First *In-Vivo* Diffuse Optics Application of a Time-Domain Multiwavelength Wearable Optode

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Abstract: The optode is an innovative, ultra-compact (few cm^3) multiwavelength system for time-domain diffuse optics. We present here the first *in-vivo* measurements that benefit from this technological breakthrough. © 2022 The Author(s)

1. The optode and its basic performances

In the last years, thanks to the technological advancement in microelectronics and photonics, time-domain diffuse optics (TD-DO) setup components (pulsed lasers, time-resolved detectors, and timing electronics) are experiencing a reduction in dimensions and costs without a significant degradation in performances. Within this stream, an innovative ultra-compact (few cm^3), stand-alone and multispectral system (the so called optode) for TD-DO has been realized as one of the outcomes of the SOLUS project (funded by the EU) [1]. The goal of the SOLUS project was, indeed, to develop a multi-modal probe where 8 optodes were arranged around the ultrasound (US) transducer used for breast imaging. The morphological information given by the US is complemented with that on composition given by the tomographic reconstruction obtained using the 8 optodes, and with the tissue' stiffness measured with Shear Wave Elastography to improve the differentiation between benignant and malignant lesions in breast.

Independent of the multimodal imaging system, the optode is a breakthrough technology since it represents a stand-alone spectroscopic system which embeds 8 laser diodes (in the wavelength range between 600 and 1100 nm, average power > 1 mW) firing at a repetition rate of 40 MHz, a large-area time-gated digital Silicon PhotoMultiplier (dSiPM) [2] and a Time-to-Digital Converter (TDC) for the recording of the Distribution of Time-of-Flight (DTOF). The optode has been characterized using the BIP, nEUROPt and MEDPHOT protocols [3], which are well assessed in the DO field. The most important features of the optode are surely its very large light harvesting capability (i.e., responsivity test defined in the BIP protocol), which is more than one order of magnitude larger than state-of-the-art systems, and the dynamic range of the Instrument Response Function (IRF) of about 5 decades. Those features make the optode a good choice for measurements aiming to detect a perturbation in depth (e.g., brain imaging or cancer detection in the breast). Several optodes can be combined to create a matrix of sources and detectors. In the minimal configuration of one source and one detector, indeed, we have demonstrated that using the laser sources of one optode and the detector and timing electronics of a second one at 2.7 cm average source-detector distance (SDD) a penetration depth of about 3.5 cm can be reached (data not shown). On the other hand, the MEDPHOT protocol on the retrieval of optical properties (absorption and reduced scattering coefficient, μ_a and μ_s' respectively) of a homogeneous medium demonstrated an acceptable accuracy and good linearity of the smart optode (with SDD = 2.7 cm) on the measurement of μ_a. A strong coupling of μ_a on the measured μ_s' and suboptimal performances in μ_s' accuracy are mitigated by the fact that the tissue composition information is conveyed by μ_a.

In this work we present the results obtained from the use of two optodes (one used only for its laser sources and second one for its detector and TDC with an average SDD of 2.7 cm) for monitoring the concentration of hemoglobin during arterial occlusion and brain activation during a finger tapping exercise.

2. *In-vivo* applications using the optode

To test the use of the optode for *in-vivo* applications we challenged it with an arterial occlusion and a finger tapping exercise. All measurements were approved by the Ethical Committee of Politecnico di Milano and conducted in compliance with the Declaration of Helsinki. Three healthy subjects were enrolled after having given their written informed consent. For the arterial occlusion, a sphygmomanometer's cuff was placed on the subject's arm and inflated at 250 mmHg to block the blood flow. After 120 s of baseline acquisition, the arterial occlusion was kept for 180 s, followed by 180 s of recovery. For what concerns the finger tapping task, the center of the probe was placed on the C3 position, and the subject was asked to perform a standard finger tapping exercise (repeated 5 times)

consisting of 20 s rest, 20 s of finger tapping with the right hand, and 20 s of recovery. The exercise was repeated also with the left hand (i.e., ipsilateral task). To assess the arterial occlusion and brain activation, it is enough to estimate the concentration over time of oxy- and deoxygenated hemoglobin (HbO_2 and HHb respectively) thus two wavelengths (670 and 830 nm) have been used. Only for the brain imaging, for each wavelength, two delays (one early and one late) have been recorded since they statistically bring information about shallower and deeper structures respectively. For each delay, an acquisition time of 1 s was set. The late delay (around 1.6 ns from IRF peak) was chosen as the latest where the achievable count-rate is about 2 Mcps. Having both early and late photons, it is possible to apply the correction reported in Ref. [4] to cancel out the effect of the superficial layer on the deep one. For both measurements, the signal was then divided into time-windows of 0.5 ns width whose position is referred to peak of the IRF. The variation in concentration of HbO_2 and HHb are computed with respect to the rest phase following the Lambert-Beer law.

Figure 1 shows the variation over time of HbO_2 and HHb. As expected, during the occlusion phase, due to the consumption of oxygen, the HbO_2 decreases while HHb increases. The behavior when the occlusion is removed (i.e., both fast increase in HbO_2 and decrease of HHb) is in-line with what reported in literature.

Figure 2 reports the results (averaged over the 5 repetitions, with standard deviation represented by the error bars) obtained on one subject for the exercise done with the controlateral (left panel of Figure 2) and ipsilateral (right panel of Figure 2) hand. The contralateral task clearly shows the fingerprint of a brain activation (i.e., increase in the HbO_2 and fainter decrease of the HHb during the task phase), while no activation is visible in the ipsilateral task. Similar results were obtained also for the other subjects. Thanks to the large responsivity of the detector, it is possible to recognize the fingerprints of brain activation even looking at the single repetition (data not shown).

In conclusion, the optode has shown a great potential in the detection of hemodynamic changes thus being a good candidate for next generation TD-DO instruments for brain imaging. Moreover, to exploit the multiwavelength capability of the optode, we tested it for spectroscopic measurements (e.g., investigation of adipose tissue for preventive purposes) (data not shown).
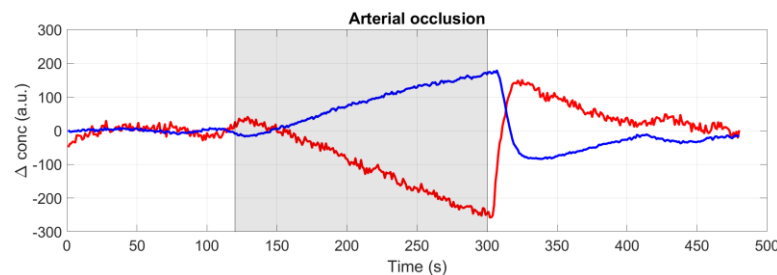

Figure 1. Variation of HbO_2 (red curve) and HHb (blue curve) obtained for arterial occlusion using a time-window of 0.5 - 1 ns. The shadowed region corresponds to the occlusion phase.
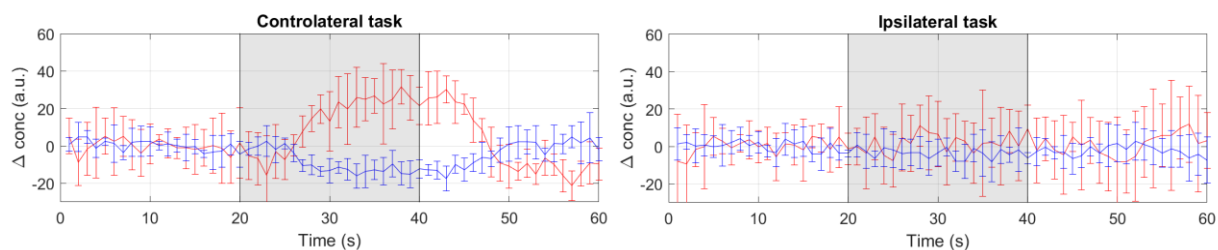

Figure 2. Mean variation of HbO_2 (red) and HHb (blue) obtained for contralateral (left) and ipsilateral (right) finger tapping using a time window of 2.5 - 3 ns. The shadowed region corresponds to the task phase.

Acknowledgements

3. References

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