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# Time-domain diffuse optics: towards next generation devices

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## ABSTRACT

Diffuse optics is a powerful tool for clinical applications ranging from oncology to neurology, but also for molecular imaging, and quality assessment of food, wood and pharmaceuticals. We show that ideally time-domain diffuse optics can give higher contrast and a higher penetration depth with respect to standard technology. In order to completely exploit the advantages of a time-domain system a distribution of sources and detectors with fast gating capabilities covering all the sample surface is needed. Here, we present the building block to build up such system. This basic component is made of a miniaturised source-detector pair embedded into the probe based on pulsed Vertical-Cavity Surface-Emitting Lasers (VCSEL) as sources and Single-Photon Avalanche Diodes (SPAD) or Silicon Photomultipliers (SiPM) as detectors. The possibility to miniaturized and dramatically increase the number of source detectors pairs open the way to an advancement of diffuse optics in terms of improvement of performances and exploration of new applications. Furthermore, availability of compact devices with reduction in size and cost can boost the application of this technique.

**Keywords:** Time Resolved Diffuse Optics, Photon Migration, SPAD, SiPM

## 1. INTRODUCTION

A common and classical method to non-invasively investigate diffusing media, like biological tissues, is to work in continuous-wave (CW) regime within the 600-1100 nm range, and detect the re-emitted light at a certain distance $\rho$ from the injection point. Deeper structures are probed if $\rho$ is increased. Such approach is severely compromised by the strong light attenuation and impaired spatial resolution due to absorption and scattering effect during light propagation in diffusive media. Working in a time-domain (TD) regime introduces one more variable (i.e. the photon time-of-flight $t$), which provides two benefits: the capability to uncouple absorption from scattering,[1] and the possibility to probe a medium in depth by exploiting long lived deep travelling photons.[2] Further, we have shown as a small/null- distance approach can optimize signal level, contrast and spatial resolution[3]. To do that an efficient gating mechanism is needed in order to extract the few late photons out of a huge burst of early photons.[4] Nowadays TD approach is limited by complexity of the system, costs, and poor signal to noise ratio as compared to CW systems. At the beginning large table-top pulsed lasers were employed as sources combined with streak-cameras as detectors. In the last decade, TD rack instruments, compatible with clinical use, based on pulsed diode lasers or fibre-based sources and on compact time-correlated single-photon counting (TCSPC) were developed. Still, the number of sources and detectors is quite limited and large fibre bundles are needed for efficient light collection. Gated intensified camera is suitable for a parallel detection scheme, but poor gating capability (suppression and dynamic range) are insufficient for the null-distance approach,[5] while the overall light harvesting is largely suboptimal. In this paper, we will first analyze potentialities of TD diffuse optics under realistic conditions, then we will present the basic building block of the envisaged TD system. Finally, we will discuss the potentialities of this new research direction.

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## 2. SIMULATIONS

Here we simulate a situation, which is common in many practical cases (such as assessment of tumor masses or brain functional activations). This problem is the detection of a focused inhomogeneity in absorption set at a certain depth $z$ within a semi-infinite highly scattering medium. We simulate an ideal system under realistic conditions, where sources and detectors cover all the free surface of the semi-infinite medium. Detectors are considered with unitary quantum efficiency and perfect gating capability, while the total laser light shined to the sample has a power density of 4mW/mm$^2$. We simulate the contrast $C=(N_0-N)/N_0$ produced by an inhomogeneity of 1 cm$^3$ (cube shaped) with a $\Delta\mu_a$ of +100% with respect to the absorption coefficient of the surrounding homogeneous turbid medium, where $N$ and $N_0$ are respectively the perturbed and unperturbed detected photons (Fig1). We compare ideal TD and CW systems for various $z$, assuming a 1 cm$^2$ square source-detector pair. Sources and detectors are set above the inclusion using a null distance approach ($\rho$=0) for TD and a classical approach (variable $\rho$) for CW. In the latter case, the contrast is plotted against the mean photon time of flight. Assuming that the inclusion can be detected if contrast is higher than 1% and the Poisson noise ($\sigma$) is lower than 1% (white region in Fig1), the CW approach is able to detect the absorption perturbation only down to z=2 cm using long source detectors separations $\rho\geq$4 cm because of low achievable contrast. Conversely, the TD approach can reach up to z=5 cm around photon time of flight around 7-8 ns. In this case, the TD contrast is several order of magnitude higher than the CW contrast.[6] However, also for z=2 cm (average depth of brain cortex in adults) the achievable contrast for the TD approach is 8-fold higher than the contrast for CW approach at $\rho$=5 cm. For comparison, we can consider that a state-of-the-art TD system[7] operating at $\rho$=3 cm can detect photons with $\sigma$<1% which travelled into the tissue at maximum of 3 ns, yielding a maximum reachable depth of z=3 cm.

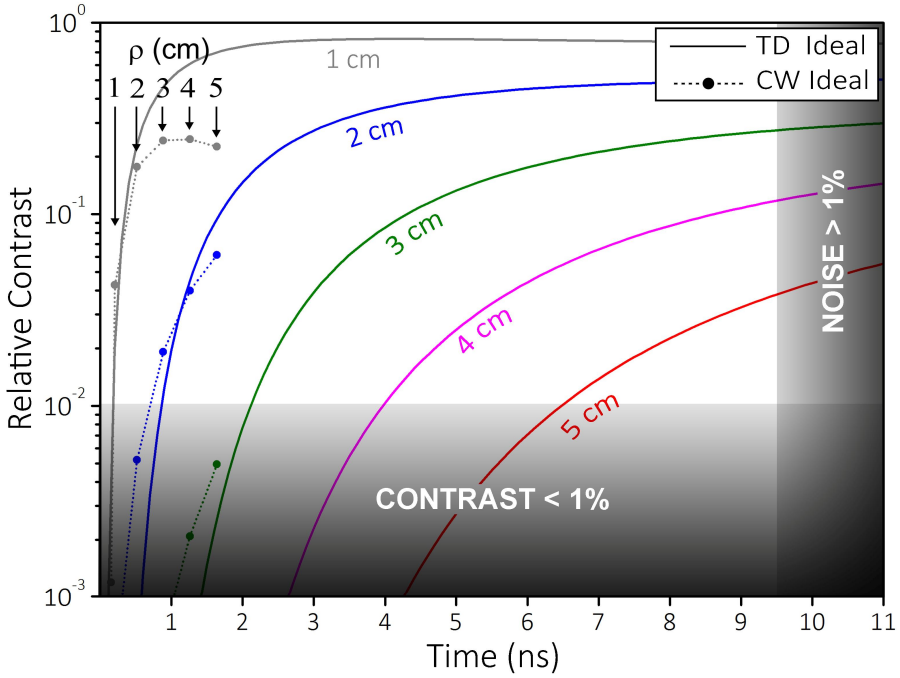


Figure 1. Simulation results.

## 3. EXPERIMENTS

A multichannel CW diffuse optics system which a number of sources and detectors sufficient in order to densely distributed them, approaching the ideal case, has already demonstrated showing exciting results in the field of functional brain imaging.[8] For the TD regime, three conditions are needed in order to fully exploit the potentialities presented in the previous paragraph: the gating capability of the detector for extracting late photons even at null source-detector distance (condition 1), a dense coverage of detectors (condition 2) and a dense coverage of sources (condition 3). Here we present the basic building block – a TD source-detector pair integrated directly onto the probe – that opens the way towards the

next generation of TD systems. For detection, we integrate on a probe a time-gated CMOS-SPAD or a free-running SiPM. The former was used in order to demonstrate the gating capability (condition 1) on a CMOS device with a still small active area (100 μm of diameter) but scalable and suitable for a dense integration. The latter still is not demonstrate to have gating capability, but it has a large (1 $mm^2$) active area, compact, low cost and densely packable, in fact it is developed for positron emission tomography systems, (condition 2). We implemented a pulsed VCSEL as source, also in this case this technology, developed for other applications, can be integrated and densely packed (condition 3). The probe is placed on the sample with ρ=0.5 cm for the SPAD based probe (SPAD-probe), and ρ=3 cm for the SiPM based probe (SiPM-probe). All the ancillary electronics (power supplies, VCSEL and SPAD gating circuit, amplifiers, TCSPC board) are still external. As a first validation we tested the SiPM-probe as a simple TD diffuse optics system retrieving the optical properties of a homogeneous medium (data not shown).[9] This probe shows a very good linearity and accuracy over the entire absorption and scattering measured range, thus demonstrating its usefulness for those applications where accurate optical properties assessment is needed (e.g. breast density assessment, fruit maturity staging). To validate the two probes for inhomogeneity detection we measured the contrast *C* generated by a 100 $mm^3$ black cylinder (equivalent to an increase in the absorption coefficient of 160% with respect to the surrounding medium over a 1 $cm^3$ sphere[10]) set at different depth within a homogeneous realistic phantom. SPAD-probe can detect the inhomogeneity (C>1%) down to 2.5 cm of depth, while SiPM-probe can reach the depth of 3.0 cm. The lower performances of SPAD-probe are probably due to the low detector area, which limits the usable temporal range. This issue can be solved employing gated detectors with larger area or gating an array of multiple detectors (as SiPM). However, SPAD-probe, in its present form, can reach a depth comparable of the depth of the adult brain cortex. To demonstrate the capabilities of the proposed approach for *in-vivo* applications we performed a standard motor cortex activation exercise (20 s of baseline, 20 s of finger tapping performed with the right hand and 20 s of recovery) positioning the SPAD-probe directly on the left hemisphere of the head over the representation of the right hand motor area.

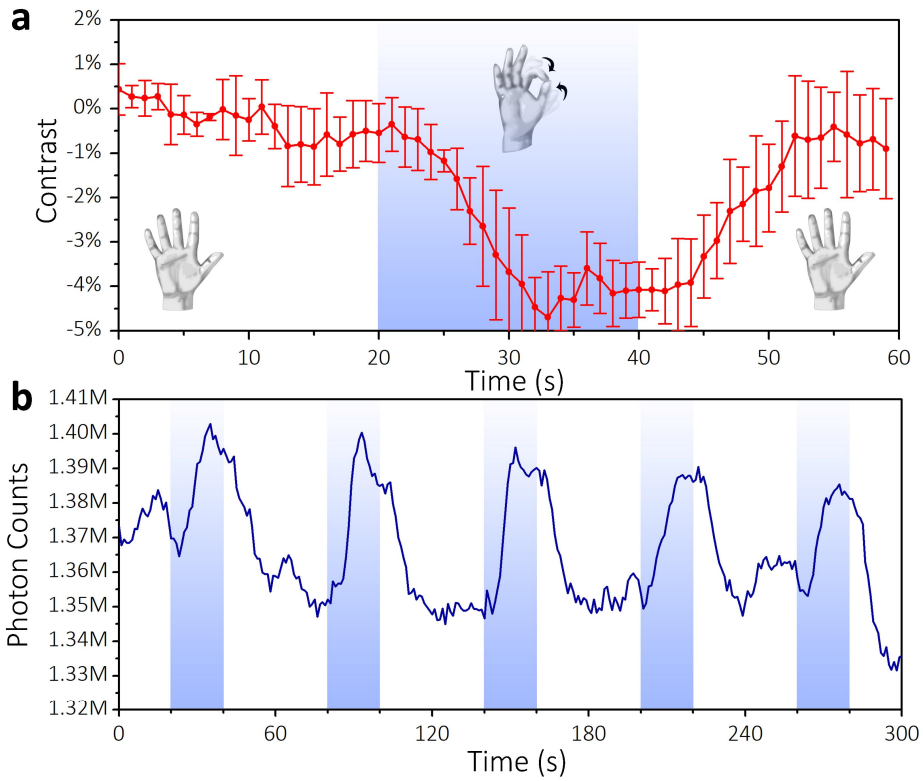


Figure 2. *In-vivo* results. a) Contrast averaged over the 5 repetitions. b) Total photon counts during the exercise.

This compact probe, which represents the single pixel of an array of the ideal TD system, can already detect standard motor-cortex activations even in this first implementation at short ρ. In fact, observing figure 2 (panel a), it is possible to clearly observe the task related change in the contrast *C* due to the brain activity. In panel a of figure 2 it is shown the

folding average of the contrast over 5 repetitions of the exercise. While in panel b of the same figure it is shown the total counts collected during the opening of the gate in the five repetitions of the exercise where it is possible to recognize the perturbation due to brain activity in all the single repetitions.

## 4. CONCLUSIONS

The demonstration of the basic integrated TD probe opens the way to a densely packed source and detector probe to fully exploit TD potential. This achievement would be a breakthrough in many ways. First, it will dramatically increase sensitivity, quantitation and localization capabilities in already existing clinical applications (e.g. optical mammography or brain imaging). Secondly, it will permit to reach non-invasively new organs too deep to be seen with conventional optical techniques, such as the lung (at the basis of many morbidities) or the heart (with the chance to detect the first onset of infarct). Looking further ahead, TD Diffuse Optics could evolve to a new generation imaging technique breaking the achievable depth limit and pushing the new limit towards 4-6 cm, comparable to other modalities such as ultrasonography, obviously with worse spatial resolution but with higher specificity (both chemical and functional). Along a parallel path, we envision small, portable/wearable, low cost TD devices, even at a single optode pair, of great interest in point-of-care or personalized health monitoring, but also in non-medical fields, such as on-line quality assessment of fruit or pharmaceuticals, monitoring of porous materials, or even development of smart-phone based consumer applications. Further steps are needed to exploit the full potential of TD systems. For the source, low-cost VCSEL production is already imminent due to the telecom interest. For detection, we easily foresee either the evolution of gated CMOS-SPAD towards larger collection area and dense parallelization, or of large area SiPMs towards fast time-gating. The additional electronics are constituted by standard blocks, suitable for smooth integration in a CMOS chip, including the TCSPC board, to be replaced by time-to-digital converters already integrated in SiPMs or SPADs. In conclusion, we have demonstrated the first building block of next generation TD systems for Diffuse Optics with sources and detectors embedded onto the probe itself.

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