A High-Bandwidth Frequency-Domain Photon Migration Instrument for Clinical Use

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ABSTRACT

We have developed a high-bandwidth frequency-domain photon migration (FDPM) instrument which is capable of noninvasively determining the optical properties of biological tissues in near-real-time. This portable, inexpensive, diode-based instrument is unique in the sense that we employ direct diode laser modulation and avalanche photodiode detection.

Diffusion models were used to extract the optical properties (absorption and transport scattering coefficients) of tissue-simulating solutions.from the 300 kHz to 1 GHz photon density wave data.

Keywords: frequency-domain photon migration, optical properties, diode laser, network analyzer, avalanche photodiode

2. INTRODUCTION

Knowledge of the optical properties of biological tissues is vital in therapeutic and diagnostic applications involving the use of lasers and other light sources. For example, in therapeutic applications, such as Photodynamic Therapy (PDT), the optical properties are required in order to determine the light distribution in pathological and normal tissues[1]. In diagnostic applications, light can be used to obtain information about structure and function. For example, differences in the optical properties between normal and pathological tissues may be exploited for imaging purposes. In addition, temporal changes may be indicative of metabollic changes. To be clinically useful, the optical properties should be determined noninvasively. This may be accomplished using frequency-domain photon migration (FDPM).

In FDPM the intensity of light incident on a material, such as biological tissue, is modulated at high frequency (10^6 - 10^9 Hz), and the diffusely reflected or transmitted signal is monitored by a phase-senstitive detector. It has been shown that the modulated wave propagates through multipe-scattering media, such as biological tissue, as diffuse photon density waves with a coherent front[2-4]. Since density wave dispersion depends on the optical properties of the material probed, the absorption (μ_a) and transport

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scattering (μ'_s) coefficients can be determined by fitting the measured frequency- and distance- dependent behavior to analytical expressions derived from diffusion theory[4].

A number of modulation-detection techniques have been developed for FDPM. The most general involves modulation of the light source (arc lamp or laser) using a Pockels cell and cross-correlation detection using conventional photomultiplier tubes[5]. However, due to its limited bandwidth (200 - 300 MHz), this technique may be insufficient for determining the optical properties of most biological tissues. For example, FDPM measurements on human uterine tissue indicate that frequencies in excess of 350 MHz are required for reliable determination of μ_a and μ'_s in a single measurement[6]. This bandwidth limitation can be overcome by use of the high harmonic content of pulsed mode-locked lasers and sensitive, fast photodetectors. Although such systems are ill suited to the clinic due to their cost and complexity, they permit recording of photon density wave dispersion with sufficient temporal resolution for optical properties to be calculated in a single measurement.

In this work we describe a relatively simple, inexpensive diode-based FDPM system operating in near real time between 300 kHz and 1 GHz which allows rapid determination of the optical properties of biological tissues from a single multifrequency measurement.

3. INSTRUMENTATION

A schematic overview of the system is shown in Figure 1. A novel feature of the system is the vector network analyzer (Hewlett-Packard Model 8753C), which measures reflection and transmission characteristics of devices and networks by applying a known swept signal and measuring the responses. The analyzer's built-in synthesized source produces a swept rf signal (300 kHz - 1 GHz) which is superimposed upon the direct current of a diode laser by means of a bias tee (Picosecond Pulse Labs Model 5575A). A small fraction of the rf is split off and used as a reference signal. The direct current is obtained from a stabilized current source (ILX Lightwave Model LDC-3742) which also provides thermoelectric cooling control for the laser diode. A directional coupler prevents reflections at the laser diode from reaching the network analyzer. An rf switch allows for the incorporation of up to four different diodes in the system. Two laser diodes are used in the present configuration: a AlGaInP (λ = 674 nm) and a GaAlAs (λ = 811 nm) both obtained from SDL, Inc. All measurements described in this work were performed using the AlGaInP diode. The laser is usually biased at 50 mA above lasing threshold (210 mA) and 14 dBm of RF power is applied. However, since no impedance matching of the laser diode to the 50 ohm source impedance was performed, the actual ac optical power is much less than 14 dBm. The diode laser output is focused through a grin lens and coupled into a 100 μm gradient-index multimode fiber. Typically, optical powers ranging from 20 - 40 mW are coupled into the sample.

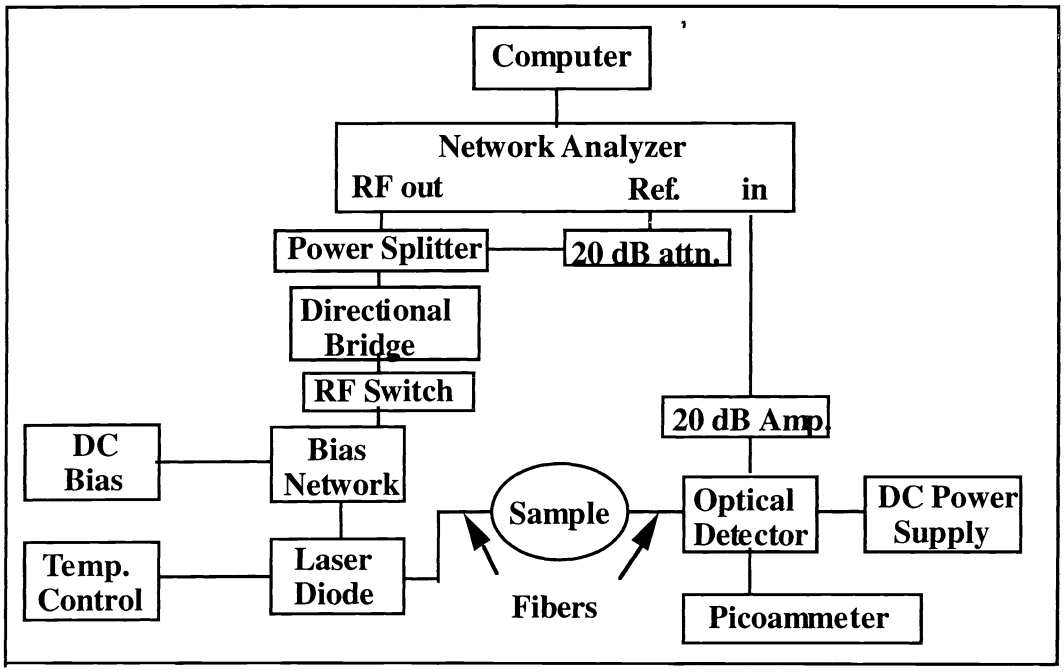

Figure 1. Schematic of the frequency-domain photon migration instument.

The optical signal is collected with a 600 μm step-index multimode fiber and transimtted to a high-gain (4 x 10^3) avalanche photodiode (APD; New Focus Inc., Model 1651) biased at 15 V. The dc output of the APD is monitored with a picoammeter (Keithley Model 485). Acquisiton times of photon-density-wave phase and amplitude over the entire 300 kHz to 1 GHz frequency spectrum are variable and depend primarily on intermediate frequency bandwidth and signal averaging parameters. Reasonable signals can be collected on the order of seconds. Shorter acquisition times can be realized by constraining the measurement bandwidth.

4. RESULTS AND DISCUSSION

The source modulation at low and high frequency is illustrated in Figure 2 for a dc bias setting of 254 mA. There is some distortion of the sinusoidal waveform at high frequency which is due to the dynamic behavior of the semiconductor laser under strong modulation[7]. The distortions become more pronounced as the dc bias approaches threshold. In practical terms, we were able to compensate for small waveform distortions by acquiring sample and reference data under identical conditions.

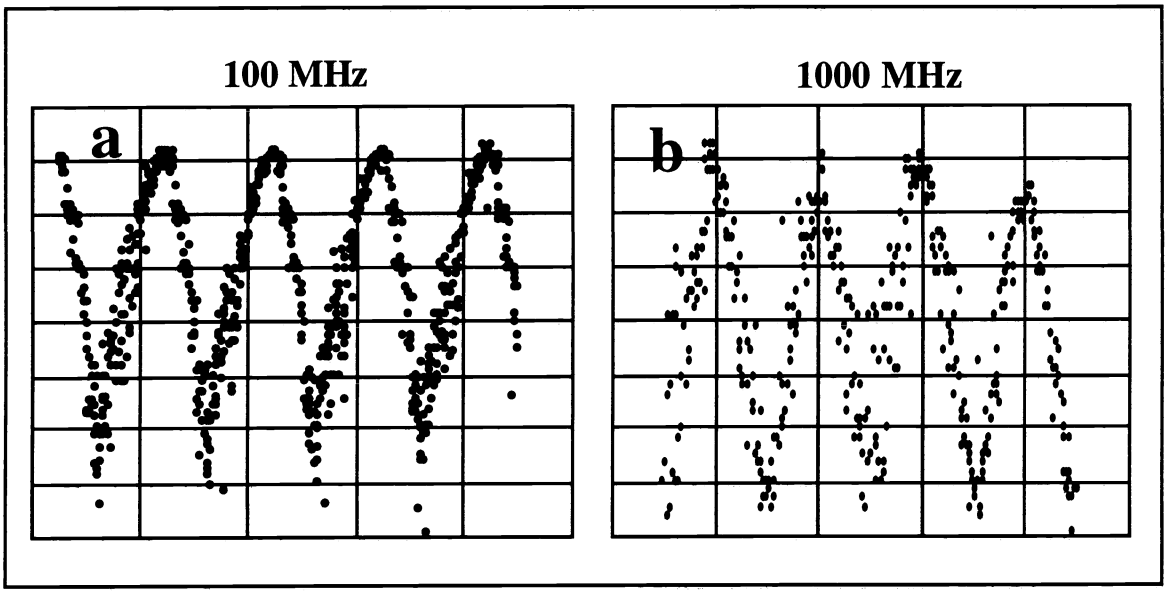

Figure 2. Source modulation at a dc bias of 254 mA and a) 100 MHz and b) 1000 MHz. The vertical scates in a) and b) are 100 and 50 mV/div. respectively. The corresponding horizontal scales are 10 and 1 ns/div. respectively.

The ability of the system to determine the optical properties of tissue-simulating solutions was tested using 2% Intralipid (Kabivitrum Inc., Clayton, NC) and 1 μg/ml of nickel tetrasulfonated phthlocyanine (NiSPC; Midcentury, Posen, Il). The concentrations of Intralipid and NiSPC were chosen to correspond to the optical properties of typical tissues. Measurements were performed in two geometries: infinite and semi-infinite (Fig. 3). In the case of the infinite geometry, the source and detector fibers were centered and placed at a depth of approximately 10 cm in a 4 L cylindrical beaker containing 3.5 L of the liquid solution. For the semi-infinite measurements, the source and detector fibers were positioned at the surface of the solution. In both cases, reference and signal measurements were made at source-detector separations of 5 and 12 mm (effective separation = 7 mm). The propagation of light in the tissue-simulating solutions was analyzed using diffusion theory. Appropriate diffusion models were fit to the infinite[4] and semi-infinite[8] data using a nonlinear least-squares fitting routine, based on a Marquardt-Levenberg algorithm.

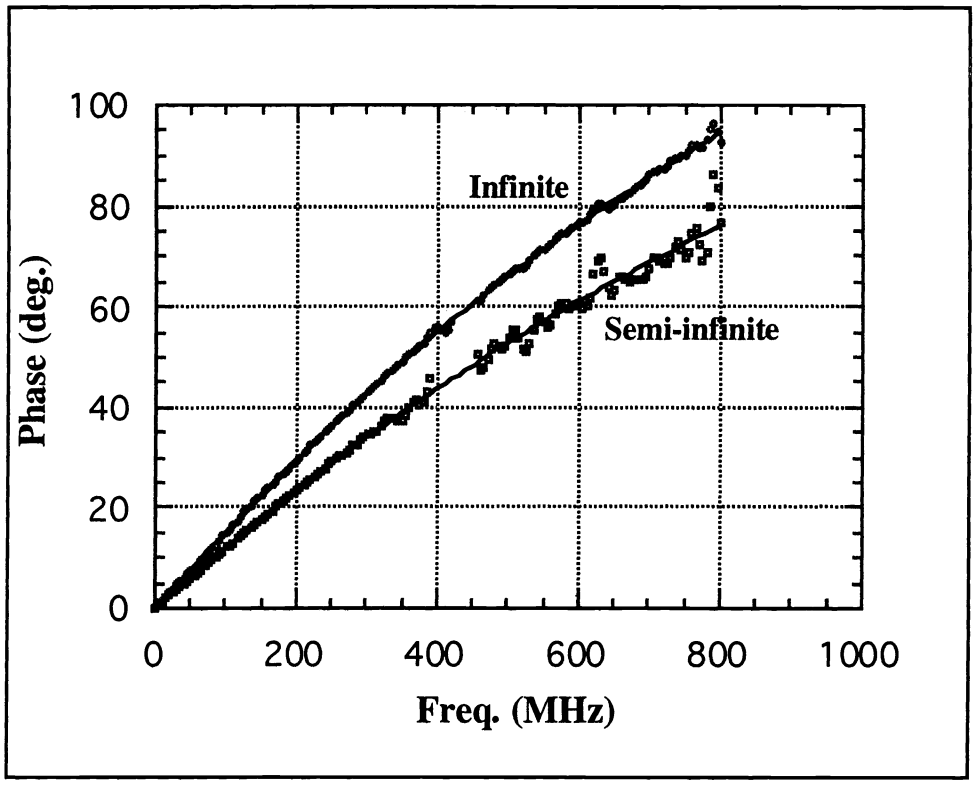

Figure 3. Phase vs. frequency response for 2% Intralipid and 1 μg/ml NiSPC tissue-simulating solutions of two geometries. In both cases, the effective source-detector separation was 7.0 mm. The curves represent best fits to the data.

Figure 3 shows the phase vs. frequency plots in the two geometries. Each data set was acquired in approximately 14 s. As expected, the phase is lower in the semi-infinite case due to tha fact that only photons propagating in the plane below the fibers contribute to the signal. The plots demonstrate that reliable phase data can be obtained in tissue-simulating solutions at frequencies up to 800 MHz. The actual and fitted optical properties are summarized in Table 1. The fitted absorption and transport scattering coefficients are in good agreement with the actual values. In the case of the transport scattering coefficient, the actual value is determined from Mie theory[9].

Table 1. Summary of fitted and actual optical properties

	Semi-infinite	**Infinite**	**Actual values**
μ_a **(mm^{-1})**	0.0087	0.0108	0.01 - 0.013
μ'_s **(mm^{-1})**	1.86	2.65	2.0 - 2.5

In general, we have been able to obtain reliable phase information up to 800 MHz at source-detector separations up to 18 mm in tissue-simulating solutions (μ_a = 0.01 mm^{-1}, μ'_s = 2.0 mm^{-1}). Rapid

attenuation of the ac signal component limits the bandwidth of the instrument at greater distances. At present, the overall system bandwidth is detector limited. The APD has a 3 dB rolloff at 1 GHz, however, the response of the detector falls by 1.5 dB at 800 MHz at the high gain settings used in these experiments.

Modifications to the present system should improve the signal-to-noise ratio and allow measurements up to the 1 GHz APD limit. These modifications include: (1) improving the optical coupling onto the small-area (200 μm dia.) detector, (2) improving the optical coupling between the laser diode and fiber, (3) improving source modulation characteristics by placing a low inductance resistor in series with the laser diode so the overall impedance is matched to the 50 ohm rf output, (4) increasing the source modulation depth (especially at high frequencies) by amplifying the network analyzer rf output, and (5) combining phase data with the ac and dc amplitude information to calculate optical properties.

5. CONCLUSIONS

We have developed a high-bandwidth FDPM instrument, which employs direct diode modulation and APD detection at multiple modulation frequencies up to 1 GHz. Access to 1 GHz multifrequency phase and amplitude information permits rapid, noninvasive characterization of the optical properties of most commonly encountered tissues in a single measurement. With the incorporation of additional wavelength diodes the system will be capable of monitoring various physiological parameters, including oxygenated and deoxygenated hemoglobin levels, drug concentration, blood volume changes, tissue hydration status, and tissue scattering properties. Since the instrument is compact, it can easily be transported to operating rooms and bedridden patient, such as neonates in intensive care. These features suggest that portable FDPM devices can be constructed to provide high-bandwidth information for a variety of applications in tissue diagnostics and imaging.

6. ACKNOWLEDGMENTS

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7. REFERENCES

1. B.C. Wilson and M. S. Patterson, Phys. Med. Biol., 31, 327-360, 1986.

2. J. Fishkin, E. Gratton, M. J. vandeVen and W. W. Mantulin, Proc. Soc. Photo-Opt. Instrum. Eng., 1431, 122, 1991.

3. M. A. O'Leary, D.A. Boas, B.C. Chance and A. G. Yodh, Phys. Rev. Lett., 69, 2658, 1992.

4. B. J. Tromberg, L. O. Svaasand, T.-T. Tsay and R. C. Haskell, Appl. Opt., 32, 607, 1993.

5. J. R. Lakowicz, *Principles of Fluorescence Spectroscopy*, Plenum, New York, 1983.

6. S. J. Madsen, P. Wyss, L. O. Svaasand, R. C. Haskell, Y. Tadir and B. J. Tromberg, Phys. Med. Biol., 39, 1191, 1994.

7. W. I. Way, J. Lightwave Technol., LT-5, 305, 1987.

8. R. C. Haskell, L. O. Svaasand, T.-T. Tsay, T.-C. Feng, M. S. McAdams and B. J. Tromberg, J. Opt. Soc. Am. A, 11 (10), 2727, 1994.\

9. H. J. Van Staveren, C. J. M. Moes, J. van Marle, S. A. Prahl and M. J. C. vanGemert, Appl. Opt. 30, 4507, 1991.