A miniaturized and low-cost sub-nanosecond fluorescence lifetime detector based on and array of CMOS SPAD detectors

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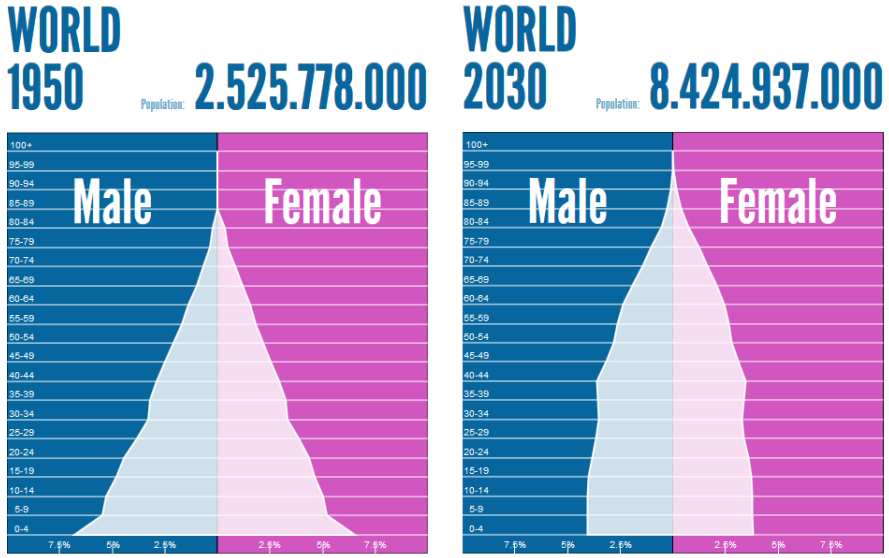
Outline

1. Motivation
2. Fluorescence as a technique for diagnosis
3. Lifetime detection based on CMOS SPADs
4. Miniaturized and low-cost sub-ns device
5. Conclusions

Motivation

❶ Healthcare is under pressure in industrialized countries



❷ Under-diagnosis in developing countries

❸ Fast diagnosis at the point of care

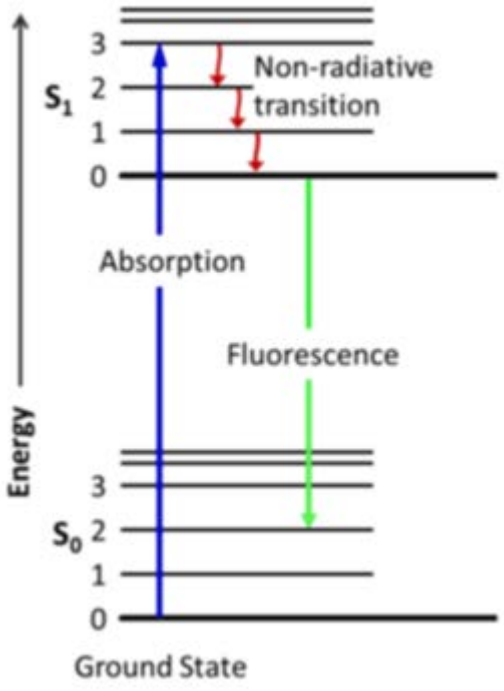
Cardiovascular diseases (like acute myocardial infarction): leading cause of death

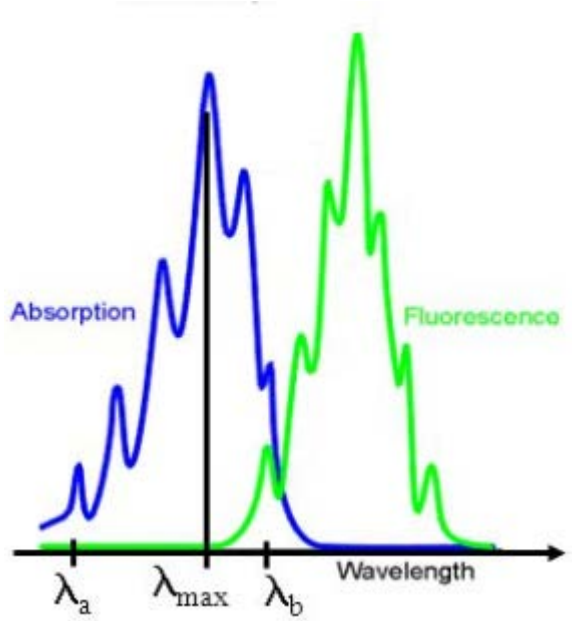
Strokes: Fast diagnosis between ischemic (TPA effective if less than 4 h) or hemorrhagic

Sepsis: One in three patients who die in a hospital have sepsis

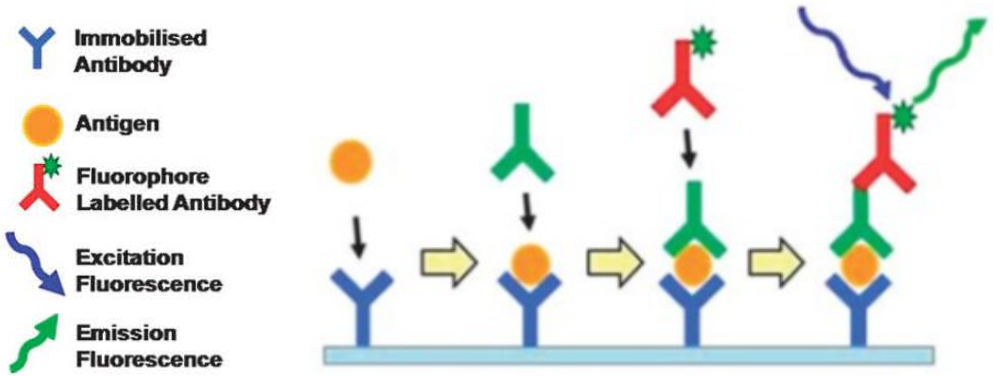
Fluorescence

1. Fluorescence is a optical transduction technique
2. Is very sensitive and selective (because few materials emit and thanks to labelling)
3. It can be measured Intensity, Lifetime and FRET (distance between fluorescent dyes)





Example of immunoassay

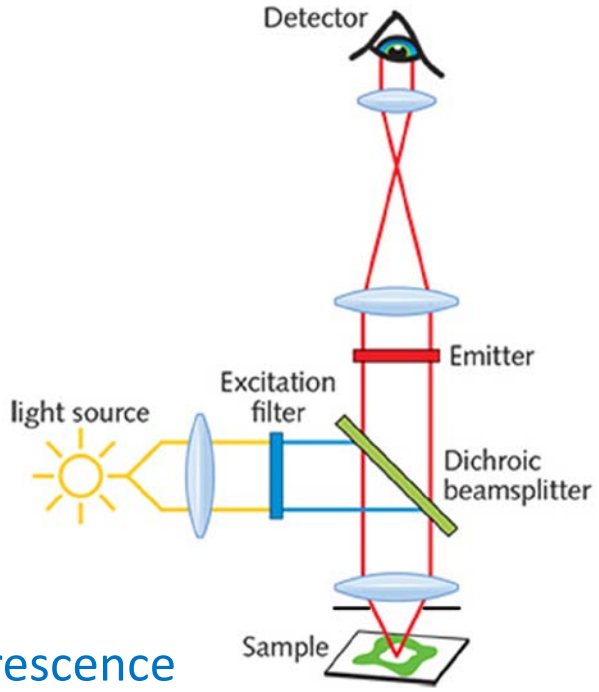


Fluorescence

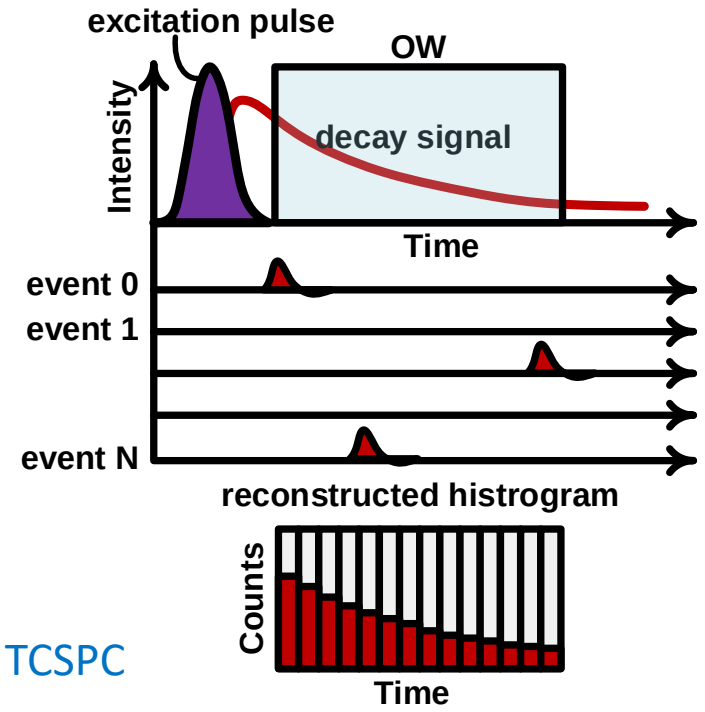
❶ Time Resolved Fluorescence is characteristic of each fluorescent molecule and the chemical composition of the environment (can be used to follow reaction mechanisms)

❷ It does not depend on excitation light intensity and concentration of fluorophores

❸ Commonly measured by TCSPC (Time Correlated Single Photon Counting)



Epifluorescence



TCSPC

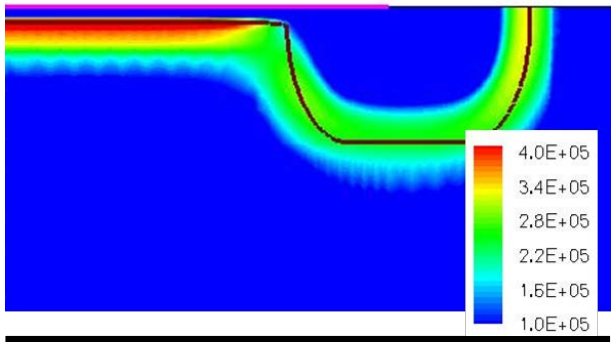
CMOS SPADs

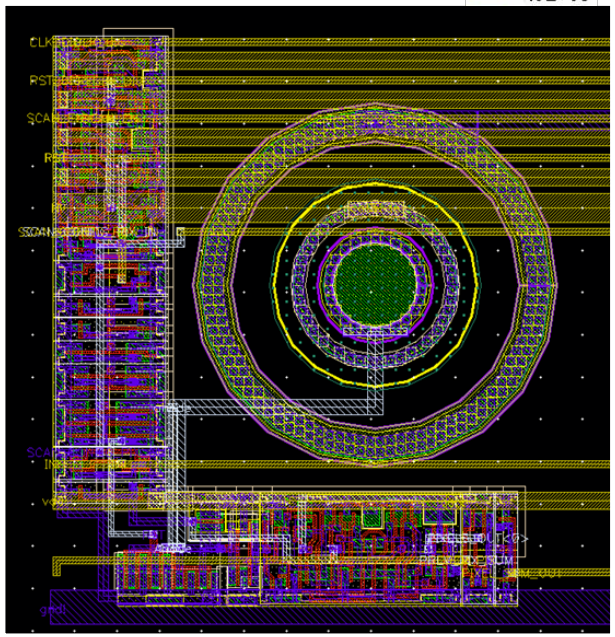
❶ CMOS SPADs work in Geiger mode (bias 10-20% above breakdown) and have ‘infinite’ gain

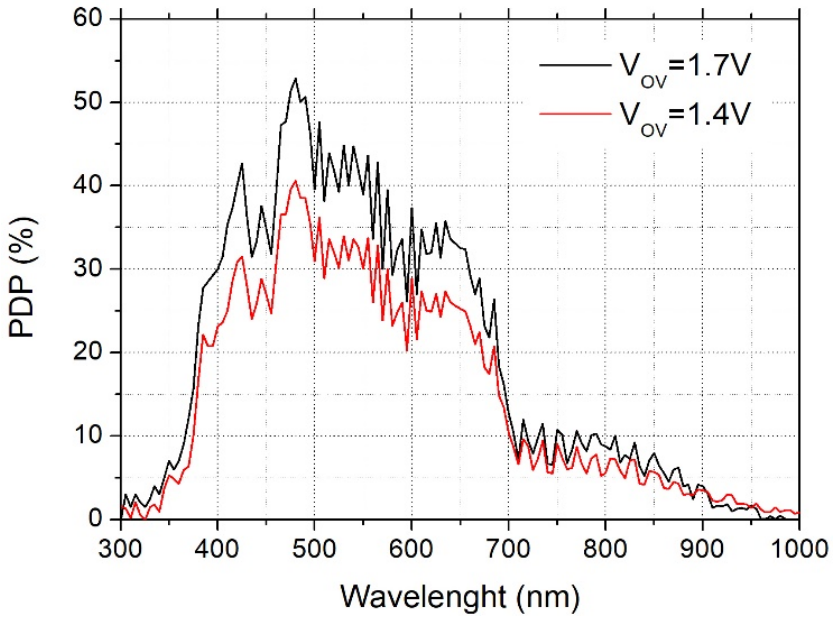
❷ Response not proportional to amount of light

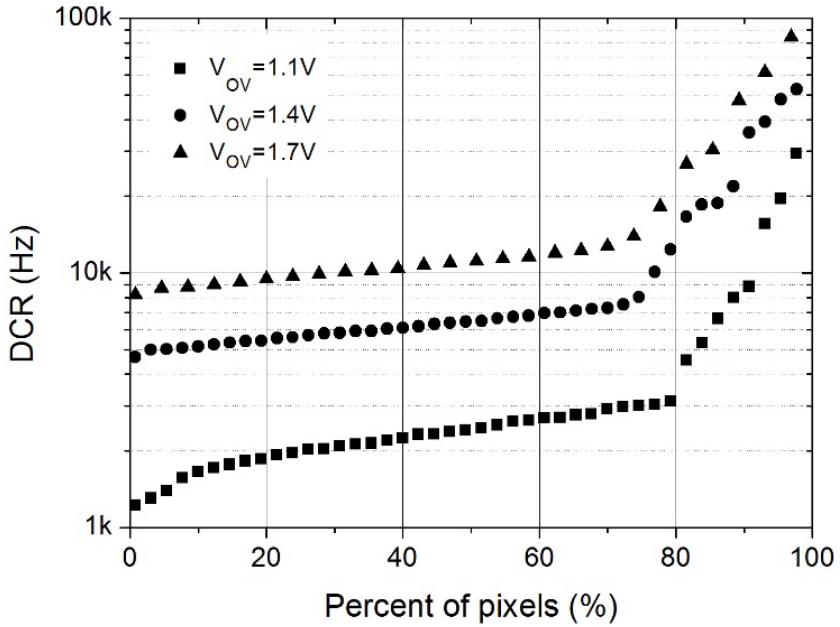
❸ Dark Count rate is an issue (~7000 cps in this work)

❹ Photo Detection Probalility in visible (~350-700 nm)

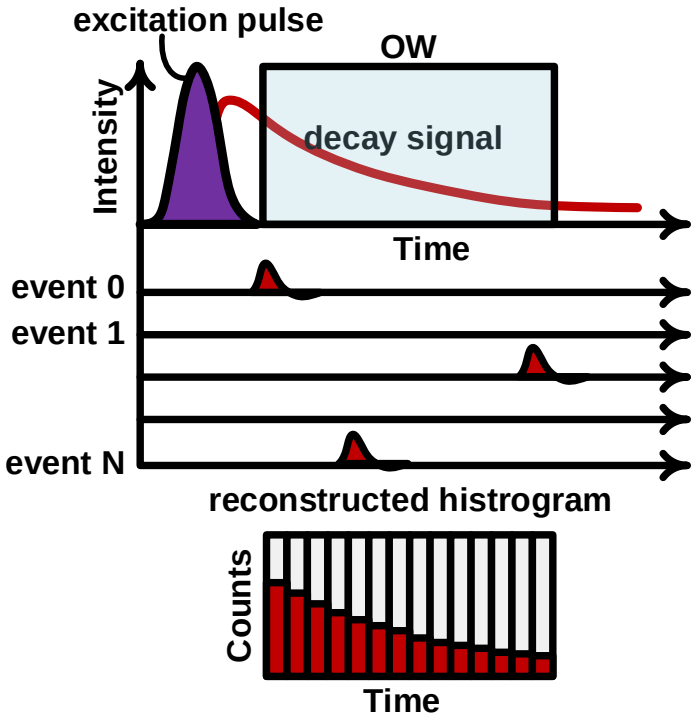


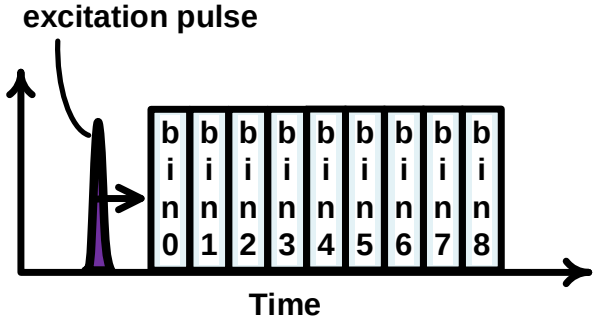


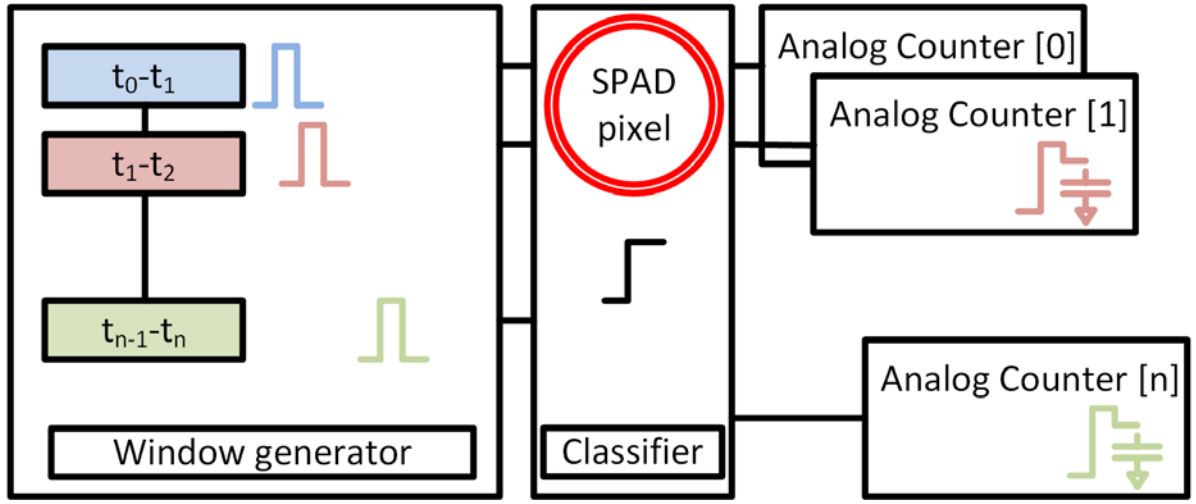


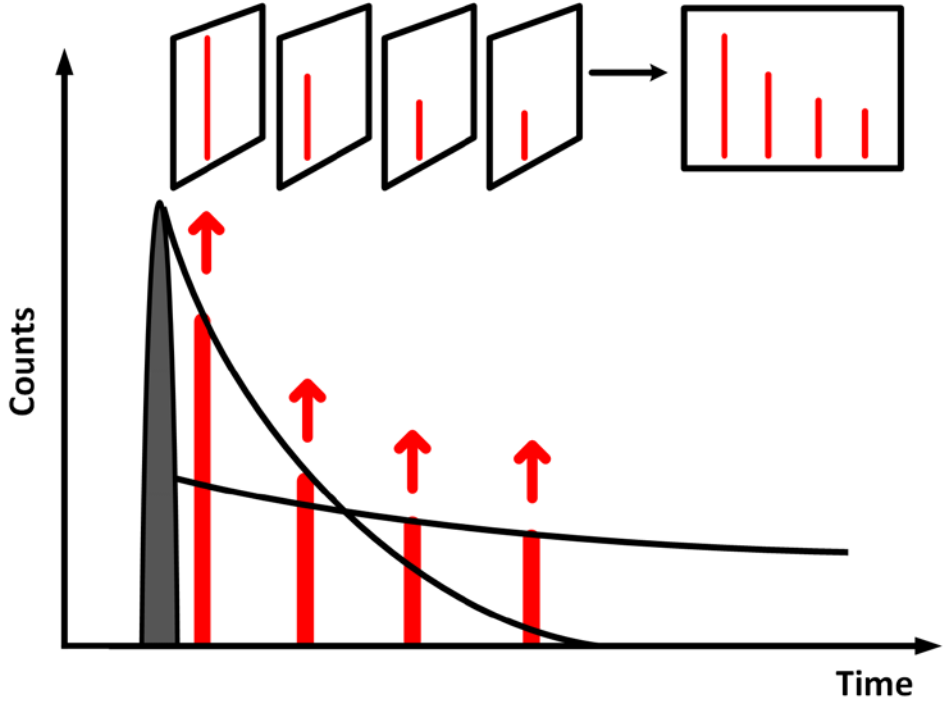


180nm CMOS process with STI


excitation pulse
OW
Intensity
decay signal
Time
event 0
event 1
event N
reconstructed histrogram
Counts
Time


excitation pulse
bin0
bin1
bin2
bin3
bin4
bin5
bin6
bin7
bin8
Time

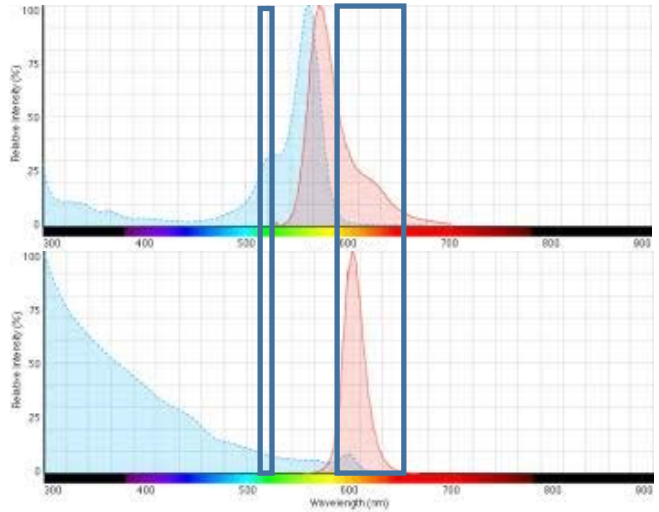

t0-t1
t1-t2
tn-1-tn
Window generator
SPAD pixel
Classifier
Analog Counter [0]
Analog Counter [1]
Analog Counter [n]

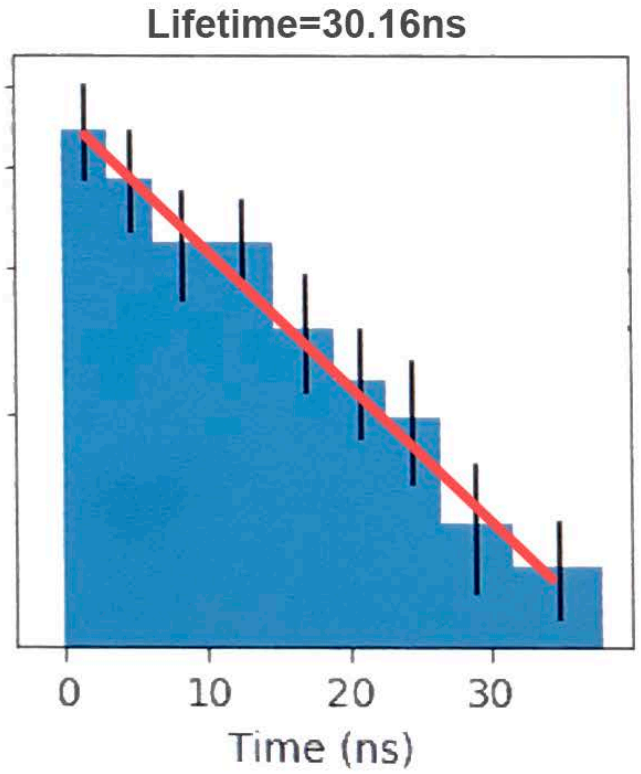

Counts
Time

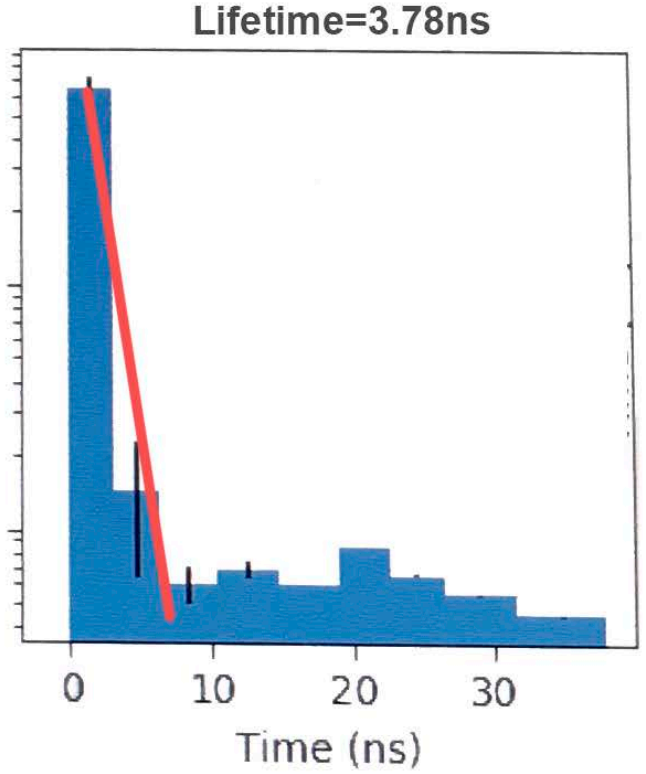
Results

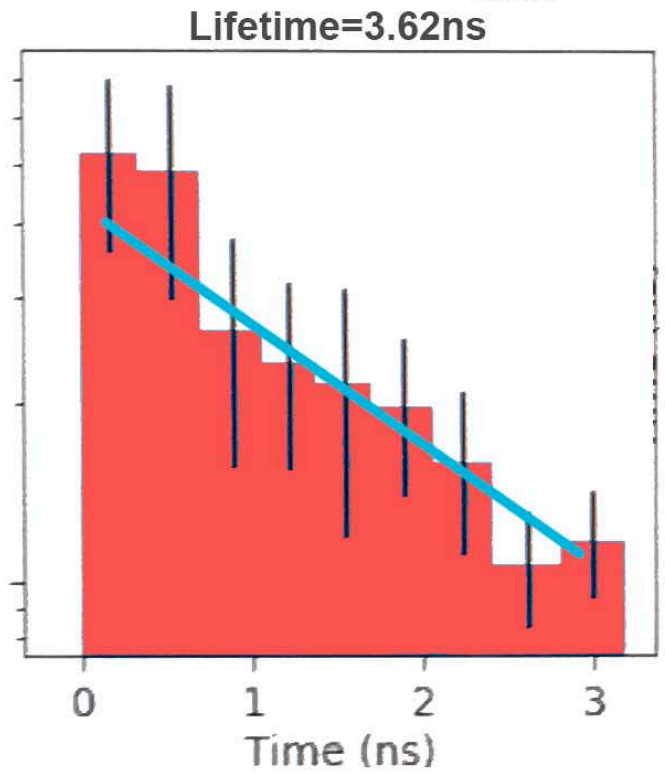
- Quantum Dot QDot605
  Excitation light 520nm, Emission light 605nm
- Alexa Fluor 546
  Excitation light 520nm, Emission light 546nm

Dichroic Filter: Reflection band 525-556nm; Transmission band: 580-650nm
Emission filter: TRITC 594-656nm

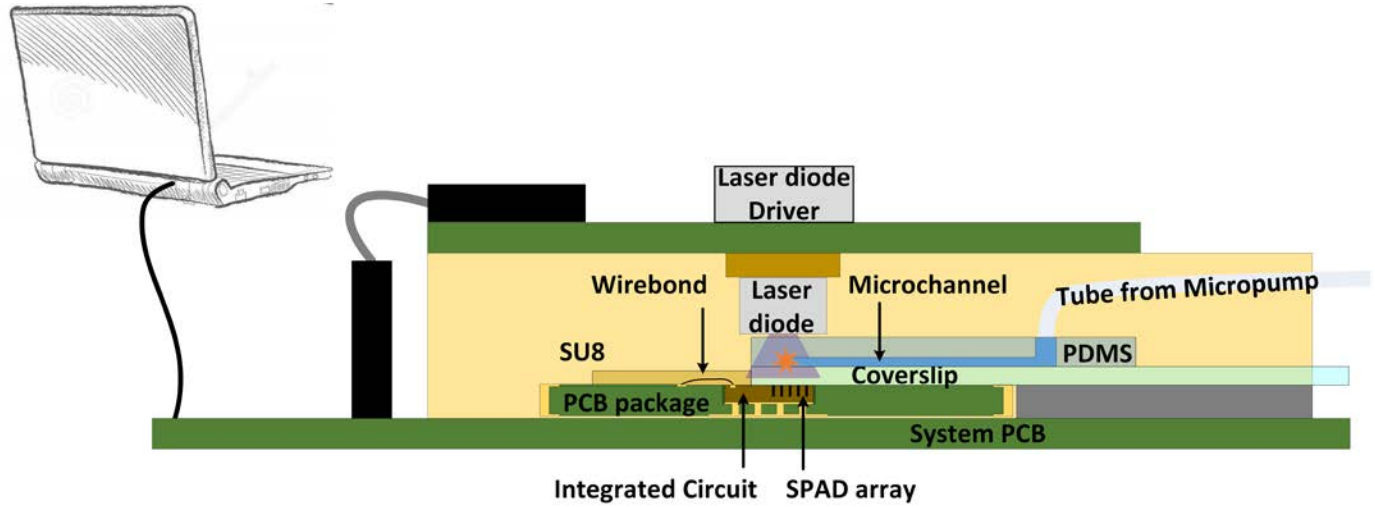


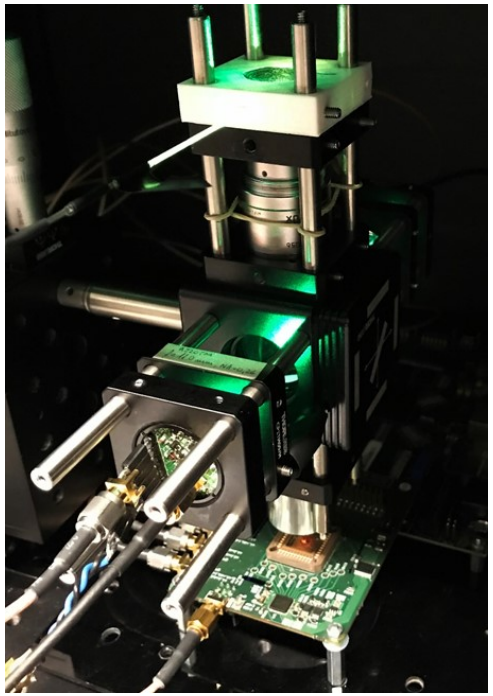


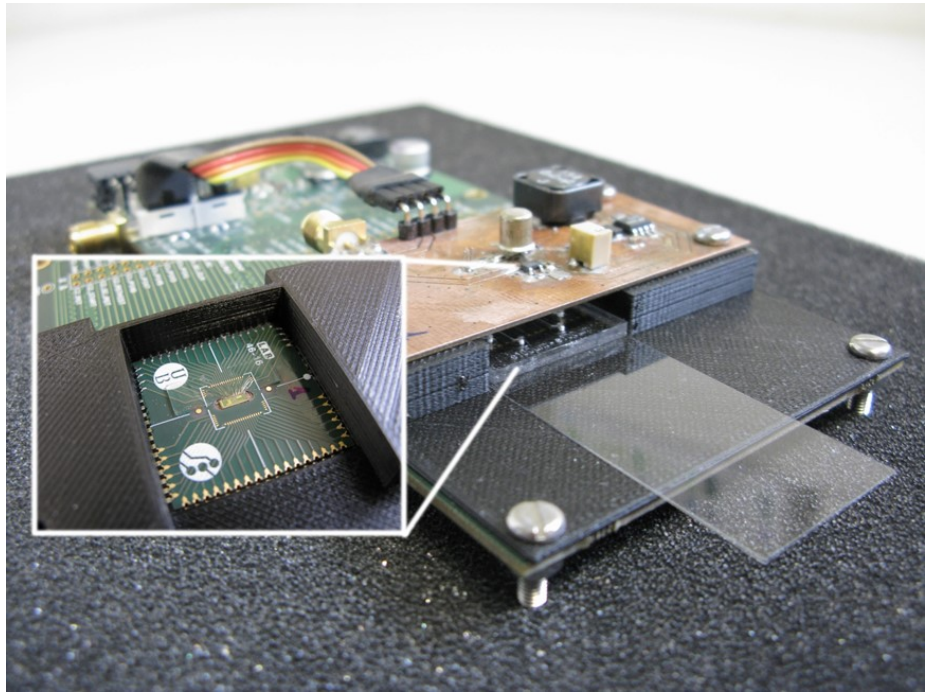




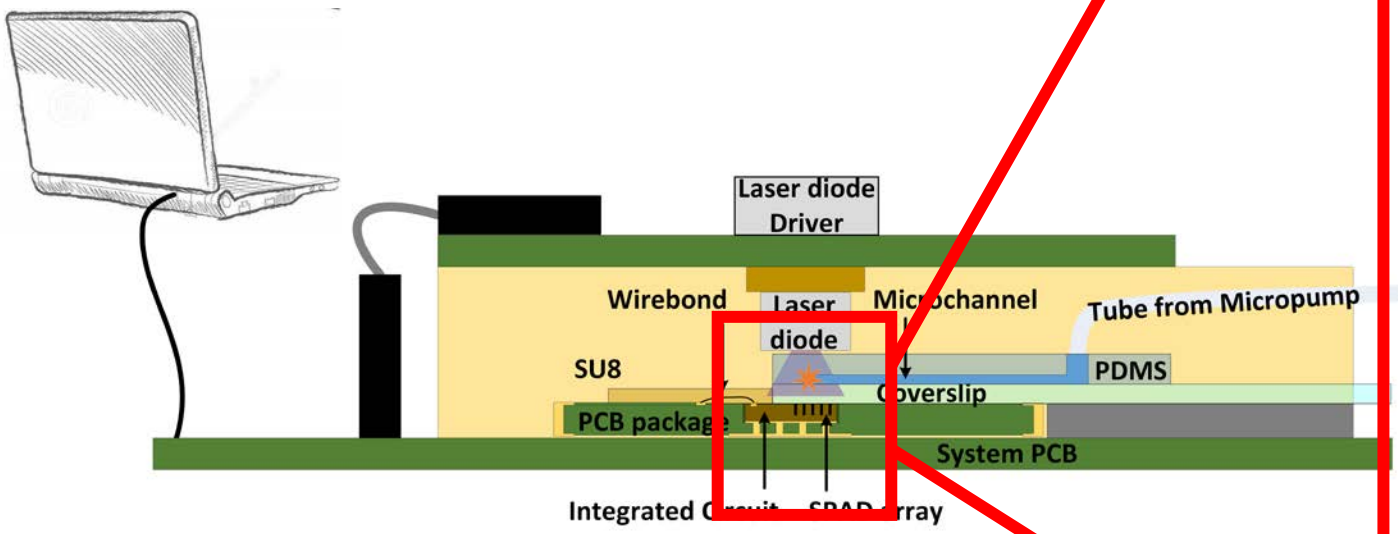
Results


Laser diode
Driver
Wirebond
Laser
diode
Microchannel
Tube from Micropump
SU8
PDMS
Coverslip
PCB package
System PCB
Integrated Circuit
SPAD array

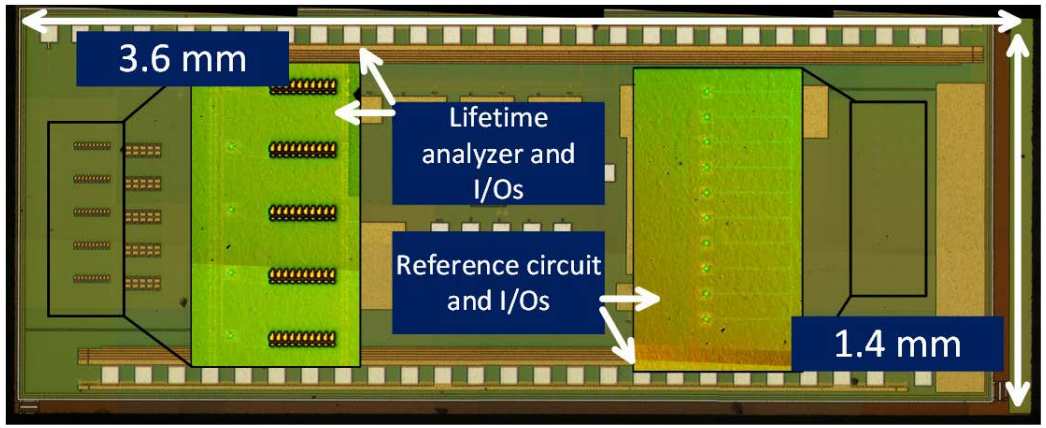


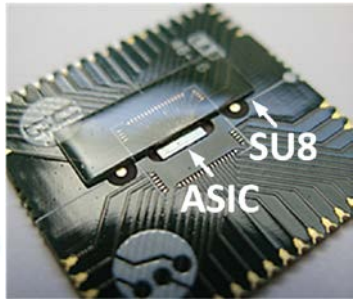


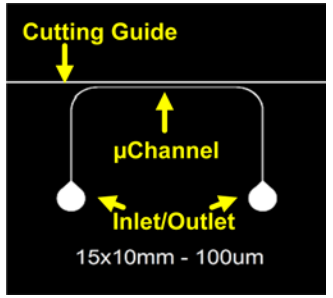
Results

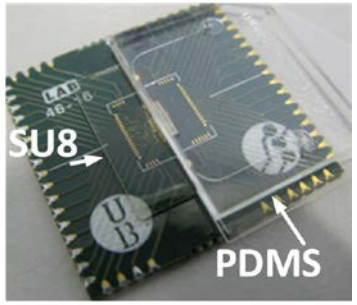


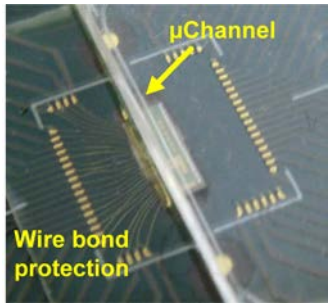
❶ SPAD array

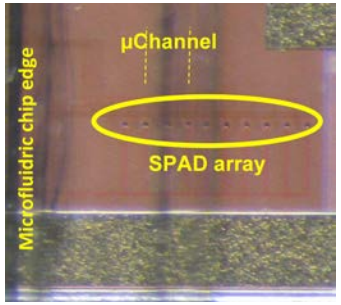




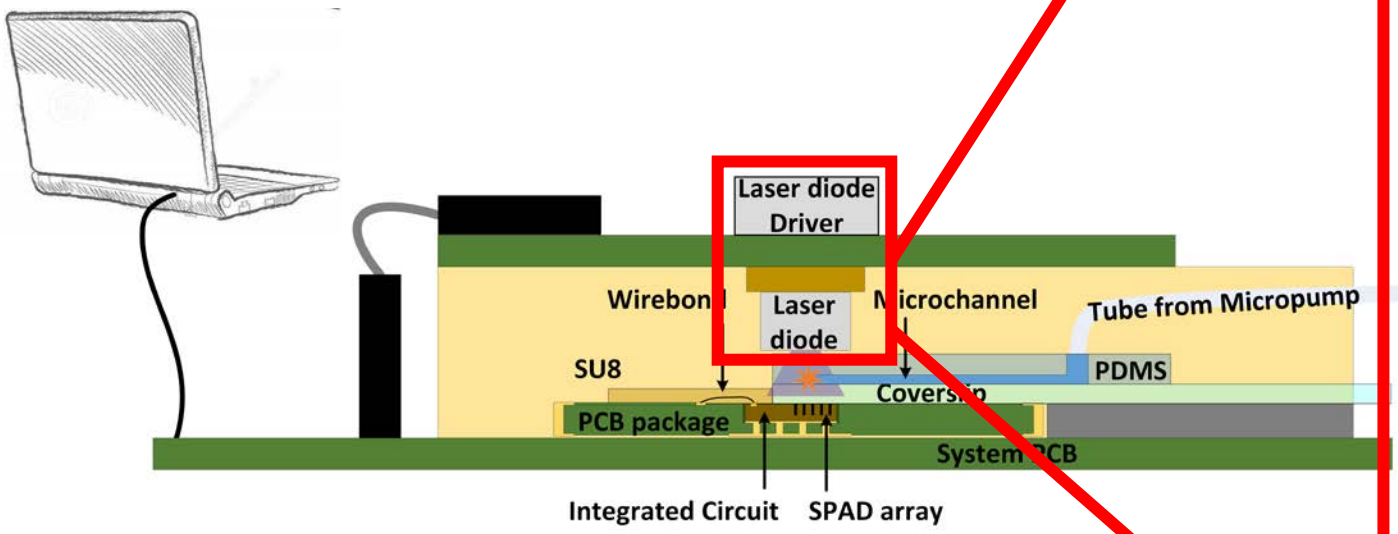




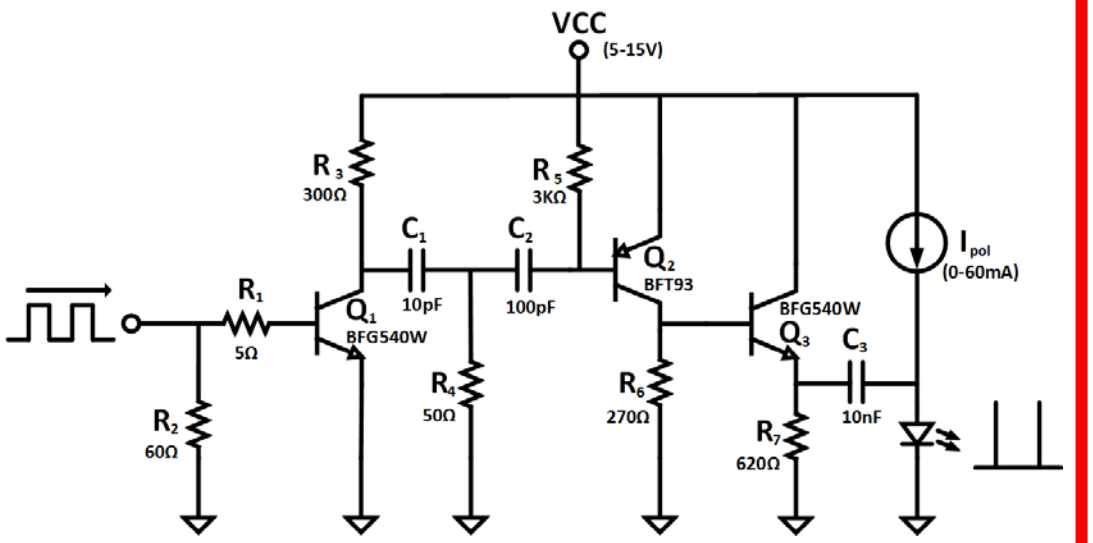


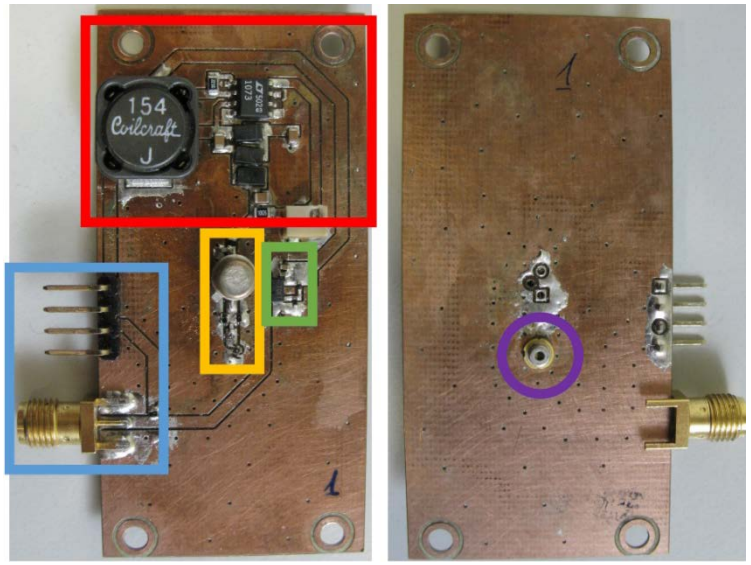


Results



❷ Laser and driver

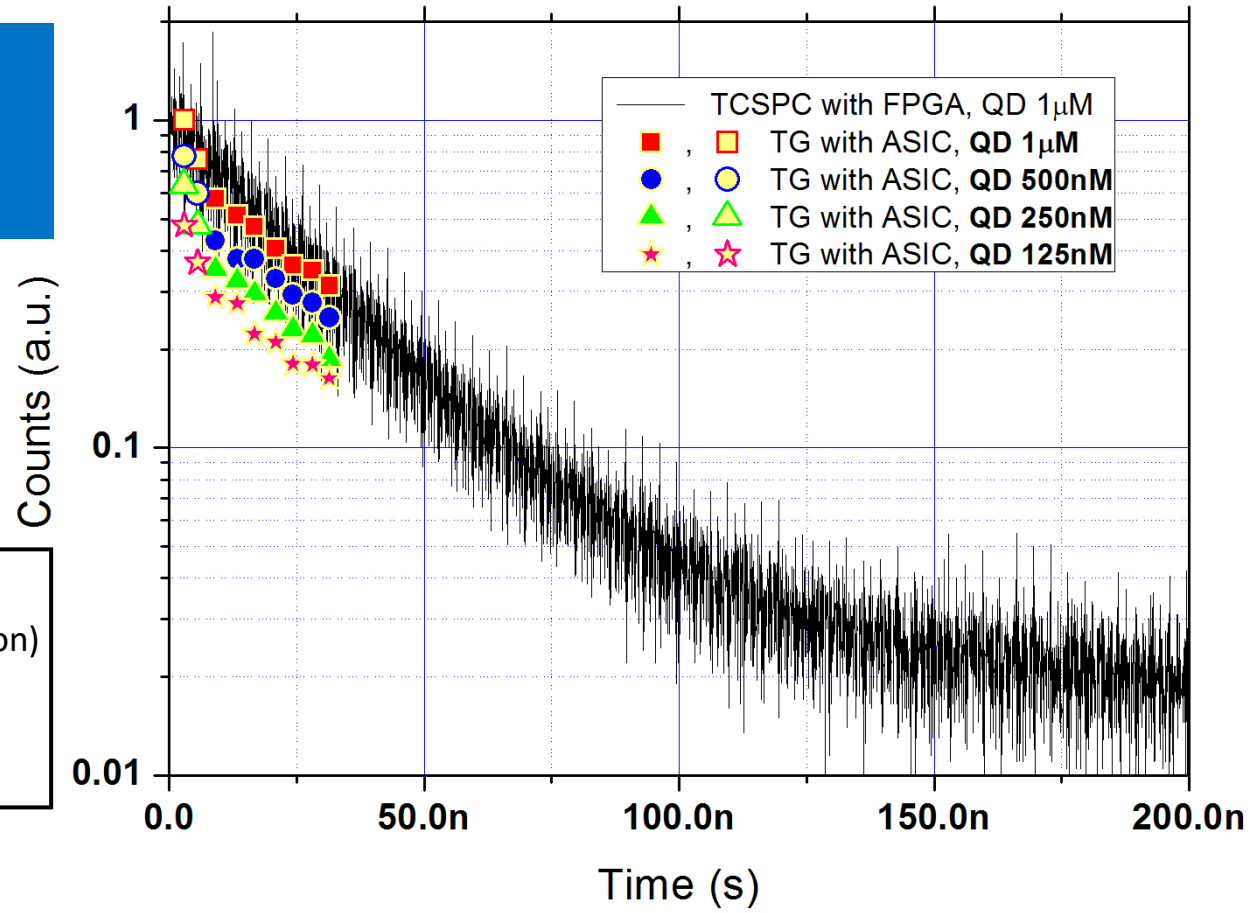




A low-cost high-repetition-rate picosecond laser diode pulse generator, W. Uhring, Ch. Zint, J. Bartringer, Proceedings of SPIE - The International Society for Optical Engineering, 2004.

Results

Vbias=900 mV (bins ~4ns)
VbiasCl=700 mV (0.76 mV/photon)
Overvoltage 1.4 V
V_{HV}=13 V
UV laser diode



5000 excitation pulses
t_{on}/t_{off} 30/20 ns
total measurement time of 250 μs

Minimum concentration 1/8 μM
(low signal-to-noise ratio impeded to measure below)

Lifetime of τ=36.1±0.105 ns
Agrees quite well with the reported value of 34.6 ns.

$$\tau = \frac{N(\Sigma t_i^2) - (\Sigma t_i)^2}{N \Sigma t_i \, lnI_i - (\Sigma t_i)(lnI_i)}$$

Q. Chen, A. Kiraz, X. Fan, Optofluidic FRET lasers using aqueous quantum dots as donors, Supplementary material, Lab. Chip., vol. 12, no. 2, pp. 353-359, 2016.

Conclusions

❶ An array of 5 CMOS SPADs has been used to build a miniaturized fluorescence lifetime detector that could be used as a POC device for time resolved fluorescence

Is able to detect with >20% efficiency photons in the visible

❷ The sample is loaded through a set of microfluidic channels

This could enable the system to perform multiplexed measurements with several biomarkers/labels

❸ The system was tested with Quantum Dots in 20nL, down to concentration of 125nM.

Better resolution could be obtained implementing the SPADs in a process with lower noise

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