Performance and reproducibility assessment across multiple time-domain near-infrared spectroscopy device replicas.

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ABSTRACT

Reproducibility between different replicas of the same device is an important aspect in the biomedical research field. Multiple replicas of a dual-wavelength, single-channel *"NIRSBOX"* device have been assembled and characterized and in this work, we present their full performance assessment. Characterization is focused on measurement accuracy, reproducibility, and reliability, following well-defined and widely adopted procedures to assess the quality of diffuse-optics instruments. The results of the performance assessment procedures are promising, showing the possibility of having highly reproducible performance over different TD/NIRS product, feature of paramount importance when it come to comparing result from different instrument, i.e. multicenter studies.

Keywords: TD-NIRS, performance, accuracy, reproducibility, biomedical, medical, covid19, quality assessment, characterization.

1. INTRODUCTION

In the biomedical research field, TD-NIRS is increasingly becoming used in many laboratories and clinics across the world. Its unique features give access to a wide variety of applications. Compared to more common NIRS techniques, such as continuous-wave (CW) NIRS and frequency-domain (FD) NIRS, it stands out thanks to its low sensitivity to motion artifacts and the possibility of retrieving optical features of multilayer diffusive media at different depths using only a single inter-fiber distance. Indeed, when probing the sample in reflection geometry (where output light detection happens few centimeters apart from the injection site) photons arriving later in time carry hemodynamic information from deeper tissue layers as compared to photons arriving earlier. Furthermore, TD-NIRS ability of disentangling absorption and reduced scattering properties make physiological measurements more accurate and reliable.

Lower cost and higher compactness are recently making TD-NIRS devices more accessible to a broader research community [1] and, additionally, their non-invasive recording of absolute concentration of oxygenated and deoxygenated hemoglobin in human tissue makes them an optimal choice in case of muscle and brain hemodynamic monitoring, form neurosciences to intensive care unit applications. As an example, a customized version of the device here presented is currently being used in the development of a multimodal optical platform for assessing microvasculature dysfunction in COVID-19 patients, in the framework of the VASCOVID European-funded research project [2].

The number of users of TD-NIRS technique is however still mainly limited to specifically trained scientists. Other than the lack of easy-to-use commercial devices, the reason for this can be affeered to the absence of agreed standards on both data analysis and device operation. Compared to CW-NIRS devices, which are more common in the global market, TD-NIRS devices can potentially lead to more reproducible results. In fact, retrieval of optical parameters relies on the different temporal shapes of the backscattered laser pulse instead of the difference in collected light intensity, leading to less variability in probe repositioning and less sensitivity to subjects' motion.

The absence of industrial standards for the manufacturing process and assessment of TD-NIRS devices' capabilities makes this task challenging and intriguing at the same time. Clear statements and results related to technical performances and reproducibility of TD-NIRS measuring systems are necessary for manufacturers and users to either control the quality of the production and to have the possibility to decide the most suitable device to be used based upon the declared capabilities. Several studies in literature managed to propose effective protocols and procedures to assess performances of research-grade diffuse optical spectroscopy (DOS) devices. In particular, MEDPHOT, BIP, NEUROPT protocols [3-5], cover a wide range of technical characterizations and are particularly suitable for TD-NIRS devices. In

collaboration with many different laboratories around the world, we have reported a project aiming to assess the performances of different laboratory-grade diffuse optical devices (including TD-NIRS and FD-NIRS technologies) following the BIP, MEDPHOT and NEUROPT protocols [6]. This work will surely be of extreme importance to start highlighting the most critical values in the characterization process and evaluation of diffuse optical devices, although the work carries the drawback of comparing a wide variety of DOS devices, including, different techniques and different technologies, characterized by a very low level of manufacturing reproducibility (being of course laboratory-grade devices). Nevertheless, it is paving the way for standardization within the DOS community.

To the best of our knowledge, quality assessment results have never been reported and compared for several replicas of the same TD-NIRS product.

2. METHODOLOGY AND RESULTS

2.1 The NIRSBOX device

The devices used in this study (*NIRSBOX*, PIONIRS srl, Italy [7]) are compact dual-wavelength TD-NIRS systems. The injection light path comprises two picosecond lasers operating at 685 nm and 830 nm, having temporal pulse-width lower than 200 ps FWHM (full-width at half-maximum). Light is injected/recollected to/from the tissue through optical fibers and a dedicated optical probe having 3 cm inter-fiber distance. Photons are collected by a custom-made wide-area single-photon detection module and DTOF (distribution of times-of-flight) curves are recorded through the TCSPC (time-correlated single-photon counting) technique, with 10 ps resolution. The system can be battery operated and acquired optical parameters and hemodynamics indicators can be processed and shown in real-time.

Figure 1 The NIRSBOX device of which 10 replicas have been tested following common performance assessment protocols.

2.2 Assessment protocols and methodology

In this comparison study, 10 commercial *NIRSBOX* systems have been characterized. In particular, the BIP protocol was followed to compare the basic technical features of the devices (in terms of instrument-response function, stability over time, responsivity, and differential nonlinearity), while the capability of accurate and precise optical parameter retrieval was assessed on a matrix of 32 different solid phantoms (following the MEDPHOT protocol). Due to customized laser wavelengths on 3 devices, only 7 out of 10 devices will be included in the MEDPHOT results comparison, while all 10 devices will be included in the BIP comparison. While only results from the BIP and MEDPHOT protocol will be presented in this manuscript, outcomes from the NEUROPT protocol show the ability of the *NIRSBOX* device to reach a penetration depth of 2.8 cm, in case of a black cylindric inclusion of 25 mm^3 volume in a homogeneous tissue-mimicking phantom (with a source-detector separation of 3 cm). The in-depth analysis will be reported elsewhere.

Data from the different devices were combined to provide specific indicators of: (i) reproducibility performance, (ii) coupling between absorption and scattering measurements and (iii) linearity. The measurements have always been performed using the same probe and optical fiber layout: horizontal 90° light-deflecting S1 probe [7], combined with a

100 um core diameter, 1.5 m long silica graded-index injection fiber bundle (FC/PC connectorized) and a 1.5 m long GI fiber with 1 mm core diameter (FC/PC connectorized). To avoid ambient light disturbances, black absorbing tissue has been used to cover the measuring probe and the phantoms. All measurements (except for stability tests) have been performed after at least 20 minutes of instrument warmup time. Measurements have been performed in one year time, due to the manufacturing timetable and availability of the devices. The tissue-mimicking solid phantom used in this study, produced by Politecnico di Milano [3], do not undergo changes in terms of mechanical structure and optical properties in an equivalent time period.

2.3 Results

From the basic instrument performance protocols (BIP) we firstly assessed the **instrument response function** (IRF) reproducibility across all the devices. IRF reproducibility is a key feature to ensure high measurement performance. Indeed, IRF shape differences could drastically affect the estimation of the sample optical parameters. Ten repeated measurements, at each wavelength, have been acquired with an integration time of 1 s and photon count rate within 700 and 1200 kcps (background counts excluded) for each *NIRSBOX* device. After background noise subtraction, the average over the repetitions have been retrieved for each device. Results were then normalized and aligned on their peak position and averaged across all devices Figure 2. The resulting averaged FWHM was 176.2 ps ± 10.4 ps (mean ± std) at 830 nm and 172.5 ps ± 12.2 ps (mean ± std) at 685 nm.
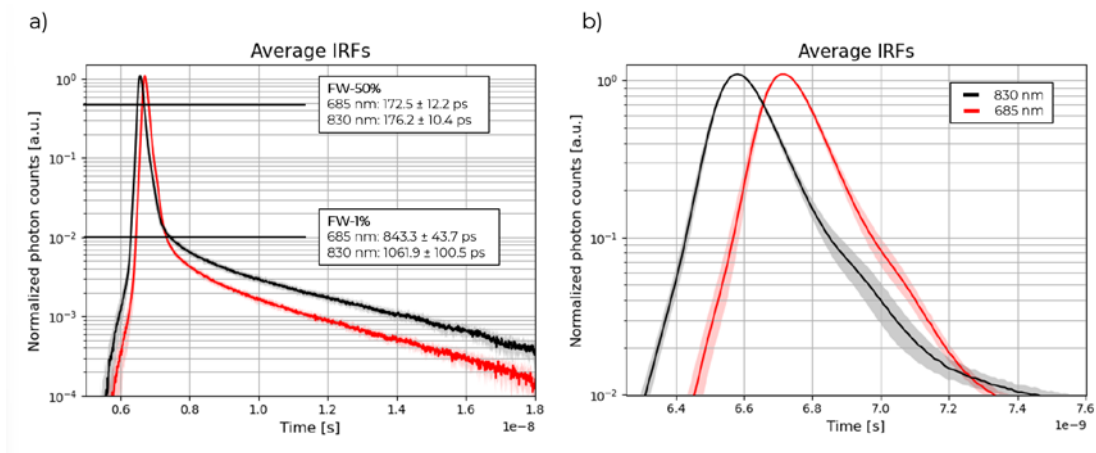

Figure 2 Averaged IRFs over 10 *NIRSBOX* devices. a) Shaded areas report the standard deviation within the averaged IRFs of 10 different devices. Full-width values are reported in "mean value ± standard deviation" at two levels of the curves' amplitudes: fifty percent amplitude (FW-50%) and at 1% amplitude (FW-1%). b) First two decades zoom of the graph in a), to better appreciate the standard deviations of the measurements for each time bin.

The second instrument feature that was tested within the BIP protocol was the device **differential non linearity** (DNL) of the detection channel. The detector active area was irradiated by uncorrelated ambient light, reaching a count rate within 700 and 1200 kcps and 300 repetitions of 1 s integration time have been acquired for each *NIRSBOX* device and each wavelength. Repetitions have been integrated and normalized over the mean value of the uncorrelated light counts' distribution. Normalized DNLs have been averaged across all devices and the standard deviation has been calculated for each time bin. In Figure 3 the average DNL across all devices is reported for both wavelengths: shaded areas indicate the standard deviation of the measurement, while solid lines report the average values. Dashed lines report the acceptable upper and lower limit variation from the mean value (± 10%).
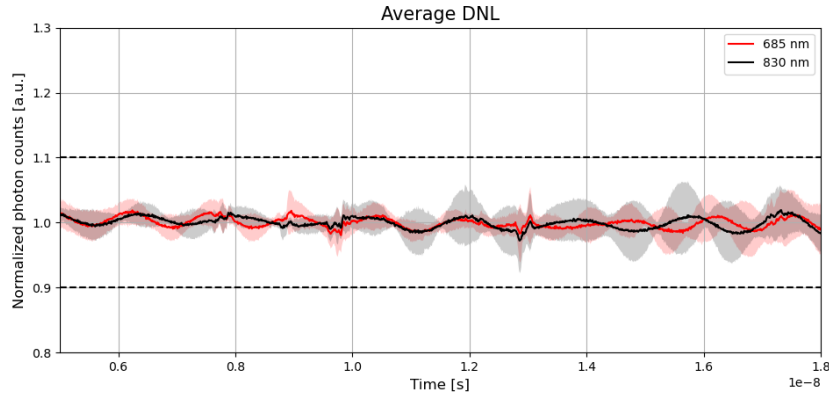
Figure 3 Average DNL over 10 *NIRSBOX* devices. Shaded areas indicate the standard deviation between measurements, while dashed lines report the acceptable upper and lower limit variation from the mean value.

Spurious oscillations in Figure 3 are mainly due to electrical cross-talk phenomena and non-idealities of the photon acquisition chain. Being well within the tolerance range, their presence do not affect optical parameter retrieval capability of the device

The **responsivity**, which represent the light harvesting capability of the system [4], has been assessed for each system and averaged across the fleet of devices. The average responsivity was: $(1.6 \pm 0.4) \times 10^{-8}$ m2sr (mean $\pm$ std) for 685 nm and $(4.7 \pm 2.1) \times 10^{-9}$ m2sr (mean $\pm$ std) for the 830 nm laser wavelength.

These results can provide a hint on the level of the reproducibility of the detection channel collection efficiency within different devices, targeting, in particular, the efficiency of the SiPM module and the replicability of its coupling optics.

Eventually, each device's **stability** has been measured by acquiring repeated DTOF at 1 s integration time for each wavelength for a total time of 3 hours (Figure 4). The probe was placed on the IRFbox [7] ensuring shielding from ambient light. Results have been normalized to the last measured value in terms of integrated counts, FWHM and peak position. The standard deviation over different devices has been calculated over normalized data, to be able to appreciate relative variations.
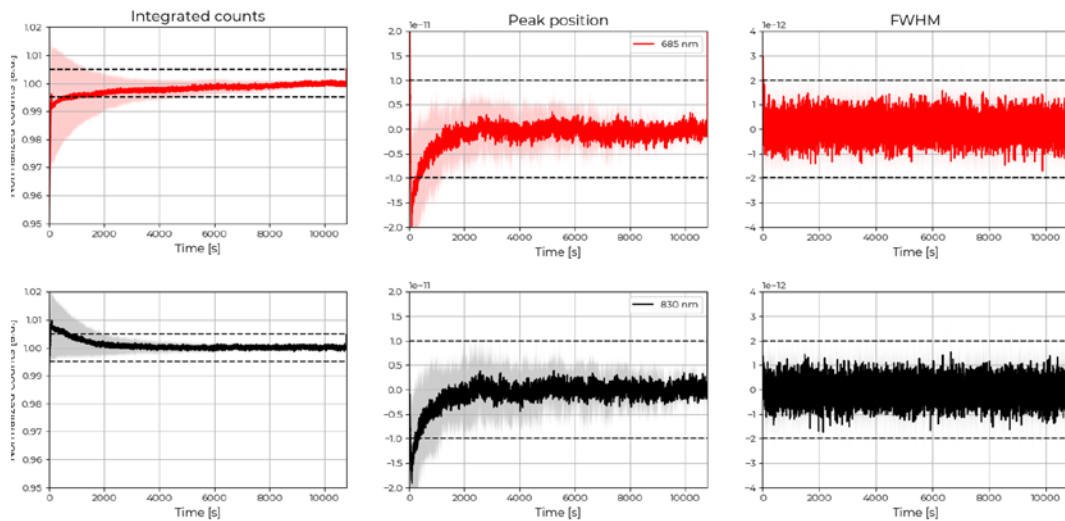

Figure 4 Results on the stability of the main IRF curve features (integrated counts, FWHM and peak position), averaged across 10 *NIRSBOX* devices. Values have been normalized on the last measured DToF, shaded areas report the normalized standard deviation.

Results retrieved from the MEDPHOT protocol are instead highlighting the reproducibility across different devices in retrieving the nominal optical parameters (absorption and reduced scattering coefficients) of known tissue-mimicking phantoms. The summarized comparison is reported in Figure 5.
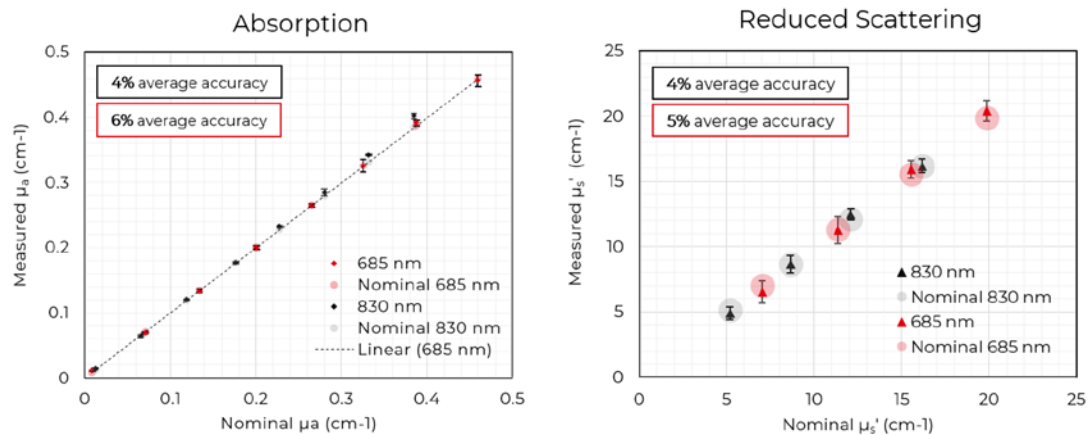

Figure 5 Average results of the METPHOT protocol across 7 different *NIRSBOX* devices. Filled dots represent the measured values while shaded discs are centered on the phantom's nominal values and have a radius equal to their average uncertainty. Error bars represent the standard deviation of the measured value across all devices. Absorption results are on the left and scattering on the right graph.

The accuracy is good over all phantom values of the MEPHOT protocol. It is even improved from what usually results from one single device, meaning that oscillations are possible in the single device but the average value converges to the nominal one (with limited deviation). Vertical error bars represent the standard deviation of the measured value across all devices while shaded discs are centered on the nominal phantom value and the disk radius reports its uncertainty values retrieved by state-of-the-art device used to characterize the phantom matrix [8]. From the graphs in Figure 5, it is possible to see that the acquisitions across all devices are highly reproducible, with error bars comparable to the error in evaluating the nominal phantom's values. Linearity is also verified to be in line with state-of-the-art systems. It is possible to appreciate that for both wavelengths, the absorption variation follows very well the trend of the nominal values (dashed line). The same conclusions can be deducted from the graph of the reduced scattering coefficient results.

3. CONCLUSION

In this work, 10 replicas of a commercial TD-NIRS device have been tested and characterized. Results and comparisons across them showed a very high level of reproducibility on the basic instrument performances and high accuracy in the retrieval of optical parameters on a well-characterized set of tissue-mimicking phantoms. Results are promising, demonstrating a high reproducibility level of TD-NIRS device manufactured in scalable production settings.

DISCLOSURE: ML, AT, AT, DC, ADM, AP, FZ, MB are co-founders of PIONIRS s.r.l.

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