Published in final edited form as:

Appl Opt. 2004 March 10; 43(8): 1654–1662.

Dual-mesh optical tomography reconstruction method with a depth correction that uses *a priori* ultrasound information

Minming Huang

Department of Electrical and Computer Engineering, University of Connecticut, Storrs, Connecticut 06269.

Quing Zhu

Department of Electrical and Computer Engineering, University of Connecticut, Storrs, Connecticut 06269. zhu@engr.uconn.edu.

Abstract

A dual-mesh reconstruction method with a depth correction for near-infrared diffused wave imaging with ultrasound localization is demonstrated by use of phantoms and clinical cancer cases. Column normalization is applied to the weight matrix obtained from the Born approximation to correct the depth-dependent problem in the reconstructed absorption maps as well as in the total hemoglobin concentration maps. With the depth correction, more uniform absorption maps for target layers at different depths are obtained from the phantoms, and the correlation between the reconstructed hemoglobin concentration maps of deeply located, large cancers and the histological microvessel density counts are dramatically improved.

1. Introduction

Optical tomography that uses near-infrared (NIR) diffusive light has huge potential for providing functional parameters for distinguishing between benign and malignant processes.¹⁻¹⁰ However, the intensive light scattering in soft tissues makes it very difficult to obtain accurate optical property maps with an acceptable spatial resolution. Recently, a combination of NIR imaging with other imaging modalities, such as ultrasound or magnetic resonance imaging (MRI), has shown promising results¹¹⁻¹⁶ in providing complementary contrasts and in overcoming NIR reconstruction problems. In these methods the NIR and the ultrasound or MRI probes have been deployed such that both modalities view the same tissue volume. As a result, the *a priori* lesion information, including tissue type, lesion location, and shape provided by coregistered ultrasound or MRI, can guide the NIR image reconstruction to localized target regions.

However, perturbations of optical properties in nontarget regions could prevent the accurate reconstruction of the optical properties in target regions. Recently, we developed a novel dual-mesh method, which divides the entire imaging volume into target regions and nontarget regions based on the coregistered ultrasound images. The image reconstruction is performed by use of fine voxels for target regions and coarse voxels for nontarget regions. As a result, the total number of voxels with unknown optical properties is significantly reduced and the inversion is well defined. By using the dual-mesh method, we have obtained encouraging results from tissue biopsies taken from a group of patients.¹⁷⁻¹⁹

However, for deeply located, highly absorbing large tumors, we have found that the reconstructed absorption values and the resulting total hemoglobin concentration are highly dependent on depth (layer).¹⁹ In other words, the reconstructed absorption coefficients of the top layer are higher than those of deeper layers. This depth-dependent reconstruction is related to the weight matrix used for image reconstruction. In our current study¹⁷⁻²⁰ a handheld probe

was used to obtain NIR measurements in the reflection geometry, and the semi-infinite boundary condition was used to compute the weight matrix. The Born approximation was used to relate the unknown optical properties of the medium to the measurements, and an inversion was performed with the conjugate gradient iterative searching method. According to Ref. 21, the resulting weights for the semiinfinite geometry can roughly be described by the so called “banana function.” The banana function causes the reconstructed optical properties²⁰ to be highly depth dependent owing to the tendency of the iterative searching method to converge along the steepest direction, i.e., the largest weight direction. As a result, even for a homogeneous target, the reconstructed absorption coefficients of the top target layers, which normally have larger weights, are higher than those of the bottom target layers, which normally have smaller weights. Therefore it is essential to scale the weight matrix according to depth before the iterative searching method is applied. In this paper we introduce a simple column normalization scheme, which can dramatically alleviate the depth-dependent problem.

2. Dual-Mesh Method with Depth Correction

The details of our dual-mesh imaging reconstruction algorithm are described in Ref. 17. Briefly, the total imaging volume is segmented into two regions, L and B , where lesion region L contains the heterogeneity measured from coregistered ultrasound images and nonlesion region B is the back-ground. Then the target and background regions are discretized with different voxel sizes, resulting in a fine grid in the lesion region and a coarse grid in the nonlesion region. In the dual-mesh method we consider the absorption changes in the medium with the assumption that the scattering heterogeneities make a negligible contribution to the measurement. Similar procedures can be applied to reconstruct scattering coefficients.²⁰ From the Born approximation, the scattered field can be approximated as

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

where $G(r_{vj}, r_{di}) U_{inc}(r_{vj}, r_{si})$ and $G(r_{vk}, r_{di}) U_{inc}(r_{vk}, r_{si})$ are weight values at the center r_{vj} of voxel j and at the center r_{vk} of voxel k in lesion volume L and in back-ground volume B , and r_{si} and r_{di} are source and depositions, respectively. Equation (1) can be written into the following matrix form:

$$[U_{sd}]_{M \times 1} = [W_L, W_B]_{M \times N} [M_L, M_B]_{N \times 1}^T, \quad (2)$$

respectively. Instead of reconstructing the $\Delta\mu_a$ distribution, we reconstruct the total absorption distribution M and then divide it by different voxel sizes of the target and the background region to obtain the $\Delta\mu_a$ distribution. In general, the target region is more absorbing than the background is, and the total absorption distribution M , which is approximately the product of $\Delta\mu_a$ times voxel size, is well scaled between the lesion region and the nonlesion region for the inversion. In the reported studies, we have used a fine grid of $0.5 \text{ cm} \times 0.5 \text{ cm} \times 0.5 \text{ cm}$ in the target region and a coarse grid of $1.5 \text{ cm} \times 1.5 \text{ cm} \times 1.0 \text{ cm}$ in the background region. As a result, the weight matrix $[W] = [W_L, W_B]$ expands to several discrete layers in depth, and the B weight matrix W_B of larger tumors also expands to two or three layers.

However, the resulting weight matrix is not well scaled in depth. If the lesion region expands to two or three layers for larger tumors, the weights of the voxels at the top target layer are normally 1-2 times larger than those at the neighboring bottom target layer. To alleviate the depth-dependent problem, we compute a diagonal matrix G to rescale the weight matrix in different layers. For convenience, the weight matrix $W_{L,B}$ is arranged such that voxels from the target small region are followed by big voxels from the background region, and in each

region voxels are grouped layer by layer from top to bottom. As a result, we have p_1 target layers and p_2 back-ground layers. To form the diagonal matrix G , the mean absolute values of the columns of the weight matrix $W_{L,B}$ are calculated and grouped into a vector F as

$$F(j) = \frac{1}{N} \sum_i |W_{L,B}(i, j)|, \quad j = 1, 2, \dots, N. \quad (3)$$

Then the maximum mean absolute values are obtained for each layer, and the ratios between the maximum mean absolute values of the layer p' and that of the reference layer p_0 are used to form the diagonal matrix G :

$$G_{ij} = 0, \quad i \neq j, \quad j = 1, 2, \dots, N, \quad (4)$$

where p' is the layer number starting from the top and p_0 is a reference layer number, which is chosen as the bottom target layer in our computation.

The rescaled weight matrix used for reconstruction can be rewritten as

$$[U_{sd}] = [W_L, W_B][G]^{-1}[M_L, M_B]^T = [W'] [M']^T, \quad (5)$$

where $[W'] = [W_L, W_B][G]^{-1}$ is the rescaled weight matrix and $[M']^T = [G][M_L, M_B]^T$ is the rescaled weight matrix and is the rescaled total absorption distribution. The conjugate gradient method is used to minimize the object function, and the iterative search quickly converges in two or three iterations. No regularization scheme is used in the inversion. The resulting solution $[M']$ is divided by matrix G to obtain the total absorption distribution M . Because the new weight matrix is more uniform across the target layers, the iterative search procedure is less sensitive to the banana function in the target region.

3. Experimental Methods

The details of our NIR imaging system have been documented in Ref. 14. Briefly, it consists of 12 pairs of dual-wavelength sources (780 and 830 nm) and 8 detectors. The light sources are laser diodes with amplitude modulated at 140 MHz, and the detectors are photon multiplier tubes (PMTs). The sources and detectors are coupled to the combined probe through optical fibers. Shown in Fig. 1 is a schematic diagram of the combined probe, a circular plate with smaller circles representing optical source fiber positions and bigger circles denoting detector fiber positions. The rectangular hole in the middle houses the ultrasound transducer, which images the volume underneath. This one-dimensional ultrasound scanner can provide a y-z view of the targets (called a B-scan), where y is the lateral dimension and z is the propagation dimension. In the phantom experiments, the probe was mechanically translated in the x direction to acquire three-dimensional (3D) volumetric image data. Windowing the 3D data in the z direction at a particular depth provides the two-dimensional (2D) target spatial images in the x-y plane (called the C-scan). C-scans are coregistered with NIR images.²² The probe is made of a black plastic plate and is designed to be handheld. For each source-detector pair, both the amplitude and the phase of the scattered wave at the detector are measured and are used to reconstruct the absorption coefficients of the targets. Therefore both matrices $[U_{sd}]_{M \times 1}$ and $[W_L, W_B]_{M \times N}$ in Eq. (2) are complex numbers.

To evaluate our modified dual-mesh reconstruction method, we performed a series of phantom studies. A 0.6% Intralipid solution was used as the homogeneous background. The calibrated μ_a and μ_s are 0.0285 and 5.88 cm⁻¹, respectively, at 780 nm. Gel absorbers were suspended inside the Intralipid solution as targets.²³ Six targets with different absorption contrasts and

different sizes were chosen. Among these 3 six targets, three were cubic, which were 1 cm in size, and the other three were ellipsoidal, which were approximately 4 cm $\times$ 4 cm $\times$ 2 cm. The diffusion coefficients of all absorbers were the same as that of the background. Because the reconstruction performances at 780 and 830 nm are similar, we only report the experimental results at the 780-nm wavelength for the phantom studies.

Clinical studies were performed at the University of Connecticut Health Center (UCHC). The UCHC Institutional Review Board committee approved the human subject protocol. Patients with palpable and nonpalpable masses that were visible on clinical ultrasounds and who were scheduled for biopsies were enrolled as research subjects. Two cases of deeply located, advanced cancers were used to demonstrate the improvement in the reconstructed absorption maps as well as in the total hemoglobin concentration maps.

4. Experimental Results

A. Phantom Results

The reconstructed results of a small target without and with the depth correction are compared in Fig. 2. The target is a cube approximately 1 cm in size. The expected absorption coefficient is 0.052 cm⁻¹ above the background 0.0285 cm⁻¹ (see Table 1, target 1). Figure 2(a) is a B-scan ultrasound image obtained simultaneously with NIR measurements, and the estimated target depth from the B-scan is $\sim$ 2.0 cm. The ultrasound C-scan image was obtained by mechanical translation of the transducer in the x direction. The resulting C-scan ultrasound images show that the estimated target size is 1.1 cm $\times$ 1.1 cm $\times$ 1 cm and that its center location is at approximately (0, -1 cm, 2.0 cm). Figure 2(b) shows the reconstructed absorption maps without the depth correction. The total imaging volume is 4 cm $\times$ 4 cm $\times$ 3.75 cm. Slice 1 is the spatial x - y image of 4 cm $\times$ 4 cm obtained at a 0.75-cm depth in the Intralipid. Slice 7 is at a 3.75-cm depth in the Intralipid, and the spacing between slices is 0.5 cm. For comparison, the mean reconstructed values of different target layers are calculated by averaging the reconstructed values of the voxels within the target regions of corresponding layers, and the mean reconstructed values of the target regions are calculated by averaging the reconstructed values of the voxels within the entire target region of all the layers. The reconstructed absorption values of the top layer are quite reasonable, whereas those of the bottom layer are too small. The mean reconstructed values of two target layers are 0.0713 and 0.0412 cm⁻¹ for the top and the bottom layers, respectively, and the mean reconstructed value in the whole target region is 0.0562 cm⁻¹, which is approximately 70% of the expected value. Figure 2(c) shows the reconstructed absorption maps with the depth correction. The mean reconstructed values of layers 1 and 2 in the target region have been improved to 0.085 and 0.077 cm⁻¹, respectively. Moreover, the mean reconstructed value in the whole target region is improved to 0.081 cm⁻¹, which is very close to the expected value of 0.0805 cm⁻¹.

Figure 3 shows the reconstructed results of an ellipsoidal target located at (0, 0, 2.5 cm). The target is homogeneous, and its absorption coefficient is approximately 0.22 cm⁻¹ over the background 0.0285 cm⁻¹. From the resulting C-scan ultrasound images, the estimated target size is 4.2 cm $\times$ 4.2 cm $\times$ 2 cm, and the depth of the target center is $\sim$ 2.5 cm. Figure 3(a) shows the reconstructed absorption maps without the depth correction. The mean reconstructed values of the four target layers are 0.203, 0.13, 0.085, and 0.062 cm⁻¹ (from top to bottom; see Table 2, target 3), respectively, and the mean reconstructed value in the entire target region is 0.116 cm⁻¹, which is $\sim$ 47% of the expected value of 0.2485 cm⁻¹. Figure 3(b) shows the reconstructed absorption maps with the depth correction, and the reconstructed image uniformity is dramatically improved. The mean reconstructed values of the four target layers are 0.157, 0.144, 0.169, and 0.235 cm⁻¹ (from top to bottom), respectively, and the mean reconstructed value in the whole target region is 0.169 cm⁻¹, which is approximately 68% of the expected

value. The mean reconstructed value within the target's full width at half-maximum region is 0.206 cm^{-1} , which is approximately 83% of the expected value.

Tables 1 and 2 summarize the experimental results of the six absorbers, three of which are 1-cm cubes and the rest are ellipsoids. Table 1 shows the comparison of the reconstructed results from three small phantoms without and with the depth correction. For targets located at approximately a 2-cm depth in the Intralipid, the improvement is obvious. Without the correction, the mean value of the top target layer can reach 88%-102% of the expected value, but the mean value of the bottom target layer is approximately 50% of the expected value. With the depth correction, both the mean value of the bottom target layers and the uniformity of the distribution improve dramatically. A comparison of the result without and with the correction shows that the difference between the mean values of the top target layer and the bottom target layer is reduced from approximately 50% to 12.2% of the expected value. For target 3 the difference between the reconstructed values obtained without the correction and those obtained with the correction is negligible due to the layer insensitivity of the banana function at that target depth.

Table 2 shows the comparison of the reconstructed results from three big phantoms without and with the depth correction. All three targets are located approximately 2.5 cm within the Intralipid solution. Without the depth correction, the mean values in the target region decrease quickly from the top layer to the bottom layer. Although the mean value of the top layer is approximately 80%-95% of the expected value, the mean value of the bottom layer reaches only 20%-35% of the expected value. With the depth correction, the mean values of the four target layers are quite uniform. Even for the highest absorber, target 6, the biggest difference between the mean reconstructed values of different layers in the target region is less than 35% of the expected value.

B. Results from Two Advanced Cancers

In Ref. 19 we reported what we believe to be the first heterogeneous hemoglobin distributions of large cancers imaged by optical tomography and also showed that the hemoglobin distributions correlate, to a large extent, with histological microvessel density counts. However, for two deeply located, highly absorbing tumors, we found that the relatively high microvessel counts obtained from posterior samples do not correlate well with the low optical absorption distribution observed in deeper slices during optical imaging. Here we show that the modified dual-mesh method dramatically improves the correlation between the hemoglobin distributions and the histological microvessel density counts for these two cancer cases.

The first example is a 33-year-old pregnant woman with a palpable $3 \text{ cm} \times 3 \text{ cm} \times 1.5 \text{ cm}$ lump located at the twelve o'clock position on her left breast. The ultrasound image showed that the lesion had discrete nodularity [see Fig. 4(a)]. The center of the lump was $\sim 2.5 \text{ cm}$ beneath the skin surface. An ultrasoundguided core biopsy revealed that the lesion was both *in situ* and an invasive ductal carcinoma, as observed on multiple cores (histologic grade 3, nuclear grade 3). Optical absorption maps, as well as the total hemoglobin concentration distribution, were obtained without and with the depth correction. Figures 4(b) and 4(d) are the resulting optical absorption maps at 780 and 830 nm, respectively, obtained by the dual-mesh method without the depth correction, and Fig. 4(f) shows the corresponding total hemoglobin concentration. Figures 4(c) and 4(e) are the optical absorption maps of Figs. 4(b) and 4(d) with the depth correction, and Fig. 4(g) shows the resulting total hemoglobin concentration. The extinction coefficients used for calculating the oxygenated and deoxygenated hemoglobin (Hb) concentrations are $\epsilon_{\text{Hb}}^{780} = 2.5448$, $\epsilon_{\text{HbO}_2}^{780} = 1.6950$, $\epsilon_{\text{Hb}}^{830} = 1.7973$, $\epsilon_{\text{HbO}_2}^{830} = 2.4198$ and obtained from Ref. 24 in a natural logarithm scale in units of inverse millimoles times inverse centimeters. The details of the calculation can be found in Ref. 17. For each figure, slice 1 is the spatial x - y image of $8 \text{ cm} \times 8 \text{ cm}$ obtained at 0.5 cm beneath the skin surface. Slice 7 is at

a 3.5-cm depth, toward the chest wall, and the spacing between slices is 0.5 cm. Obviously, the uniformity of the absorption and the total hemoglobin distribution was improved with the depth correction. For quantitative comparison, the measured average absorption coefficients within 6 dB of the maximum value at two wavelengths, 780 and 830 nm, and the average total hemoglobin concentration within 6 dB of the maximum value were calculated for each target layer (see Table 3, ID number 23). For the absorption coefficient maps at 780 nm [Figs. 4(b) and 4(c)], the average values for three target layers were increased from 0.107, 0.022, and 0.0119 cm^{-1} to 0.149, 0.0296, and 0.0135 cm^{-1} , respectively. For the absorption coefficient maps at 830 nm [Figs. 4(d) and 4(e)], the average values for three target layers were increased from 0.247, 0.086, 0.037 cm^{-1} and to 0.234, 0.26, and 0.23 cm^{-1} , respectively. As a result, the average total hemoglobin concentrations for three target layers were increased from 93.3, 33, and 18.4 $\mu\text{mol/l}$ to 97, 77.4, and 61.7 $\mu\text{mol/l}$, respectively. As reported in Ref. 19, the total histological microvessel counts were 60 (anterior/lateral), 88 (anterior/medial), and 152 (posterior), respectively, over 10 consecutive fields. The counts obtained from the anterior and the lateral samples correlated with the optical absorption and the total hemoglobin concentration shown in slice 3 of Figs. 4(b), 4(d), and 4(f). However, the high total counts obtained from a posterior sample did not correlate well with the low total hemoglobin distribution shown in slices 4 and 5 of Fig. 4(f), which was computed with the dual-mesh method. With the depth correction, the correlation of the high total counts with the hemoglobin concentration seen in the deeper slices 4 and 5 of Fig. 4(g) was dramatically improved.

The other example was obtained from a 53-year-old women with a palpable mass, but a normal mammo-gram. An ultrasound revealed an irregularly shaped lesion of 2 cm $\times$ 2 cm $\times$ 1.3 cm, and an ultrasound-guided surgical biopsy confirmed it to be an invasive and *in situ* ductal carcinoma (histological grade 2, nuclear grade 2). The lesion center was $\sim$ 2.4 cm in depth relative to the skin. As in the previous case, the optical absorption maps, as well as the total hemoglobin concentration distribution, were obtained without and with the depth correction, and the measured average values within 6 dB of the maximum value for each target layer were calculated (Table 3, ID number 21). With the depth correction, the average total hemoglobin concentrations for three target layers were improved from 103.7, 44.8, and 33 $\mu\text{mol/l}$ to 99.6, 106.3, and 80.6 $\mu\text{mol/l}$, respectively. The improved light absorption and hemoglobin concentration correlate well with the total number of microvessels, which were 83 (anterior), 121 (posterior/lateral), and 124 (posterior), respectively, over 10 consecutive fields, as reported in Ref. 19.

Table 3 summarizes the results of the two deeply located, large cancer cases. Similar to the phantom experimental results shown in Subsection 4.A, the reconstructed results from the modified dual-mesh method are less depth dependent. Dramatic improvement was obtained for the values at the bottom layers, with a small change in the reconstructed values at the first target layer. With the depth correction, both cases show improved correlation between the reconstructed total hemoglobin distributions and the histological microvessel density counts.

5. Discussion and Summary

The experiment results presented in Section 4 have shown that the modified dual-mesh algorithm with the depth correction alleviates the depth-dependent problem, which is related largely to the varying sensitivity with depth in a reflection geometry.²¹ However, as we see from Tables 1 and 2, the reconstructed mean value in the target region can reach only 68%-75% of the expected value for large phantom targets, which have a μ_a higher than 0.17 cm^{-1} . For large absorbers with a μ_a higher than 0.17 cm^{-1} , the reconstructed μ_a may be underestimated due to linear suppression.²⁵ In the reported two large cancer cases, the reconstructed μ_a values are higher than 0.17 cm^{-1} , which might be beyond the linear range. Fortunately, the tumor sizes are not as large as those of the bigger phantoms; therefore, the accuracy of the reconstructed

absorption coefficients should be better than 68%-75%. Nonlinear forward models, such as the finite-element method, may avoid this problem by updating the weight matrix with the trade-off of increased computation time. We are currently pursuing investigations along these lines.

In conclusion, the dual-mesh algorithm with a depth correction can significantly improve the reconstructed absorption distributions in deeper-target layers. The experimental results of phantoms have shown that the reconstructed absorption maps are more uniform for phantom targets. The clinical results of two deeply located, large cancers have shown improved correlation between the reconstructed total hemoglobin concentrations and the histological microvessel density counts.

Acknowledgements

Scott Kurtzman and Poornima Hegde are thanked for their clinical consultations and microvessel density counting. NanGuang Chen, Daqing Piao, and graduate students Puyun Guo and Shikui Yan are acknowledged for their continuous help on NIR system and probe modifications. We thank the following funding agents for their support: U.S. Department of Defense Army Breast Cancer Program (DAMD17-00-1-0217, DAMD17-03-1-0690), Donaghue Foundation, and the National Institutes of Health (8R01EB002136-02).

References

1. Tromberg B, Shah N, Lanning R, Cerussi A, Espinoza J, Pham T, Svaasand L, Butler J. "Non-invasive *in vivo* characterization of breast tumors using photon migration spectroscopy,". *Neoplasia* 2000;2:26–40. [PubMed: 10933066]
2. Danen RM, Wang Y, Li XD, Thayer WS, Yodh AG. "Regional imager for low resolution functional imaging of the brain with diffusing near-infrared light,". *Photochem. Photo-biol* 1998;67:33–40.
3. Franceschini MA, Moesta KT, Fantini S, Gaida G, Gratton E, Jess H, Seeber M, Schlag PM, Kashke M. "Frequency-domain techniques enhance optical mammography: initial clinical results,". *Proc. Natl. Acad. Sci. USA* 1997;94:6468–6473. [PubMed: 9177241]
4. Li X, Durduran T, Yodh A, Chance B, Pattanayak DN. "Diffraction tomography for biomedical imaging with diffuse-photon density waves,". *Opt. Lett* 1998;22:573–575. [PubMed: 18183271]
5. Matson C, Liu H. "Analysis of the forward problem with diffuse photon density waves in turbid media by use of a diffraction tomography model,". *J. Opt. Soc. Am. A* 1999;16:455–466.
6. Paulsen K, Jiang H. "Spatially varying optical property reconstruction using a finite element diffusion equation approximation,". *Med. Phys* 1995;22:691–701. [PubMed: 7565358]
7. Arridge S, Schweiger M. "Photon-measurement density functions, Part I: Analytical forms,". *Appl. Opt* 1995;34:7395–7409.
8. Arridge S, Schweiger M. "Photon-measurement density functions, Part II: Finite-element-method calculations,". *Appl. Opt* 1995;34:8026–8037.
9. Jiang H, Paulsen K, Osterberg U, Pogue B, Patterson M. "Optical image reconstruction using frequency-domain data: simulations and experiments,". *J. Opt. Soc. Am. A* 1995;2:253–266.
10. Yao Y, Wang Y, Pei Y, Zhu W, Barbour RL. "Frequency-domain optical imaging of absorption and scattering distributions by a Born iterative method,". *J. Opt. Soc. Am. A* 1997;14:325–341.
11. Zhu Q, Durduran T, Holboke M, Ntziachristos V, Yodh A. "Imager that combines near infrared diffusive light and ultrasound,". *Opt. Lett* 1999;24:1050–1052. [PubMed: 18073937]
12. Zhu Q, Conant E, Chance B. "Optical imaging as an adjunct to sonograph in differentiating benign from malignant breast lesions,". *J. Biomed. Opt* 2000;5:229–236. [PubMed: 10938788]
13. Zhu Q, Chen NG, Piao DQ, Guo PY, Ding XH. "Design of near infrared imaging probe with the assistance of ultrasound localization,". *Appl. Opt* 2001;40:3288–3303. [PubMed: 11958271]
14. Chen NG, Guo PY, Yan SK, Piao DQ, Zhu Q. "Simultaneous near infrared diffusive light and ultrasound imaging,". *Appl. Opt* 2001;40:6367–6380.
15. Carraresi S, Shatir TSM, Martelli F, Zaccanti G. "Accuracy of a perturbation model to predict the effect of scattering and absorbing inhomogeneities on photon migration,". *Appl. Opt* 2001;40:4622–4632.

16. Ntziachristos V, Ma XH, Chance B. "Time-correlated single photon counting imager for simultaneous magnetic resonance and near-infrared mammography,". *Rev. Sci. Instrum* 1998;69:4221–4233.
17. Zhu Q, Chen NG, Kurtzman S. "Imaging tumor angiogenesis using combined near infrared diffusive light and ultrasound,". *Opt. Lett* 2003;28:337–339. [PubMed: 12659436]
18. Zhu Q, Huang M, Chen NG, Zarfes K, Jagjivan B, Kane M, Hegde P, Kurtzman S. "Ultrasound-guided optical tomographic imaging of malignant and benign breast lesions: initial clinical results of 19 cases,". *Neoplasia* 2003;5:379–388. [PubMed: 14670175]
19. Zhu Q, Kurtzman S, Hegde P, Huang M, Chen NG, Jagjivan B, Kane M, Zarfes K. "Imaging heterogeneous tumor hemoglobin distributions of advanced breast cancers by optical tomography with ultrasound localization,". *Proc. Natl. Acad. Sci.* (to be published)
20. Huang, M.; Chen, NG.; Yuan, B.; Zhu, Q. "3D simultaneous absorption and scattering coefficient reconstruction for the reflection geometry," in *Optical Tomography and Spectroscopy of Tissue V*. In: Chance, B.; Alfano, RR.; Tromberg, BJ.; Tamura, M.; Sevick-Muraca, EM., editors. *Proc. SPIE*. 4955. 2003. p. 52-58.
21. Fantini, S.; Franceschini, M.; Walker, SA.; Maier, JS.; Gratton, E. "Photon path distributions in turbid media: applications for imaging in optical tomography," in *Photon Migration and Spectroscopy of Tissue and Model Media: Theory, Human Studies and Instrumentation*. In: Chance, B.; Alfano, RR., editors. *Proc. SPIE*. 2389. 1995. p. 340-349.
22. Huang M, Xie TQ, Chen NG, Zhu Q. "Simultaneous reconstruction of absorption and scattering maps with ultrasound localization: feasibility study using transmission geometry,". *Appl. Opt* 2003;42:4102–4114. [PubMed: 12868853]
23. Zhu Q, Sullivan D, Chance B, Dambro T. "Combined ultrasound and near infrared diffusive light imaging,". *IEEE Trans. Ultrason. Ferroelectr. Freq. Control* 1999;46:665–678.
24. Cope, M. University College; London, UK: 1991. "The application of near infrared spectroscopy to non invasive monitoring of cerebral oxygenation in the newborn infant,". Ph.D. dissertation
25. Carraresi S, Shatir TSM, Martelli F, Zaccanti G. "Accuracy of a perturbation model to predict the effect of scattering and absorbing inhomogeneities on photon migration,". *Appl. Opt* 2001;40:4622–4632.

Fig. 1. Sensor distribution of the combined probe. Smaller circles are optical source fiber positions and larger circles are detector fiber positions. An ultrasound probe is located at the center of the combined probe, and the optical source and detector fibers are distributed at the periphery of the ultrasound probe.

Fig. 2.

Comparison of the reconstruction results of a small 1-cm³ cubic target located at (0,-1cm,2cm) inside the Intralipid. (a) B-scan ultrasound image. The dotted markers spaced 1 cm apart on the right side of the image indicate the scale in depth. (b) Optical absorption map (780 nm) obtained from the dual-mesh scheme without the depth correction. (c) Optical absorption map (780 nm) obtained from the dual-mesh scheme with the depth correction. The total imaging volume is 4 cm × 4 cm × 3.75 cm. Slice 1 is the spatial x-y image of 4 cm × 4 cm obtained at a depth of 0.75 cm in the Intralipid. Slice 7 is 3.75 cm deep within the Intralipid, and the spacing between slices is 0.5 cm. The unit for the absorption coefficient is cm⁻¹.

(a)

(b)

Fig. 3.

Comparison of the reconstruction results of a large ellipsoidal phantom target located at (0, 0, 2.5 cm) inside the Intralipid. (a) Optical absorption map (780 nm) obtained from the dual-mesh scheme without the depth correction. (b) Optical absorption map (780 nm) obtained from the modified dual-mesh scheme with the depth correction. The total imaging volume is $8\text{ cm} \times 8\text{ cm} \times 3.75\text{ cm}$. Slice 1 is the spatial x - y image of $8\text{ cm} \times 8\text{ cm}$ obtained at a depth of 0.75 cm in the Intralipid. Slice 7 is 3.75 cm deep within the Intralipid, and the spacing between slices is 0.5 cm. The unit for the absorption coefficient is cm^{-1} .

Fig. 4.

(ID 23P7). (a) Ultrasound image of a 33-year-old woman with a highly suspicious breast lesion located at the twelve o'clock position and measuring 3 cm $\times$ 3 cm $\times$ 1.5 cm. The ultrasound shows the discrete nodularity of the lesion. (b) Optical absorption map (780 nm) obtained from the dual-mesh scheme without the depth correction. (c) Optical absorption map (780 nm) obtained from the modified dual-mesh scheme with the depth correction. (d) Optical absorption map (830 nm) obtained from the dual-mesh scheme without the depth correction. (e) Optical absorption map (830 nm) obtained from the modified dual-mesh scheme. (f) Total hemoglobin concentration of the lesion obtained from the dual-mesh scheme without the depth correction. (g) Total hemoglobin concentration of the lesion obtained from the modified dual-mesh scheme. The total imaging volume is 8 cm $\times$ 8 cm $\times$ 3.5 cm. Slice 1 is the spatial x - y image of 8 cm $\times$ 8 cm obtained at 0.5 cm beneath the skin. Slice 7 is 3.5 cm beneath the skin, toward the chest wall, and the spacing between slices is 0.5 cm. The unit for the absorption coefficient is cm^{-1} , and the unit for the total hemoglobin concentration is $\mu\text{mol/liter}$.)

Fig. 4. (Continued)

Table 1
Comparison of the Reconstructed μ_a Values from Phantom Experiment without and with Depth Correction Small Phantoms

Target Contrast	Small Targets (1-cm ³ cube)				
	Target 1 [0, -1 cm, 2 cm]	Target 1 [0, 0, 2 cm]	Target 2 [0, -1 cm, 2 cm]	Target 2 [0, 0, 2 cm]	Target 3 [0, -1 cm, 1 cm]
ROI					
Expected μ_a (cm ⁻¹)	1.2 × 1.2 × 1 cm	1.2 × 1.2 × 1 cm	1.2 × 1.2 × 1 cm	1.2 × 1.2 × 1 cm	1.2 × 1.2 × 1 cm
Reconstructed μ_a (cm ⁻¹)	0.0805	0.0805	0.18	0.18	0.103
Without normalization	0.0713/0.0411 (0.0562 [†])	0.079/0.0364 (0.0577 [†])	0.177/0.093 (0.135 [†])	0.182/0.089 (0.135 [†])	0.104/0.108 (0.106 [†])
Without normalization	0.0853/0.0771 (0.081 [†])	0.0773/0.0738 (0.0756 [†])	0.165/0.143 (0.154 [†])	0.14/0.134 (0.137 [†])	0.109/0.1 (0.105 [†])
					0.0924/0.0958 (0.0941 [†])
					0.098/0.089 (0.0935 [†])

ROI: Region of interest, fine mesh.

* Mean values obtained within the target region for each target layer. The mean values are calculated by averaging the reconstructed values of the voxels within the target region for the corresponding layers.

[†] Mean values obtained within the entire target region. The mean value is calculated by averaging the reconstructed values of the voxels within the entire target region.

Table 2

Comparison of the Reconstructed μ_a Values from Phantom Experiment without and with Depth CorrectionBig
Phantoms

Target Contrast	Big Targets (4 cm × 4 cm × 2 cm ellipsoidal shape)		
	Target 4 [0, -0.5 cm, 2.7 cm]	Target 5 [0, -0.5 cm, 2.5 cm]	Target 6 [0, 0, 2.5 cm]
ROI	4.2 × 4.2 × 2 cm	4.2 × 4.2 × 2 cm	4.2 × 4.2 × 2 cm
Expected μ_a (cm ⁻¹)	0.178	0.93	0.2485
Reconstructed* μ_a (cm ⁻¹)			
Without normalization	0.165/0.107/0.072/0.057 (0.097) [†]	0.101/0.068/0.0476/0.03 (0.062) [†]	0.203/0.13/0.085/0.062 (0.116) [†]
With normalization	0.165/0.130/0.127/0.119/0.132 [†]	0.08/0.076/0.079/0.077/0.079 [†]	0.157/0.144/0.169/0.235/0.169 [†]

ROI: Region of interest, fine mesh.

* Mean values obtained within the target region for each target layer. The mean values are calculated by averaging the reconstructed values of the voxels within the target region for the corresponding layers.

[†] Mean values obtained within the entire target region. The mean is calculated by averaging the reconstructed values of the voxels within the entire target region.

Table 3

Comparison of the Reconstructed Results of the Two Cancer Cases without and with Depth Correction

Target Contrast	ID Number 21 (ROI: $8 \times 8 \times 1.3$ cm)		ID Number 23 (ROI: $7 \times 7 \times 1.66$ cm)	
	Without Norm	With Norm	Without Norm	With Norm
Reconstructed [*] ave. 6 dB μ_a (cm^{-1})				
780 nm	0.15/0.033/0.027	0.189/0.167/0.079	0.107/0.02/0.012	0.149/0.03/0.0135
830 nm	0.21/0.089/0.057	0.169/0.232/0.27	0.25/0.086/0.037	0.234/0.26/0.23
Reconstructed [*] ave. 6 dB Hb (μ mol/l)	103.7/44.8/33	99.6/106.3/80.6	93.3/33/18.4	97/77.4/61.7

ID: Identification.

ROI: Region of interest, fine mesh.

Hb: Hemoglobin.

* Mean values obtained within the target region for each target layer. The mean values offerent target layers are calculated by averaging the reconstructed values of the voxels within the target region for corresponding layers.