Innovative single-photon large-area optical probe for diffuse optical spectroscopy (SP-LADOS)

Fabio Acerbi[1*], Laura Di Sieno[2], Anurag Behera[2], Alberto Dalla Mora[2], Alberto Gola[1]

[1] Fondazione Bruno Kessler (FBK), Centre for material and microsystems (CMM), via Sommarive 18, I-38123, Trento, Italy;
[2] Politecnico di Milano, Dipartimento di Fisica, piazza Leonardo da Vinci 32, 20133 Milano, Italy
*Corresponding author: acerbi@fbk.eu

ABSTRACT
Light is a powerful tool for non-invasive functional investigation of tissues. Time domain diffuse optical spectroscopy is a promising technique used in neurology, oncology, and quality assessment of food, wood, and pharmaceuticals. The SP-LADOS project focused on development of a new high-performance detection module for such technique, based on large-area (10x10 mm^2) single-photon detector, with significantly reduced noise, good detection efficiency and improved signal extraction. Such detector can improve by a factor >100 the state-of-the-art performance, paving the way to completely novel applications. So far, we obtained very good results, with responsivity much better than current research and clinical systems.

Keywords: single-photon; diffuse optics; time-resolution; detection module; large-area; responsivity.

1. INTRODUCTION

In the last decades, a great attention has been posed on the use of light to look inside the body recovering information about functionality and composition of tissues. SP-LADOS is a project inserted in the time-domain diffuse optics (TD-DO) field, where it could bring large innovation. TD-DO is a completely non-invasive technique that exploits fast light pulses to give information about functionality and composition of tissues in depth [1]. Moreover, it allows to disentangle scattering from absorption (respectively linked to tissue's microstructure and chemical composition).

SP-LADOS project is developing a novel detector capable of increasing the light harvesting efficiency in TD-DO by two orders of magnitude, while maintaining a good performance in terms of timing resolution and a low dark count rate (DCR). This will allow overcoming the limited depth sensitivity of currently available systems, paving the way to completely novel spectroscopy approaches, e.g. non-invasive study of the functionality and compositions of lungs, heart or chest (even in transmittance geometry), as well as to new generation of low-cost clinical devices, for clinical applications not explored up to now with optical techniques. For these reasons, the SP-LADOS project is developing a very-large area silicon photomultiplier (SiPM) of 10x10 mm^2 with possibly enhanced NIR sensitivity, with a moderately-low level of DCR (<2 Mcps, counts per second) and with good single-photon time resolution (SPTR). The project focused not only on the detector chip, but also a complete detection module, with front-end electronics and cooling control.

SP-LADOS project so far has demonstrated very good results. We already developed and validated a compact module (5x5x4 cm^3) based on a 6x6 mm^2 SiPM, being the largest-area detector ever demonstrated in TD-DO systems. Signal extraction has been improved with optimized SiPM layout, and DCR has been limited thanks to Peltier cooling and augmented DCR-temperature dependence. The measured responsivity (i.e. diffused light harvesting capability [1]) at 670 nm is the highest ever reported for SiPM detectors with a value of $7.54 \cdot 10^6$ m^2sr, significantly better than currently available cutting edge research technologies.

2. STATE OF THE ART

TD-DO systems exhibit important advantages over concurrent solutions, like continuous-wave approach. For example, source-detector separation (SDS) can be chosen freely, down to null separation, and it is not related to the investigation depth, which is instead just linked to photons' arrival time. However, TD-DO systems are usually extremely limited in the light harvesting efficiency requiring single-photon detector with high timing resolution.

To improve the responsivity and the performance of TD systems several efforts have been done. The laser sources have improved the power and reduced the size while, on the detector side, some groups started to use probe-hosted SiPMs instead of fiber-based signal collection with photocathode-based detectors or single-photon avalanche diodes (SPADs), with great advantages

in terms of light harvesting capability [1]. Despite being around for years, SiPMs started only recently to be successfully used in TD-DO, due to important performance optimization, especially the reduction of DCR down to ~100 kcps/mm^2 level. After a first phase where good performances in terms of SPTR and DCR were achieved, the replacement of standard photocathode-based detectors have been done to improve the systems' sensitivity and reducing cost and dimensions. For example SiPMs with active area of 1-1.7 mm^2 (with fill-factor of 50-74%) featuring a SPTR down to 57 ps FWHM have been employed in TD-DO [1]. Thanks to this achievement, compact systems have been realized, with dimension of a book (20x16x5 cm^3) and low power consumption (10 W), compatible with battery operation [1]. Finally, shrinking as much as possible the detection module size, to realize a miniaturized detector module, hosted into small caps compatible with EEG headdress, it is possible a time resolution of 250 ps FWHM [1].

However, for unprecedented breakthroughs (e.g. probing deep structures like heart or lung), detectors with larger area still represent an unmet need.

3. BREAKTHROUGH CHARACTER OF THE PROJECT

The ideal detector for TD-DO should have large active area (like PMTs) but also advantages of SPADs in terms of compactness, ruggedness, good SPTR and detection efficiency [1]. SiPMs can meet the large area, compactness and ruggedness requirements, therefore they are nowadays the detector of choice, but it is absolutely not easy to combine large area, low noise and good SPTR. with active areas bigger than ~3x3 mm^2. Indeed, the noise level increases to levels that generally saturates timing electronics capabilities and SPTR worsen because of signal degradation.

The ambitious goal of SP-LADOS project was to overcome such limitation, thus providing what can be considered the best detector for TD-DO. This is a large area SiPM (1 cm^2, much bigger than what reported up to now) with: i) enhanced performance, particularly higher NIR sensitivity, ii) better signal extraction to obtain a good SPTR and iii) significant noise reduction (target <2 Mcps on the whole 1 cm^2 area). These are three key advancements with respect to current state-of-the-art performance reported in TD-DO systems all at once, and they can be possible with the design of a completely new SiPM (designed and fabricated in FBK) with improved layout and optimized technology with enhanced NIR sensitivity. Moreover, cooling and proper signal extraction and amplification are mandatory to have a suitable detector for TD-DO application. This can be obtained with a dedicated detection-module design and implementation, including Peltier cooler and low-noise controller circuitry. A comparison between state-of-the-art and new SP-LADOS SiPM-based detectors is presented in Table 1.

Table 1. Comparison of responsivity (670 nm), DCR and timing resolution (at FWHM) of SiPM-based TD-DO detectors.

Nom. Area [mm^2]	Eff. Area [mm^2]	Responsivity (670nm) [m^{2}sr]	DCR total [kcps]	SPTR FWHM [ps]	Ref
1	0.5	0.5 E-6	~100	~140	[1]
9*	7.38	~3 E-6	~500	~300	[4]
36	32.1	7.5 E-6	~200	~600	This work
100**	~93-97	expected ~2-5 E-5	<1000	<900	**

* cutting-edge ongoing research (validation still in progress)
** upcoming SP-LADOS detection module.

Furthermore, in SP-LADOS project the great and unique experience of PoliMi group in TD-DO systems development and validation was crucial to conceive the requirements of the detector and its validation. Indeed, before detector design, the existing FBK technologies have been studied and, thanks to the simulation tool developed in PoliMi, the most crucial parameters (e.g. background level, SPTR etc.) to have the required performances in TD-DO were identified. The final goal is a device featuring a boosted responsivity (a factor ~100 with respect to state-of-the-art). This can pave the way to completely novel applications, e.g. non-invasive study of the functionality and composition of lungs or of the heart, or event the investigation of the human chest in transmittance geometry (as opposed to the "conventional" reflectance geometry), generating a completely novel investigation paradigm: the "whole-body optical radiography". These innovations will be tremendous for medical imaging applications.

4. PROJECT RESULTS

The SP-LADOS project already obtained very good results. After an initial pre-characterization of existing FBK SiPM technologies, we developed a first version of large-area detection module. As shown in Fig. 1, this is compact (5x5x4 cm^3) and it is based on a medium/large area SiPM, with a ~6x6 mm^2 active area, made by 4 different SiPM chips (~3x3 mm^2, with 35 µm cell pitch) placed side by side, all in parallel. SiPMs have been designed and fabricated in FBK. The cell fill factor is >80%, whereas considering the chip fill-factor, the total effective active area is about 32.1 mm^2 (Table 1). The SiPMs are based on p-on-n junction technology [2], chosen due to lower primary and correlated noise, as well as the greater reduction of noise with cooling (due to lower electric field). The SiPMs are Peltier cooled at about -15°C, inside a vacuum-sealed TO8 package. The module also contains a custom made front-end electronics, trans-impedance gain ~10000 V/A, and the TEC temperature controller, which has been optimized to

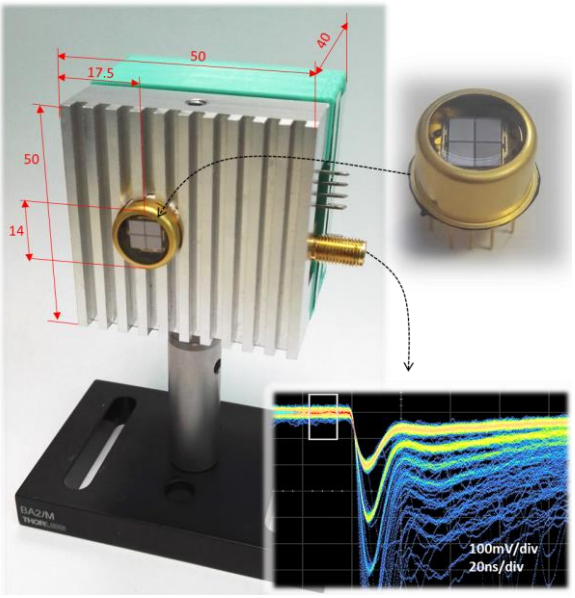

Fig. 3. Picture and dimension of the SP-LADOS detection module, based on a 6x6 mm^2 SiPM. On bottom/right: example of persistency-trace of output signals (5.3 V excess bias).

reduce voltage interference on the SiPM signal (very important for precise timing applications as TD-DO.

The SiPMs have been characterized in FBK as described in [2]. The primary noise is around 80 kcps/mm^2 (kilo counts per second per 1mm^2 area) at 20°C, with 38 V bias (5.8 V excess bias). At -15°C it reduces to ~7 kcps/mm^2, thus ~200 kcps on 6x6 mm^2. Afterpulsing probability is lower than 1%, the crosstalk probability is ~34% and the photon detection efficiency (PDE) is ~17% at 700 nm, increasing up to 25% with 10 V excess bias. Moreover, a special metal-grid layout has been chosen to have an improved signal extraction. As seen in Fig. 1, the signal amplitude is in the order of 200 mV, with a signal to noise ratio of approximatively 20 (5.3 V excess bias).

The performance of the SiPM detection module have been characterized also with internationally accepted protocols for performance assessment of diffuse optics instrument, namely Basic instrument performance (BIP), nEUROPt and MEDPHOT protocols (see [3]). BIP protocol aims to characterize individual component of the system. We firstly characterized the spectral responsivity of the detector. Fig. 2 shows it in comparison with cutting-edge research technology [4], state-of-the-art research [1] and clinical technology [5]. (to the best of our knowledge). Responsivity at 670 nm is the highest ever reported for SiPM detectors (~7.5·10^{-6} m^{2}sr). Fig. 3 shows instrument response function (IRF) and its FWHM. IRF tail slope increase with wavelength while, the afterpulsing ratio (0.234 ±0.14) is independent on wavelength. The detector was also found to be very stable over time: photon counting rate, DCR and SPTR (FWHM) have been tested for 10 hours, showing stability within 1%, or 10 ps respectively. This in important for contrast measurements and retrieval of tissue optical properties.

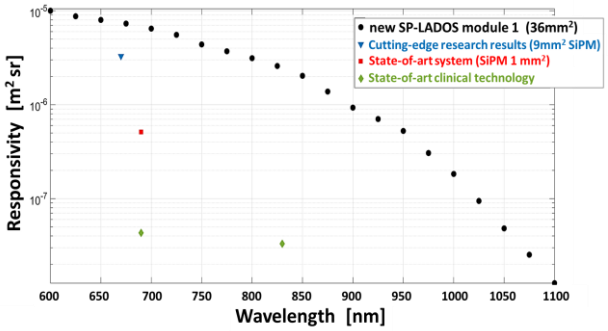

Fig. 1. Spectral responsivity of SP-LADOS detection module, compared with state-of-the-art. The obtained results are better than the best reported cutting-edge research detector.

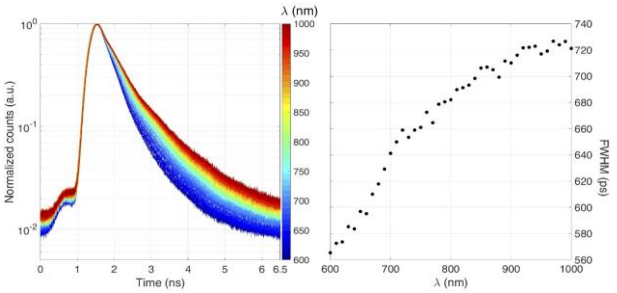

Fig. 2. Measured instrument response function (IFR) of the 36mm^2 detection module, and its full-width at half-maximum (FWHM) value. Measurements done between 600 nm and 1000 nm with step of 10 nm.

MEDPHOT protocol evaluates the ability to reliably measure optical properties of homogeneous media using 32 homogeneous solid phantoms spanning a wide range of absorption (0 to 0.35 cm^{-1}) and reduced scattering coefficient (0 to 20 cm^{-1}). Measurements were performed in transmittance geometry and the detector was able to reliably measure optical properties as high as μ_a = 0.47 cm^{-1} and μ_s' = 20 cm^{-1}. This exceeds over state-of-the-art. Additionally, in the range of biological tissues, a good linearity in the retrieval of coefficient was found and the accuracy is respectively 7.5% and 5.9% respectively. It was also verified a negligible coupling between recovered scattering and absorption values.

The nEUROPt protocol evaluates the ability of the system in detecting local absorption changes within a homogeneous background. The measurements have been done in reflectance geometry, with different source-detector separation (SDS). As shown in Fig. 4, with proper choice of the SDS, the module is able to see local perturbation down to a depth of about 30 mm, with contrast >1% and contrast to noise ratio (CNR) > 1 (i.e. theoretical limits for detectability [1]). This is a good achievement and it starts to pave the way to first measurements in transmission geometry thanks to the extreme responsivity that allowed the use of these very large SDSs.

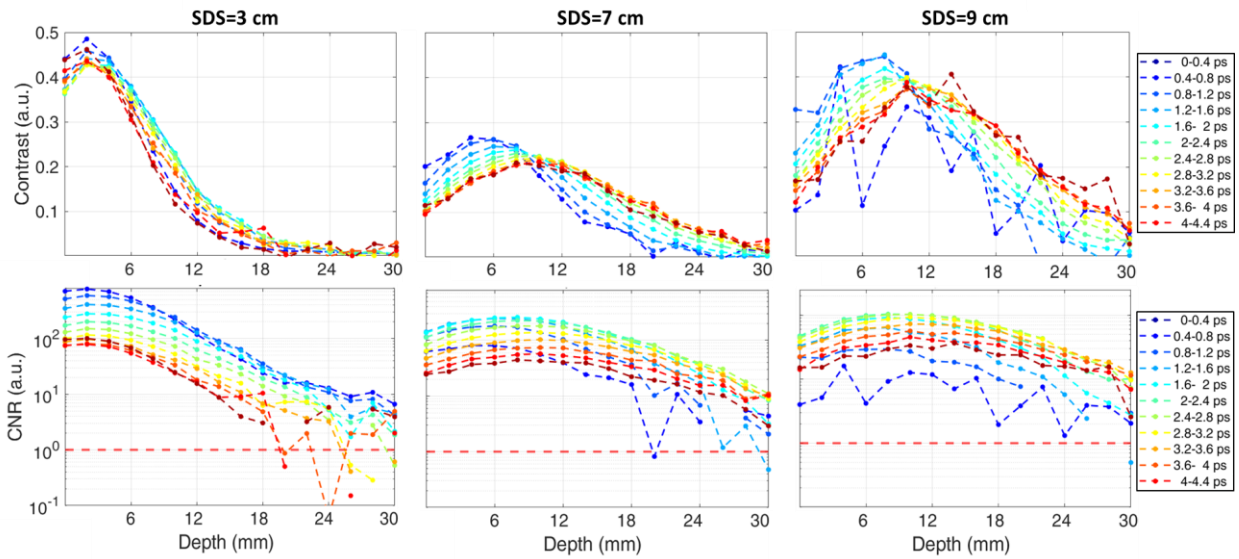

Fig. 4. Contrast and contrast-to-noise ratio (CNR) measured with nEUROPt protocol [3], with the new 36 mm^2 detection module, as a function of the local inclusion depth, for different source-detector separation (SDS) and different time-windows [3]. It can be seen that it is possible to see local perturbation down to a depth of about 30 mm, with CNR much greater than 1.

5. FUTURE PROJECT VISION

5.1. Technology Scaling

Aiming to a more compact and versatile system, as well as targeting to TRL 5-7, the chip and the electronics should be scalable. The detector here reported is produced in FBK clean-room with a CMOS compatible technology, thus with large room for scalability. The SiPM technology can be transferred to external foundry. FBK has already experience in such processes. Moreover, the number of channels (detectors and lasers) can be scaled up. PoliMi had a proven experience in scaling of the dimensions and cost of the TD-DO systems. Given the great potentiality of the SP-LADOS technology, we can see different development scenarios, all with great impact on society and health. Their choice will be evaluated depending also on the outcome of other ATTRACT-Phase1 projects.

On possible strategy is to use SP-LADOS technology to go further in investigation potentiality, creating new multi-imaging techniques, (e.g. brain investigation) improving the diagnostic capabilities. Merging SP-LADOS with other ATTRACT-Phase1 project would be a feasible way and some preliminary investigation have been done. This will be possible with a dedicate research project, requiring ~2-3 years development stage.

Another strategy is to go towards the demonstration of the first "whole-body optical-radiography" system. The breakthrough would be performing deep investigations, despite the low spatial resolution, providing sensitivity to chemical composition (e.g. functionality of deep organs or even the oxygenation of a foetus in the womb). This would be revolutionary in the non-invasive and label/radiation-free imaging field. It requires experts in: i) pulsed lasers, ii) in high-throughput timing electronics, iii) clinical applications. It will require ~3 years for the development and advancement in TRL 5.

Finally, another possible development direction, with great impact on wellbeing, is the creation of consumer systems for wearable and smart personal non-invasive health monitoring device, for example for sportsman.

5.2. Project Synergies and Outreach

For the ATTRACT-Phase2 two main strategies can be appealing: i) building a bigger consortium for superior clinical investigation tools, ii) creating a partnership for the industrialization of the new TD-DO instrument. Clustering with other projects is important, going towards multi-imaging techniques, giving the unique potentiality for diagnosis or study of new mechanisms behind the onset of diseases. For example, with the morphological imaging power of ultra-sounds for non-invasive tumour diagnosis, or combining with Electroencephalography/ Magnetoencephalography. Other ATTRACT-Phase1 projects worked specifically on these aspects and the outcome of those projects will be fundamental.

Dissemination in SP-LADOS project is a priority to rise the interest from stakeholders and potential users. The new detector can be considered an enabling technology for many types of investigations. It is important to reveal the performance, starting with non-invasive measurements on human tissues, investigating unexplored regions of head and chest. As an example, TD-DO could benefit from these innovations to probe down in the chest, reaching the lung, with potential in the management of e.g. Covid-19 patients. This will also pave the way to similar investigation in food or pharmaceutical.

5.3. Technology application and demonstration cases

SP-LADOS technology can have direct applications in the health sector. The goal of the developed system, as well of the possible new investigation methods is the functional investigation, with non-invasive techniques, of several human body regions and tissues, like the deep structure of the brain and the chest. This is very important, also looking towards possible compact and portable devices for every-day care and health monitoring. Moreover, the developed technology can be a very useful sub-system, integrated with other clinical investigation machines, and combined with other techniques. For example, giving functional information to other imaging techniques. Diffuse optics systems combined with ultrasound or MEG/EEG probes, would create a very promising investigation technology. SP-LADOS could have important application in advanced clinical tools.

5.4. Technology commercialization

The technology developed in this project is capable of rising the interest of different investors for the commercialization of a biomedical product. Some steps are needed at this stage to make a commercial product, as well as the necessary clinical validations. Moving to development stage, to reach TRL-5-7 it will be important to have private investors or commercial partners in the biomedical field and/or business incubators taking part also of the development itself, creating an important synergy for the transformation of the prototype demonstrator into a product. Indeed, some preliminary interest from private company has emerged, both to be partner in improving the performance of the single parts of the system, and to partner on the commercialization of the complete investigation system.

5.5. Envisioned risks

One important risk can be the loss in the spatial resolution of TD-DO technique when employing large SDS (e.g. 10 cm) that can demote the performance in parameters retrieval. In this situation, at the expenses of additional instrumental and computational cost, the system can evolve towards tomographic apparatuses, which are capable of compensating the low spatial resolution, as demonstrated for breast imaging.

Generally, the risks associated with the next development stage are on the technology validation. This procedure can be expensive and time consuming. Finally, considering miniaturization of the current system, the transformation of all the benchtop instruments is not straightforward. It would be beneficial to create cooperation with a partner having instrumentation and experience in the biomedical analysis, allowing a proper tool-to-tool comparison and direct performance and potentiality estimation of the new techniques.

5.6. Liaison with Student Teams and Socio-Economic Study

A possible SP-LADOS Phase2 would benefit from the collaboration of MSc student teams. Not only the technology is now at a very interesting development phase, but it can be associated with other diagnostic technique. The work on the very first demonstrators, the design of proper and comfortable bed for optical-radiography, or the design of a portable diagnosis device, addressing important societal challenges, can be a perfect task for a young and creating student minds. Given the multidisciplinary nature of the project, we will organize a summer school to allow them to familiarize with the main concepts on detectors, TD-DO techniques and clinical challenges, providing also the proper material for the students. We will also designate a proper person to take care of this school and of subsequent collaboration phase, as well as for helping in the with relevant information for socio-economical studies of the ATRACT projects..

6. ACKNOWLEDGEMENT

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