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Quantitative spectroscopy of superficial turbid media

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We report a novel diffuse optical spectroscopy probe design for determining optical properties of superficial volumes of turbid samples. The fiber-based probe employs a highly scattering layer placed in contact with the sample of interest. This layer diffuses photons from a collimated light source before they enter the sample and provides a basis for describing light transported in superficial media by the diffusion approximation. We compare the performance of this modified two-layer diffusion model with Monte Carlo simulations. A set of experiments that demonstrate the feasibility of this method in turbid tissue phantoms is also presented. Optical properties deduced by this approach are in good agreement with those derived by use of a benchmark method for determining optical properties. The average interrogation depth of the probe design investigated here is estimated to be less than 1 mm. © 2005 Optical Society of America

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Optical techniques such as diffuse optical spectroscopy (DOS) promise a fast and noninvasive way to quantify tissue composition and function *in vivo*.[1,2] DOS can be used for accurate determination of optical absorption (μ_a) and reduced scattering properties (μ_s') and for access to functional information, such as water and lipid concentrations and blood oxygen saturation of bulk biological tissues.[1] In a typical DOS measurement, a volume of tissue can be probed by use of a source–detector geometry similar to that illustrated in Fig. 1(a). To quantitatively deduce optical properties of turbid samples by using DOS requires a theoretical model that relates scattering and absorption coefficients to the measured reflectance. Inverse modeling based on the diffusion approximation to the radiative transport equation[3,4] can be computationally efficient and is commonly employed in DOS. The standard diffusion model assumes that (1) $\mu_s' \gg \mu_a$ in the sample and (2) that the radiance is the sum of an isotropic fluence term and a small directional flux term. DOS methods have performed quite well in the 600–1000 nm spectral range for determining optical properties and chromophore concentrations for applications such as monitoring breast cancer therapy.[1] In these applications, tissues are sufficiently thick and source–detector separations are larger than 10 transport mean free paths, so assumption (2) is reasonable.

Unfortunately, more than 80% of all cancers originate in epithelial tissue volumes that are 1 mm or less below the tissue surface. At this depth, diffusion-based methods have proved ineffective for quantitative examination of tissue because assumption (2) in the diffusion approximation mentioned above is no longer met.[5]

To address this need we have developed a novel probe in which a layer of a highly scattering ($\mu_s' = 47.35$/mm at 661 nm), low absorption ($\mu_a = 10^{-7}$/mm) material of known thickness is placed on the surface of the sample under investigation, as depicted in Fig. 1(b). We modified the two-layer geometry such that the detection fiber is in direct contact with the sample's surface. This modified two-layer (MTL) configuration results in highly diffused light and enables us to employ a MTL diffusion model to predict the optical properties of superficial volumes of interest.

The MTL model is an extension of a general two-layer diffusion model proposed by Kienle *et al.*[6] Following Kienle's derivation of a two-layer model, the diffusion equation can be written as $\{(1/c_i)(\partial/\partial t) + \mu_{ai} - \nabla[D_i(r)\nabla]\}\Phi_i(r,t) = S_i(r,t)$, where $D = 1/3(\mu_a + \mu_s')$ and Φ are the diffusion constant and the fluence rate, respectively, S is the source term, c is the speed of light in the medium, and $i = 1, 2$ is the layer number. The source is modeled as a point-source pulse located beneath the air–layer 1 boundary at a distance of $z_0 = 1/(\mu_a + \mu_s')$, and therefore the source terms can be written as $S_1 = \delta(x, y, z - z_0)$ and $S_2 = 0$. Extrapolated boundary conditions[4] are applied, and the fluence rate and the z component of the flux of different layers are continuous at the boundary of the first and second layers.[6] The fluence rates for this system of diffusion equations can be solved in the Fourier domain. Because the second layer corresponds to the sample volume of interest and is of immediate interest here, we focus on a description of the fluence rate of the second layer in the Fourier domain:

$$\phi_2(z,Q) = \frac{\sinh[\alpha_1(z_b + z_0)]\exp[\alpha_2(l - z)]}{D_1\alpha_1 \cosh[\alpha_1(l + z_b)] + D_2\alpha_2 \sinh[\alpha_1(l + z_b)]},$$
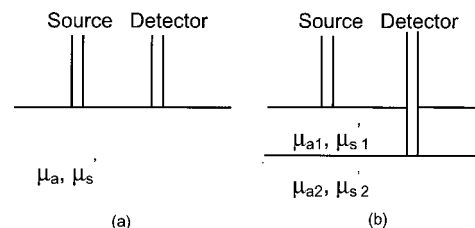
where

Fig. 1. (a) Typical DOS and (b) modified two-layer measurement geometries.

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$$\phi_2(z,Q) = \int_{-\infty}^{\infty} \int_{-\infty}^{\infty} \Phi_2(x,y,z)\exp[i(Q_1 x + Q_2 y)]\mathrm{d}x\mathrm{d}y,$$

$$\alpha_2{}^2 = (D_2 Q^2 + \mu_{a2} + j\omega/c_2)/D_2,$$

ω is the source modulation frequency, l is the thickness of the first layer, and $Q^2 = Q_1{}^2 + Q_2{}^2$. By numerically performing an inverse Fourier transformation of the solution, we obtain the fluence rate in the bottom layer. The spatially resolved reflectance is the integral of radiance L in the bottom layer, $L_2 = \Phi_2 + 3D_2(\partial\Phi_2/\partial z)\cos\theta$, over the backward hemisphere: $R(\rho) = \int_{2\pi}[1 - R_{\mathrm{Fres}}(\theta)]\cos\theta(L_2/4\pi)\mathrm{d}\Omega$, where $R_{\mathrm{Fres}}(\theta)$ is the Fresnel reflection coefficient for a photon with incident angle θ relative to the normal to the boundary. In this Letter we compare the performance of the MTL diffusion model with Monte Carlo simulation. Experimental results that demonstrate the feasibility of a MTL method that uses turbid phantoms are also presented.

Monte Carlo simulations of the MTL measurement geometry [Fig. 1(b)] were carried out to validate our modeling approach. The optical properties of the top layer (scattering layer) and the bottom layer (sample) were $\mu_{a1} = 1 \times 10^{-6}$/mm, $\mu'_{s1} = 50$/mm, $n_1 = 1.33$, $\mu_{a2} = 0.04$/mm, $\mu'_{s2} = 0.7$/mm, and $n_2 = 1.33$, respectively. The numerical apertures of the source fiber and of the detection fiber were both set at 1.33 to be consistent with our MTL diffusion model. The top layer's thickness and the source–detector separation were set to 3 and 2.5 mm, respectively. The sample thickness for this simulation was semi-infinite. The amplitude and phase data from a Monte Carlo simulation (asterisks) and from a MTL diffusion model (solid curves) are shown in Fig. 2. Amplitude and phase differences between the Monte Carlo simulation and the MTL diffusion model are within 1.3% and 4.6%, respectively, over the source modulation frequency range 50–500 MHz. Small differences between amplitude and phase data generated from Monte Carlo simulation and two-layer diffusion model were also observed by Kienle et al.[6] By fitting the Monte Carlo simulated data to the MTL diffusion model with a nonlinear regression algorithm, we recovered the optical properties of the sample layer to be $\mu_{a2} = 0.03156$/mm and $\mu'_{s2} = 0.664$/mm, which deviate from the designed values by 21% and 5%, respectively. We calculated the probe depth from the simulation by averaging and weighting the depths of scattering events in the sample layer experienced by detected photons. Probe depths of 676 and 658 μm were obtained when the source modulation frequencies were 50 and 500 MHz, respectively.

We performed an additional Monte Carlo simulation to illustrate that the MTL geometry is relatively insensitive to deep sample optical properties. In this simulation, the sample itself is stratified, with an upper-layer thickness of 2 mm (optical properties as used in the previous simulation) and an underlying semi-infinite layer that has distinctly different optical properties of $\mu_{a3} = 0.08$/mm, $\mu'_{s3} = 1.4$/mm, and in-
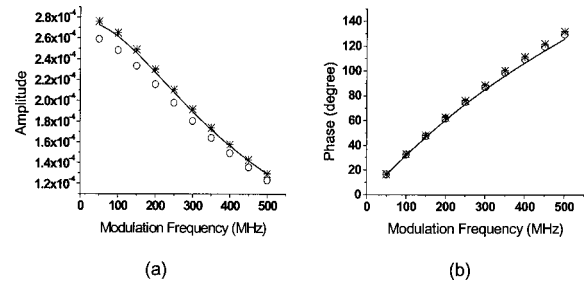

Fig. 2. (a) Amplitude and (b) phase versus source modulation frequencies generated from a MTL diffusion model (solid curve) and a Monte Carlo simulation (asterisks). See text for parameters used. Monte Carlo simulation results (squares) were generated with a layered sample composed of a 2 mm thick layer ($\mu_{a2} = 0.04$/mm, $\mu'_{s2} = 0.7$/mm) with an underlying semi-infinite layer ($\mu_{a3} = 0.08$/mm, $\mu'_{s3} = 1.4$/mm).

dex of refraction $n = 1.33$. Optical properties of the semi-infinite layer are not meant to represent those of any particular *in vivo* tissues but were chosen to illustrate the superficial probing aspects of the MTL probe design. Monte Carlo simulated amplitude and phase in this geometry are shown as squares in Fig. 2, and the recovered optical properties of the sample are $\mu_{a2} = 0.03268$/mm and $\mu'_{s2} = 0.706$/mm, which correspond closely to the uppermost 2 mm of the sample. The maximum differences in amplitude and phase between the two Monte Carlo simulations (asterisks and squares) are 6.1% and 1.1%, respectively, and illustrate that the influence of the third layer on the recovered sample's optical properties is small and that the majority of photons detected by use of our MTL geometry have traveled within the most superficial 2 mm of the sample.

Next, we carried out experiments on tissue phantoms, using a frequency-domain photon migration instrument that has been described in detail elsewhere.[1] Six laser diodes, 661, 681, 783, 806, 823, and 850 nm, were used in all our measurements, and a fiber-coupled avalanche photodiode was used for detection.

We fabricated five homogeneous liquid phantoms with different optical properties by using 10% Lyposin (Abbott Laboratories, Chicago, Ill.) as a scatterer, the water-soluble dye Nigrosin (Sigma, St. Louis, Mo.) as an absorber, and water. We determined the benchmark properties for each phantom by placing each phantom in a 1500 ml beaker. Source and detector fibers were submerged 80 mm below the surface and 70 mm from the sides of the container to prevent the occurrence of boundary effects. Measurements of amplitude and phase were carried out with source and detection fibers separated by 8 and by 10 mm. Source modulation frequencies ranged from 50 to 500 MHz in 400 equal steps. The optical properties of the five phantoms at 660 nm are listed in Table 1.

Next, we carried out measurements of each phantom in the semi-infinite and MTL geometries. For MTL measurements, the source fiber (610 μm; N.A., 0.37) was glued with epoxy to the top of a 70 mm $\times$ 70 mm, 3 mm thick Spectralon layer (Labsphere, North Sutton, NH). A small hole was

drilled through the Spectralon layer such that the center-to-center distance for the source and detection fibers (610 μm; N.A., 0.37) was 2.5 mm. We placed the probe in gentle contact with the surface of each sample and carried out frequency-domain photon migration measurements. The index mismatch between the probe and the phantom is small because the index refraction of Spectralon is 1.35 and the water-based phantoms have refractive indices of $\sim$1.33. The modulation frequencies ranged from 50 to 300 MHz in 200 equal steps. Inasmuch as Spectralon is highly attenuating, with $\mu_a = 10^{-7}$/mm and $\mu_s' = 47.35$/mm at 661 nm, the reflectance data collected at modulation frequencies higher than 300 MHz were noisy and were therefore neglected for this set of measurements. For semi-infinite measurements, the source–detector separation was 5 mm and the source modulation frequency range and the diameters of the source and detection fibers were the same as those used in MTL measurements.

We determined instrument response by measuring a liquid phantom with known optical properties and subsequently used it to calibrate the raw data from each phantom. We employed a MTL diffusion model and a P_1 diffusion model[4] to recover the optical properties from MTL and semi-infinite geometry measurements, respectively. A least-squares fit to amplitude demodulation and phase shift based on these models was used to recover the optical properties for each sample.

Figure 3 shows the results of using three different measurement geometries for liquid phantom 3, which has optical properties similar to those of oral cheek tissue.[7] The properties determined in the MTL geometry (circles) are in good agreement with those deter-

mined from infinite-medium measurements (asterisks), and the deviations between the results of the two measurement geometries are less than 5%. Error bars for MTL and infinite measurement results are not apparent in Fig. 3 because the error bars are smaller than the symbols used to identify the data. We calculated the deviation of optical properties deduced by MTL measurements from benchmark properties for all five phantoms at 661 nm. MTL measurement results showed small deviations (less than 8%) from benchmark results for all phantoms studied here, as listed in Table 1. The deviations do not demonstrate a noticeable dependence on a samples' optical properties.

In comparison, results from semi-infinite geometry (triangles) deviate from benchmark properties, and the error bars are too small to be discernible in Fig. 3. Optical properties from the semi-infinite measurement do not share the same trend with the benchmark values because the standard diffusion model does not describe photon transport accurately in this regime. The deviations of recovered optical properties from benchmark values are as high as 100% and 60% for μ_a and μ_s', respectively. Instrument phase and amplitude noise gradually degrades the detected signal as the photon path lengths decrease. As source–detector separation decreases in this geometry, we expect optical properties to deviate increasingly from benchmark values.

In conclusion, the MTL approach provides an efficient and reliable way to quantify the optical properties of superficial volumes of samples. The average interrogation depth of the MTL probe given the parameters investigated here is less than 1 mm. Our future research will include a detailed characterization of the probe's performance as a function of parameters such as top-layer scattering coefficient, source–detector separation, range of source modulation frequencies, and sample optical properties.

Table 1. Benchmark Optical Properties at 661 nm of Five Liquid Phantoms and Deviations of Optical Properties Determined by Use of MTL Measurements from Benchmark Values

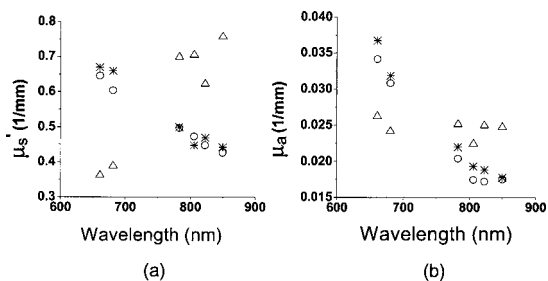| Phantom | μ_a (mm^{-1}) | μ_s' (mm^{-1}) | Deviation (%) | |
			μ_a	μ_s'
LP1	0.0198	1.0865	−2.07	1.42
LP2	0.0396	1.0746	3.58	−0.71
LP3	0.0367	0.6896	−6.94	−6.33
LP4	0.0118	1.1098	1.87	−6.65
LP5	0.0195	0.6698	3.90	7.49

Fig. 3. (a) Reduced scattering coefficients μ_s' and (b) absorption coefficients μ_a of the liquid phantom recovered from infinite-medium (asterisks), MTL (circles), and 5 mm semi-infinite (triangles) measurements at six wavelengths.

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