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Non-contact photoacoustic tomography and ultrasonography for brain imaging

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ABSTRACT

Photoacoustic tomography (PAT) and ultrasonography (US) of biological tissues usually rely on transducer arrays for the detection of ultrasound. Obtaining the best sensitivity requires a physical contact with the tissue using an intermediate coupling fluid (water or gel). This type of contact is a major drawback for several applications such as neurosurgery. Laser-ultrasonics is an established optical technique for the non-contact generation and detection of ultrasound in industrial materials. In this paper, the non-contact detection scheme used in laser-ultrasonics is adapted to allow probing of ultrasound in biological tissues while remaining below laser exposure safety limits. Both non-contact PAT (NCPAT) and non-contact US (NCUS) are demonstrated experimentally using a single-frequency detection laser emitting suitably shaped pulses and a confocal Fabry-Perot interferometer. It is shown that an acceptable sensitivity is obtained while remaining below the maximum permissible exposure (MPE) of biological tissues. Results obtained *ex vivo* with a calf brain specimen show that sub-mm endogenous and exogenous inclusions can be detected at depths exceeding 1 cm. When fully developed, the technique could be a unique diagnostic tool in neurosurgery providing deep imaging of blood vessels, blood clots and blood oxygenation.

Keywords: biomedical imaging, photoacoustic tomography, ultrasonography, non-contact detection, neurosurgery, brain, blood oxygenation, ischemia

1. INTRODUCTION

Biomedical imaging techniques are presently intensively developed [1]. Photoacoustic tomography (PAT), which provides images of the optical absorption contrast, holds promise for many biomedical applications [2,3]. Ultrasonography (US) is a well established imaging modality providing acoustic properties of tissues. Both PAT and US usually rely on ultrasonic transducers in contact with the tissue using a coupling fluid (water or gel). Unfortunately, a physical contact is not suitable for many applications [4]. For example, during brain surgery, the transducer array must be inserted in a sterile sleeve and the sterile saline solution used as coupling medium requires a horizontal working plane. Most extracorporeal applications can use coupling fluids but some, such as burn diagnostic, cannot. Applications related to ophthalmology may also benefit from a non-contact detection of acoustic signals [5]. For small animal imaging, immersion in water significantly complicates the procedure [6]. Consequently, non-contact optical detection of ultrasound in biological tissues is of great interest. Moreover, generation and detection of ultrasound by remote optical means would facilitate endoscopic implementations of PAT and US as well as compatibility with other imaging modalities such as optical coherence tomography (OCT) [2,5,7]. Air-coupled transducers [8] have been considered for PAT but their limited sensitivity could be difficult to overcome, especially when spatial resolution is needed. Attempts have been made to replace piezoelectric transducers by optical means but most of these attempts require a contact with the tissue [9-12].

Laser ultrasonics (LU) is a well established optical technique allowing non-contact generation and detection of ultrasound [13]. LU is mostly applied to industrial materials such as metals, plastics and polymer-matrix composites. Ultrasound is laser generated by thermoelastic expansion or by slight ablation at the surface of the material and acoustic reflections coming back to the surface are detected using a laser beam reflected/backscattered by the material. The reflected/backscattered light, which is phase modulated by the surface displacement, is demodulated with a large throughput interferometer such as a confocal Fabry-Perot interferometer (CFPI) [14,15] or a photorefractive

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interferometer [16,17]. High sensitivity is obtained by using a high power detection laser and operating in a shot-noise-limited detection regime. The challenge in applying the optical detection scheme used in LU to biomedical imaging consists in obtaining an acceptable sensitivity without exceeding laser exposure safety limits [18]. Non-contact PAT has been recently demonstrated on materials [19] but, to our knowledge, not on biological tissues for which the optical properties can differ significantly and laser safety limits cannot be ignored.

In this work, the optical detection scheme used in industrial LU is adapted to the safe detection of ultrasound in biological tissues. The technique does not require any contact, coupling medium or surface preparation. Non-contact PAT and US (NCPAT and NCUS) are implemented using a single apparatus, the difference between both imaging modes being found in the reconstruction algorithms. This demonstration is based on three strategies. First, a safe level of laser radiation is achieved by shortening high-energy detection laser pulses to the propagation time of ultrasound. Second, quantum-limited sensitivity is reached using an optical phase demodulator in differential configuration. Third, nearly diffraction-limited images are obtained by sensing remotely the surface profile of the tissue. Those strategies allow a safe detection of inclusions exhibiting optical and acoustic contrasts. The technique is expected to be applicable *in vivo* on beating/moving internal organs or skin.

2. EXPERIMENTAL SETUP

2.1 Laser sources

Using laser beams to generate and detect ultrasound in biological tissues immediately leads to opposite requirements. First, the sensitivity of the measurement can only be increased by using a higher power of laser radiation. Second, the laser power is limited by safety limits, namely, the maximum permissible exposure (MPE), to avoid damaging the biological tissue [18]. Those opposite requirements necessitate an appropriate laser exposure management.

Efficient laser generation of acoustic waves is obtained with sufficiently short laser pulses compared to thermal and stress relaxation times [1]. Typically, few nanosecond pulses produced by Q-switched lasers are appropriate. In practice, the tissue must be exposed on a large surface area to obtain a uniform illumination inside the tissue and the generation laser pulse energy is limited by the MPE for a repetitive exposure [18]. In the absence of free parameters for the generation laser, the laser exposure management is thus related to the detection laser.

When probing soft tissues at depths limited to 1 or 2 cm, the maximum propagation delay of ultrasonic waves is about 25 μs since the propagation velocity is about 1.5 mm/ μs in soft tissues. In order to minimize laser exposure, the detection laser illumination should be limited to the ultrasound propagation delay. For most industrial applications, a master oscillator power amplifier (MOPA) emitting powerful long pulses is appropriate. Such a laser source can be adapted to biomedical applications by limiting the pulse duration without losing energy in the laser system. This is done by adding an intensity modulator (IMOD) between the single-frequency continuous wave (cw) master oscillator and the following pulsed power amplifier. A schematic diagram of such a laser source is shown in Fig. 1a.

Fig. 1 (a) Layout of the detection laser. MO, Nd:YAG cw master oscillator; ISO, optical isolator; HW, half-wave plate; PBS, polarizing beam splitter; AM, amplitude modulator; IMOD, intensity modulator; TFP, thin-film polarizer; LR, Nd:YAG laser rod; FL, flashlamp; QW, quarter-wave plate. Other components are plane dielectric mirrors. (b) Pulse shape at the output of the detection laser without pulse shaping. (c) Pulse shape tailored for the experiment using the IMOD. The generation laser pulse occurs at $t = 0 \mu\text{s}$ (green lines in b and c).

The IMOD allows inhibiting the amplifier output at the beginning of each pumping flash by setting its transmission to zero. The energy then builds up in the amplifier laser rods (LRs). Before the end of each pumping flash, the transmission of the IMOD is increased gradually to release the stored energy and obtain the desired pulse duration and shape at the amplifier output. Without pulse shaping (Fig. 1b), the output pulses at the exit of the pulsed power amplifier have an energy of 35 mJ, a peak power of 280 W and a duration of 110 μ s (FWHM: full width at half maximum). With pulse shaping (Fig. 1c), the output pulses tailored for this experiment have an energy of 14 mJ, a peak power of 560 W and a duration of 24 μ s (FWHM). Reducing the pulse duration thus increases the available peak power. More importantly, the peak power for a given energy is about 5 times higher with the tailored pulses. We have chosen using a tailored pulse shape with an increasing instantaneous power for two reasons. First, this eliminates strong signal oscillations at the output of high-pass filters preceding signal digitization. Second, the sensitivity increases with time to facilitate the detection of weaker signals arriving at larger time delays (coming from larger depths in the tissue).

2.2 Scanning and detection systems

A schematic diagram of the scanning setup is shown in Fig. 2a. The generation laser (not shown) is a Q-switched laser emitting 5 ns pulses at 532 nm with a repetition frequency of 10 Hz. The generation laser beam (shown in green) is directed toward the biological tissue specimen after beam expansion and transmission through a line mask blocking the generation laser on the detection scan line. The purpose of the line mask was to eliminate any overlap between the detection and generation laser illumination during the entire scan to increase the allowed laser power (see also Subsection 3.2). This allows using the single shot safety limit for the detection laser and the repetitive exposure safety limit for the generation laser. The detection laser beam (shown in red) is transmitted to the setup with a multimode optical fiber. A sample of the detection laser beam is first deflected by a beam splitter (BS) and coupled into an optical fiber as a reference beam for phase noise elimination. The detection laser beam is then focused on a 400 μ m diameter spot on the tissue specimen. A small prism mirror (P) in front of the collecting optics is used to direct the detection laser beam to the tissue without coupling stray light into the collecting optics. The resulting illumination/detection geometry is shown in the inset (Fig. 2a) where the elliptic green area is the generation laser spot (masked on the scan line) and the red area is the detection laser spot. The collecting optical system uses two lenses assemblies (LAs) for collimating and coupling the reflected/backscattered light (shown in yellow) into the optical fiber (400 μ m core diameter, 0.39 numerical aperture) carrying the signal beam. The biological tissue specimen is located on a computer-controlled motorized stage allowing displacements along the scanning axis x and the focusing axis z . The working distance between the biological tissue and the collecting optics was about 25 mm.

Fig. 2 (a) Schematic diagram of the biological tissue scanning setup: LA, lenses assembly; L, lens; M, plane mirror; BS, beam splitter; P, gold coated hypotenuse prism. (b) Schematic diagram of the CFPI in differential configuration: PBS, polarizing beam splitter; PZM, piezoelectrically actuated mirror mount; VA, variable attenuator; DD, differential detector.

The phase demodulation of the collected light is done with an actively stabilized CFPI mounted in differential configuration to achieve both intensity and phase noise reduction (Fig. 2b) [20]. The horizontal polarization is used to analyze light from the tissue specimen (signal beam) and the vertical polarization is used to measure the phase noise of the detection laser (reference beam). The CFPI is a 1 m long cavity with mirrors' reflectivity of 94.5%. The back mirror is mounted on a piezoelectrically actuated mount (PZM) fed by a 10 Hz servo loop ensuring stabilization at half-maximum of the carrier frequency transmission. The optical system inertia ensures a good stability within each measurement time window of about 20 μ s. Such a CFPI is thus already compatible with *in-vivo* measurements. The demodulation response of the CFPI presents a peak demodulation response around 2 MHz and remains significant between 400 kHz and 9 MHz. For both reference and signal beams, a differential detector (DD) was used to remove intensity noise (Fig. 2b). Each DD uses two InGaAs photodiodes in series DC-coupled to a transimpedance amplifier followed by a high-pass filter (300 kHz cutoff frequency) and a voltage amplifier. Phase noise of the detection laser was eliminated by the active filtering explained as follows. First, the amplitude of the signal channel before the generation laser pulse was multiplied to obtain an rms noise equal to that of the reference channel in the same time window. Then, iterations around this first value have allowed determining the optimum amplitude multiplication factor to minimize the residual noise on the difference between both channels. Typically, the residual noise was comparable to the shot noise level calculated from nominal values of the transimpedance gain and InGaAs photodiodes' quantum efficiency. The spectrum of the residual noise was practically white in the frequency range kept for the analysis (0.5 to 3 MHz).

3. METHODOLOGY

3.1 Image reconstruction

A typical image is obtained from 60 to 80 A-scans, each measured with a single detection laser pulse (no averaging). All A-scans are grouped in a raw B-scan image which is processed with the synthetic aperture focusing technique (SAFT) [21]. The SAFT algorithm was applied in the time domain and modified to take into account the surface profile of the biological tissue. When measuring remotely on curved surfaces with non negligible height variations compared to the minimum ultrasonic wavelength (about 0.5 mm at 3 MHz), the surface profile is an essential input for a reliable image reconstruction. In our experiment, the surface profile was measured prior to the scan using a time-domain OCT system. Each raw B-scan image, once linked with the surface profile, contains the necessary information for both NCPAT and NCUS reconstructions; the only difference being related to the expression of the propagation delay.

In the case of NCPAT, the optically scattering tissue is considered to have a low background absorption at the generation laser wavelength, except for optically absorbing inclusions such as blood vessels. In this case, the thermoelastic generation occurs on each inclusion with a strength related to the product of the local laser fluence and the absorption coefficient of the inclusion. Ultrasonic waves then propagate up to the surface where they can be detected.

Fig. 3 Reconstruction methods. (a) One-way path used in NCPAT imaging mode. (b) Two-way path used in NCUS imaging mode. Same color code as in Fig. 2.

In the case of NCUS, the combination of the weak endogenous optical absorption at the generation laser wavelength with the high generation laser light fluence at the surface of the biological tissue (or close to it) is considered to be sufficiently large to produce an acoustic wave by thermoelastic generation. The unprepared surface of the tissue is thus the source of a probing ultrasonic wave which has an initial wavefront following the surface topography. Ultrasonic reflections produced by inclusions exhibiting an acoustic impedance mismatch with the surrounding tissue go back to the

Fig. 4 Images of a calf brain specimen. (a) NCPAT image obtained with the following embedded objects (respective diameters in parenthesis): *i*, white painted metal wire (0.8 mm) *ii*, blood vessel phantom (0.7 mm); *iii*, blood vessel phantom (0.5 mm); *iv*, blood vessel phantom (0.3 mm). (b) Corresponding NCUS image. All scales are in mm except for amplitude profiles (in arbitrary units).

5. CONCLUSION

The results presented herein demonstrate that NCPAT and NCUS can be performed *ex vivo* on soft biological tissues. Sub-millimeter endogenous and exogenous inclusions have been detected at depths exceeding 1 cm. It is clearly shown that the highly scattering surface of a soft tissue provides a sufficiently strong diffused reflectivity to measure the ultrasonic displacement of the surface while remaining below the MPE. This however requires limiting the pulse duration of the detection laser to the propagation time of ultrasound. Using a differential configuration of the CFPI has also been essential to reach a quantum-limited sensitivity by removing both intensity and phase noise of the detection laser. For NCPAT, the 1D surface profile measurement with an OCT system has been sufficient to obtain nearly diffraction-limited images using time-domain SAFT. However, for the NCUS imaging mode, a 2D surface topography measurement and a better modelling of the probing ultrasonic wave would be essential to achieve diffraction-limited images.

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