Characterizing liquid turbid media by frequency-domain photon-migration spectroscopy

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Abstract. We present a wavelength-tunable frequency-domain instrument for the characterization of liquid turbid media. The instrument employs a tunable titanium-sapphire laser modulated by an acousto-optic modulator. The absorption and reduced scattering coefficient of Intralipid® 20%, diluted to concentrations of 0.94 to 4.00%, are measured over the wavelength range 710 to 850 nm at 10-nm intervals. The standard measurement errors for the absorption and reduced scattering coefficients are 1 and 2.5%, respectively. Extrapolation to 0% Intralipid® concentration gives an absorption coefficient that closely follows that of water, overestimating the absorption of pure water by less than 10%. The reduced scattering coefficient is compared at 750 nm with published results and is found consistent within the experimental error. We compare the reduced scattering coefficient to an estimate based on Mie theory and find the reduced scattering coefficient underestimated the Mie theory result by about 9%. [DOI: 10.1117/1.3119282]

Keywords: frequency domain spectroscopy; photon migration spectroscopy; intralipid; absorption; scattering; reduced scattering.

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1 Introduction

Light transport in turbid media has been a focus of intense research because of its application in the biomedical, chemical, and pharmaceutical fields as well as for nondestructive quality assessment of agricultural produce.[1–4] The propagation of light in turbid media is generally described by the diffusion approximation to radiative transport theory,[5] which characterizes turbid media by the absorption (μ_a) and reduced scattering coefficient (μ_s'). A comprehensive overview of diffuse light transport was recently presented by Jacques and Pogue.[6]

In many studies, phantoms that mimic the optical properties of human or animal tissue are investigated.[7] A common liquid phantom used to simulate scattering properties of biological tissue is Intralipid®, but the optical properties reported in the literature show considerable variation.[8] Because of the discrepancies in the results, there has been an effort to assess the performance of the instruments that measure these optical properties.[9] The authors reported measurements made in a solid phantom with eight different instruments and found that the reduced scattering coefficient varied by up to 41% at some wavelengths. Measurement techniques can be grouped into continuous wave, time domain, and frequency-domain methods; however, a frequency-domain instrument was not included in that study.

The frequency domain technique employs an intensity-modulated source to separate the effect of absorption and scattering in turbid media.[10] The modulation frequencies typically extend from a few megahertz to a few hundred megahertz. The modulated light generates a density wave of diffuse photons inside the medium. The characteristics of this wave depend on the modulation frequency and optical properties of the medium. If measurements of phase and amplitude are collected for at least two modulation frequencies or two path lengths, the optical properties of the medium can be calculated. Sun et al.[11] showed that calculating optical properties from ac amplitude and phase measurement at multiple source-detector separations gives the most accurate results, but they found the precision of these measurements is poorer than the multifrequency approach. Currently all the frequency-domain instruments report optical properties of Intralipid® at a few discrete wavelengths. These wavelengths are often constrained to the availability of semiconductor diode lasers: Coquoz et al.[12] report at 674, 811, and 849 nm; Madsen et al.[13] at 670 nm; Xu and Patterson[14] at 750 nm; and Bevilacqua et al.[15] at 672, 800, 806, 852, 896, 913, and 978 nm.

In this paper, we describe a broadband tunable instrument to estimate the absorption and reduced scattering coefficients of turbid media from measurements of ac amplitude and phase at a range of optical path lengths in the medium. A tunable, continuous wave, titanium-sapphire laser was used to enable measurements across a wide range of wavelengths, 700 to 1100 nm. The laser is modulated using an acousto-optic modulator. The setup was tested by measuring the optical properties of Intralipid®-20%, at five dilutions, in the therapeutic window between 710 and 850 nm at 10-nm intervals. The instrument performance was evaluated by comparing the measured optical properties with published data and

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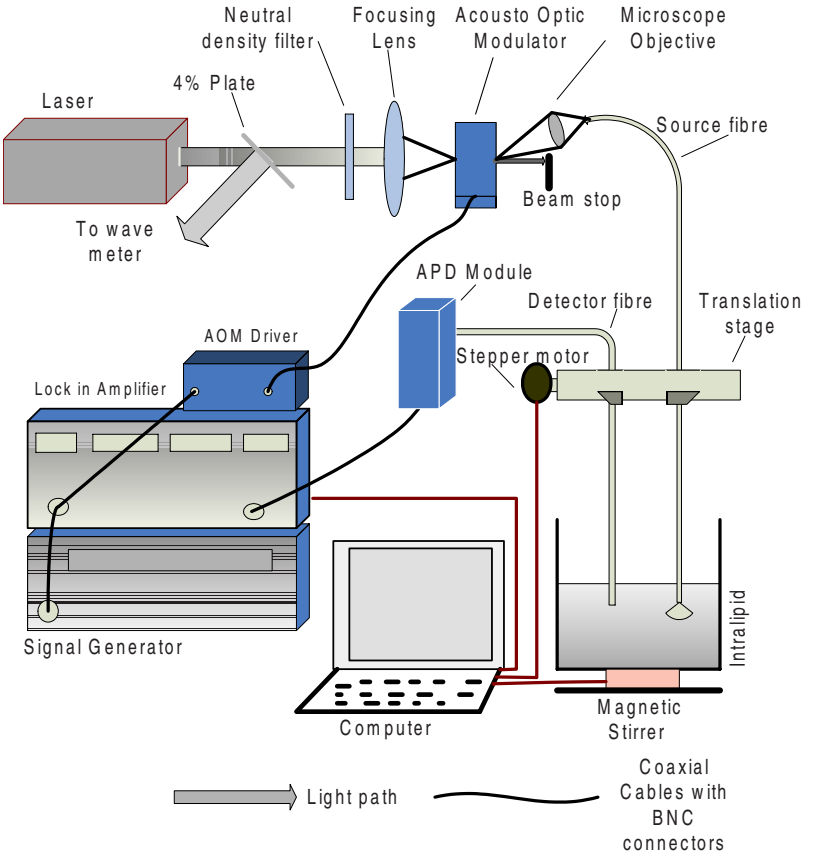

Fig. 1 Schematic diagram of the experiment setup.

Mie theory predictions based on particle size measurements.

2 Theory

Light transport in highly scattering media is generally analyzed using the diffusion approximation to the Boltzmann transport equation.[5,16] Fishkin et al.[17] suggested the propagation of modulated light inside turbid media could be used to estimate optical properties. Fishkin and Gratton[10] reported a solution to the diffusion equation for a sinusoidal intensity modulated point source and obtained an expression for the photon density at a distance r from the source. From this, the following expressions for absorption (μ_a) and reduced scattering (μ_s') coefficients were calculated.[18]

$$\mu_a = \frac{\omega}{2v}\left[\frac{M_{\mathrm{PH}}}{M_{\mathrm{ac}}} - \frac{M_{\mathrm{ac}}}{M_{\mathrm{PH}}}\right],$$

$$\mu_s' = \frac{M_{\mathrm{ac}}^2 - M_{\mathrm{PH}}^2}{3\mu_a} - \mu_a. \tag{1}$$

Here, ω is the angular frequency of the source modulation, v is the speed of light in the medium, M_{PH} is the slope of the phase plotted against the source-detector separation r, M_{ac} is the slope of $\ln(A \times r)$ plotted against r; and A is the amplitude of the photon density wave a distance r from the source.

3 Method

The experimental setup is illustrated in Fig. 1. The instrumentation is a phase-sensitive detection system that measures the amplitude and phase of modulated light propagating through a liquid medium. A tunable laser is used to obtain measurements from 710 to 850 nm in 10-nm intervals.

The light source consists of a continuous wave titanium-sapphire laser (899-LC, Coherent, USA), which is tunable from 700 to 1100 nm. The titanium-sapphire laser is pumped by a frequency-doubled, solid state laser (Verdi-V5, Coherent, USA). The operating wavelength is monitored by diverting a small fraction of the beam to a wavemeter (WA 1150, Burleigh, USA) using a glass plate. The beam amplitude is modulated at 50 MHz using an acousto-optic modulator (AOM; GPM 800-200-950, Brimrose, USA) and a fixed-frequency driver (FFA-800-B1-F1, Brimrose, USA). The modulation signal is supplied by a high-frequency signal generator (SMY-02, Rohde & Schwarz, Germany). The beam is focused into the acousto-optic crystal using a 10-cm-focal-length lens with an antireflection coating.

The modulated source is delivered to the turbid sample via an optical fiber with a numerical aperture of 0.48 (air) and core diameter of 1 mm (BFL 48-1000, Thorlabs, USA). A microscope objective couples the output of the AOM into the fiber. A second identical fiber collects light transmitted through the sample for measurement by an avalanche photodiode (APD) module (C5331-30, Hamamatsu, Japan). Both

optical fibers face down into the solution and are threaded through stainless steel tubes (diameter 6 mm) to provide rigidity. The source fiber is fixed at the center of the sample; the collection fiber is mounted on a translation stage. The distance between the source and collection fibers is computer controlled to a precision better than 10 μm. The minimum separation possible with our setup is 10 mm.

The amplitude and phase shift of the transmitted signal is measured using a lock-in amplifier (SR844, Stanford Research Systems, USA). A phase reference for the lock-in is obtained from the source modulation signal. Typical amplitude measurements are between −25 and −60 dBm, with an intrinsic noise floor of −70 dBm. The lock-in amplifier and translation stage are controlled by custom software implemented in LabView (National Instruments, USA) and MATLAB (The Math Works, USA) for automatic data collection.

To validate the instrument performance, the optical properties of the tissue phantom Intralipid®-20% (Pharmaco, New Zealand) were measured after dilution with distilled water to lipid concentrations of 0.94, 1.80, 2.59, 3.32, and $4.00 \pm 0.01\%$ (w/w). Measurements were made in a large (10-L, 26-cm-diam, 21-cm-height) stainless steel pot filled with 5.5 to 6 L of solution. To prevent settling and maintain a uniform temperature distribution, the solution was gently stirred with a magnetic stirrer (VELP Scintifica, Italy). A loose polythene sheet covered the top of the steel pot to prevent water evaporation. The temperature of the solution was monitored during measurements and found to be $22 \pm 0.5\ ^\circ\mathrm{C}$ throughout the experiment.

The distance between source and detector fibers was varied from 10 to 30 mm in 0.8-mm steps. Five replicate measurements of amplitude and phase delay were collected at each position. The optical properties were calculated from these measurements at each wavelength and concentration using Eq. (1).

To provide a separate estimate of the reduced scattering coefficient of the turbid sample, the particle size distribution of a 1% solution of our Intralipid®-20% stock solution was measured using a Mastersizer 2000 (Malvern Instruments Ltd., UK). The reduced scattering coefficient was calculated from the particle size distribution using Mie theory.[19,20]

4 Results

Figure 2 illustrates the ac amplitude and phase measured at a wavelength of 750 nm for 10 replicate measurements at five concentrations. Both the phase and the logarithm of source-detector separation multiplied by ac amplitude vary linearly with source-detector separation. The amplitude was normalized to −1 dBm at 1 cm and phase shift was normalized to 1 rad at 1 cm for clarity. This eliminates small source drifts between measurements from the plot, but does not affect the optical properties reported here, which are all based on slopes.

Across all wavelengths, we observed that the magnitude of the amplitude-separation slope increased with concentration. The same was true for phase, which also showed a consistent relationship with concentration.

The particle size distribution measured with the Mastersizer 2000 is plotted in Fig. 3. The particle distribution of Intralipid®-10% reported by van Staveren et al.[19] is included for comparison. We have presented the particle distribution as a volume fraction here, as particle size, rather than mass, more directly affects scatter cross section; the large number of small particles identified by van Staveren et al.[19] will make only a small contribution to the reduced scattering coefficient. Both results show consistency in a peak particle size between 200 and 300 nm. The peak in van Staveren et al.'s[19] data around 425 nm is caused by noise in their data, which is exaggerated for small numbers by our conversion from number density to volume fraction.

The average absorption and reduced scattering coefficients at each concentration and wavelength were calculated using Eq. (1). Errors were estimated by propagation of uncertainties from the replicate measurements.

The calculated absorption coefficient is plotted in Fig. 4. It shows a characteristic water absorption peak around 740 nm and the tail of the 970-nm water absorption peak, as might be expected from a solution that is predominantly water. In general, the absorption coefficient decreases as the concentration of Intralipid® increases. The absorption coefficient of 0.53% (solid fraction) Intralipid®-10%, reported by Pifferi et al.,[21] is included for comparison. Pifferi et al.[21] used time-correlated single-photon counting to obtain their estimate of the absorption coefficient. The absorption coefficient agrees in shape but is lower from 740 to 810 nm and higher from 820 to 850 nm than our results. This is not consistent with the relationship between concentration and absorption observed in our data; we will explore this further below.

Figure 5 shows the reduced scattering coefficient calculated from the frequency-domain measurements and Mie theory using the particle size distribution plotted in Fig. 3. Intralipid® concentrations of 0.94, 2.59, and 4% were used in the Mie theory calculation to facilitate comparison with the frequency-domain result. Again, there is a clear correlation with the reduced scattering coefficient increasing as Intralipid® concentration increases. Both frequency-domain and Mie results show a steady decrease in the reduced scattering coefficient as wavelength increases as reported elsewhere.[15,22] However, we found the Mie theory estimate of the reduced scattering coefficient overestimated our frequency-domain result by about 6%. This is significantly larger than the random error in the frequency-domain result (approximately 0.01%). It may reflect a systematic error in one, or both, of the methods.

5 Discussion

Collecting absorption measurements at many concentrations enabled us to extrapolate and estimate the absorption coefficient of the pure absorber. In the near-IR, the main absorbing species of Intralipid® is water,[19,23] which provides an independent validation of the absorption measurement. Water concentration was calculated by dividing the mass of water by the total mass of the Intralipid® sample to allow for soluble constituents. Figure 6 illustrates a typical relationship, measured at 750 nm, between absorption and concentration. A linear fit, with 95% confidence intervals is included. For comparison, water absorption reported by six other groups[24–29] and absorption of Intralipid® (0.53%) reported by Pifferi et al.[21] are included. In this case, the extrapolated absorption coefficient overestimates the most recent water absorption measurements by about 12%, though the error is not the same at all wave-

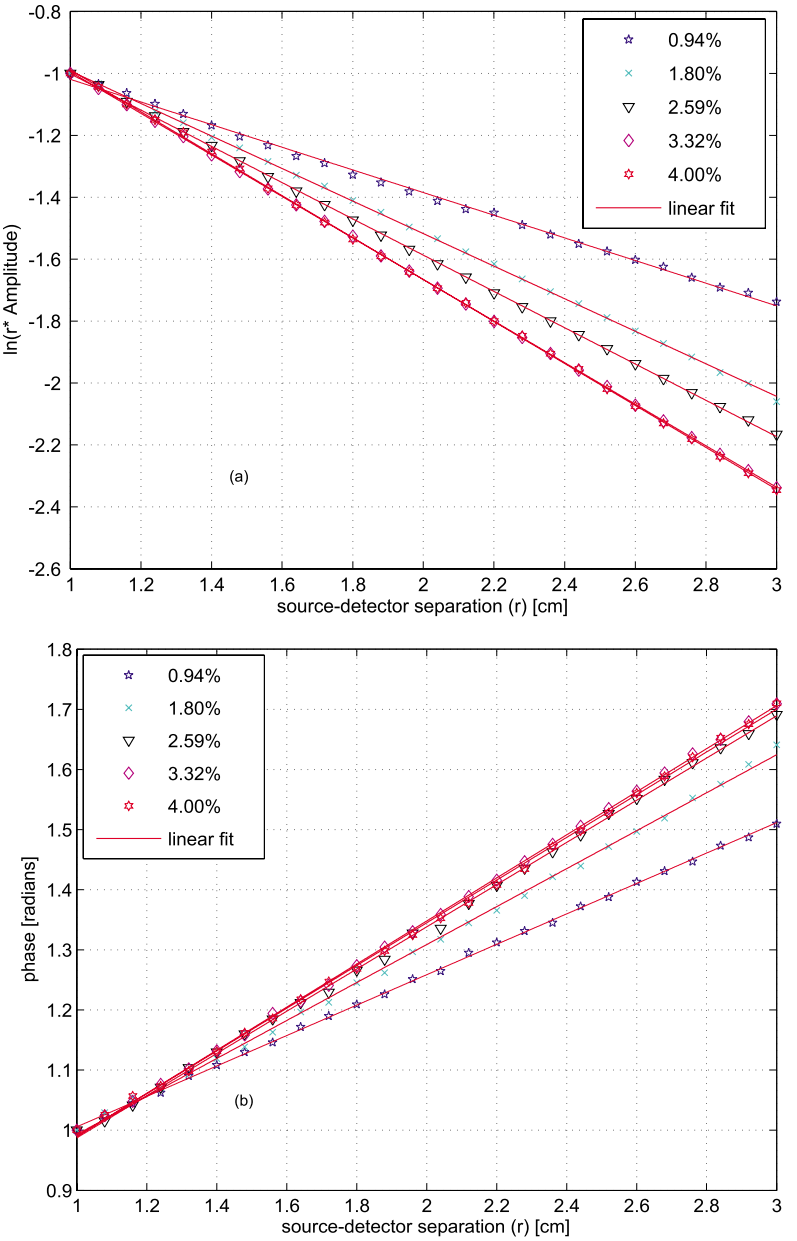

Fig. 2 (a) Logarithm of source-detector separation times normalized ac amplitude and (b) normalized phase variation versus source-detector separation at 750 nm for five Intralipid® concentrations.

lengths. At 750 nm, the measurement reported by Pifferi et al.[21] is about 11% below the extrapolated value for 0.53% Intralipid®. However, as Fig. 4 shows, this discrepancy also varies with wavelength.

The extrapolation shown in Fig. 6 can be applied across all wavelengths to estimate the spectrum of the pure absorber (Fig. 7). The water absorption data reported by Kou et al.[28] are included for comparison; these data were also measured at 22 °C, include standard errors, and show good agreement with the work of Downing and Williams[30] and Palmer and Williams[25] who used similar methods. With water as the main absorbing constituent of Intralipid®, it is not surprising to find our extrapolated absorption coefficient closely follows that of water. However, a weighted mean difference of 0.0022 ± 0.0003 cm^{-1} indicates a statistically significant discrepancy between the two data sets. This probably indicates systematic problems in the measurements or flaws in the underlying theory. We believe there are no other absorbers in Intralipid®-20% strong enough to introduce this discrepancy. In any case, we found this provides a robust, quantitative approach to validating an instrument's measurement of the absorption coefficient.

A similar analysis can be applied to the reduced scattering coefficient, though it is not sensible to extrapolate to a pure scattering medium. At high scatter concentrations, the relationship between the scattering coefficient and concentration is not linear because individual scattering particles can mask their neighbors. Figure 8 shows the reduced scattering coeffi-

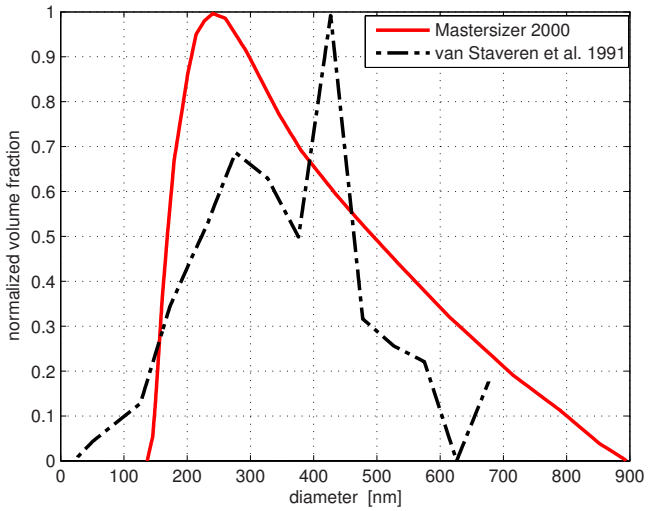

Fig. 3 Volume fraction of Intralipid®-20% particles measured with a Mastersizer 2000. This distribution is used in our Mie theory calculations. Data by van Staveren et al.,[19] converted to volume fraction, are included for comparison.

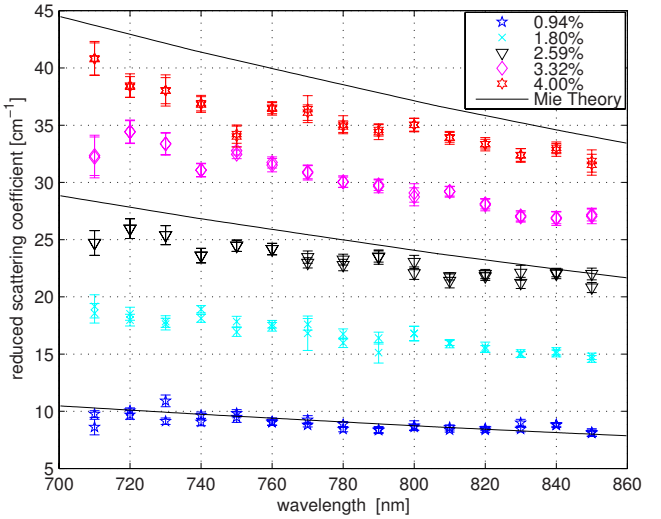

Fig. 5 Reduced scattering coefficient of Intralipid®. The solid line corresponds to a Mie theory calculation based on our particle-size measurements. The error bars indicate a 95% confidence interval.

cient at 750 nm plotted against Intralipid® concentration. Reduced scattering values calculated by Mie theory using our measured volume fractions are included for comparison. At lower concentrations the theory values agree well with the measured reduced scattering coefficients. As the concentration of Intralipid® increases, the measured reduced scattering coefficient drops below the Mie theory values. Previous reports[31,32] have shown that the linear relationship between reduced scattering coefficient and particle concentration breaks down at higher Intralipid® concentrations, though van Staveren et al.[19] reported that a linear relationship between concentration and the reduced scattering coefficient holds reasonably well up to 4% at 1100 nm.

To compare with other published data we have linearly interpolated our data and linearly scaled literature data to 2% Intralipid® concentration, well within the linear range. Figure 9 shows the result. Included are the reduced scattering coefficient for Intralipid®-20% (2% solution) reported by other frequency domain,[12,14] time resolved,[33] and continuous wave[34] methods. Xu and Patterson[14] report scattering data at 750 nm by making measurements in diluted samples of Intralipid®-20% in water from 0.3 to 2% concentration. Coquos et al.[12] report reduced scattering coefficients at 811 and 849 nm by making measurements in a solution of Intralipid® with an added absorber. The reduced scattering reported by Spinelli et al.[33] and Martelli and Zaccanti[34] for Intralipid®-20% is scaled down to a 2% concentration for comparison. Overall, our results are in good agreement with other measured data. The scattering values reported by Chen et al.[35] are 30% lower than our and other published results and are not included in the diagram.

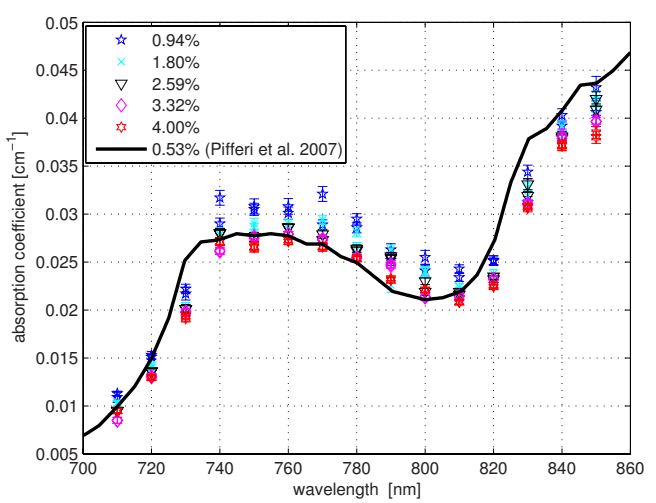

Fig. 4 Absorption coefficient of Intralipid. Data reported by Pifferi et al.[21] (solid line) are included for comparison. The error bars indicate a 95% confidence interval.

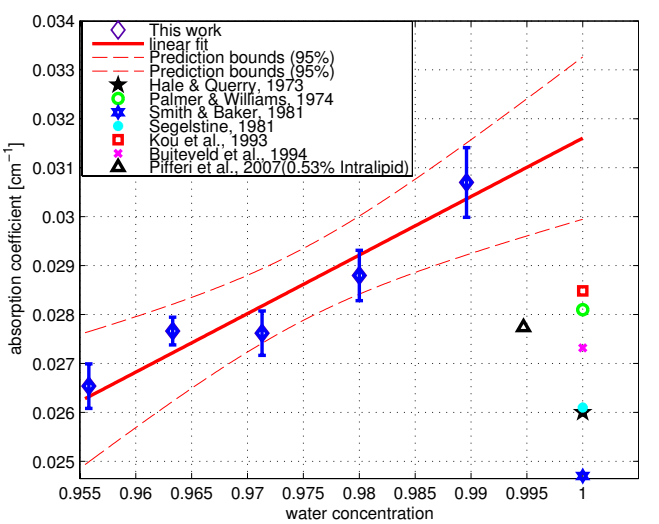

Fig. 6 Absorption coefficient of Intralipid® at 750 nm plotted against water concentration along with literature data. The dotted lines indicate 95% confidence interval for the linear fit.

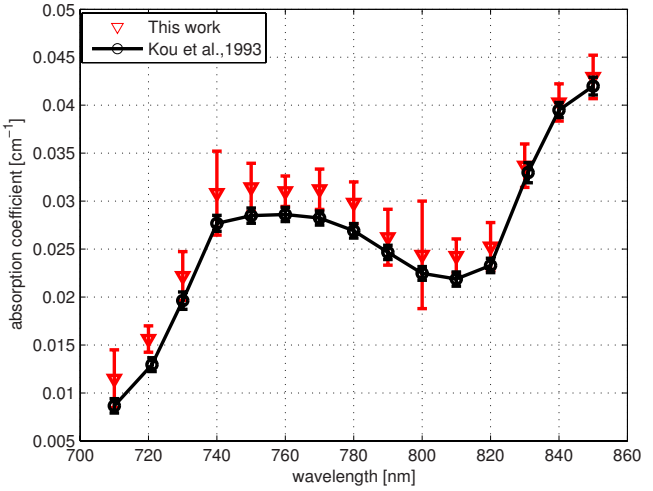

Fig. 7 Extrapolated absorption coefficient (triangular markers with error bars) for water from Intralipid® measurements versus wavelength. The solid curve represents water absorption data reported by Kou et al.[28] The error bars correspond to ±2 standard deviations.

Figure 9 also shows the reduced scattering coefficient calculated by Mie theory using our particle size measurement, as well as values derived from the van Staveren et al.[19] Mie theory fit. Calculated values reported by Michels et al.[36] for Intralipid®-20% are scaled down to a 2% concentration and closely follow our theoretical data. Our experimental results are below our Mie calculations by about 6%, with a larger deviation at lower wavelengths. The discrepancy between our experimental results and van Staveren et al.'s[19] values is about 11% across the whole wavelength range. This may be due to a change in size distribution because of a slight differences in manufacturing recipes for Intralipid®.[36] A discrepancy between experimental and Mie theory values has also been reported for measurements in a microsphere suspension.[12] The

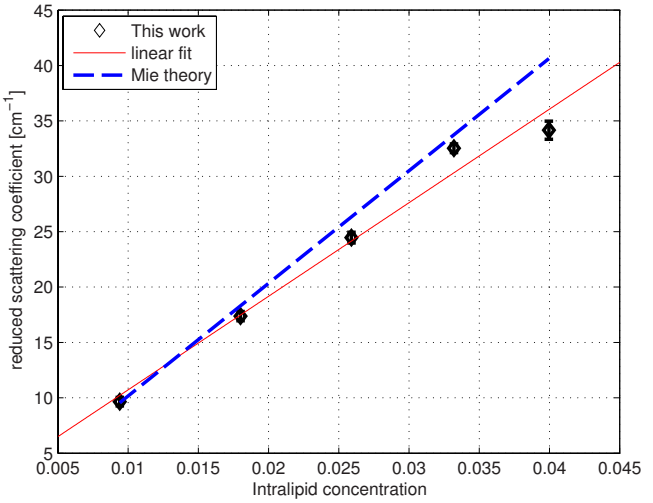

Fig. 8 Reduced scattering coefficients at 750 nm versus Intralipid® concentration. The errorbars indicate 95% confidence intervals. The solid line is a linear fit to the experimental data. The dashed line shows the Mie theory results.

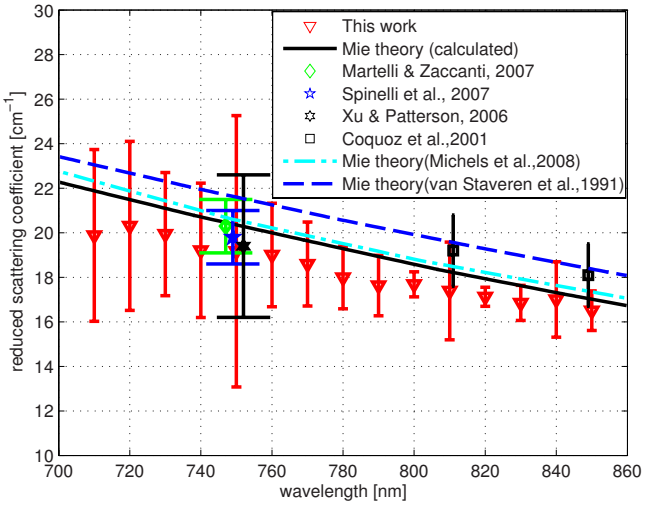

Fig. 9 Reduced scattering coefficient (triangular markers with error bars) values for a 2% solution of Intralipid® plotted against wavelength. The solid line corresponds to the Mie theory values calculated based on our particle size measurement. Data reported at 750 nm are staggered a little to make them visible. The error bars indicate 95% confidence interval.

Coquoz et al.[12] experimental results overestimated the reduced scattering by 6.5 to 28% at 811 nm and 1 to 8% at 849 nm compared to Mie theory values.

Our results are consistent with the literature and confirm that the experimental setup is capable of measuring the absorption and reduced scattering coefficient of Intralipid®. Using acousto-optic modulation of a tunable laser in a frequency-domain photon-migration instrument is a viable approach to measure the optical properties of liquid turbid media.

6 Conclusion

We presented frequency-domain measurements from a tunable titanium-sapphire laser modulated with an AOM at 50 MHz. The instrument performance was evaluated with measurements of Intralipid®-20%, at five concentrations (0.94 to 4.0%), in the therapeutic window (710 to 850 nm). We obtained measurements with standard errors of 1% for the absorption coefficient and less than 2.5% for the reduced scattering coefficient.

We found the absorption coefficient decreased as Intralipid® concentration increased, consistent with the liquid phase being the dominant absorber. We extrapolated the relationship between absorption and concentration to estimate the absorption of the liquid phase. The absorption of the liquid phase was found to follow closely that of pure water, but overestimating it by about 10%. It was not clear from our measurements whether this difference was due to additional absorbing species in the liquid phase or systematic errors in the measurements. In either case, we found comparison with water absorption a useful technique for validation of Intralipid® measurements.

We found a clear linear correlation between reduced scattering coefficient and concentration across all wavelengths. We interpolated our measurements and results reported in the

literature at 750 nm to a common concentration of 2%. Our results were consistent with prior literature at discrete wavelengths, within experimental error. The reduced scattering coefficient was also compared with an estimate calculated from particle-size distribution using Mie theory. We found the Mie theory calculation overestimated our frequency-domain measurement and previous reports in the literature by about 6%.

These results show that a tunable laser can be used with an AOM to measure the absorbing and scattering properties of turbid liquids over a moderate wavelength range. Collecting data over a broader range than has been previously explored has aided comparison with the intrinsic properties of the turbid medium's constituents. Potential systematic discrepancies between the different techniques have been highlighted.

Acknowledgments

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