Use of bioresorbable fibers for interstitial time-domain diffuse optical spectroscopy using fast-gating

Use of Bioresorbable fibers for Interstitial Time-Domain Diffuse Optical Spectroscopy using Fast-Gating

Vamshi Damagatla[a], Nadia G. Boetti[b], Laura Di Sieno[a], Diego Pugliese[c], Davide Janner[c], Alberto Dalla Mora[a], and Antonio Pifferi[a]

[a]Politecnico di Milano, Dipartimento di Fisica, Milano, Italy
[b]Fondazione LINKS-Leading Innovation and Knowledge for Society, Torino, Italy
[c]Politecnico di Torino, Dipartimento di Scienza Applicata e Tecnologia and INSTM research unit, Torino, Italy

ABSTRACT

Bioresorbable materials have gained interest for implantable optical components such as fibers for medical devices and have been demonstrated as suitable to perform diffuse optical measurements. In this work, we demonstrate interstitial, broadband, time-domain diffuse optical spectroscopy measurements using bioresorbable fibers, by employing a single-photon avalanche diode operated in an ultrafast time-gate mode for photon detection. Using tissue equivalent liquid phantoms, we test the system absorption linearity as per the MEDPHOT protocol and demonstrate the scattering independent absorption retrieval of the water spectrum in the 600-920 nm range. Consequently, we also attempt to distinguish the spectral changes due to the presence of optically denser speck inclusion in a tissue equivalent liquid phantom.

1. INTRODUCTION

Interstitial Fiber Spectroscopy (IFS) is an attractive research area for use as guidance tool in minimally invasive *in vivo* surgical procedures[1] and together with Time-Domain Diffuse Optical Spectroscopy (TD-DOS) — based on the detection of the Distribution of Time-of-Flight (DTOF) of photons in the tissue — offers certain advantages like extended probed depth, disentanglement of optical coefficients, independence from amplitude fluctuations. It has the potential to support with functional volumetric assessment in endoscopic procedures, perform needle-based 'optical biopsies', help in characterization and monitoring of photodynamic therapy, and help in the shift to minimally invasive surgery. An exciting way to perform these is with the use of biocompatible and bioresorbable optical fibers which offer the novelty of implantation in the human body for monitoring of therapy, tissue healing, medication uptake among many others. Studies have been performed, and the feasibility of bioresorbable fibers for TD-DOS measurements at standard source detector separations has been shown previously.[2]

However, to test their use as implantable devices, we also need to perform IFS measurements using a Null Source-Detector Separation (NSDS) approach. To overcome the drawback of the overwhelming number of early photons in NSDS which outnumber the late photons by many orders of magnitude and saturate standard detectors, we have exploited an in house built, Single Photon Avalanche Diode (SPAD) running in an ultrafast gated mode to quench the early photon burst and acquire the DTOFs with a high dynamic range.[3]

2. MATERIALS AND METHODOLOGY

The Phosphate based bioresorbable fiber was manufactured by tuning core and cladding phosphate glass compositions so as to get a numerical aperture of 0.20. The stretched core glass was placed in the extruded cladding glass tube to obtain by rod-in-tube technique a core/cladding preform and the optical fiber was drawn using an in house developed drawing tower with core/cladding dimensions of 200/400 µm.

Picosecond pulses (40MHz repetition rate) from a supercontinuum laser (SuperK Extreme, NKT Photonics) were spatially dispersed to obtain a broadband spectrum (600-980 nm) and were injected into a 50/125 µm graded index silica fiber which was mechanically coupled to the bioresorbable fiber to be incident on the liquid phantoms i.e. calibrated aqueous solutions of Intralipid (IL) and India ink with desired optical properties.[4] As shown in Figure 1(a), the diffusely reflected photons were again detected with a 200 µm core bioresorbable fiber

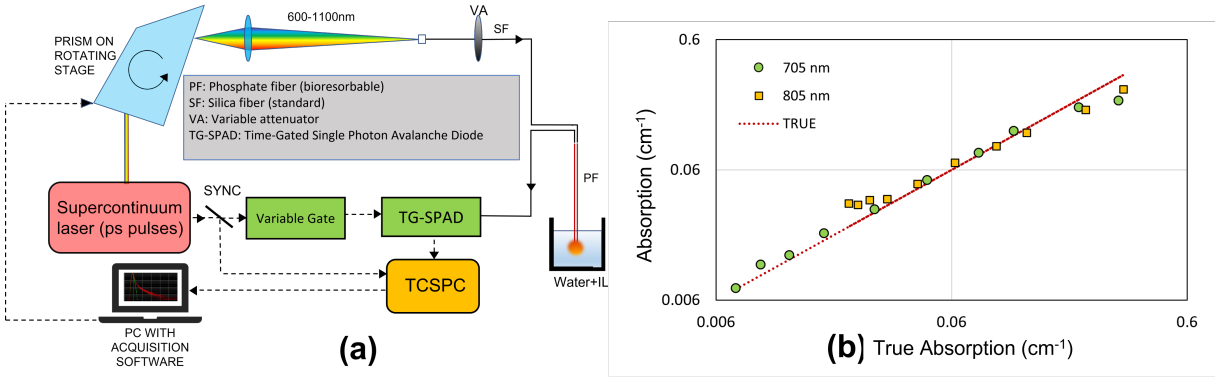

Figure 1. (a) Experimental setup; solid lines are optical paths and dashed lines are electronic paths; (b) absorption linearity using Intralipid phantoms

mechanically coupled with a silica fiber and were incident on the SPAD (100 µm active area diameter). Three types of measurements were performed - 1) to test the system linearity[5] 2) retrieve the water absorption spectrum and study the effect of variation of scattering (μ_s') on recovered absorption (μ_a) 3) to retrieve the changes in spectra upon approaching an compositionally different inclusion in a homogeneous medium.

The Instrument Response Function (IRF) was taken in reflectance mode through a diffusing teflon layer atop a glass surface (reflecting). The DTOFs were acquired as slices of the pulse, obtained by fast gating the detector in steps of 50 ps and consequently increasing the power for each gate by the use of the Variable Attenuator (VA), so as to reach a set photon count goal (350000 counts in this case). In total 40 gates were applied to get a total delay of 2 ns. The curves were then normalized based on the power calibration of the VA and joined together to obtain a reconstructed DTOF with about 5 decades of dynamic range.[3] The measurement DTOFs were obtained similarly but using only 20 gates in steps of 100 ps width. The optical properties are recovered by solving the inverse problem for the reconstructed curves - fitting the convolution of the IRF and the analytical solution of the Diffusion Equation (DE) in a homogeneous infinite medium (Eq. 1), to the experimental data. From (Eq. 1), we can see that at source-detector separation (ρ) = 0, the dependence of fluence (ϕ) on μ_s'(=1/3D) theoretically vanishes and thus, we can attempt scattering independent μ_a retrieval by 'selecting' only the late photons for fitting from the tail of the DTOF.

$$\phi(r,t) = \frac{v}{(4\pi Dvt)^{(3/2)}} \exp\left(-\frac{\rho^2}{4Dvt}\right) \exp(-\mu_a vt) \qquad ; where \quad v = Speed\ of\ light \tag{1}$$

For the linearity measurements, water+IL phantoms were prepared with nominal scattering of 10 cm^{-1} (750 nm) and ink was added to increase the absorption. To test the scattering independence of absorption retrieval, the scattering of the phantom was changed by adding calibrated quantities of Intralipid to obtain μ_s'=10, 15, 20 cm^{-1}.[4] Finally, a 2 x 2 x 2 cm cubic speck inclusion (porcine muscle) was placed in an Intralipid phantom of μ_s'=10 cm^{-1} and no added absorbers (nominal values at 750nm). The spectra were then measured with the phosphate fibers while approaching the inclusion at various distances, beginning from 20 mm to the final position on the surface of the speck inclusion.

3. RESULTS AND DISCUSSION

The absorption linearity was tested at two different wavelengths of 705 and 805 nm and the system was found to be linear (Figure 1(b)) over a combined μ_a range of 0.007-0.35 cm^{-1} with less than 13% relative error (barring a few outliers). Also, we were able to recover the water spectrum in the range of 700-920 nm, within a 20% error and consequently, as shown in Figure 2(a) we also found marginal variation in absorption upon changing the scattering values for μ_s'=10 cm^{-1} or more, confirming the scattering independent absorption retrieval proposal from the late photons. Finally, Figure 2(b) shows the change in the shape of the spectra as one moves towards the inclusion - from 20 mm away upto its surface. At distances away from the inclusion (20 mm) we obtain a spectrum

similar to that water, whose absorption increases as we go into the NIR region, and this can be attributed to the presence of the homogeneous aqueous liquid phantom. However, as we go closer to the inclusion, there is not just an overall increase in the absorption, but also a change in the shape of the spectrum, specifically below 700 nm. We observe a significant increase in the μ_a below 700 nm and this can be attributed to the presence of haemoglobin and other blood components in the speck inclusion (the exact composition of which is unknown due to obvious changes while processing, storage, etc).

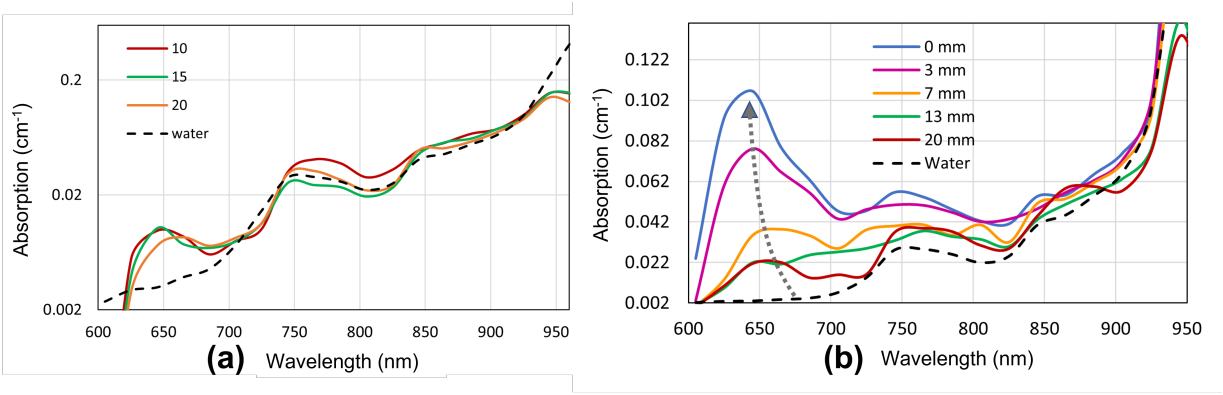

Figure 2. (a) Absorption spectrum of water+Intralipid solution with variation of μ_s', as compared to that of pure water from literature; (b) Variation of spectra due to a cubic speck inclusion in an Intralipid based liquid phantom, the arrow represents the direction of approach to the inclusion

4. CONCLUSIONS

We have demonstrated broadband interstitial TD-DOS measurements using bioresorbable fibers in NSDS regime by using an ultrafast gated SPAD for detection. By obtaining about 50 dB of dynamic raange through gating, we were able to test the system's absorption linearity and were able recover the absorption independent of the scattering. We also were able to distinguish spectrally, the presence of a meat inclusion in aqueous phantom by observing the change in the spectrum due presence of haemoglobin.

ACKNOWLEDGEMENTS

The authors would like to acknowledge funding from the PHAST-ETN project under European Union's Horizon 2020 research and innovation programme (Marie Sklodowska-Curie grant agreement No. 860185).

REFERENCES

[1] Svensson, T., Andersson-Engels, S., Einarsdóttír, M., and Svanberg, K., "In vivo optical characterization of human prostate tissue using near-infrared time-resolved spectroscopy," *Journal of Biomedical Optics* **12**, 014022 (2007).

[2] Sieno, L. D., Boetti, N. G., Mora, A. D., Pugliese, D., Farina, A., Sekar, S. K. V., Ceci-Ginistrelli, E., Janner, D., Pifferi, A., and Milanese, D., "Towards the use of bioresorbable fibers in time-domain diffuse optics," *Journal of Biophotonics* **11** (1 2018).

[3] Dalla Mora, A., Tosi, A., Zappa, F., Cova, S., Contini, D., Pifferi, A., Spinelli, L., Torricelli, A., and Cubeddu, R., "Fast-gated single-photon avalanche diode for wide dynamic range near infrared spectroscopy," *IEEE Journal of Selected Topics in Quantum Electronics* **16**(4), 1023–1030 (2009).

[4] Spinelli, L., Botwicz, M., Zolek, N., Kacprzak, M., Milej, D., Sawosz, P., Liebert, A., Weigel, U., Durduran, T., Foschum, F., et al., "Determination of reference values for optical properties of liquid phantoms based on intralipid and india ink," *Biomedical optics express* **5**(7), 2037–2053 (2014).

[5] Pifferi, A., Torricelli, A., Bassi, A., Taroni, P., Cubeddu, R., Wabnitz, H., Grosenick, D., Möller, M., Macdonald, R., Swartling, J., et al., "Performance assessment of photon migration instruments: the medphot protocol," *Applied optics* **44**(11), 2104–2114 (2005).