Large-format SPAD arrays and imagers for molecular imaging

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MEDAMI 2022, Portorož, Slovenia
05/09/2022

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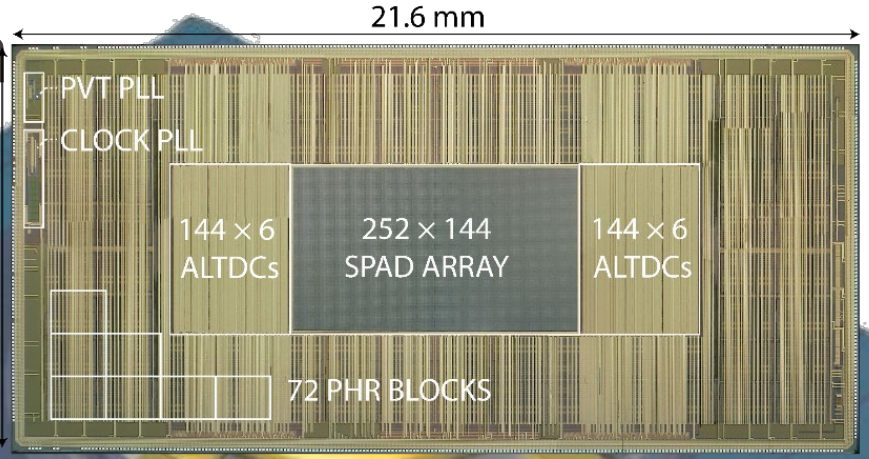
Outline

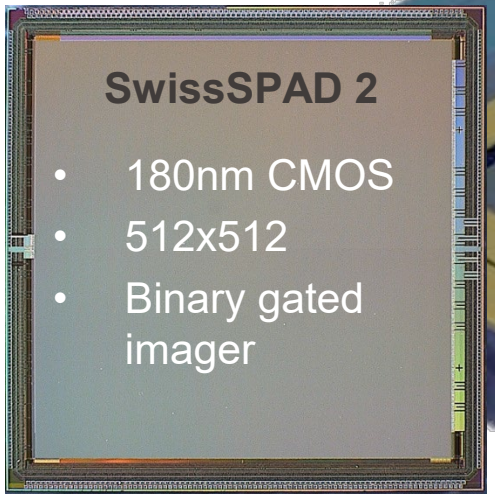
- Introduction
- SPAD arrays for PET
- SPAD imagers for molecular imaging
- Conclusions

Introduction – SPAD, SPAD arrays & imagers, SiPM

SPAD: single-photon avalanche diode
SiPM: silicon photomultiplier

AQUA – SPAD Design Examples





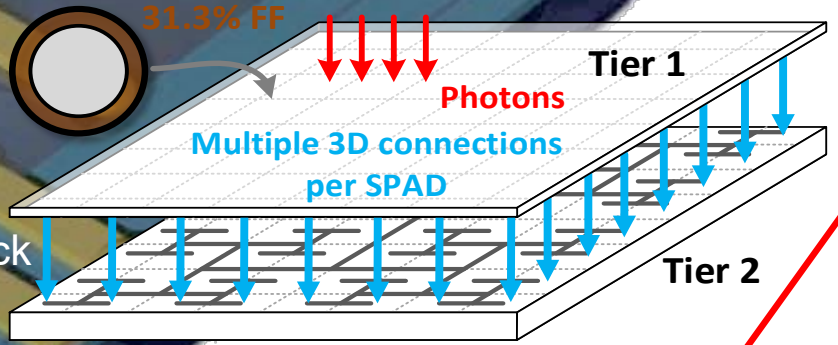
SwissSPAD 2

- 180nm CMOS
- 512x512
- Binary gated imager

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

- 45nm/65nm CMOS 3D stack

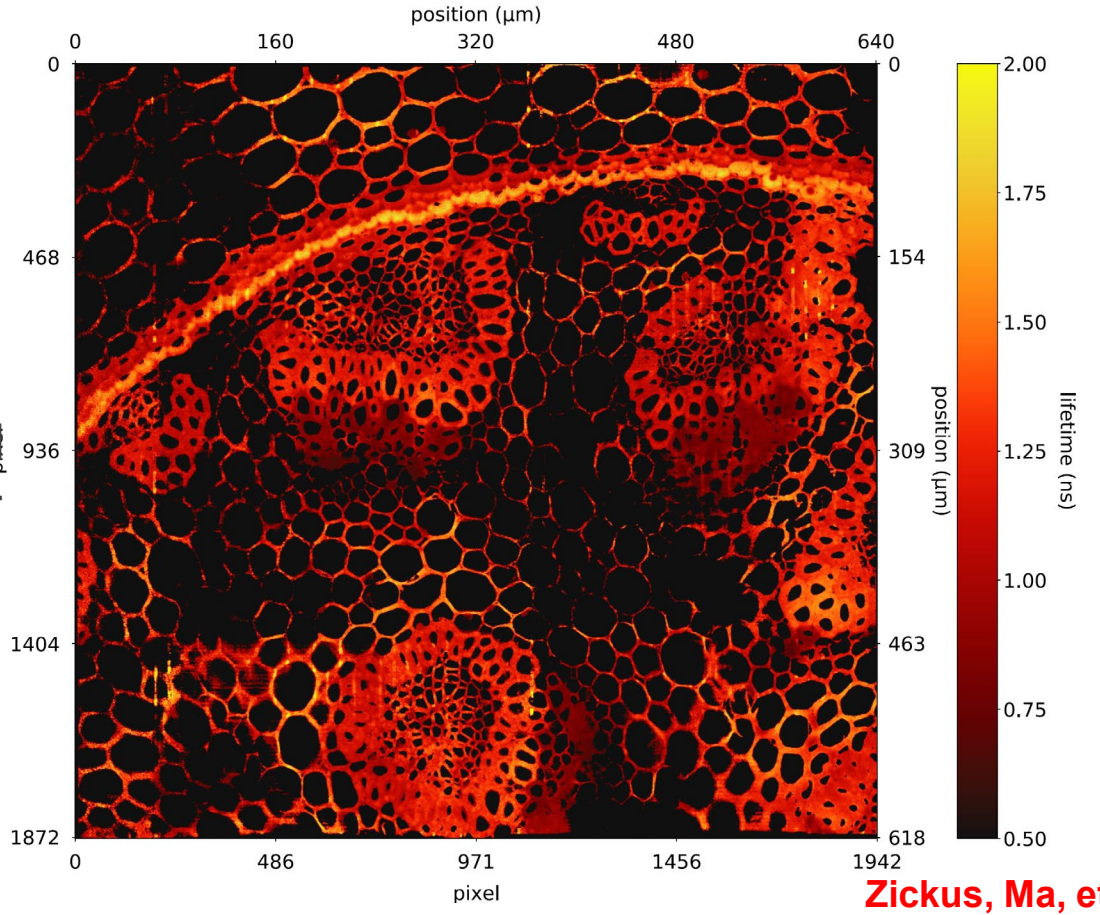
Mantis



- First 3D stacked direct time-of-flight sensor in CMOS

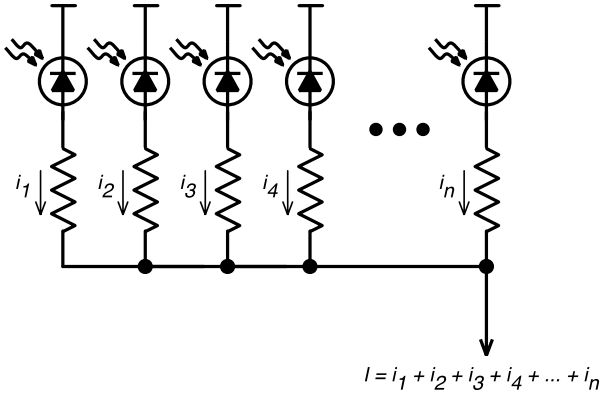
Example: FLIM image

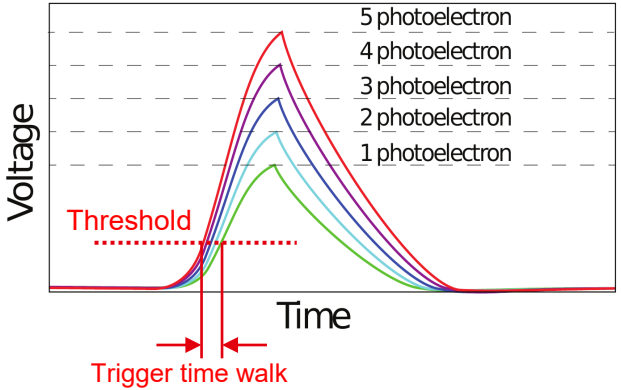
- FLIM: Fluorescence Lifetime Imaging Microscopy
- Widefield, stitched (3.64 Mpx)+ ANN-based lifetime processing

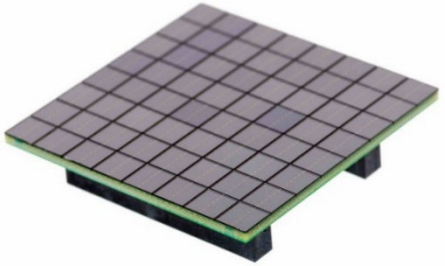


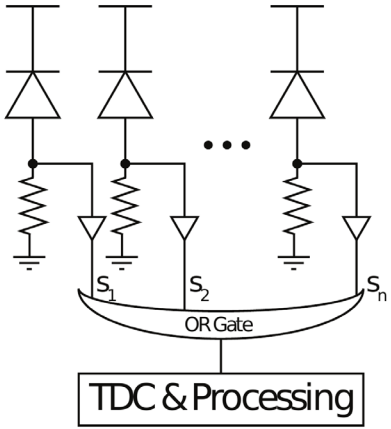
Zickus, Ma, et al, Sci Rep 2020

Analog vs. Digital Silicon Photomultiplier

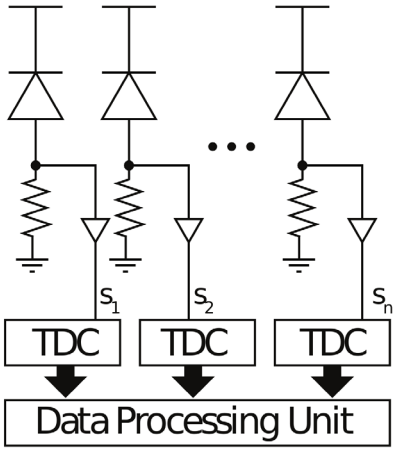








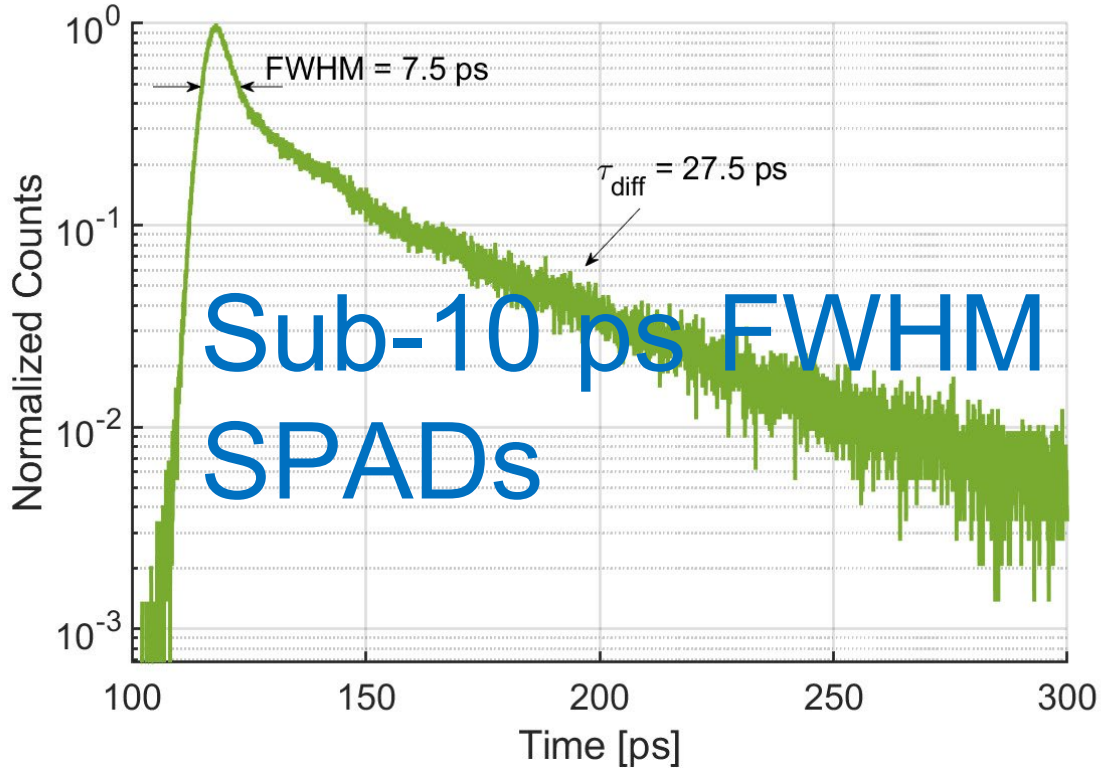
Standard dSiPM



Ideal dSiPM

SPAD arrays for PET

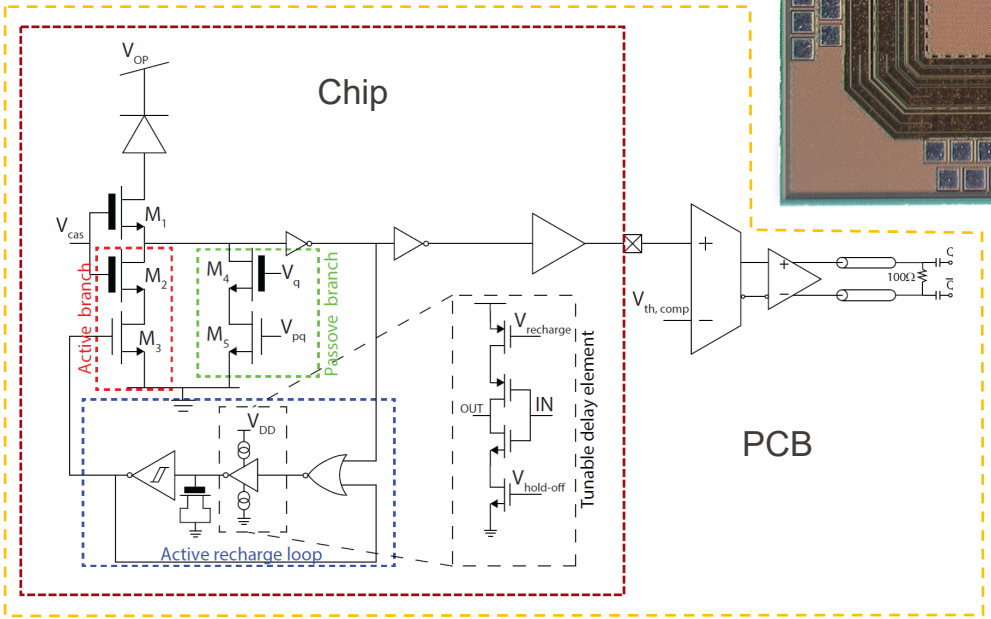
Device-level optimisation

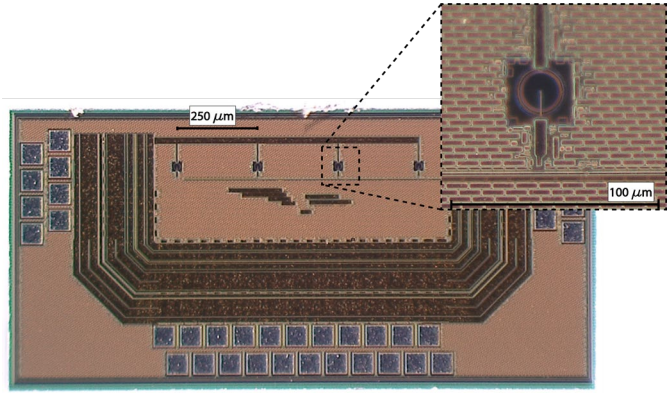


Claudio Bruschini & Edoardo Charbon, EPFL

SPAD & chip structure and read-out PCB

No pre-amplifier





Size: ~149.6 μm^2

Chip:

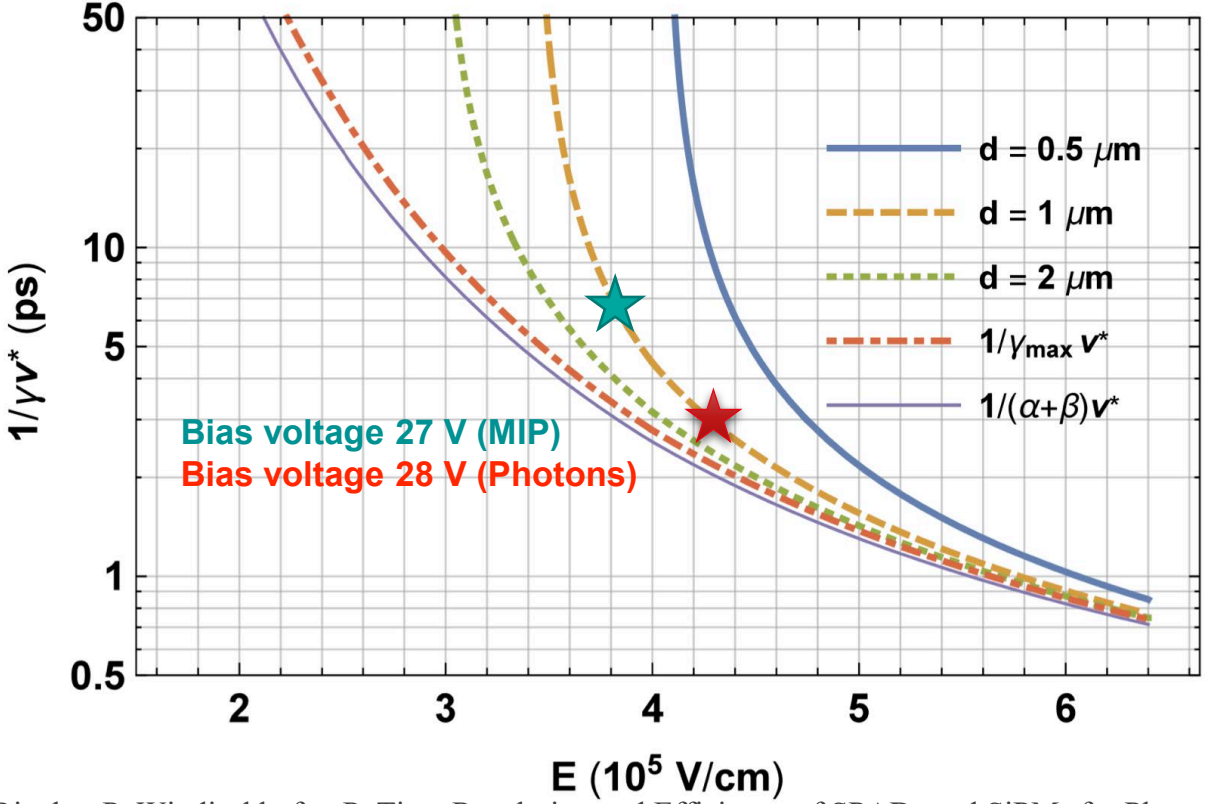
- 25 μm diameter CMOS SPAD
- Passive quenching and active reset circuit
- Tunable dead time (down to 3 ns)

System-on-board:

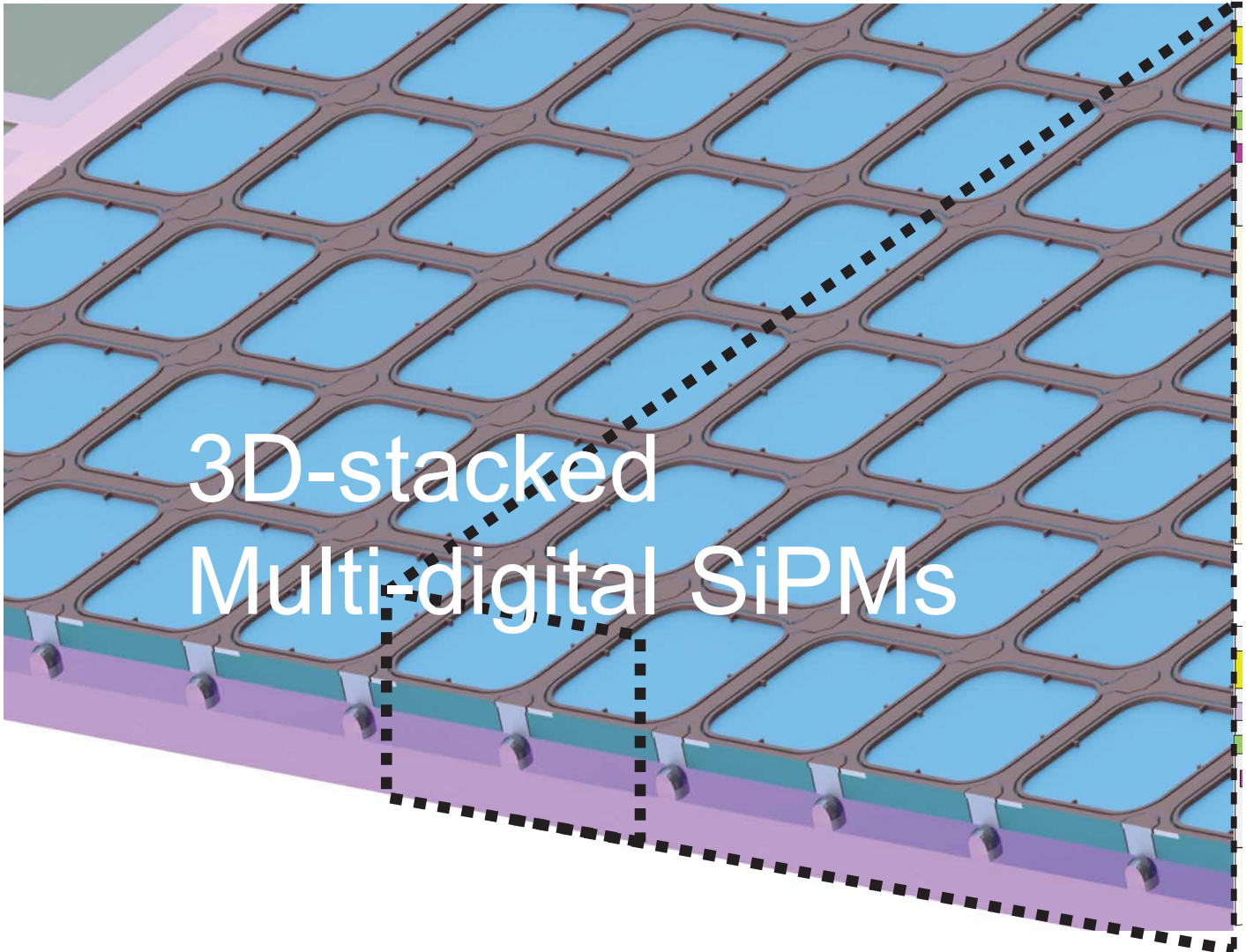
- Single external power supply source
- All voltages provided through DACs controlled with serial protocol, reduced cable noise
- Si-Ge comparator for 50 Ohm coupling
- High signal slew rate (≥ 1.6 V/ns)

- Lindner, *et al.* IEEE EDL 2018, F. Gramuglia, *et al.*, JSTQE 2021

Time resolution with SPADs

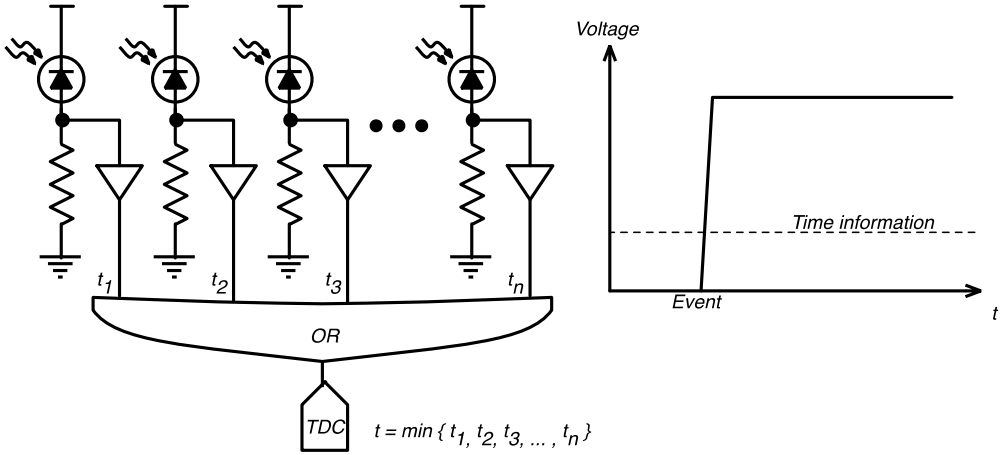


W. Riegler, P. Windischhofer, P. Time Resolution and Efficiency of SPADs and SiPMs for Photons and Charged Particles. *Nucl Instr Methods Phys Res Section A: Acc Spectrometers, Detectors Associated Equipment* (2021)

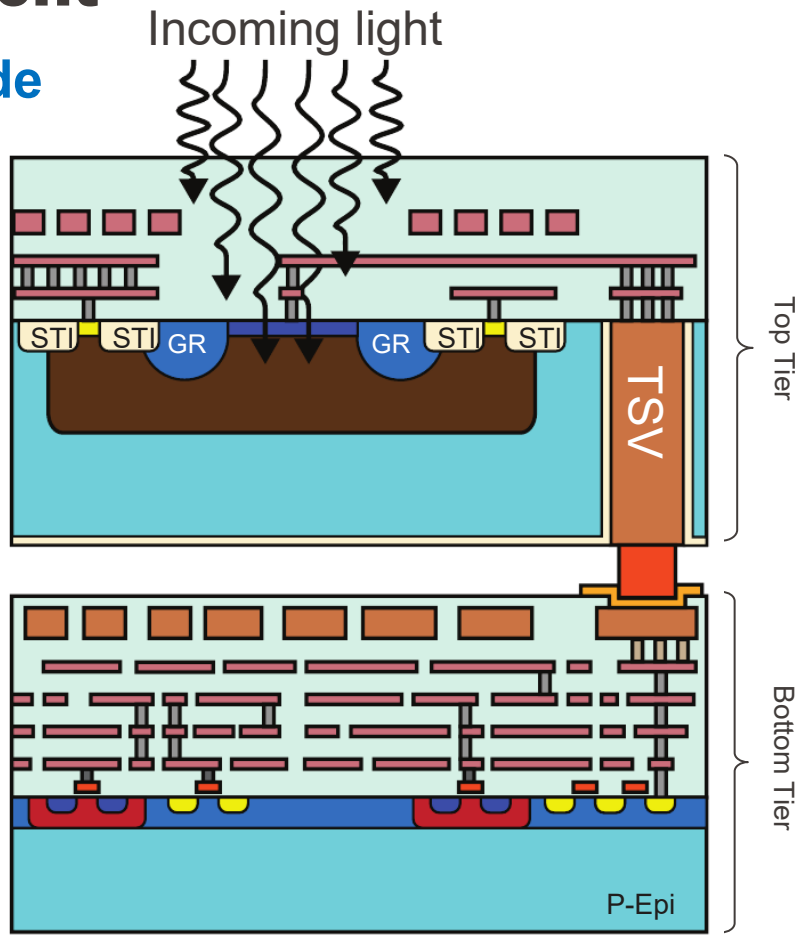

3D-stacked
Multi-digital SiPMs

Detector Concept Development

Digital SiPM



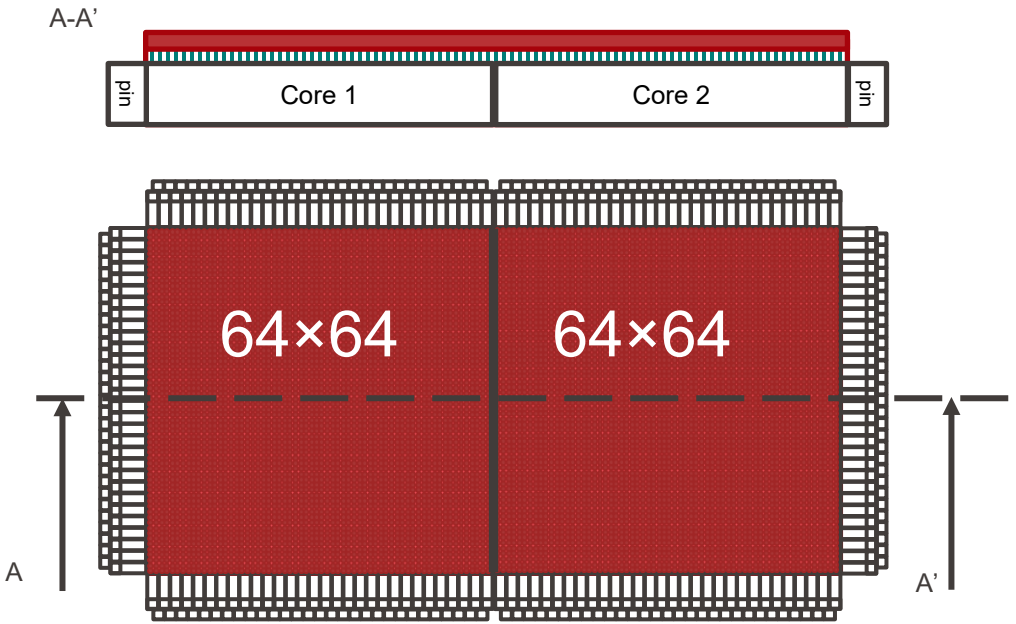
3D front-side illuminated



Chip Architecture

Multi digital SiPM:

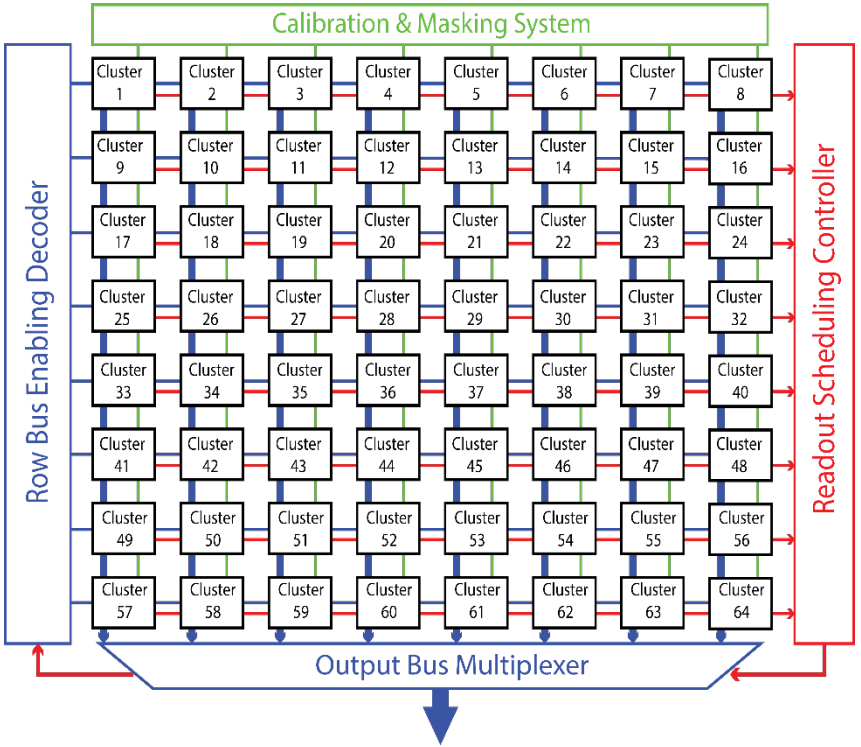
- 2 cores
- 64 clusters per core
- 64 SPADs per cluster
- Array of 8192 SPADs (2×4096)



Chip Architecture

Multi digital SiPM:

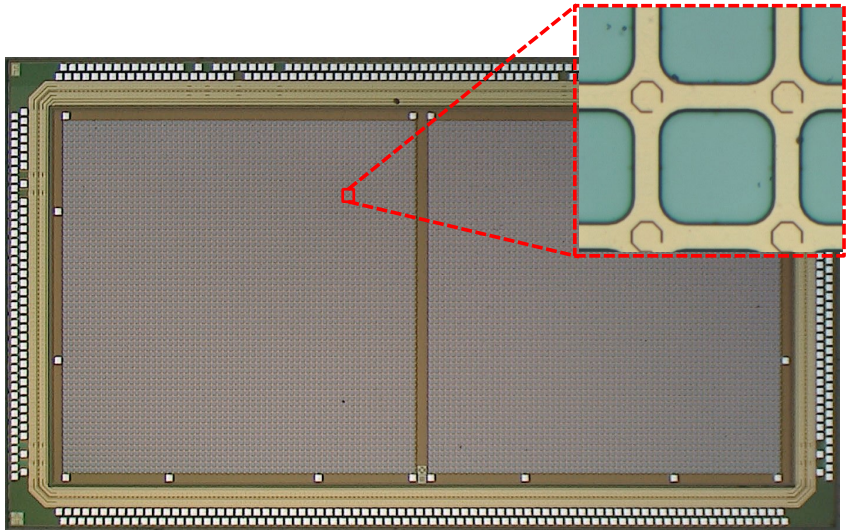
- 64 clusters per core
- 64 SPADs per cluster
- Random access readout architecture
- Single SPAD masking
- TDC calibration
- Fixed priority scheduling system

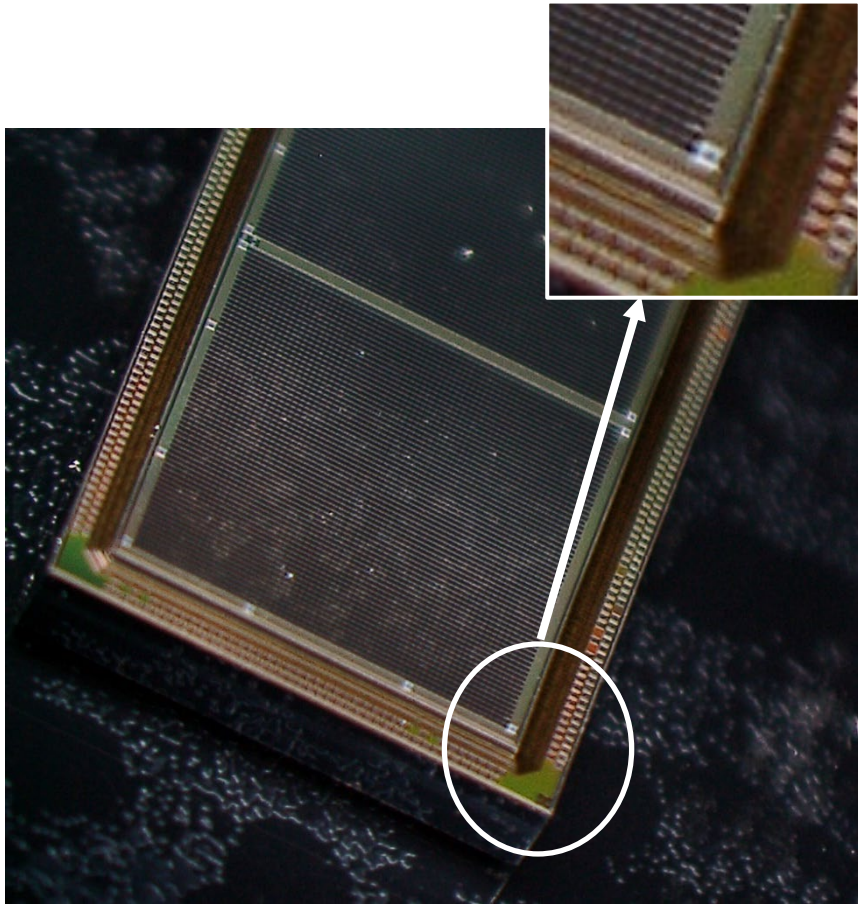


Blueberry TOF Sensor

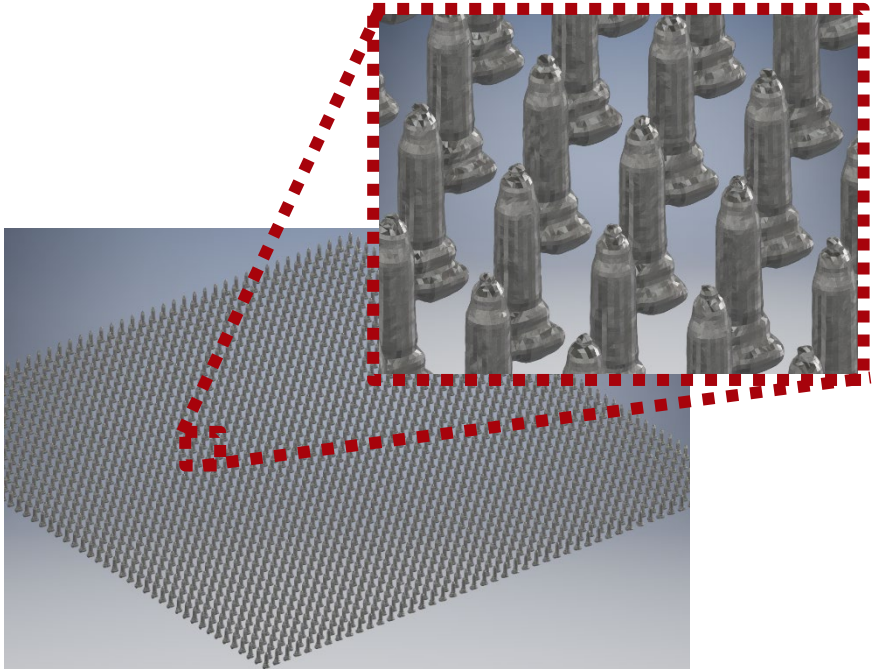
3D Stacked Chip:

- Array size: ~ 7.5×4.2mm^2
- Number of SPADs: 8192
- Technology node: 180nm CMOS

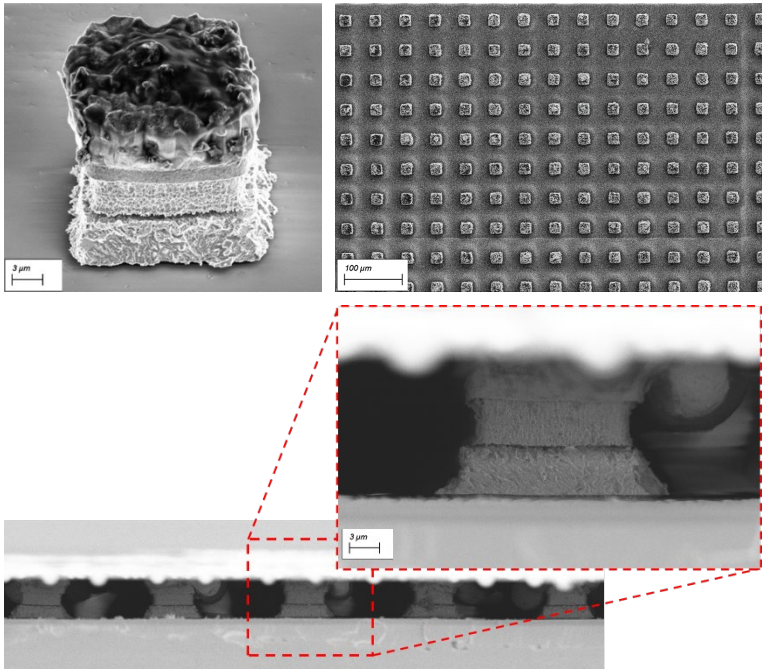




Imaging Inspection



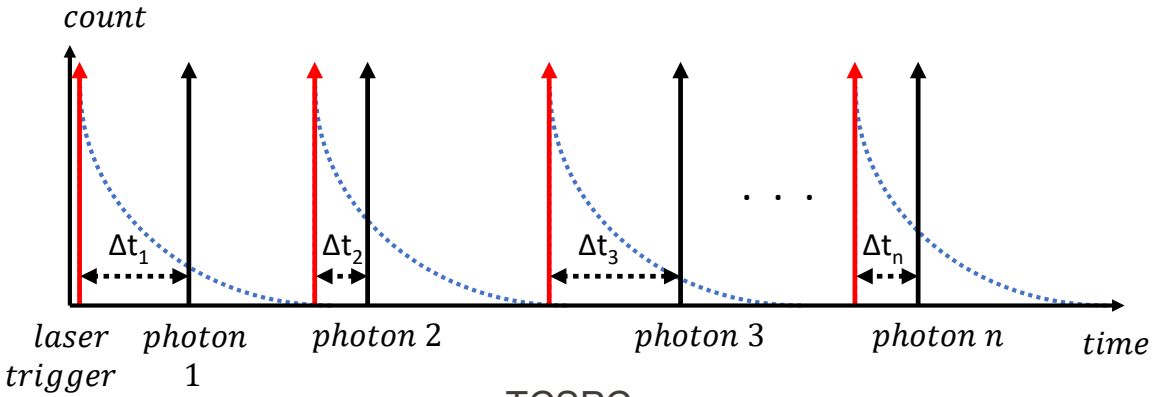
- X-Ray tomography
  - Voxel 1.42 µm
  - Not destructive inspection of TSV structure on large area

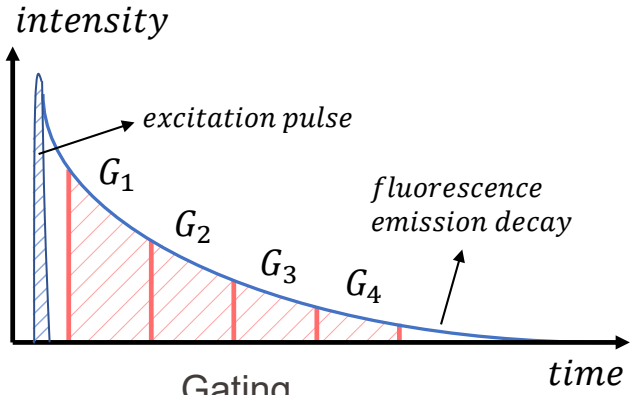


- SEM images of Microbump detail before (top) and after (bottom) 3D bonding

SPAD imagers for molecular imaging

Widefield Fluorescence Lifetime – time-resolved



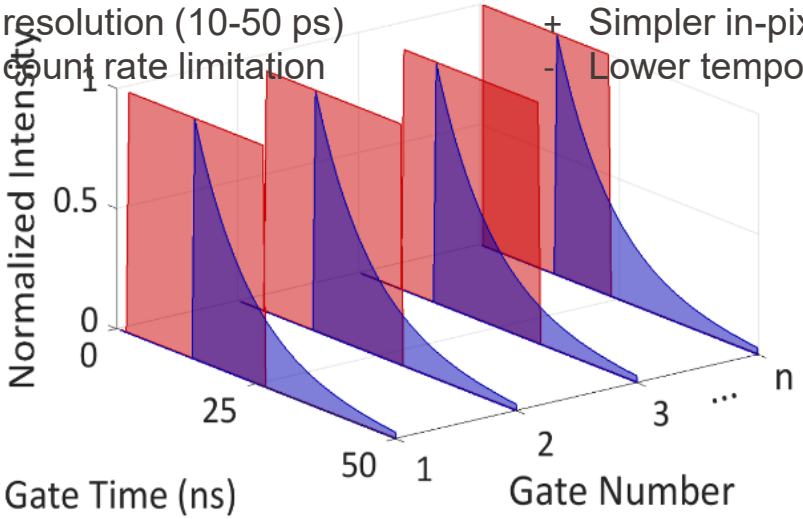


TCSPC

+ 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)

SPAD imagers for molecular imaging
#1 Drug target engagement

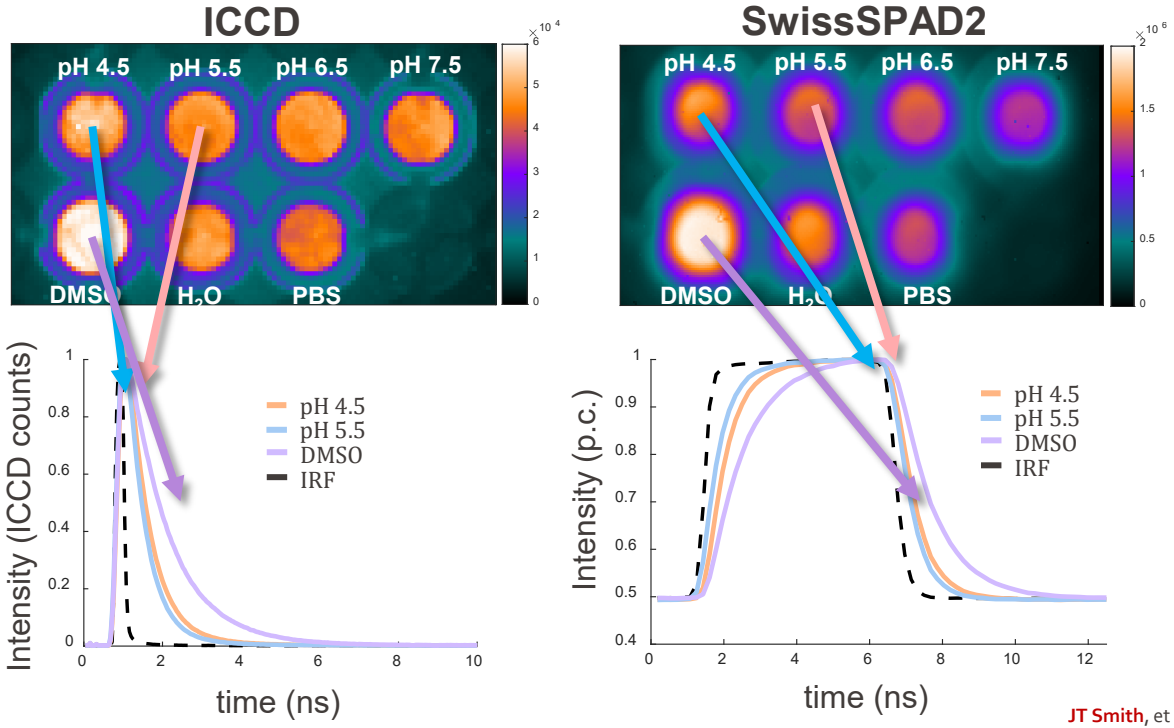
Jason T. Smith, Alena Rudkouskaya, Shan Gao, Arin Ulku, Claudio Bruschini, Edoardo Charbon, Shimon Weiss, Margarida Barroso, Xavier Intes and Xavier Michalet, *Optica* 9(5), 2022, DOI: 10.1364/OPTICA.454790

NIR MFLI (Macroscopic FLI) validation *in vitro*

Short lifetime measurements: IRDye 800CW-2DG

Photon → decay → lifetime → local environment influence

Intensity Images

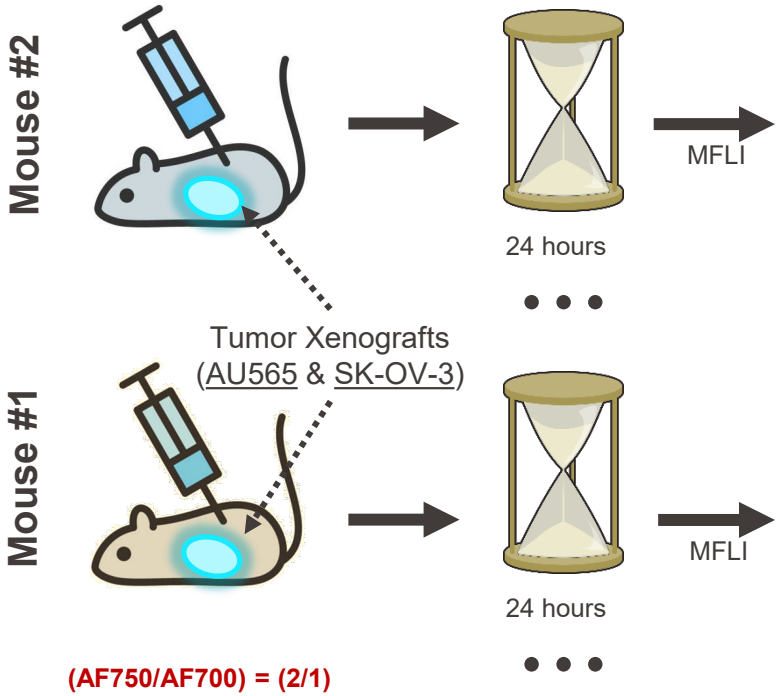


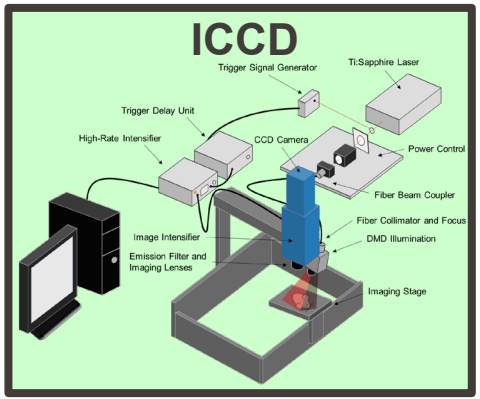
JT Smith, et al. Optica. (2022)

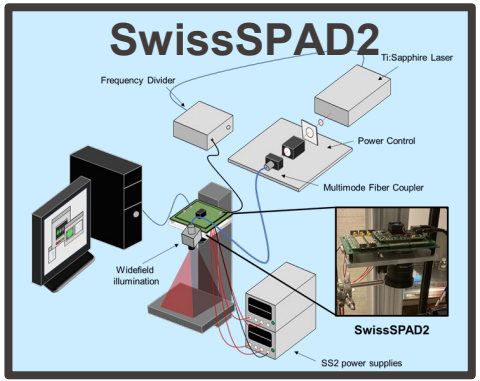
Noninvasive NIR MFLI-FRET: Trastuzumab

Experimental Design

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



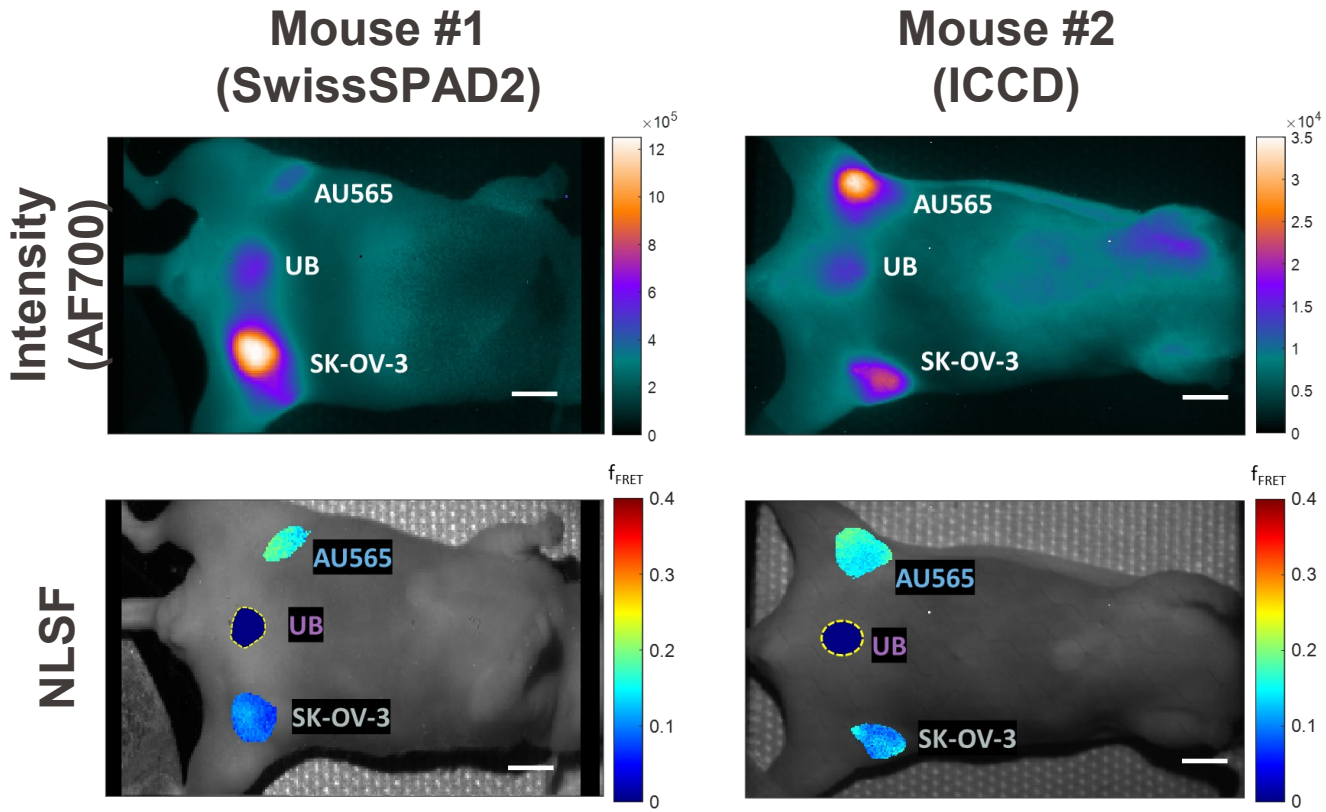


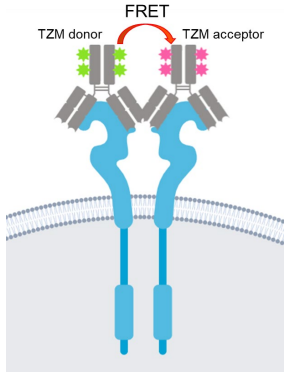


(AF750/AF700) = (2/1)

Noninvasive NIR MFLI-FRET: Trastuzumab

FLI-FRET Quantification





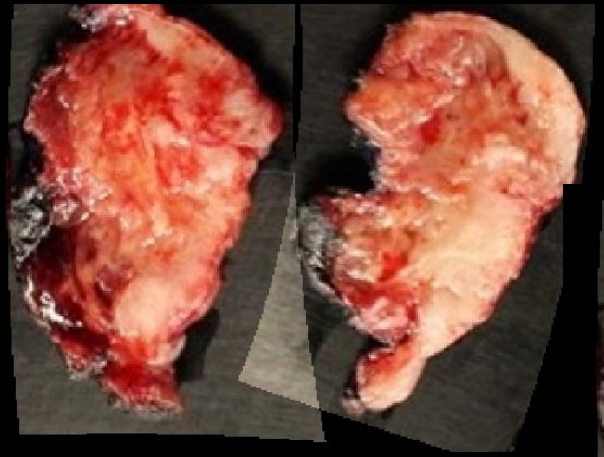
JT Smith, et al. **Optica.** (2022)

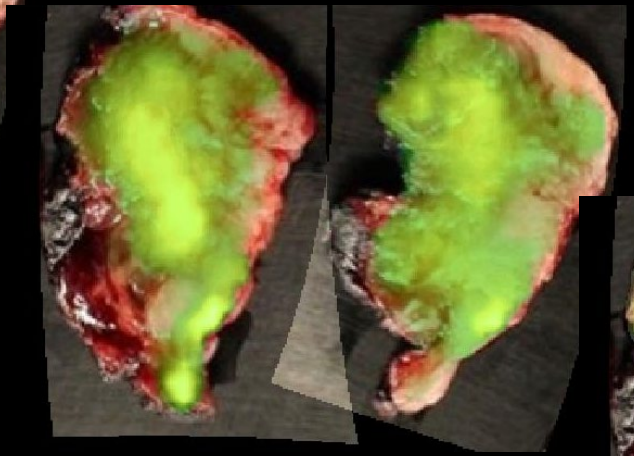
SPAD imagers for molecular imaging #2 Depth profiling

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

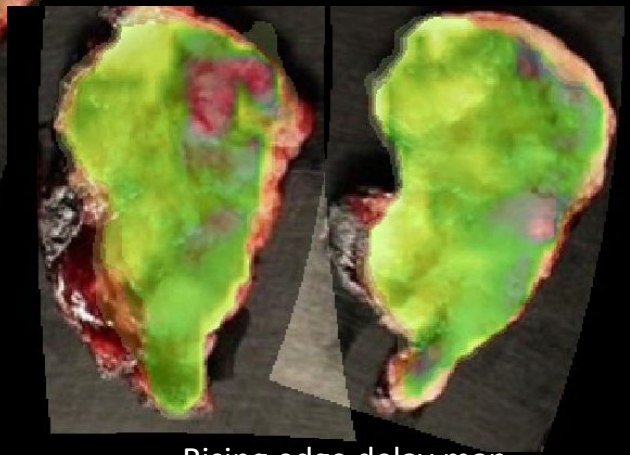
First ex-vivo fluorescence LiDAR data with SPAD – head & neck tumor

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





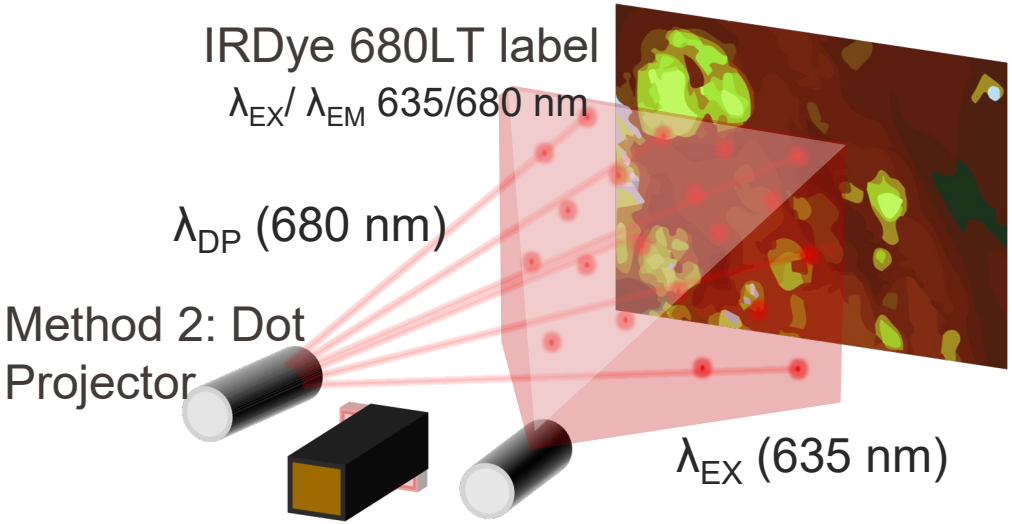
Integral fluorescence intensity map

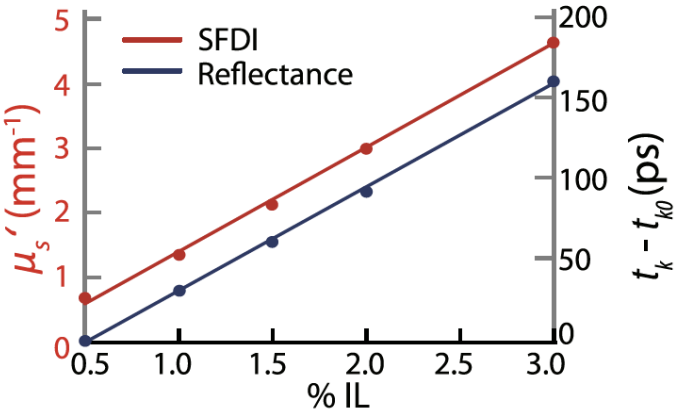


Rising edge delay map

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

Fluorescence LIDAR

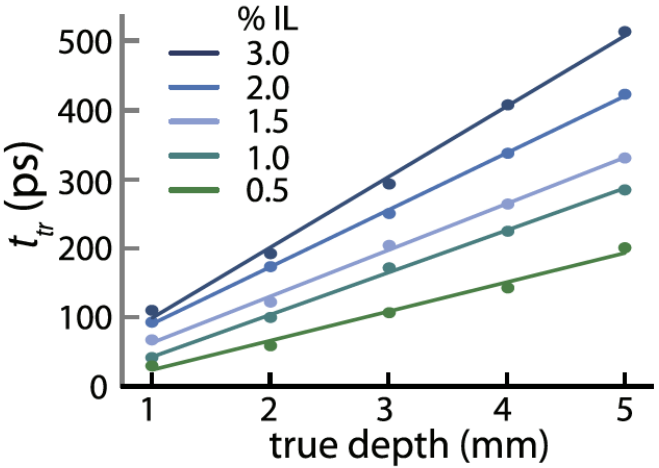


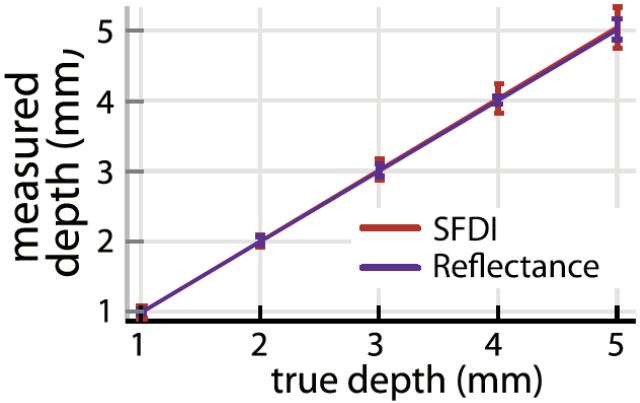


SFDI: Spatial Frequency-Domain Imaging

Fluorescence LIDAR

Calibrating fluorescence response for tissue optical properties (simple lookup table of μ_a, μ_s')





Sub-millimeter resolution for simple objects

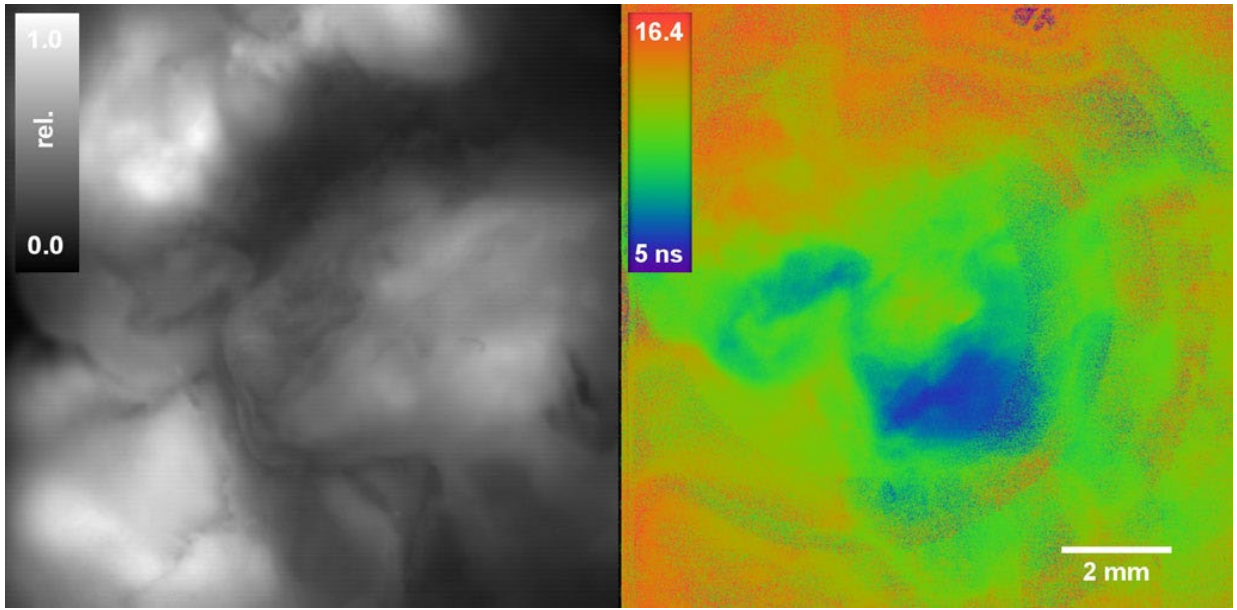
pi imaging

SPAD imagers for molecular imaging #3 Neurosurgery

Michel Antolovic, ISSW 2022, Les Diablerets (CH)

Protoporphyrin IX Fluorescence Imaging

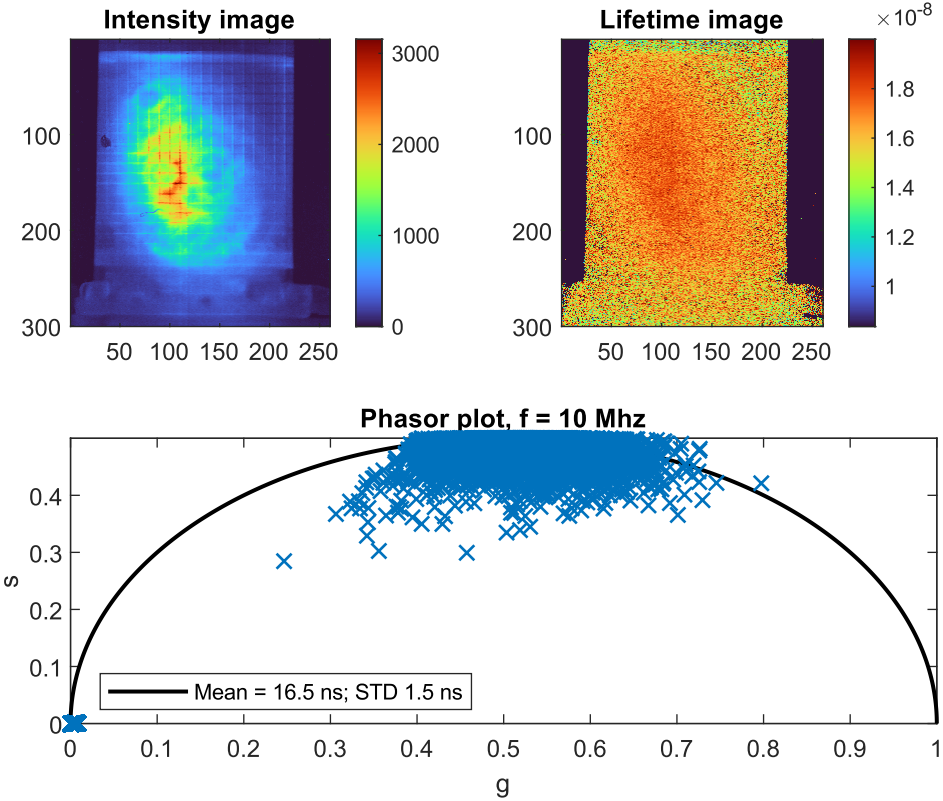
- Visualizing 5-ALA-induced PpIX fluorescence in malignant glioma surgery



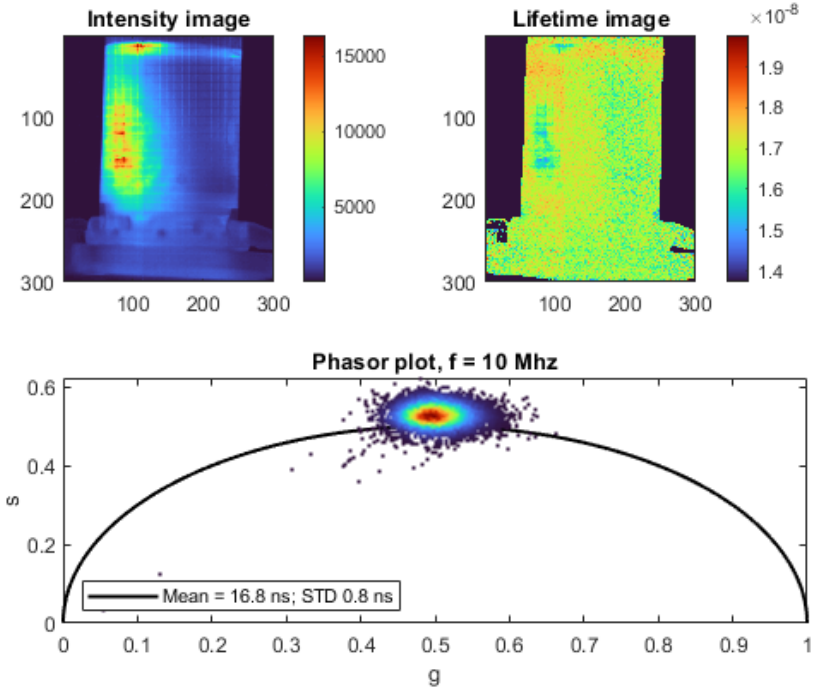
Mikael T. Erkkilä, *et al.*, ”Widefield fluorescence lifetime imaging of protoporphyrin IX for fluorescence-guided neurosurgery: An ex vivo feasibility study”, J. Biophotonics. 2019;12:e201800378. DOI: 10.1002/jbio.201800378

PpIX Lifetime Imaging

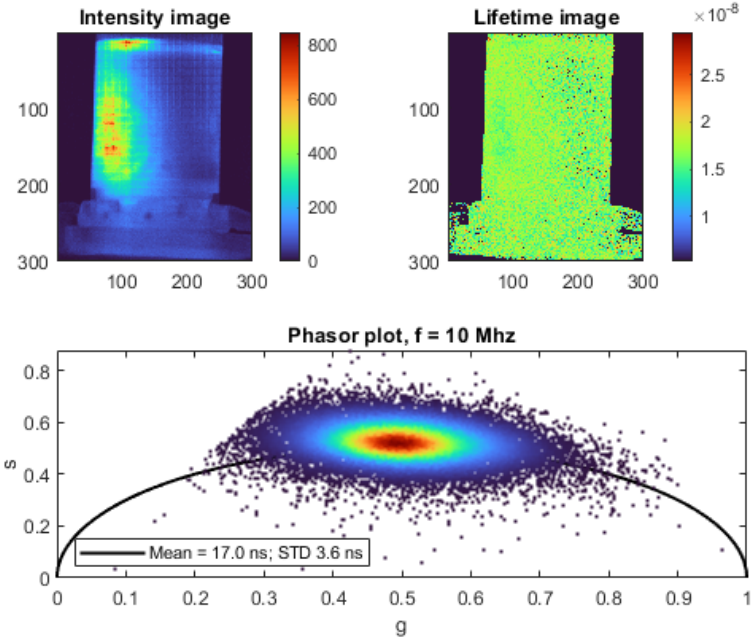
- PpIX dissolved in DMSO exhibits strong mono-exponential fluorescence signal
- One can retrieve a lifetime of 16.5±1.5 ns coherent with literature



PpIX Lifetime Imaging – increasing frame rate



234 gate positions



15 gate positions

Acknowledgments & Sources

FNSNF KIST T-Micro

SPAD arrays for PET:

- **Sub-10 ps FWHM SPADs**: Francesco Gramuglia, Ming-Lo Wu, Myung-Jae Lee, Claudio Bruschini, Edoardo Charbon
  - JSTQE(28) 2021, Frontiers in Physics(10) 2022
- **3D-stacked digital SiPM** (“Blueberry”): Francesco Gramuglia, Andrada Muntean, Carlo Alberto Fenoglio, Esteban Venialgo, Myung-Jae Lee, Scott Lindner, Makoto Motoyoshi, Andrei Ardelean, Claudio Bruschini, Edoardo Charbon
  - NSS-MIC 2021, IISW 2021
- **MIP detection**: Francesco Gramuglia, Emanuele Ripiccini, Carlo Alberto Fenoglio, Ming-Lo Wu, Lorenzo Paolozzi, Claudio Bruschini, Edoardo Charbon
  - Frontiers in Physics(10) 2022

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
- **#3 Neurosurgery**: Michel Antolovic and colleagues @Pi Imaging
  - ISSW 2022

Rensselaer

pi imaging