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Improved photoacoustic dosimetry for retinal laser surgery

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ABSTRACT

Lasers are employed for numerous medical interventions by exploiting ablative, disruptive or thermal effects. In ocular procedures, lasers have been used for decades to treat diseases such as diabetic retinopathy, macular edema and aged related macular degeneration via photocoagulation of retinal tissues. Although laser photocoagulation is well established in today's practice, efforts to improve clinical outcomes by reducing the collateral damage from thermal diffusion is leading to novel treatments using shorter (μs) laser pulses (e.g. selective retinal therapy) which result in physical rather than thermal damage. However, for these new techniques to be widely utilized, a method is required to ensure safe but sufficient dosage has been applied, since no visible effects can be seen by ophthalmoscopy directly post treatment. Photoacoustic feedback presents an attractive solution, as the signal is dependent directly on absorbed dosage. Here, we present a method that takes advantage of temporal pulse formatting technology to minimize variation in absorbed dose in ophthalmic laser treatment and provide intelligent dosimetry feedback based on photoacoustic (PA) response. This method tailors the pulse to match the frequency response of the sample and/or detection chain. Depending on the system, this may include the absorbing particle size, the laser beam diameter, the laser pulse duration, tissue acoustic properties and the acoustic detector frequency response. A significant improvement (>7x) of photoacoustic signal-to-noise ratio over equivalent traditional pulse formats have been achieved, while spectral analysis of the detected signal provides indications of cavitation events and other sample properties.

Keywords: photoacoustic, laser surgery, fiber laser, dosimetry, retina

1. INTRODUCTION

Since the middle of the twentieth century, ophthalmologists have used photocoagulation to treat retinal diseases such as aged-related macular degeneration and diabetic retinopathies [1-3]. The Xenon arc-lamps used in the first coagulators were rapidly replaced by laser sources and since then retinal laser therapies have constantly been improved [4, 5]. Today, photocoagulation protocols use long (several microseconds to milliseconds) laser pulses to create thermal damage. There is, however, a trend towards lesser damaging protocols that favor shorter laser pulses (microsecond or sub-microsecond). When the laser pulse duration approaches the thermal confinement time constant, the temperature increases and results in micro-evaporations (often referred to as cavitations). The nature of damage induced with shorter laser pulses is thus mechanical rather than thermal and this leads to an enhanced damage confinement. This method is known as Selective Retinal Therapy (SRT). Due to high levels of inhomogeneity in the optical absorption and scattering properties both within and between tissues in the same individual, as well as between different individuals, consistent dosing of laser energy to a target remains challenging. Feedback of absorbed dosage by tissue is thus desired to provide consistent and repeatable treatment regimes. Pioneering work demonstrated that monitoring the photoacoustic (PA) waves generated during retinal laser surgery treatment was a promising method to control SRT dose [6-8]. However, due to the stress confinement dynamics of biological tissue, microsecond laser pulses used in SRT are not optimal for PA generation.

The recent advent of fiber lasers with flexible pulse formats [9] offers a much greater potential for photoacoustic optimization when compared to traditional laser technologies (e.g. Q-switch and mode-locked lasers) having limited time-domain capabilities. Pulse shape tailoring is already being applied for precise microfabrication processes [10, 11] and cavitation control [12]. Use of a digitally programmable, semiconductor seed diode, which is fiber amplified, can be tailored to provide on demand pulses of any temporal shape having a 1 ns resolution (minimal pulse width ≅ 3 ns). This capability allows full control of energy deposition rates for photoacoustic measurements in frequencies under 300 MHz. As a result, this laser represents an extremely flexible tool that can be used to control energy deposition rates. Here, in a fashion similar to what is being done in frequency domain PA spectroscopy, the treating laser pulse was modulated to fit the acoustic frequency response of the sample and detection chain. The generated acoustic wave was recorded and filtered to isolate signal at the modulation frequency to improve the signal-to-noise (SNR) ratio.

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2. METHODS

2.1 Experiment setup

Figure 1 is a schematic representation of the experimental setup used to measure the effect of pulse formatting on the photoacoustic feedback induced during laser treatment.

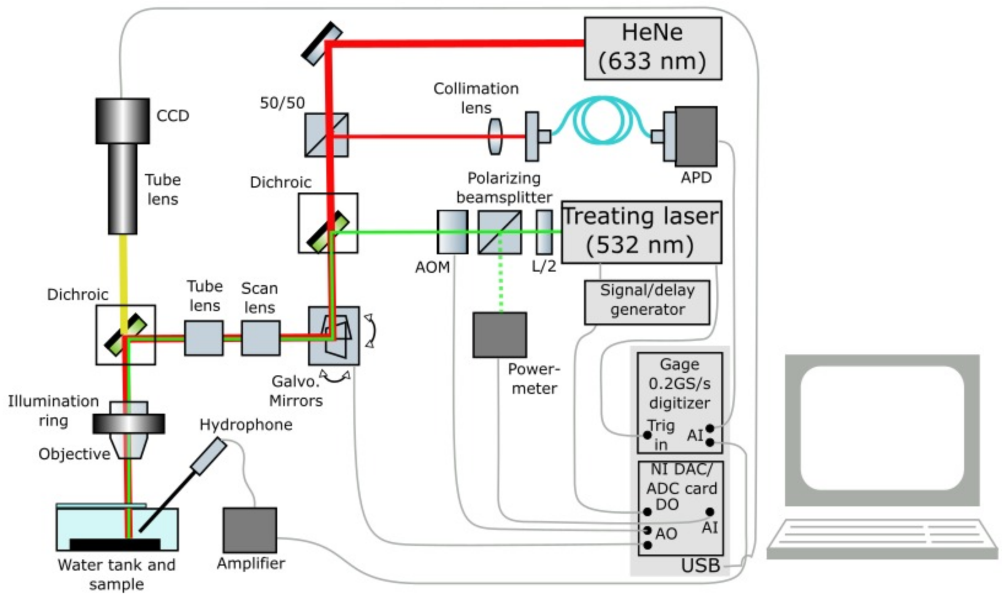

Figure 1. Laser therapy with photoacoustic dosimetry experimental setup. AOM: Acousto-optic Modulator and APD: Avalanche Photodiode.

The beam of a custom INO-built Master Oscillator Programmable Amplitude Wave (MOPAW, 1064 nm fundamental wavelength) frequency doubled (532 nm) fiber laser [9] was directed and focused onto an absorbing sample (PVC-P dyed phantom (INO), dried inks (black and red sharpie markers) or leporine retinal explants) with a set of mirrors and optics. These optics included motorized galvanometer mirrors (Thorlabs, GVSM002) for beam displacement on the sample and an acousto-optic modulator to control the laser treatment pulse energy. Pulse energy was determined with a joulemeter tap (Coherent, J-10Si-Le) and the pulse shape was monitored using a fast photodetector (Electro-Optics Technology Inc., GaAS PIN detector ET-4000). Laser spot size was measured to be 28 µm by imaging the spot on a camera and taking the $1/e^2$ width. Acoustic waves were captured with hydrophone model HNC-1000 (Onda) coupled to an AH1100 20dB amplifier (Onda) with a 20 MHz bandwidth. A HeNe laser at 633 nm (Melles Griot, 5 mW) was also used as an aiming beam and a reflection probe. The reflection probe signal was monitored with an avalanche photodetector (ThorLabs, APD 120A2). A CCD camera was used to help position the sample, the hydrophone and the beams. A labVIEW program was designed to scan samples with the treating beams, control the treating laser pulse energy and acquire the photoacoustic signals for each treated zones. Two cards (NI PCIe-6323 and GaGe CSE1222-4G) were used to control the galvanometric mirrors, the acousto-optic modulator and acquire data from the hydrophone, the powermeter and the avalanche photodiode.

2.2 Sample preparation

Experiments were conducted on photoacoustic phantom, dried inks at the bottom of a petri dish or retinal explants. Phantoms were prepared from a commercial PVC-P formulation (701-89 Vynaflex plastisol compound, Gripworks). The selected black pigmented PVC-P mixture was chosen for its elevated coefficient of absorption, μ_a, mimicking the highly absorbent pigmented retinal epithelium layer, and for efficiently generating a strong repeatable acoustic response. The RPE explants were prepared from fresh adult rabbit eyes obtained from a local slaughterhouse, in accordance with the ARVO Animal Statement and our institution's guidelines. Following enucleation, eyes were cut around the iris region. The anterior part, the vitreous humor and the retinal layer were carefully removed. The remaining posterior globe was incised and pinned to the bottom of a small petri dish (see water tank in Fig. 1).

2.3 Data analysis

PA signal amplitude, PA power spectral density and acoustic wave's spectrograms calculation as well as image reconstruction were done with the help of MATLAB scripts.

3. RESULTS

3.1 Modulated PA feedback

We evaluated the frequency response of our system by using a 3 ns laser impulsion (defined here as the impulse frequency response influenced by the sample, the transducer and amplifier individual responses). We found a maximal response around 4.2 MHz. Laser pulses of 600 ns duration and different modulation frequencies were used on a PA phantom. The generated acoustic waves were digitally filtered (2 MHz bandwidth) and the SNR calculated. SNR results are summarized in figure 2. Much larger SNRs could be observed in the frequency bands expected to have higher acoustic response (based on the impulse system frequency response). Maximal SNR was obtained for the 4.2 MHz modulated pulses, when the 3.2-5.2 MHz bandpass filter was applied resulting in a 7-fold increase in SNR ratio as compared to the 600 ns square pulse with the same filter, or a 14-fold increase over the SNR of the raw signal. While the modulated pulses are expected to have a 2-fold increase in peak excitation power over the square pulse due to the duty cycle (50% vs 100%), this is not sufficient to explain the increase in SNR.

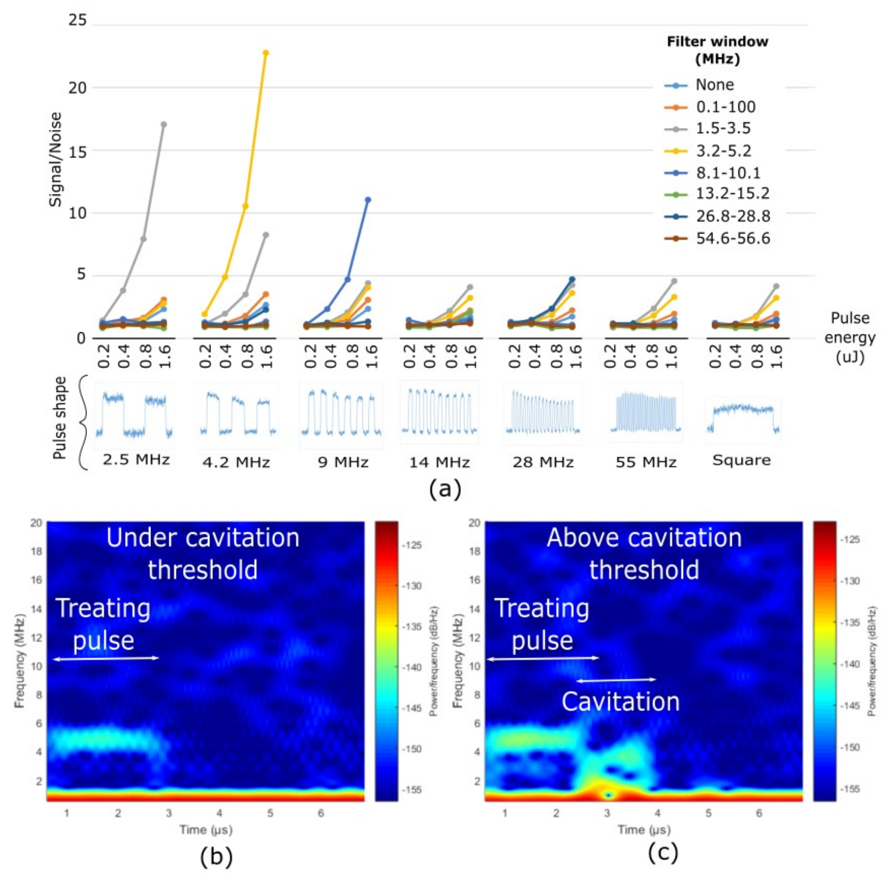

Figure 2. a) SNR ratio obtained with different modulated pulse shapes. Representative pulse shapes are illustrated below the x-axis, where all overall pulse envelopes are 600 ns in length. Pulse energies and modulation frequency are listed in the x-axis labels. Bandpass frequency filters are defined in the figure legend. Each data point is the average of 8 PA measurements. b-c) Spectrograms of the PA response before, during and after 2 µs treatment pulses modulated at 5 MHz under (b) and above (c) cavitation threshold.

When using modulated light pulses on more complex samples (leporine retinal explants), the ultrasound generated was characterized by a strong band at the laser pulse modulation frequency (5 MHz). Given that the very fine spectral response induced by a modulated treating laser pulse differs from the cavitation-induced frequency response, spectral analysis help recover information on the nature of the light/tissue interaction at the treated zone. Spectrograms of the PA response below and above cavitation threshold are represented figure 2(b-c).

3.2 Treatment uniformity

In the context of selective retinal therapy, maintenance of treatment uniformity can be obtained by increasing the pulse energy incrementally until desired mechanical damage is monitored for each pre-established treatment zone [8]. Alternatively, if the operator could measure the treatment threshold for a given treatment point and measure the absorption map of the retina at the laser wavelength, the threshold for each desired treatment zone can easily be calculated. A way to do this would be to pre-acquire a sub-threshold PA image of the sample and titrate the treatment energy according to the PA response for a given coordinate set. Using a pre-acquired PA image of a sample and an acousto-optic modulator we could obtain a uniform treatment response over the sample as demonstrated in figure 3. The sample used in that case were inks of different colors (i.e. different absorption properties) at the bottom of a petri dish.

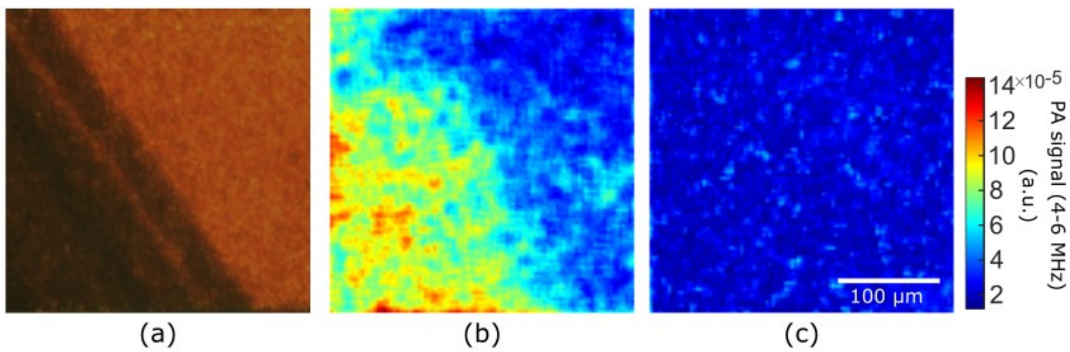

Figure 3. a) CCD microscopic image of a non-uniform sample (black ink was applied in the lower left corner and red ink was applied in the upper right corner). Corresponding PA image of the sample imaged on the left (b) and PA feedback image obtained with treatment titration (c). Note that treatment effect is uniform over the sample despite spatial absorption variations. Scale bar applies to (a), (b) and (c). PA signal scale applies to (b) and (c).

4. CONCLUSION

As discussed above, microsecond laser pulses are not optimal for high amplitude PA wave generation. These results demonstrate that modulated microsecond treating laser pulses and acoustic spectral analysis can be beneficial to PA feedback dosimetry (for a given pulse energy the SNR improvement factor is 7X) and cavitation detection. Use of modulated instead of standard pulses could be paired with the use of highly sensitive resonant acoustic transducers to help map selective retinal therapy outcomes. This could also allow improved photoacoustic feedback image quality while remaining below maximal permissible exposure prescribed by ANSI (American National Standards Institute) guidelines. Experiments performed in this work were limited to a small laser spot size (28 µm), and remain to be repeated for larger treatment spot sizes more representative of those currently used in SRT.

Moreover, this work demonstrated preliminary results showing that a sub-threshold PA map can be used to calculate the spatial correction map to allow uniform energy absorption to be deposited over a spatially variable absorbing surface. We showed a significant improvement in the uniformity of the PA signal representative of the absorbed optical dose over a non-uniform sample (Fig. 3c).

Finally, due to their flexibility, programmable fiber lasers can be used for improved treatments as well as dosimetry in laser based retinal therapies.

5. ACKNOWLEDGEMENTS

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