

SPECTROSCOPY AND TOMOGRAPHY OF TISSUES IN THE FREQUENCY-DOMAIN

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1. FREQUENCY DOMAIN METHODS IN TISSUE SPECTROSCOPY AND IMAGING

Substantial progress in the field of light spectroscopy and imaging of tissues was achieved when the group of Chance, Patterson and Wilson showed that the optical parameters of a turbid medium can be obtained from time resolved measurements of short light pulses propagating in the medium (Patterson et al, 1991a). Essentially, a fit of the intensity as a function of time, measured at some distance from the source, can provide separately the values of the absorption and of the reduced scattering coefficients. This demonstration was important because the focus was shifted from attempts to separate the scattering from absorption, using empirical corrections to the Beer-Lambert law, to a rigorous application of a physical model. During the same period, our lab proposed employing the Fourier transform equivalent concept using an intensity modulated light source (Gratton et al, 1990). Since frequency domain methods have better resolution and sensitivity and are much faster than the time domain methods, our proposal was followed by many others including Chance, Patterson and Wilson (Boas et al, 1993,1994; Cui and Ostrander, 1993; Duncan et al, 1993; Kaltenbach and Kaschke, 1993; O'Leary et al, 1992; Patterson et al, 1991b; Tromberg et al, 1993). It is well known that time domain and frequency domain measurements are mathematically equivalent, when the frequency domain measurement is carried out using a wide range of modulation frequencies (Gratton et al, 1983; Alcalá et al, 1984). However, frequency domain measurements can be made at a single modulation frequency, thereby sacrificing some of the information. The advantage of measurements at a single frequency is that they can be very fast, accurate and have an excellent signal-to-noise ratio. The question is whether the information that is lost by measuring the values of the phase shift, DC and AC at a single frequency, instead of using a frequency range, is essential or not. In the diffusive regime in a homogeneous medium, only two parameters are required to fully define the properties of the medium; namely the reduced scattering and the absorption coefficient. A measurement at a single frequency provides three independent quantities: phase, AC and DC. In the

diffusive regime, from any combination of two of them, it is possible to obtain the reduced scattering and the absorption coefficient. Which pair of quantities is used depends only on signal-to-noise considerations. This approach provides the technical basis for the development of instruments capable of measuring the reduced scattering and absorption coefficients.

2. FREQUENCY-DOMAIN DESCRIPTION OF LIGHT PROPAGATION IN HOMOGENEOUS STRONGLY SCATTERING MEDIA

In the range of source-detector distances used in our experiments and for relatively small values of the absorption coefficient (compared to the scattering coefficient), the physical model based on the diffusion approximation to the Boltzmann transport equation is adequate to describe the propagation of light in highly scattering materials, such as tissues. The theory of light propagation in tissue has been extensively described in the context of the transport theory (Case and Zweifel, 1967; Ishimaru, 1978). The diffusion approximation of the transport equation is shown below

$$v\mu_a U(r,t) + \frac{\partial U(r,t)}{\partial t} - vD\nabla^2 U(r,t) = vS(r,t) \quad (1)$$

where $U(r,t)$ represents the photon density in units of photons/cm³, $vD = v/(3\mu_a + 3\mu'_s)$ is the diffusion coefficient in units of cm²/s, μ'_s is the reduced scattering coefficient in cm⁻¹, μ_a is the absorption coefficient in cm⁻¹, v the velocity of light in the medium in cm/s and r the distance between the source and the detector in cm. The source term $S(r,t)$ on the right side of the equation is a sinusoidally intensity modulated source at an angular frequency ω . The solution of this equation in an infinite homogeneous medium has been reported by us (Fishkin and Gratton, 1993) and by others. The expressions for the phase, DC and AC parts are repeated below for convenience.

$$\phi = r \left[\frac{v^2 \mu_a^2 + \omega^2}{v^2 D^2} \right]^{\frac{1}{4}} \sin \left[\frac{1}{2} \arctan \left(\frac{\omega}{v\mu_a} \right) \right] + \varepsilon \quad (2)$$

$$\ln(rU_{DC}) = -r \sqrt{\frac{\mu_a}{D}} + \ln \left(\frac{S_o}{4\pi v D} \right) \quad (3)$$

$$\ln(rU_{AC}) = -r \left[\frac{v^2 \mu_a^2 + \omega^2}{v^2 D^2} \right]^{\frac{1}{4}} \cos \left[\frac{1}{2} \arctan \left(\frac{\omega}{v\mu_a} \right) \right] + \ln \left(\frac{S_o A}{4\pi v D} \right) \quad (4)$$

Note that expressions 2-4 contain the reduced scattering and absorption coefficients, but also some other unknowns; S_o , A and ε , representing the strength, the modulation and the phase of the light source, respectively. Unless the source constants are precisely known, they need to be measured. In our work, after analysis of several possibilities, we have found it more convenient to measure the values of the phase, DC and AC at several source-detector separations from the source (Fantini et al, 1994). We then used only the slope of the plots of phase, $\ln(rDC)$ and $\ln(rAC)$ as a function of the distance to obtain the values of the reduced

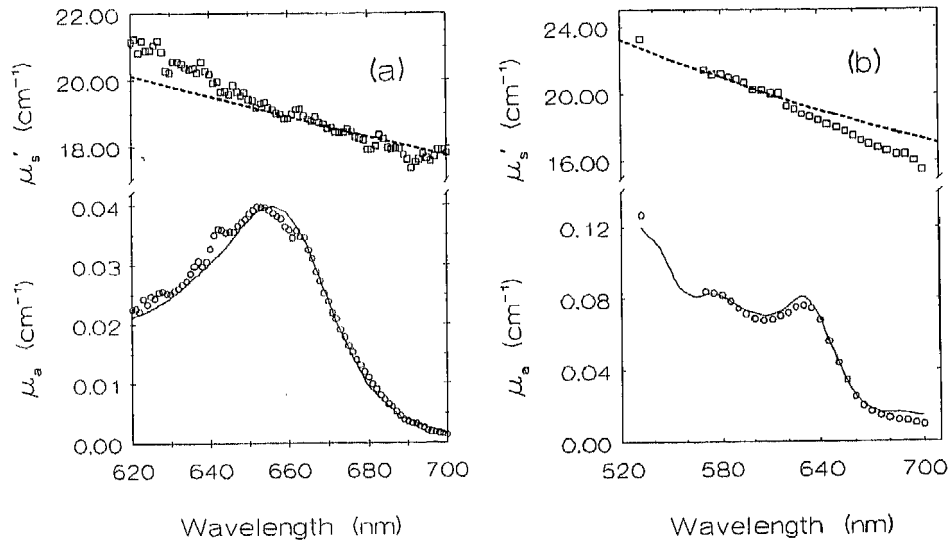


Figure 1. a) Absorption and scattering spectrum of methylene blue in Intralipid. The upper curve is the scattering spectrum. The dashed line is the predicted scattering spectrum based on the average Intralipid size particles. The lower solid curve is the spectrum of the same solution of methylene blue before the addition of Intralipid. b) Absorption and scattering spectrum of a suspension of methemoglobin in Intralipid. The solid line represents the spectrum measured with a normal spectrophotometer before the addition of the Intralipid.

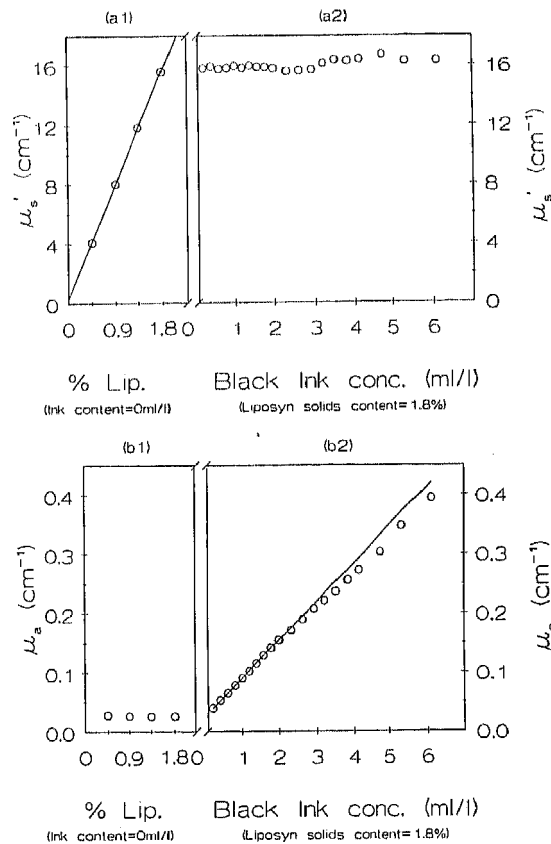


Figure 2. Independence of the measurement of the scattering coefficient from the absorption coefficient. In part 1 (left) the addition of scatterers does not affect the absorption value. In part 2 (right), the addition of absorbers does not affect the value of the scattering coefficient. The scatterer is Intralipid and the absorber is black India ink.

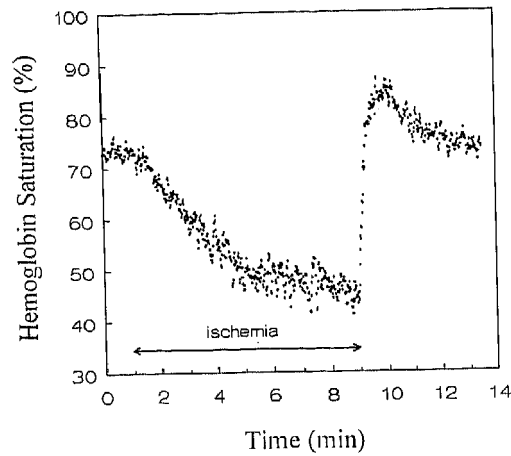


Figure 3. Continuous monitoring of muscle oxygenation. After about 1 minute, the blood flow was stopped by an external pneumatic cuff. The circulation was allowed again after about 6 minutes. Note the overshoot of the muscle oxygenation and the recovery of the normal oxygenation value.

scattering and absorption coefficients. The details of the method have been described in Fantini et al, 1995. The key point is that the method is based on a physical model rather than on empirical corrections or prior separate estimation of the scattering contribution or path length. The measurement is fast, e.g., each determination of the scattering and of the absorption coefficient can be obtained in few milliseconds with high precision and accuracy. The separation of the scattering from the absorption is complete. Cross talk between the two measurements is minimal for the entire range of scattering and absorption values of normal tissues. An example of simultaneous measurement of the scattering and of the absorption coefficients of a strongly scattering suspension is shown in Figures 1 and 2.

On the basis of this idea and using the solution of the diffusion equation taking into account the boundary between air and tissue, an instrument was built that operates simultaneously at two wavelengths, 715 nm and 850 nm. At these wavelengths, the major contributions to absorption in tissues are due to deoxyhemoglobin and oxyhemoglobin, respectively. Since absorption can be measured free of the scattering contribution, an absolute estimation of hemoglobin saturation can easily be obtained. An example of the operation of this instrument is shown in Figure 3. It reports an experiment in which the hemoglobin saturation in a muscle was changed by constricting the circulation with an externally applied pressure cuff. A more detailed description of measurements on a number of subjects is reported in De Blasi et al (1995)

3. HETEROGENEOUS MEDIA

One of the assumptions of the multiple distance method for the measurement of the reduced scattering and absorption coefficients in turbid media is that the medium is homogeneous. By contrast, tissues are heterogeneous. In practice, for measurements of tissue masses such as large muscles, the effect of the skin layer is very small using the multidistance method. The reason is that the photon trajectories spend very little time in the skin and the effect on the measured parameters, using the multiple distance method, is very small. Also, the contact of the optical elements with the skin, which is very important for intensity

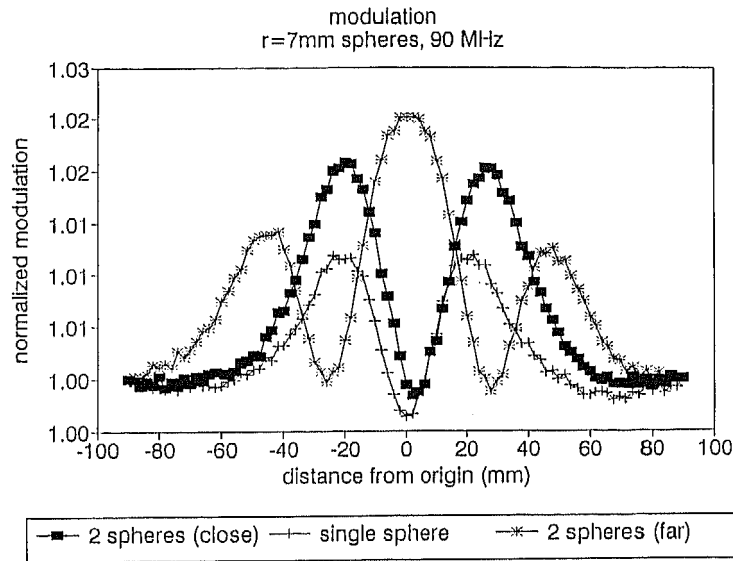


Figure 4. Photon density wave diffraction due to totally absorbing spheres. The diffraction pattern due to two spheres is very close to the sum of the diffraction patterns of each sphere when they are close and when they are far apart.

measurements, produces no appreciable effect, using the multiple distance measurement protocol.

We are interested in detecting and quantifying macroscopic regions of different optical properties in tissues. In general, the problem of reconstructing the optical properties of tissues is referred to as the inverse problem. From measurements at a large number of locations at the surface of the tissue one wishes to reconstruct the map of the optical parameters at every volume element inside the tissue. Since the diffusion of light in tissues is a non-linear process, the solution of the inverse problem presents a formidable challenge. Several groups have proposed reconstruction algorithms, some of which seem to be quite successful, but invariably all are computationally intensive and require relatively long times on large computers (Arridge et al, 1991; Arridge, 1993; Barbour et al, 1993; Graber et al, 1993; Singer et al, 1990). The problem is complicated by the non-linear nature of the light propagation process. An object at a given location can influence the light distribution at another location. However, the diffusion model shows that the effect of one object decreases at least exponentially as the distance from the object increases.

As a consequence, the influence of an object on distant objects is not very large, as shown in Figure 4, which reports the measurement of the diffraction pattern due to the presence of one and two absorbing spheres.

Note that the diffraction pattern obtained in the two-sphere experiments is approximately the sum of the diffraction patterns of each individual object. The objects used for the experiments of Figure 4 are totally absorbing spheres immersed in an Intralipid® suspension. In practice, tissue regions are not totally absorbing and the effect of one object on the other should be even smaller than that shown in the measurements of Figure 4. On the basis of these and other considerations, we used a simple linear superposition algorithm as a model for reconstruction of the tissue interior. Several ingredients are necessary for this approach to be valid and some preliminary tests have been performed as discussed below. Other labs have proposed a similar approach based on the perturbation method (O'Leary et al. 1995).

4. LINEAR SUPERPOSITION IN A LIGHT BUNDLE

We have used a perturbation approach for reconstructing the map of the scattering and absorption coefficients of tissues based on the linear superposition of light bundles. Our approach does not use iterations. The method is a simple weighted back-projection scheme intended for rapid display. The basic idea is that we can divide the object under study in voxels and that every voxel produces an independent effect at the detector point. Strictly speaking, this assumption should not be valid. The photon density waves scatter out of every object in the medium. The scattered density wave can then be scattered again from the other objects present in the medium giving rise to higher order scattered waves. In the perturbation approach, we only consider the first scattering events. We should distinguish the scattering of the photon density wave due to the macroscopic objects of the medium from the multiple scattering of the light from the microscopic particles of the medium. This latter effect gives rise to propagation of light by diffusion. Using the concept of photon density waves and light bundles, we have used a mathematical theory that is linear in the local variations of the scattering and absorption coefficient due to the macroscopic inhomogeneities. Schematically, we describe the photon density wave from a source using the following representation

$$w(r, t) \propto W_o(r, t) \frac{e^{-kr}}{r} \quad (5)$$

$$k^2 = \frac{v\mu_a - i\omega}{vD} \quad (6)$$

This expression describes the photon density wave, k is the complex wave vector and contains the scattering and absorption parameters of the uniform medium. When the wave reaches an inhomogeneity of the medium at a location r_i , either absorbing or scattering, a new wave propagates from this location. In the first order perturbation, the scattered wave W_s has the same mathematical form as the incoming wave, but a different amplitude that depends on the optical properties of the inhomogeneity. For example, for an absorbing inhomogeneity of absorption coefficient $\Delta\mu_a$ different from the surrounding medium, the scattered wave gives the following contribution at the detector located at r_d

$$w_{sd}(r, t) \propto \Delta\mu_{ai} \frac{e^{-kr_{si}}}{r_{si}} \frac{e^{-kr_{id}}}{r_{id}} \quad (7)$$

Equation 7 is mathematically identical to the equation describing the light bundle (Feng et al, 1994), where $\Delta\mu_{ai}$ represents the perturbation of the light bundle.

Although equations 5-7 are valid for an infinite medium, expressions for the light bundle for a semiinfinite medium, with both source and detector at the medium surface, are also available (Kaltenbach and Kaschke, 1993). The same reference by Kaschke's group also reports the expression for different boundary conditions such as the slab geometry. The expressions for a scattering inhomogeneity have a more complex form, because a scattering inhomogeneity contributes to the intensity at the detector with a dipole term rather than with the monopole term described by equation 7. In the linear approximation, if a number, N , of objects scatter the photon density wave, the effect at the detector is given by the sum of the contributions from each object:

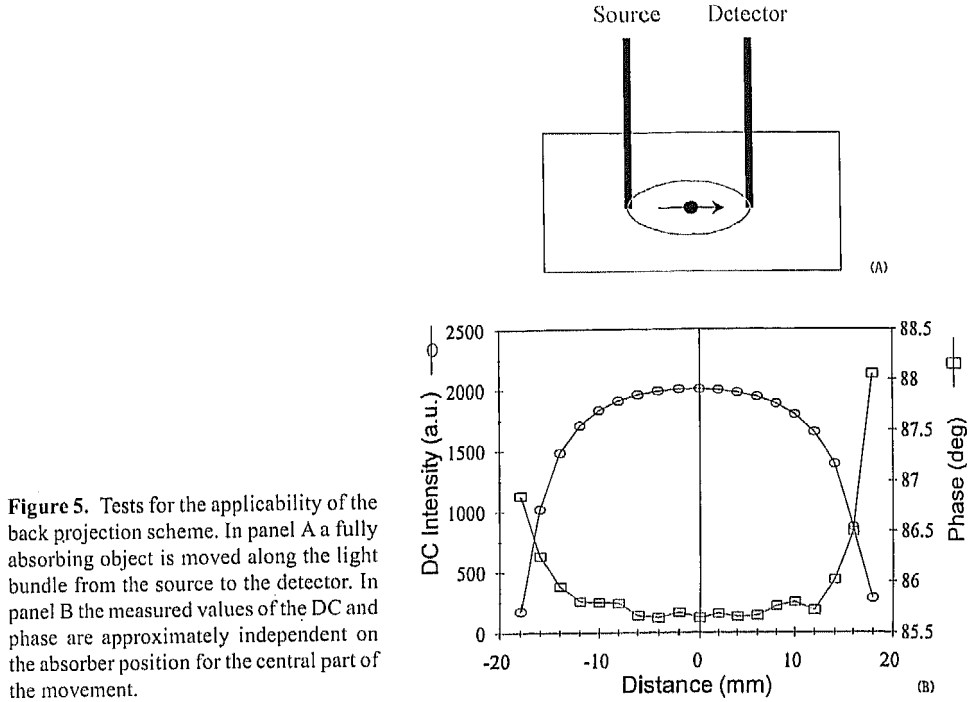


Figure 5. Tests for the applicability of the back projection scheme. In panel A a fully absorbing object is moved along the light bundle from the source to the detector. In panel B the measured values of the DC and phase are approximately independent on the absorber position for the central part of the movement.

$$w_{sd}(r, t) = \sum_{i=1, N} \Delta\mu_{ai} \frac{e^{-kr_{si}} e^{-kr_{id}}}{r_{si} r_{id}} \quad (8)$$

Equation 8 can be rewritten for every source-detector pair. If the number of those pairs is equal or larger than the number of voxels, then the inversion of the linear system of equations represented by equation 8 can, in principle, provides the value of the absorption and scattering coefficient at every voxel. An important issue is the inversion of the system of equations represented by expression 8, given the ill-posed character of this problem. There are also a number of questions related to signal-to-noise ratio concerning the effect of the scattered photon density wave at the detector. Is this wave of sufficient amplitude to be detected as a variation of the unscattered photon density wave? How accurate can be the recovered scattering and absorption parameters? Are the semiinfinite medium and the slab geometry equivalent in regard to the sensitivity of the perturbing object?

An alternative way to describe the propagation of light in tissue is to consider the set of all possible trajectories that photons can follow from the source to the detector. This concept has been recently discussed (Maier and Gratton, 1993; Feng et al, 1994) and an analytical expression for the bundle of photon trajectories in a homogeneous medium, both infinite and semi-infinite, has been presented. Along the light trajectory, the intensity decreases exponentially due to absorption and we can apply the Beer-Lambert law. We have performed some tests to better understand if this concept can be applied to real situations. The test was performed in the simplest possible situation, i.e., in a uniform, infinite, scattering and absorbing medium. An absorbing object was moved along the line from the source to the detector as shown in Figure 5a. In the infinite medium this path is, of course, the most probable photon trajectory.

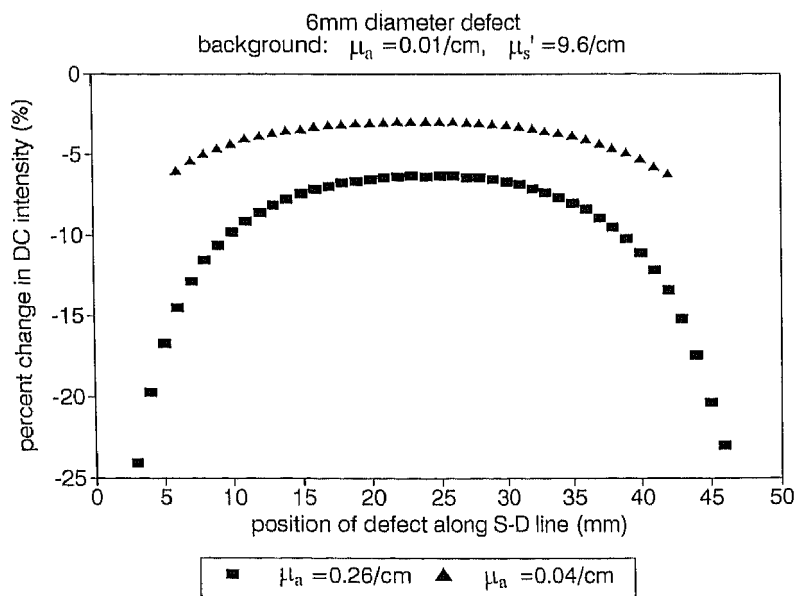


Figure 6. DC value of an absorbing object as it moves from the source to the detector for two different values of the absorption coefficient of the object. The scattering coefficient of the object is the same as that of the background.

One condition for the linear approximation to be valid is that the particular position of the object along the source-detector line should not matter, since the extinction due to absorption should be the same along the photon trajectory. Figure 5b shows the values of the phase and DC measured at different positions along the source-detector line. Clearly, at least for this particular case, the values of phase and DC are not strongly dependent upon the position of the object and consequently neither are the absorption nor the reduced scattering coefficients. Also note that this experiment was performed using a totally absorbing object of about 5 mm in size. Figure 6 shows a similar experiment, but now the object has an absorption coefficient a factor of four larger than the background and the same scattering as the background. For this experiment the deviations from linearity are even smaller than for the measurements using a fully absorbing object. For these experiments the medium is a suspension of 1.5% dry weight of Intralipid and the absorption was increased by ink additions. The background scattering and absorption were measured using the multidistance method and resulted in 6.3 cm^{-1} and 0.2 cm^{-1} for the scattering and absorption coefficients, respectively.

A second condition for the linear superposition idea to be valid is that two equal objects along the line should cause twice the effect. We have confirmed this prediction using phantom studies. Finally, we repeated the experiments with an object that is twice as absorbing as the first object, and the effect approximately doubled. We know that the superposition method should fail when the objects are very absorbing or very scattering as compared with the surrounding medium. We have shown that deviations from linearity are observed for totally absorbing objects (Figure 6), but the effect is not very large.

The important question concerns measuring values of the scattering and absorption coefficients in real tissue inhomogeneities. Our experiments only show, that under some controlled conditions, the idea of superposition can be safely applied. These results were

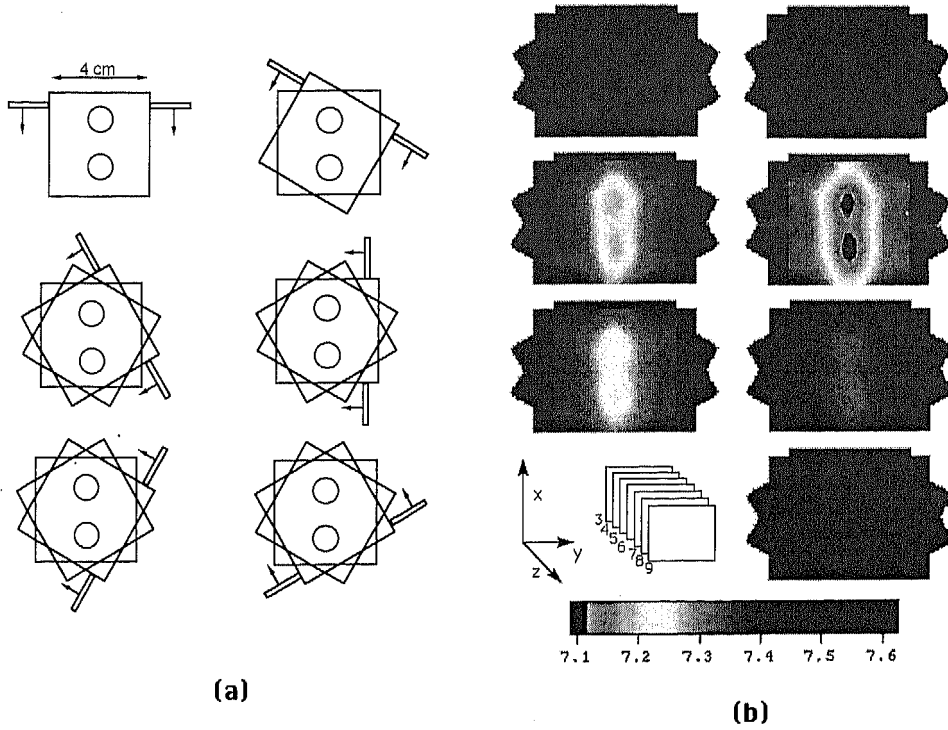


Figure 7. Back projection reconstruction of two glass spheres. a). The circles indicate the positions of the two glass spheres. The larger squares indicate the scan area. Six scans at 30 degrees interval were collected for the back projection. b) The gray scale indicates the scattering coefficient levels in cm^{-1} . The panels from #3 to #9 show the back projection reconstruction at seven different planes. c) 3D reconstruction of the two spheres using the SLICER program. This program is designed to interpolate different z-planes and to draw a particular isosurface at a selected value of the scattering coefficient. The shadow at the border of the reconstruction area is an artifact of the back projection process. This region, which is outside of the reconstruction region was left to better visualize the size of the glass particles with respect to the reconstruction region. The medium is a suspension of 1.5% solid content of Intralipid.

obtained in the infinite medium. However, we have analytical expressions and experimental measurements of the light bundle in the semi-infinite geometry. Finally, we show in Figure 7 the reconstruction of absorbing objects using the linear superposition principle and a back projection algorithm (in the infinite geometry) similar in principle to the one used in x-ray computed tomography.

To obtain this reconstruction, we have measured the value of the absorption and scattering coefficients at a number of source-detector positions using our frequency domain scanner. To calculate the value of the absorption and scattering coefficient we used the reference method described in Walker et al (1995). We weighted the measured value of the absorption and reduced scattering values in the line joining source-detector using the light bundle density along that line. This operation was repeated for different sample orientations. Finally, the back projected image was low-pass filtered to obtain the reconstructed images of Figure 7. The 3-D reconstruction region has a size of about 4x4x4 cm. The panel to the right #3 shows the map at one plane of the scattering coefficient in the reconstruction region well above the objects. The gray scale below indicates the scattering coefficient levels in cm^{-1} . The background scattering is very uniform. The sample consisted of a suspension of 1.5% Intralipid solid content. When two glass spheres of 1 cm diameter separated by 2 cm (center to center) filled with the same intralipid suspension as that of the background were inserted into the scattering medium as shown in Figure 7a, the maps of the absorption coefficient shown in Figure 7b were obtained for each particular z-plane. To obtain this figure, the source and detector optical fibers were scanned simultaneously and the data were collected at 0.4 mm intervals in the x-y plane. Then the two spheres were moved by an angle of 30 degrees and a new scan was acquired. Six scans were acquired at 30 degrees rotation intervals. To obtain a new plane for the 3-D reconstruction, the object was moved in the z direction by 4 mm steps. A total of 11 planes were acquired (only planes from 3 to 9 are shown; the other planes are very uniform). The back projection algorithm was applied for each plane to obtain the images of panel b. Finally, the back projections obtained at the different planes were processed by the SLICER software by SPYGLASS to interpolate the 3-D image shown in the Figure 7c. The important point is that the weakly scattering objects can be easily distinguished and the general shape of the object (two spheres) can be recognized.

Although we only show the scattering coefficient map, the absorption coefficient map is equally well resolved. The processing time per plane is less than a second on the 486DX66 PC computer. The acquisition time per plane (6 rotations) is about 60 seconds. Each plane image is displayed essentially in real time. The total acquisition time for the 3-D image was about 10 minutes. Although this time is still relatively long for clinical applications, we have obtained equally sharp images scanning the objects using a 1 millimeter step in the x, y plane.

ABSTRACT

Frequency-domain methods provide a simple approach to spectroscopy and tomography of tissues. Non-invasive tissue spectroscopy can be achieved with complete separation of the scattering from the absorption contribution. A non-invasive monitor of tissue oxygenation based on a dual-wavelength multidistance method is presented. The effect of tissue inhomogeneities is analyzed using a perturbative approach and a backprojection reconstruction algorithm. The backprojection algorithm directly produces maps of the scattering and absorption coefficients.

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