TITLE PAGE

Citation Format:

1. S. K. V. Sekar, A. Farina, E. Martinenghi, A. Dalla Mora, P. Taroni, A. Pifferi, T. Durduran, M. Pagliazzi, C. Lindner, P. Farzam, M. Mora, M. Squarcia, and A. Urbano-Ispizua, "Broadband Time-Resolved Diffuse Optical Spectrometer for Clinical Diagnostics: Characterization and in-vivo Measurements in the 600-1350 nm spectral range," in *DIFFUSE OPTICAL IMAGING V*, Dehghani, H and Taroni, P, ed., Proceedings of SPIE, Vol. 9538, 95380R, 2015.

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DOI abstract link:

http://dx.doi.org/10.1117/12.2183835

Broadband Time-Resolved Diffuse Optical Spectrometer for Clinical Diagnostics: Characterization and in-vivo Measurements in the 600-1350 nm spectral range.

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ABSTRACT

We report on the design, performance assessment, and first in vivo measurement of a Time-Resolved Diffuse Optical system for broadband (600-1350 nm) nm measurement of absorption and scattering spectra of biological tissues for non-invasive clinical diagnostics. Two strategies to reduce drift and enhance responsivity are adopted. The system was enrolled in a first in vivo test phase on healthy volunteers, carrying out non-invasive, in vivo quantification of key tissue constituents (oxy- and deoxy-hemoglobin, water, lipids, collagen) and tissue micro-structure (scatterer size and density).

Keywords: time-resolved spectroscopy, scattering, absorption, detector, MEDPHOT protocol, silicon photomultiplier (SiPM), in-vivo.

1. INTRODUCTION

Diffuse optical spectroscopy as a non-invasive tool is being applied with increasing success to investigate highly scattering media. Powered by the evolution of novel lasers and detectors the field of photon migration has rapidly grown in numerous applications in the field of non-invasive characterisation of biological media such as optical mammography[1,2]and brain oxymetry[4], in vivo spectroscopy of biological tissue, investigation of bone, bone marrow[5] and joint pathologies[6], and so on. In particular, time-domain approaches decouple absorption from scattering contributions, which in case of biological media can be related to the physiological or pathological status of the tissue and can be effectively used for functional studies and non-invasive clinical diagnostics. Moreover, in most in-vivo studies due to limited number of wavelengths, water, oxy-, and deoxy-hemoglobin are assumed as the only absorbers while other significant absorbers in tissue specifically in bone could be the lipid and the bone mineral. Taking advantage of broadband spectroscopy, we can decouple the effect of other absorbers in the tissue, which provides valuable biological information.

Most of the broadband systems developed in the literature, due to lack of broadband detectors and sources cover only a part[7] of the therapeutic window (600-1200 nm). Additionally, in biological media the range of 900-1000 nm where lipid, water, and collagen show important absorption peaks is quite challenging due to high absorption demanding for high detection responsivity and good temporal resolution. One more important problem faced by time-resolved systems is the uncertainty crept into the estimated values of absorption and scattering due to drift and distortion caused by the laser and the detector. Adopting strategies that makes the system independent of the above mentioned uncertainties can improvise the overall stability and reproducibility of the system.

The aim of the present work is to identify the best detection strategy for developing a time-domain diffusive optical spectroscopic system that operates efficiently over the range of 600-1350 nm along with real time drift and distortion compensation. Moreover, issues such are portability and robustness are addressed in view of clinical use.

Diffuse Optical Imaging V, edited by Hamid Dehghani, Paola Taroni, Proc. of SPIE Vol. 9538, 95380R · © 2015 SPIE · CCC code: 1605-7422/15/$18 · doi: 10.1117/12.2183835

2. MATERIALS AND METHODS

2.1 System setup

Figure 1 shows the schematic diagram of the optical chain of the portable time resolved system. The source is provided by a photonic crystal based supercontinuum fiber laser (SC450, Fianium,UK) with 6 W overall power over a spectral range 450-1750 nm. The pulse width of few picoseconds is generated at a 40 MHz repetition rate. Spectral tunability is achieved by dispersing the source with a Pellin Broca prism and coupling the selected wavelength into fiber.

The system was designed to work efficiently over the range of 600-1350 nm. To have high responsivity[10] over the whole range, two different detectors are used, namely a Silicon Photomultiplier (SiPM) (Hamamatsu S10362-11-050C) driven by a dedicated electronics developed at Politecnico di Milano[11,13] and an InGaAs photomultiplier (Hamamatsu). Exploiting their complementary spectral sensitivity (600-940 nm and 940-1350 nm, respectively) it is possible to cover a wide range with high responsivity. The signal from the sample is selectively directed onto the two detectors using a 45/55 pellicle beam-splitter with the spectral changeover point at 940 nm. Figure 1 shows the overall responsivity of the combined detector system.

To compensate for the temporal drift and keep track of the overall laser and detector time response, a reference line is inserted, acquiring the instrumental transfer function (IRF) synchronously with a constant delay with respect to the signal. These strategies are depicted in Figure 1(right).

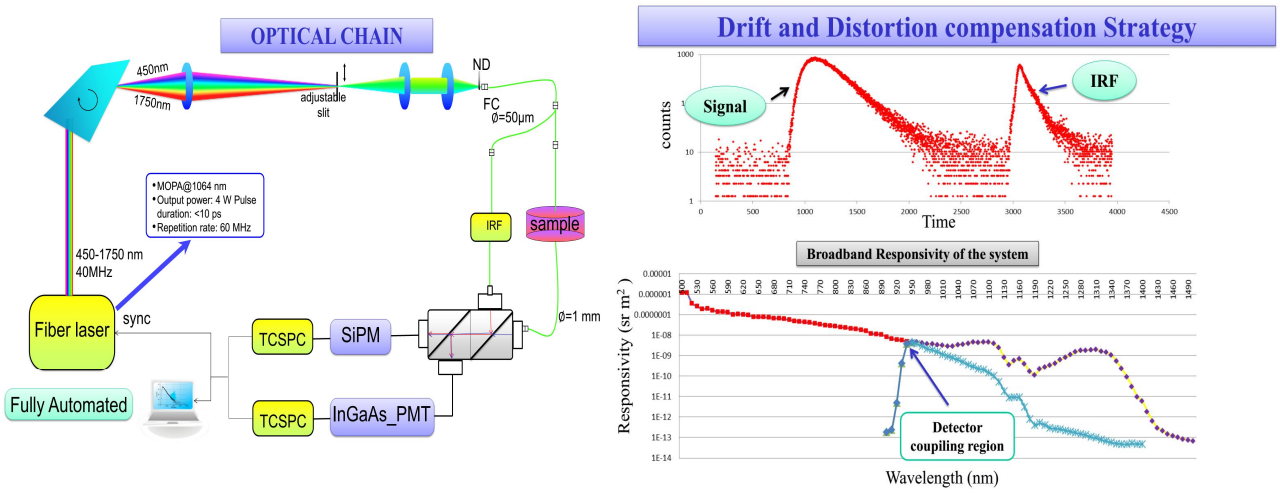


Figure 1: Compensation of drift and distortion by means of simultaneous acquisition of data and IRF (right above); combination of two detectors covering complementary spectra ranges (right below); block diagram of system optical in measurements (left).

2.2 Measurement Protocol

The system performance was assessed by the well-established MEDPHOT[8] protocol, which estimates the system performance in terms of finally extracted parameters of interest (absorption and scattering coefficients) rather than of hardware specification. A total of 16 phantoms were measured, combining in a matrix form, 4 increasing absorption coefficients (0.1, 0.2, 0.3, 0.4 cm^{-1}) with 4 increasing scattering coefficients (5, 10, 15, 20 cm^{-1}). All the assays were performed over the broad operating wavelength range of 600-1350 nm with 10 nm as step size. Reflectance geometry with a source detector separation of 2 cm was employed in the protocol.

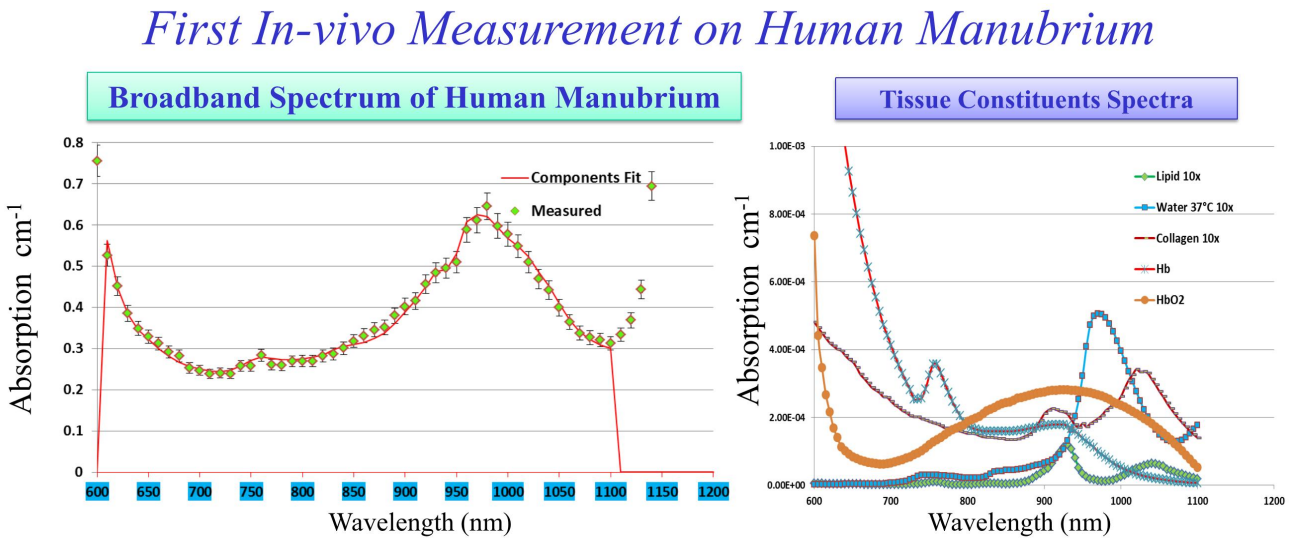
The system was finally enrolled in first in vivo measurements on the human manubrium. Reflectance geometry with 2.5 cm as a source detector separation was used for this measurement. The quantification of tissue constituents was achieved by fitting broadband absorption values with a linear combination of tissue constituent spectra.

3. DATA ANALYSIS

Absorption (μ_a) and reduced scattering coefficient (μ'_s) of experimentally acquired curves at each wavelength were fitted with an analytical solution of the diffusion approximation to the transport equation for a homogeneous semi-infinite medium[9]. Extrapolated boundary conditions were used. Theoretically predicted curves were convolved with the IRF and normalized to the experimentally acquired curve. The fitting range included 80% of peak value on the rising edge of the curve and 1% on the tail.

4. RESULTS AND CONCLUSION

The developed system was successfully tested by its first measurements on the human manubrium. The scatter plot in figure 2 (left) displays the experimentally measured values, where the solid line represents the linear combination of tissue constituent spectra. The percentage tissue constituents water(H2O), lipid, collagen and oxy, deoxy- hemoglobin (HbO_2 and Hb), total hemoglobin(tHb) in micromolar(uM) concentrations were quantified and are tabulated in figure 2(table bottom). The absorption spectrum of individual key tissue constituents used for the extraction of their concentrations from measured spectrum is shown in the figure2 (right). Though the system can perform measurements over 600-1350nm range, the spectrum of in vivo measurement was truncated at 1200 nm owing to high water absorption above 1150 nm.



•The above spectrum shows the secondary fit results of first invivo data with components spectrum

Hb[uM]	HbO2[uM]	Lipid[%]	H2O[%]	Collagen[%]	Background[cm-1]	tHb(uM)	StO2
6.5	48.2	43.9	37.5	18.5	0.1	54	88%

Figure 2: First Broadband in vivo spectrum of measured(green squares) and fitted(red solid line) of human manubrium(left), Tissue constituents spectra(right), fitted human manubrium tissue constituent values(table bottom).

In conclusion, we developed and characterised the first portable hybrid clinical system for time-resolved diffuse optical spectroscopy covering the range of 600-1350 nm. The first in vivo broadband time-resolved measurement on the human manubrium is presented, revealing the spectral features of the key absorption constituents in this wide range and permitting to quantify their content. This instrument can be used in exploratory clinical studies aiming at full spectral characterisation of either pathological or physiological conditions. Translation to point-of-care, compact and cost-effective portable devices is the feasible in the next years due to the impressive growth of photonics components [12]

ACKNOWLEDGMENTS

The research leading to these results has partially received funding from the EC's Seventh Framework Programme under the projects LASERLAB-EUROPE (grant agreement n. 284464,) and OILTEBIA (grant agreement n. 317526), Fundacio Cellex Barcelona, Marie Curie IRG (FP7, RTPAMON), Ministerio de Economia y Competitividad (PHOTOSTROKE), Obra Social La Caixa (LlumMedBCN), LASERLAB- EUROPE III (BIOPTHICAL).

REFERENCES

[1] Torricelli A., et al. , "Use of a nonlinear perturbation approach for *in vivo* breast lesion characterization by multiwavelength time-resolved optical mammography," Opt. Express 11(8), 853–867 (2003).

[2] Taroni, P., Pifferi, A., Salvagnini, E., Spinelli, L., Torricelli, A., Cubeddu, R. Seven-wavelength time-resolved optical mammography extending beyond 1000 nm for breast collagen quantification (2009) Optics Express, 17 (18), pp. 15932-15946.

[3] Torricelli, A., Quaresima, V., Pifferi, A., Biscotti, G., Spinelli, L., Taroni, P., Ferrari, M., Cubeddu, R. Mapping of calf muscle oxygenation and haemoglobin content during dynamic plantar flexion exercise by multi-channel time-resolved near-infrared spectroscopy (2004) Physics in Medicine and Biology, 49 (5), pp. 685-699.

[4] De Blasi R. A., et al. , "Cerebral and muscle oxygen saturation measurement by frequency-domain near-infrared spectrometer," Med. Biol. Eng. Comput. 33(2), 228–230 (1995).

[5] Farzam P, et al. , "Noninvasive characterization of the healthy human manubrium using diffuse optical spectroscopies", Physiol Meas 35, 1469-1491 (2014).

[6] Hielscher A. H., et al. , "Frequency-domain optical tomographic imaging of arthritic finger joints," IEEE Trans. Instrum. Meas. 30(10), 1725–1736 (2011).

[7] Pifferi, A. Torricelli, P. Taroni, D. Comelli, A. Bassi, R. Cubeddu, "Fully automated time domain spectrometer for the absorption and scattering characterization of diffusive media," Rev. Sci. Instrum. 78, 053103 (2007).

[8] Pifferi A., et al. , "Performance assessment of photon migration instruments: the MEDPHOT protocol,"Appl. Opt. 44(11), 210414 (2005).

[9] M. S. Patterson, B. Chance, and B. C. Wilson, ''Time resolved reflectance and transmittance for the non-invasive measurement of optical properties,''Appl. Opt.28, 2331–2336 (1989).

[10] Wabnitz, H. *et al.* Performance assessment of time-domain optical brain imagers, part 1: basic instrumental performance protocol. *J. Biomed. Opt.* **19,** 86010 (2014).

[11] A. Dalla Mora, E. Martinenghi, D. Contini, A. Tosi, G. Boso, T. Durduran, S. Arridge, F. Martelli, A. Farina, A. Torricelli, and A. Pifferi, "Fast silicon photomultiplier improves signal harvesting and reduces complexity in time-domain diffuse optics," Opt. Express, vol. 23, no. 11, p. 13937, 2015.]

[12] A. Dalla Mora, D. Contini, S. Arridge, F. Martelli, A. Tosi, G. Boso, A. Farina, T. Durduran, E. Martinenghi, A. Torricelli, and A. Pifferi, "Towards next-generation time-domain diffuse optics for extreme depth penetration and sensitivity," Biomed. Opt. Express, vol. 6, no. 5, p. 1749, 2015.

[13] A. Dalla Mora, D. Contini, S. Arridge, F. Martelli, A. Tosi, G. Boso, A. Farina*, T. Durduran, E. Martinenghi, A. Torricelli, A. Pifferi, "Towards next-generation time-domain diffuse optics for extreme depth penetration and sensitivity," Biomedical Optics Express, vol. 6, no. 5, pp. 1749-1760, 20 April 2015.