SPAD position sensitive detectors: Application in life sciences & biology

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PSD'13, Oxford, UK
07/09/2023

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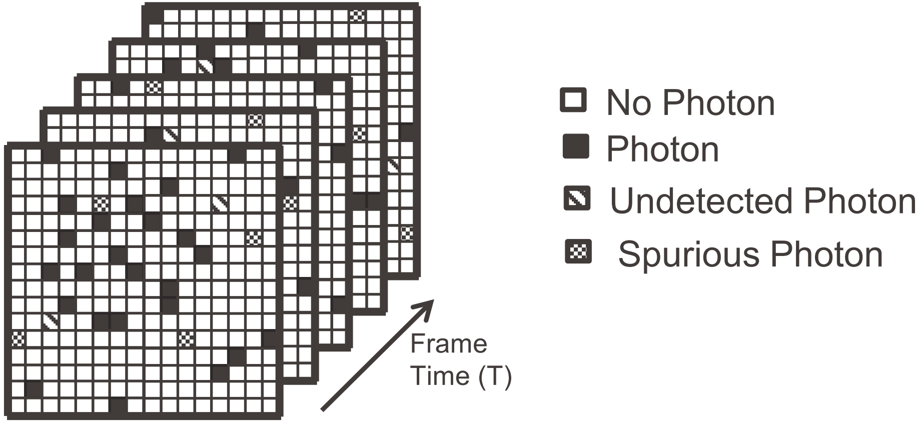
Introduction – SPAD arrays & Single-photon imaging

SPAD: single-photon avalanche diode
SiPM: silicon photomultiplier

Single-Photon Imaging Basics

(CMOS) SPAD: Single-Photon Avalanche Photodiode



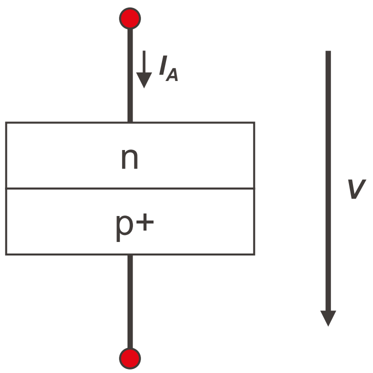
+ **time-of-arrival**, energy/wavelength, polarisation, etc.

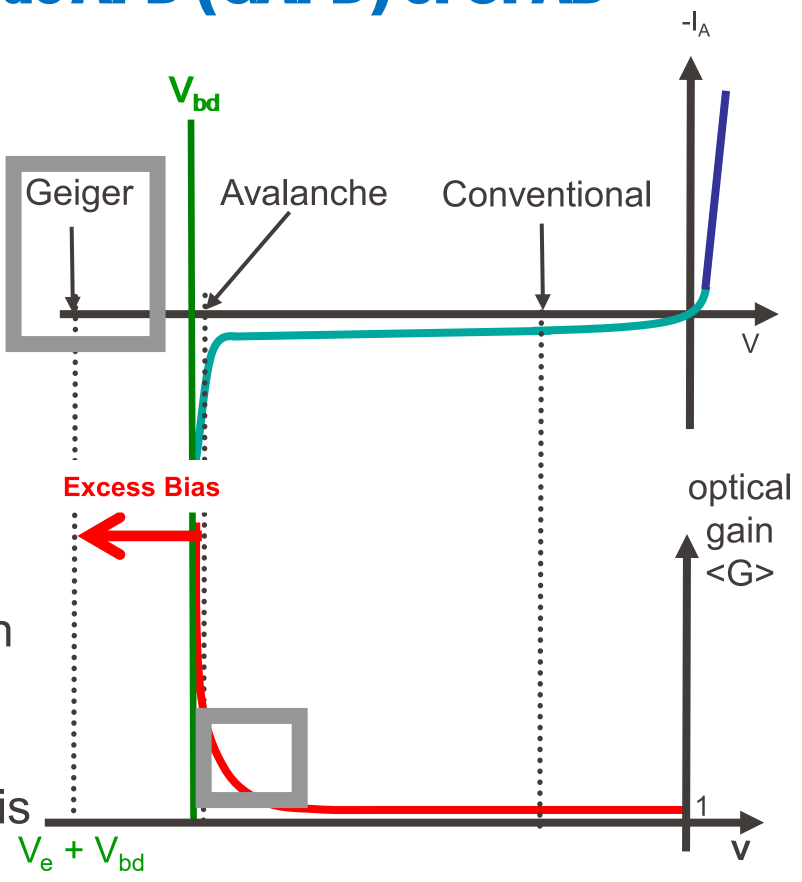
Perfect single photon detection limited by

1. Photon detection efficiency (PDE) = QE x FF
2. Temporal Aperture Ratio
3. Dark Count Rate

R. Henderson, Edinburgh Univ., ISSCC 2013 – E. Fossum, IISW 2013

Geiger-mode APD (GAPD) or SPAD



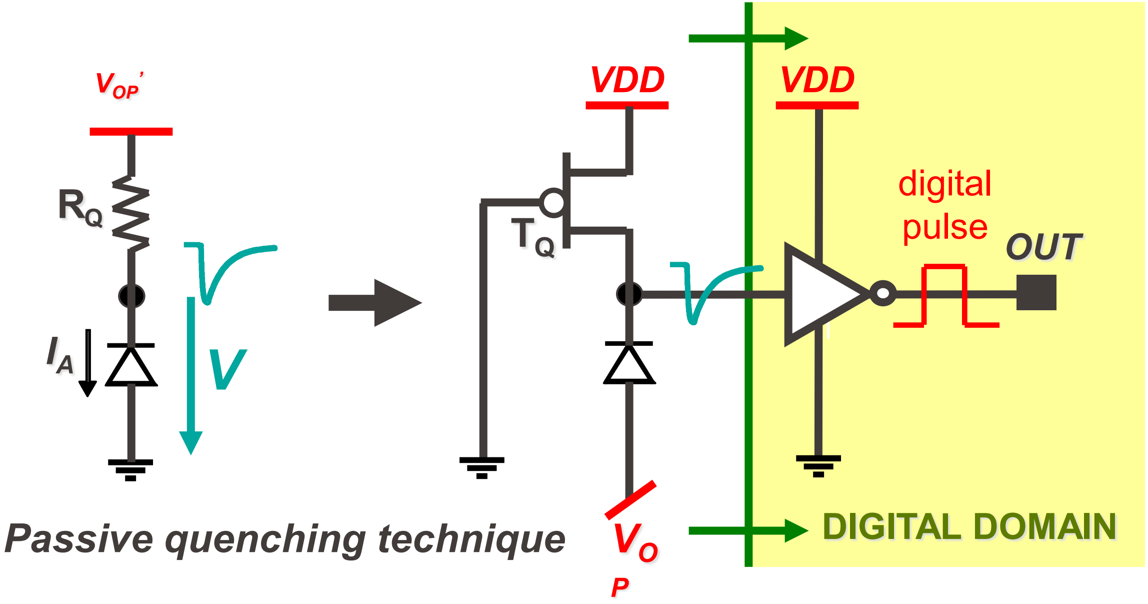


- One can achieve a virtually infinite gain biasing above breakdown…

Thus gain variability is meaningless

Quenching (and gating) a SPAD in CMOS

- The SPAD becomes like any other digital device but it is triggered by a photon!



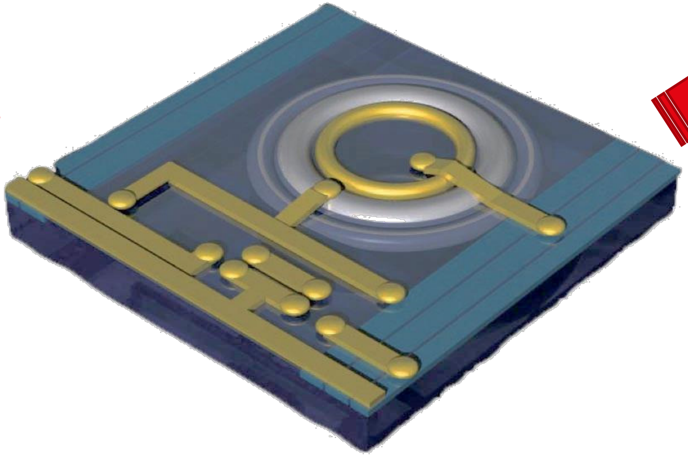
- With two more switches one can gate sensitivity

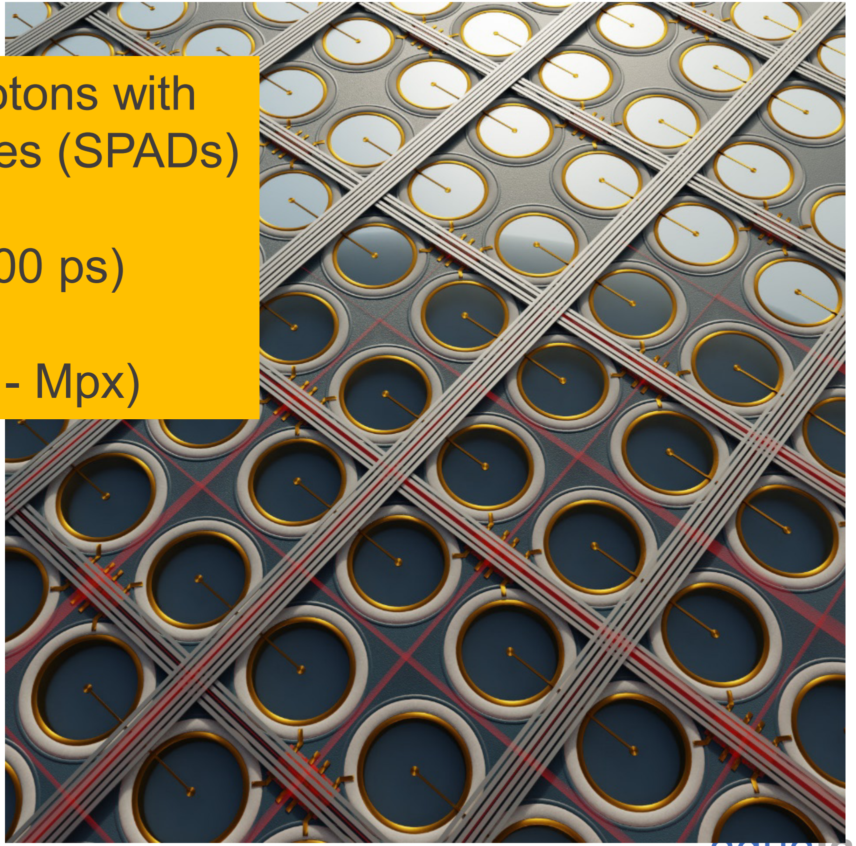
Quantum Imaging

Detect/time-stamp single optical photons with CMOS Single-photon Avalanche Diodes (SPADs)

Excellent timing resolution (10-100 ps)

Increasing spatial resolution (kpx - Mpx)





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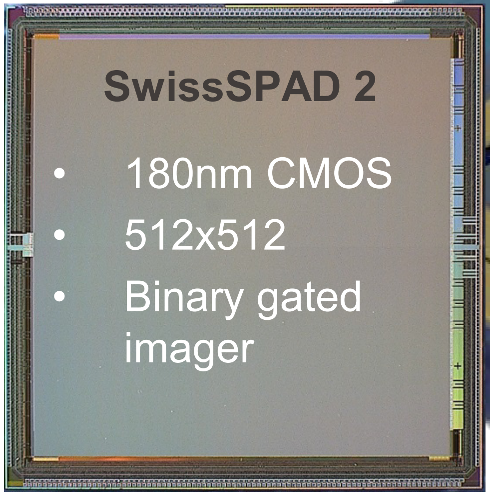
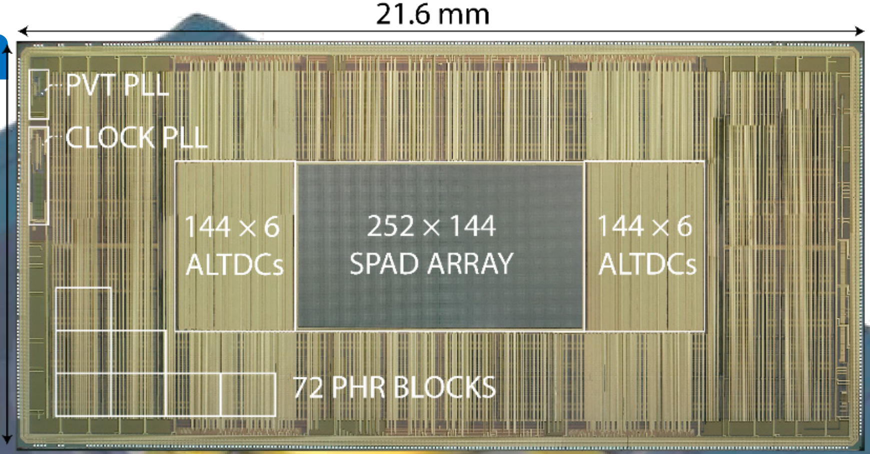
SPAD array architectures & imaging examples

AQUA – SPAD Design Examples

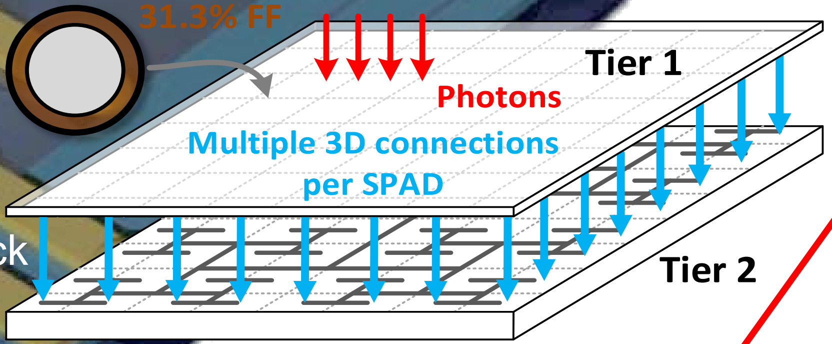


- 180nm CMOS
- 512x512
- Binary gated imager



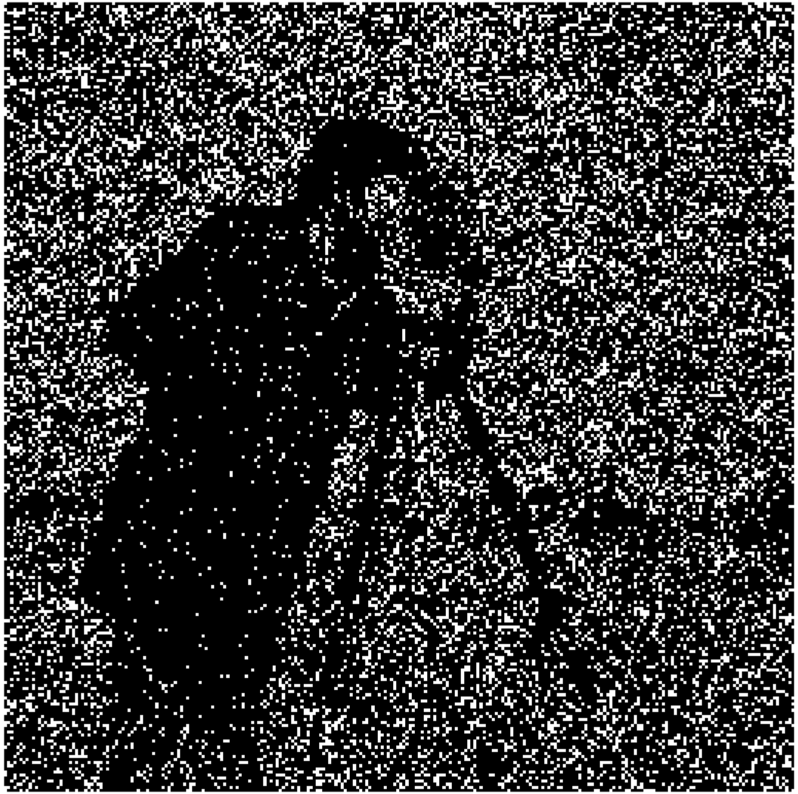
- 180nm CMOS
- 11.2 Gbit/s output data bandwidth

Mantis

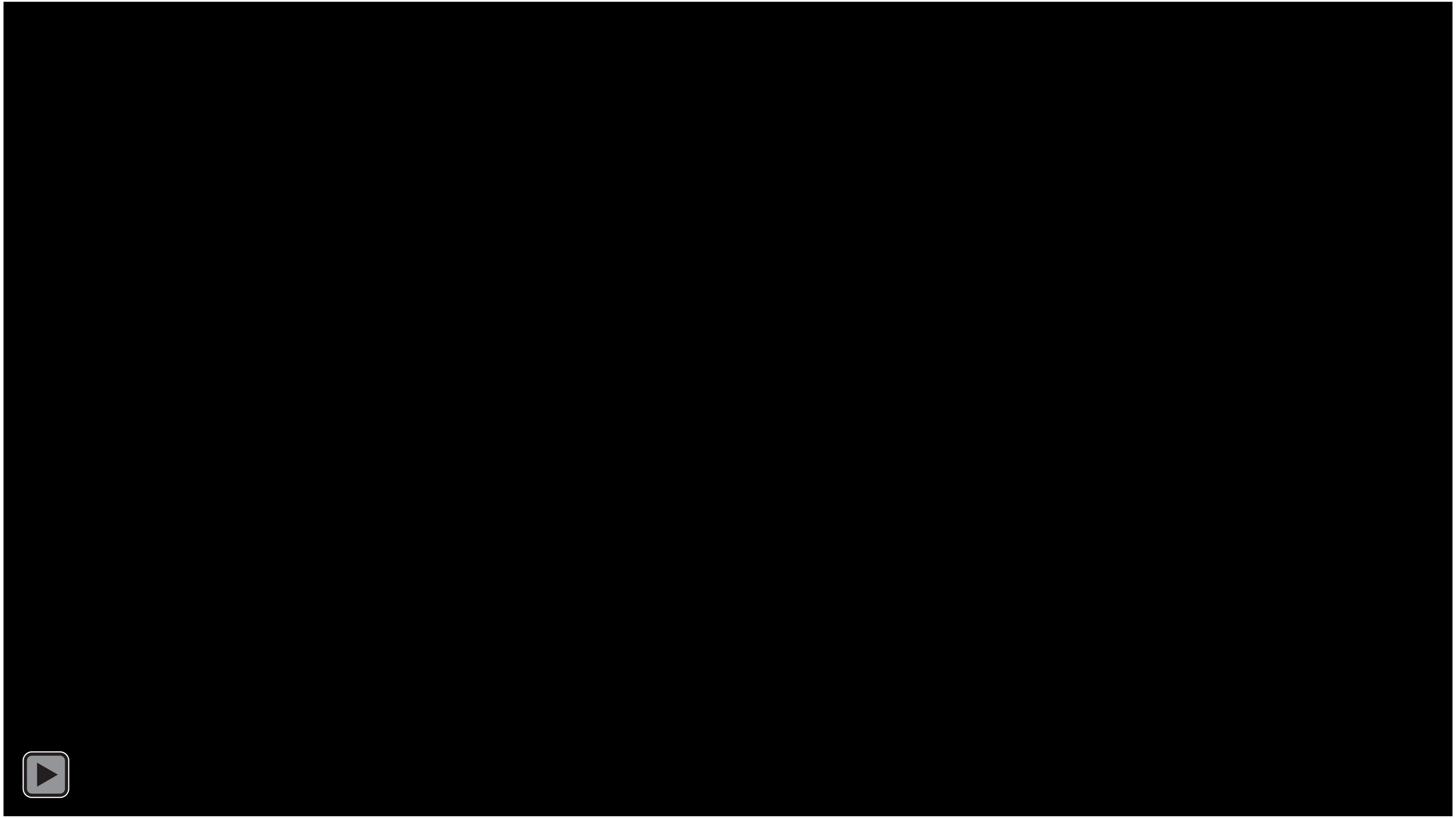


- 45nm/65nm CMOS 3D stack
- First 3D stacked direct time-of-flight sensor in CMOS

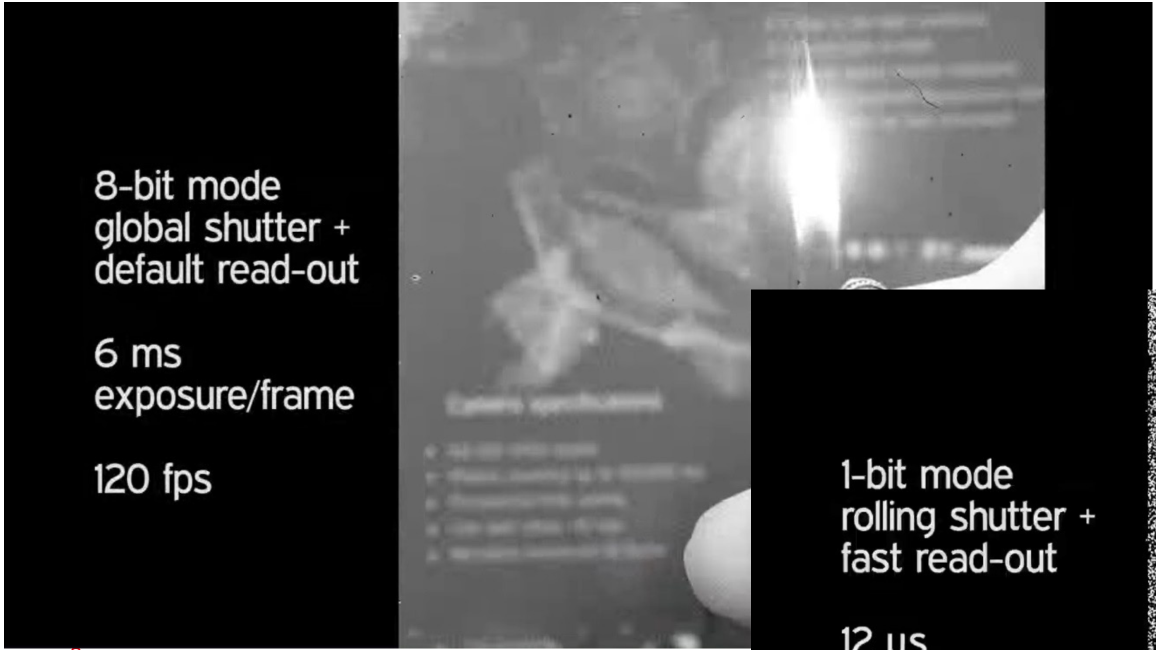
Quanta imaging – 1 bit

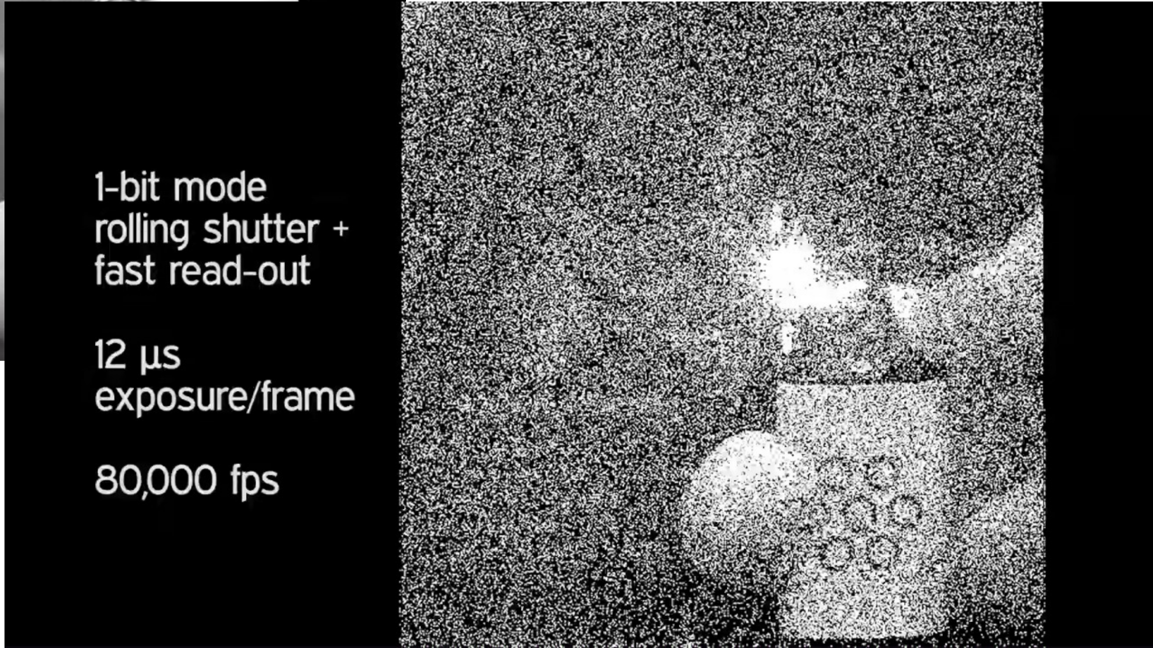


Light-in-flight (time gating)



High-speed imaging (intensity)

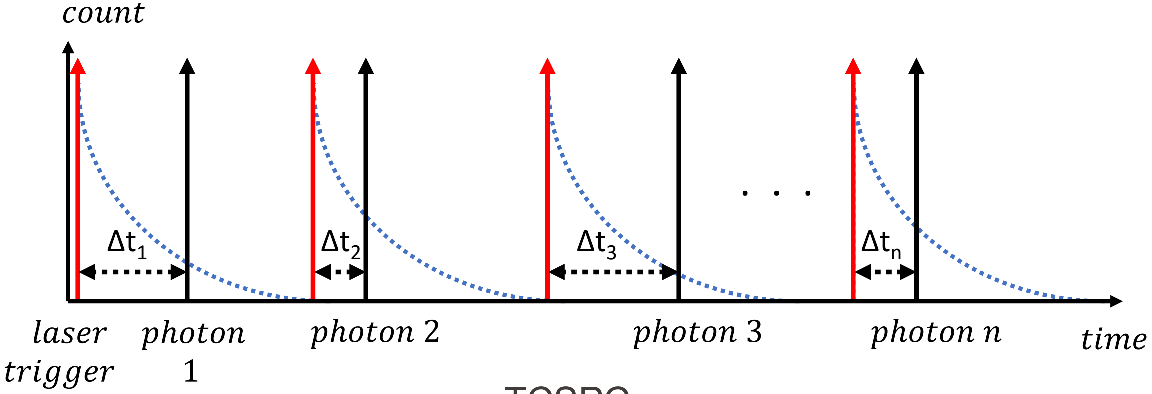


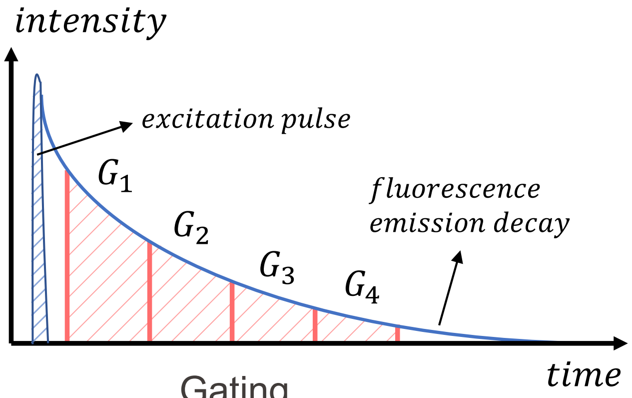


Applications in life sciences & biology

Claudio Bruschini & Edoardo Charbon, EPFL

Widefield Fluorescence Lifetime – time-resolved





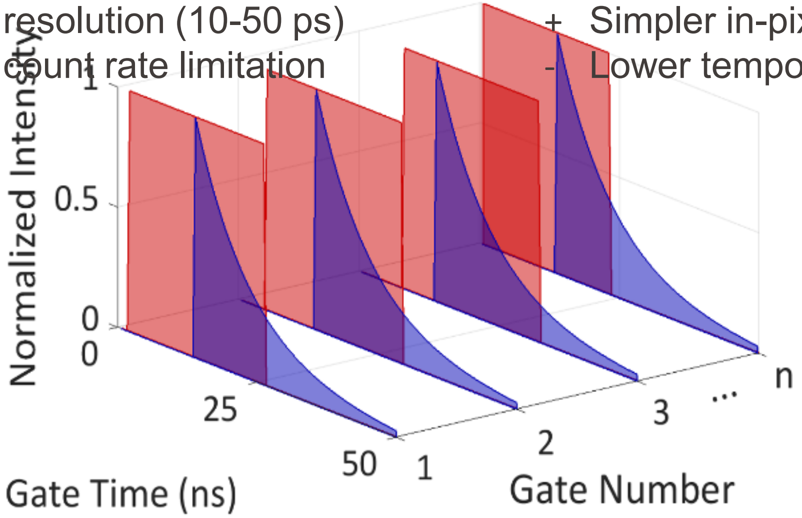
TCSPC

+ High temporal resolution (10-50 ps)
- Global photon count rate limitation

Gating

+ Simpler in-pixel implementation/high GCR
- Lower temporal resolution (large width)

[A. Ulku, EPFL, PhD, 2021]

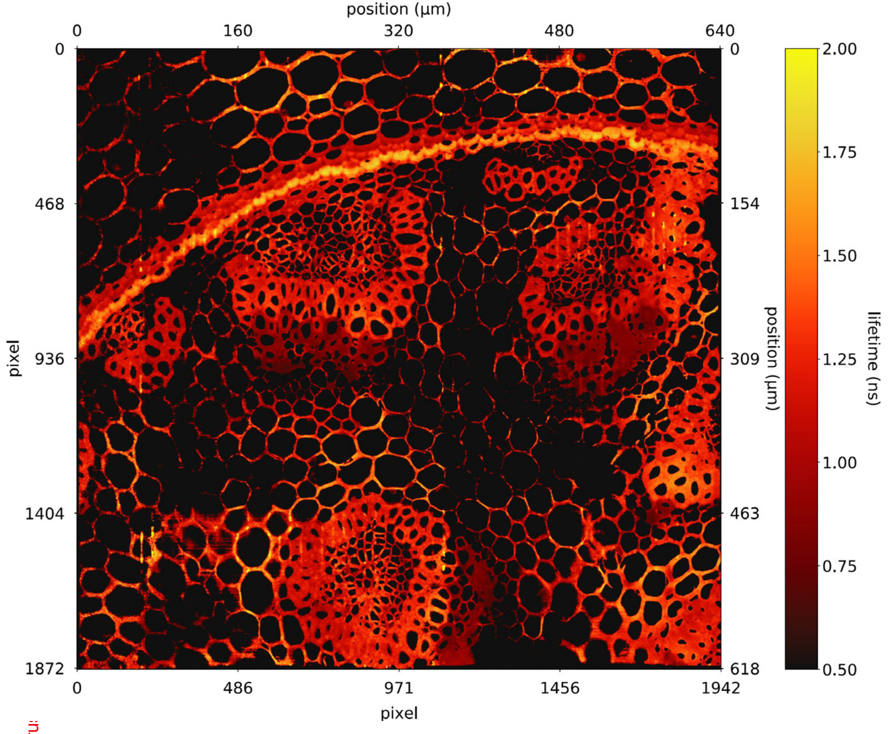


Gate shifts as small as 18 ps!

(A. Ulku et al., MAF, 2020)

FLIM Examples: From micro to macroscopic

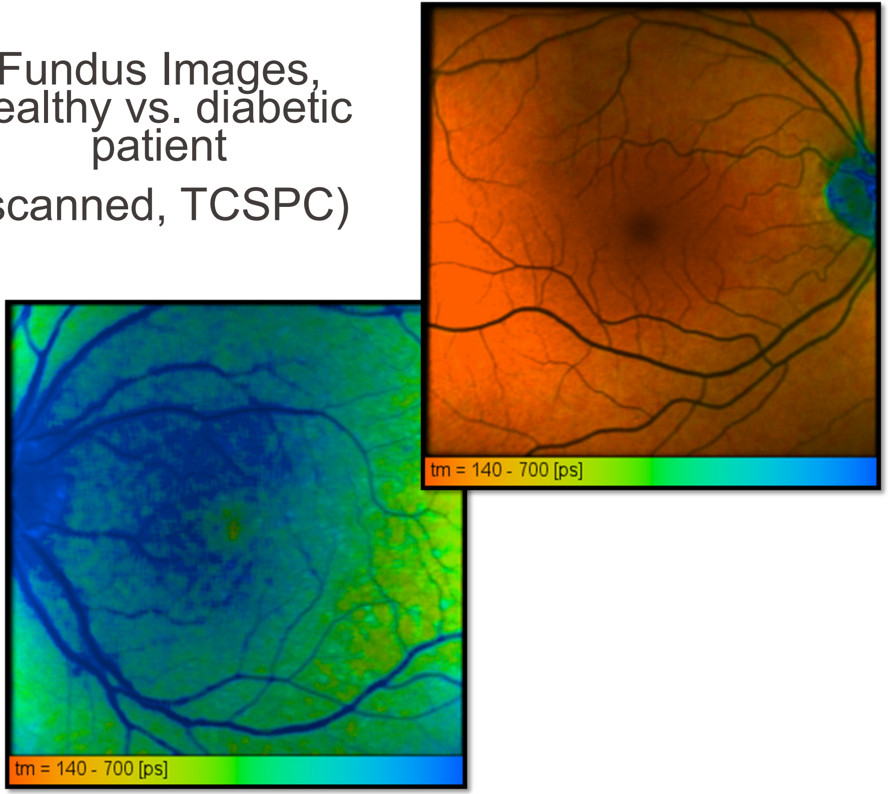
- Widefield, stiched (3.64 Mpx)+ ANN



Zickus, Ma, et al, Sci Rep 2020

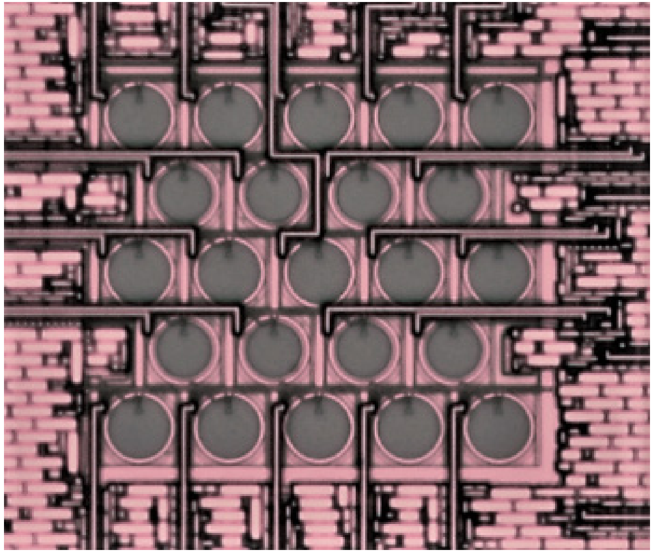
Fundus Images, healthy vs. diabetic patient

(scanned, TCSPC)

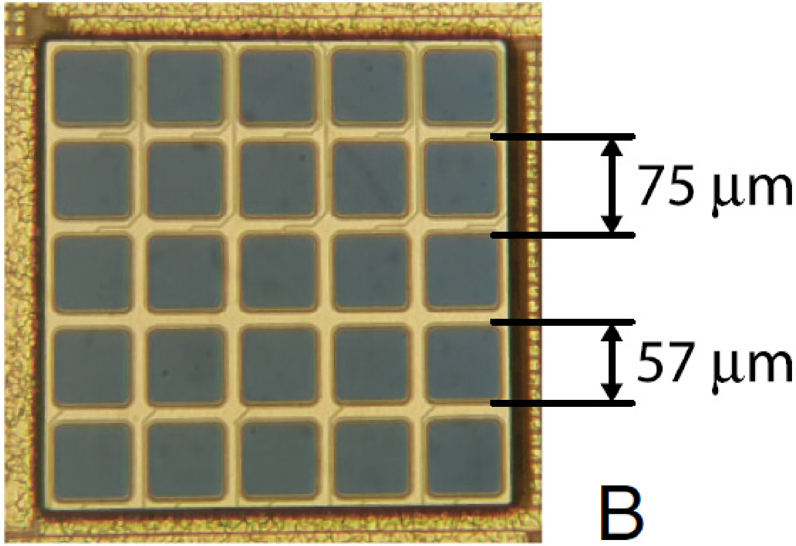


[M. Hammer, Univ. Hospital Jena, 2015]

Small-format high-performance SPAD imagers



Antolović et al, Optics Express 2018,
FOM 2019 - 0.18 µm
SPAD23 array (Pi Imaging Technology)



Buttafava et al, Optica 2020
0.16 µm BCD

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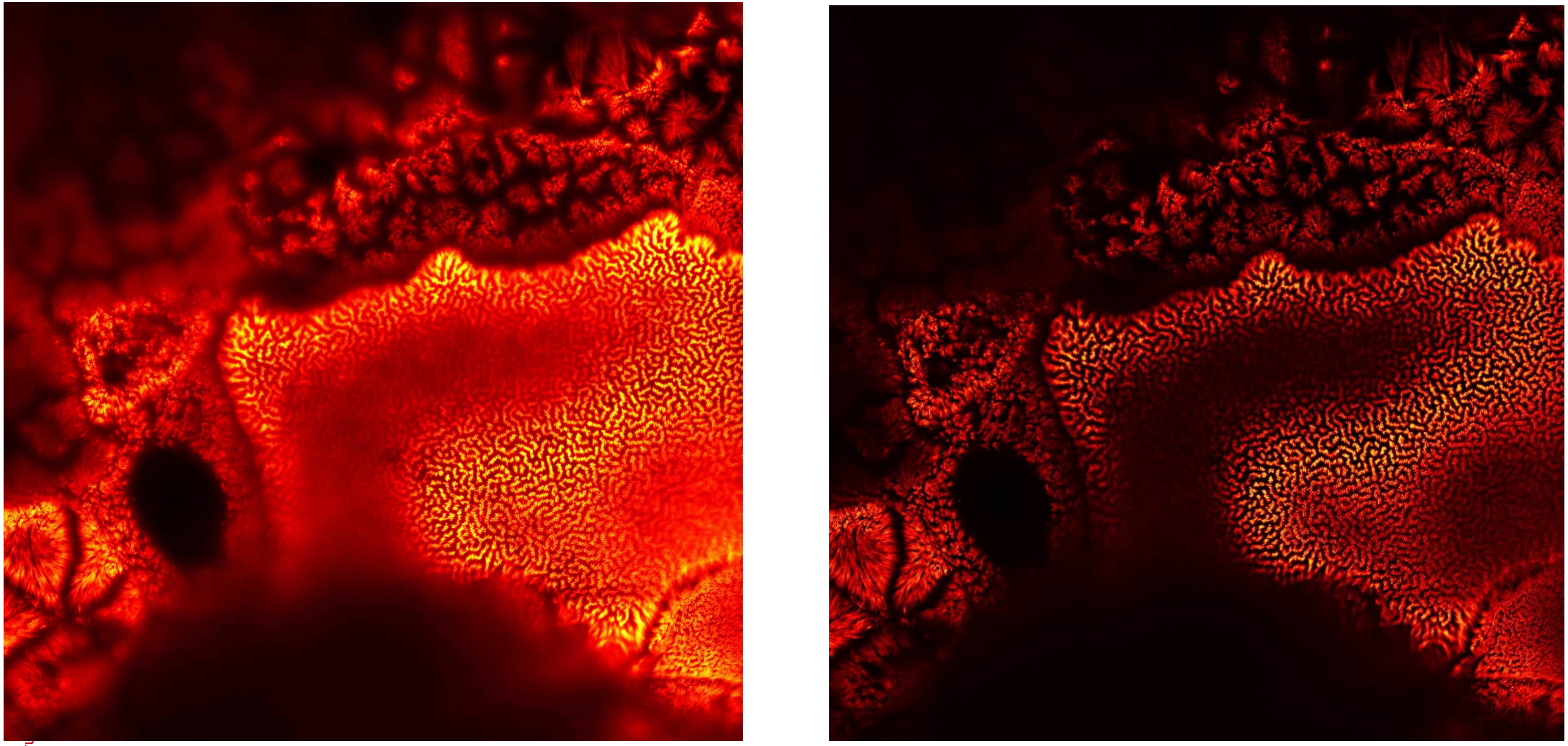
Microscopy applications



Abberior 2D STED, samples: Charité –Berlin

C. Br

- Actin in microvilli of Caco2 cells. Fixed cells were stained with abberior STAR RED phalloidin. *MATRIX* detection -> background signal removal and optical sectioning improvement (2D-STED).

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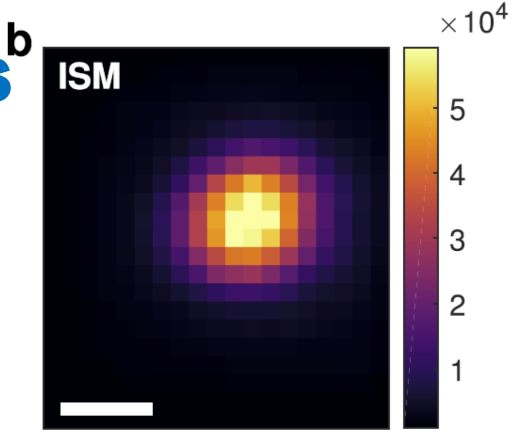
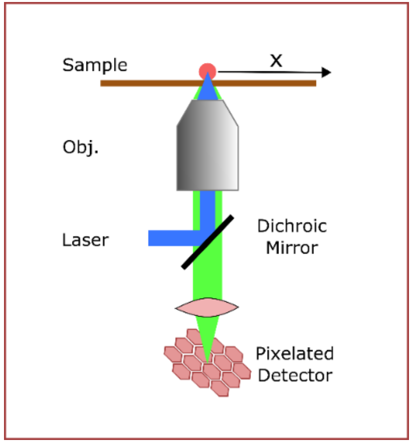
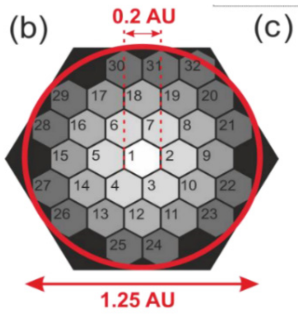
(Quantum) Microscopy applications

ISM (Image Scanning Microscopy): i) Exchange pinhole with a detector array, ii) Scan sample, iii) Shift images and sum

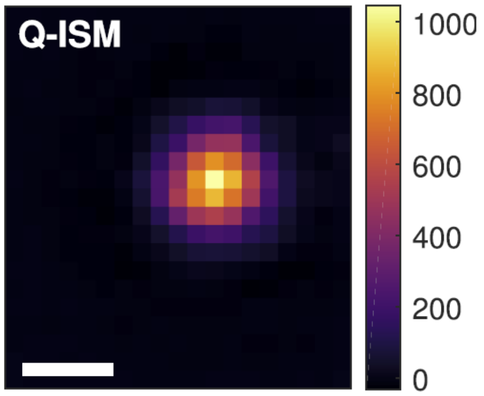


A pixelated confocal detector





Q-ISM: exploit quantum correlations



Tenne et al, SPIE PW 2019; Lubin et al OpEx (23) 2019

Sheppard, C. J. R. *Optik (Stuttg).* 80, 53–54 (1988), Muller and Enderlein, PRL, 2010

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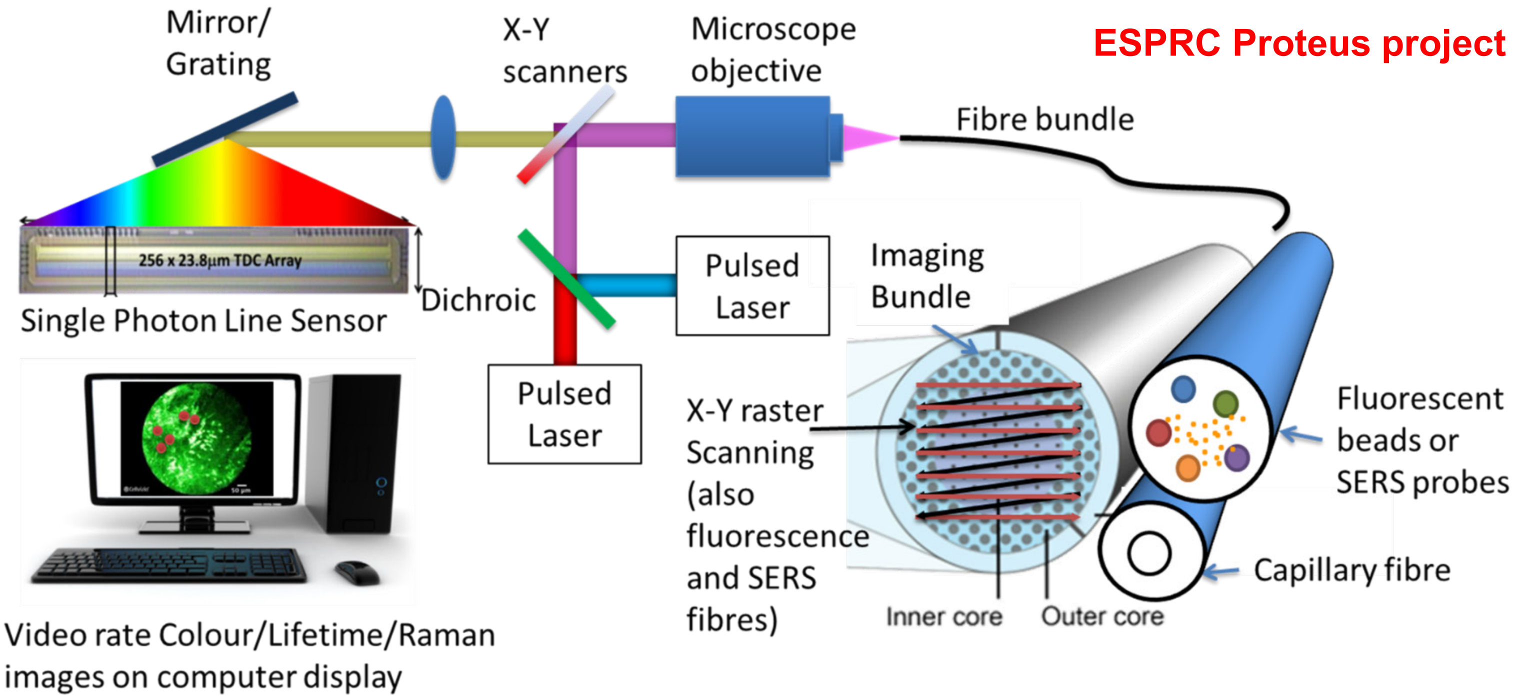
Endoscopic FLIM & Raman

ESPRC Proteus project



R. Henderson, Edinburgh Univ. 2017

SPIE BIOS 2017: Choudhury, [10041-10], Pedretti, [10041-21], Ehrlich, [10058-16]

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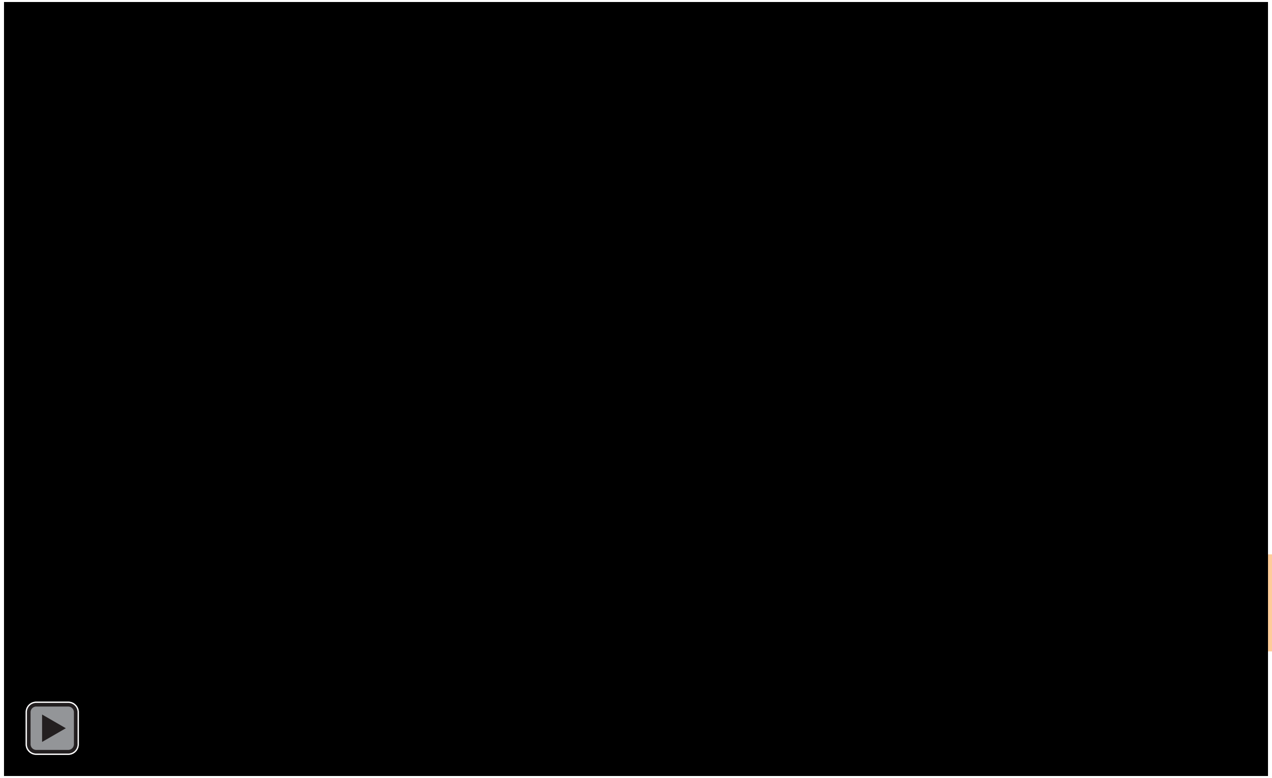
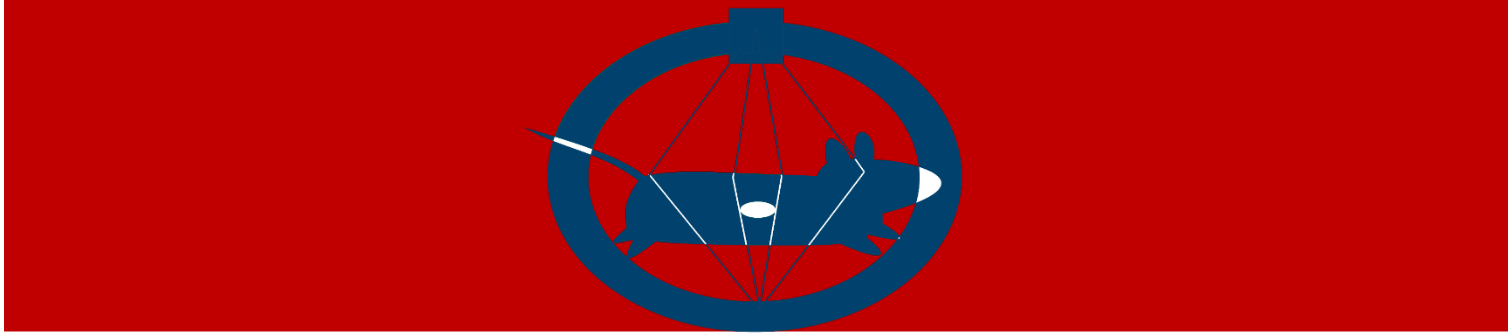
Real-time TCPSC FLIM

Fast Fluorescence Lifetime Imaging using on-FPGA recurrent neural networks & photon detection timestamps



Yang Lin, EPFL 2022

SPAD imagers for molecular imaging



SPAD imagers for molecular imaging
#1 Drug target engagement

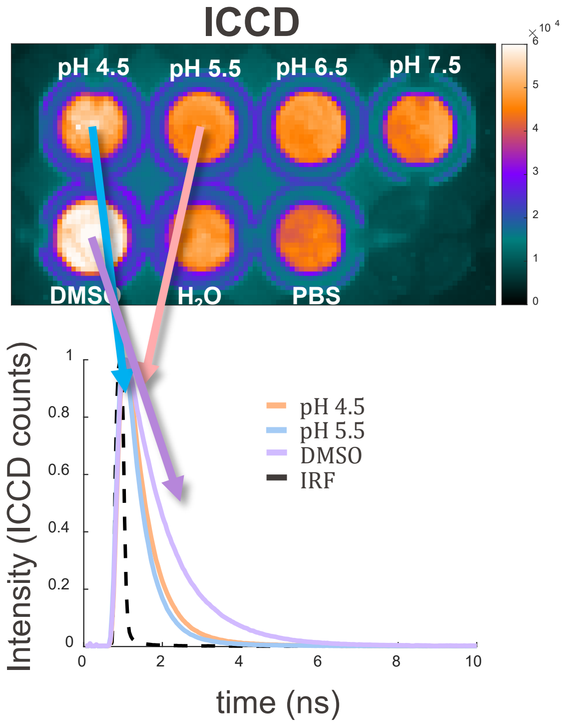
Jason T. Smith, Alena Rudkouskaya, Shan Gao, Arin Ulku, Claudio Bruschini, Edoardo Charbon, Shimon Weiss, Margarida Barroso, Xavier Intes and Xavier Michalet, *Optica* 9(5), 2022, DOI: 10.1364/OPTICA.454790

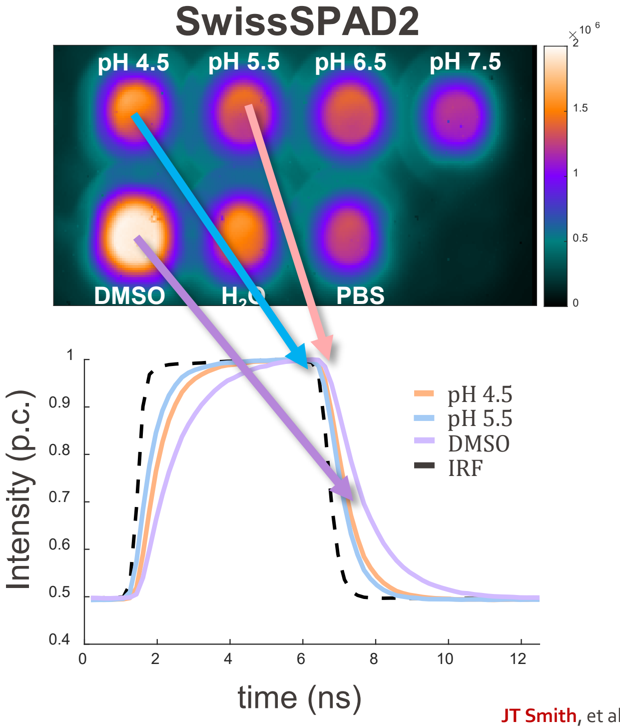
NIR MFLI (Macroscopic FLI) validation *in vitro*

Short lifetime measurements: IRDye 800CW-2DG

Photon → decay → lifetime → local environment influence

Intensity Images



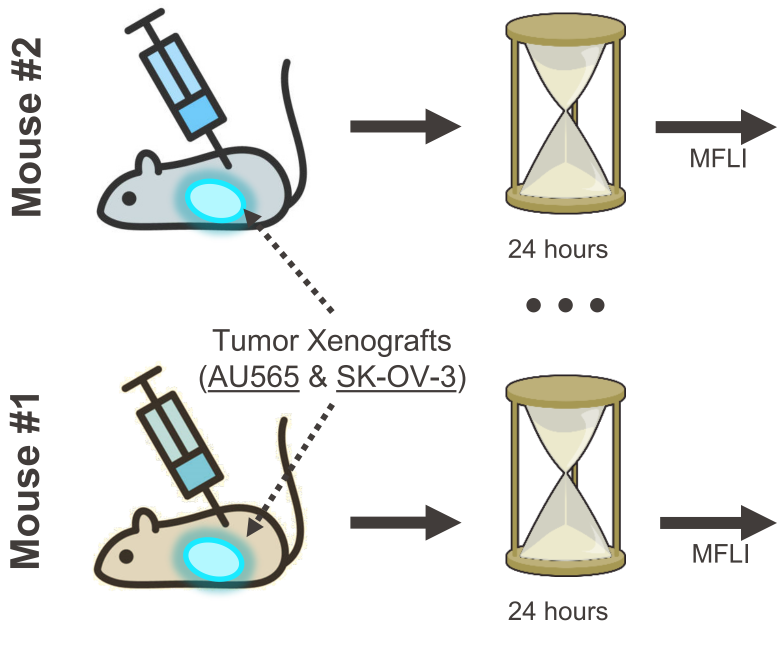


JT Smith, et al. **Optica.** (2022)

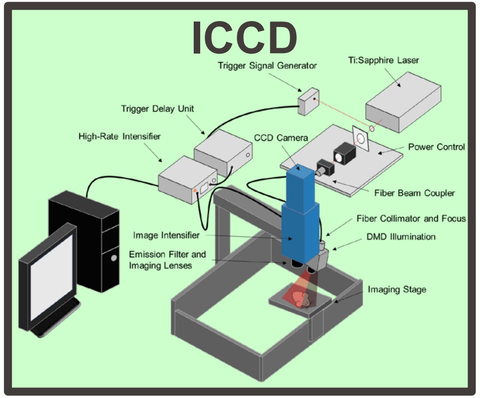
Noninvasive NIR MFLI-FRET: Trastuzumab

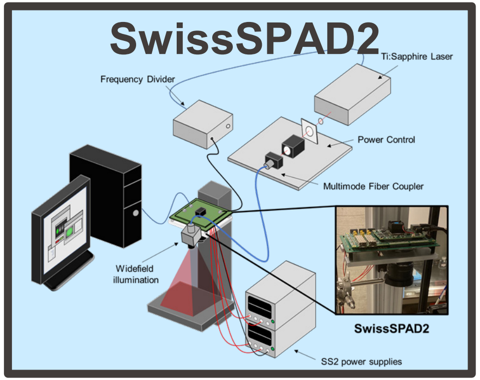
Experimental Design

Trastuzumab (anti-HER2 Ab) tagged with **AF700 & AF750**



(AF750/AF700) = (2/1)





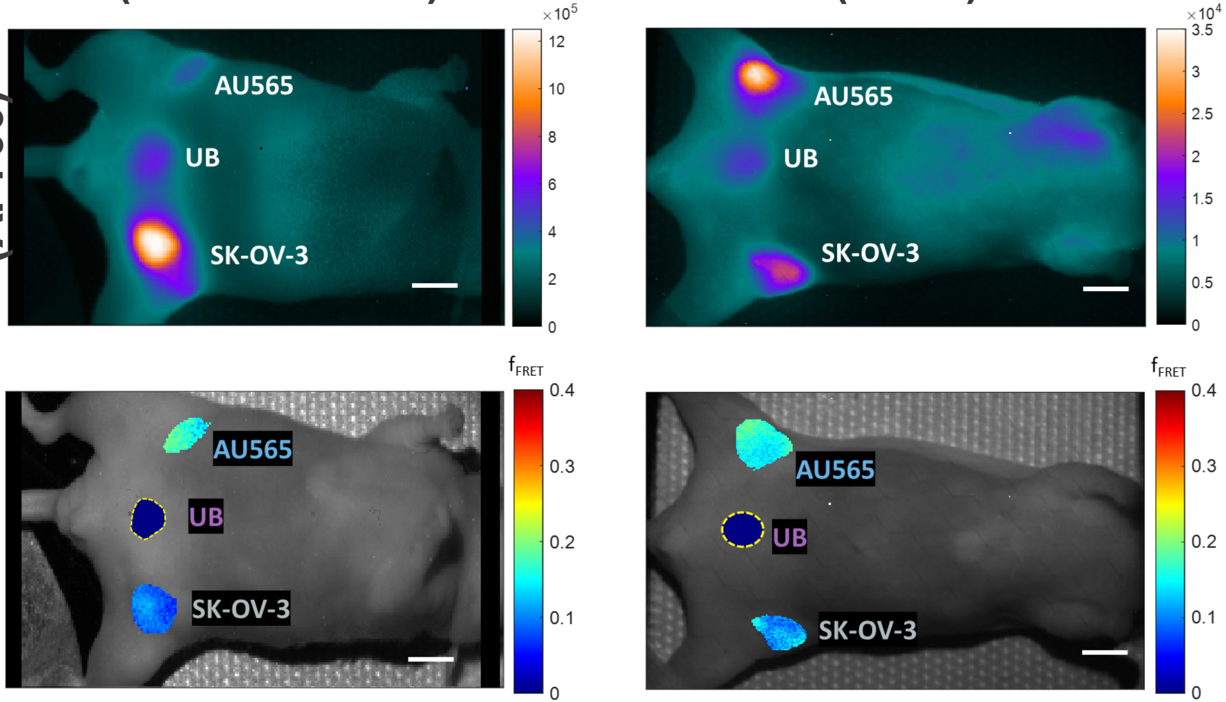
Noninvasive NIR MFLI-FRET: Trastuzumab

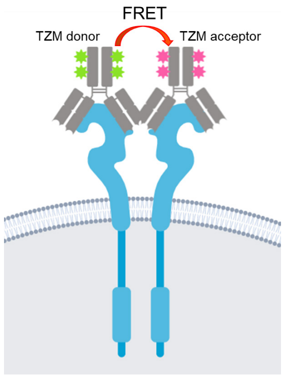
FLI-FRET Quantification

Mouse #1 (SwissSPAD2) | Mouse #2 (ICCD)

Intensity (AF700)

NLSF





JT Smith, et al. Optica. (2022)

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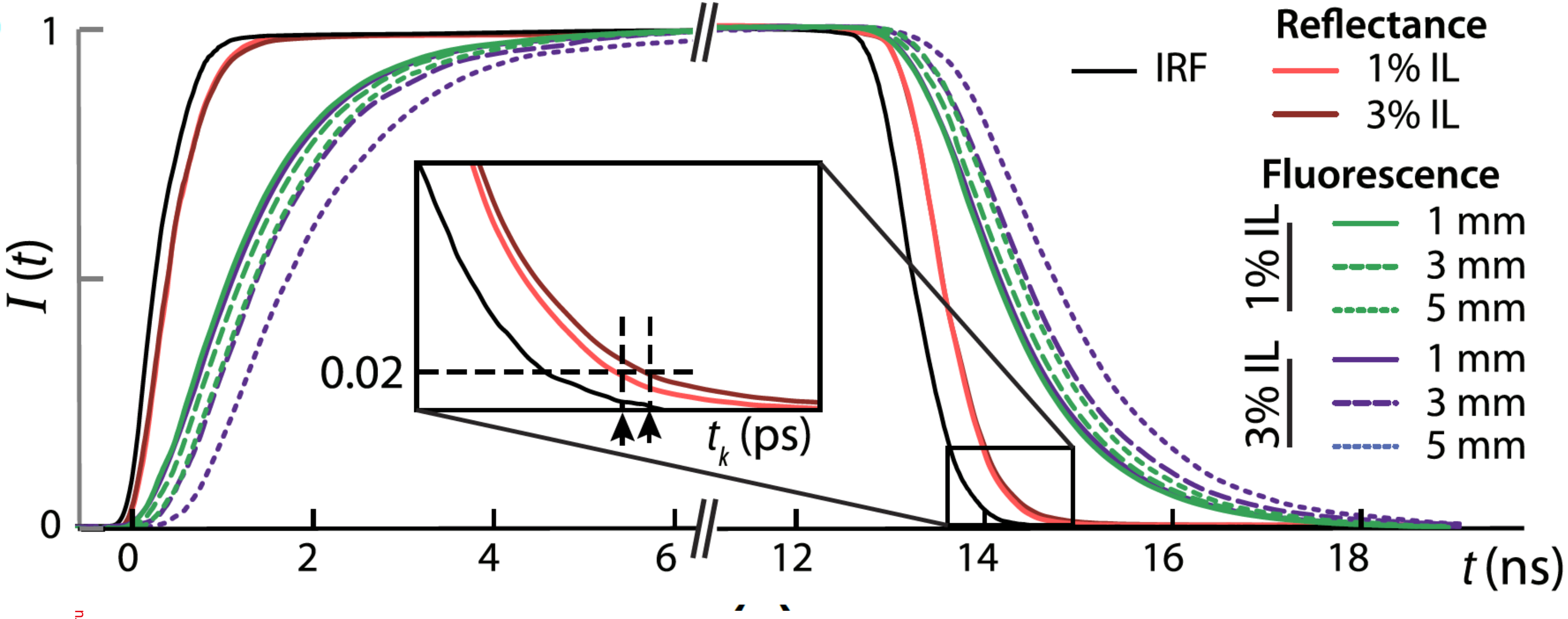
SPAD imagers for molecular imaging #2 Depth profiling

Petr Bruza, Arthur Petusseau, Arin Ulku, Jason Gunn, Samuel Streeter, Kimberley Samkoe, Claudio Bruschini, Edoardo Charbon, and Brian Pogue, ***Optica*** **8(8), 2021, DOI: 10.1364/OPTICA.431521**

Subsurface fluorescence LIDAR



C. Bru

Temporal profiles of reflectance and fluorescence of IRDye 680RD inclusion at varying depth

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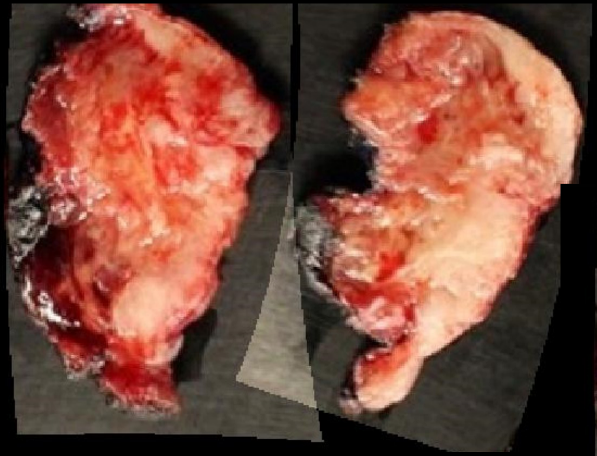
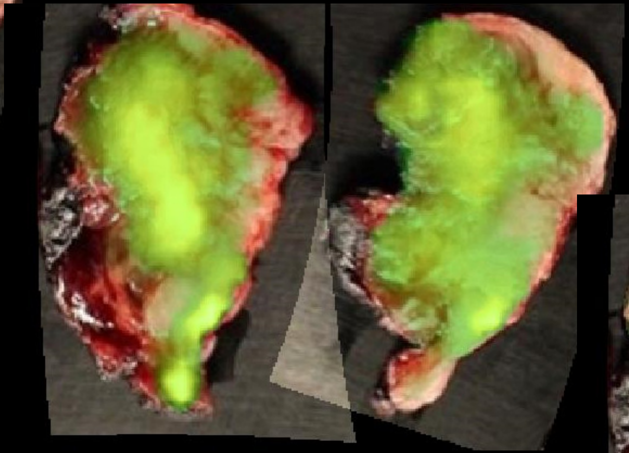
First ex-vivo fluorescence LiDAR data with SPAD – head & neck tumor

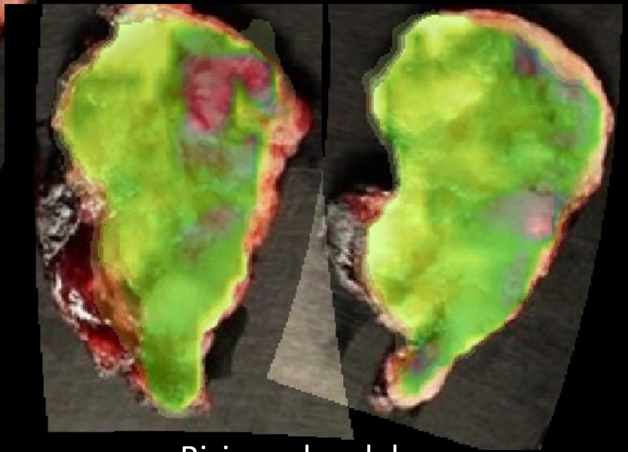
ABY-029 (anti-epithelial growth factor receptor Affibody molecule coupled with IRDye 800CW, 0.63 ns lifetime)





Integral fluorescence intensity map

$\bar{I}$ (a.u.) 0 0.5 1

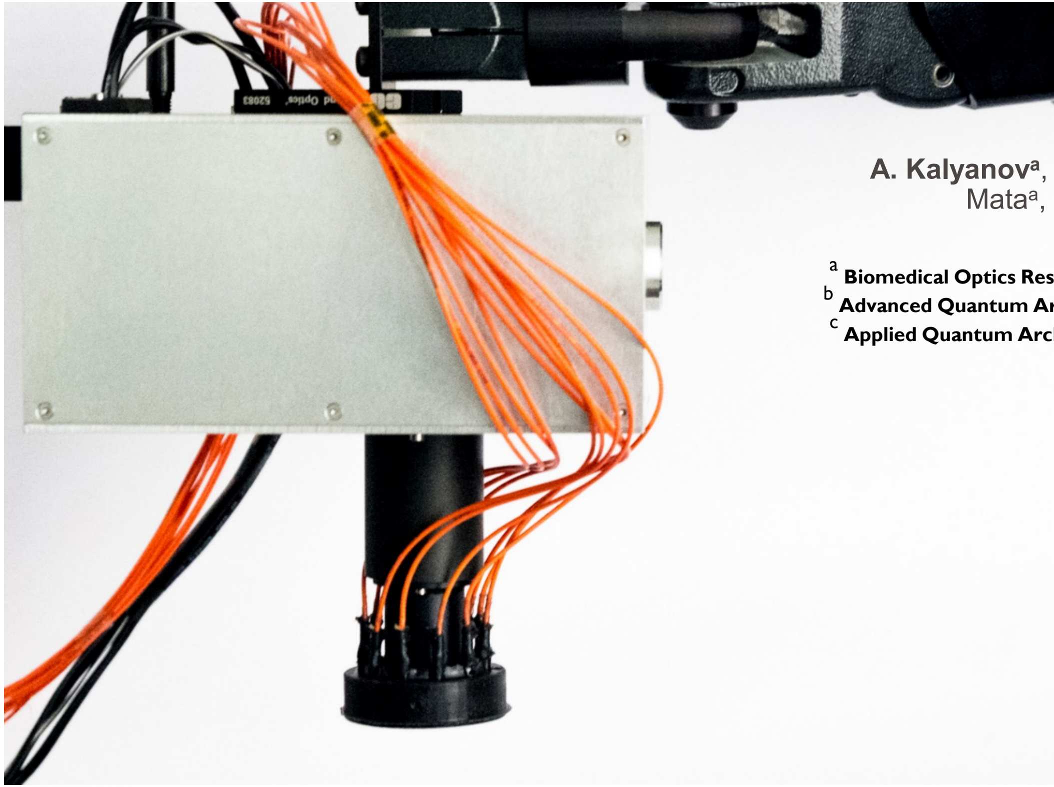


Rising edge delay map

t_{tr} (ns) 0.5 1.0 1.5 2.0

Bruza P, et al. Optica 8(8), 2021.

Imaging in Diffusive Media (e.g. tissue)



A. Kalyanov[a], J. Jiang[a], S. Lindner[ab], L. Ahnen[a], A. Di Costanzo Mata[a], J. Mata Pavia[a], S. Sanchez Majos[a], C. Zhang[c], E. Charbon[bc], Martin Wolf[a]

[a] **Biomedical Optics Research Laboratory (BORL)**, Dept. of Neonatology, University of Zurich
[b] **Advanced Quantum Architecture laboratory (AQUA)**, School of Engineering, EPFL Lausanne
[c] **Applied Quantum Architectures (AQUA)**, Delft University of Technology, Delft, Netherlands.

‘Pioneer’ system for preterm brain imaging

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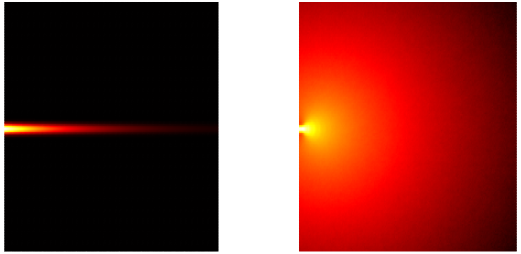
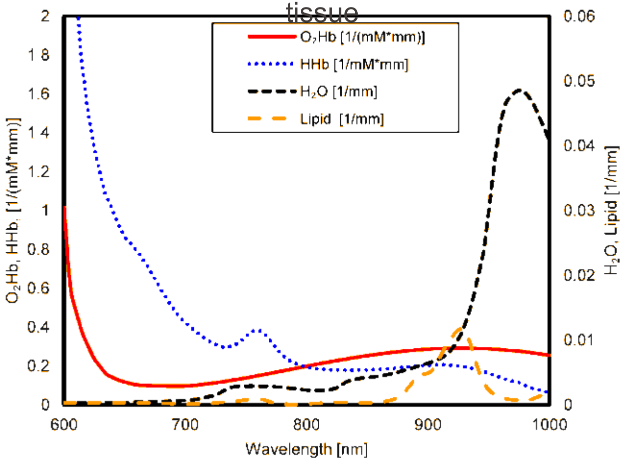
Near-infrared optical tomography (NIROT)

- Measures oxy- and deoxyhemoglobin concentration in tissue.
- No dyes are necessary to produce contrast.
- Compact, bedside applicable systems are commercially available.

Absorption Scattering



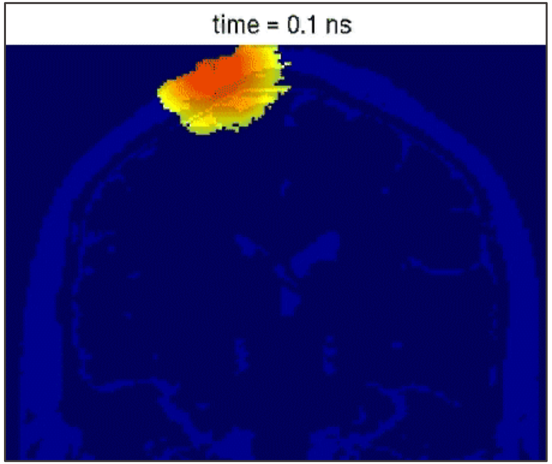
Absorption spectra of chomophores in tissue



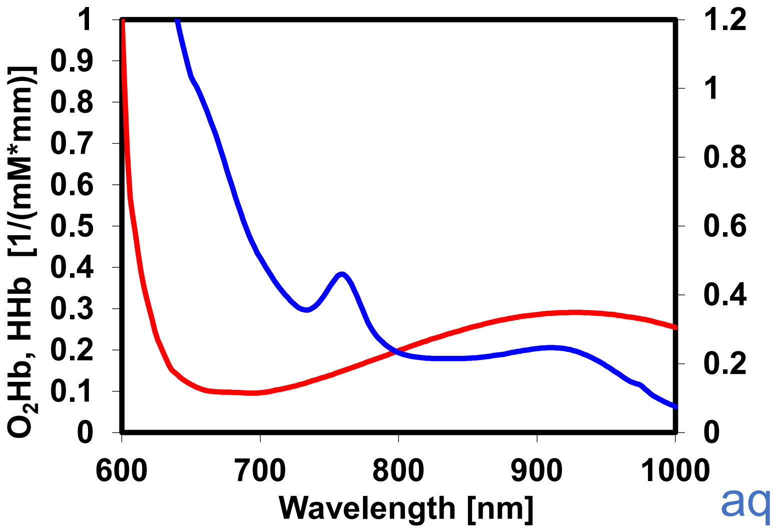
Courtesy J. Mata Pavia, PhD Defence, 2014

Near-infrared Optical Tomography Basics

- Contrast: Oxy-, deoxyhemoglobin
- Strongest absorbers in tissue in NIR
- $StO_2 = O_2Hb / tHb$ is equivalent to pO_2
- **Quantitative, non-invasive, harmless, frequently repeatable**



Credit: D. Boas



Summary & Conclusions

Summary & Conclusions

- Significant improvements in (CMOS) SPAD imagers in past 18y
- Keywords:
  - **Single-photon, SNR**
  - **Speed**
  - **Time-resolved**
  - **Zero read-out noise**
  - **Miniaturization, all-solid-state**
  - **Quantum imaging/correlations**
- Competition from other single-photon or established technologies

→ Imagers/arrays available from:

- PhotonForce (UK), MPD (I), Pi Imaging Systems (CH), Horiba (FLIMera), others – Biophotonics, microscopy, spectroscopy, "quantum imaging"
- Consumer: Sony (LIDAR), Canon (safety & security), STMicroelectronics (LIDAR), Bosch (ranging), OEMs (industrial vision & automation)

C. Bruschini, H. Homulle, et al., Light LSA (8), 2019

Acknowledgments & Sources

FNSNF

- Edoardo Charbon & the whole aqualab Team! Special thanks:
  - Former members: M. Antolovic, A. Ulku
- Robert Henderson (Univ. of Edinburgh)
- Mohit Gupta, University of Wisconsin
- Alexander Kalyanov, Martin Wolf, UZH (CH)
- Gur Lubin, Dan Oron, Ron Tenne, Weizmann Institute of Science (IL)
- Martin Hammer, Univ. Hospital Jena (D)
- Xavier Michalet, UCLA
- Pi Imaging Technology S.A., Lausanne (CH)
- abberior Instruments GmbH

pi imaging

Acknowledgments & Sources

FNSNF

SPAD imagers for molecular imaging

- **#1 Drug target engagement:** Arin Ulku, Claudio Bruschini, Edoardo Charbon; Jason Smith, Xavier Intes, Xavier Michalet, and colleagues @RPI
  - *Optica* 9(5), 2022, DOI: 10.1364/OPTICA.454790; SPIE PW 2022
- **#2 Fluorescence LIDAR:** Arin Ulku, Claudio Bruschini, Edoardo Charbon; Petr Bruza, Arthur Petusseau, Brian Pogue, and colleagues @Dartmouth
  - *Optica* 8(8), 2021, DOI: 10.1364/OPTICA.431521

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