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Photorefractive detection of tagged photons in ultrasound modulated optical tomography of thick biological tissues

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Abstract: We present a new and simple method to obtain ultrasound modulated optical tomography images in thick biological tissues with the use of a photorefractive crystal. The technique offers the advantage of spatially adapting the output speckle wavefront by analysing the signal diffracted by the interference pattern between this output field and a reference beam, recorded inside the photorefractive crystal. Averaging out due to random phases of the speckle grains vanishes, and we can use a fast single photodetector to measure the ultrasound modulated optical contrast. This technique offers a promising way to make direct measurements within the decorrelation time scale of living tissues.

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1. Introduction

The use of light to image areas exhibiting optical contrast embedded inside thick biological tissues is a challenge because of complex light scattering in such media, resulting in a blurring of the image. Multiple scattering is quantified by an effective diffusion length ℓ^* , after which a photon has lost the memory of its direction, phase, and polarisation. This length is of the order of 200 μm in biological tissues, making impossible to obtain direct optical images through centimeter thick samples. Furthermore, such samples exhibit very low transmission even in the so-called therapeutic window (750-950 nm) where optical absorption of biological tissues is low. A $t = 4$ cm thick sample with $\ell^* = 200 \mu\text{m}$ transmits only $10^{-8} - 10^{-9}$ of the incoming power.

In this paper we will show that using a photorefractive based detection scheme in an ultrasound modulated optical tomography imaging setup, a fast detection technique currently developed by our group and others [1], allows to image through 4 cm of biological tissue with millimeter resolution with a single detector. Until now, such performances were only attainable with parallel multi-detector schemes.

2. Ultrasound modulated optical tomography

Ultrasound modulated optical tomography aims at overcoming the difficulties linked to multiple diffusion by using the interaction of light and ultrasound. Light crossing an insonified volume is phase modulated because the ultrasound (US) modulates the optical path through both a change of the refractive index of the medium and a periodic motion of the scatterers. This corresponds to a frequency shifting of the photons involved and is often referred to as *photon tagging* [2, 3]. The concept of acousto-optical (AO) imaging relies upon an interference measurement between these *tagged* photons and coherent photons that have not crossed the insonified volume. When the US scan points out a volume presenting an optical contrast (e.g. local absorbance and/or scattering properties) like tumors, the quantity of *tagged* photons is modified. Localisation and resolution (1mm) of objects are made possible because of the good directionality of the US within biological tissues.

Important complications arise due the statistical nature of the output light (speckle). For a time-dependent perturbation on the system (e.g., an acoustic wave), the resulting information is averaged out because each grain of speckle exhibits a spatial random phase variations $\phi_S(x, y, z, t)$. More tricky is the temporal evolution of the signal obtained through living tissues because motion, e.g., brownian, circulation) decorrelates the phase of light during its propagation. This phenomenon, usually quantified as *speckle decorrelation time* τ_c , has subtle effects

on the signal to noise ratio (detection can be severely hindered for some cases, e.g., blood vessels, where τ_c is small), and measurements must be done faster than τ_c to reduce averaging effects.

A great *etendue*, and a fast and frequency selective response are required. But these characteristics are yet not satisfied on a unique setup, and various approaches have been used for the detection of the interference pattern. In a single detector scheme, a unique grain of speckle is imaged [4]. The signal is detected at high frequency (US), far from the low frequency noise of the system and much higher than the decorrelation time equivalent high-pass filter as well, that authors measure to be at least 1 kHz [5, 6]. Since the ultrasound modulation efficiency is of the order of 1%, the signal coming from a single grain can be very small. For such a reason, CCD's camera can be preferred, each grain *flux* being measured and processed independently on a single pixel of the camera. Though high-flux sensitive, the response is slow (some hundreds of Hz) compared to a single detector (MHz and more) because of the large number of pixels (some tens of 10^4). Moreover, the huge amount of data to transfer can compromise real-time analysis. Many works have been done with cameras and a phase stepping acquisition technique [7, 8]. However, low frequency noise exists because the signal is also shifted to a low frequency term. The ultrasound modulated optical tomography signal can be isolated with digital holography using a Mach-Zehnder interferometer and a rectangular aperture at the output of the sample, with a performance close to *shot-noise* [9].

3. Photorefractive holography

The idea to fully optimise the output *flux* on a large aperture, fast single detector, implies to deal with speckle averaging of the interferogram on its surface, that is to make spatially coherent the signal and the local oscillator in the detector plane. This situation has been previously solved for the measurement of surface vibrations on rough objects (backscattered light), by a so-called *self-adaptive* wavefront holography, using a photorefractive (PR) crystal, in a two-beams coupling [10] or in a four-wave mixing scheme [11]. In these experiments, one measures very small phases differences with relatively high flux levels. Our situation is slightly different because we must measure very small flux, and control the phase of the US. In this aspect, it approaches the PR beam splitter used to detect phase modulated telecommunications signals [12]. We will see how to adapt this concept to ultrasound modulated optical tomography of biological tissues.

Photorefractive effect arises in materials that present both electrooptic effect and photoconductivity, which combination allows to transform a non uniform illumination of the material into a spatial variation of the refractive index [13]. When illuminated by the interference between an object and a reference beam, the material records a hologram, i.e., the amplitude and phase of the object beam. This hologram is dynamic meaning that it can follow the interference pattern fluctuations slower than the response time τ_{PR} of the material, also meaning that *only* slowly moving hologram are recorded. In PR materials the time response is inversely proportional to the incident power density, with values as short as some microseconds observed in some crystals with high power cw-lasers [14]. The PR effect is not wavelength resonant and has been observed in several kind of materials covering a large spectral range from the visible to near infrared (400 nm to 1600 nm). For the first experiment, we have chosen a single crystal of GaAs, sensitive in the near infrared (1064 nm here), where biological tissues, though scattering, are quite transparent.

The setup (Fig. 1) is an interferometer, where the recombination plate is a photorefractive crystal. The scattering media (B) is chicken breast, insonified by a transducer (T) (*Panametrics*, *focal length*= 68 mm, *Diameter*= 40mm). It operates in a *cw* regime at $\omega_{US} = 2MHz$ with a $35V_{pp}$ peak to peak excitation. This corresponds to an acoustic pressure of about 0.1MPa in

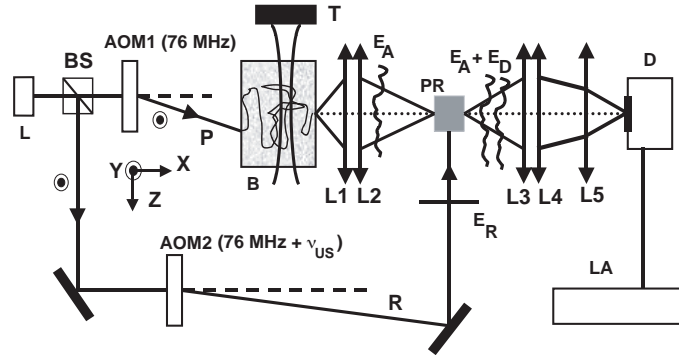


Fig. 1. Experimental setup. L: Single axial mode YAG: Nd³⁺ laser ($\lambda = 1064\text{nm}$). BS: splits the laser beam into a probe (P) and a reference (R) beam. T: US piezo-transducer. AOM1,2: Acousto-optic modulators. E_A, E_S (not drawn), E_D : fields associated to the speckle wavefronts (see text). E_R reference field. D: silicon photodetector ($S = 4.9\text{mm}^2$). L1,2,3,4,5: wide aperture $NA = 1$ aspherical lenses. B: chicken breast. PR: GaAs photorefractive crystal. LA: Lock-in amplifier.

the center of the pencil shaped focal zone, whose diameter is 2mm in the acoustic transverse direction (x, y), and 20mm in the longitudinal direction (z). The ensemble (B+T) is immersed in a water tank to ensure coupling of the US. The light source (L) is a $TEM_{0,0}$ single axial mode YAG : Nd³⁺ laser (*Lightwave electronics*: $\lambda = 1064\text{ nm}$, $P = 100\text{ mW}$), linearly polarized along the y -direction. The laser beam (frequency ω_L) is split into a reference beam R going outside the sample, and a probe beam P crossing the sample. They are *shifted* in frequency ($\omega_{AOM1} = 76\text{ MHz}$, $\omega_{AOM2} = 76\text{ MHz} + \omega_{US}$) with acousto-optic modulators AOM1,2 (*Crystal Technologies*) having a 50% efficiency, so that we measure on both arm of the interferometer a power of 25mW . Finally, they recombine inside a ($1 \times 1 \times 1\text{ cm}^3$) PR crystal (undoped GaAs, grown by Liquid Encapsulated Czochralski method) oriented in an energy transfer configuration [13]. The R and P beams respectively enter the orthogonally (001) and (110) faces of the crystal in order to reduce scattering effects. It also allows to work close to the maximum response of the crystal, regarding the grating spacing, and to collect the signal (on the crystal and on the photodiode) with large aperture aspherical lenses ($\phi = 4\text{cm}$, focal length = 4cm). The minimum time response we have measured with this configuration is $\tau_{PR} \simeq 5\text{ms}$ in a conventional two beam-coupling experiment (without any sample) using an averaged *flux* of 75mW within the crystal. In our experiments, the *flux* within the crystal is typically 25mW , and τ_{PR} approaches 15ms .

Our technique differs from the one proposed by Sui *et al.* [1]. In our case, the frequency shifting of the reference beam by the acousto-optic modulators ensures that the photorefractive detection is applied only to the *tagged* photons. The field within the PR crystal contains three components: the scattered field $\mathbf{E}_S e^{j\omega_0 t}$, the tagged photons field $\mathbf{E}_A e^{j\omega_1 t}$, and the reference field $\mathbf{E}_R e^{j\omega_1 t}$ with ($\omega_0 = \omega_L + \omega_{AOM1}$ and $\omega_1 = \omega_0 + \omega_{US}$). Both \mathbf{E}_S and \mathbf{E}_A fields are *de-polarized*, and exhibit uncorrelated speckle patterns. We have verified this point experimentally by measuring, within a few seconds both \mathbf{E}_S and \mathbf{E}_A complex fields. The measurement is made by the heterodyne holography method [9, 15]: by choosing the proper frequencies for the acousto-optical modulators, one can tune the heterodyne receiver in order to measure \mathbf{E}_S or \mathbf{E}_A . The field intensity I within the crystal is a time dependent speckle interference pattern: $I = |\mathbf{E}_S e^{j\omega_0 t} + \mathbf{E}_A e^{j\omega_1 t} + \mathbf{E}_R e^{j\omega_1 t}|^2$. The $\mathbf{E}_S \mathbf{E}_A^*$, and $\mathbf{E}_S \mathbf{E}_R^*$ terms yield to fast moving fringes at

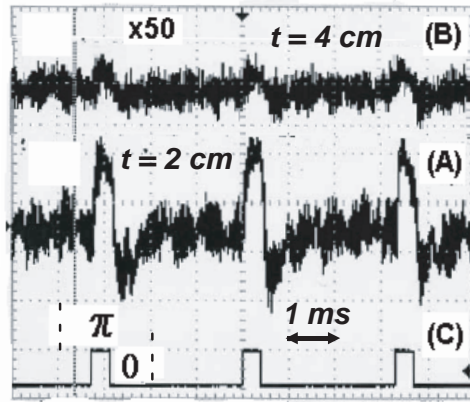


Fig. 2. Normalised one shot *ac*-signal obtained with thicknesses $t = 2 \text{ cm}$ (A) and 128 averaged (B) with $t = 4 \text{ cm} (\times 50)$ chicken breast and $P = 0.1 \text{ MPa}$. Trace (C) shows the phase modulation of the US ($\omega_{mod} = 305 \text{ Hz}$, cyclic ratio = $1/8$).

$\omega_{US} = 2 \text{ MHz}$, and do not write a hologram. The *tagged* photons term $\mathbf{E}_A \mathbf{E}_R^*$ is static and creates, by PR effect, a volume hologram, i.e. a spatial modulation $\delta n \propto \langle \mathbf{E}_A \mathbf{E}_R^* \rangle_t / I$ of the PR crystal index of refraction n (here $\langle \rangle_t$ denotes time-averaging over τ_{PR}). According to Bragg's condition, \mathbf{E}_R is diffracted by the volume hologram into a field \mathbf{E}_D with the *same* wavefront as \mathbf{E}_A i.e. \mathbf{E}_D is *spatially* and *temporally* coherent with \mathbf{E}_A . Since $I \cong |\mathbf{E}_R|^2$, one gets $\mathbf{E}_D \cong \eta \langle \mathbf{E}_A \rangle_t$. Here η is a proportionality efficiency factor depending on the electrooptic constants of the crystal, approaching 30% in our case.

\mathbf{E}_D and \mathbf{E}_A interfere on a silicon photodiode, yielding the photorefractive signal $\mathbf{E}_A \mathbf{E}_D^*$. To make this signal time varying, and to extract it from the various low frequency noise contributions, we apply on the US, a rectangular phase modulation $\psi(t) = (0, \pi)$ at $\omega_{mod} = 305 \text{ Hz}$ (Fig. 2C), so that \mathbf{E}_A is phase modulated. Now \mathbf{E}_A must be replaced, in the calculation of the signal, by $e^{j\psi(t)} \mathbf{E}_A = \pm \mathbf{E}_A$. Since the modulation is fast ($\omega_{mod} \gg 1/\tau_{PR}$), the hologram cannot follow it and it will then stay static. Since the cycling ratio ($\frac{1}{8} \ll 1$) is small, the hologram depth δn , and thus \mathbf{E}_D , reach nearly the same stationary values, than without modulation (within a factor $\langle e^{j\psi(t)} \rangle_t = 0.75$). One then gets a large rectangular optical modulation ($\cong 1.5 \eta |\mathbf{E}_A|^2$ peak to peak) on the PR signal $\mathbf{E}_A \mathbf{E}_D^*$.

4. Experimental results

We achieved tests on chicken breast tissue. Fig. 2 shows the PR signal seen by the photodiode with a $RC = 1 \text{ ms}$ high pass filter ($R = 1 \text{ k}\Omega$, $C = 1 \text{ }\mu\text{F}$). For thickness $t = 2 \text{ cm}$, the *real-time* signal to noise ratio (SNR) seen on Fig. 2A is about 3. For thickness $t = 4 \text{ cm}$ (Fig. 2B) we have measured $SNR \cong 5$ with a lock-in detection (200 ms time-constant). As previously stated, ultrasound modulated optical tomography of thick biological tissues had only been achieved with the rather slow multi-detector scheme mentioned above and with poorer SNR [8]. In this sense, our results are an important and promising step towards the development of an instrument with performances suitable for clinical studies.

As a last evidence of the method, Fig. 3 shows a lateral *1D*-scan of the US focused in a 2 cm thick chicken samples containing an ink inclusion ($\sim 2 \times 2 \times 2 \text{ mm}^3$). The lateral width of the AO response ($FHMW = 9.4 \text{ mm}$) is in good agreement with the size of the expected illuminated zone in the sample. As shown on the figure, the extracted optical contrast (curve B)

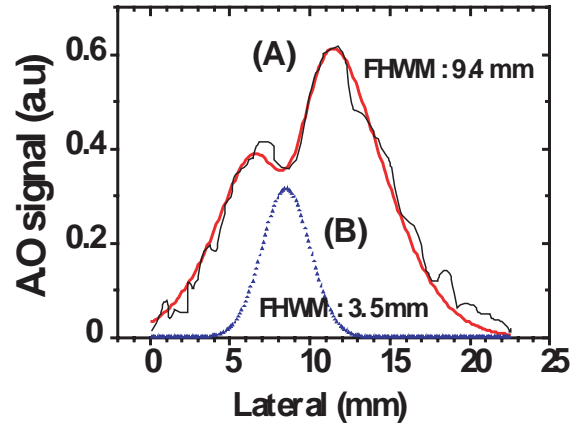


Fig. 3. Lateral 1D-scan (A) of a $t = 2$ cm thick chicken breast containing a 2 mm ink inclusion. The absorbing contribution of the inclusion corresponds to curve (B).

gives a $FHWM = 3.5\text{mm}$. This value is reasonable since it represents the convolution product between the inclusion size (2mm) and the US width at the focus point (2mm).

5. Discussion and conclusion

The results presented here are encouraging considering the relatively low acoustic pressure (0.1 MPa) used, and the many possible improvements. With *co*-directional coupling (typically 45° between the beams) one can get a faster PR response ($\sim 1\text{ms}$) with still good efficiency ($\eta \approx 15\%$), with in counterpart more scattering of the reference beam by the optical imaging setup. We expect to get a better diffraction efficiency in the 90° coupling geometry with a thicker crystal, where the signal and the reference beams respectively enter the $(11\sqrt{2})$ and $(11 - \sqrt{2})$ faces in order to have a grating oriented along $\langle 001 \rangle$. In this configuration, the effective electrooptic coefficient is $r_{eff} = -r_{41}$ (we have at present $r_{eff} = r_{41}/\sqrt{2}$). We plan to use a large area cooled InGaAs photodetector, more sensitive in this spectral region than silicon detectors. Using of a polarizer after the sample should remove half of the *un-tagged* photons noise contribution. The laser incoming power used here is quite low (25 mW on both arms) and could be enhanced at least by a factor of 10, in order to study thicker samples and to reduce the PR time response τ_{PR} . We are also looking towards crystals sensitive within the *therapeutic window* (600 – 900 nm), to get functional informations on biological sample, particularly around 800 nm, where tumors exhibit an anomalous $[HbO_2]/[HbO]$ ratio, detectable through absorption variations.

In summary, we have presented a new method for direct biological acousto-optic imaging of thick tissues using a single detector and a photorefractive GaAs single-crystal. This method, which combines good flux sensitivity (large detector area, large collection angle), high frequency response (photodiode), and simple acquisition technique (mono detector), will contribute to get images of thick biological tissues.

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