In order to perform the demodulation (Appendix G: Demodulation.c) for a given detector channel, the algorithm must first extract all 150 samples that belong to each detector channel. It does so sequentially by looping through the data memory (IDA and IDB) extracts each of the 150 samples which are stored at 16 row intervals. The loop starts with row 0 and loop through all 16 possible starting offset rows (index i loops from 0 to 15).

```
for i from 0 to 15 //each possible starting offset row
  for j from 0 to 149 //find each of the 150 samples
    datMatA[j] = (double) IDA[i+16*j];
    datMatB[j] = (double) IDB[i+16*j];
  end
  OUTPUT[(Det_Hash[i]] = demodulate(datMatA);
  OUTPUT[(Det_Hash[i+16]] = demodulate(datMatB);
end
```

Once the DSP has extracted the 150 samples from the IDA and IDB memory banks, it now has a complete waveform for one detector from each channel (datMatA and datMatB). At this point it can perform the demodulation to compute the amplitude of the waveform. Then, when writing the result to the output array (an array that contains 32 elements - one for each detector channel), it carefully matches the data extracted from memory to the actual detector value according to the following hash table according to Table 5-5. The hash table references detector values from 0 to 31.

```
Det_Hash[DETECTORS] = { 2,0,10,8,18,16,26,24,3,1,11,9,19,17,27,25,
  6,4,14,12,22,20,30,28,7,5,15,13,23,21,31,29};
```
5.5 Digital Lock-in Detection

Each DSP is responsible for demodulating the incoming data to extract the amplitude of the signal. The digital lock-in detection algorithm employed by this system was previously described in detail by Masciotti et al. [65]. The key feature of the algorithm is that it uses a simple averaging filter to extract the amplitude of the signal, but requires a specific relationship between \( f_m \), the frequency of the signal (7 kHz and 5 kHz in this system), and \( N_s \), the number of samples acquired, as shown in Eq. 5.1.

\[
f_m = \frac{k f_s}{N_s}, 1 \leq k < \frac{N_s}{2} \quad (5.1)
\]

Using the relationship given in Eq. 5.1 the digital demodulation can be implemented as derived in [65] and shown in Eq. 5.2 where \( Data \) is a 1x150 array of the samples from the detector channel containing the measurement from one wavelength set that contains two wavelengths: one modulated at 5 kHz and one modulated at 7 kHz. \( InPhaseRef \) is a 150x2 array of a 5 kHz and 7 kHz in-phase waveform with 150 samples taken at 75 kHz. \( Quad \) is a 150x2 array consisting of a 5 kHz and 7 kHz quadrature waveform, shifted by \( \frac{1}{4} \) of the phase period, with 150 samples taken at 75 kHz. Both \( InPhaseRef \) and \( Quad \) are stored on the DSP. The \( Scaling \) parameter is used to convert the final amplitude from an integer ranging from 0 to \( 2^{16} - 1 \) into a relative voltage ranging from 0 to 5 V, so \( Scaling \) in our system equals 13107.

\[
InPhase_{2x1} = Data_{1x150} * InPhaseRef_{150x2}; \quad Quad_{2x1} = Data_{1x150} * QuadRef_{150x2};
\]

\[
Output_{WL1} = \frac{\sqrt{|InPhase[0]|^2 + |Quad[0]|^2}}{150 * Scaling}; \quad Output_{WL2} = \frac{\sqrt{|InPhase[1]|^2 + |Quad[1]|^2}}{150 * Scaling} \quad (5.2)
\]
Performing the lock-in detection digitally using a DSP chip as opposed to using traditional analog circuitry not only reduces the amount of hardware required for demodulation, but also provides a more robust solution with better noise performance [66, 67]. Simply by reprogramming the DSP chip it is possible to adjust the lock-in frequency, filtering, and the number of detectors. In addition, DSP-based demodulation is less sensitive to analog component tolerances that can vary with temperature and age as well as between detector channels [68].

5.6 Coordinated Data Transfer

The demodulated amplitude for each detector is stored as a 32-bit floating point number that must be transferred to the host. This transfer takes place through output buffers that are located on the Master and Slave DSP Boards. The DSP writes the data to the output buffer, triggering a read request to the host PC. The host PC then asynchronously chooses to read the result from the output buffer.

Each pair of DSP chips (mDSP & sDSP1 and sDSP2 & sDSP3) share an 8,192 x 9-bit dual synchronous FIFO (IDT 72851, Integrated Device Technologies) through which the data is sent back to the host computer. Each DSP must break up the 32-bit floating point number into four 8-bit writes to the FIFO. These writes are accomplished through the DMACH10, which is programmed to transmit 32 32-bit words according to its internal counter (CEP0) and 4*32=128 8-bit words according to its external counter (ECEP0). A full tomographic data set consists of 4 writes/detector * 32 detectors * 32 sources * 4 wavelength = 16,384 writes. The output buffer FIFO used here can accommodate half of a full tomographic data set (8,192). This provides
flexibility in the event that the host PC cannot immediately service the read request from the output buffer.

Any data sitting in the output buffer FIFO causes the empty flag (FIFO_EF/) to deassert, thereby triggering a request to the host PC. The host PC then grants the request and triggers a read to the FIFO, which sends the data to the host PC, via a Data Acquisition Card (DAQ). As such, the FIFO is essentially a data buffer that is responsible for holding the data until the host computer is ready. The control signals from the host PC are passed to the detector hardware through a DAQ (PCI-6503, National Instruments) that has a 24-bit digital I/O interface. The data from the DSP chips is acquired by the host PC through a second DAQ (PCI-6533, National Instruments) that provides 32 digital data lines that are individually configurable as inputs or outputs, grouped into four 8-bit ports. Each group of 8-bit ports is devoted to one DSP in order to handle the data transfer to the host computer. The connections between the DAQ cards and the detection unit are illustrated in Fig. 5-13.
Any data present in the output buffer causes the FIFO_EF/ signal to go low, initiating the burst-transfer protocol. The burst-transfer protocol, controlled by the DAQ, is a protocol that uses acknowledgement (ACK) and request (REQ) signals in addition to sharing a clock (PCLK). The Glue Logic Board contains the hardware that synchronizes the FIFO_EF/ signal with the PCLK line to generate the REQ signal to the DAQ. The DAQ responds by asserting the ACK signal to indicate it is ready to acquire the data. Data transfer occurs on the rising edge of the PCLK signal (which is connected to the FIFO_R/ pin) until the data buffer is empty and FIFO_EF/ goes high. The PCLK is generated by the DAQ and can be controlled through the user interface (it is currently set to 60 kHz). The Glue Logic Board plays a large role in generating the correct
handshaking signals for the data transfer and also provides connectors for the two DAQ cables, and the cable to the optical switch. The Schematic, Board Layout, and BOM for the Glue Logic Board are included in Appendix I. Fig. 5-14 contains the timing diagram for the burst transfer of the data from the output buffer to the host PC.

![Timing Diagram](image)

Figure 5-14. Timing diagram for the burst-transfer protocol from the DSP output data buffers to the host computer.

For each source, the DSP dumps the demodulated result for 32 channels of data at 2 wavelengths as a series of four 8-bit writes into the output buffers. Ideally, the host PC should empty the output buffer in time for the DSP to write the data from the next source position. This gives the host PC 9 ms to retrieve the data (7 ms of source settling, plus another 2 ms while the DSP is acquiring the data from the ADCs). It takes approximately 1.7 ms to demodulate the data, which leaves 7.3 ms to transfer the data to the host PC. The PCLK determines how quickly this data transfer takes place. We use a PCLK of 60 kHz, which allows us to transfer the data in 4.3 ms \(\frac{1}{60} \text{kHz} \times 32 \text{ channels} \times 4 \text{ transfers/channel} \times 2 \text{ wavelengths}\). The PCLK speed can be increased if more channels or wavelengths are added to the system, but a slower PCLK improves the data acquisition stability by reducing the likelihood of race conditions on the REQ, ACK, and PCLK lines.
5.7 Master DSP Board Design

The mDSP, mCPLD, and sDSP1 are all mounted on the Master DSP printed circuit board, shown in Fig. 5-15. The board is the same height and size as the detector boards, and can connect to a standard 6U/4HP front panel (Vero Technologies). The boards connect to the backplane of the detection unit via to 96-pin connectors (650473-5, Tyco Electronics). The four-layer PCB has a top and bottom copper layer for part placement and routing, one dedicated inner ground layer, and one inner layer for power planes. The Master DSP uses on-board voltage regulators to convert the incoming 5 V and 12 V lines into 1.8 V, 3.3 V, and 5 V. The board also has both a digital and analog ground planes. There are two clocks on the Master DSP Board: a 30 MHz clock for the CPLD (PLD CLK) and a 25 MHz clock for the DSP (DSP CLK). The CPLD and EEPROM chips can all be removed from the board for reprogramming the behavior of the system. The Master DSP Board schematic, bill of materials, and layout are included in Appendix J.
5.8 Slave DSP Board Design

The sCPLD, sDSP2 and sDSP3 are mounted on the Slave DSP printed circuit board, shown in Fig. 5-16. The board is the same height and size as the Detector and Master DSP boards, and can connect to a standard 6U/4HP front panel (Vero Technologies) The board connects to the backplane of the detection unit via two 96-pin connectors (650473-5, Tyco Electronics). The four-layer PCB has a top and bottom copper layer for part placement and routing, one dedicated inner ground layer, and one inner layer for power planes. The Slave DSP uses on-board voltage regulators to convert the incoming 5 V and 12 V lines into 1.8 V, 3.3 V, and 5 V. The board also has both digital and analog ground planes. There is one clock on the Slave DSP Board: a 25 MHz clock for the sDSPs (DSP CLK). The clock for the sCPLD is routed from the
Master DSP board to ensure both CPLDs are synchronized. The CPLD and EEPROM chips can be removed from the board for reprogramming the behavior of the system. The Slave DSP Board schematic, bill of materials, and layout are included in Appendix K.

5.9 Detection Backplane and Enclosure

The Detection Backplane is a PCB board whose primary role is to connect all of the boards of the Detection Unit (16 Detector Boards, 1 Master DSP Board, 1 Slave DSP Board, 1 Glue Logic Board). In addition, the Detection Backplane provides the connector (PCIH47M400A1, Positronic) for a 400 W Compact Peripheral Component Interconnect (cPCI) Power Supply (cPWR-59401, Chroma) that provides voltage rails +5 V (50 A), +3.3 V (50 A), +12 V (12 A), and -12 V (2 A). As the -12 V line in our system requires over 2 A, which exceeds the 2 A max rating
of most cPCI power supplies, we supplement the -12 V line with a 1 W external power supply (MW1212-760, Elpac).

The Detection Backplane also provides connectors for two quiet fans (SF12025C, Vizo/Vantec) that require 12 V and provide 38 cubic feet of air flow per minute (CFM). The Detection Backplane also contains a power resistor for each of the voltage lines (FPS2-T220, Reidon) to ensure that even when no boards are plugged in, the minimum current is still drawn from the cPCI supply. The Detection Backplane is 10.3 inches by 16.925 inches and is compatible with a 19 inch x 6U Elma Enclosure. The BOM, Layout, and Schematic for the Detection Backplane are included in Appendix L. Fig. 5-17 shows how the various PCB boards are connected to the Detection Backplane to make up the Detection Unit.

![Diagram of the physical configuration of the PCBs that make up the Detection Unit.](image)

The Detection Backplane is a very long PCB that routes signals as far as 17 inches. Over this long distance, the reflections and termination of the line may impact the digital signals. Reflections can cause the rising or falling edge of the digital signal to fluctuate. In some cases
this fluctuation can incorrectly triggering the signal. In our system this can cause issues shifting in the gain bits as well as reading of the ADC data. To reduce digital reflections, the following lines were updated with an RC line termination (typically with a ~1 MΩ resistor and a ~10 pF capacitor): RCK, SCK, CLK, CNVST/, CS1/, CS2/, CS3/, CS4/, A0/.
Chapter 6 : Software Interface

The software interface gives the user control over the operation of the system, automatically computes the optimal gain bits for an experiment, and displays real-time imaging data. The software interface communicates with the electronics via two DAQs, and consists of a graphical user interface (GUI) written in LabVIEW (LabVIEW 6.0, National Instruments). The user interface is comprised of a series of tabs that compartmentalize the various operations: Experiment Setup, Imaging Parameters, Gain Bits, and Imaging. Upon launching the GUI the user must input the parameters to be used for the experiment including: the number of sources, detectors, and wavelengths to be used for each breast (Fig. 6-1).

![Choose The Parameters for this Experiment]

Figure 6-1. User interface launch screen.
The launch screen accepts the parameters for the experiment including the number of sources, detectors, and wavelengths for each breast.

6.1 Imaging Parameters

The Experiment Parameters tab provides advanced options for the control of the system. These features are primarily used for the development and debugging of the system, and are not used in a typical experiment. The data acquisition clock, handshaking, and data ports can
be controlled through this tab, as well as the output ports to the \( m \)DSP (such as DIO_PC0, DIO_PC1, SOFT_RST/, etc). In addition, the user can adjust the lower and upper signal thresholds \( (S_{\text{min}} = 0.2 \text{ V and } S_{\text{max}} = 1.5 \text{ V}) \), and can modify the timing of the automatic gain bit detection routine. Any LabVIEW and data acquisition errors that occur can be seen on this tab.

A screen shot of Imaging Parameters tab is shown in Fig. 6-2.

![Digital Optical Tomographic Breast Imager](image)

**Figure 6-2.** Screen shot of user interface Imaging Parameters tab.

### 6.2 Experiment Setup

The Experiment Setup tab gives the user with the ability to change the number of sources, detectors, and wavelengths for an ongoing experiment. In addition, the gain bits can be saved to a text file, or loaded from a text file. This is an important feature that allows the same gain settings to be used across multiple experiments. The number of averages to be used during
each measurement on the Gain Settings tab is also modifiable through this tab ($N_{avg}$, typically set to 3). The tables on the right side of the tab inform the operator of the detectors that do not have measured values in the optimal range. Finally, in the event of a problem with the detection electronics, this tab allows the user to perform a soft reset of the hardware. Following the soft reset the user must end the program and restart. A screen shot of the Experiment Setup tab is shown in Fig. 6-3.

![Screen shot of the user interface Experiment Setup tab.](image)

**Figure 6-3.** Screen shot of the user interface Experiment Setup tab.

### 6.3 Gain Settings

The Gain Settings tab is one of the more important tools provided by the user interface. By pressing the “CONFIRM” button the system uploads the gain, takes 3 measurements (as specified on the Experiment Setup tab), and displays the result for each source-detector pair for each wavelength set. If the measured signal for a given source-detector pair is below the lower threshold ($S_{min}$) then the indicator is yellow; if it is above the upper threshold ($S_{max}$) then the
indicator is red, and if the value falls in the optimal range \( S_{\text{min}} < S < S_{\text{max}} \) then the indicator is green. This allows the user visually assess the performance of the current gain bits. The amount of gain for each source-detector pair at each wavelength set can be manually controlled by a slider. With each increment of the slider the gain applied to the source-detector channel increases by a factor of 10. Both wavelengths belonging to a Wavelength Set must share the same gain setting (the wavelengths are not demodulated and separated until after the analog gain stages). The user can switch between Wavelength Sets as well as the Left and Right breast via tabs on the Gain Settings page. A screen shot of the Gain Settings tab is shown in Fig. 6-4.
A key feature of the Gain Settings interface is the “AUTO” button that calls a routine that automatically detects the optimal gain settings for each source-detector pair for each wavelength set and breast. This is important, since for 2 breasts, each with 64 detectors, 32 sources, and 2 wavelength sets, there are over four thousand gain settings that must be programmed. Without the “AUTO” feature, the user would need to adjust over 4000 gain bits for each experiment. The automatic gain routine starts with the lowest gain setting, programs...
the gain across the channels, takes the average of $N_{av}=3$ samples at that gain setting, and then evaluates if that gain setting provides a signal above the minimum threshold ($S_{min}$). If the signal for a channel is within the optimal range, then the LabVIEW records that gain setting, and no longer updates the gain bits on that channel for the rest of the iterations. By no longer increasing the gain bits on channels that are already at an acceptable level, we avoid unnecessarily saturating those channels with too much gain. In the next iteration the routine applies the next highest gain setting, acquires $N_{av}$ samples, and records the channels that are now within the optimal range. The routine continues looping until it has tested all of the gain settings, at which point it ends and displays the optimal gain setting and signal received at the gain setting for each source-detector channel at both wavelength sets and for both the left and right breast.

The automatic gain routine begins with the lowest possible gain setting and gradually increments the setting until the signal reaches the optimal range for the detected signal. This is important design because saturation or clipping of the detected sinusoidal waveform can occur if too much gain is applied to a detector channel. Clipping of the sinusoid will cause the DSP to measure signal power at our modulation frequencies of 5 kHz or 7 kHz frequency, despite the fact that the amplitude of the signal is ‘bigger’. When demodulated, a clipped sinusoid signal has a lower value than an unclipped sinusoid with a smaller amplitude. For this reason, it is important that the user be aware of the fact that detector values that are too high, or that are not $\sim 10$ times higher than the previous gain stage, are at risk of saturation.
6.4 Data Acquisition

Prior to acquiring the data for an experiment, the gain bits should be optimally set on the Gain Settings tab. Next, the imaging can be performed through operations on the Data Acquisition tab. This tab allows the user to specify the number of frames to acquire and the location where the data should be stored. The data is stored according to the name entered in the ‘File Name’ with _Left and _Right appended for the data from the left and right breast, respectively. The extensions .wl1, .wl2, .wl3, and .wl4 are also appended to the files corresponding to the data acquired at 808 nm, 765 nm, 905 nm, and 827 nm wavelengths. Each imaging frame is written to the files as a separate row. Each frame, or row, contains 32x64 space-separated values written in the following order, where S1D1 represents source 1 detector channel 1:

\[
S1D1 \ S1D2 \ ... \ S1D64 \ S2D1 \ S1D2 \ ... \ S2D64 \ ... \ S32D64
\]

The user can start, stop, and pause the imaging using the SCAN, PAUSE, and STOP buttons located on the Data Acquisition tab. The data acquired from the left and right breasts is displayed on two tabs that can be easily switched between during the experiment to monitor the data acquisition from each breast. The data for all the detectors for one source position and one wavelength is displayed on the graph. Sliders below the graph allow the user to display different source positions and wavelengths. In some cases it is useful to display only some of the detector channels – these can be selected from the checkboxes to the right of the plot. A screen shot of the Data Acquisition tab is shown in Fig. 6-5, below.
While the user operation of the Data Acquisition tab is relatively straightforward, the LabVIEW interface plays an important role in processing the incoming data from the system. As described in Section 5.7, the data in the output buffers on the DSP boards is stored as 4 8-bit writes. These 8-bit writes are read from the dual FIFO output buffer as a 16-bit value combining the data from MDSP and sDSP1 and as another 16-bit value combining the data for sDSP2 and sDSP3. The LabVIEW must unpack the incoming data into the 32-bit floating point
numbers for each of the channels. Fig. 6-6 shows how the incoming data for a single source is unpacked in the LabVIEW (Scan_2_mx.vi whose block diagram is included in Appendix M).

![Figure 6-6. Diagram showing the unpacking of data arriving from the DSP. This diagram shows the data collection from a single source.](image)

**Chapter 7 : System Overview and Performance**

In Chapter 2, a number of system requirements were specified: Speed, Number of Channels, Sensitivity and Dynamic Range, Linearity, Stability, Size, and Scalability. Here we discuss how each of these requirements was satisfied by the design of the digital optical tomography breast imaging system. The performance of the system is tested in phantom experiments involving three different absorbing inclusions.
7.1 Speed

The speed of acquisition is an essential parameter for dynamic imaging experiments. The temporal response of the system is limited by the settling time of the optical switch and the number of source positions and wavelengths that it must switch between. The switch requires 7 ms to settle after switching positions, followed by 2 ms to acquire the data for all detectors at that source position. This brings the imaging time to 9 ms per source position. Since we image the two wavelength sets sequentially, the imaging rate also depends on the number of wavelength sets. Consequently, the fastest the system can image is to collect one frame in 0.009 seconds with one source and 2 wavelengths (111 Hz). Or, with 32 sources and 2 wavelengths it can acquire a frame in 0.288 seconds (3.5 Hz). Finally, the slowest configuration is to use all 32 sources and 4 wavelengths in which case it takes 0.576 seconds to acquire one frame (1.7 Hz).

7.2 Channels

The system has 32 source positions, 64 detector positions, and 4 wavelengths per breast. This provides a total of 16,384 data points per image frame. A rough estimate for a C-cup breast assuming a 6 cm radius and a half-sphere shape for the breast indicates that the system has one detector every 4 cm$^2$.

7.3 Sensitivity and Dynamic Range

The dark noise is the measured signal when no incident light is present, and thus represents the smallest measurement that can be reliably performed with the system. Fig. 7-1 shows the dark noise measured for each gain setting with the standard deviation of the
measurements across all detectors indicated by the error bars. As expected, with increasing amplification in the PGA stage and eventually in the TIA stage we see increasing noise present. At the lower gain stages we see noise levels below 50 μV, but as the gain increases we see increasing noise until at the highest gain stage of 10 GV/A we observe an RMS dark noise of 22 mV. The slightly higher noise at the 1 M versus the 10 M setting represents the fact that the 1 M setting uses less TIA gain and more PGA gain, whereas the 10 M setting uses more TIA gain and less PGA gain. While TIA gain improves the signal to noise ratio (SNR), PGA gain does not. This finding demonstrates that increasing the gain at the TIA stages is preferred over increasing the gain at the PGA stage.

![Figure 7.1](image)

Figure 7.1. Logarithmic plot of the root mean squared (RMS) dark noise for each detector gain setting. Error bars represent the standard deviation of all detectors.

The Noise Equivalent Power (NEP) is an indication of the detector sensitivity to light and can be computed for an SNR of unity using the dark noise of the highest gain setting. Taking the mean of the root-mean-squared (RMS) detector noise at the highest gain setting and using the known 0.5 W/A property of the silicon photodetector in the given wavelength range, the
NEP is approximately 4.5 pW RMS. The NEP represents the smallest light signal that can be detected. The largest light signal that can be detected uses the full detector range for the lowest gain setting, which in this case is to detect a 2.5 V peak-to-peak voltage on the 10 kV/A gain setting. Using these values we can calculate the dynamic range of the system to be 108 (or 158 dB).

Using the Beer-Lambert Law specified in Chapter 1 (Eq. 1.3) we can estimate the amount of light that will arrive at the detector after passing through 10 cm of breast tissue. Assuming typical optical properties of breast tissue ($\mu_a=0.1 \text{ cm}^{-1}$ and $\mu_s'=10 \text{ cm}^{-1}$) we can calculate the light intensity arriving at a detector separated by 10 cm from an input source of 5 mW as shown in Eq. 7.1. Here we roughly account for the effects of scattering on the path length by using $\mu_{eff} = \sqrt{3\mu_a (\mu_a + \mu_s')}$. Our calculation shows that our sensitivity (4.5 pW) is still two orders of magnitude better than the sensitivity of light required to detect 5 mW of light through 10 cm of breast tissue (138 pW).

$$I(x) = 1.38 \times 10^{-10} \text{ mW} = 5 \text{ mW} \times e^{-1.74 \times 10} = I_0 \times e^{-\mu_{eff} dx} \quad (7.1)$$

Using the same calculation for the smallest source-detector separation of 1 cm we find that the system must accommodate a range of light intensities from 138 pW to 0.8 mW. This works out to a dynamic range of 136 dB. Our system exceeds that requirement by 24 dB.

### 7.4 Linearity

System linearity was examined by using the same incident light on a detector and then measuring the detected voltage across all possible gain settings. This was repeated four times in order to cover all gain settings. The results are plotted in Fig. 7-2, where we see that a linear
relationship across the gain settings is generally maintained. We expect to see a 10x gain factor between each gain setting measuring the same signal. An exponential fit of the data in Fig. 7-2 should give an equation of $e^{-2.3}$ in a perfectly linear 10x relationship between gain settings. For the curves below we see good linearity with fits of $e^{-2.31}$ ($R=1$), $e^{-2.27}$ ($R=0.9999$), $e^{-2.30}$ ($R=1$), and $e^{-2.02}$ ($R=0.9955$) for S1 through S4. We expect the decreased linearity at the highest gain settings (reflected by S4), since those settings also introduce higher noise levels.

![Figure 7-2. Linearity across all gain settings measured through four optical samples (S1-S4).](image)

Each sample reflects the same input intensity measured across multiple gain settings.

### 7.5 Coefficient of Variation and Long Term Stability

The coefficient of variation (CV), shown in Eq. 7.2 is calculated here for a static breast-shaped phantom with breast optical properties over a period of 5 minutes (500 frames) with the full number of sources and detectors.

$$CV = \frac{\sigma}{\mu}, \quad SNR = 20 \log_{10} \frac{1}{CV}$$  \hspace{1cm} (7.2)

Fig. 7-3 shows the mean of the CV calculated for all detectors at the given gain setting for each wavelength. Up until 100 MV/A the CV is as low as 0.15% for some wavelengths but by the highest gain setting it increases to approximately 3%. The SNR for each of these settings can be
calculated according to Eq. 7.2 giving us an average SNR of 51 dB for the lowest gain setting and 30 dB for the highest gain setting.

![Figure 7-3](image.png)

Figure 7-3. The mean CV of the detectors at each gain setting for each wavelength. Errors bars represent the standard deviation across source-detector pairs.

To assess the long term stability of the system we measured the same static breast phantom over 40,000 frames (~38 minutes). Taking the mean of measured values at frame 1 and calculating the percentage change between that and the mean at frame 40,000 there is a 0.7% change in the measured value.

7.6 Size

The electronic components and software interface described in the previous chapters are combined into a single system that is contained in a custom-made portable cart, as shown in Fig. 7-4. The instrument cart measures 104x79x66 cm and is on wheels so that it can be moved around in a clinical setting. All of the electronics are completely encased by semi-transparent doors to the cart, while the computer monitor, keyboard, and mouse sit on top of the cart.
Figure 7-4. Photograph of the instrument.
Shown are (a) the portable cart enclosing all the electronics and (b) the cart with the doors open to display the various electronic components.

There are four shelves inside of the cart that hold the various modules of the system. The top shelf holds the optical switch, the shelf below it contains the input unit, the largest middle shelf contains the detection electronics, and the bottom shelf holds the host computer (Fig. 7-4b). The optical fibers emerge from the opposite side of the cart (not shown) and can be configured in a number of geometries, as discussed in Chapter 8.

There are two power lines in the cart that provide power to the computer on the primary line, and the rest of the electronics on the secondary line. The secondary line has an emergency stop button and can be turned on and off without affecting the computer. The secondary line also provides power to a 12 V DC power supply that powers two fans (4212, ebmpapst) that each provide 50 CFM. One fan brings cool air into the cart while the other fan expels the warm air. Originally we designed the cart to use more powerful fans, but found that
the noise generated by the fans was not ideal for use in the clinical setting. The noisier, higher CFM fans should be used for studies that require running the system for more than 3 hours.

7.7 Scalability
An ideal instrument design will provide the flexibility for a number of experimental applications, and for the scaling of the system for future applications. Already our system provides the ability to image with 1 to 32 sources and 1 to 64 detectors with 2 or 4 wavelengths. In addition, the use of digital components provides a scalable design that can be adjusted to accommodate more sources, wavelengths, and channels without a significant design effort. More sources can be introduced by adding laser diodes and using the Input Unit microcontroller to program a unique frequency within the 3-9 kHz band. The DSP chips can be programmed to demodulate at any frequency, and can accommodate any number of wavelengths and sources. To increase the number of detectors the master-slave architecture can be expanded to include an increasing number of slave DSP chips and DAQ cards, without affecting the processing time or significantly increasing the size of the system.

7.8 Phantom Measurements of Absorbing Inclusions
To test the ability of the instrument to identify an absorbing inclusion, similar to a tumor located inside the breast, we performed a series of phantom experiments with an Intralipid and Ink solution as the background breast-like tissue, and with a scattering silicon and ink solid cube to mimic a tumor. The background intralipid was mixed to approximate breast optical properties of \( \mu_a = 0.1 \text{ cm}^{-1} \) and \( \mu_s' = 8 \text{ cm}^{-1} \) by combining 40 mL of 20% Intralipid (Baxter) with 3 mL of a 1% dilution of India Ink in 1.5L of solution. Three 2x2x2 cm solid tumor-like cubes were
suspended in the background mixture. The lightest cube had a slightly higher absorption and scattering than the background mixture, the medium cube had 2x the absorption of the lightest cube, and the dark cube had 3x the absorption of the lightest cube. A photograph of the three inclusions are shown in Fig. 7-5.

![Image of three cubes with different absorptions](image1.png)

Figure 7-5. Photograph of the absorbing inclusions used in the phantom experiments. Shown from left to right are the light, medium, and dark inclusions.

25 frames of data were acquired and averaged for both the background reference as well as the background with each inclusion and the results were reconstructed using the diffusion approximation, as discussed in detail in Section 9.3. The results of the phantom reconstructions are shown in Fig. 7-6. The inclusion is identified as a region of increased absorption in all three cases. The darkest inclusion has a reconstructed absorption of \( \mu_a = 0.2 \text{ cm}^{-1} \), while the middle inclusion has \( \mu_a = 0.16 \text{ cm}^{-1} \) and the lightest inclusion has \( \mu_a = 0.12 \text{ cm}^{-1} \). These values agree with the known ratios of ink introduced into each inclusion.

![Image of absorption profiles](image2.png)

Figure 7-6. Phantom experiment with DOT images shown for three inclusions of increasing absorption.

The images show the absorption profile (in cm\(^{-1}\)) of a (a) the lightest inclusion, (b) the medium inclusion, and (c) the darkest inclusion.
7.9 System Summary

Table 7-1 summarizes the system performance. The cost to produce the prototype instrument is approximately $100,000, but future iterations and mass production would significantly decrease that cost. As such, the digital optical breast imaging system is a fairly low-cost, portable, non-ionizing, clinically translatable imaging system.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sources</td>
<td>32 per breast, 64 total</td>
</tr>
<tr>
<td>Detectors</td>
<td>64 per breast, 128 total</td>
</tr>
<tr>
<td>Wavelengths</td>
<td>&lt;5 mW at 765 nm, &lt;5 mW at 808 nm, &lt;5 mW at 827 nm, &lt;5 mW at 905 nm</td>
</tr>
<tr>
<td>Temporal Response</td>
<td>111 Hz (1 source, 2 wavelengths), 3.5 Hz (32 source positions, 2 wavelengths), 1.7 Hz (32 source positions, 4 wavelengths)</td>
</tr>
<tr>
<td>Dynamic Range</td>
<td>(~10^8) (158 dB)</td>
</tr>
<tr>
<td>Noise Equivalent Power</td>
<td>(~4.5) pW RMS</td>
</tr>
<tr>
<td>Dark Noise Amplitude</td>
<td>&lt;10 µV RMS (at lowest gain setting), &lt;22 mV RMS (at highest gain setting)</td>
</tr>
<tr>
<td>Long Term Stability</td>
<td>0.7% over 40 minutes</td>
</tr>
<tr>
<td>System Size</td>
<td>104 cm x 79 cm x 66 cm</td>
</tr>
<tr>
<td>Power Consumption</td>
<td>3.5 Amps @ 120 V AC</td>
</tr>
</tbody>
</table>

Table 7-2 presents a comparison between the new digital breast imaging system and the small animal digital imaging system presented by Lasker et al. [58]. The most important difference between the digital breast imaging system described in this thesis and the small-animal digital imaging system lies in the dramatic increase in sources, detectors, and wavelengths for the application to breast imaging, bringing the number of data points collected per frame from 1024 in the original system to 16,384 in the breast imaging system. Despite this 16 fold increase in data, there is only a 5 fold decrease in system speed, from 8.9 Hz to 1.7 Hz.
In fact, the decrease in imaging speeds comes primarily from the increased number of sources and wavelengths, and not from the 4 fold increase in detectors. This is accomplished by the new master-slave architecture implemented for simultaneous data detection and demodulation from 128 detectors. In addition, despite the large increase in detectors, sources, and wavelengths, the size of the entire breast imaging system (including the cart) is only slightly larger than the original digital imaging system. This is due to more compact digital detection boards (8 channels per board as opposed to 4) as well as the master-slave DSP-based architecture that can scale effortlessly with the number of detectors.

The breast imaging system uses less low gain settings and adds more high gain settings to handle the larger imaging volumes. This accounts for the lower dynamic range as well as the fact that the higher gain settings lead to slightly higher dark noise and CV%. Overall, the system performance is similar between the two systems as they are based upon the same detection techniques - both have coefficients of variation of less than 1% for most gain settings and have very low dark noise (<50µV for most gain settings).

Table 7-2. Comparison of system characteristics for the digital small-animal imager and the digital breast imager.

<table>
<thead>
<tr>
<th>Property</th>
<th>Digital Small-Animal Imaging System</th>
<th>Digital Breast Imaging System</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mode of Operation</td>
<td>CW</td>
<td>CW</td>
</tr>
<tr>
<td>Sources</td>
<td>16</td>
<td>64</td>
</tr>
<tr>
<td>Detectors</td>
<td>32</td>
<td>128</td>
</tr>
<tr>
<td>Wavelengths</td>
<td>1-2</td>
<td>1-4</td>
</tr>
<tr>
<td>Total Data Points</td>
<td>1024</td>
<td>16,384</td>
</tr>
<tr>
<td>Frame Rate</td>
<td>8.9-140 Hz</td>
<td>1.7-111 Hz</td>
</tr>
<tr>
<td>Dynamic Range</td>
<td>~180 dB</td>
<td>~160 dB</td>
</tr>
<tr>
<td>Dark Noise</td>
<td>20-400 µV</td>
<td>10 µV-22 mV</td>
</tr>
<tr>
<td>CV (%)</td>
<td>0.05-0.5%</td>
<td>0.3-3%</td>
</tr>
<tr>
<td>Number of DSP Chips</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>System Size (including cart)</td>
<td>81 x 61 x 64 cm</td>
<td>104 x 79 x 66 cm</td>
</tr>
</tbody>
</table>
7.10 Future Improvements

During the design, validation, and clinical use of the system there were certain features that would be valuable to include in future implementations of this design. In many cases the value of these features wasn’t apparent until the device was built and in use, preventing us from implementing them in this version of the device.

The first feature that would be valuable for use in debugging and in calibrating the system is software control of each individual laser diode. Due to the fact that two wavelengths are present on each wavelength set, it is impossible to measure the intensity of one wavelength without unplugging the laser driver from the input backplane, which is clearly not an ideal solution. In addition, software control of the laser diodes would allow the user to turn laser diodes for wavelengths not required for the experiment. This feature could be fairly simply implemented by passing 4 additional signals from the host pc, via the DAQ1, routed through the backplane to a connector that would bring the signals to the input unit. The laser diode on/off signal could then be input directly to the ON pin of the relevant laser driver.

Detecting signal saturation due to too much amplification is an essential feature that should be included in the next design of the system. When signals saturate they provide incorrect demodulated values that can often be difficult to detect. Unfortunately, the only place where saturation or clipping can be detected is prior to demodulation on the DSP chip. I believe this could be made possible through an algorithm that looks for repeated samples at the maximum or minimum values. If this situation is identified the DSP should transmit a special character along with the data to warn the host computer that that signal may be subject
to saturation. The implementation of this feature would require significant planning and possible changes to the hardware design of the DSP to Host PC data transmission.

A simple enhancement to this system would involve the addition of an even lower amplification setting for the TIA. Currently the lowest setting is 10 kV/Å, and in some situations this low gain setting still risks saturation for the co-located source-detector fibers. It would be suitable to add a 1 kV/Å gain stage. This would have the added benefit of further increasing the dynamic range of the system.

While 4 wavelengths of light provides an improvement over previous 2-wavelength systems, adding an additional 2 wavelengths to bring the system to 6 wavelengths would provide even more spectral information to better resolve the optical chromophores in the breast, specifically water and fat. These wavelengths could be incorporated into the current system by adding 2 laser diodes and accompanying drivers. The light from each laser could be combined into each of the two current light streams, but with modulation frequencies at 3 kHz. Each light stream would contain a 3 kHz, 5 kHz, and 7 kHz modulated wavelength to be demodulated by the DSP in the detection unit.

Although the system is portable and can be moved between the lab and the clinic, the cart is very heavy, and moving the system could be made much easier by transitioning to a lighter, narrower cart.
Chapter 8: Breast-Fiber Interface

One of the goals in designing the digital optical tomography system for breast imaging was to image the breast via direct contact in a fully 3D geometry. This allows the imaging to be performed without compression and without the use of a matching fluid, two features that are clinically desirable. Imaging the breast in a fully 3D geometry provides more angles for measurements through the breast, improving the 3D resolution and removing the need for compression that other geometries necessitate (specifically parallel plate geometry). However, designing a clinically translatable breast-fiber interfaced is challenging for a number of reasons:

1. Accommodating a range of breast sizes: There is a very large range of breasts sizes that the interface must accommodate – from A to DDD+.

2. Getting close to the chest wall: It is difficult to get the breast away from the stomach and to allow the interface to get under the breast and close to the chest wall.

3. Making good contact with the breast: If the interface allows the fibers to conform entirely to the patient’s breast then the contact with the breast will be good, but it becomes very difficult to know the positioning of the individual fibers. If the fibers are in a rigid geometry it is easy to know the positioning, but it becomes harder to make good contact with the breast. Both issues are important: without good contact with the breast the imaging may miss regions of the breast or introduce artifacts to the images. Inexact source-detector positions introduce artifacts to the reconstructions and can make longitudinal studies challenging.
In the studies described in the following chapters two different breast interfaces were tested. Each interface addresses the tradeoffs listed above in slightly different ways. The first interface described is an articulating-finger interface that has more degrees of freedom for making contact with the breast and is ideal for dynamic studies where knowledge of the exact fiber positioning is not as important. The second interface is a translating-ring interface with precise positioning that is suitable for longitudinal studies and absolute imaging where it is more important to know the precise fiber positioning for repeatable measurements.

8.1 Articulating-Finger Fiber-Breast Interface

The articulating-finger fiber-breast interface was designed and built by the Optical Tomography group at the State University of New York Downstate Medical Center. The patient can be imaged in either a standing or seated position. The interface uses two adjustable arms that bring 64 fibers in contact with each breast. There is a flat bottom plate that comes up under the breast, bringing 4 rows of 8 fibers each (32 total fibers including 32 detectors and 16 colocated sources). The top part of the interface is comprised of eight articulating fingers, each holding 4 optical fibers that can be individually adjusted to make gentle contact with top part of the breast. 32 fibers make contact with the top of the breast including 32 detectors and 16 colocated sources. The angle of the articulating fingers can be increased to accommodate larger breasts. A photograph of the articulating fiber interface is shown in Fig. 8-1.
The articulating-finger interface provides a fast way to make good contact with breasts from a C-D cup. The interface is not optimized for smaller breasts (A-B cup), where the breast is not large enough to cover the optical fibers on the lower plate. Conversely, for very large breasts, it is difficult to bring the interface in close proximity to the chest wall, and the fibers only cover a limited portion of the breast.

One important consideration in using the articulating-finger interface is that due to the flexibility of the interface, it is difficult to know the precise location of the optical fibers. As such, the interface does not lend itself to the generation of a unique finite element meshes for each individual patient. In addition, due to the grasping nature of the interface, the articulating fingers must be released to remove the breasts, prohibiting the use of an optical reference imaged under the same settings as the breast that can be to calibrate the system for absolute measurements. These are not issues for dynamic imaging, where the temporal change in
optical signal is used to solve for changes in the optical chromophores in tissue. All measurements are normalized to a baseline breast measurement, which significantly reduces the importance of the mesh and fiber positions. Fig. 8-2 shows the finite element mesh used for all patients imaged with the articulating-finger interface. The mesh uses typical fiber positions and tissue boundary for a C-cup breast. The mesh contains ~6500 voxels.

![Figure 8-2. Finite-element mesh used to approximate the breast geometry for the articulating-finger interface. There are 4 rows of 8 fibers on the bottom plate and 4 articulating fingers with 4 fibers each covering the top of the breast. Red dots indicate fiber positions.](image)

### 8.2 Translating-Ring Fiber-Breast Interface

A second fiber-breast interface was designed specifically for the longitudinal imaging required to monitor tumor response to therapy. This interface was designed to accommodate a large range of breast sizes, while allowing for the precise repositioning of the interface at each imaging time point. In addition, the interface allows for precise localization of the fibers, and a liquid optical reference can be placed into the interface after imaging the patient, allowing for better calibration. The precise fiber positioning and use of an optical reference allow for absolute measurements of breast optical chromophores.
The design consists of four rings of increasing diameter (4, 8, 12, 16 cm). As the rings increase in size, they contain more positions for source and detector fibers (8, 12, 16, 28). Further, the angle of the fibers changes as the ring size increases (60°, 45°, 30°, 15°). This variable angle helps to keep the fibers normal to the breast tissue. With the exception of the smallest ring, the rings can be removed to accommodate breast sizes from A (smallest 2 rings used) to DDD (all 4 rings used). In addition, the rings can translate vertically to conform to each patient’s breast. This translation is accomplished manually and secured by spring plungers that interact with shafts that have holes every 5mm. Two shafts attach to each ring and hold it in place. Each optical fiber is held in place by a shaft collar that secures to the metal part of the fiber tip.

This new interface was designed for optimal patient comfort, and thus provides a number of adjustable features. The separation between the left and right breast can be changed, as can the height of the rings. In addition, each set of rings is attached to a camera mount (Manfrotto 229 Super Pro Head) which provides three degrees of freedom for aligning the ring structures with the patient's breasts. The camera mounts used in this design have recordable positioning indicators so that in longitudinal studies, precise positioning can be maintained across imaging time points. The device is currently constructed for imaging of the patient in a seated position, similar to a massage chair. The patient sits on a stool and leans over the rings while holding onto a set of handlebars. The handlebars also serve as a strain release for the optical fibers. There is a foam head rest where the patient can rest her chin or forehead. The device is built around a modified computer cart (Neo-Flex Laptop Cart) that is on
wheels. A photograph of the digital optical breast imaging system with the optical fibers connected to the translating ring interface is shown in Fig. 8-3, below.

![Photograph of the translating ring breast interface.](image)

Figure 8-3. Photograph of the translating ring breast interface.

The rings were designed and prototyped with the help of Keith Yeager and the facilities provided through the Biomedical Engineering Machine Shop. Our fabrication technique involved a 3D printed design infiltrated with plastic. The design of the rings was done using Solidworks and then printed using a 3D Printer (310 Plus, ZCorp). Creating the rings through the use of a 3D Printer not only simplifies the manufacturing process, but also allows for more sophisticated geometries than cannot be easily machined. The printed parts were left to dry in the printer overnight, and then were dried further through baking in a vacuum chamber.
Infiltration of the rings was performed with an ultra-low viscosity liquid plastic casting resin (Smooth-Cast 310, Smooth-On, Inc.) with a 20 minute pot life and 2-4 hour demold time. The plastic is naturally white, but can be dyed grey or black using Ultra-Black dye that is mixed into the liquid plastic. To infiltrate the rings, the liquid plastic was mixed thoroughly in a pan deep enough to cover each ring, and then the ring was submerged into the liquid. The entire pan was then placed into a vacuum chamber for 3-5 minutes to improve the infiltration of the plastic through the ring. After removing the pan from the vacuum chamber the extra plastic was blown off of the ring using pressurized air. The ring was then placed back into the vacuum chamber for 2-3 minutes and then blown off with pressurized air one more time. This process helped to avoid excess plastic pooling on the surface of the rings. The rings were then left to dry and harden overnight. The final result is a very strong plastic material that can be machined, drilled, sanded, and painted. In this application, we chose not to paint the rings, and simply sanded them by hand to a smooth and comfortable surface for the patient.

A key benefit of the translating ring interface is the precise localization of the optical fibers. The position of the optical fibers never changes in the x or y dimensions. However, as the rings are adjusted, the fiber positions translate accordingly in the z direction. In addition, if the largest ring is removed, then those fibers are excluded from the mesh and subsequent image reconstruction. For each patient, a unique mesh was generated in GiD according to the ring positioning. The mesh extended 2 cm beyond the last ring to account for the presence of the chest wall. A sample mesh involving three of the translating rings is shown for a patient with a B cup breast in Fig. 8-4.
Figure 8-4. Sample finite-element mesh to approximate the breast geometry for the translating-ring fiber-breast interface.

The mesh shown here uses 3 of the rings with more, smaller voxels placed near the optical fibers.
Chapter 9 : Dynamic Optical Imaging of Breast Cancer

To investigate the performance of the system in a clinical setting, we gathered preliminary imaging data from 21 subjects including 3 healthy subjects and 18 subjects with breast masses. The goal of the study was to explore the use of dynamic imaging techniques to detect and characterize breast tumors. Previous studies looking at the dynamic response of breast tissue to a stimulus have shown promising preliminary results, but have been limited to case studies of only a few subjects [39, 42-44]. Here we aim to more completely explore the rich spatial and temporal dataset that dynamic imaging provides in a larger subject group containing healthy breasts and well as breasts with benign and malignant masses.

9.1 Experimental Protocol

In this study, which was compliant with the Health Insurance Portability and Accountability Act (HIPAA) and approved by the Columbia University Institutional Review Board (IRB-AAAD7133), written consent was obtained from all 21 subjects who were compensated for their participation. The subjects were asked to stand in a comfortable position while the breast interface was brought into contact and adjusted for each breast. Each fiber-bearing finger of the interface was adjusted until gentle contact with the breast was established for all fibers, starting with the outer fingers and progressing to the central fingers. During this time the patient was asked to identify any fibers that were causing discomfort, and such fibers were then readjusted.

Prior to the measurements, each participant was trained on how to perform a valsalva-like breath hold by maintaining pressure in their mouth and lower abdomen. Participants were
also informed about the importance of minimizing motion during the imaging sequences. The
valsalva maneuver is a commonly used tool in a number of clinical diagnoses including many
cardiac and brain abnormalities [69]. It involves a prolonged expiratory effort that results in
increased intra-thoracic pressure which results in decreased venous return to the heart. It is
expected that this decrease in venous return will correlate to a measureable increase in
hemoglobin levels in the breast tissue as shown by Schmitz et al. [42]. Hemoglobin levels are
relevant to the detection of breast cancer because they provide contrast between normal
tissue vascularization and increased, disorderly tumor vascularization.

In order to minimize the patient’s discomfort and the risk of motion artifacts the
imaging sequence was compressed to be as fast as possible, while still maintaining time for the
dynamic effects to settle. The imaging sequence, shown in Fig. 9-1, involved a 60-180 second
baseline followed by a 30 second breath hold and 90 second recovery which was repeated
three times. Three trials were performed in order to achieve one trial with minimal motion and
suitable breath hold duration; in most subjects the second trial was selected for reconstruction.
This resulted in a total imaging duration of approximately 10 minutes. During the breath hold
the subject was asked to avoid any large inhalation and simply stop breathing, while
maintaining pressure in the mouth and stomach. In the event that the patient could not
complete the 30 second breath hold, she was asked to indicate the end of the breath hold by
opening her mouth (5 patients).
9.2 DOT Imaging

All imaging for this study was performed using the digital diffuse optical breast imaging system described in Chapters 2 through 7. The articulating-finger breast interface described in Section 8.1 was used to bring the optical fibers in contact with the breast. With all 32 sources, 4 wavelengths, and 128 detectors used in this configuration the system acquires data from both breasts at a frame rate of 1.7 Hz. Automatic gain settings were calculated for each patient prior to the imaging sequence.

*Imaging Reconstruction Algorithm*

The data collected from the 128 detectors, 32 sources, and 4 wavelengths (16,384 data points) are measurements obtained from the surface of the tissue. A reconstruction algorithm is required to transform the surface measurements into three-dimensional images of the chromophores throughout the tissue volume. The surface measurements can be inverted according to the Beer-Lambert law (Eq. 1.1) that describes the absorption of electromagnetic energy as it passes along a given path through an absorptive medium. Unlike x-ray imaging, the path that light takes as it travels through the tissue is not a straight line between the source and detector. The propagation of light through tissue can be accurately modeled using the equation of radiative transfer. However, light propagation in scattering-dominant media such
as breast tissue is well described by the diffusion approximation (DA) to the equation of radiative transfer as:

\[-\nabla \cdot D(\vec{r})\nabla u(\vec{r}) + \mu_a u(\vec{r}) = f(\vec{r}) \text{ in } X \text{ s.t. } u(\vec{r}) + 2D(\vec{r})A \frac{\partial u(\vec{r})}{\partial n} = 0 \text{ in } \partial X, \tag{9.1}\]

where \(A\) is related to the reflection due to mismatched refractive indices, \(u(\vec{r})\) is the light radiation density, and \(D(\vec{r})\) is the diffusion coefficient given by \(D = 1/(3(\mu_a + \mu_s'))\). The solution to (9.1) provides a prediction \(P_\lambda = Qu_\lambda\) of the measurement at the medium surface where \(Q\) represents a measurement operator that projects the forward solution \(u(\vec{r})\) onto the measurable quantity by our digital dynamic imaging system. The basic idea behind DOT imaging of tissue chromophores is to exploit the linear correlation between the tissue absorption and the concentrations of chromophores (Eq. 1.2).

The major chromophores relevant to breast imaging are oxygenated hemoglobin (HbO₂), deoxygenated hemoglobin (Hb), water (H₂O), and lipid, whose molar extinction coefficients are well documented in the literature [15]. The multi-spectral inverse model can directly recover the spatial distributions of chromophore concentrations by using data from all wavelengths simultaneously during the reconstruction [70]. In this experimental study, we focus on the reconstruction of two major chromophore concentrations, \([\text{HbO}_2]\) and \([\text{Hb}]\), by using data from two wavelengths (\(\lambda = 765\) nm and 835 nm) since these two chromophores are closely associated with tumor vascularity and are the chromophores most relevant to a breath hold stimulus.

For each patient a 50-frame data set (~30 s) acquired immediately prior to the onset of the breath hold was used as a baseline. Relative changes in oxygenated hemoglobin ([HbO₂])
and deoxygenated hemoglobin ([Hb]) were reconstructed relative to this baseline, and therefore all images indicate a change in the concentration of oxygenated hemoglobin (Δ[HbO$_2$]%) and deoxygenated hemoglobin (Δ[Hb]%). Any source-detector channels with greater than 15 dB of noise during the baseline period were excluded from the reconstruction as this noisy data can cause numerical instability and produce artifacts in the reconstructed image. Further, we assumed typical breast tissue values for baseline [HbO$_2$] and [Hb] of 18 uM and 9 uM respectively. Although these values may not be exact for all patients, we are most concerned with the dynamic (therefore relative) changes that the breast undergoes during the course of a breath hold, and absolute chromophore values are not necessary for that analysis. In fact, one of the advantages of using dynamic biomarkers lies in the fact that they do not require absolute chromophore concentrations. 100-frame time sequences were reconstructed starting from the onset of the breath hold and lasting through the recovery period. The total reconstruction time for one image frame was approximately 20 mins on a Dual Core Intel Xeon 3.33GHz processor.

*Image Quantification*

The reconstructed images provide a visual representation of the breast showing the distribution of the percentage change in chromophores (Δ[Hb]% and Δ[HbO$_2$]%). There are many ways to quantify the chromophore change in the tumor region. We chose to select the average chromophore value over a 1-cm-radius sphere around the voxel of maximum change. The position of the sphere can change with each image frame. We chose to enhance a previous published technique that involves using the maximum voxel [71] be averaging over a sphere
around that voxel to create a more stable parameter. By allowing the sphere to move with
each imaging frame, the algorithm is free to track the tumor in the breast, which is relevant to
the post-breath hold period where respiratory motion can cause the tumor position in the
breast to vary slightly with time. By allowing the sphere to move to the voxel of peak intensity,
the algorithm does not require any prior knowledge of the tumor location. Similarly, using a 1-
cm-sphere provides a standard algorithm, as opposed to selecting a variable radius depending
on prior knowledge of the tumor size.

9.3 Subject Summary

Dynamic DOT measurements were performed on 21 subjects over the course of one year.
Three of the subjects were healthy volunteers, while the other eighteen had a benign or
malignant mass. 13 of the 21 subjects were post-menopausal with a mean age of 54±10 years
and a mean BMI of 30±4. There was no significant difference in the age or BMI between
healthy, benign, and malignant groups. 14 subjects had a malignant mass in one breast of
which 4 were invasive ductal carcinomas (IDC), 1 was an invasive lobular carcinoma (ILC), 2
were ductal carcinomas in situ (DCIS), and 7 were a combination of IDC, ILC, and DCIS. Three
subjects had a benign mass in one breast, and one subject had benign masses in both breasts.
Three subjects with tumor-bearing breasts also had a contra-lateral breast with a benign mass.
Of the eight benign masses, 1 was atypical ductal hyperplasia (ADH), 4 were fibroadenomas
(FA), 1 was a cyst, 1 was sclerosing adenosis (SA), and 1 was unbiopsied. The average mass size
was 1.6 cm ranging from 0.1 to 4 cm.
All subjects in this study had prior mammograms for comparison. In most cases ultrasound and DCE-MRI images were also available and were used to verify the tumor location and size. A summary of the subjects who participated in the study is shown in Table 9-1.

Table 9-1. Summary of subjects and pathologies.

<table>
<thead>
<tr>
<th>Subject</th>
<th>Age</th>
<th>BMI</th>
<th>Cup</th>
<th>Pathology</th>
<th>Location</th>
<th>Size$^1$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>41</td>
<td>22.6</td>
<td>C</td>
<td>Healthy</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>61$^{PM}$</td>
<td>32.9</td>
<td>DD</td>
<td>Healthy</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>63$^{PM}$</td>
<td>31</td>
<td>C</td>
<td>Healthy</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>4</td>
<td>44</td>
<td>22.4</td>
<td>B</td>
<td>Poorly diff. IDC + DCIS</td>
<td>Right, 1:00, 5 cm FN</td>
<td>2.7</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Benign (SA)</td>
<td>Left 2:30, 6 cm FN</td>
<td>0.5</td>
</tr>
<tr>
<td>5</td>
<td>49</td>
<td>29.2</td>
<td>D</td>
<td>Moderately diff. IDC + ILC</td>
<td>Left 3:00, Posterior</td>
<td>1.9</td>
</tr>
<tr>
<td>6</td>
<td>70$^{PM}$</td>
<td>28.7</td>
<td>DDD</td>
<td>Poorly diff. IDC</td>
<td>Right 2:00, 10 cm FN</td>
<td>2.2</td>
</tr>
<tr>
<td>7</td>
<td>63$^{PM}$</td>
<td>31.5</td>
<td>DDD</td>
<td>Poorly diff. IDC</td>
<td>Right 1:30, Posterior</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Benign (Cyst)</td>
<td>Left 2:00, 5 cm FN</td>
<td>0.6</td>
</tr>
<tr>
<td>8</td>
<td>41</td>
<td>27.4</td>
<td>D</td>
<td>Moderately diff. ILC</td>
<td>Right 10:00, Posterior</td>
<td>2.6</td>
</tr>
<tr>
<td>9</td>
<td>58$^{PM}$</td>
<td>28.7</td>
<td>C</td>
<td>IDC + ILC</td>
<td>Left 2:30, 10 cm FN</td>
<td>2.1</td>
</tr>
<tr>
<td>10</td>
<td>56$^{PM}$</td>
<td>30.2</td>
<td>C</td>
<td>Poorly diff. IDC + ILC</td>
<td>Right 9:00-10:00</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Benign (FA)</td>
<td>Left 2:00</td>
<td>0.1</td>
</tr>
<tr>
<td>11</td>
<td>63$^{PM}$</td>
<td>25.8</td>
<td>C</td>
<td>DCIS</td>
<td>Right 11:00, 5 cm FN</td>
<td>2.2</td>
</tr>
<tr>
<td>12</td>
<td>64$^{PM}$</td>
<td>26.7</td>
<td>B</td>
<td>Moderately diff. IDC + ILC + DCIS</td>
<td>Right 1:00, 3 cm FN</td>
<td>1.4</td>
</tr>
<tr>
<td>13</td>
<td>42</td>
<td>43.1</td>
<td>D</td>
<td>Moderately diff. IDC + ILC + DCIS</td>
<td>Left 1:30, 13 cm FN</td>
<td>1.3</td>
</tr>
<tr>
<td>14</td>
<td>68$^{PM}$</td>
<td>32.3</td>
<td>C</td>
<td>Poorly diff. IDC</td>
<td>Right Upper Outer Quad$^2$</td>
<td>2</td>
</tr>
<tr>
<td>15</td>
<td>38</td>
<td>30.4</td>
<td>D</td>
<td>Poorly diff. IDC</td>
<td>Right 9-10:00, 5 cm FN</td>
<td>1.5</td>
</tr>
<tr>
<td>16</td>
<td>58$^{PM}$</td>
<td>30.4</td>
<td>C</td>
<td>DCIS</td>
<td>Left 2:00, 6 cm FN</td>
<td>1.8</td>
</tr>
<tr>
<td>17</td>
<td>57$^{PM}$</td>
<td>28.6</td>
<td>B</td>
<td>Poorly diff. IDC+ ILC</td>
<td>Right 11:00, 1 cm FN</td>
<td>0.5</td>
</tr>
<tr>
<td>18</td>
<td>42</td>
<td>31</td>
<td>DD</td>
<td>Benign (FA)</td>
<td>Left 7:00, 3 cm FN</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Benign (FA)</td>
<td>Right 5:00, 8 cm FN</td>
<td>1</td>
</tr>
<tr>
<td>19</td>
<td>47</td>
<td>31.4</td>
<td>C</td>
<td>Benign (unbiopsied)</td>
<td>Right 7:30, 5 cm FN</td>
<td>1</td>
</tr>
<tr>
<td>20</td>
<td>55$^{PM}$</td>
<td>23.2</td>
<td>C</td>
<td>Benign (FA)</td>
<td>Right 6:00, 6 cm FN</td>
<td>0.7</td>
</tr>
<tr>
<td>21</td>
<td>61$^{PM}$</td>
<td>28.3</td>
<td>DDD</td>
<td>ADH</td>
<td>Left 11:00, 3 cm FN</td>
<td>1.1</td>
</tr>
</tbody>
</table>

$^{PM}$ Indicates the subject is post-menopausal.

$^1$ Size of the largest dimension of the tumor (in cm).

$^2$ Extremely dense breasts - precise location and size not known.

With the onset of the breath hold we observe an increase in [Hb] and [HbO$_2$] levels in the breast. Upon resuming normal breathing, the [Hb] and [HbO$_2$] levels return to baseline levels. In tumor bearing breasts, there is a notable difference in the hemodynamic response over the course of the breath hold as compared to healthy breasts. Fig. 9-2 shows the $\Delta$[Hb]%,...
calculated as the spherical average over the peak voxel as described in Section 9.2, for the left and right breast of a breast cancer patient (Fig. 9-2a) and a healthy subject (Fig. 9-2b). Fig. 9-2a shows the Δ[Hb]% response over the course of a 20-second breath hold and recovery for a 64-year old subject with a 1.4 cm tumor in the right breast identified as Subject 12 (S12) in Table 9-1. The tumor-bearing breast has a greater increase in [Hb] during the breath hold, followed by a slower return to baseline values. Although both the healthy left and tumor-bearing right breasts were imaged during the same breath hold, their hemodynamic response is markedly different (Fig. 9-2a), as compared with a 63 year-old healthy subject (S3) where both the left and right breasts are healthy and have nearly identical responses to a 30-second breath hold (Fig. 9-2b).

Figure 9-2. Percentage change in deoxy-hemoglobin (Δ[Hb]%) over the course of a breath hold for (a) a breast cancer patient and (b) a healthy subject.

Shown here for (a) a 64 year-old subject (S12) with a 1.4 cm tumor in the right breast (solid black line) and (b) a 63 year-old healthy subject (S3). In (a) the breath hold lasted 20 seconds while in (b) the breath hold lasted 30 seconds.

Fig. 9-3a shows coronal slices through the left and right breast for multiple points during the breath hold and recovery sequence from a 57 year-old post-menopausal woman (S17). The tumor, an invasive ductal and lobular carcinoma located at 11:00 in the right breast, is most
visible during the mid-recovery time point. In reconstructed images at the mid-recovery time point, we observe an enhancement in $\Delta [\text{Hb}]\%$ in the tumor region, as shown in Fig. 9-3b. There is also an enhancement in $\Delta [\text{HbO}_2]\%$ (Fig. 9-3c) although it is lesser than that of $\Delta [\text{Hb}]\%$.

Figure 9-3. DOT images of the left and right breast for a breast cancer patient shown at four time points over the course of a breath hold.

Shown are (a) Coronal slices looking at the $\Delta [\text{Hb}]\%$ in the Left (top) and Right (bottom) breast at four different time points over the course of the breath hold. There is an invasive carcinoma at 11:00 in the right breast (S17), which is most visible during the mid-recovery time point. Coronal slices showing (a) $\Delta [\text{Hb}]\%$ and (b) $\Delta [\text{HbO}_2]\%$ demonstrate that while an enhancement of $\Delta [\text{HbO}_2]\%$ is seen in the tumor region, the contrast is not as great as in $\Delta [\text{Hb}]\%$.

9.4 Mid-Recovery Tumor Visualization

As illustrated in Fig. 9-3, the mid-recovery time point provides the greatest contrast between tumor and healthy breast tissue. For this reason we chose to investigate the mid-recovery time point, 15 seconds following the end of the breath hold, as a means for breast cancer visualization and detection. Fig. 9-4 shows mid-recovery images from a pre-menopausal 38 year-old female subject (S15) with a 1.5-2cm invasive ductal carcinoma located at 9-10:00 in the right breast, 5 cm from the nipple (FN). Fig. 9-4a/b/c illustrates the three different two-
dimensional slices that are commonly used to display medical images: sagittal, coronal, and axial. For this subject, the tumor is visualized in all three planes by a marked increase in mid-recovery $\Delta[Hb]\%$. To compare the DOT images to other modalities, we show here corresponding mammogram (Fig. 9-4d) and DOT (Fig. 9-4e) axial views. The tumor region, identified by an increased density in the upper outer quadrant in the mammogram, corresponds to an increased region of $\Delta[Hb]\%$ in the DOT image. Likewise, corresponding sagittal views from DCE-MRI (Fig. 9-4f) and DOT (Fig. 9-4g) show the tumor in the mid-upper region as an increase area of contrast enhancement corresponding to an increase in $\Delta[Hb]\%$ in the DOT image. The DOT sagittal image shows the area of enhancement to be approximately 5cm from the nipple, which agrees with the other modalities. The region of enhancement in the DOT image appears larger than the actual tumor area due to the blurring introduced by the tissue scattering of light and the ill-posed nature of the inverse problem.
Figure 9-4. Correlation of the DOT $\Delta[Hb]$% images of the mid-recovery time point with DCE-MRI and mammogram images.

Shown are three slices: (a) sagittal, (b) coronal, and (c) axial for a subject (S15) with a 2 cm tumor in the Right breast, 5 cm FN at 9-10:00. A mammogram of the tumor is shown in (d) with the corresponding axial DOT slice (e) showing an enhancement of $\Delta[Hb]$% at the mid-recovery time point. A sagittal DCE-MRI slice shows the location of the tumor in (f) with the corresponding DOT slice showing a matching $\Delta[Hb]$% enhancement 5 cm from the nipple in (g).

The increase in $\Delta[Hb]$% at the mid-recovery time point is observed across multiple pathologies including IDC, ILC, and DCIS but not in healthy breasts, as shown in Fig. 9-5. An enhancing region can be seen in the correct location for each of the cancerous pathologies (Fig. 9-5a/b/c/d) but no enhancing regions are visible in the case of a benign pathology (Fig. 9-5e) or in a healthy subject (Fig. 9-5f). Fig. 5a shows coronal slices of $\Delta[Hb]$% for the left and right breast of a 44 year-old pre-menopausal woman (S4) with an IDC of 2.7 cm at 1:00 in the right breast. Fig. 9-5b shows coronal slices of $\Delta[Hb]$% for the left and right breast of a 58 year-old
post-menopausal woman (S9) with an IDC and ILC of size 2.1 cm at 2:30 in the left breast. Fig. 9-5c shows coronal slices of $\Delta[Hb]\%$ from a 41 year-old pre-menopausal woman (S8) with a 2.6 cm ILC at 10:00 in the right breast. The regions corresponding to the tumor locations show an increase in $\Delta[Hb]\%$ as compared to the surrounding healthy tissue and the healthy contralateral breast. Fig. 9-5d shows coronal slices for a 58 year-old post-menopausal woman (S16) with DCIS at 2:00 in the left breast of approximately 1.8 cm. Similar to an invasive tumor, the DCIS is identified by increased $\Delta[Hb]\%$ following the breath hold. Fig. 9-5e shows coronal slices for a 61 year-old post-menopausal woman (S21) with ADH of size 1.1 cm at 11:00 in the left breast. ADH, a benign pre-cancerous cellular change, appears as a region of minimal enhancement of a magnitude also seen in the contralateral breast. Finally Fig. 9-5f shows a 63 year-old healthy subject (S3) where both breasts demonstrate a very homogenous level of $\Delta[Hb]\%$ with no regions of pronounced enhancement.

![Figure 9-5](image)

Figure 9-5. Mid-recovery images showing the $\Delta[Hb]\%$ for the left and right breast for six different pathologies.

The pathologies shown include (a) an IDC at 1:00 in the right breast (S4); (b) an IDC and ILC at 2:30 in the left breast (S9); (c) an ILC at 10:00 in the right breast (d) ductal carcinoma in situ at
2:00 in the left breast; (e) ADH at 11:00 in the left breast; and (f) a healthy subject with no breast nodules.

9.5 Quantification of Mid-Recovery $\Delta[Hb]$

The tomographic images show that $d[Hb] \%$ is elevated in the region of the tumor at the mid-recovery time point. Fig. 9-6a shows the average over the 1-cm-radius sphere of peak $d[Hb] \%$ for healthy subjects ($n=6$), benign masses ($n=8$), and tumors ($n=14$). At the mid-recovery time point healthy breasts have almost returned to baseline ($1.6 \pm 0.5 \%$), while the tumors still have some $d[Hb] \%$ lingering through the recovery period ($6.8 \pm 3.6 \%$). The benign masses fall between the healthy and tumor values ($4.9 \pm 2.7 \%$). There is a significant difference in $d[Hb] \%$ between healthy and tumor-bearing breasts ($p=0.0002$), as well as between the healthy and benign breasts ($p=0.014$).

To standardized the technique for better comparison across subjects, we normalized each breast to the peak $d[Hb] \%$ in either breast for each subject. The normalized change in deoxy-hemoglobin ($d[Hb]n$) at the mid-recovery time point is shown in Fig. 9-6b. Similar to the results found in Fig. 9-6a, the healthy and benign breasts have much smaller $d[Hb]n$ (Healthy: $0.17 \pm 0.1$, Benign: $0.31 \pm 0.22$) while the tumor bearing breasts have a larger fraction of $d[Hb]n$ remaining at the mid-recovery time point ($0.45 \pm 0.27$). There is a significant difference between the healthy breasts and the breasts with tumors ($p=0.004$).
Figure 9-6. Average $\Delta[Hb]\%$ at the mid-recovery time point for healthy, benign, and tumor-bearing breasts.

Shown are the (a) average and (b) normalized average change in $\Delta[Hb]\%$ for all healthy ($n=6$), benign ($n=8$), and tumor-bearing ($n=14$) breasts.

(*$p<0.05$, #$p<0.01$).

9.6 Bilateral Hemodynamic Correlation

Subjects with healthy breasts ($n=3$) or benign nodules ($n=4$) have a very similar hemodynamic response to the breath hold in both the left and right breasts, as shown in Fig 9-2b. This is captured by the high correlation of the $d[Hb]\%$ profile shown in Fig. 9-7 (Healthy: $0.85\pm0.2$; Benign: $0.92\pm0.05$; Combined Healthy & Benign: $0.89\pm0.13$), while subjects with cancer ($n=14$) had a lower correlation between the two breasts ($0.68\pm0.21$). There is a significant difference between the combined correlation for all non-cancer subjects (healthy and benign) and cancer subjects ($p=0.043$) as well as between benign and cancer subjects ($p=0.007$).
9.7 Exponential Fitting of Dynamic Data

With the onset of the breath hold we observed an increase in the total hemoglobin levels in the breast, likely due to impeded venous return to the heart \[42\]. Upon resuming normal breathing, the hemoglobin levels in the breast return to their baseline levels. While the tumor-bearing breasts had a similar profile to the healthy breasts, there was a noticeably slower return to baseline during the recovery period following the end of the breath hold, as shown in Fig. 9-8a. To capture this difference, we fit an exponential function to the breath hold and minimized the root mean squared error between the exponential function and the actual data.

The exponential function was characterized by the following equation:

\[
f(t) = f_{sd}(t) \frac{(1-e^{-\frac{t}{\tau_r}})}{(1-e^{-\frac{t_{BH}}{\tau_f}})} + f_{su}(t) \frac{e^{-\frac{t-t_{BH}}{\tau_f}}}{(1-e^{-\frac{t_{BH}}{\tau_r}})}
\]  \hspace{1cm} (9.2)

where \( t \) is the time from the onset of the breath hold, \( \tau_r \) is the rise time constant and \( \tau_f \) is the fall time constant. For each patient \( t_{BH} \) is automatically determined as the point during the breath
hold range (0-30 seconds) where the curve reaches its maximum. The functions \( f_{sd} \) and \( f_{su} \) are step down and step up functions, respectively, defined as follows:

\[
\begin{align*}
  f_{sd}(t) &= \begin{cases} 
  1, & 0 < t < t_{BH} \\
  0.5, & t = t_{BH} \\
  0, & t > t_{BH} 
  \end{cases} \\
  f_{su}(t) &= \begin{cases} 
  0, & 0 < t < t_{BH} \\
  0.5, & t = t_{BH} \\
  1, & t > t_{BH} 
  \end{cases}
\end{align*}
\]

(9.3)

All exponential fitting was performed on normalized experimental data in order to characterize the shape of the curve without considering the amplitude of change, and for this reason, Eq. 9.2 is normalized to unity at time \( t_{BH} \).

Fig. 9-8a shows the time traces for the percentage change in deoxyhemoglobin concentration \( \Delta[Hb] \% \) from baseline for a healthy (solid black) and tumor-bearing (solid grey) breast as well as the exponential fit (dashed lines) over the course of a breath hold. Fig. 9-8b shows the average rise time \( (\tau_r) \) for the healthy \((n=6)\), benign \((n=8)\), and tumor-bearing breasts \((n=14)\). The \( \tau_r \) for the tumor-bearing breasts is smaller than for the healthy breasts (Healthy: 39.7±30.1%; Tumor: 25.2±27.1%; \( p=0.33 \)). However, the greatest difference in the tissue hemodynamics occurs following the breath hold, as characterized by \( \tau_f \), shown in Fig. 9-8c. Tumor-bearing breasts have a much slower washout rate, reflected by the fact that \( \tau_f \) is larger in the tumor-bearing breasts than in the healthy breasts (Healthy: 14.3±9.5%; Tumor: 29.9±29.5%; \( p=0.09 \)). The benign masses fall in between the healthy and tumor-bearing breasts for both \( \tau_r \) and \( \tau_f \). Though not statistically significant, this trend confirms the source of the contrast that provides good tumor visualization at the mid-recovery time point.
Figure 9-8. Exponential fitting of the transient response to a breath hold.

(a) The change in [Hb] normalized to the peak change for a healthy (solid black line) and tumor bearing (solid grey line) breast over the course of a breath hold. Overlayed are the exponential fits for the healthy breast (dashed black line) and tumor-bearing breast (dotted grey line).

Average (b) Rise and (c) Fall time constants of the exponential fit for healthy, benign, and tumor bearing breasts.

9.8 False Negative and False Positive Cases

In four tumor-bearing breasts, we were unable to visualize the tumor at the mid-recovery time point. Two of these cases (S6, S13) involved large-breasted subjects with tumors near the chest wall. In these cases, it is possible that the fiber interface did not make adequate contact with the region of the breast that contained the tumor. As a result, the fiber interface was primarily
imaging the healthy portion of the breast, reflected in our images that show a healthy profile of $\Delta[\text{Hb}]\%$. In the third case (S16) suspicious nodules with tumor-like profiles were observed in the contra-lateral breast. These nodules were unbiopsied so it is not clear how our finding relates to the pathology. In the fourth case (S14), the subject had very dense breasts.

In one of the breasts with a benign mass (S19) our imaging showed a tumor-like region in the corresponding location. The mass has not been biopsied and the subject is scheduled for a follow-up visit in 6 months. Since the pathology of the mass is unknown we cannot be sure that our finding is incorrect.

9.9 Discussion

In this study we demonstrated that there are hemodynamic biomarkers of breast cancer that can be detected with dynamic optical tomography imaging during a breath hold. Respiratory maneuvers such as a breath hold or valsalva maneuver have been previously explored in brain DOT imaging, where an increased blood volume is observed in the region overlying valveless cerebral veins that experience hypertension during the respiratory maneuver [72]. While the effect of respiratory maneuvers is not as well studied in the breast, increased blood volume has been reported in pilot DOT imaging studies of the breast during a valsalva maneuver or breath hold [42, 73], which is believed to be caused by increased intrathoracic pressure that is transmitted through the vascular tree, resulting in an increased arterial and venous pressure [69]. In addition to the increased blood volume during the maneuver, these studies have also reported that the change in deoxy-hemoglobin in the breast appears to be more sensitive to respiratory maneuvers, similar to our observations.
The source of dynamic contrast comes from differences in the architecture and structure between normal and tumor vasculature. Growing tumors require increased vasculature in order to supply nutrients and oxygen, while also removing waste products from the expanding tumor. Once tumors surpass approximately 200 microns the tumor cells can no longer rely on diffusion from the nearby vessels and therefore must recruit new blood vessels by releasing pro-angiogenic growth factors. The newly formed vasculature is tortuous, disorganized, and hyper-permeable [6]. There are many shunts and stunted vessels that disrupt the normal artery-capillary-vein vascular hierarchy. Due to this disorganized structure, despite increased vasculature, the tumor perfusion remains poor. Poor perfusion combined with the high metabolic activity of tumor cells causes tumors to be more hypoxic than surrounding healthy tissue [74].

In our study, the hemodynamic response of the tumor tissue differed from that of the healthy tissue. In healthy subjects we saw a rise in [Hb] and [HbO₂] levels during the breath hold, followed by a rapid return to baseline levels upon the resumption of normal breathing. In tumor regions of the breast we observed an increase in [Hb] and [HbO₂] levels during the breath hold followed by a much slower return to baseline than in healthy subjects. This effect was most pronounced in the [Hb] levels. We believe that this sluggish return to baseline is due to the combined effect of the disorganized vasculature that affects blood flow in the tumor region, as well as the hypoxic nature of oxygen-hungry tumors. Our results confirm those of pilot studies looking at respiratory dynamics using DOT that reported a phase delay in the
transient response of tumor tissue [44] and a sluggish recovery of [Hb] levels following a breath hold [42].

*Study Limitations*

While this work included benign masses for analysis, its primary focus was on differentiating healthy tissue from malignant masses. Due to the variety of benign masses sampled, coupled with the small sample size, it was not possible to infer strong statistical value from the benign subject data. While the work here shows some promising trends in the benign masses (typically falling in between healthy and malignant values), it is clear that a larger, more controlled study would be necessary to fully explore these findings.

In performing one of the largest diffuse optical imaging studies involving a breath hold we discovered a few important clinical advantages and disadvantages associated with this work. Some of the clinically advantageous features of our study include the lack of compression during imaging, direct fiber contact with the breast which means no coupling fluid is required, and the use of endogenous contrast. The main disadvantage involves the variability in breath holds performed by subjects. One of four false negative subjects also suffered from asthma (S6), where poor breath hold execution likely affected the DOT results. Asthma should be considered as a contraindication to future breath hold studies. Two subjects had large breasts with tumors located close to the chest wall. In those cases, we had difficulty getting the tumor region into our optical breast interface due to the size of the breast, resulting in poor visualization of the tumor region. This was one of the factors that led to the design of the translating ring fiber-breast interface described in Section 8.2.
Conclusions

We conducted a study exploring the hemodynamic changes in the breast during a breath hold in 21 subjects (6 healthy breasts, 14 tumor-bearing breasts, and 8 breasts with benign masses). Using a newly designed dynamic DOT system that can acquire data simultaneously from both breasts at 1.7 Hz, we were able to analyze the transient response of the breast to a breath hold. Healthy breasts showed an increase in [Hb] levels during the breath hold followed by a return to baseline upon the resumption of breathing. In tumor-bearing breasts the tumor region could be identified by its much slower recovery from the breath hold. We quantified this slower recovery of the tumor by fitting an exponential curve to the breath hold deoxy-hemoglobin levels and found that the washout time constant τf was greater for the tumor region than in the healthy breast. In addition, at a time point 15 seconds following the end of the breath hold the tumor region can be visualized as an area of increased Δ[Hb]%, while the surrounding healthy tissue and contra-lateral breast show a fairly uniform return to baseline values by that time point (Healthy: 1.6±0.5%; Tumor: 6.1±3.7%; p=0.007). Our analysis of the correlation between the Δ[Hb]% transient response in the left and right breast showed a very high correlation in healthy and benign subjects (0.89±0.13) and poorer correlation in subjects with cancer (0.68±0.2). We believe that these findings reflect the effect of the disorganized tumor vasculature on the tissue hemodynamic response.

While these optical biomarkers appear to hold some promise in understanding the differences between benign and malignant masses, a larger, prospective study with more biopsied benign cases would be necessary to confirm the trends shown here. Overall our study
shows that dynamic optical markers have value in identifying breast tumors without the need for injected contrast agents or painful compression. These findings provide a basis for analyzing transient responses for the detection of breast cancer in the hopes that this will provide another dimension for characterizing tumors to improve sensitivity, specificity, or better predict tumor response to therapy.
Chapter 10: Monitoring Tumor Response to Therapy: Pre-Clinical

The emergence of a number of therapeutic agents over the past 10 years has improved the treatment of both advanced and early stage breast cancer in both the pre-surgery (neoadjuvant) and post-surgery (adjuvant) settings [75]. However, despite these advances, the optimal therapeutic agent for a specific patient cannot be determined a priori. There is a clinical need for patient specific metrics through rapid noninvasive imaging to tailor drug treatment by optimizing dosages, timing of drug cycles, and duration of therapy, thereby reducing toxicity and cost and improving patient outcome. The use of non-ionizing radiation, coupled with high sensitivity to HbO$_2$ and Hb, short imaging times, and no need for exogenous contrast agents make DOT an attractive imaging solution to this problem.

In particular, treatments that target blood vessel development in tumors have been highly effective in subsets of patients and in select types of cancer. However, the variability in efficacy, combined with the high cost and toxicity of these novel treatments suggest that a rapid noninvasive means of benchmarking tumor response to therapy would be useful. In the experiment described here, we study how diffuse optical tomography (DOT) can be used for monitoring tumor vascularization. Using two small animal xenograft model systems with previously well-characterized responses to vascular endothelial growth factor (VEGF) inhibition, we use DOT to distinguish responder from non-responder tumor types within a few days of starting treatment.
10.1 Anti-Angiogenic Drug Therapy

The field of anti-angiogenic research was pioneered by Judah Folkman who, 40 years ago, first suggested that the prevention of new vessel formation could result in tumor dormancy and could therefore be a novel cancer therapy [76]. Since that time, there has been considerable effort invested in developing new anti-angiogenic agents that have been tested in a number of pre-clinical and clinical studies. The majority of these agents target pro-angiogenic growth factors, specifically, the vascular endothelial growth factor (VEGF). It has been shown that VEGF is expressed in almost all human tumors and higher levels of VEGF correlated with increased tumor vascularity, growth, invasion and metastasis [77]. The first successful human clinical trial showed that an anti-VEGF monoclonal antibody (bevacizumab) substantially increased the time to progression in metastatic colon cancer, and led to FDA approval of bevacizumab in 2004 [78, 79]. Bevacizumab (BV) is now approved for non-small cell lung cancer, metastatic HER2 negative breast cancer, metastatic renal cell carcinoma, and second line treatment of glioblastoma [80].

Despite these promising clinical results, the effectiveness of BV is heavily dependent on the type of tumor, and it has been shown that different types of tumors can show significantly different responses to VEGF blockade [81]. In addition to variability in effectiveness across tumor types, another difficulty that anti-angiogenic drugs face is that over time, tumors are able to find a way around the VEGF pathway and resume angiogenesis [82]. Furthermore, VEGF inhibitors can have significant toxicities, increasing the importance of targeting therapy to responders [83]. As a result of these difficulties in anti-angiogenic therapy, it is clear that being
able to monitor the tumor progression and response to treatment in vivo will be valuable for improving effectiveness.

Current methods that have been explored for visualizing tumor angiogenesis and drug responsiveness include positron emission tomography (PET), magnetic resonance imaging (MRI), and ultrasound imaging (US). PET imaging uses radioactive tracers such as fluorodeoxyglucose (FDG) or $^{15}$O to look at tumor metabolism or perfusion [84]. MRI studies looking at angiogenesis typically focus on dynamic contrast enhanced MRI (DCE-MRI) which uses an injected paramagnetic contrast agent to generate maps of blood flow or permeability [85]. Ultrasound imaging of angiogenesis typically uses either power doppler to assess the larger vessels, or injected microbubbles as a contrast agent to image blood flow in the smaller vessels (known as contrast enhanced ultrasound (CEUS)) [86]. PET, DCE-MRI, and CEUS all require an injection of an exogenous contrast agent. Contrast agents can have adverse effects [87], increase the time required for imaging protocols, and the injection of these agents introduces an additional variable that can be difficult to control in longitudinal studies.

### 10.2 Experiment Design

In this study, we used DOT to monitor two tumor models with previously characterized and divergent responses to VEGF inhibition. Xenografts from the SK-NEP-1 human Ewing family tumor cell line [88], are highly responsive to various anti-VEGF agents, with significant loss of vasculature and inhibition of growth. In contrast, xenografts from the NGP human neuroblastoma cell line continue to grow with only slight restriction and minimally destabilized vessels [89-92]. We asked, using DOT, whether differences in perfusion-related parameters
could differentiate between the responder (SK-NEP-1) and non-responder (NGP) tumor models, and whether such changes could be detected within days of the start of treatment with the anti-VEGF antibody BV. We found that DOT can distinguish responders from non-responders, as early as one day after treatment, and confirmed these findings with MRI T2 relaxometry and lectin perfusion imaging. Our findings suggest that a DOT can provide a rapid readout of tumor responsiveness to VEGF inhibition.

10^6 NGP or SK-NEP-1 cells were injected intrarenally into 4-6 week old NCR female nude mice (Taconic, Germantown, NY) as previously described [89, 92] and the resulting xenografts were monitored for growth using bioluminescence. At a threshold corresponding to 1-2 g, tumors were randomized to control or treatment groups (cohort size 5-6 mice per treatment group). DOT and MRI imaging of the tumors was performed at day 0, 1, 3, and 5. An injection of 0.2 mL of BV (2.5 mg/mL) was administered intravenously via the tail vein following the imaging sessions on days 0 and 3. Albumin was used as a placebo for control studies (Con). Animals were euthanized by CO₂ inhalation at day 5 after serial imaging studies (DOT and MRI), and at days 0, 1, 3, and 5 for lectin perfusion analysis. All animal experiments were approved by the Columbia University Institutional Animal Care and Use Committee (IACUC, AC-AAAA9639).

**Optical Imaging Protocol**

Optical imaging was performed using a DOT system designed in our laboratory for small animal imaging [58]. The small animal imaging system is a scaled-down version of the digital breast imaging system; it uses 16 sources to illuminate the target with two wavelengths (765 nm and
830 nm) and 32 fibers to detect the scattered and transmitted light through the target. The optical fibers surround a cylinder made of white Delrin material with a wall thickness of 1.7 mm, a diameter of 3.2 cm and a height of 10 cm (Fig. 10-1a). The fibers are arranged in two rings separated by 1.25 cm and with an alternating pattern of source-detector-detector-source. The animals were suspended vertically in the cylinder and held in place by a nose code that was also used to administer anesthesia (isofluorane gas 1-2%). For each imaging time point the spine of the mouse was aligned with the same source fiber and the ears were carefully positioned to maintain precise vertical alignment. Intralipid 1% (diluted from Intralipid 20%, Baxter Healthcare Corp.) was used as a matching liquid surrounding the mouse to prevent edge artifacts. The Intralipid 1% was warmed to 37°C in order to maintain a stable mouse body temperature. Either prior to or following the mouse imaging a reference measurement was also acquired using Intralipid 1%.

Data was acquired at 6.9 Hz with a dynamic range of ~190dB. 300 frames of data (45 seconds of data) were collected at days 0, 1, 3, and 5 along with a homogeneous reference image of Intralipid 1%. The 300 frames were averaged to compute the mean and standard deviation data for each source-detector pair and then normalized to the homogenous reference prior to reconstruction into 3D images of [HbO₂], [Hb], and total hemoglobin concentration ([THb]). We assumed that changes in absorption (i.e. [HbO₂], [Hb], [THb]) would most strongly reflect tumor responsiveness to BV, and thus did not include scattering parameters in our reconstruction. All image reconstructions were performed using a recently developed partial-differential equation (PDE)-constrained multispectral imaging method [93] that employs the
equation of radiative transfer as a light propagation model. The 3D volume mesh used in these reconstructions involved approximately 16,000 tetrahedral elements and the total reconstruction time for one image was approximately 2 hrs on a Dual Core Intel Xeon 3.33GHz processor.

MRI T2 Relaxometry

MRI is routinely used for high-resolution anatomical and physiological imaging in numerous clinical applications, including determination of tumor size, location, and perfusion [94]. MRI studies that visualize hemodynamic parameters typically employ gadolinium-based contrast agents [95]. To circumvent the potential complications due to contrast agents, we have adapted an approach first introduced by Teicher et al. [96] that uses T2 relaxometry to derive information about blood volume without the use of contrast agents. Here we applied this approach to determine relative blood volume fractions in tumors.

A vertical 9.4 T microimaging system (DRX400, Bruker Biospin, Billerica, MA, USA) was used to perform abdominal MR imaging. The mice were anesthetized using isoflurane gas (1-2%) and their respiration was monitored and gated during the experiment. All experiments were carried out with a single-element 30-mm-diameter birdcage RF coil. T2-weighted images were acquired using 2D axial and coronal rapid acquisition with relaxation enhancement (RARE) pulse sequences. Imaging parameters included a pulse echo time of TE = 50 ms, a repetition time (TR) varying from 2700 to 3900 ms, an echo train of 8, a matrix size of 128×128, a slice thickness of 1 mm, an interslice gap of 0.2 mm and a field of view (FOV) varying from 2.5 to 3 cm.
The T2 images were used to calculate the relative blood volume fraction in the tumors. Previous studies [97-99] have reported a linear relationship between the changes in the transverse relaxation rate (ΔR2) and the changes in deoxy-hemoglobin concentration (Δ[Hb]), a marker for blood volume. The relationship between R2 and [Hb] is linear, as shown in Eq. 10.1.

\[ R2 = R0 + k_2[Hb] \Rightarrow \Delta R2 = \Delta R0 + k_2\Delta[Hb] \]  

(10.1)

where \( \Delta R0 \) is the relaxometry contribution of \( \Delta R2 \) that is not the result of [Hb] changes and \( k_2 \) is a tissue-specific constant. If we assume that the relaxation rate changes are caused by changes in the deoxy-hemoglobin concentration only, then \( \Delta R0 \) is zero. To reduce physiological variations that could affect \( R0 \), we maintained standard scan times and respiratory rates across all mice.

In a spin-echo sequence the transverse relaxation rate change is related to the signal intensity using the logarithmic expression shown in Eq. 10.2.

\[ \Delta R2 = \ln(S_{pre}/S_{post})/TE \]  

(10.2)

where TE is the effective echo time and \( S_{pre}, S_{post} \) are the signal intensities of the region of interest (ROI) in the corresponding T2 images before and after treatment respectively. T2 images were preferred to T1 for the blood volume measurements because they provided significantly improved anatomical information [100]. T2 images were also preferred to T2* images due the their superior performance in depicting heterogeneous distributions of small-field disturbances (derived from arterioles, capillaries, and venules) as opposed to large vessels [97].
The coronal T2 view allowed the selection of a larger region of interest (ROI) within the tumors, since the tumors appeared to expand more on the anteroposterior axis than on the lateral or dorsoventral axis across the 5 day treatment period. However, axial T2 images were used for the ΔR2 measurements in cases where the depiction of the tumor was not clear in the coronal view. The ROI signal intensities were normalized over the signal intensity of the urine (reference signal) on the unaffected kidney. In selecting the ROI we chose a region with very homogeneous contrast and attempted to avoid large vessels within the tumor as well as necrotic and possibly hypoxic regions in the tumor core. The selected image plane, slice, and ROI dimensions remained as consistent as possible across the different days. The same operator processed all the images.

Lectin Perfusion Studies

At euthanasia, mice were injected with fluorescein-labeled Lycopersicon esculentum lectin (100μg/100μl PBS, Vector Laboratories, Burlingame, CA). Vasculature was fixed by infusing 1% paraformaldehyde. 40-μm sections were cut using a vibratome, and digital images were subjected to computer-assisted quantitative analysis of tumor vessel architecture [101, 102]. After binarization, microvessel density (MVD) was estimated by the total number of white pixels per field as determined by the method of Wild et al. [101]. The total number of images analyzed ranged from 35-67 for SK-NEP-1 and from 51-74 for NGP.

Statistical Methods

To assess overall differences between the groups of mice, a linear mixed effects regression model was implemented using the SAS PROC MIXED procedure (SAS Software Version 9.1, SAS
Institute, Cary, NC). The model estimates linear trajectories for each cohort over time, while accounting for comparisons among repeated measurements from the same mice. The intercept was treated as a random effect and covariate to account for the differences between mice at baseline. The maximum likelihood method was used to estimate the regression coefficients.

DOT imaging employed a linear model for the [THb] at days 0, 1, 3, and 5, using the slope of linear fit for comparison between cohorts. MRI imaging employed a linear model for relative signal change at days 1, 3, and 5, using the intercept of the linear fit for comparison between cohorts. Comparisons of DOT and MRI parameters between BV-treated and control tumors at days 1, 3, and 5 were calculated using unpaired two-tailed Student’s t-tests, with alpha set at 0.05. Lectin perfusion data was analyzed with one-way ANOVA and post-analysis with Tukey’s multiple comparison test (GraphPad Prism 5.0 Software, San Diego, CA).

10.3 DOT Imaging Results

Continuous-wave DOT was performed using near-infrared light to illuminate the target sequentially from multiple angles while measuring transmitted and reflected light intensities, allowing sensitive detection of changes in concentrations of chromophores (e.g. oxy, deoxy-hemoglobin, and total hemoglobin). Fig. 10-1d shows 3D volume images of total hemoglobin [THb]. Overall, we observed a strong decrease in total hemoglobin [THb] at least once over the 5 day experimental period in BV-treated SK-NEP-1 tumors. In Fig. 10-1d, [THb] in the BV-treated SK-NEP-1 tumors reached a nadir at day 3 and then had partial recovery at day 5. In contrast, in control SK-NEP-1 tumors, and both control and BV-treated NGP tumors, [THb] steadily increased over the 5-day period.
Figure 10-1. DOT small-imaging setup and representative 3D reconstructions of total hemoglobin concentration ([THb]) for each cohort at day 0, 1, 3, 5.

(a) The experimental setup showing a mouse surrounded by intralipid in the imaging cylinder with the two rings of optical fibers surrounding the tumor region. Also shown are diagrams outlining (b) the region of the mouse shown in the 3D volume images and (c) the orientation of the mouse and tumor in the 2D axial images.

(d) 3D [THb] images showing a 2x3 cm cylindrical volume encompassing the tumor-bearing portion of a representative mouse from each cohort at days 0, 1, 3, 5. A steady increase in [THb] over the 5 days is noticeable in the SK-NEP-1 Con, NGP BV, and NGP Con cohorts. In contrast, the SK-NEP-1 BV cohort showed a strong decrease in [THb] at days 1 and 3 followed by a rebound at day 5.

The observed effects are further illustrated through axial slices taken from the 3D reconstruction through the plane of peak [THb]. Fig. 10-2a shows four mice from the BV-treated SK-NEP-1 cohort and Fig. 10-2b shows four mice from the BV-treated NGP cohort. At some point over the 5 days all BV-treated SK-NEP-1 mice show a drop in [THb], while in NGP mice there is an increase in [THb] over the 5 days. It appears as though some BV-treated NGP
mice do show mild signs of suppressed vascularization (Fig. 10-2b, rows 3 and 4) due to the drug, although the effect is much smaller than in the SK-NEP-1 cohort.

![Figure 10-2. 2D axial slices through the plane of peak [THb] for treated (a) responsive and (b) non-responsive tumors at day 0,1,3,5. Four representative animals from the (a) BV-treated SK-NEP-1 cohort and (b) BV-treated NGP cohort are presented here. The images are oriented with the tumor at 9:00, as shown in Fig. 10-1c.](image)

To quantify these effects, a 5 mm$^3$ cube was selected centered around the highest-intensity voxel, and mean [THb] of the voxels within that cube was calculated. Fig. 10-3 shows the mean [THb] over the 5 days with a linear fit generated by a mixed-effects model [103]. For SK-NEP-1 tumors, mean [THb] showed a divergent trend between BV-treated and control groups with a significant difference in the slope of the linear fit for each group (P=0.02). In contrast, for NGP tumors, the mean [THb] increased in both BV-treated and control groups over the five days with no significant difference in the slope of the linear fit for each group (P=0.81).
Figure 10-3. Average [THb] for each cohort plotted over 5 days.

Shown is the response for the control and treated cohorts for the (a) SK-NEP-1 responsive tumor type and (b) the NGP non-responsive tumor type. [THb] was quantified in the tumor region by selecting a 5 mm³ cube surrounding the peak voxel. The slope of the linear fit is significantly different between the SK-NEP-1 BV-treated (BV) and control (Con) cohorts (p=0.02). No such significance is seen between the NGP BV-treated and control cohorts (p=0.81).

Fig. 10-4 shows that the percentage change in mean [THb] from day 0 significantly distinguished between SK-NEP-1 BV-treated and control groups at day 1 (BV: 18±15%, n=5; Con: 19±27%, n=5; P=0.034) and day 5 (BV: -9±22%, n=5; Con: 42±37%, n=5; P=0.034). No such distinction was seen in NGP BV-treated and control groups, which showed an overall increase by day 5 (BV: 5±14%, n=6; Con: 5±33%, n=6; P=0.99). Oxy- and deoxy-hemoglobin concentrations, [HbO₂] and [Hb], followed similar trends to [THb], with BV causing a decrease in [HbO₂] and [Hb] in SK-NEP-1 but not in NGP (Fig. 10-4a/b). This finding suggests that a blood volume reduction is the leading cause for this observation, rather than a change in blood oxygen saturation.
Figure 10-4. Average total-, oxy- and deoxy-hemoglobin concentrations, [THb], [HbO₂] and [Hb], for each cohort over the five days.

[HbO₂] and [Hb] followed similar trends to [THb], with BV causing a decrease in (a) SK-NEP-1 but not in (b) NGP tumors.

(*P<0.05).

10.4 MRI T2 Relaxometry Results

MRI T2 relaxometry has previously been used to derive steady-state blood flow measures in brain [96]. We have adapted this technique to determine relative blood volume in tumors, by using the T2 images to determine the transverse relaxation rate (ΔR2). Since the change in the transverse relaxation rate (ΔR2) is linearly related to the change in the deoxygenated hemoglobin concentration Δ[Hb] [97-99], ΔR2 can be used to determine relative blood volume. Fig. 10-5 shows axial examples of T2-weighted MR images taken just before the injection of BV (day 0), and 1, 3, and 5 days after the injection. In the BV-treated SK-NEP-1 tumors there is a visible increase in the T2 signal intensity (brightness). This indicates that ΔR2, and thus the relative blood volume, decreases with BV treatment. In comparison, the T2 signal intensity in control SK-NEP-1 tumors and both control and BV-treated NGP tumors remained relatively
constant or decreased, indicating that the relative blood volume remained constant or increased, respectively.

Figure 10-5. Representative T2 spin-echo axial MR images for each group at days 0, 1, 3, 5. The axial slices were obtained at days 0, 1, 3, and 5 after an initial injection with either bevacizumab (BV) or albumin control (Con) at day 0.

Quantifying the transverse relaxation rate (ΔR2), we found that BV caused a rapid (after 1 day), decrease in the relative blood volume in SK-NEP-1 tumors as determined by a significant decrease of 3.47±2.77 s⁻¹ (p=0.021) in the ΔR2 (Fig. 10-6). By day 3 and day 5, the effect of BV on the relative blood volume persisted but lessened (reduction of 0.91±2.22 s⁻¹ and 1.1±1.95 s⁻¹, respectively). SK-NEP-1 control tumors exhibited no statistically significant changes in the ΔR2. BV-treated and control NGP tumors exhibited either stable or increased ΔR2 over time. To
statistically evaluate the overall response over the entire five days of the study, we employed a linear mixed-effects model [103]. A linear fit to days 1, 3 and 5 demonstrated a significant difference between the intercept of the SK-NEP-1 BV-treated cohort and the control group (p=0.0014), but no such difference between the NGP BV-treated cohort and the control group (p=0.1037).

Figure 10-6. Average change in the transverse relaxation rate (ΔR2) plotted for each cohort over 5 days.

The changes in ΔR2 were quantified in a specific region of interest with homogeneous tissue contrast within the tumor. The same region was selected throughout the tumor images over the five days.

The slope of the linear fit is significantly different between the SK-NEP-1 BV-treated and control cohorts (p=0.0014). No such significance is seen between the NGP BV-treated and control cohorts (p=0.1037).

In addition to the transverse relaxation rate, we quantified the tumor mass from MR images. This was performed by manually outlining the left kidney in the axial T2 images and generating 3D reconstructed views of the tumors. The mass value was estimated from the product of the total number of voxels within the boundary of each tumor and the voxel resolution, also taking into consideration the interslice gap of the 2D MR images. Treatment of
SK-NEP-1 mice with BV essentially arrested tumor growth over the 5 day period, compared with continued growth in the control tumors (Fig. 10-7). Growth of NGP tumors was unaffected by BV treatment. These results along with the analysis of lectin perfusion studies of the vasculature, shown in Section 10.5, verify our DOT classification of SK-NEP-1 as a responder and NGP as a non-responder to VEGF blockade therapy.

![Graph showing tumor volume changes](image)

Figure 10-7. The temporal progression of the percentage mass volume-changes of the tumors as computed by 3D reconstructed T2 MRI views of the tumors.

BV treatment significantly inhibited tumor growth in SK-NEP-1 xenografts at days 3 and 5 in comparison to control, but not in NGP xenografts. (*p<0.05).

### 10.5 Lectin Perfusion Results

Established SK-NEP-1 and NGP tumors were injected IV with fluorescein-labeled L. esculentum lectin, prior to sacrifice at day 0, or after 1, 3, or 5 days of treatment with either the control vehicle or BV (Fig. 10-8a). There is a noticeable decrease in the tumor vascularization in the SK-
NEP-1 BV-treated tumors by day 1, which persists at day 3 and day 5. This decrease in vascularization is not evident in NGP BV-treated tumors.

Figure 10-8. Lectin perfusion results confirm the vascular responsiveness of SK-NEP-1 and non-responsiveness of NGP tumors to treatment.

Representative fluorescent images are shown in (a) for BV-treated SK-NEP-1 and NGP tumors at days 0, 1, 3 and 5. A noticeable decline in vasculature is observed by day 1 in SK-NEP-1 BV-treated mice, but not in NGP BV-treated mice.

There is a significant drop in MVD (b) in SK-NEP-1 BV-treated tumors at days 1, 3, 5 (**p<0.001) compared with day 0 control tumors, and with a significant difference in MVD between Con and BV-treated tumors at days 1, 3, 5 (#p<0.001). NGP BV-treated mice show a drop at day 3 (*p<0.01) with a rebound at day 5 and no significant differences between Con and BV-treated tumors on any day.

Quantified changes in lectin perfusion studies of tumor vasculature were consistent with changes detected by DOT and MRI T2 relaxometry (Fig. 10-8b). As compared to day 0 controls,
microvessel density (MVD) in BV-treated SK-NEP-1 tumors decreased by 65% at day 1, 74% at day 3, and 77% at day 5 (p<0.001, each) and differed significantly from control SK-NEP-1 tumors at days 1, 3, and 5 (p<0.001, each). MVD decreased by 51% in BV-treated NGP tumors at day 3 (p<0.01) followed by a rebound back to baseline levels at day 5. There was no significant difference between control and BV-treated NGP tumors at any day.

10.6 Discussion
Biologically targeted agents hold promise for increasing effectiveness of cancer treatment, yet optimizing their use may require the development of new assessment strategies. In this set of preclinical studies, we have demonstrated that it is possible to clearly distinguish responder from non-responder tumors within 5 days of BV treatment (Fig. 10-3). Changes in total hemoglobin identified by DOT at early imaging time points correlates to changes in microvessel density (as observed by lectin perfusion imaging) and relative blood volume (as observed by MRI T2 relaxometry). The DOT images show a significant decrease in total hemoglobin in the tumor region over the five days, but no significant change in the blood oxygen saturation (Fig. 10-4), leading us to believe that a blood volume reduction is the leading cause for this observation. This is confirmed by the change in relative blood volume observed in BV-treated SK-NEP-1 by the MRI T2 relaxometry studies (Fig. 10-6).

The results shown here underscore the importance of visualizing the tumor vascularity non-invasively for longitudinal studies. In both the DOT (Fig. 10-3) and MRI (Fig. 10-6) quantification of tumor [THb] and blood volume there are signs of rebounding effects in the BV-treated SK-NEP-1 and NGP tumors. This transitive response can be measured in vivo using DOT
and provides valuable insight into the temporal dynamics of the vasculature in response to anti-angiogenic therapy. Further work would be necessary to correlate how these observed transitive responses relate to changes in the vascular structure, namely normalization of vessel architecture [104, 105]. In addition, the incorporation of other optical imaging techniques such as diffuse correlation spectroscopy (DCS) [106] and contrast-enhanced optical techniques [107] could enhance this work by further quantifying the changes in tumor perfusion and oxygenation due to BV treatment. More sophisticated image classification algorithms could also provide alternative ways of quantifying tumor response and could extend this work to use multiple image parameters to discriminate responders from non-responders, similar to work that has been performed using optical images for classification in rheumatoid arthritis [108] and breast cancer [109].

DOT's advantages lie in its low cost, short imaging times, and use of non-invasive and non-ionizing radiation. In addition, with no need for exogenous contrast agents, DOT is well suited to longitudinal studies that require repeated imaging. Our findings open the door for a number of non-invasive, longitudinal, pre-clinical studies, to improve our understanding of the subtleties of anti-angiogenic agents in an effort to increase the efficacy of these drugs. Further, this study provides pre-clinical background as the optical imaging field looks to translate these findings into therapy monitoring in the clinic [2].

Overall, these results suggest that the development of rapid, imaging-based assessments for human patients is feasible. Coordinated clinical use of DOT data could provide significant benefits for patients by enabling earlier and more effective clinical decision-making.
For individuals with nonresponsive tumors, alternate regimens could be considered without waiting for overt therapeutic failure to occur, avoiding needless toxicity. Alternatively, those patients whose tumors demonstrated responsiveness could remain on treatment. Lastly, given the high cost of biologically-targeted therapies like BV, such early assessment of drug effectiveness could reduce the economic strains of cancer treatment for patients and families.
Chapter 11: Monitoring Tumor Response to Therapy (Clinical)

Neoadjuvant chemotherapy (NACT) consists of drug therapy that is administered prior to surgery. It is the standard of care for locally advanced breast cancer, which involves breast tumors that may be large, and may have spread to lymph nodes or tissue near the breast, but that have not spread beyond the breast region to other parts of the body. NACT can reduce tumor size and allow for breast conserving surgery in patients who would have otherwise required mastectomy [47]. In addition, NACT provides an in vivo assessment of tumor responsiveness to therapy and has become a useful strategy for evaluating the biologic effects of new cancer therapies. NACT also has the added effect of systemically treating any micrometastases that may be present in the body.

Following NACT the patient undergoes surgery, at which point the pathological effect of the treatment can be assessed. A complete pathological response (pCR) occurs when no residual tumor cells are observed in the pathological specimen obtained during surgery. Studies have shown that pCR correlates with the more traditional cancer endpoints of 5-year and 10-year disease-free-survival [48, 49]. The NSABP B18 study showed that women who achieved a pathologic complete response (pCR) with NACT have significantly improved disease free and overall survival [110].

However, only 3-27% of women achieve a pCR after months of NACT [50]. These low response rates have motivated a number of studies looking to predict response to neoadjuvant chemotherapy, with the notion that detecting non-responders early in treatment would allow for a change in treatment to improve response and patient outcomes. There is currently no
modality that is ideal for assessing early response to NACT. Physical exam, mammogram, ultrasound, and magnetic resonance imaging (MRI) are based on measuring tumor size changes and are insensitive to early the vascular response of the tumor. In a retrospective study of 141 women, Chagpar et al. found that size estimates by palpation, US, and mammography were only moderately correlated with residual tumor size following NACT (reported correlation coefficients of 0.42, 0.42, and 0.41 respectively) [51]. Similarly, Schott et al. evaluated 41 patients with physical exam, mammogram, US, and MRI and found the sensitivity of each modality in detecting a pCR was 50, 50, 25, and 25%, respectively [111]. PET-CT, has shown promise in predicting response to NACT; however, in addition to the high cost ($1000 per study) [52], successive PET-CT exposes the patient to radioactive isotopes and ionizing radiation.

Given the success of the pre-clinical study discussed in Chapter 10, we hypothesize that early changes in DOT parameters can be used to predict individual patient response to NACT. As it is fast, less expensive, and requires neither ionizing radiation nor exogenous contrast, serial DOT measurements during NACT can be used to track tumor changes more frequently than other imaging modalities. Preliminary optical imaging studies have shown promising results in small patient groups and suggest that optical techniques may be able to identify responsive tumors within the first week of treatment [54-56, 112].

11.1 Clinical Protocol

A HIPAA-compliant, Columbia IRB-approved (IRB-AAA10480) pilot study of 20 women began recruitment at the Columbia University Medical Center in June 2011. The inclusion criteria is specified in the protocol as English or Spanish speaking women over the age of 18 with recently
diagnosed invasive breast cancer deemed eligible to receive neoadjuvant chemotherapy with weekly taxane followed by dose-dense doxorubicin and cyclophosphamide. Patients should have a tumor size ≥ 1 cm by clinical measurement, bra cup size ≥ B, and be scheduled to undergo NACT with 12 cycles of weekly paclitaxel (80mg/m²) (T) followed by 4 cycles of doxorubicin (60mg/m²) and cyclophosphamide (600 mg/m2)(AC) given biweekly.

Upon or prior to enrollment, each study participant underwent a targeted physical exam including height, weight, blood pressure, pulse, and breast exam including bra cup size as reported by the patient. Measurement of the breast tumor size was documented using standardized calipers with the patient lying in the supine position with the ipsilateral arm placed behind the head (or in the same position on all subsequent exams). Baseline imaging (MRI and mammogram) and diagnostic breast tumor core biopsy for future analysis of Ki-67 and microvessel density were also obtained.

During the baseline visit, each participant underwent DOT imaging for determination of oxy-hemoglobin ([HbO₂]), deoxy-hemoglobin ([Hb]), and scattering (μ′) content in the breasts. DOT imaging was performed at six time points:

- Baseline (prior to treatment)
- Week 2 (before cycle 3 of paclitaxel)
- Week 4 (before cycle 5 of paclitaxel)
- Week 0 AC (prior to starting AC treatment)
- Week 2 AC (before cycle 2 of AC)
- Pre-Surgery
Before surgery mammography and breast MRI were repeated. Fig. 11-1 shows the timing of the various components of the study.

![Figure 11-1. Timing of NACT treatment, physical exams, MRI, and DOT imaging.](image)

**11.2 Optical Imaging Protocol**

All diffuse optical imaging measurements were performing with the digital optical imaging system described in Chapters 2 through 7. The translating ring breast-fiber interface described in Section 8.2 was designed specifically for this experiment in order to perform longitudinal measurements of the absolute optical properties of the breast. Fig. 11-2 shows a photograph of a patient being imaged with diffuse optical tomography. At each imaging time point 1,000 frames of data were collected from the patient. A stable region of fifty frames was selected and the average and standard deviation for each source-detector measurement was computed. Any source-detector pairs with a signal to noise ratio (SNR) below 15 dB were excluded from the reconstruction to reduce noise artifacts. Three-dimensional reconstructions were obtained using a the diffusion approximation as a model for light propagation, as described in Section 9.3
However, in this case the algorithm reconstructs absolute values of the chromophore concentrations (in this case \([\text{Hb}], [\text{HbO}_2]\), and scattering). Absolute reconstructions are similar to the differential reconstructions described in Section 9-3, except for that in this case the baseline is an Intralipid reference, and the images of the subject’s breasts are reconstructed relative to that reference. Since the optical properties of the Intralipid reference are known, we can compute the actual optical properties of the breast.

Figure 11-2. Photograph of diffuse optical tomography imaging of a study participant.

A reference image was performed immediately following the patient imaging using a combination of 20% Intralipid (Baxter) and 1% India Ink (Higgins) diluted and mixed to yield similar optical properties to breast tissue (\(\mu_o=0.12 \ \text{cm}^{-1}, \ \mu_s'=8.13 \ \text{cm}^{-1}\)). We chose to mix the Intralipid reference with a slightly higher absorption than the average breast to avoid saturation.
during the reference measurement. The Intralipid reference measurement was performed with identical settings to the patient (including the gain settlings controlling the amplification of the detect channels). The Intralipid reference (1.5 L held in a clear plastic bag) was placed into the translating ring interface and 100 frames of data were acquired, of which 50 frames were selected as the baseline reference, an input to the reconstruction algorithm.

The 3D reconstruction was performed on a finite element mesh with ~46,000 voxels, with more, smaller voxels placed near the sources and detectors. A unique mesh was created for each patient using the known geometry of the rings holding the sources and detectors. Since the rings for the patient interface are adjustable in the coronal direction, the position of the sources and detectors remains fixed in x and y, but varies in the z direction depending on the patient’s breast size. Therefore, a different mesh is generated for each patient according to the coronal translation of the rings. The mesh was extended 2 cm from the largest ring to account for the chest wall (see Fig. 8-4 for a sample mesh). Sagittal slices showing the tumor location were selected from the tumor-bearing breast, and the same slice from the contralateral breast was also selected for visualization. Images from all time points were plotted on the same scale for longitudinal analysis.

11.3 Preliminary Imaging Results

Included here are preliminary results for the initial patients who have enrolled in the study. Study enrollment is ongoing and this study will likely continue until early 2013.
**Case Study 1**

A 47 year-old premenopausal woman enrolled as the first patient in the study in June 2011 and underwent NACT for poorly differentiated invasive ductal carcinoma at New York-Presbyterian Hospital. Her baseline BMI was 27.3 with a bra size of 36B. She obtained bilateral US and MRI images that confirmed that there was a mass in the right breast with approximate dimensions of 1.4 cm, and 2.3x1.5x2.0 cm determined by each imaging modality, respectively. Fig. 11-3 shows PET-CT, Mammogram, and US images obtained at baseline.

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**Figure 11-3. Case Study 1: Baseline PET-CT, mammogram, and US images.**

(a) An axial slice through the body with the tumor region in the breast shown an a highly enhancing node (bright yellow).

(b) A craniocaudal (axial) mammogram of the right breast. The red circle shows the malignant region.

(c) An US image of the tumor with a 1.4 cm diameter.
Figure 11-4. Case Study 1: Graphical representation of tumor position in the breast.
(a) View looking at the patient with the tumor located at 1 o’clock. The grey circle represents the
tumor, and the solid line shows the sagittal slice taken 1.7 cm from the nipple, thought the tumor
region.
(b) Sagittal view of the slice through the tumor.
(c) Sagittal DOT image with the tumor region outlined with the black dashed line.

Fig. 11-4 graphically illustrates the location of the tumor in the breast with the position
of the sagittal axial slice selected 1 cm to the left of the nipple. The same slice was selected for
both the left breast (top three rows) and right breast (bottom three rows) at all time points, as
shown in Fig. 11-5. For each breast the images are organized as [HbO₂] (topmost row), [Hb]
(middle row), and μᵣ (bottom row). The scale goes from blue (low chromophore
concentration) to red (high chromophore concentration), and is constant across both breasts,
and all imaging time points. At baseline, there is a region of high [HbO₂], [Hb] and scattering in
the right breast compared to the surrounding tissue (Fig. 11-5a). The region of enhancement is
located at approximately 12 o’clock and 4 cm from the nipple. This correlates well with the
mammogram and MRI tumor localization (11 o’clock and 6 cm for the nipple). In our imaging
geometry the patient leans into the rings, likely causing some minor coronal compression of the
breast which likely results in the tumor appearing slightly closer to the nipple in the DOT
images.

After the first two cycles of paclitaxel (Fig. 11-5b/c) were administered the tumor could
no longer be visualized and by Week 0 AC (Fig. 11-5d) the DOT images showed similar [HbO₂],
[Hb], and μᵣ in both the left and right breast. A smaller ring geometry was used for the pre-
surgery imaging time point (Fig 11-5f) due to changes in the patient’s breast size.
Figure 11-5. Case Study 1: DOT images of \([\text{HbO}_2]\), \([\text{Hb}]\), and \(\mu_\text{s}'\) for the left (healthy, top three rows) and right (tumor bearing, bottom three rows) breast during NACT. Shown are images taken at (a) Baseline, (b) Week 2, (c) Week 4, (d) Week 0 AC, (e) Week 2 AC and (f) Pre-Surgery.
The change in optical parameters was quantified by averaging the chromophore values within a 1-cm-radius sphere around the tumor location in the DOT image. The radius of 1 cm was selected to match the tumor size (2 cm diameter) at Baseline. The quantified values for the [HbO₂], [Hb], and μₜ are shown in Fig. 11-6. Also shown in Fig. 11-6a is the largest tumor dimension taken from the caliper measurements. The caliper measurements correlate with the observed DOT changes. This patient was very responsive to treatment, as visualized by the DOT imaging.

Figure 11-6. Case Study 1: Response to therapy over treatment as assessed by (a) caliper measurement, (b) [HbO₂], (c) [Hb], and (d) scattering (μₜ).

Chromophore measurements are quantified as the average value over a 1-cm-radius sphere taken around the tumor location.
Case Study 2

The second case study involves a 66 year-old postmenopausal woman who enrolled in the study in September 2011 and is undergoing NACT for a poorly differentiated invasive ductal carcinoma located in the right breast. MRI images show a mass at 1 o’clock in the right breast 6 cm from the nipple with dimensions of 2.3x1.5x2.0 cm. Fig. 11-7 shows PET-CT, MRI, and US images obtained at baseline.

![Figure 11-7. Case Study 2: Baseline PET-CT, MRI, and US images.](image)

(a) An axial slice through the body with the tumor region in the breast shows a highly enhancing node (bright yellow).
(b) An axial bilateral MRI. The red circle shows the malignant region.
(c) An US image of the tumor with a 1.3 cm diameter.

![Figure 11-8. Case Study 2: Graphical representation of tumor position in the breast.](image)

(a) View looking at the patient with the tumor located at 1 o’clock. The grey circle represents the tumor, and the solid line shows the sagittal slice taken 1 cm from the nipple, thought the tumor region.
(b) Sagittal view of the slice through the tumor.
(c) Sagittal DOT image with the tumor region outlined with the black dashed line.
Fig. 11-8 graphically illustrates the location of the tumor in the breast with the position of the sagittal axial slice selected 1 cm to the left of the nipple. The same slice was selected for both the left breast (top three rows) and right breast (bottom three rows) at all time points, as shown in Fig. 11-9. For each breast the images are organized as [HbO$_2$] (top row), [Hb] (middle row), and $\mu_s'$ (bottom row). The scale goes from blue (low chromophore concentration) to red (high chromophore concentration), and is constant across both breasts, and all imaging time points. There is a region of high [HbO$_2$] and $\mu_s'$ (and moderate [Hb]) in the right breast compared to the surrounding tissue and the contralateral breast at baseline (Fig. 11-9a). The region of enhancement is located at approximately 1 o’clock and 3-4 cm from the nipple, again this correlates with the MRI localization when we consider the coronal compression of the breast in our imaging geometry.

After the first two weeks of paclitaxel treatment (Fig. 11-9b/c) there is a dramatic decrease in the chromophores in the tumor region. By Week 0 AC (Fig. 11-9d) the DOT images show a more homogenous chromophore distribution across the right breast, and there are more similar concentrations in the left and right breasts.
Figure 11-9. Case Study 2: Sagittal DOT images of \([\text{HbO}_2]\), \([\text{Hb}]\), and \(\mu'_s\) for the left (healthy) and right (tumor bearing) breast during NACT.

Shown are images at (a) Baseline, (b) Week 2, (c) Week 4, (d) Week 0 AC and (e) Week 2 AC.
As with Case Study 1, the change in optical parameters was quantified by averaging the chromophore values within a 1-cm-radius sphere around the tumor location in the DOT image. The radius of 1 cm was selected to approximate the tumor size (2 cm diameter) at Baseline. The quantified values for the $[\text{HbO}_2]$, $[\text{Hb}]$, and $\mu_s'$ are shown in Fig. 11-10. Also shown in Fig. 11-10a is the largest tumor dimension taken from the caliper measurements. The caliper measurements generally correlate with the observed DOT changes. This patient was responsive to treatment, as visualized by the DOT imaging. Interesting to note is that there is an increase in deoxy-hemoglobin in the tumor region at Week 4, corresponding to a decrease in oxy-hemoglobin. This may represent necrosis occurring in the tumor region during treatment.

After week 4 the caliper measurements provide little information about the tumor response, while the DOT parameters continue to show meaningful changes. Specifically, there is a persistent decrease in $[\text{Hb}]$ from Week 4 to Week 2 AC and an observed rebound effect in $[\text{HbO}_2]$ over the same time. This may reflect the changing oxygen saturation of the tumor region, moving from a more hypoxic and necrotic tissue to a more normally perfused tissue.
11.4 Discussion

We have developed instrumentation and methods for the visualization of breast tumors in longitudinal studies. Our current techniques can extract [HbO₂], [Hb] and scattering for use in studying the vascularization of advanced breast tumors in response to neoadjuvant chemotherapy.

Our preliminary findings show that DOT can identify the tumor region at baseline by an increased [HbO₂], [Hb], and scattering as compared to the surrounding healthy tissue. Increased [HbO₂] and [Hb] are observed at baseline due to the higher levels of vascularization in the tumor region due to angiogenesis. Increased scattering may reflect the increased cellularity
(increased cell density) as well as the enlarged nuclei that are hallmarks of cancerous tissue. Increased [Hb], [HbO$_2$], and scattering in tumor regions is well documented in literature [21, 26]. The observed DOT measurements correlate well with the tumor dimensions obtained through caliper measurements, and suggest that as early as 2 to 4 weeks after beginning treatment DOT can predict that the tumor is responding to treatment. These results agree with results from other clinical studies that show significant decreases in optical parameters in responding patients within weeks of initiating therapy [54, 56, 113].

In both case studies we observed a strong decrease in absorption and scattering within 4 weeks of starting NACT. Paclitaxel is a microtubule-damaging anti-cancer agent that is known to have anti-angiogenic properties [114, 115]. In these two case studies we see an almost 30% reduction in [HbO$_2$] and a 10% reduction in [Hb], reflecting the decreased vascularization of the tumor region. There is approximately 60% and 20% reduction in scattering over the NACT treatment for Case Study 1 and 2, respectively. This decrease in scattering reflects the return to more normal tissue cellularity caused by the chemotherapy drugs. Similar changes in [Hb], [HbO$_2$], and scattering have been reported by Soliman et al. in a DOT study of 10 patients [56], and by Cerussi et al. in a diffuse optical spectroscopy study of 34 patients [54], and by Jiang et al. in a diffuse optical tomography study of 7 patients [112]. Soliman et al. showed that [Hb], [HbO$_2$], and scattering changes can be used to differentiated between responders and non-responders, while Cerussi et al. and Jiang et al. showed that only [Hb] and [HbT], respectively, differentiated between groups. As further data is collected in our ongoing study, we will be
able to add to these preliminary findings in an effort to understand which optical biomarkers are most sensitive to NACT response.

This study is ongoing and will ultimately aim to explore these promising preliminary results in a population of 20 patients. The study will improve upon existing studies by including better pathological endpoints to evaluate the tumor responsiveness. The biologic response will be assessed by Ki-67 reduction which is associated with cellular proliferation. A reduction in Ki-67 during NACT has been shown to correlate with clinical outcome [116]. DOT-measured hemoglobin concentrations have also been shown to correlate with Ki-67 [117]. This study will allow for the correlation between longitudinal changes in Ki-67 and DOT parameters through Ki-67 assessment at baseline, surgery, and in some patients at mid-treatment. In addition, prior studies have had non-uniform treatment schedules and chemotherapy agents, while our study controls for those factors.

DOT has a number of advantageous characteristics that make it well suited to therapy monitoring. It’s non-ionizing, inexpensive, and portable technology makes it a clinically appealing solution for longitudinal measurements at the point of care. The principle advantage that DOT has over other breast imaging modalities (US, MRI, and Mammography) is its sensitivity to the endogenous tumor changes in vascularity and cellularity. Tumor hemoglobin content and scattering appear to be more sensitive and provide an earlier indication of tumor response than tumor size.
Chapter 12: Wireless Handheld Optical Imaging Probe

In chemotherapy monitoring applications, where the location of the tumor in the breast is already known, and is, in many cases, large and palpable, it may be possible to simplify the instrumentation for easier clinical use. A number of handheld optical imaging probes have been developed for detecting breast tumors and monitoring tumor response to therapy [54, 113, 118, 119]. However, all of them are either fiber or camera-based systems where the handheld portion of the probe connects to a much larger instrument. In this chapter we present the design of a handheld device that miniaturizes the detection hardware so that all processing is performed at the detector and transmitted wirelessly to the host computer. This design eliminates the need for optical fibers or a camera-based design and allows for a hand-held device whose small form factor and ease of use make it suitable for a number of clinical applications.

Most of the current handheld probes for optical breast imaging detect light in reflectance geometry with a 0.5 to 3.5 cm source-detector separation in order to probe beneath the tissue surface. They use a range of near-infrared wavelengths to determine the concentration of chromophores relevant to detecting tumors including oxy- and deoxy-hemoglobin, lipid, water, and scattering. Many of these probes operate in the frequency domain (FD), where the source light is modulated in intensity at frequencies between 100 and 1000 MHz. These systems can extract both the change in phase and amplitude from the detected light. Current handheld FD imaging systems require bundles of optical fibers to bring the detected light back to large systems that house the detection hardware.
Continuous-wave (CW) systems use illumination with constant (or radio-frequency modulated) light intensities and, as a result, only extract the change in amplitude of the light through the tissue. Although less information is collected as compared to FD systems, CW systems are much less expensive, allow for faster data acquisition, and the detection electronics can be miniaturized. Recently, Xu et al. demonstrated a handheld CW system for pressure-induced dynamic breast imaging [113, 120]. Their approach integrates the detection electronics into the handheld portion of the device and relays the measured data to a laptop computer via a serial port. No wireless handheld breast imaging devices have been published to date.

In other areas, wireless optical imaging devices have recently been developed for wearable technologies [121, 122], and endoscopy [123, 124]. A wearable patch-like device designed by Muehlemann et al. uses 4 CW sources and 4 detectors with 2 wavelengths [121]. A flexible printed circuit board holds the illumination, detection, and wireless transmission electronics. Similarly, a larger, but still portable wearable brain-imaging system developed by Atsumori et al. [122] uses 8 CW sources and 8 detectors with 2 wavelengths for imaging the frontal cortex. Along with a portable pack that attaches to the subject's waist, the wireless system allows the subject to move around during imaging. Both of these systems focus on differential imaging and use the modified Beer-Lambert law to look at relative changes in the concentration of oxy- and deoxy-hemoglobin. In endoscopy, capsule-like wireless devices have been designed for spectral, fluorescent, and bright field imaging of the gastrointestinal tract [123, 124]. These devices use small complementary metal-oxide semiconductor (CMOS) or
charged couple device (CCD) sensors to perform qualitative imaging for identifying suspicious regions at the surface of the tissue.

Despite this progress, there are currently no wireless optical imaging devices that perform diffuse optical tissue measurements with absolute reconstruction of the concentrations of tissue chromophores, including the contribution of tissue scattering. Here we present the first prototype of such a device. Our new system is handheld, wireless, and can resolve actual optical properties of scattering, oxy- and deoxy-hemoglobin using four source wavelengths and two detectors at 2.3 Hz. The device uses radio-frequency modulated illumination to eliminate background light and reduce noise artifacts. Using digital detection techniques described earlier in Chapters 4 and 5, we are able to perform the majority of the signal detection and demodulation in the digital domain, which allows for the wireless transmission of the final signal amplitude. The device is inexpensive, portable, runs off of a 9V D-type battery, and can seamlessly interface via Bluetooth to a host computer. A multispectral evolution algorithm uses the measured light intensity to calculate absolute values for tissue-scattering, and concentrations of oxy- and deoxy-hemoglobin in tissue.

12.1 Wireless Handheld Probe Design

The instrument uses four near-infrared wavelengths of light to illuminate tissue. The light passes through the sample and is absorbed and scattered as it travels to two detectors configured in reflectance geometry and located 1.8-2.4 cm and 2.7-3.3 cm away from the sources as shown in Fig. 12-1.
The light is detected by a silicon photodiode and both quantized and demodulated by a microcontroller that passes the result back to the host computer via Bluetooth. The instrument is powered by a 9V D-type battery. A block diagram of the system is shown in Fig. 12-2.

![System block diagram for the wireless handheld probe.](image)

The current version of the device is a prototype that is enclosed by a plastic case measuring 11.5 x 16 x 2.5 cm. This makes the device easy to hold and it can be brought in contact with a wide variety of tissue surfaces. A photograph of the probe is shown in Fig. 12-3a. Fig. 12-3b shows the instrument with the enclosure opened to expose the inner electronics.
Figure 12-3. Photograph of the handheld wireless probe.
Shown are photographs of (a) the device and (b) with the enclosure opened to expose the electronics.

**Light Illumination**

The input light is generated by 10 mW 5.6 mm-diameter laser diodes at wavelengths of 780 nm, 808 nm, 850 nm, and 904 nm (L780P010, L808P010, L850P010, L904P010, ThorLabs). The wavelengths are selected to provide a range of spectral information to reconstruct oxygenated hemoglobin ([HbO$_2$]), deoxygenated hemoglobin ([Hb]) and scattering ($\mu_s'$), while working within the limited selection of wavelengths available in this small package. The laser diodes are driven by a 15 V Laser Diode Driver (iC-WKN, iC Haus). Each wavelength has the ability to modulate the amplitude at a frequency ranging from 1 to 8 KHz, controllable by 20 kΩ
potentiometers. The modulation signal is generated using a combination of a 1 kHz to 33 MHz
Oscillator (LTC1799, Linear Technologies), a binary counter (M74HC4820, STMicroelectronics)
and a low-pass filter (LTC1067, Linear Technologies). The power of the laser diode can be
controlled using a 20 kΩ potentiometer that regulates the current to the laser driver.

The modulation of the input light provides several advantages including superior noise
rejection (including ambient light) as well as the ability to illuminate the tissue simultaneously
with multiple wavelengths. Due to the fact that the speed of this particular system is limited by
the processing power of the microcontroller, the probe is configured to sequentially illuminate
the target which each wavelength. However, future iterations of this design involving a more
powerful microcontroller could simultaneously illuminate the sample with all wavelengths,
modulated at different frequencies, thereby improving the frame rate by a factor of 4.

Light Detection

Light is detected using a silicon photodiode (SiPD) (S1337-33BR, Hamamatsu) and a trans-
impedance amplifier (TIA). The amplifier has 4 possible gain settings including 10 kV/A, 100
kV/A, 1 MV/A, and 10 MV/A. For laser power between 1 and 5 mW, the closer detector (d1)
uses the 1 MV/A setting for most applications, while the further detector (d2) uses the 10 MV/A
setting. The 1 MV/A and 10 MV/A gain settings utilize a bandwidth-extension technique
previously described in Section 4.2. Following the TIA, the signal is high-pass filtered to remove
any DC offset. The signal is also passive low-pass filtered to prevent aliasing at the analog-to-
digital converter (ADC). In the final stage the signal is offset to 1.5V to fully optimize the 0 to 3
V dynamic range of the input to the ADC.
The microcontroller used in this design (ADUC7020, Analog Devices) has a built-in 12-bit analog-to-digital converter (ADC). The ADC logic is configured to sample at 75 kHz and to acquire 150 samples for each measurement. Upon acquisition, the microcontroller performs digital lock-in detection to extract the amplitude from the detected sinusoidal signal. This algorithm, previously outlined in Section 5.6, uses averaging filters combined with modulation and sampling constraints to digitally extract the amplitude while reducing noise. The demodulated amplitude is transmitted to the Bluetooth Module via a universal asynchronous receiver/transmitter (UART) interface.

The Bluetooth Module (RN-41, Roving Networks) was selected for this instrument due to its small form factor (13.4 x 25.8 x 2.0 mm) and low power consumption (<100 mA @ 3 V). The RN-41 Bluetooth Module provides secure communication with 128-bit encryption, error correction for guaranteed packet transfer, and a Class 1 antenna that provides up to 100m of wireless range. Any Bluetooth-capable computer can pair with the Bluetooth Module (by providing the correct pairing code) and communicate via a virtual serial communication port to a LabVIEW user interface.

**Power Supply**

All power to the device is supplied by a 9 V D-type battery. This could easily be replaced with any battery that can provide more than 120 mA at 3 V. Care was taken in selecting components for the device that operate at 3 V so that only one voltage rail is required for the device operation. A low-dropout voltage regulator takes any input voltage between 3 and 12 V and converts it to 3 V.
12.2 System Performance

With no incident light on the detector the dark noise of the system is 160 µV. This is far below the typical values recorded for tissue of between 0.05 and 1 V. The largest possible input value is 3 V peak-to-peak, giving the device a dynamic range of 85 dB for the single 10 MV/A gain setting. From measurements made on a tissue-like optical phantom, the SNR was between 36 dB and 51 dB. This range is due in part to the differences in absorption at the various wavelengths.

The system speed is currently limited by the time required to demodulate the acquired signal. It takes 2 ms to acquire 150 samples followed by 52 ms to demodulate the data and send it to the Bluetooth module. This 54 ms acquisition time must be repeated for each of the four wavelengths and each of the detectors, ultimately giving a sampling speed of 2.3 Hz. It takes the laser diodes approximately 5 ms to settle following switching. This settling time is coordinated to take place during the time that the microcontroller is demodulating the data from the previous wavelength. A summary of the probe’s parameters and performance is shown in Table 12-1.

<table>
<thead>
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<th>Parameter</th>
<th>Value</th>
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</thead>
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<td>Detectors</td>
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<td>Mode</td>
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<td>Frame Rate</td>
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</tr>
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<td>Dynamic Range</td>
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<tr>
<td>Dark Noise</td>
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<tr>
<td>SNR</td>
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<tr>
<td>Power Consumption</td>
<td>120 mA @ 3 V</td>
</tr>
<tr>
<td>Size</td>
<td>11.5 x 16 x 2.5 cm</td>
</tr>
</tbody>
</table>
12.3 Evolutionary Reconstruction Algorithm

The wireless handheld probe provides measurements of the light that scattered through the light and returned to the detector at the surface, as shown in Fig. 12-4.

![Diagram of light propagation in a back-reflection geometry.](image)

Photons that are emitted from the source into the medium scatter and return to a detector located $d$ away from the source. As the source-detector separation increases, the photons that arrive at the detector are more likely to have travelled deeper into the sample (in $z$).

By performing reflectance measurements at multiple locations on the surface of the medium with multiple wavelengths we can compute the optical properties of the tissue. The diffuse reflectance depends solely on the absorption coefficient $\mu_a$, the reduced scattering coefficient $\mu_s'$, and the source-detector separation $d$. Under the assumption of a semi-infinite homogeneous medium, there is a closed-form analytic solution for the spatially resolved reflectance. It is given by Farrell et al. [125] as:

$$R(d)_{DC} = \frac{1}{4\pi \mu_t'} \left[ (\mu_{eff} + \frac{1}{r_1^2}) \exp(-\mu_{eff}r_1) + \left( \frac{4}{3} A + 1 \right) (\mu_{eff} + \frac{1}{r_2^2}) \exp(-\mu_{eff}r_2) \right]$$  \hspace{1cm} (12.1)

where

$$r_1 = \sqrt{\left( \frac{1}{\mu_t'} \right)^2 + d^2} \quad \text{and} \quad r_2 = \sqrt{\left( \frac{\frac{3}{2} A + 1}{\mu_t'} \right)^2 + d^2}$$ \hspace{1cm} (12.2)
Here $\mu_{\text{eff}}$ is the effective attenuation coefficient ($\mu_{\text{eff}} = \sqrt[3]{\mu_a \mu_s}$), $\mu_t'$ is the total transport coefficient ($\mu_t' = \mu_a + \mu_s'$) and $A$ is the internal reflection parameter [126] that takes into account the refractive index mismatch at the air-tissue interface.

The common approach to find $\mu_a$ and $\mu_s'$ is to fit the analytic solution (Eq. 12.1) to the measured values of $R(d)$, which makes use of the linear correlation between $R(d)$ and $d$. In other words, a plot of $\log(d^2R(d))$ versus $d$ can be used to estimate $\mu_{\text{eff}}$. To separate $\mu_a$ and $\mu_s'$, Patterson et al. [127] used the absolute overall diffuse reflectance over the entire surface, whereas Farrell et al. [125] exploited the reflectance at small $d$ to obtain $\mu_s'$, while Liu et al. [128] used the intercept of $d^2R(d)$ versus $d$ to estimate $\mu_s'$, and Matcher et al. [129] simply use time-resolved techniques to assume $\mu_s'$. Once $\mu_a$ and $\mu_s'$ are obtained at multiple wavelengths, the results are then combined to obtain the chromophore concentrations (e.g. [HbO$_2$] and [Hb]). Clinical applications of this technique can be found in literature [130-134].

Although the slope-based approach is widely used, it is highly sensitive to noise. Small errors in the measurement can lead to a large error in the slope obtained through a least squares fitting procedure. To reduce this error, one can increase the number of data points by increasing the number of detectors, which in turn leads to an increase in the size of a probe, a solution that is not preferred in the design of hand-held probes. To overcome the difficulties with the slope-based approach, we employ a multispectral evolutionary algorithm that uses data from all wavelengths simultaneously to estimate the optical properties.

Evolution algorithms imitate the principles of evolution and heredity in nature for inverse problems in engineering applications. The general structure of the algorithm involves a
population of individuals \( P_k = (x_1, ..., x_n)_k \) that can recombine and mutate to create offspring. On each iteration, the offspring is evaluated against an objective function only a subset of the offspring is selected as the population for the next iteration \( P_{k+1} = (x_1, ..., x_n)_{k+1} \). Once the objective function has reached an acceptably small value, that offspring is identified as the solution to the problem.

### 12.4 Phantom Measurements

Experimental studies on an optical phantom were performed to validate the handheld probe. Using a liquid phantom we explored the relationship between the expected value of absorption and scattering and our reconstructed value. To reconstruct the absolute values of absorption and scattering parameters in the medium, we normalized the target measurement data to a reference medium with known optical properties. Measurements were made at the surface of an 8 cm × 8 cm × 8 cm box filled with 500 ml of 30 different solutions. Each solution consisted of an aqueous mixture made up of Intralipid (Baxter Intralipid 20% Fat Emulsion), black ink (Higgins India Ink), and near-infrared dye (Epolight 2735, Epolin Inc.). We chose Intralipid for its well-documented optical properties and prior use in phantom studies to mimic tissue optical properties [135, 136]. Likewise, black India ink is commonly used in optical phantoms and is a water-soluble absorber that has a flat absorption spectrum in our wavelength range. Epolight 2375 is a water-soluble near-infrared dye that has peak absorption at 970 nm, and therefore displays a different spectral response from India ink in the near-infrared range. The ranges for \( \mu_a \) and \( \mu_s' \) were selected based on the typical optical properties of breast tissue [21].
In the first experiment we used a reference solution of 3.2% by volume (32 ml/l) of Intralipid 20% with no added ink. This provides a medium where the absorption is predominantly due to water, which results in higher absorption at higher wavelengths (expected $\mu_a$: 0.023, 0.019, 0.042, 0.068 cm$^{-1}$ @ 780, 808, 850, 904) [17]. The scattering in the medium is due to the Intralipid scattering and decreases at higher wavelengths (expected $\mu_s'$: 6.74, 6.48, 6.12, 5.70 cm$^{-1}$ @ 780, 808, 850, 904 nm) [135, 136]. We increased the reduced scattering coefficient by increasing the concentration of Intralipid from 3.4% (34 ml/l) to 5.2% (52 ml/l) in increments of 0.2% (2 ml/l) resulting in a $\mu_s'$ ranging from ~6-10 cm$^{-1}$. Note that an increase in the Intralipid concentration does not change the absorption of the solution. In Fig. 12-5a we show both the theoretical (solid and dashed lines) and the experimentally-derived values for $\mu_a$ for varying concentrations of Intralipid. As expected, $\mu_a$ shows no dependence on the Intralipid concentration and the calculated values for absorption closely match the expected values for water absorption. Conversely, Fig. 12-5b shows that $\mu_s'$ increases linearly with the increasing Intralipid concentration due to the increased concentration of scatterers. Our setup tends to underestimate the reduced scattering and has an average relative error of 6%.
Figure 12-5. Phantom experiment using the wireless probe to measure increasing absorption and scattering.

Reconstructed values of (a) $\mu_a$ and (b) $\mu'_a$ for linearly increasing amounts of Intralipid added to the phantom; and reconstructed values of (c) $\mu_a$ and (b) $\mu'_a$ for linearly increasing amounts of Ink added to the phantom.

For the second experiment we used a reference solution of 4.8% (48 ml/l) Intralipid and 0.024 ml/l of our ink dilution. In this case the absorption is due to both water and ink (expected $\mu_a$: 0.042, 0.038, 0.060, 0.086 cm$^{-1}$ @ 780, 808, 850, 904 nm) while scattering is due to Intralipid (expected $\mu'_s$: 9.84, 9.46, 8.93, 8.31 cm$^{-1}$ @ 780, 808, 850, 904 nm). We increased the absorption coefficient by increasing the ink concentration by 0.024 ml/l per step from 0.048 ml/l to 0.24 ml/l (resulting in an increase in $\mu'_a$ of $\sim$0.0192 cm$^{-1}$ per step). Note that increasing
the ink concentration does not significantly affect the scattering properties of the medium. The results are shown in Fig. 12-5c/d where the theoretical values of absorption and scattering are shown by the solid and dashed lines and the experimentally derived values are shown by the markers. In Fig. 12-5c, $\mu_o$ shows a linear relationship to the ink concentration with an average relative error of 3%. The increased ink concentration does not affect the scattering of the solution, as reflected by Fig. 12-4d, where $\mu_s'$ is constant across the various concentrations of ink. Similar to the first experiment the scattering is underestimated by 7% on average, an effect that appears accentuated at the longer wavelengths. This may be due to the fact that, although black ink is commonly considered to be a perfect absorber, it may have a scattering component that can lead to an underestimation of scattering [137].

In order to explore the probe’s ability to accurately separate two chromophores (such as oxy- and deoxy-hemoglobin), we performed measurements on a series of liquid optical phantoms with varying amounts of ink (Black India Ink) and dye (Epolight 2735, 0.05 g in 50 ml deionized water). In each experiment, we used a low and high absorbing solution to calibrate the probe. In the first experiment, we measured a solution of 4% Intralipid (40 ml/l), 0.5 ml/l of dye, and 1.5 ml/l to 3.5 ml/l of ink in steps of 0.5 ml/l (Phantom 1 through 5). The expected and measured values of the ink and dye volumes are shown in Fig. 12-6a. In the second experiment, we measured a solution of 4% Intralipid (40 ml/l), 1 ml/l of a 1% ink dilution, and 1 ml/l to 3 ml/l of dye in steps of 0.5 ml/l (Phantom 6 through 10). The expected and measured values of the ink and dye volumes are shown in Fig. 12-6b. Note that increasing the ink or dye concentration does not affect the scattering properties of the medium. The expected and
measured values for the scattering parameter $A$ are shown for the increasing ink (Fig. 12-6c) and increasing dye (Fig. 12-6d) experiments. The results shown in Fig. 12-6 demonstrate that the probe can distinguish between two different optically absorbing chromophores. The small error in deriving the precise ink and dye volumes is due to the fact that the wavelengths used in the probe are optimized for differentiating oxy- and deoxyhemoglobin, not for differentiating the spectra of ink and dye.

Figure 12-6. Reconstructed volumes of ink (grey) and dye (black) in Intralipid solution for (a) linearly increasing amounts of ink and (b) linearly increasing amounts of dye. Also shown is the reconstructed scattering $A$ for each experiment (c/d). Dashed lines represent the actual values, while the markers indicated measured values.
12.5 Discussion

We have presented a new hand-held wireless device for diffuse optical tissue spectroscopy. The prototype was created for less than $400 and presents an inexpensive, portable, and user-friendly device for clinical optical measurements. The size of the device is currently suited for hand-held operation, but could be further scaled down in size by selecting smaller component footprints, a smaller battery, and denser board layout. Furthermore, while the device can image at 2.3 Hz, which is suitable for most dynamic imaging experiments, the speed could be increased by selecting a more powerful microcontroller and using simultaneous illumination by multiple wavelengths. Using four wavelengths and two detector positions we have demonstrated that we can accurately resolve absolute measurements of absorption and scattering using a multispectral evolutionary reconstruction algorithm.

This device will facilitate future clinical studies exploring the optical signatures of tumor regions in the breast, but is not limited to breast imaging. Indeed, this device provides a fast and easy way to make static and dynamic measurements on many other tissues, including, for example, brain or limbs, without the need for specific interfaces for each application. The ease of use, portability, and low cost of this device will complement many existing clinical optical studies by providing real-time measurements, and will create opportunities for new clinical applications.
Chapter 13: Summary and Future Work

13.1 Summary

This thesis focuses on the development of a new optical tomography system for dynamic and static imaging of breast cancer. The system uses digital detection techniques combined with a master-slave digital-signal-processor (DSP) architecture. The digital demodulation and timing control of the system enable frame rates of 1.7 – 111 Hz. The ability to store a unique gain bit setting for each source-detector pair provides a large dynamic range (160 dB) that is important for imaging the breast. The instrument has 32 sources and 64 detectors per breast, and can image at four wavelengths (765, 808, 827, and 905 nm). Two fiber-breast interfaces were used for clinical studies: an articulating-finger breast interface for dynamic imaging and a translating ring breast interface for longitudinal studies for absolute measurements.

The contrast derived from the difference in optical absorption and scattering by various tissue chromophores (namely oxygenated and deoxygenated hemoglobin) can be used to create three-dimensional maps that provide insight into the physiology of the tissue. In cancer, the increased vasculature that forms around a growing tumor can be used to identify suspicious tissue. In addition, tumor vasculature is poorly formed, shunted, and dilated, features that cause a tumor tissue to respond differently to a stimulus. We conducted two clinical studies and one pre-clinical study exploiting this biological source of optical contrast.

In a study of 21 subjects, we explored dynamic features that can be used to identify breast masses during the hemodynamic response of the breast to a breath hold. Specifically, there is poor correlation in the transient response between the left and right breast in subjects...
with breast cancer. In addition, during the recovery period from the breath hold, the tumor can be visualized by an increased presence of deoxygenated hemoglobin. Exponential fitting of the transient response suggests that the source of this contrast in the recovery period comes from the slower washout rate of deoxygenated hemoglobin from the tumor region. This slow washout rate is due to the disorganized tumor vasculature.

In a pre-clinical study involving 22 mice we used DOT to differentiate between responsive tumors and non-responsive tumors within 5 days of anti-angiogenic drug treatment. A significant decrease in total hemoglobin was observed in the responsive, treated mice as early as one day after treatment, while untreated, and treated non-responsive mice showed an increase in total hemoglobin over the 5 days. These changes in total hemoglobin correlated with changes in microvessel density (observed by lectin perfusion imaging) and relative blood volume (observed by MRI T2 relaxometry).

Based on the results of the pre-clinical therapy-monitoring study, as well as the growing need for a technique to improve the effectiveness of neoadjuvant chemotherapy in breast cancer, we designed a clinical study using DOT to predict individual patient response to neoadjuvant breast cancer therapy. Case studies of two breast cancer patients suggest that DOT can predict the patient’s response to therapy as early as two weeks after beginning treatment. In both cases, a strong reduction in absorption due to decreased vasculature in the tumor region is observed as early as 2 weeks after commencing treatment, representing the early anti-angiogenic effects of the chemotherapy agents. Strong reductions in scattering were
also observed, reflecting changes in tumor cellularity. These preliminary results will be further explored in an ongoing study of 20 patients undergoing NACT.

The clinical use of the digital optical breast imaging system led to the design of a complementary handheld probe for fast, simple, local optical measurements. This compact wireless probe can make dynamic measurements at 2.4 Hz or static measurements. Its design requires contact with a 4 cm section of tissue, removing the need for a complex fiber-breast interface and enabling a large variety of clinical studies. Phantom experiments with the device show that it can resolve optical properties of absorption and scattering with good accuracy.

Overall, this thesis has focused on the design and clinical translation of new digital instrumentation for optical tomography. We have seen promising results in studies using the device for breast cancer detection and therapy monitoring. It is our hope that these results provide the basis for further studies refining the techniques and clinical use of DOT for improvements in breast cancer management.

13.2 Future Work

Instrumentation

The digital optical tomography system has been in clinical use at the Herbert Irving Comprehensive Cancer Center (HICCC) for 3 years. Over the past six months, staff at the HICCC have been trained and are now proficient at operating the system. Training clinicians to operate the system opens up a larger range of clinical studies and use of the device. This process can be further facilitated in the future by improving the software user interface to simplify the use of the device in a clinical setting.
Chapter 8 described two fiber-breast interfaces with different approaches for making contact with the breast. Further improvement to these interfaces can significantly improve the quality of the DOT images by providing better breast-fiber contact over the entire breast volume for patients of all breast sizes and body types. Software-controlled positioning of the interface would be an ideal extension of the existing system, with motors to control the precise positioning of the interface. The importance and difficulty of designing clinically implementable fiber-breast interfaces across a broad range of patient sizes should not be underestimated in future DOT breast imaging studies.

From a technical standpoint, there are a few enhancements to the system that could improve its clinical use and operation. These improvements are outlined in detail in Section 9.10.

*Dynamic Breast Imaging*

There are many other aspects of breast cancer management in which DOT may be able to improve patient outcomes. The study described in Chapter 9 showed that dynamic DOT can be used to visualize breast tumors. In addition, it also showed promising trends in using dynamic signatures of tumors to differentiate benign from malignant pathologies. While a more controlled, larger, prospective study would be required to fully investigate these trends, DOT may have a complementary role to mammography as a secondary screening tool. It is also possible that dynamic DOT may provide information about the tumor vasculature which could be used to predict how the tumor will respond to therapy.
Dynamic contrast mechanisms can provide additional information about tumor vascularity. However, in many cases, the biological mechanism causing the optical contrast is not clear. Preliminary attempts to understand the source of contrast during a breath hold have been performed by creating a 3-compartment Windkessel vascular model, as described in Appendix N. This model can be further enhanced to validate and complement the experimental results of dynamic imaging.

**DOT Monitoring of Neoadjuvant Chemotherapy**

There is a significant need in the neoadjuvant chemotherapy setting to find new ways to predict and monitor response to therapy. DOT is perfectly suited to this application, as it is fast, non-ionizing, and sensitive to the early changes in the tumor physiology. The study described here showed promising results in two case studies, where the tumor response could be visualized by decreases in hemoglobin and scattering within two weeks. This study is ongoing and will hopefully provide the basis for a number of other investigations into the use of DOT in optimizing treatment schedules and therapy selection with the goal of improving patient outcomes.

In addition to the longer NACT study described here, there are a number of 2-week studies that explore the short term tumor response to treatment prior to surgery. DOT imaging of these studies would provide a quantitative *in vivo* assessment of the tumor response. These studies not only generate additional clinical information to guide patient care, but also provide an opportunity to explore the effects of new therapies in vivo. The shorter timeframe allows
for more rapid results and could provide an ideal setting for testing new DOT instrumentation and protocols.

**DOT in Pre-Clinical Applications**

While clinical translation of this tool is one of the more exciting aspects of this work, the value of DOT in pre-clinical studies should not be ignored. In fact, the ability to conduct small-animal studies to complement and parallel the clinical therapy monitoring studies is a strong benefit of optical imaging. Pre-clinical studies can also allow for the refinement of the imaging techniques, including the imaging protocols, optical references, and reconstruction algorithms. Pre-clinical studies benefit not only from a well-controlled setting, but also from a wide range of well-characterized tumor models and treatments.

In our study of bevacizumab-treated renal tumors we observed an overall decrease in total hemoglobin over the 5 days. However, individual mice showed varying rebound effects which may reflect vascular normalization in response to treatment. Tumors are known to find alternate pathways in response to anti-angiogenic treatment in order to continue vascular development. DOT would enable further exploration of these effects, especially in studies looking at combinations of anti-angiogenic treatments.

**Wireless Handheld Probe**

Optical imaging is an inexpensive, non-ionizing, compact technology that can provide physiologically-relevant information about tissue at the point of care. Designing portable, widely useable technologies such as the wireless handheld imaging probe described in Chapter 12 will allow for optical imaging to be translated into any number of clinical applications. The
work here focused on the design of the handheld probe for breast imaging, but the probe is not limited to breast tissue. There is interest in also applying the use of this probe to skin imaging, particularly in observing the behavior of pediatric hemangiomas. Although the technology and acquired data is significantly simplified from the DOT instrumentation described in Chapters 2 through 9, the handheld probe complements more sophisticated DOT imaging studies and opens up a wide range of new applications.

13.2 Conclusions

Over the past 15 years the field of diffuse optical tomography has progressed from theoretical applications to bench top demonstrations and, more recently, into the clinic. With increasing interest in using safe, lower-cost imaging techniques, DOT continues to find clinical applications where its sensitivity to tissue physiology makes it a valuable medical tool. DOT can provide physiologically-relevant information for detecting, characterizing, and monitoring tumors in both clinical and pre-clinical settings. In particular, optical imaging shows particular promise in breast cancer applications. The role of optical imaging in breast cancer management will be better understood in coming years by the research community through studies ranging from preliminary case studies to recently-initiated multi-center prospective clinical trials.
References


# APPENDIX A – DDS BOARD BOM, SCHEMATIC, AND BOARD LAYOUT

## A1. Bill of Materials

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<td>SMT 0805</td>
<td>1/8 W, 1%</td>
<td>Yageo: 9C08052A1743FKHFT</td>
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<tr>
<td>36</td>
<td>2</td>
<td>R29, R47</td>
<td>165k</td>
<td>SMT 0805</td>
<td>1/8 W, 1%</td>
<td>Yageo: 9C08052A1653FKHFT</td>
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<tr>
<td>37</td>
<td>2</td>
<td>R32, R50</td>
<td>10k Potentiometer</td>
<td>Thru-Hole</td>
<td>3/8&quot; SQ CERM SL MT</td>
<td>Bourns: 3299W-1-103</td>
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<tr>
<td>38</td>
<td>1</td>
<td>R31</td>
<td>2.0k</td>
<td>SMT-1206</td>
<td>1/4W 5%</td>
<td>Yageo: 9C12063A2001JLHFT</td>
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<tr>
<td>39</td>
<td>2</td>
<td>R33, R51</td>
<td>1.78k</td>
<td>SMT-1206</td>
<td>1/4W 1%</td>
<td>Yageo: 9C12063A1781FKHFT</td>
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<tr>
<td>40</td>
<td>2</td>
<td>R34, R52</td>
<td>49.9 Ohm</td>
<td>SMT-1206</td>
<td>1/4W 1%</td>
<td>Yageo: 9C12063A4990FKHFT</td>
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<tr>
<td>41</td>
<td>2</td>
<td>R49, R53</td>
<td>0.0 Ohm</td>
<td>SMT-1206</td>
<td>1/4W 5%</td>
<td>Yageo: 9C12063A0R00JLHFT</td>
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<tr>
<td>42</td>
<td>2</td>
<td>U1, U2</td>
<td>DDS</td>
<td>TQFP-80</td>
<td>DDS CMOS 80-LQFP</td>
<td>Analog Devices: AD9854AST</td>
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<td>43</td>
<td>2</td>
<td>U8, U9</td>
<td>SOT-223</td>
<td>2.0 Amps</td>
<td>Analog Dev: ADP3338AKCZ-3.3</td>
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<td>44</td>
<td>1</td>
<td>U6</td>
<td>SOT23-3</td>
<td>200 mA, Low Dropout</td>
<td>Linear Technology: LT1964ESS-5</td>
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<tr>
<td>45</td>
<td>1</td>
<td>U3</td>
<td>8SOIC</td>
<td>IC RECEIVER ECL DIFF 3.3V</td>
<td>ON: MC100LVEL16DG</td>
<td></td>
</tr>
</tbody>
</table>
A2. Schematic
A3. Board Layout
APPENDIX B – INPUT UNIT MICROCONTROLLER CODE

// ddsdriver.C

#include <REG52.H> /* special function register declarations for the intended 8051 derivative */
#include <intrins.h> /* call to invoke _nop_() (one cpu circle, 100ns) for time delay*/

sbit WR1 = P1^0;
sbit UDCLK1 = P1^2;
sbit WR2 = P1^1;
sbit UDCLK2 = P1^3;
sbit WR3 = P1^4;
sbit UDCLK3 = P1^6;
sbit WR4 = P1^5;
sbit UDCLK4 = P1^7;
sbit RST = P3^7;
int i;

void main (void) // The main C function. Program execution starts here after stack initialization.
{
    // time delay
    for (i = 0; i < 1000; i++) delay _nop_();

    // Initializing four DDS
    UDCLK1 = 1;
    UDCLK2 = 1;
    UDCLK3 = 1;
    UDCLK4 = 1;

    WR1 = 1;
    WR2 = 1;
    WR3 = 1;
    WR4 = 1;

    // Resetting four DDS
    RST = 0;
    for (i = 0; i < 1000; i++) delay _nop_();
    RST = 1;
    for (i = 0; i < 1000; i++) delay _nop_();
    RST = 0;
    for (i = 0; i < 10000; i++) delay _nop_(); // _nop_() is used to guarantee that the timing requirement of the DDS is met.

    // Choosing the operation mode and the source of update clock
    _nop_(); _nop_(); _nop_(); _nop_(); _nop_();
    P3 = 0x1f; // Address for corresponding register
    P2 = 0x00; // Single tone and external update clock

    _nop_(); _nop_(); _nop_(); _nop_(); _nop_();
    WR1 = 0; // Writing I/O buffer
    WR2 = 0;
    WR3 = 0;
    WR4 = 0;

    _nop_(); _nop_(); _nop_(); _nop_(); _nop_();
    WR1 = 1;
WR2 = 1;
WR3 = 1;
WR4 = 1;

// Bypassing inverse sinc function
_nop_();_nop_();_nop_();_nop_();
P3 = 0x20; // Address for corresponding register
P2 = 0x40;

_nop_();_nop_();_nop_();_nop_();_nop_();
WR1 = 0; // Writing I/O buffer
WR2 = 0;
WR3 = 0;
WR4 = 0;

_nop_();_nop_();_nop_();_nop_();_nop_();
WR1 = 1;
WR2 = 1;
WR3 = 1;
WR4 = 1;

// Setting up the frequency tuning words 5000hz->20c49ba5e3 for DDS I
_nop_();_nop_();_nop_();_nop_();_nop_();
P3 = 0x09; // Address for corresponding register
P2 = 0xe3;

_nop_();_nop_();_nop_();_nop_();_nop_();
WR1 = 0; // Writing I/O buffer
_nop_();_nop_();_nop_();_nop_();_nop_();
WR1 = 1;

_nop_();_nop_();_nop_();_nop_();_nop_();
P3 = 0x08; // Address for corresponding register
P2 = 0xa5;

_nop_();_nop_();_nop_();_nop_();_nop_();
WR1 = 0; // Writing I/O buffer
_nop_();_nop_();_nop_();_nop_();_nop_();
WR1 = 1;

_nop_();_nop_();_nop_();_nop_();_nop_();
P3 = 0x07; // Address for corresponding register
P2 = 0x9b;

_nop_();_nop_();_nop_();_nop_();_nop_();
WR1 = 0; // Writing I/O buffer
_nop_();_nop_();_nop_();_nop_();_nop_();
WR1 = 1;

_nop_();_nop_();_nop_();_nop_();_nop_();
P3 = 0x06; // Address for corresponding register
P2 = 0xc4;

_nop_();_nop_();_nop_();_nop_();_nop_();
WR1 = 0; // Writing I/O buffer
_nop_();_nop_();_nop_();_nop_();_nop_();
WR1 = 1;

_nop_();_nop_();_nop_();_nop_();_nop_();
P3 = 0x05; // Address for corresponding register
P2 = 0x20;

_nop_();_nop_();_nop_();_nop_();_nop_();
WR1 = 0; // Writing I/O buffer
WR1 = 1; // Setting up the frequency tuning words 7000hz->2de00d1b71 for DDS II
P3 = 0x09; // Address for corresponding register
P2 = 0x71;

WR2 = 0; // Writing I/O buffer
WR2 = 1;

P3 = 0x08; // Address for corresponding register
P2 = 0x1b;

WR2 = 0; // Writing I/O buffer
WR2 = 1;

P3 = 0x07; // Address for corresponding register
P2 = 0x0d;

WR2 = 0; // Writing I/O buffer
WR2 = 1;

P3 = 0x06; // Address for corresponding register
P2 = 0xe0;

WR2 = 0; // Writing I/O buffer
WR2 = 1;

P3 = 0x05; // Address for corresponding register
P2 = 0x2d;

WR2 = 0; // Writing I/O buffer
WR2 = 1;

// Setting up the frequency tuning words 5000hz->20c49ba5e3 for DDS III
P3 = 0x08; // Address for corresponding register
P2 = 0xe0;

WR3 = 0; // Writing I/O buffer
WR3 = 1;

P3 = 0x0b; // Address for corresponding register
P2 = 0xa5;
WR3 = 0; // Writing I/O buffer
_nop_();_nop_();_nop_();_nop_();_nop_();
WR3 = 1;

_nop_();_nop_();_nop_();_nop_();_nop_();
P3 = 0x07; // Address for corresponding register
P2 = 0x9b;

_nop_();_nop_();_nop_();_nop_();_nop_();
WR3 = 0; // Writing I/O buffer
_nop_();_nop_();_nop_();_nop_();_nop_();
WR3 = 1;

_nop_();_nop_();_nop_();_nop_();_nop_();
P3 = 0x06; // Address for corresponding register
P2 = 0xc4;

_nop_();_nop_();_nop_();_nop_();_nop_();
WR3 = 0; // Writing I/O buffer
_nop_();_nop_();_nop_();_nop_();_nop_();
WR3 = 1;

_nop_();_nop_();_nop_();_nop_();_nop_();
P3 = 0x05; // Address for corresponding register
P2 = 0x20;

_nop_();_nop_();_nop_();_nop_();_nop_();
WR3 = 0; // Writing I/O buffer
_nop_();_nop_();_nop_();_nop_();_nop_();
WR3 = 1;

// Setting up the frequency tuning words 7000hz->2de00d1b71 for DDS IV
_nop_();_nop_();_nop_();_nop_();_nop_();
P3 = 0x09; // Address for corresponding register
P2 = 0x71;

_nop_();_nop_();_nop_();_nop_();_nop_();
WR4 = 0; // Writing I/O buffer
_nop_();_nop_();_nop_();_nop_();_nop_();
WR4 = 1;

_nop_();_nop_();_nop_();_nop_();_nop_();
P3 = 0x08; // Address for corresponding register
P2 = 0x1b;

_nop_();_nop_();_nop_();_nop_();_nop_();
WR4 = 0; // Writing I/O buffer
_nop_();_nop_();_nop_();_nop_();_nop_();
WR4 = 1;

_nop_();_nop_();_nop_();_nop_();_nop_();
P3 = 0x07; // Address for corresponding register
P2 = 0x0d;

_nop_();_nop_();_nop_();_nop_();_nop_();
WR4 = 0; // Writing I/O buffer
_nop_();_nop_();_nop_();_nop_();_nop_();
WR4 = 1;

_nop_();_nop_();_nop_();_nop_();_nop_();
P3 = 0x06; // Address for corresponding register
P2 = 0xe0;

_nop_();_nop_();_nop_();_nop_();_nop_();
WR4 = 0; // Writing I/O buffer
_nop_();_nop_();_nop_();_nop_();_nop_();
WR4 = 1;

_nop_();_nop_();_nop_();_nop_();_nop_();
P3 = 0x05; // Address for corresponding register
P2 = 0x2d;

_nop_();_nop_();_nop_();_nop_();_nop_();
WR4 = 0; // Writing I/O buffer
_nop_();_nop_();_nop_();_nop_();_nop_();
WR4 = 1;

// Update the four DDS
for (i = 0;i < 1000;i++) // Time delay
    _nop_();
UDCLK1 = 0;
UDCLK2 = 0;
UDCLK3 = 0;
UDCLK4 = 0;

for (i = 0;i < 1000;i++) // Time delay
    _nop_();
UDCLK1 = 1; // Externally updating both DDS
UDCLK2 = 1;
UDCLK3 = 1;
UDCLK4 = 1;

for (i = 0;i < 1000;i++) // Time delay
    _nop_();
UDCLK1 = 0;
UDCLK2 = 0;
UDCLK3 = 0;
UDCLK4 = 0;

while(1);
## APPENDIX C – INPUT UNIT BACKPLANE BOM, SCHEMATIC, AND BOARD LAYOUT

### C1. Bill of Materials

<table>
<thead>
<tr>
<th>Item</th>
<th>Ref</th>
<th>Part Desc.</th>
<th>Package</th>
<th>Specification</th>
<th>Manufacturer/Source: PN</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>R7, R8</td>
<td>0 Ohm</td>
<td>SMT-1206</td>
<td>Thick film, 1/4W 5%</td>
<td>Yageo: 9C12063A0R00JLHFT</td>
</tr>
<tr>
<td>2</td>
<td>R2</td>
<td>33 Ohm</td>
<td>SMT-1206</td>
<td>Thick film, 1/4W 1%</td>
<td>Yageo: RC1206FR-0733RL</td>
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<tr>
<td>3</td>
<td>R5, R6</td>
<td>50 Ohm</td>
<td>SMT-1206</td>
<td>Thick film, 1/4W 1%</td>
<td>Yageo: RC1206FR-0749R9L</td>
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<tr>
<td>4</td>
<td>R1, R3</td>
<td>10k</td>
<td>SMT-1206</td>
<td>Thick film, 1/4W 1%</td>
<td>Yageo: 9C12063A1002FKHFT</td>
</tr>
<tr>
<td>5</td>
<td>R4</td>
<td>2k</td>
<td>SMT-1206</td>
<td>Thick film, 1/4W 5%</td>
<td>Yageo: 9C12063A2001JLHFT</td>
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<tr>
<td>6</td>
<td>C1, C3, C6, C8, C9, C12, C13, C14, C16</td>
<td>0.01uF</td>
<td>SMT-0805</td>
<td>CERAMIC 10% 50V X7R</td>
<td>AVX: 0805SC103KAT2A</td>
</tr>
<tr>
<td>7</td>
<td>C15</td>
<td>0.047uF</td>
<td>SMT-0805</td>
<td>CERM .047UF 10% 50V X7R</td>
<td>AVX: 0805SC473KAT2A</td>
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<td>8</td>
<td>C2, C4, C11, C18, C19, C24</td>
<td>0.1uF</td>
<td>SMT-0805</td>
<td>CERM, 10%, 50V X7R</td>
<td>Kemet: C0805C104K5RACTU</td>
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<td>9</td>
<td>C5, C7, C10, C17, C20, C21, C25</td>
<td>10uF</td>
<td>EIA-3216</td>
<td>Tantalum, 10V 10%</td>
<td>AVX: TAJA106K010R</td>
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<tr>
<td>10</td>
<td>C22, C23</td>
<td>250uF</td>
<td>Radial FC</td>
<td>CERAMIC POL, 25V</td>
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<tr>
<td>11</td>
<td>IC6</td>
<td>SOL-14</td>
<td>Schmitt Trigger Hex, Inverter</td>
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<tr>
<td>12</td>
<td>IC2</td>
<td>SOL-14</td>
<td>Quad, And gate</td>
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<td>13</td>
<td>IC1</td>
<td>QSOP-16</td>
<td>2:1 Mux</td>
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<td>14</td>
<td>IC4</td>
<td>PLCC44</td>
<td>Microcontroller</td>
<td>Atmel: AT89S8252</td>
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<td>15</td>
<td>U8</td>
<td>SOT-223</td>
<td>3.3V 2A Power Regulator</td>
<td>Analog Dev: ADP3338AKCZ-3.3</td>
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<td>IC5</td>
<td>TO-220</td>
<td>LDO REG FIXED 5V 1.5A</td>
<td>Linear Technology: LT1086CT-5</td>
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<td>17</td>
<td>U$57</td>
<td>DIL08-4</td>
<td>10 MHz Crystal Oscillator CMOS PROG 3.3V 0E</td>
<td>Epson: SG-8002DC-MPT</td>
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<td>18</td>
<td>JP1</td>
<td>DIL-3</td>
<td>CONN HEADER VERT 3POS .100 TIN</td>
<td>AMP/Tyco: 640452-3</td>
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<tr>
<td>19</td>
<td>SW1</td>
<td>Gull-Wing</td>
<td>SPST Switch TACT MOM SLD G-WING SMD</td>
<td>C&amp;K: KT11P2SM</td>
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<td>20</td>
<td>IC5</td>
<td>TO-220</td>
<td>LDO REG FIXED 5V 1.5A</td>
<td>Linear Technology: LT1086CT-5</td>
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<tr>
<td>21</td>
<td>U1</td>
<td>SOIC-8</td>
<td>IC RECEIVER ECL DIFF 3.3V 8SOIC</td>
<td>ON Semi: MC100LVE16D</td>
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<tr>
<td>22</td>
<td>Switch Connector</td>
<td>DIL-3</td>
<td>CONN HEADER VERT 3POS .100 TIN</td>
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<td></td>
</tr>
<tr>
<td>23</td>
<td>L1, L2</td>
<td>SMD</td>
<td>Wide Band Choke</td>
<td>Sample</td>
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C2. Schematic
C3. Board Layout
APPENDIX D – LASER DIODE SPECIFICATIONS

D1. Laser Diode Drawing
D2. Laser Diode Specifications

<table>
<thead>
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<th>Device Type: HPD1005-HHLF-TEC-FAC</th>
<th>Customer: SUNY</th>
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<tbody>
<tr>
<td>Serial Number: 3</td>
<td>Temp: 25</td>
</tr>
</tbody>
</table>

- **I<sub>max</sub>**: 0.90 Amps
- **P<sub>max</sub>**: 0.35 Watts
- **V<sub>max</sub>**: 1.99 Volts
- **I<sub>th</sub>**: 0.20 Amps
- **SE**: 0.53 W/A
- **V<sub>f</sub>**: 1.66 Volts
- **R<sub>S</sub>**: 369.95 mOhms
- **R**: 332.00 uAAW

**Wavelength**: 764.9 nm

**FWHM**: 0.4 nm

<table>
<thead>
<tr>
<th>CURRENT (A)</th>
<th>VOLTAGE (V)</th>
<th>POWER (W)</th>
<th>DETECTOR (uA)</th>
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</thead>
<tbody>
<tr>
<td>0.000</td>
<td>1.479</td>
<td>0.000</td>
<td>0.0</td>
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<tr>
<td>0.050</td>
<td>1.511</td>
<td>0.000</td>
<td>0.0</td>
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<td>0.100</td>
<td>1.658</td>
<td>0.000</td>
<td>0.0</td>
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<tr>
<td>0.150</td>
<td>1.793</td>
<td>0.000</td>
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<td>0.200</td>
<td>1.746</td>
<td>0.019</td>
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<td>0.250</td>
<td>1.767</td>
<td>0.047</td>
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<td>0.300</td>
<td>1.787</td>
<td>0.074</td>
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<td>0.350</td>
<td>1.807</td>
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<td>1.826</td>
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<td>0.450</td>
<td>1.846</td>
<td>0.159</td>
<td>47.0</td>
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<tr>
<td>0.500</td>
<td>1.865</td>
<td>0.189</td>
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<td>0.600</td>
<td>1.883</td>
<td>0.213</td>
<td>61.7</td>
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<td>0.650</td>
<td>1.902</td>
<td>0.239</td>
<td>71.2</td>
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<td>0.700</td>
<td>1.920</td>
<td>0.265</td>
<td>79.7</td>
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<tr>
<td>0.750</td>
<td>1.938</td>
<td>0.289</td>
<td>88.3</td>
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<tr>
<td>0.800</td>
<td>1.956</td>
<td>0.311</td>
<td>97.7</td>
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<tr>
<td>0.850</td>
<td>1.973</td>
<td>0.330</td>
<td>106.1</td>
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<tr>
<td>0.900</td>
<td>1.990</td>
<td>0.352</td>
<td>117.0</td>
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**Notes:**

**Graphs:**
- Voltage (V) vs. Current (A)
- Power (W) vs. Voltage (V)
- Intensity vs. Wavelength (nm)
### Device Information

<table>
<thead>
<tr>
<th>Device Type:</th>
<th>HPO1005-HHLF-TEC-FAC</th>
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<tbody>
<tr>
<td>Device Number:</td>
<td>18432-4</td>
</tr>
<tr>
<td>Serial Number:</td>
<td>4</td>
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<table>
<thead>
<tr>
<th>Parameters</th>
<th>Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>I max</td>
<td>0.66 Amps</td>
</tr>
<tr>
<td>P max</td>
<td>0.37 Watts</td>
</tr>
<tr>
<td>V max</td>
<td>1.77 Volts</td>
</tr>
<tr>
<td>Ith</td>
<td>0.19 Amps</td>
</tr>
<tr>
<td>SE</td>
<td>0.81 W/A</td>
</tr>
<tr>
<td>VT</td>
<td>1.57 Volts</td>
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<tr>
<td>RS</td>
<td>327.00 mOhms</td>
</tr>
<tr>
<td>R</td>
<td>165.47 uAW</td>
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### Wavelength and FWHM

- Wavelength: 808.5 nm
- FWHM: 0.5 nm

### Current-Voltage-Intensity Table

<table>
<thead>
<tr>
<th>CURRENT (A)</th>
<th>VOLTAGE (V)</th>
<th>POWER (W)</th>
<th>DETECTOR (uA)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.000</td>
<td>1.399</td>
<td>0.000</td>
<td>0.0</td>
</tr>
<tr>
<td>0.050</td>
<td>1.630</td>
<td>0.000</td>
<td>0.3</td>
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### Graphs

- **Top Graph**: (Power vs. Voltage and Current)
- **Bottom Graph**: (Intensity vs. Wavelength)
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**Notes:**

**Wavelength:** 826.5 nm

**FWHM:** 1.4 nm
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Notes:

- Wavelength: 904.8 nm
- FWHM: 0.3 nm
APPENDIX E – DETECTION UNIT TIA AND RC HIGH-PASS FREQUENCY RESPONSE

E1. TIA Frequency Response
E2. RC High-Pass Frequency Response
### Appenidex F – Detector Board BOM, Schematic, and Board Layout

#### F1. Detection BOM

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<th>Ref</th>
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<th>Package</th>
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<td>3.3V 1K X 9 ASYNCH FIFO</td>
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F2. Schematic
F3. Board Layout
APPENDIX G – DSP CODE

G1. Main.c

#include "def21161.h"
#include "Experiment_Parameters.h"
#include <processor_include.h> // for idle();
#include <signal.h>
#include <sysreg.h>

// global variables
int src = 0; // # of sources
int det = 0; // # of detectors
int wl_set = 0; // # of wavelength sets
int im_cnt = 0; // # of image count

double IDA[DETECTORS*SAMPLES/2] = {0}; // incoming ADC data for one source, 16 detectors, 150 samples(last det)
double IDB[DETECTORS*SAMPLES/2] = {0}; // incoming ADC data for one source, 16 detectors
double OUTPUT_W1[DETECTORS] = {0}; // demodulated date for wavelength 1
double OUTPUT_W2[DETECTORS] = {0}; // demodulated date for wavelength 2

// function declarations
void Initialize_DSP(void);
void Initialize_DMA(void);
void Turn_on_LED(void);
void getImage(void);
void get_PCins();
void irqINTR();
void ep0INTR();
void ep1INTR();
void sp0INTR();
void sp1INTR();
void tmINTR();

void main(void)
{
    im_cnt = 0;

    Initialize_DSP(); // initialize registers upon starting up
    Initialize_DMA(); // initialize DMA register

    #ifdef MASTER_DSP // MASTER code

    sysreg_bit_set(sysreg_IMASK, IRQ0i);

    interrupt(SIG_IRQ0,irqINTR);
    interrupt(SIG_EP0I,ep0INTR); // EXT.port buffer 0 interrupt
    interrupt(SIG_EP1I,ep1INTR); // EXT.port buffer 1 interrupt
    interrupt(SIG_SP0I,sp0INTR); // sport0 interrupt
    interrupt(SIG_SP1I,sp1INTR); // sport1 interrupt
    interrupt(SIG_TM0,tmINTR); // low priority timer interrupt

    Turn_on_LED();
    get_PCins();

    while(1) {
        idle (); // wait for /IRQ0 interrupt
    }
G2. Initialize_DSP.c

#include "Experiment_Parameters.h"
#include <def21161.h>
#include <sysreg.h>

void Initialize_DSP()
{
    #ifdef MASTER_DSP
        // configure flag lines direction
        *(volatile int *)IOFLAG = FLG5O | FLG9O; //select flag5,9 as output
        *(volatile int *)IOFLAG &= ~FLG5; // output low, default
        *(volatile int *)IOFLAG &= ~FLG9; // output low, default

        // Configure interrupt registers
        sysreg_bit_clr(sysreg_MODE1, IRPTEN); // disable global interrupt
        sysreg_bit_set(sysreg_MODE2, IRQOE); // set IRQ0 interrupts as edge-sensitive
    #endif

    sysreg_bit_clr(sysreg_MODE1, NESTM); // disable interrupt nesting

    // Configure serial port register
    *(volatile int *)DIV0 = 0; //clear serial port0 divisor register
    *(volatile int *)DIV1 = 0x0010007; //select the FS divisor for internal FS. the FS frequency under this
        //value is about 12. (see page 10-36)
    *(volatile int *)SPCTL0 = SLEN16 | CKRE | FSR | LAFS; // initialize SPORT0 register
        // enable 16 bit word length
        // use rising edge for sampling data,
        // require frame sync
        //late FS
    *(volatile int *)SPCTL1 = DDIR | SLEN32 | CKRE | FSR | LAFS | IFS; // enable transmit buffers (output port),
        // choose and late transmit frame sync.
        // use internal Frame sync
        // require frame sync
        // use rising edge for sampling data
        // enable 32 bit word length

    void Initialize_DMA()
    {
        // initialize external port 0 DMA
        *(volatile int *)DMAC10 = MASTER|MSWF|PMODE6|TRAN;
            // disable external handshake mode, enable master
            // mode (DSP is master),MSW first during packing, 8 bit external
            // to 32/64 bit internal packing,
            // transmit data from internal memory for the
            // DMA channel 10 external port FIFO buffer.

    void Initialize_DMA()
    {
        // initialize external port 1 DMA
    }
}

*(volatile int *)SYSCON |= HBW16; // set host bus width to 16 bit
*(volatile int *)DMAC11 = HSHAKE | MASTER | PMODE1; // enable handshake mode, enable master
// mode (DSP is master), LSW first during packing, 16 bit external
// to 32/64 bit internal packing,
// receive data from external memory for the
// DMA channel 10 external port FIFO buffer.
// initialize serial port 0 DMA
// initialize serial port 1 DMA

G3. myIRQ.c

#include "def21161.h"
#include <signal.h>
#include <processor_include.h>
#include <sysreg.h>

void get_PCins();

void irqINTR() // IRQ interrupt from PC
{
    get_PCins();
}

void ep0INTR() // External port 0 uploads demodulated imaging data to DAQ
{
    *(volatile int*)DMAC10 &= ~DEN; // disable EXT. port 0 DMA
}

void ep1INTR() // External port 1 downloads imaging parameter and gainbits from DAQ
{
    //
    sysreg_bit_clr(sysreg_IMASK, EP1I); // clear the DMA1 interrupt
    *(volatile int*)DMAC11 &= ~DEN; // disable EXT. port 1 DMA
}

void sp0INTR() // serial port 0 receives modulated imaging data
// DMA is automatically disabled
{
    sysreg_bit_clr(sysreg_IMASK, SP0I); // disable SPORT0 interrupt
    *(volatile int *)SPCTL0 &= ~SPEN_A; // disable serial port 0A
    *(volatile int *)SPCTL0 &= ~SPEN_B; // disable serial port 0B
    *(volatile int *)SPCTL0 &= ~SDEN_A; // disable serial port 0A DMA
    *(volatile int *)SPCTL0 &= ~SDEN_B; // disable serial port 0B DMA
}

void sp1INTR() // serial port 1 sends gainbit data to CPLD
// DMA is automatically disabled
{
    sysreg_bit_clr(sysreg_IMASK, SP1I); // disable SPORT1 interrupt
    *(volatile int *)SPCTL1 &= ~SPEN_A; // disable serial port 1A
    *(volatile int *)SPCTL1 &= ~SPEN_B; // disable serial port 1B
    *(volatile int *)SPCTL1 &= ~SDEN_A; // disable serial port 1A DMA
    *(volatile int *)SPCTL1 &= ~SDEN_B; // disable serial port 1B DMA
}

void tmINTR() // timer interrupt
{
    sysreg_bit_clr(sysreg_IRPTL, TMZHI | TMZLI);
sysreg_bit_clr(sysreg_IMASK, TMZHI);// disable timer interrupt with high priority
timer_off();// disable timer

G4. Pc_instruction.c

#include "def21161.h"
#include "Experiment_Parameters.h"

// function declarations
void Turn_off_LED(void);
void Turn_on_LED(void);
void getImpar(void);
void downGbit(void);
void getImage(void);

void get_PCins()
{
    Turn_off_LED();
    *(volatile int*)IRQ0I = 0;// disable IRQ0 interrupt
    while(1)
    {
        while(1);// hold until flag2=1
        {
            if ( poll_flag_in(DIO_PLD0,5) == 1 ) break;// CPLD sends out 1 while in standby
        }

        // if flag0=0 and flag1=0 then turn on LED and keep rolling
        if ( poll_flag_in(DIO_PC0,5) == 0 && poll_flag_in(DIO_PC1,5) == 0 )
        {
            Turn_on_LED();
            break;
        }

        // if flag0=1 and flag1=0 then get imaging parameters from PC
        if ( poll_flag_in(DIO_PC0,5) == 1 && poll_flag_in(DIO_PC1,5) == 0 ) getImpar();

        // if flag0=0 and flag1=1 then download gainbits from PC
        if ( poll_flag_in(DIO_PC0,5) == 0 && poll_flag_in(DIO_PC1,5) == 1 ) downGbit();

        // if flag1=1 and flag1=1 then take new image
        if ( poll_flag_in(DIO_PC0,5) == 1 && poll_flag_in(DIO_PC1,5) == 1 ) getImage();
    }
}

G5. LED.c

#include "def21161.h"
#include "Experiment_Parameters.h"

void Turn_on_LED(void)
{
    *(volatile int*)OFLAG |= FLG9; // output high;
}

void Turn_off_LED(void)
#include "def21161.h"
#include "Experiment_Parameters.h"
#include <processor_include.h>
#include <sysreg.h>

extern int src; // # of sources
extern int det; // # of detectors
extern int wl_set; // # of wavelength sets (0: 1 wl set, 1: 2 wl sets)

void getImpar(void)
{
    // Labview sends the source/detector information to the DSP
    // This subroutine sets up the data transfer between the PC and DSP using a small DMA sequence.

    *(volatile int*)IIEP1 = (int) (&src); // DMA Ch11 Index Register set to address of src
    *(volatile int*)IMEP1 = 0x1; // DMA Ch11 Modify Register = 1
    *(volatile int*)CEP1 = 0x1; // DMA Ch11 Count Register = 1
    *(volatile int*)GPEP1 = 0; // DMA Ch11 General Purpose Register = 0
    *(volatile int*)EIEP1 = 0x0C000000; // DMA Ch11 External Index Register = 0x0C000000
    *(volatile int*)EMEP1 = 0x1; // DMA Ch11 External Modify Register = 1
    *(volatile int*)ECEP1 = 0x2; // DMA CH11 External Count Register = 2
    *(volatile int*)CPEP1 = 0; // DMA CH11 Chain Pointer Register = 0 (no chaining)

    // sysreg_bit_set(sysreg_IMASK, EP1I); // enable DMA 11 interrupt
    *(volatile int*)DMAC11 |= DEN; // DEN=1 // Enable DMA channel 11

    while(1) {
        if(sysreg_bit_tst(sysreg_IRPTL, EP1I)) {
            sysreg_bit_clr(sysreg_IRPTL, EP1I);
            *(volatile int*)DMAC11 &= ~DEN; // this bit shows if the interrupt has fired
            break;
        }
    }

    // Splits the data word into variables src (16 LSB) and det (16 MSB)
    while(1) // Make sure that we're not requesting an IRQ anymore so that we can return to standby
    {
        if ( poll_flag_in(DIO_PC0, 5) == 0 ) break;
    }

    int temp;
    temp = src;
    src = src & 0x0000003F; // clear 16 MSB of src (plus additional 8MBS for now)

    // Extract the number wavelength sets embedded in the source number
    if((temp & 0x00000040) > 0) { wl_set = 2; }
    else { wl_set = 1; }

    det = temp >> 0x10; // right shit temp by 16 bits, set det to the 16 MSB of src
det = det & 0x000000FF; // clear 16 MSB of src (plus additional 8MBS for now)
extern int src; // # of sources  
extern int det; // # of detectors  
extern int wl_set; // # of wavelength sets  

void downGbit(void) // Ext. Port Buffer 1 DMA  
{  
    if ( poll_flag_in(DIO_PC1,5) == 0 )  
        return; // double-check  
    else  
    {  
        // compute the size of memory used for gain bits  
        int total_word32 = ceil(SOURCES * wl_set * det * GAINBITS / 32);  
        int count_size = det * GAINBITS / 32;  
        *(volatile int*)DMAC11 &= ~DEN;  

        // set up transfer channels over the external port  
        *(volatile int*)IEP1 = (int)(&GB); // DMA Ch11 Index Register set to address  
        *(volatile int*)CEP1 = total_word32*2; // DMA Ch11 Count Register = total_word32 * 2 for left and right  
        *(volatile int*)EPEP1 = 0; // DMA Ch11 General Purpose Register = 0  
        *(volatile int*)EIEP1 = 0x0C000000; // DMA Ch11 External Index Register = 0x0C000000  
        *(volatile int*)GPEP1 = 0; // DMA Ch11 General Purpose Register = 0  
        *(volatile int*)ECEP1 = 4 * total_word32; // DMA CH11 External Count Register = 2 x total_word32, because the buffer is 16 bits.  
        *(volatile int*)IMEP1 = 0x1; // DMA Ch11 Modify Register = 1  
        *(volatile int*)EP1I = 1; // enable DMA 11 interrupt  
        *(volatile int*)DMAC11 |= ~DEN; // Enable DMA channel 11 transfer of gain bits from Labview to DSP - also enable chaining  

        while(1) {  
            if(sysreg_bit_tst(sysreg_IRPTL, EP1I)) {  
                sysreg_bit_clr(sysreg_IRPTL, EP1I);  
                *(volatile int*)DMAC11 &= ~DEN;  
                break; // this bit shows if the interrupt has fired  
            }  
        }  

        // Make sure to disable any dma on the sport1 channel so that we can  
        // first put the cpld into gb and send the # of sources  
        *(volatile int*)SPCTL1 &= (~SDEN_A & ~SDEN_B & ~SENDN & ~SPEN_B & ~SPEN_A);  

        // configure the DMA for serial port 1A  
        *(volatile int*)II1A = (int)GB;  
        *(volatile int*)GP1A = 0; // DMA General purpose register = 0  
        *(volatile int*)CP1A = 0; // DMA chain pointer register=0  
        *(volatile int*)IM1A = 0x1; // DMA internal modify register=1  
        *(volatile int*)CI1A = total_word32; // DMA internal counter register  

        // configure the DMA for serial port 1B  
        *(volatile int*)II1B = (int)GB + total_word32;  
        *(volatile int*)GP1B = 0; // DMA General purpose register = 0  
        *(volatile int*)CP1B = 0; // DMA chain pointer register=0  
        *(volatile int*)IM1B = 0x1; // DMA internal modify register=1
*(volatile int*)C1B = total_word32; // DMA internal counter register

// Tell CPLD to go to gainbit state by setting FS for a word at port 1A (data = 0).
sysreg_bit_clr(sysreg_IMASK, SP1I); // enable sport 1 interrupt
*(volatile int*)SPCTL1 |= ~FS_BOTH; // enable sport 1A
*(volatile int*)TX1A = 0;
*(volatile int*)SPCTL1 |= SPEN_A; // enable sport 1A
poll_flag_in(DIO_PLD1,0); // wait for CPLD to confirm it is in gainbit state (flag3 pulses high)

// send src # and wl_set# to CPLD before sending gainbit through 1A
sysreg_bit_clr(sysreg_IMASK, SP1I); // enable sport 1 interrupt
*(volatile int*)SPCTL1 |= SPEN_A; // enable sport 1A
*(volatile int*)TX1A = (src*wl_set) | ((wl_set-1) << 0x07);
poll_flag_in(DIO_PLD1,0);

int src_pos = 0;
while ( src_pos < src*wl_set ) {
    *(volatile int*)SPCTL1 &= (~SDEN_A & ~SDEN_B);
    *(volatile int*)SPCTL1 |= (SENDN | SPEN_A | SPEN_B);

    // configure the DMA for serial port 1A
    *(volatile int*)II1A = (int)GB + src_pos*count_size;
    *(volatile int*)GP1A = 0; // DMA General purpose register =0
    *(volatile int*)CP1A = 0; // DMA chain pointer register=0
    *(volatile int*)IM1A = 0x1; // DMA internal modify register=1
    *(volatile int*)C1A = count_size; // DMA internal counter register

    // configure the DMA for serial port 1B
    *(volatile int*)II1B = (int)GB + total_word32 + src_pos*count_size;
    *(volatile int*)GP1B = 0; // DMA General purpose register =0
    *(volatile int*)CP1B = 0; // DMA chain pointer register=0
    *(volatile int*)IM1B = 0x1; // DMA internal modify register=1
    *(volatile int*)C1B = count_size; // DMA internal counter register

    src_pos++;

    // send gainbits
    //sysreg_bit_set(sysreg_IMASK, SP1I); // enable sport 1 interrupt
    *(volatile int*)SPCTL1 |= (SDEN_A | SDEN_B); // LSB first, enable sport1 and its DMA for both A and B
    //idle(); // wait for interrupt;
poll_flag_in(DIO_PLD1,0);
}
poll_flag_in(DIO_PLD0,2); //wait for CPLD to get into standby state (flag2=1)

while(1) //Make sure that we're not requesting an IRQ anymore so that we can return to standby
{
    if ( poll_flag_in(DIO_PC1,5) == 0 ) break;
}
G8. Imaging.c

#include "def21161.h"
#include "Experiment_Parameters.h"
#include <processor_include.h>
#include <sysreg.h>

extern int im_cnt;// # of image count
extern int IDA[]; // incoming ADC data
extern int IDB[]; // incoming ADC data
extern double OUTPUT_W1;// demodulated date for wavelength 1
extern double OUTPUT_W2;// demodulated date for wavelength 2
extern int src; // # of sources
extern int det; // # of detectors
extern int wl_set; // # of wavelength sets

// function declarations
void deModulation(void);
void getImage()
{
    im_cnt++; // for each frame

    // set general purpose register and chain pointer registers for DMA serial port 0
    *(volatile int *)GP0A = 0;
    *(volatile int *)GP0B = 0;
    *(volatile int *)CP0A = 0;
    *(volatile int *)CP0B = 0;
    *(volatile int *)C0A = 16*SAMPLES;//32 src * 32 det * 150 samples / 2
    *(volatile int *)COB = 16*SAMPLES;//

    // set internal modify register = 1
    *(volatile int *)IM0A = 1;
    *(volatile int *)IM0B = 1;

    // set internal index register -> IDA
    *(volatile int *)II0A = (int) (&IDA);

    // set internal index register -> IDB
    *(volatile int *)II0B = (int) (&IDB);

    *(volatile int*)DMAC10 &= ~DEN; //Disable DMA channel 10 until we’re ready
    //configure Ext. Port Buffer 0 for sending demodulated data to PC
    *(volatile int*)IIEP0 = (int) (&OUTPUT_W1);//DMA Ch10 Index Register set to address of OUTPUT_W1
    *(volatile int*)IMEP0 = 0x1;//DMA Ch10 Modify Register = 1
    *(volatile int*)CEP0 = DETECTORS * 0x2; //DMA Ch10 Count Register = 2*32
    *(volatile int*)GPPEP0 = 0; //DMA Ch10 General Purpose Register = 0
    *(volatile int*)IPEP0 = 0x08000000; //DMA Ch10 External Index Register = 0xOC000000,us2 cleared, write to FIFO
    *(volatile int*)EIEPO = 0x1; //DMA Ch10 External Modify Register = 1
    *(volatile int*)ECRPO = DETECTORS * 0x8; //DMA Ch10 External Count Register = 4*32

    sysreg_bit_clr(sysreg_IRPTL, EP0I | SP0I | TM2H);
    int src_pos = 0;
    int count_val = 0;

    #ifdef MASTER_DSP //only the Master DSP needs to control the CPLD (put it into imaging state, start the timer)
    // set timer for the settling time
timer_off();
    //timer_set (0x7A120, 0x7A120); // 5ms
timer_set (0xAAE60, 0xAAE60); // 7ms
    #endif
}
//timer_set (0x927C0, 0x927C0); // 6ms
sysreg_bit_clr(sysreg_IMASK, TMZLI);

// DSP notify CPLD to start passing the first source imaging data
*(volatile int *)IOFLAG |= FLG5; // send imaging request to CPLD
while (src_pos < src*w_set)
{
    while(1)
    {
        if (poll_flag_in(DIO_PLD1,5) == 1)
        {
            break; // FLAG3 tells DSP to start the timer (switch settled)
        }
    }
    sysreg_bit_set(sysreg_IMASK, SP0I | TMZHI); // enable timer interrupt with high priority and enable sport 0 interrupt
timer_set (0xAAE60, 0xAAE60);
timer_on(); // start timer
}
#endif
while (src_pos < 2*SOURCES) // when it is the slave running it just waits for the CPLD to be finished
{
    // the CPLD knows # of sources it needs to send, but Slave DSP doesn’t
    // (max # of iterations is 32 sources * 2 wavelength sets)
syrsreg_bit_set(sysreg_IMASK, sp0I); // enable sport 0 interrupt
#endif
// Send out the data to the PC from the previous source while we’re waiting for the timer to expire
// This takes ~1.7ms, fast enough that it will complete before the 5ms timer
if(src_pos > 0) {
    deModulation();
    // Configure the External DMA register to send WL1 data
    *(volatile int*)IIEP0 = (int)&OUTPUT_W1; // DMA Ch10 Index Register set to address of OUTPUT_W1
    *(volatile int*)CEP0 = DETECTORS; // DMA Ch10 Count Register = 32
    *(volatile int*)ECEP0 = DETECTORS * 0x4; // DMA CH10 External Count Register = 4*32 (Each 32-bit word is broken up into 4 8-bit writes)
    *(volatile int*)EIEP0 = 0x08000000; // DMA Ch10 External Index Register = 0x0C000000, us2 cleared, write to FIFO
    *(volatile int*)DMAC10 |= DEN; // Enable DMA channel 10, send WL1 data to buffer
    while(1) {
        if(sysreg_bit_tst(sysreg_IRPTL, EP0I)) {
            sysreg_bit_clr(sysreg_IRPTL, EP0I);
            *(volatile int*)DMAC10 &= ~DEN;
            break; // this bit shows if the interrupt has fired
        }
    }
    // Configure the External DMA register to send WL2 data
    *(volatile int*)IIEP0 = 0x08000000; // DMA Ch10 Index Register set to address of OUTPUT_W1
    *(volatile int*)CEP0 = DETECTORS; // DMA Ch10 Count Register = 32
    *(volatile int*)ECEP0 = DETECTORS * 0x4; // DMA CH10 External Count Register = 4*32 (Each 32-bit word is broken up into 4 8-bit writes)
    *(volatile int*)EIEP0 = 0x08000000; // us2 cleared, write to FIFO
    *(volatile int*)DMAC10 |= DEN; // Enable DMA channel 10, send WL1 data to buffer
    while(1) {
        if(sysreg_bit_tst(sysreg_IRPTL, EP0I)) {
            sysreg_bit_clr(sysreg_IRPTL, EP0I);
            *(volatile int*)DMAC10 &= ~DEN;
            break; // this bit shows if the interrupt has fired
        }
    }
// Reconfigure the SPORT0 DMA registers so that they're ready to go again
*(volatile int *)II0A = (int) (&IDA); // set internal index register -> IDA
*(volatile int *)II0B = (int) (&IDB); // set internal index register -> IDB
*(volatile int *)C0A = 16*SAMPLES; // 32 det * 150 samples / 2 (A&B streams)
*(volatile int *)C0B = 16*SAMPLES; //

*(volatile int *)SPCTL0 |= ( SPEN_A | SDEN_A | SPEN_B | SDEN_B ); // enable sport0, start taking in ADC data

// Wait for the Sport interrupt to let us know we've received the data
#ifdef MASTER_DSP
while(1) {
    count_val = *(volatile int *)C0A; //A and B have the same sync, so once one of them
    if(count_val == 0) {  // when count_val==0 then we know they are both done. This could be done more
        //elegantly with SPOI, but I couldn't get the interrupt to trigger properly.
        //if(sysreg_bit_tst(sysreg_IRPTL, SP0I)) {
            sysreg_bit_clr(sysreg_IRPTL, SP0I | TM2HI);
            *(volatile int *)SPCTL0 &= ~( SPEN_A | SDEN_A | SPEN_B | SDEN_B );
            break;  //this bit shows if the interrupt has fired
        } else if(count_val == 4*SAMPLES) {
            *(volatile int *)IOFLAG &= ~FLG5; // now that CPLD has understood, stop sending IMST
        }
    }
#else
while(1) {
    count_val = *(volatile int *)C0A; //A and B have the same sync, so once one of them
    if(count_val == 0) {
        //if(sysreg_bit_tst(sysreg_IRPTL, SP0I) || poll_flag_in(DIO_PLD0,5) == 1) {
            sysreg_bit_clr(sysreg_IRPTL, SP0I);
            *(volatile int *)SPCTL0 &= ~( SPEN_A | SDEN_A | SPEN_B | SDEN_B );
            break;  //this bit shows if the interrupt has fired
        }
    }
#endif

src_pos = src_pos+1;
if ( poll_flag_in(DIO_PLD0,5) == 1 ) break; // FLAG2 tells DSP that data acquisition is complete because we're back in standby.

// We still have one source worth of data to send back to the PC
demodulation();

// Configure the External DMA register to send WL1 data
*(volatile int *)IIEP0 = (int) (OUTGW_L1); // DMA Ch10 Index Register set to address of OUTPUT_L1
*(volatile int *)CEP0 = DETECTORS; // DMA Ch10 Count Register = 2*32
*(volatile int *)ECEP0 = DETECTORS * 0x4; // DMA Ch10 External Count Register = 8*32
*(volatile int *)EIEP0 = 0x08000000; // DMA Ch10 External Index Register = 0x0C000000, us2 cleared, write to FIFO
*(volatile int *)DMAC10 |= DEN; // Enable DMA channel 10, send WL1 data to buffer

while(1) {
    if(sysreg_bit_tst(sysreg_IRPTL, EPOI)) {
        sysreg_bit_clr(sysreg_IRPTL, EPOI);
        *(volatile int *)DMAC10 &= ~DEN;
        break; // this bit shows if the interrupt has fired
    }
}

// Configure the External DMA register to send WL2 data
*(volatile int*)IIEP0 = (int) (&OUTPUT_W2); //DMA Ch10 Index Register set to address of OUTPUT_W1
*(volatile int*)CEP0 = DETECTORS; //DMA Ch10 Count Register = 2*32
*(volatile int*)ECEP0 = DETECTORS * 0x4; //DMA CH10 External Count Register = 8*32
*(volatile int*)EIEP0 = 0x08000000; // us2 cleared, write to FIFO
*(volatile int*)DMAC10 |= DEN; //Enable DMA channel 10, send WL1 data to buffer

while(1) {
    if(sysreg_bit_tst(sysreg_IRPTL, EP0I)) {
        sysreg_bit_clr(sysreg_IRPTL, EP0I);
        *(volatile int*)DMAC10 &= ~DEN;
        break; //this bit shows if the interrupt has fired
    }
}
*(volatile int *)IOFLAG &= ~FLG5;

G9. Demodulation.c

#include "def21161.h"
#include "Experiment_Parameters.h"
#include <matrix.h>
#include <math.h>
#include "Ref_sig.h"
extern int IDA[];
extern int IDB[];
extern double OUTPUT_W1[];
extern double OUTPUT_W2[];
extern double RI5k7k[];
extern double RQ5k7k[];
void deModulation(void)
{
    int j; // index for samples
    int i; // index for det
    double scaling = 13107; //((2^16)-1)/5 : divide by this factor to turn the number into a voltage;

    //Inphase Reference Matrix
    double *m1 = (double *) (&RI5k7k);
    //Quadrature Reference Matrix
    double *m2 = (double *) (&RQ5k7k);
    //Sample Matrix
    double datMat[SAMPLES];
    double *m0 = (double *) (&datMat);
    //Mixed Matrix
    double XMat[COLOURS][1]; // inphase
    double YMat[COLOURS][1]; // quadrature
    double *m3 = (double *) (&XMat), *m4 = (double *) (&YMat);

    //This hash is required in order to resort the detectors back into their correct order (undoes the muxing from chip select, etc).
    int Det_Hash[DETECTORS] = {2, 0, 10, 8, 18, 16, 26, 24, 3, 1, 11, 9, 19, 17, 27, 25, 6, 4, 14, 12, 22, 20, 30, 28, 7, 5, 15, 13, 23, 21, 31, 29};

    // compute chain A (port A data)
    for ( i = 0; i < (DETECTORS/2) ; i++ )
    {
        
    
}
://get the sample matrix
for (j = 0; j < SAMPLES; j++)
    datMat[j] = (double) IDA[1+16*j];
//datMat[j] = (double) IDA[i+16*j]; // Extract the samples from the given detector (always spaced 16 entries apart)

//multiply the matrices
matmmlt (m3, m1, m0, COLOURS, SAMPLES, 1); //inphase mix
matmmlt (m4, m2, m0, COLOURS, SAMPLES, 1); //quadrature mix

//take the square root of the real part squared plus the imag. part squared to get the amplitude.
OUTPUT_W1[Det_Hash[i]] = sqrtf( (XMat[0][0] - 2.5) * (XMat[0][0] - 2.5) + (YM at[0][0] - 2.5) * (YMat[0][0] - 2.5) ) / SAMPLES / scaling;
OUTPUT_W2[Det_Hash[i]] = sqrtf( XMat[1][0] * XMat[1][0] + YMat[1][0] * YMat[1][0] ) / SAMPLES / scaling;

};
int det_div_2 = DETECTORS/2;

// compute chain B (port B data)
for (i = det_div_2; i < DETECTORS; i++)
{
    //get the sample matrix
    for (j = 0; j < SAMPLES; j++)
        datMat[j] = (double) IDB[i-det_div_2+16*j]; // Extract the samples from the given detector (always spaced 16 entries apart)

    //multiply the matrices
    matmmlt (m3, m1, m0, COLOURS, SAMPLES, 1); //inphase mix
    matmmlt (m4, m2, m0, COLOURS, SAMPLES, 1); //quadrature mix

    //take the square root of the real part squared plus the imag. part squared to get the amplitude.
    OUTPUT_W1[Det_Hash[i]] = sqrtf( XMat[0][0] * XMat[0][0] + YMat[0][0] * YMat[0][0] ) / SAMPLES / scaling;
    OUTPUT_W2[Det_Hash[i]] = sqrtf( XMat[1][0] * XMat[1][0] + YMat[1][0] * YMat[1][0] ) / SAMPLES / scaling;

};

G10. ExperimentParameters.h

#define MASTER_DSP  // Define whether we are compiling master or slave code
#define PCI 0x20000  //bit 17 - enables per-chain interrupts
#define GAINBITS 3
#define SOURCES 32
#define DETECTORS 32  // two DSPs on each board, so 64/2=32
#define SAMPLES 150
#define COLOURS 2  //number of wavelengths per set
#define DIO_PC0 0
#define DIO_PC1 1
#define DIO_PLD0 2
#define DIO_PLD1 3
#define DIO_IMST FLG5
#define DIO_LED FLG9
APPENDIX H – CPLD CODE

H1. CPLD_breast_imager_master.pld

/* *************** INPUT PINS **********************/
PIN 12 = en; /* Enable */
PIN 83 = clk; /* PLD Clock */
PIN 75 = timexp; /* Timer from DSP*/
PIN 20 = TF; /* DSP Transmit Frame */
PIN 21 = TDA; /* DSP Transmit Data A */
PIN 22 = TDB; /* DSP Transmit Data B */
PIN 35 = IMST; /* Imaging Start from DSP - active low*/

/* TEMP DEBUG PINS */
PIN 27 = dbg1;
PIN 28 = dbg2;
PIN 39 = dbg3;
PIN 40 = dbg4;
PIN 41 = dbg5;

/* *************** OUTPUT PINS **********************/
PIN 70 = FG2; /* Control line to DSP 1 */
PIN 15 = FG3; /* Control line to DSP 2 */
PIN 17 = fr; /* FIFO read signal */
PIN 81 = fw; /* FIFO write signal */
PIN 79 = ffrst; /* FIFO reset signal */
PIN 68 = frrt; /* FIFO retransmit signal */
PIN 69 = GBL; /* Output to left-breast shift register */
PIN 74 = GBR; /* Output to right-breast shift register */
PIN 16 = ssclk; /* To be AND gated with clock and then becomes shift register input clock */
PIN 24 = scrclk; /* To be AND gated with clock and then becomes shift register output clock */
PIN 25 = scl; /* Clear the shift register */
PIN 18 = cnvst; /* Convert State - Used to switch between ADC cores */
PIN 80 = A0; /* Channel address bit sent to every ADC */
PIN 56 = cs1; /* Chip select signal for cards 1&2&3&4 */
PIN 54 = cs2; /* Chip select signal for cards 5&6&7&8 */
PIN 57 = cs3; /* Chip select signal for cards 9&10&11&12 */
PIN 55 = cs4; /* Chip select signal for cards 13&14&15&16 */
PIN 29 = PS0; /* Output to optical switch */
PIN 30 = PS1; /* Output to optical switch */
PIN 31 = PS2; /* Output to optical switch */
PIN 33 = PS3; /* Output to optical switch */
PIN 34 = PS4; /* Output to optical switch */
PIN 36 = PS5; /* Output to optical switch */
PIN 37 = PS6; /* Output to optical switch */

/* *************** PINNODES **********************/
/* Main State Machine Variables */
PINNODE = M1;
PINNODE = M0;

/* Inputs from the DSP - TF is the frame synchronizer and TDA and TDB are the data lines */
PINNODE = TF_0;
PINNODE = TF_1;
PINNODE = TDA_0;
PINNODE = TDA_1;
PINNODE = TDA_2;
PINNODE = TDA_3;
PINNODE = TDA_4;
PINNODE = TDA_5;
PINNODE = TDA_6;
PINNODE = TDA_7;
PINNODE = TDA_8;
PINNODE = TDB_0;
PINNODE = IMST_0;

/* Gainbit State Machine Variables */
PINNODE = G2;
PINNODE = G1;
PINNODE = G0;

/* Signal to increment the source counter */
PINNODE = src_cntr;

/* Holds the number of sources programmed at the beginning of the gainbit state */
PINNODE = src0;
PINNODE = src1;
PINNODE = src2;
PINNODE = src3;
PINNODE = src4;
PINNODE = src5;
PINNODE = src6;
PINNODE = wl_sets;

/* Counts which source we are programming the gainbits for */
PINNODE = gsc0;
PINNODE = gsc1;
PINNODE = gsc2;
PINNODE = gsc3;
PINNODE = gsc4;
PINNODE = gsc5;
PINNODE = gsc6;

/* Imaging State Machine Variables */
PINNODE = IM0;
PINNODE = IM1;
PINNODE = IM2;

/* Finished Imaging (all samples, sources, and cs) */
PINNODE = f_img;

/* Counters for source positions, samples, and the sample enable (whether to allow the sample counter to run */
PINNODE = srcpos_cntr;
PINNODE = smpl_cntr;
PINNODE = smpl_en;

/* Flopped version of the TIMEXP input from the DSP */
PINNODE = time;

/* Conversion state counters - counts to 70 cycles (time for the ADC to convert */
PINNODE = cwc0;
PINNODE = cwc1;
PINNODE = cwc2;
PINNODE = cwc3;
PINNODE = cwc4;
PINNODE = cwc5;
PINNODE = cwc6;
PINNODE = f_cnvt; /*Finished the conversion state 70 cycle delay*/

/* Sample Counter counts to 300 (150 samples for each detector A0=0 and A0=1) */
PINNODE = csmp0;
PINNODE = csmp1;
PINNODE = csmp2;
PINNODE = csmp3;
PINNODE = csmp4;
PINNODE = csmp5;
PINNODE = csmp6;
PINNODE = csmp7;
PINNODE = csmp8;
PINNODE = f_smpl; /* Goes high when csmp has counted to 300 */

/* Send Data Counter - counts to 126 */
PINNODE = sdc0;
PINNODE = sdc1;
PINNODE = sdc2;
PINNODE = sdc3;
PINNODE = sdc4;
PINNODE = sdc5;
PINNODE = sdc6;
PINNODE = f_sd; /*Finished sending all 126 bits of data - 16 bits per detector, 2 detectors per ADC and 4 cs*/

PINNODE = ls; /* Goes high when imaging data has been sent for every source */

/* Source position counter - keeps track while imaging, which source positions have been completed */
PINNODE = spc0;
PINNODE = spc1;
PINNODE = spc2;
PINNODE = spc3;
PINNODE = spc4;
PINNODE = spc5;
PINNODE = spc6;

/*flag3 and flag3_d are in order to spread out the FG3 output to the DSP to make it longer, thus giving it a higher chance of the DSP catching it */
PINNODE = flag3;
PINNODE = flag3_d;

/*Optical Switch Timer Counters*/
PINNODE = swtch_cntr0;
PINNODE = swtch_cntr1;
PINNODE = swtch_cntr2;
PINNODE = swtch_cntr3;
PINNODE = swtch_cntr4;
PINNODE = swtch_cntr5;
PINNODE = swtch_cntr6;
PINNODE = swtch_cntr7;
PINNODE = swtch_cntr8;
PINNODE = swtch_cntr9;

/*For expanding the read clock pulse*/
PINNODE = fr1;
PINNODE = fr2;
PINNODE = fr3;

/*Optical Switch stobe counters & state machine pinnodes */
PINNODE = T0;
PINNODE = T1;
PINNODE = strobe;
PINNODE = strobe_counter;
PINNODE = strobe_init;
PINNODE = switch_cntr_hold;

/* *************** MAIN STATE MACHINE ****************** */

field MSM = [M1..0];
$define initial 'b'00
$define standby 'b'01
$define gainbit 'b'10
$define imaging 'b'11

[M1..0].ck = clk;

SEQUENCED MSM {
    present initial
        if (len)
            if (en & !IMST_0)
                next initial;
            next standby;
    present standby
        if (len)
            next initial;
        if (en & !IMST_0)
            next gainbit
            out ffrst
            out flag3;
        if (en & !TF_0 & TF_1 & !TDA_1)
            next gainbit
            out ffrst
            out flag3;
        if (en & IMST_0)
            next imaging
            out flag3;
        default
            next standby;
    present gainbit
        if (len)
            next initial;
        if (en & f_gb)
            next standby;
        if (en & !f_gb)
            next gainbit;
    present imaging
        if (len)
            next initial;
        if (en & f_img)
            next imaging;
        if (en & !f_img)
            next imaging;
}

ffrst.ck = clk;
FG2.ck = clk;
FG2.d = en & IM1 & M0;

flag3.ck = clk;
flag3_d.ck = clk;
flag3_d.d = flag3;

FG3.ck = clk;
FG3.d = flag3 & flag3_d;

IMST_0.d = IMST;
IMST_0.ck = clk;

TF_0.d = TF;
TF_1.d = TF_0;
TDA_0.d = TDA;
TDB_0.d = TDB;
[TDA_1..8].d = [TDA_0..7];
[TF_0..1].ck = clk;
[TDA_0..8].ck = clk;
TDB_0.ck = clk;

/* *************** GAINBIT STATE MACHINE ****************** */

field GB5M = [G2..0];
$define gb_init 'b'000
$define gb_getsrc 'b'001
$define gb_cnt96 'b'010
$define gb_shift 'b'011
$define gb_fifo 'b'100
$define gb_loop 'b'101
$define gb_UNDEF1 'b'110
$define gb_UNDEF2 'b'111

[G2..0].ck = clk;

SEQUENCED GB5M {

  present gb_init
  if [en & M1 & !M0 & ffrst]
  next gb_getsrc
  out flag3;

  present gb_getsrc
  if [en & M1 & !M0 & f_getsrc]
  next gb_cnt96
  out flag3 out src_cntr;

  present gb_cnt96
  if [en & M1 & !M0 & f_gb_upload]
  next gb_fifo
  out src_cntr;

  present gb_fifo
  if [en & M1 & !M0 & f_gb_upload]
  next gb_loop
  out src_cntr;

  present gb_loop
  if [en & M1 & !M0 & f_gb_getsrc]
  next gb_loop
  out src_cntr;

  present gb_UNDEF1
  next gb_init;

  present gb_UNDEF2
  next gb_init;
}

f_getsrc = !TF_0 & TF_1 & !G2 & !G1 & G0;

fw.ck = clk;

src_cntr.ck = clk;

/* Counter for keeping track of how many sources have been programmed for the experiment */
[src0..6].ck = clk;
src0.d = TDA_1 & f_getsrc # src0 & !f_getsrc;
src1.d = TDA_2 & f_getsrc # src1 & !f_getsrc;
src2.d = TDA_3 & f_getsrc # src2 & !f_getsrc;
src3.d = TDA_4 & f_getsrc # src3 & !f_getsrc;
src4.d = TDA_5 & f_getsrc # src4 & !f_getsrc;
src5.d = TDA_6 & f_getsrc # src5 & !f_getsrc;
src6.d = TDA_7 & f_getsrc # src6 & !f_getsrc;
wl_sets.ck = clk;
wl_sets.d = TDA_8 & f_getsrc # wl_sets & !f_getsrc;

/* Counter for keeping track of the source number (to make sure we have shifted in gain bits for every source) */
[gsc0..6].ck = clk;
append gsc0.d = !gsc0 & src_cntr & M1 & !M0;
append gsc0.d = gsc0 & !src_cntr & M1 & !M0;
append gsc1.d = gsc1 & !gsc0 & src_cntr & M1 & !M0;
append gsc1.d = gsc1 & !src_cntr & M1 & !M0;
append gsc1.d = gsc1 & !gsc0 & M1 & !M0;
append gsc2.d = gsc2 & gsc1 & !gsc0 & src_cntr & M1 & !M0;
append gsc2.d = gsc2 & !gsc1 & src_cntr & M1 & !M0;
append gsc2.d = gsc2 & gsc1 & !src_cntr & M1 & !M0;
append gsc2.d = gsc2 & !gsc1 & src_cntr & M1 & !M0;
append gsc3.d = !gsc3 & gsc2 & gsc1 & gsc0 & src_cntr & M1 & !M0;
append gsc3.d = gsc3 & !src_cntr & M1 & !M0;
append gsc3.d = gsc3 & !gsc0 & M1 & !M0;
append gsc3.d = gsc3 & !gsc1 & M1 & !M0;
append gsc3.d = gsc3 & !gsc2 & M1 & !M0;
append gsc4.d = !gsc4 & gsc3 & gsc2 & gsc1 & gsc0 & src_cntr & M1 & !M0;
append gsc4.d = gsc4 & !src_cntr & M1 & !M0;
append gsc4.d = gsc4 & !gsc0 & M1 & !M0;
append gsc4.d = gsc4 & !gsc1 & M1 & !M0;
append gsc4.d = gsc4 & !gsc2 & M1 & !M0;
append gsc5.d = !gsc5 & gsc4 & gsc3 & gsc2 & gsc1 & gsc0 & src_cntr & M1 & !M0;
append gsc5.d = gsc5 & !src_cntr & M1 & !M0;
append gsc5.d = gsc5 & !gsc0 & M1 & !M0;
append gsc5.d = gsc5 & !gsc1 & M1 & !M0;
append gsc5.d = gsc5 & !gsc2 & M1 & !M0;
append gsc6.d = !gsc6 & gsc5 & gsc4 & gsc3 & gsc2 & gsc1 & gsc0 & src_cntr & M1 & !M0;
append gsc6.d = gsc6 & !src_cntr & M1 & !M0;
append gsc6.d = gsc6 & !gsc0 & M1 & !M0;
append gsc6.d = gsc6 & !gsc1 & M1 & !M0;
append gsc6.d = gsc6 & !gsc2 & M1 & !M0;
append gsc6.d = gsc6 & !gsc3 & M1 & !M0;
append gsc6.d = gsc6 & !gsc4 & M1 & !M0;
append gsc6.d = gsc6 & !gsc5 & M1 & !M0;

/* Determine whether or not we are finished programming the gainbits for all of the enabled sources */
f_gb = !(src0 $ gsc0) # (src1 $ gsc1) # (src2 $ gsc2) # (src3 $ gsc3) #
    (src4 $ gsc4) # (src5 $ gsc5) # (src6 $ gsc6) # !G0 # G1 # !G2);

/* Outputs to the shift registers */
scl.ck = clk;
GBL.d = en & TDA_0 & !G2 & G1 & !G0;
GBR.d = en & TDB_0 & !G2 & G1 & !G0;
GBL.ck = clk;
GBR.ck = clk;
ssclk.d = en & TF_0 & !G2 & G1 & !G0;
ssclk.ck = !clk;
srclk.ck = !clk;

/* Since both ssclk and srclk are ANDed with the clock after leaving the CPLD, we shift them by half a clock cycle to give more stability to the system. */

/* Finished uploading the gainbits whenever the DSP stops sending them */
/* NOTE - no checking done by CPLD to make sure correct number of gainbits were transferred */
f_gb_upload = TF_0 & TF_1 & !G2 & G1 & !G0;

/* *************** IMAGING STATE MACHINE ********************** */
/* NOTE: The strobe_init signal is what actually tells the switch to move positions. */
/* The srcpos_cntr is just keeping track of the next position */

field IMSM = [IM2..0];
$define i_init 'b'000 /* Initial state */
$define i_wait 'b'001 /* State where the optical source is updating (~5ms) */
$define i_update 'b'010 /* State where the DSP is updating its settings - is this state needed? */
$define i_conversion 'b'011 /* Give the ADC time to convert the signals from analog to digital (~70 clocks) */
$define i_send_data 'b'100 /* Send the data to the DSP - 150 samples per detector/source combo */
$define i_finish1 'b'101 /* Finished state */
$define i_finish2 'b'110
$define i_switch 'b'111
IM2.0.ck = clk;

SEQUENCED IMSM {

present i_init if (len # IM1 # IM0) next i_init;
    if (en & M1 & M0) next i_switch;
    /*the first time through the switch is already in the right spot - don't need to change positions*/

present i_switch if (len # IM1 # IM0) next i_init;
    if (en & M1 & M0) next i_wait out strobe_init;

present i_wait if (len # IM1 # IM0) next i_init;
    if (en & M1 & M0 & time) next i_update out srcpos_cntr;
    default next i_wait out flag3;
    /*outputing flag3 the entire time we are in i_wait tells the DSP to start the 5ms timer*/

present i_update if (len # IM1 # IM0) next i_init;
    if (en & M1 & M0) next i_cnvrt out smpl_en;
    default next i_update;

present i_cnvrt if (len # IM1 # IM0) next i_init;
    if (en & M1 & M0 & f_cnvrt) next i_sndta out smpl_cntr out smpl_en;
    default next i_cnvrt out smpl_en;

present i_sndta if (len # IM1 # IM0) next i_init;
    if (en & M1 & M0 & f_sd & !f_smpl) next i_cnvrt out smpl_en;
    if (en & M1 & M0 & f_sd & f_smpl & !ls) next i_switch;
    if (en & M1 & M0 & f_sd & f_smpl & ls) next i_finish1 out f_img;
    default next i_sndta out smpl_en;

present i_finish1

present i_finish2 next i_init;

}

f_img.ck = clk;
srcpos_cntr.ck = clk;
smpl_cntr.ck = clk;
smpl_en.ck = clk;
strobe_init.ck = clk;
/* Fifo Retransmit - Set low for one cycle after imaging state is completed */
!frt.d = ((IM2 & !IM1 & IM0) # (IM2 & IM1 & !IM0));
frt.ck = clk;

/* Convert State signal to ADC */
!cnvst.d = !IM2 & IM1 & IM0;
cnvst.ck = clk;
/* Fifo Read Signal - output to the Gainbit Fifo */
fr1.d = (((IM2 & !IM1 & IM0) # (IM2 & IM1 & IM0) # (IM2 & IM1 & IM0) # (IM2 & IM1 & IM0) # (IM2 & IM1 & IM0)));
fr1.ck = clk;

/* Need to expand the read pulse to avoid glitches*/
fr2.ck = clk;
fr2.d = fr1;
fr3.ck = clk;
fr3.d = fr2;
fr.d = fr1 # fr2 # fr3;
fr.ck = clk;

/* Timer input from the DSP */
time.d = timexp;

/* Counter for the conversion state (counts for 70 cycles) */

[cwc0..6].ck = clk;

append cwc0.d = !cwc0 & !IM2 & IM1 & IM0;
append cwc1.d = !cwc1 & cwc0 & !IM2 & IM1 & IM0;
append cwc1.d = cwc1 & !cwc0 & !IM2 & IM1 & IM0;
append cwc2.d = !cwc2 & cwc1 & cwc0 & !IM2 & IM1 & IM0;
append cwc2.d = cwc2 & !cwc0 & !IM2 & IM1 & IM0;
append cwc2.d = cwc2 & !cwc1 & !IM2 & IM1 & IM0;
append cwc3.d = !cwc3 & cwc2 & cwc1 & cwc0 & !IM2 & IM1 & IM0;
append cwc3.d = cwc3 & !cwc0 & !IM2 & IM1 & IM0;
append cwc3.d = cwc3 & !cwc1 & !IM2 & IM1 & IM0;
append cwc3.d = cwc3 & !cwc2 & !IM2 & IM1 & IM0;
append cwc4.d = !cwc4 & cwc3 & cwc2 & cwc1 & cwc0 & !IM2 & IM1 & IM0;
append cwc4.d = cwc4 & !cwc0 & !IM2 & IM1 & IM0;
append cwc4.d = cwc4 & !cwc1 & !IM2 & IM1 & IM0;
append cwc4.d = cwc4 & !cwc2 & !IM2 & IM1 & IM0;
append cwc4.d = cwc4 & !cwc3 & !IM2 & IM1 & IM0;
append cwc5.d = !cwc5 & cwc4 & cwc3 & cwc2 & cwc1 & cwc0 & !IM2 & IM1 & IM0;
append cwc5.d = cwc5 & !cwc0 & !IM2 & IM1 & IM0;
append cwc5.d = cwc5 & !cwc1 & !IM2 & IM1 & IM0;
append cwc5.d = cwc5 & !cwc2 & !IM2 & IM1 & IM0;
append cwc5.d = cwc5 & !cwc3 & !IM2 & IM1 & IM0;
append cwc5.d = cwc5 & !cwc4 & !IM2 & IM1 & IM0;
append cwc6.d = !cwc5 & cwc4 & cwc3 & cwc2 & cwc1 & cwc0 & !IM2 & IM1 & IM0;
append cwc6.d = cwc6 & !cwc0 & !IM2 & IM1 & IM0;
append cwc6.d = cwc6 & !cwc1 & !IM2 & IM1 & IM0;
append cwc6.d = cwc6 & !cwc2 & !IM2 & IM1 & IM0;
append cwc6.d = cwc6 & !cwc3 & !IM2 & IM1 & IM0;
append cwc6.d = cwc6 & !cwc4 & !IM2 & IM1 & IM0;
append cwc6.d = cwc6 & !cwc5 & !IM2 & IM1 & IM0;

f_cnvt.d = !cwc6 & !cwc5 & !cwc4 & !cwc3 & cwc2 & cwc1 & !cwc0; /*70*/
f_cnvt.ck = clk;

/* Counting the number of samples (counts to 300 - 150 for each ADC address 0 and 1) */

[csmp0..8].ck = clk;

append csmp0.d = !csmp0 & smpl_cntr & smpl_en;
append csmp0.d = csmp0 & !smpl_cntr & smpl_en;
append csmp1.d = !csmp1 & csmp0 & smpl_cntr & smpl_en;
append csmp1.d = csmp1 & !smpl_cntr & smpl_en;
append csmp1.d = csmp1 & !csmp0 & smpl_en;
append csmp2.d = !csmp2 & csmp1 & csmp0 & smpl_cntr & smpl_en;
append csmp2.d = csmp2 & !smpl_cntr & smpl_en;
append csmp2.d = csmp2 & !csmp0 & smpl_en;
append csmp3.d = !csmp3 & csmp2 & csmp1 & csmp0 & smpl_cntr & smpl_en;
append csmp3.d = csmp3 & !smpl_cntr & smpl_en;
append csmp3.d = csmp3 & !csmp0 & smpl_en;
append csmp3.d = csmp3 & !csmp1 & smpl_en;
append csmp3.d = csmp3 & !csmp2 & smpl_en;
append csmp4.d = !csmp4 & csmp3 & csmp2 & csmp1 & csmp0 & smpl_cntr & smpl_en;
append csmp4.d = csmp4 & !smpl_cntr & smpl_en;
append csmp4.d = csmp4 & !csmp0 & smpl_en;
append csmp4.d = csmp4 & !csmp1 & smpl_en;
append csmp4.d = csmp4 & !csmp2 & smpl_en;
append csmp4.d = csmp4 & !csmp3 & smpl_en;
append csmp5.d = !csmp5 & csmp4 & csmp3 & csmp2 & csmp1 & csmp0 & smpl_cntr & smpl_en;
append csmp5.d = csmp5 & !smpl_cntr & smpl_en;
append csmp5.d = csmp5 & !csmp0 & smpl_en;
append csmp5.d = csmp5 & !csmp1 & smpl_en;
append csmp5.d = csmp5 & !csmp2 & smpl_en;
append csmp5.d = csmp5 & !csmp3 & smpl_en;
append csmp5.d = csmp5 & !csmp4 & smpl_en;
append csmp6.d = !csmp6 & csmp5 & csmp4 & csmp3 & csmp2 & csmp1 & csmp0 & smpl_cntr & smpl_en;
append csmp6.d = csmp6 & !smpl_cntr & smpl_en;
append csmp6.d = csmp6 & !csmp0 & smpl_en;
append csmp6.d = csmp6 & !csmp1 & smpl_en;
append csmp6.d = csmp6 & !csmp2 & smpl_en;
append csmp6.d = csmp6 & !csmp3 & smpl_en;
append csmp6.d = csmp6 & !csmp4 & smpl_en;
append csmp6.d = csmp6 & !csmp5 & smpl_en;
append csmp7.d = !csmp7 & csmp6 & csmp5 & csmp4 & csmp3 & csmp2 & csmp1 & csmp0 & smpl_cntr & smpl_en;
append csmp7.d = csmp7 & !smpl_cntr & smpl_en;
append csmp7.d = csmp7 & !csmp0 & smpl_en;
append csmp7.d = csmp7 & !csmp1 & smpl_en;
append csmp7.d = csmp7 & !csmp2 & smpl_en;
append csmp7.d = csmp7 & !csmp3 & smpl_en;
append csmp7.d = csmp7 & !csmp4 & smpl_en;
append csmp7.d = csmp7 & !csmp6 & smpl_en;
append csmp8.d = !csmp8 & csmp7 & csmp6 & csmp5 & csmp4 & csmp3 & csmp2 & csmp1 & csmp0 & smpl_cntr & smpl_en;
append csmp8.d = csmp8 & !smpl_cntr & smpl_en;
append csmp8.d = csmp8 & !csmp0 & smpl_en;
append csmp8.d = csmp8 & !csmp1 & smpl_en;
append csmp8.d = csmp8 & !csmp2 & smpl_en;
append csmp8.d = csmp8 & !csmp3 & smpl_en;
append csmp8.d = csmp8 & !csmp4 & smpl_en;
append csmp8.d = csmp8 & !csmp5 & smpl_en;
append csmp8.d = csmp8 & !csmp6 & smpl_en;
append csmp8.d = csmp8 & !csmp7 & smpl_en;

/* Address select to ADC */
A0.d = csmp0;
A0.ck = clk;
f_smpl.d = csmp8 & !csmp7 & csmp6 & csmp5 & csmp4 & csmp3 & csmp2 & csmp1 & csmp0 & smpl_cntr & smpl_en;
append csmp8.d = csmp8 & !smpl_cntr & smpl_en;
append csmp8.d = csmp8 & !csmp0 & smpl_en;
append csmp8.d = csmp8 & !csmp1 & smpl_en;
append csmp8.d = csmp8 & !csmp2 & smpl_en;
append csmp8.d = csmp8 & !csmp3 & smpl_en;
append csmp8.d = csmp8 & !csmp4 & smpl_en;
append csmp8.d = csmp8 & !csmp5 & smpl_en;
append csmp8.d = csmp8 & !csmp6 & smpl_en;
append csmp8.d = csmp8 & !csmp7 & smpl_en;

/* Counter for sending the data from ADC to DSP */
[sdc0.6].ck = clk;
append sdc0.d = en & !sdc0 & IM2 & !IM0 & !IM1;
append sdc1.d = en & !sdc1 & sdc0 & IM2 & !IM0 & !IM1;
append sdc1.d = en & !sdc1 & !sdc0 & IM2 & !IM0 & !IM1;
append sdc2.d = en & !sdc2 & sdc1 & sdc0 & IM2 & !IM0 & !IM1;
append sdc2.d = en & !sdc2 & !sdc0 & IM2 & !IM0 & !IM1;
append sdc2.d = en & !sdc2 & !sdc1 & IM2 & !IM0 & !IM1;
append sdc2.d = en & !sdc2 & !sdc1 & !sdc0 & IM2 & !IM0 & !IM1;
append sdc3.d = en & !sdc3 & sdc2 & sdc1 & sdc0 & IM2 & !IM0 & !IM1;
append sdc3.d = en & !sdc3 & !sdc2 & sdc1 & sdc0 & IM2 & !IM0 & !IM1;
append sdc3.d = en & !sdc3 & !sdc2 & !sdc1 & sdc0 & IM2 & !IM0 & !IM1;
append sdc3.d = en & !sdc3 & !sdc2 & !sdc1 & !sdc0 & IM2 & !IM0 & !IM1;
append sdc4.d = en & !sdc4 & sdc3 & sdc2 & sdc1 & sdc0 & IM2 & !IM0 & !IM1;
append sdc4.d = en & !sdc4 & !sdc3 & sdc2 & sdc1 & sdc0 & IM2 & !IM0 & !IM1;
append sdc4.d = en & !sdc4 & !sdc3 & !sdc2 & sdc1 & sdc0 & IM2 & !IM0 & !IM1;
append sdc4.d = en & !sdc4 & !sdc3 & !sdc2 & !sdc1 & sdc0 & IM2 & !IM0 & !IM1;
append sdc5.d = en & !sdc5 & sdc4 & sdc3 & sdc2 & sdc1 & sdc0 & IM2 & !IM0 & !IM1;
append sdc5.d = en & !sdc5 & !sdc4 & sdc3 & sdc2 & sdc1 & sdc0 & IM2 & !IM0 & !IM1;
append sdc5.d = en & !sdc5 & !sdc4 & !sdc3 & sdc2 & sdc1 & sdc0 & IM2 & !IM0 & !IM1;
append sdc5.d = en & !sdc5 & !sdc4 & !sdc3 & !sdc2 & sdc1 & sdc0 & IM2 & !IM0 & !IM1;
append sdc6.d = en & !sdc6 & sdc5 & sdc4 & sdc3 & sdc2 & sdc1 & sdc0 & IM2 & !IM0 & !IM1;
append sdc6.d = en & !sdc6 & !sdc5 & sdc4 & sdc3 & sdc2 & sdc1 & sdc0 & IM2 & !IM0 & !IM1;
append sdc6.d = en & !sdc6 & !sdc5 & !sdc4 & sdc3 & sdc2 & sdc1 & sdc0 & IM2 & !IM0 & !IM1;
append sdc6.d = en & !sdc6 & !sdc5 & !sdc4 & !sdc3 & sdc2 & sdc1 & sdc0 & IM2 & !IM0 & !IM1;
append sdc6.d = en & !sdc6 & !sdc5 & !sdc4 & !sdc3 & !sdc2 & sdc1 & sdc0 & IM2 & !IM0 & !IM1;
append sdc6.d = en & !sdc6 & !sdc5 & !sdc4 & !sdc3 & !sdc2 & !sdc1 & sdc0 & IM2 & !IM0 & !IM1;
append sdc6.d = en & !sdc6 & !sdc5 & !sdc4 & !sdc3 & !sdc2 & !sdc1 & !sdc0 & IM2 & !IM0 & !IM1;
append sdc6.d = en & !sdc6 & !sdc5 & !sdc4 & !sdc3 & !sdc2 & !sdc1 & !sdc0 & !IM0 & !IM1;
append sdc6.d = en & sdc6 & !sdc2 & IM2 & !IM0 & !IM1;
append sdc6.d = en & sdc6 & !sdc3 & IM2 & !IM0 & !IM1;
append sdc6.d = en & sdc6 & !sdc4 & IM2 & !IM0 & !IM1;
append sdc6.d = en & sdc6 & !sdc5 & IM2 & !IM0 & !IM1;
append sdc6.d = en & sdc6 & sdc5 & IM2 & !IM0 & !IM1;

f_sd.d = sdc6 & sdc5 & sdc4 & sdc3 & sdc2 & sdc1 & !sdc0;

/*126*/
f_sd.ck = clk;

/* Logic for the chip selects (active low select) */
!cs1.d = !sdc6 & !sdc5 & IM2 & !IM0 & !IM1 & en;
!cs2.d = !sdc6 & sdc5 & IM2 & !IM0 & !IM1 & en;
!cs3.d = sdc6 & !sdc5 & IM2 & !IM0 & !IM1 & en;
!cs4.d = sdc6 & sdc5 & IM2 & !IM0 & !IM1 & en;
[cs1..4].ck = clk;

/* Signal that determines when all of the enabled sources have been imaged */
l.s.d = (src0 $ spc0) # (src1 $ spc1) # (src2 $ spc2) # (src3 $ spc3) # (src4 $ spc4) # (src5 $ spc5) # (src6 $ spc6);
l.s.ck = clk;

/* Counter for source positions */
[spc0..6].ck = clk;
append spc0.d = !spc0 & srcpos_cntr & M1 & M0;
append spc0.d = spc0 & !srcpos_cntr & M1 & M0;
append spc1.d = !spc1 & srcpos_cntr & M1 & M0;
append spc1.d = spc1 & !srcpos_cntr & M1 & M0;
append spc2.d = !spc2 & srcpos_cntr & M1 & M0;
append spc2.d = spc2 & !srcpos_cntr & M1 & M0;
append spc3.d = !spc3 & srcpos_cntr & M1 & M0;
append spc3.d = spc3 & !srcpos_cntr & M1 & M0;
append spc4.d = !spc4 & srcpos_cntr & M1 & M0;
append spc4.d = spc4 & !srcpos_cntr & M1 & M0;
append spc5.d = !spc5 & srcpos_cntr & M1 & M0;
append spc5.d = spc5 & !srcpos_cntr & M1 & M0;
append spc6.d = !spc6 & srcpos_cntr & M1 & M0;
append spc6.d = spc6 & !srcpos_cntr & M1 & M0;

/* Logic to control the optical switch */
[swtch_cntr0..9].ck = clk;
append swtch_cntr0.d = !swtch_cntr0 & strobe_counter;
append swtch_cntr1.d = !swtch_cntr1 & swtch_cntr0 & strobe_counter;
append swtch_cntr1.d = swtch_cntr1 & lswtch_cntr0 & strobe_counter;
append swtch_cntr2.d = lswtch_cntr2 & swtch_cntr1 & swtch_cntr0 & strobe_counter;
append swtch_cntr2.d = swtch_cntr2 & lswtch_cntr0 & strobe_counter;
append swtch_cntr2.d = swtch_cntr2 & lswtch_cntr1 & strobe_counter;
append swtch_cntr3.d = lswtch_cntr3 & swtch_cntr2 & swtch_cntr1 & lswtch_cntr0 & strobe_counter;
append swtch_cntr3.d = swtch_cntr3 & lswtch_cntr0 & strobe_counter;
append swtch_cntr3.d = swtch_cntr3 & lswtch_cntr1 & strobe_counter;
append swtch_cntr3.d = swtch_cntr3 & lswtch_cntr2 & strobe_counter;
append swtch_cntr4.d = swtch_cntr4 & lswtch_cntr3 & swtch_cntr2 & swtch_cntr1 & swtch_cntr0 & strobe_counter;
append swtch_cntr4.d = swtch_cntr4 & lswtch_cntr0 & strobe_counter;
append swtch_cntr4.d = swtch_cntr4 & lswtch_cntr1 & strobe_counter;
append swtch_cntr4.d = swtch_cntr4 & lswtch_cntr2 & strobe_counter;
append swtch_cntr5.d = lswtch_cntr5 & swtch_cntr4 & swtch_cntr3 & swtch_cntr2 & swtch_cntr1 & lswtch_cntr0 & strobe_counter;
append swtch_cntr5.d = swtch_cntr5 & lswtch_cntr0 & strobe_counter;
append swtch_cntr5.d = swtch_cntr5 & lswtch_cntr1 & strobe_counter;
append swtch_cntr5.d = swtch_cntr5 & lswtch_cntr2 & strobe_counter;
append swtch_cntr5.d = swtch_cntr5 & lswtch_cntr3 & strobe_counter;
append swtch_cntr5.d = swtch_cntr5 & lswtch_cntr4 & strobe_counter;
append swtch_cntr5.d = swtch_cntr5 & lswtch_cntr6 & strobe_counter;
append swtch_cntr6.d = lswtch_cntr6 & swtch_cntr5 & swtch_cntr3 & swtch_cntr4 & swtch_cntr2 & swtch_cntr1 & lswtch_cntr0 & strobe_counter;
append swtch_cntr6.d = swtch_cntr6 & lswtch_cntr0 & strobe_counter;
append swtch_cntr6.d = swtch_cntr6 & lswtch_cntr1 & strobe_counter;
append swtch_cntr6.d = swtch_cntr6 & lswtch_cntr2 & strobe_counter;
append swtch_cntr6.d = swtch_cntr6 & lswtch_cntr3 & strobe_counter;
append swtch_cntr6.d = swtch_cntr6 & lswtch_cntr4 & strobe_counter;
append swtch_cntr6.d = swtch_cntr6 & lswtch_cntr5 & strobe_counter;
append swtch_cntr6.d = swtch_cntr6 & lswtch_cntr7 & strobe_counter;
append swtch_cntr7.d = lswtch_cntr7 & swtch_cntr6 & swtch_cntr5 & swtch_cntr4 & swtch_cntr3 & swtch_cntr2 & swtch_cntr1 & lswtch_cntr0 & strobe_counter;
append swtch_cntr7.d = swtch_cntr7 & lswtch_cntr0 & strobe_counter;
append swtch_cntr7.d = swtch_cntr7 & lswtch_cntr1 & strobe_counter;
append swtch_cntr7.d = swtch_cntr7 & lswtch_cntr2 & strobe_counter;
append swtch_cntr7.d = swtch_cntr7 & lswtch_cntr3 & strobe_counter;
append swtch_cntr7.d = swtch_cntr7 & lswtch_cntr4 & strobe_counter;
append swtch_cntr7.d = swtch_cntr7 & lswtch_cntr5 & strobe_counter;
append swtch_cntr7.d = swtch_cntr7 & lswtch_cntr6 & strobe_counter;
append swtch_cntr8.d = lswtch_cntr8 & swtch_cntr7 & swtch_cntr6 & swtch_cntr5 & swtch_cntr4 & swtch_cntr3 & swtch_cntr2 & swtch_cntr1 & lswtch_cntr0 & strobe_counter;
append swtch_cntr8.d = swtch_cntr8 & lswtch_cntr0 & strobe_counter;
append swtch_cntr8.d = swtch_cntr8 & lswtch_cntr1 & strobe_counter;
append swtch_cntr8.d = swtch_cntr8 & lswtch_cntr2 & strobe_counter;
append swtch_cntr8.d = swtch_cntr8 & lswtch_cntr3 & strobe_counter;
append swtch_cntr8.d = swtch_cntr8 & lswtch_cntr4 & strobe_counter;
append swtch_cntr8.d = swtch_cntr8 & lswtch_cntr5 & strobe_counter;
append swtch_cntr8.d = swtch_cntr8 & lswtch_cntr6 & strobe_counter;
append swtch_cntr8.d = swtch_cntr8 & lswtch_cntr7 & strobe_counter;
append swtch_cntr8.d = swtch_cntr8 & lswtch_cntr9 & strobe_counter;
append swtch_cntr9.d = lswtch_cntr9 & swtch_cntr8 & swtch_cntr7 & swtch_cntr6 & swtch_cntr5 & swtch_cntr4 & swtch_cntr3 & swtch_cntr2 & swtch_cntr1 & lswtch_cntr0 & strobe_counter;
append swtch_cntr9.d = swtch_cntr9 & lswtch_cntr0 & strobe_counter;
append swtch_cntr9.d = swtch_cntr9 & lswtch_cntr1 & strobe_counter;
append swtch_cntr9.d = swtch_cntr9 & lswtch_cntr2 & strobe_counter;
append swtch_cntr9.d = swtch_cntr9 & lswtch_cntr3 & strobe_counter;
append swtch_cntr9.d = swtch_cntr9 & lswtch_cntr4 & strobe_counter;
append swtch_cntr9.d = swtch_cntr9 & lswtch_cntr5 & strobe_counter;
append swtch_cntr9.d = swtch_cntr9 & lswtch_cntr6 & strobe_counter;
append swtch_cntr9.d = swtch_cntr9 & lswtch_cntr7 & strobe_counter;
append swtch_cntr9.d = swtch_cntr9 & lswtch_cntr8 & strobe_counter;
append swtch_cntr9.d = swtch_cntr9 & lswtch_cntr9 & strobe_counter;

/* switch_cntr_hold goes high when counter reaches 788 ~26usec */
switch_cntr_hold.ck = clk;
switch_cntr_hold.d = swtch_cntr9 & swtch_cntr8 & lswtch_cntr7 & lswtch_cntr6 & lswtch_cntr5 & swtch_cntr4 & lswtch_cntr3 & swtch_cntr2 & lswtch_cntr1 & lswtch_cntr0;
/* *************** STATE MACHINE FOR STROBE ***************** */
field T1SM = [T1..0];
$define t1_idle  'b'00
$define t1_cnt_hold 'b'01
$define t1_error  'b'10
$define t1_error2 'b'11
[T1..0].ck = clk;
strobe.ck = clk;
strobe_counter.ck = clk;

SEQUENCED T1SM {
    present t1_idle
        if (strobe_init) next t1_cnt_hold out strobe_counter;
        default next t1_idle;
    present t1_cnt_hold
        if (switch_cntr_hold) next t1_idle;
        default next t1_cnt_hold out strobe_counter out strobe;
    present t1_error next t1_idle;
    present t1_error2 next t1_idle;
}

/* Cycle through source positions from 1 to 32 and 1or2 wavelength sets */
[PS6..0].ck = clk;

PS0.d = !strobe;

/* Depending on how many wavelength sets we're using (1 or 2) we may or may not want to do the A1/A2 selection */
PS1.d = spc0 & wl_sets; /*(A1/A2 selection on switch = wavelength selection)*/
PS2.d = (spc1 & wl_sets) # (spc0 & !wl_sets); /*(Data0 for B1..B32 selection)*/
PS3.d = (spc2 & wl_sets) # (spc1 & !wl_sets); /*(Data1 for B1..B32 selection)*/
PS4.d = (spc3 & wl_sets) # (spc2 & !wl_sets); /*(Data2 for B1..B32 selection)*/
PS5.d = (spc4 & wl_sets) # (spc3 & !wl_sets); /*(Data3 for B1..B32 selection)*/
PS6.d = (spc5 & wl_sets) # (spc4 & !wl_sets); /*(Data4 for B1..B32 selection)*/
H2. CPLD_breast_imager_slave.pld

/* *************** INPUT PINS ***********************/

PIN 83 = clk; /* PLD Clock */
PIN 56 = cs1; /* chip select 1 */
PIN 54 = cs2; /* chip select 2 */
PIN 57 = cs3; /* chip select 3 */
PIN 55 = cs4; /* chip select 4 */

PIN 4  = ind1a; /* Input from ADC 1A */
PIN 5  = ind2a; /* Input from ADC 2A */
PIN 6  = ind3a; /* Input from ADC 3A */
PIN 8  = ind4a; /* Input from ADC 4A */
PIN 9  = ind5a; /* Input from ADC 5A */
PIN 10 = ind6a; /* Input from ADC 6A */
PIN 11 = ind7a; /* Input from ADC 7A */
PIN 15 = ind8a; /* Input from ADC 8A */

PIN 16 = ind1b; /* Input from ADC 1B */
PIN 17 = ind2b; /* Input from ADC 2B */
PIN 18 = ind3b; /* Input from ADC 3B */
PIN 20 = ind4b; /* Input from ADC 4B */
PIN 21 = ind5b; /* Input from ADC 5B */
PIN 22 = ind6b; /* Input from ADC 6B */
PIN 24 = ind7b; /* Input from ADC 7B */
PIN 25 = ind8b; /* Input from ADC 8B */

PIN 27 = ind1c; /* Input from ADC 1C */
PIN 28 = ind2c; /* Input from ADC 2C */
PIN 29 = ind3c; /* Input from ADC 3C */
PIN 30 = ind4c; /* Input from ADC 4C */
PIN 31 = ind5c; /* Input from ADC 5C */
PIN 33 = ind6c; /* Input from ADC 6C */
PIN 34 = ind7c; /* Input from ADC 7C */
PIN 35 = ind8c; /* Input from ADC 8C */

PIN 36 = ind1d; /* Input from ADC 1D */
PIN 37 = ind2d; /* Input from ADC 2D */
PIN 39 = ind3d; /* Input from ADC 3D */
PIN 40 = ind4d; /* Input from ADC 4D */
PIN 41 = ind5d; /* Input from ADC 5D */
PIN 44 = ind6d; /* Input from ADC 6D */
PIN 46 = ind7d; /* Input from ADC 7D */
PIN 48 = ind8d; /* Input from ADC 8D */

/* *************** OUTPUT PINS **********************/

PIN 60 = outd1a; /* Output Data to DSP 0A */
PIN 61 = outd1b; /* Output Data to DSP 0B */
PIN 63 = outd2a; /* Output Data to DSP 1A */
PIN 64 = outd2b; /* Output Data to DSP 1B */
PIN 65 = outd3a; /* Output Data to DSP 2A */
PIN 67 = outd3b; /* Output Data to DSP 2B */
PIN 68 = outd4a; /* Output Data to DSP 3A */
PIN 69 = outd4b; /* Output Data to DSP 3B */
PIN 58  = sync; /* Sync output for Data to DSPs */

/* *************** PINNODES **********************/

PINNODE = sp1;
PINNODE = sp2;
PINNODE = sp3;
PINNODE = sp4;

/* *************** DATA MUXING *********************** */

sp1.d = !cs1;
sp2.d = !cs2;
sp3.d = !cs3;
sp4.d = !cs4;

[sp1..4].ck = clk;

sync.d = sp1 # sp2 # sp3 # sp4;
sync.ck = clk;

/* Right Side */
outd1a.d = sp1 & ind1c # sp2 & ind3c # sp3 & ind5c # sp4 & ind7c;
outd1b.d = sp1 & ind2c # sp2 & ind4c # sp3 & ind6c # sp4 & ind8c;

outd2a.d = sp1 & ind1d # sp2 & ind3d # sp3 & ind5d # sp4 & ind7d;
outd2b.d = sp1 & ind2d # sp2 & ind4d # sp3 & ind6d # sp4 & ind8d;

/* Left Side */
outd3a.d = sp1 & ind1a # sp2 & ind3a # sp3 & ind5a # sp4 & ind7a;
outd3b.d = sp1 & ind2a # sp2 & ind4a # sp3 & ind6a # sp4 & ind8a;

outd4a.d = sp1 & ind1b # sp2 & ind3b # sp3 & ind5b # sp4 & ind7b;
outd4b.d = sp1 & ind2b # sp2 & ind4b # sp3 & ind6b # sp4 & ind8b;

outd1a.ck = clk;
outd1b.ck = clk;
outd2a.ck = clk;
outd2b.ck = clk;
outd3a.ck = clk;
outd3b.ck = clk;
outd4a.ck = clk;
outd4b.ck = clk;
## APPENDIX I – GLUE LOGIC BOARD BOM, LAYOUT, and SCHEMATIC

### I1. Bill of Materials

<table>
<thead>
<tr>
<th>Item</th>
<th>Reference</th>
<th>Value</th>
<th>Package</th>
<th>Description</th>
<th>Dist.</th>
<th>Dist. PN</th>
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<td>0.1u</td>
<td>805</td>
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<td>805</td>
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<td>IC 5.0V 250MA LDO REG 8-SOIC</td>
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I2. Schematic
I3. Board Layout
## APPENDIX J – MASTER DSP BOARD BOM, SCHEMATIC, AND BOARD LAYOUT

### J1. Bill of Materials

<table>
<thead>
<tr>
<th>Item</th>
<th>Qty</th>
<th>Reference</th>
<th>Value</th>
<th>Package</th>
<th>Description</th>
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<td>0.01 uF</td>
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<td>D1,D2,D3</td>
<td>RED-SMT</td>
<td>(3mm x 2.2mm x 1.5mm)</td>
<td>LED RED ULTRA BRIGHT GW SMD</td>
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J2. Schematic
J3. Board Layout
### APPENDIX K – SLAVE DSP BOARD BOM, SCHEMATIC, AND BOARD LAYOUT

#### K1. Bill of Materials

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<tr>
<th>Item</th>
<th>Reference</th>
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K2. Schematic
K3. Board Layout
APPENDIX L – DETECTOR UNIT BACKPLANE BOM, LAYOUT, AND SCHEMATIC

L1. Bill of Materials

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<th>Item</th>
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<td>SV_PWR_RES, 3.3V_PWR_RES</td>
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<td>RES 5.000 OHM 15W 1% SMD TO-220</td>
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<td>FPS2-T2205.000CT-ND</td>
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<td>12V_PWR_RES</td>
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<td>TO-220</td>
<td>RES 50.000 OHM 15W 1% SMD TO-220</td>
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<td>R1,R2,R3,R5,R6</td>
<td>10k</td>
<td>0805 SMD</td>
<td>RES 10K OHM 1/8W 5% 0805 SMD</td>
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<td>R4</td>
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<td>2512 SMD</td>
<td>RES 300 OHM 1W 5% 2512 SMD</td>
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<td>New Egg</td>
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<td>CONN DB9 MALE SOLDIER CUP NICKEL</td>
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<td>FUSE DRAWER</td>
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<td>Chroma</td>
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<td>19 INCH 6U ENCLOSURE</td>
<td>Elma</td>
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</table>
L2. Schematic
L3. Board Layout
APPENDIX M – LABVIEW BLOCK DIAGRAMS

M1. Data Acquisition

Initialization of DAQ digital input channels. Sets acquisition rate, samples, and mode (burst).
Preparation for reading a single frame of data. Lower left corner writes DIO_PC0 and DIO_PC1 to 1 to instruct mDSP to begin data acquisition.

For each frame of data the LabVIEW unpacks the 8-bit packets in Data_converter_mx.vi and then reorganizes the arrays in preparation for displaying the data.
Data_converter_mx.vi is responsible for organizing the 8-bit packets received on the data bus and formatting them into 32-bit floating point data points for each source, detector, and wavelength.

Data acquired from the DAQ is converted into the appropriate arrays and then written to 4 files (one for each wavelength) and also output to the Data Acquisition plot. Only the selected wavelength and detectors are displayed, but all values are written to the file.
When the data acquisition is complete, and the correct number of frames have been acquired, the LabVIEW instructs the mDSP to leave the imaging state by setting DIO_PC0 and DIO_PC1 low.

M2. Gain Bit Programming

When the 'CONFIRM' button is pressed, the LabVIEW uploads the current gain bits to the mDSP, waits, and then reads back 'Average Over' number of frames and then averages the result.
Automatic gain settings are calculated when the ‘AUTO’ button is pressed. This code starts with the lowest gain setting and then keeps increasing the gain until the data detected for a given channel falls within the acceptable range (as set by the Imaging Parameters tab). When a channel has found an acceptable gain setting, it preserves that gain setting and ceases to continue testing higher gain settings, in order to avoid saturation of the detection channel.
APPENDIX N – WINDKESSEL VASCULAR MODEL

To understand the physiological mechanism that causes an increase in blood volume in the breast during the breath hold, we created a three-compartment vascular model for the breast. Vascular models have been used to understand the biological mechanisms for dynamic optical contrast in the brain [N1, N2].

![Fig. N-1. Analog electrical equivalent for a 3-compartment Windkessel model of the vascular system.](image)

Fig. N-1 shows the analog electrical equivalent of the 3-compartment (arterial, capillary, venous) Windkessel model of the vascular system. Each vascular compartment is modeled with two resistors and a capacitor, while the arterial and venous blood pressures are modeled by voltage sources. The resistors account for the vascular resistance to blood flow, while the capacitors model the vascular compliance and ability to store blood. The voltage sources cause a current to flow through the electrical equivalent circuit, representing the flow of blood. The blood volume in a given compartment is equal to the difference between the flow out and the flow into that compartment. Table 9-2 shows the resistance and capacitance values used for each compartment, which were adapted from literature [N3].
Table N-1. Descriptions and values of the parameters used in the 3-compartment vascular model.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Description</th>
<th>Value</th>
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<tr>
<td>$P_a$</td>
<td>Arterial blood pressure</td>
<td>60 mmHg</td>
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<tr>
<td>$P_v$</td>
<td>Venous blood pressure</td>
<td>25 mmHg</td>
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<tr>
<td>$R_{a1}$</td>
<td>Input resistance of the arterial vasculature</td>
<td>0.0075 mmHg/s/ml</td>
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<tr>
<td>$R_{a2}$</td>
<td>Output resistance of the arterial vasculature</td>
<td>0.038 mmHg/s/ml</td>
</tr>
<tr>
<td>$R_{c1}$</td>
<td>Input resistance of the capillary vasculature</td>
<td>12.1 mmHg/s/ml</td>
</tr>
<tr>
<td>$R_{c2}$</td>
<td>Output resistance of the capillary vasculature</td>
<td>2.42 mmHg/s/ml</td>
</tr>
<tr>
<td>$R_{v1}$</td>
<td>Input resistance of the venous vasculature</td>
<td>2.43 mmHg/s/ml</td>
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<tr>
<td>$R_{v2}$</td>
<td>Input resistance of the venous vasculature</td>
<td>0.013 mmHg/s/ml</td>
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<tr>
<td>$C_a$</td>
<td>Capacitance of the arterial vasculature</td>
<td>0.91 ml/mmHg</td>
</tr>
<tr>
<td>$C_c$</td>
<td>Capacitance of the capillary vasculature</td>
<td>2.7 ml/mmHg</td>
</tr>
<tr>
<td>$C_v$</td>
<td>Capacitance of the venous vasculature</td>
<td>13.3 ml/mmHg</td>
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</table>

The breath hold is implemented in the Windkessel model as an increase in venous blood pressure ($P_v$) by 5 mmHg, simulating the increase in thoracic pressure impeding the venous return. The parameters in Table N-1 are those used to model healthy breast tissue. To model tumor vasculature we increase the capillary resistances ($R_{c1}$ and $R_{c2}$) by 10 times and decrease the capillary compliance ($C_c$) by 2 times. The results of the breath hold simulation performed using a Windkessel model in response to a breath hold, as run using a Simulink (MATLAB, Mathworks Inc.) program. The program is included in Fig. N-2.
The results of the model are shown in Fig. N-3. The blue line represents the % change in total blood volume for a healthy breast in response to a breath hold, while the blue response represents the response of a tumor-bearing breast. Similar to the clinical results shown in Chapter 9, the greatest contrast between the tumor and healthy vasculature occurs in the recovery period following the breath hold. Further improvements to this model could account for oxygen consumption by the tissue, and provide insight into the transient response of oxygenated and deoxygenated hemoglobin as opposed to just total blood volume. In addition, validation of the model by both experimental data and other physical parameters such as heart
rate, blood pressure, and oxygen saturation could strengthen this work and provide a greater understanding of the biological mechanism from which we derive the optical contrast during a breath hold.

Figure N-3. Plot showing the % change in blood volume for a healthy breast vascular model and a tumor vascular model.

References:

