A Multimodal Breast Cancer Imaging System Using Coregistered Dynamic Diffuse Optical Tomography and Digital Breast Tomosynthesis

by

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MSc ETH EEIT, ETH Zürich (2009)

Submitted to the Department of Electrical Engineering and Computer Science in partial fulfillment of the requirements for the degree of Doctor of Philosophy at the MASSACHUSETTS INSTITUTE OF TECHNOLOGY June 2017

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Abstract

Diffuse optical tomography (DOT) is an emerging noninvasive functional imaging method for breast cancer diagnosis and neoadjuvant chemotherapy monitoring. In particular, the multimodal approach of combining DOT with x-ray digital breast tomosynthesis (DBT) is especially synergistic as DBT prior information can be used to enhance the DOT reconstruction. DOT, in turn, provides a functional information overlay onto the mammographic images, increasing sensitivity and specificity to cancer pathology.

We describe a dynamic DOT apparatus designed for tight integration with commercial DBT scanners and providing a fast (1 Hz+) image acquisition rate to enable tracking of hemodynamic changes induced by the mammographic breast compression. The most significant advance enabling fast acquisition was the design and construction of a direct analog-to-digital conversion frequency-domain near-infrared spectroscopy (FD-NIRS) component. It achieves simultaneous dual wavelength operation at 685 nm and 830 nm by concurrent 67.5 MHz and 75 MHz frequency modulation of each laser source, respectively, followed by digitization using a high-speed analog to digital converter and real-time hybrid FPGA-assisted demodulation by discrete Fourier transform (DFT).

The overall DOT system integrates 96 CW-NIRS and 24 FD-NIRS source locations, as well as 32 CW-NIRS and 20 FD-NIRS detection locations into low-profile plates that mate to the DBT compression paddle and x-ray detector cover, respectively. The plates and the embedded optical fibers are made of plastic to minimize x-ray absorption and thus allow true simultaneous acquisition of the DBT image.

We first characterize each major system component individually, and then demonstrate overall performance using static and dynamic tissue-like phantoms, as well as in vivo images acquired from the pool of patients recalled for breast biopsies at the Massachusetts General Hospital Breast Imaging Division.

Thesis Supervisor: David A. Boas
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Chapter 1

Introduction

Breast cancer is the most prevalent cancer form in women worldwide and it generally also has the highest mortality rate, with the exception of some regions, such as the United States (US), where it is surpassed by lung cancer [1]. In this dissertation we present our contribution to hopefully enhance breast cancer detection and monitoring, which in turn would lead to improved patient outcomes.

Diffuse optical tomography (DOT) is a noninvasive, nonionizing, and safe imaging modality capable of generating three-dimensional (3D) concentration maps of chromophores, such as oxyhemoglobin (HbO) and de-oxyhemoglobin (Hb), by sending near-infrared light through tissue. These maps can reveal information about tissue metabolic status, which is otherwise not directly accessible with structural imaging methods such as x-ray mammography.

Striving to make this additional information accessible to clinicians, and thus allowing them to make more informed decisions, we have designed a DOT add-on to a commercial digital breast tomosynthesis (DBT) system. DBT, or colloquially called 3D mammography, is an x-ray based technology that, similarly to computed tomography (CT), provides 3D structural images of the tissue, albeit at a considerably reduced resolution along the axis perpendicular to the compression plane due to limited projection angles. A combined DOT/DBT system can therefore provide a functional overlay over the structural volume slices obtained by the DBT system, and thus present the clinician the additional functional information in a clear and
familiar fashion. Ideally such a system will retain the benefits of each individual modality, which are high spatial resolution in the case of DBT, and provision of functional information in the case of DOT, and at the same time also take advantage of synergies between the two technologies, such as providing prior information to the DBT image reconstruction.

While other DOT/DBT combination systems have been published before, our second generation tomographic optical breast imager (TOBI2), which we present here, has the potential to be a significant step towards clinical feasibility. It is to our knowledge the first system to feature an x-ray translucent optical probe which allows true simultaneous data acquisition, and thus enables exploitation of the full benefits of coregistration. This is in contrast to previous systems, where at least parts of the optical probe had to be removed for DBT image capture, or the breast even had to be recompressed due to the use of separate systems, and consequently the complexity of image fusion and prior extraction was much higher.

Also, as part of TOBI2, we built and published [2] to our knowledge the first frequency-domain near-infrared spectroscopy (FD-NIRS) system with frequency encoded light sources, as well as direct digital sampling and demodulation. These improvements over previously available systems, with the target of increased acquisition speed, were motivated by the desire to capture tissue dynamics during mechanical stimulation (e.g. mammographic compression), a promising contrast mechanism yet to be fully explored.

Due to its planned location in a clinical space and number of subjects we hope to acquire, the system was built to a near-commercial standard. Initial characterization shows that it performs at the expected level, and as designed is much faster than the previous generation instrument. Performance was further confirmed by tests using custom silicone phantoms featuring liquid filled cavities free of glass or other foreign materials which could distort our results due to light piping. Finally, we have acquired initial patient images showing expected trends based on previous publications, but to reach final conclusions regarding clinical performance of TOBI2, a larger number of subjects has to be acquired and their data have to be processed.
1.1 Thesis outline and bibliographical notes

The remainder of this dissertation is organized as follows. In chapter 2 we will describe our motivation in more detail, give a brief introduction to DOT, and then further explain our rationale to build a new DOT system. In chapter 3 we will present the system, the image reconstruction methods, as well as the phantoms we made to test the system in detail. In chapter 4 we present the characterization results for the main components of TOBI2, and also demonstrate results showing the overall system performance, such as phantom experiments and a first patient image. In chapter 5 we discuss the results and present potential future developments and alternative design decisions.

The contents of this thesis are mainly based on our previous journal publications, covering the FD-NIRS component including the demodulation algorithm and the overall TOBI2, respectively:


Additionally we have presented our work at the following conferences:

- B. Zimmermann, J. Selb, S. Carp, Q. Fang, J. Stadtmiller, R. Dewsnap, R. Altman, and D. Boas, “A frequency domain near-infrared spectroscopy oximeter using high-speed, direct analog to digital conversion,” in *Biomedical Optics and*


And finally, Massachusetts General Hospital has also decided to apply for patents covering aspects of the FD-NIRS component and the optical probe:


Chapter 2

Background and Significance

In this chapter we will first illustrate the need for improved breast cancer detection and monitoring, then give a brief introduction to DOT and the progress made in the field in recent years. Finally, we will explain the benefits of combining DOT with a structural imaging modality, and elucidate why we built a new and faster instrument.

2.1 Clinical need for improved breast cancer detection

The American Cancer Society estimates that in 2017, 252,710 women will be diagnosed with invasive breast cancer in the US alone. When excluding non-melanoma skin cancer, the breast is the most common cancer site in females (see Tab. 2.1) with a share of 29% of new cases, and the overall lifetime probability of developing breast cancer is estimated at 12.4% [10]. Even though the survival rate has significantly increased in the last 30 years (see Fig. 2-1), earlier detection and improved treatment remain a priority.

X-ray mammography and its extension to 3D imaging, DBT, are the most widely used screening modalities, and have been attributed a 14% to 32% relative reduction in breast cancer mortality for women aged 39 to 69 years [11]. Both of these techniques can offer greater than 80% sensitivity [12]–[14], but poor specificity in clinical use
<table>
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<th>World Deaths</th>
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Table 2.1: Estimated cancer incidence and mortality in women in 2012. Numbers in thousands. *excluding non-melanoma skin cancer. (Data from [1].)

Figure 2-1: Breast cancer incidence and mortality rates for US females in the years 1984 to 2014. The growing difference between new cases and deaths illustrates the increasing survival rate. (Data from [24].)

[15]–[17], resulting in benign biopsies over 70% of the time [18], remains a challenge. These biopsies that ultimately show no evidence of cancer can cause significant stress to the patients and their families.

Women with mammographically dense breasts, which make up 43.3% of the US female population aged 40 to 74 [19], present an additional complication. Dense breasts are a significant risk factor for breast cancer [20], [21], yet at the same time mammographic sensitivity and specificity is reduced in these patients [22], [23].

Efforts to overcome these shortcomings are being made in multiple areas. DBT, due to its 3D imaging of the breast, is able to offer moderately increased sensitivity and specificity by reducing the confusing superposition of layers of breast tissue present in
traditional digital mammography [25]–[27]. Furthermore, functional methods such as contrast-enhanced magnetic resonance imaging (MRI) [28]–[32] and positron emission tomography (PET) [33]–[35], are gaining ground with respect to specificity [36]–[40]. Unfortunately, the cost and availability of these technologies, and the injection of tracers [40] prevent them from wide adoption for screening exams.

2.2 Introduction to near-infrared diffuse optical tomography (DOT)

Near-infrared DOT, an emerging technology for tissue functional imaging, can offer a relatively inexpensive, non-invasive, and non-ionizing alternative to the high-cost methods mentioned in the previous section. Near-infrared DOT uses wavelengths in the range of 650 nm to 950 nm, the so-called first optical window, where light absorption is minimal compared to shorter or longer wavelengths, at which point hemoglobin or water absorption coefficients are large respectively. Chromophore absorption contributions in typical breast tissue are shown in Fig. 2-2. Other windows at longer wavelengths exist, but the first window has the additional advantage that common silicon photodetectors offer high quantum efficiency throughout the range (see red line in Fig. 2-2), whereas at longer wavelengths more exotic and expensive materials would have to be employed.

DOT builds upon the technique of near-infrared spectroscopy (NIRS) to provide 3D tissue chromophore concentration maps. DOT works by sending near-infrared light of the wavelengths mentioned in the previous paragraph along multiple paths through tissue, and in the simplest case measuring the attenuation of a continuous-wave (CW) light source, or additionally the phase shift of a radio frequency (RF) power-modulated light source. These methods are called CW-NIRS and FD-NIRS respectively. Alternatively, with time-domain near-infrared spectroscopy (TD-NIRS) the attenuation and broadening in the time-domain of a pulsed light source is measured [41]. FD-NIRS and TD-NIRS measurements allow the disentanglement of ab-
Figure 2-2: (blue) Tissue absorption contributions of HbO, Hb, water, and fat in the wavelength region of the first optical window. Assuming HbT of 30 μM, SO2 of 75%, tissue water and fat concentrations of 45% and 55% respectively. Extinction coefficients of hemoglobin from [42] with data from Gratzer and Kollias, water from [43], [44], and fat from [45]. (red) Typical quantum efficiency of a silicon photodetector. Data from [46].

Sorptive and scattering effects. By fitting a light diffusion model to measurements acquired from source and detector arrays that at least partially encompass the tissue, localized absorption and scattering coefficients can be reconstructed. Finally, by combining results from two or more wavelengths, the above mentioned 3D concentration maps of tissue chromophores, such as HbO, Hb, and total hemoglobin (HbT), as well as oxygen saturation (SO2) can be obtained.

One of the main difficulties using DOT is the need for a good model of the measurement, because due to the ill-posedness of the problem, induced by the necessarily sparse sampling, small model-data mismatches can be amplified in the inversion, and thus lead to significant inaccuracies in the reconstructed chromophore maps [47]. To overcome this problem, researchers in the field have proposed various solutions to address the most detrimental error mechanisms, and thus made DOT image reconstruction more robust.

For example, 3D modeling of the breast tissue [48], [49] has largely replaced the 2D models prevalent in the early phase of DOT. At the same time the diffuse pho-
ton propagation model has been augmented with coupling coefficients to account for varying and imperfect contact of the fibers with the skin [50], and to compensate for fluctuations of local skin pigment and hair density [51]. Methods are also being introduced to detect and correct light leakage even before the measurement [52], or completely reject optodes with insufficient signal quality.

Reconstructing chromophore concentrations directly, as opposed to first reconstructing absorption coefficients at discrete wavelengths and then calculating concentrations, lets one take advantage of prior information of their absorption spectra (so called spectrally constrained reconstruction). This approach has proven to result in significantly improved image quality compared to the indirect method [53]–[55].

Finally regularization techniques, used to prevent overfitting due to the underdetermined nature of the problem, are becoming more and more sophisticated. Researchers inform the regularization parameters with structural information obtained by a second high-resolution imaging modality [56], such as MRI [57]–[59], and also have devised methods to reduce crosstalk between chromophores in spectrally constrained reconstructions [60]. Most of the improvements mentioned in the previous paragraphs are standard procedure nowadays, and readily available software packages such as Redbird [61], [62], NIRFAST [63], [64], and TOAST++ [65] incorporate them.

On the hardware side, innovative stand-alone DOT-based optical breast imaging systems having circular [66], [67], pentagonal [68], cup shaped [69], as well as parallel plate [70]–[72] optode geometries have been reported. Using instruments with aforementioned configurations and algorithms, multiple research groups have started exploratory studies, looking for markers of lesions [73], [74], and also acquiring healthy baseline functional properties [75]. More recently, those studies have expanded in the number of measured subjects [76], and even multi-center trials [77] have been completed. Researchers have been able to detect abnormal deep-tissue angiogenesis and metabolism, and were able to identify elevated HbT as one of the primary markers for cancer detection with DOT [78]. Finally, monitoring of neoadjuvant chemotherapy with DOT has been another focus of interest [79]–[83], as it plays to the advantages of the technology, i.e. observing functional changes in underlying tumor physiology,
which are known to manifest earlier than the actual tumor shrinkage [84], [85], but also avoiding the technologies shortcomings, i.e. low spatial resolution, because the tumors to be monitored are often already fairly large.

Despite these encouraging results, stand-alone DOT has not yet managed to establish itself as a useful tool in daily clinical routine, and it is becoming more evident that a further breakthrough is required to achieve sufficiently high specificity.

2.3 The case for multi-modal imaging

Inspired by the success of other multi-modal imaging technologies, especially positron emission tomography combined with computed tomography (PET/CT), researchers began to explore the possibility of combining DOT with structural imaging modalities for breast cancer imaging. Combining low-resolution functional imaging with high-resolution structural imaging in a spatially and temporally co-registered manner creates a win-win strategy: on the one hand, utilizing the high-resolution structure images as a prior, the functional imaging modality can yield improved image quality and reduced artifacts [57], [62], [86] to deliver a more accurate representation of the functional status of tissue; on the other hand, specificity of the structural imaging modalities can be improved by adding complementary physiological information, such as hemoglobin concentration, blood flow, and other metabolic activity, from the functional imaging modality. Moreover, coregistration of two modalities can facilitate the extrapolation of image findings interpreted from one modality to the other, and ease in the acceptance of new technologies by the radiology community.

Co-registration of DOT with ultrasound [87] and MRI [88]–[90] has been investigated by various groups both for cancer detection, and chemotherapy monitoring [91]. However, combining DOT with DBT or x-ray mammography is more promising in terms of clinical translation due to the gold-standard status, high-prevalence, fairly low-cost, and high-resolution nature of these x-ray technologies. In particular, adding the functional diagnostic information of the low-cost and non-ionizing DOT technology to the well established x-ray technique, instead of introducing a completely
new tool, might prove to be a gentle way to establish the new technology and allay concerns by clinicians.

Several DOT/DBT studies have been published [92]–[94], including the results from our own first generation tomographic optical breast imager (TOBI1) [61], [95], [96], demonstrating the potential of the technology to differentiate malignant from benign lesions.

2.4 Motivation to build an improved system

In recent years it has been discovered that monitoring dynamic changes in the breast due to breath maneuvers [97], [98], gas inhalation [99], or mechanical stimulation [100]–[104] can yield valuable additional information. Evaluating dynamic contrast due to mechanical stimulation in combined DOT/DBT systems is particularly efficient, because the breast will be readily under compression during mammography in any case.

Our group has already investigated hemodynamic responses of breasts under partial or full mammographic compression using a stand-alone DOT system, finding statistically different pressure responses of tumor tissue compared to healthy tissue [105], [106], and even being able to estimate volumetric blood flow and oxygen consumption [107]. Increased blood flow has previously been shown to coincide with tumor regions [108]. Additionally the stiffness disparity of healthy versus malignant tissue might lead to new cancer markers which could be revealed in the future.

To take full advantage of this promising contrast mechanism, we built a second generation DOT/DBT system (TOBI2) with dynamic imaging in mind. The main benefit of TOBI2 over the previous system [96] is a much higher acquisition speed achieved by using a combination of frequency encoding, fast source switching, and parallel detection. Overall, up to 34 lasers can be powered at the same time, and all 52 detectors can be acquired simultaneously. The resulting fast frame rate and short frame acquisition period minimizes image artifacts caused by changing tissue optical properties and non-concurrent sampling of all channels due to time-multiplexed
sources, similar to the rolling shutter effect known in digital cameras.

A main innovation of TOBI2 is its completely custom built FD-NIRS component. Unlike CW-NIRS systems which have achieved high imaging rates through a combination of frequency and time multiplexing [69], [109]–[111], traditional FD-NIRS imagers still require fairly long acquisition times (up to 60 s) to obtain a full set of tomographic data. The lengthy measurement is a result of sequential cycling through all laser wavelengths and output fibers, where sufficient integration time is needed for each data point to overcome the inherently lower signal-to-noise ratio (SNR) of FD-NIRS measurements.

The multiwavelength FD-NIRS system design we present in this dissertation combines a fast galvo-based fiber multiplexer on the source side with direct analog-to-digital conversion on the detection side. The direct sampling method, enabled by advances in high-speed analog-to-digital converters (ADCs), offers two significant advantages compared to the commonly used homo- and heterodyne I/Q demodulation schemes [112]. On the one hand, multiple modulation frequencies can be used simultaneously in conjunction with discrete Fourier transform (DFT) demodulation before detector saturation or decreased noise performance become a concern. This allows operation of multiple laser sources without the need for multiple, frequency specific I/Q circuits, as required in homodyne demodulation; on the other hand, by placing the ADC close to the photodetector module the RF analog circuit design is simplified and there is much less chance for RF leakage, interference, and channel-to-channel crosstalk.

While the direct sampling approach has been increasingly used in the telecommunications field (e.g. software defined radios), the instrument built as part of TOBI2 was, to the best of our knowledge, the first FD-NIRS system using direct digital sampling and frequency encoding. Since our initial publication [2], other groups have also presented direct sampling, frequency encoded systems [113], [114], and frequency encoded FD-NIRS systems using more traditional demodulation techniques [68].

Additional advantages of TOBI2, over our first generation system, are an increased optode density, which results in higher image resolution, as well as x-ray translucent
source and detector plates. Employing x-ray translucent optical probes eliminates
the necessity to remove them before x-ray imaging, and thus enables true simulta-
neous dual-modal imaging, and reduces the time spent in compression compared to
sequential optical and x-ray imaging, thereby increasing patient comfort.
Chapter 3

Methods and System Description

In this chapter, we will first give an overview of the TOBI2 system. Then we will describe the individual system components in more detail. Finally, we will explain the construction of some of the phantoms we created for performance testing, and outline the image reconstruction methods used for the results presented in chapter 4.

3.1 System overview

TOBI2, the main subject of this dissertation, is a hybrid CW-FD-NIRS dynamic DOT system with an x-ray translucent optical fiber probe designed to mount on a commercial DBT machine. A hybrid solution for the NIRS instrumentation was chosen to leverage the advantages of both technologies. While the FD-NIRS system can provide phase delay information to obtain absolute tissue optical properties, the CW-NIRS system is technologically easier to build and thus cheaper on a per-channel basis, offers greater parallelism and therefore increased duty cycle and speed due to the larger number of available modulation frequencies, and finally its lower bandwidth detectors feature a 20 times lower noise-equivalent power (NEP), resulting in more long separation source detector pairs being above the noise floor.

The complete system, together with its schematic drawing, is shown in Fig. 3-1 and Fig. 3-2, respectively. The source plate, sending light through the compressed breast, is attached to the upper compression paddle of a Hologic Selenia Dimensions
DBT machine. The detector plate, which collects the light transmitted through the breast, slides onto the x-ray detector cover of the DBT machine. Both probe plates are connected to the instrument tower via glass fibers, which are protected by black plastic sleeves. The tower houses both the FD-NIRS and CW-NIRS components, as can be seen in Fig. 3-1(b). Due to the necessity to locate TOBI2 in an active clinical space, the tower is normally fully enclosed. On the outside of the tower, a shelf is supporting the laptop which controls the optical system. Holders for the optical probe, located on the front of the tower, allow for stowage when the DBT machine is used stand-alone. A foot pedal is available to mark specific time points during the measurement. The following sections describe each component in more detail.

3.2 FD-NIRS component

The FD-NIRS component discussed in the following subsections was specifically designed to integrate into the multimodal DOT/DBT breast imager described in this thesis. However, the FD-NIRS component can equally well be used stand-alone as a FD-NIRS system for brain, breast, muscle or other NIRS studies.

To get an initial overview, a simplified schematic of the FD-NIRS component is shown as part of Fig. 3-2 (green boxes). A more detailed schematic, depicting all major components, can be seen in Fig. 3-3. The FD-NIRS subsystem consists of two enclosures, the source unit, and the detector unit, shown in the upper half of Fig. 3-1(b). The two units are linked by command and clock routing cables. The detector unit is also connected to the laptop for data acquisition, as well as to the CW-NIRS component for synchronization.

3.2.1 FD-NIRS source unit description

The two main components contained in the FD-NIRS source unit shown in Fig. 3-4 are the clock generator and the light source assembly. The purpose of the clock generator is to generate the modulation frequencies for both lasers, as well as the clock for the ADCs in the detector unit. Since the phase delay incurred by the light
Figure 3-1: (a) Complete TOBI2 system. The optical probe is attached to the DBT machine. Optical fiber bundles connect the optodes in the probe to the instruments inside the enclosed tower. (b) Inside view of the instrument tower. From top to bottom: The FD-NIRS detectors, FD-NIRS sources, (2x) CW-NIRS source expansion boxes, and the CW6 main instrument.
Figure 3-2: Schematic overview of the TOBI2 system. CW-NIRS components are shaded in yellow, FD-NIRS components are shaded in light green, DBT system components are shaded in gray, and fiber optics are represented in blue.

when traveling through tissue is one of the two principal measurements required to compute absolute tissue optical properties, the phase differences between the two modulation signals and the ADC clock have to be stable, meaning the relative phase is not allowed to drift, and the relative as well as the absolute phase noise should be kept to a minimum.

To eliminate phase drift, it is necessary to derive all signals from a common reference. Furthermore, to minimize phase noise, we decided to generate all three signals from a common oscillator by integer division only. Other options would have been to generate each frequency by separate phase-locked loops (PLLs) locked to a common reference, or to generate the signals via direct digital synthesis (DDS) integrated circuits (ICs) again clocked from a common high speed clock.

A custom printed circuit board (PCB), shown in Fig. 3-5, was designed to house the main clocking components. On it a 50 MHz reference clock for the instrument is generated by a temperature-compensated crystal oscillator (TCXO) (Connor-Winfield D75J). A 2.7 GHz clock signal is derived from this reference by a PLL (Analog Devices AD9517). 2.7 GHz is the least common multiple of the chosen laser modulation
Figure 3-3: Schematic showing all major components of the ED-NIRS system.
Figure 3-4: FD-NIRS source unit interior. Top left: Clock generator and the two laser driver cards. Bottom left: Free-space optical cage assembly with collimators, beam combiner, galvanometer, and fiber array. Top right: Galvo drivers. Bottom right: Fiber connectors to probe.
Figure 3-5: Custom clock generator. The TCXO reference clock, the PLL with the main oscillator, as well as the divider generating the ADC sampling clock are located under the left shield. The dividers generating the two double-rate modulation frequencies are located under the right shield, maximizing separation from the sampling clock.

frequencies (67.5 MHz and 75 MHz) and the ADC sampling clock (180 MHz). The ADC sampling clock is derived from the 2.7 GHz clock by an internal divider of the AD9517 IC, which is set to a divisor of 15. It is then sent over two coaxial cables to the backplanes of the detector unit for further distribution.

The main 2.7 GHz PLL clock is also sent via low-voltage positive emitter-coupled logic (LVPECL) to a divide-by-2 IC (Micrel SY100EP32V), which creates a 1.35 GHz signal compatible with the secondary clock divider and distribution IC (Analog Devices AD9513). This IC, which is separately shielded to prevent electromagnetic interference (EMI) into the sample clock, creates 135 MHz and 150 MHz signals by division with 10 and 9, respectively. Those signals are then sent to the corresponding two laser driver cards.

The high impedance nodes in the avalanche photo diode (APD) modules on the detector cards are very sensitive to EMI. Any signal at the modulation frequencies of the lasers coupled into these nodes will look like a real (optical) signal. Thus great
care has been taken to electrically shield both the APDs, but more importantly also the laser diodes and laser driver circuits, as high currents swinging at the modulation frequencies are present on these boards. To simplify shielding at the source side, we designed the clock generator and laser driver PCBs in such a way as to keep the final modulation frequencies as localized as possible. This is mainly achieved by performing the final division by two only on the driver boards themselves. Additionally, conducted EMI, which could reach the detector box via the ADC clock cables, or other data lines, is suppressed by appropriate filters on all signal, data, and power lines.

The laser driver boards, an example is shown in Fig. 3-6, are again custom PCBs. The double-rate modulation signal entering the board is first sent through a band-pass filter (Mini-Circuits SXBP-140+/SXBP-150+) to prevent any back-propagation of the final modulation signal, as mentioned in the previous paragraph. Next the signal frequency is divided by 2 with a flip-flop, and then sent through another band-pass filter (Mini-Circuits SXBP-70+) to convert the square wave to a sinusoidal signal by removing the odd harmonics. The final laser driver stage consists of an op-amp (Analog Devices AD8038) and a RF NPN transistor (CEL NE46134) as an output buffer. Two 10 turn trim potentiometers allow the adjustment of modulation amplitude and offset. They are usually set so that the optical output power of the connected laser diode varies between 3.75 mW and 46.25 mW over a modulation cycle, resulting in a 85% modulation depth and 25 mW average power.

The light sources consist of one 50 mW 685 nm laser diode (Opnext HL6750MG) modulated at 67.5 MHz and a 50 mW 830 nm laser diode (Opnext HL8338MG) modulated at 75 MHz. The light of both diodes is collimated, and the beams are then combined by a long-pass dichroic beamsplitter (Semrock FF757-Di01) with a reflection band of 450 nm to 746 nm, and a transmission band of 768 nm to 1100 nm. To adjust the beams so that they are parallel and overlapping, the diodes and collimator packages are mounted on kinematic and translation mounts. The combined beam is then launched via a two-dimensional (2D) scanning galvanometer (ThorLabs GVS002) and two achromatic doublet lenses (ThorLabs AC254-075-B) into 200 μm
Figure 3-6: Custom laser driver. The double-rate modulation signal is fed into the left SMA connector, then passes through the first band-pass to reach the frequency divider under the small shield. The resulting square wave is then converted to a sinusoidal wave in the second band-pass and fed to the driver circuit under the large shield on the right.

Multimode silica fibers. Twenty-five fibers are arranged in a 5x5 array so that the illuminated fiber can be selected by steering the galvanometer to the appropriate angle. Simulations by ThorLabs show that the doublet lenses concentrate the beam into a maximal spot size of 21.2 μm, much smaller than the diameter of the multi-mode fibers used here. Additionally, the beam can be steered into a beam dump, which allows the system to acquire the dark signal.

Using an off-the-shelf galvanometer instead of a traditional optical switch as an optical multiplexer offers a cost-effective solution to allow dynamic adjustment of scanning patterns and to accommodate additional source locations in the future without needing additional electronic hardware.

The galvanometer is controlled by its own dedicated micro-controller (Atmel AT-mega 2560) via 2 digital-to-analog converters (DACs) (Texas Instruments PCM56U) mounted on a custom PCB to ensure fast switching between fibers. Calibration of the galvo positions is performed by sequentially connecting a patch fiber from each source fiber port to a photodiode mounted in a SMA mating sleeve. The diode is connected via a trans-impedance amplifier to the ADC internal to the micro-controller. The micro-controller can then perform a successively refined search pattern to find the location of maximal light intensity. By turning the laser sources on independently, it can also display information about the co-alignment of the two laser sources in two
axes.

With this arrangement, when switching between neighboring source fibers, as it is typically the case during a measurement, we achieve a switch time of 600μs from trigger to illumination of the target fiber. Stabilization of the signal is achieved within 2ms. In the worst case transition, diagonally across the array, we achieve a switch time of 2ms, and the signal is completely settled within 3ms.

### 3.2.2 FD-NIRS detector unit description

Each of the 20 detection channels is built on its own printed circuit board (see Fig. 3-7) to allow for easy replacement and future expandability. The diffusely re-emitted light arriving at the detector boards via fused silica fiber bundles is converted to electrical signals by an APD which is part of an APD module (Hamamatsu C5331-04). The module also contains the first gain stage in the form of a low noise trans-impedance amplifier, as well as the necessary high voltage supply to bias the APD. The bias voltage is temperature compensated to keep the gain of the APD constant. This module features an APD operating in linear mode with a 3mm diameter, peak sensitivity at 800 nm, a pass band of 4kHz to 80 MHz, and a typical noise equivalent power of 0.4 pW/√Hz (maximum 0.8 pW/√Hz). The choice of APD module is primarily determined by a tradeoff between bandwidth and active area. Larger APDs tend to have a larger junction capacitance, and thus limit the bandwidth available from the trans-impedance amplifier stage. The selected APD has just enough bandwidth for our application, and thus allows us to maximize the active area and collect as much light as possible.

The overall gain of the APD module is only $2.3 \times 10^4$ V/W, correspondingly a 1nW optical signal would only produce an electrical signal with 23μV amplitude. Therefore, to match the signal to the input range of the ADC (2.25V full-scale), further amplification is needed. The first stage after the APD module is a high-speed, low noise current feedback op-amp (Analog Devices AD8000) providing 20 dB of gain. The AD8000 was chosen for its bandwidth and its low input voltage noise, which is approximately 70 fW/√Hz when referred to the optical input, and thus much
Figure 3-7: Detector card. TOBI2 contains 20 of these cards. On the left, the APD module with SMA optical connector is visible. The gain chain, comprising several amplifiers and the band-pass filter, followed by the ADC and field-programmable gate array (FPGA), are located to the right of the APD module. The backplane connector is mounted on the right edge. In addition to the smaller shields on the card, the whole card can be covered with a large shield to further decrease cross-talk to the neighboring detectors and EMI sensitivity.

Then the signal is filtered with a bandpass filter with a $63\text{ MHz}$ to $77\text{ MHz}$ passband (maximum attenuation $1.5\text{ dB}$) and $>20\text{ dB}$ rejection below $50\text{ MHz}$ and above $95\text{ MHz}$ (Mini-Circuits SXBP-70+) in order to block other interference (e.g., in our breast tomography system, light coming from the CW-NIRS component, which could otherwise saturate the ADCs and reduce dynamic range). In the next step, the signal is further amplified by another AD8000 op-amp and then the single ended signal is converted into a differential signal by a transformer. It is then fed into a differential amplifier (Linear Technology LTC6409) which serves as the last gain stage ($20\text{ dB}$), as well as ADC buffer and additional anti-aliasing low-pass filter. Each section of the analog signal chain is individually shielded to prevent interchannel crosstalk between neighboring detector cards, as well as leakage across the gain chain.

Finally, the signal is sampled 180 million times per second (180 MSPS) with 16-bit resolution by a high-speed ADC (Linear Technology LT2209). The ADC has its own built-in voltage reference, and is directly connected to its own dedicated low-cost FPGA (Xilinx Spartan-6 LX9), which demodulates the signal, as described in
Sec. 3.2.3. The FPGA loads its firmware from the attached flash memory, or via the back-plane over a JTAG chain. Additionally, each board contains its own voltage regulators for the various components, as well as a temperature sensor.

The detector box features two backplanes, each connecting 10 detector cards to the common control card, shown in Fig. 3-8. Additional to the signal and power lines, each backplane also contains a low-voltage differential signaling (LVDS) clock fanout buffer (Analog Devices ADCLK854), distributing the clock coming from the clock generator card in the source unit to the ADCs on the individual detector cards.

On the detector unit control card, a microcontroller (Atmel ATmega2560) clocked at 8 MHz, collects the data from all 20 detector cards via a 4 MHz serial peripheral interface (SPI) bus over multipoint LVDS (M-LVDS). The data are then sent on to the personal computer (PC) via a parallel to universal serial bus (USB) converter (FTDI FT245R) for further signal processing and data recording. The microcontroller on the control card also signals the microcontroller in the source unit to illuminate the next source location in the sequence, and sends synchronization pulses to the CW-NIRS.
component. Additionally, the source unit microcontroller can set the detector cards in a diagnostic mode and transfer card temperature as well as raw, not-demodulated data from the ADCs.

The detection unit was built collaboratively with our industrial partner. The author initially built a single source, single detector prototype. The author then provided the component selection, schematic for the analog front end (including ADC and FPGA), and firmware for the scaled up unit as described in this section. TechEn Inc. handled the PCB layout with input from the author, as well as manufacturing of the cards and assembly of the chassis.

3.2.3 Demodulation algorithm

As mentioned in the previous section, the analog signal is sampled 180 million times per second at 16-bit resolution. From this raw data stream, the signals of the 685 nm and 830 nm lasers have to be extracted. In a traditional analog instrument, this would be accomplished using homo- or heterodyne detection with a mixer for down conversion, and then a slow ADC for sampling the in-phase and quadrature signals [112]. In our instrument, however, we have chosen to do this digitally. One possibility would be to use a fast Fourier transform (FFT) algorithm. However, a fairly large amount of frequency bins is required to keep the width of each individual bin small enough, and thus the memory and computational requirements would be very high, and a cost-effective solution for a 20 channel instrument is not possible. The FFT algorithm computes all \( N \) bins simultaneously while for our application we only need to obtain the values from two bins. Therefore, another possibility is to directly implement a DFT, where we compute the two bins we are interested in individually, without the need of having to compute all the other bins. In our design, we achieve a frequency bin width comparable to a 4 million point FFT at a much lower computational cost. We have also further optimized the DFT algorithm, as described below, to avoid multiplication in the high frequency (180 MHz) section.

The standard DFT \( X[k] \) is computed as shown in Eq. 3.1, where \( x[r] \) is the input
signal, \( W_N = e^{-j(2\pi/N)} \), and \( k \) denotes the frequency bin to be computed.

\[
X[k] = \sum_{r=0}^{N-1} x[r]W_N^{kr} \tag{3.1}
\]

This algorithm requires fast complex multiplications, and all the complex factors \( W_N^{kr} \) have to be computed on the fly or stored in a lookup table. Thus, a direct implementation of this equation in an FPGA is no easy task. To simplify, we turn to the Goertzel algorithm. As shown in Ref. [115], the \( k \)th bin of the \( N \)-point DFT can be computed by feeding the signal into a system with impulse response \( W_N^{-kn}u[n] \) which is initially at rest (i.e., all registers are initialized to zero). \( u[n] \) is the unit step function. The desired result is then the \( N \)'th output value [see Eqs. 3.2 and 3.3] of the system. See also flow graph in Fig. 3-9.

\[
X[k] = y_k[n]|n = N \tag{3.2}
\]

\[
y_k[n] = W_N^{-k}y_k[n - 1] + x[n] \tag{3.3}
\]

The resulting modified algorithm is much better suited for implementation in a FPGA; the multiplication factor is constant, and the complete input sequence does not need to be kept in memory. But there are still some deficiencies. The algorithm still requires one complex multiplication or four real multiplications per input sample. Further, the required adder and multiplier in the recursive loop can only have a combined latency of one clock cycle, which is not possible to implement in low cost
Figure 3-10: Flow graph of the Goertzel algorithm with an additional delay in the recursive loop.

FPGAs at the required numerical resolution and speed. To overcome the problem of insufficient latency in the recursive loop, we have changed the one sample delay element \( z^{-1} \) to an \( l \) sample delay element \( z^{-l} \). The resulting flow graph is shown in Fig. 3-10. Note that some non-recursive elements have been added to compensate for the added delay and keep the overall transfer function unchanged. The transfer function of the system of Fig. 3-10 is shown in Eq. 3.4 for the case when \( l = 2 \).

\[
H_k(z) = \frac{1 + z^{-1}W_N^{-k}}{1 - z^{-2}W_N^{-2k}}
\]  
(3.4)

The structure can be further simplified by multiplying the numerator and denominator with a common factor as shown in Eqs. 3.5 and then expanding the terms, as shown in Eq. 3.6 (similar as in Ref. [115]).

\[
H_k(z) = \frac{(1 + z^{-1}W_N^{-k})(1 - z^{-2}W_N^{2k})}{(1 - z^{-2}W_N^{-2k})(1 - z^{-2}W_N^{2k})}
\]  
(3.5)

\[
H_k(z) = \frac{1 + z^{-1}W_N^{-k} - z^{-2}W_N^{2k} - z^{-3}W_N^{k}}{1 - 2\cos(\frac{3\pi}{N}2k)z^{-2} + z^{-4}}
\]  
(3.6)

The result is shown in Fig. 3-11. The complex multiplication in the recursive loop is replaced with a real multiplication at the expense of an additional term in the non-recursive part. The modulation frequencies of the instrument can be chosen
freely within a certain range. Thus, if we choose the modulation frequency of one laser as $3/8 \cdot 180\,\text{MHz} = 67.5\,\text{MHz}$ corresponding to $k = 3/8 \cdot N$, the cosine becomes zero, and thus the structure can be further simplified as shown in Fig. 3-12. The recursive loop is now reduced to a simple adder, for a real input sequence $x[n]$ the numbers stay real in this part of the computation. A similar structure can be found for the case of $l = 3$ and $k = 5/12 \cdot N$, resulting in a modulation frequency of $75\,\text{MHz}$ for the second laser. The corresponding transfer function is shown in Eq. 3.7.

$$H_k(z) = \frac{1 + z^{-1}W_N^{-k} + z^{-2}W_N^{-2k} - z^{-3}W_N^{3k} - z^{-4}W_N^{2k} - z^{-5}W_N^k}{1 + z^{-6}} \quad (3.7)$$
As highlighted in Fig. 3-12, this novel algorithm can be implemented in a hybrid fashion, splitting the workload between a FPGA and a PC. On the FPGA the resource requirements are minimal. Specifically, for a 4 million point DFT computation only one 36-bit adder is required for guaranteed overflow-free computation, and by absorbing the delay element in the loop, the adder can have a latency of up to four clock cycles, which allows us to employ pipelining in its implementation. The complex multiplications in the non-recursive structure can all be done in real time, e.g., in MATLAB on a PC, since only the last four results of the recursive structure are needed, and thus the amount of data to be transferred and the amount of computation are fairly low.

We implemented the above algorithm on the FPGA of each detector card. For each modulation frequency, we continuously calculate two DFTs with 50% overlap and length of \( N = 4 \cdot 10^6 \) in real time. This results in an output data rate of 90 Hz. All 180 million samples per second each ADC acquires are actually used for calculation of the output data. For this implementation only four 36 bit adders and some control logic are required per card. Everything fits even in the smallest FPGA model of Xilinx’s low cost Spartan-6 line, with room to add additional frequencies if required later on. On the PC side, MATLAB has to perform three and five complex multiplications, and three and five complex additions per sample per channel for the first and second modulation frequency respectively. This results in a total workload of \( 20 \text{ ch} \cdot 90 \text{ Hz} \cdot (5 + 3) = 14400 \) complex multiplications and additions per second overall to decode and record the amplitude and phase raw data in real-time, a task any recent computer can easily handle.

### 3.3 CW-NIRS component

The CW-NIRS imaging unit, shown in Fig. 3-1(b) bottom half and in Fig. 3-2 in yellow, was manufactured by TechEn Inc. (Milford, MA). It consists of the main commercially available CW6 system (modified to control the two supplemental source units mentioned below) containing 32 detectors and 32 lasers diodes split evenly
between the wavelengths of 690 nm and 830 nm. Two custom supplemental source units boxes, each containing 32 lasers split again evenly between 690 nm and 830 nm, increase the total of CW lasers to 96. Each laser is modulated with a square wave at one of 32 discrete frequencies between 6.4 kHz and 12.6 kHz. The frequencies are chosen to span less than one octave, so that harmonics do not fall on other modulation frequencies. The system powers the lasers in the main CW6 unit and the supplemental boxes in a sequential, electronically switched order, so that only 32 lasers are on simultaneously (only 32 modulation frequencies are available, thus they have to be shared between the main unit and the supplemental units). The dwell time in each state is specified in multiples of 40 ms, and for the data shown in this thesis we used a dwell time of 1 s, thus resulting in a frame rate of 1/3 Hz.

On the detection side, each channel consists of a Hamamatsu APD module (C5460-01). Similar to the module used in the FD-NIRS component, described in Sec. 3.2.2, this module features an APD with 3 mm diameter active area, integrated trans-impedance amplifier, and temperature compensated biasing. However, the frequency response is tailored to the CW-NIRS application with a pass-band of DC to 100 kHz. The lower cut-off frequency allows for a much higher gain of $1.5 \times 10^8 \text{V/W}$ at 800 nm and thus a reduced typical noise equivalent power of $20 \text{fW/}\sqrt{\text{Hz}}$ (maximum $40 \text{fW/}\sqrt{\text{Hz}}$). The higher gain unfortunately also results in a saturation limit of 60 nW, which is significantly lower than the limit of the APD used in the FD-NIRS component.

The APD module is followed by a high-pass filter, variable gain amplifier, anti-aliasing filter, and digitizer. FPGAs and digital signal processors on a central control card demodulate the signals by calculating the FFT of each detection channel, and send the raw intensity data of the appropriate FFT bins to the controlling computer via a USB connection at a rate of 25 samples/s. The CW-NIRS component also acquires analog auxiliary channels containing synchronization information from the FD-NIRS component, as well as foot pedal presses indicating events during the measurement period. A functionally similar instrument (CW5) has previously been described in Refs. [109], [116]. The main difference is that the older CW5 instrument
Figure 3-13: Close-up view of the source plate, including detail of the 45° polish.

lacks built in decoding capabilities, and thus the signals have to be demodulated off-line on a computer.

3.4 Optical probe construction

The optical probe consists of a source plate, shown in Fig. 3-13, which is permanently attached to a DBT machine compression paddle, and a detector plate, shown in Fig. 3-14, which fits on the x-ray detector cover of the DBT machine. Figure 3-15 shows the probe attached to the DBT machine. Both the detector plate and the compression paddle with the source plate can be detached within seconds to return the DBT machine into its normal clinical configuration. We also built a protection case for the detector plate, and both plates can be hanged on the side of the instrument tower for storage.

The source plate contains 120 500 µm Poly(methyl methacrylate) (PMMA) fibers,
placed individually in milled channels in a 3.175 mm thick clear polycarbonate plate. A clear plate was chosen to facilitate positioning of the breast by the research mammographer. At the edge of the source plate, the PMMA fibers are illuminated by 500 µm glass fibers that are terminated with SMA connectors at the other end, where they attach to the optical instrumentation. At the light emitting ends, the PMMA fibers are polished at 45° angles to send light into the breast tissue by total internal reflection. A 45° termination, as opposed to small prisms or bent fiber, was chosen to minimize source plate thickness and thus x-ray absorption. To prevent light leakage through the clear source plate, the fiber channels end within 5 mm black plastic disks, and the fibers are painted black.

Efficient 45° polishing was achieved by fixating 12-15 PMMA fibers in a plastic tube using water soluble wax (Freeman Sol-u-carv), and then polishing the whole bundle on a commercial fiber polishing machine (Seikoh Giken SFP-510) using a custom angled fixture. After completion, the fibers are easily freed by dissolving the wax in warm water.

The detector plate consists of a quarter inch thick black acrylonitrile butadiene styrene (ABS) plate, into which 54 channels containing 2 mm diameter PMMA fibers
Figure 3-15: Detailed view of the DBT machine with attached optical probe. The compression paddle with the glued on optical source plate is installed in the paddle holding mechanism. The detector plate is resting on the bottom compression paddle.
are milled. On the light collection side, the fibers are terminated with 45° plastic prisms, and at the edge of the detector plate they are coupled into SMA terminated 2.5 mm diameter glass fiber bundles that route the light back into the instrument tower and to the detectors.

The optode locations on the source and detector plates are shown in Fig. 3-16. The coverage area is approximately a semi-circle with 160 mm diameter and was chosen so to give full breast coverage in 80% of patients, as determined by breast outlines obtained from DBT images from our previous study [96]. The optodes on the source plate were arranged in an oblique lattice, where the spacing of 10 mm was largely determined by the number of available sources in the CW-NIRS and FD-NIRS components. The detector optodes are not arranged in a grid shape. Even tough we strove to achieve a uniform distribution, their locations are determined by the need to route-out the fibers from the innermost optodes to the lateral plate edges. While this is obviously also necessary for the detector plate, the 2 mm diameter (plus margin for the channel) of the PMMA detector fibers, and their greater minimum bending radius, limit the routing options in-between the outer optodes to a larger degree. To obtain a metric of optode spacing in the detector plate we calculated the average distance to the nearest neighbor, which results in 12 mm.

To achieve x-ray translucency and therefore the possibility of true simultaneous co-registration, we have chosen to not use glass fibers or any metal in the field of
view of the DBT system. As discussed further in Sec. 5.1 and shown in Tab. 5.1, glass severely absorbs x-rays of the energies used in DBT. Additionally, the plates and fibers were chosen to be of similar materials to minimize x-ray contrast and thus further simplify artifact removal.

3.5 Probe optode assignment optimization

As mentioned previously, the optical subsystem consists of two distinct instruments, the CW-NIRS component (Sec. 3.3) and the FD-NIRS component (Sec. 3.2) with 96 sources and 32 detectors, and 24 sources and 20 detectors respectively. Each imager has its own advantages. The FD-NIRS instrument provides phase measurements and two wavelengths at each source location. The CW-NIRS instrument has higher temporal resolution and lower noise equivalent power, but no phase measurements and only one wavelength at each source location. The sources and detectors of each imager have to be assigned optimally to the 120 source and 54 detector optodes of our breast probe in order to obtain the maximum amount of information per measurement, and thus be able to generate the best possible reconstruction image quality. The problem of optimal optode assignment and distribution not only exists in breast imaging, but potentially also in the design of high density diffuse optical tomography head probes used increasingly in functional near-infrared spectroscopy [17].

To solve the optimal partition problem we took a creative approach - crowd-sourcing - to efficiently explore human-guided optimization and numerical algorithms. To this end a Javascript based web-app was developed, and lab members were invited to layout and fine-tune the probe design on-line. Each submitted design was ranked in real-time, according to a score based on the slope of the singular spectrum of the Jacobian matrix, a measure of the ill-posedness of the system [118]. Obviously an exhaustive search is prohibitive due to the enormous number of possible solutions. Therefore the participants had to find appropriate strategies to maximize their score. Even though the maximum possible score for our design constraints is unknown, we can estimate how close the solutions are based on an upper bound for the score.
Create 200 random solutions (first generation).

Calculate score for all solutions of current generation

Computing time used up or solution stagnant over many generations?

Create next generation, consisting of the 20 best previous solutions, plus 9 children of each of the 20 best previous solutions. Each child has one random optode permutation.

Done.

Figure 3-17: Flow diagram of the genetic algorithm used to obtain the best optode partition.

10 lab members submitted over 400 possible designs. Generally the scores of the human inspired designs were well above the mean score of 810 for purely random designs. However, the human designs were surpassed by solutions found by algorithms. The best solution was found by using a genetic algorithm. The flow diagram is shown in Fig. 3-17. After several trials a score of 888.6 was obtained, which is fairly close to a theoretical upper bound of 942 obtained by assigning FD-NIRS lasers to all source locations, and FD-NIRS detectors to all detector locations. Another algorithm, producing a score of 885, and thus almost as good as the above mentioned genetic algorithm, was derived by a co-investigator based on the mixture of a graph theory algorithm and human-guided optimization.

Contrary to our initial assumptions, high scoring solutions tend to have the optodes not distributed uniformly or randomly, but seem to have the FD-NIRS optodes, especially the detectors, clustered in the center of the probe, while pushing the CW-NIRS optodes to the boundary. Figure 3-18 shows the 'best' solution, as well as a uniform and a random solution for comparison.

It remains up to further investigation to determine the exact impact of a higher score on the resulting real life image contrast. Also, so far the different noise char-
Figure 3-18: Random, uniform, and best found optode partition patterns, including their score.
acteristics, as well as the duty cycles, have not yet been taken into account. Finally one has to also consider that only a few breasts will cover all optodes as we assumed in our slab geometry. Nonetheless we are confident that our 'best' partition is close to optimal, and we believe concentrating FD-NIRS optodes in the center also makes sense for actual breasts, as the center of the probe will almost always be covered by tissue, and thus the optodes generating the most information per fiber will always be in use. Hence the here presented 'best' solution is the one we implemented in our system.

3.6 Performance testing phantoms

To measure the temporal and spatial resolution of TOBI2, we created two phantoms. The first phantom features one centrally located spherical cavity with a diameter of 19 mm. The second phantom features three spherical cavities of 13 mm, 19 mm, and 25 mm diameter with a 45 mm center to center distance. The cavities can be filled with liquids of varying optical properties through the channels embedded in the phantom, to either match with or to create contrast to the background optical properties.

Each phantom was constructed from 2.8 L silicone (Smooth-On Ecoflex 00-50) mixed with 2660 mg of white pigment and 78 mg of black pigment (Smooth-On Silc Pig White & Black). The amount of pigments was experimentally determined to approximately result in optical properties similar to that of human breast tissue. To avoid light piping, the inclusions were made without glass, or any other material that could guide light around the inclusion and thus distort our results.

Specifically, as seen in Fig. 3-19(a) and (b), the inclusions were made of water-soluble wax spheres (Freeman Sol-U-Carv) and were mounted in the mold with 2.4 mm diameter steel tubes. After pouring and curing of the vacuum-degassed silicone, the tubes were removed, and the wax spheres were dissolved by flowing warm water through the channels. The finished phantoms, as shown in Fig. 3-19(c), have a thickness of 52 mm. The size and separation of inclusions were further confirmed by DBT
3.7 Image reconstruction methods

Optical image reconstructions, for the results presented in chapter 4, are performed on a pair of tetrahedral meshes, a finer one for solving the optical forward problem, and a coarser one for solving the inversion. The meshes are generated using the MATLAB-based toolbox 'iso2mesh' [49] (iso2mesh.sourceforge.net). A slab geometry is used to generate the phantom meshes, whereas 3D DBT images are used to extract the breast shape for patient scans. Raw optical measurements are first calibrated against a homogeneous silicone phantom with known optical properties and then fitted for bulk optical properties. Non-linear, spectrally constrained inversion of
the finite-element representation of the diffusion approximation using the Tikhonov-regulated Gauss-Newton approach is performed for 9 iterations using our in-house software, i.e., Redbird [61], to reconstruct optical images shown in sections 4.4 and 4.5. When solving the inverse problem, compositional structural priors are used as soft constraints in our structural-prior guided reconstruction algorithm described previously [62].

In phantoms, a sphere located at the inclusion center, and with its diameter matched, is used to derive the structural prior for each phantom inclusion, and the prior for background is set to enforce unity of both tissue compositions on each mesh node. For patients, a dual-Gaussian segmentation algorithm [62] is used to automatically derive adipose and fibroglandular compositional priors from DBT images. Similar to the phantom inclusion prior, a Gaussian sphere profile is used to generate an additional lesion prior with known centroid and size information provided by an experienced radiologist.
Chapter 4

Results: System Characterization and First Patient Images

In this chapter we will first present the results of performance tests conducted on the individual system components. Thereafter we will show phantom and initial patient images to demonstrate the capability of the final, combined system.

4.1 FD-NIRS component characterization

In this section we will first report the results of some basic system characteristics tests. Then we will show that the FD-NIRS component can recover optical properties of a tissue-like phantom.

4.1.1 Noise floor and phase measurement

To test basic functionality of the APD module, the gain chain, and the ADC converter on each detector card, the FPGAs were set into raw data acquisition mode, and 16,368 sample segments were obtained. FFTs of each segment were calculated, and for Fig. 4-1 100 of those FFTs were averaged. Figure 4-1 clearly shows two peaks at the laser modulation frequencies, as expected. No aliased harmonics, or other spurious signals are visible. Finally, the noise floor shows the shape of the band-pass filter in the
These positive results allow us to proceed to the next measurements. From here on we use the FPGA implemented DFT algorithm described in Sec. 3.2.3 to obtain signal amplitudes and phases. To measure NEP, amplitude-phase crosstalk, and inter-channel crosstalk, we implemented a setup where we can send light coming from the source unit through two automated filter wheels with five different neutral density filters and one empty slot each, allowing for 36 different absorption values ranging from 0 OD to 10 OD nominal (actual maximal attenuation at 685 nm is 8.06 OD and 5.69 OD at 830 nm). The resulting attenuated light is sent via a fiber to the detection component. Light outputs at different filter settings are calibrated with a sensitive optical power meter.

Figure 4-2(a) shows a typical plot of signal magnitude versus incident optical power of our system, obtained with the aforementioned setup. The optical powers given are corrected for modulation depth, which is typically 85%. The intersection of the gray asymptotes drawn in the figure indicates the optical power corresponding to an SNR of one. We typically measure a noise equivalent power of less than 1.4 pW/√Hz, which is approaching the manufacturer specified maximum noise equivalent power of the APD module of 0.8 pW/√Hz at 800 nm or approximately 1 pW/√Hz at 685 nm.
Figure 4-2: (a) Measured signal amplitude vs. incident optical power. Each point corresponds to 1 s of data. The blue line represents the driven detector, the red lines the three neighboring detectors. The grey asymptotes intersect at 1.25 pW, which represents the NEP of the system. The difference between the blue and red line represents the channel separation, shown in dark grey. (b) Measured signal phase vs. incident optical power. Each point represents 90 samples, corresponding to 1 s of data. The grey line is placed at the NEP of the system, as determined in (a). For both (a) and (b) 685 nm data is shown. The system behaves similarly at 830 nm with a NEP of 1.37 pW.
In the same figure, the responses of the three neighboring (left, right, below), non-driven detectors are plotted in red. As can be seen, even at high optical input power into the main, driven detector, the neighboring, non-driven detectors show no signal. Only when the optical power reaches above 1\( \mu \)W one of the neighboring detectors registers a signal. The channel separation on the detector side is thus larger than 100\( \text{dB} \) (five orders of magnitude). However, on the laser source side there is some measurable crosstalk between sources, most likely due to stray light generated by reflections in the optics coupling into unintended fibers, or because of the proximity of the fibers in, and right after the array plate in the optical multiplexer. We measure a channel separation of more than 80\( \text{dB} \) in the source component. The overall system is thus limited by the optical multiplexer and shows a channel separation of over 80\( \text{dB} \).

Saturation can be observed when a signal of approximately 1.2\( \mu \)W at 830 nm is fed to the APD. The same effect can be seen in Fig. 4-2(a) for powers above 1.5\( \mu \)W, where the system response becomes non-linear. This saturation power level is more than an order of magnitude higher than the performance of our commercial CW-NIRS system, and it is also much higher than the signals typically encountered in the transmission type measurements used in our breast scanner. Together with the noise floor of 1.4\( \text{pW} \) this results in an instantaneous dynamic range of more than 115\( \text{dB} \). At 685 nm, the dynamic range is even slightly larger because saturation is only reached at 1.5\( \mu \)W signal power. We were not able to observe any inter-wavelength crosstalk up to the maximum specified input power of 1.5\( \mu \)W.

Figure 4-2(b) shows the measured phase when the optical power is varied. From the flat response we can conclude that we do not observe any amplitude phase crosstalk. Also, the measured phase noise of the output signal is smaller than 6\( \text{mrad}/\sqrt{\text{Hz}} \) at 100\( \text{pW} \) input power. So far the measured phase has been held constant. To verify that the phase changes as expected, measurements on a setup where the optical path length can be changed with a linear translation stage were performed. The results can be seen in Fig. 4-3. For simplicity, the phase change has been converted to distance. The measured phase changes as expected.

Finally we also wanted to characterize the stability of the system. This is not
so much an issue because we intend to use the instrument for long measurements (the breast compression must be limited to a few minutes for reasons of patient tolerability), but because, depending on protocol, significant time might elapse from calibration measurement to subject measurements. First we measured signal magnitude and phase at system start-up when the optical path was held constant. In parallel, temperatures from the internal sensors, and additional external sensors were also recorded. The results can be seen in Fig. 4-4. Warm-up changes of approximately 0.35 dB or 4% magnitude and 20 mrad phase can be observed in the first 15 min. These changes are on a comparable timescale to the temperature increase measured on the detector card, and at the exhaust of the detector box, as shown in Fig. 4-4(b). Temperatures in the source unit increase to a far smaller degree, which is commensurate to its low power consumption. Stability after a 1 h warm-up period has been confirmed with a 10 h test (not shown), where the measured amplitude drifted by less than 1.5% and the phase less than 3 mrad at approximately 5 nW and 685 nm.
Figure 4-4: (a) Magnitude and phase change observed when powering on a cold FD-NIRS system. Measured at approximately 5 nW and 685 nm. (b) Temperatures measured during warm up at various locations in the system.
4.1.2 Tissue-like phantom optical property recovery

To test the ability of the instrument to recover absolute optical properties, we performed several titration experiments using a mixture of water, whole milk bought at the local grocery store, and black India ink (Higgins 44204). The measurements were performed in multi-distance reflectance mode, with source detector separations of 15, 20, 25 and 30 mm, and analyzed using the semi-infinite form of the diffusion approximation as described in Refs. [119], [120]. Ten equally spaced milk concentrations between 7% to 37% were used. For each milk concentration, we took measurements over a series of 20 absorption steps corresponding to 0 to 45.6 ppm of ink, resulting in a total of 200 different mixtures. The upper concentration limits correspond to maximal optical properties typically observed in patients [73].

Each phantom started as a 1500 mL mixture of milk (7% to 37%) and water (to 100%; no ink was present in the phantom at baseline). The probe was held in place by a holder on the surface of the liquid, approximately 1 mm submerged to ensure good optical contact. Ink was then added to the milk and water mixture by a computer-controlled syringe pump. Measurements were taken in between each ink adding step. To ensure proper mixing of all three components, we used a magnetic stirrer, and waited 30 s after each ink addition. This experiment was repeated 10 times, for each level of milk concentration. Measurements to calibrate the light magnitude and phase of our optodes, similar to those described in [121], were taken before and after the whole measurement sequence on a calibration phantom manufactured by ISS Inc..

The results can be seen in Figs. 4-5 and 4-6. The leftmost graphs (a) and (d) show that the recovered absorption and scattering coefficients change linearly with ink and milk concentrations, respectively. The closeness of the lines also shows that the recovered absorption coefficients are largely independent of milk concentration, and that recovered scattering coefficients are largely independent of ink concentrations. The middle graphs (b) and (e) show again the independence of recovered reduced scattering coefficients with changing ink concentration, and recovered absorption coefficients with changing milk concentrations. We observe that our results are close to the ideal.
Figure 4-5: Absorption stepping. (a) Recovered absorption coefficient versus ink concentration. The different lines represent different milk concentrations (the lowest line corresponds to the lowest milk concentration). (b) Recovered reduced scattering coefficient versus ink concentration. The different lines again represent different milk concentrations, with the lowest milk concentration corresponding to the lowest line. (c) The blue line shows the y-intercepts of linear fits to the curves in (a). Ideally, it would be constant at the level of water absorption indicated by the light blue line (0.0049 cm⁻¹). The red line shows the relative crosstalk from recovered absorption coefficient to recovered reduced scattering coefficient at different milk concentrations, derived from the slopes and mean magnitudes of the lines in (a) and (b). (d-f) show the same plots as (a-c), but for 830 nm. Water absorption at 830 nm is 0.0291 cm⁻¹.
Figure 4-6: Scattering stepping. (a) Recovered reduced scattering coefficient versus milk concentration. The different lines represent different ink concentrations. (b) Recovered absorption coefficient versus milk concentration. The different lines again represent different ink concentrations, with the lowest ink concentration corresponding to the lowest line. (c) The blue line shows the y-intercepts of linear fits to the curves in (a). Ideally, it would be constant at zero. The red line shows the relative crosstalk from recovered reduced scattering coefficient to recovered absorption coefficient at different ink concentrations, derived from the slopes and mean magnitudes of the lines in (a) and (b). (d-f) show the same plots as (a-c), but for 830 nm.
The blue lines in Figs. 4-5(c,f) and 4-6(c,f) show the y-intercept of a linear fit to each of the curves in Figs. 4-5(a,d) and 4-6(a,d), respectively. Ideally the blue curve in Fig. 4-5(c,f) would be constant at the level of water absorption (0.0049 cm\(^{-1}\) at 685 nm and 0.0291 cm\(^{-1}\) at 830 nm), because at the y-intercept the ink concentration is zero, and thus the only remaining absorber is water. We can see that the reported values are nearly independent of milk concentration, but slightly above the ideal values mentioned before. One possible explanation is contamination of the mixture with another absorber.

The blue line in Fig. 4-6(c,f) extrapolates the recovered scattering coefficient to zero milk concentration for different ink concentrations. We would expect this value to be zero, because without milk the mixtures do not contain any scatterer. The results are fairly close to the ideal, and show only a small positive correlation with ink concentration. The slight increase in scattering coefficient with increased ink could be explained by scattering from the ink particles.

The red line in Fig. 4-5(c,f) shows the slope of the linear fit to the lines in Fig. 4-5(b,e), normalized by the slopes of the linear fits to the lines shown in Fig. 4-5(a,d). Ideally the slopes of the lines in Fig. 4-5(b,e) would be zero, representing zero crosstalk from absorption to scattering coefficients. The red line in Fig. 4-6(c,f) shows the reciprocal measurement. We can see that in the absorption stepping the crosstalk generally is small, and only approaches 10% for low milk concentrations, where possibly the diffusion approximation used to analyze the data starts to break down. In the scattering stepping the crosstalk is a bit larger than in the absorption stepping, but generally also stays below 10%. A possible explanation for the worse result in the scattering stepping is that the milk titration, as opposed to the ink titration, was done by hand and thus additional errors were introduced.

Of note, we observed that the values of y-intercepts and crosstalk depend strongly on the assumed optical properties of the calibration phantom. We measured these properties with our commercial ISS Imagent FD-NIRS system, described in Ref. [121], but we assume that the Imagent measurements have a precision of approximately 5% to 10%. We therefore optimized the assumed optical properties of the phantom.
within that range to minimize y-intercepts and crosstalk. The optimized calibration phantom optical properties were consistent between multiple titration datasets (data not shown).

4.2 CW-NIRS component characterization

As mentioned before, an older but functionally similar system to our CW-NIRS instrument (TechEn CW6) has been characterized in Refs. [109], [116], so only a reduced set of tests, focused on the variable gain setting, has been performed here. We used the same multi-attenuation filter wheel setup as in Sec. 4.1.1, and chose gain settings of 1 to 200 for the variable gain amplifier in the CW-NIRS system. The results can be seen in Fig. 4-7(a). Figure 4-7(b) shows the noise equivalent power for each gain setting, as determined from the intersections of the light blue asymptotes in (a). The dynamic range, calculated as the difference between saturation power (yellow line in (a)) and noise floor, is also shown. We did not measure the saturation limit with a gain of 1 directly, because even at the lowest attenuation setting the light throughput of the filter wheel was not strong enough. However, from the APD datasheet we know that the detector will typically saturate at 75 nW at 690 nm (represented by the vertical part of the yellow line in (a)), thus this power was used as the saturation limit.

We observe that at high gain settings, when considering the 25 Hz system bandwidth, the measured NEP approaches the typical value of \( 20 \text{fW/}\sqrt{\text{Hz}} \cdot \sqrt{25 \text{Hz}} = 0.1 \text{pW} \) given in the APD datasheet. Thus at these higher gains the noise floor is determined by the electronic noise in the APD, and the instrument does not add additional noise. At low gain settings the measured magnitude of the noise floor does not shift; components after the variable gain amplifier are the dominant noise contributors.

The optimal gain range is thus found at medium settings of 2 to 50, where a dynamic range of up to 95 dB can be obtained. At higher gains the NEP does not decrease further, while still penalizing the dynamic range. On the other end, choosing
Figure 4-7: (a) Measured signal magnitude vs. optical power of the CW-NIRS system at various gain settings (indicated). 9 s of data at 690 nm and 25 Hz. (b) NEP and dynamic range vs. gain setting. NEP calculated from the light blue asymptotes in (a). Dynamic range calculated as difference between light blue noise floor line and yellow saturation line in (a). Dynamic range for gain of 1 is extrapolated.

A gain of less than 2 does not increase the saturation power level, while negatively affecting the NEP and dynamic range.

Crosstalk between channels was not observed. However, if one channel saturates a detector, obviously all channels terminating in that detector experience distortion. Additionally, if one channel is received at near saturation power in a detector, all other 15 detectors in the same bank will experience some crosstalk for that source only.

4.3 Optical probe performance

Analysis of the probe performance centers around two points: light throughput and impact on DBT x-ray images. To quantify the additional losses incurred due to choosing an x-ray translucent optical probe design, we measured the light transmission of both the source as well as the detector fibers and compared overall throughput vs. a simple design where glass fibers directly touch the tissue. On the source side, power is reduced by approximately 3.3 dB, and on the detection side by 6.4 dB, resulting in a total loss of 9.7 dB or 89% at 830 nm. At 690 nm the losses are slightly less due
Figure 4-8: Schematic showing the additional optical losses incurred due to the hybrid PMMA/glass fiber design vs. a minimal fiber-to-tissue approach.

to the better transmissivity of the PMMA fibers at this wavelength. The detailed results are shown in Fig. 4-8.

To assess the impact on x-ray images, DBT slices of a patient’s breast have been taken with the optical probe plates in place, and are shown in Figs. 4-9(a-c). In Fig. 4-9(a), on the upper surface of the breast, the small source fibers are only barely visible, whereas in Fig. 4-9(b), on the lower surface of the breast, the larger detector fibers and prisms are clearly visible, but their artifacts do not exceed the dynamic range of the x-ray detector. Figure 4-9(c) shows a center slice, which can be compared to a center slice of the same patient taken without the optical probe attached (Fig. 4-9(d)). It is evident that in the center of the breast the DBT reconstruction algorithm already largely removes the artifacts.

### 4.4 Phantom images

To test our complete system with all its components, we performed a series of phantom experiments. As a first test, to determine the maximal usable source-detector separation, we measured the single-inclusion phantom described in Sec. 3.6 with the liquid inside the inclusion matched to the bulk optical properties, which in turn are comparable to those of a typical human breast ($\mu_a = 0.075\,\text{cm}^{-1}$ at 690 nm and $\mu_a = 0.052\,\text{cm}^{-1}$ at 830 nm, $\mu'_a = 8.4\,\text{cm}^{-1}$ at 690 nm and $\mu'_a = 7.1\,\text{cm}^{-1}$ at 830 nm). The resulting calibrated signal magnitudes versus source-detector separations can be seen in Fig. 4-10. From this figure we observe that separations of less than approximately 9 cm result in detectable signals above the noise floor, whereas instrument
Figure 4-9: Impact of optical plates on the DBT images. (a) Top slice of breast DBT volume taken with the optical probe attached. The source fibers and mounting holes are clearly visible. (b) Bottom slice of breast DBT volume taken with the optical probes attached. The detector fibers and prisms are clearly visible. The high absorption patches are the result of small pieces of electrical tape used in the construction of the probe. They were removed subsequently. (c) Middle slice of breast DBT image taken with the optical probe attached. Faint shadows of the detector fibers can be seen. (d) For comparison, a middle slice of the separately acquired clinical breast DBT image taken on the same patient (no optical components present).
Figure 4-10: Plot of the signal amplitude of all possible source-detector combinations versus the corresponding source-detector distances, as measured in the single inclusion silicone phantom. The optical properties of the inclusion are matched to the bulk, which in turn has properties comparable to a human breast. The signals are expected to decay exponentially with distance.

noise dominates in measurements with source-detector separations of more than 9 cm.

To demonstrate the image reconstruction algorithm and evaluate the spatial resolution, we also imaged the triple-inclusion phantom described in Sec. 3.6. All three inclusions were filled with a water, milk, and India ink mixture, with the scattering coefficient matching the bulk of the phantom and the absorption coefficient being 1.81 times the value of the bulk at 690 nm. Figure 4-11(a) shows an absorption image representing the middle slice of the reconstructed 3D absorption map. The three inclusions can easily be seen, and the centroids are at the expected locations. The reconstructed absorption values at 690 nm are 0.138 cm\(^{-1}\), 0.142 cm\(^{-1}\) and 0.146 cm\(^{-1}\), which represent contrast of 1.59, 1.63 and 1.68, respectively, to the reconstructed bulk absorption coefficient of 0.087 cm\(^{-1}\) at 690 nm.

For testing the temporal dynamic performance of the system, the single-inclusion phantom was imaged over 165 seconds, with one image being reconstructed for every 3 s of data. During the first third of the measurement period, the water, milk, and India ink mixture in the inclusion was matched to the bulk optical properties both in absorption and scattering. During the middle third of the measurement, the
Figure 4-11: (a) Middle slice showing the reconstructed absorption map of the triple-inclusion phantom. (b) Middle slice showing the reconstructed absorption map of the single-inclusion phantom during the last third of the measurement. (c) Time course of the reconstructed absorption coefficients of the single-inclusion phantom at the location of the inclusion (blue), and at a control location approximately 4 cm left of the inclusion (red). All values at 690 nm.
absorption was increased to 1.54x the baseline value by injecting a different liquid mixture with higher ink concentration into the inclusion. For the last third of the measurement period, the absorption was further increased to 2.82x of the baseline value.

Figure 4-11(b) shows an absorption image representing the middle slice of the reconstructed 3D absorption map during the last third of the measurement. Figure 4-11(c) shows the time course of the reconstructed absorption values at the location of the inclusion, as well as at a control location approximately 4 cm left of the inclusion. The reconstructed absorption value at the control location has an average of 0.08 cm\(^{-1}\) and stays constant within ±6 percent. The average values of the reconstructed absorption coefficients at the inclusion centroid during each third of the measurement are 0.072 cm\(^{-1}\), 0.108 cm\(^{-1}\) and 0.166 cm\(^{-1}\), respectively. Compared to the targeted 1.54x and 2.82x contrast, the reconstructed contrast during the middle and last thirds of the dynamic measurement are 1.5x and 2.31x, respectively. The two visible spikes are presumably due to an expansion of the cavity due to increased liquid pressure when changing the mixture.

4.5 First patient images

4.5.1 Patient

A 47-year-old non-Hispanic white female with a breast cancer diagnosis was imaged on our system. An ultrasound guided left breast core biopsy indicated the presence of grade 3 invasive ductal carcinoma at 5 o'clock position, located 3 cm from the nipple, measuring 1.8 cm × 1.2 cm × 1.1 cm. An axillary lymph node core biopsy found lymph nodes with metastatic ductal carcinoma. Patient consent was obtained in accordance with the policies and guidelines of the Massachusetts General Hospital / Partners Healthcare institutional review board. The subject’s breast was imaged under partial compression (half mammographic force, 21.8 N for this patient, as measured by the DBT system built-in pressure sensor) first, followed by imaging under
full mammographic compression (44.5 N for this patient). The imaging session lasted approximately 3 minutes.

4.5.2 Results

Figures 4-12(a) and 4-12(b) display the slice of the HbT map passing through the center of the lesion, overlaid on the corresponding slice of the DBT from the patient scan. Optical images were reconstructed using the adipose and fibro-glandular tissue fractions as priors derived from the x-ray information [62]. In addition, we used a Gaussian sphere tumor prior with a diameter of 15 mm at the centroid of the lesion [62], as determined by our collaborating radiologist. Figure 4-12(a) shows the absolute HbT concentration and Fig. 4-12(b) shows the change in HbT due to increasing the compression level from partial to full mammographic force. To facilitate the visibility of hemodynamic changes in the tumor, the color scale in Fig. 4-12(a) is chosen such that values below 25 μM, which are representative of normal tissues, are transparent. Similarly, the color scale in Fig. 4-12(b) is chosen to show positive HbT changes as transparent. In both images the tumor area displays localized contrast, increased HbT concentration in the absolute image, and a compression-induced further reduction in HbT in the relative changes image. Figure 4-13(c) shows the time course of the mean HbT values in both the tumor region, and in the rest of the breast, respectively. During the first (half-force) compression period, HbT displays a slowly increasing trend in both the tumor and the normal tissues, but the tumor area exhibits what appears to be blood volume oscillations that are not as evident in the normal tissue. The second compression period was rather short, and the distinguishing feature is the substantial decrease in tumor HbT vs. half-compression while only a small further decrease occurs in the normal tissues.
Figure 4-12: (a) Absolute total hemoglobin concentration map of the slice corresponding to the tumor centroid, overlaid over the corresponding x-ray DBT slice. The red line denotes the tumor outline as marked by our collaborating radiologist. (b) Change in total hemoglobin concentration as the compression is increased from half to full mammographic force. The red line denotes the tumor outline as marked by our collaborating radiologist.

Figure 4-13: Time course of reconstructed total hemoglobin concentration (HbT) in the tumor region and normal breast tissue, respectively during the entire measurement session (the vertical bar and break in the timeline indicate where compression was increased from half to full mammographic compression).
Chapter 5

Discussion and Conclusion

5.1 Discussion

In this thesis, we have described and demonstrated our second-generation tomo-
graphic optical breast imager (TOBI2). One of the main goals of the development of
this new instrument was to increase acquisition speed to avoid artifacts due to hemo-
dynamic changes during breast compression, and in fact be able to capture these
dynamics as additional biomarkers. We reached this goal by a combination of intro-
ducing frequency division multiplexing in the FD-NIRS component, increasing the
switching speed of the time division multiplexing for both the CW and the FD-NIRS
component, and using many parallel detection channels.

Frequency division multiplexing in the FD-NIRS component was achieved by
building a completely new system, using a direct digital sampling approach, which al-
 lows the instrument to illuminate multiple wavelengths at the same time. Modularity
was emphasized during the construction of the instrument, resulting in the possibility
to easily fit additional sources and detectors if required. In fact in the future we plan
to build laser source cards built to fit directly into the same slots currently used for
the detector cards.

With a measured NEP of less than $1.4 \text{ pW}/\sqrt{\text{Hz}}$, the FD-NIRS component per-
forms near the APD manufacturer's specification. The employed direct digital sam-
pling and digital demodulation is however independent of the particular detector used.
Therefore, if an even lower noise floor is required, photomultiplier tubes (PMTs) could be used instead of APDs for example, but at the disadvantage of higher cost, potentially smaller dynamic range and the introduction of amplitude–phase crosstalk [122].

We also developed a signal decoding algorithm for use in the FD-NIRS component, which employs only adders in the high speed section of the filter structure, thus allowing the use of low cost FPGAs. Currently our system is limited to wavelengths of 685 nm and 830 nm, sufficient to distinguish oxy- and deoxy-hemoglobin. If required, it would easily be possible to increase the number of decoded frequencies to at least four, thus allowing a four wavelength instrument, or alternatively in a two wavelength system increase the speed by increasing parallelism and having two active RF-modulated laser sources per wavelength at any time. These changes could be made with minimal additional hardware, and no decrease in duty cycle. If even more frequencies need to be decoded, or if frequency sweeping is desired, a digital implementation of a more traditional demodulation scheme, e.g. homodyne or heterodyne detection, would become more competitive resource-wise. For this purpose, a larger and more expensive FPGA might be necessary.

Our FD-NIRS system characterization data also demonstrate an instantaneous dynamic range of greater than 115 dB at a maximum system bandwidth of 90 Hz, matching or exceeding other reported FD-NIRS diffuse optical spectrometers and imagers, such as those described in Refs. [70], [92], [113], [123].

Furthermore, the fast switching time (<2 ms worst case) of the galvo multiplexing system compares favorably to commercial optical switches which often have tens of milliseconds long switching times (e.g. 15 ms for Newport MPSN-62-12), and requires us to discard only two samples (due to the overlapping DFT sequences) per transition between illuminated source positions. Consequently, if one aims for a 50% overall duty cycle (individual sources will have obviously a lower duty cycle), all the data from all possible combinations of sources and detectors can be acquired in 1.16 s. In our particular application, we are aiming for a duty cycle above 90%, and hence chose settings that result in a 10 s cycle time and 94% duty cycle.

As mentioned before, to the best of our knowledge, the here presented FD-NIRS
component was at time of initial publication [2] the first FD-NIRS system to use frequency encoding, and the first to use direct digital sampling without prior down conversion.

In the CW-NIRS component, we have completely eliminated mechanical switching by dedicating a laser to each source fiber and then rotating electronically between laser banks. This approach could also be used in the FD-NIRS component, but at the cost of increased complexity in preventing EMI due to the less-localized footprint of this approach. Another possibility would be to use MEMS based optical switches, which can achieve sub-millisecond performance (e.g. Thorlabs OSW8108 typ. 0.5 ms). However, the availability of suitable MEMS switches is still limited, as most are optimized for the longer wavelengths used in telecommunications, and their price is still very high, especially when considering that multiple switches would have to be stacked to achieve the same number of source optodes. In any case, reducing the number of lost samples per switching event to one would require a significant synchronization effort to time the switching to occur exactly at a sequence boundary. Losing no sample at all is not possible with our overlapping decoding scheme.

Currently we have settled on a frame acquisition duration of 3 s for the CW-NIRS component, as this seems to represent a good compromise between duty cycle and frame rate. Three seconds per frame is already an order of magnitude faster than our previous system [96] (and many other breast optical tomography systems). If necessary in the future, we can easily acquire data at faster speeds (e.g. more than 1 Hz), with a small penalty in signal quality.

The second goal of this new system was to create an x-ray translucent optical probe to enable true simultaneous co-registration of DBT and DOT, which provides improvements in the DOT reconstruction accuracy, DOT and DBT image fusion, as well as reduction in acquisition and breast compression time. To make it possible to leave the optical probe in place during x-ray acquisition, the first priority is to keep its x-ray absorption variation low. Added absorption in the x-ray field of view can be compensated up to a certain degree by using a larger dose, but if the probe absorption varies too much, the detector dynamic range can be exceeded, and information will
Material | X-ray Density $(\log(I_{\text{transmitted}} / I_0))$ | % of Breast Phantom
--- | --- | ---
Mammographic Breast Phantom | 1.12 | 100%
2.5 mm Glass Fiber Bundle | 1.02 | 91%
400 $\mu$m Glass Fiber | 0.09 | 8%
3 mm Plastic Fiber | 0.08 | 7%
6.4 mm Acrylic Plate | 0.18 | 16%

Table 5.1: X-ray absorption of glass and plastic fibers compared to a standard mammographic breast phantom.

be lost.

Before construction of the optical probe, initial measurements of the x-ray absorption of typical probe materials were made by our group (summarized in Tab. 5.1). As expected, the measurements show that glass has a large x-ray absorption at the energies used for mammography. For example, a glass fiber bundle absorbs approximately as much as the whole breast. Even a 400 $\mu$m multi-mode glass fiber will leave a strong shadow in the x-ray image. For this reason, we decided early on in the design phase to only use plastic fibers. To minimize contrast in both the detection and source side, we embedded the plastic fibers into plastic plates by milling precise channels, thus keeping the x-ray absorption length fairly uniform. Due to the large optical attenuation of the used PMMA fibers at near-infrared wavelengths (especially at 830 nm in our case), it was necessary to minimize their length and transition to glass fibers right at the edge of the probe, just outside of the x-ray field of view.

The choice whether to mount the optical detector plate to the x-ray detector plate, and the source plate to the compression paddle, or vice versa, was again largely guided by the goal of artifact reduction. We expect that artifact removal for the bottom plate, which is directly attached to the x-ray detector, is easier than for the top plate. This is because the bottom plate stays stationary with respect to the x-ray detector, and thus a simple static calibration might be used, whereas the top plate moves with the compression paddle from patient to patient, and therefore a more complicated removal algorithm will have to be used. Consequently, we decided to mount the detector plate on the bottom, to have the possibility to compensate for the larger expected artifacts.
created by the large diameter fibers, and attach the source plate, which is thinner and only contains small diameter fibers, on top.

As can be seen in Figs. 4-9(a-c), artifacts from the probe are visible in the DBT images, but are within the dynamic range of the x-ray detector, so we are confident that they can be removed in post-processing. In fact, as seen in Fig. 4-9(c), when compared to Fig. 4-9(d), the native Hologic DBT image reconstruction algorithm already removes a large fraction of the artifacts. Further improvements could be achieved by performing an image subtraction on raw DBT projection images.

The light budget penalty of almost 10 dB or 90%, when compared to a traditional glass-fiber only probe, might seem excessive, but a quick back of the envelope calculation, using the signal decay profile from Fig. 4-10, shows that an attenuation by a factor of 10x only reduces the maximum useful source-detector distance by approximately 1.3 cm, or 13% in a typical breast. This seems to be an acceptable compromise. The biggest loss results from the transition between detector PMMA fiber to glass fiber bundle, mostly because of the inevitably low fill factor of the bundle. This could be alleviated in the future by locating the detectors directly at the edge of the probe, making the bundle obsolete. Another option we have explored would be the use of perfluorinated plastic (Cytop) fibers. These fibers have both a small x-ray and near-infrared absorption, and thus would allow a single fiber type probe, eliminating lossy couplers. Unfortunately they are currently still very costly, and also delicate and brittle, and thus not yet suitable for daily clinical use. Finally, the large losses due to the 45° polish of the source fibers (visible in Fig. 3-14) could probably be reduced by coating the angled surface with a metallic finish.

As mentioned in the introduction, to the best of our knowledge, TOBI2 was at the time of its first publication [5] the only DOT/DBT system featuring an x-ray translucent probe allowing truly simultaneous acquisition of x-ray and optical images.

As reported above, the raw performance of the three main individual components of TOBI2 improved in every way on our previous system, and hence exceeded our expectations. Testing of the combined system performance using phantoms show that we can clearly image inclusions smaller than 13 mm diameter, and dynamic changes
are represented correctly. The contrast recovery is up to approximately 20% below our expectations, especially for the higher absorption cases. Since this underestimation is also size dependent, with the smaller inclusions experiencing a larger effect, we believe smoothing from the image reconstruction algorithm to be responsible for this, despite our use of a soft prior.

Initial in vivo imaging results are encouraging as well. Values of absolute HbT shown in Fig. 4-12(a) are consistent with the expected increased HbT contrast of malignant tumors reported by numerous other studies [77], [124]. Dynamic contrast induced by compression changes is also clearly seen in the ΔHbT image and time course (Figs. 4-12(b) and 4-13), demonstrating the capability of dynamic optical imaging using TOBI2. The tumor dynamic signatures shown here are meant as an example of the data that can be acquired with the TOBI2 system. Group analysis over a larger patient sample is needed to determine whether these signatures are representative. The slow recovery in HbT as the breast is kept under compression, likely due to the steady decrease in compression force due to tissue relaxation, is consistent with previous publications [106], [125] from our group. However, due to the complexity of the iterative DBT clinical breast positioning procedure, the optical image acquisition did not begin until approximately 20 s to 30 s after the breast tissue initially experienced compression. As a result, the early response is not captured in the presented data. Previously, using a standalone dynamic optical imaging system with a computer controlled compression mechanism, an early decrease in tumor HbT during compression [106], [125] has been seen. However, in the example TOBI2 scan, this early decrease has likely occurred before the measurement was initiated (while the radiology technician was positioning the breast under compression to match clinical standards). The significantly larger decrease in tumor HbT observed after the transition to full compression vs. the surrounding normal tissue (likely related to the higher stiffness of tumor tissue) may be a useful tumor marker, and will be further characterized in future work.

These encouraging results give us confidence that combining dynamic optical imaging with x-ray digital breast tomosynthesis in true simultaneous co-registration can
ing with x-ray digital breast tomosynthesis in true simultaneous co-registration can provide a reliable platform for both breast cancer detection and chemotherapy guidance. Additional possible improvements are the addition of extra wavelengths to the FD-NIRS component, the optimization of the acquisition software, automation of x-ray artifact removal, and improving the DOT reconstruction algorithm by incorporating temporal regularization. Also, the long-term durability of the plastic optical fiber probe remains to be explored.

5.2 Conclusion

In this work, we have presented a fast, hybrid tomographic optical breast imaging system featuring 3072 CW-NIRS channels (96 CW sources x 32 CW detectors), 480 FD-NIRS channels (24 FD sources x 20 FD detectors), up to 1 Hz acquisition rate, and an x-ray translucent probe. A main innovation is the incorporated purpose-built high-performance direct digital sampling FD-NIRS imager, which achieves high temporal resolution while matching the performance of other slower instruments in the field. The key metrics presented in chapter 4 are summarized in Tab. 5.2.

Tests show that our second-generation system exceeds the basic performance metrics of our previous optical-DBT system, and meets our expectations. Using phantoms with glass-free inclusions, we demonstrate that we can image features of less than 13 mm diameter with good quantitative accuracy by employing soft-prior constrained reconstruction, and capture their dynamics. DBT images taken with the optical probe attached show that the resulting artifacts are small enough for us to be confident that it will be possible to remove them automatically in the future. First patient images testify to the usefulness of these new features. These results pave the way for future clinical studies, in conjunction with improvements in our data acquisition interface and image reconstruction pipeline.
<table>
<thead>
<tr>
<th>Source, Detectors</th>
<th>Acquisition Speed</th>
<th>Noise Floor</th>
<th>Phase Noise</th>
<th>Max. Input Power</th>
<th>Dynamic Range</th>
<th>Channel Separation</th>
<th>Amplitude Stability</th>
<th>Phase Stability</th>
</tr>
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<tbody>
<tr>
<td>FD-NIRS</td>
<td>25, 20</td>
<td>&lt;1.4 pW/√Hz</td>
<td>&lt;6 mrad at 100 pW</td>
<td>1.5 μW</td>
<td>&gt;115 dB (20 · \log_{10})</td>
<td>&gt;80 dB (20 · \log_{10})</td>
<td>±1.5% at 5 nW, 10 h</td>
<td>3 mrad at 5 nW, 10 h</td>
</tr>
<tr>
<td>CW-NIRS</td>
<td>96, 32</td>
<td>22 fW/√Hz to 366 fW/√Hz</td>
<td>0.6 nW to 75 nW</td>
<td>72 dB to 95 dB (20 · \log_{10})</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

Table 5.2: Summary of key performance metrics of the FD-NIRS and CW-NIRS instruments. CW-NIRS values depend on gain setting (see also Fig. 4-7).
Abbreviations

3D three-dimensional. 13, 17–20, 69, 71

ABS acrylonitrile butadiene styrene. 46

ADC analog-to-digital converter. 24, 28, 30, 33–39, 43, 55, 56

APD avalanche photo diode. 33, 34, 36, 37, 44, 55, 56, 58, 65, 75

CT computed tomography. 13

CW continuous-wave. 19, 43, 75, 81

CW-NIRS continuous-wave near-infrared spectroscopy. 3, 19, 24, 27–30, 37, 38, 43, 44, 48–50, 58, 65, 66, 77, 81

DAC digital-to-analog converter. 35


DCS Diffuse Correlation Spectroscopy. 5

DDS direct digital synthesis. 30

DFT discrete Fourier transform. 3, 24, 39, 40, 42, 43, 56, 76


EMI electromagnetic interference. 33, 34, 37, 77
FD frequency domain. 81

FD-NIRS frequency-domain near-infrared spectroscopy. 3, 14–16, 19, 24, 27–32, 44, 48–50, 55, 60, 64, 75–77, 80, 81

FFT fast Fourier transform. 39, 44, 55, 56

fNIRS functional near-infrared spectroscopy. 5

FPGA field-programmable gate array. 3, 37, 40, 42–44, 55, 56, 76

Hb de-oxyhemoglobin. 13, 20

HbO oxyhemoglobin. 13, 20

HbT total hemoglobin. 20, 21, 72, 73, 80

IC integrated circuit. 30, 33

JTAG Joint Test Action Group. 37

LVDS low-voltage differential signaling. 38, 84

LVPECL low-voltage positive emitter-coupled logic. 33

MEMS micro-electro-mechanical systems. 77

M-LVDS multipoint LVDS. 38

MRI magnetic resonance imaging. 19, 21

NEP noise-equivalent power. 27, 56, 57, 65, 66, 75

NIRS near-infrared spectroscopy. 19, 27, 28

PC personal computer. 38, 42, 43

PCB printed circuit board. 30, 34, 35, 39
**PET** positron emission tomography. 19

**PLL** phase-locked loop. 30, 33

**PMMA** Poly(methyl methacrylate). 45, 46, 48, 67, 78, 79

**PMT** photomultiplier tube. 75

**RF** radio frequency. 19, 24, 34, 76

**SNR** signal-to-noise ratio. 24, 56

**SO2** oxygen saturation. 20

**SPI** serial peripheral interface. 38

**TCXO** temperature-compensated crystal oscillator. 30, 33

**TD-NIRS** time-domain near-infrared spectroscopy. 19

**TOBI2** tomographic optical breast imager 2. 14, 15, 23, 24, 27–30, 37, 52, 75, 79, 80

**US** United States. 13, 18

**USB** universal serial bus. 38, 44
References


