The SiPM revolution in time-domain diffuse optics

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Abstract: Time-domain diffuse optics is a powerful non-invasive, non-ionizing and label-free technique based on the use of picosecond pulsed laser light to probe highly scattering media like biological tissues down to a depth of few centimeters to obtain functional and compositional information. This technique is opening new perspectives in various fields spanning from oncology (e.g. characterization of breast or thyroid lesions, etc.) to neurology (e.g. diagnosis and monitoring of traumatic brain injuries, functional brain imaging, etc.), as well as in non-biomedical fields (e.g. characterization of fruits, wood, etc.). Time-domain diffuse optics is nowadays undergoing fascinating technology advancements, permitting for the first time the design of low-cost compact/wearable high performance systems. This revolution has been made possible also taking advantage from Silicon PhotoMultiplier (SiPM) progresses, originally driven by other applications, since time-domain diffuse optics is highly demanding in terms of performance, in particular requiring single-photon detectors with large collection area, high fill-factor, high single-photon timing resolution, low power dissipation and compact high-throughput front-end electronics. This work will review the recent advancements introduced by SiPMs in time-domain diffuse optics, mostly thanks to the support of different running EU H2020 projects (e.g. SOLUS -G.A.731877-, LUCA -G.A.688303-, BITMAP -G.A.675332-, ATTRACT -G.A.777222-, Laserlab-Europe -G.A.654148-), showing their present performances in this field, the inherent advantages that allowed the design of innovative diffuse optical imaging systems, as well as highlighting their present limitations in order to push forward the research towards the perfect SiPM for time-domain diffuse optics.

Keywords: time-domain diffuse optics, silicon photomultiplier, single-photon avalanche diode, photon scattering, near-infrared spectroscopy, time-correlated single-photon counting.

1 Introduction

The use of light for probing highly scattering media (i.e. diffuse optics, -DO-) is drawing attention in different biomedical and not biomedical fields [1]-[5]. Many different biological media are quite transparent in the wavelength range between 600 and 1100 nm as scattering dominates with respect to absorption, leading to the possibility to probe them down to a depth of 2-3 cm when a reflectance geometry measurement scheme is adopted [6]. In this scheme, light is injected and collected at the same side of the medium under investigation, with certain distance between such points (ρ). By exploiting light sources at different wavelengths it is possible to retrieve the absorption (μ_a) and reduced scattering coefficients (μ_s') spectra of the medium, respectively linked to its chemical composition and microstructure [7]. This opens up to a plenty of applications like: functional brain imaging or muscle oximetry (where the technique commonly takes the name of functional Near-Infrared Spectroscopy -fNIRS-) [8], optical mammography [9], thyroid nodules characterization [10], bone pathologies examinations [11] as

well as non-biomedical applications like the non-destructive quality assessment of food [12], wood [13], pharmaceutical [14] and semiconductor powders [15]. As DO only relies on the use of light, the technique is non-invasive, non-ionizing and label-free. Depending on the different possible light modulation, one can operate a DO system in different ways. Among the most common adoptions it is worth mentioning the continuous-wave (CW) regime, the time-domain (TD) and the frequency-domain (FD) [16]. It is well known that CW DO is the simplest approach to the measurement, but at the same time the information content of a measurement performed with a single source-detector pair is the lowest. On the other side, among other techniques TD DO is the most demanding in terms of cost and complexity of the instrumentation, but the information content of a single measurement is the highest [16]. In particular, by monitoring just the intensity of light backscattered by the tissue, a single CW DO channel cannot disentangle μ_a and μ_s' information. Instead, TD DO relies on the injection of light pulses in the picosecond range and time-resolved detection of single-photons re-emitted by the medium under investigations, followed by their classification with Time-Correlated Single-Photon Counting technique (TCSPC) [17]. The re-emitted light pulse at a certain source-detector separation from the injection point is broadened and attenuated due to both scattering and absorption. However, as scattering mainly affects the pulse width and delay, while absorption mainly affects the pulse decay tail, μ_a and μ_s' can be separately assessed [16]. For this reason, TD DO is also less prone to motion artifacts as they often result into a signal attenuation, which can be detrimental only for CW DO. Additionally, using CW DO the penetration depth is dependent on the source-detector distance ρ. Hence, depth penetration can be increased by increasing ρ, at the expenses of the signal-to-noise ratio, as the signal level exponentially decreases upon increasing ρ, thus resulting into a trade-off between signal level and depth penetration. On the contrary, with TD DO the average investigated depth is: i) independent of ρ (thus allowing the use of short ρ to increase the signal instead of forcing the use of large ρ as in the case of CW DO) [18] and ii) encoded in the photons' time of flight [19],[20]. It is therefore sufficient to analyze photons detected at longer delays with respect to the injection time of the laser pulse into the medium to maximize the penetration depth. For this reason, TD DO shows the highest depth selectivity when there is the need to disentangle information about structures set at different depths inside biological tissues (e.g. in disentangling hemodynamic changes occurring within skin/skull and those occurring in the brain) [21]. It has been first theorized [22] and then demonstrated [23],[24] that one can even adopt a null or small (few mm) ρ, adding further advantages to the TD approach. First, the volume probed in the medium (i.e. the sensitivity shape) is much more symmetrical and confined, acquiring a drop-like shape instead of the classical banana-like shape [23], thus increasing the spatial resolution of the technique. Moreover, as more photons result confined into a smaller volume, the contrast produced by a possible localized perturbation (e.g. a localized functional activation of the brain, as well as a tumor) inside the sensitivity shape and the number of photons reaching the detector are higher at all the arrival delays with respect to the laser injection time within the tissue [23]. Unfortunately, upon decreasing ρ, the amount of early-arriving photons increases much faster than that of late photons, thus increasing the information related to the outer regions of the probed volume, up to the saturation of the single-photon detection chain. Pushing this up to the limit (i.e. null ρ, where the source and detector are in the same point, as it can be achieved with a single fiber [25]) the direct reflection from medium surface is detected. Being a few percent fraction of the injected light, this signal results extremely above the single-photon regime. In these condition, a time-gated photon-detection scheme should be adopted, using single-photon detectors that can survive

to trillions of photons impinging during the OFF state (i.e. early-photons), with quite unaltered performance in the following ON state, where late-photons must be recorded. Up to now, this has been possible only using single-photon avalanche diodes (SPADs) [26],[27] (i.e. the main building block of the silicon photomultiplier, SiPM) as the photocathode of intensified photomultiplier tubes (PMTs) can be damaged by high photon fluxes. In the following, we take advantage of the expertise and collaborations of our research group to provide an overview of the recent technological advancements in TD DO, focusing in particular on those introduced by SiPMs, mostly thanks to the support of different running EU H2020 projects (e.g. SOLUS [28], LUCA [29], BITMAP [30], ATTRACT [31], Laserlab-Europe [32]), showing their present performances in this field, the inherent advantages that allowed the design of innovative diffuse optical imaging systems, as well as highlighting their present limitations in order to push forward the research towards the perfect SiPM for TD DO.

2 State of the art and trends

Table 1 shows the main theoretical and practical advantages and disadvantages of TD DO before 2015, which represents the starting point of a revolution in the field, with fast technological advancements that are still running. The expected features of next generation of TD DO devices is shown after 2020 for comparison. As discussed above, with respect to CW DO, TD DO allows to freely set the ρ as the investigated depth does not depend on this choice. Thus, theoretically, many measurement points can be arranged into a small area allowing to fabricate dense measurements grids, with no gap between sources and detectors. Additionally, as a small ρ approach allows to confine the sensitivity shape within the medium as well as to increase the number of photons collected at all the arrival delays, the operation in the TD allows higher spatial resolution and sensitivity to deeper structures. Thanks to the possibility to analyze photons arriving with different delays to retrieve information coming from different depths, TD DO has the highest depth selectivity. Finally, exploiting an information encoded in the shape of the re-emitted pulse, TD DO results more informative with respect to CW DO, and less prone to motion artifacts.

As a matter of fact, despite decades of research in TD DO, only CW and FD devices have pervaded the market of biomedical optics. It is worth noting that, to the best of our knowledge, there is only one company on the market (in Japan) with TD fNIRS devices [33]. The main reasons behind this are listed in the bottom rows of Table 1. TD instrumentation is much more expensive and bulky with respect to CW devices. Hence, the adoption of a large number of collection points similar to cutting-edge CW systems recently reported in the literature [34] are not feasible at the moment in a TD approach. For the above mentioned reasons, before 2015 devising wearable and/or battery-operated TD systems was considered science fiction.

As a matter of fact, TD DO instruments underwent strong technological advances already well before 2015. Two decades ago, for instance, first TD instruments were indeed based on bulky, delicate and expensive titanium sapphire lasers [35]. Then, new sources appeared on the market like supercontinuum pulsed fiber lasers or pulsed diode lasers. Exploiting these technologies, it was possible to fabricate rack-based TD systems, for the first time suitable to enter in the clinical environment [8], as well as to fabricate first TD multichannel systems for topographic or tomographic optical imaging [36]-[39]. Still, the high fabrication cost (in the order of hundred

thousand euros) as well as the fridge-like dimension, prevented a widespread adoption of these technologies in both the research environment and, consequently, in the clinical practice.

Table 1 Advantages of TD DO before the SiPM revolution and its future perspective after 2020.

FEATURE	Time Domain (before 2015)	Time Domain (after 2020)
Free selection of ρ	YES	YES
Dense grid of measurement points	YES	YES
High spatial resolution	YES	YES
High depth sensitivity	YES	YES
High depth selectivity	YES	YES
High accuracy	YES	YES
Low Cost	NO	YES
Compact	NO	YES
Many parallel channels	NO	YES
Wearable	NO	YES
Battery operated	NO	YES

It is worth nothing that the miniaturization of TD systems down to wearable devices is attractive not only due to an increased versatility, but also for increasing the performances. Indeed, although photocathode-based detectors can exhibit active areas of different square millimeters, practically they cannot be used in contact with the tissue under investigation, thus requiring the use of optical fibers to drive the light from the collection point on the sample to the detector, limiting both the collection area and the numerical aperture, often losing more than one order of magnitude of useful signal.

Figure 1 shows a simulated comparison between the ultimate performance achievable by CW and TD techniques [40]. For this purpose, the simulated ideal scenario doesn't take into account any technological limitation assuming for instance for TD the possibility to use a detector with delta-Dirac timing response, 100% photon detection efficiency and a large active area of 1 cm^2, in direct contact with the tissue under investigation to avoid signal losses, with perfect time-gating capability to reject early-arriving photons. Equivalently, on the source side, it is assumed the possibility to use the maximum amount of laser light that can be injected in the tissue in an area of 1 cm^2 without overcoming the maximum permissible exposure limits for skin. A high throughput timing electronics is considered, so as to avoid any loss due to the saturation of the

digital stage that allows to retrieve the distribution of the photons' time of flight. For CW, different ρ (expressed in cm in Figure 1) are considered, so as to enable probing tissues at different depths. For TD, only null ρ is simulated, as the depth selectivity is ensured thanks to the possibility to process photons at the different arriving delays (in ns in Figure 1). In Figure 1a it is simulated the contrast (i.e. the relative change in the number of photon counts [40]) produced by a localized absorption perturbation ($\Delta\mu_a$ = 0.1 cm^{-1}) set at different depths inside a homogeneous scattering medium characterized by μ_a = 0.1 cm^{-1} and μ_s' = 10 cm^{-1}. The shadowed regions limit the detectability where contrast is > 1% (which is considered distinguishable within the biological variability) and where the Poisson noise does not exceed 1%, so that the contrast is statistically robust. As it can be seen, the TD contrast is always much higher than the CW one, independently of the depth of the perturbation, and it extends well beyond the CW maximum depth, allowing to probe tissues down to a depth of 6 cm provided that photons with a delay of more than 9 ns are detected. As a further proof, the use of the same simulated ideal systems for tomographic reconstruction (see Figure 1b) of the same absorption perturbation set at a depth of 4 cm completely fails with CW and succeeds with TD, thanks with the much higher contrast at this depth, while the contrast of the ideal CW system at a depth of 4 cm is considerably below the detectability threshold of 1%.

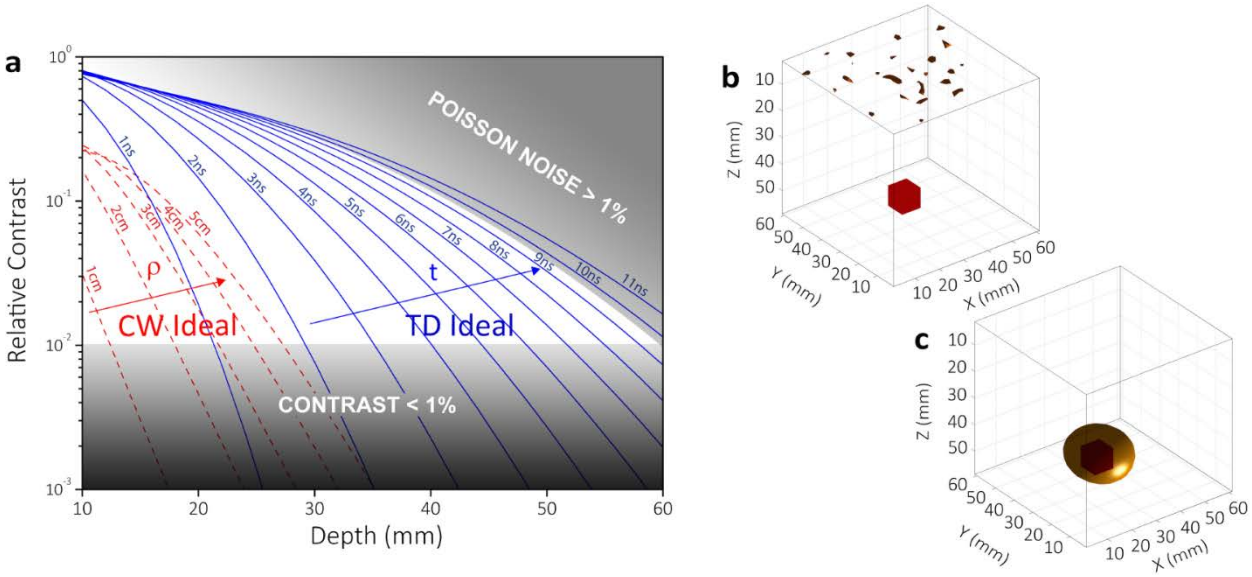

Fig. 1 (a) Simulated contrasts for ideal CW- (dashed lines, depth increased by increasing ρ) and TD DO (solid lines, results at null ρ) systems given by a localized 100% absorption perturbation as a function of its depth inside a homogenous scattering media (μ_a = 0.1 cm^{-1}, μ_s' = 10 cm^{-1}). (b) Optical tomography performed using the same ideal systems and the same perturbation set at a depth of 40 mm (the simulated cubic perturbation is depicted in red). Reprinted with permission from [40] © The Optical Society.

Notwithstanding this impressive scenario, TD systems are presently able to reach a penetration depth in the order of 2-3 cm. The main conditions to overcome this limit are therefore the possibility to have wearable systems with: i) dense distribution of probe-hosted (avoiding optical

fibers) pulsed laser sources to maximize the light power that can be injected into biological media; ii) an equivalent dense distribution of probe-hosted time-resolved single-photon detectors to maximize the amount of collected photons; iii) the time-gating capability to extract the few late photons out of the overwhelming burst of early photons; iv) a high throughput miniaturized timing electronics able to process all photon counts without losses.

It is worth noting that, although being highly challenging technological goals, all these have been already demonstrated (or partially demonstrated) in the literature [41]. What is still missing is merging all of them into a single TD system.

In a recent work by some of the Authors [40] the possibility to directly place into a wearable probe an array of pulsed vertical-cavity surface emitting lasers has been demonstrated, still using external fast voltage pulse generators to trigger the laser emission. In a later work [42], the use of laser drivers fully integrated into a single silicon chip was introduced in TD DO. Both technologies were validated on phantoms and in-vivo following rigorous protocols for performance assessment of DO systems [43]-[45]. In this way, the assembly of dense arrangements of sources into a small area, if not demonstrated yet, was at least enabled.

As a first step towards the second and third conditions, initially another recent work by some of us [40], then other research groups [46],[47] demonstrated the possibility to squeeze the time-gated SPAD technology down to a size compatible with wearable probes. However, SPADs are well known for their limited active area size. Indeed, in Ref. [47] the detector has an active area diameter of 10 µm. In our previous work [40], we made use of a SPAD with a diameter of 200 µm. However, in both cases we are still far from the simulated 1 cm^2 collection area.

Finally, the last condition is fulfilled in different research prototypes of time-to-digital converters that were published in recent years, allowing to reach throughputs in the order of magnitude of billions of counts per second (cps) in the size of a small piece of silicon [48]-[50].

3 The SiPM revolution

It is clear, as discussed before, that the ideal detector for TD DO should exhibit the large active area of PMTs, while showing the typical advantages of SPADs like their compactness and ruggedness. Additionally, good single-photon timing resolution and low noise are required. Even if SiPMs are available since two decades, being optimized for photon-number resolving detection, their use in TD DO was not considered before recent years due to their initial very high dark count rate at the single-photon level, often overcoming 1 Mcps in a 1 mm^2 device, as well as inadequate single-photon timing resolution. However, the SiPM technology underwent strong advancements during the last decade by considerably lowering both DCR and timing jitter. Thus, in 2014 we started exploring these devices for TD DO and this represented a revolution.

In a previous work by some of the Authors, the single-photon timing resolution (SPTR) of Hamamatsu Photonics (HP) and Excelitas Technologies (ET) devices has been studied when SiPMs are hosted inside very compact and wearable probes suitable for direct contact with the medium under investigation [51]. In these conditions, from 1.3 x 1.3 mm^2 devices by HP (S13081-050CS) it was possible to achieve a SPTR = 57 ps full-width at half maximum (FWHM), as well as a remarkable SPTR = 67 ps FWHM from 1 x 1 mm^2 devices by ET (C3074011050C). Moving to even larger active areas, from 3 x 3 mm^2 devices by ET (C3074233050C) it was possible to achieve a SPTR = 115 ps FWHM, as well as an SPTR = 135

ps FWHM from 3 x 3 mm^2 devices by HP (S13082-4084). Similarly to SPADs [52], SiPMs exhibit a first tail in the SPTR response shape with time constant of 60-130 ps (depending on the considered model) due to photons absorbed within the neutral region of the reverse biased p-n junction [53] and a second long tail with time constant of 1-4 ns (depending on the considered model) probably due to the same subtle background phenomena giving rise to the so-called memory effect in SPADs [54]-[56].

The field of DO relies on well-defined internationally agreed figures of merit for evaluating the performance of components and system, one of this is the "diffuse optical responsivity" (R), which can be assessed following the procedure described in [44] using a calibrated phantom. To give an idea of the improvement in the signal level given by SiPMs, it is worth mentioning that the R of TD DO systems based on a 1 mm^2 probe-hosted SiPM can overcome the value of previous state-of-the-art devices by 1-2 orders of magnitude, and obviously the use of a 9 mm^2 can lead to a gain approaching the 3 orders of magnitude.

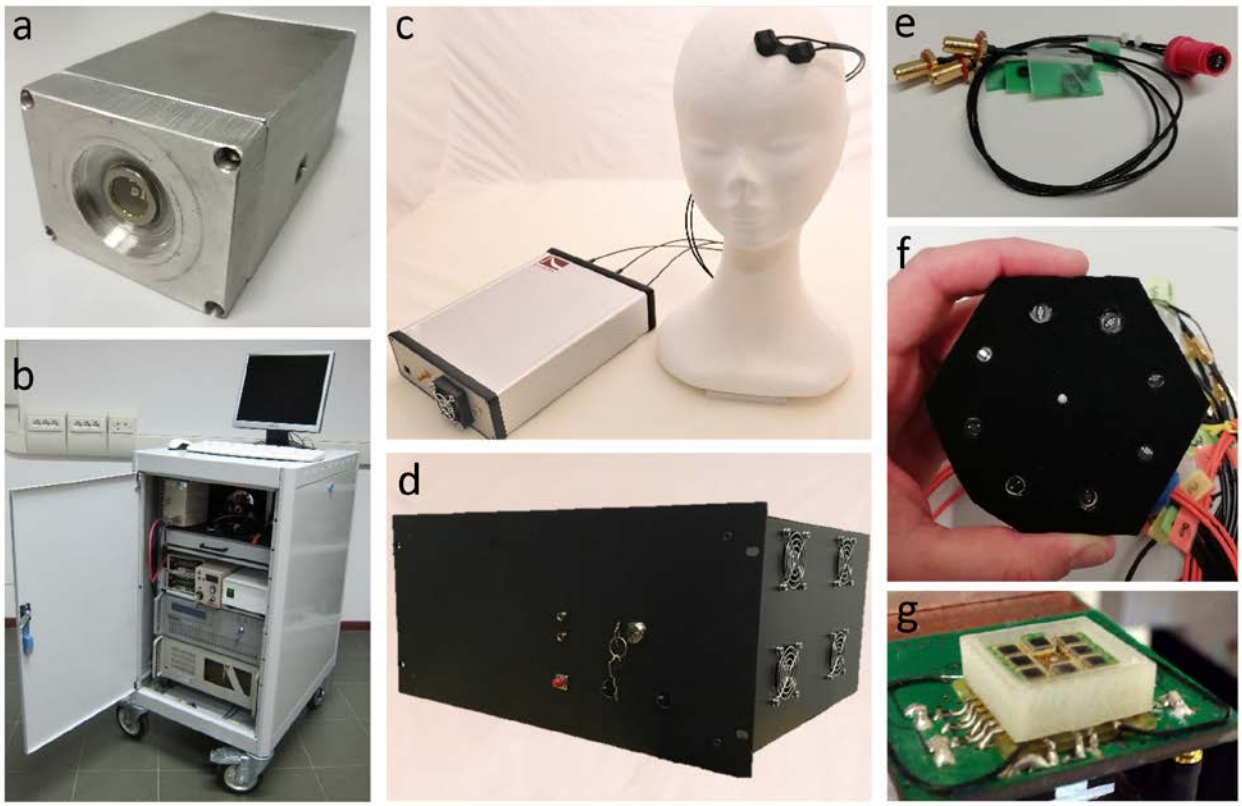

Fig. 2 SiPM-based TD DO components and systems: (a) single-photon timing module [60], (b) broadband time-resolved spectroscopy system [61], (c) compact TD fNIRS system [68], (d) 8-wavelength dual detection channel near-infrared spectroscopy system [70], (e) wearable time-resolved single-photon detector probe [72] and (f) tomographic probe based on the same detector [73], (g) detection stage of a new optical mammography system [75].

SiPMs were in the following validated in different scenarios of possible TD DO applications like: i) the accurate measurement of optical properties of homogeneous media (highlighting in particular the capability to linearly follow changes in optical properties and proper uncoupling of absorption from reduced scattering coefficients), where they showed performance in line with

the state of the art [57], ii) the capability of detecting localized perturbations inside the medium in depth, where they showed improved performances thanks to their increased efficiency in the collection of diffused light, thus allowing the detection of a larger number of late-arriving photons [40], iii) the possibility of exploitation in diffuse optical tomography (DOT) systems at a single wavelength to reconstruct 3D maps of optical properties [58], as well as in multispectral DOT to reconstruct 3D maps of different chemical constituents of the sample under investigation [59], in both cases showing impressive performances.

Three different parallel branches of SiPM exploitation started: i) replacing PMTs or hybrid PMTs in state-of-the-art bulky systems; ii) designing hybrid systems (still fiber based) between the previous and the next-generation, taking advantage of parallel development of compact laser sources; iii) designing innovative wearable detection chains with high performance thanks to the use of SiPMs directly embedded in the probe in contact with the medium under investigation.

To enable the first path, a compact ($5 \times 4 \times 10$ cm^3), robust and easy to use SiPM-based single-photon detection module was designed (see Figure 2a) [60]. It embeds an SiPM integrated with a suitable Peltier cooling stage together with the read-out and signal conditioning circuit for avalanche pulses, the biasing electronics and a driver for the thermoelectric cooler. The module uses a detector with a total photosensitive area of 1 mm^2 (with 51% cell fill factor, release 1) or 1.7 mm^2 (with 74% cell fill factor, release 2). The detector exhibits an SPTR of ~140 ps FWHM (release 1) or ~75 ps FWHM (release 2). This detector was used to replace PMTs in different TD DO systems like a broadband TD optical spectroscopy system (see Figure 2b) [61] and in systems devised for the evaluation of fruit quality [62]. These SiPM-based systems were used in the following years for different pre-clinical studies like the non-invasive characterization of human bones [11] and abdominal fat heterogeneities [63], as well as to retrieve optical properties of basic tissue constituents like collagen [64], elastin [65] and various thyroid chromophores [66]. It is worth mentioning that, in parallel, Hamamatsu Photonics developed a new version of its TD DO system (i.e. the tNIRS-1, a clinical tissue oxygen meter) with 2 SiPM-based detection channels, featuring an overall SPTR of about 1.5 ns FWHM [67].

On the second exploitation path, SiPM modules were used to fabricate the first TD system so compact and light-weight to enable unprecedented TD DO application on freely moving subjects, by hosting it into a backpack (see Figure 2c) [68]. Thanks to new compact laser sources (2 wavelengths are embedded for tissue oximetry applications) and to the use of 1 SiPM module and 1 integrated time-to-digital converter (TDC) [69] instead of a classical TCSPC board/system, these devices have roughly the size of a book ($20 \times 16 \times 5$ cm^3) and a weight of about 2 kg. Its power consumption lower than 10 W also enables the battery operation. The high performance of lasers, SiPM and TDC, as well as the accurate design of optics and fiber optics components lead to an overall SPTR better than 300 ps at both wavelengths. The same technologies (lasers, SiPM modules and TDCs) were adopted also for developing an 8-wavelength and dual detection channel instrument for diffuse optical spectroscopy (see Figure 2d) [70]. Thanks to further efforts in improving the laser pulse shapes, as well as to the second release of the SiPM module with improved timing resolution, this instrument features an SPTR better than 160 ps FWHM at all the wavelengths, granting high accuracy in the application. Due to a higher system complexity (e.g. the need to embed an optical fiber switch for multiplexing lasers at different wavelengths into the same injection point in the tissue, as well as the need to embed automatic attenuators for each wavelength to adjust the signal to fit the single-photon level) the device has a size of $48 \times 38 \times 20$ cm^3, with possibility of being hosted inside a standard 5U 19” rack case. Indeed, this instrument was designed aiming at a primary use inside the LUCA device [71], a

multi-modal system exploiting the combination of ultrasound imaging, TD DO and diffuse correlation spectroscopy [16] for characterization of thyroid nodules, aiming at replacing expensive and uncomfortable biopsies with a non-invasive and cheaper examination [29].
On the last exploitation path, exploiting the relative simplicity in the front-end electronics required to operate SiPMs, miniaturized single-photon detector modules were designed (see Figure 2e) [72]. These modules require an external bias generator and embed the detector (either a 1×1 mm^2 SiPM C30742-11-050 by ET [72] or a 1.3×1.3 mm^2 SiPM S13081-050CS by HP [73]) together with front-end and avalanche amplification electronics. It is so compact (about $0.6 \times 0.5 \times 2$ cm^3) that can be hosted either into small plastic caps compatible with the EEG standard headdress (thus easily allowing fNIRS studies) or into arrangements of different detectors inside a wearable tomographic probe (see Figure 2f). Due to constraints of the compact footprint, these modules feature a SPTR of about 250 ps FWHM. The technology was validated both for muscle oximetry and for monitoring brain functional activations during standard finger-tapping exercises [72] and, in combination with an 8-channel TDC (SC-TDC-1000/08 S, Surface Concept, Germany), for real-time diffuse optical tomography on phantom and in-vivo [73]. Similarly, SiPMs were exploited for improving the performance of a previously developed 7-wavelength optical mammography system. It operates in transmittance geometry, with the breast slightly compressed between two parallel glass plates. In its original conditions, the full breast area was raster-scanned moving simultaneously an injection fiber (where different laser pulses at different wavelengths are multiplexed) and a large area collection fiber bundle, which was bifurcated providing the collected signal to 2 PMTs, one optimized for the visible range and one for the near-infrared range, each one connected to a PC-hosted TCSPC board [74]. SiPMs were used to entirely replace this detection chain [75]. 8 SiPMs with 1.3 x 1.3 mm^2 active area and 74% fill factor (S13360-1350PE by HP) were arranged in just a 1 x 1 cm^2 area to act together as a single TD DO detector of equivalent active area of about 10 mm^2 (see Figure 2g), directly replacing the fiber bundle at the collection side. However, to maximize the throughput, each detector is connected to an individual avalanche signal discrimination electronic board and to an independent input channel of a commercially available 8-channel TDC (SC-TDC-1000/08 S, Surface Concept, Germany). In this way, it was possible to reach a gain in signal of minimum 70 and maximum 3100 (depending on the wavelength considered) in the spectral range of interest, with a single detector technology replacing both the visible and the near-infrared optimized PMTs.

Conclusions and perspectives

In this paper we have shown how SiPMs recently fostered a revolution in the design of TD DO systems thanks to their superior performance and versatility with respect to PMTs. This revolution is however just at the beginning, being mostly confined where this technology has been first introduced in the field of DO, but it will probably spread all over the world. Additionally, further impressive breakthroughs are expected in the years to come as the full potential of SiPMs still has to be unleashed. Just to mention a couple of examples, while SiPM performance in the visible range is much more attractive than that in the near-infrared one, these detectors have been used to cover the entire spectral range of interest for DO, thus large signal gains are expected when InGaAs SPADs [76],[77] will be used to fabricate structures similar to SiPMs, which seems to be a current trend [78],[79]. Further, we have seen that the conditions for a breakthrough require the combination of a large detection area with fast time-gating capability.

Thus, the development of a detector embedding these two features is expected to bring additional advantages and orders of magnitude of gain in the dynamic range of TD DO measurements. This is what is pursued by the H2020 EC-funded SOLUS project [28], which aims at exploiting the combination of ultrasound imaging, shear-wave elastography and diffuse optical tomography for improving the specificity of breast cancer examinations. To this purpose, a compact optode is being developed, which embeds pulsed lasers and a time-gated detector [80]. Some of these optodes will be integrated into a single multimodal probe together with the ultrasound transducer and shear-wave elastography electronics. However, the optode will have a big potential also as a stand-alone object, with envisioned revolutionary impact in TD DO, enabling for the first time a widespread adoption of the technique.

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