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Bioresorbable fibers for time-domain diffuse optical measurements: a step toward next generation optical implantable devices

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ABSTRACT

The use of bioresorbable fibers represents an innovative way to build optical implantable devices and to look inside the body. Recently, a new kind of bioresorbable fibers, based on calcium-phosphate glasses, has been introduced by some of us. They show a good biocompatibility and improved attenuation loss coefficient with respect to other bioresorbable fibers. In this work, we used those fibers to explore their suitability in diffuse optics. Indeed, the time-domain technique is a non-invasive methodology which allows to have an absolute estimate of the absorption and reduced scattering spectra of the diffusive medium. It allows to bring information about concentration of chemical components (water, oxy- and deoxy-hemoglobin), thus conveying information about the functional status and/or the scattering properties (changes in tissue microstructure, edema). Such information can then be related to the tissue regeneration, healing process, or to a harmful evolution. This makes the time domain optical spectroscopy coupled to bioresorbable fibers a good candidate for future medical devices. Here we demonstrate the suitability of these fibers for diffuse optics by means of standardized tests and then we use them for a proof-of-principle measurement on ex-vivo chicken breast, obtaining results comparable with standard fibers. Thanks to the encouraging results, we are working on a system based on a single fiber (serving as both injection and collection fiber) to go closer to a single interstitial fiber which can lessen the effect of the implant.

Keywords: time-domain diffuse optics, bioresorbable fibers, diffusive media, interstitial measurements, implantable devices.

1. INTRODUCTION

In the last decade, the use of light as a tool to non-invasively investigate tissues has gained a lot of interest, due also to the promising exploitation in biomedicine. Indeed, tissues are diffusive media[1], thus, when photons are injected inside them, they undergo many scattering events. If working in the so-called "therapeutic window" (600-1100 nm), there is a weak absorption of the light by tissues thus, when working in the so-called "reflectance geometry", the diffusing photons are easily re-emitted after having travelled in depth (e.g. more than 1 cm below the skin). For this reason, they bring information about the structural and chemical properties of the tissue (linked to scattering and absorption coefficient, respectively).

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The use of Time-Domain (TD) approach relies on the injection of short (in the order of tens of ps) laser pulses in the sample and on the reconstruction of the temporal profile of the re-emitted photons (Distribution of Time of Flight, DTOF). With respect to Continuous Wave approach[2] (which relies on the use of a steady-state source), the TD approach allows to retrieve separately absorption and reduced scattering coefficients (μ_a and μ_s', respectively)[3]. In addition, when using the reflectance geometry, the mean depth reached by the photons is encoded in their arrival time. Indeed, the later the photons are re-emitted, the longer is their path-length, thus the higher is the probability they probed a deep region of the tissue. For those two reasons, the TD approach is claimed to have a higher information content with respect to CW one, in particular if a single source-detector distance is used.

Within the TD acquisition, the so called "short or null source-detector distance approach"[4] (i.e. injection and collection fibers are apart of few mm or in the same point) allows to increase the number of photons detected at any time as well as to improve the spatial resolution and the contrast produced by localized perturbations at all photon arrival times. The main drawback of this technique is the large increase of the "early photons" (i.e. those photons that are reflected or scarcely diffused, thus not bringing any useful information) which can cause the saturation (or even the damage) of the detector. To reject this peak of early photons, a detector which can be turned on in few hundreds of ps is needed, so as to acquire only late photons (the so called "fast-gated" technique). Additionally, the possibility to acquire only a portion of the DTOF allows to increase the dynamic range of the acquisition, thus reaching up to 7 decades (see Ref.[5] for details). It has been demonstrated in literature the improvement given by the fast-gated technique in spatial resolution, penetration depth and also quantification[6–8].

In the last years, a great technological improvement for both TD source and detector[9] has been done thus pushing toward the use of TD-approach for wearable devices.

On the other hand, several groups work on the development of bioresorbable materials in order to create devices that, once implanted and exploited, are then destroyed by the human body without leaving any harmful residual. If bioresorbable stitches are nowadays a common procedure for surgeries, optical bioresorbable components are attracting the attention of many scientists for their potentialities. More in detail, several works have been published presenting bioresorbable fibers and devices suitable for implant[10–14]. Among the different solutions proposed, calcium-phosphate glasses (CPGs) had been widely validated as a bioresorbable and biocompatible material for application in both hard and soft tissue engineering[15,16]. In Ref.[17], CPGs have been proposed also as a material for bioresorbable optical fibers. Indeed, they show a good biocompatibility and very low batch-to-batch variability and, thanks to the study of optimal composition, it was possible to overcome their main limitation such as high attenuation and poor transparency[16] obtaining an attenuation loss coefficient of 1.9 and 4.7 dB m^{-1} (at 1300 and 633 nm respectively) which are 1 or 2 orders of magnitude better than the values reported for other bioresorbable fibers.

The availability of bioresorbable fibers paves the path to new devices for clinical applications. Indeed, they could be implanted during the surgery and then left in place to periodically monitor the follow-up of the patient, studying the evolution of possible healing or inflammation processes. On the other hand, bioresorbable fibers can be successfully exploited for interstitial photodynamic and photothermal therapies with in-situ irradiation[18,19].

To this extent, it is fundamental firstly to assess the aptness of bioresorbable fibers for TD spectroscopy. To achieve this first objective we used internationally agreed protocols for performance assessment of TD instrument (such as BIP[20] and MEDPHOT[21] ones). We then challenged the system based on bioresorbable fibers in the retrieval of the spectrum of both absorption and reduced scattering coefficient of an *ex-vivo* sample (chicken breast). As a last step toward implantable devices, we tried to acquire measurements in the single-fiber configuration[22]. The single fiber approach, indeed, will lessen the impact of the implant (only one fiber will be implanted) and allows to exploit the advantages given by the use of the "null source-detector distance approach".

2. MATERIAL AND METHODS

2.1 Suitability of bioresorbable fibers for TD measurements: phantom measurements

The suitability of the bioresorbable fibers for TD-diffuse optics has been assessed using tests defined within an internationally recognized protocol. More in detail, we made use of the Instrument Response Function (IRF) test (BIP protocol) to check the absence of possible fluorescence or back reflections caused by the bioresorbable fibers which can

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be detrimental for TD-measurement. Due to the rigidity of the fibers, the IRF was measured putting collection and injection fibers close one to the other onto a piece of white paper, which acts as a diffuser.

In addition to IRF recording, we applied the MEDPHOT test to assess the capability of the system based on bioresorbable fibers to properly retrieve the optical properties of the medium. We made use of liquid phantoms (based on water) whose optical properties were obtained adding calibrated quantities of Indian ink (as absorber) and Intralipid (acting as a scatterer). After the phantom test, we moved to an *ex-vivo* sample to check the capability of the current system based on bioresorbable fibers to retrieve the spectrum of both absorption and scattering over a wide range (600-1100 nm). For both MEDPHOT and *ex-vivo* tests, we used a 20 mm interfiber distance and the fibers were about 3 cm in depth with respect to the surface of the sample. The measurements were carried on using setups and procedures presented with more details in Ref.[23].

In all cases, we used bioresorable fibers with a core diameter of 100 µm (cladding: 300 µm) and a numerical aperture of 0.17 at 633 nm. They have been produced using the procedure fully described in Ref.[23].

2.2 Single fiber measurements

To go toward the use of a single bioresorbable fiber, we modified the setup used for previously described measurements. The new schematics of the setup is reported in Figure 1. The laser source was a supercontinuum laser (SuperK Extreme, NKT Photonics, Denmark) working at 40 MHz repetition rate. The monochromatic light was then attenuated by means of a calibrated Variable Optical Attenuator and coupled to one of the input fiber of the optical coupler (Fiber Optic Network Technology Co, Canada). Half of the signal was sent to a tank containing black ink to be sure to minimize the back reflection at the fiber tip. The other half of the input signal was sent to the phantom ("sample" in Figure 1) through one of the output fibers, which was then coupled to the bioresorbable fiber (0.25 m long) using a 3-axis micrometric translation stage. The collected photons are then delivered to the detector through the fourth branch of the coupler which is directly connected to its focusing optics. All input and output fibers of the optical coupler were 2.5 m long.

The detector used is a fast-gated SPAD (100 µm diameter active area), which can be turned on and off in less than 200 ps. When a photon impinges on the detector, the generated avalanche is detected and a concurrent "start" signal is generated. This signal is fed to the Time-Correlated Single Photon Counting[24] (TCSPC) board (SPC 130, Becker and Hickl GmbH) as a "start" signal. On the other hand, the "stop" one is sent to the TCSPC board from the laser which generates an electrical pulse ("sync") synchronous with the generation of optical pulse. The FG-SPAD gate's opening time was set using the laser "sync" signal properly delayed by means of an home-made transmission-line-based delayer (not shown in Figure 1). For the characterization, the sample was substituted with a piece of white paper to perform the IRF of the system.

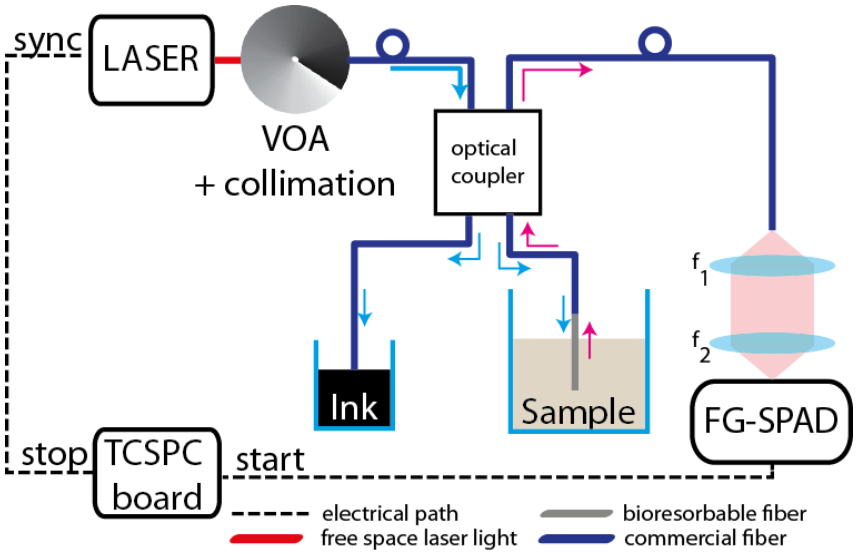

Figure 1. Schematics of the setup used for single-fiber measurements.

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3. RESULTS AND DISCUSSION

3.1 Suitability of bioresorbable fibers for TD measurements: phantom and *ex-vivo* measurements

The basic characterization of bioresorbable fibers started with the IRF acquisition. As an example, in Figure 2 is reported the IRF recorded with the supercontinuum laser at 820 nm where it is clearly noticeable the absence of any fluorescence or back reflection issue. It has to be noted that the presence of the exponential decay after the IRF peak is due to the diffusion tail[25] of the detector used. The same behavior was observed in all wavelength range (data not shown).

For what concerns the MEDPHOT protocol, the results are reported in Figure 3(a-d). In the graphs are reported the measured ("meas.") values of absorption and reduced scattering coefficients against the true ones. Figure 3(a) and (d) demonstrate that the system is linear in recording absorption and reduced scattering values, for a phantom with $\mu_a \leq 0.690$ cm^{-1}. Furthermore, there is a good independency in recovering scattering and absorption parameters (see Figure 3(b) and (c)), meaning that the recovered absorption/scattering value is pretty stable when changing the scattering/absorption coefficient of the measured phantom). Deviations from ideality are probably due to the low signal, which impairs the fitting procedure.

With those two tests (IRF and MEDPHOT protocols) we assessed the suitability of bioresorbable fibers for TD diffuse optical spectroscopy. Hence we tested our system with an *ex-vivo* measurement on a chicken breast. The absorption and reduced scattering spectra recovered are reported in Figure 3(e-f). It is possible to notice the presence of two peaks at 550 nm and 970 nm: the former is due to the presence of deoxy-hemoglobin, while the latter to the water[26]. For what concerns the reduced scattering, its value is low in amplitude (< 3 cm^{-1}) and, as expected, it shows an overall decrease for longer wavelength. The two peaks at 550 and 970 nm are fingerprint of absorption-to-scattering coupling, which is due to the failure of the diffusion approximation used for fitting procedure.

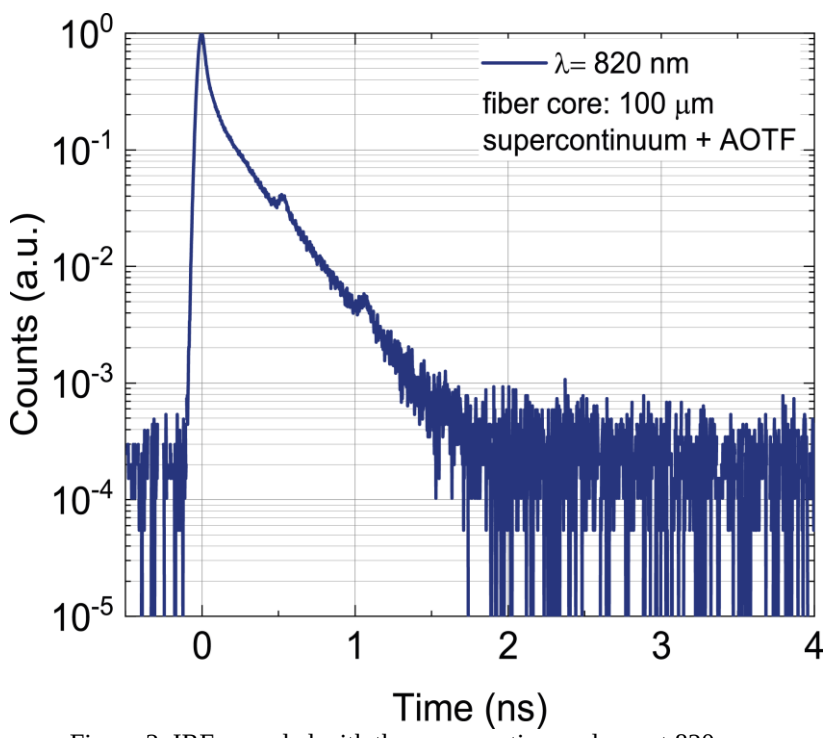

Figure 2. IRF recorded with the supercontinuum laser at 820 nm.

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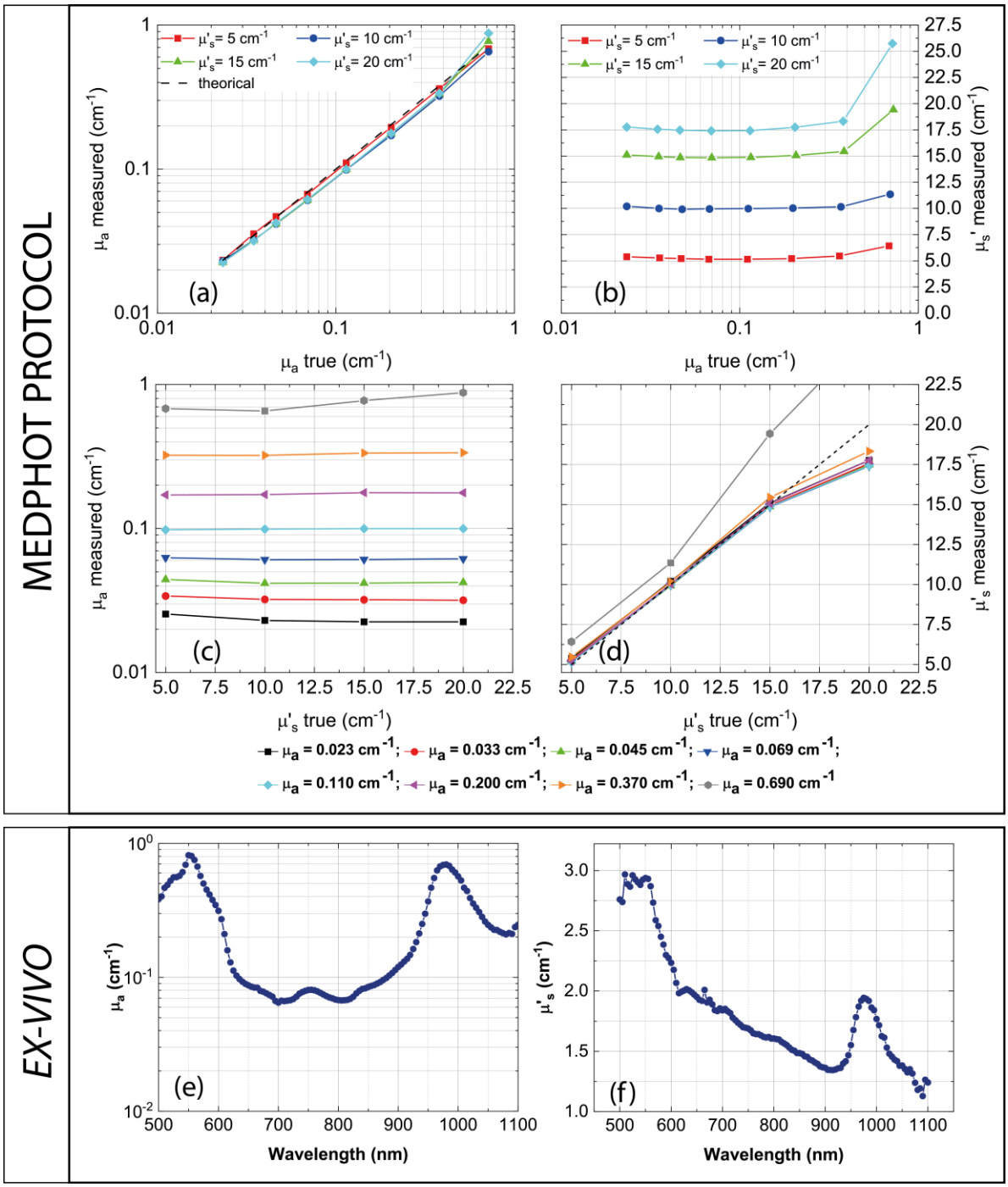

Figure 3. (a-b) MEDPHOT linearity plots; (c-d) recovered spectra of a chicken breast.

3.2 Single fiber measurements

Figure 4 represents a sketch of the recorded shape of signal, containing the IRF together with other non-idealities. The "A" peak represents the pulse created by the Fresnel reflection of the laser pulse at the connection between the coupler's fiber and the tip of the bioresorbable fiber. 2.5 ns later (corresponding to a round-trip of the 0.25 m long bioresorbable fiber), the "B" peak is recorded: this corresponds to the useful IRF (i.e. the reflection at the tip of the bioresorbable fiber coupled with the paper).

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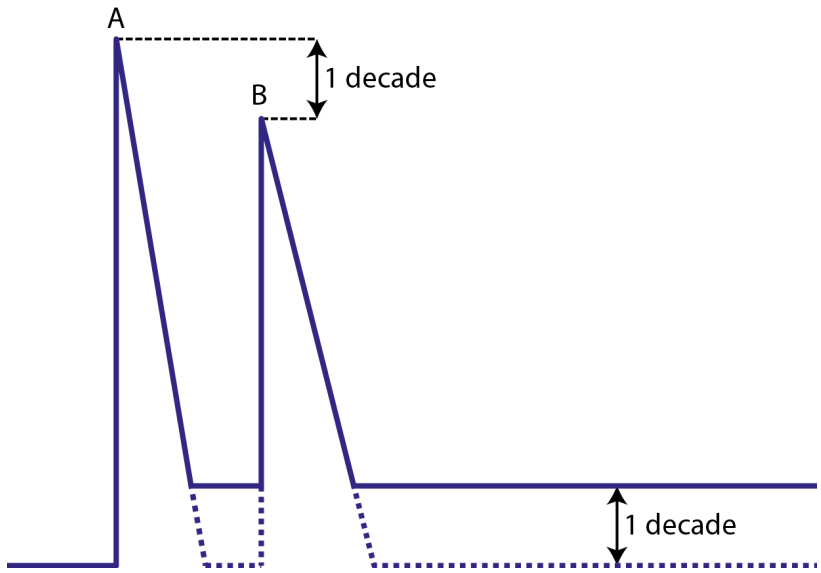

Figure 4. Schematic representation of the signal collected at the TCSPC board for 1 period of the laser (25 ns).

It is worth noting that the peak "B" has an amplitude which is about 1 decade lower than "A" peak, due to the losses of the biofiber itself and to the amount of light collected at the tip of the bioresorbable fiber. The flat region after "B" peak represents the useful region that can be used for measurements. It is dominated by the so called "memory effect" of the detector (i.e. a long time constant decay tail, which limits further increase in the dynamic range operating in time-gated regime[27]). Indeed, the presence of the strong reflection "A" before the main signal "B" triggers the "memory effect", thus increasing the baseline signal level in the useful region and reducing the dynamic range available for measurements (solid line -real case with "memory effect"- *vs*. dashed line -ideal case with whole dynamic range available- in Figure 4). Single-fiber measurements resulted currently unfeasible due to this issue since, as reported in Ref[22], the information about optical properties are concentrated in the bottom part of the DTOF, several orders of magnitude below the IRF peak and close to the "memory effect" level. Currently, our efforts are oriented to the reduction of the amplitude of the peak "A" reflection to increase the dynamic range of the IRF.

4. CONCLUSIONS AND FUTURE PERSPECTIVES

We firstly investigated the suitability of bioresorbable optical fibers for TD diffuse optical spectroscopy. We made use of some tests of BIP and MEDPHOT protocols to assess the suitability of the IRF of the system and its capability to properly recover optical properties of a homogeneous medium. Additionally, we also challenged our system with an *ex-vivo* measurement on a chicken breast.

After a first validation of the suitability of bioresorbable fibers for TD diffuse optical spectroscopy, we investigated the possibility to use a single-fiber approach. Preliminary measurements have enlightened an issue due the coupling between a standard fiber and a bioresorbable one. This issue causes a decrease of the dynamic range of the system, thus preventing the measurement. We are currently exploring technical solutions to improve the coupling of the light between standard and bioresorbable fibers to solve this problem.

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