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Time-Domain Diffuse Optics using Bioresorbable Fibers: a Proof-of-Principle Study

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Abstract: We show for the first time the aptness of Calcium Phosphate Glass-based bioresorbable fibers for time-domain diffuse optics using tests described by a standardized protocol and we also present a spectroscopic measurement on a chicken breast.

OCIS codes: (110.7050) Turbid media; (300.6500) Spectroscopy, time resolved; (170.5280) Photon migration; (170.3660) Light propagation in tissue; (170.1610) Clinical applications; (060.2290) Fiber materials; (160.2750) Glass and other amorphous materials; (160.1435) Biomaterials.

1. Introduction

In the last years bioresorbable materials are gaining increasing interest, as they eliminate the need for follow-up explant surgery. Indeed, they have been used for several applications, thus increasing the range of applicability of optical tools in clinics and further decreasing the impact of minimally invasive methods.

Among the materials employed for applications in hard and soft tissue engineering, Calcium Phosphate Glasses (CPGs) are widely studied and their biocompatibility and resorbability have been demonstrated both in-vivo and in-vitro [1,2]. The feasibility of bioresorbable optical fibers using CPGs was previously proved [3] and the attenuation losses are 1 up to 2 orders of magnitude lower as compared to what reported so far for bioresorbable waveguides [4,5].

In this work we study the aptness of CPG fibers for time-domain diffuse optical spectroscopy (TD-DOS) deep into biological tissues. Indeed, TD-DOS can provide an absolute estimate of the absorption and reduced scattering spectra of the diffusive medium [6], thus allowing to recover quantitative information on the chemical composition (water, oxy- and deoxy-hemoglobin, water, lipids, collagen [7]), on the scattering properties (change of microstructure, edema) and on the functional status (e.g. oxygenation [8,9]) of the samples. By analyzing all those parameters, some information about the tissue (e.g. tissue regeneration, healing process, etc.) can be inferred.

In this paper, we made use of the same CPG fibers used in [10], characterized by a relatively high numerical aperture (0.17) so as to improve the light harvesting. To study the suitability of CPG fibers for TD-DOS we used tests taken from a standardized protocol for the objective performance assessment of diffuse optics instruments: the Instrument Response Function (IRF) described in the Basic Instrumental Performance (BIP) protocol [11] and the linearity test contained in the MEDPHOT protocol [12]. The former test characterizes the overall time resolution of the instrument as a whole and it is fundamental to assess the intrinsic suitability of the setup for DOS measurements. The latter allows us to ascertain the performance of a system in retrieving the optical properties (absorption and reduced scattering) of a reference homogeneous diffusive medium.

We finally used the system in a more realistic environment by inserting the fibers into a cut of chicken breast and performing a spectral analysis in the 500-1100 nm range. Taking into account the results obtained in [10], in this work we used the fibers with a core diameter of 200 μm to increase the light harvesting and the measurements Signal-to-Noise Ratio (SNR).

2. Setup and measurements

The experimental setup was the same used in [10] and is schematically depicted in Fig. 1a. Two different laser sources are shown: indeed we switched from one to the other depending on the experiment. For the linearity measurements, a high power laser is required to span a wide range of optical properties. For this reason, we used a four-wave mixing prototype (Fianium Ltd, UK), providing optical pulses at 820 nm at a rate of 40 MHz. On the other hand, for spectroscopy measurements we employed a supercontinuum laser (SuperK Extreme, NKT Photonics,

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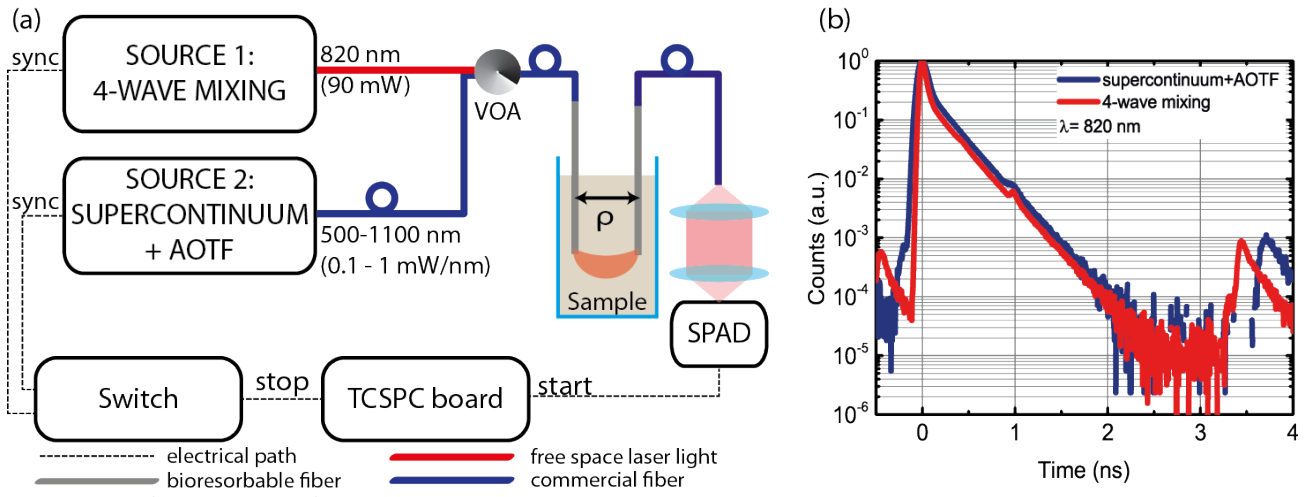

Fig. 1. On the left (a), schematics of the setup. On the right (b), IRF taken at 820 nm using both laser sources.

Denmark) coupled to a dual-channel Acousto-Optical Tunable Filter: in this way we were able to provide optical pulses at 80 MHz with a wavelength tunable in the 500-1100 nm range.

In both cases, the light provided by the laser source was attenuated using a Variable Optical Attenuator (VOA) and delivered to the sample through bioresorbable optical fibers (grey solid lines in Fig. 1a) with a core diameter of 200 μm, that were connected to commercial silica ones (blue solid lines). The distribution of time-of-flight was then recorded by a Time Correlated Single-Photon Counting (TCSPC) board.

The fibers were immersed by about 30 mm into the sample so as to mimic an interstitial measurement and they were separated by 20 mm (source-detector distance, ρ). The photons harvested by the collection fiber were focused onto the detector (100 μm active area diameter SPAD, Micro Photon Devices Srl, Italy) through a doublet of lenses with a demagnification factor of 2.

Fig. 1b shows the IRF of the built system using both sources at a given wavelength (820 nm). The full width at half maximum is always lower than 150 ps, the dynamic range is larger than 4 decades and there is no evidence of back reflections or fluorescence. For the supercontinuum laser, we also verified that the IRF did not change significantly in the whole wavelength range (data not shown here, see Ref. [10] for further details). Hence, we can state that the proposed setup is suitable for TD-DOS.

For the linearity measurements, we used liquid phantoms composed of water, ink (acting as absorber) and Intralipid (providing scattering property). The desired ("conv. true" in Fig. 2) optical properties of the phantom were obtained by a proper mixture of the components [13] reported above. In this way, phantoms combining 4 values for the scattering coefficient (μ'_s = 5, 10, 15 and 20 cm^{-1} at 820 nm) with 8 values for the absorption one (μ_a ranging from 0.023 to about 0.690 cm^{-1}) were synthesized. For each phantom, we acquired 60 repetitions of 1 s which were then summed up to increase the SNR. The optical properties were then recovered by fitting the experimental measurements to an analytical model obtained under the Diffusion Approximation, which describes the photon transport in an infinite diffusive medium [14]. For further details on data analysis, see Ref. [10].

In Fig. 2, four plots showing the measured ("meas.") values of absorption and reduced scattering coefficients against the true ones are reported. It is worthwhile noting that the system, for a phantom with $\mu_a < 0.690$ cm^{-1}, is linear in both absorption and scattering (see first and last graphs) and that there is a good independency between the scattering and absorption parameters (see second and third graphs, where the recovered absorption/scattering value is pretty stable upon a change in the scattering/absorption coefficient of the measured phantom). The deviation from ideality for phantoms featuring $\mu_a = 0.690$ cm^{-1} and $\mu'_s > 10$ cm^{-1} can be ascribed to the low signal which impairs the fitting procedure.

Once the system had been validated in terms of linearity, we tested it with a spectroscopic measurement on a chicken breast. The absorption and reduced scattering spectra are reported in Fig. 3. In the absorption spectrum, two main peaks (at 550 nm and 970 nm) are clearly distinguishable. The former (550 nm) is due to deoxy-hemoglobin (whose presence is confirmed by the observation of a third broad peak at about 750 nm), while the peak at 970 nm is a fingerprint of the water [15]. The recovered scattering spectrum is low in amplitude (< 3 cm^{-1}) and it shows, except in the region around 550 and 970 nm, a decreasing trend with the wavelength, which is compatible with the data reported in literature [15]. The peaks in the μ'_s spectrum at the same wavelengths of the absorption ones are due to the failure of the diffusion approximation (low scattering and high absorption) which leads to an absorption-to-scattering coupling.

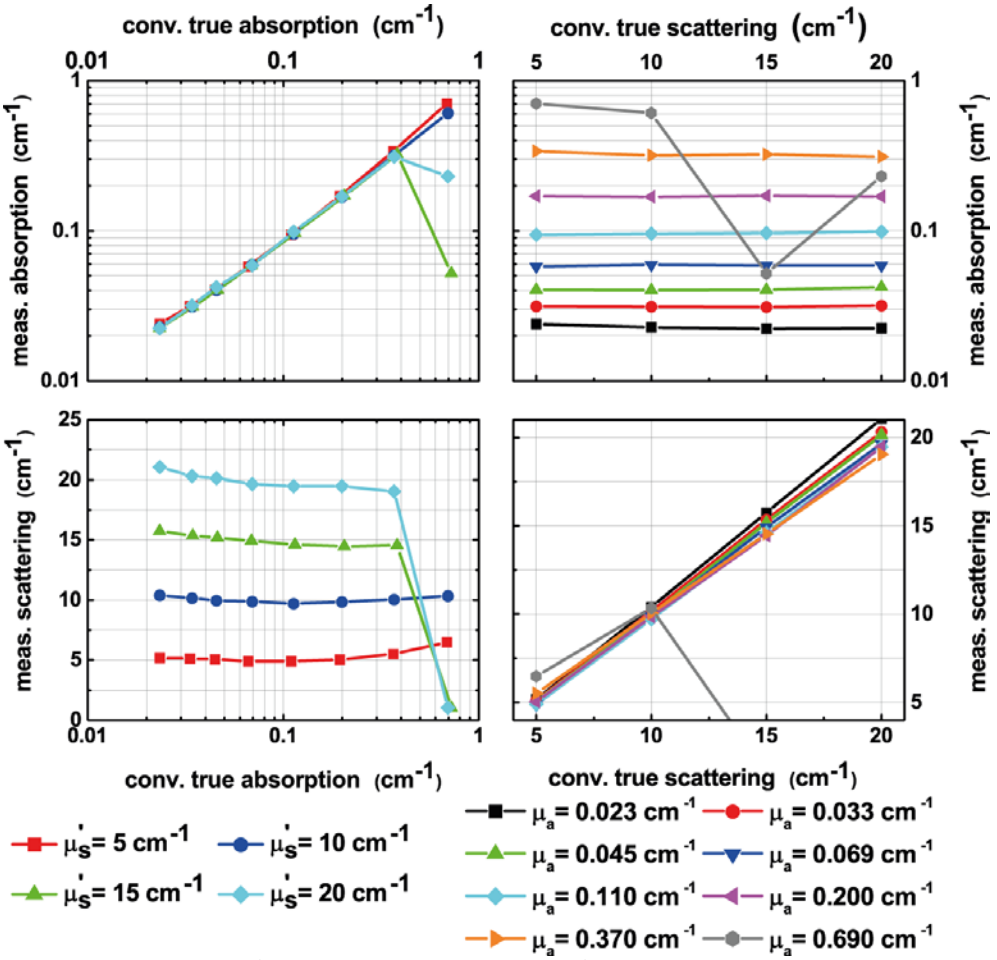

Fig. 2. Results of the linearity test on liquid phantoms featuring 4 μ'_s and 8 μ_a values.

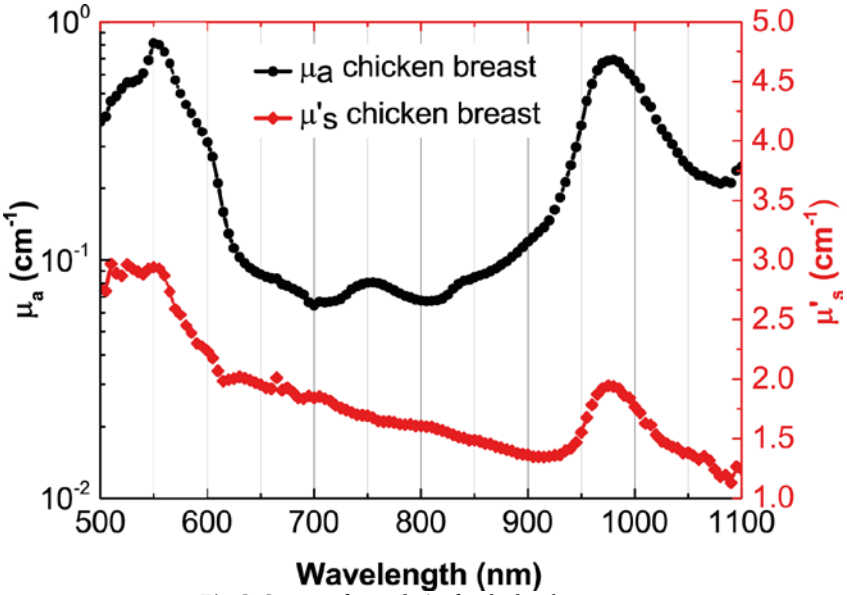

Fig. 3. Spectra of μ_a and μ'_s of a chicken breast.

We noticed that the use of a detector with larger area but also higher dark count rate (e.g. the SiPM module [16] used in a state-of-the-art spectroscopic system [17]) bring to a significant difference in the spectra (data not shown). For this reason, a detector featuring a low noise is in any case fundamental in this measurements where, notwithstanding the larger core of fibers, the system still suffers from a limited light harvesting.

3. Conclusions and future perspectives

In this work we validated the use of CPG fibers for time-domain diffuse optics measurements. Bioresorbable fibers with an increased numerical aperture were employed so as to improve the light harvesting. After having checked the IRF of the proposed system, we proved its capability to properly recover optical properties of phantoms on a wide range of absorption and scattering coefficients. Additionally, we performed an ex-vivo validation on a chicken breast using a large fiber core (200 μm) to improve the light harvesting. From all those measurements, we proved the aptness of bioresorbable fibers in the TD-DOS.

The exploitation of bioresorbable fibers for the TD-DOS technique paves the way toward a wide number of clinical applications that can be explored in the future. For example, the fibers could be used: (i) during interventions where they can be inserted (and left in place) to detect inflammation or abnormal response (e.g. assessment of flap viability [18]); (ii) to track the regeneration of tissues in implants with no burden since the fiber can be eventually reabsorbed; (iii) in the brain, to monitor deep hypoxia or hemorrhage in the sub-acute phase after brain injury [19]; (iv) for interstitial photodynamic and photothermal therapies with in-situ irradiation [20,21].

In all cases, the advantages of the bioresorbable fibers (no need for an explant surgery) and of the TD-DOS technique (providing quantitative information on optical properties and so on tissue composition, functional status and structure) are fundamental for the development of a new generation of clinical applications in which the impact of inserted optical fibers is lessened. Additionally, the use of detectors which exhibit higher quantum efficiency in the near-infrared wavelength [22] region will allow to recover also information on collagen and lipids whose content is related to the possible pathogenesis of diseases. Further developments of the current setup can also be envisaged: an increase of the numerical aperture of the bioresorbable fibers up to 0.22 can improve the light harvesting and a different composition of glasses can lead to a more flexible fibers. Additionally, the setup can be simplified thus reducing its cost for example by substituting the TCSPC board with a gated counter [23] or a Time-to-Digital Converter [24].

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