Medical Transillumination Imaging Using Short-pulse Diode-lasers

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Medical transillumination imaging using short-pulse diode lasers

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The recently introduced time-resolved technique for enhanced medical transillumination imaging has been demonstrated for the important case of a diode laser transmitter. This type of gated-viewing technique utilizes early received light only to reject multiply scattered, delayed light, normally blurring the image. Human breast-cancer detection is demonstrated *in vitro*, and the observations are explained by using theoretical modeling and tissue phantom experiments.

Key words: Medical diagnostics, transillumination, picosecond spectroscopy, diode lasers, mammography, multiple scattering, imaging, gated viewing, cancer detection.

Introduction

Recently there has been a strong interest in enhanced viewing through turbid media motivated particularly by medical applications.[1] Based on previous work, demonstrating first enhanced-contrast medical-transillumination imaging *in vivo*[2] by using a time-gated laser technique,[3,4] we now present the extension of the technique to diode-laser utilization. In view of these results, practical medical use, in particular mammography, seems to be quite realistic.

Visible light transillumination of tissue (diaphanography) is a modality for tumor diagnostics based on the characteristic absorption of light in malignant tumors owing to the surrounding neovascularization.[5–7] When visible light in optical transillumination is used, wavelengths with low absorption must be used, i.e., red or near-IR light. The main problem is that in this wavelength region the dominating attenuation effect is not the absorption but the scattering. The scattering coefficient is of the order of 10 cm^{-1}, while the absorption coefficient is of the order of 0.1 cm^{-1}.[8–10] The large scattering coefficient induces a pronounced multiple scattering in the tissue. The effect causes a decreased contrast when tissue transillumination is performed. The effect of light scattering can be reduced by time gating as demonstrated in our previous work.[4,2]

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The time-gating technique is based on the concept that the tissue is transilluminated with very short (picosecond) laser pulses, and the transmitted light is detected with time resolution. The light that leaves the transilluminated tissue first travels a shorter and straighter path in the tissue than the light exiting later. Thus the early part of the light contains more information about the spatial localization of different optical properties.

To achieve time-resolved detection, different approaches can be used. Optical streak cameras have good temporal resolution but need rather high light levels to obtain good signal-to-noise ratio.[11–13] Optical Kerr gates and other nonlinear optical shutters have high temporal resolution.[14] Duncan *et al.*[15] have used stimulated Raman amplification to create a time gate with high temporal resolution and high sensitivity. These techniques, however, need high power to open the shutters.

Time-correlated single-photon counting has the advantages of high sensitivity, but the temporal resolution is not that good. A closely related technique is to work in the Fourier plane of the time-gated techniques by using high-frequency intensity-modulated light and detect the phase and intensity modulation.[16]

Recently several other approaches to imaging through turbid media have been presented. Some groups have used holographic techniques in which the transmitted light is detected on a hologram or a CCD by means of a reference beam acting as an ultrafast light shutter (light in flight).[17–19] Toida *et al.*[20] have used a technique based on heterodyne detection.

We present a technique for performing imaging

through turbid media by using short-pulse diode lasers. First we present a theory making it possible to explain the behavior of photons propagating in tissue. The experimental setup is described, and then some experimental results on human tissue and a tissue phantom are given. Finally we draw some conclusions from the work presented.

Theoretical Modeling

Different models can be used to simulate the photon propagation in tissue. One way is to use Monte Carlo simulations.[21] With this approach the path of a single photon in the tissue is tracked. The tissue is characterized by the scattering coefficient μs, the absorption coefficient μ_a, and the mean cosine of the scattering angle g, which is a way of expressing the anisotropic scattering of the photons. The effective scattering coefficient μ_s' is defined as $\mu_s^*(1-g)$. By tracking a large number of photons it is possible to simulate the behavior of the light in tissue. This is an extremely time-consuming approach, since a large number of photons have to be tracked to obtain good statistics, especially when photons propagating through a slab of tissue are observed.

Another model is based on the diffusion equation:

$$(1/c)^{\partial\Phi(r,t)}/\partial t - D\nabla^2\Phi(r,t) + \mu a\Phi(r,t) = S(r,t), \quad (1)$$

where $\Phi(r, t)$ is the diffuse photon fluence rate, c is the speed of light in the tissue, D is the diffusion coefficient ($D = \{3[\mu a + (1-g)\mu s]\}^{-1}$), and $S(r, t)$ is the photon source. The equation can be solved numerically with a computer, and thus the light propagation can be calculated for different kinds of tissue. Patterson *et al.*[22] and Madsen *et al.*[23] have solved the equation analytically for transillumination of a homogeneous tissue slab. The analytical solution to the diffusion equation (1) can be verified by a least-squares fit to an experimental curve obtained with a phantom with known optical properties.[24,25] Tissue phantoms with different optical properties can be made by mixing liquids with a known scattering coefficient (Intralipid) and absorption coefficient (ink). For a sample with unknown optical properties the parameters can be estimated by a least-squares fit between the experimentally obtained curve and the convolution between the analytical expression and the system impulse response function.

The theoretical modeling makes it possible to understand experimental observations and can provide guidance for improved measurement strategies.

Experimental Setup

The experimental setup used in our present studies of photon migration in tissue is shown in Fig. 1. The light source is a Hamamatsu picosecond near-IR PLP-01 diode laser with a laser head emitting at 815 nm. The pulses from the laser are 30 ps wide according to the manufacturer's test sheet, and the pulse rate is 10 MHz, with a peak power of 300 mW. Thus the average power of the device is ~0.1 mW. The use of a diode laser instead of an argon-ion-pumped dye laser constitutes a great simplification. The laser pulses irradiate the object, and the light is detected on the opposite side. The detector assembly consists of an optical fiber and a lens that focuses the light onto a photon-counting MCP/PMT (Hamamatsu R2566-07). Delayed-coincidence techniques are used to achieve time-resolved detection. The signal from the MCP is fed through a fast amplifier and a constant fraction discriminator (CFD) to a time-to-amplitude converter (TAC). This signal is the start signal for the TAC. The stop signal comes from the laser driver unit, and this pulse is also fed through a CFD. The output signal from the TAC is fed to a multichannel analyzer, in which a histogram of arrival time for the photons is formed, i.e., a temporal dispersion curve. The curves can be transferred to a computer (PC) for evaluation. The impulse response function for the system is ~50 ps (full width at half-maximum). A small fraction of the incident light is brought to the detector through an optical fiber to create a small peak after every curve. Thus the peak is a reference in time and enables comparison and temporal matching between different detected curves.

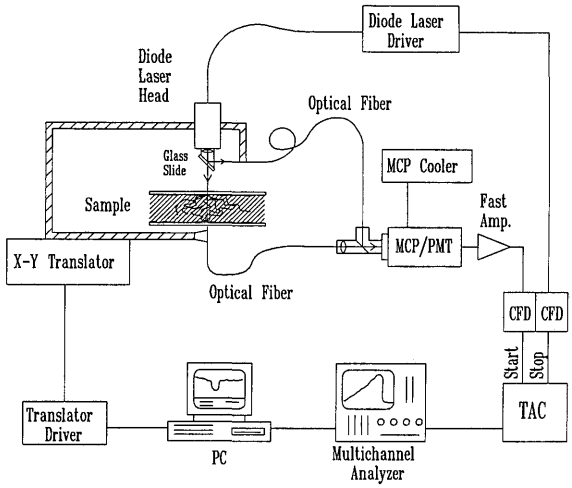

Fig. 1. Experimental setup used in the study of time-resolved migration of photons in tissue: CFD, constant fraction discriminator; TAC, time-to-amplitude converter; MCP/PMT, microchannel plate/photomultiplier tube.

The laser diode and the detector fiber can be translated across the sample, and thus scanning in two dimensions can be performed without moving the sample. The translators and the detector system are controlled from the computer.

Measurements and Results

Measurements were performed on a human-tissue sample as well as on a tissue phantom constructed to simulate the tissue behavior. Theoretical calculations based on the diffusion equation were made to interpret the observations.

Female Breast *in Vitro*

Figure 2 shows a logarithmic representation of the temporal dispersion curve obtained when a 30-mm-

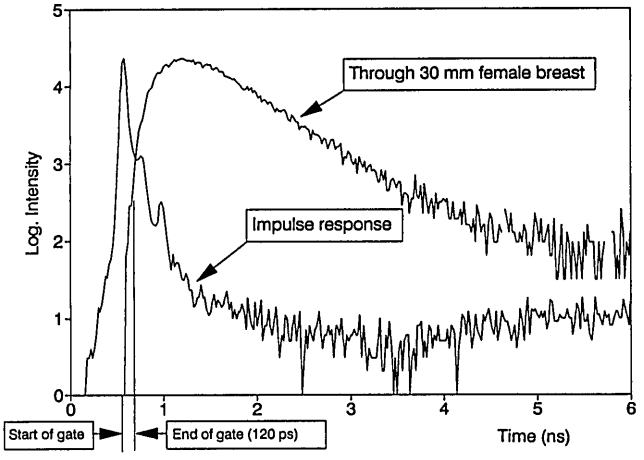

Fig. 2. Light detected through a 30-mm-thick breast-tissue sample and the impulse response of the system. A time-gate window of 120 ps is indicated on the curve detected through the sample.

thick female breast sample was transilluminated *in vitro*. The mastectomy contained an invasive ductal carcinoma. The sample was placed between two glass plates and compressed to an even thickness over the sample. The breast was a mammographically dense breast, which usually denotes connective-tissue hyperplasia,[26] and it was extremely difficult to detect the tumor by means of x rays. The impulse response for the system is also shown in the figure.

The temporal location of a time-gate window of 120 ps is indicated in the dispersion curve. The start of the time-gate window is where the detected light rises above the noise level, and it can be seen in the figure that no direct unscattered light can be detected through the tissue. The light used in the time-gated technique is thus not unscattered light. The gate window is fixed in time to the previously mentioned reference peak, and the window is kept constant when we scan over the sample. This presumes that the sample thickness is constant and that the refractive index does not change considerably over the sample. A two-dimensional scan was performed over the sample over a 60 × 20-mm area with a step length of 4 mm. The sampling time at each point was 20 s.

Figure 3 shows the image obtained from the scan. The upper image shows the total amount of light detected at every point, i.e., the integral of each detected dispersion curve. This image represents in some way the image obtained when conventional diaphanography is used. The middle image shows the light detected during the first 120 ps of every dispersion curve, and the lower image shows the early light divided by the total amount of light detected. By performing this division it is possible to eliminate artifacts such as variances in the laser output power or detection efficiency and the influence of absorbing dirt on the glass plates. As can be seen there is a considerable increase in early light in the lower right corner of the image. The tumor is located there. The increase in early light can be explained by theoretical modeling in terms of the differences in

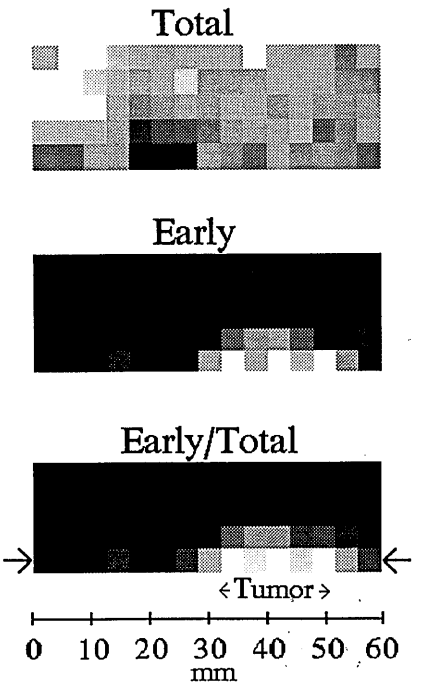

Fig. 3. Gray scale images of a scan over a 30-mm-thick female breast sample *in vitro* with an invasive ductal carcinoma. Top, total detected light intensity. Middle, light intensity detected during the first 120 ps. Bottom, light intensity detected during the first 120 ps divided by the total amount of light.

scattering coefficients.[24,27] The tumor tissue has a lower scattering coefficient compared with the normal tissue. This causes the leading edge of the temporal dispersion curve to move toward earlier times, and more photons fall in the selected temporal window. Thus the tumor signal is positive. As can be seen the tumor cannot be detected in the total light image. Figure 4 shows a scan through the lower image in Fig. 3, where the arrows show the contrast. The tumor size was of the order of 20 mm.

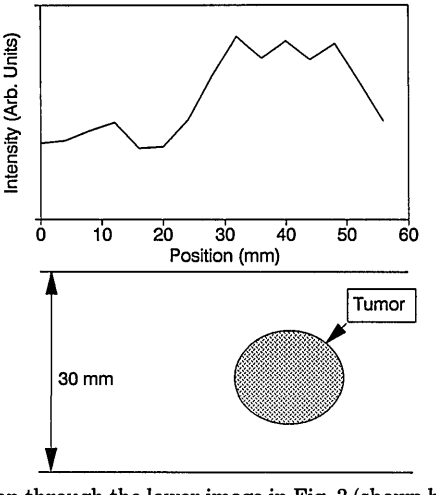

Fig. 4. Scan through the lower image in Fig. 3 (shown by arrows) showing the contrast in the image.

Tissue Model

To be able to simulate a tumor model with low scattering inside a tissue slab, an animal fat model was made. The model consisted of a 120 mm × 100 mm block of animal fat, which was 30 mm thick. In the middle of the block a 15-mm-diameter, 4-mm-thick transparent plastic disk was molded. The optical properties of the fat were estimated to $\mu_s' = 8.0\ \text{cm}^{-1}$ and $\mu_a = 0.020\ \text{cm}^{-1}$ by a fit to the solution to Eq. (1). The plastic disk is totally transparent; thus μ_s' and μ_a are both zero for the disk. A two-dimensional scan was performed over an area of 60 mm × 60 mm in steps of 2 mm. The sampling time at every point was 10 s.

Figure 5 shows the images obtained. The upper left image is the spatial distribution of the total light intensity. The upper right frame shows the time-gated image with a temporal gate of 160 ps. The lower figure is a sketch of the sample with the plastic disk indicated. As can be seen the disk can be clearly observed in the time-gated image, but it is not noticeable in the total light image. The structures shown in the right part of the images are due to thickness variations in the block of fat that was not pressed between glass plates. The time-gated technique is extremely sensitive to variations in sample thickness. Any regular thickness variations could be compensated for when the curves are evaluated, but in this case it is a quite local artifact on the surface of the fat. Figure 6 shows the contrast obtained over the disk when different time gates are used. As can be seen a smaller time gate gives a better contrast, but the noise is stronger. The size of the plastic disk and its location are indicated in the figure. The total light obtained over the disk is also indicated in the figure, and as can be seen there is no

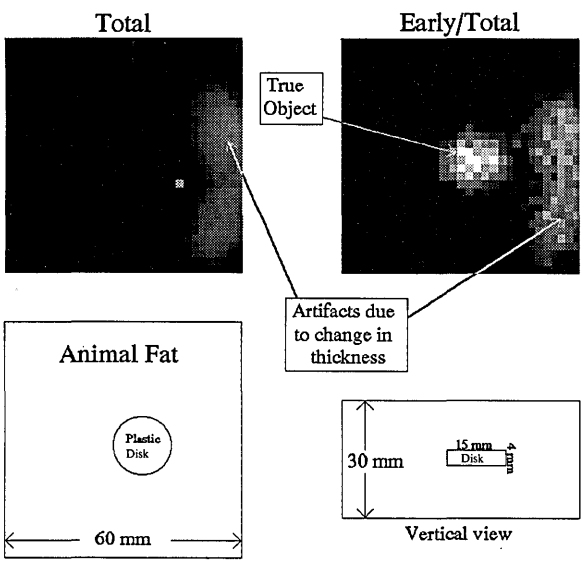

Fig. 5. Gray scale images obtained when a 30-mm-thick tissue phantom of animal fat with a transparent plastic disk in the middle are transilluminated. Top left, total detected light. Top right, light detected during the first 160 ps divided by the total light. Bottom, left and right, location and size of the plastic disk.

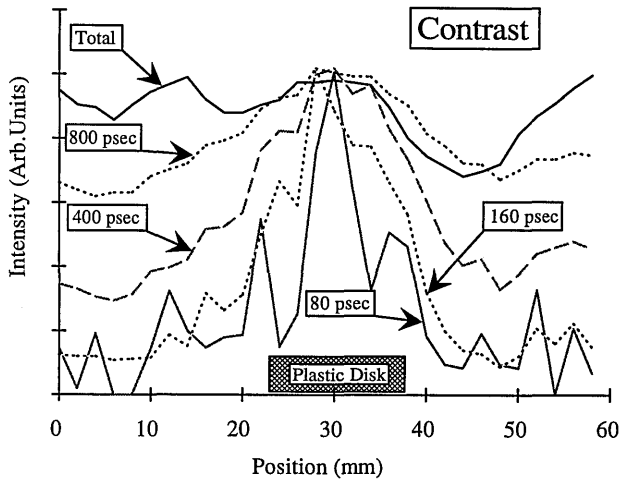

Fig. 6. Contrast obtained over the plastic disk in Fig. 5 when different time gates are used.

sign of the disk in this curve. It should be noted that there is still a small demarcation of the disk in the curve representing the 800-ps gate. It should also be noted that the curve representing a gate of 160 ps, the gate that we used in Fig. 5, has a contrast (full width at half-maximum) of approximately the same size as the plastic disk. This gate width is thus chosen empirically.

Figure 7 shows two dispersion curves obtained when the fat phantom is transilluminated; one is on the plastic disk, and one is 12 mm from the center of the plastic disk. The bottom curve in the figure shows the ratio between the accumulated integral of the two curves, i.e., the integral from left to right of the curve obtained on the plastic disk divided by the integral of the curve obtained 12 mm from the plastic disk. This curve shows how large the contrast difference is as a function of the size of the time gate. As can be seen an increased demarcation of the disk

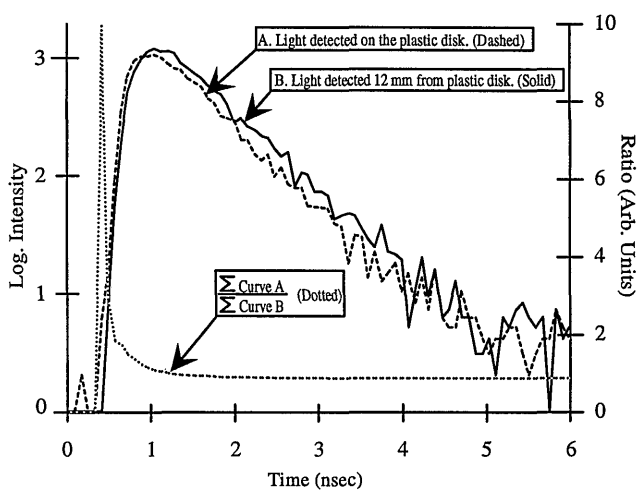

Fig. 7. Temporal dispersion curves obtained (A) on the plastic disk and (B) 12 mm from the center of the disk. The dotted curve shows the ratio between the integral of curve A and the integral of curve B from left to right.

occurs for shorter gate widths, starting at almost 1 ns.

Conclusions

Our new experiments show again that the time-gated technique can be used to enhance the spatial resolution when a highly scattering medium such as tissue is transilluminated. We demonstrate that it is possible to perform tissue transillumination by using pulsed diode lasers. Such lasers are small and inexpensive, and this implies that this concept is realistic for developing a diagnostic equipment based on nonionizing radiation. Still many improvements are needed and are possible to implement. The measuring time could be cut drastically with higher-power lasers and with a detector with a higher quantum efficiency. Our present MCP has a quantum efficiency of only 0.2% at the wavelength used. Single-photon counting avalanche diodes provide an attractive alternative.

Traditional diaphanography is based on the concept that the tumors have a higher sbsorption than the surrounding healthy tissue. Our experiments show that this is not always the case. Rather we show that the difference in the scattering coefficient can be the dominating optical property that discriminates between tumor and healthy tissue. The work of Peters *et al.*[8] indicates that the scattering coefficient is lower in carcinoma compared with glandular tissue, although it is not statistically significant. In glandular-rich breasts it is more difficult to detect tumors by means of x rays. In traditional diaphanography it is not possible to detect variations in the scattering coefficient. The time-gated technique thus brings about a new parameter to evaluate.[27] Improved data evaluation and procedures employing response function deconvolution and utilizing scattering as well as absorption properties should increase the image contrast further.

Because of the limit on the temporal resolution of our system the spatial resolution is limited. Figure 6 shows that we would not increase the spatial resolution by using shorter scanning steps. Lasers with shorter pulses, e.g., a mode-locked diode laser, and faster detectors would increase the temporal resolution and thus increase the spatial resolution. However, because of the lack of unscattered light for realistically thick biological samples, even in the time-gated technique, the spatial resolution is limited with respect to the shortness of the pulse.

Finally the use of optical radiation permits molecular-spectroscopy aspects to be used for the selective enhancement of tissue areas characterized by certain chromophores. These can be added naturally or artificially. In particular, tumor-seeking agents, such as hematopophyrin derivatives, and in the future more suitable agents can be employed when differential absorption properties are used. The tunability of diode lasers is of particular interest for such spectroscopic transillumination imaging when the gated-viewing concept for spatial contrast enhancement is employed.

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