The EndoTOFPET-US project

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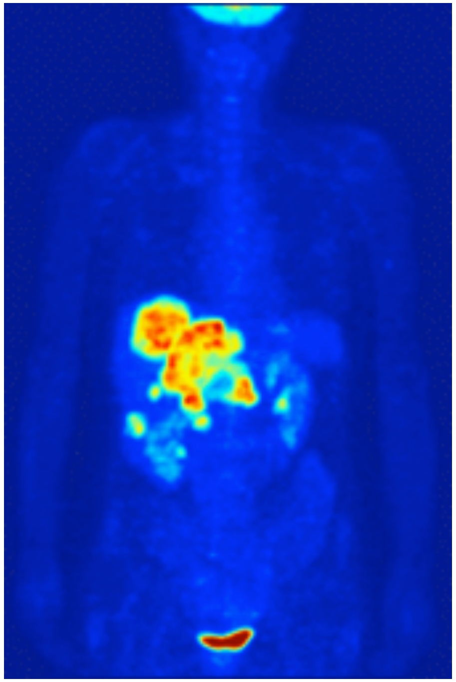


Erika Garutti

This work has been partly funded by the European Union 7th Framework Program (FP7/2007-2013) under Grant Agreement No. 256984 EndoTOFPET-US, and supported by a Marie Curie Early Initial Training Network Fellowship of the European Union 7th Framework Program (PITN-.-GA-.-2011-.-289355-.-PicoSEC-MCNet)

The EndoTOFPET-US project

Endo = Endoscopic

TOF = Time of Flight

PET = Positron Emission Tomography

US = Ultrasound

The EndoTOFPET-US project

The tool

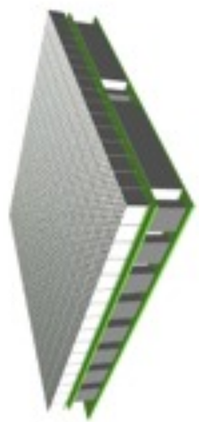
- Endo = Endoscopic
- TOF = Time of Flight
- PET = Positron Emission Tomography
- US = Ultrasound

The goals:

1) development of biomarkers for prostate and pancreas tumor

2) intra-operative imaging of prostatic and pancreatic lesions (guided surgery / biopsy)

The EndoTOFPET-US project



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- Enhanced resolution due to proximity
- Combination with biopsy needle

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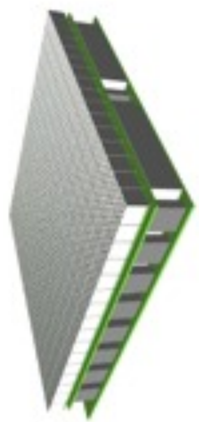


The tool

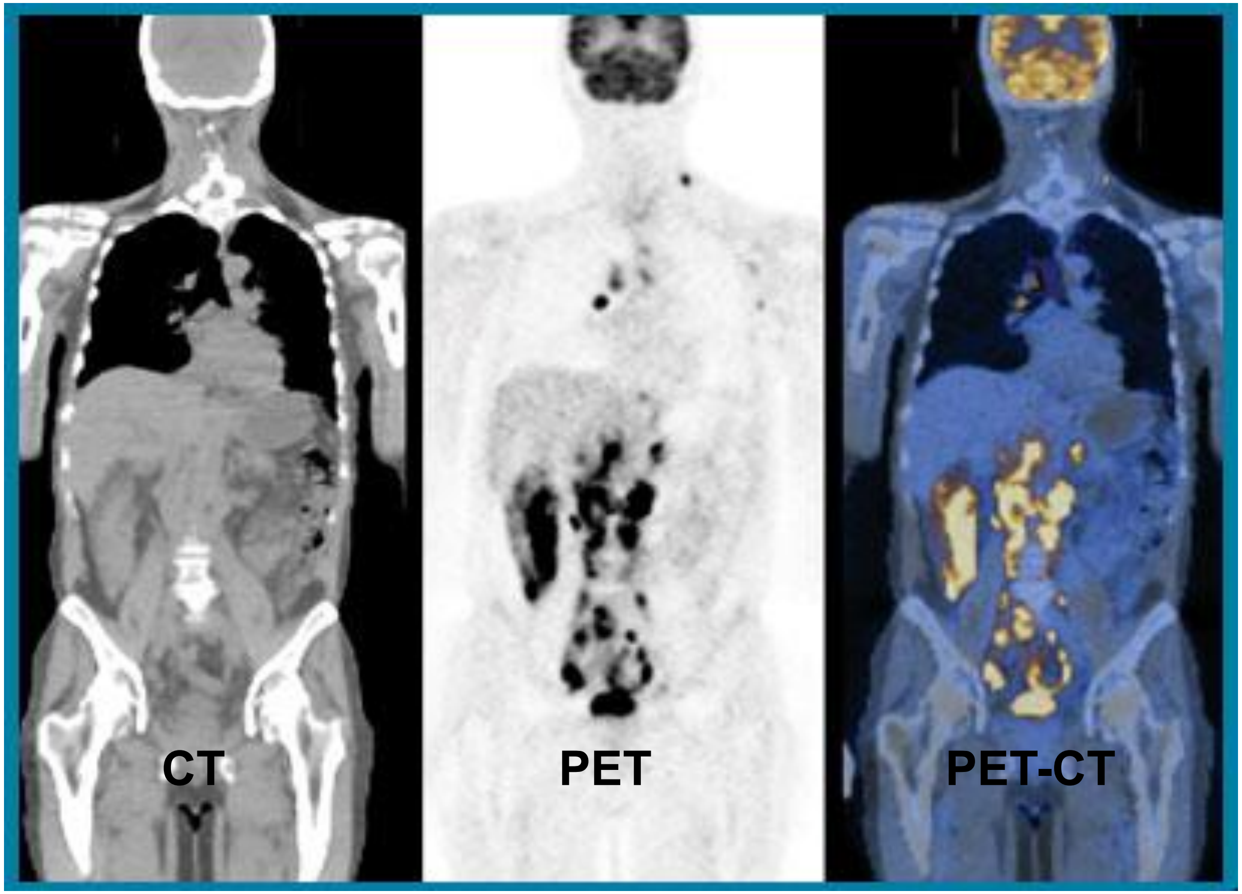
- Enhanced resolution due to proximity
- Combination with biopsy needle

Endo = Endoscopic
TOF = Time of Flight
PET = Positron Emission Tomography
US = Ultrasound

Multi-modal instrument:
high resolution metabolic imaging (PET)
plus anatomical imaging (US)

The goals:
1) development of biomarkers for prostate and pancreas tumor
2) intra-operative imaging of prostatic and pancreatic lesions (guided surgery / biopsy)

Multi-modality imaging



First concept by D. Towsend and Prof. Donath (CERN+CHUG)

Development by University of Pittsburgh and CTI

TWO IS BETTER THAN ONE !

Computed tomography (CT) provides excellent anatomical image = localization

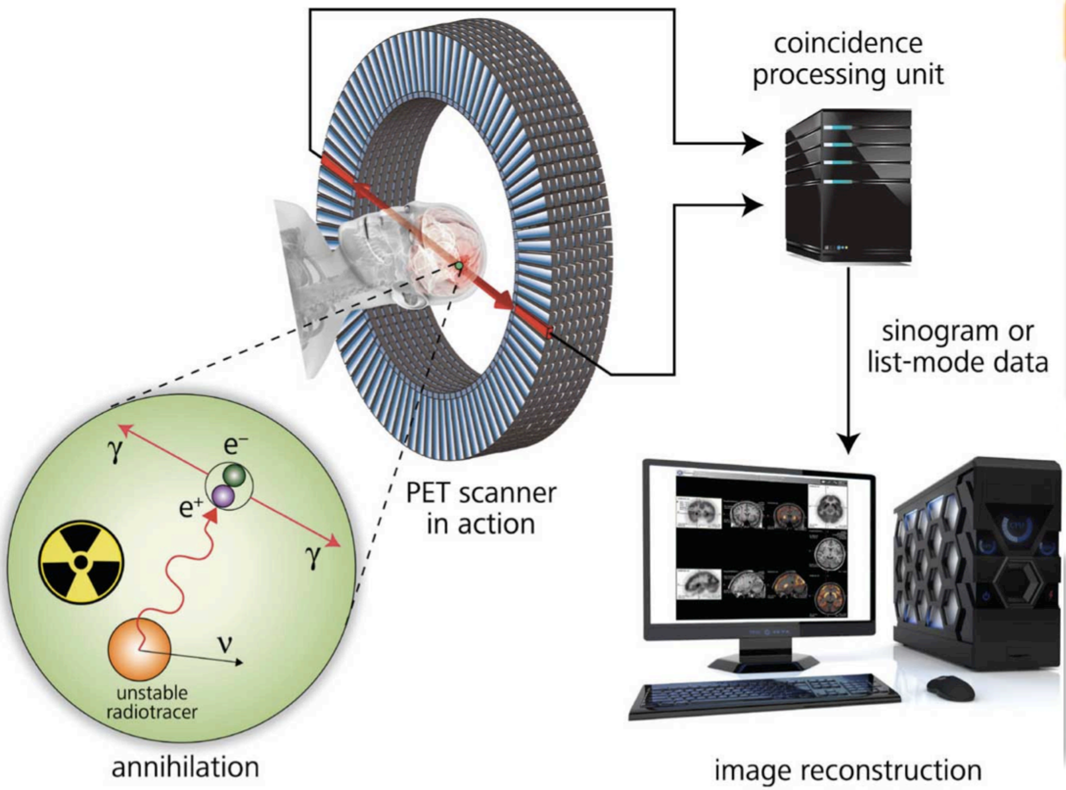
PET adds the functional information = finds tumor

Image fusion from a multi-modal systems

What is Positron Emission Tomography ?

PET Imaging

- PET is in-vivo functional imaging technique
- It produces a quantitative image of the radiotracer concentration
- Image of the body metabolism



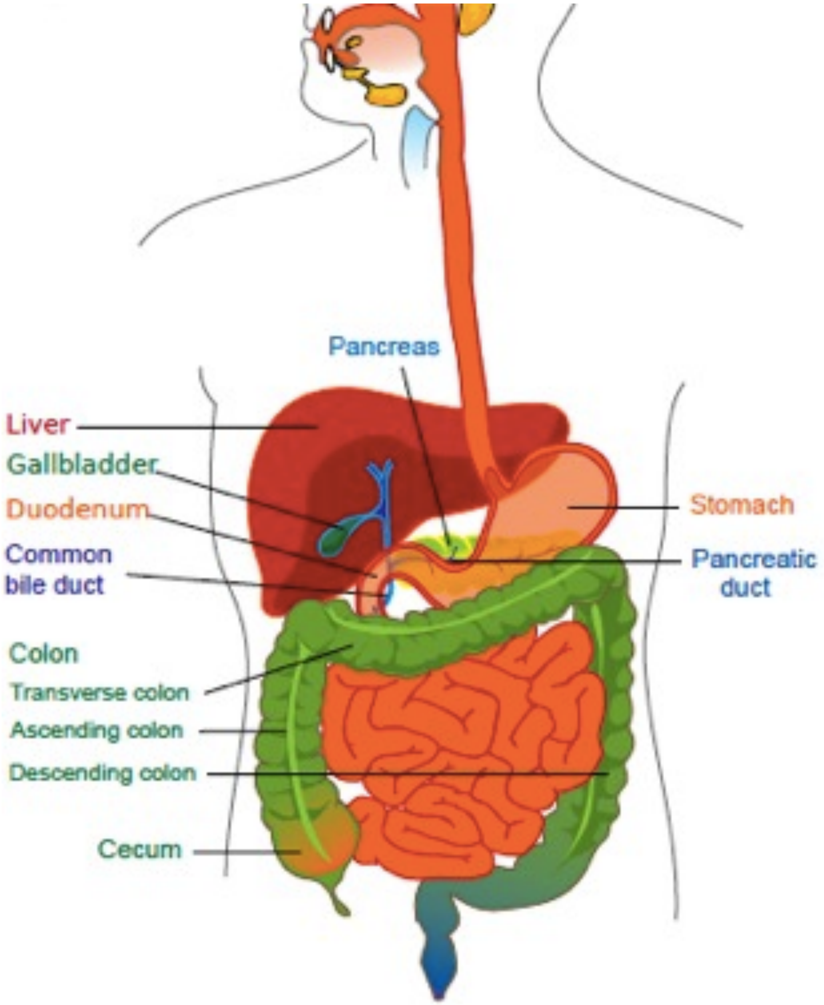
PET Principle

- Radiotracer (β^+ emitter) concentrates in the metabolical active areas
- $e^+e^- \rightarrow 2\gamma$ (back-to-back, 511 keV each)
- Detect two opposite events occurring "simultaneously" (in *coincidence*)
- Take projections from many angles

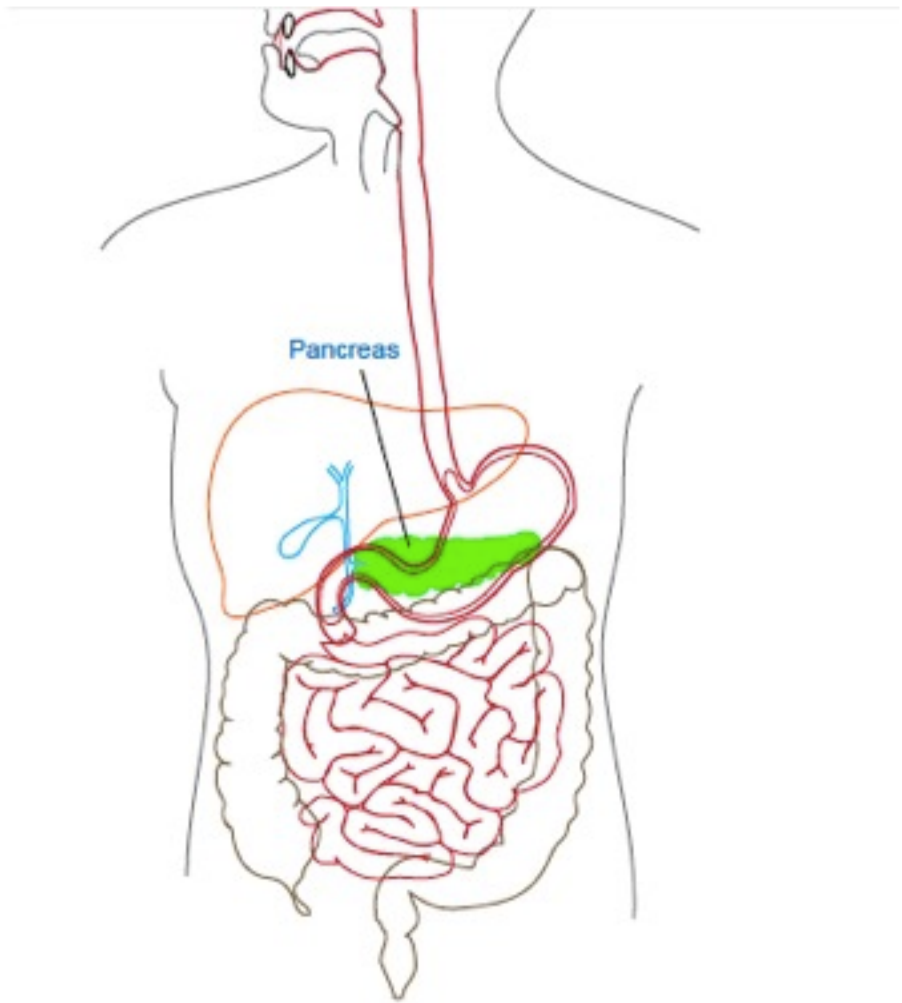
In Practice

- Inject radiotracer ($3 - 7$ MBq per kg)
- Wait for uptake (≈ 1 h)
- Acquire data (≈ 0.5 h for full body)
- Reconstruct the data

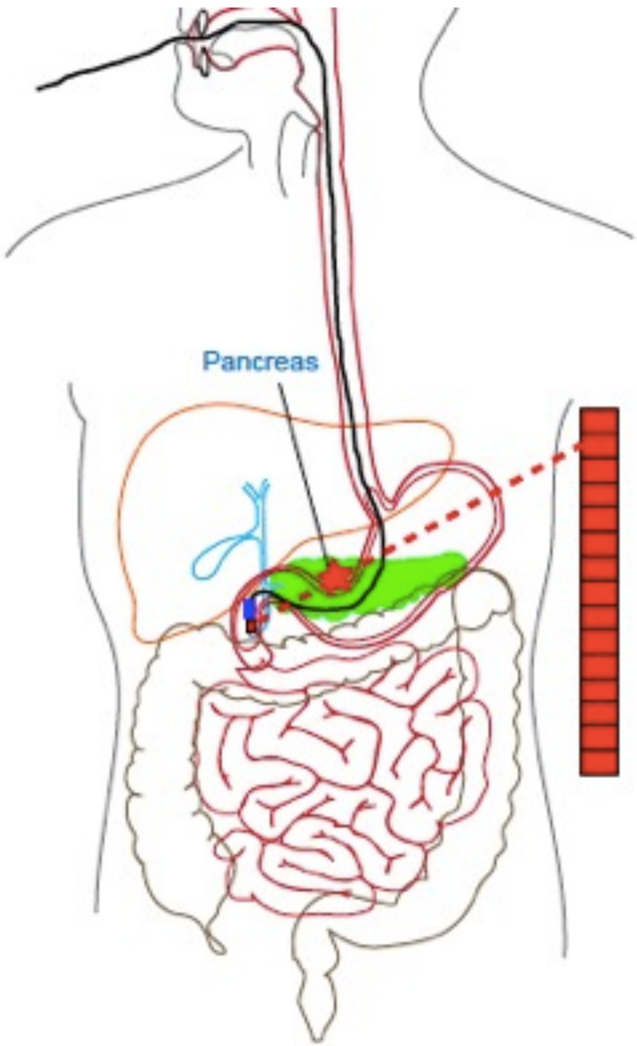
How does endoscopic PET work?



How does endoscopic PET work?

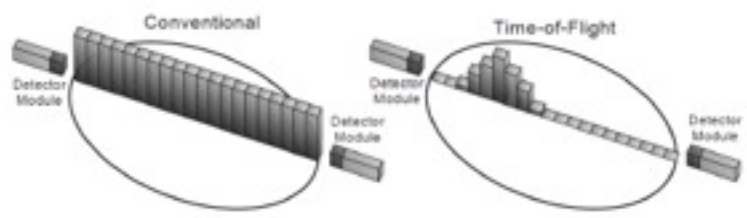


How does endoscopic PET work?



PET image from the line of response obtained between two detectors in coincidence

1) External PET plate
2) Internal PET head mounted on the tip of an endoscopic US transducer



Time of Flight: to reject false coincidences from near by organs.

What are bio-markers?

The goals:

1) development of biomarkers for prostate and pancreas tumor

A traceable substance introduced into an organism as a mean to examine the organ functionality or health

Examples:

rubidium chloride (radioactive isotope) ➔ heart muscle perfusion

prostate-specific antigen (PSA) ➔ high concentration potentially indicate cancer

The biomarker concentration correlates with the risk of a disease or the susceptibility of the disease to a given treatment.

Project motivation

Why these targets?

Pancreatic Cancer

4th leading cause in Western countries for cancer-related death ...

An extremely poor prognosis ... with very low 5-year survival rates ...

Standard imaging methods: US & CT ...

Both lack metabolic information ...

No reliable early detection method ...

Prostatic Cancer

The 6th leading cause amongst males for cancer-related death ...

Relatively good prognosis if confined and aggressively treated ...

Standard imaging methods: US & MRI

Both lack of metabolic information ...

Challenge: Detect small size tumors in large background environment ... [e.g. liver, heart, bladder]

Project motivation

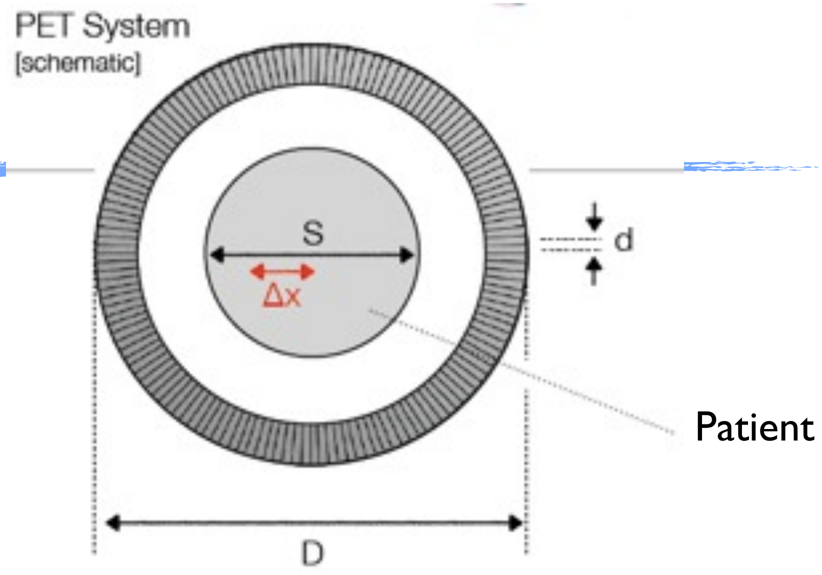
Why Endoscopic?

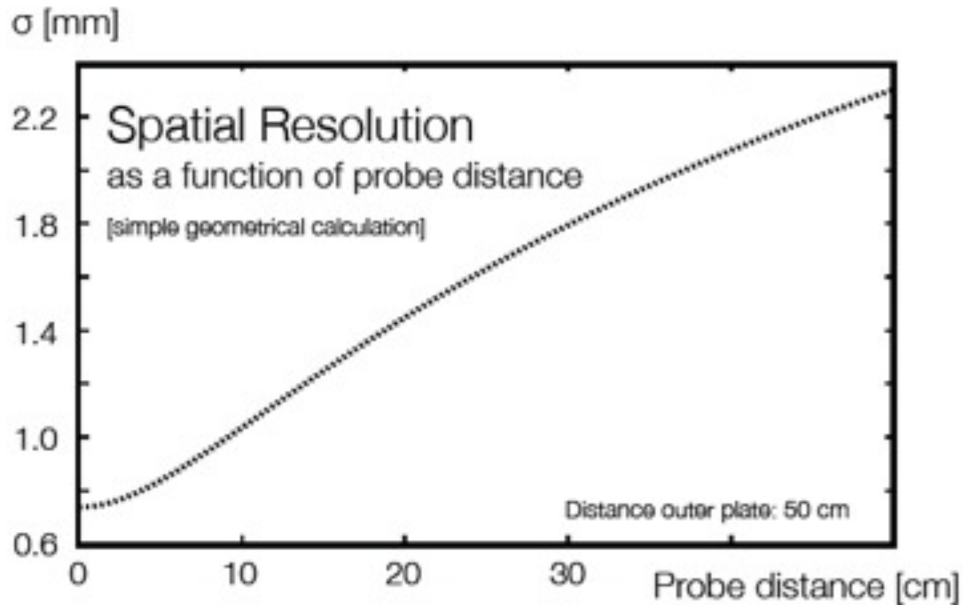
PET image resolution:

$$\sigma^2 \propto r^2 + (d/2)^2 + (.0022D)^2$$

r : Positron range [ca. 0.5 mm]
d : Detector size [ca. 1.0 mm; inner probe]
D : Detector distance

[see e.g. R.Lecomte, NIM A 526]
[zero position decoding error]





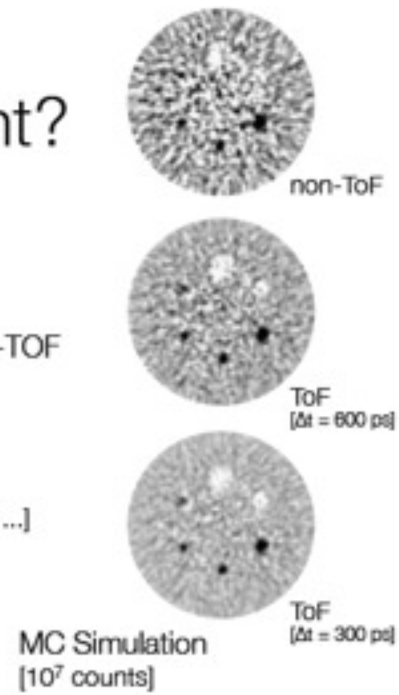
Why Time-of-Flight?

Sensitivity improvement:

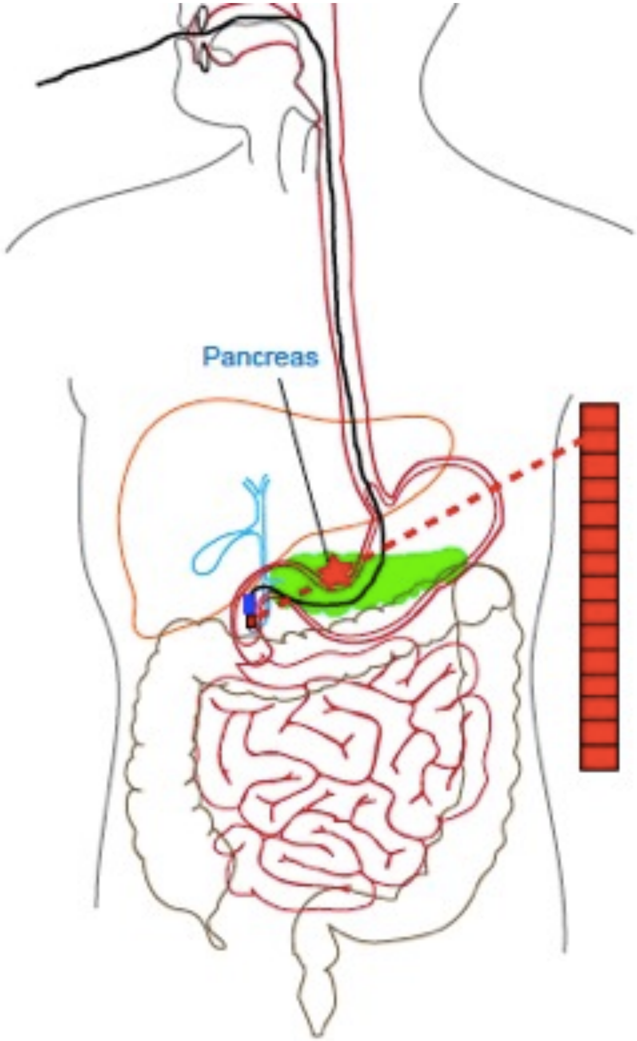
$$SNR^2_{TOF} \propto \frac{S}{\Delta x} \times SNR^2_{non\text{-}TOF}$$

S : Size of patient
Δx : Source localization using ToF

[M.Conti, Eur. J Nucl. Med Mol. Imag. 38 ...]



Project challenges



Technical Challenges:

- Extreme miniaturization
- Coincidence time resolution 200 ps FWHM (~3cm background rejection)
- Fast crystals & ultra-fast photo-detection
- Image reconstruction for free-hand imaging,
- O(mm) spatial resolution ➔ tracking
- Fusion of US and PET images

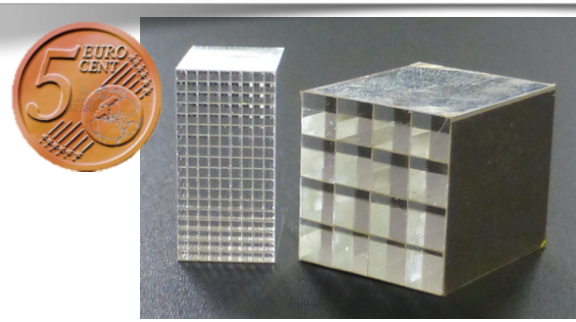
Extreme miniaturization + fast detector

Conventional PET module

Extreme miniaturization + fast detector

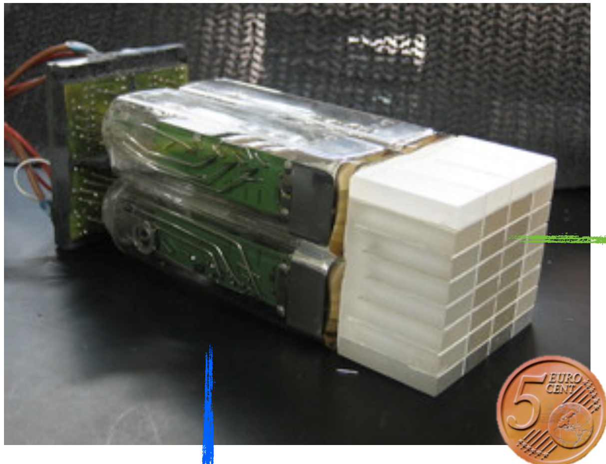
Conventional PET module

better crystals

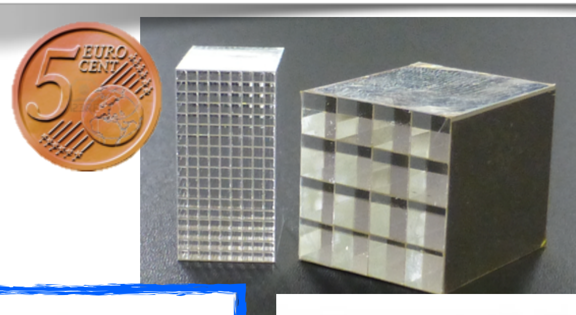


Extreme miniaturization + fast detector

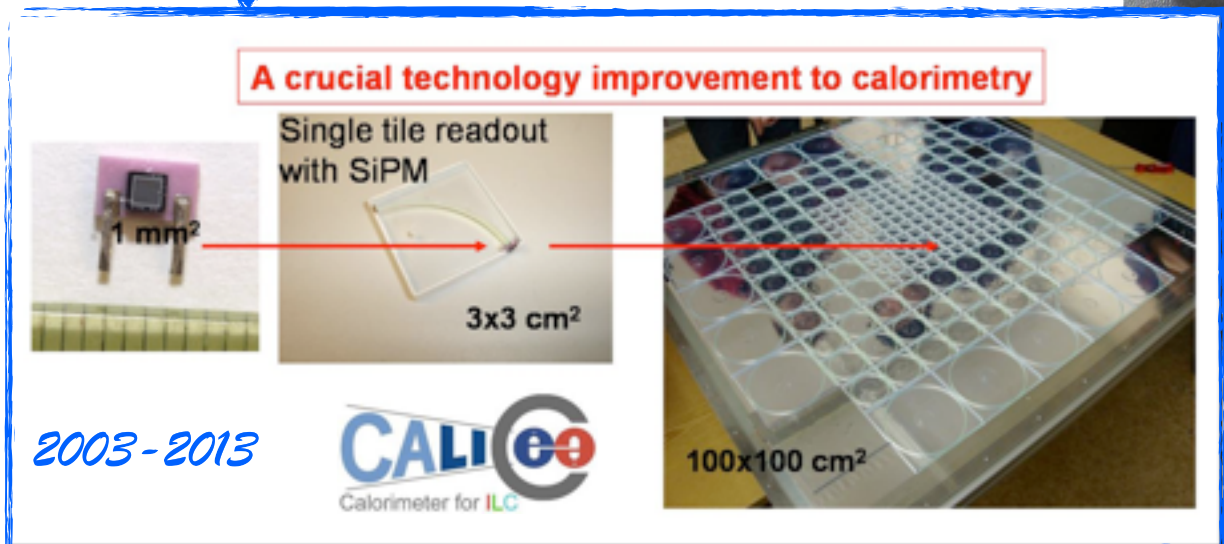
Conventional PET module

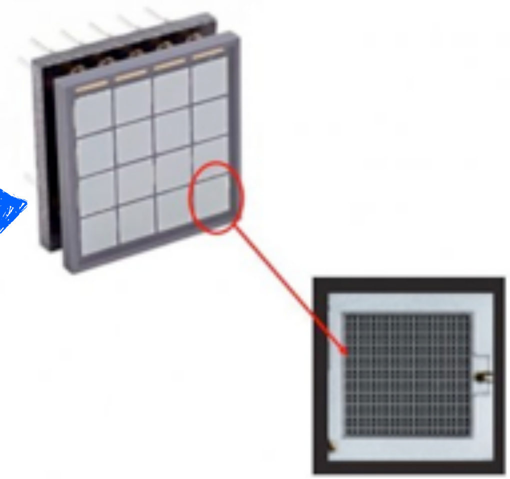


better crystals



better photo-detectors





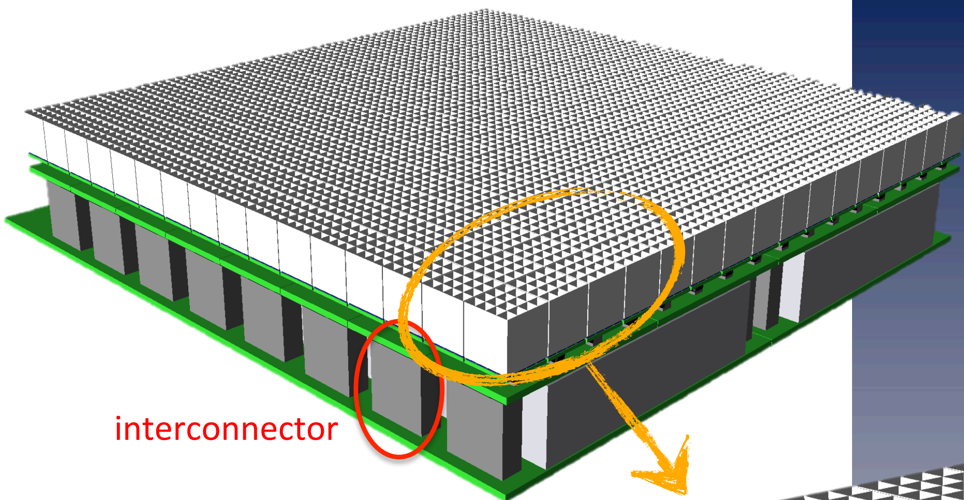
Project structure and funding

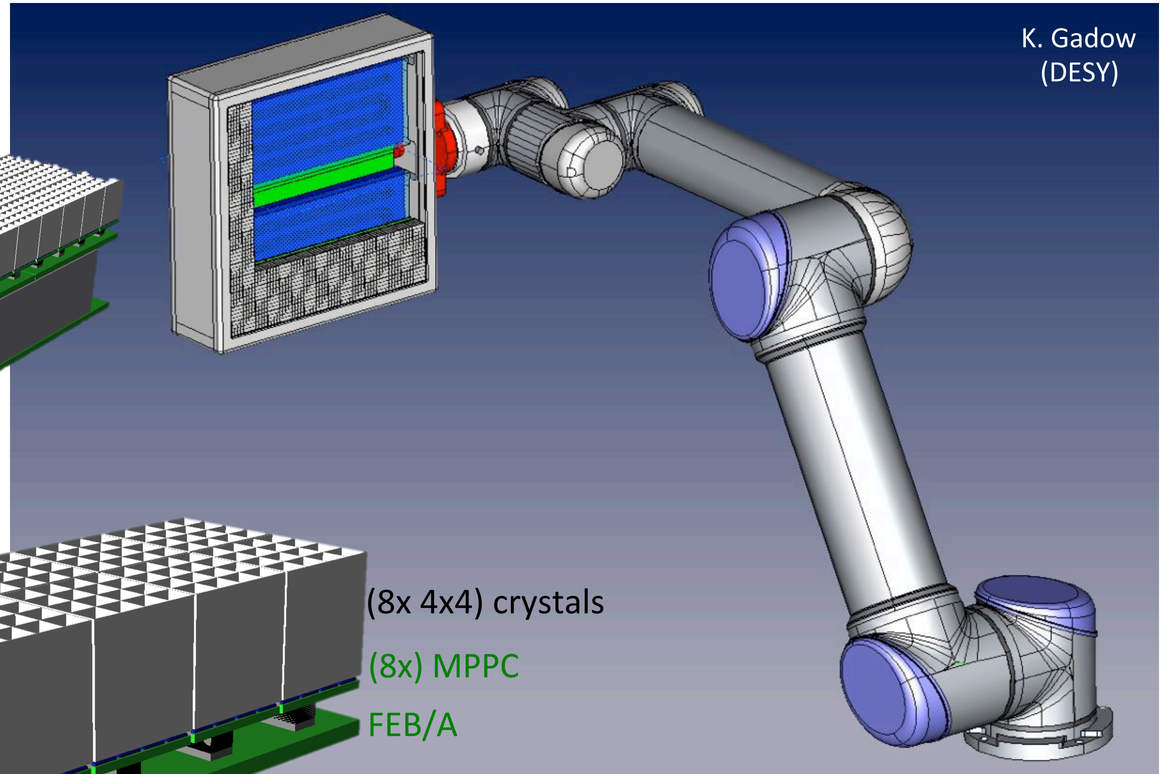
- EU funded project (FP7-health)
- Running period: 2011-2014
- Total budget: 5.5 M€ (DESY ~10%)
- Partners ➔
- Work packages:

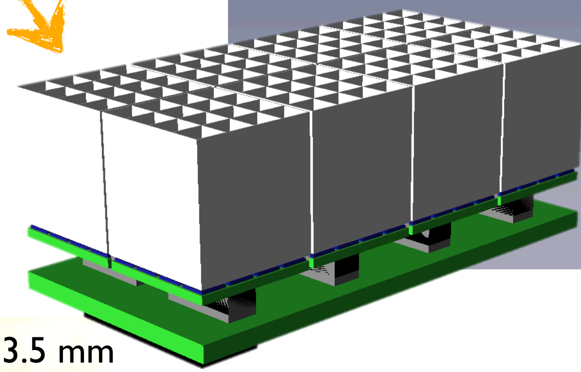
WP 1	Project Coordination
WP 2	Crystals and optics
WP 3	Photodetector
WP 4	Front End (FE) and Data Acquisition (DAQ) electronics
WP 5	Detector integration
WP 6	Clinical requirements & preclinical and pilot clinical studies

EndoTOFPET-US - DESY group

External PET plate - detector design



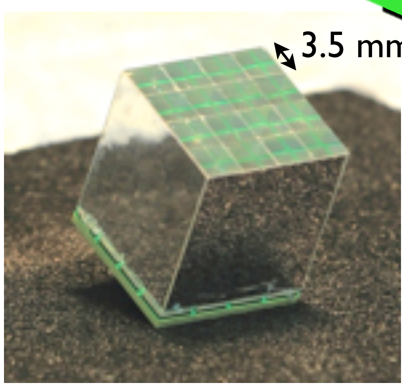




MPPC

+

LYSO



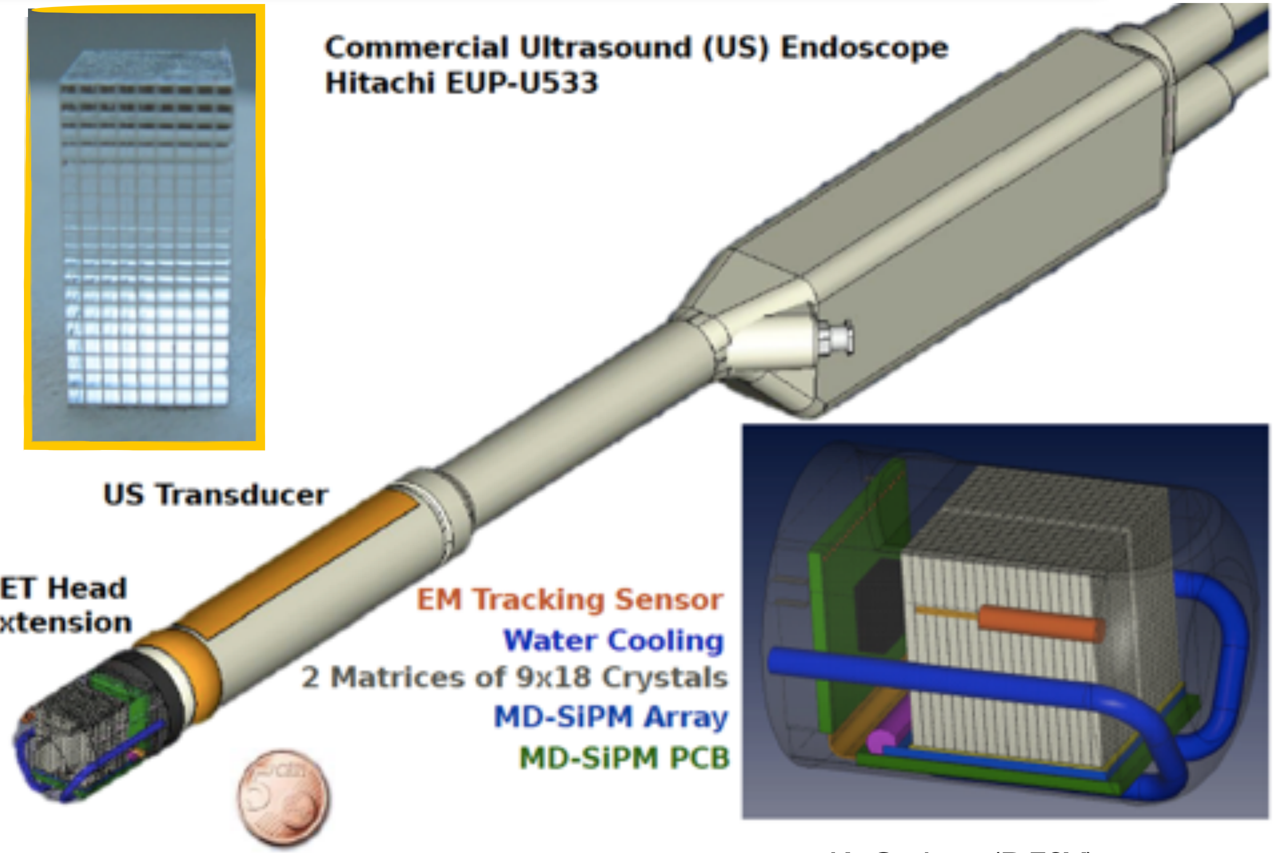
- Plate area: 23×23 cm^2
- 4096 LYSO crystals à $3.5 \times 3.5 \times 15$ mm^3
- Coupled to SiPMs (Discrete Through-Silicon Via MPPC arrays from Hamamatsu)
- Dedicated fast 64-channel ASIC & cooling plate embedded in detector housing
- Mounted on moveable arm

Internal PET head - detector design

Endoscopic PET Detector

- PET extension mounted on a transrectal US endoscope
- Clamped on endoscope head without alterations of the endoscope
- PET head volume: $23 \times 23 \times 40\ \mathrm{mm}^3$

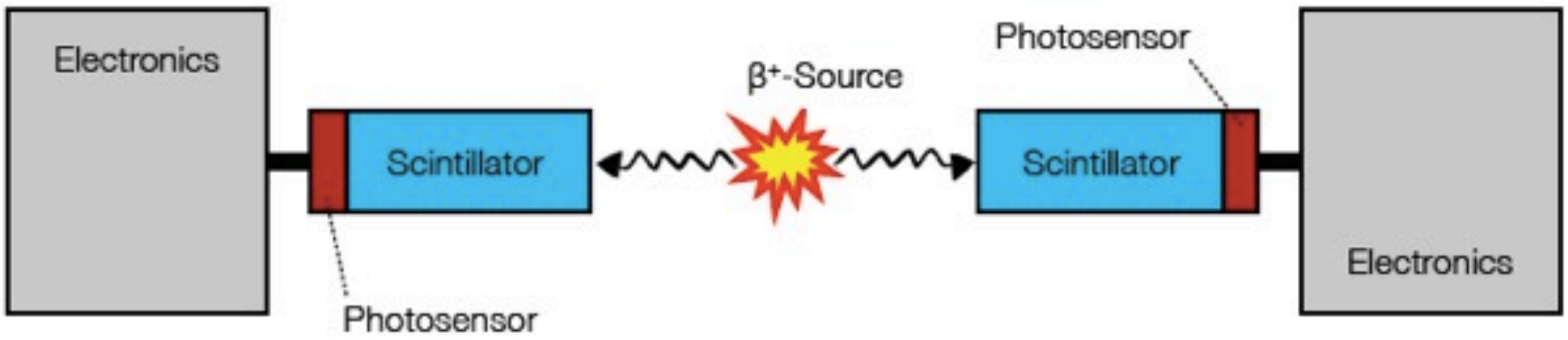
- 2 matrices of 9×18 crystals $0.71 \times 0.71 \times 15\ \mathrm{mm}^3$
- High granularity for excellent spatial resolution
- Coupled to Multichannel -Digital SiPMs (MD-SiPM)
- Readout: digital output of SPADs via interconnection PCB to DAQ
- Cooling via water pipes

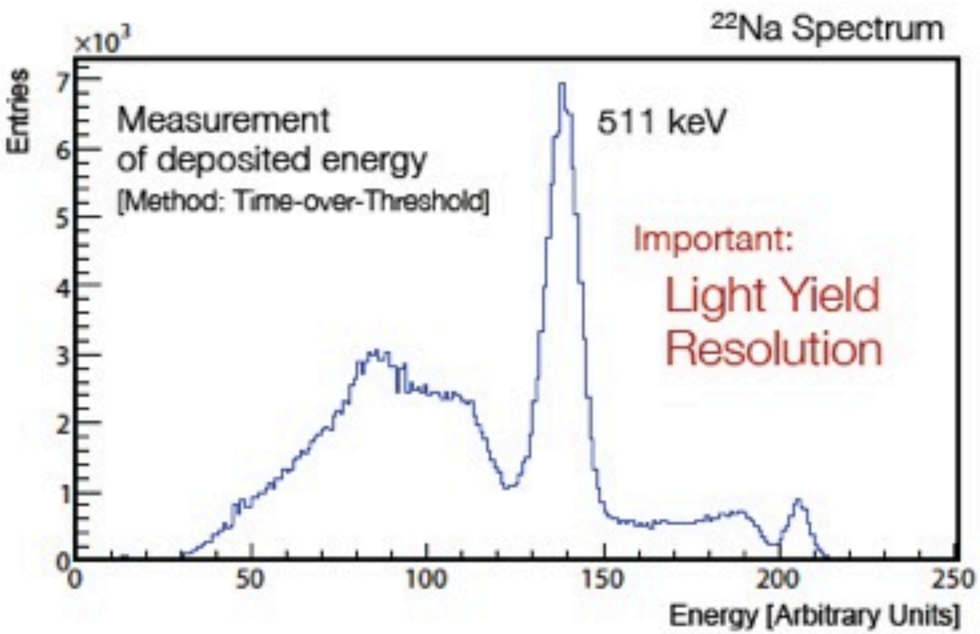


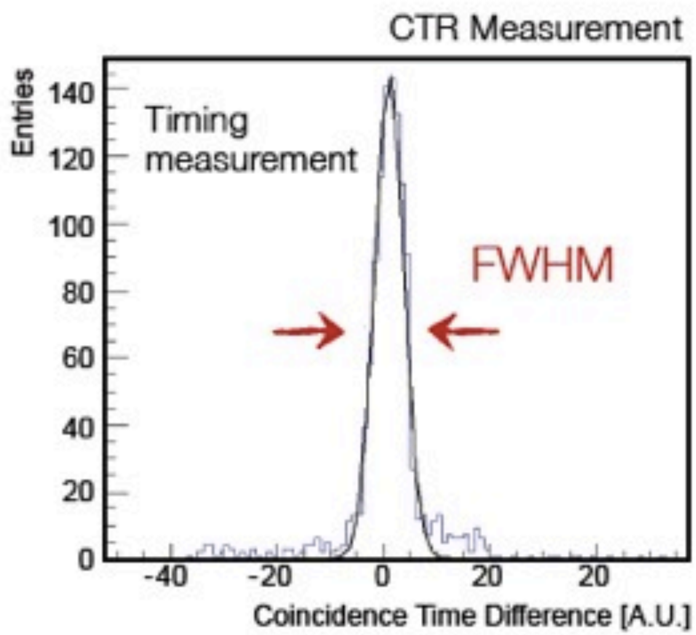
K. Gadow (DESY)

System characterization

System characterization



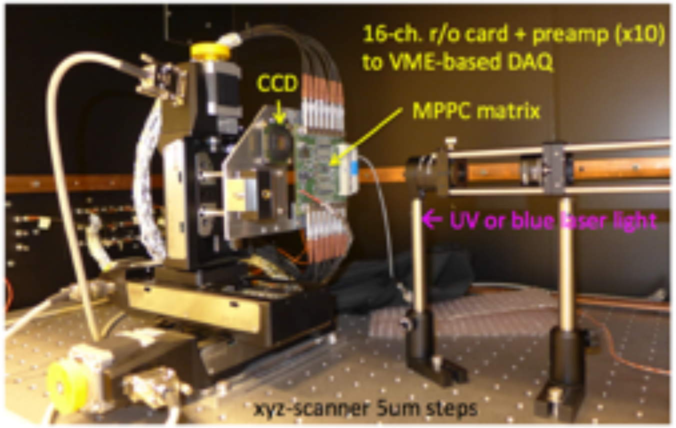


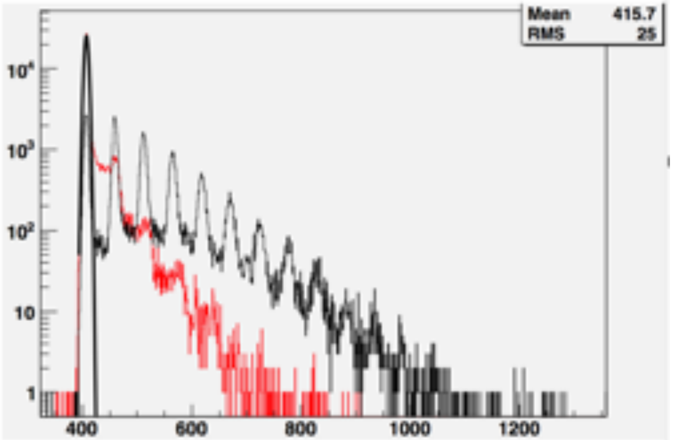


Erika Garutti

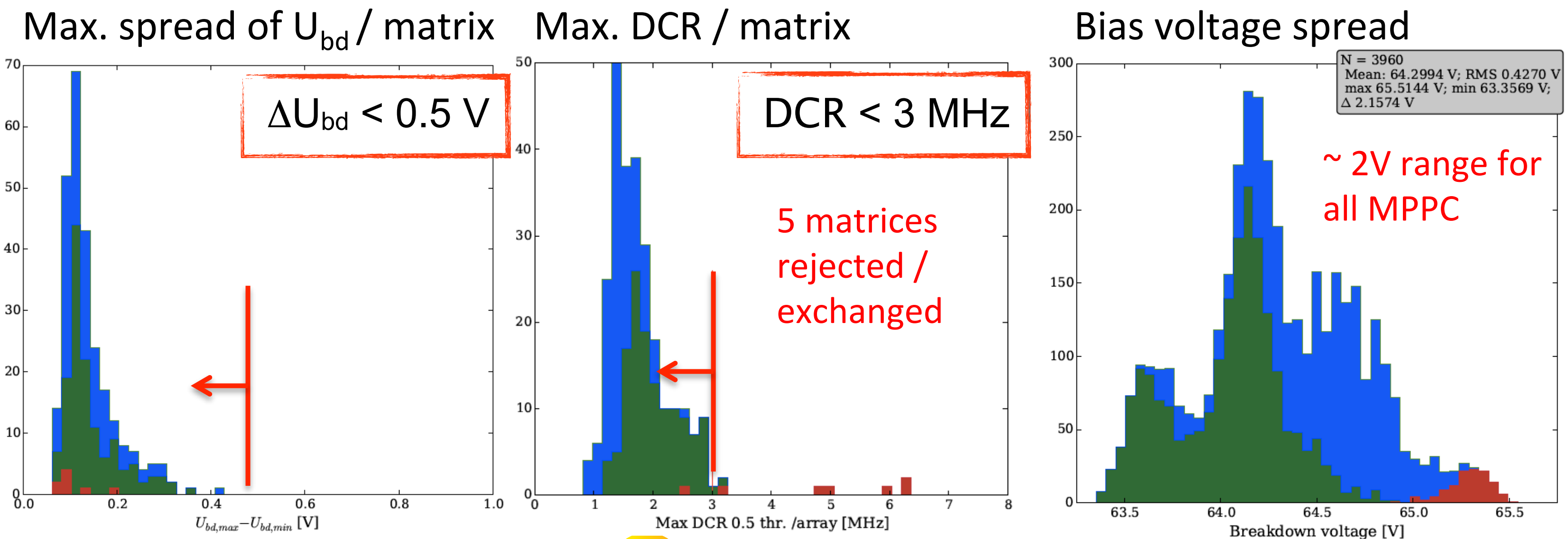
ENDO TOFPET US
Endoscopic TOFPET & Ultrasound

External PET plate - Photo-detector - SiPM





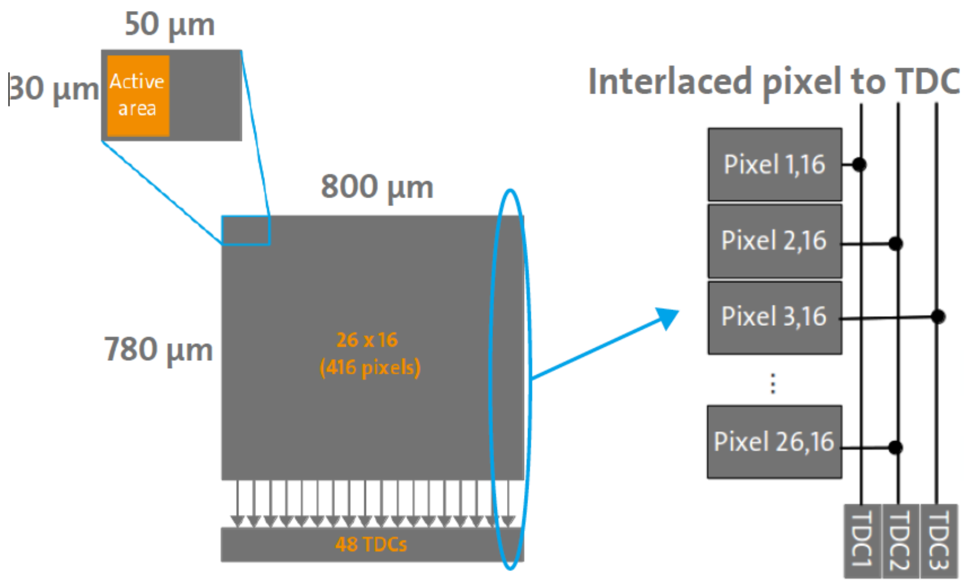
Char. set-up: collect laser light (black) and dark (red) spectra from 276 MPPC matrices
Verify producers parameters: Gain, DCR, breakdown V spread



Wednesday, April 16, 14

Inner PET head - Photo-detector - MD-SiPM

- **TU Delft's MD-SiPM prototype specification:**
  - 30x50 µm² pixel size with 57% fill factor
  - 416 SPAD pixels (26x16) per cluster
  - 780x800 µm² cluster size
  - Photon Detection Efficiency (PDE) up to 17%
  - 48 column-wise shared TDC
  - 45 ps per TDC bin



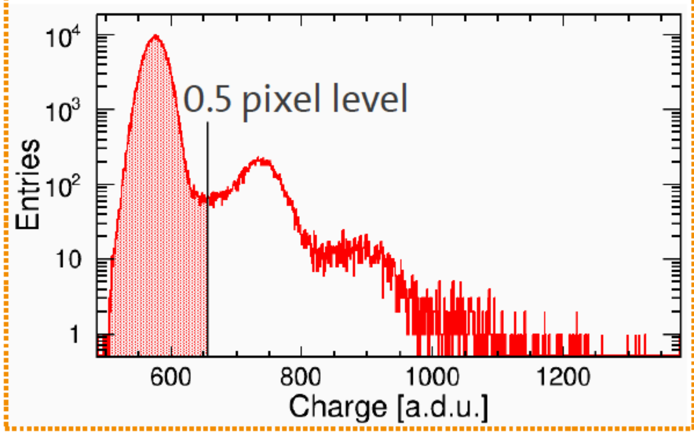
Courtesy of E. Charbon, Delft

MD-SiPM - dark count rate

- **Rate of randomly discharged pixels due to thermal excitation, tunneling effect**
  - **Occurrence of dark counts follow Poisson statistic**
  - **Using zero counts to calculate the rate**

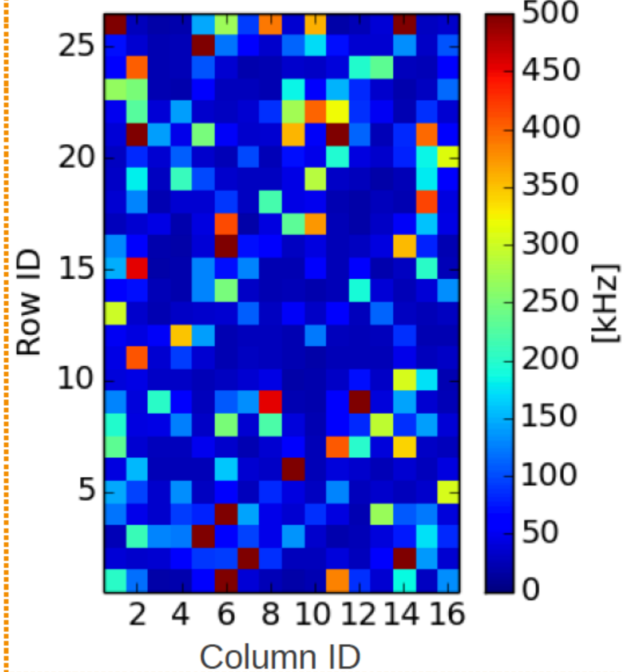
DCR has non-linear dependence on:
- **Excess bias voltage over break down**
- **Temperature**

DCR of MPPC (400 pixels)



- **Room temperature**
- **1.4 V excess bias**
- **Charge integration time: 100 ns**

Pixel-by-pixel DCR of MD-SiPM

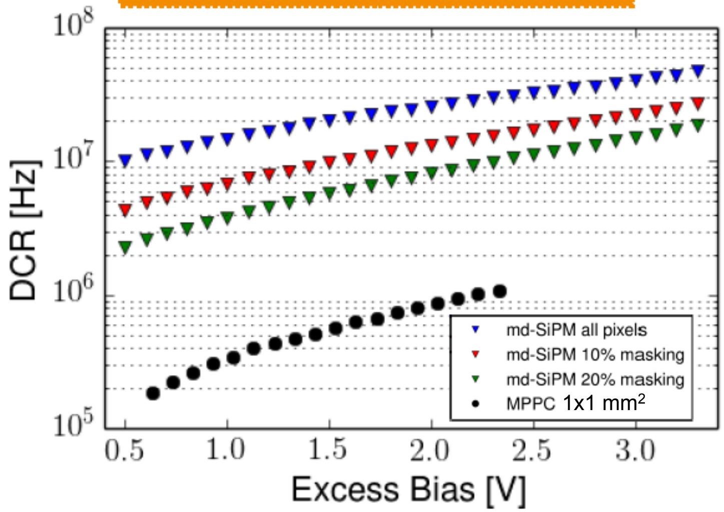


- **Room temperature**
- **2.5 V excess bias**
- **Readout frame of 100 ns**

MD-SiPM - dark count rate

- **Compare to MPPC**

Sensor DCR Comparison

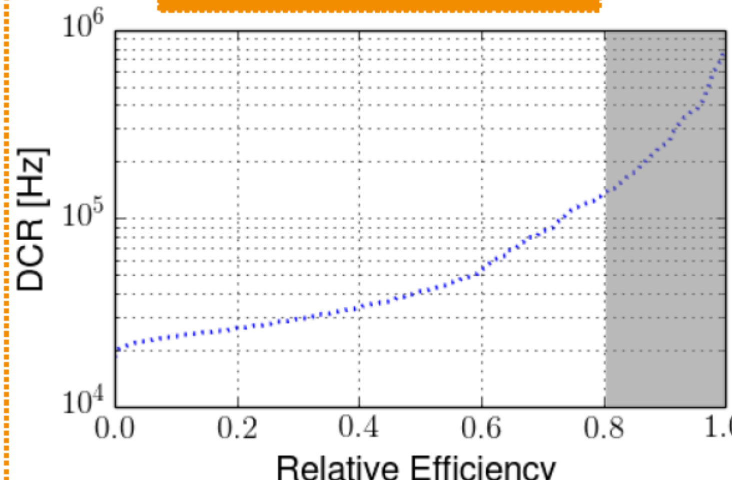


- **DCR per µm² of the two sensors at nominal operating voltage, room temperature**

MPPC	MD-SiPM
~ 1 Hz/µm²	~ 50 Hz/µm²

- **DCR Suppression:**
  - **Cool the sensor**
  - **Turn noisy pixel off (lost in efficiency)**

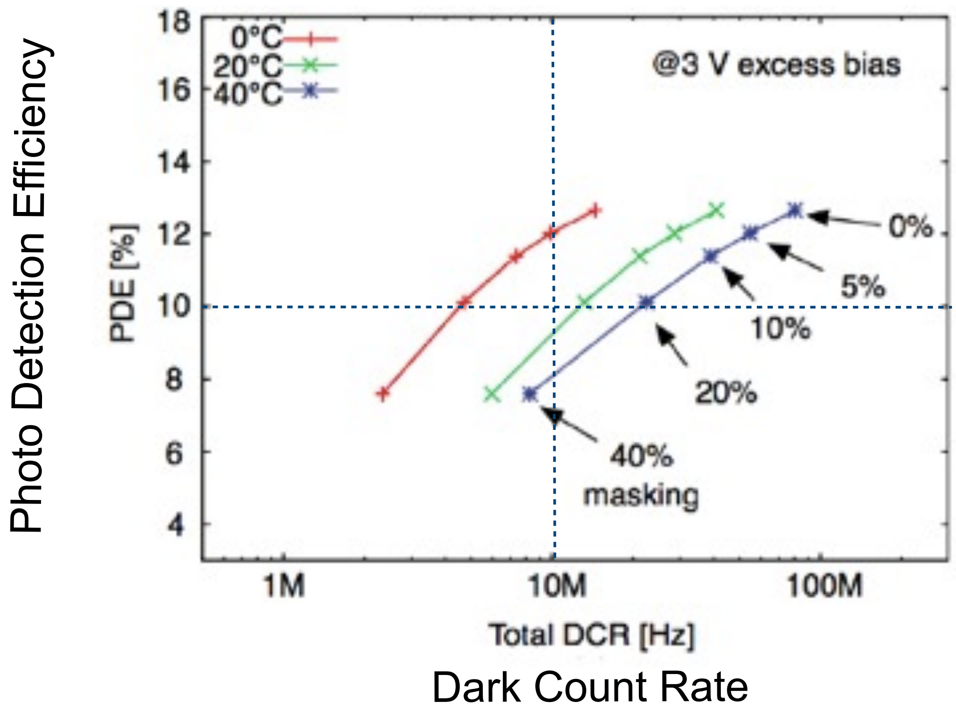
Cumulative Pixel DCR



- Room temperature
- 2.5 V excess bias
- Readout frame of 100 ns

MD-SiPM - cooling requirement

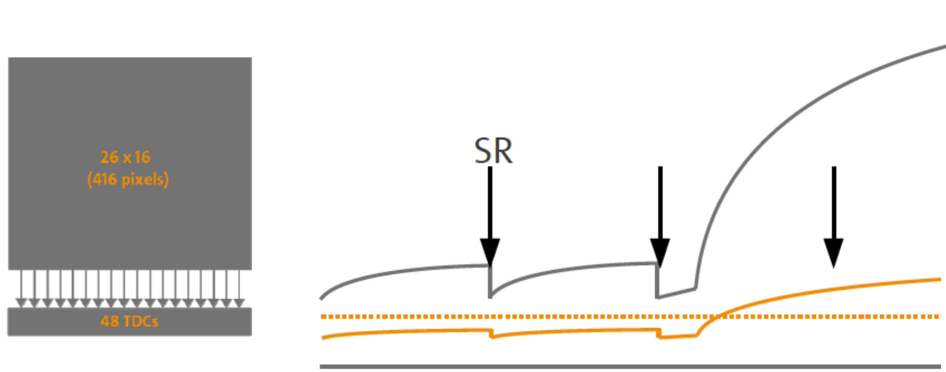
Design goal: 200 ps coincident time resolution
Requirement: PDE > 10% & DCR < 10 MHz

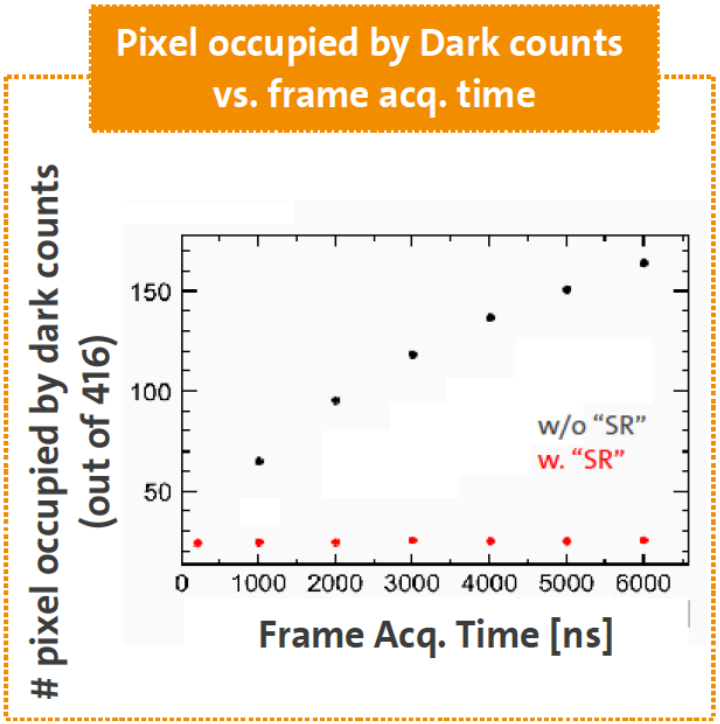


→ reachable only with sensor cooled < 20 °C

MD-SiPM - trigger validation

- "Smart Reset" (SR): Reset pixels and TDCs if there is no TDC activation burst
  - Comparing to pixel memory, number of activated TDCs can be faster read out
  - Threshold on number of activated TDCs is "energy-like"

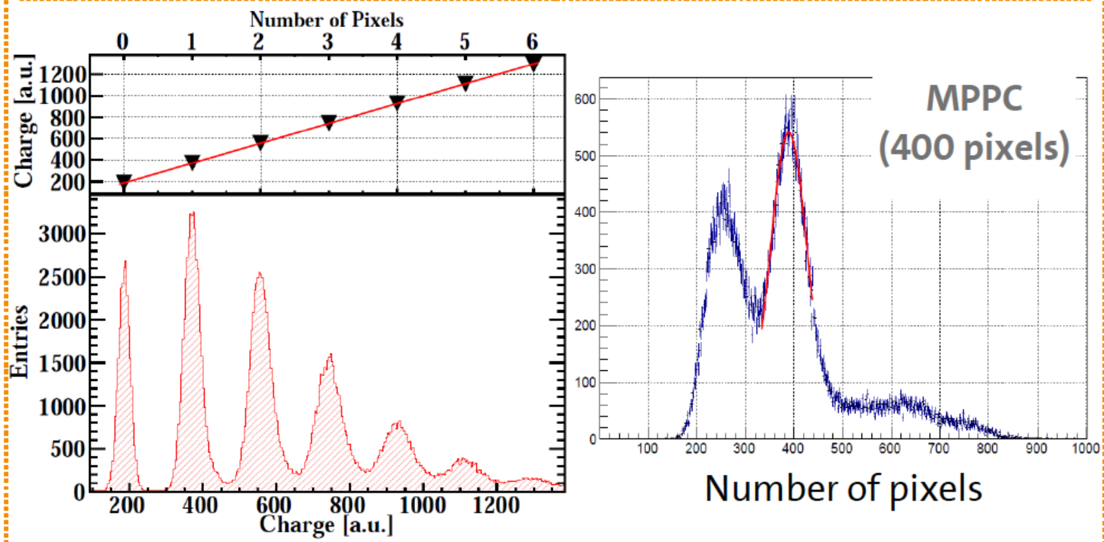




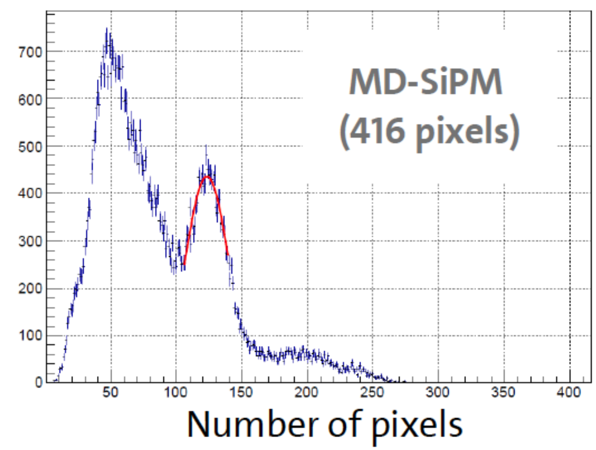
Detector response

^{22}Na source + 1x1x15 mm^3 LYSO crystal, dry contact, without wrapping

^{22}Na spectrum by MPPC (calibrated to number of fired pixels)



^{22}Na spectrum by MD-SiPM



- 1x1 mm^2 device
- Gain measurement uses blue LED light
- Energy spectrum of ^{22}Na is calibrated to number of fired pixels:

  Number of pixels = Charge/Gain

- 0.78x0.8 mm^2 device

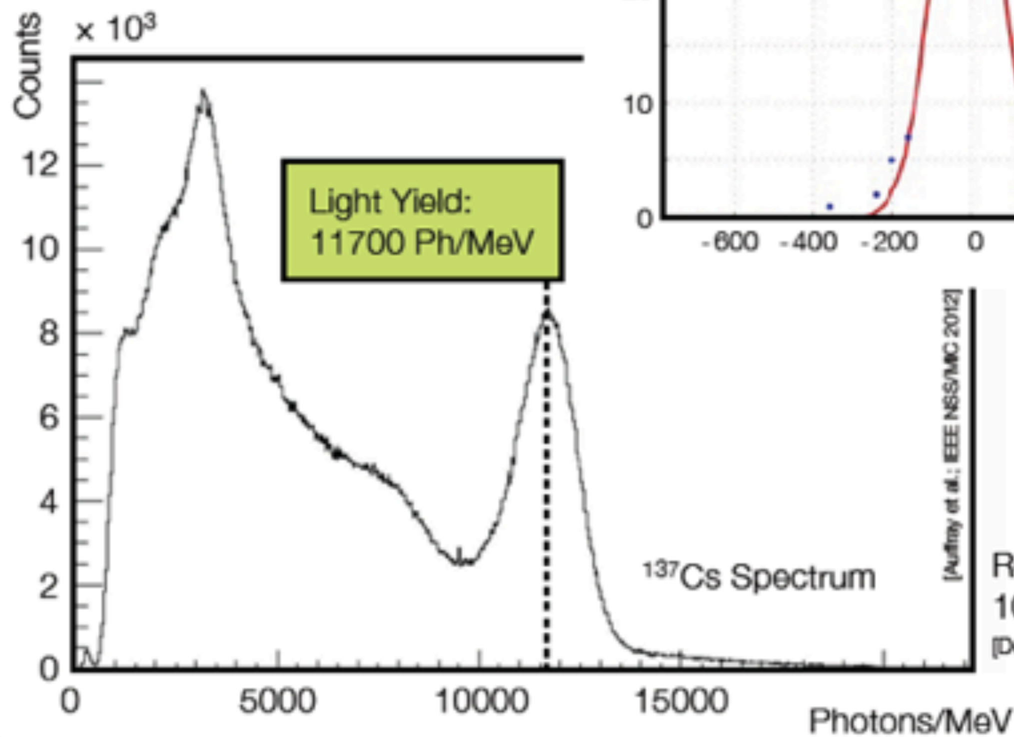
Inner PET head - Scintillator crystals

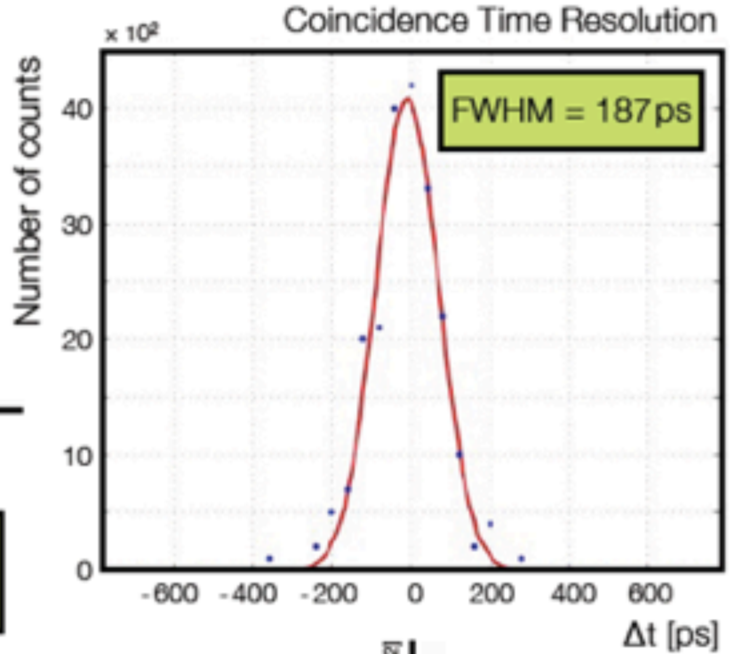
Crystal Matrix – Inner Probe

Scintillator : LYSO; ESR reflector by 3M;
Photosensor : Hamamatsu 1x1 mm² MPPC [CTR meas.]
Photonics PMT [LY meas.]
Electronics : Nino Chip + HPTDC

[Note: dry contact to photosensor]

LYSO matrix [Proteus]
9x18 crystals; each: 0.71x0.71x15 mm³





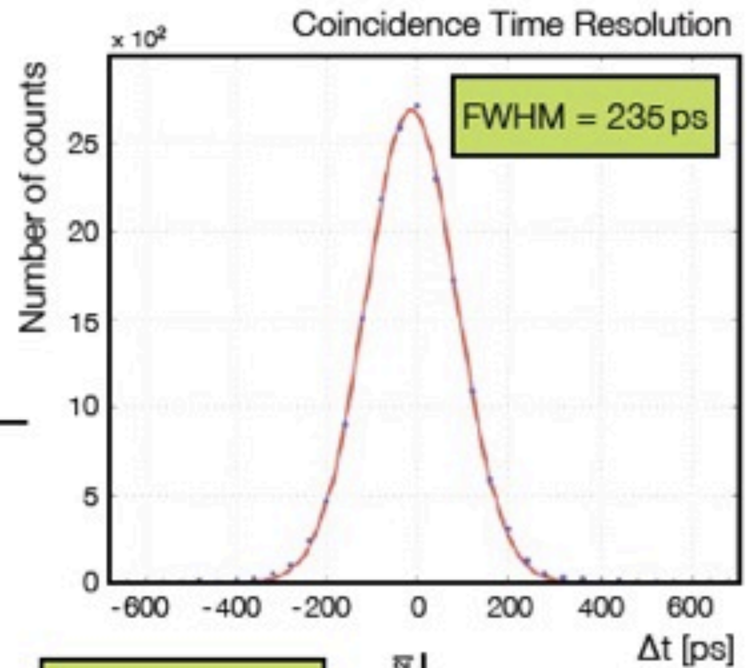
Requirement:
10000 - 15000 Ph/MeV
[Depends on SiPM properties etc.]

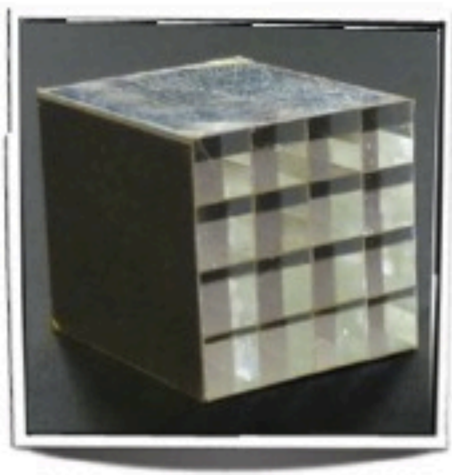
External PET plate - Scintillator crystals

Crystal Matrix – Outer Plate

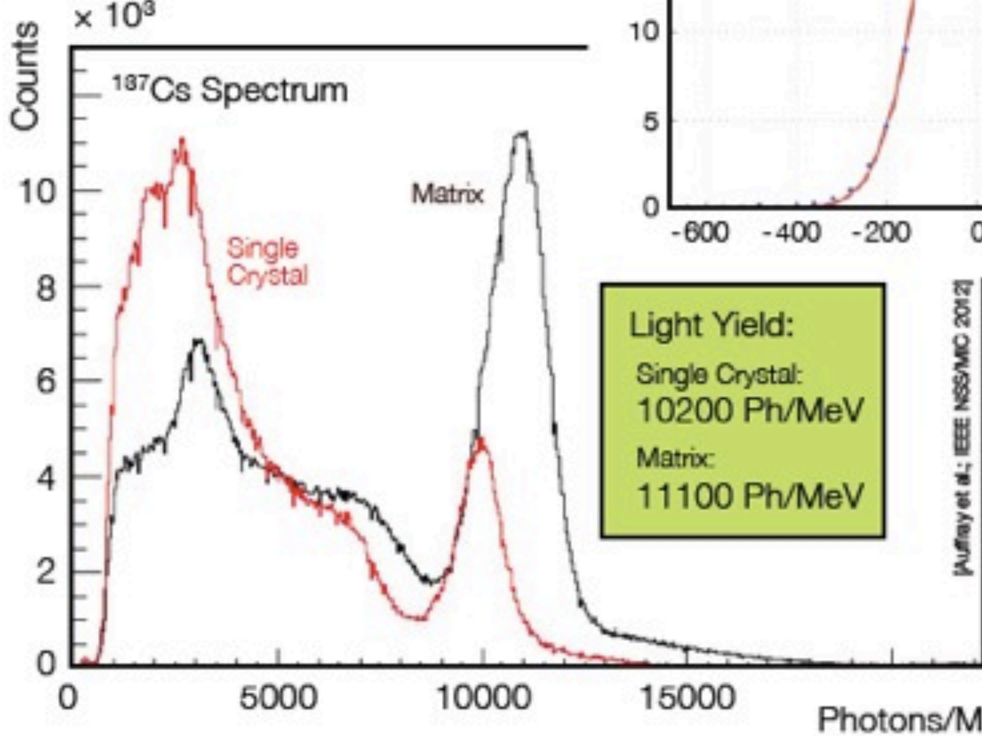
Scintillator : LYSO; ESR reflector by 3M;
Photosensor : Hamamatsu 3x3 mm² MPPC [CTR meas.]
Photonics PMT [LY meas.]
Electronics : Nino Chip + HPTDC

[Note: dry contact to photosensor]



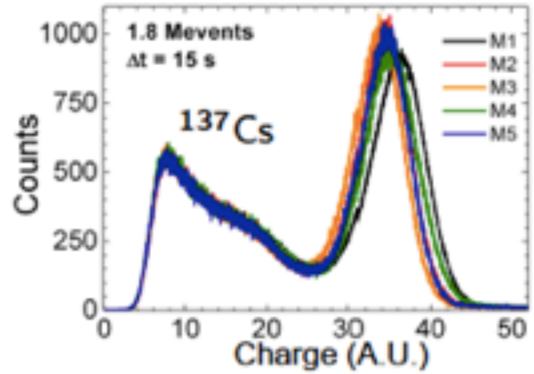


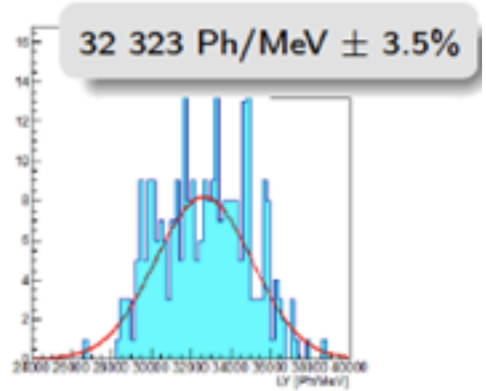
LYSO matrix
[CPI prototype]
Outer PET plate
4x4 crystals; each: 3.1 x 3.1 x 15 mm³



Requirement:
10000 - 15000 Ph/MeV
[Depends on SiPM properties etc.]

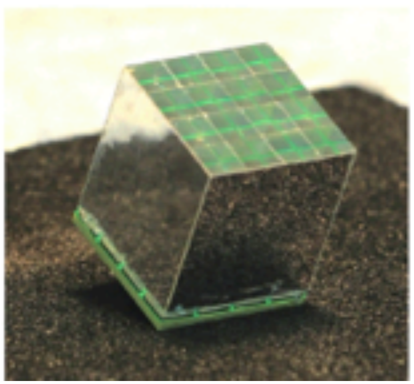
Crystal matrices - light yield & gluing





- Time resolution improves with higher light yield (LY)
- Measure LY with a photomultiplier tube (PMT); correct for air gap, glue & wrapping
- Average LY: 32 200 ph/MeV for the external plate crystal matrices
- Energy resolution $\approx 13\%$, similar for probe

- Quality assurance of gluing: I-V curves before and after gluing

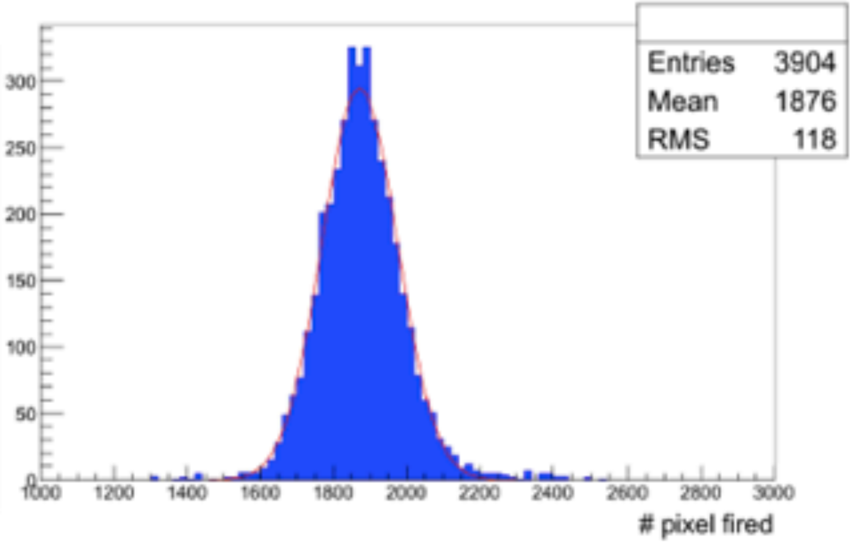


- Gluing: Automised alignment setup
- Visual inspection
- Wrapped with reflector foil + cap

Crystal + SiPM modules

Light Output

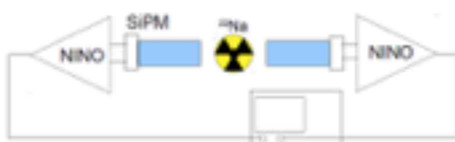
- Operate every channel at the same gain ($G = 1.25 \cdot 10^6$)
- Temperature monitoring and correction
- Mean number of fired pixels (511 keV) 1876 ± 118
- Mean spread within one module $\approx 15\%$
- Mean energy resolution (511 keV) $\approx 12.8\%$

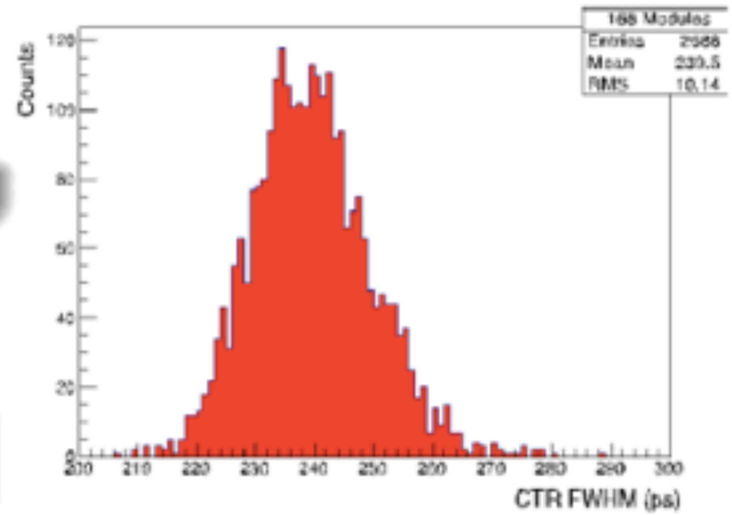


CTR coincidence time res.

- Measure all modules in coincidence with a reference module
- Time-over-threshold with ultra-fast amplifier-discriminator chip (NINO) plus TDC

$\text{CTR} = 239.5 \pm 10$ ps



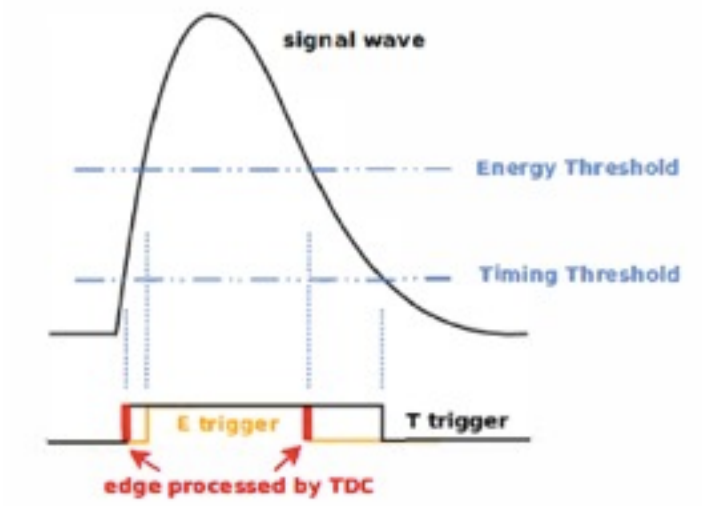


Two dedicated fast SiPM r/o ASICs

Measure time and energy information

Timing via leading-edge technique

Energy using time-over-threshold method

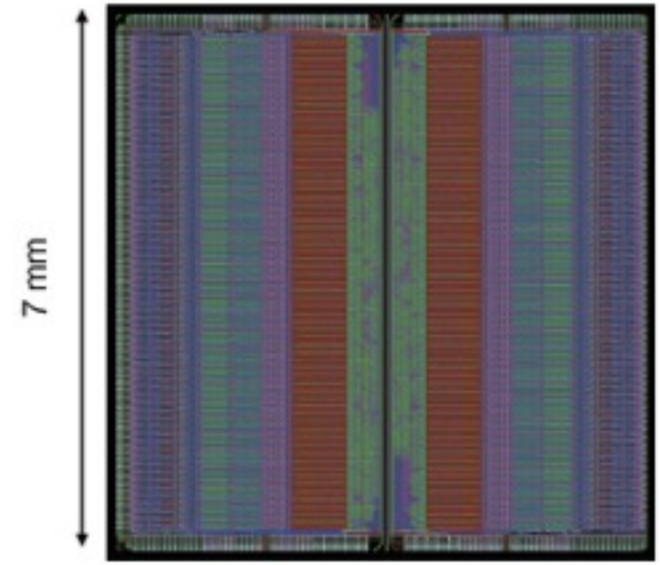


Large channel density
4000 channels within 20 x 20 cm²

Low noise, low timing jitter
Aim: smaller 30 ps ...

Low power consumption
Aim: smaller 10-20 mW/channel ...

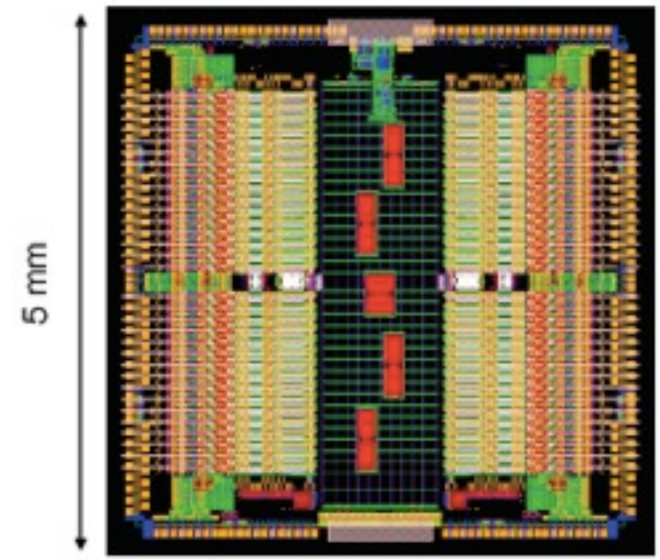
SiPM bias tuning
Adjustment range: 500 mV



ToFPET ASIC

128 channels

[LIP]

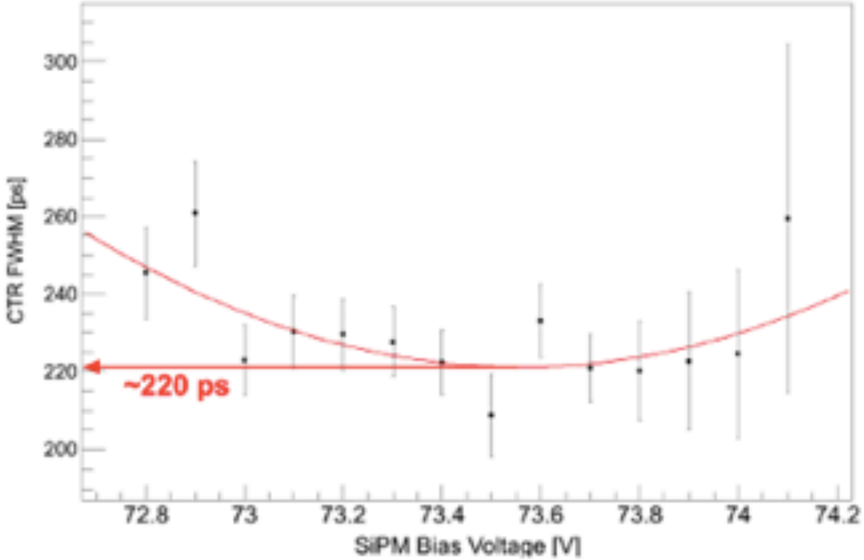


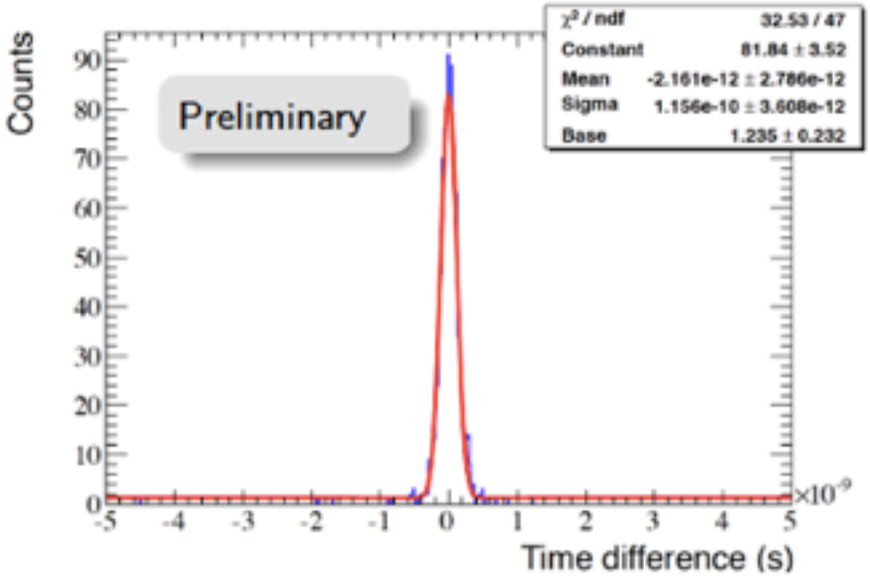
STiC 3.0 ASIC

64 channels

[KIP]

ASICs characterization





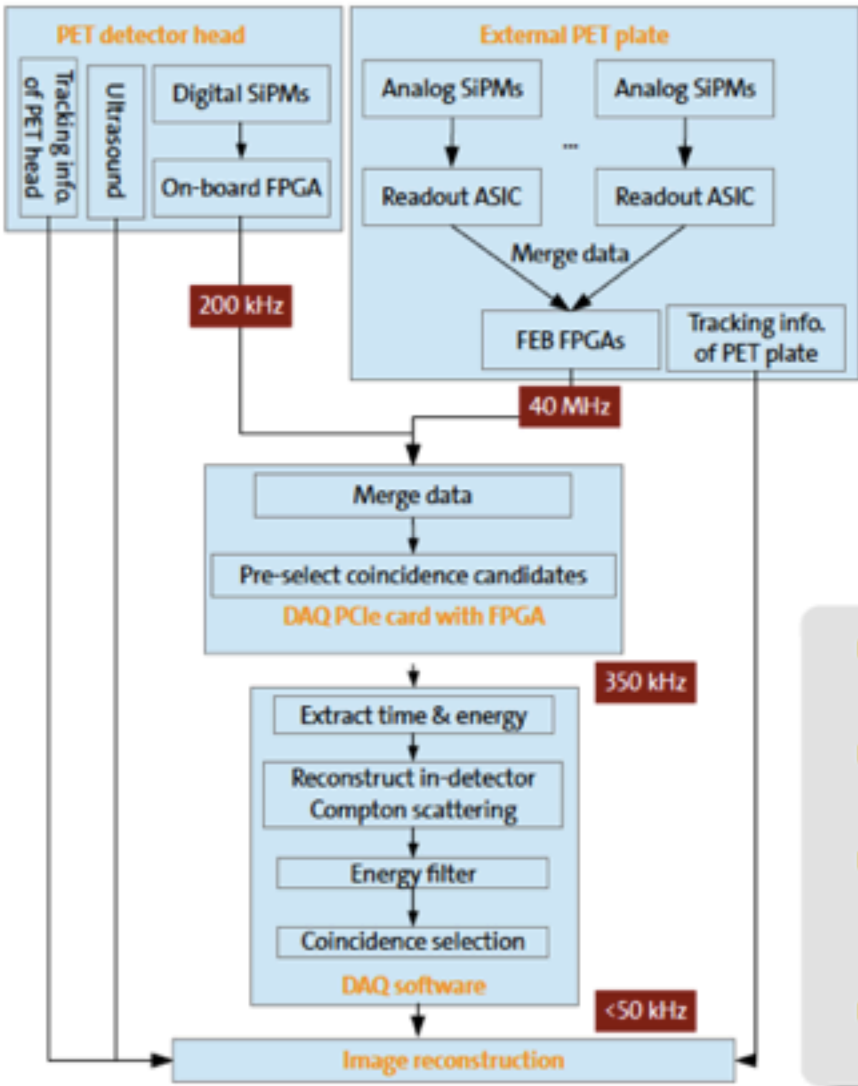
16-channel STiC Chip

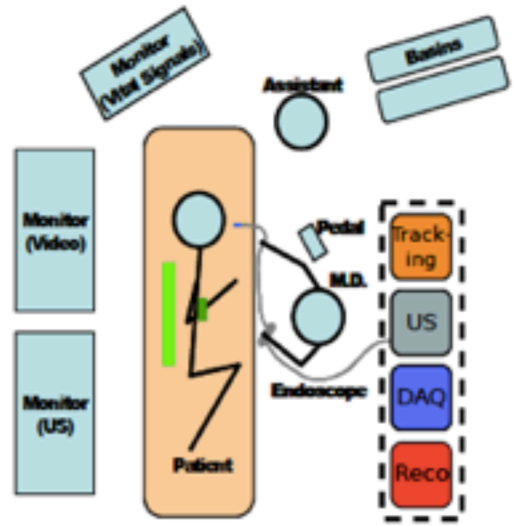
- ^{22}Na source, 3.1x3.1x15 mm LYSO crystals coupled to MPPC
- Connected to STiC chip using differential readout
- Energy resolution of 511 keV peak is $\approx 12\%$
- Measured CTR at optimal HV-settings is 220 ps FWHM
- 64 channel STiC chip delivered, tests ongoing

64-channel TOFPET Chip

- ^{22}Na source, 3.1x3.1x15 mm LYSO crystals coupled to MPPC
- Connected to TOFPET chip using single-ended readout
- Measured CTR: 270 ps FWHM (preliminary)

Data acquisition





- DAQ backend implemented in PCI-e board interfacing to DAQ PC
- Firmware to communicate with ASIC and probe developed and tested
- Medical data communication framework (control communication between multiple imaging & tracking devices)
- Graphical user interface, incl. PET/US fusion

Tracking system

External Plate

- External plate held by mechanical, lockable arm
- Tracked by optical tracking system
- Expected accuracy: $\approx$ 0.5 mm/ 0.5°

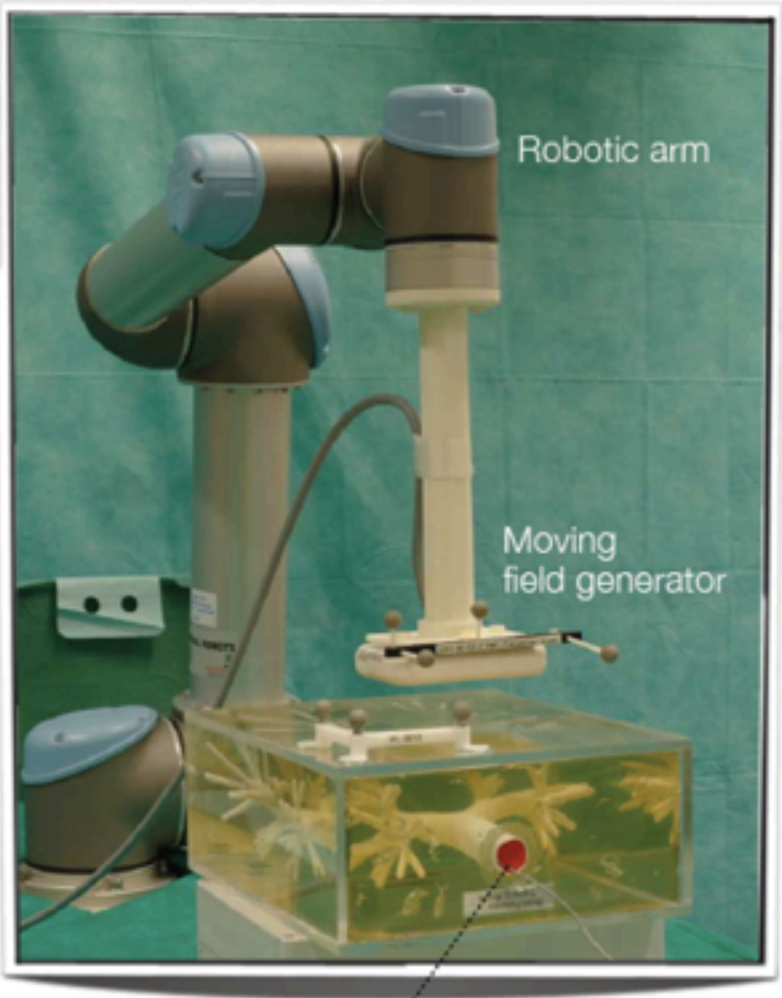
Prostatic Endoscope

- Needed tracking precision $\approx$ 1 mm
- Magnetic tracking limited to 4.1 mm / 1.46° if endoscope in movement
- Improved to 1.44 mm / 1.66° if endoscope static
- Track device optically (and mechanically?)
- Pancreas: No optical tracking possible

Tracking Precision

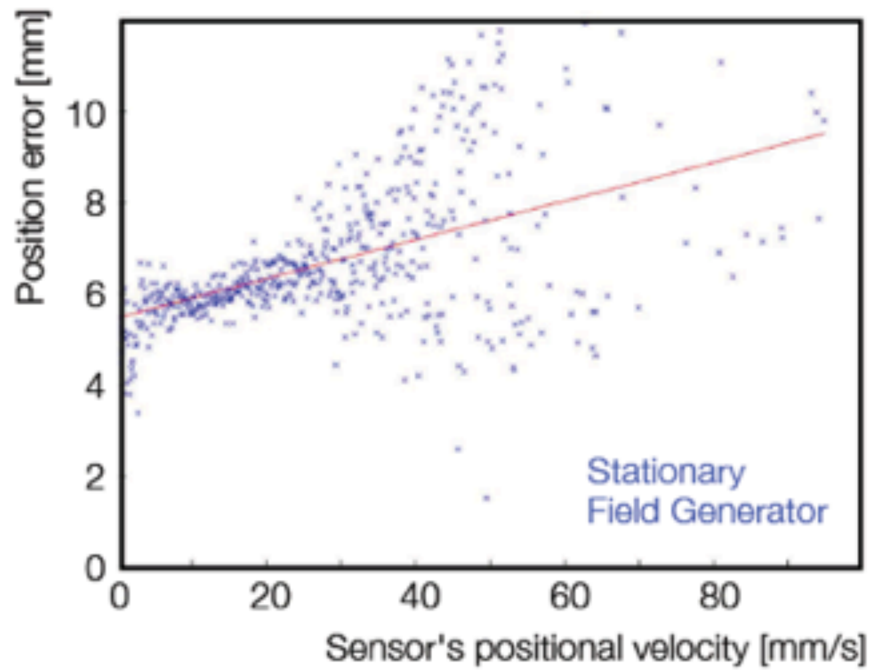
- Electromagnetic: $\approx 3 - 4$ mm
- Optical: $\approx 0.1 - 0.5$ mm
- Mechanic: $\approx 50\,\mu\text{m} - 0.1\,\text{mm}$

Electromagnetic tracking system



	Position Accuracy	Orientation Accuracy
Dynamic, stationary FG	6.64 ± 7.86 mm	2.70 ± 1.56 °
Dynamic, moving FG	3.83 ± 6.43 mm	1.34 ± 0.52 °
Static acquisition	1.55 ± 0.62 mm	1.46 ± 1.07 °

Reichl et al., IEEE 2013



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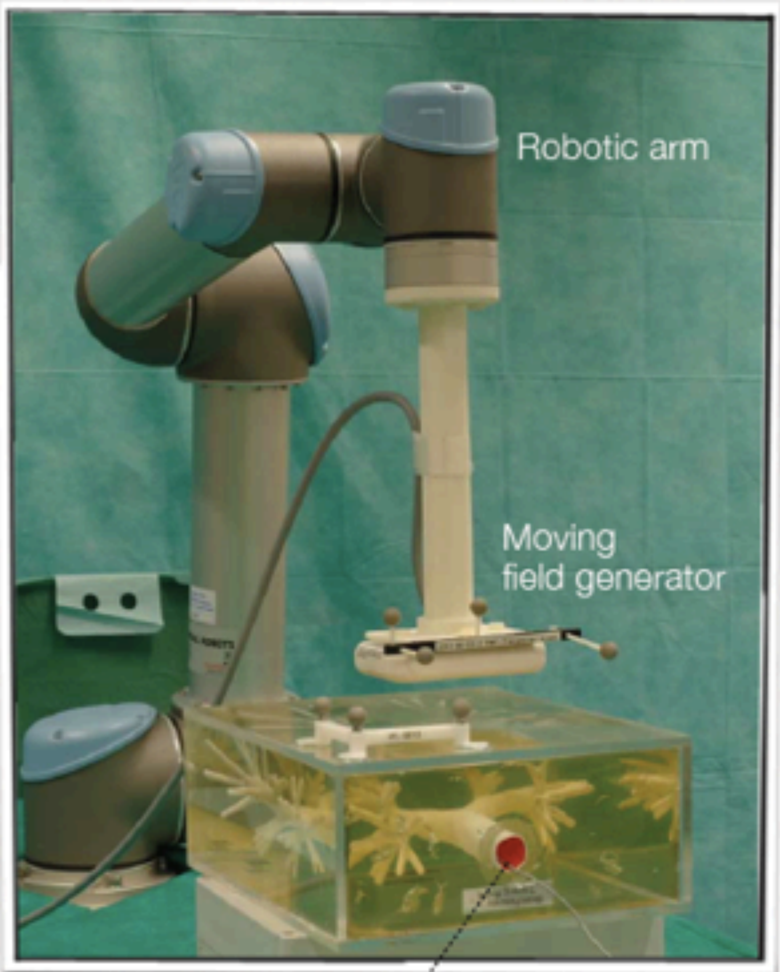
Electromagnetic tracking system



Moving sensor
[within bronchoscopy training phantom]

	Position Accuracy	Orientation Accuracy
Dynamic, stationary FG	6.64 ± 7.86 mm	2.70 ± 1.56 °
Dynamic, moving FG	3.83 ± 6.43 mm	1.34 ± 0.52 °
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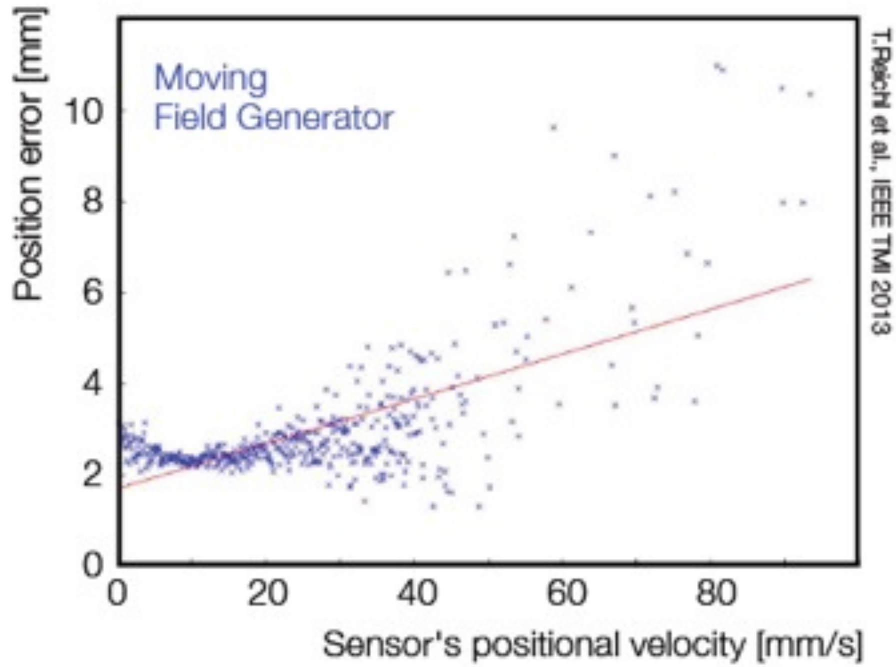
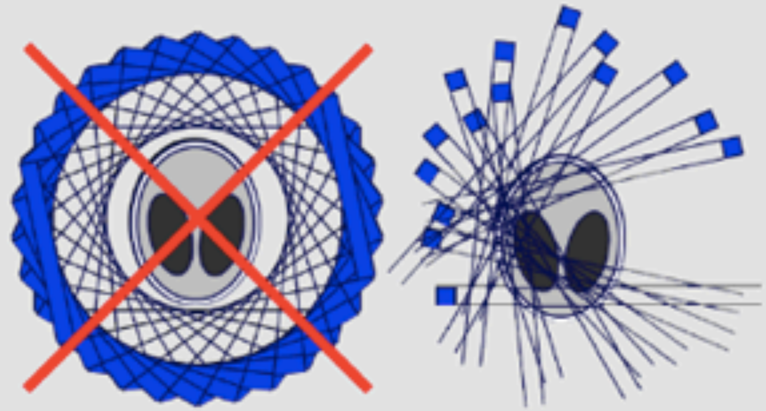


PET image reconstruction

Challenges

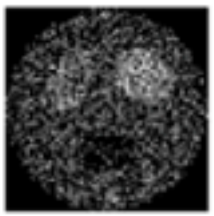
- Time of flight (TOF)
- Limited angle problem
- Freehand
  → undefined volume of interest
- Low sensitivity, high noise
- Reconstruct the image on-line to provide guidance for the physician



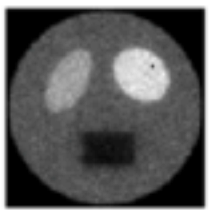
Solution

- Maximum Likelihood - Expectation Maximisation (ML-EM) iterative reconstruction: Good performance in case of Poissonian noise
- GPU Computation: Solving a massively parallel problem (4 × GTX690 à 3072 cores)

Original Image



Filtered Backprojection (ramp filter)



Maximum-Likelihood (ML-EM)

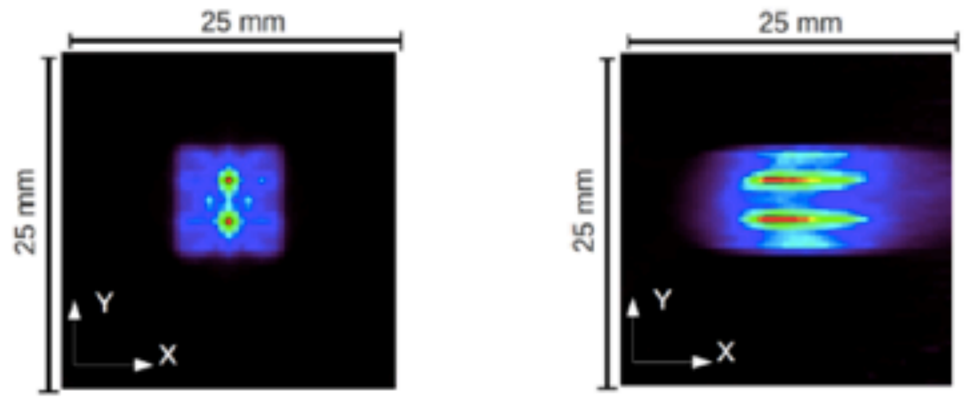
- GPU speedup by factor $\mathcal{O}(10)$
- Image reconstruction in $\mathcal{O}(\text{min.})$

Reconstructed image quality

Best image resolution under ideal conditions:

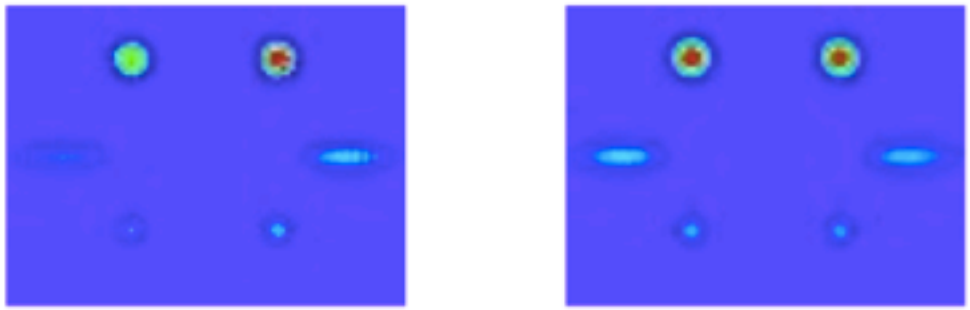
- $d = 0.5$ mm source: 0.667 ± 0.002 mm FWHM
- $d = 2$ mm source: 1.657 ± 0.064 mm FWHM

In a noisy environment with limited view, the image quality degrades



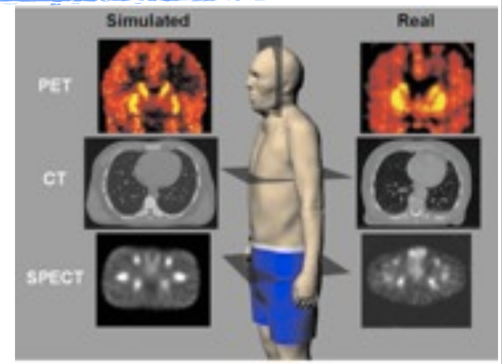
Full Rotation   Limited Rotation

Simulation of sphere and elipsoid sources
Left half in water, right half in vacuum



No attenuation/scatter modelling   With attenuation/scatter modelling

Full body simulation with GAMOS



Geant4-based Architecture for Medical-Oriented Simulation

- Allows asymmetric detectors → use in-built coincidence sorter
- Possibility to import whole body phantom (i.e. visible human)

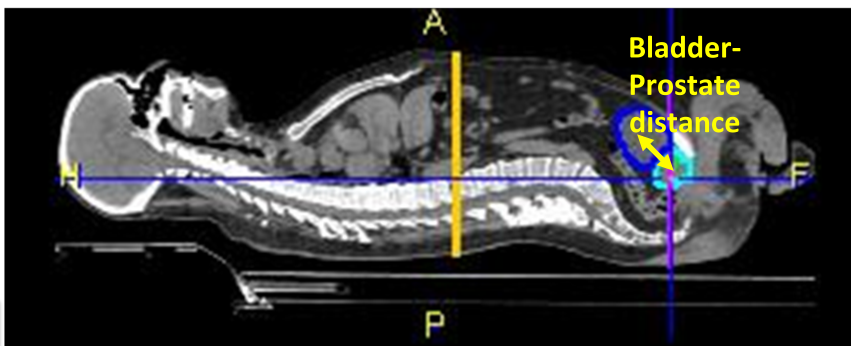
- Ability to tune all parameters according to patient data

Number Patient Examination Date0	Patient 1 27.10.2011	Patient 4 17.03.2010
Prostate Volume	96 ml	75 ml
Bladder Volume	232 ml	121 ml
Thickness of Pelvis Bone (at the prostate level)	2.3 cm	2.4 cm
Uptake Prostate (average)	1.9 kBq/ml	1.9 kBq/ml
Uptake Bladder (average)	1.4 KBq/ml	1 kBq/ml
Uptake of prostatic lesions (average)	3.3 kBq/ml	6.7 kBq/ml
Volume of prostatic lesions	8.5 ml	3.4 ml

Signal / Background ~ 1/10 – 1/20

- Anonymous databank of measured prostate lesions from CHUV, Lausanne

- Possibility to import directly clinical data from PET/CT



What about the bio-markers?

Aix Marseille université

The goals:

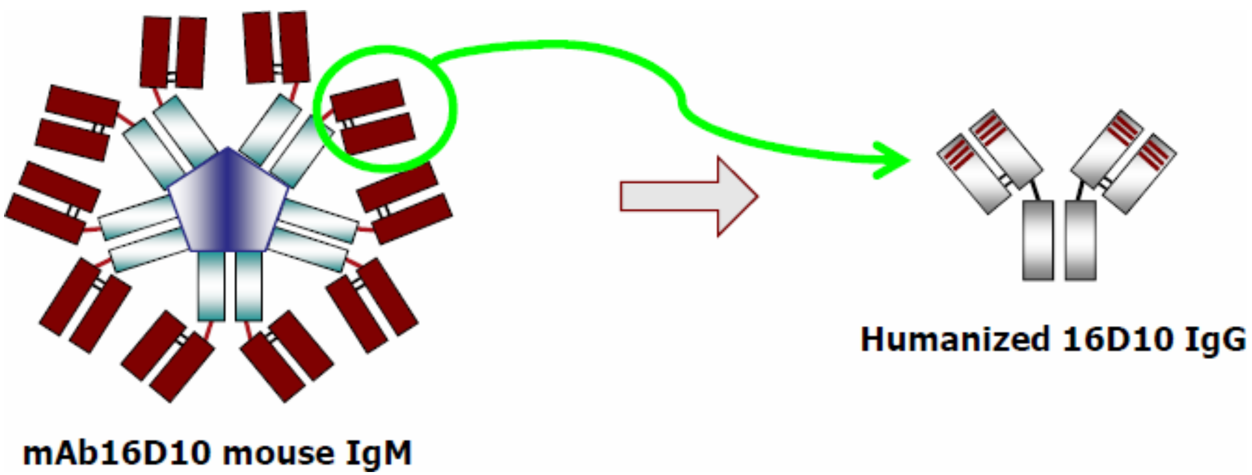
1) development of biomarkers for prostate and pancreas tumor

New Biomarker for Pancreatic Cancer: mAb16D10

developed within the project objectives

- Recognition of human pancreatic tumoral cells and tissues
- Therapeutic properties
- Diagnostic properties

→ Development of new humanized 16D10 IgG forms of mAb16D10



What about the bio-markers?

The goals:

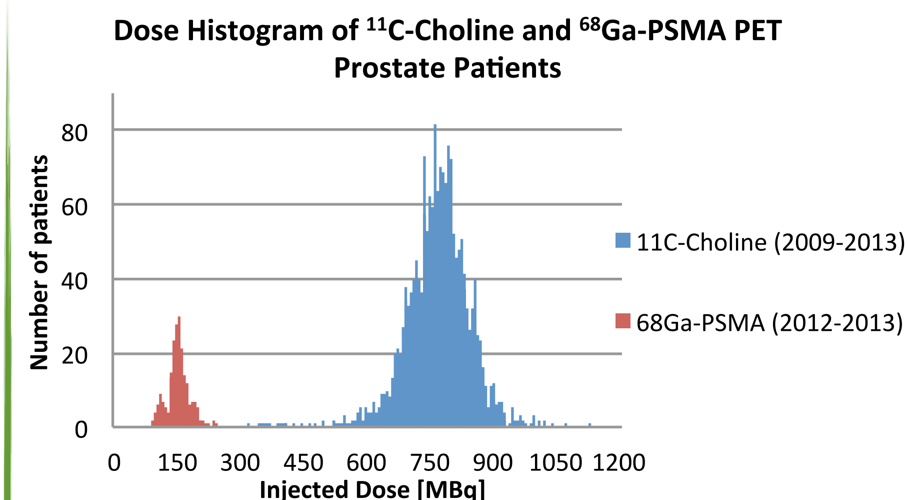
1) development of biomarkers for prostate and pancreas tumor

New Radiotracer for Prostate Carcinoma: ^{68}Ga-PSMA

From [1]:

- 37 patients with PCa biochemical recurrence
- ^{18}F-fluoromethylcholine (CHO) and ^{68}G-PSMA PET/CT
- detection rates 70.3% (CHO) and 86.5% (PSMA)

~360 patients scanned at TUM in 12/2013

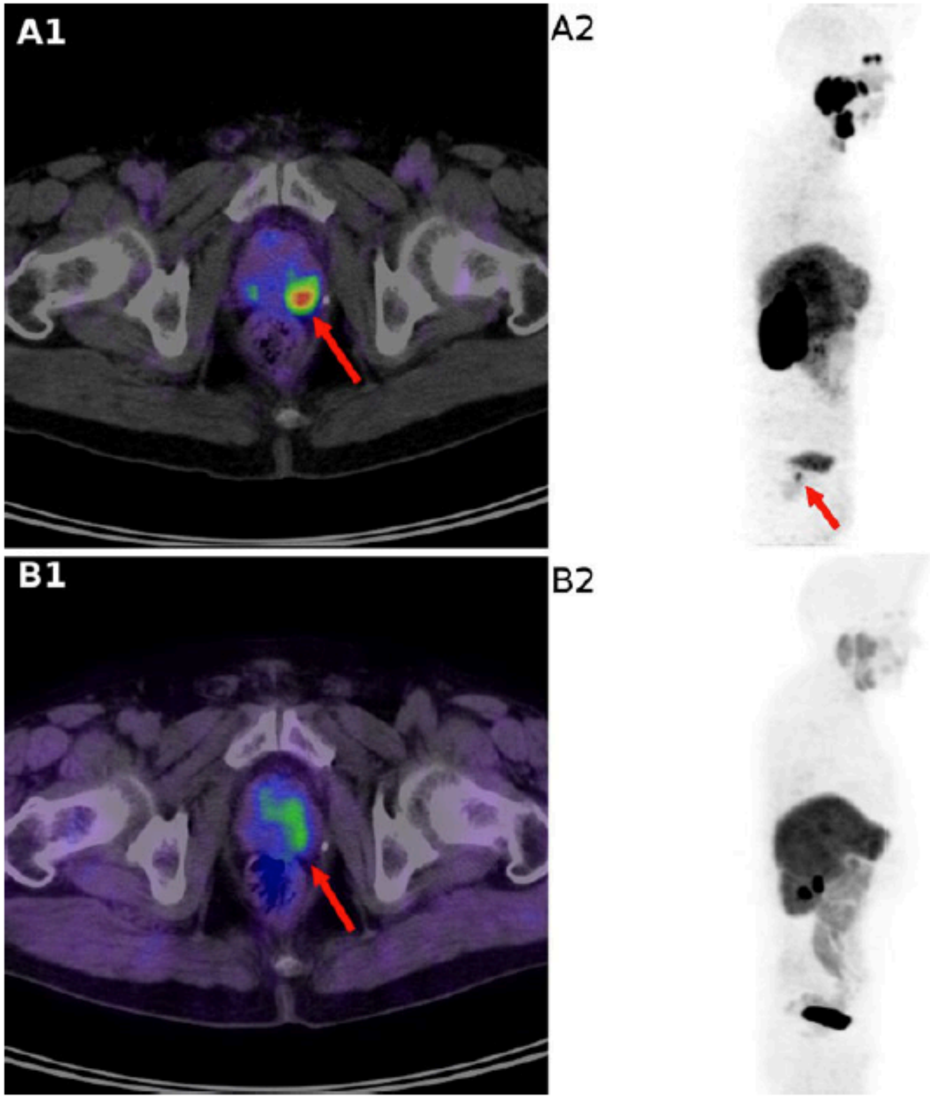


- PSMA performs better at low PSA values
- Higher uptake by PCa lesions
- Low background signal
- Improved detection of metastasis
- Detection of small lymph nodes

^{68}Ga: generator produced, half-life 68 min

[1] Afshar-Oromieh A., Haberkorn U., et al., “Comparison of PET imaging with a ^{68}Ga-labelled PSMA ligand and ^{18}F-choline-based PET/CT for the diagnosis of recurrent prostate cancer”. EJNMMI 2014; 41:11—20

^{68}Ga-PSMA PET/CT in prostate cancer



^{68}Ga-PSMA PET/CT

67-year-old patient
RT + hormonal treatment
Increasing of PSA
(2002:1, 2011: 7.4)

^{68}F-FCH PET/CT

Conclusions

EndoTOFPET-US ...

... a novel multimodal endoscopic ToFPET/US imaging system
for improved prostate and pancreas tumor diagnostics

... requires frontline research concerning

Novel Photosensors
Ultra-fast readout electronics
Scintillating crystals & optical systems
Tracking and image reconstruction
Biomarkers

... entails knowledge transfer between HEP and medicine ...

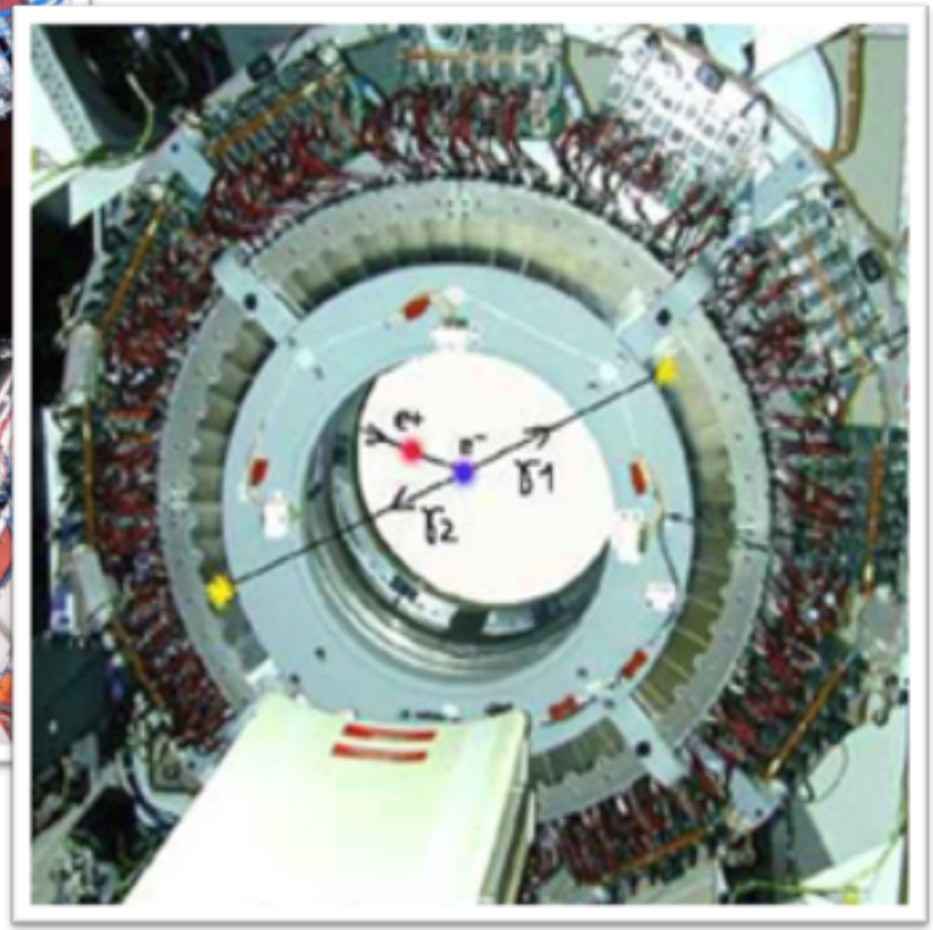
Time Schedule:

Originally, pre-clinical trials to be started in January 2014
Current status:

System Integration: Spring 2014
System Commissioning/Validation: Summer 2014
Delivery to medical hospital: Autumn/End 2014

THANK YOU FOR YOUR ATTENTION !

PET calorimeter system
(a laying human fits into the detector bore)



CMS calorimeter system at LHC (CERN)
(the humans are not part of the experiment)

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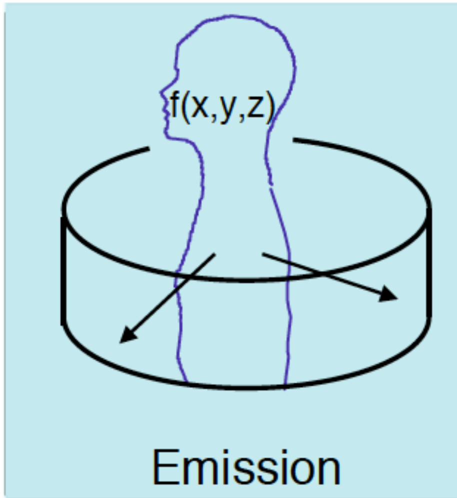
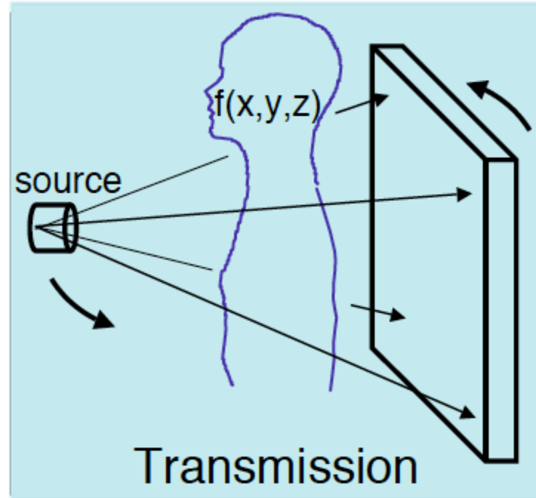
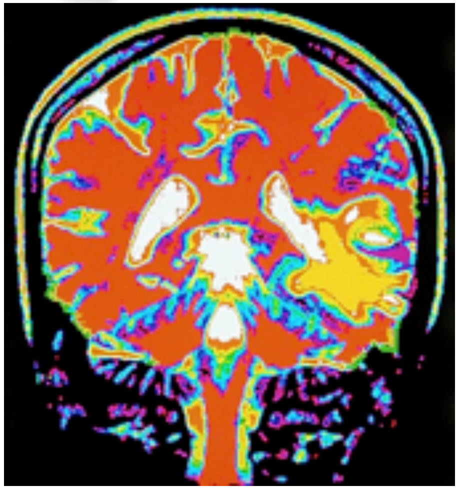
Look inside the human body



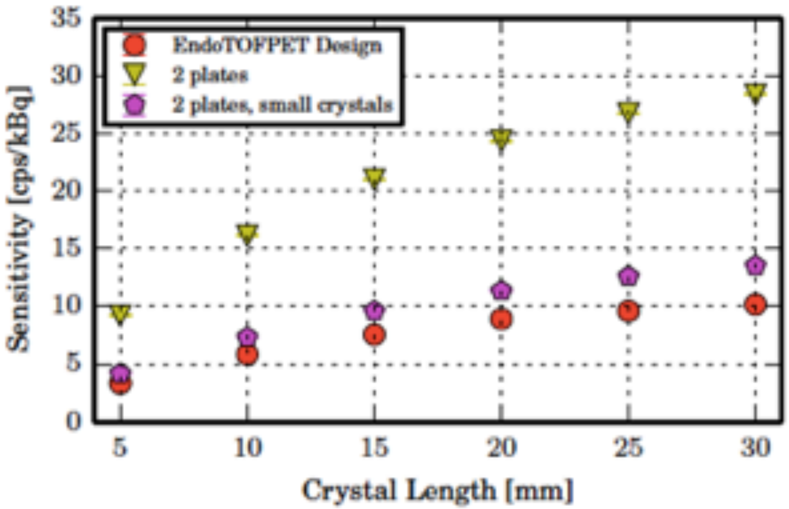


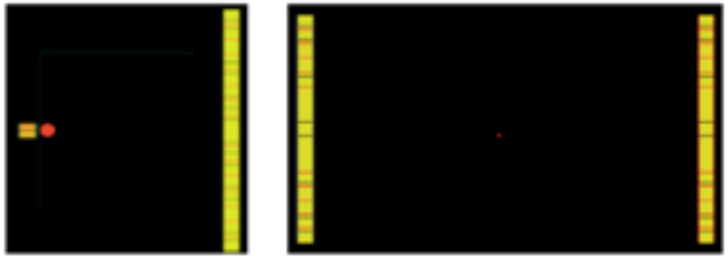
functional image



anatomical image

Project motivation





Asymmetric crystal segmentation: Granularity of internal probe is crucial

	Image resolution [mm]		Sensitivity [cps/kBq] (rounded)
	w/o DOI	w/ DOI	
EndoTOFPET	1.84 ± 0.003	1.84 ± 0.003	7
2 plates	2.80 ± 0.05	2.23 ± 0.04	21

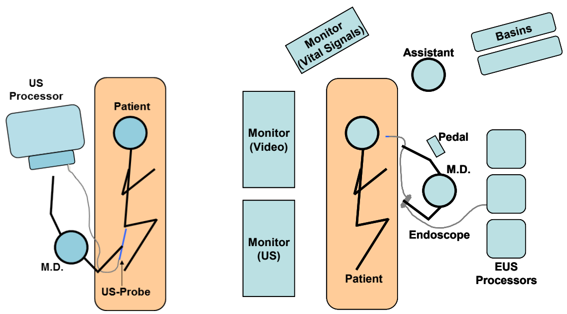
Advantages of endoscopic approach:

- High spatial image resolution
- Double-sided readout not needed (depth-of interaction (DOI))
- Freehand → interventional imaging (Intra-operative)
- Sensitivity not key issue

Radiation safety: personnel exposure (Indico → WP6)

- International Commission on Radiological Protection (ICRP):
    - 20 mSv effective dose / calendar year (avg. over 5 years)
    - Shouldn't exceed 50 mSv in any single year

- Previous studies: occupational exposure during radioguided surgeries ▪ 10 ^{18}F-FDG radioguided surgical procedures
    - Surgeon at D = 0.3 to 0.6 m from patient
    - Mean Surgeon exposure: 61±57 (6-261) µSv/h [1]
    - → Operator of EndoTOFPET-US device could perform a large number of interventions per year



Prostate US   Pancreas EUS

- People involved in trials at CERIMED will be monitored!

[6] S. Povoski, et al., "Comprehensive evaluation of occupational radiation exposure to intraoperative and perioperative personnel from 18F-FDG radioguided surgical procedures". EJNMMI 2008; 35:2026-2034