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Tumor Detection Using Time-resolved Light Transillumination

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ABSTRACT

We demonstrate a time-gated technique to reduce the effect of light scattering when transilluminating turbid media such as tissue. The concept is based on transillumination with picosecond laser pulses and time-resolved detection. By detecting only the photons with the shortest travelling time, and thus the least scattered photons, the contrast can be enhanced. Measurements on a tissue phantom as well as breast tissue *in vitro* are presented. It is demonstrated that the spatial resolution can be enhanced by using the time-gated technique. We also show that differences in scattering properties may be more pronounced than differences in absorption properties when demarcating tumor from normal tissue.

1. INTRODUCTION

Visible light transillumination of tissue is a modality for tumor diagnostics based on the characteristic absorption of light in malignant tumors due to the surrounding neovascularization.[1-6] When using visible light in optical transillumination, wavelengths with low absorption have to be used, i.e. red or near-infrared 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 in the order of 100 cm^{-1}, while the absorption coefficient is in the order of 1 cm^{-1}.[7-9] The large scattering coefficient induces a pronounced multiple scattering in the tissue. The effect causes a decreased contrast when tissue transillumination is performed. We demonstrate a time-gating technique to reduce the effect of light scattering.[10-11]
The time-gating technique is based on the concept that light which leaves the transilluminated tissue first has travelled a shorter and straighter path in the tissue than light exiting later[12-14]. Thus, the "early" part of the light contains more information about the spatial localization of different optical properties.
Recently several other approaches have been presented. Spears *et al.* have used a technique called chrono-coherent imaging in which the transmitted light is detected on a hologram by means of a reference beam acting as an ultrafast light shutter (Light in flight)[15]. Toida *et al.* have used a technique based on heterodyne detection.[16]

2. THEORETICAL MODELS

Different models can be used to simulate the photon propagation in tissue. One way is to use Monte Carlo simulations. In this approach the path of a single photon in the tissue is tracked. The tissue is characterized by the scattering coefficient (μ_s), the absorption coefficient (μ_a) and the mean cosine of the scattering angle

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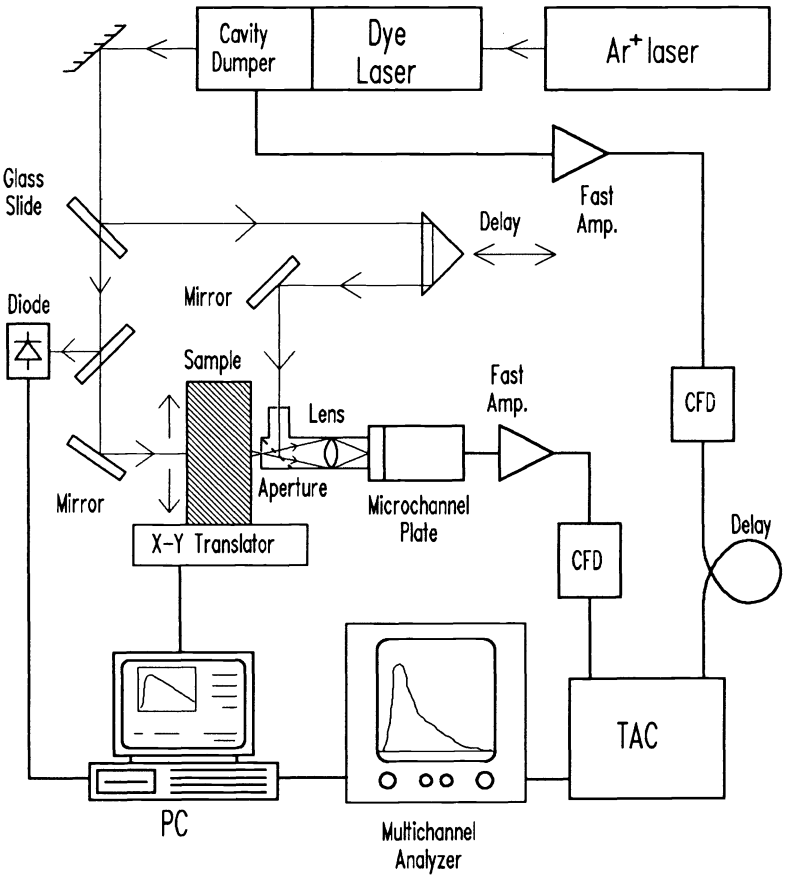


Fig. 1. *Experimental set-up used in the study of time-resolved migration of photons in tissue.*

(g), which is a way of expressing the anisotropic scattering of the photons. By tracking a large number of photons it is possible to simulate the behavior of the light in tissue.
Another model is based on the diffusion equation:

$$(1/c)\,\frac{\partial\Phi(\mathbf{r},t)}{\partial t} - D\nabla^2\Phi(\mathbf{r},t) + \mu_a\Phi(\mathbf{r},t) = S(\mathbf{r},t) \qquad (1)$$

where $\Phi(\mathbf{r},t)$ 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 $S(\mathbf{r},t)$ is the photon source. The equation can be solved numerically by using a computer and thus the light propagation can be calculated for different kinds of tissue. Patterson *et al.* have solved the equation analytically for transillumination of a homogeneous tissue slab[17]. Tissue phantoms with different optical properties can be made by mixing liquids with known scattering coefficient (Intralipid) and absorption coefficient (ink). The optical properties of the mixture can be estimated by doing a least-square fit to the analytical solution to the diffusion equation.[18]

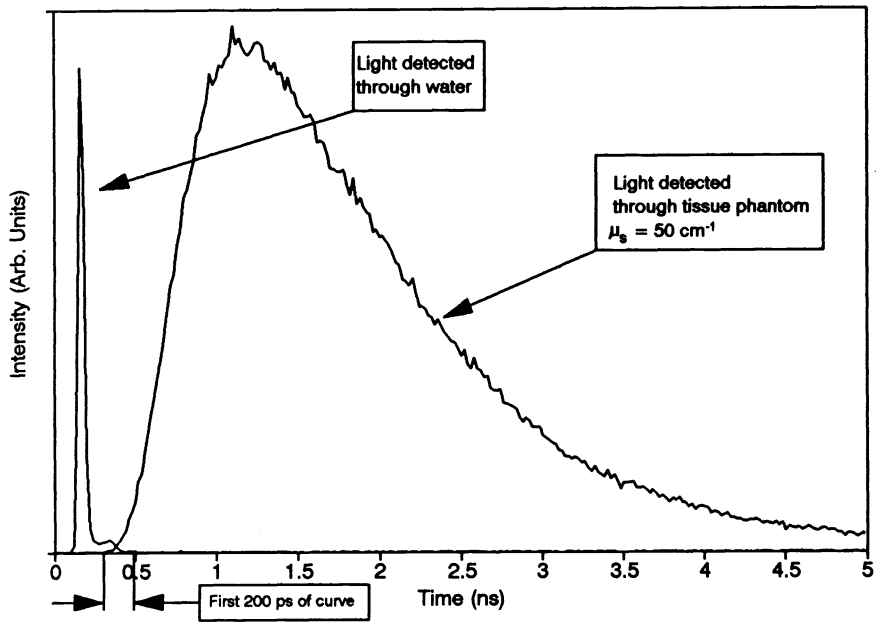


Fig. 2. *Light detected through a 35 mm thick tissue phantom and through 35 mm of water. A time gate window of 200 psec is indicated on the curve detected through the phantom.*

3. EXPERIMENTAL SET-UP

The experimental set-up used in our studies of photon migration in tissue is shown in Fig. 3. The light source was a mode-locked Coherent CR-12 Ar-ion laser pumping a Coherent CR-599 dye laser equipped with a cavity dumper. The pulses from the dye laser were measured to be 6 psec wide by using an autocorrelator. The laser pulses irradiated the object, and the light was detected on the opposite side. The detector assembly consists of a small aperture and a lens that focuses the light onto a photon-counting microchannel plate photomultiplier tube (Hamamatsu R2566-07). Delayed coincidence techniques were used to achieve time-resolved detection. The signal from the microchannel plate 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 time-to-amplitude converter. The stop signal comes from the cavity dumper driver and this pulse is also fed through a fast amplifier and a CFD. The output signal from the time-to-amplitude converter 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 approximately 50 ps (FWHM). A small fraction of the incident light is brought to the detector through an optical delay line to create a small peak after every curve. Thus, the peak is a reference in time and enables comparison between different detected curves.

The transilluminated sample can be translated across the beam-detector axis and scanning in two dimensions can be performed. The translator is controlled from the computer. A photodiode, which is monitored by the computer, is used to compensate for any variations in the laser intensity during measurements.

4. RESULTS

4.1 Tissue phantom

In Fig. 2 a temporal dispersion curve obtained when transilluminating a tissue phantom consisting of a 35 mm cuvette filled with 10 g solid Intralipid in 1200 ml water is shown. The scattering coefficient is estimated to 50 cm^{-1}. The figure also shows the light detected when the phantom is substituted with water, i.e. the impulse response for the system. The location in time of a time gate window of 200 psec 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 phantom. The large scattering coefficient also indicates that the detected early light is not unscattered light because the amount of unscattered light should be too small to detect. The gate window is fixed in time to the previously mentioned reference peak and the window is kept constant when scanning over the sample. This presumes that the sample thickness is constant and that the refractive index does not change considerably over the sample.

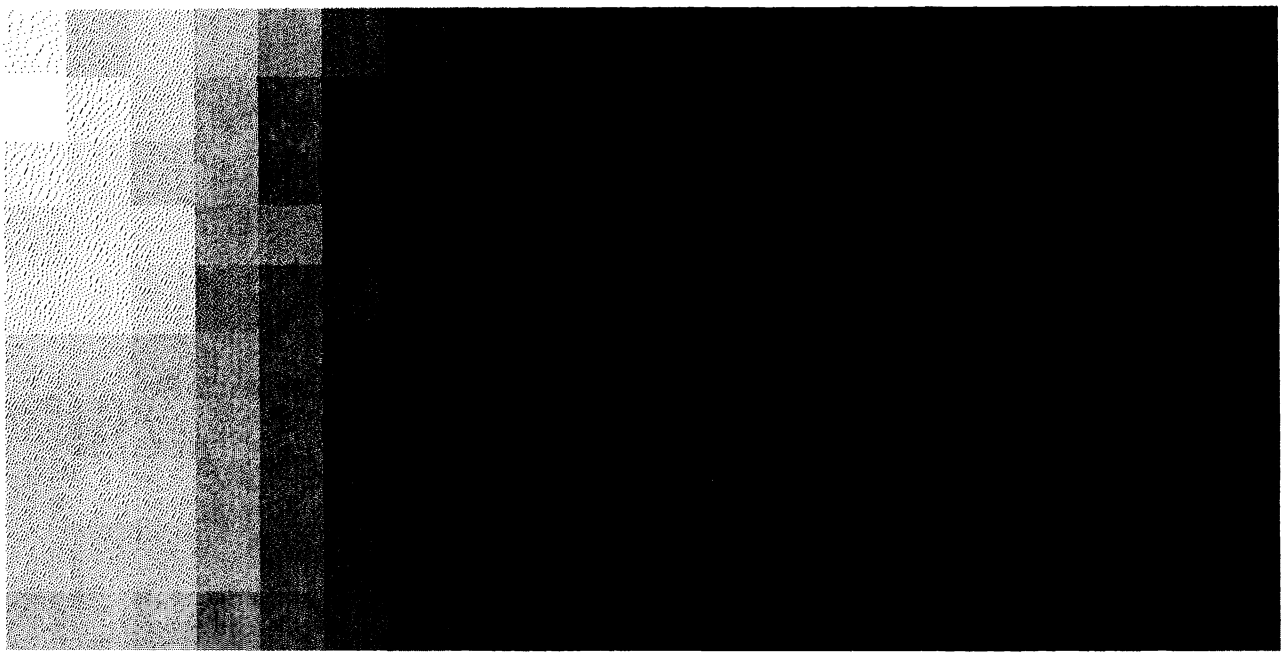
A 27 mm diameter black rubber ring with a 11 mm hole is put in the middle of the cuvette. A dispersion curve is recorded for 10 sec. every 3 mm over a 30×60 mm area. The laser wavelength was 600 nm. In Fig. 3A a 256 grey scale image of the total detected light at each point is shown. The total detected light is obtained by taking the integral of every dispersion curve. Thus, the image represents the result obtained with traditional diaphanography. In Fig. 3B the result when the time-gated technique is used is shown. The figure is a 256 grey scale image of the light recorded during the first 200 ps of every dispersion curve divided by the total amount of light at each point. The division gives a normalization of the data. Fig. 4A shows the same image but with another grey scale to enhance the contrast. In Fig. 4B a sketch of the tissue phantom with the localization of the rubber ring is shown.

As can be seen in the figures the hole in the rubber ring can be detected when the time-gated technique is used. In Fig. 3A no sign at all of the hole can be recognized. The time-gated image is slightly asymmetric and the reason for this we do not know yet.

4.1 Breast tissue

In Fig. 5 a scan through a 16 mm thick slab of a female breast *in vitro* with a malignant tumor is shown. The diameter of the tumor, an invasive ductal carcinoma, was approximately 18 mm. The laser wavelength in this case was 640 nm. A temporal dispersion curve was sampled every 2 mm for 60 sec. The triangles in Fig. 5 show the total amount of light received at every point (Time Integrated) and the squares show the light received during the first 120 psec of every dispersion curve (Time Gated). As can be seen there is a distinct demarcation of the tumor when the time gated technique is used. In this case the amount of early light increases through the tumor while the total amount of light remains almost constant. The reason for this can be found in the difference in scattering coefficient. By doing a least-square fit to the analytical solution to equation (1) the optical properties of the tissue can be estimated. It gives $\mu_s = 68$ cm^{-1} and $\mu_a = 0.22$ cm^{-1} for the tumor and $\mu_s = 98$ cm^{-1} and $\mu_a = 0.21$ cm^{-1} for the healthy tissue just next to the tumor. This is calculated with $g = 0.8$. The over-all slope of the curves in Fig. 5 is due to a varying absorption coefficient over the sample.

A



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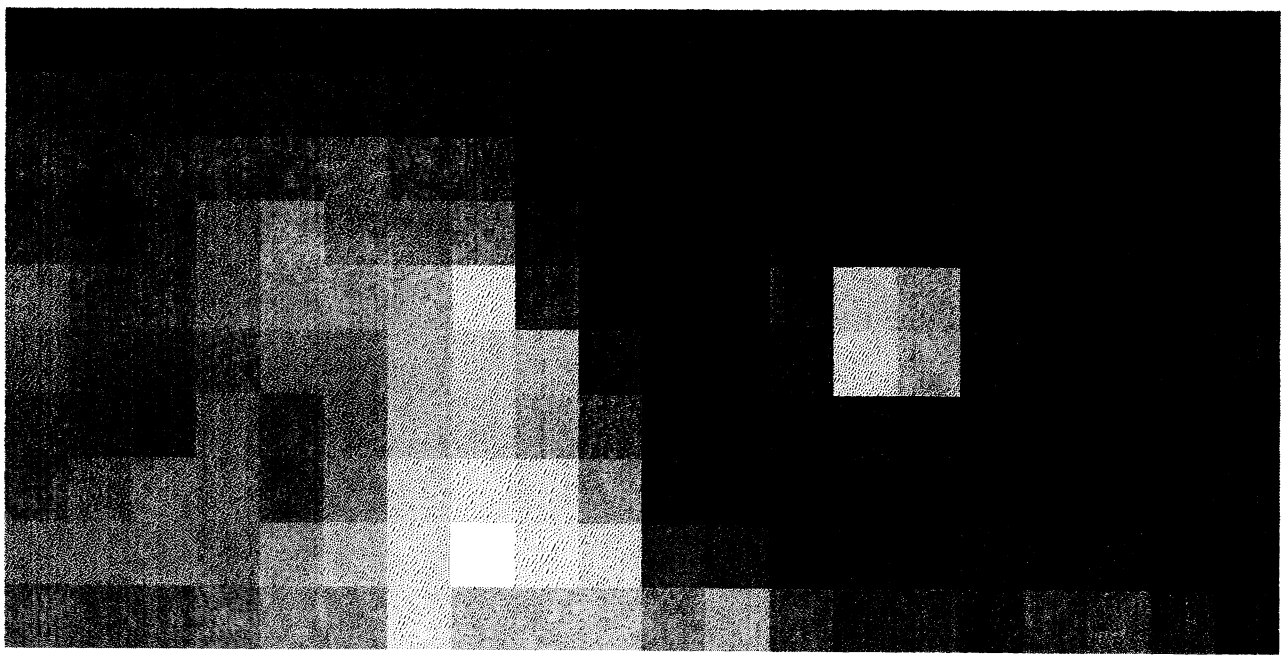
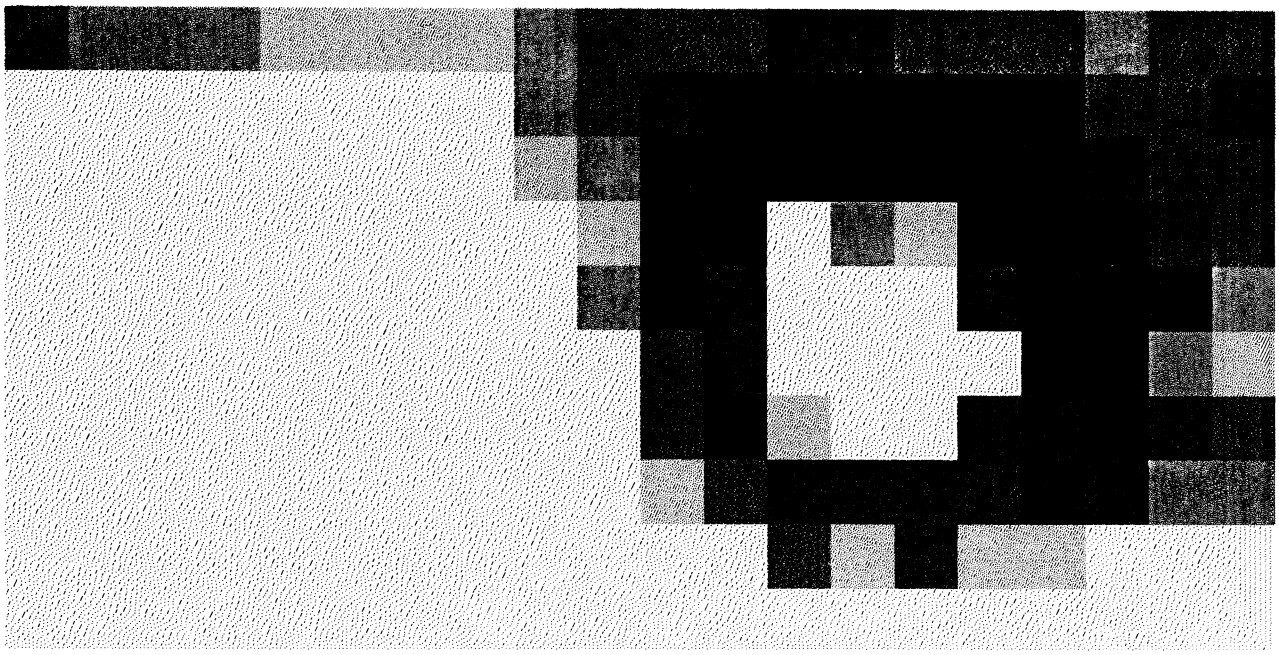


Fig. 3. *256 gray scale images of a black rubber ring in a 30×60 mm tissue phantom, 35 mm thick. A (Upper): Total detected light intensity. B (Lower): Light intensity detected during the first 200 ps divided by the total amount of light.*

A



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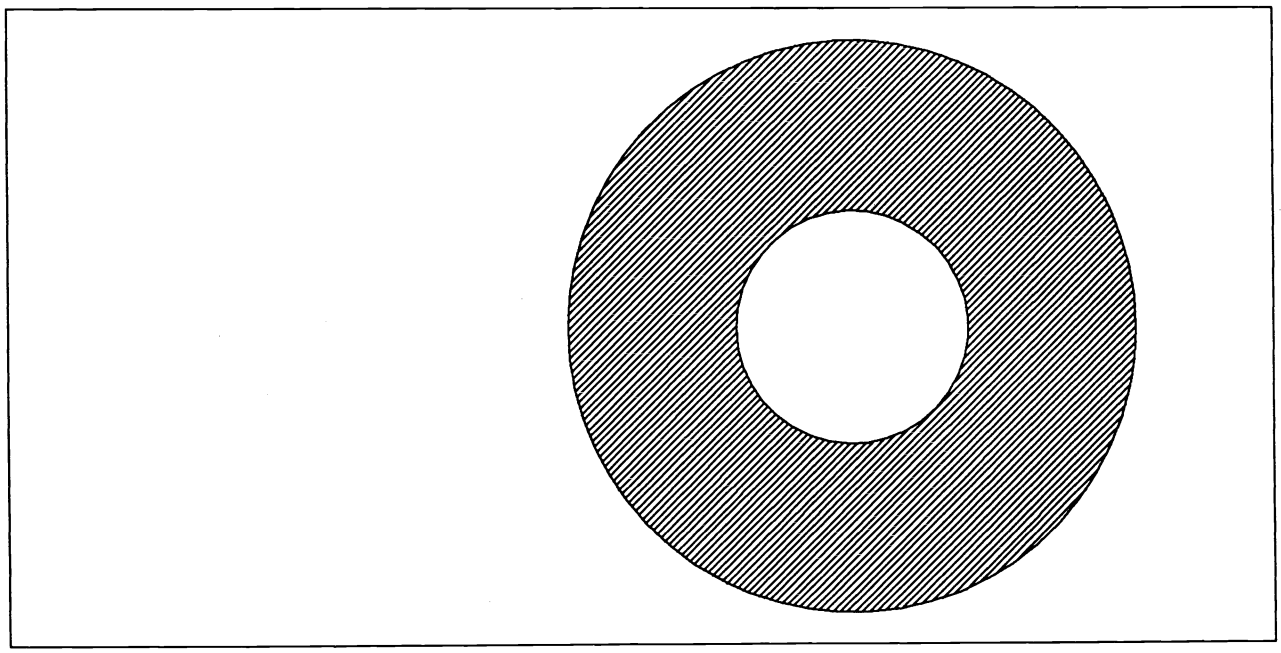

Fig. 4. *A (Upper): The same image as in Fig. 3B but in another grey scale. B (Lower): Sketch of the tissue phantom and the rubber ring.*

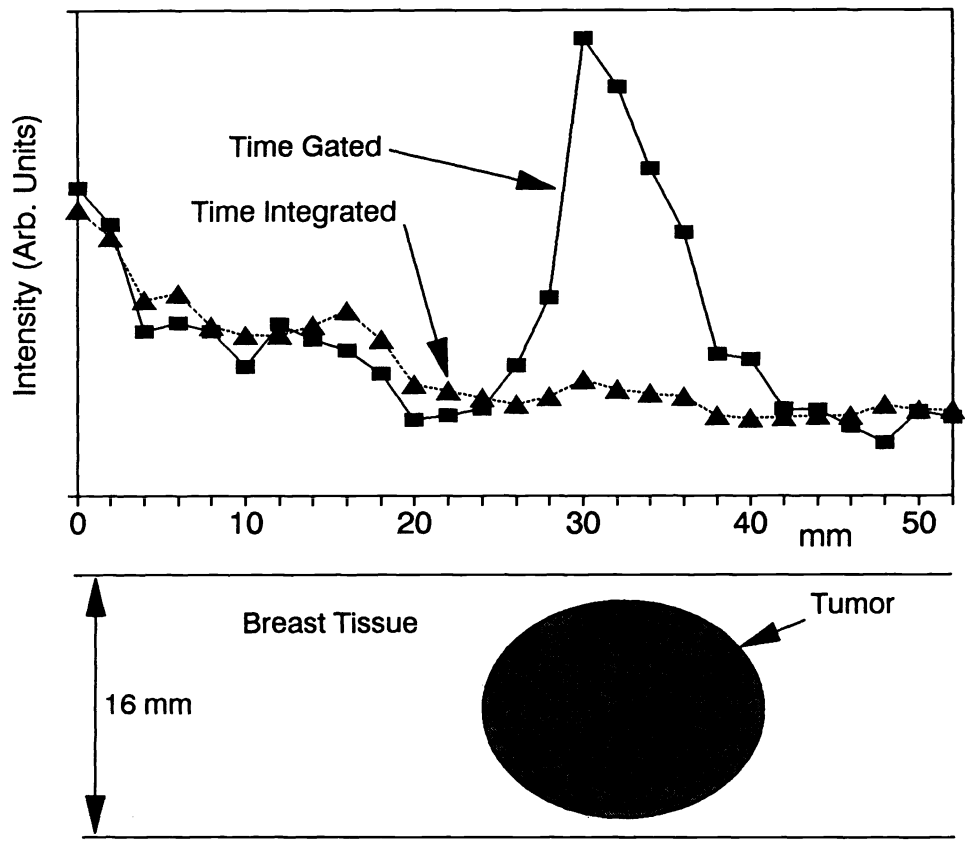

Fig. 5. *Detected light intensity when scanning* in vitro *across a 16 mm thick slab of female breast with a malignant tumor. Triangles: Total detected light intensity. Squares: Light detected during the first 120 ps.*

5. DISCUSSION

Our experiments show that the time-gated technique can be used to enhance the spatial resolution when transilluminating a highly scattering medium such as tissue. The width of the time gate is a compromise between the contrast and the signal-to-noise ratio (SNR): the smaller window the better contrast and spatial resolution but the larger SNR.
Traditional diaphanography is based on the concept that the tumors have a higher absorption than the surrounding healthy tissue. Our experiments show that this is not always the case. Our results show that the difference in scattering coefficient can be the dominating optical property that differs between tumor and healthy tissue. By using the time gated technique and detecting only the early light the demarcation of the tumor can be strongly enhanced.

6. ACKNOWLEDGEMENTS

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