Optical Ranging of Muscle and Brain.

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ABSTRACT

Radar and optical ranging under conditions of poor propagation through scattering media have similarities in detection and imaging of brain biochemistry. In the intensely scattering properties of the brain, chemical identification of altered states of hemoglobin oxygenation are described and approaches to localization of brain bleeding are outlined. Both time domain and frequency domain employ similar technology. In brain study, a pulse time resolution of 400 ps and in phase modulation frequencies in the vicinity of 200 MHz can be employed. In both systems, global or localized data acquisition detects or images brain hypoxia or localized bleeding.

INTRODUCTION

The propagation of electromagnetic waves through scattering media is one of the problems that besets most long distance communication and radar systems. Similarly, optical spectroscopy of the body organs is beset by intense scattering as studied by Raleigh (1) and there has been an unsolved problem as to how to obtain quantitative optical data from such systems. Nevertheless, several conventional optical systems have been constructed for measuring the absorption of hemoglobin, and also fat, protein, and water in body tissues. Recent studies focus on the quantitation of photo-sensitizing dyes for tumor therapy or optical systems for detecting biliverdin in neonatal liver disease. In such cases, the length of the optical path is derived from studies of large concentration changes of hemoglobin in model systems, for example, the cat brain has been used as a model for the neonate brain (2). However, transferability, while previously accepted as valid, is now found to be questionable and in fact transferability of optical parameters (scattering (μ_s) and absorption (μ_a) from one human subject to another, is now under question.

Picosecond light pulses have been used in the study of light transmission through the skin and many thin tissues; but the first attempt to obtain data from animal and then human brain was made three years ago (3,4) and the results of studies shortly thereafter reported in a book entitled "Photon Migration in Tissues" (5). The theoretical studies of photon migration in tissues using either Monte Carlo or diffusion equation calculations were for the first time correlated with actual measurements on human subjects, and fits for reasonable values of absorption and scattering were achieved (6,7). At the same time, it was found empirically that the terminal slopes of the photon kinetics in the human head and in animal models followed exponential kinetics over many decades of intensity. Most important, the rate of exponential decay was dependent upon the concentration of the absorber. This was soon confirmed in the solution of the diffusion equation for long times where with semi-infinite models, the absorber was the principal factor governing the rate of photon decay in brain tissue.

The diffusion equation appears applicable to tissue studies under these limitations is described by Patterson, these abstracts. Both theory and experiment identified a novel method for quantifying concentrations in tissues by the simple algorithm

$$(-1/L) \log I = \varepsilon C = \mu_a \qquad (1)$$

essentially the Beer-Lambert Law where ε is the extinction coefficient and C the concentration have usual meanings and units, whilst L, the optical path, is determined from the velocity of light in tissue (~23 cm/ns) and - log I represents the exponential decay of photon

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intensity, in a semi-infinite sample, where μ_a is the absorption coefficient expressed in reciprocal length scale.

Geometric factors in photon decay measurements are important and generally photons are injected in one temple and measured at various places at various distances of input/output separation (ρ) between the two temples. In such studies values of ρ greater than 5 cm appear to give absorption independent of the input/output distance, suggesting that at longer times photons very nearly uniformly fill the experimental object, i.e., the head.

EXPERIMENTAL STUDY

The time resolved spectrometer which we have developed specially for studies of the brain is shown in the block diagram of Fig. 1. It is seen that a pulsed laser diode of 5 mW output power and pulse width of 100 ps can be used at repetition rates between 10 and 100 MHz to provide adequate illumination of the head and a duty ratio between 10^{-3} and 10^{-2} at a wavelength of 670 nm. Fiber optic coupling to the head is acceptable and the peak and average powers are acceptable for human subject studies.

The pick-up of migrating photons from the skin surface is effected by direct coupling to a 10x20 mm photocathode of the squirrel cage PMT type R928. This is an extended red PMT appropriate to laser diodes in the 750-800 nm region. The pulse output of the PMT is amplified and coupled to the usual upper and lower level discriminator (SCA), time to amplitude converter (TAC), and multichannel analyzer (MCA) display. With the geometry shown, typical count rates can be as high 10,000/sec assuring speedy data acquisition. Such a chart is shown in the middle display where the input/output distance is 5 cm and the acquisition time 30 sec, satisfactory for a number of clinical studies. The response time of the PMT directly from the laser diode is shown in Fig.1C for a fixed delay between the pulses. It is seen that the instrument function is adequately short compared to the photon migration pattern from the brain and thus, under these conditions, ultrafast PMT's such as microchannel plate tubes are not absolutely essential. As indicated in analysis by Patterson (these abstracts) it is straightforward to calculate the scattering factor from the peak time delay and the absorption factor from the slope of the photon decay especially in the brain where the hemoglobin present in the capillary bed is the principal absorber.

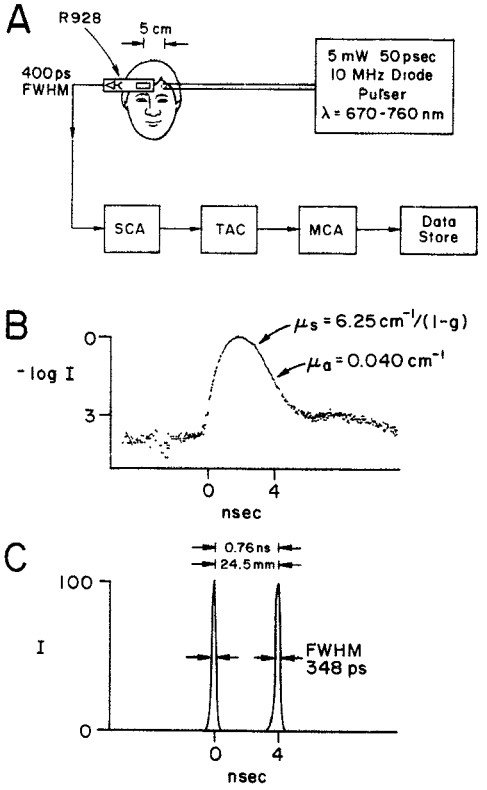

Fig.1. Experimental measurement of photon migration in the adult human head using time resolved spectroscopy. The laser wavelength is 670 nm.

Deoxygenation of hemoglobin occurring during pathological conditions, stroke, etc., will cause increases of absorption at 670 nm. Thus under these conditions, the time delay is the same but the slope is increased and direct calculation of the amount of deoxy-hemoglobin present is obtained directly from the ratio or the difference of the slopes.

Frequency Domain Studies

Just as in pulse radar, phase and frequency modulation systems were important as indeed as in radar altimeters, the Omni position finding and many systems that rely upon doppler effects. Phase modulation systems have the same advantages as they do in radar; compactness and economy for the very simple reason that the duty ratio of a phase modula-

tion system can be high compared to that of most pulse systems, and the difference may be several orders of magnitude. Thus we have concentrated upon development of a low power phase modulation system for optical studies, for which the diffusion equation can be rewritten as follows (as quoted directly from Ref. 7, and from Patterson, these abstracts).

Instead of $R(\rho,t)$, the observable quantities are the modulation, $M(\rho,f)$ and phase $\phi(\rho,f)$ of the detected signal observed at a distance ρ and frequency f. To examine how the modulation and phase are related to the optical properties of the tissue, the Fourier transform of Eq. (1) can be obtained using the integral expression of Gradshteyn and Ryzhik (8). After some algebraic manipulation we have

$$M(\rho,f)=\frac{(1+\psi_o^2+2\psi_i)^{\left(\frac{1}{2}\right)}}{(1+\psi_\infty)}\exp(\psi_\infty-\psi_i) \qquad (2)$$

$$\phi(\rho,f)=\psi_r-\tan^{-1}\left(\frac{\psi_r}{1+\psi_i}\right) \qquad (3)$$

where

$$\psi_o=\left[3(\mu_a+(1-g)\mu_s)(\rho^2+z_o^2)([\mu_a c]^2+[2\pi f]^2)^{\frac{1}{2}}c^{-1}\right]^{\frac{1}{2}} \qquad (4)$$

$$\psi_r=-\psi_o\sin\left(\frac{\theta}{2}\right) \qquad (5)$$

$$\psi_i=\psi_o\cos\left(\frac{\theta}{2}\right) \qquad (6)$$

$$\theta=\tan^{-1}\left(\frac{2\pi f}{\mu_a c}\right) \qquad (7)$$

and

$$\psi_\infty=\psi_o(f=0)=\psi_i(f=0)=[3\mu_a(\mu_a+(1-g)\mu_s)(\rho^2+z_o^2)]^{\frac{1}{2}} \qquad (8)$$

If $M(\rho,f)$ and $\phi(\rho,f)$ are measured as functions of frequency, μ_a and $(1\text{-}g)\mu_s$ may be estimated by fitting the data to Eqs. (2) and (3) in a manner analogous to the discussion of the diffusion equation.

Since phase is amplitude independent and the unit may have to be employed under surgical operating conditions where ambient light can be a factor, the phase detection system is currently in use. In such a case, measurement at two absorption wavelengths and indeed two frequencies can readily be employed to eliminate zero sets due to fixed phase delays. Under these conditions the ratio of the phase angles at the two wavelengths approximates the ratio of the values of μ_a.

Global detection. The above studies of time resolved spectroscopy, the photons are allowed to migrate globally in the brain in order to identify clinically important desaturation. It should be noted that measurement of long pathlengths, i.e., longer times of TRS and lower frequencies for PMS will eventually come to a point where any input/output combination will serve to detect a deficiency of oxygen delivery any where within the large volume filled by photons, an excellent global scan mode.

Localization. One of the key features of radar is precision of location, both in range and bearing, and when dealing with coherent radiation, specular reflections and predictable angular distributions of reflected light are obtainable. However, with scattered radiation, no pencil beam is available. Instead, the space surrounding the object is gradually filled with photons in the absence of boundary conditions (Fig. 2A,B). When an object is close to a boundary, for example as in a brain hemorrhage near the skull, then probability distributions are significantly different depending upon the point of entry and point of exit of the radiation (Fig. 2D). For example, the chance of photons surviving the passage past the absorbing object and the boundary of the system, for example, the edge of the brain and the skull, the photon has little chance of survival of that track (Fig. 2D). Thus tracks distant from the object and not near the boundary are favored so that the longest lived photons congregate in a zone opposite the absorber (Fig.1D) (See Haselgrove, this vol.).

Thus, the uniquely different aspects of imaging the brain and imaging a moving target in free space is: a) photons escape from the boundaries of the object, for example, escape from the skin and skull to the outer space, and b) absorption by a target within the brain.

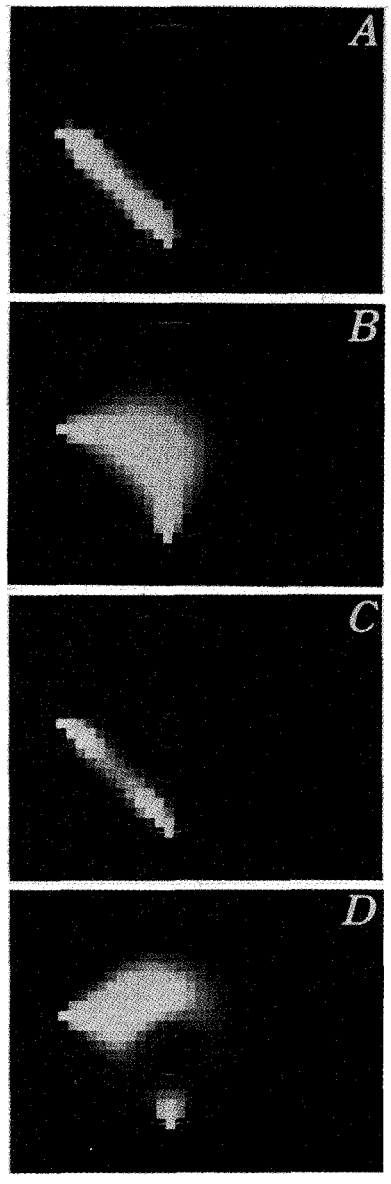

Fig. 2. Solutions to the diffusion equations for a 90° input/output positions at 6 and 9 o'clock. A and C represent early and B and D late development of migration pattern shown as bright portions of the pictures. In A and B, no absorber is present whilst in C and D and absorber is present within the model at 8 o'clock (See J. Haselgrove, these abstracts).

Coherent or Ballistic Photons. If a localized area of brain bleeding is in a straight line between input and output fibers, then coherent or ballistic photons will be used as in a C.T. image system (see Fig. 2A,C). Such photons may not be deviated from the direct pathlength and the time of flight is measured by the straight line distance between input and output. However, in highly scattering human tissues, the number of straight line or ballistic (coherent) photons is so small that extremely long averaging times are required. Instead, it is advantageous to acquire photon migration data from a number of strategic points around the periphery of the head where the brain bleeding is suspected due to clinical evaluations of functional disability (Fig. 2B,D). In this case, shortened tracks are measured for those inputs which are proximal to the localized absorber, whilst longer tracks are recorded when the input/output combination is distal to the localized absorber (Fig. 2D).

Imaging Algorithms. The algorithms used in direct time of flight measurements such as CT, PET and ultrasound are applicable to direct or ballistic optical measurements (Fig 2A,C). As mentioned above, because of the small number of such photons such studies are too time consuming for clinical studies. Imaging based upon the changing patterns of photon migration at different input/output combinations are employed to image a localized absorber (Fig. 2D). At present, the diffusion equation or Monte Carlo methods are employed to generate appropriate photon kinetics measured at various input/output combinations. These are compared to the corresponding kinetics or time delay values measured experimentally on the human subject. Alteration of the parameters of the model in order to improve the correspondence of the two sets of data are expected to give a satisfactory fit to the observed data. Under these conditions the model itself becomes the image of the brain containing the particular localized absorber.

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REFERENCES

(1) Lord Raleigh, *Phil. Mag.* 37:321 (1919) (2) Jobsis, F.F. (1977) Science 198:1264-1267. (3) Chance, B., Leigh, J.S., Miyake, H., Smith, D.S., et al (1988) Proc. Natl. Acad. Sci. USA 85:4971-4975. 4. Chance, B., Nioka, S., Kent, J., McCully, K., et al. (1988) Anal. Biochem. 174:698-707. 5. Chance, B., ed. (1989) Photon Migration in Tissues, Plenum Publ. New York. 6. Patterson, M.S., Chance, B. & Wilson, B.C. (1989) J. Appl. Optics 28:2331-2336. 7. Patterson, M.S., Moulton, J.D., Wilson, B.C. & Chance, B. (1990) SPIE 1203:62-75. 8. Gradsteyn, I.S. and Ryzhik, I.M. (1980) Table of Integrals, Series and Products, p. 340, Academic Press, New York.