Feasibility of near-infrared diffuse optical spectroscopy on patients undergoing image-guided core-needle biopsy

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Abstract: We describe a side-firing fiber optic sensor based on near-infrared spectroscopy for guiding core needle biopsy diagnosis of breast cancer. The sensor is composed of three side firing optical fibers (two source fibers and one detection fiber), providing two source-detector separations. The entire assembly is inserted into a core biopsy needle, allowing for sampling to occur at the biopsy site. A multi-wavelength frequency-domain near-infrared instrument is used to collect diffuse reflectance in the breast tissue through an aperture on the biopsy needle before the tissue is removed for histology. Preliminary in vivo measurements performed on 10 normal or benign breast tissues from 5 women undergoing stereo- or ultrasound-guided core needle biopsy show the ability of the system to determine tissue optical properties and constituent concentrations, which are correlated with breast tissue composition derived from histopathology.

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1. Introduction

Percutaneous, image-guided core needle biopsy is now commonly used for the diagnosis of image-detected, nonpalpable breast lesions. An estimated 1.4 million breast needle biopsies are performed annually in the U.S. [1]. Compared to surgical excision, this procedure offers multiple advantages: it is faster, less invasive, less expensive, minimizes deformity, leaves little or no scarring and has a shorter recovery time [2-6]. Needle biopsy can obviate the need for surgery in women with benign lesions [3-5, 7] and reduce the number of diagnostic surgical procedures performed in women with breast cancer [3-5, 8-10]. However, the procedure has limited sampling accuracy because only a finite number of tissue sites are biopsied and sent for histology. In some cases, sampling of the suspicious mass may be missed altogether (due to displacement of the lesion relative to the tip of the biopsy needle). As a result, needle biopsy procedures have a false-negative rate of 1% - 7% [11-13] when verified with follow up mammography, and a repeat biopsy rate of 9% - 18% [13-15]. Furthermore, approximately 80 percent of women who undergo core needle biopsy are ultimately found to only have benign lesions [16, 17]. These unnecessary procedures carry a substantial physical and emotional burden for patients, and financial cost.

Fiber optic sensors based on near infrared (NIR) diffuse optical spectroscopy have the potential to improve the sampling yield of image-guided core needle biopsy. In the NIR spectral region between 650 -1000 nm, the number of light scattering events in tissue is approximately two orders of magnitude greater than the number of absorption events. This allows light to penetrate up to several centimeters into breast tissues before being absorbed by the tissue or collected by a detector. The NIR absorption and scattering properties of tissue can be quantitatively described using a model of light propagation based on the diffusion approximation to the radiative transport equation [18, 19]. The diffusion equation can be used to calculate the absorption and scattering coefficients of tissue from NIR spectroscopic measurements of diffusely reflected light, from which tissue composition can be derived [18-20]. Endogenous absorbers in breast tissue include oxygenated hemoglobin (HbO₂), deoxygenated hemoglobin (Hb), water and lipids. Endogenous scattering is associated with microscopic variations in the size, shape and refractive indices of both intracellular and extracellular components. Tissue vascularity, hemoglobin saturation and water content have all been identified as diagnostic markers of breast cancer using a variety of different techniques including immunohistochemistry, needle oxygen electrodes and magnetic resonance spectroscopy. Breast cancers are more vascularized [21, 22], have hypoxic regions [23-25] and an elevated water content [26-28] compared to normal breast tissues. Thus, NIR diffuse optical spectroscopy offers a rapid and quantitative assessment of tissue physiological and structural properties for characterizing breast tissue composition and for the diagnosis of breast cancer in vivo. NIR diffuse optical spectroscopy has been widely used for intact breast tumor characterization [18, 28-30], monitoring of tumors in the intact breast in response to neoadjuvant chemotherapy [31-33], quantifying the effects of menopausal status on breast tissue properties [34, 35], and breast tissue perfusion studies [36].

NIR diffuse optical spectroscopy can be implemented for breast cancer applications via several different approaches [18, 28-30]. Traditionally, multiple fiber optic sensors placed in a matrix have been used to image the optical properties of intact tumors within the breast (non-invasive) [32, 37]. Alternatively, fiber optic sensors can be designed and adapted to endoscopes or biopsy needles for minimally invasive characterization of the local tumor optical properties within the breast prior to biopsy [38]. Our goal is to exploit the latter approach to improve the sampling accuracy of image-guided breast needle biopsy procedures. When inserted into the biopsy needle, the probe should be able to (1) survey multiple sites without the need for tissue removal, (2) sample a much larger volume of the lesion than can be biopsied, and (3) provide accurate and immediate feedback of malignant tissue sites to biopsy. The sensor would indicate whether tissue at different points is normal, benign or malignant and potentially guide the needle to be advanced deeper, or have its position changed, before the biopsy is actually sampled.
We have previously developed a 2.4 mm diameter fiber optic probe for NIR diffuse optical spectroscopy which can be inserted into the breast through a Suros ATEC biopsy needle. This probe was tested on homogenous tissue phantoms with optical properties that are representative of normal and diseased human breast tissue [38]. The retrieved absorption coefficient ($\mu_a$) was within 10% of the theoretical value from 0.02 to 0.15 cm$^{-1}$ and the retrieved reduced scattering coefficient ($\mu_s'$) was within 30% of the theoretical value (10 cm$^{-1}$). In this paper, we demonstrate the feasibility of performing NIR diffuse optical spectroscopy \textit{in vivo} with the side-firing probe in patients undergoing image-guided core-needle biopsy and the relationship between the optically measured and histologically derived tissue composition. Optical measurements were made from a total of 10 tissue sites in 5 patients using a three-wavelength frequency-domain NIR system and the side-firing fiber optic probe. The measurements were analyzed using the diffusion equation to extract the absorption and scattering coefficients at each wavelength. Beer’s law was used to extract the concentrations of the constituent absorbers, Hb and HbO$_2$ from the absorption coefficients at the three wavelengths. Hemoglobin saturation (SO$_2$) and the total hemoglobin concentration (THC) were calculated. Pearson’s correlation coefficients were calculated between the extracted tissue optical properties ($\mu_a$ and $\mu_s'$), physiological properties (THC and SO$_2$) and histologically derived tissue composition (adipose, fibroglandular and blood content derived from histo pathology of the biopsied tissue site).

2. Materials and methods

This section describes the operating principles of the side-firing fiber optic probe and the frequency-domain NIR instrument, the clinical study design, pathologic evaluation and the data analysis methods that were used in extraction of optical properties and corresponding physiological and structural information of breast tissues.

2.1 Side-firing fiber optic probe

A side-firing fiber optic sensor has been previously developed by our group for making NIR diffuse optical spectroscopy measurements via a 9 gauge needle during image-guided core needle biopsy [38]. Figure 1 shows (a) a schematic of the side-firing probe inside a biopsy needle and (b) a photograph of the entire probe next to the Suros ATEC biopsy needle (9 gauge). The Suros 9G biopsy needle is designed to be used with vacuum-assisted stereotactic systems for breast biopsy and for partial or complete removal of benign breast lesions. The key feature of the needle is a side-facing aperture (20 mm long and 3.6 mm wide) through which tissue biopsies are sampled. Side-viewing source and detector optical fibers can be inserted into the needle, such that NIR diffuse optical spectroscopy measurements of the breast can be made along the length of the aperture. Moreover, the hand piece of the needle, which can rotate the aperture and the side-firing probe, will enable diffuse optical spectroscopy measurements at up to 12 clock positions (essentially rotating the bore of the needle and hence, the aperture over an angle of 360 degrees) around the needle.
The proximal end of the fiber optic probe consists of two side-firing source fibers with a core diameter of 200 μm and a numerical aperture (NA) of 0.22 and a side-firing detection fiber with a core diameter of 600 μm and a NA of 0.22. The source-detector separations, which are defined as the distance from the tip of the detection fiber to those of the two source fibers, are 5 mm and 10 mm, respectively. An optical quartz cap with a length of 15 mm and an outer diameter of 2.4 mm seals the tip. All fiber tips are polished at an angle of 43° and radially oriented such that the light from each fiber is normal to the circumference of the quartz cap, minimizing specular reflection into the detector fiber. These fibers are relayed to the instrument via flexible Tygon tubing, which is connected to the quartz cap. The relative placement and orientation of the fiber tips was fixed by gluing the fibers together. Epoxy at the junction of the rigid cap and the Tygon tubing fixed the fibers inside the cap. The quartz cap, tubing as well as the epoxy used to bond them together are all biocompatible. FC/APC connectors interface the distal end of the tubing to a frequency-domain NIR instrument that will be described in detail in the following section. Finally, an adaptor with labels for the different clock positions is attached to the Tygon tubing [see Fig. 1(b)] in order to enable alignment the tip of the optical fibers along the aperture of the needle.

2.2 Frequency-domain NIR instrument

The instrument to which the probe is coupled, is a frequency-domain NIR spectroscopy system (shown in Fig. 2) similar to the FDPM instrument reported by T. Pham, et al [39]. The operating principle of the FDPM system has been described in detail in the literature [18, 39, 40] and is briefly described here.
The light sources are three laser diodes that generate far red (660 nm, ML101J21, Mitsubishi Electric, Japan) and NIR light (811 and 849 nm, SDL-5401, JDS Uniphase Corp., Milpitas, CA). The laser diodes are DC-biased and temperature-controlled by a multi-channel laser diode controller (LDC-3908, ILX Lightwave, Bozeman, MT). An RF switch (8769K and 11713A, both from Agilent Technology, Palo Alto, CA) is used to select the laser diode that is to be modulated by the RF power of a network analyzer (Agilent 8712ET, Agilent Technology, Palo Alto, CA). To directly modulate the laser diode modules, the high frequency AC modulation current and the DC bias current are combined into a single output by a built-in Bias-T in each laser diode mount (LDM 4980 series, ILX Lightwave, Bozeman, MT). The bias currents are selected such that all diodes operate within the linear range of their power-current (P-I) curves when an RF power of 11.3 dBm is applied. The intensity-modulated light is delivered to the tissue site through the two source fibers in the side-firing probe that are sequentially controlled by an 8×8 optical switch (GP700, DiCon Fiberoptics, Inc., Richmond, CA). The average power (DC) delivered at the probe tip is approximately 1.0 mW for 660 nm and 5 mW for 811 and 849 nm. The modulation frequency is scanned from 50 to 150 MHz in 1 MHz increments, resulting in 101 data points in each scan. The light then propagates through the tissue and undergoes attenuation and a phase shift. The diffusely reflected signal is collected by the detection side-firing fiber and relayed to an avalanche photodiode (APD) module (C5658, Hamamatsu Corp., Japan). The AC output of APD module is post-amplified by a 19-dB RF amplifier (ZFL-500HLN, Mini-Circuits, Brooklyn, NY). The network analyzer measures the amplitude and phase using heterodyne detection at a bandwidth of 15 Hz. A laptop computer and LabVIEW VI’s (National Instruments Corporation, Austin, Texas) are employed to control all the devices and for data acquisition. At each tissue site, the following scanning sequence is used: The amplitude and phase are measured over 50 to 150 MHz at 660 nm for the source fiber 1-detection fiber pair, and then the source fiber 2-detection fiber pair. This is repeated for 811 and 849 nm. A single scan takes about eight seconds and the total measurement time required at each tissue site was about one minute.

2.3 Clinical study design

The clinical protocol for this study was approved by the Institutional Review Boards at the University of Wisconsin - Madison. NIR diffuse optical spectroscopy was performed on patients undergoing image-guided core needle biopsy at the University of Wisconsin Hospital (UWH). The fiber optic probe was utilized in both stereotactic and ultrasound guided biopsy
procedures. Before the core needle biopsy procedure, the fiber optic probe was sterilized using cold gas (ethylene oxide, ETO) sterilization. In the stereotactic procedure, the needle was fired into the lesion with guidance from mammography. Once the tip of the needle was in the lesion, the cutter in the needle was retracted such that the side-facing aperture on the needle was open. Low vacuum suctioning was used to remove residual blood from the field. Then the side-firing fiber optic probe was inserted into the needle and oriented to face the aperture and NIR diffuse reflectance spectroscopy measurements were made from the tissue site adjacent to the side facing aperture. Then, the optical sensor was removed. Vacuum suctioning was applied to pull the optically interrogated tissue into the aperture and then the cutter was advanced to biopsy that site. Vacuum suctioning was applied again to pull the biopsied core out of the needle into a tissue collection chamber at the back of the needle. Then the cutter was advanced to close the aperture and rotated to the next clock position and the optical measurement was repeated. Clock position refers to the direction the side-facing aperture is oriented upon rotation of the needle, where the direction is represented by the location of each hour on the face of a clock (for example, if the aperture were facing up at 12 o’clock, it would be rotated by 60 degrees at 2 o’clock, 120 degrees at 4 o’clock and so forth). Optical measurements were only taken from sites where biopsies were taken for diagnostic histopathology. The experimental protocol was essentially the same in the ultrasound-guided procedure in that optical measurements were taken immediately prior to biopsy at each given location. Ultrasound biopsies are less dependent on clock-face position and based instead on real-time feedback from the ultrasound images which guide biopsy positioning.

After the optical spectroscopy procedure was completed, calibration measurements were made from a group of three breast tissue phantoms with known optical properties (fixed $\mu_s'=10\text{cm}^{-1}$, and $\mu_a=0.07$, 0.12 and 0.17 $\text{cm}^{-1}$, all at 811 nm). The calibration procedure is discussed in detail in the next section. Finally, probe light leakage (light that travels directly from illumination to collection fibers) was recorded at all wavelengths and all frequencies using an almost opaque ink solution ($\mu_a > 50 \text{ cm}^{-1}$).

2.4 Pathology

Tissue samples taken from the measured sites were placed in separate formalin containers and sent to the UWH pathology department for histopathology. The tissue was routinely processed and one paraffin section covering the length of each biopsy core was cut, hematoxylin and eosin (H&E) stained, and microscopically examined. Microscopic evaluation of the stained section was performed and recorded by the board certified pathologist (J.H.). The tissue composition was recorded as estimated percentages of adipose tissue, fibrous tissue, normal ducts/lobules, benign tissue, and extravascular blood due to hemorrhage during the procedure (the reason fresh hemorrhage is still present after tissue processing is that it most likely clots prior to the placement of the specimen in formalin, and thus is stabilized by fibrin). Benign tissues were further categorized as adenosis, fibroadenoma, cyst, fibrocystic change and reparative changes.

2.5 Data analysis methods

The amplitude and phase data was collected and analyzed using the diffusion approximation in the frequency domain [41] to extract the absorption coefficient and reduced scattering coefficient of the tissue at each wavelength. Two source-detector separations were used to eliminate instrumentation artifacts due to modulation-dependence of the light sources and instrument response [42, 43]. For a fiber optic probe with two different source-detector separations ($r_0$ and $r$), the relative amplitude of the photon-density oscillation $AC_{rel}$ and the relative phase shift $\Delta \Phi_{rel}$ are given by [39, 42, 43]

$$\ln \left( \frac{r}{r_0} \cdot AC_{rel} \right) = \ln \left( \frac{r \cdot AC(r)}{r_0 \cdot AC(r_0)} \right) = -(r - r_0) \frac{3\mu_s (\mu_a + \mu_s')}{2} / \left[ 1 + \left( \frac{\alpha}{\nu \mu_a} \right)^2 + 1 \right]^{1/2}$$

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where $AC(r_0)$ and $AC(r)$ are the AC component of the amplitude detected by the collection fiber due to diffuse reflectance of the two sinusoidally intensity-modulated light sources, respectively. $\Phi(r_0)$ and $\Phi(r)$ are the phase-shift for the two separations, respectively. $\omega=2\pi f$ is the angular modulation frequency, where $f$ is the modulation frequency, and $v$ is the speed of light in the medium. The attenuation and the phase-shift of these photon density waves in an infinite medium are determined by three wave characteristics, the frequency $f$, the source-detector separations ($r_0$ and $r$), and the medium characteristics ($\mu_a$ and $\mu_s'$). Tissue optical properties were independently extracted by fitting the NIR spectroscopic data to the theoretical model based on Eq. (1) and Eq. (2). The data analysis algorithm was implemented in MATLAB 7.1 (MathWorks, Inc.). A Levenberg-Marquardt nonlinear least square minimization algorithm was adapted to simultaneously fit the relative amplitude $AC_{rel}$ and phase-shift $\Delta \Phi_{rel}$ with equal weight. The phase-shift in degrees was converted to radians prior to fitting so that the $AC_{rel}$ and $\Delta \Phi_{rel}$ were on the same level. Various initial guesses of ($\mu_a$, $\mu_s'$) were used to guarantee that the chi-squared value (goodness-of-fit metric) was at the global minimum.

Prior to the fitting, the amplitude and phase data were background subtracted using the light leakage measured from the ink solution. In addition, to account for differences in the attenuation and optical path length of the two source fibers, the amplitude and phase data obtained from the three reference phantoms were fit to the diffusion model to generate three correction factors at each wavelength $\lambda$: a multiplication factor $X(\lambda)$, and two offset factors $Y(\lambda)$ and $Z(\lambda)$ for the amplitude and phase shift, respectively. This is given by Eqs. (3) and (4):

$$AC_{rel\_theoretical}(\lambda_i) = X(\lambda_i) \cdot AC_{rel\_phantom}(\lambda_i) + Y(\lambda_i)$$

$$\Delta \phi_{rel\_theoretical}(\lambda_i) = \Delta \phi_{rel\_theoretical}(\lambda_i) + Z(\lambda_i)$$

The correction factors were then used to calibrate the amplitude and phase measurements obtained from the patients.

Next, the concentrations of the two absorbers, Hb and HbO$_2$ were derived from the linear fits to the absorption coefficients ($\mu_a(\lambda_i)$) at the three wavelengths, using Beer’s law as shown in Eq. (5).

$$\mu_a(\lambda_i) = 2.303 \times [\varepsilon_{\text{Hb}}(\lambda_i)C_{\text{Hb}} + \varepsilon_{\text{HbO2}}(\lambda_i)C_{\text{HbO2}} + \varepsilon_{\text{lipid}}(\lambda_i)C_{\text{lipid}} + \varepsilon_{\text{water}}(\lambda_i)C_{\text{water}}]$$

where, $\varepsilon$ is the extinction coefficient of the absorbers and $C$ is the concentration of the absorbers. These equations have four unknowns (the concentrations of the four absorbers), and therefore requires at least four equations to solve. Because we only used three wavelengths in our NIR instrument, the background water and lipid concentration were assumed to be constant, $C_{\text{water}}=31\%$, $C_{\text{lipid}}=57\%$, respectively [44, 45].

3. Results
3.1 Pathology results

A total of 12 subjects scheduled for a core needle biopsy procedure were consented to the optical study, including 4 PRE (premenopausal) subjects, 2 HRT (hormone replacement treatment) subjects, and 6 POST (postmenopausal) subjects. From each subject, optical measurements and biopsies were taken anywhere from 2 to 6 clock locations (12, 2, 4, 6, 8 and 10) within the same breast. Unfortunately, 7 of these subjects were excluded from the final data analysis, for a number of reasons. Two patients were excluded because the probe broke during calibration (both POST subjects); one patient was excluded due to an instrument...
malfunction (a PRE subject); data from 3 other patients (all POST subjects) did not converge during numerical analysis and curve fitting – optical measurements from these patients were made with a side-firing probe that had a significant amount of light leakage, which was comparable to the signal. One patient was excluded because the needle hit a vein before the first optical measurement took place. In the five patients that remained, only the first few measurements (varies from subject to subject as shown in Table 1) were used for further analysis. The reason for this was that in the current study design, a biopsy was taken after each optical measurement. Thus, there was progressively more bleeding with each biopsy which affected the subsequent optical measurements. After a thorough examination of the data, we concluded that that only the first few measurements in each patient had an acceptable signal level (SNR>10), i.e. the signal was not completely attenuated by blood in the cavity (inversion of these results gave absorption coefficients that were an order of magnitude higher than that in the physiological range) [18, 34, 44, 46-50]. This resulted in a total of 10 sites from 5 patients. The age, menopausal status and histological breakdown for tissue sites obtained from 10 samples from the remaining 5 patients are given in Table 1.

Table 1: Age and Menopausal Status of the Subjects and Histological Breakdown of the Optically Interrogated Tissue Sites in These Patients.

| Subject No. | Age | Menopausal Status | Sample No. | Adipose (%) | Fibroglandular (%) | Blood (%) |
|-------------|-----|-------------------|------------|-------------|--------------------|----------|
| 16          | 40  | PRE               | 1          | 50          | 50                 | 0        |
|             |     |                   | 2          | 5           | 45                 | 50       |
|             |     |                   | 3          | 0           | 0                  | 100      |
|             |     |                   | 4          | 10          | 10                 | 80       |
| 30          | 61.8| HRT               | 1          | 60          | 40                 | 0        |
| 14R         | 70.5| POST              | 1          | 55          | 35                 | 10       |
|             |     |                   | 2          | 90          | 10                 | 0        |
| 18          | 75  | POST              | 1          | 60          | 10                 | 30       |
|             |     |                   | 2          | 50          | 0                  | 50       |
| 25          | 59  | POST              | 1          | 45          | 25                 | 30       |

Pearson’s correlation analysis was carried out to determine the relationship between the biographical (age, menopausal status) and histological variables shown in Table 1. Figure 3 shows the Pearson’s correlation between age and (a) adipose content; (b) fibroglandular content; and (c) blood content in normal/benign breast tissues. The solid lines represent a linear fit across all the samples. Figure 3(a) indicates that, in normal/benign breast tissue, adipose content is positively correlated to subject age as would be expected. In addition, the adipose tissue content of post-menopausal women is greater than that of pre-menopausal women (Wilcoxon Rank Sum test: p<0.05). However, as shown in Figs. 3(b) and 3(c), fibroglandular and blood content do not appear to be correlated with subject age and there were no statistically significant differences in these two parameters between pre- and post-menopausal women. The fibroglandular is expected to decrease with age and with menopause. Thus, in this study, Pearson’s correlations were carried out between the optical measured and histologically derived tissue composition, which is a direct measure of tissue composition.
Fig. 3. Pearson’s correlation between age and (a) adipose content; (b) fibroglandular content; and (c) blood content in normal/benign female breast tissues. Filled squares represent PRE samples, open triangles represent the HRT sample, open circle represent POST samples, and solid lines represent a linear fit across all the samples. Pearson’s coefficient was used in calculating the correlations.

3.2 Optical properties of normal/benign breast tissue

Figures 4(a)-4(f) shows a scatter plot of extracted $\mu_a$ and $\mu_s'$ at 849 nm versus tissue constituents (adipose, fibroglandular and blood content, respectively) for all ten samples. An average $\mu_a$ of 0.145±0.034 cm$^{-1}$ and 0.108±0.011 cm$^{-1}$ was measured for Pre- and Post-menopausal subjects, respectively. The Wilcoxon Rank Sum test indicated a statistically significant difference between the absorption coefficients of PRE and POST subjects ($p < 0.05$). The reduced scattering coefficients for PRE subjects (average $\mu_s'$ 8.8±3.1 cm$^{-1}$) and POST subjects (average $\mu_s'$ 8.5±2.7 cm$^{-1}$) did not show any significant differences ($p > 0.1$).

Pearson’s correlation analysis was carried out to evaluate the relationship between the optical variables and the histological variables. Figures 4(a), 4(c), and 4(e) indicate that the absorption coefficient is inversely correlated with adipose tissue content ($p<0.05$) and
Fig. 4. $\mu_a$ and $\mu_s'$ at 849 nm versus percent adipose, fibroglandular and blood contents. Filled squares represent PRE samples, open triangles represent the HRT sample, open circle represent POST samples, and solid lines represent a linear fit across all the samples. Pearson’s coefficient was used in calculating the correlations.

positively correlated with blood content as measured by histology (p<0.05), but is not significantly correlated with fibroglandular content (p>0.1). Figures 4(b), 4(d), and 4(f) indicate that $\mu_s'$ is positively correlated with the fibroglandular content (p<0.05), but has no
significant dependence on the adipose tissue content or blood content (p>0.05). It should be noted that the 849 nm data is representative of correlations at other wavelengths.

### 3.3 Tissue Physiological Properties

Figure 5(a)-5(f) shows the extracted total hemoglobin concentration (THC) and blood oxygen saturation (SO2) plotted versus the tissue adipose, fibroglandular and blood content. The THC ranges from 30~75 μM and has a strong negative dependence on adipose tissue content (p<0.05) and positive correlation with blood content as measured by histology (p<0.05), but no significant correlation with the fibroglandular tissue content. An average blood oxygen saturation of 84±10% was measured across all the 10 samples. Blood saturation didn’t show significant correlation with any of the tissue constituents. The Wilcoxon Rank Sum test did not show significant differences in the THC and SO2 between pre- and post-menopausal subjects.

### 4. Discussion

The goal of this work was to investigate the feasibility of performing frequency-domain NIR spectroscopy via a side-firing probe in patients undergoing image-guided breast needle biopsy. We used the side-firing probe to quantify the optical properties (absorption and scattering) and physiological properties (total hemoglobin concentration and hemoglobin oxygen saturation) of normal/benign breast tissues from 10 sites in 5 patients in vivo. The subjects of this in vivo study were patients with non-palpable mammographically-suspect lesions and thus were scheduled for a stereo- or ultrasound-guided core needle biopsy. A positive correlation was observed between the adipose content and subject age as seen in Fig. 3(a). It is widely accepted that adipose content increases with age in the female breast and is a result of adipose tissue progressively replacing the fibroglandular tissue during menopause [47, 51]. Although the breast of young women are composed primarily of dense fibroglandular tissue that is known to contain more blood vessels, no direct dependence of the fibroglandular tissue and blood content on subject age was observed as seen in Fig. 3(b) and (c). One would expect a negative correlation between fibroglandular content with age [52]. One likely explanation for this lack of correlation is that the adipose tissue content ranges from 0-100%, thus including predominantly adipose tissues, while the maximum fibroglandular tissue content found in the biopsies was less than 50%. Having predominantly fibroglandular tissues and a larger sample size of this tissue type may have improved the correlation between this parameter and age. The lack of correlation between blood content and age maybe due to the fact that the blood content is due to extravascular hemorrhage rather than blood in vessels.

Body-mass-index (BMI), a parameter associated with breast cancer risk [53], is often used in optical mammography [45, 47, 54]. In general, based on clinical intuition, we would expect a positive correlation between adipose content and BMI. In contrast, we would expect an inverse correlation between fibroglandular content and adipose content because these two components combine to constitute the breast (higher proportion of one implies lower proportion of the other). Therefore, because adipose content and BMI are positively correlated, BMI will also be inversely correlated with fibroglandular content. Finally, because blood content is increased in the more active fibroglandular component of the breast it would be positively correlated with fibroglandular content and inversely correlated with adipose content and BMI. However, BMI is an indirect, coarse estimation of breast adipose content and thus not evaluated in this study.

A negative correlation was observed between the absorption coefficient at 849 nm and adipose tissue content and is likely due to the fact that adipose tissue is less vascular than fibroglandular tissue and thus, increased adipose tissue content reflects decreased tissue vascularity. This result is consistent with Suzuki’s finding in 30 healthy Japanese women where the absorption coefficient was negatively correlated with subject’s age [46]). A positive
correlation was observed between the absorption coefficient at 849 nm and blood content obtained histologically. The blood content measured from the histological samples is
primarily due to fresh hemorrhage. This suggests that there was biopsy induced bleeding in
the breast that influenced the measurement of the absorption coefficient. Although
fibroglandular tissue is known to contain more blood vessels and therefore a greater blood
supply than adipose tissue, no direct dependence of the absorption coefficient on
fibroglandular tissue content was observed. This might be attributed in part to the fact that the
absorption coefficient is not only affected by the intravascular blood volume, but also by
extravascular hemorrhage as suggested in Fig. 4(e). A positive correlation was observed
between the reduced scattering coefficient at 849 nm and percent fibroglandular tissue. It has
previously been shown that fibroglandular and ductal tissues result in increased scattering
compared to adipose tissues [55-57]. No significant correlation was found between the
reduced scattering coefficient at 849 nm and adipose tissue content. No previous studies in the
literature have shown any correlations between the reduced scattering coefficient and subject
age [44, 54, 58], which is positively correlated with adipose tissue in the healthy female
breast. In summary, the absorption coefficient appears to be sensitive to adipose tissue content
while the reduced scattering coefficient is correlated with the fibroglandular tissue content in
normal breast tissues.

The THC from our study varied from 30 ~ 75 μM, which falls in the higher end of the
ranges reported in the literature. In previous studies, Cerussi et al. measured a THC range
from 5 to 60 μM using a seven-wavelength FDPM probe in the breasts of 28 healthy women
aged 18-64 years [35], Shah et al. reported a THC varying from 3 to 25 μM in 14 normal
subjects including PRE, HRT and POST women using the same technology [34], Pogue et al.
measured THC values from 9 to 45 μM in thirty-nine normal subjects with diffuse optical
tomography (DOT) [59], and Cubbedu et al. measured values from 35 to 80 μM on the left
breast of a healthy 36 year old volunteer in the different phases of the menstrual cycle using
time-resolved reflectance and transmittance spectroscopy [49]. A common feature of these
studies is that the measurements were obtained on the surface of intact breasts. The relatively
high THC is likely due to some bleeding of the tissue during the biopsy procedure as seen in
Fig. 5(e) and also due to the fact that these measurements are made in direct contact with the
tissue of interest (local measurements). There is a negative correlation between THC and
adipose content [Fig. 5(a)]. Adipose tissues have fewer blood vessels and a smaller blood
supply than fibroglandular tissues and thus increased adipose tissue content would suggest
decreased THC. However, there is lack of an expected negative correlation between THC and
fibroglandular tissue content. When a tissue section is examined where there has been
hemorrhage, the surface area made up of intravascular blood is generally much, much less
than that made up by areas of extravascular blood (hemorrhage). In our study, it appears that a
larger contribution to THC comes from extravascular blood due to hemorrhage, rather than
from the intravascular component, which is why there may be a lack of correlation between
THC and the fibroglandular content. The reason the extravascular hemorrhage does not appear
to affect the correlation between THC and adipose tissue content is that adipose tissues are
inherently less vascular than fibroglandular tissue, and thus less prone to hemorrhage during
the procedure. In fibroglandular tissue, if we were only measuring the vessels and the blood
contained within those vessels the correlation might be preserved. But since there is a
somewhat increased chance of hemorrhage in these more vascular tissues, the THC could
have a greater contribution from extravascular as opposed to intravascular blood, thus
confounding the expected correlation between the intravascular THC and fibroglandular
content.

An average blood oxygen saturation of 84 ± 10% was measured across all the 10 samples.
Srinivasan et al. measured an average SO2 of 68.3 ± 7.2% for 60 healthy subjects [58], and
Cerussi et al. measured an averaged SO2 of 76.3 ± 6.4% for 15 healthy premenopausal
subjects and 81.9 ± 8.8% for 6 postmenopausal subjects with FDPM instrument and a laser
breast scanner (LBS) [35], but Veen et al. reported a much higher oxygen saturation of 93 ±
7% in 24 normal breast tissues using a fiber optic needle probe with differential path-length
spectroscopy (DPS) [50]. The SO2 of this study is higher than those reported by Srinivasan

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and Cerussi, but lower than that reported by Veen. It should be noted that both Srinivasan’s and Cerussi’s results were obtained from intact healthy female breasts and are an average over a larger tissue volume, whereas Veen’s and our study used minimally invasive fiber optic probes and thus yield information on the local tissue blood oxygenation and blood content. However, it should also be noted that Veen did not report the THC measurements in their paper [50]. In our study we found that there is no significant correlation between blood saturation and the histological parameters. This is consistent with similar findings in literature, which show that there is no significant correlation between blood saturation and subject age or body mass index (BMI) [44, 60]. Our results also suggest that even though there is some bleeding, blood saturation measurements are not susceptible to bleeding during core needle biopsy as seen in Fig. 5(f).

Subject bleeding during the biopsy procedure is expected to contribute to attenuation of the photon density waves. In the current study, the first optical measurement was always performed before any biopsy sample was removed, but subsequent measurements taken after each biopsy, would be progressively more susceptible to bleeding. Although a vacuum chamber was used to suck out the majority of the blood in the cavity and in the needle between optical measurements, residual blood and bleeding during the spectroscopy was still a concern, particularly after the second measurement. The bleeding can result in higher total hemoglobin concentration than otherwise measured on intact healthy breasts. This may explain the higher THC measured in this study as compared to those found by Cerussi [35] and Pogue [59]. A revised procedure was recently adopted to reduce the subject bleeding. In this procedure, optical measurements are taken at all the clock positions first and then followed by tissue biopsy at each site.

Another important factor that should be addressed is the number of wavelengths used in the fitting algorithm. Currently, only three wavelengths were used in this feasibility study, even though four principal absorbers exist in breast tissue. Although water and lipid contribute significantly less to the total absorption compared to oxy- and deoxy-hemoglobin at these wavelengths, ignoring their contributions or their concentration variations from subject to subject can be a significant source of error [54]. It has also been indicated that inclusion of more wavelengths in the FDPM instrument may increase robustness in the amplitude and phase fitting in the presence of noise and provide the capability of extracting other chromophores in the tissue [61]. To alleviate this source of error, additional wavelengths will be incorporated for future clinical studies.

Finally, we believe that significant light leakage associated with the probes used in the clinical studies rendered some data unusable. The light leakage reduces the signal-to-noise ratio of the clinical signal, resulting in errors in the amplitude and phase measurements. To reduce the probe light leakage, a baffle will be mounted in between the tips of the collection fiber and the illumination fibers of new side-firing probes for future clinical studies.

5. Conclusion

We performed NIR diffuse optical spectroscopy in vivo with a side-firing fiber-optic probe in patients undergoing image-guided core-needle biopsy. The study shows that the measured tissue optical absorption is sensitive to adipose tissue content as well as fresh hemorrhage while the measured optical scattering is sensitive to fibroglandular tissue content in normal or benign female breasts. The side-firing probe based on NIR spectroscopy may eventually provide a practical, minimally invasive means for enhancing the sampling yield of image-guide core needle biopsy for breast cancer diagnosis.

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