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Imaging tumor angiogenesis by use of combined near-infrared diffusive light and ultrasound

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Abstract

A novel two-step reconstruction scheme using a combined near-infrared and ultrasound technique and its utility in imaging distributions of optical absorption and hemoglobin concentration of breast lesions are demonstrated. In the first-step image reconstruction, the entire tissue volume is segmented based on initial coregistered ultrasound measurements into lesion and background regions. Reconstruction is performed by use of a finer grid for lesion region and a coarse grid for the background tissue. As a result, the total number of voxels with unknown absorption can be maintained on the same order of total measurements, and the matrix with unknown total absorption distribution is appropriately scaled for inversion. In the second step, image reconstruction is refined by optimization of lesion parameters measured from ultrasound images. It is shown that detailed distributions of wavelength-dependent absorption and hemoglobin concentration of breast carcinoma can be obtained with the new reconstruction scheme.

Tumor blood volume and microvascular density are parameters that are anatomically and functionally associated with tumor angiogenesis. During the past decade, modeling of light propagation in the near-infrared (NIR) region, combined with advancements of light source and detectors, has improved diffused light measurements and made possible the application of tomographic techniques for characterizing and imaging tumor angiogenesis.^{1,2} However, the NIR technique has not been widely used in clinics, and the fundamental problem of intense light scattering remains. As a result, diffusive light probes a widespread region instead of providing information along a straight line, and tomographic image reconstruction is, in general, underdetermined and ill-posed. Zhu *et al.*³ and Chen *et al.*⁴ demonstrated a combined imaging technique, using *a priori* lesion structure information provided by coregistered ultrasound images to assist NIR imaging reconstruction in phantom studies.^{3,4} As a result, the NIR image reconstruction is well defined and less sensitive to noise. In this Letter we report on our novel two-step image reconstruction scheme that uses the combined approach and demonstrate its utility in imaging tumor absorption and hemoglobin distributions. It is shown that detailed heterogeneous distributions of wavelength-dependent optical absorption and hemoglobin concentration of a breast carcinoma can be obtained. To the best of our knowledge, such detailed distributions have not been reported in the literature.

A picture of our combined hand-held probe used in clinical studies is shown in Fig. 1(a), and the probe dimensions and optical sensor distributions are shown in Fig. 1(b). The combined probe consists of a commercial ultrasound one-dimensional array located at the center of the probe and optical source and detector fibers distributed at the periphery and connected to the NIR imager. The NIR imager consists of 12 dual-wavelength source channels and 8 parallel receiving channels.⁴ In the transmission part, 12 pairs of dual-wavelength (780- and 830-nm) laser diodes are amplitude modulated at 140 MHz. In the reception part, 8 photomultiplier tubes detect diffusely reflected light from the tissue. Both the amplitude and phase at each source–

detector pair are obtained, and the resulting total number of measurements is $12 \times 8 \times 2 = 192$. The combined probe is made of a black plastic plate 10 cm in diameter; therefore, a semi-infinite boundary condition can be used for the NIR measurement geometry. The amplitude and phase measured from the normal side of the breast are used to calculate the background absorption μ_a and reduced scattering coefficient μ_s' .⁴ In our two-step image reconstruction, we first segment tissue volume into two regions, L and B , that contain a lesion as measured from coregistered ultrasound images and background tissue, respectively. We use the Born approximation to relate the scattered field $U_{sc}'(r_{si}, r_{di}, \omega)$ measured at source–detector pair i to absorption variations $\Delta\mu_a(r')$ in each volume element of two regions within the sample, where r_{si} and r_{di} are the source and detector positions, respectively. We then discretize the lesion volume and the background volume with different voxel sizes (a finer grid for lesion volume and a coarse grid for background). The scattered field can then be approximated as

$$U_{sc}'(r_{si}, r_{di}, \omega) \approx -\frac{1}{D} \times \left[\sum_{Lj} G(r_{vj}, r_{di}) U_{inc}(r_{vj}, r_{si}) \int \Delta\mu_a(r') d^3r' + \sum_{Bk} G(r_{vk}, r_{di}) U_{inc}(r_{vk}, r_{si}) \int \Delta\mu_a(r') d^3r' \right], \quad (1)$$

where r_{vj} and r_{vk} are the centers of voxels j and k in lesion volume L and background volume B , respectively², and $U_{inc}(r', r_{si})$ and $G(r', r_{di})$ are the incident wave and the Green function of the semi-infinite geometry, respectively. The matrix form of relation (1) is given as

$$[U_{sd}]_{MX1} = [W_L, W_B]_{MXN} [M_L, M_B]^T, \quad (2)$$

where $W_L = [-1/DG(r_{vj}, r_{di})U_{inc}(r_{vj}, r_{si})]_{M \times N_L}$ and $W_B = [-1/DG(r_{vk}, r_{di})U_{inc}(r_{vk}, r_{si})]_{M \times N_B}$ are weight matrices for the lesion volume and the background volume, respectively; $[M_L] = [\int_{1L} \Delta\mu_a(r') d^3r', \dots, \int_{N_L} \Delta\mu_a(r') d^3r']$ and $[M_B] = [\int_{1B} \Delta\mu_a(r') d^3r', \dots, \int_{N_B} \Delta\mu_a(r') d^3r']$ are the total absorption distributions of the lesion volume and the background volume, respectively.

Instead of reconstructing the $\Delta\mu_a$ distribution directly as the standard Born approximation, we reconstruct total absorption distribution M and then divide the total by different voxel sizes of lesion and background tissue to obtain $\Delta\mu_a$ distribution. By choosing a finer grid for the lesion and a coarse grid for the background tissue, we can maintain the total number of voxels with unknown absorption on the same scale of the total measurements. As a result, the inverse problem is less underdetermined and ill-posed. In addition, since the lesion absorption coefficient is higher than that of the background tissue, in general, the total absorption of the lesion over a smaller voxel is on the same scale of total absorption of the background over a bigger voxel, and therefore the matrix $[M_L, M_B]$ is appropriately scaled for inversion. The reconstruction is formulated as a least-squares problem. The unknown distribution M can be iteratively calculated with the conjugate-gradient search method.

The lesion location and volume from coregistered ultrasound is estimated as follows: Since the commercial one-dimensional ultrasound probe that we use acquires two-dimensional ultrasound images in the $y-z$ plane (z is the propagation direction) and the two-dimensional NIR probe provides three-dimensional images, the coregistration is limited to an interception plane. However, if we approximate a lesion as an ellipsoid, we are able to estimate its center and radii from two orthogonal ultrasound images and therefore obtain the lesion volume. Three sources of error may lead to inaccurate estimation of the lesion center and radii and therefore to cause errors in reconstructed optical properties. First, the lesion boundaries may not be well defined in ultrasound images. Second, two separate orthogonal ultrasound images are used to estimate

the radii and the center, and these parameters depend on the ultrasound probe position and compression of the hand-held probe. Third, the target volumes or shapes seen by different modalities may be different because of different contrast mechanisms. In the second step, we refine image reconstruction by perturbing the center c_0 and then the radii r_0 and choosing the optimal set of parameters (c_{opt} , r_{opt}).

Clinical studies were performed at the Health Center of the University of Connecticut, and the human subject protocol was approved by the Health Center IRB committee. Patients with palpable and nonpal-pable masses that were visible on clinical ultrasound were used as subjects. These subjects were scanned with the combined probe, and ultrasound images and optical measurements were acquired at multiple locations, including the lesion region that was scanned at two orthogonal positions, and a normal region of the contralateral breast scanned at two orthogonal positions.

An example is given in this Letter to demonstrate the use of our reconstruction scheme. Figure 2(a) shows a gray-scale ultrasound image of a palpable lump in a 44-year-old woman. The lesion was located at the 6 to 8 o'clock position of the left breast at approximately 1.5-cm depth. Ultrasound showed an irregular poorly defined hypoechoic mass, and the lesion was considered highly suspicious for malignancy. An ultrasound guided-core needle biopsy was recommended. Biopsy results (after NIR imaging) revealed that the lesion was a high-grade *in situ* ductal carcinoma with necrosis.

Multiple optical measurements at two orthogonal positions were simultaneously made with ultrasound images at the lesion location as well as at approximately the same location of the contralateral normal breast. The fitted average tissue background measured on the normal side of the breast at both wavelengths was $\mu_a^{780} = 0.03 \text{ cm}^{-1}$, $\mu_a^{830} = 0.05 \text{ cm}^{-1}$, $\mu_s'^{780} = 9.22 \text{ cm}^{-1}$, and $\mu_s'^{830} = 7.58 \text{ cm}^{-1}$. The perturbations for both wavelengths used to calculate absorption maps were normalized as $U_{sc}'(r_{si}, r_{di}, \omega) = [U_L(r_{si}, r_{di}, \omega) - U_N(r_{si}, r_{di}, \omega)] U_B(r_{si}, r_{di}, \omega) / U_N(r_{si}, r_{di}, \omega)$, where $U_L(r_{si}, r_{di}, \omega)$ and $U_N(r_{si}, r_{di}, \omega)$ were measurements obtained from the lesion region and the contralateral normal region, respectively, and $U_B(r_{si}, r_{di}, \omega)$ was the incident field calculated with fitted background μ_a and $D = 1 / 3 \mu_s$. This procedure cancels unknown system gains associated with different sources and detectors as well as electronic channels. The initial estimates of the lesion center and diameter in two orthogonal ultrasound images were (0, 0.39 cm, 1.7 cm) and 3.44 cm $\times$ 4.38 cm $\times$ 1.76 cm, respectively. A finer grid of 0.5 cm $\times$ 0.5 cm $\times$ 0.5 cm and a coarse grid of 1.5 cm $\times$ 1.5 cm $\times$ 1.0 cm were chosen for the lesion and background tissue, respectively. The total reconstruction volume was chosen to be 9 cm $\times$ 9 cm $\times$ 4 cm, and the total number of voxels with unknown optical absorption was 190, which was of the same order as the 192 total measurements. Image reconstruction was performed with the NIR data simultaneously acquired with the ultrasound image shown in Fig. 2(a). The second-step refined reconstruction revealed optimal lesion centers at approximately (−1.1 cm, 0.3 cm, 1.7 cm) for 780 nm and (−0.9 cm, −0.7 cm, 1.7 cm) for 830 nm and optimal diameters of 4.28 cm $\times$ 5.18 cm $\times$ 1.96 cm. The detailed absorption maps with high absorption nonuniformly distributed around the lesion boundaries at both wavelengths are shown in Figs. 2(b) and 2(c). By assuming that the major chromophores are oxygenated (oxyHb) and deoxygenated (deoxyHb) hemoglobin molecules in the wavelength range studied, we can estimate the distribution of total hemoglobin concentration as shown in Fig. 2(d). The measured average cancer and background total hemoglobin concentrations were 55.8 μmol and 20.7 μmol , respectively.

It is interesting to note that the absorption distributions at both wavelengths as well as the total hemoglobin concentration were distributed heterogeneously at the cancer periphery. To the best of our knowledge, such fine distributions have not been obtained by use of NIR-only

reconstruction techniques. However, this finding agrees with the published literature showing that breast cancers have higher blood volumes than nonmalignant tissue because of angiogenesis, especially at the cancer periphery. In addition, the carcinoma reported here had a necrotic core, which could lead to the low absorption observed at both wavelengths in the center region.

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Fig. 1.

(a) Hand-held combined probe and a frequency-domain NIR imager. (b) Sensor distribution of the combined probe (diameter, 10 cm). The smaller circles are optical source fibers, and the bigger circles are detector fibers. A commercial ultrasound probe is located at the center and its dimensions are 5.6 cm by 1 cm.

Fig. 2.

(a) Gray-scale ultrasound image of a palpable lump of a 44-year-old woman. Ultrasound showed an irregular poorly defined hypoechoic mass, and the lesion was considered as highly suspicious for malignancy. Reconstructed optical absorption maps at (b) 780 nm and (c) 830 nm. The vertical color bars are the absorption coefficient [cm^{-1}]. (d) Total hemoglobin concentration map. The vertical color bars are μmol . The NIR data were simultaneously acquired with the ultrasound image shown in (a). Each image consists of seven slices obtained in 0.5-cm spacing from 0.5 to 3.5 cm in depth. The vertical and horizontal axes correspond to x and y dimensions of 9 cm by 9 cm.