POLITECNICO
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Time-Domain Near Infrared Spectroscopy

Davide Contini
Politecnico di Milano – Physics Department

davide.contini@polimi.it

Outline

1. Introduction
2. TD-NIRS
3. SiPMs for TD-NIRS
4. SPADs for TD-NIRS
5. Conclusion

davide.contini@polimi.it

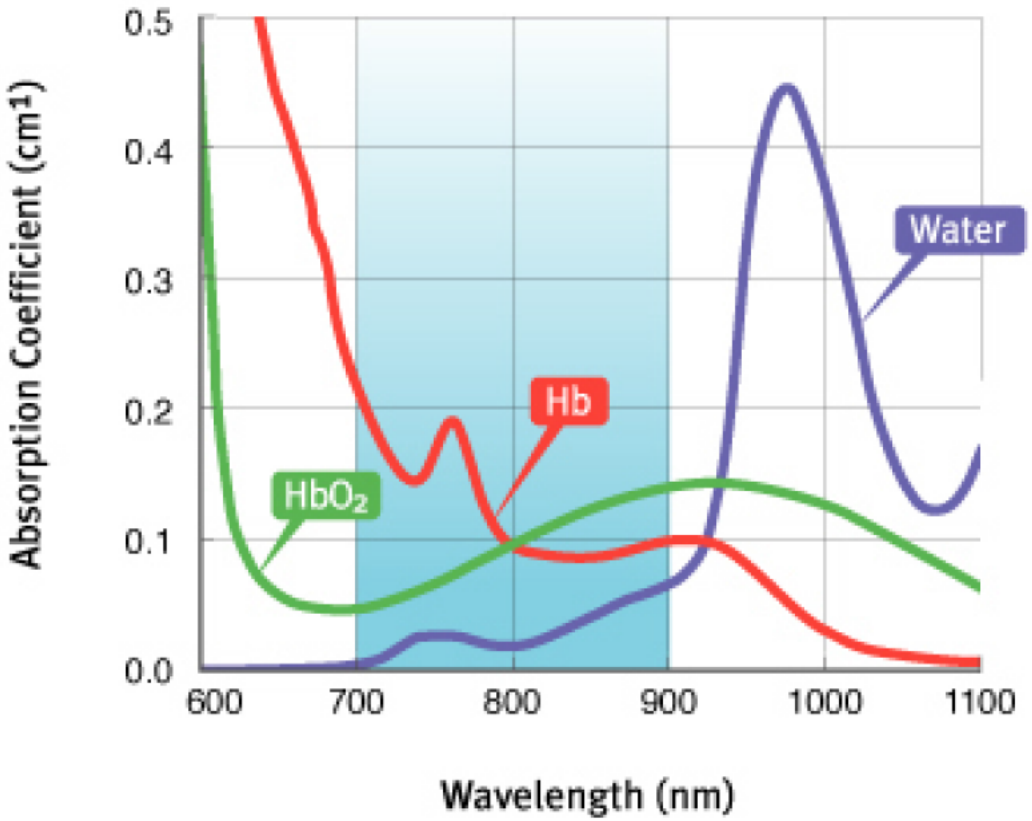
Can light penetrate turbid medium light biological tissues?

Georges de La Tour (1593 – 1652)

St Joseph, 1642, Louvre, Paris

davide.contini@polimi.it

Therapeutic window



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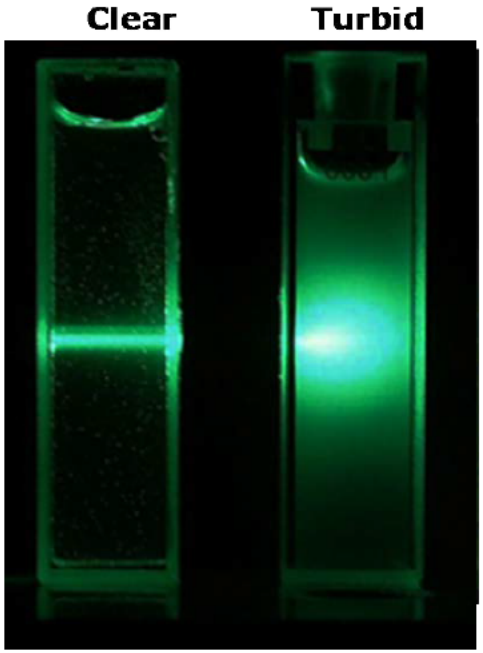
Photon migration in turbid media



- **Scattering effect dominant**
- **Path-length unknown**

Absorption: related to tissue components

Absorption coefficient:

$\mu_a = 1/\ell_a$ (cm^{-1})

Scattering: related to tissue structure

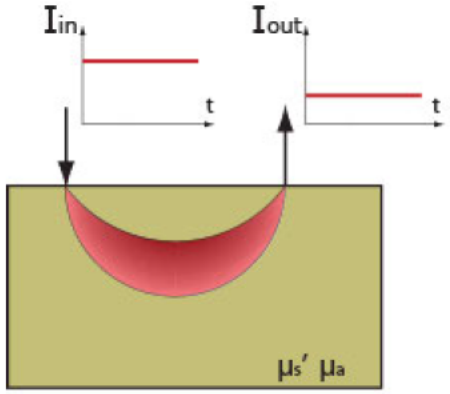
Scattering coefficient:

$\mu_s = 1/\ell_s$ (cm^{-1})

davide.contini@polimi.it

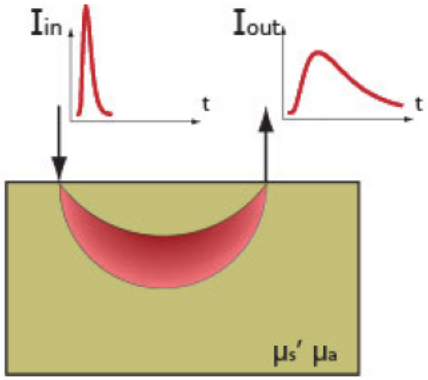
Near Infrared Spectroscopy modalities

CW



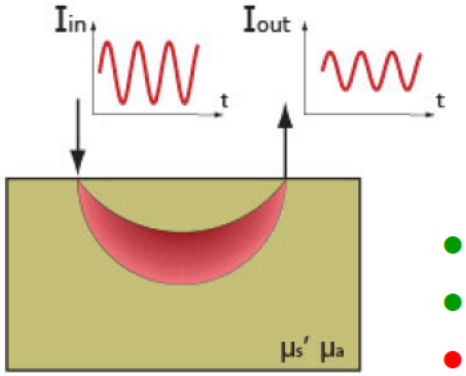
- Sampling rate
- Size and simplicity
- No absolute values
- Penetration depth

TD



- Absolute values
- Penetration depth
- Spatial resolution
- Complexity

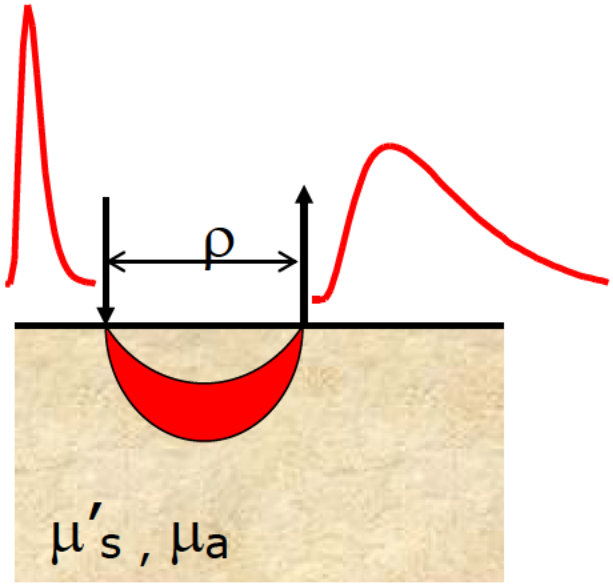
FD



- Absolute values
- Sampling rate
- Penetration depth

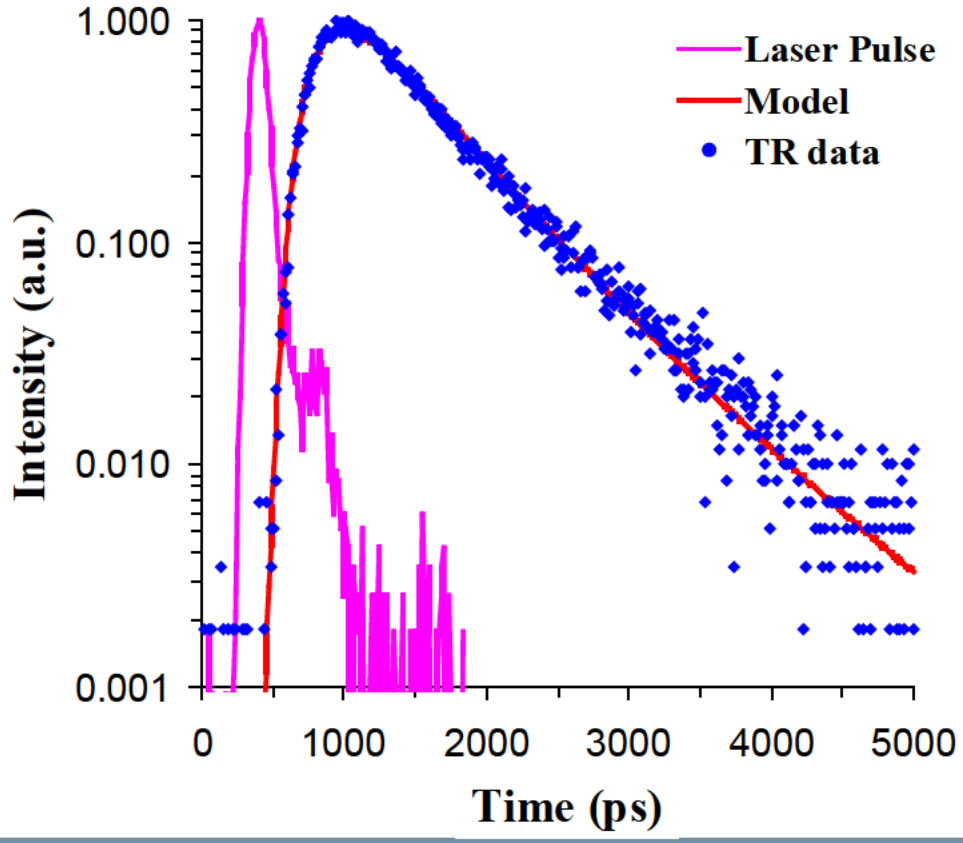
davide.contini@polimi.it

Time-Domain Near Infrared Spectroscopy: Accuracy



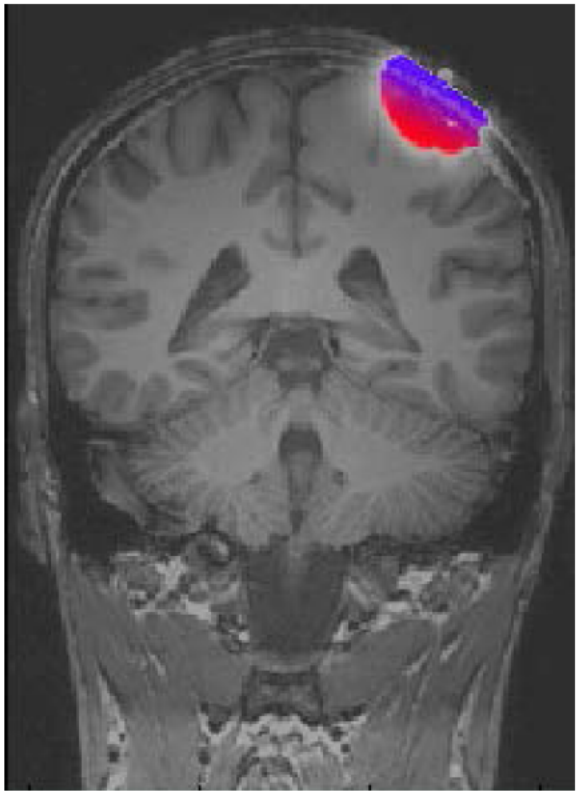
Diffusion equation:

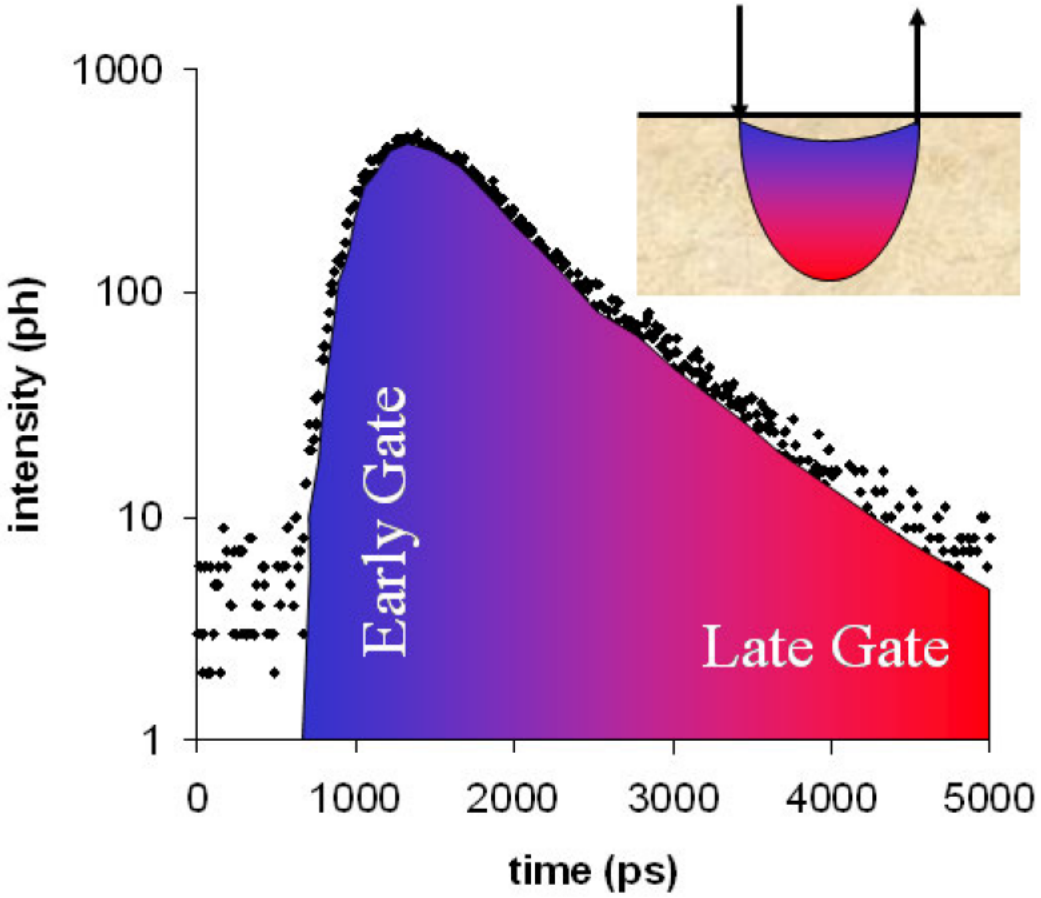
$$R(\rho,t) \cong A\, t^{-5/2} \left(\mu_s'\right)^{1/2} exp\left(-\frac{3\mu_s'\rho^2}{4vt}\right) exp\left(-\mu_a vt\right)$$



davide.contini@polimi.it

Time-Domain Near Infrared Spectroscopy: Depth sensitivity



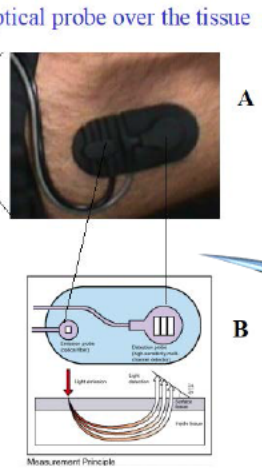


davide.contini@polimi.it

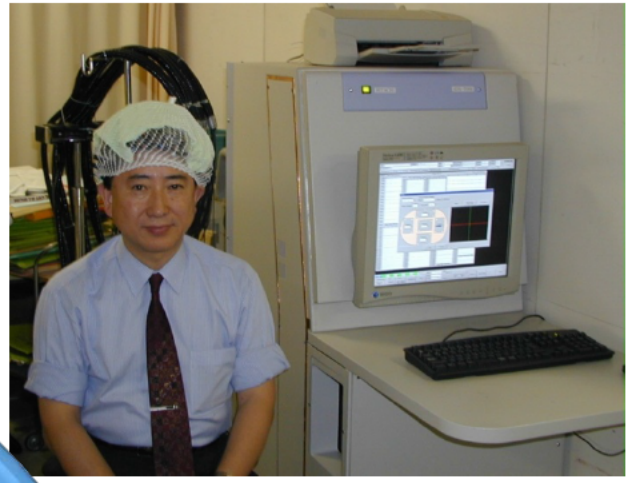
Physics told us a story but reality is different….(1 of 2)

Hamamatsu, KK

Single-channel

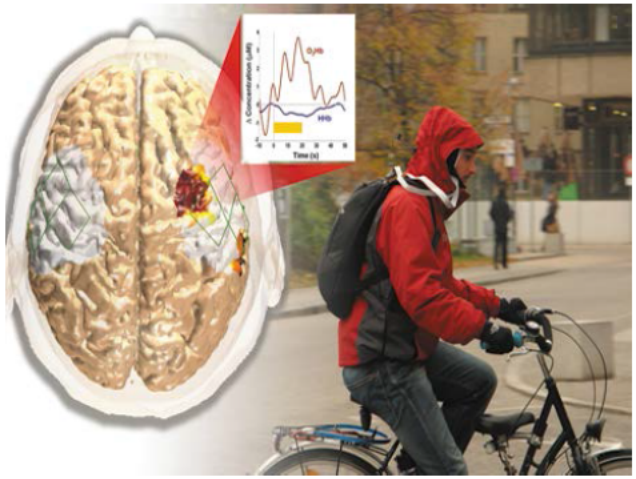


1992



Hitachi Medical, KK

Multi-channel



NIRx, USA

2014

Wearable

M.Ferrari & V.Quaresima, Neuroimage 63:921-935 (2012)

davide.contini@polimi.it

Physics told us a story but reality is different….(2 of 2)

Research


(a)


(b)


(c)


(d)


(e)

(a) fOXY PoliMi (b) Brain imager IBBE (c) Brain imager PTB (d) MONSTIR2 UCL (e) TGI-2 MGH

Commercial

Hamamatsu Photonics K.K., Japan
Fujisaka et al. ISOTT 2015

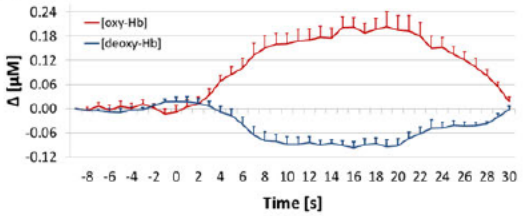
davide.contini@polimi.it

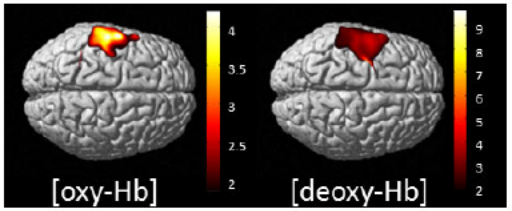
State of the art system (1 of 3)

healthy

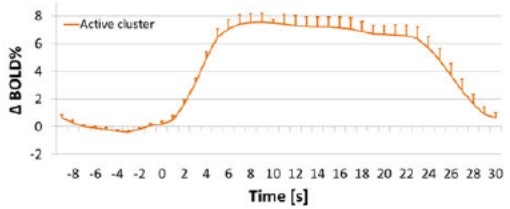
ULD patients

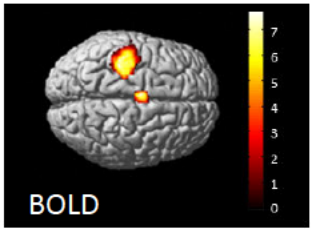
A



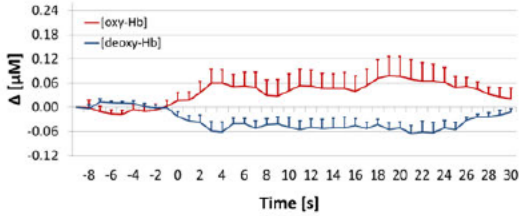


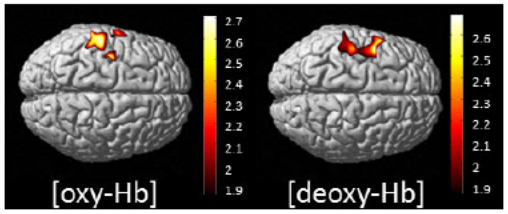
B



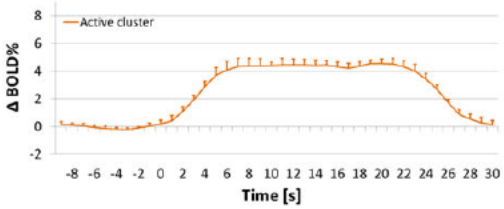


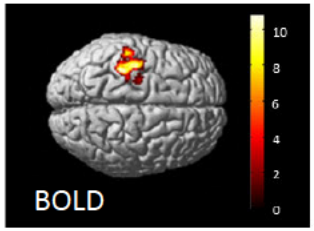
D

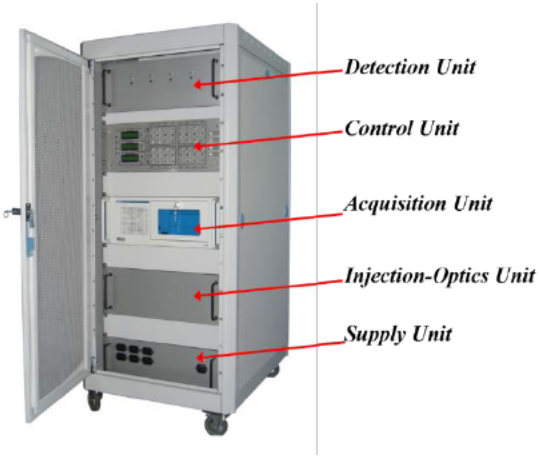




E







Contini *et al.*, Opt Expr, 14: 5418-5432 (2006).

NEUROPt
Non-invasive imaging of brain function and disease by pulsed near infrared light

Visani *et al.* Brain Topography *DOI: 10.1007/s10548-014-0402-6* (2014)

davide.contini@polimi.it

State of the art system (2 of 3)

BABYLUX

davide.contini@polimi.it

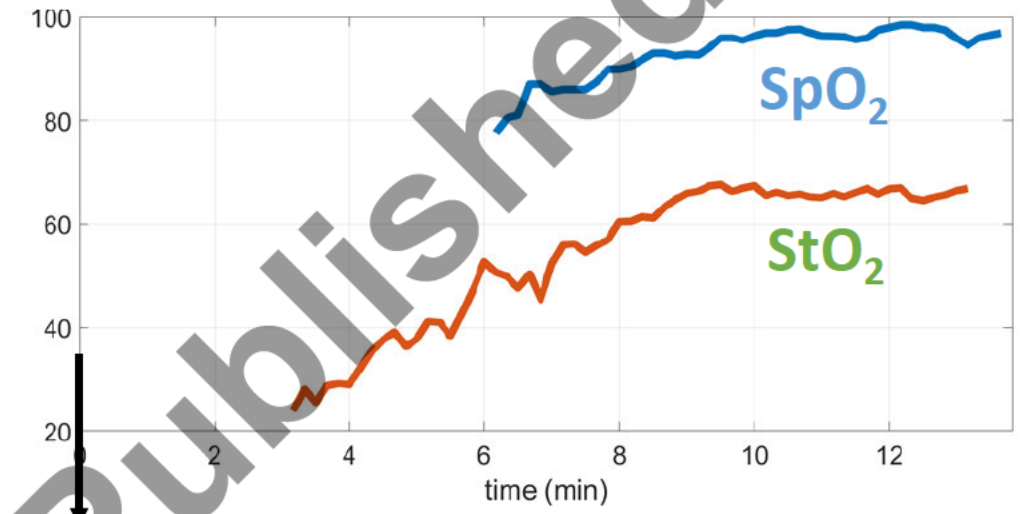
State of the art system (3 of 3)

Inclusion criteria

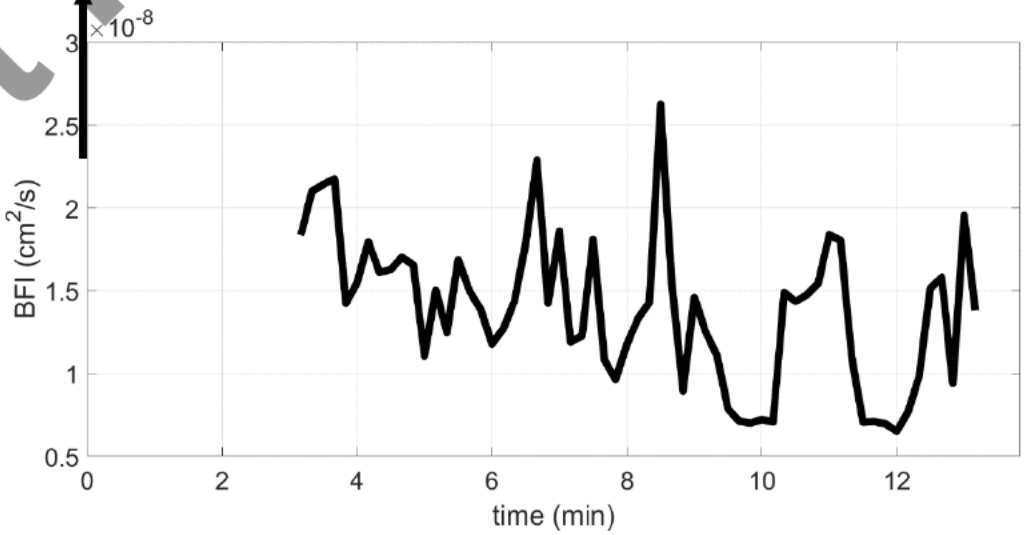
- term newborns (with a gestational age > 37 weeks)
- planned to be delivered by an uncomplicated elective caesarean section

Physiological raise in oxygenation

- Already measured with cerebral oximetry [Pichler et al., (2013), *Journal of Pediatrics*.]

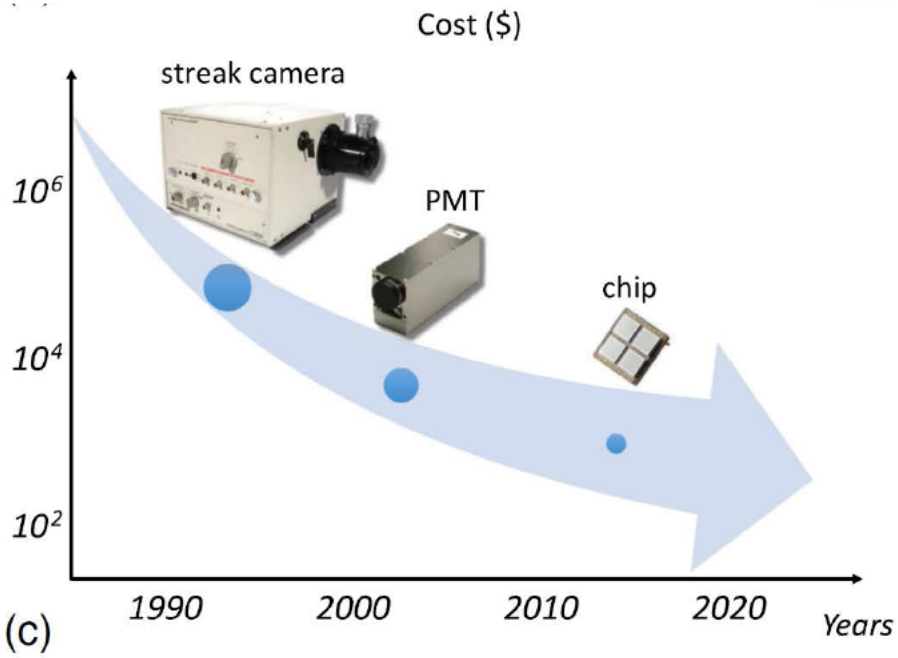


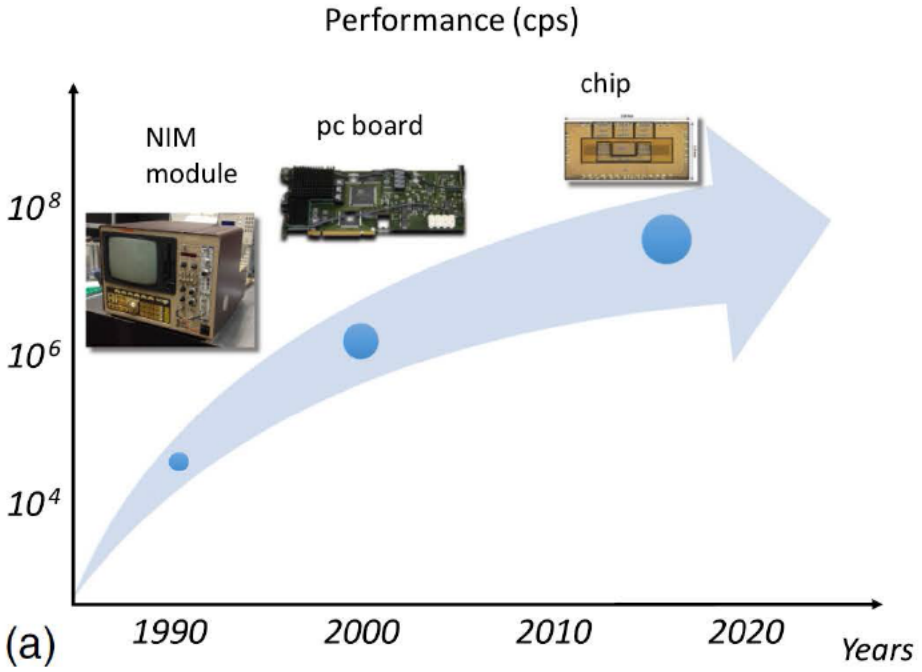
Time of birth



davide.contini@polimi.it

Towards Next generation system



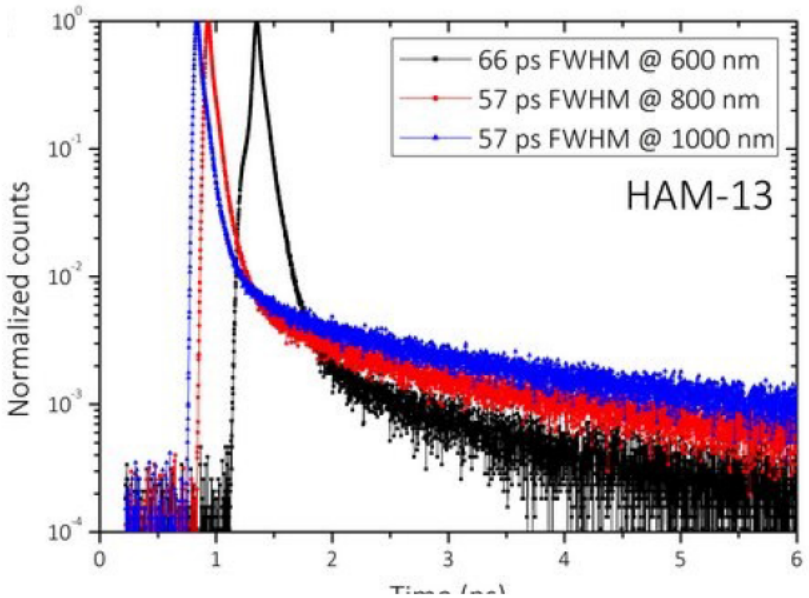


Pifferi et al. **JBO**, 21 (9) (2016)

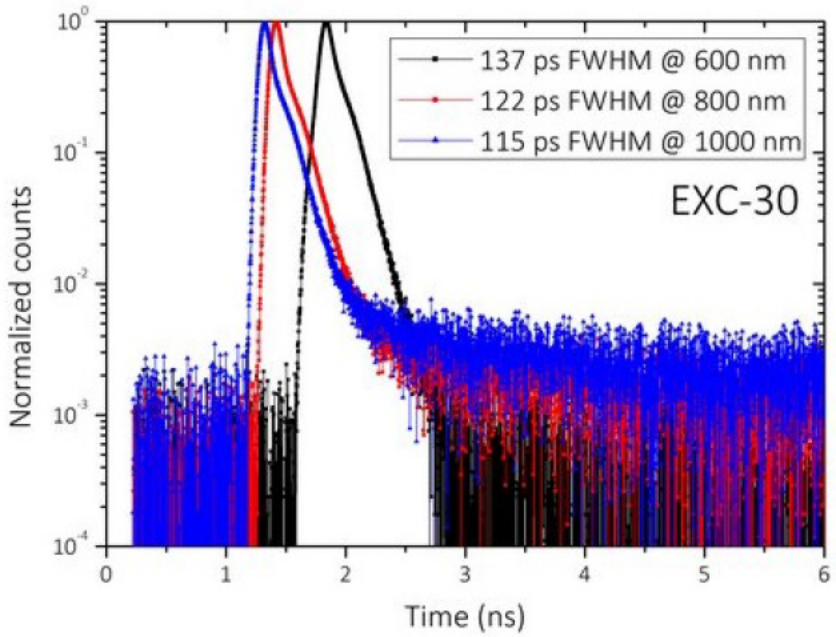
davide.contini@polimi.it

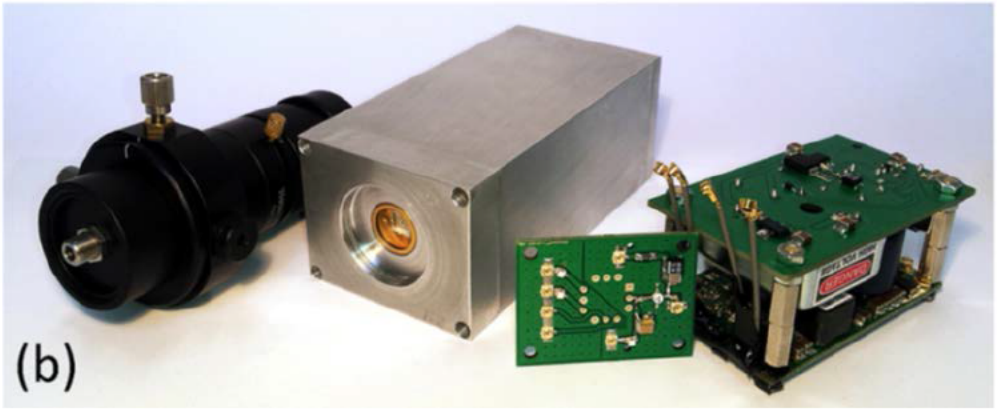
Towards Next generation system: SiPM

1.7 mm² SiPM



9 mm² SiPM





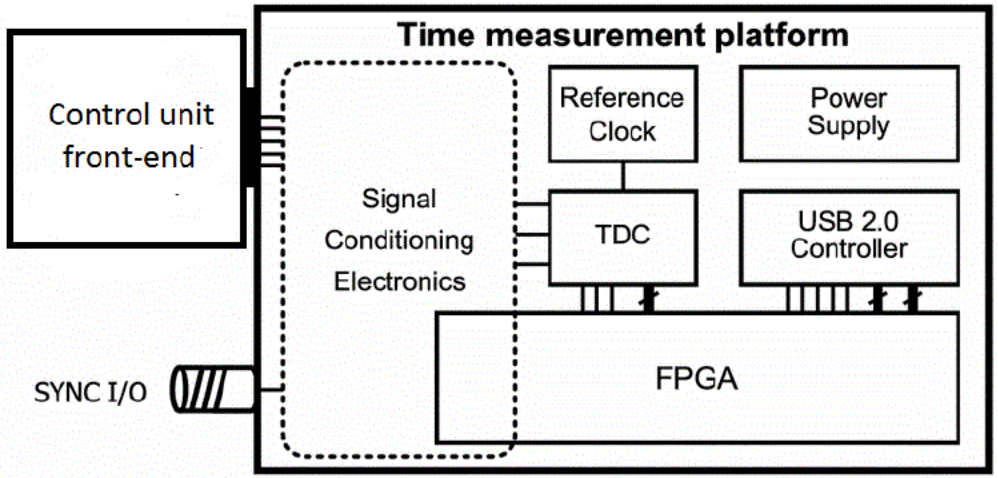
- ✓ Active area = 1.7 mm²
- ✓ Microcells fill-factor ≥ 74%
- ✓ QE @ 650 nm ~ 20%, @ 900 nm ~ 2%
- ✓ Timing resolution ~ 80 ps (FWHM)
- ✓ Background noise ~ 20 kcps
- ✓ Count rate > 2 Mcps

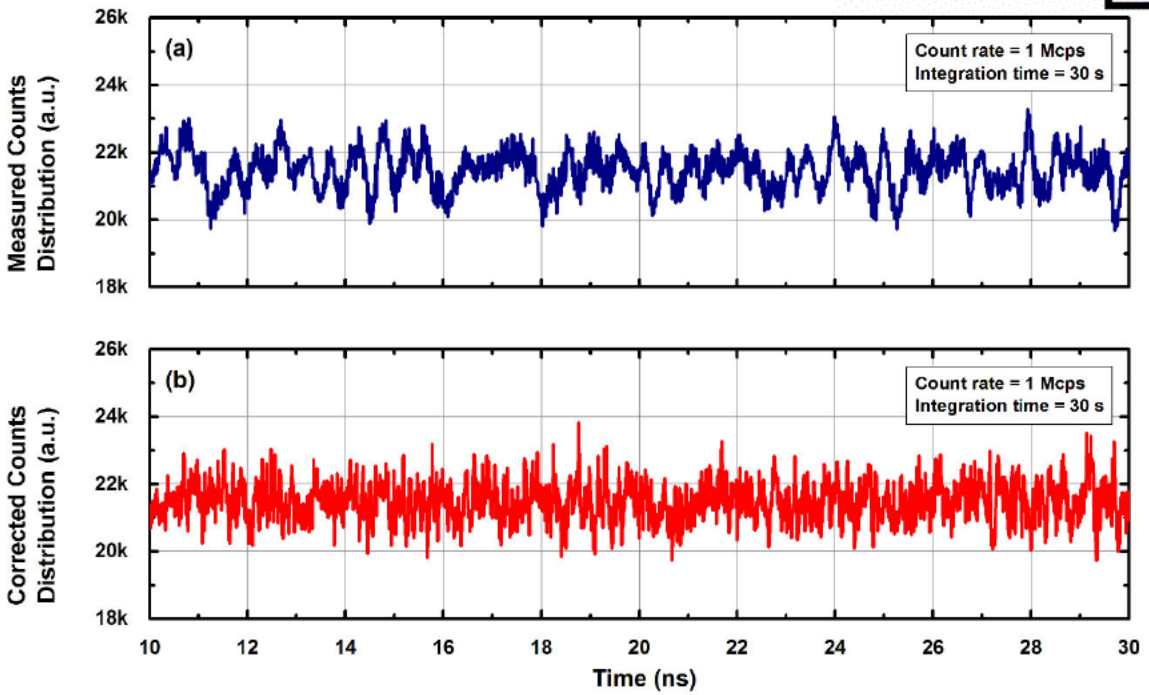
Dalla Mora et al. **Opt Expr**, 23:13937 (2015)
Martinenghi et al. **RSI**, 87 (2016)

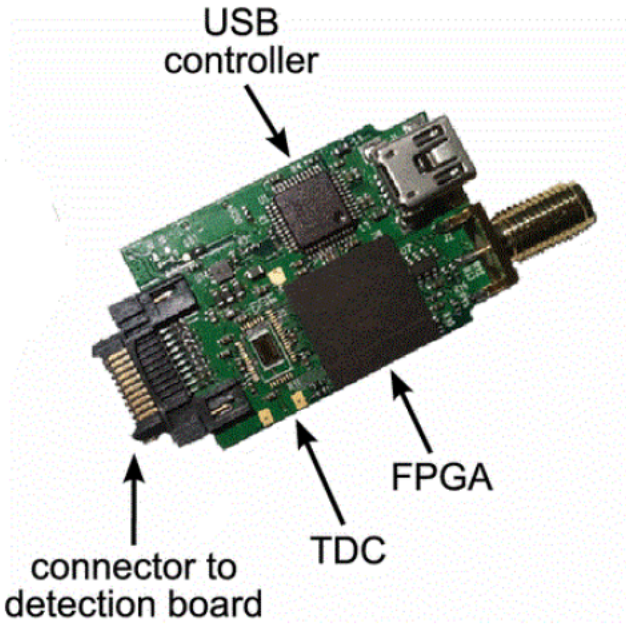
davide.contini@polimi.it

Towards Next generation system: TDC

- ✓ Based on FPGA and custom CMOS technology
- ✓ Temporal resolution: 10 ps
- ✓ Single shot precision: 40 ps
- ✓ DNL: Extremely repeatable
- ✓ DNL: 3% down to 1% with correction



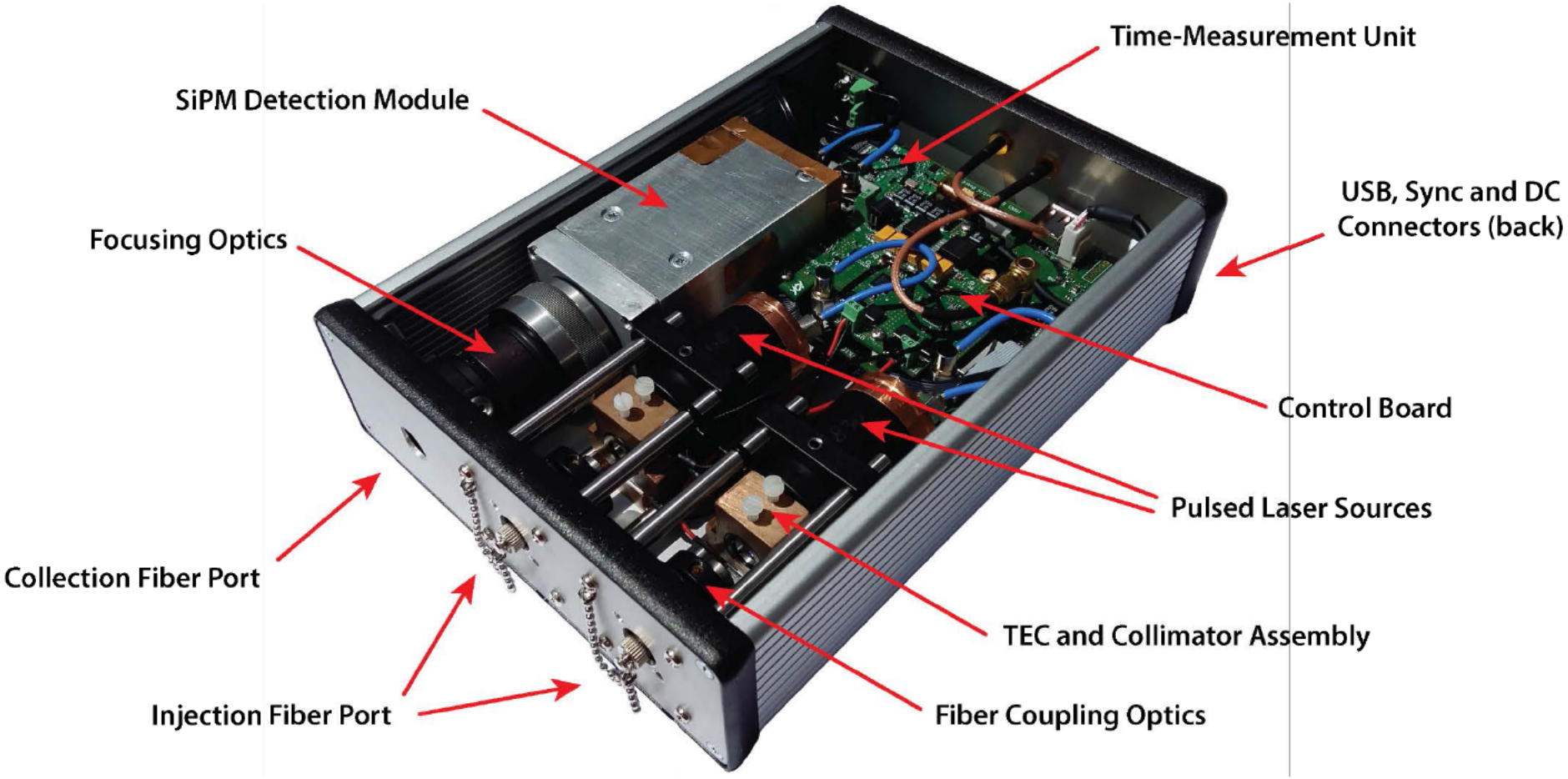




Developed by Electronics Departments of Politecnico di Milano

davide.contini@polimi.it

Next generation system



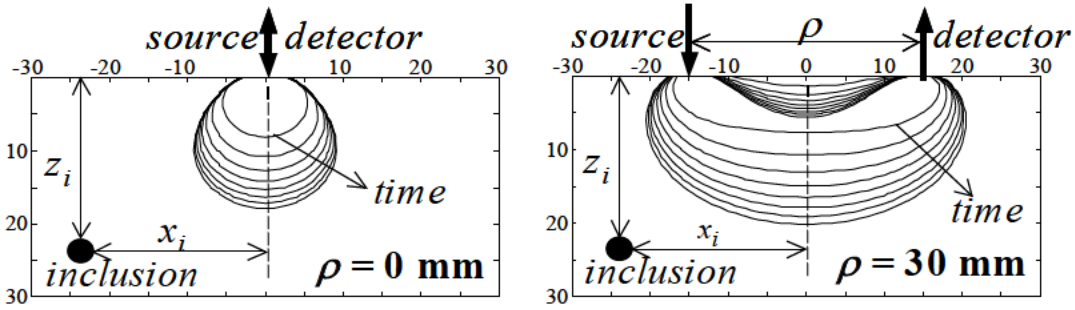
Collaboration between Physics and Electronics Departments of Politecnico di Milano

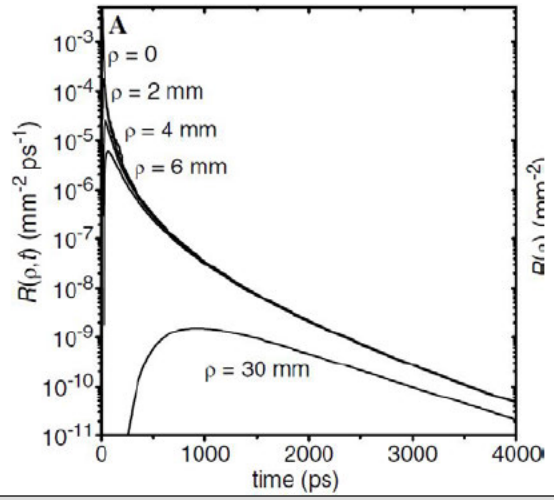
M. Buttafava *et al.*, *IEEE Photonics Journal*, vol. 9(1) (2017)

davide.contini@polimi.it

Small source-detector distance approach

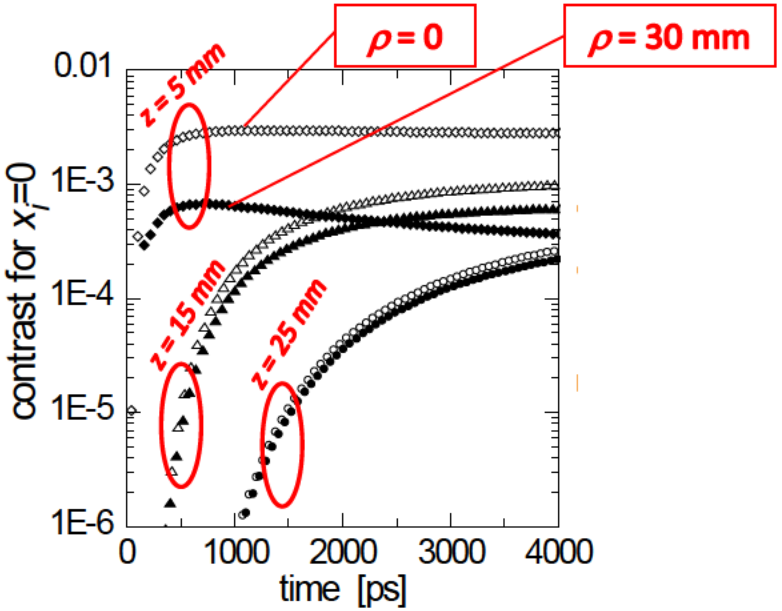
Torricelli et al. **Phys. Rev. Lett.**, 95:078101 (2005)

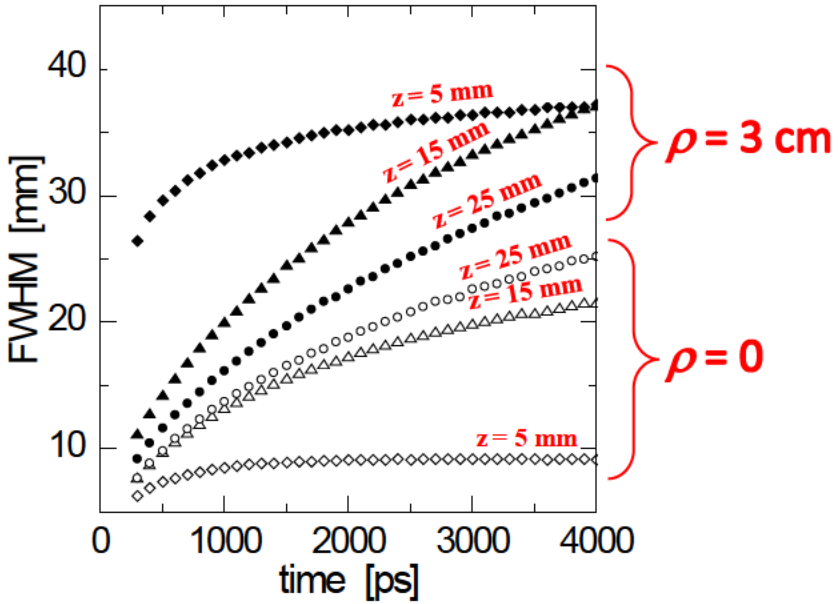




⇒ More **confined** and simmetrical sensitivity region for $\rho = 0$

⇒ **SIGNAL INTENSITY** always **BETTER** at $\forall$ t for $\rho = 0$



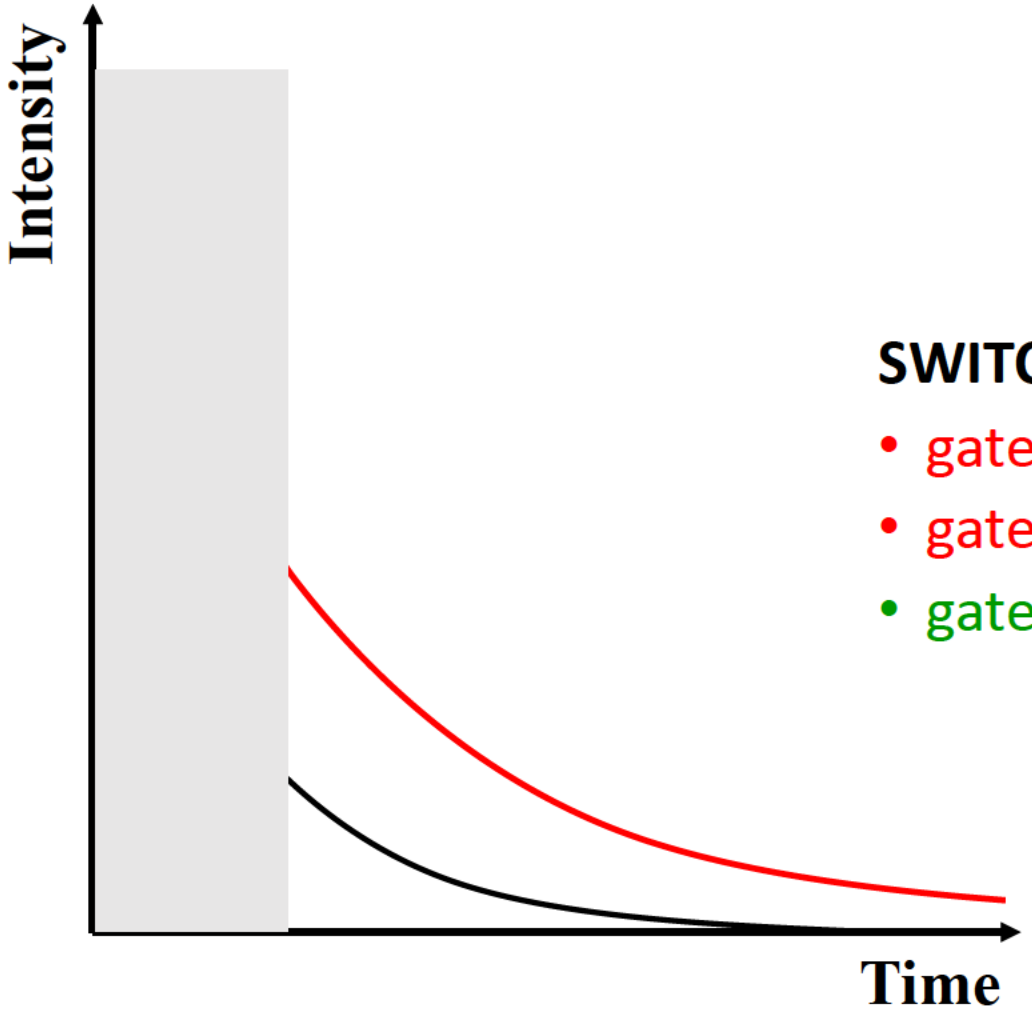


⇒ **CONTRAST** always **BETTER** at $\forall$ t for $\rho = 0$

⇒ **SPATIAL RESOLUTION** always **BETTER** at $\forall$ t for $\rho = 0$

davide.contini@polimi.it

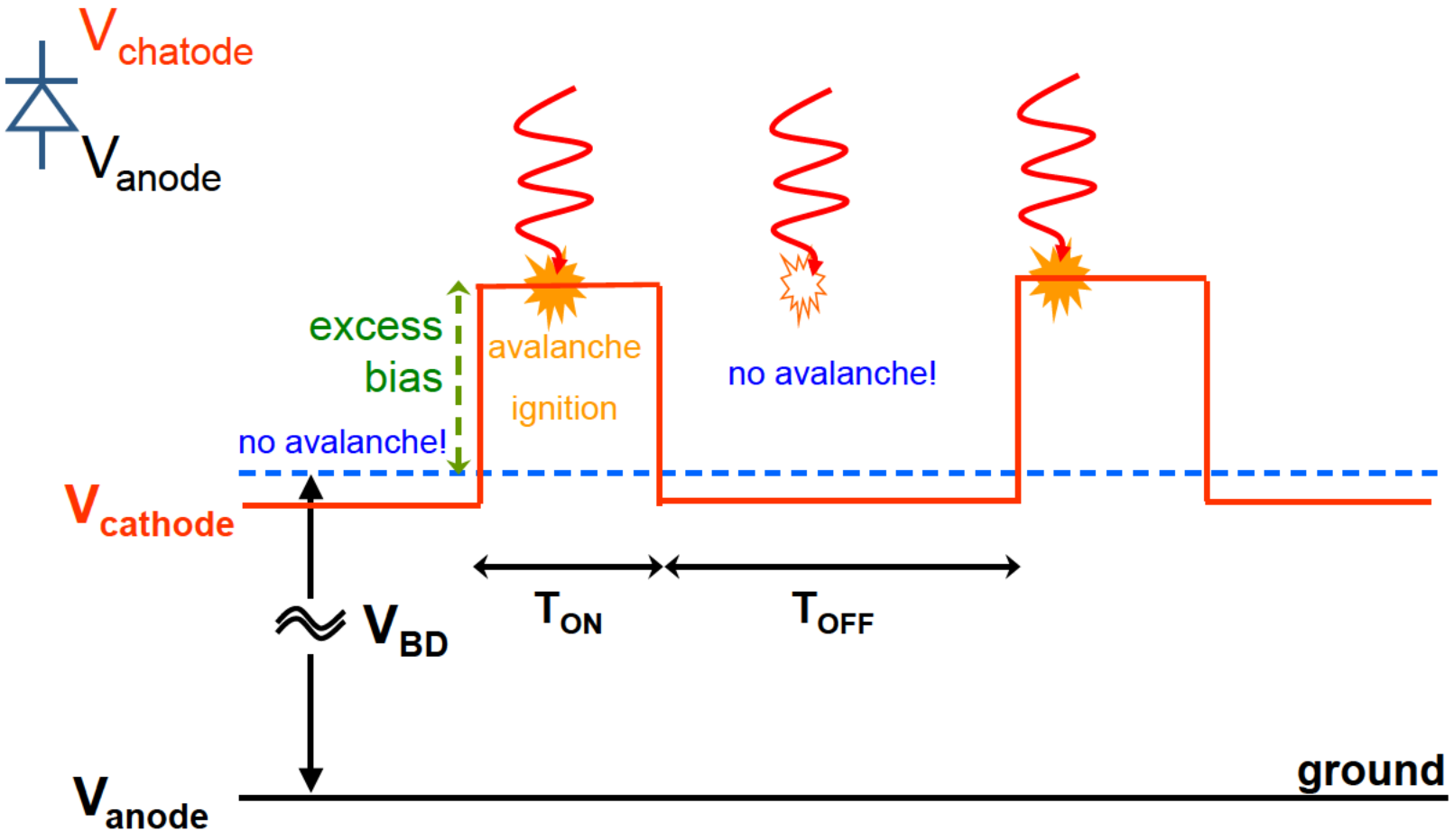
How to practically suppress early photons ?



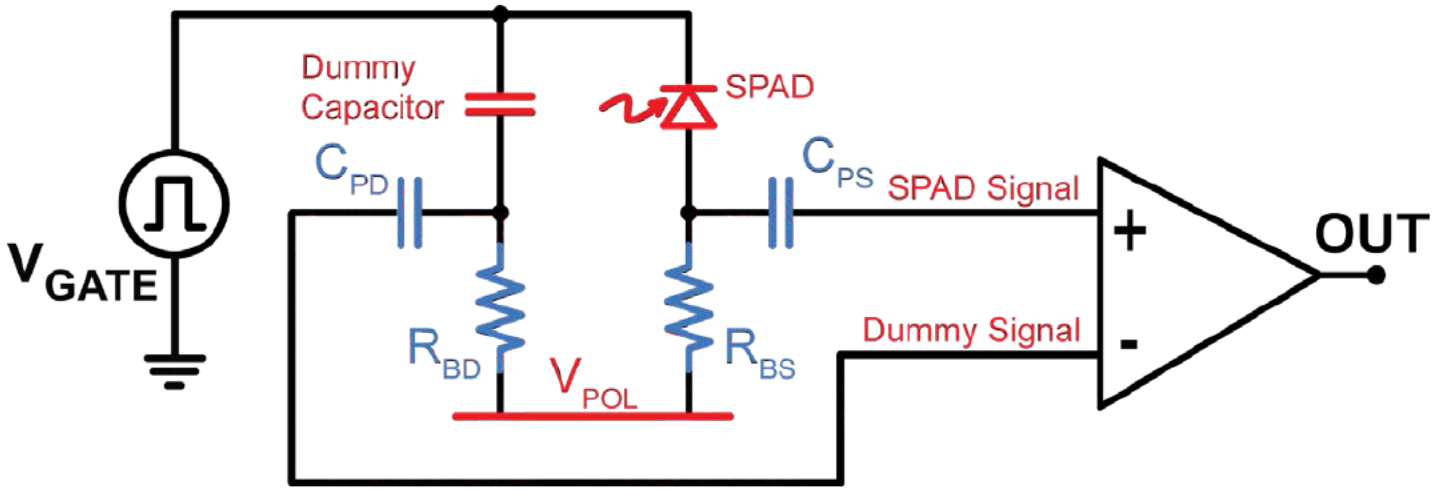
SWITCH OFF THE DETECTOR

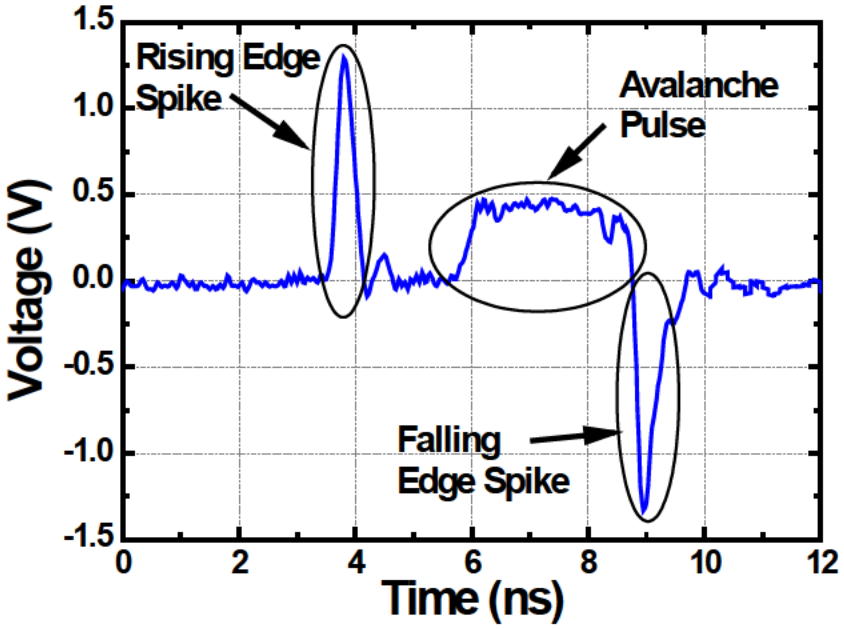
- gated MCP → probably NO
- gated ICCD → probably NO
- gated SPAD → probably YES

Gated-mode operation of SPADs



Passive quenching, dummy path and differential sensing

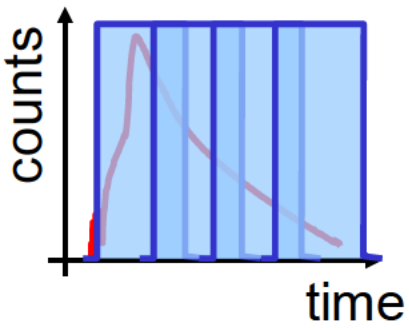




rise/fall transitions = 200 ps

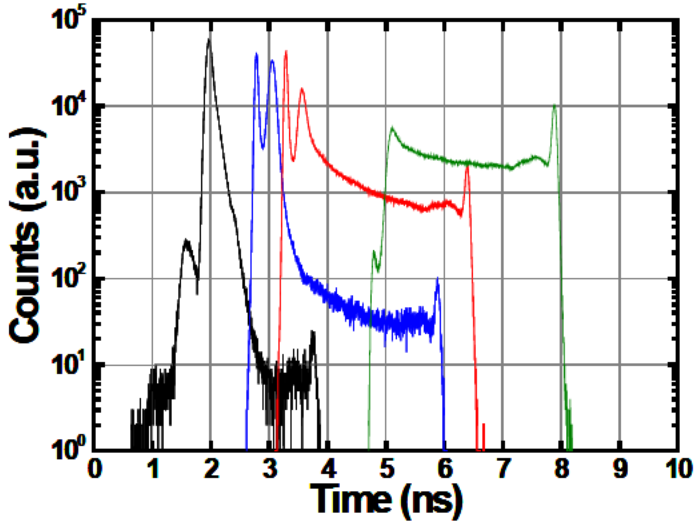
capacitive
feed-through spikes
are **3 times higher** than
the avalanche pulse

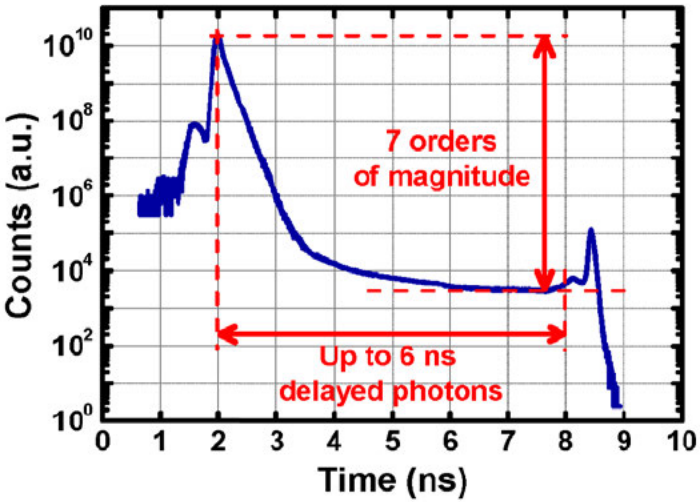
TD-NIRS at small source-detector separation: layout



Thanks to fast gating
→ early (previous) photons are rejected
→ **laser power can be increased**

The fast-gated SPAD module developed by the Electronics Dept. of Politecnico di Milano



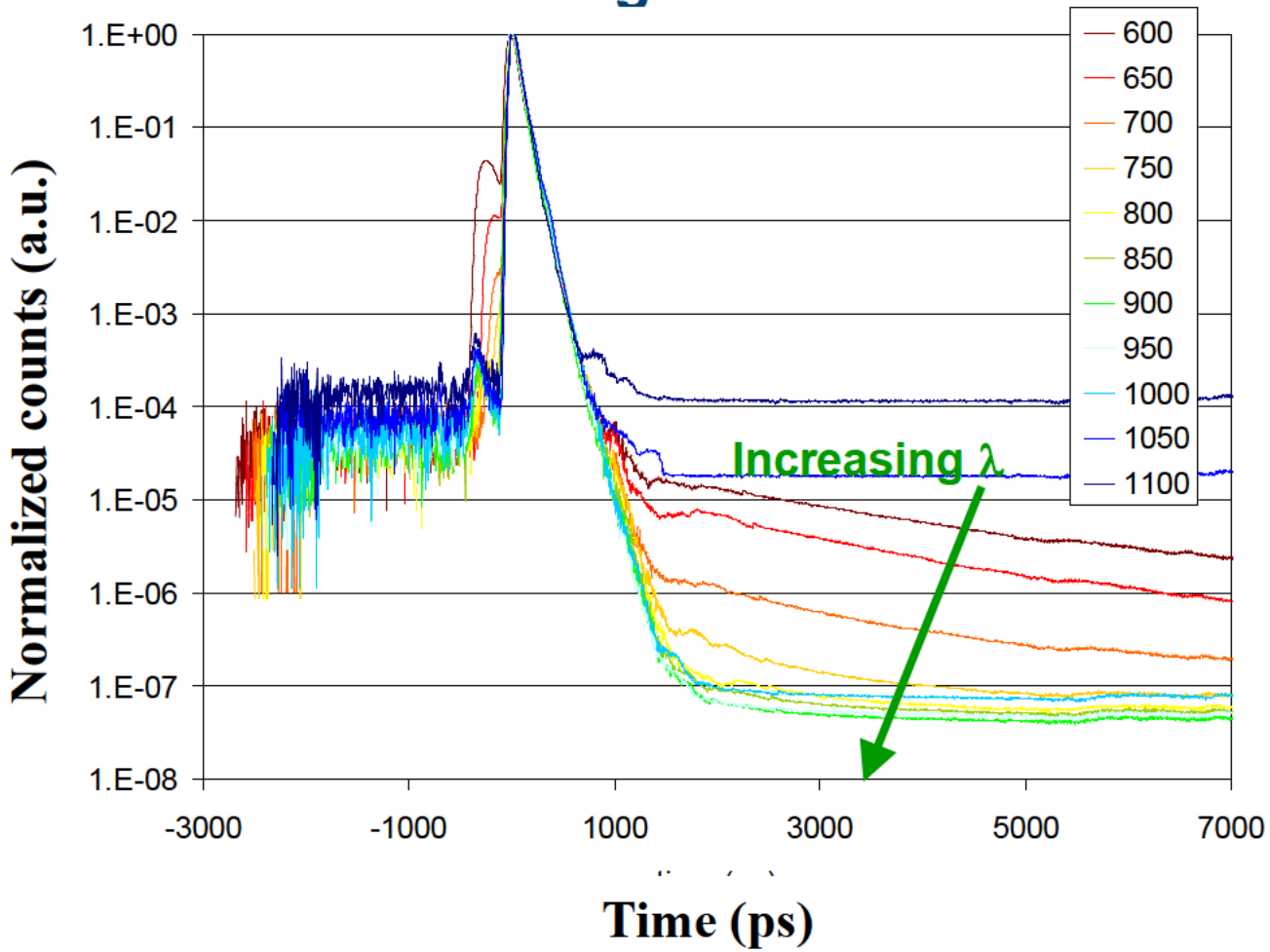


Pifferi et al., **Phys Rev Lett** 100:138101 (2008)

Dalla Mora et al, **IEEE J Sel Top Quant Electr** 16:1023 (2010)

Tosi et al., **Opt Exp** 19 :10735 (2011)

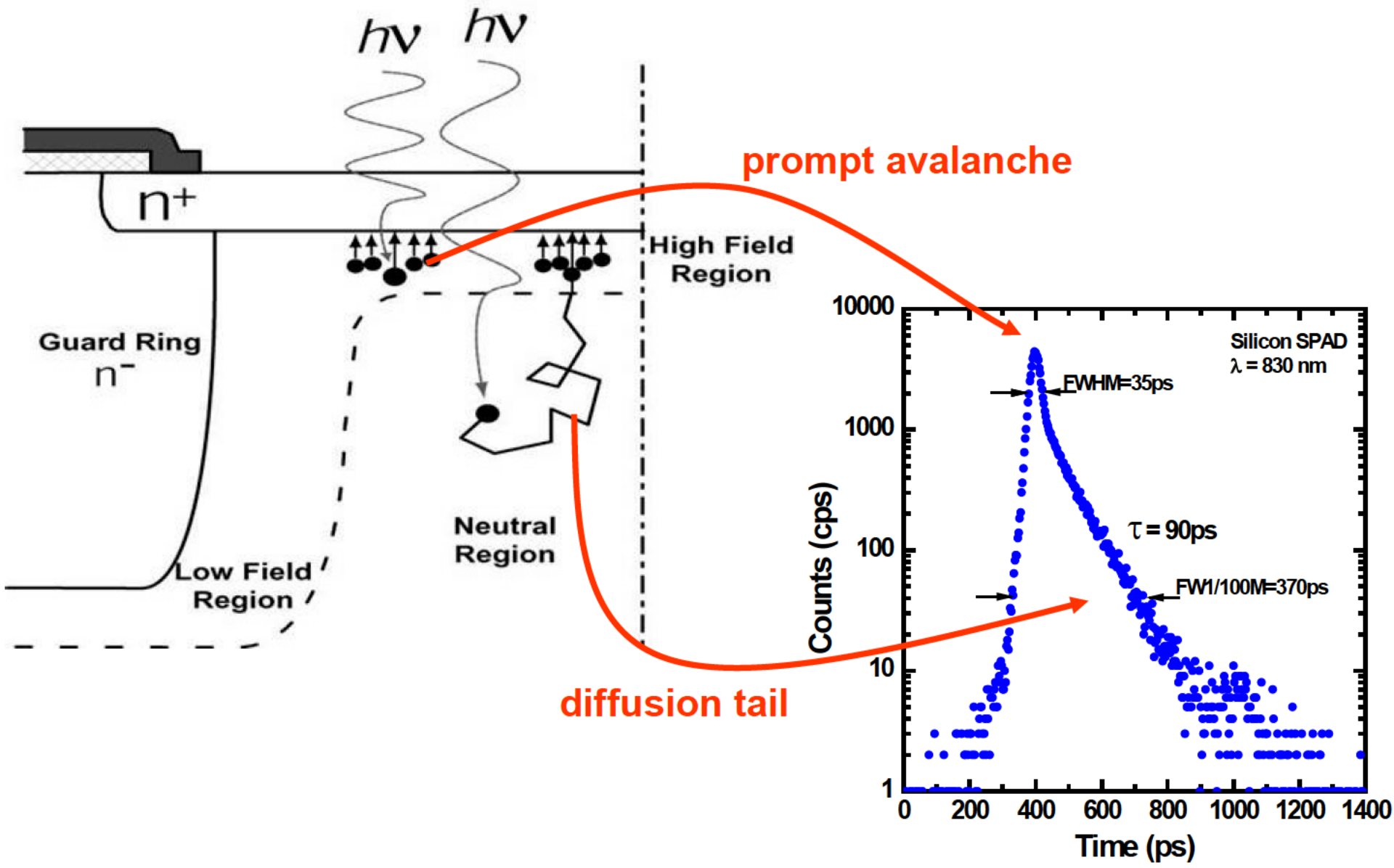
Measurements (100µm SPAD): IRF at different wavelengths



Dynamic Range limited by:

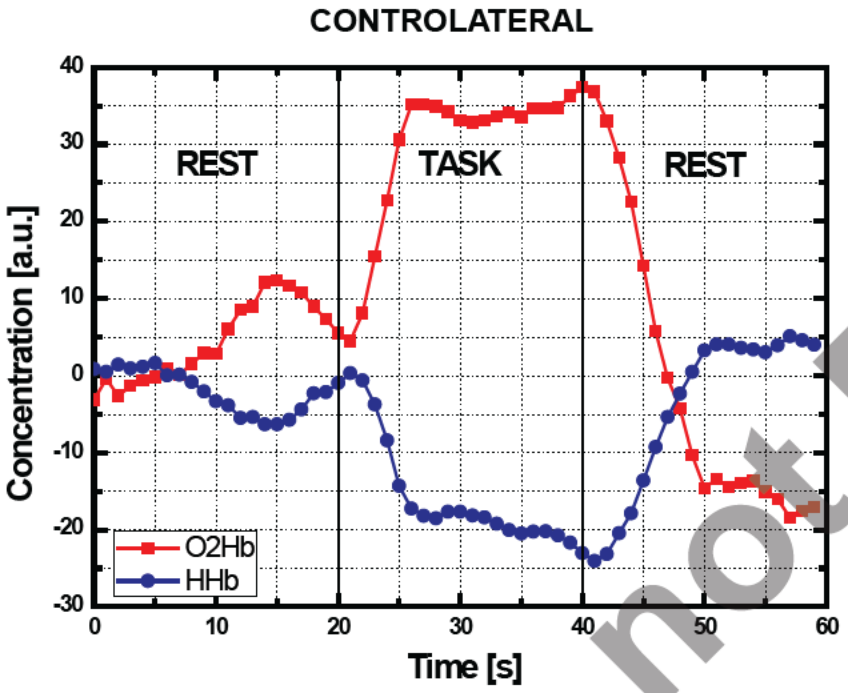
- **memory effect**

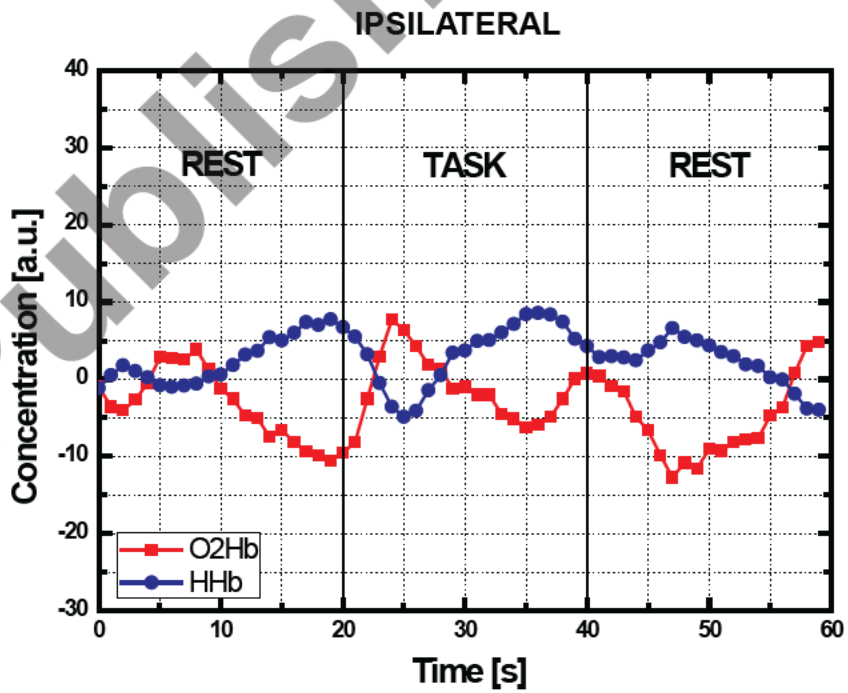
Carrier diffusion tail



TD-NIRS at small source-detector separation: Brain

IN VIVO detection of brain activity during MOTOR TASK excercise

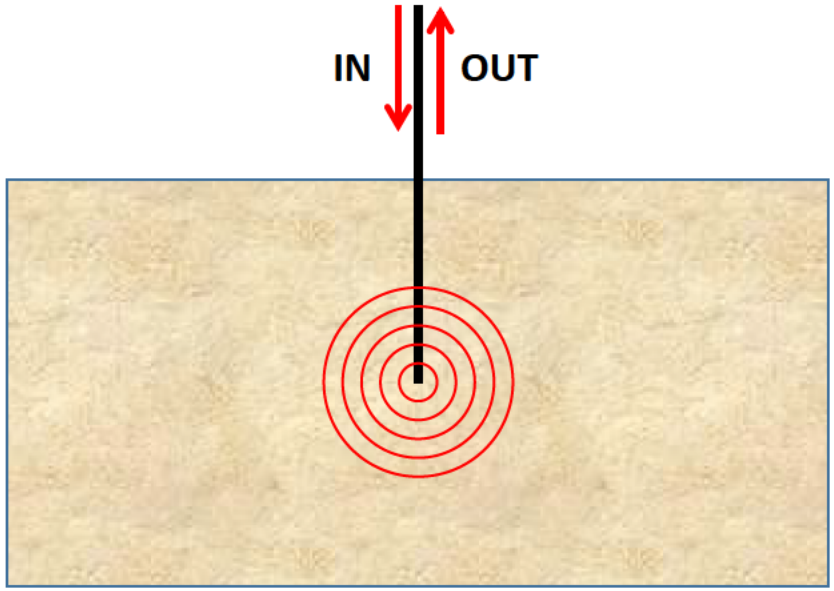




⇒ Feasibility of fNIRS at short distances with high SNR

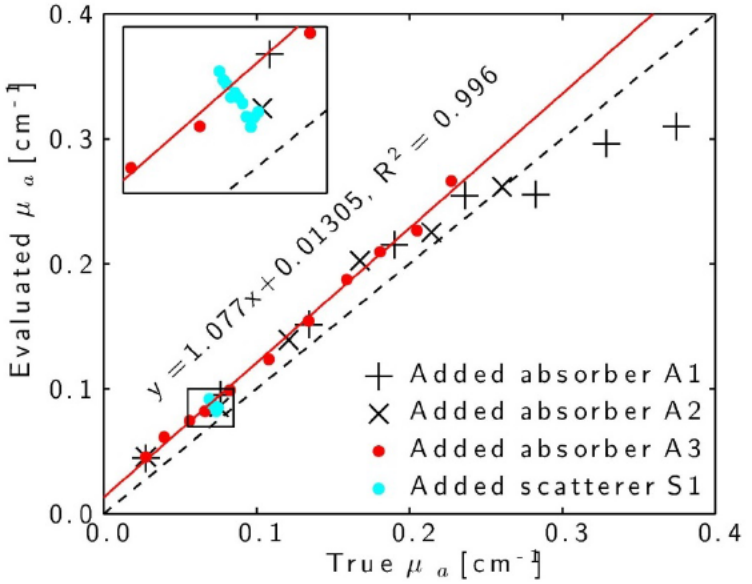
TD-NIRS at small source-detector separation: Spectroscopy

Collaboration:
S.Andersson-Engels, Lund University



Rejection of STRONG direct reflection by early photons suppression

PHANTOM RESULTS

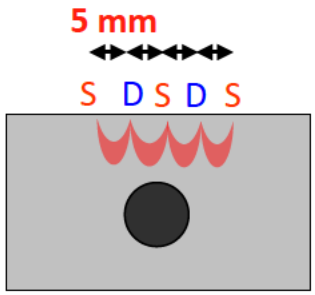


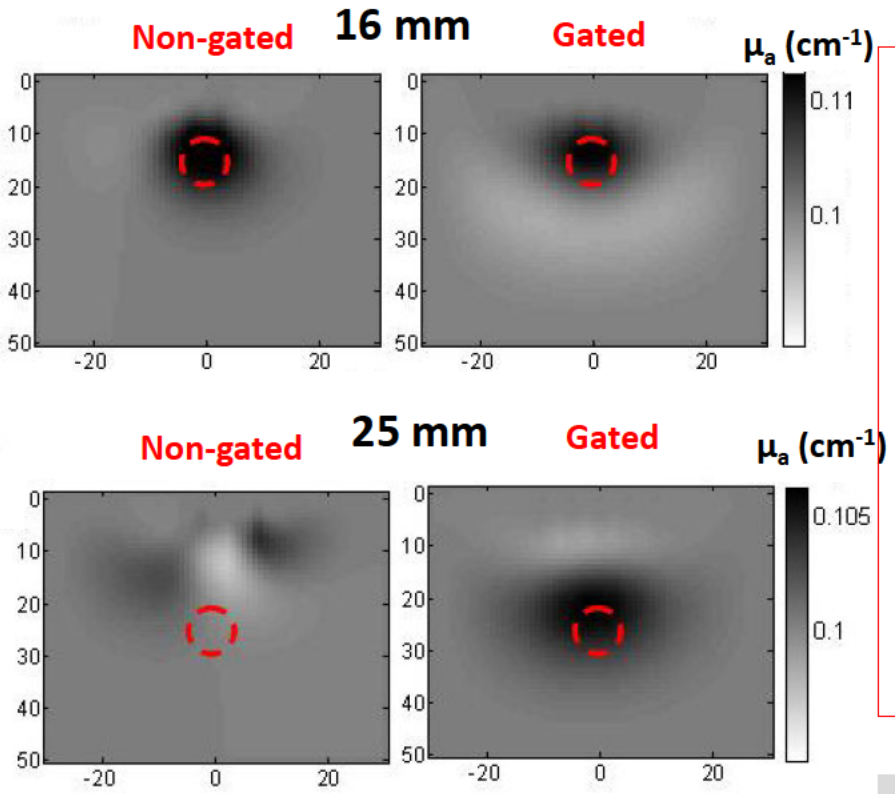
Alerstam et al. **Opt Lett**, 37:2877 (2012)

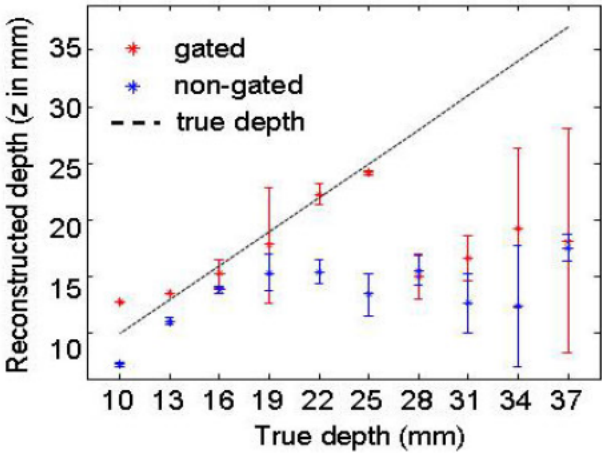
⇒ **Feasibility of single-fiber interstitial spectroscopy**

TD-NIRS at small source-detector separation: Tomography

Collboration:
A. Planat Chretien, CEA, Grenoble



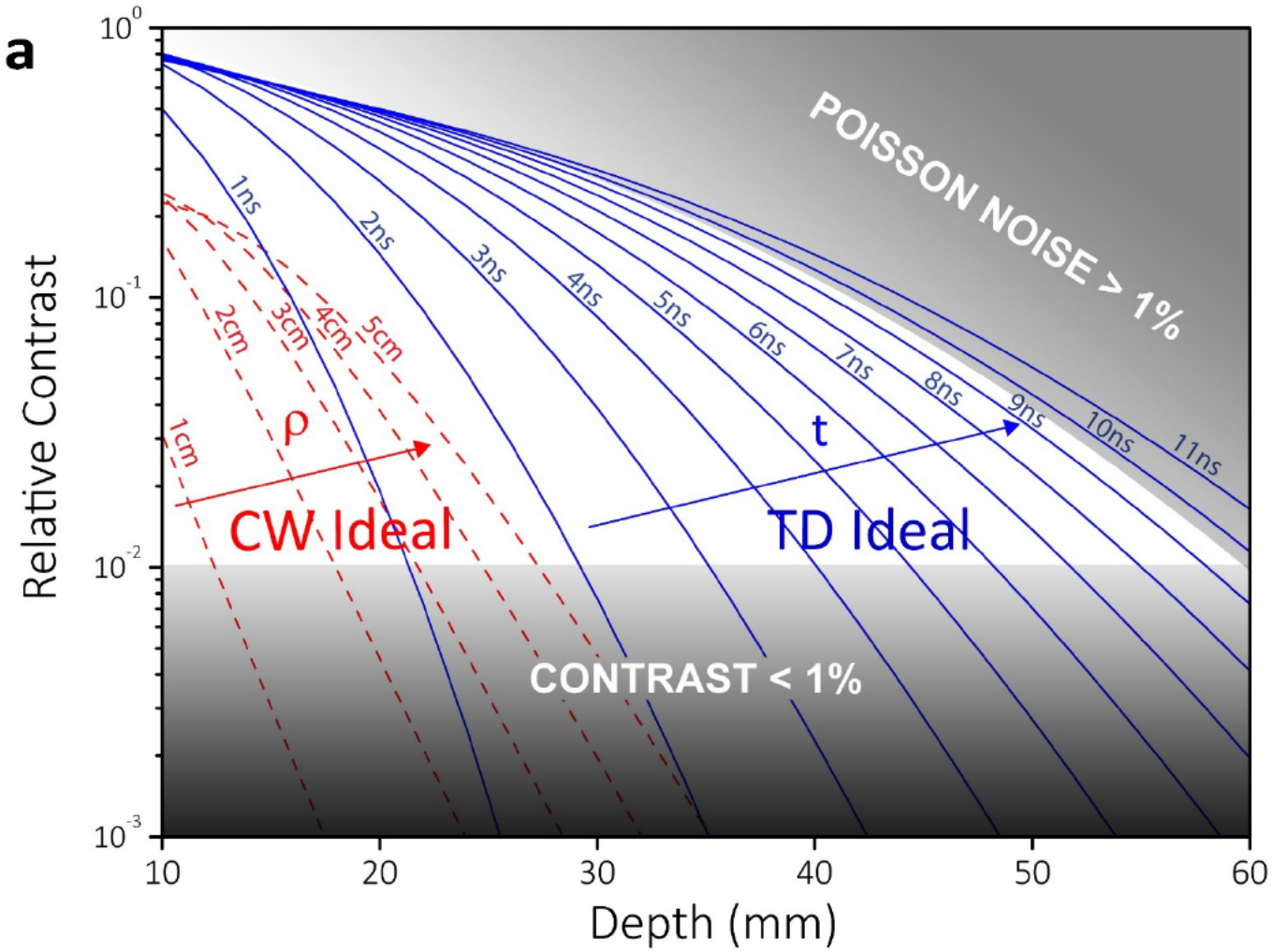


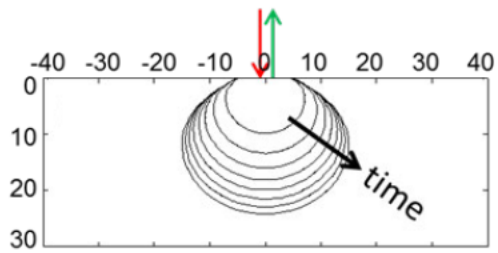


Puszka et al. **Biomed Opt Expr**, 4:1351 (2013)

⇒ Tomographic reconstruction down to 25 mm with fast-gated SPAD

Limits of CW and TD NIRS (1 of 2)





- 1 cm² optodes
- Power = 4 mW/mm²
- ideal time response
- shot noise
- acquisition time = 1 s
- $\Delta\mu_a$ = 0.1 cm^{-1}, V=1 cm³
- μ_a=0.1 cm^{-1}, μ'_s=10 cm^{-1}

⇒ identify extreme physical limits of TD diffuse optics

davide.contini@polimi.it

Which are the ingredients?

CONDITION 1

- dense distribution of pulsed sources for maximizing injected photons

CONDITION 2

- dense distribution of time-resolved detectors for maximizing light harvesting

CONDITION 3

- Perfect time-gating to reject early photons

CONDITION 4

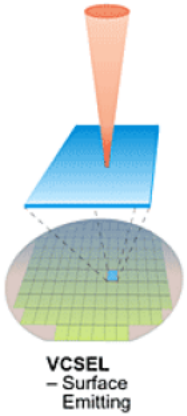
- High throughput compact timing electronics

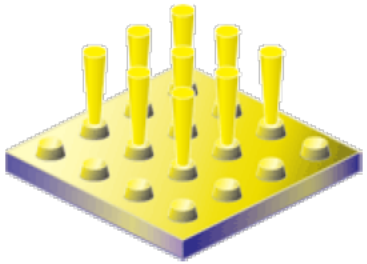
⇒ highly challeging technological goals

davide.contini@polimi.it

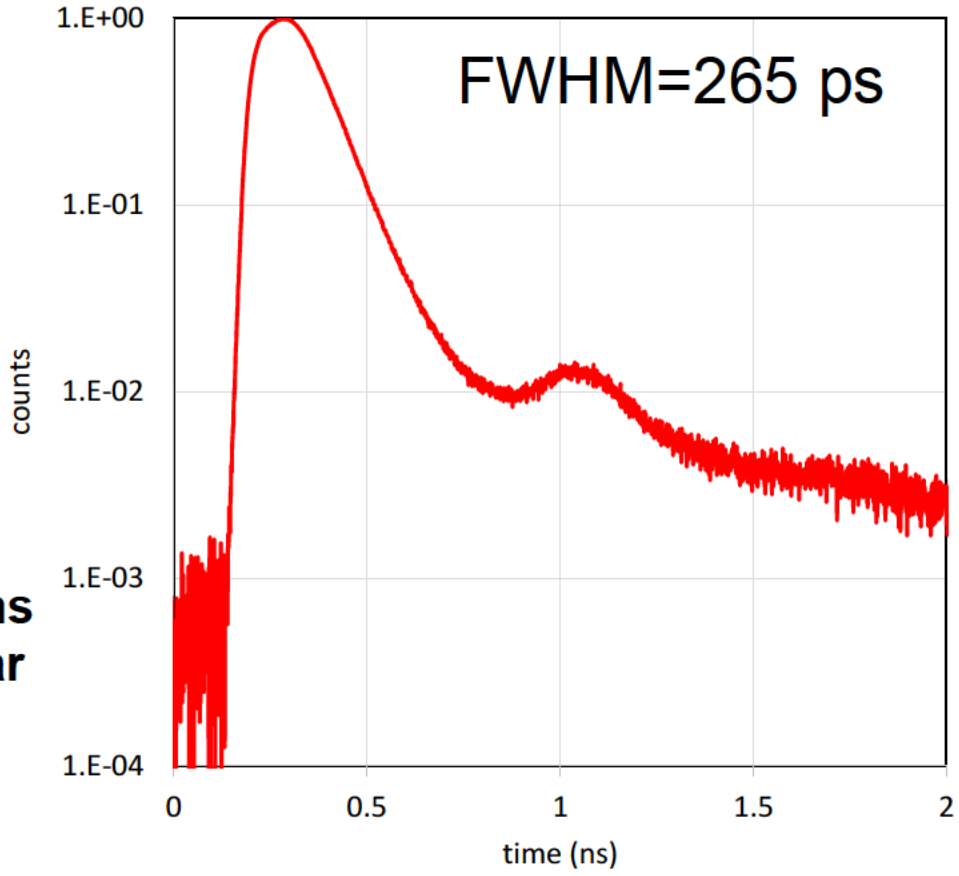
Vertical-Cavity Surface-Emitting Laser (VCSEL)

Vixar





Pulsing of a VCSEL die
(driver by Politecnico, dept. Electronics)

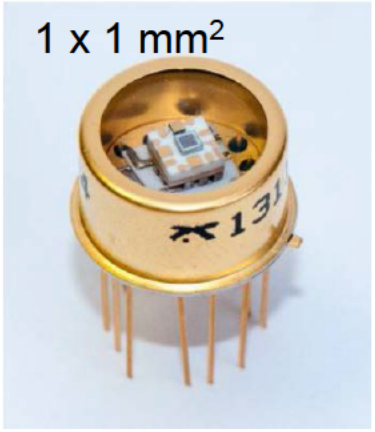


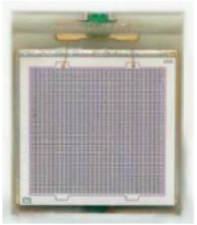
VCSELs are perfect candidates for dense pulsed source distributions onto the probe, but never tried so far in time-domain diffuse optics

⇒ Suitability of VCSEL for TD-diffuse optics (→ condition 1)

davide.contini@polimi.it

Silicon Photomultipliers (SiPM)

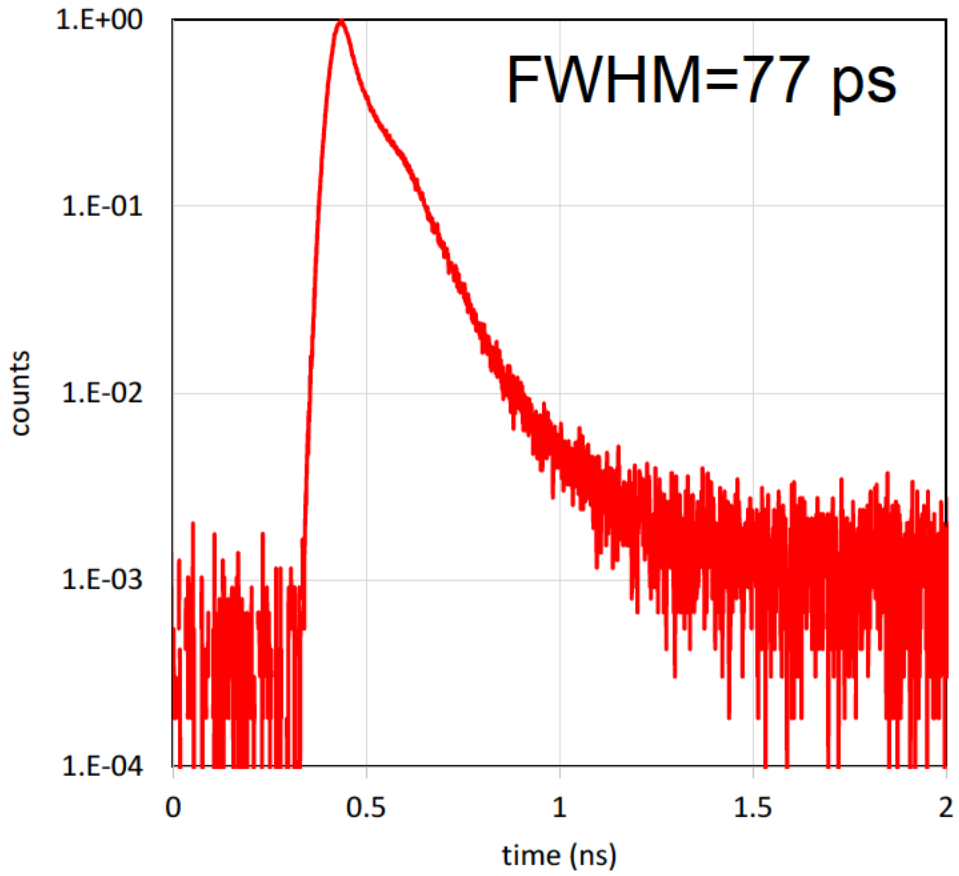




New developments fostered by PET systems and high-energy physics

compact, low cost, large area, scalable

SiPM with TCSPC
(electronics by Politecnico, dept. Physics)

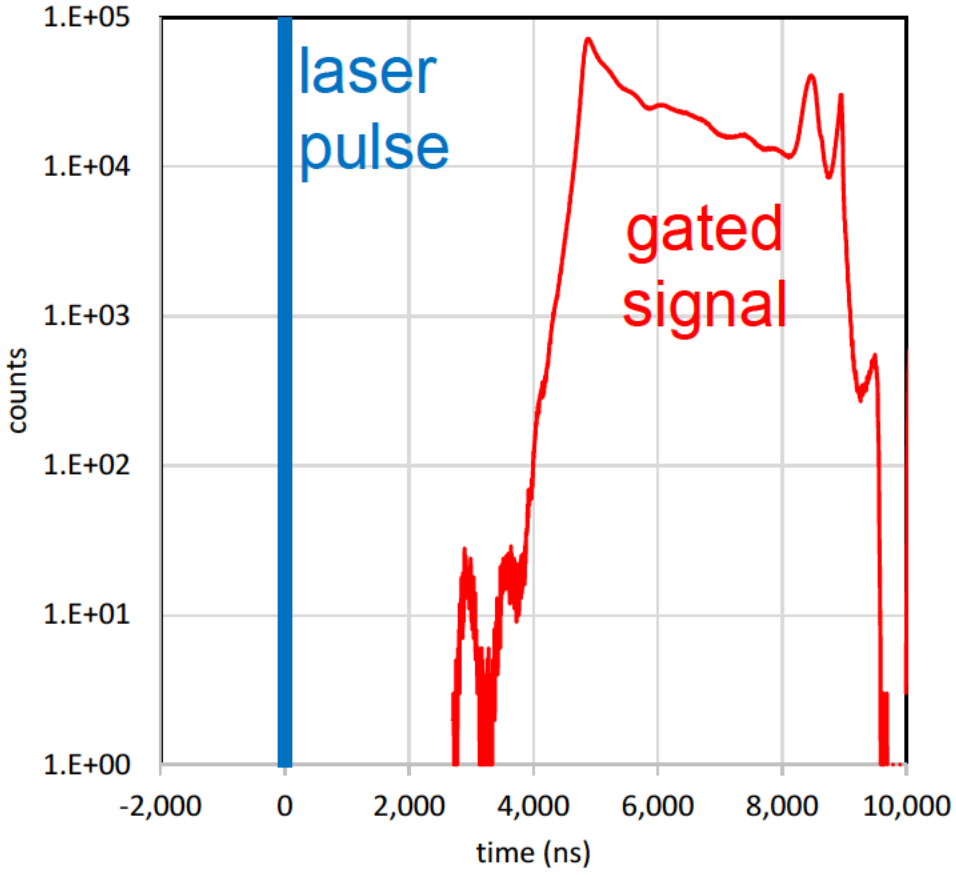


⇒ suitability of SiPM for TD-diffuse optics (→ condition 2)

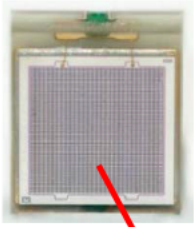
davide.contini@polimi.it

Time-Gated Single-Photon Avalanche Diode (SPAD)

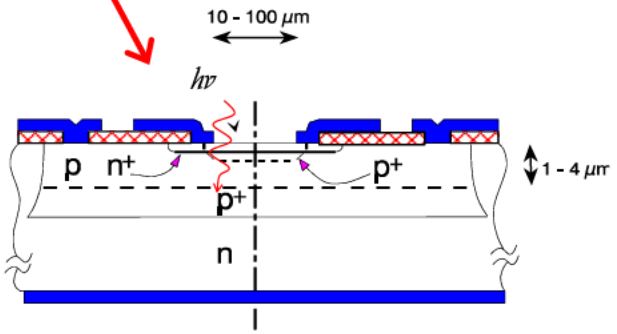
fast gating of a CMOS SPAD (Politecnico, dept. Electronics)



SiPM



a single cell of a SiPM is a SPAD



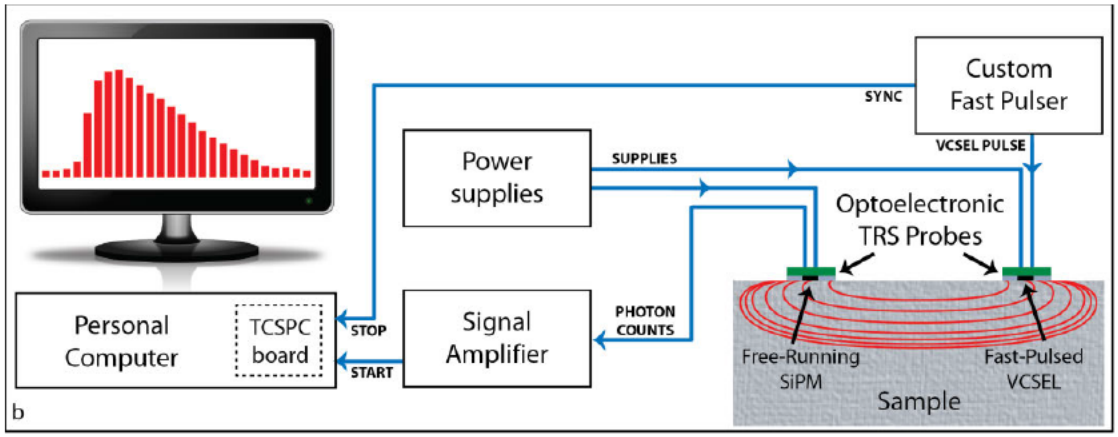
SPAD

⇒ gating of CMOS SPAD – basic element of SiPM (→ condition 3)

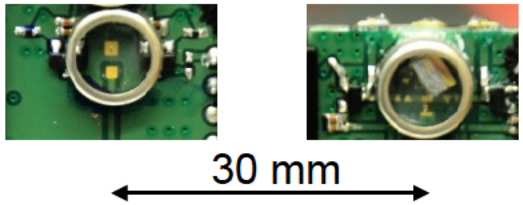
davide.contini@polimi.it

Technological demonstrator
Probes with embedded TD Source + Detector

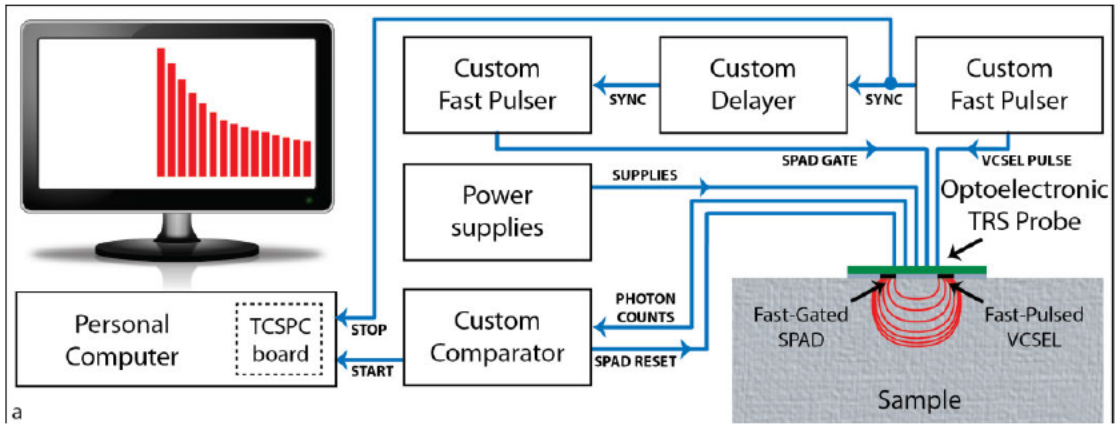
PROBE1 = VCSEL + SiPM



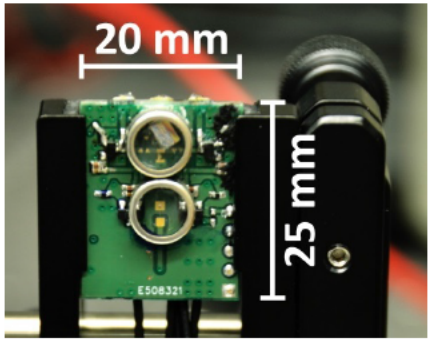
ρ = 30 mm



PROBE2 = VCSEL + gated SPAD

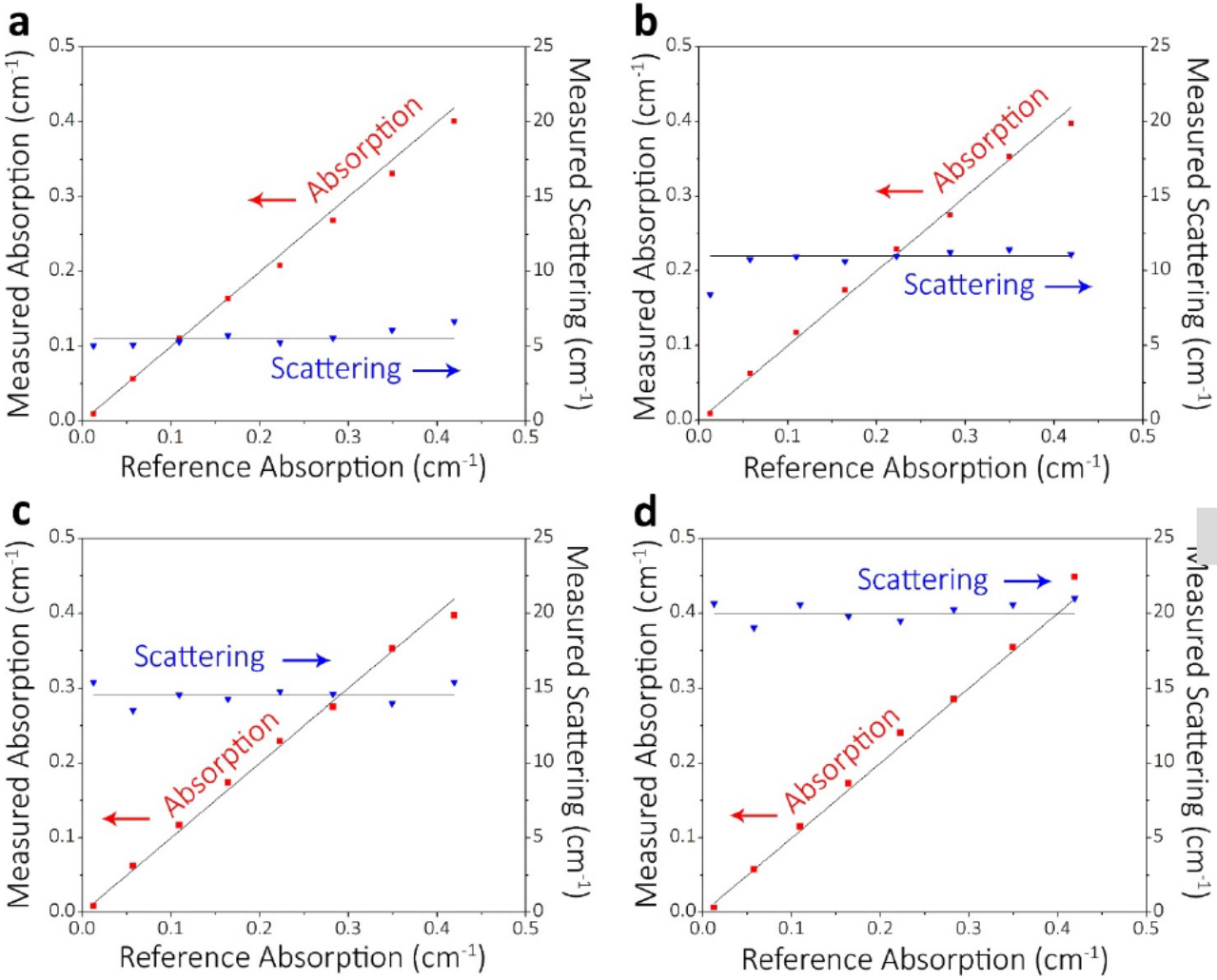


ρ = 5 mm

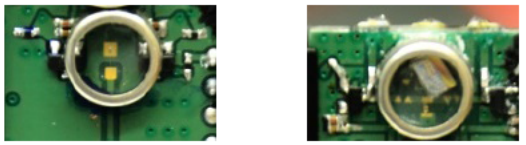


davide.contini@polimi.it

Phantom Measurements: Diffuse Spectroscopy on homogeneous media



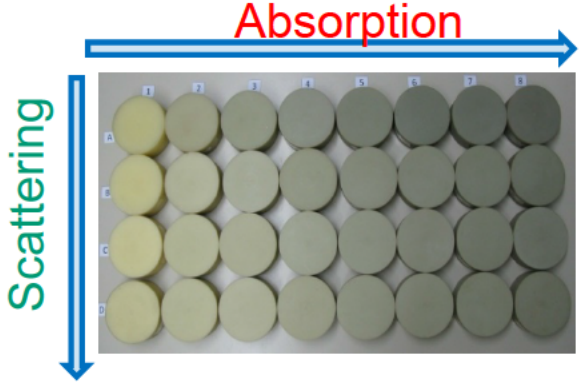
PROBE1



MEDPHOT Protocol

performance assessment on homogeneous media

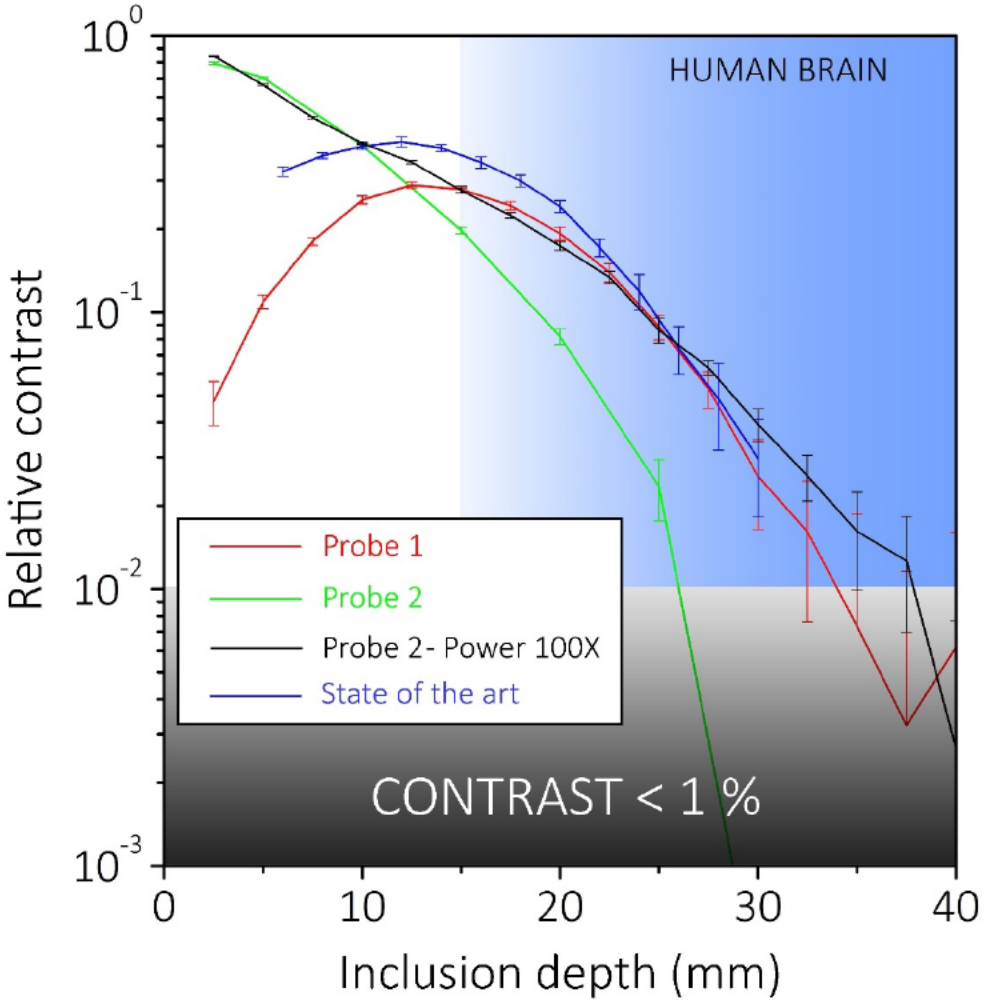
Pifferi et al. **Appl. Opt.**, 44:210414 (2005)

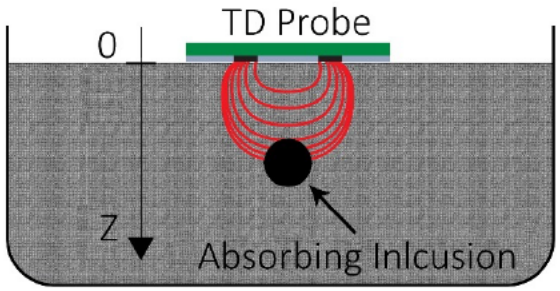


⇒ validation for spectroscopy of homogeneous media

davide.contini@polimi.it

Phantom Measurements: Relative contrast for embedded perturbation





$\Delta\mu_a = 0.16\ cm^{-1}\ V = 1\ cm^3$

$$C = \frac{N_{hom} - N_{hpert}}{N_{hom}}$$

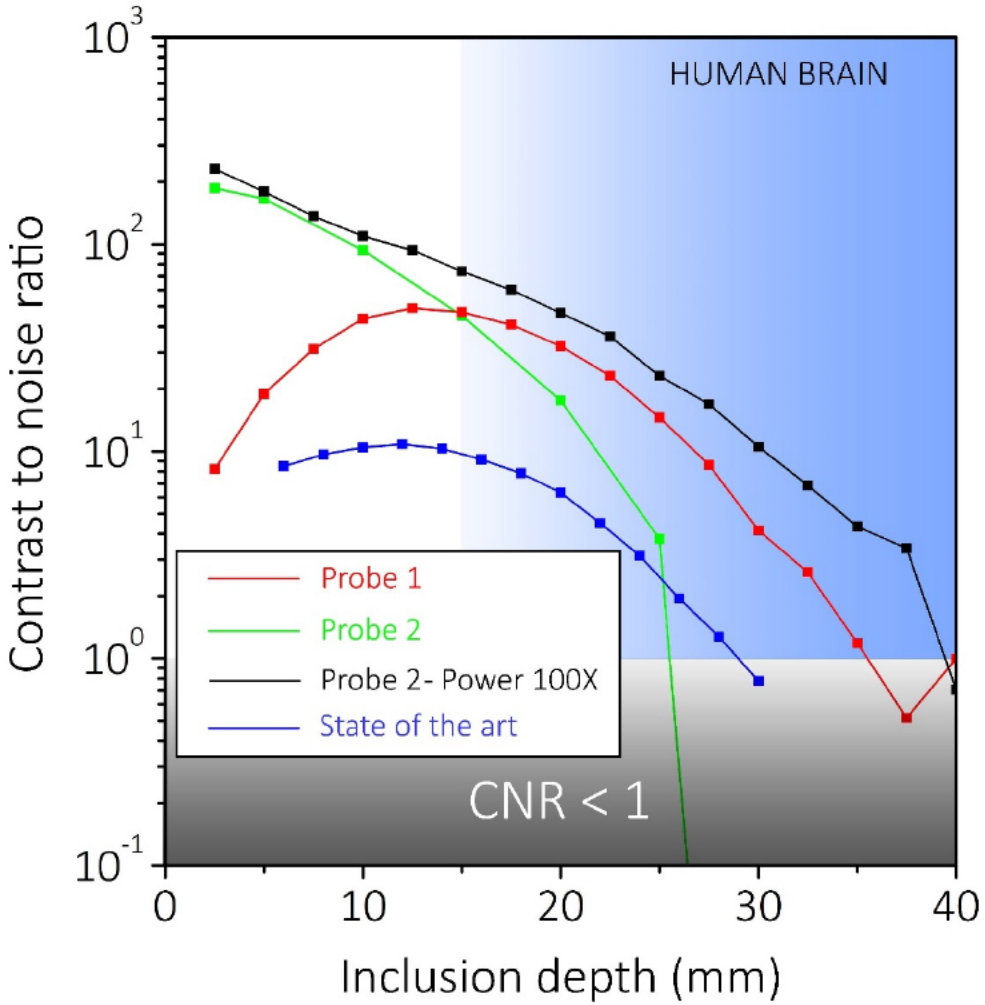
NEUROPT Protocol
performance assessment
on heterogeneous media

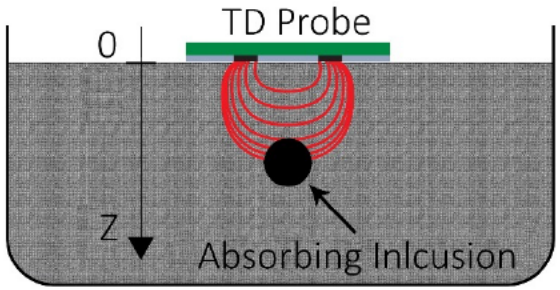
Wabnitz et al. **J. Biomed. Opt**, 19:086012 (2015)

⇒ performances comparable to bulky state-of-the-art system

davide.contini@polimi.it

Phantom Measurements: CNR for embedded perturbation





$\Delta\mu_a = 0.16\ cm^{-1}\ V = 1\ cm^3$

acquisition = 1 s

$$CNR = \frac{N_{hom} - N_{hpert}}{\sigma(N_{hom})}$$

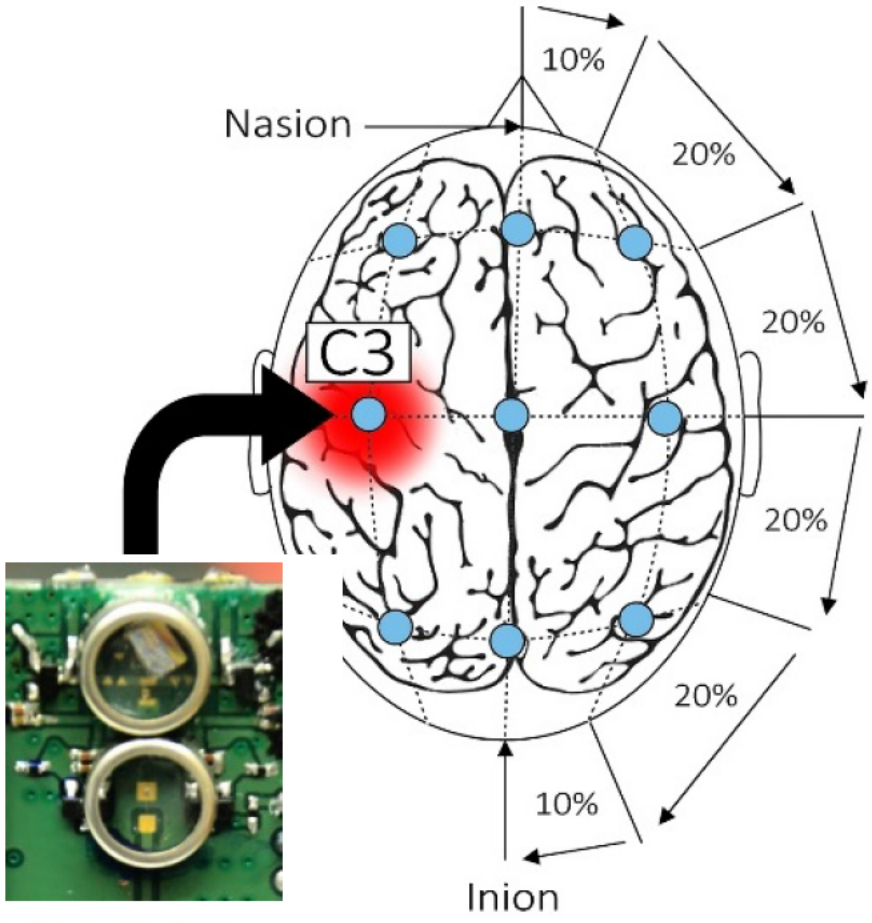
NEUROPT Protocol

Wabnitz et al. **J. Biomed. Opt**, 19:086012 (2015)

⇒ performances better then bulky state-of-the-art system

davide.contini@polimi.it

In vivo Measurements: Preliminary results (1 of 2)



Probe directly in contact with the scalp on C3

Source-detector distance 5 mm

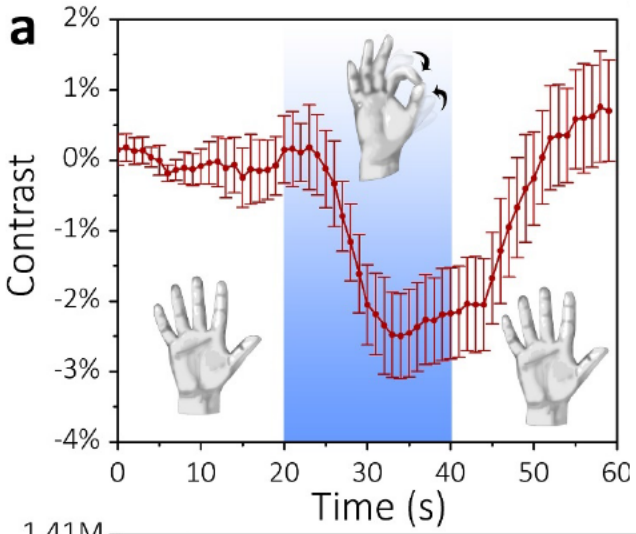
Finger tapping experiment

10 trials

20 s rest, 20 s task, 20 s recovery

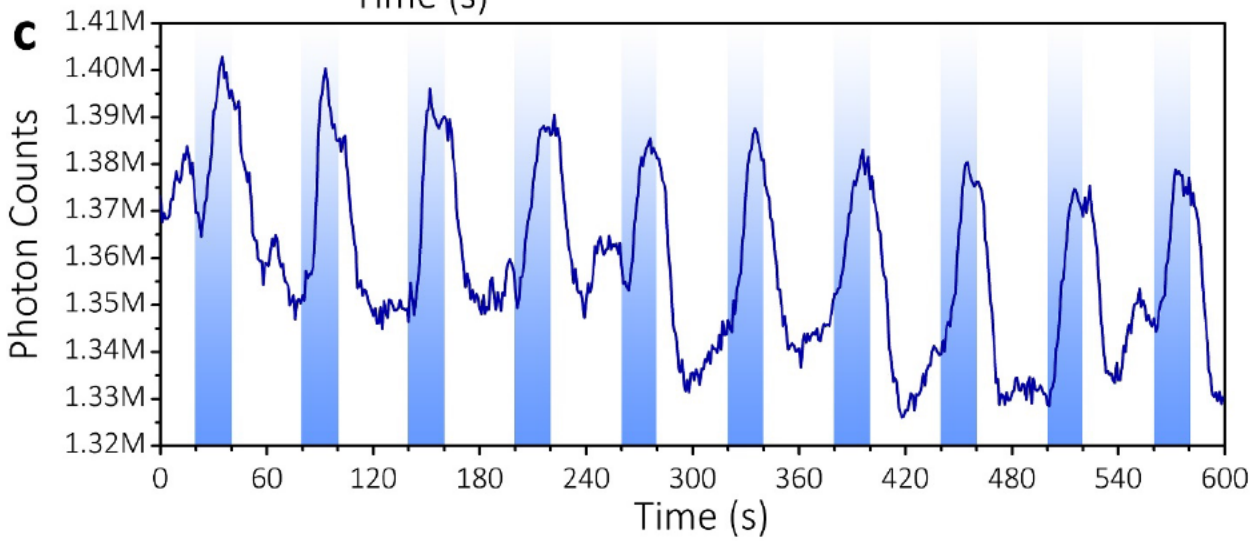
davide.contini@polimi.it

In vivo Measurements: Preliminary results (2 of 2)



folding average

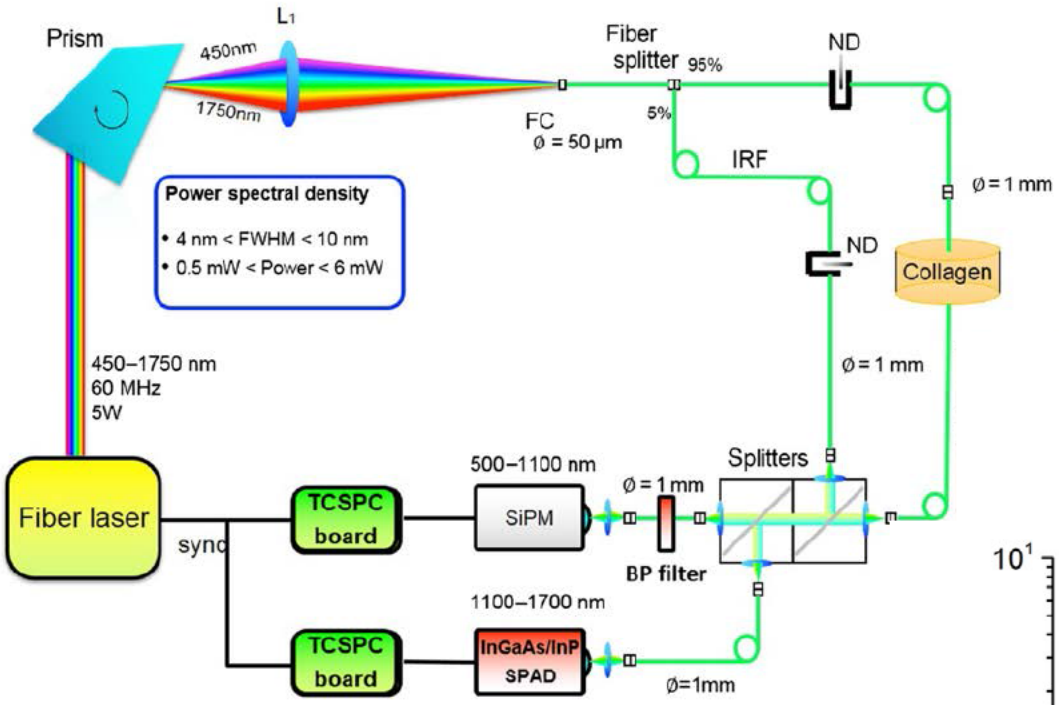
single repetitions

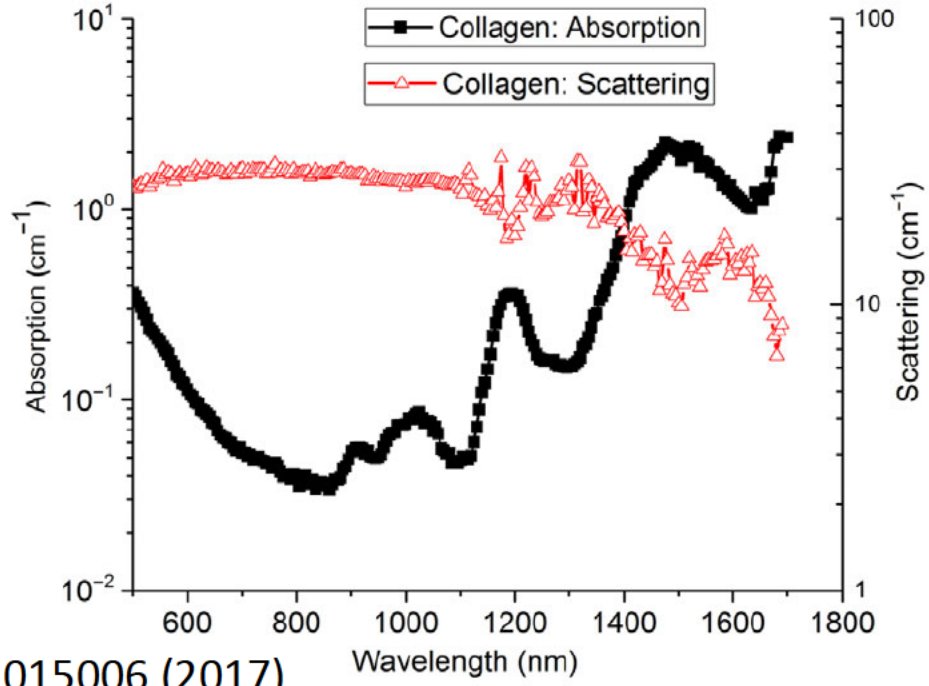


⇒ initial in vivo use of the probe

davide.contini@polimi.it

InGaAs/InP Spad for TD-NIR spectroscopy





S. Konugolu Venkata Sekar J. Biomed. Opt. 22(1), 015006 (2017)

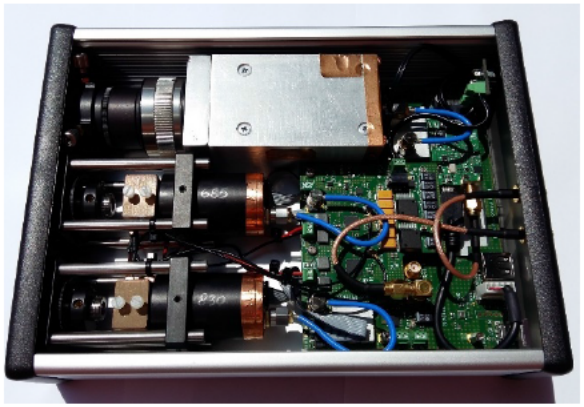
davide.contini@polimi.it

Conclusion (1 of 3)

PAST

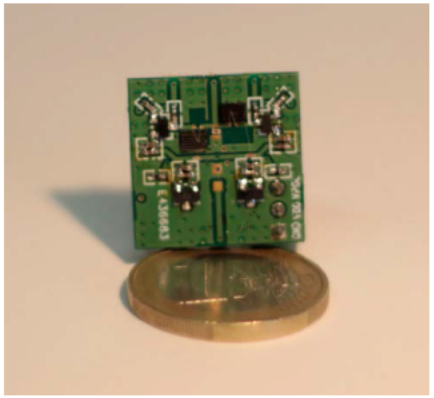
- Multichannel
- Bulky
- Complex
- Expensive

PRESENT



- 1 or 2 channels
- Compact
- Easy to use
- Cheap

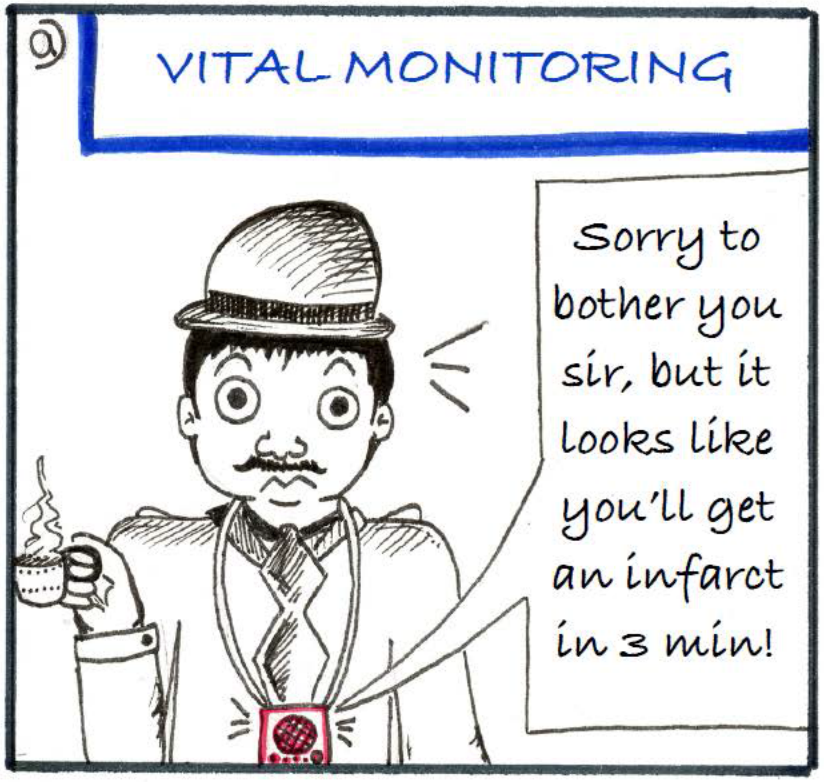
FUTURE

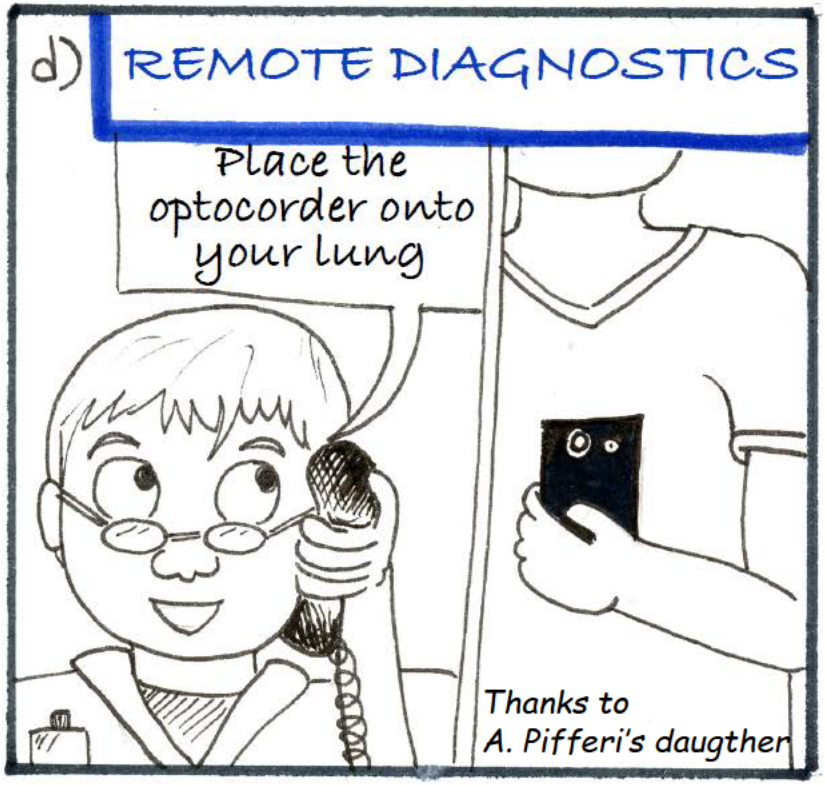


- Multichannels
- Very Compact
- Easy to use
- Very Cheap
- Under development

davide.contini@polimi.it

Conclusion (2 of 3)

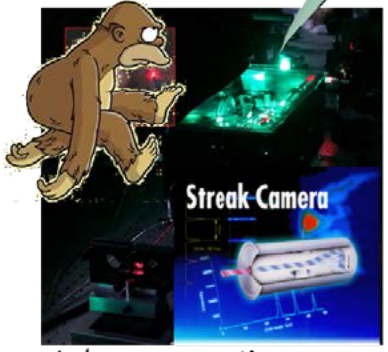




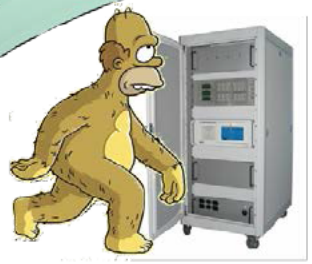
davide.contini@polimi.it

Conclusions (3 of 3)

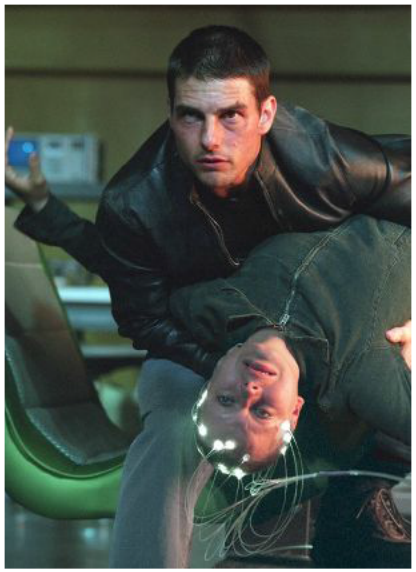
TD-diffuse optics
(r)EVOLUTION



1st generation



2nd generation



Philip K. Dick, "The Minority Report" (1956)
Steven Spielberg, "Minority Report" (2002)

<<Medical technology: The hand-held diagnostic devices seen on "Star Trek" are inspiring a host of medical add-ons for smartphones>>, Dec 1st 2012 | The Economist

davide.contini@polimi.it

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MPD

Andrea Giudice, Simone Tisa....

Other institution

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LUCA

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PHOTONICS 21

PHOTONICS PUBLIC PRIVATE PARTNERSHIP

BABYLUX

(Grant agreement n. 620996)

SOLUS

SMART OPTICAL AND ULTRASOUND DIAGNOSTICS OF BREAST CANCER

This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 731877.

PHOTONICS 21

PHOTONICS PUBLIC PRIVATE PARTNERSHIP

PhD student and Post Doc positions available contact: davide.contini@polimi.it

POLITECNICO
MILANO 1863

PhD student and Post Doc positions available on TD-NIRS development and application

Contact: davide.contini@polimi.it