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Tissue optical parameter map generated with frequency-domain spectroscopy

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ABSTRACT

Near infrared optical imaging is emerging as a potentially important imaging modality, because it offers real time data access, portability, cost-effectiveness, and the relatively safe use of non-ionizing radiation. Reconstruction of images by optical tomography is complicated by the diffusive character of light propagation in optically heterogeneous tissue. The spatial volume element probed by the light path between the light source and optical detector is rather wide and depends on a variety of experimental and instrumental factors. We have published an optical image of the hand in air based on photon density wave distribution characteristics, using both steady-state (intensity) and frequency-domain (phase and modulation)¹ experimental conditions. Since then, we have developed new instrumentation, better measurement protocols, some reconstruction algorithms and a more complete theoretical understanding of photon diffusion in both homogeneous and heterogeneous media. We have now performed frequency-domain measurements (at a modulation frequency of 160 MHz with 760 nm near infrared light) with the hand immersed in a scattering fluid (the infinite geometry arrangement). The advantages of our current approach include the spectroscopic resolution of physiologically interesting tissue regions, greater spatial resolution, the generation of absorption and reduced scattering coefficient maps of the image, rapid data acquisition, real time simultaneous display of the experimental parameters and calculated optical parameters and the possibility of obtaining some tomographic reconstruction.

Keywords: Optical imaging, frequency domain, optical parameter map, tissue image

1. INTRODUCTION

The appeal of near infrared radiation as an imaging tool was apparent many years ago in the pioneering mammography studies of Cutler.² The advantages that optical imaging offers include real-time data access, complementary information from tissue spectroscopy reflective of physiological function, non-invasiveness, portability, cost-effectiveness, and the relatively safe use of non-ionizing radiation. Reconstruction of images by optical tomography is complicated by the diffusive character of light in highly scattering and optically heterogeneous tissues. In recent years, our group and several others have used the diffusion approximation to describe photon density wave propagation in an infinite, homogeneous, and scattering medium.³⁻⁷ Frequency-domain methods, which permit variation in a) modulation frequency, b) source detector separations, and c) probing wavelength, allow for examination of different tissue volumes by the propagating radiation. In a recent manuscript,¹ we presented the theory of photon migration in scattering media and illustrated the utility of the frequency domain experimental approach in producing an optical image. These early images,

specifically of the human hand, were presented as raw, unmodified data. Acquired by frequency-domain methods, the images of the hand presented a view from steady-state (intensity of average DC level), or time-resolved perspectives (phase shift Φ and modulation ratio of AC to DC levels). These images showed the information content of the frequency-domain representations to be richer in detail and complementary to the intensity (DC) image. The drawback of those early images, was the lack of information about the optical properties of the tissue, namely, the absorption and reduced scattering coefficients. In addition, the images of the hand were collected in air and consequently they provided a skewing of the image to highlight superficial structures. After advances in our theoretical understanding of light migration in scattering media^{8,9} new methods for obtaining absolute values of the optical parameters^{10,11} improvements to our instrumentation, and introduction of facile image processing routines we have revisited the image of the hand.

Under our experimental conditions, namely, i) a strongly scattering and homogeneous medium (i.e. absorption much less than scattering), ii) physical boundaries and sources at a far distance, greatly exceeding the photon mean free path—the diffusion approximation to the Boltzman transport equation is valid.⁹ The time dependent solution to the equation was articulated by Patterson *et al.*¹² and the analytical solution for a sinusoidally modulated intensity source was derived by Fishkin and Gratton.³ This solution is represented in equation (1) for the photon density $U(r,t)$ in space (r) and time (t)

$$U(r,t) = \frac{S}{4\pi v D r} \exp\left(-r\sqrt{\frac{\mu_a}{D}}\right) + \frac{SA}{4\pi v D r} \exp\left(-r\left(\frac{v^2\mu_a^2 + \omega^2}{v^2 D^2}\right)^{1/4} \cos\left(\frac{1}{2} \tan^{-1}\left(\frac{\omega}{v\mu_a}\right)\right)\right) \times \\ \exp\left(ir\left(\frac{v^2\mu_a^2 + \omega^2}{v^2 D^2}\right)^{1/4} \sin\left(\frac{1}{2} \tan^{-1}\left(\frac{\omega}{v\mu_a}\right)\right) - i(\omega t + \varepsilon)\right) \quad (1)$$

where S is the source strength (in photons per second), A is the modulation of the source, ω is the angular modulation frequency of the source, ε is an arbitrary phase and v is the speed of a photon in the transporting medium (water in most tissues). D corresponds to the diffusion coefficient

$$D = 1/3 [\mu_a + \mu_s'] \quad (2)$$

with units in distance. The linear absorption coefficient, μ_a , carries units of inverse distance and represents the inverse mean free path for photon absorption. The reduced scattering coefficient, μ_s' , (in units of inverse distance) is related to the linear scattering coefficient, the inverse mean free path for photon scattering, through g , the average of the cosine of the photon scattering angle:

$$\mu_s' = (1 - g) \mu_s \quad (3)$$

In frequency domain experiments, the three measured parameters are the phase shift (Φ), the DC level and the AC level. In an imaging experiment all these parameters can be expressed as a function of the distance, r , between source and detector. Consequently, from measurements of Φ , DC and AC signals at various distances r , one can calculate absolute values of μ_a and μ_s' .^{10,11} A similar derivation is possible with multiple modulation frequencies and a fixed distance. The light bundle probing the medium at different separation distances r interrogate different spatial volumes. Thus, the μ_a and μ_s' properties of the homogeneous medium can be independently determined, the source

term S is readily calculated. Under these conditions, optical imaging at a fixed distance and a single frequency becomes feasible.¹³

2. METHODS

2.1. Materials and Instrumentation

We conducted our scan of the human hand by immersing it in a highly scattering aqueous solution of Liposyn III (20%), which is an intravenous fat emulsion from Abbott Laboratories (Chicago, IL). To partially compensate for limits on the detector's dynamic range, we approximately matched the absorption and scattering properties of the Liposyn III to those of the hand, by diluting the emulsion with water (40mL Liposyn III to 1L water) to a total volume of 38 liters. Matching the absorption coefficient was accomplished by serial additions of black India ink. The hand was linearly scanned by a computer controlled raster scanning robotic device (Techon, New York) with software control and automation provided by ISS, Inc. (Champaign, IL). The hand scan followed a grid pattern with a nonlinear advance (data collection in one direction only) of the source and detector optical fibers (see Figure 1). The hand was immobilized by resting on a brace, consisting of a frame with a fine grid of nylon filaments. The frequency domain, laser imaging instrument shown in Figure 1 was very similar to that used in our previous study,¹ except that the laser source was changed. Briefly, the mode-locked Titanium Sapphire laser source was pumped by an argon ion laser. The optical signal (760 nm) was modulated at 160 MHz. The Titanium Sapphire laser acts as the master oscillator in this scheme. The electronics included a radio frequency amplifier (A_1), a frequency synthesizer (S_1), and photomultiplier tube detectors (PMT, reference and sample). The S_1 frequency synthesizer injects a radio frequency signal, offset from 160 MHz, into the dynode chain of the PMT. This heterodyned mixing produces a cross correlation signal, carrying the same phase and amplitude information, as the original signal. After filtering, the cross correlation signal is processed by the data acquisition computer for display. The cross correlation signal, essentially a sine wave, was processed by sampling the waveform in at least four signal defining quadrants. If necessary, signal to noise can be increased by a greater sampling density of the waveform or by averaging multiple sequential wave forms. When imaging a relatively large tissue area, the data collection protocol per pixel necessitates a rapid accumulation of data to maintain a reasonable total time frame for the measurement. To that end, we have improved our wave form processing capabilities, so that the cross correlation frequency in this experiment was 1250 Hz, allowing for sub-second data integration times per pixel (10^4 total pixels) and resulting in a total measurement time of approximately 10 minutes. Higher cross correlation frequencies are available (up to 20KHz), but in this particular experiment the time required for registration of each line scan in the robotic device precluded a fast data acquisition routine.

2.2. Measurement protocol

The measurement protocol involved scanning an 8 x 8 cm grid in a gradation of 101 steps (0.8 mm/step). To accurately determine the optical properties of the background matching fluid a series of full grid scans was performed, in which the source detector separation distance was varied between 3 to 5 cm in 0.5 cm increments. The measured optical properties of the background medium were $\mu_a = 0.17 \text{ cm}^{-1}$ and $\mu_s' = 5.6 \text{ cm}^{-1}$. The hand was then immersed in the background medium and scanned with a source

Figure 1. The laser based, optical imaging device consists of various optical, electronic and mechanical components. The laser source (Mira 900, Coherent, Palo Alto, CA) was a mode-locked Titanium Sapphire. The pump laser was a 8 watt argon ion (Innora 300, Coherent, Palo Alto, CA). The radio- frequency amplifier (Model 603L, ENI, Rochester, NY) and frequency synthesizer (Model 20222A, Marconi, Allendale, NJ) are phase locked with the laser source and the detectors. Both reference and sample photomultiplier tube (PMT) detectors were from Hamamatsu (Model R928, Hamamatsu City, Japan). The fiber optic bundles (Oriel, Stratford, CT) delivering the illuminating 760nm light and the detected signal were 3mm in diameter. The computer controlled data acquisition and processing system was produced in part by ISS, Inc. (Champaign, IL). The electronic output of the Titanium Sapphire laser, which is phase locked to the laser light at 80MHz, is divided in the digital divider circuit (DDC) and provides the 10 MHz input to the synthesizer (S_1) phase locked loop. S_1 then outputs a 80MHz (or a harmonic multiple) signal plus a cross correlation (Φ_c) carrier to the PMT's.

detector separation of 4.2 cm. During the scan, real time images are displayed on the computer monitor's screen. The images on the monitor continuously update the DC intensity, AC intensity, phase Φ , μ_a and μ_s' . Numerical values of these parameters for the line currently being acquired are also displayed. An auto scaling function in the acquisition routine extends the dynamic range of data acquisition. At the completion of the scan the data files are transportable for future processing and archiving. Most of the image processing, such as smoothing, filtering, and scaling, was performed with a commercial software package (Spyglass, Champaign, IL).

3. RESULTS AND DISCUSSION

Figures 2A through 2E show spatial maps for the raw data and the calculated absorption and scattering coefficients of a human hand. The digitized pixels (101 by 101) in the figures correspond to a 8 x 8 cm grid. The thumb is in the region of row 75 and

Figure 2. Optical images of the hand (80×80mm). The arrow in panel a identifies the knuckle that joins the proximal phalange to the fourth metacarpal bone. Panels a-c represent experimental data that have been processed by a nearest neighbor smoothing function. Panel a: the DC intensity image in a grey scale of PMT counts. Panel b: the AC intensity image in a grey scale of PMT counts. Panel c: the phase shift image in a grey scale of degrees. Panel d: the calculated reduced scattering coefficient image. Image processing consists of smoothing, logarithmic transformation, and filtering by a percent deviation from local average function. Panel e: the calculated absorption coefficient image. The image processing was the same as in Panel d.

column 75. The arrow in Figure 2A corresponds to the knuckle joining the proximal phalange to the fourth metacarpal bone. Panels A-C of Figure 2 are experimental data. The representative images are: Panel A, DC intensity; Panel B, AC intensity; and Panel C, phase shift in degrees. The images in Panel A-C have been processed in a pixel by pixel manner with a nearest neighbor smoothing function, that acts as a spatial high frequency filter. In 2E the calculated absorption coefficient image is further transformed to a logarithmic scale. The image is then further processed by subtracting the smoothed $\log \mu_a$ from the $\log \mu_a$ value calculated from the raw data. This difference is divided by the average value of the total image to obtain a percentage change in the local average of $\log \mu_a$. For example, a region of the image corresponding to a grey scale of 4 refers to a relative 4% decrease in the absorption coefficient at that region. In Figure 2D, the same mathematical processing was performed with the μ_s' image. Several observations can be made about these images. The first observation is that these images are obtained very rapidly. This scan of the hand was accomplished in 10 minutes, rather than the several hour registration time of our previously published image¹ of the hand. This technical advance now places optical imaging in a practical time frame for further studies in a clinical setting. The current μ_a image (Figure 2E) differs from the μ_s' image (Figure 2D) in that these spatial maps show that variations in the two coefficients are not necessarily coupled. Bones, tendons, or other "hard" structures, such as knuckles, presumably provide the scattering signal in Figure 2D. Since the μ_a image in Figure 2E was collected with 760nm light, it is quite likely that the absorbing regions in the fingers and the hand primarily correspond to the vasculature, as well as blood associated with the bone. The images in Figure 2 present a relatively good image quality of hard tissue with resolution, in the range of 3-5mm. The resolution and contrast available by optical imaging maps of soft tissues now begins to rival that of ultrasound and x-ray images, in the absence of injected contrast agents. Some of the vessels in the hand are clearly resolved (Fig 2E), and regions corresponding to major vessels or clusters of vessels are also discernible. This observation is in line with the estimated resolution of several millimeters. It is interesting to speculate that differences in μ_a in various regions of the hand image, where bone is present, may correspond to varying amounts of blood perfusing different bones. This information may prove helpful in evaluating degenerative diseases of the bone. It is important to recall, that the light bundle interrogating the tissue is non-linear and tends to "average" the optical coefficients in some weighted manner. We are currently investigating weighted backprojection techniques to obtain more realistic optical images.^{8,13} In our earlier work,¹ the images of the hand generated by observation through air, did not include the scattering and absorbing background fluid, and consequently those images highlighted somewhat superficial structures. The presence of the background fluid minimizes that aspect of measurement.

Figure 3 explores a small subset of image processing options available to present the optical data in a more accessible fashion, that may highlight anatomical structures of interest. Figure 3A shows the smoothed DC intensity image discussed in Figure 2A. The next panel (3B) shows the logarithmic transformation of 3A. Contrast and resolution are not vastly improved. However, in 3C after the smoothing, logarithmic transformation and filtering (percent deviation from local average) described in the preceding paragraph, some of the major vessels of the hand become visible. One now has the option of various overlays of this enhanced experimental data with the physical map (μ_a and μ_s') images to highlight regions of interest. Clearly, many other image processing modalities are available. It may well be that the utility of optical imaging will rely more on detection of differences in the spatial coefficient maps corresponding to

physiologically based events altering the spectroscopy of soft tissues, rather than on shear resolving power akin to radiology of hard tissue structures.

Figure 3. The DC intensity image of the hand. Panel a represents the nearest neighbor smoothing of the experimental DC intensity data with the grey scale in PMT counts. Panel b shows the logarithmic transformation of panel a. Panel c shows the image transformation of panel b by a filtering function presented as a percent deviation from local average values (range -5% to 2%).

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