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Near-infrared tomography of breast cancer hemoglobin, water, lipid, and scattering using combined frequency domain and cw measurement

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Abstract

In this study, near-IR tomography was implemented in the wavelength range from 661 to 948 nm to characterize breast tumors *in vivo*. Frequency-domain measurements provide amplitude and phase transmitted at wavelengths below 850 nm, where photomultiplier tube detection is efficient. Continuous-wave detection at additional longer wavelengths (903, 912, and 948 nm) was collected using a CCD-based spectrometer. Phantom validation experiments showed improved accuracy in hemoglobin and water concentrations using this technique. Three women with malignant breast tumors were studied. The addition of cw data at longer wavelengths increased the recovered contrast of water in the tumor region relative to surrounding tissue and allowed quantification of lipid.

Near-IR (NIR) spectroscopy and tomography of breast cancer is being studied for management of breast cancer. NIR shows the unique advantage of providing molecular-level contrast with noninvasive, nonionizing signals. Cerussi *et al.* demonstrated diffuse optical spectroscopy (DOS) of malignant breast tumors [1] using a single-surface detector with spectral data from 650 to 1000 nm. This wide-bandwidth spectrum provides sufficient spectral information to estimate all major absorbers in breast tissue, including oxy-hemoglobin (HbO₂), deoxy-hemoglobin (Hb), water, and lipid. This approach could ideally be extended to a tomographic imaging geometry where each spectral feature is spatially resolved. Diffuse optical tomography (DOT) has been used for imaging benign and malignant breast tumors with cw [2,3], frequency-domain (FD) [4], and time-domain (TD) [5] approaches, each with slightly different numbers of wavelengths used. Almost universally in these previous attempts, the measurement wavelengths used have been below 850 nm, primarily because of instrumentation limitations, which unfortunately leads to difficulty in accurate quantification of water and lipid content [6]. Several DOT studies have utilized combined FD and cw systems for breast imaging [7–9], where the distribution of hemoglobin concentration and blood oxygen saturation was reconstructed. However, in most instances, the water and lipid concentrations were assumed to be homogeneous, which is clearly not the case in breast composition. Jakubowski *et al.* [10] and Cerussi *et al.* [1] reported significant water and lipid contrast for cancerous tissues using DOS. Ignoring the water contribution can cause error propagation into the estimation of hemoglobin concentration [6,11]. In this Letter, a hybrid approach to combine FD and cw measurement

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is presented to image malignant tumors *in vivo* with DOT. By extending the spectral detection up to 948 nm wavelength, the contribution of water and lipids can be estimated, together with HbO₂ and Hb, as well as total hemoglobin (HbT=HbO₂ +Hb) and oxygen saturation (StO₂ =HbO₂/HbT). Scattering properties were modeled based on the reduced scattering coefficient model: $\mu'_s = a\lambda^{-b}$, where a is the scattering amplitude and b is the scattering power. This study was designed to contribute preliminary data on the contrast between normal and tumor tissues in all major chromophores and scatterers with the DOT imaging approach.

As shown in Fig. 1, the hybrid imaging strategy was implemented with the FD measurement system using photomultiplier tubes (PMTs) and the cw detection system comprised of sixteen CCD-based spectrometers. Six intensity-modulated laser diodes (661, 761, 785, 808, 826, and 849 nm) were used in the FD system for the measurement of amplitude and phase at each wavelength [4]. The spectrometer detection system was discussed in previous work [12]. To add data at longer wavelengths, the outputs of three laser diodes (903, 912, and 948 nm) were directed into a 3×1 fiber combiner as a single cw light source. Two sets of sixteen bifurcated fiber bundles were used for source detection. As indicated in Fig. 1(a), fiber bundles of the two systems were located at two vertically adjacent planes with about 1 cm height difference.

During imaging, subjects lay prone on the examination platform, with one breast pendant within the fiber-optic array [13]. The circular fiber array was moved into even contact pressure with the breast. In the reconstruction, the part of the Jacobian matrix of each wavelength was calculated and then combined together to initially estimate the concentration of HbO₂, Hb, water, and lipid, as well as scattering amplitude and scattering power.

The major motivation of including longer wavelengths was to improve the quantification of water and HbO₂ [6,11,14,15]. To validate this effect, phantom experiments were completed to explore the ability to better separate water and HbO₂ with this combined approach. As shown in Fig. 2(a), the gelatin background of the phantom was composed of 11 μ M blood, and the cylindrical hole was filled with solution of 22 μ M blood, providing a 2:1 contrast in HbT value. The reconstruction results are shown in Fig. 2. There was significant overestimation of the HbT value that can be explained as resulting from that the use of too few wavelengths without dominant spectral features, leading to crosstalk error [11,15,16]. When the additional three cw wavelengths were added, the HbT image was significantly improved, as shown in Fig. 2(c). The average of recovered values of HbT and water in the background and inclusion are listed in Table 1. The water content in the gelatin background was found to be near 100%, which is consistent with the volume percentage of water used in the phantom. This enhanced water recovery consequently decreases the error in HbT estimation.

Three female subjects with malignant breast tumors were studied using the hybrid NIR tomography system. The study was approved by the institutional review board, and all subjects gave informed consent to participate. Figure 3 shows the NIR images as well as MR images of the subject with a 2.7×1.8×3.4 cm infiltrating ductal carcinoma. The fiber bundle array was paced over the tumor position as given by the MR images [Fig. 3(a)]. Figures 3(a)–3(c) are contrast-difference MR images that were acquired with the patient on a 1.5 T scanner (GE Signa, GE Healthcare, Waukesha, Wisc.). The tumor position was indicted by arrows in coronal plane. In Fig. 3(d), spectral reconstruction images with FD only were compared with results using combined FD and cw data sets in Fig. 3(e). The HbT image shows a localized increase at the site of the tumor, indicating the increased vascularity due to angiogenic activity. The optical images show excellent spatial agreement in tumor

localization with the MR imaging (MRI) results. The lipid estimation using only the FD data was not included because of its relatively low absorption below 850 nm. To compare the properties of tumor and surrounding normal tissue, the region of interest (ROI) of the tumor was obtained using the FWHM in the Hb image. With longer wavelengths added into the spectral reconstruction, contrast (ROI/background) in water concentration improved from 1.10 to 1.44, along with an inverse contrast of 0.82 in the lipid image. The increase in water and the decrease in lipid content at the tumor position has also been found in other studies of malignant breast tumors using spectroscopic reflectance measurements in a similar wavelength range [1]. The average and standard deviation of the ROI and background tissue properties of three patients are summarized in Table 2. For patient 1 (shown in Fig. 3) the average tumor HbT was 27.3 μM , with 14.9 μM in the background. The tumor also had higher water concentration at 31.3%, as compared with background at 21.8%. The average lipid content decreased from 80.6% in the background to 66.3% in the tumor. In this subject, an increase in scattering power was observed in the tumor region. This has been hypothesized to be due to the malignant transformation of the tissue cells, which leads to a change in the effective scatter size of the tissue. The tumor region of all three patients showed an increase in HbO₂ and Hb relative to the surrounding normal tissue; however, the value of StO₂ in the tumor did not show a consistent decrease among all patients. The oxygen saturation changes around a tumor are complex and likely heterogeneous on a microscopic distance scale.

The recovery of contrast of water concentration was enhanced by including cw data at wavelengths above 850 nm, and lipid distribution was also able to be quantified. Taking into consideration all major chromophores is important to accurately estimate each of them. Spatial localization could be improved by incorporation into clinical imaging modalities, such as MRI, so that spatial reconstruction can be replaced by three-dimensional parameter estimation with known positions of fiber interfaces and interior tissue structures, as is ongoing in an MRI/NIR imaging system.

In summary, the quantification of water and hemoglobin concentrations was improved, as verified in phantom experiments. The contrast of water and lipid was better quantified with *in vivo* imaging of breast tumors.

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Fig. 1.

(Color online) (a) Schematic diagram of combined breast-imaging platform, using PMT-based FD and spectrometer-based cw detection systems. The FD imaging system, shown in (b), uses six intensity-modulated laser diodes and the examination bed where a patient lies in the prone position. (c) Spectrometer-based detection system for cw tomography with 16 CCD-coupled imaging monochromators.

Fig. 2.

(Color online) (a) Expected gelatin phantom properties. (b) Reconstructed images from data acquired with the FD system (661, 761, 785, 808, 826, and 849 nm). (c) Reconstructed images with cw data at three longer wavelengths (903, 912, and 948 nm) added to FD data set.

Fig. 3. (Color online) Dynamic-contrast MRI images of patient 1 in the orthogonal views: (a) axial, (b) coronal, and (c) sagittal. The reconstructed NIR coronal view images of chromophore and scattering parameters of the breast with (d) six wavelengths of FD measurements and (e) nine wavelengths of combined FD and cw data.

Table 1 Comparison of Phantom Experimental Results Using FD-Only and Combined Approaches^a

	<u>HbT (μM)</u>		<u>Water (%)</u>	
	BG	IC	BG	IC
True properties	11	22	98	97
FD (661–849 nm)	21.4	29.4	56.5	62.2
FD+cw (661–948 nm)	15.9	23.2	95.7	89.2

^a BG, background; IC, inclusion

Table 2
Results of Background versus Tumor Properties Using Combined FD and cw Measurement

Parameters	Patient 1		Patient 2		Patient 3	
	Background	Tumor	Background	Tumor	Background	Tumor
HbT (μ M)	14.9 $\pm$ 2.5	27.3 $\pm$ 4.5	14.6 $\pm$ 2.1	23.4 $\pm$ 3.0	22.1 $\pm$ 6.3	32.6 $\pm$ 6.4
StO ₂ (%)	57.3 $\pm$ 4.4	63.3 $\pm$ 4.5	70.7 $\pm$ 3.9	65.8 $\pm$ 3.3	76.8 $\pm$ 5.3	64.5 $\pm$ 7.2
HbO ₂ (μ M)	8.6 $\pm$ 2.0	17.5 $\pm$ 4.1	10.3 $\pm$ 1.6	15.4 $\pm$ 2.6	17.1 $\pm$ 5.6	21.4 $\pm$ 6.3
Hb (μ M)	6.3 $\pm$ 0.7	9.8 $\pm$ 0.7	4.3 $\pm$ 0.8	7.9 $\pm$ 0.7	5.0 $\pm$ 1.3	11.2 $\pm$ 1.1
Water (%)	21.8 $\pm$ 4.4	31.3 $\pm$ 2.3	9.0 $\pm$ 2.4	18.1 $\pm$ 1.8	14.7 $\pm$ 4.5	28.2 $\pm$ 2.8
Lipid (%)	80.6 $\pm$ 13.4	66.3 $\pm$ 10.6	73.2 $\pm$ 13.2	50.4 $\pm$ 6.3	53.8 $\pm$ 26.1	18.5 $\pm$ 4.5
Scatt. Amp.	1.0 $\pm$ 0.3	1.1 $\pm$ 0.2	1.0 $\pm$ 0.3	1.0 $\pm$ 0.2	0.9 $\pm$ 0.2	0.9 $\pm$ 0.1
Scatt. Power	1.2 $\pm$ 0.3	1.5 $\pm$ 0.2	0.4 $\pm$ 0.1	0.6 $\pm$ 0.1	1.5 $\pm$ 0.1	1.8 $\pm$ 0.2