

Detectors for medical applications: X-ray and Gamma imaging

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INFN - Trieste

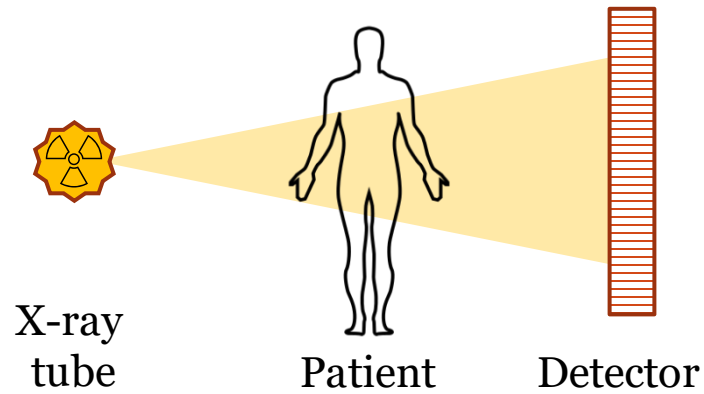
Outline

1. X and γ -ray detection in medical imaging applications
2. X-ray detectors developments and applications @ INFN
 - Photon-counting and spectral imaging: SYRMA₃D, KEST, PEPI
 - Next generation hybrid pixel detector: MEDIPIX4
 - Innovative material/sensors: PEROV
3. γ -ray detectors developments and applications @ and around INFN
 - γ and β imaging detectors: synergy with ISOLPHARM
 - ALPIDE – based detector for β -imaging
 - X and γ -ray spectrometer
 - SiPMs for Time of Flight PET @ FBK
 - Radiometabolic therapy and radioguided surgery
 - WIDIMapp: a Wearable Individual Dose Monitoring Apparatus
 - CHIRONE/CHIR2: Beta RadioGuided Surgery with β radiation

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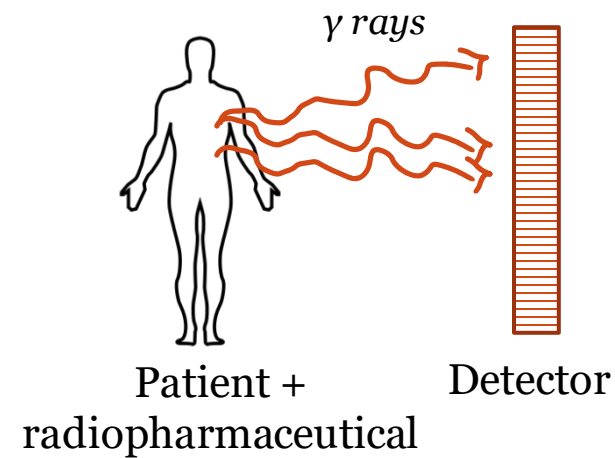
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X-ray imaging

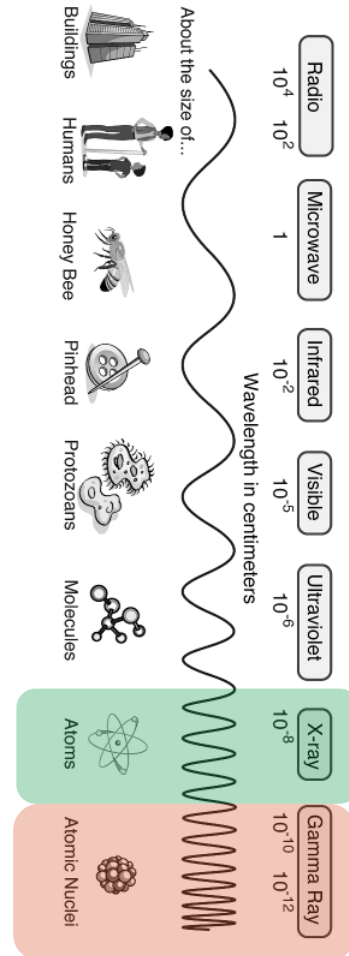


- Planar radiography
- Computed Tomography (CT)
- Fluoroscopy
- ...

γ imaging



- Positron Emission Tomography (PET)
- Single Photon Emission Tomography (SPECT)
- ...



X-ray imaging detectors

- Energy range \rightarrow 10 – 150 keV
- High spatial resolution & large FOV
 \rightarrow down to 100 μm & several cm^2
- High flux \rightarrow up to $\sim 10^9$ ph/ mm^2/s in modern CT
- Photon-counting \rightarrow Higher soft tissue visibility
- Spectral \rightarrow Chemical information
- High efficiency \rightarrow Minimize the patient dose

γ imaging detectors

- Energy range \rightarrow 100 – 1000 keV
- High efficiency \rightarrow “Few” events available
 $\sim 10^2$ counts/s
- High efficiency \rightarrow minimize use of pharmaceuticals
- Time resolution \rightarrow coincidence imaging in PET
- Low-cost wearable \rightarrow long time-span measurements

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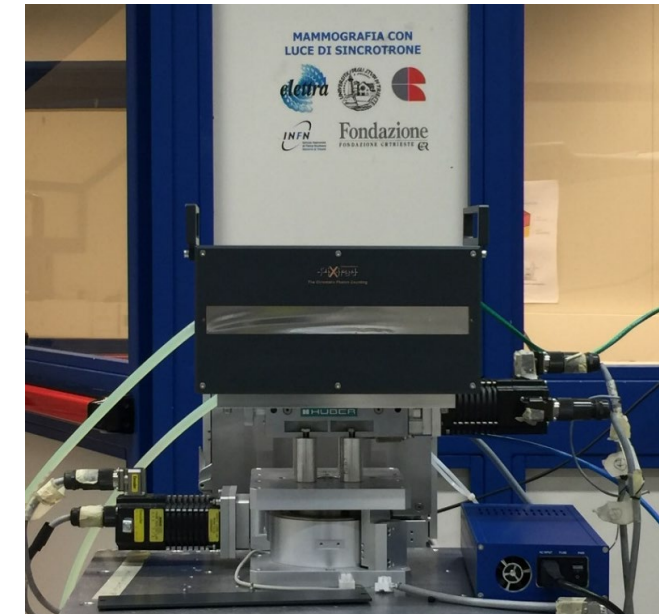
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Photon-counting and spectral imaging: SYRMA3D, KEST, PEPI

- PIXIRAD (spinoff INFN-Pisa) developed hybrid detector for X-ray imaging based on PIXIE chip. Sold to PANalytical in 2017.
- Used in several bio-medical imaging applications within INFN-CSN5
 - SYRMA-CT/3D – Synchrotron Radiation Mammography
TS, BO, CA, FE, PI, NA
 - KEST – K-Edge Spectral Tomography
TS, PI
 - PEPI – Photon-counting Edge-Illumination Phase-contrast Imaging
TS

SYRMA-CT/3D (2014-2019)

- Development and optimization for phase-contrast breast-CT clinical trial @ Elettra
 - **Large area CdTe single-photon-counting PIXIRAD-8 – PixieII chip**



PROS

- High efficiency
 - Large area ($25 \times 2.5 \text{ cm}^2$)
 - Small pixel ($60 \mu\text{m}$ pitch)
 - Dead Time Free Mode
 - Tunable Threshold
 - No electronic noise
- 3-sides buttable \rightarrow gap between modules
 - Time/exposure dependent charge trapping effects

CONS

Requires detector-specific pre-processing

Bellazzini, R., et al. JINST 8.02 (2013): C02028.

Delogu, P., et al. JINST 11.01 (2016): P01015.

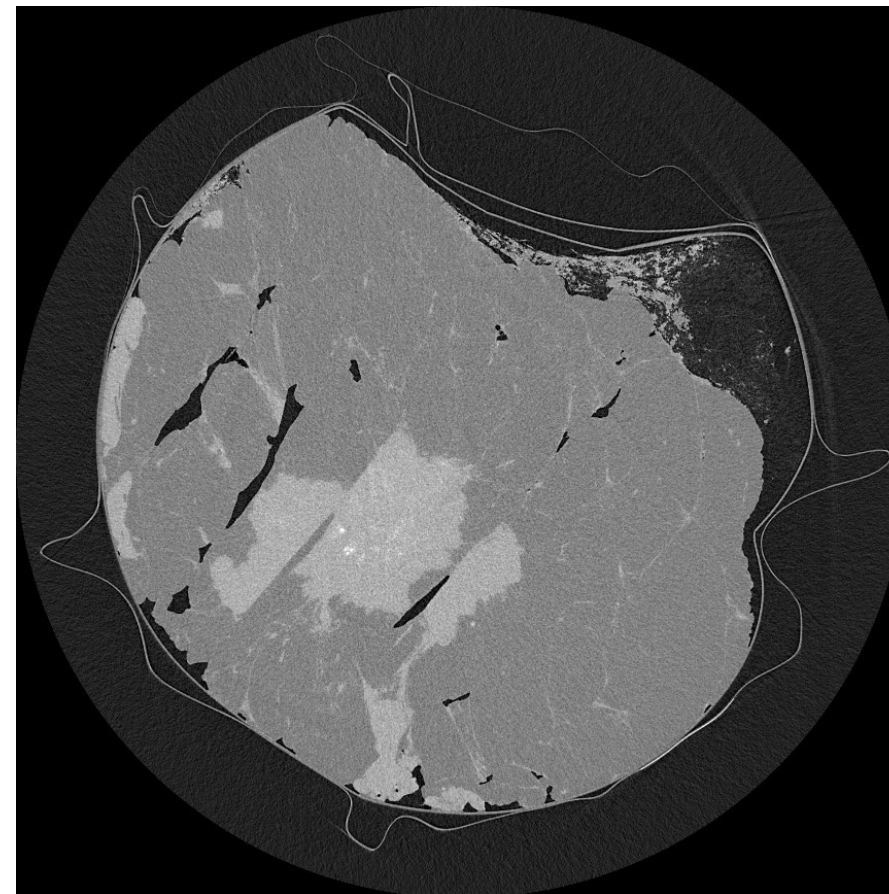
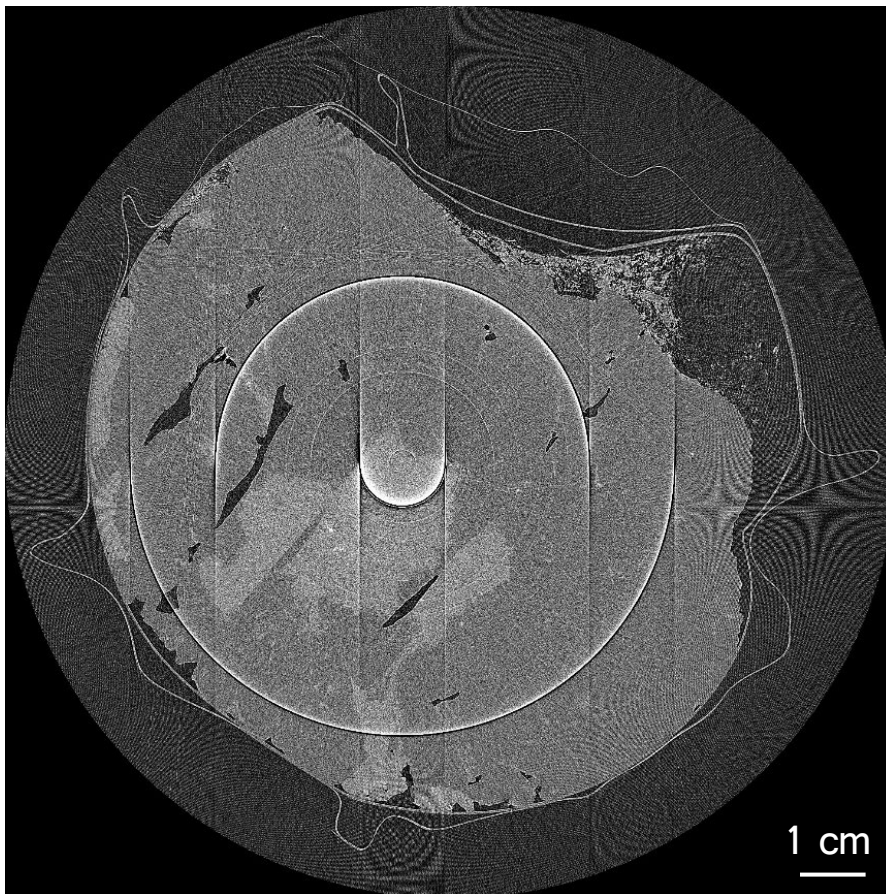
Delogu, P., et al. JINST 12.11 (2017): C11014.

Photon-counting specific pre-preprocessing

Without pre-processing



With pre-processing

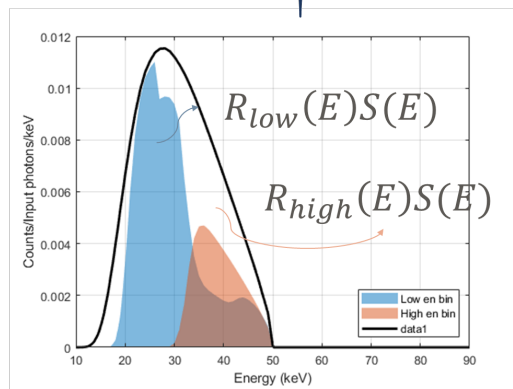
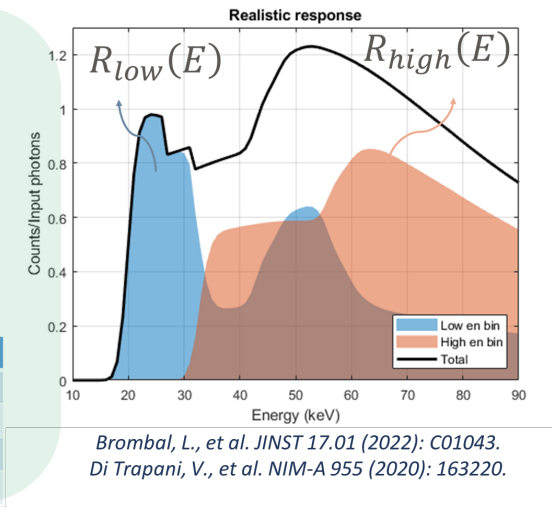
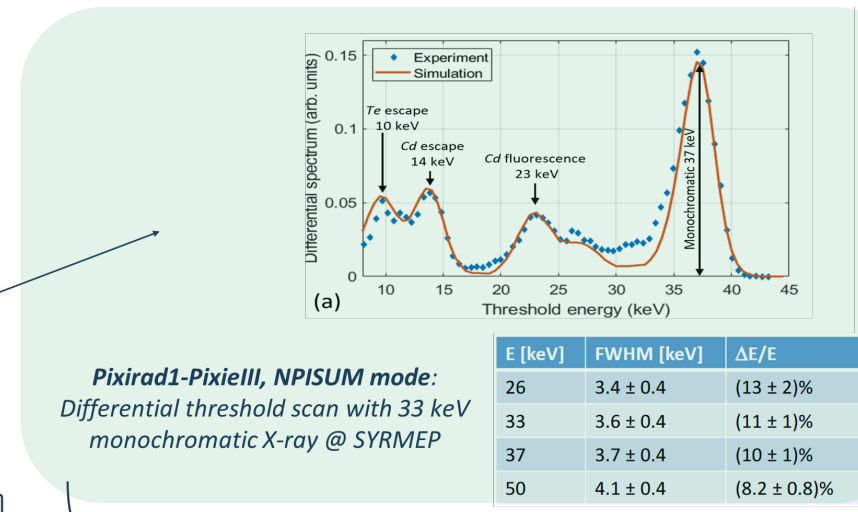
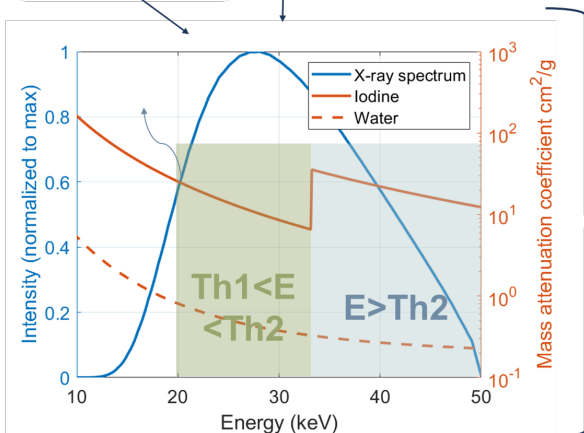
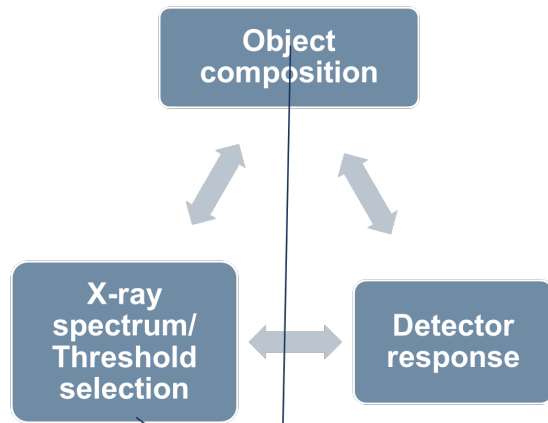


- CT scan on a breast tissue surgical specimen @ Elettra
- 1200 angular views projections
- X-ray energy: 32 keV
- Dose 20 mGy

KEST (2017-2018) PEPI (2021 - 2022)

Detector characterization is critical in spectral imaging

PIXIRAD1 – PixieIII chip



Material decomposition matrix

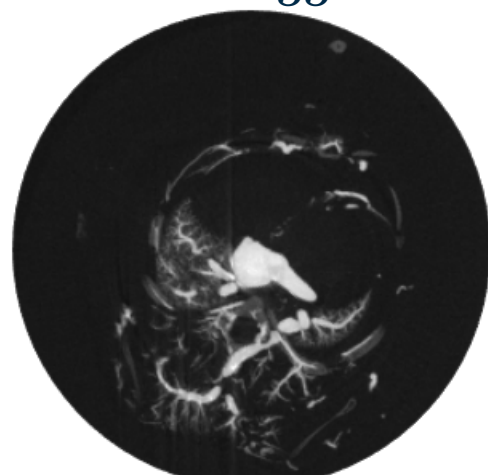
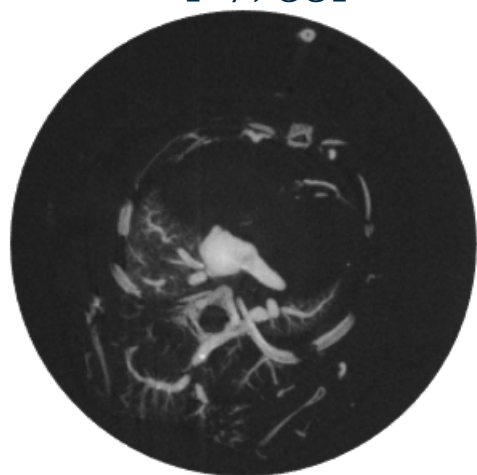
$$A_i^j = \frac{\int S(E)R_i(E)\mu/\rho_j(E)dE}{\int S(E)R_i(E)dE}$$

Di Trapani, V., et al. *Optics Express* 30.24 (2022): 42995-43011.
Brombal, L., et al. *JINST* 17.01 (2022): C01043.

KEST (2017-2019) PEPI (2021 - 2022)

Bin1 [27, 33] keV

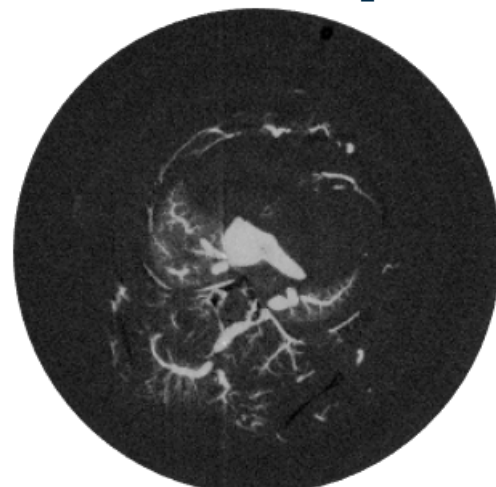
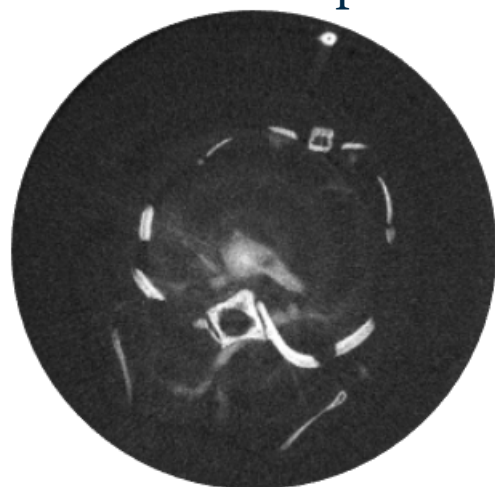
Bin2 >33 keV



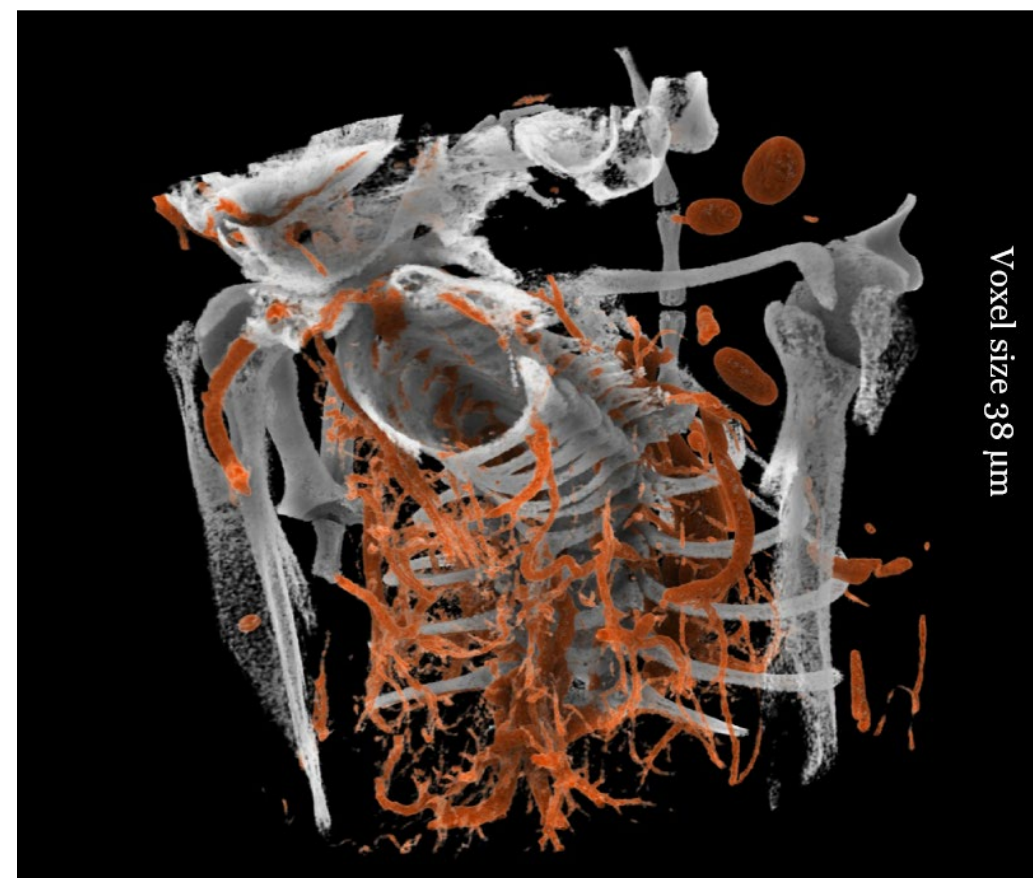
1 cm

Bone map

Iodine map



VIDEO IN THE ORIGINAL PRESENTATION

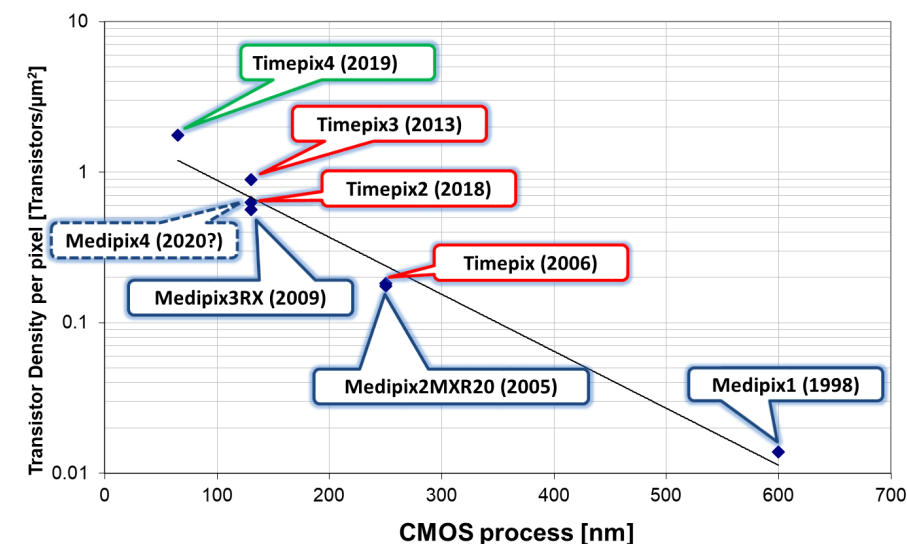


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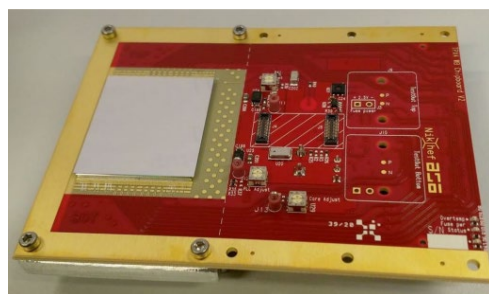
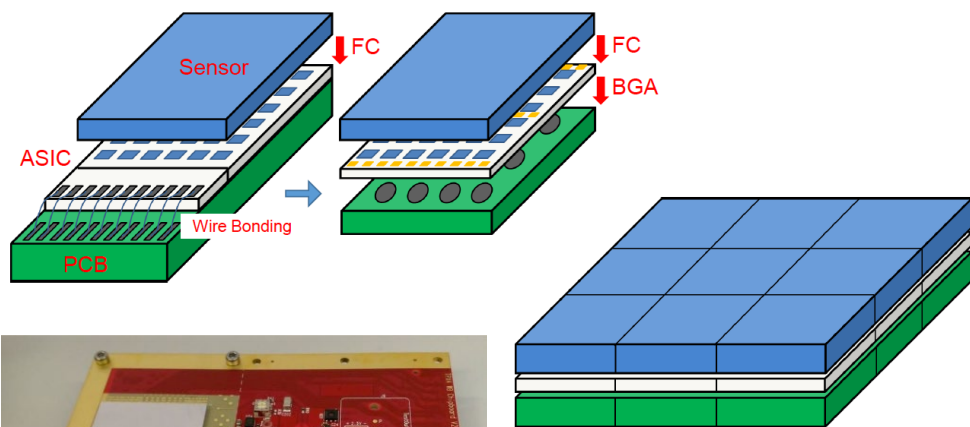
Medipix 4 collaboration

- INFN became official member of the Medipix4 Collaboration in November 2020
- Collaboration based at CERN with 18 members
- Two new ASICs produced:
 - **Timepix4**
4-side buttable large single-threshold particle tracking detector chip with improved energy and time resolution and with high-rate imaging capabilities
 - **Medipix4**
Will target spectroscopic X-ray imaging at rates compatible with medical CT scans



Timepix4 ASIC specifications

- 4-side buttable pixel arrangement
- Target to build large area detectors by combining smaller modules
- The **Through-Silicon Vias (TSVs)** is the key technology for this paradigm shift



		Timepix3 (2013)	Timepix4 (2019)	
Technology		130nm – 8 metal	65nm – 10 metal	
Pixel Size		55 x 55 μm	55 x 55 μm	
Pixel arrangement		3-side buttable 256 x 256	4-side buttable 512 x 448 3.5x	
Sensitive area		1.98 cm^2	6.94 cm^2	
Readout Modes	Data driven (Tracking)	Mode	TOT and TOA	
		Event Packet	48-bit	64-bit 33%
		Max rate	0.43x10 ⁶ hits/mm ² /s	3.58x10⁶ hits/mm²/s
	Frame based (Imaging)	Max Pix rate	1.3 KHz/pixel	10.8 KHz/pixel 8x
		Mode	PC (10-bit) and iTOT (14-bit)	CRW: PC (8 or 16-bit)
		Max count rate	~0.82 x 10 ⁹ hits/mm ² /s	~5 x 10 ⁹ hits/mm ² /s 5x
TOT energy resolution		< 2KeV	< 1KeV 2x	
TOA binning resolution		1.56ns	195ps 8x	
TOA dynamic range		409.6 μs (14-bits @ 40MHz)	1.6384 ms (16-bits @ 40MHz) 4x	
Readout bandwidth		$\leq 5.12\text{Gb}$ (8x SLVS@640 Mbps)	$\leq 163.84\text{Gbps}$ (16x @10.24 Gbps) 32x	
Target global minimum threshold		<500 e ⁻	<500 e ⁻	

MEDIPIX4 - CSN5 (2021-2023)

aimed at the exploitation of the family of application-specific integrated circuits (ASICs) developed by the Medipix4 Collaboration at CERN

5 INFN Division involved (FE, LNS, NA, PI, TS), National Resp: M. Fiorini (Ferrara University and INFN)

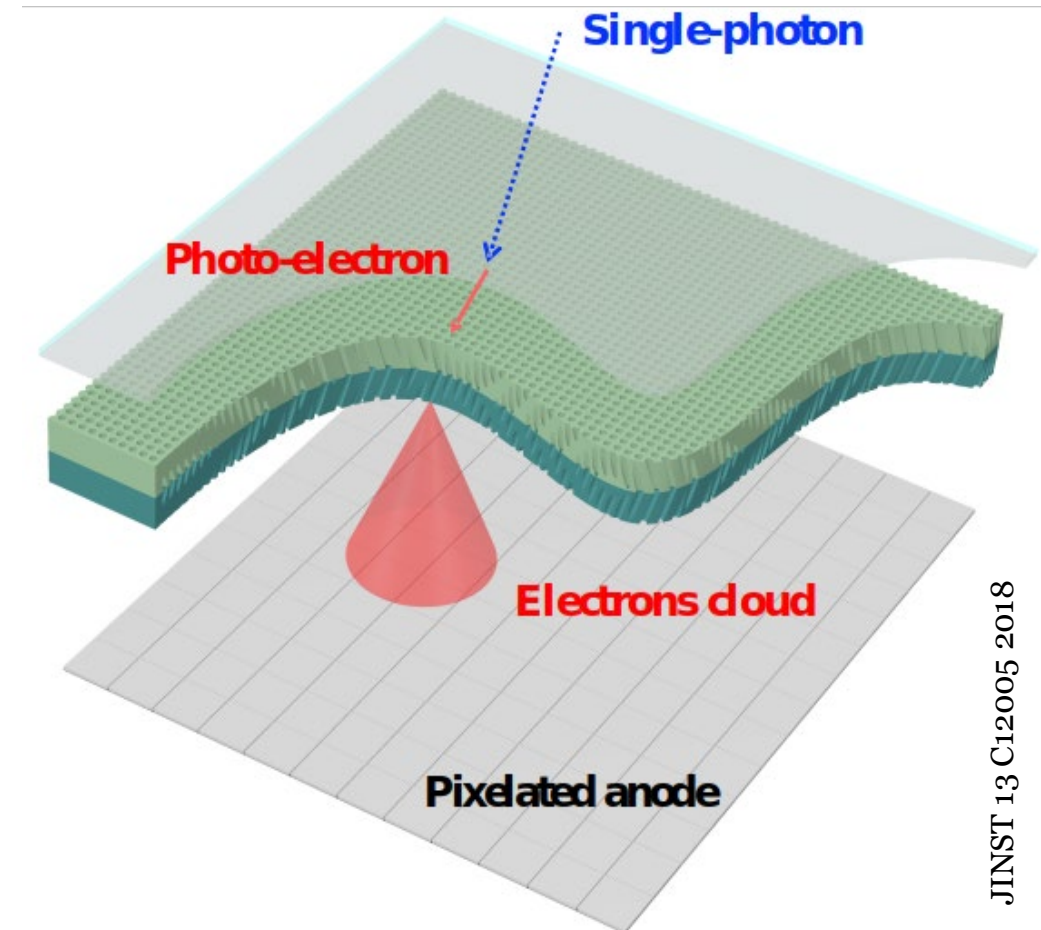
- **WP1: Electronics/software/cooling** (WP Leader: FE; Participating Groups: NA,PI)
- **WP2: New sensors development** (SiC, UV) (WP Leader: LNS; Participating Groups: Ferrara, LNS, Napoli) → see Giada Petringa's talk
- **WP3: Dosimetry and Nuclear Medicine** (WP Leader: NA, Participating Group: PI, LNS)
 - Nuclear Medicine - Compact gamma camera (NA)
 - Dosimetry - Gamma-ray detector for dosimetry and MV X-rays (NA), Diagnostic X-ray beams (PI), charged particles (LNS)
- **WP4: X-ray imaging** (WP Leader: Pisa; Participating Groups: FE, NA, PI and TS)
 - Spectral imaging (TS, PI, FE)
 - Phase Contrast Imaging (TS, NA)

Courtesy of M. Fiorini

Hybrid MCP development

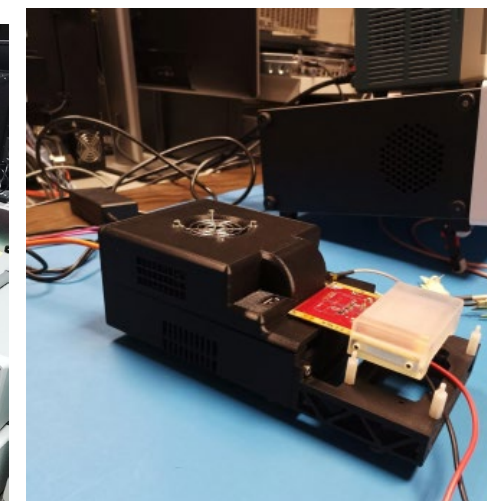


- Hybrid vacuum photo-detector development
 - photocathode + MCP multiplication + Timepix4 anode in vacuum tube
 - **Funded by ERC: 4DPHOTON** (INFN, CERN, UniFE)
- **Synergies with MEDIPIX4 CSN5 project:**
 - Development of FPGA-based read-out electronics for the Timepix4 ASIC
 - Development of open-source control and data acquisition software
 - Strong expertise available to the INFN community



Current status

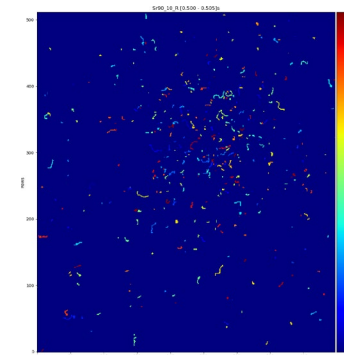
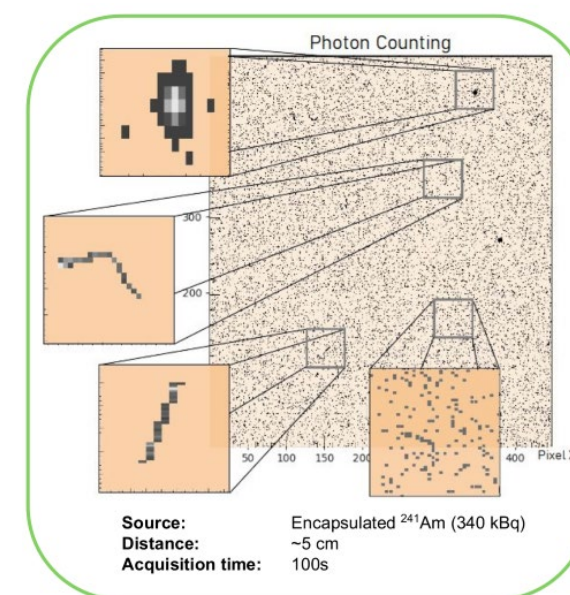
- First Timepix4_v2 bump-bonded assemblies (300 μm Si sensors, Advacam) available September 2022 and currently under test in Ferrara
- Software for slow-control and fast readout of Timepix4 under development in Ferrara, first release ready soon
- Production of assemblies with 0.5-2.0 mm CdTe sensors will be launched at the beginning of 2023



Future activities

- 2022 Medipix4 chip produced
- 2023 test of Timepix4 Si assembly + procurement of CdTe assembly
- Medipix4 assemblies production planned 2023

Courtesy of M. Fiorini



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PEROV (2020-2023)

- R&D for photodetectors based on Organo-Metal Halide Perovskite (OMHP) materials
- Involving LNF-INFN, INFN-Roma1, Universita' di Roma "La Sapienza", UniRoma2, UniMI, CNR

OMHP are class of hybrid organic-inorganic semiconductor materials with a perovskite unit-cell structure ABX_3 with:

- $A = CH_3NH_3^+$, $B =$ metallic cation (PB^{2+}), $X =$ halide anions (Cl^- , Br^- , I^-)

Organic semiconductors:

- Disordered system
- Localized electronic states
- Hopping transport \Rightarrow low mobility
- **Low cost, low temperature processing**
- **Can be solution processed**
- **Scalable to large area**

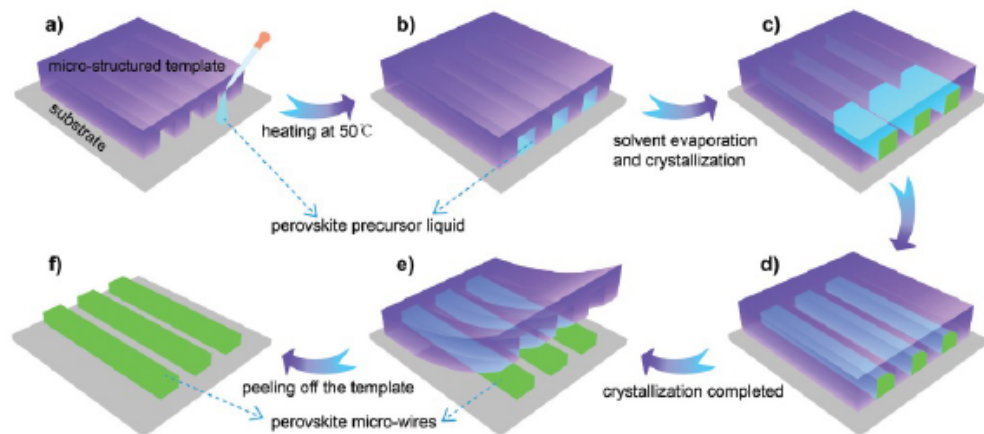
Inorganic semiconductors:

- **Ordered periodic crystal \Rightarrow band structure**
- **Delocalized Bloch states**
- **band transport \Rightarrow high mobility**
- Usually wafer based technology
- Costly, high temperature processes

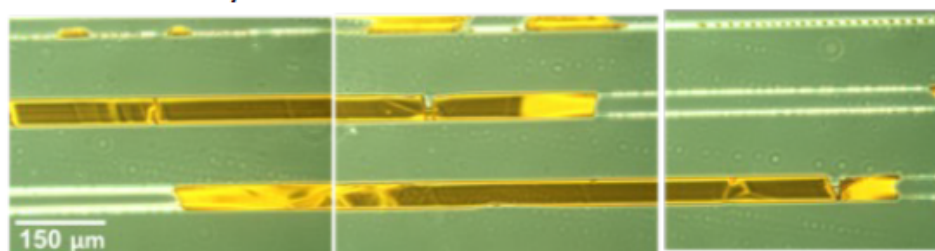
	Silicon	$CH_3NH_3Pb(I,Br)_3$
Density	2.33 g/cm ³	4.15 g/cm ³
Band gap (eV)	1.12 (indirect)	1.5-1.6 / 2.24 (direct)
Mobility (cm ² /Vs)	electrons	1400
	holes	450
Absorption (cm ⁻¹)	< 10 ⁴	> 4x10 ⁴
Threshold energy for impact ionization (eV)	1.2	~2 / 2.5 (estimated)
Mean free path (nm)	≤ 100	~100 (theory)

- OHMP band gap tunable changing halide (I,Br,Cl) 😊
- OMHP contain highly mobile defects and have instabilities issues 😞

Micro-fluidics for perovskite crystals production:



Typical dimension: $W \times L \times H = 150 \mu\text{m} \times 500 \mu\text{m} \times 6(2) \mu\text{m}$
 Production by CNR - Nanotec



- Device realized with $\text{CH}_3\text{NH}_3\text{PbBr}$ deposition on **patterned** Indium Tin Oxide/ $\text{CH}_3\text{NH}_3\text{PbBr}_3$ and Au evaporation
 - Innovative technique
 - Deposited patent (INFN + CNR) 102022000010469 (*)
- Gain observed at larger bias for thickness of 2 and 6 μm

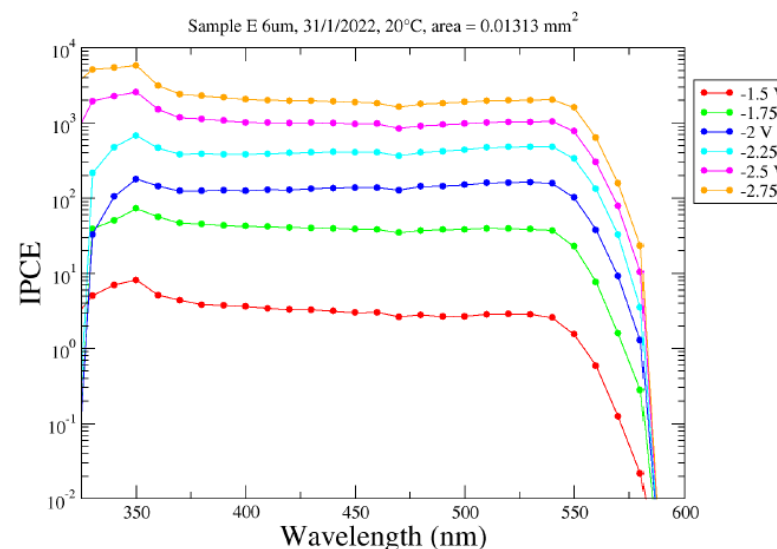
Pro:

- large flexibility in dimension
- moderate area
- pixelization
- flexible substrate
- Deposited directly on substrate

Contra:

- need high optimization of parameters (pressure, temperature,..)

(*) M. Testa, I. Viola, L. De Marco, M. Auf der Maur, F. Matteocci



- Goal: the feasibility of a hybrid X-ray detector structure combining a perovskite absorption layer and a CMOS silicon active layer
 - Principle: X-ray-generated electrons in the perovskite layer are transferred to silicon and collected by low-capacitance sensing sites coupled to in-pixel readout electronics
- The CMOS chips with an area of the order of 1cm² are available from ARCADIA INFN project
- On going activity:
 - Test on deposition of perovskite micro-channels through microfluidics technique on CMOS substrates with aluminium pads, used as passive substrates

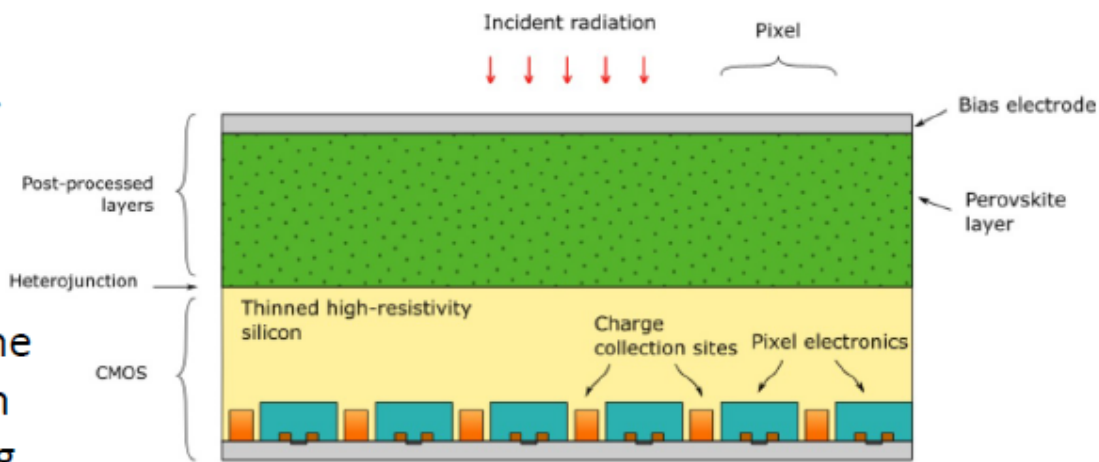
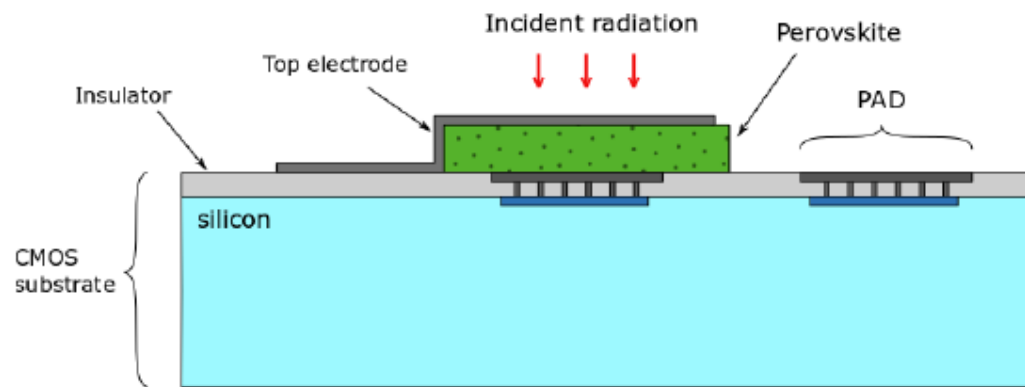


Figure 1. Simplified cross section of the proposed hybrid detector

PRIN 2022 project proposal
L.Pancheri, M. Testa, I.Viola



Courtesy of M. Testa – INFN LNF

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ISOLPHARM

- Aims at the production of wide set of high-purity radionuclides for diagnosis and therapy
- Uses the Isotope Separation On-Line (ISOL) technique @ LNL
- Many partners involved:
 - Within INFN: LNL, TIFPA, PD, PV, LNS, BO, PI
- Many activities including detector development:
 - Beta imaging (e.g. microscopy applications)
 - Gamma imaging (e.g., high-energy gamma camera)

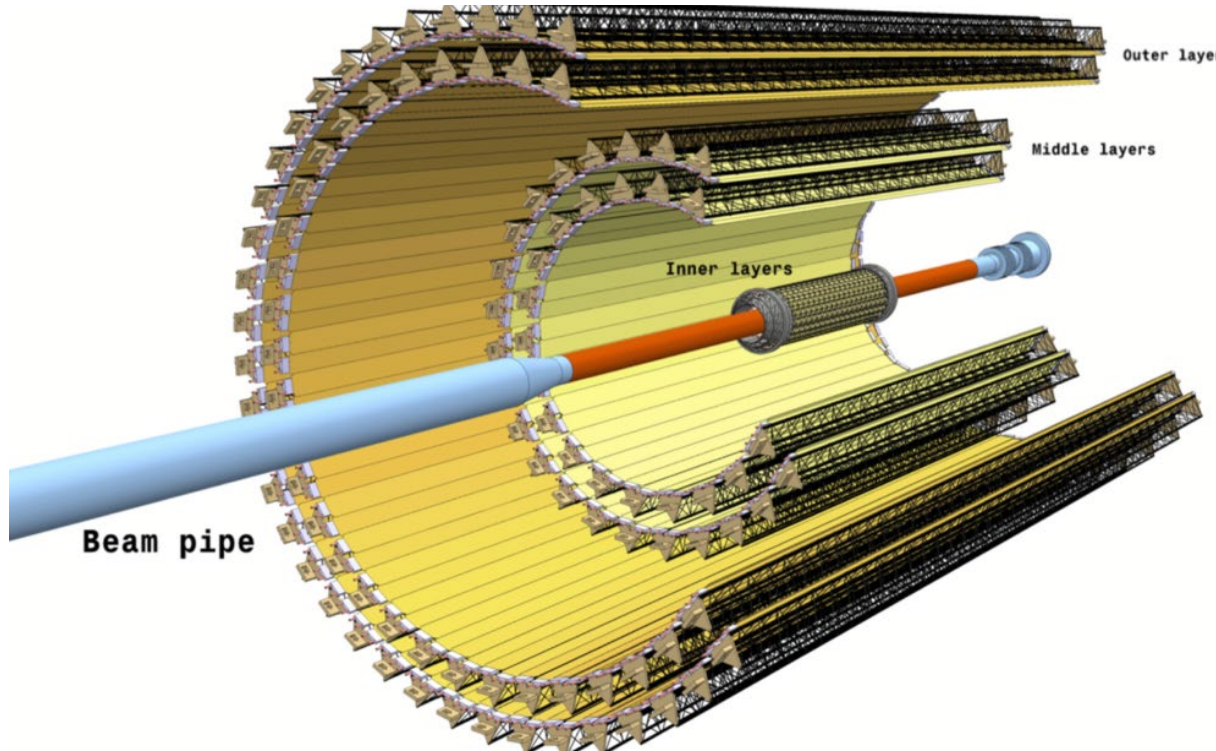


High energy physics



Biomedical application

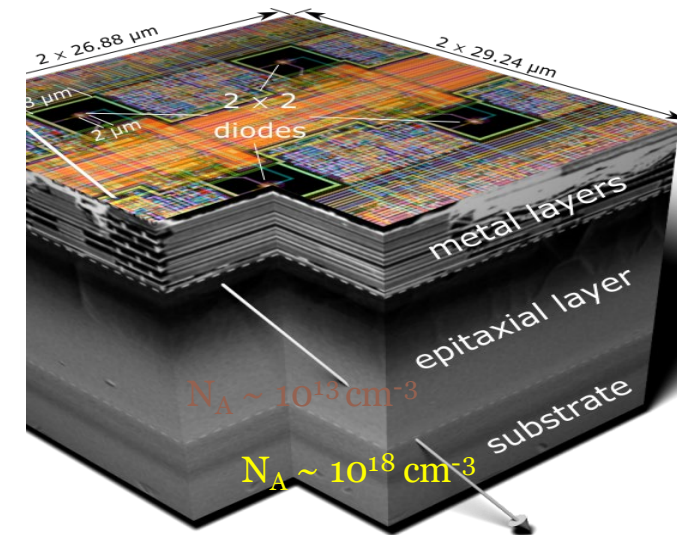
ALICE Inner Tracking System



ALPIDE design

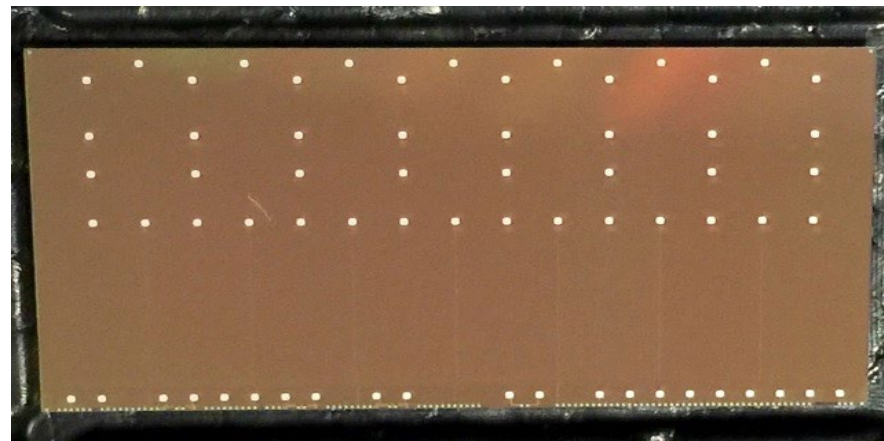
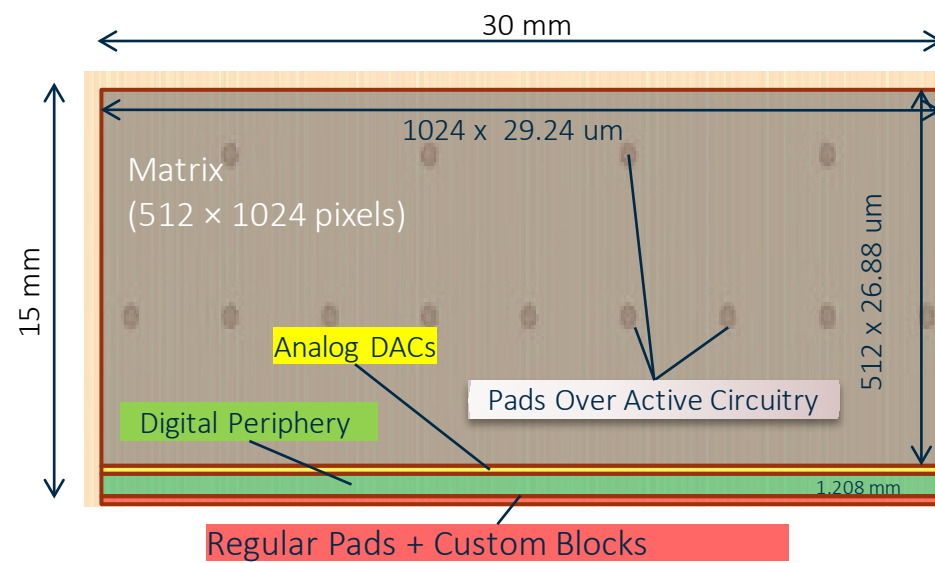
Pixel Sensor CMOS 180 nm Imaging Process (TowerJazz) 3 nm thin gate oxide, 6 metal layers

Courtesy of P. Giubilato – INFN LNL



Mager, M., and ALICE collaboration. *NIMA* 824 (2016): 434-438.

15 x 30 mm² area, 100% fill factor, 1-side pads (or pads over the matrix, but more difficult)

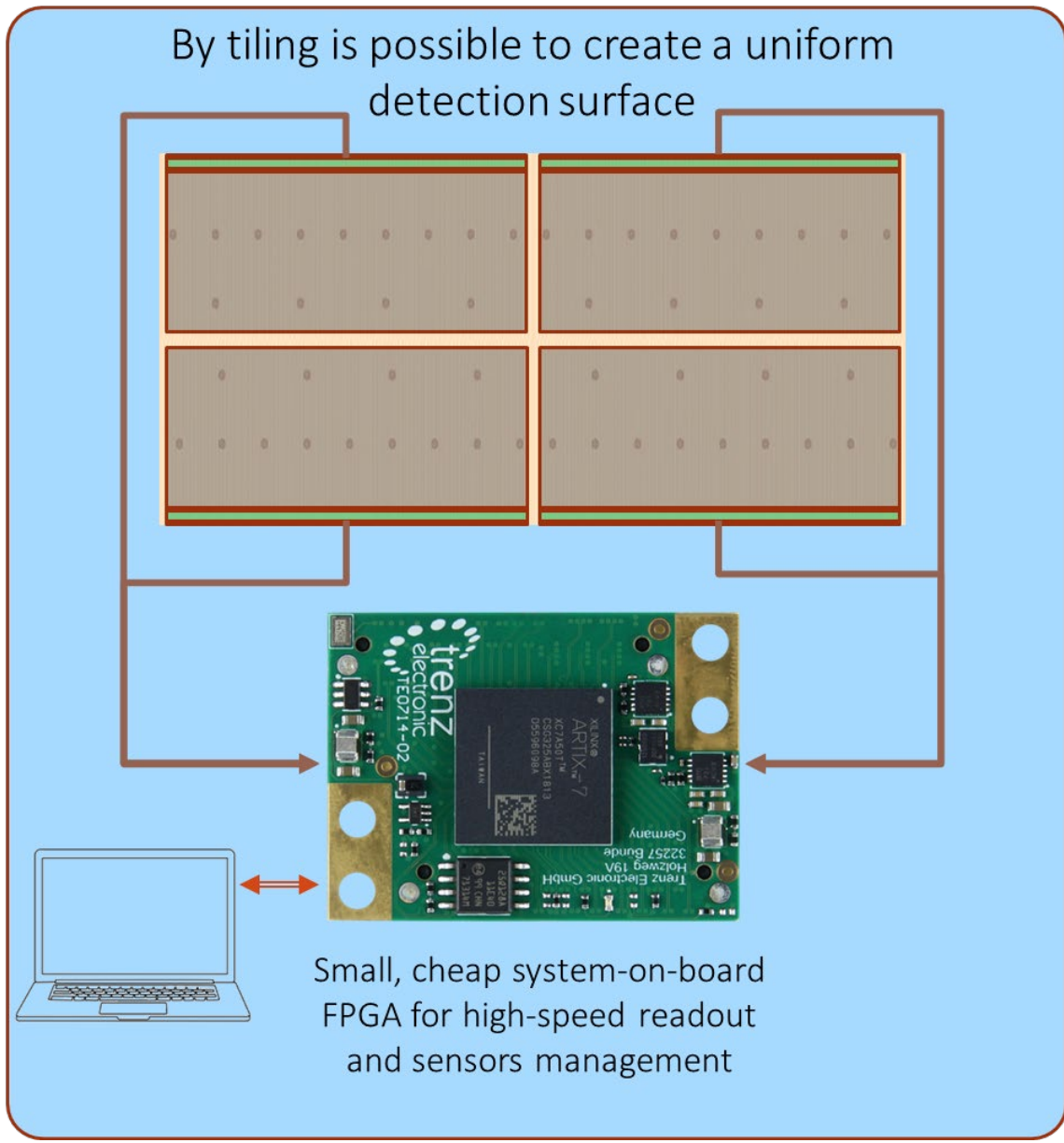


ALPIDE

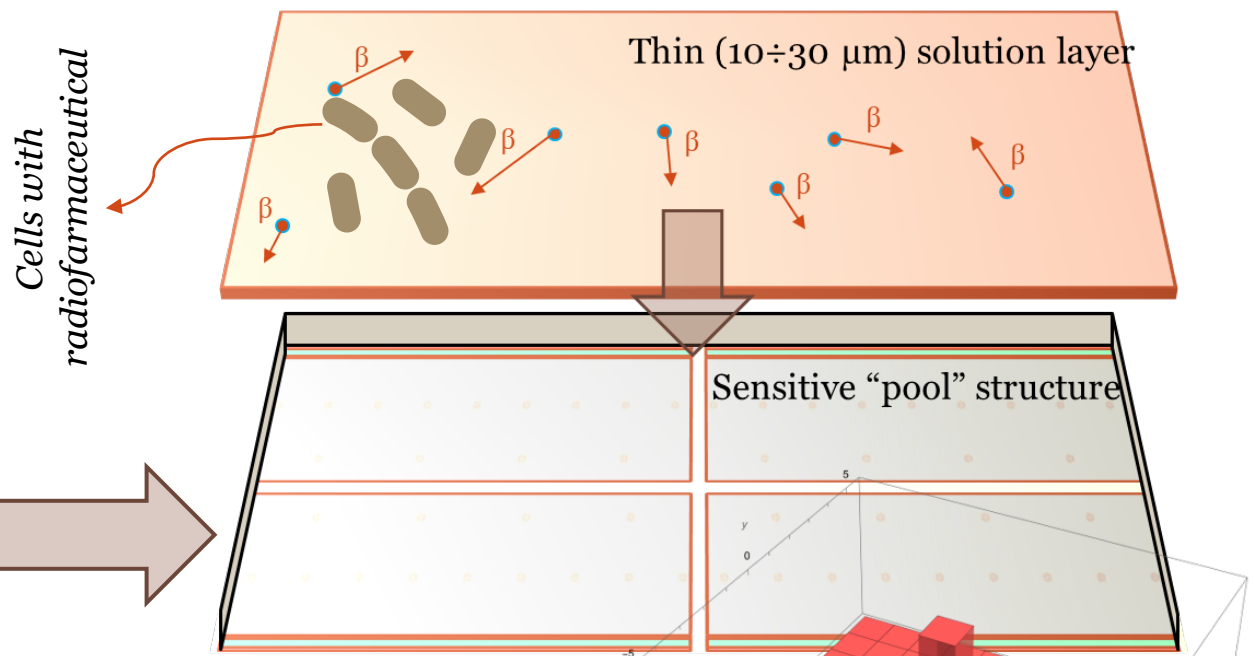
Courtesy of P. Giubilato – INFN LNL

Parameter	ALPIDE
Chip size (mm x mm)	15 x 30
Chip thickness (μm)	50 / 100
Spatial resolution (μm)	5
Detection efficiency	>99%
Fake hit rate	<< 10 ⁻⁶ (<10 ⁻⁸)
Integration time (μs)	< 6
Power density (mW/cm ²)	~40
Hit rate (cm ⁻²)	> 1 MHz

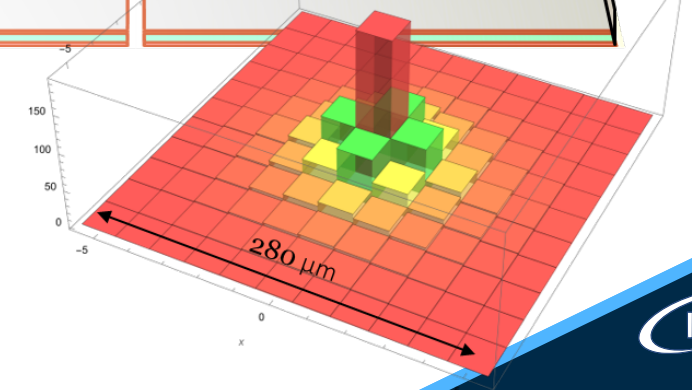
High-rate detection possible thanks to in-sensor data sparsification performed at pixel level



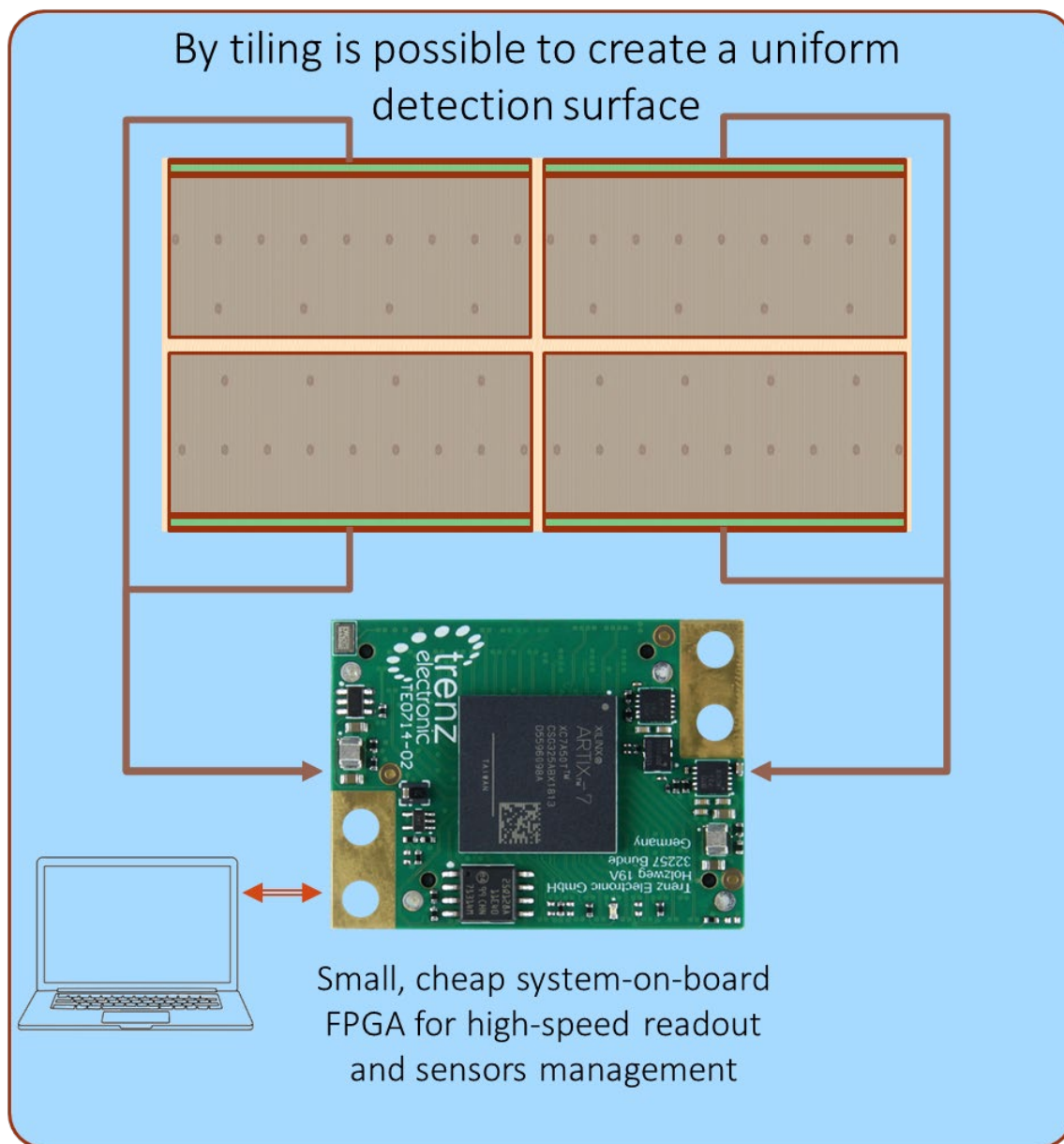
A “detecting pool” allows β detection over a very large area, in parallel, with $\approx 10 \mu\text{m}$ resolution (Lambertian)



Lambertian illumination for 4π emission at a distance of $30 \mu\text{m}$ from the sensor ($28 \mu\text{m}$ pixel). The signal remains strongly clustered, allowing precise position determination



Courtesy of P. Giubilato – INFN LNL



Courtesy of P. Giubilato – INFN LNL

Production

Large scalability potential

- Detector are produced with the same processes as in smartphones sensor
- Cheap (few USD per cm²)

Future

Stacked structure for 3D high granularity sensor for other medical applications

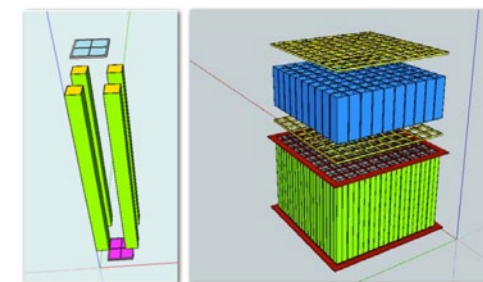
- X-ray detection
- Gamma detector (low energy)
- Sensor for Photo Electron Emission Microscopy (PEEMS)

Compact and modular position-sensitive gamma detectors for medical and space applications

XGS, a compact and modular X and gamma-ray spectrometer with CsI scintillators and double-readout Silicon Drift Detectors with dedicated electronics for the THESEUS mission by ESA.



The ProtoXGS-2 prototype. A single 4.5 x 4.5 x 45 mm³ scintillator bar is coupled at both ends with single cell, 5 x 5 cm² SDDs each with a PA-001 preamplifier.



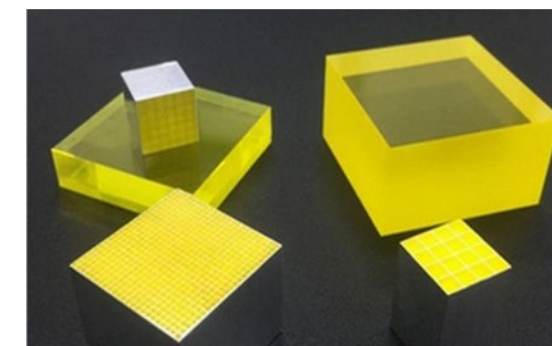
Layout of the XGS module

In the context of the **ISOLPHARM** project, a new gamma camera module optimized for the gamma radiation emitted by Ag-111 (main line 342 keV, 7%) will be developed during the next 3 years.



50 x 50 mm² collimator used in an experimental γ -camera (INFN former Scintirad Project);

It foresees the modern GAGG scintillators already tested in Bologna as part of other projects (ASI HERMES nanosatellites), SiPM and fast readout electronics.

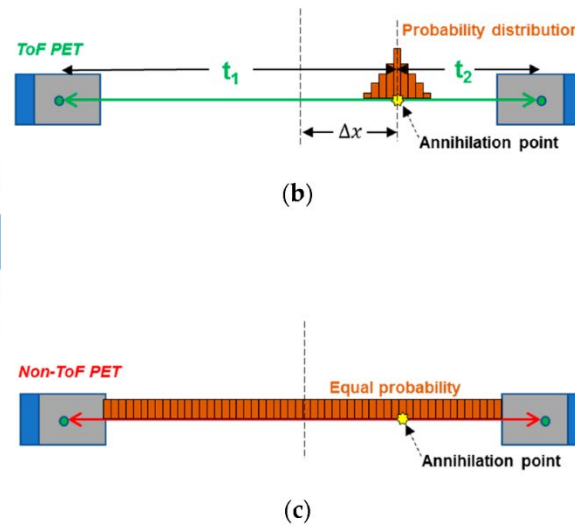
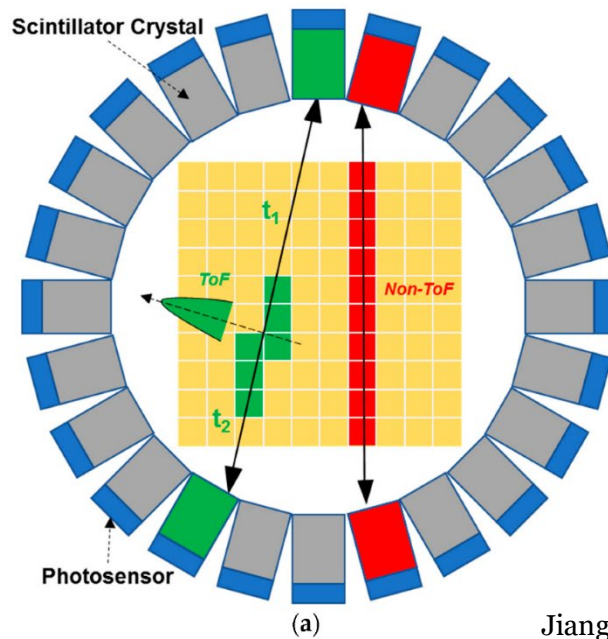


GAGG scintillators in slab and matrix produced by Epic-Crystal in the framework of the FAMU experiment.

Outline

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 - **SiPMs for Time of Flight PET @ FBK**
 - Radiometabolic therapy and radioguided surgery
 - WIDIMapp: a Wearable Individual Dose Monitoring Apparatus
 - CHIRONE/CHIR2: Beta RadioGuided Surgery with β radiation

PET and ToF PET

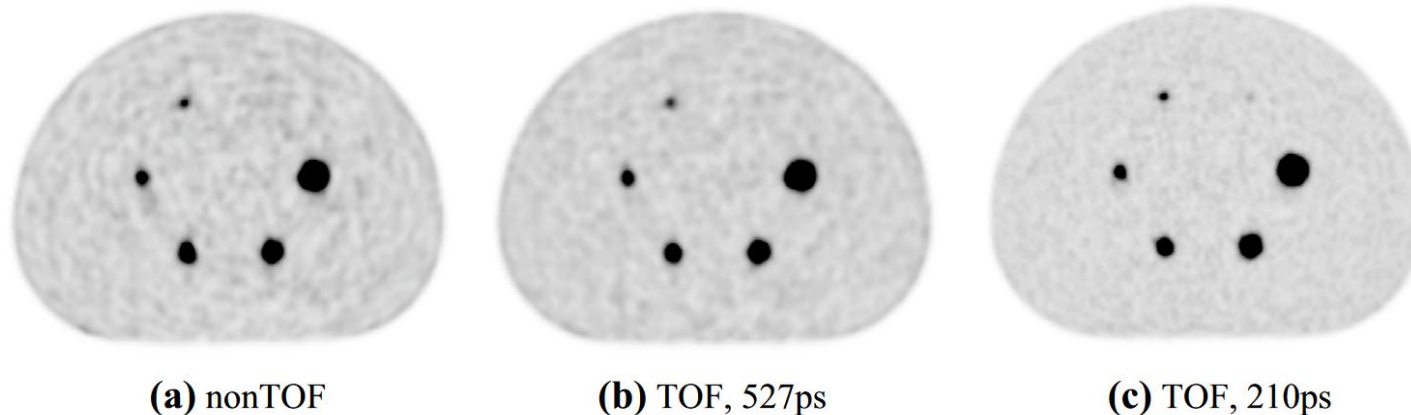


Jiang, Wei, *Sensors* 19.22 (2019): 5019.

Time-of-Flight (TOF) PET



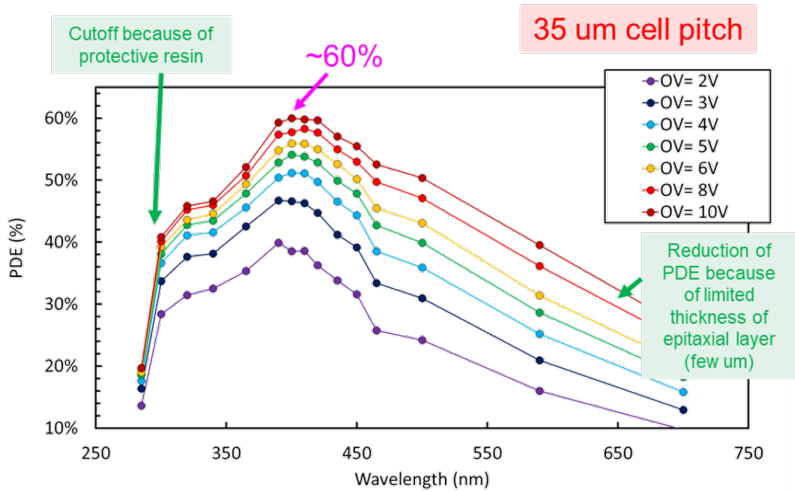
Conventional PET



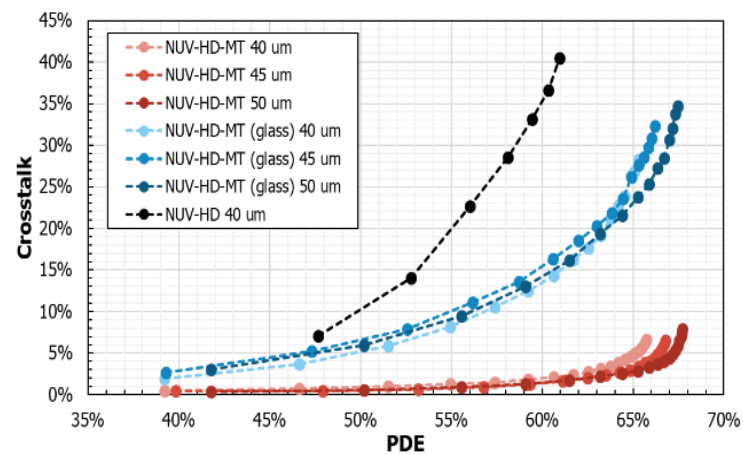
Conti, Maurizio *Clinical and Translational Imaging* 7.2 (2019): 139-147.

SiPMs for PET @ FBK

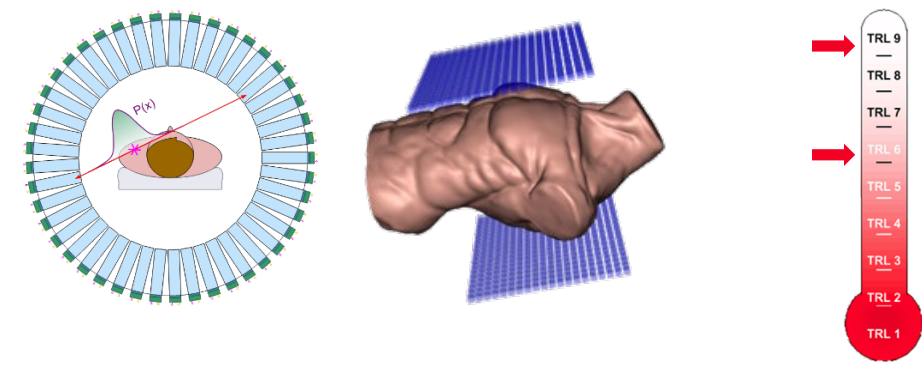
State of the art PDE and noise



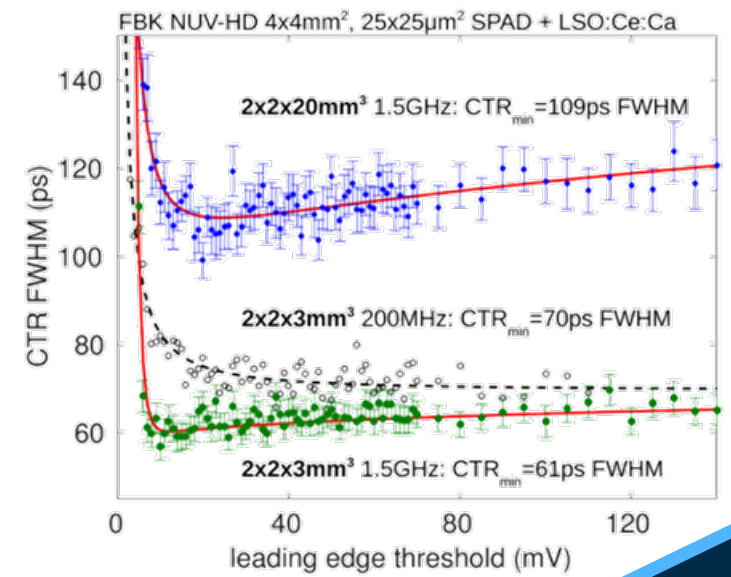
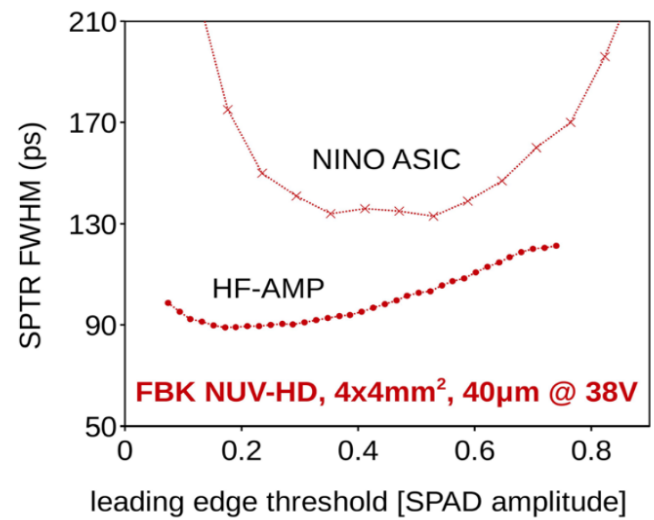
Gola, A et al. (2019). "NUV-Sensitive Silicon Photomultiplier Technologies Developed at Fondazione Bruno Kessler." *Sensors*, 19(2), 308.



Optical crosstalk vs. PDE at 420 nm measured on NUV-HD-MT technology.

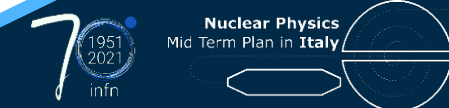


World-leading performance in PET



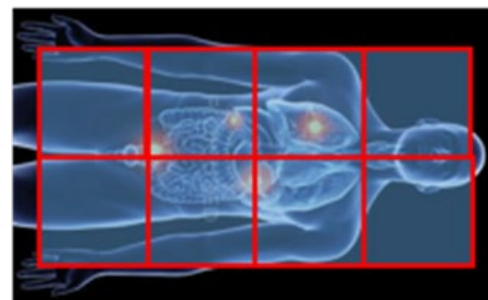
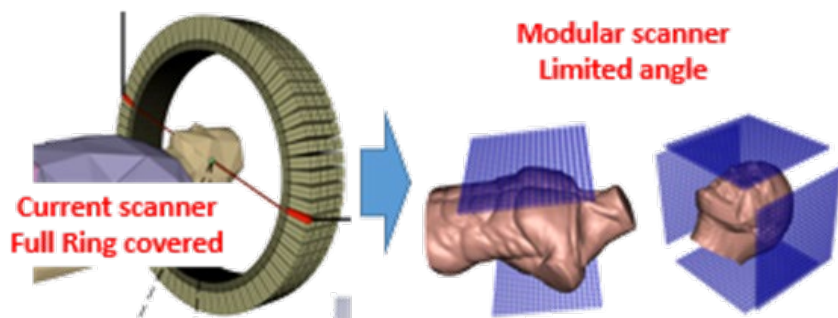
World record timing resolution: Single Photon Time resolution (SPTR, left) and Coincidence Resolving Time (CRT) in LYSO readout (right).

Courtesy of A. Gola– FBK

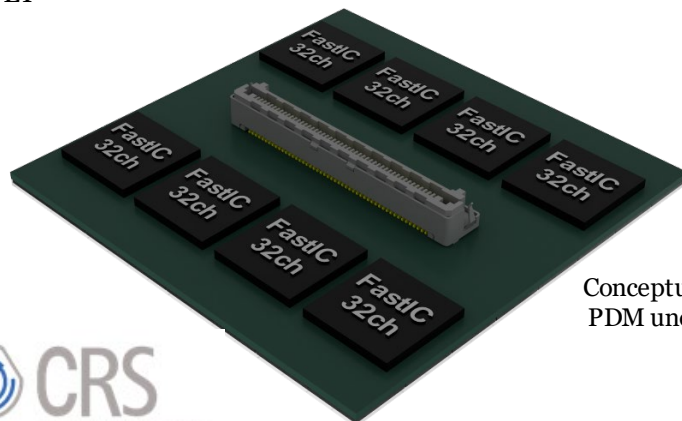


Development of large ToF-PET panels @ FBK

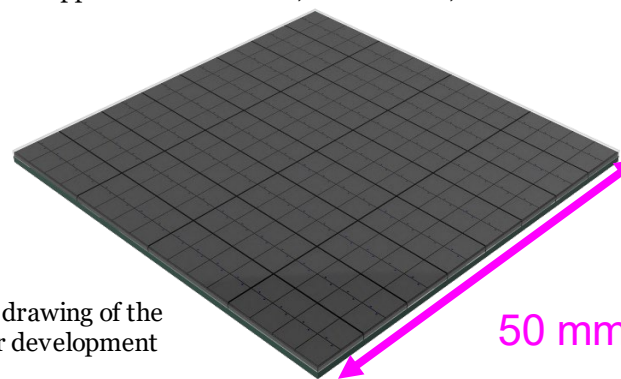
- 3D integration of SiPMs with TSV technology
- Development of 50x50 mm² PDMs to form *30x30 cm² ToF-PET panels*
- Used for limited-angle ToF-PET systems, for brain PET, Cardiac PET and full-body scanners.



Application of the PDM to build large panes used in new, limited-angle PET applications: Brain Pet, Cardiac PET, whole-body PET

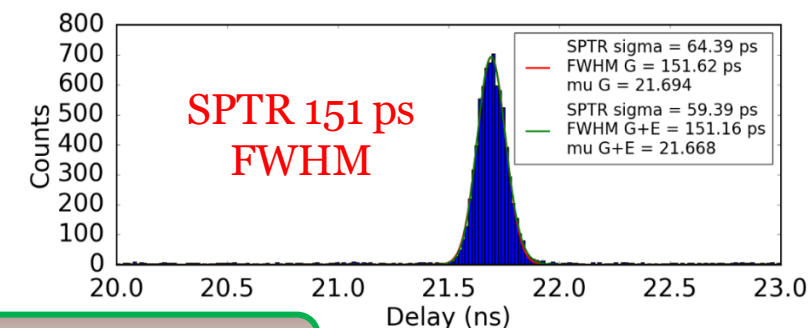


Conceptual drawing of the PDM under development

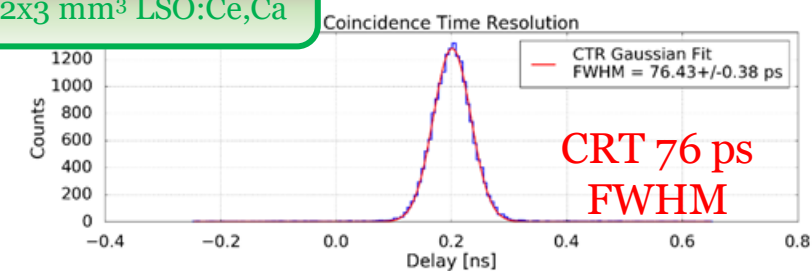


50 mm

Courtesy of A. Gola – FBK



2x2x3 mm³ LSO:Ce,Ca



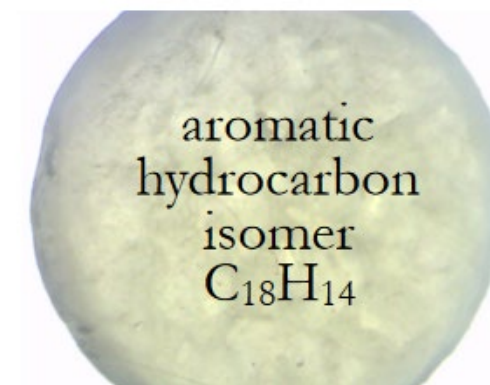
SPTR and CRT measured at FBK NUV-HD-SiPMs read by the FastICASIC developed by ICCUB.
Sensor: NUV-HD-LFv2 SiPMs, 3x3 mm²
Scintillator: 2x2x3 mm³ LSO:Ce,Ca
Power consumption: 3 mW/ channel

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WIDMApp

- Wearable Individual Dose Monitoring Apparatus
- Rationale
 - Targeted Radionuclide Therapy (TRT) effectiveness is related to reconstruction of absorbed dose in lesions and OARs
- The device
 - Wearable multi-channel sensor for gamma and beta detection
 - Thin, lightweight, robust, biocompatible
- Innovation with respect to state of the art
 - Much high accuracy in dosimetry
 - Real treatment personalization
 - Massive logistical simplification with respect to standard of care
- Possible developments in the next 5 years
 - Tests on patients
 - Detector optimization
 - Detector engineering



By
R. Mirabelli
E. Solfaroli-Camilloci

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Istituto Nazionale di Fisica Nucleare
Sezione di Roma

WIDMAApp

a **W**earable **I**ndividual **D**ose **M**onitoring **A**pparatus

Received: 11 March 2021 | Revised: 30 September 2021 | Accepted: 11 October 2021

DOI: 10.1002/imp.15311

TECHNICAL NOTE

MEDICAL PHYSICS

Technical note: A wearable radiation measurement system for collection of patient-specific time-activity data in radiopharmaceutical therapy: system design and Monte Carlo simulation results

Silvio Morganti¹ | Francesco Collamati¹ | Riccardo Faccini^{1,2} |
Giuseppe Iaccarino³ | Carlo Mancini-Terracciano^{1,2} | Riccardo Mirabelli^{1,2} |
Francesca Nicolanti^{1,2} | Massimiliano Pacilio⁴ | Antonella Soriani³ |
Elena Solfaroli-Camilloci^{1,2,5}



CHIRONE (2014-2016) - CHIR2 (2017-2019)

- CHIRONE and CHIR2 projects involved INFN-RM1, INFN-PG
- Many other partners (also clinical):
 - IIT, Sapienza, ISS, IEO, Carlo Besta ...
- Goal:
 - Development of a β – detector for radio-guided surgery
- Innovation with respect to state of the art:
 - Much more precise and accurate with respect to gamma-based technique
 - Allows radio guided surgery also in case of elevated background
 - Much handier detector, for example in robotic surgery
- Possible developments in the next 5 years:
 - Detector engineering beyond prototype
 - Extended tests on patients

Beta RadioGuided Surgery with β radiation

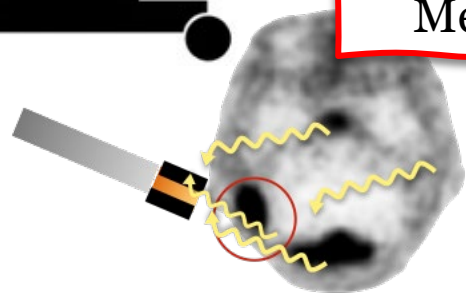
- Standard use: γ emitter + γ probe
 - E.g. ^{99}Tc : $E_\gamma = 140 \text{ keV}$

[1] A novel radioguided surgery technique exploiting β^- decays, Camillocci ES et al., Sci Rep 2015;4:4401. doi:10.1038/srep04401



FACT:
1/3 of these photons traverse more than 8 cm in human tissue

LIMITATIONS:
Healthy organs background
Detector shielding
Medical staff exposure



CHANGE IN PARADIGM:
CHIRONE (2014)
 β^- emitter + β^- detector

e.g.: ^{90}Y , pure β^- decay,
2.2 MeV \leftrightarrow ~mm penetration
 ^{68}Ga , β^+ decay,
1.92 MeV

ADVANTAGES:
No background from healthy tissue
Smaller probe
Reduced exposure

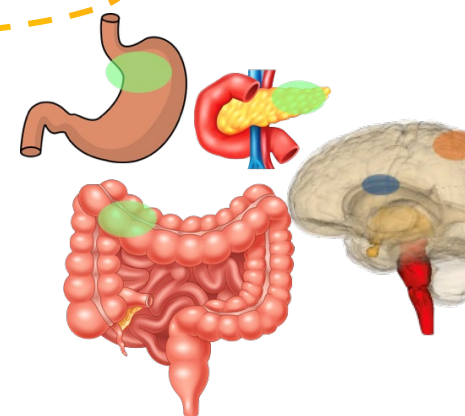
Courtesy of F. Collamati

Beta RadioGuided Surgery with β radiation



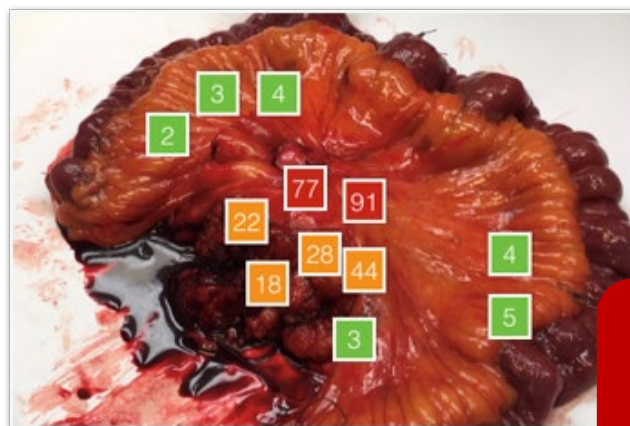
DETECTOR DEVELOPMENT

Scintillating crystal (5mm diam.) of *p-terpheyanyl*:
→ High sensitivity to β
→ Transparency to γ



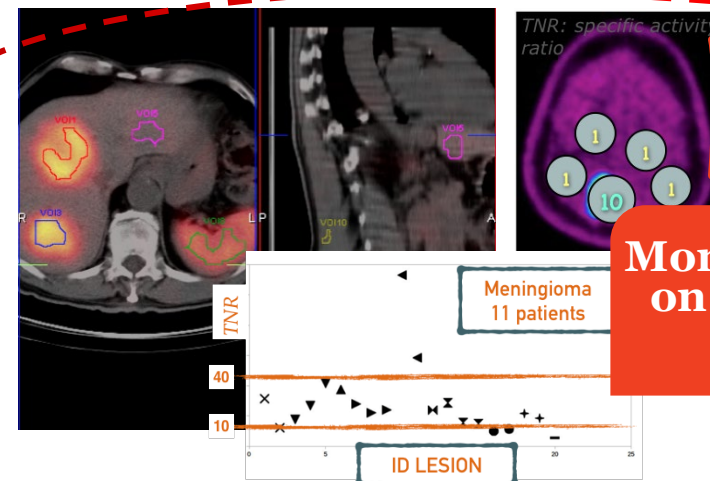
USE CASE IDENTIFICATION

β - Meningioma, Glioma and NETs, with ^{90}Y -DOTATOC
 β^+ : NETs with ^{68}Ga -DOTATOC
Prostate Cancer with ^{68}Ga -PSMA



EXPERIMENTAL VALIDATION

Ex-vivo tests on Meningioma and GEP-NET samples @IEO (Milan)



FEASIBILITY STUDIES

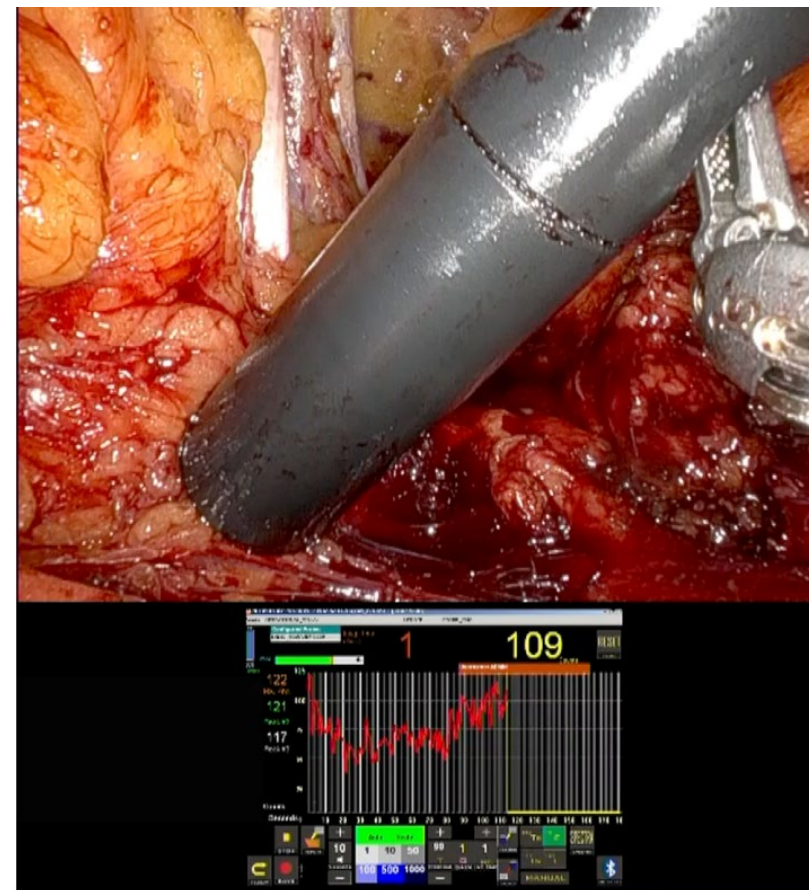
Monte Carlo simulations on PET/SPECT patient uptakes

Beta RadioGuided Surgery with β radiation

Ongoing activities:

- **Feasibility studies** of β -RGS with ^{18}F
 - Cervical Cancer (^{18}F -FDG)
- **Monte Carlo simulations** allowed to foresee probe counting due to signal and background;
- **Experimental Studies** on Detector characterization and optimization for ^{18}F β^+ detection (endpoint 633 keV)
- First **in-vivo** tests with ^{68}Ga ongoing @*IEO-Milan*
 - Prostate Cancer (*PSMA*)
 - NETs (*DOTATOC*)
- **Results** are strongly **confirming** not only the technique **capabilities**, but also the **accuracy** of our previous **simulations**!

VIDEO IN THE FINAL PRESENTATION



Courtesy of F. Collamati

Contributors list

- Luca Brombal (INFN-Trieste, Università di Trieste)
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- Piero Giubilato (INFN Padova, Università di Padova)
- Alberto Gola (FBK)
- Marcello Lunardon (INFN Padova, Università di Padova)
- Carlo Mancini Terracciano (INFN-Roma1, Università La Sapienza”)
- Marianna Testa (INFN-LNS)

Conclusions and summary

That's not my job, this is the reason why we have conveners!



THANK YOU!