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Near-infrared multispectral photoacoustic microscopy using a graded-index fiber amplifier

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ABSTRACT

We demonstrate optical resolution photoacoustic microscopy (OR-PAM) of lipid-rich tissue using a multi-wavelength pulsed laser based on nonlinear fiber optics. 1047 nm laser pulses are converted to 1098, 1153, 1215, and 1270 nm pulses via stimulated Raman scattering in a graded-index multimode fiber. Multispectral PAM of a lipid phantom is demonstrated with our low-cost and simple technique.

1. Introduction

Photoacoustic microscopy (PAM) [1,2] of lipid-rich tissue, such as atherosclerotic plaques [3–6] or myelinated peripheral nerves [7,8], typically requires near-infrared laser wavelengths near 1210 nm or 1720 nm. These wavelengths correspond to the second and first overtone optical absorption of C—H bonds in lipids [7]. Unfortunately, neither of these wavelengths are produced by commonly available pulsed lasers (e.g. Nd:YAG). Therefore, expensive optical parametric oscillators (OPOs) are necessary to perform PAM of lipids. OPOs have high pulse energy, large wavelength tuning range, and repetition rates in the several kHz range. However, the very high cost and slow wavelength tuning are major drawbacks for practical applications, where multiple wavelengths are preferred to distinguish lipids from surrounding tissue.

We have been exploring techniques based on nonlinear fiber optics to develop cost-effective lasers for PAM of lipid-rich tissue. Nanosecond laser pulses from a fixed-wavelength laser are sent through an optical fiber, where nonlinear propagation produces multiple wavelengths. The wavelength distribution depends on the laser pulse parameters and fiber properties. When nanosecond pulses pump an optical fiber near the zero-dispersion wavelength, extreme spectral broadening occurs due to several nonlinear mechanisms such as modulation instability, soliton dynamics, and phase-matched four-wave mixing [9]. Photonic crystal fibers pumped in this manner produce a supercontinuum spanning from visible to near-infrared wavelengths. In contrast, an optical fiber pumped in the normal dispersion region produces discrete wavelengths via stimulated Raman scattering (SRS) [10].

We demonstrated the first application of both techniques for PAM, where the desired wavelength is selected by a band-pass filter [11,12]. Supercontinuum generation has very broad wavelength coverage but low pulse energy (e.g. 150 nJ or less) in a specific spectral band (e.g. 10 nm width) [11,13,14]. SRS concentrates energy into fewer discrete wavelengths, leading to higher pulse energy [15,16]. Hajizera performed in-vivo blood oxygenation PAM at 532, 545, 558, and 590 nm using a high repetition rate fiber laser with an optical fiber [16]. We recently demonstrated this technique for near-infrared PAM, where a birefringent optical fiber converted a 1064 nm laser to 1097, 1150, 1215, 1275, and 1325 nm [17].

A major advantage of our technique is its simplicity, as it uses a low-cost pulsed laser followed by an optical fiber. However, an important drawback is the low pulse energy, typically a few hundred nJ [17]. Such low pulse energies require significant signal averaging for optical-resolution PAM (OR-PAM) of lipids. In this paper, we demonstrate an improved system with an over 10-fold increase in laser pulse energy at 1215 nm, corresponding to the optical absorption peak of lipids. Pulse energies of several μJ make it possible to image lipid-rich tissue with little to no signal averaging, an important step towards practical applications.

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2. Methods

2.1. Near-infrared multi-wavelength pulsed laser

Fig. 1a shows the schematic of our multi-wavelength pulsed laser. A Q-switched Nd:YLF laser (CrystaLas Corp) produces 140 mJ pulses at a wavelength of 1047 nm. The pulse duration is 14 ns and the repetition rate is 1 kHz. The laser pulses are coupled into 95 m of a graded-index multimode fiber (GIMF) with a 50 μm core diameter and 0.22 numerical aperture (GIF-50C, Thorlabs). The fiber output is collimated with a 15 mm focal length aspheric lens and sent through a filter wheel containing hard-coated band pass filters (Edmund Optics) at 1050, 1100, 1150, 1225, and 1275 nm. The 1050 nm filter has a 10 nm bandwidth and 80% transmission. All other filters have a 50 nm bandwidth and 80% transmission.

Although pulsed Nd:YLF lasers at 1053 nm are more common, systems operating at 1047 nm are also commercially available. For our particular system, the 1047 nm wavelength is important to generate pulses at 1215 nm, which lies close to the optical absorption peak of many lipids (Fig. 1b) [18,19]. Our technique relies on stimulated Raman scattering (SRS), which describes the interaction of a laser with the vibrational modes of an optical medium. SRS produces a series of frequency down-converted "Stokes lines" separated by 13.2 THz, corresponding to the peak of the Raman gain spectrum in fused silica [10,20]. An input laser at 1047 nm propagating through a silica optical fiber should produce Stokes lines at 1098, 1153, 1215, and 1284 nm.

The GIMF core has a parabolic refractive index, in contrast to the uniform profile of conventional step-index optical fibers [21]. Despite being a multimode fiber, a GIMF has several advantages. First, it exhibits an interesting "beam clean-up" property, where an input pump laser with poor spatial beam quality produces Stokes wavelengths with good spatial beam quality [22,23]. This is clearly an important feature for achieving fine spatial resolution in OR-PAM. Second, the larger diameter core permits scaling to higher pulse energies by suppressing optical damage. Furthermore, higher energy Stokes pulses can develop before saturation occurs [17]. Third, robust and high fiber coupling efficiency (e.g. 65%) is easily achieved without elaborate positioning mounts.

2.2. OR-PAM system

Fig. 1a also shows our transmission-mode OR-PAM system, where the focused optical excitation and acoustic detection are on opposite sides of the sample. The selected wavelength from the multi-wavelength source is focused with a 50 mm focal length achromat. The photoacoustic signal is detected by a 25 MHz f/2 transducer (Olympus NDT), amplified by 60 dB (Miteq), sent through a 50 MHz low pass filter (Mini-Circuits), and finally acquired by a digitizer board operating at 250 MS/s (National Instruments). Two-dimensional scanning of the object is performed with a computer controlled positioning system (Velmex). Data acquisition is performed with LabVIEW while data processing and reconstruction are performed off-line in MATLAB.

3. Experiments and results

3.1. Spectral characterization of the GIMF output

The spectral properties of the GIMF output were measured with a scanning monochromator (Optometrics). Fig. 2a shows the spectrum at "full power", corresponding to an input pulse energy of 140 μJ. The input pump (P = 1047 nm) and first three Stokes lines (S1 = 1098 nm, S2 = 1153 nm, S3 = 1215 nm) are clearly visible. The measured Stokes wavelengths closely agree with the expected values from SRS in fused silica. The Stokes line S4 is lower in peak spectral intensity but much broader in bandwidth. The expected peak wavelength of S4 is 1284 nm, but the actual value is near 1270 nm. This broadening and peak shift are most likely due to the presence of phase-matched four-wave mixing (FWM). FWM describes the nonlinear interaction between two input waves at frequencies f_1 and f_2 to produce two new waves at frequencies f_3 and f_4. Efficient FWM occurs near 1300 nm in silica fibers, where low chromatic dispersion permits phase matching between all four waves [20].

Approximately two-thirds of the laser energy coupled into the fiber remains at 1047 nm, while the remaining third is distributed among the Stokes wavelengths. Table 1 shows the measured pulse energy after each dielectric band-pass filter. The pulse energy is 7 μJ after the 1225 nm filter (50 nm bandwidth), corresponding to the Stokes peak at 1215 nm (S3). This energy is over ten times higher than our previous system [17]. Although peak S3 has a fairly broad linewidth (32 nm), we have successfully demonstrated multispectral PAM of lipids with this laser source. The spectral broadening of the higher Stokes orders is most likely due to FWM [10,20].

In theory, SRS produces a new Stokes line when the pump power is increased by a discrete amount [20]. This threshold behavior is confirmed in Fig. 2b, where the fiber output spectrum is shown at various input laser energy levels. A new Stokes line is

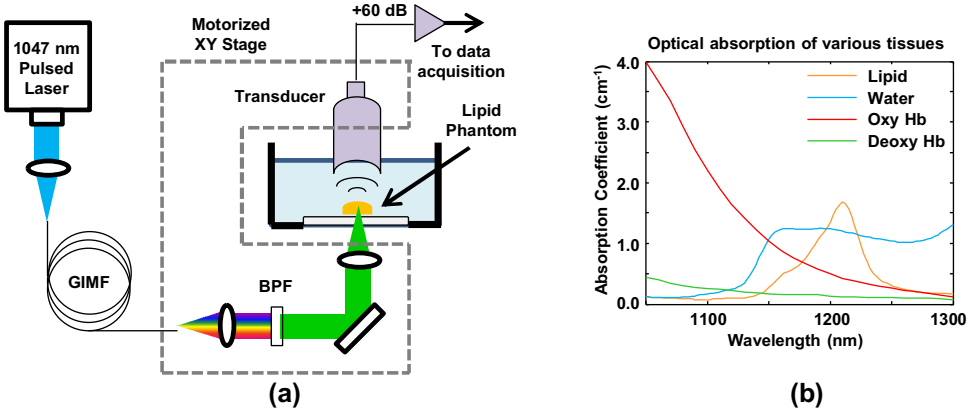

Fig. 1. (a) Schematic of the multi-wavelength pulsed laser based on a graded-index multimode fiber (GIMF). A dielectric band-pass filter (BPF) selects the desired wavelength for OR-PAM. The components within the dashed box are mounted on a motorized 2-D positioning stage. (b) Near-infrared optical absorption spectra of lipid (orange), water (blue), oxy-hemoglobin (red), and deoxy-hemoglobin (green) [18,19].