Medical applications of SiPMs

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IRIS group **http://ific.uv.es/iris**

SENSE Detector School

Ringberg Castle, Tegernsee, 19-22 June 2019

Outline

- Detectors in medical imaging.
- Overview of status, trends and some recent developments in detectors for nuclear imaging, with emphasis in SiPMs.
  - Single photon imaging / SPECT / Compton imaging.
  - Positron Emission Tomography (PET).
- Detectors for therapy.
- (Bioluminescence imaging).
- (Cherenkov imaging).

Detectors

Diagnostics	X-rays	Films, a-selenium+TFT, scintillator+ TFT/CCD
	Single photon emission	Scintillator + photodetector. Other: CZT
	Positron emission	Experimental: plastic scintillators, silicon, CdTe, LXe, LAr, gaseous,
	Optical imaging	CCDs, PMTs, SiPMs.
Therapy control	Dosimetry in radiotherapy	Ionization chambers, thermoluminescence dosimeters, films, gel, MOSFET, diamond, scintillator.
	Beam monitoring	Ionization chambers
	Treatment monitoring	*Radiotherapy:* EPID: Ionization chambers, fluoroscopic screens, semiconductor arrays *Hadron therapy:* PET, Collimated cameras, Compton cameras, other.

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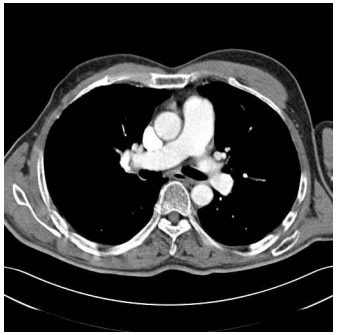
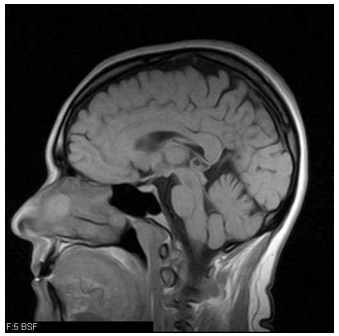
Medical imaging modalities

Structural

X-rays/ CT



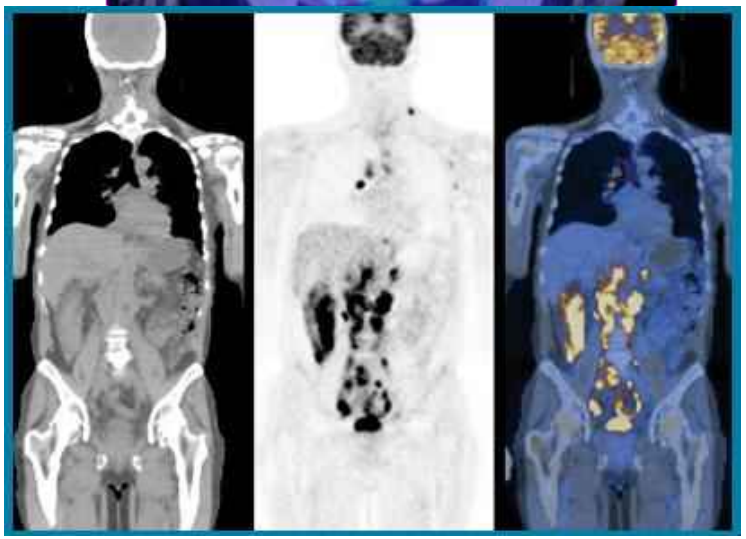
MRI



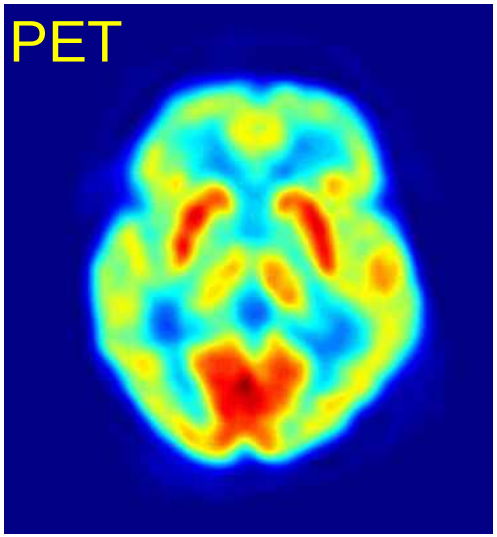
Ultrasound

Multimodality

PET-CT



Functional



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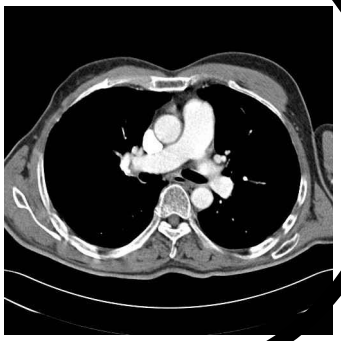
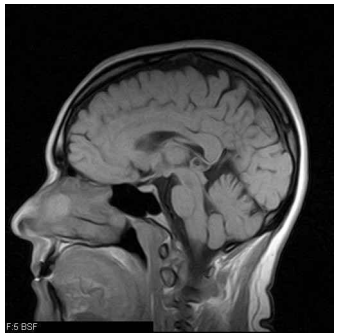


MRI



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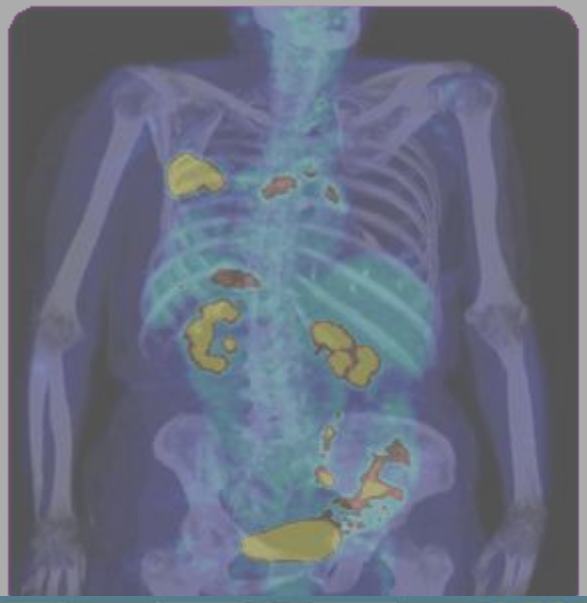
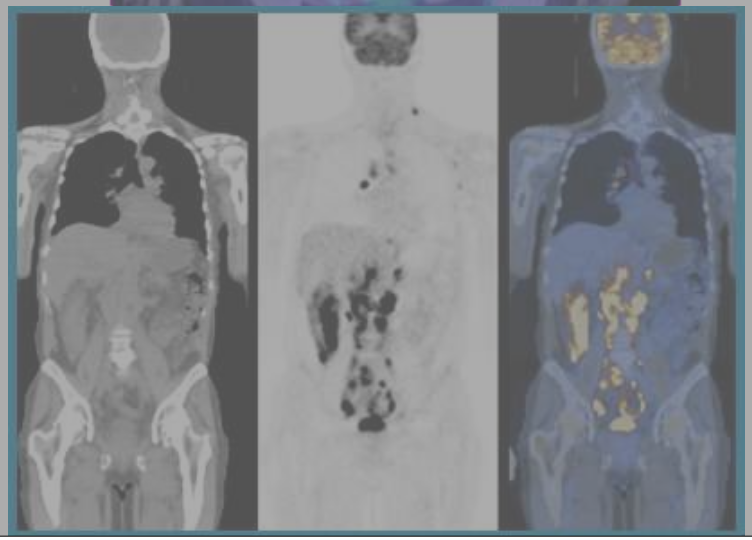
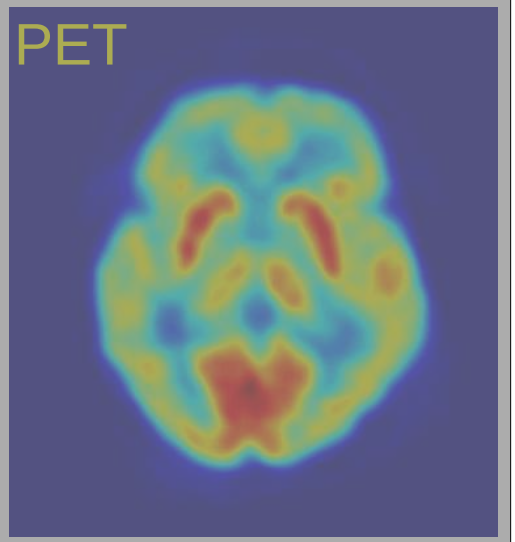




Functional

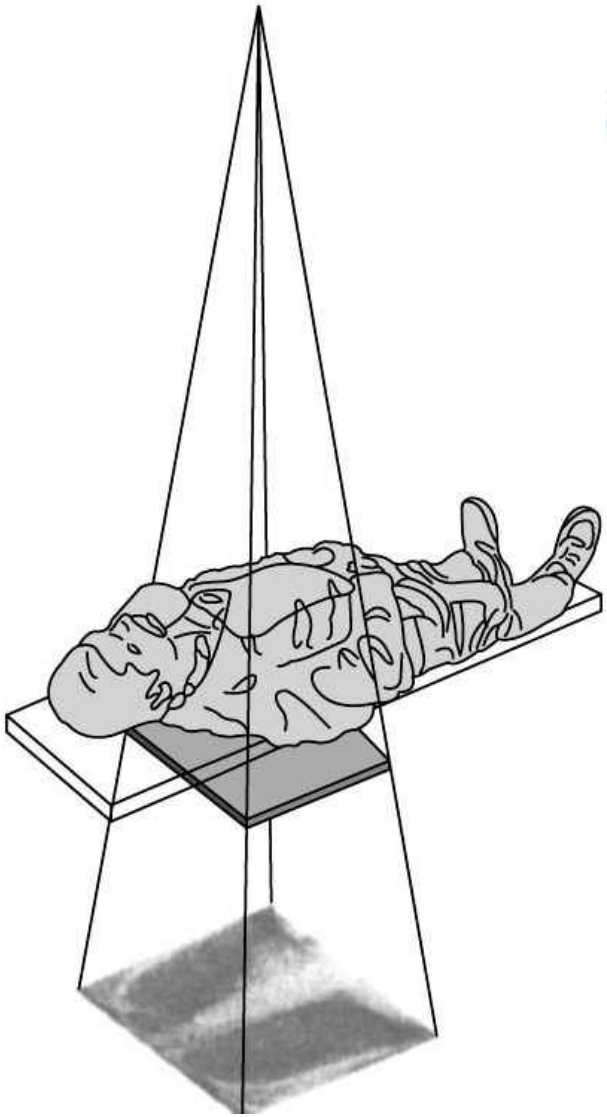
PET

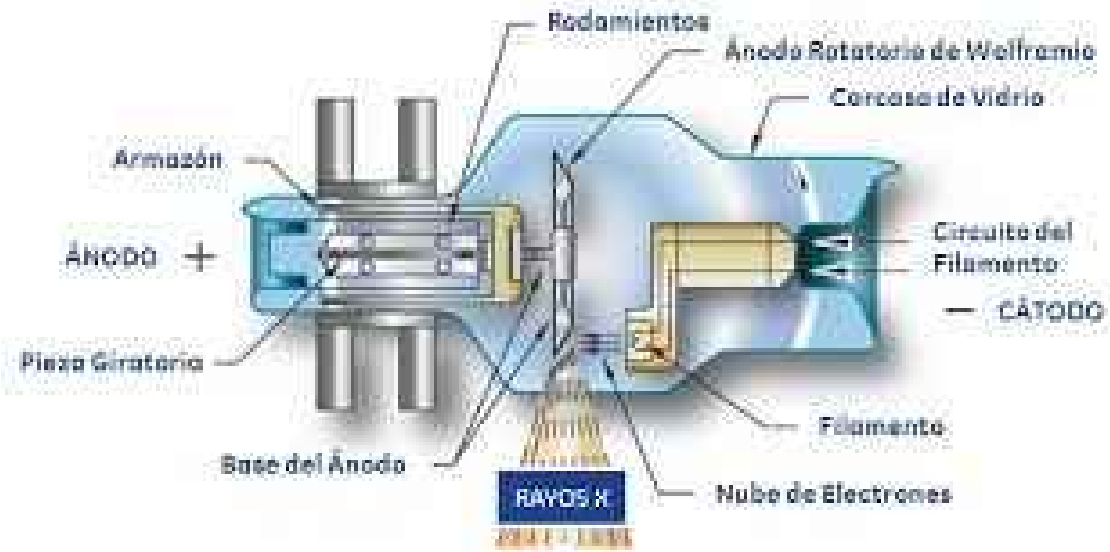


SPECT

X-rays

X-ray generator





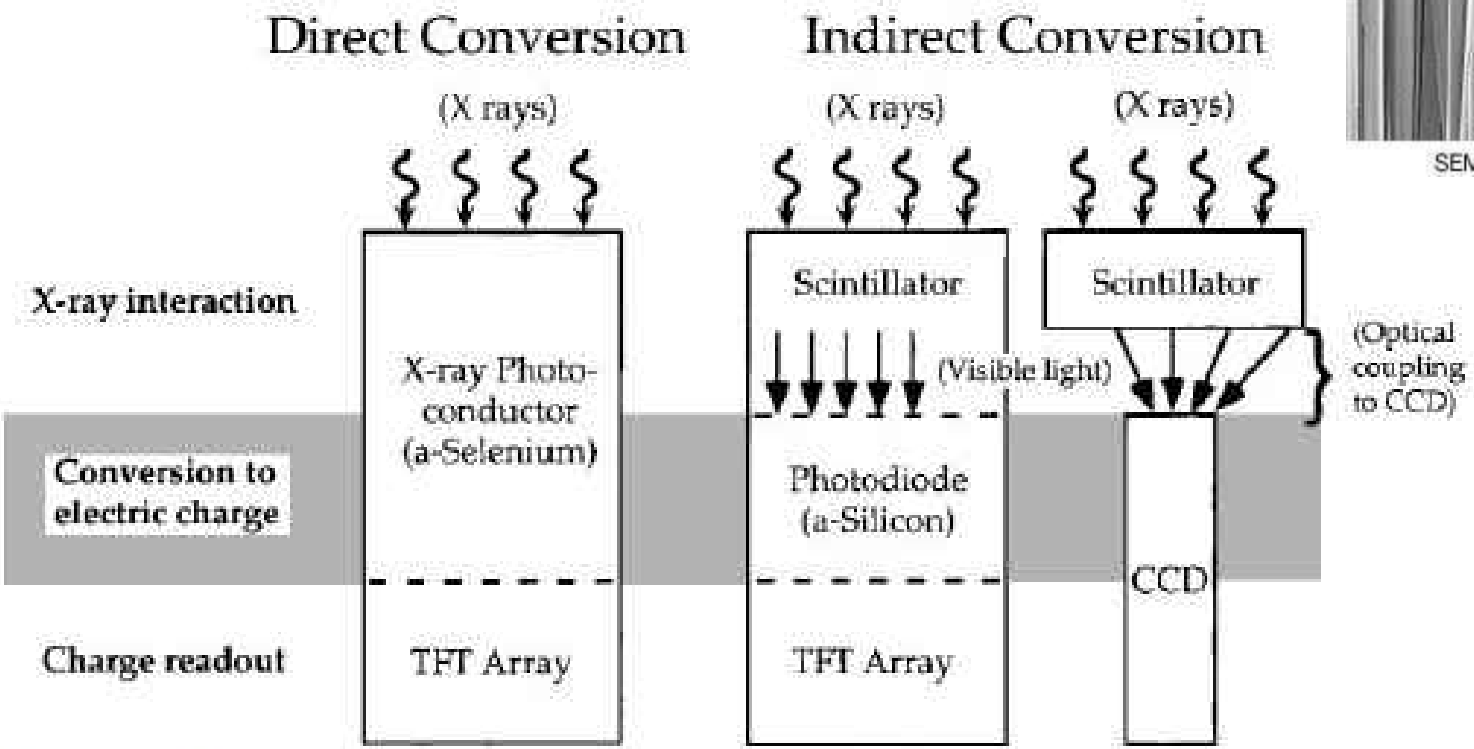
Detector

- Film still used in radiography.
- Digital: flat panel.

X-rays

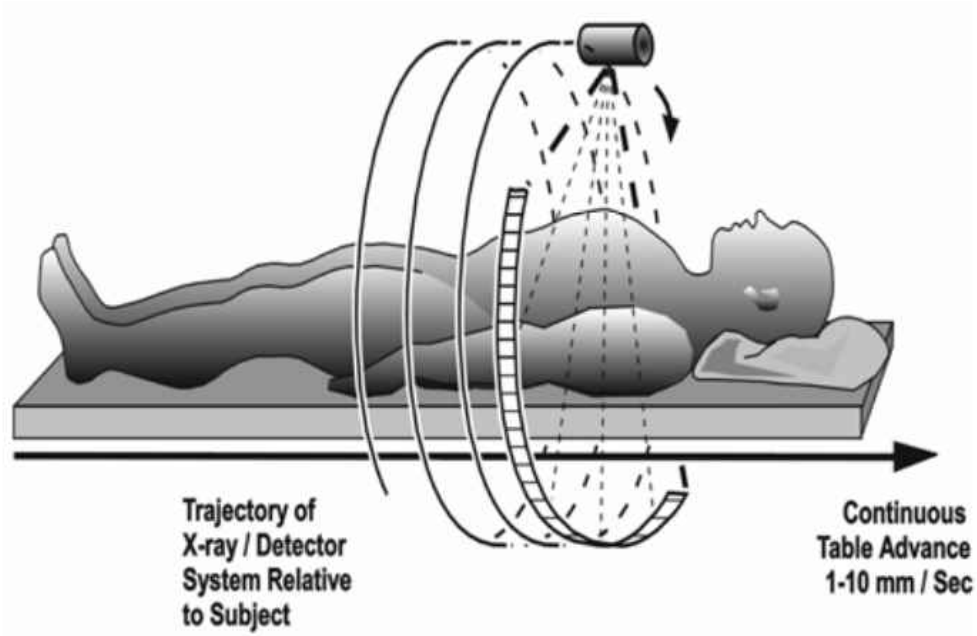
- Flat panel: Better efficiency, high resolution, low noise, large dynamic range and fast processing.
  - scint+photodetector: CsI,Gd_2O_2S + aSi-TFT or CCD.
  - Direct semiconductor: a-Selenium.

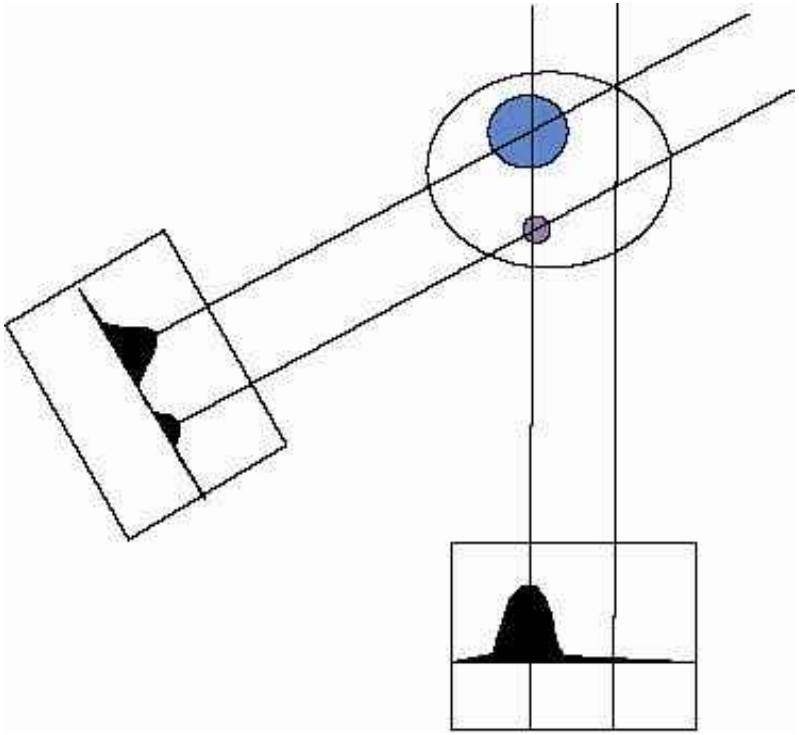
SEM image of CsI crystals

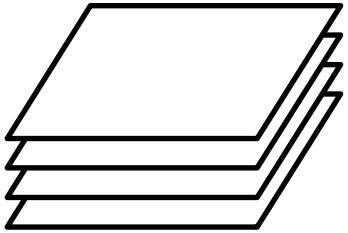


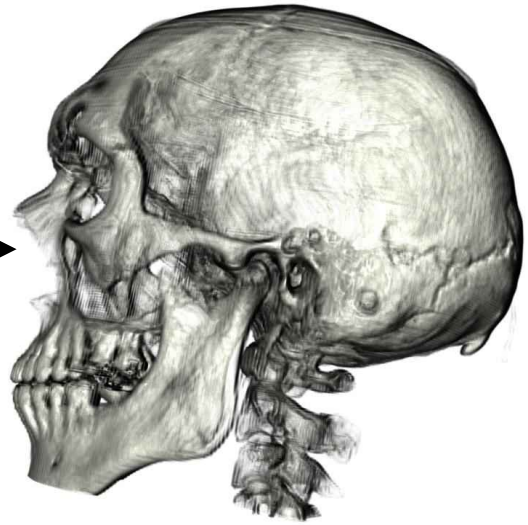
X-rays

Computed Tomography









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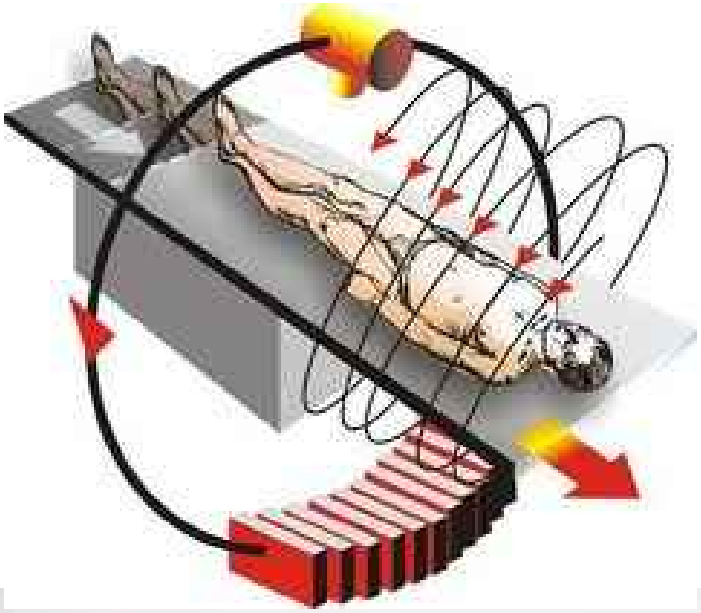

Medical imaging modalities

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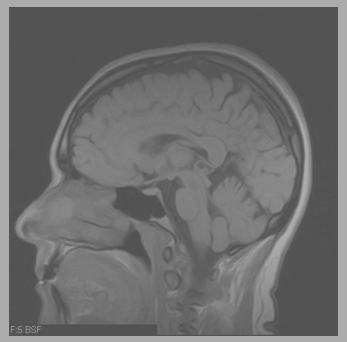
X-rays/ CT

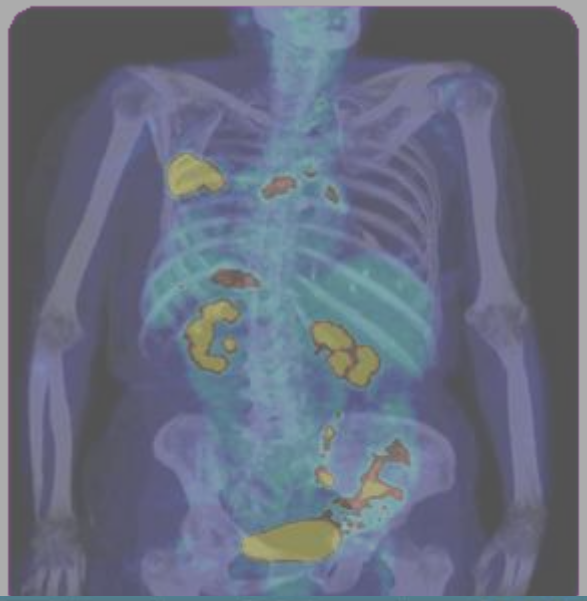
MRI

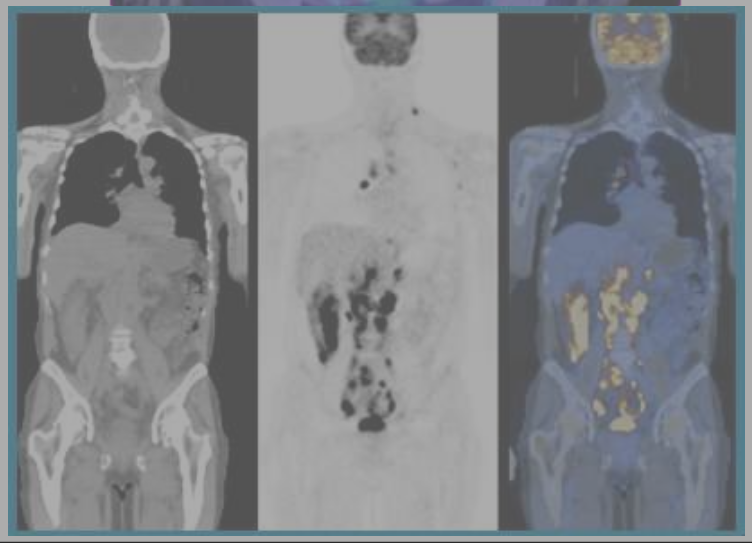


Ultrasound

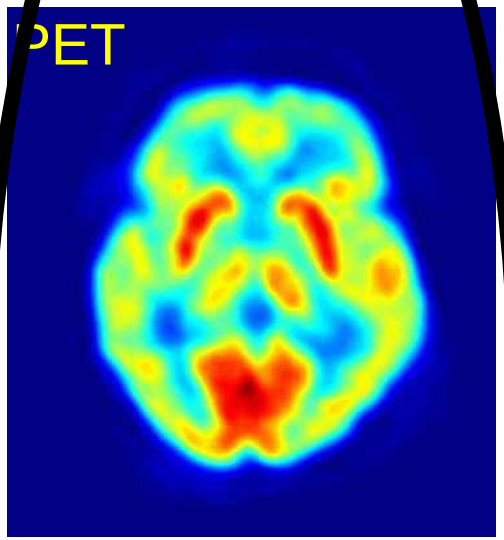
Multimodality

PET-CT



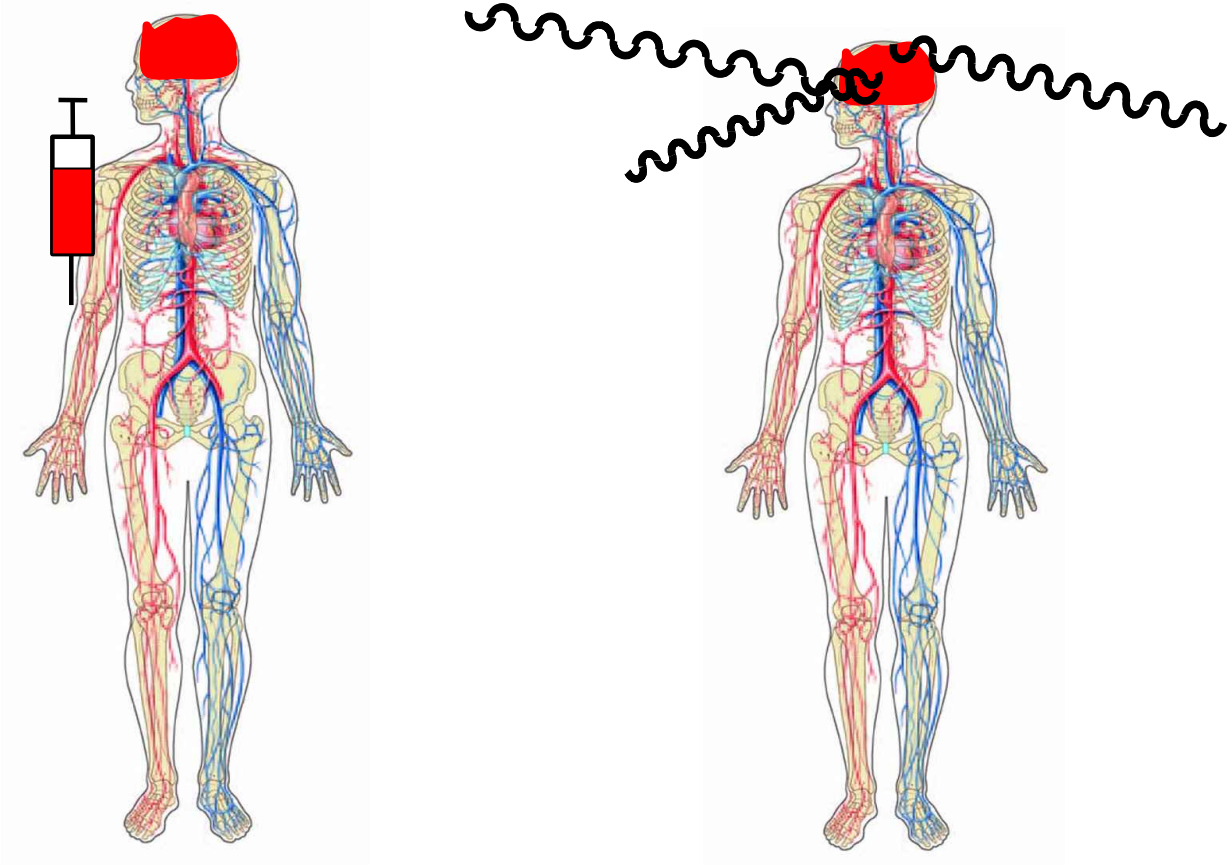


Functional



Nuclear medicine

- A radiotracer is administered to the patient, prepared to accumulate in the organ we want to image.
- It is labeled with a radioactive component that decays emitting different types of particles.
- Photons travel to the outside of the body and are detected in the scanner.



Nuclear medicine

- Isotopes with energies between 80-511 keV.
  - They can escape the body with low interaction.
  - Detectors have high efficiency at such energies.
- Detector requisites:
  - High detection efficiency (photoabsorption).
  - High energy resolution = > scatter rejection.
- Anger: first gamma camera in 1953.
  - First version with film
  - Short after with PMT
  - Still in use:
    - Good image quality
    - Good efficiency
    - Low cost

Detectors in nuclear medicine

- Scintillators + photodetectors in nuclear medicine:
  - Very good performance at affordable cost. Easy to use.
  - Dominate the market, in particular for clinical devices.
  - Improved performance with SiPMs, compact, cost effective =>

UNBEATABLE

https://www.siemens-healthineers.com/molecular-imaging/pet-ct/biograph-vision#TECHNICAL_DETAILS

Siemens Biograph Vision™ PET/CT

Detectors for nuclear medicine

- APDs (small animal PET: MADPET, LABPET, clinical).
- Solid state detectors: CZT, CdTe → Dedicated systems
  - Excellent performance in some aspects (efficiency, energy and spatial resolution), at high cost.
  - Still not perfect uniformity. Worse timing resolution.
  - Small detectors: portable cameras, small animal.
- Gaseous (liquid) detectors:
  - Lower efficiency. Timing?
  - Low cost. Good for large areas (total body)?
  - Difficult segmentation for very high resolution.

The Triumph™ Trimodality, fully integrated SPECT/PET/CT

SPECT-CZT
PET-LYSO

Scintillator crystals

	NaI(Tl)	CsI(Tl)	BGO	LSO(Ce)	LYSO(Ce)	LaBr3(Ce)
Effective atomic number (Zeff).	51	52	74	66	60	47
Linear att. Coef. (cm-1)	0.34	0.5	0.92	0.87	0.86	0.47
Density (g cm-3)	3.67	4.51	7.13	7.4	7.1	5.3
Light yield (photons keV^{-1} / %NaI)	44/100	56/127	8.2/25	27/75	34/80	70/160
Peak wavelength (nm)	410	530	480	420	420	370
Decay constant (ns)	230	600	300	40	41	25
Hygroscopic	Yes	No/slightly	No	No	No	Yes

Single photon imaging

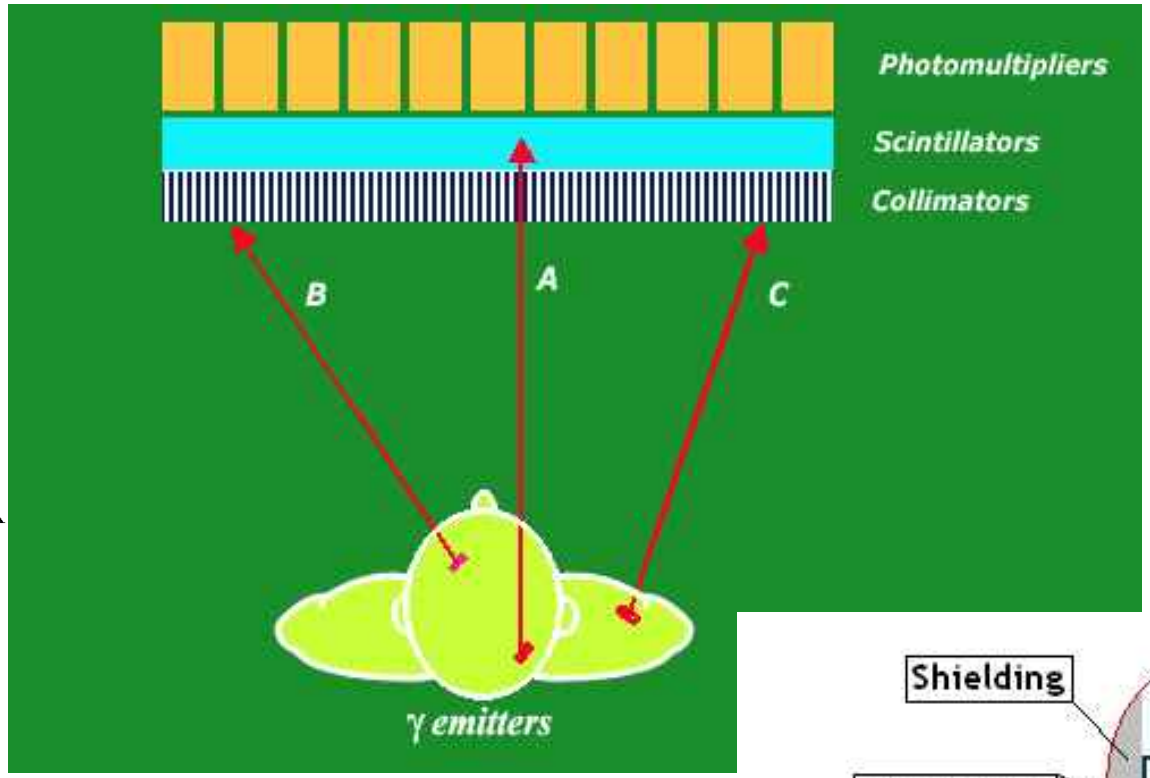
- Single photon emitting isotopes: Tc-99m (140 keV), I-123, I-131 (159 keV), In-111 (171 y 245 keV).

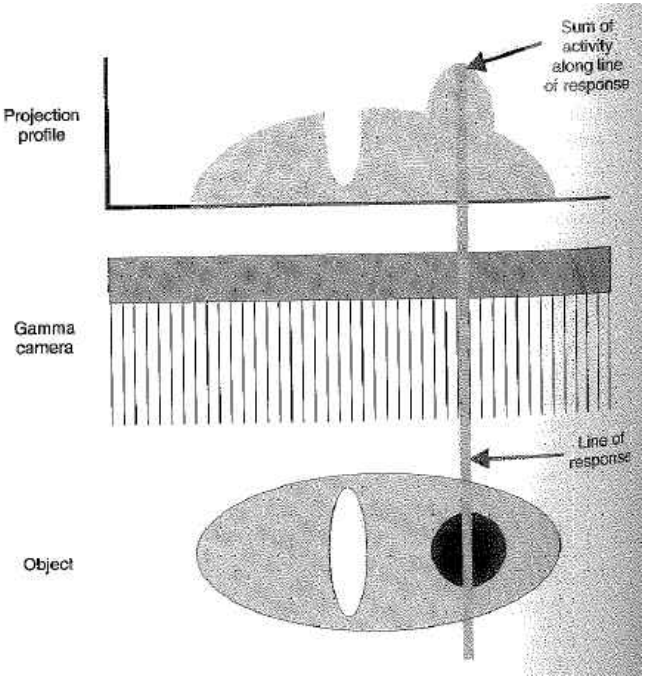
Technetium-99m: E=140 keV, half life=6 hours
Indium-111: E=159 keV, half life=13 hours

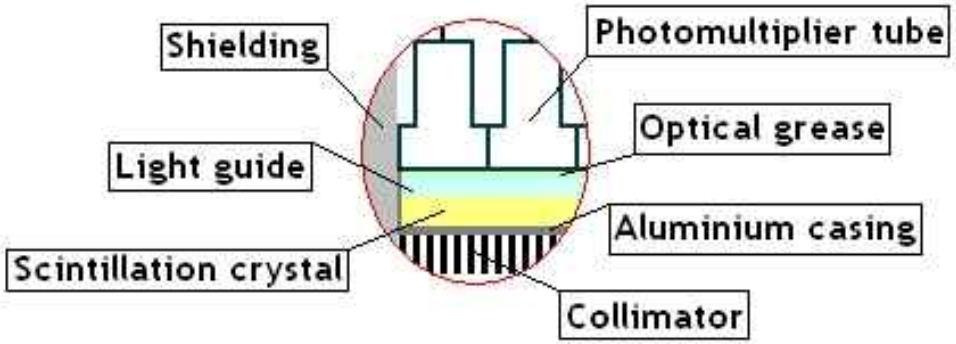
- Different compounds:

Tc-99m compound	Study
MDP	Bone metabolism
Sestamibi	Miocardic perfusion
MAG3	Renal function
HMPAO	Cerebral blood flow

Gamma cameras



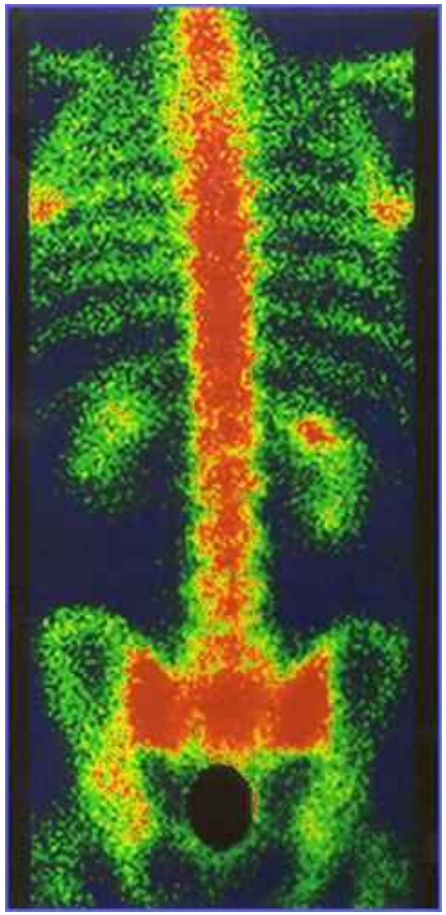


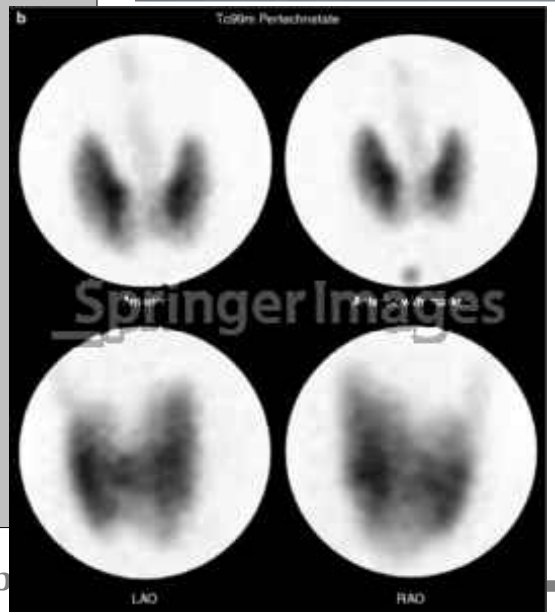


Performance influenced by collimator

- Large systems dominated by scintillators (+ PMTs).
- Dedicated systems: Scintillators (+ SiPMs), solid state (e.g. CZT in cardiac or breast commercial systems), gas.

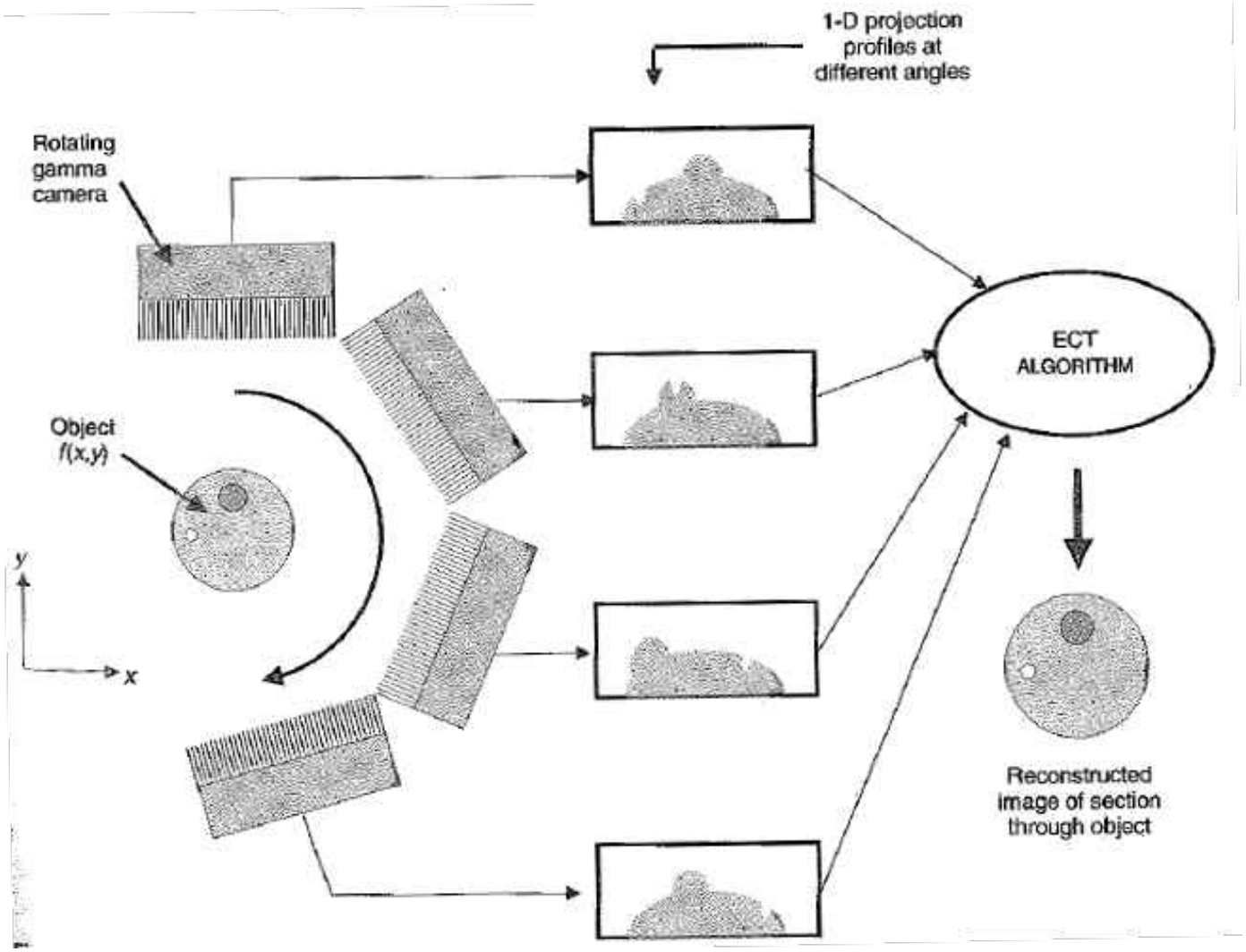
Single photon imaging



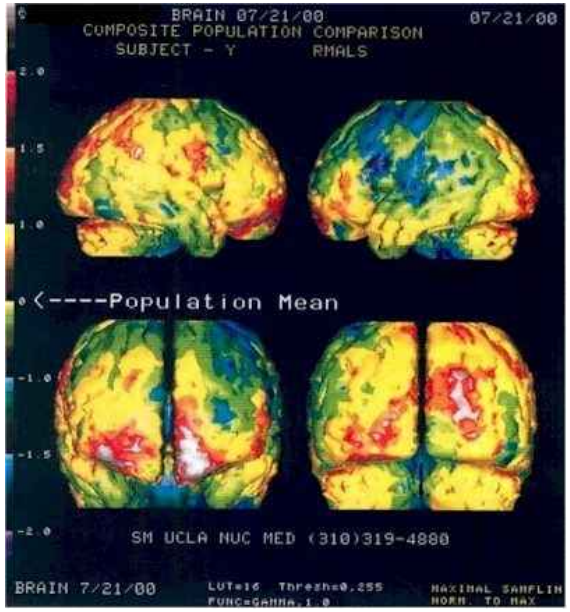


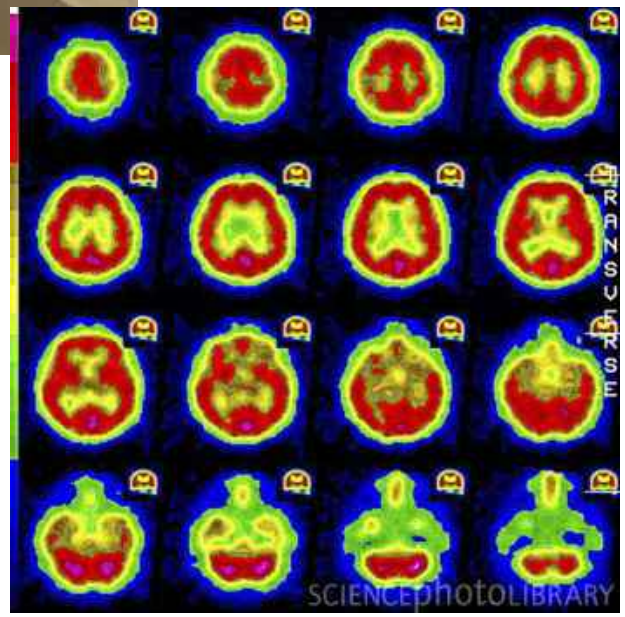
SPECT

- The detector rotates around the patient.
- Image reconstruction yields tomographic images.



SPECT


BRAIN 07/21/00
07/21/00
COMPOSITE POPULATION COMPARISON
SUBJECT - Y
RMALS
<----Population Mean
SM UCLA NUC MED (310)319-4880
BRAIN 7/21/00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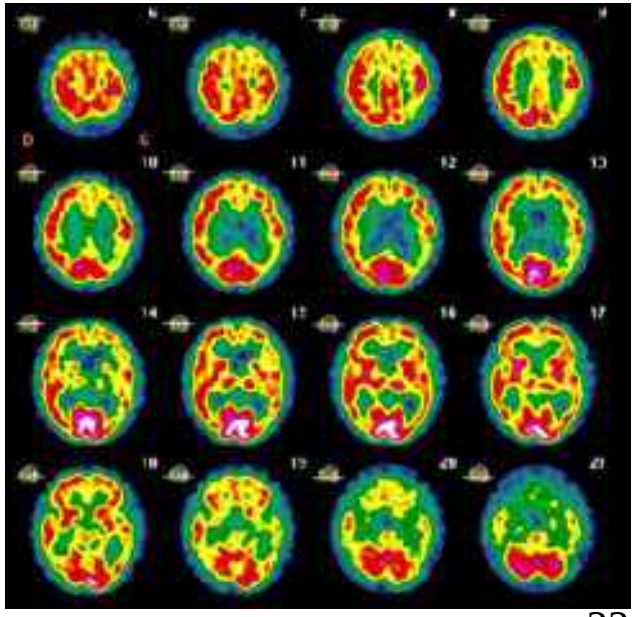
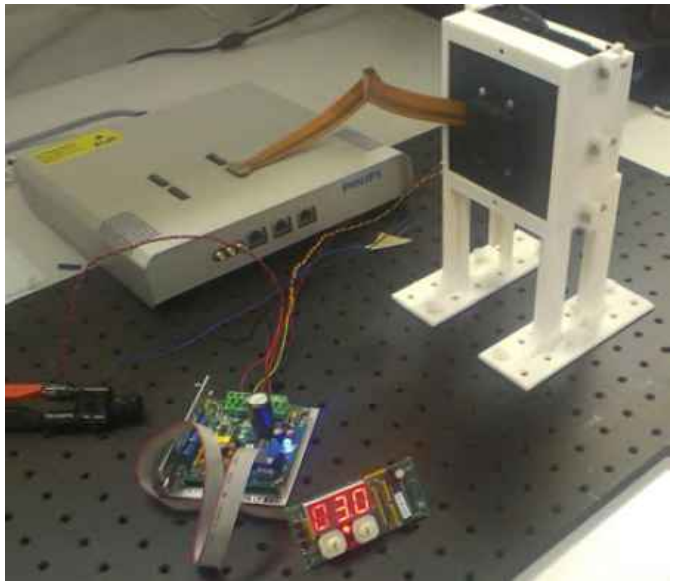
SCIENCEphotoLIBRARY

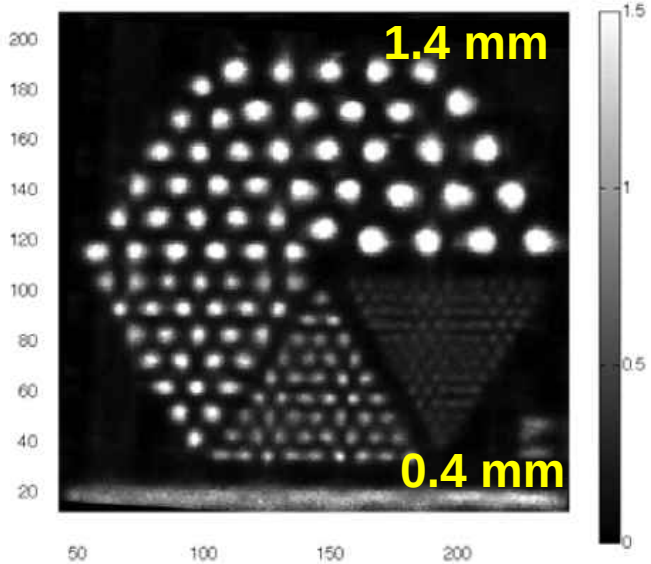


Gamma cameras

- In small systems:
  - Excellent intrinsic resolution (<0.5 mm).
  - Static ring systems → Much higher efficiency.
  - MRI compatible.
  - Multi-isotope SPECT.
- Quantitation studies

Monolithic 32 x 32 x 2 mm^3
LYSO crystal + dSiPM

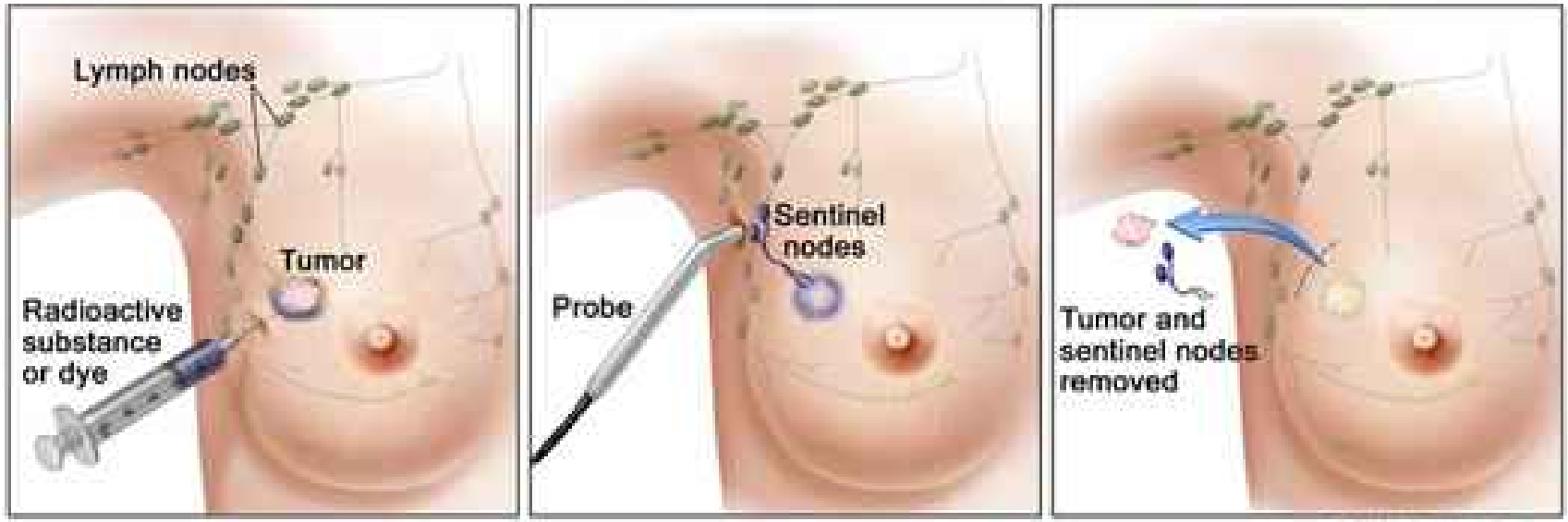




C. Bouckaert. 2013 IEEE NSS MIC. M14-7.

Intraoperative probes

- Intra-operative imaging of tumours helps the surgeon to determine precisely the tumour extension and separate from healthy tissue.
- Typical application: sentinel lymph node.



Intraoperative probes

- Beta and gamma intraoperative probes (photon counting) and mini gamma cameras (imaging).

X and $\gamma < 511$ keV

$\gamma = 511$ keV

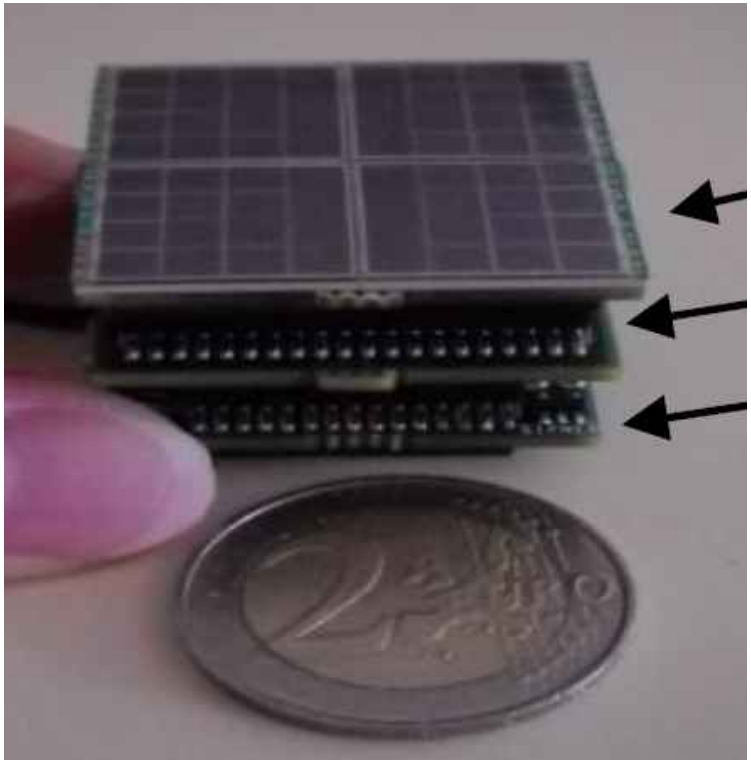
β

Heller and Zanzonico Seminars in Nuclear Medicine

- Probes have small FOV
- Need large FOV (5x5 cm^2) with excellent spatial resolution while portable and small.
- Recently solid state or scintillator + SiPMs (lower cost)

Mini gamma cameras

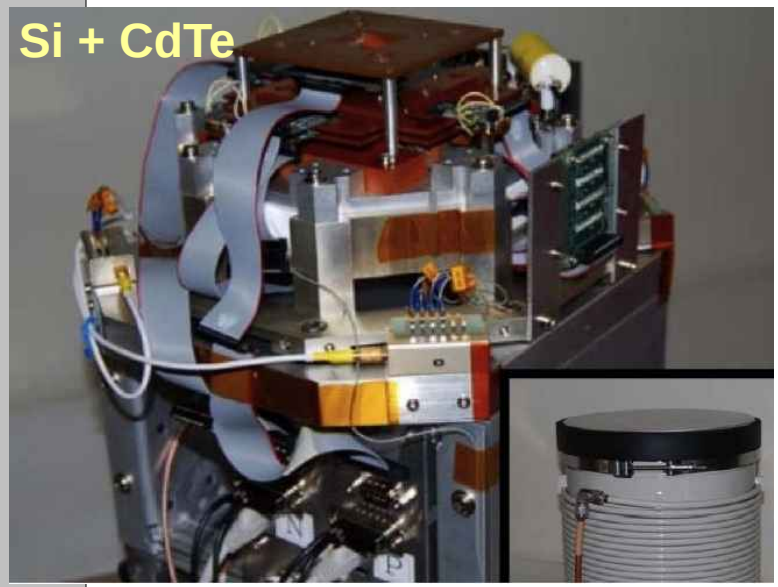
- SIPMED:
  - $LaBr_3$ scintillator 5.5 cm x 5.5cm
  - ~ 6 cm thick, 700 g; 256 readout channels
  - E resolution: 10.5% FWHM @ 122 keV
  - Spatial resolution: 1.23 mm FWHM @ 122 keV

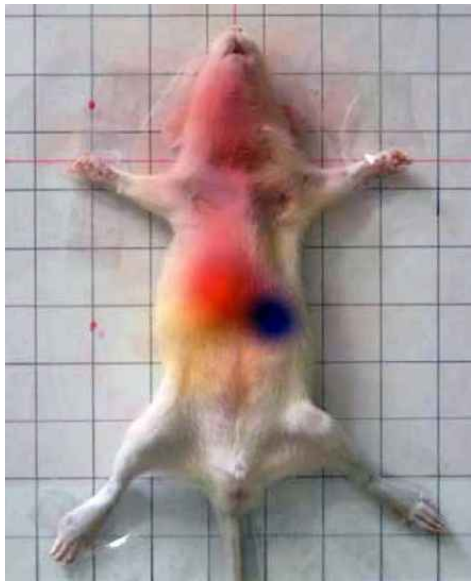


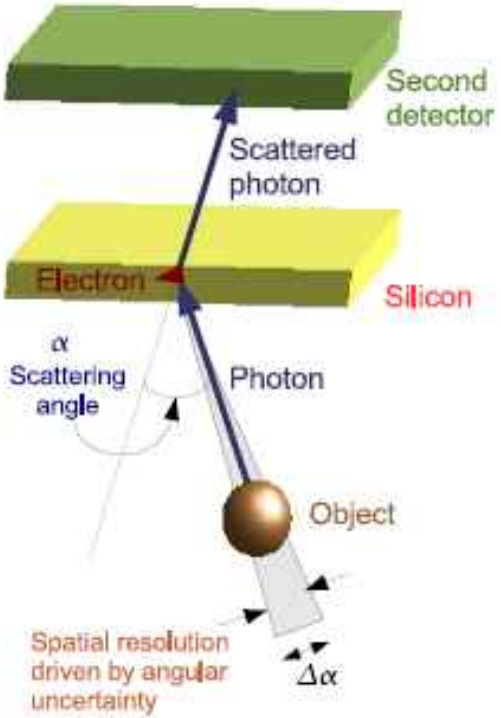
Imando et al. PoS 2012.
N. Dinu et al. NDIP 2013.

Compton Imaging

- Applied in different fields. Made of different materials. Commercial products.
- Advantages: improvement of resolution and efficiency, improvement at high energies...
- Renewed interest with SiPMs.

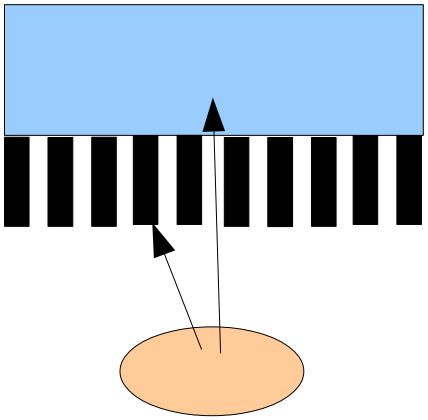




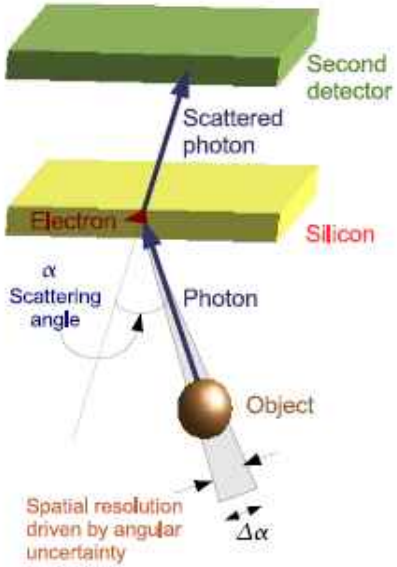


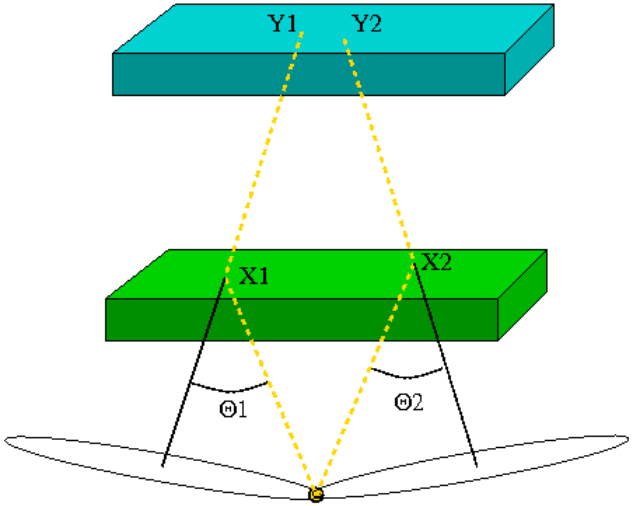
Compton Imaging

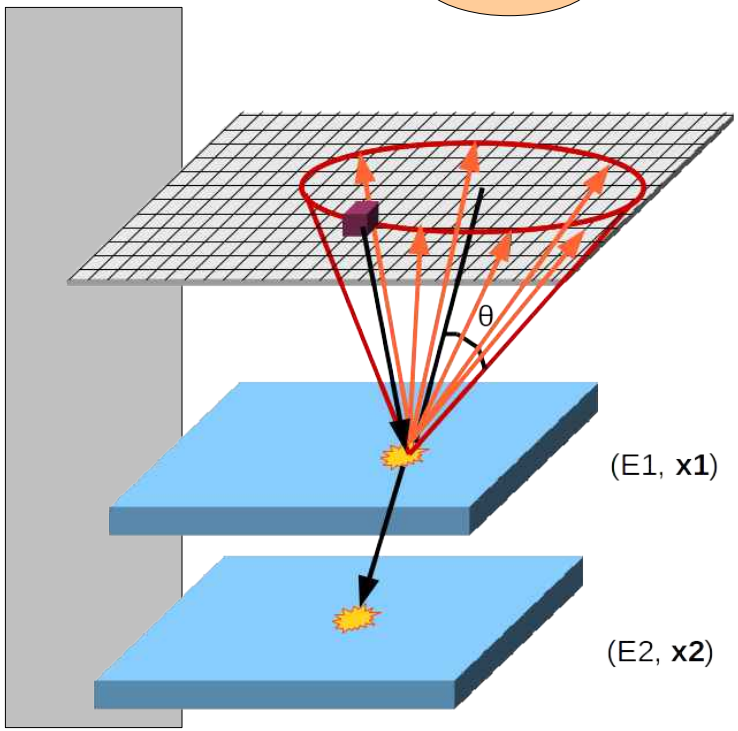
GAMMA CAMERA

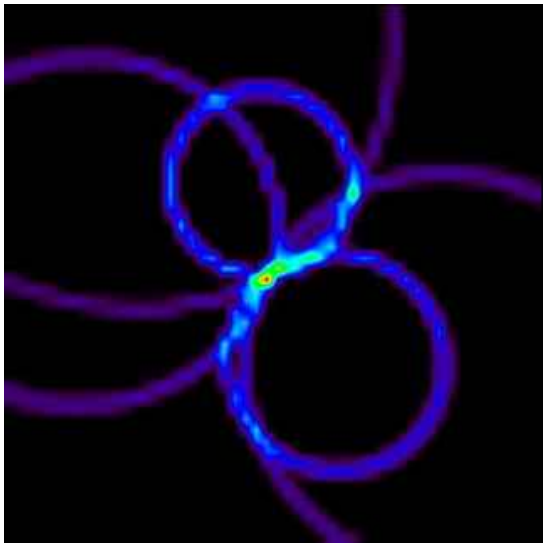


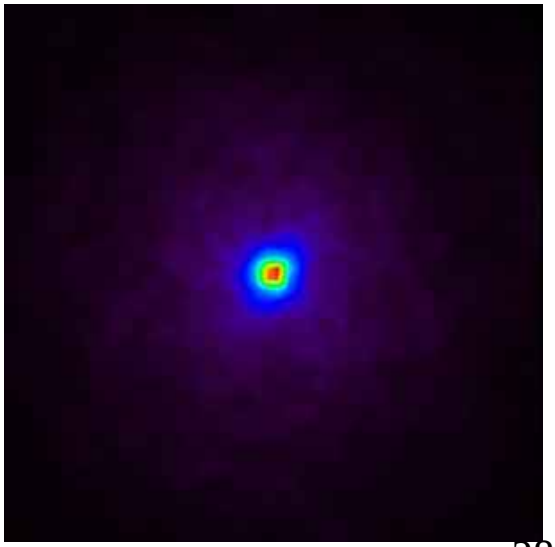
COMPTON CAMERA











Compton Imaging

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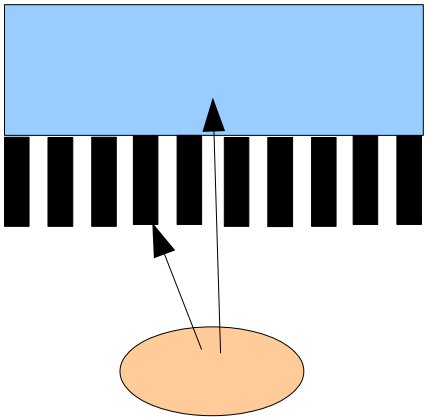
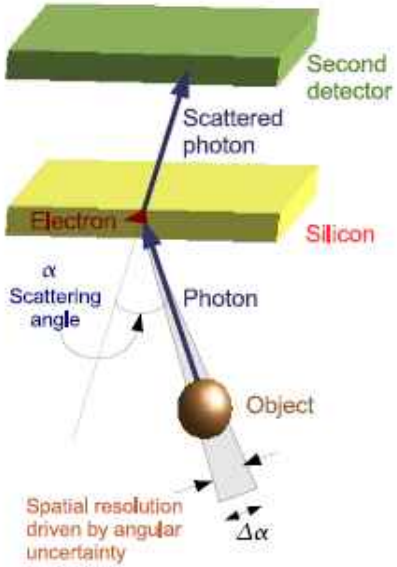
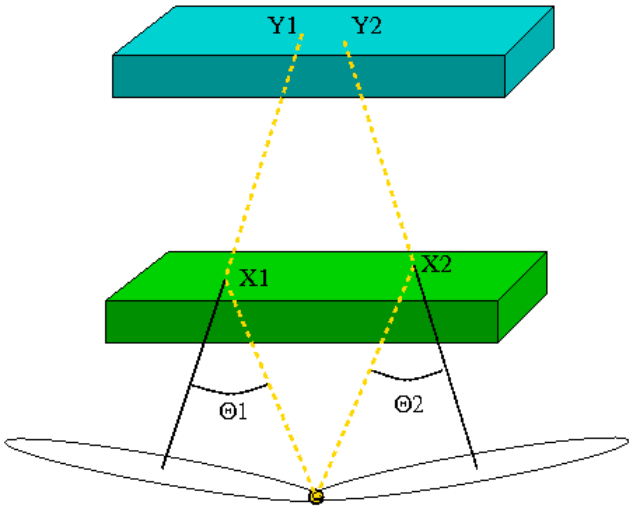
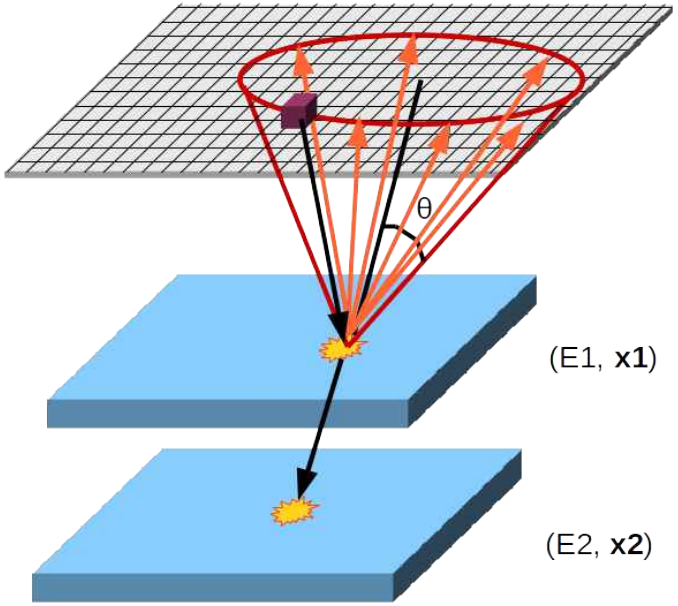


COMPTON CAMERA



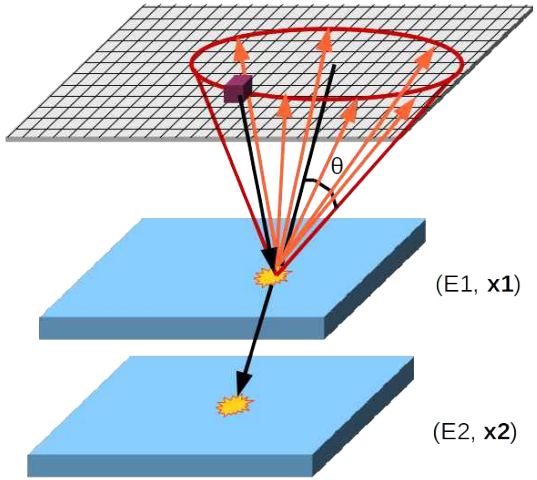




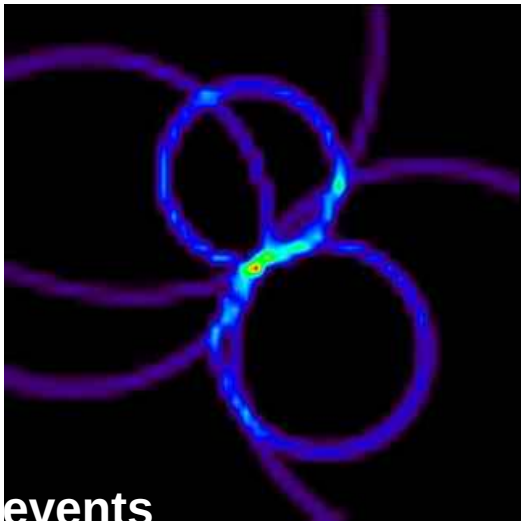
$$cos\theta = 1 - m_0c^2\left(\frac{1}{E_0 - E_e} - \frac{1}{E_0}\right)$$

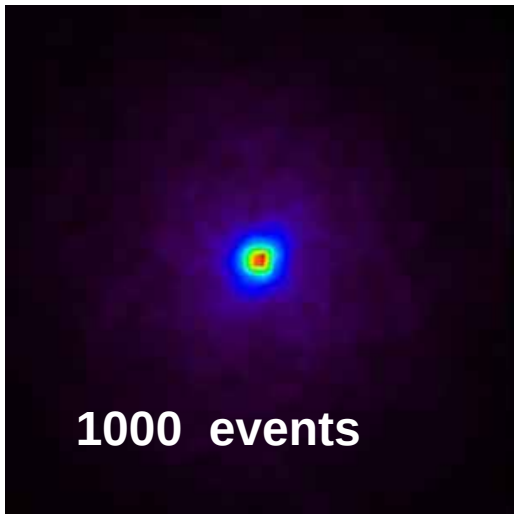
Compton cameras

- The cone surface is projected to the reconstruction volume.
- The intersection of several cone surfaces yields the position of the source.
- Not (yet?) used in medical imaging.



Backprojection

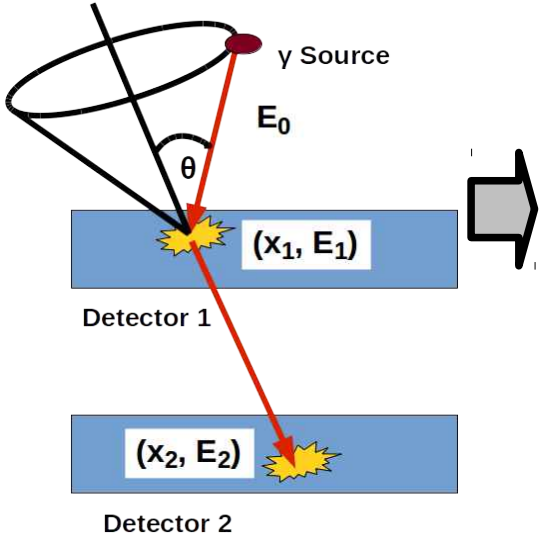




+ Image reconstruction algorithm

$$\lambda_j^{n+1} = \frac{\lambda_j^n}{s_j} \sum_{i=0}^{N} \frac{t_{ij}}{\sum_k t_{ik} \lambda_k^n}$$

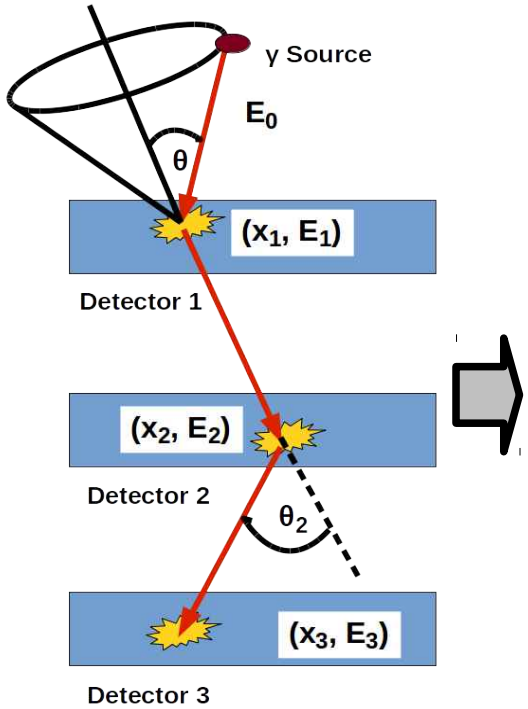
Compton camera configurations



Scatterer + absorber: 2 interactions

Problems if the photon energy is unknown or if it can escape (MeV)

$$cos\theta = 1 - m_0c^2\left(\frac{1}{E_0 - E_e} - \frac{1}{E_0}\right)$$



Multilayer: 3 interactions in 3 detectors (+ correct ordering):

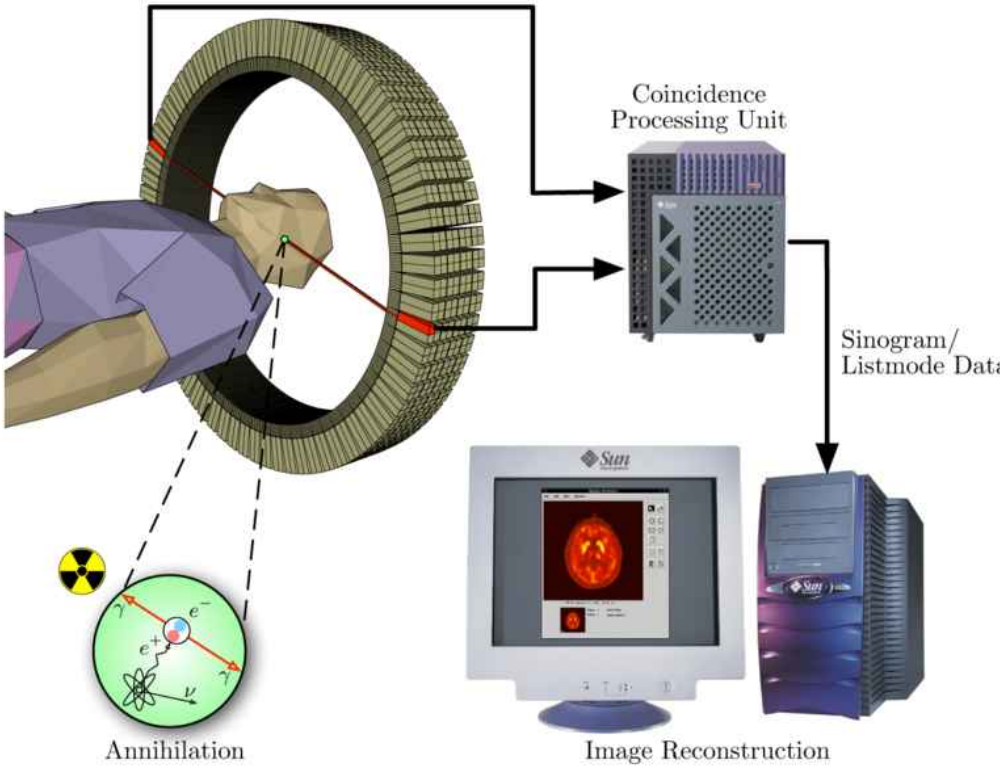
- Energy determined
- lower efficiency

$$\cos(\theta) = 1 - \frac{E_1 m_e c^2}{E_0(E_0 - E_1)}$$

$$E_0 = E_1 + \frac{1}{2}\left(E_2 + \sqrt{E_2^{\,2} + 4\frac{E_2 m_e c^2}{1 - \cos\theta_2}}\right)$$

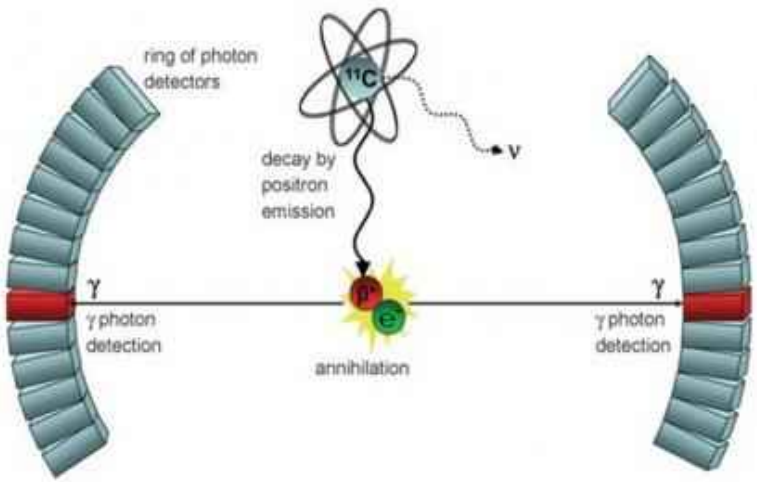
Positron Emission Tomography

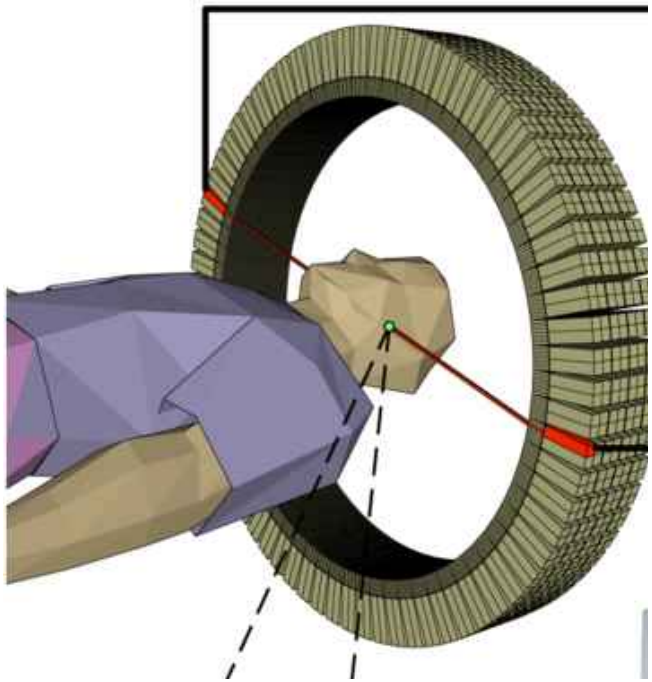
- Depth Of Interaction (DOI).
- Time-Of-Flight.
- PET-MR.
- Total Body PET (EXPLORER, J-PET).

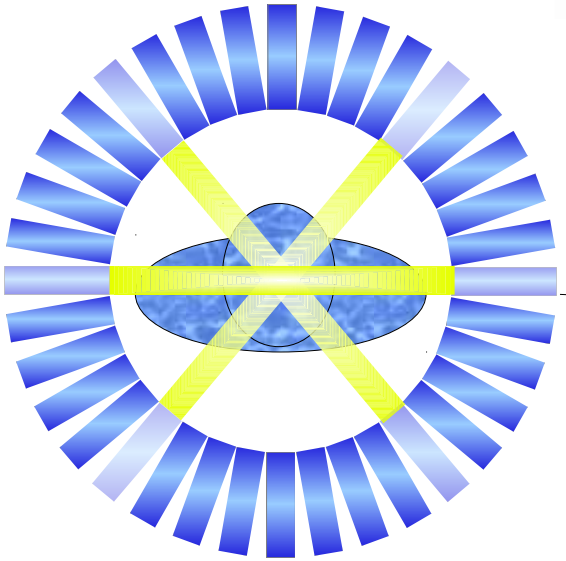


Positron Emission Tomography

- Radiotracers 18F-FDG – C11, N-13, O-15.



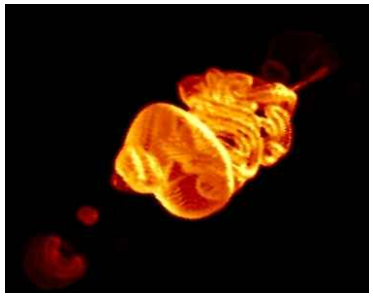




Data acquisition

$$n_j^{k+1} = \frac{n_j^k}{\sum_{i=1}^{I} a_{ij}} \sum_{i=1}^{I} a_{ij} \frac{m_i}{q_i^k}$$

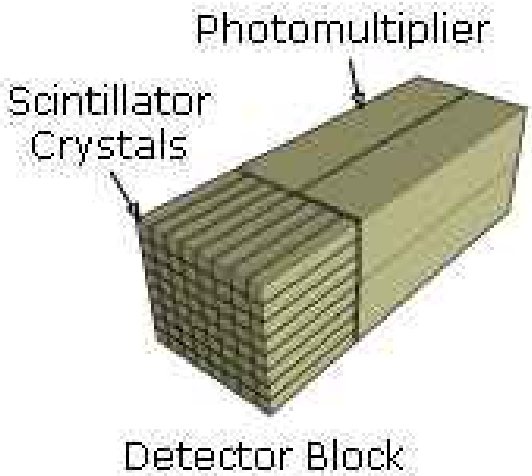
Image reconstruction

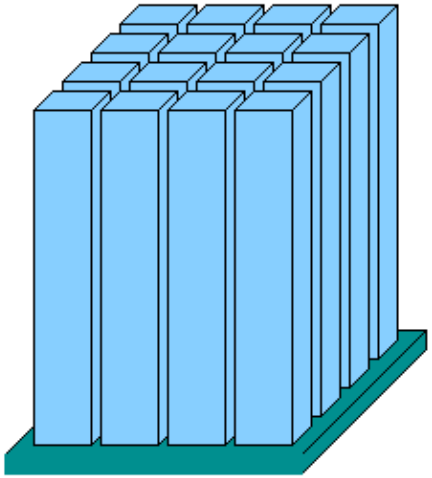


Image

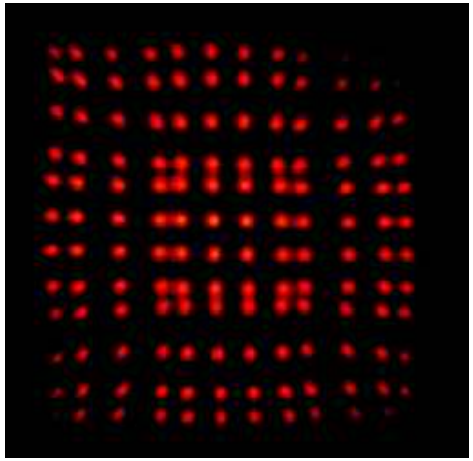
Positron Emission Tomography

- Conventional PET detector

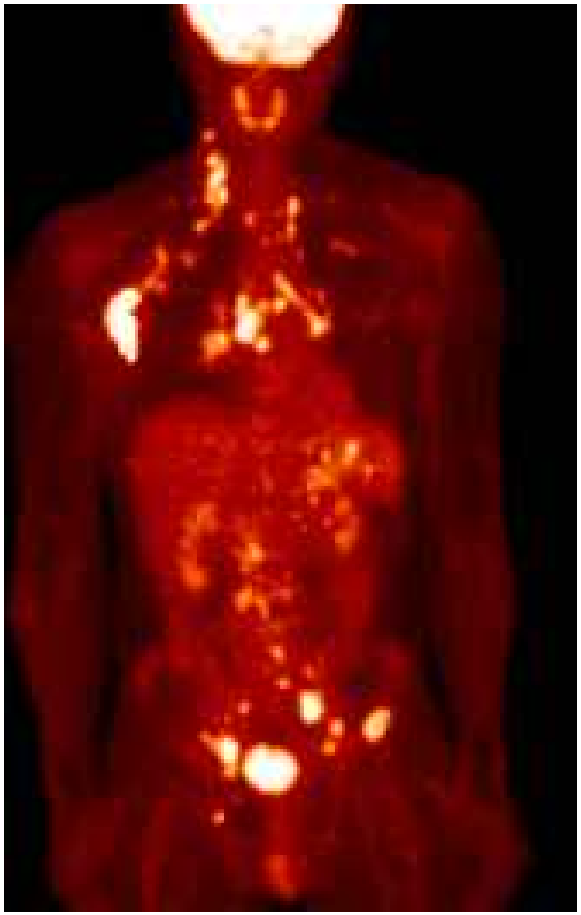




- Dedicated/animal systems with solid state / other.
- Scintillators + SiPMs

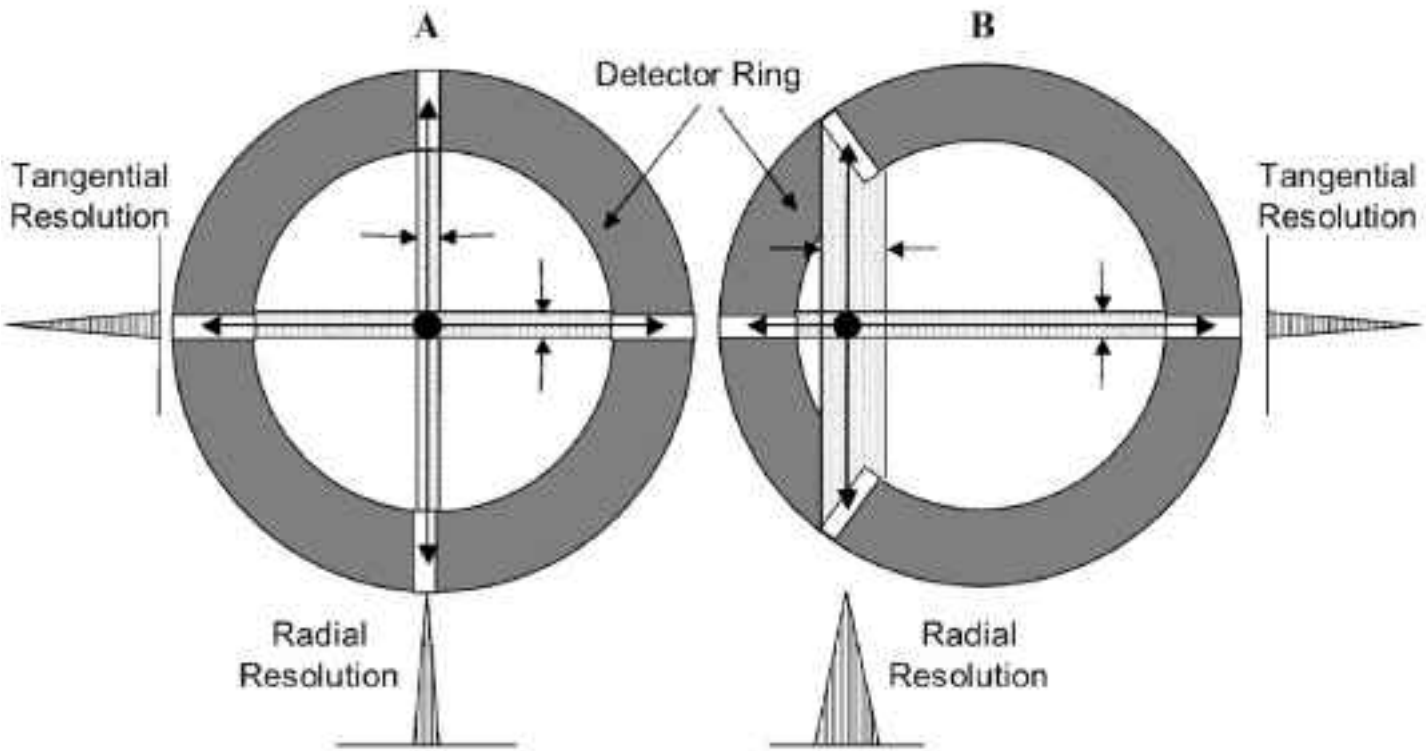


Positron Emission Tomography



Depth Of Interaction (DOI) determination

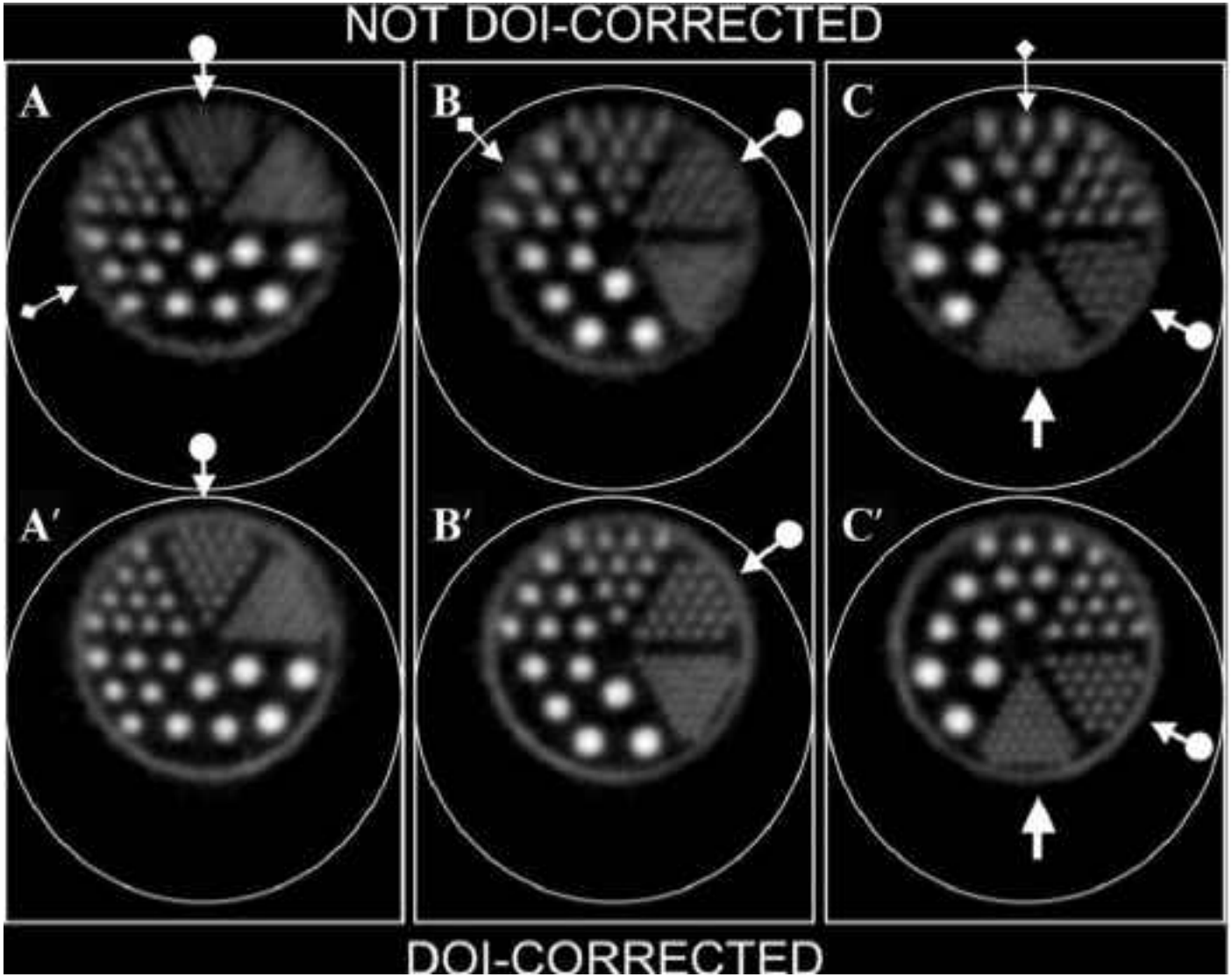
Parallax error



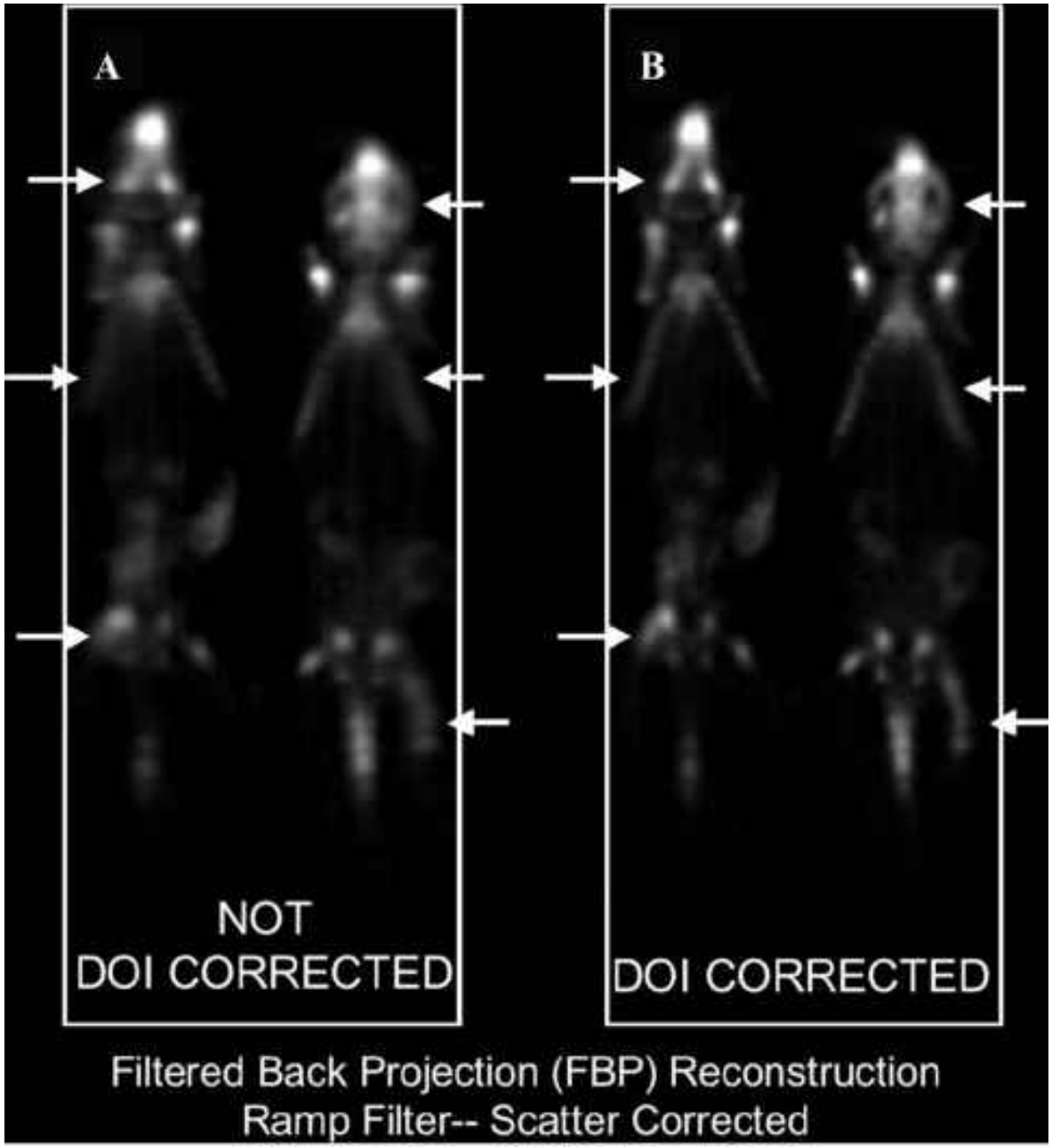
Green et al.
Molec. Im. 9(6) 2010

DOI determination

Green et al.Molec. Im. 9(6) 2010



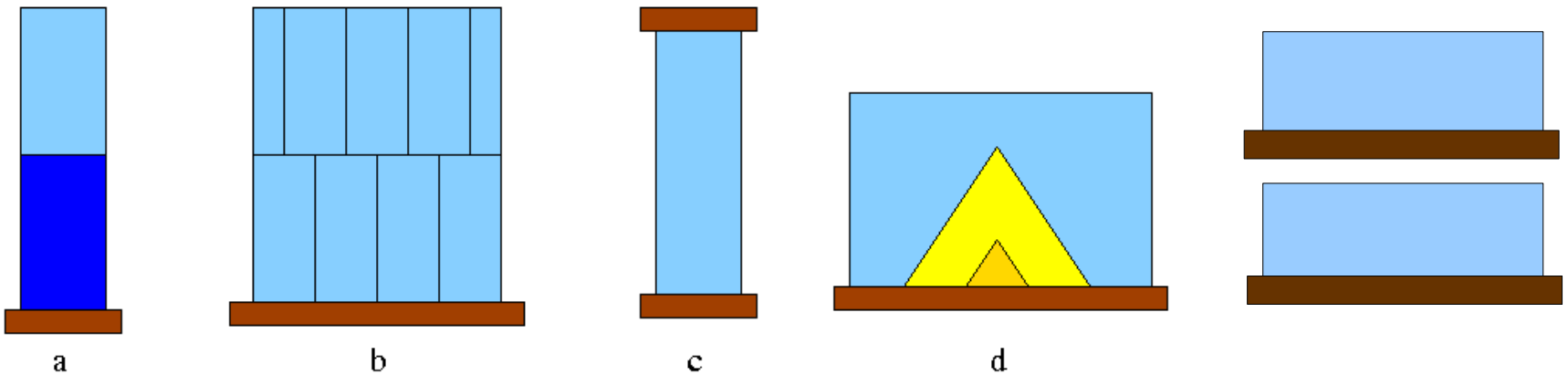
DOI determination



Green et al.
Molec. Im. 9(6) 2010

Depth Of Interaction (DOI) determination

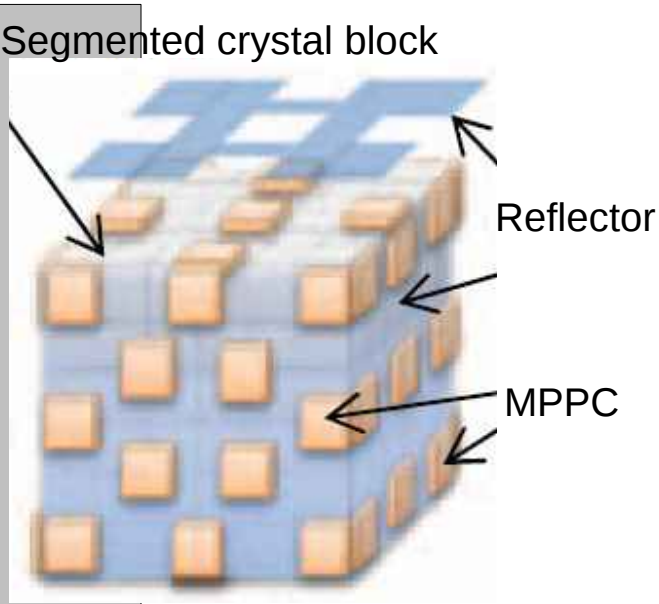
DOI determination

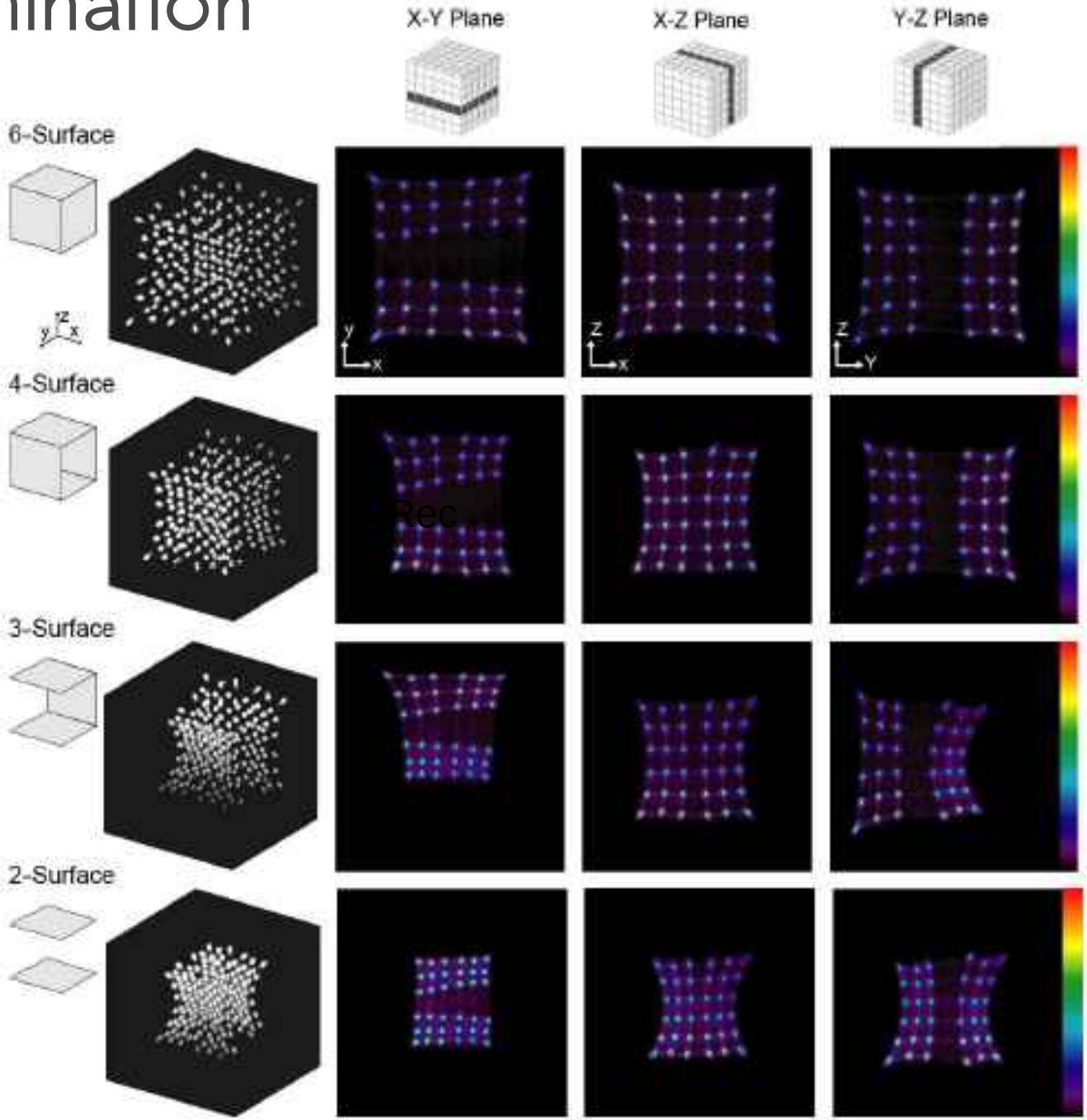


DOI determination

X'tal cube

- 3D position determination
- 1 mm3 cubes

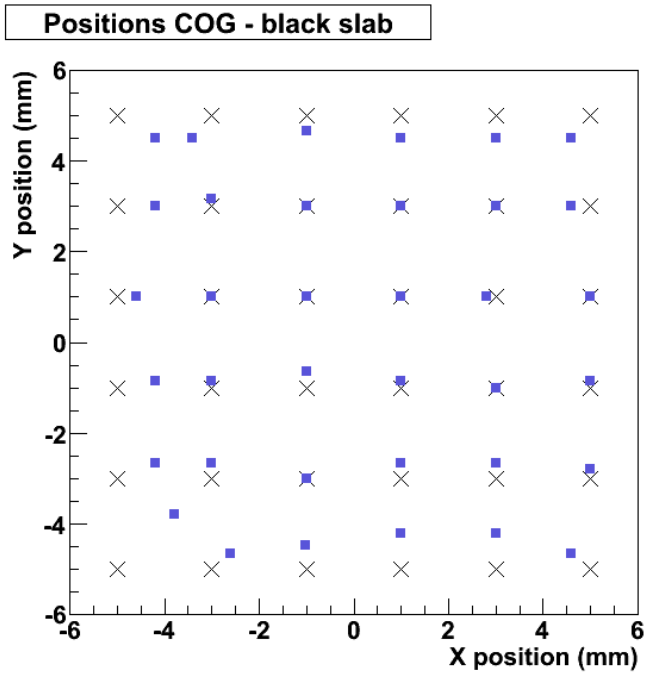


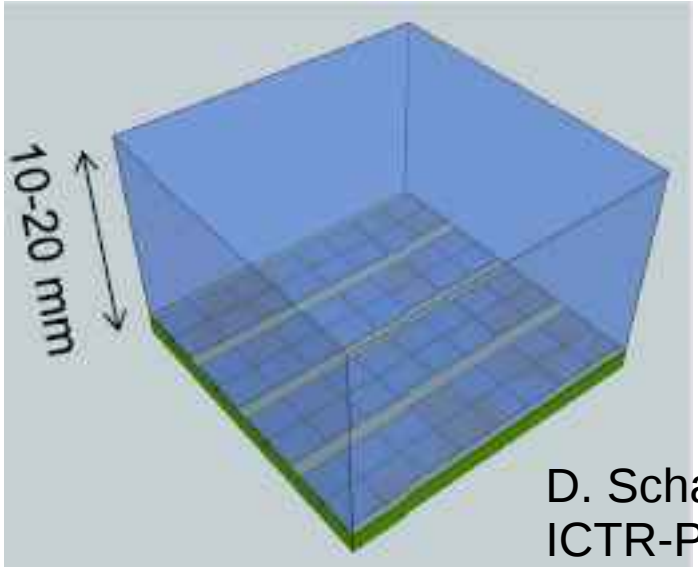


Y. Yazaki et al. 2009 IEEE NSS MIC Conf Rec

Monolithic crystals

- Much improved results with monolithic crystals + SiPMs



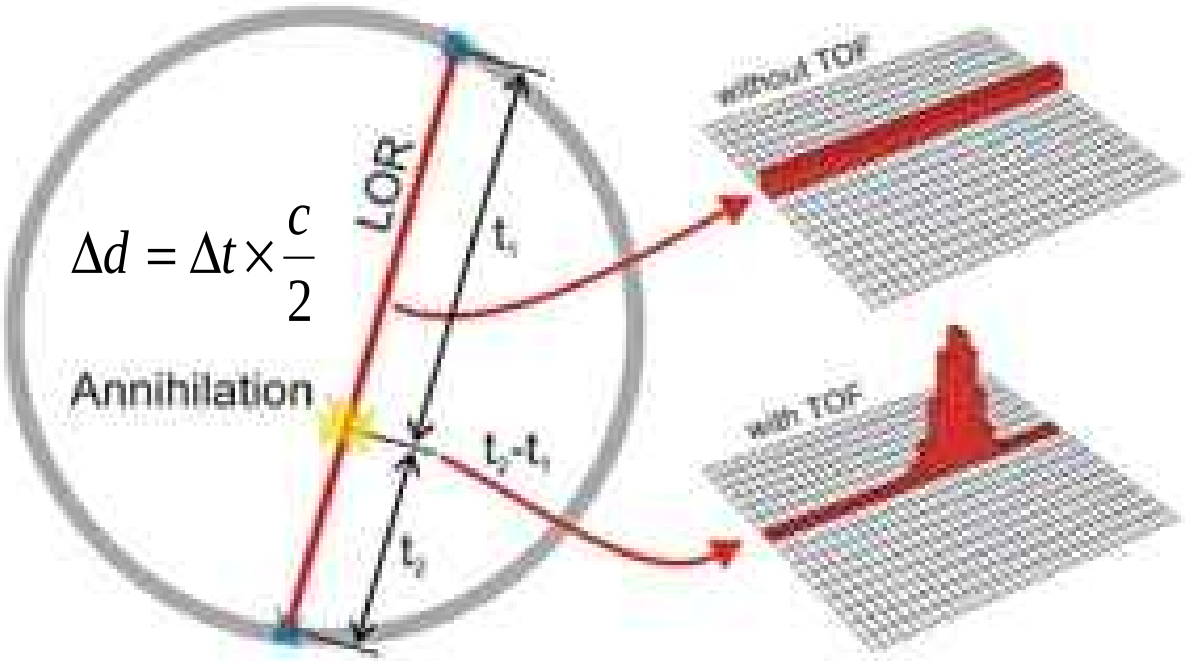


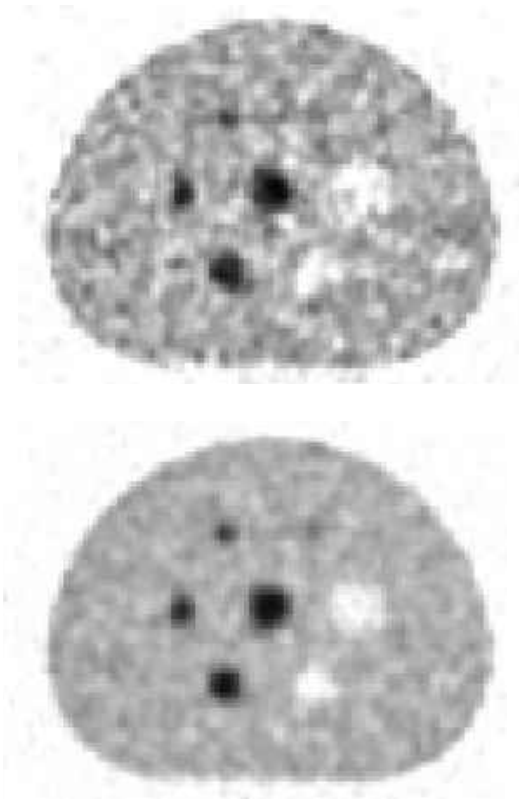
D. Schaart.
ICTR-PHE 2014

Performance parameter		Monolithic	State of the art
Energy resolution	(% FWHM)	11 - 12	~12
Spatial resolution	(mm FWHM)	1.0 - 1.6	4 - 6
DOI resolution	(mm FWHM)	3 - 5 mm	None
CRT	(ps FWHM)	160 - 185	500 - 650

Time of Flight PET

- Good timing resol. allows to reject accidental coincidences
- Very good: TOF-PET=> SNR improvement





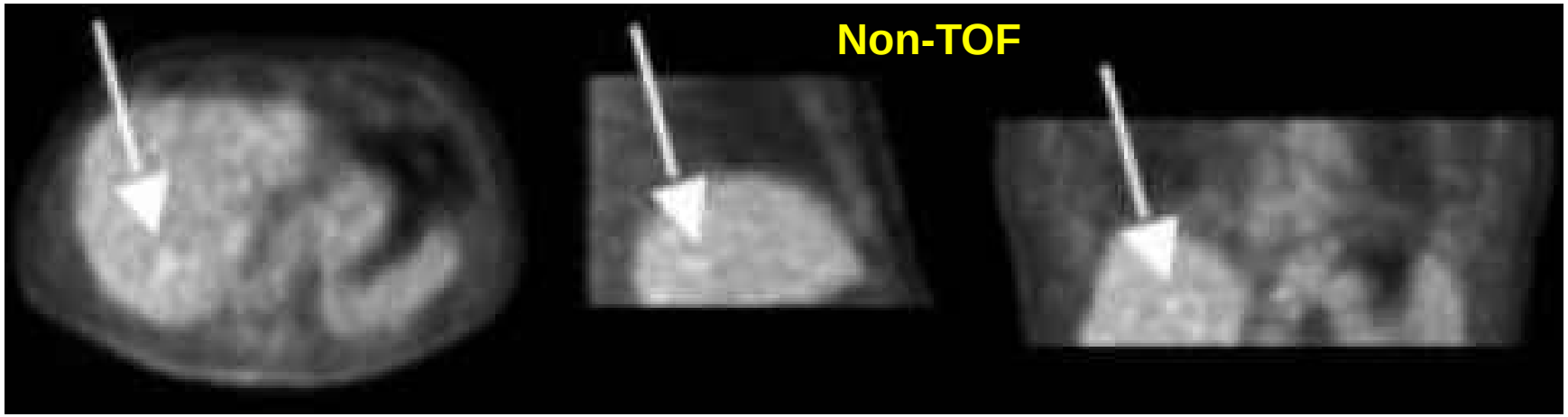
First commercial TOF-PET systems: coincidence timing resolution ~ 500 ps FWHM.

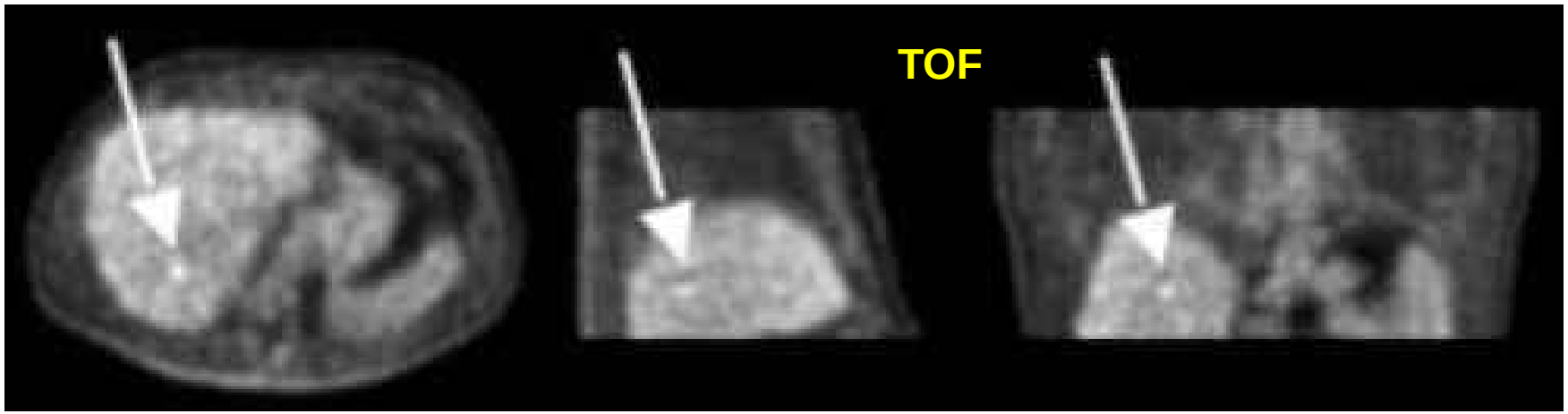
No TOF-PET in preclinical systems, but improved images

TOF-PET

Surti et al.
J Nucl Med 52(5). 2011

- Liver lesion





- Photodetectors: PMTs, MCPs, SiPMs, DSiPMs

TOF-PET

- Some of the first results better than 200 ps with small crystals.

101 ps FWHM with

- $LaBr_3$:Ce crystals
  3 x 3 x 5 mm^3
- Hamamatsu MPPCs 3x3mm^3, 50 x 50μm^3 microcells
- Own electronics

D. Schaart et al, PMB 2010

170 ps FWHM with

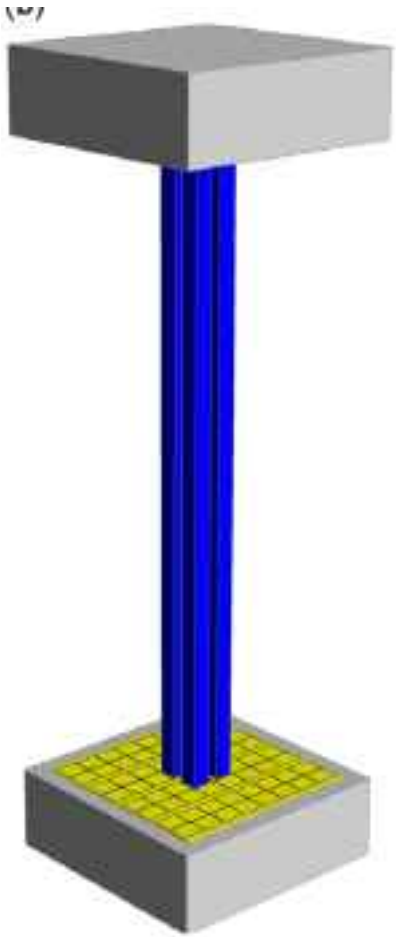
- LSO_3:CeCa crystals
  2 x 2 x 20 mm^3
- Hamamatsu MPPCs 3x3mm^3, 50 x 50μm^3 microcells
- NINO ASIC

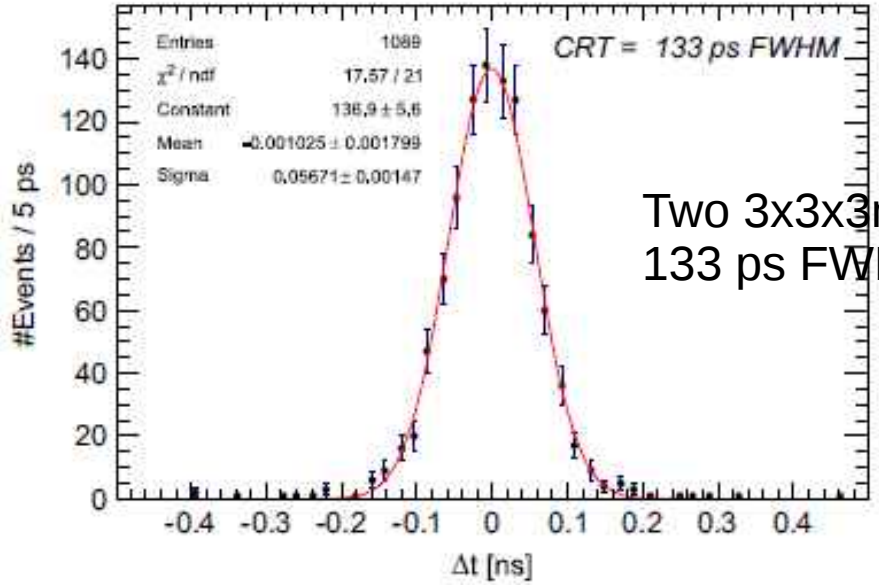
E. Auffray et al, 2011 IEEE NSS MIC CR

TOF-PET

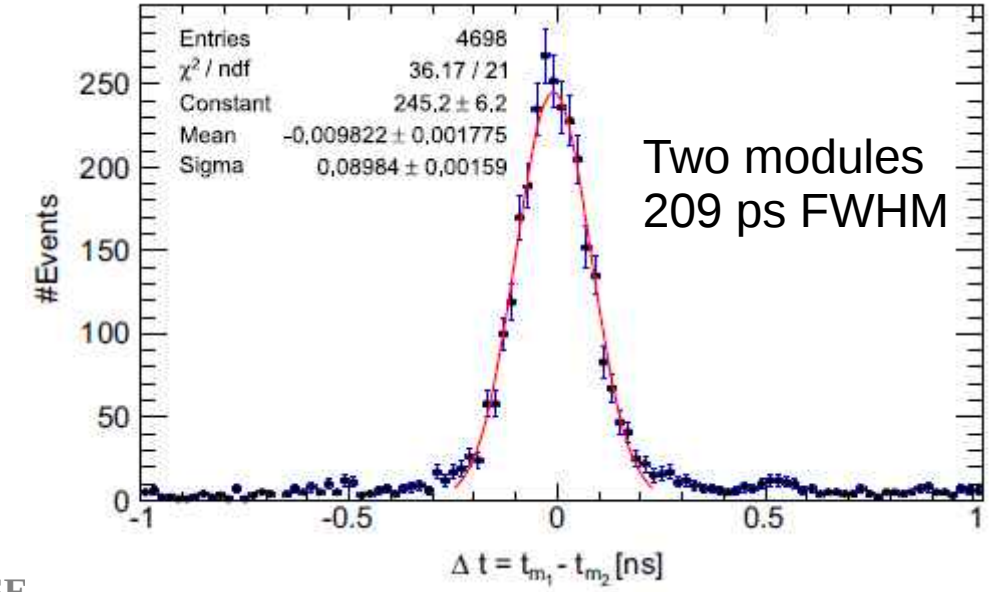
Casella et al. NIMA 736, 2014

- Module: four 100 mm LYSO crystals coupled to dSiPMs on both sides





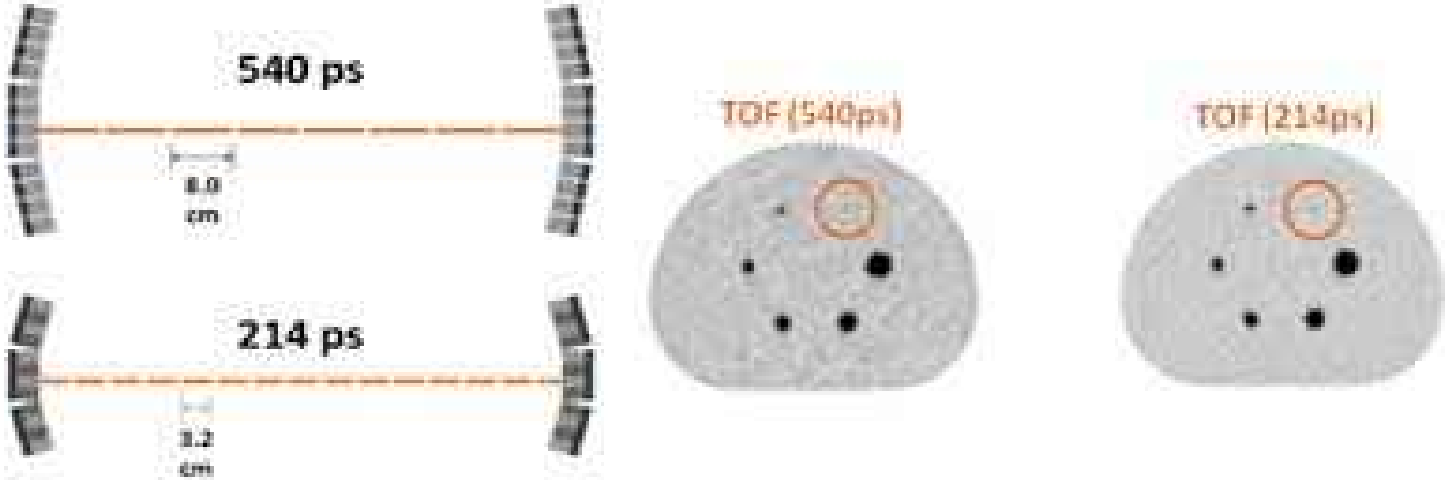
Two 3x3x3mm crystals
133 ps FWHM



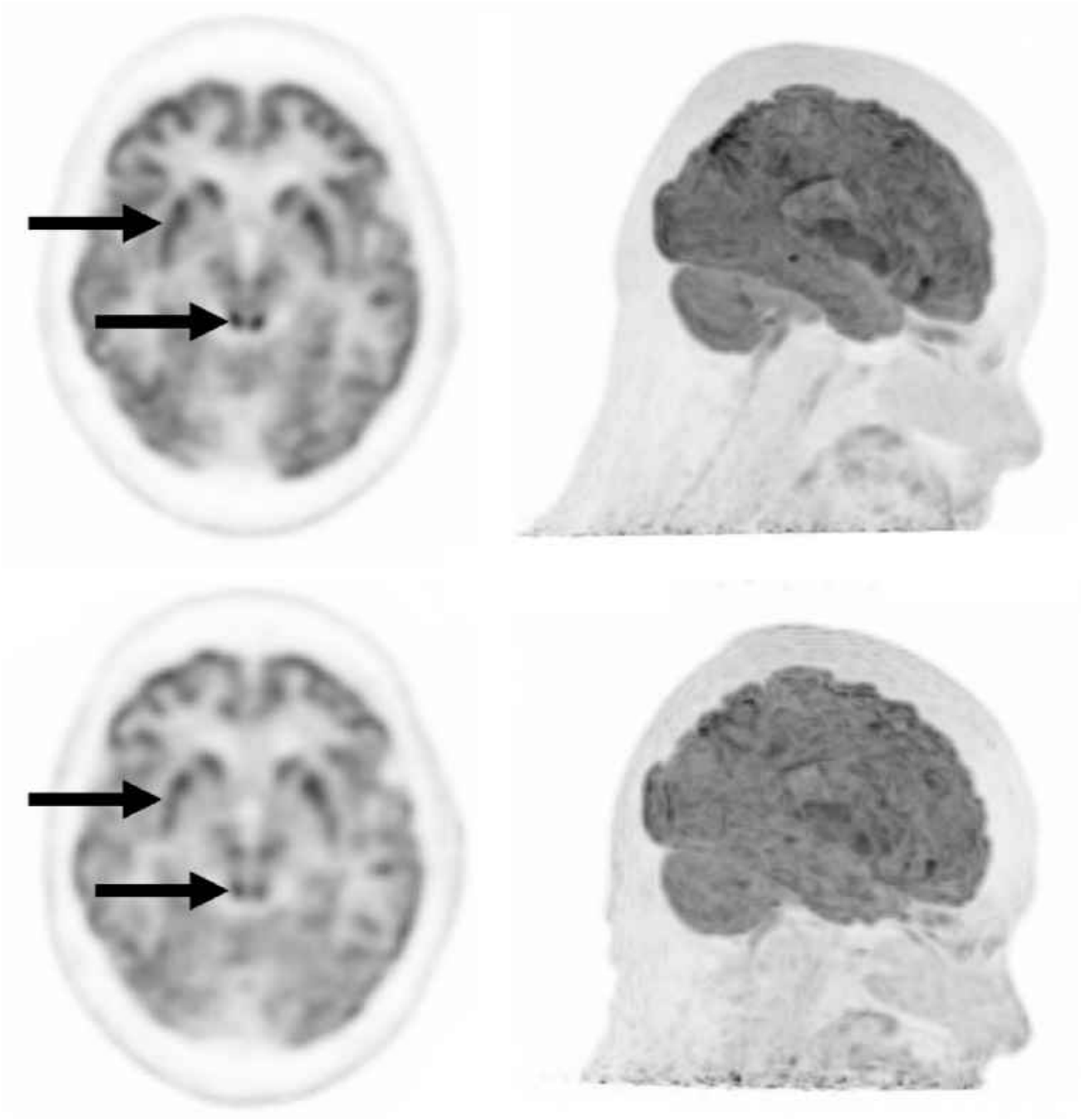
Two modules
209 ps FWHM

TOF-PET

- Siemens Biograph Vision (LSO+SiPMs, 250 ps FWHM TOF - articles quote ~ 205 ps).



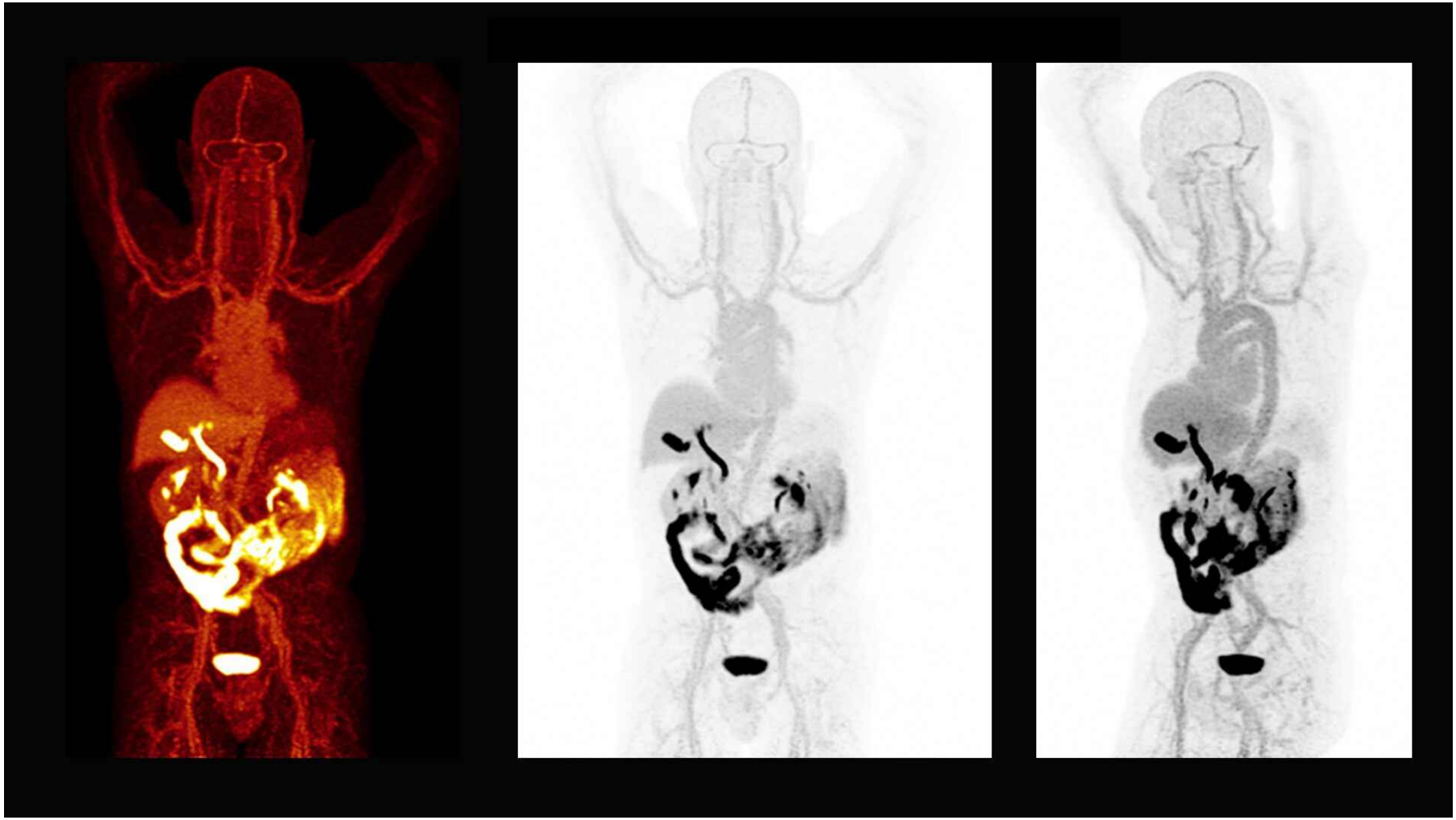
TOF-PET



Van Sluis et al.

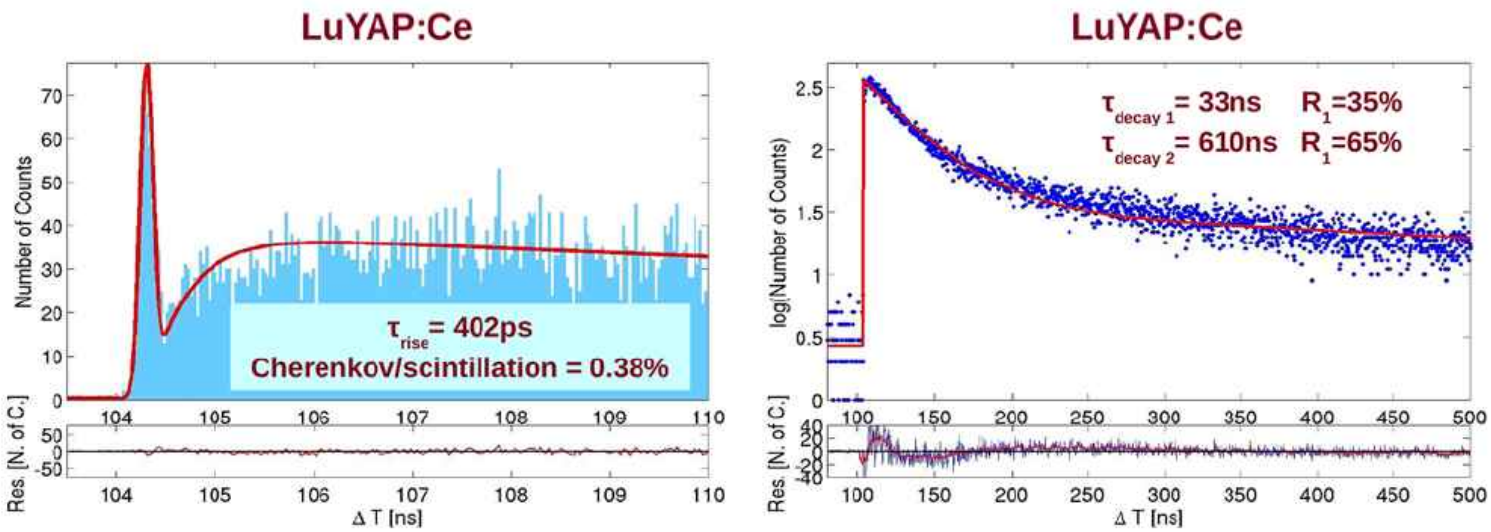
J Nuc Med 2019

TOF-PET



TOF-PET

- Research towards 10 ps timing resolution.
- FAST COST action: achieve scintillator-based detectors with timing precision better than 100 ps.
- Studies on possibility on triggering on prompt and Cherenkov photons from scintillator crystals - prompt photons produced along with scintillation photons can significantly reduce the CTR, if the single photon time resolution of the SiPM is low enough.



S. Gundacker et al. Phys. Med. Biol. 61 (2016)

Figure 25. The rise time of LuYAP:Ce was measured to 402 ps. The duration of the measurement was 34 d; a well resolved 'prompt' photon peak smeared by the IRF can be seen. The bin width is 30 ps for the rise time plot (left histogram).

Cherenkov PET

- Coincident 511 keV annihilation photons.
- ~ 10 Cherenkov photons.
- PbF_2 + MCP PMTs.
- Measured coincidence timing resolution: 36 ps sigma.
- Tests with refrigereted SiPMs also carried out.

S. Korpar et al.

Physics Procedia 37 (2012)

S. Korpar et al. / Physics Procedia 37 (2012) 1531 – 1536

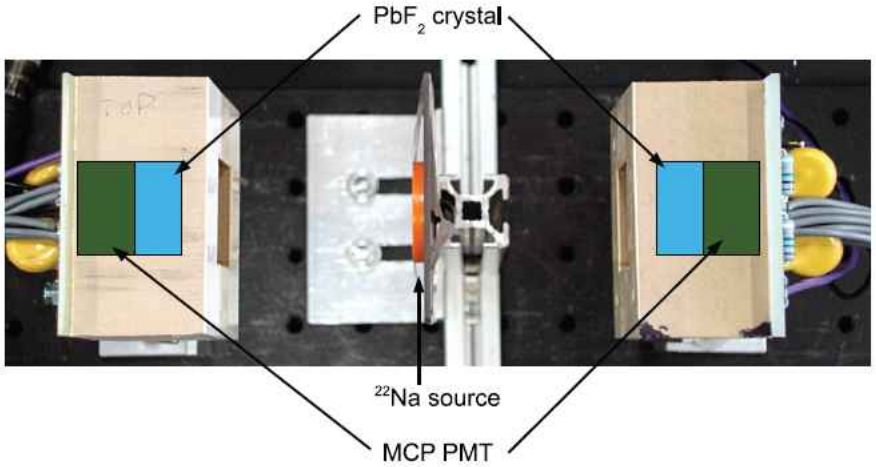


Fig. 1. The experimental setup with ^{22}Na source in between the two PbF_2 crystals coupled to MCP PMTs.

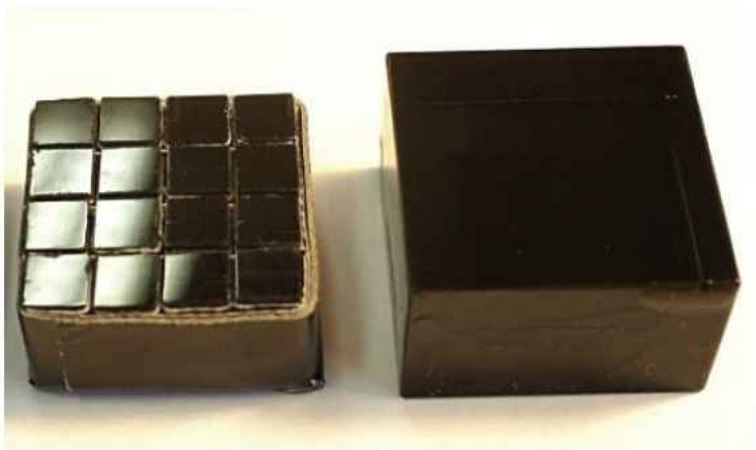
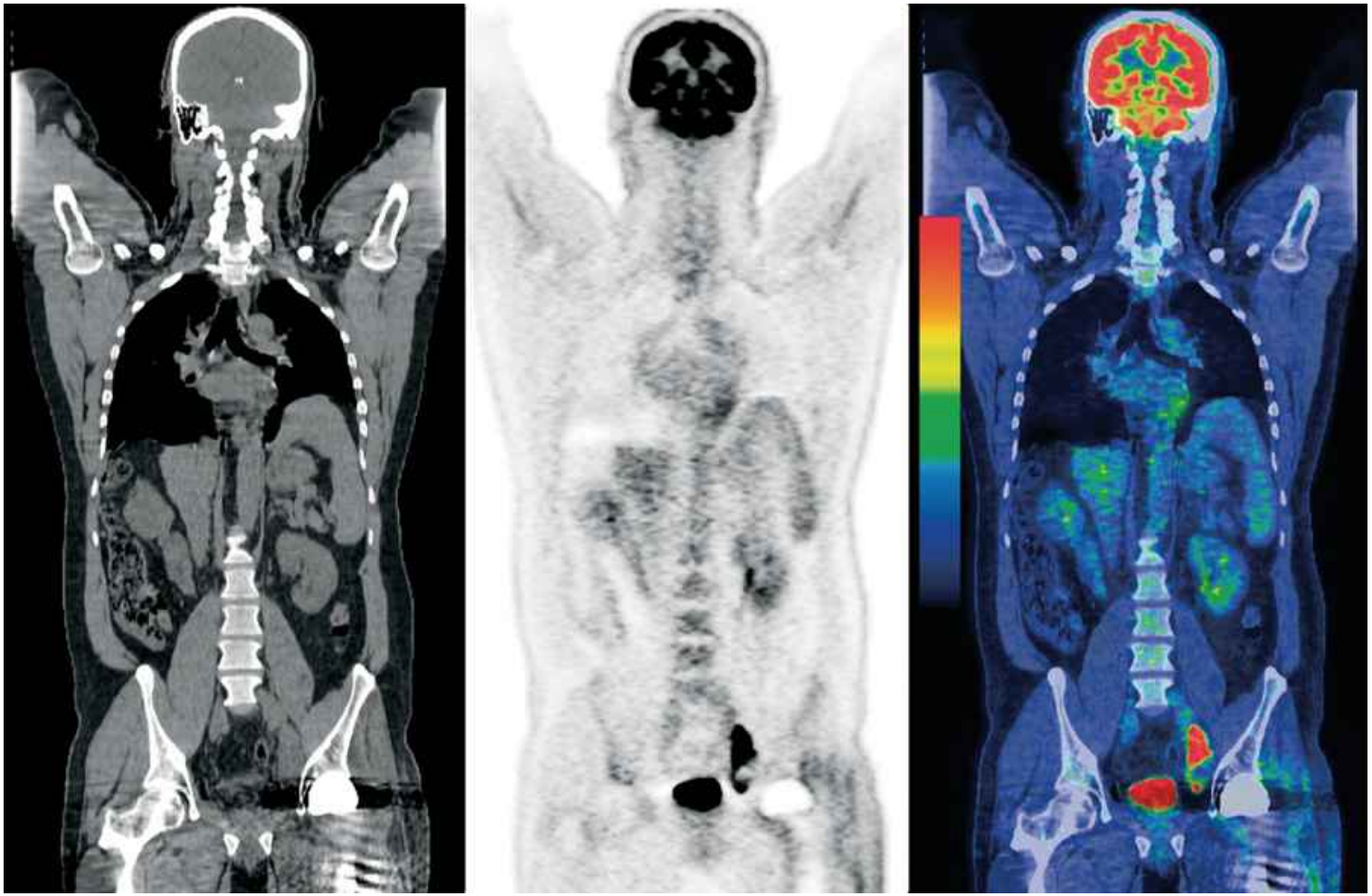


Fig. 2. Cherenkov radiator crystals used for detection of 511 keV photons in the present experiment.

PET-CT / PET-MR

- Combining anatomical and functional images increases diagnostic accuracy
- PET-CT is now the standard. PET-MR already exists.

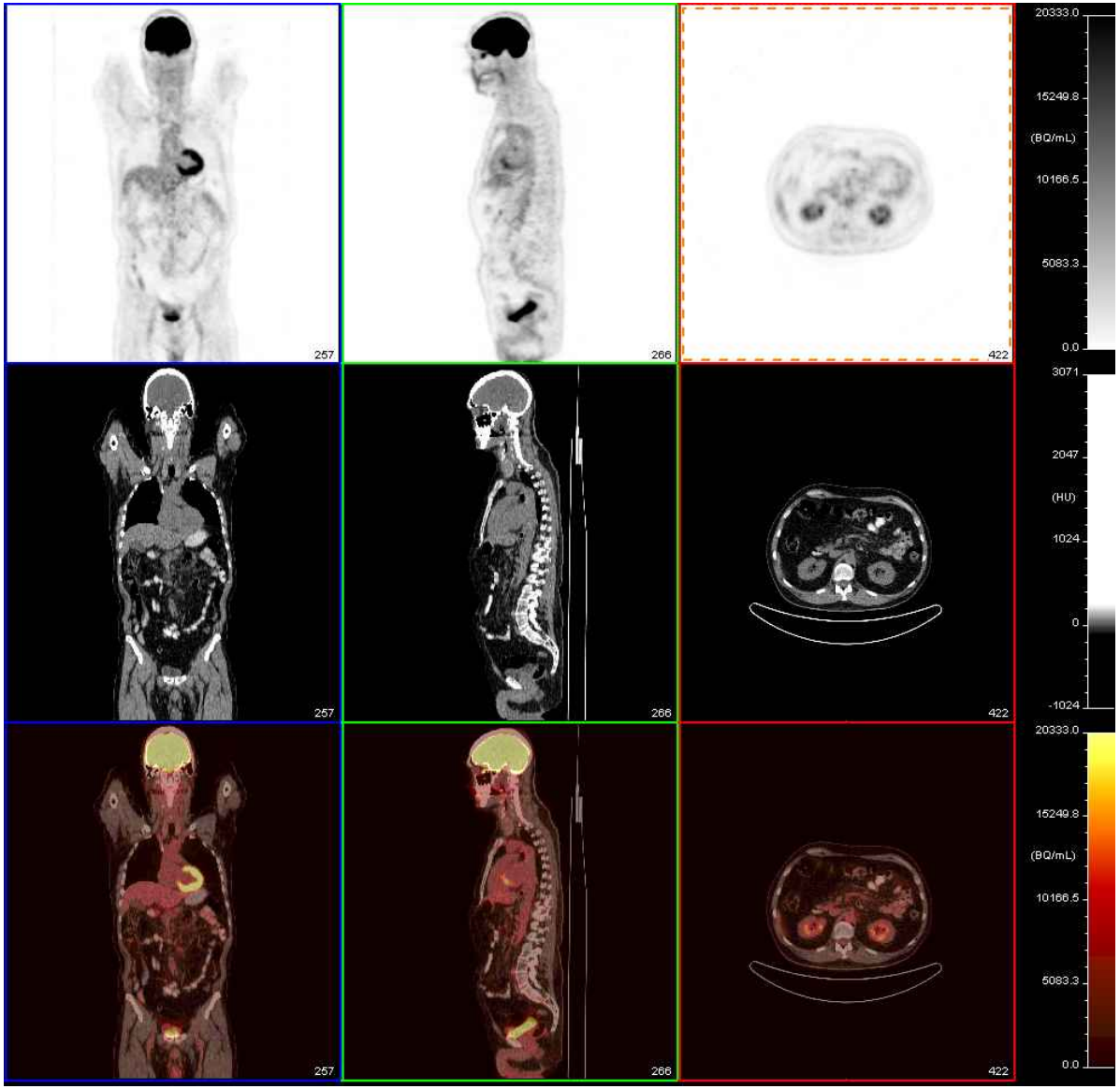


Multimodality

PET

CT

PET + CT

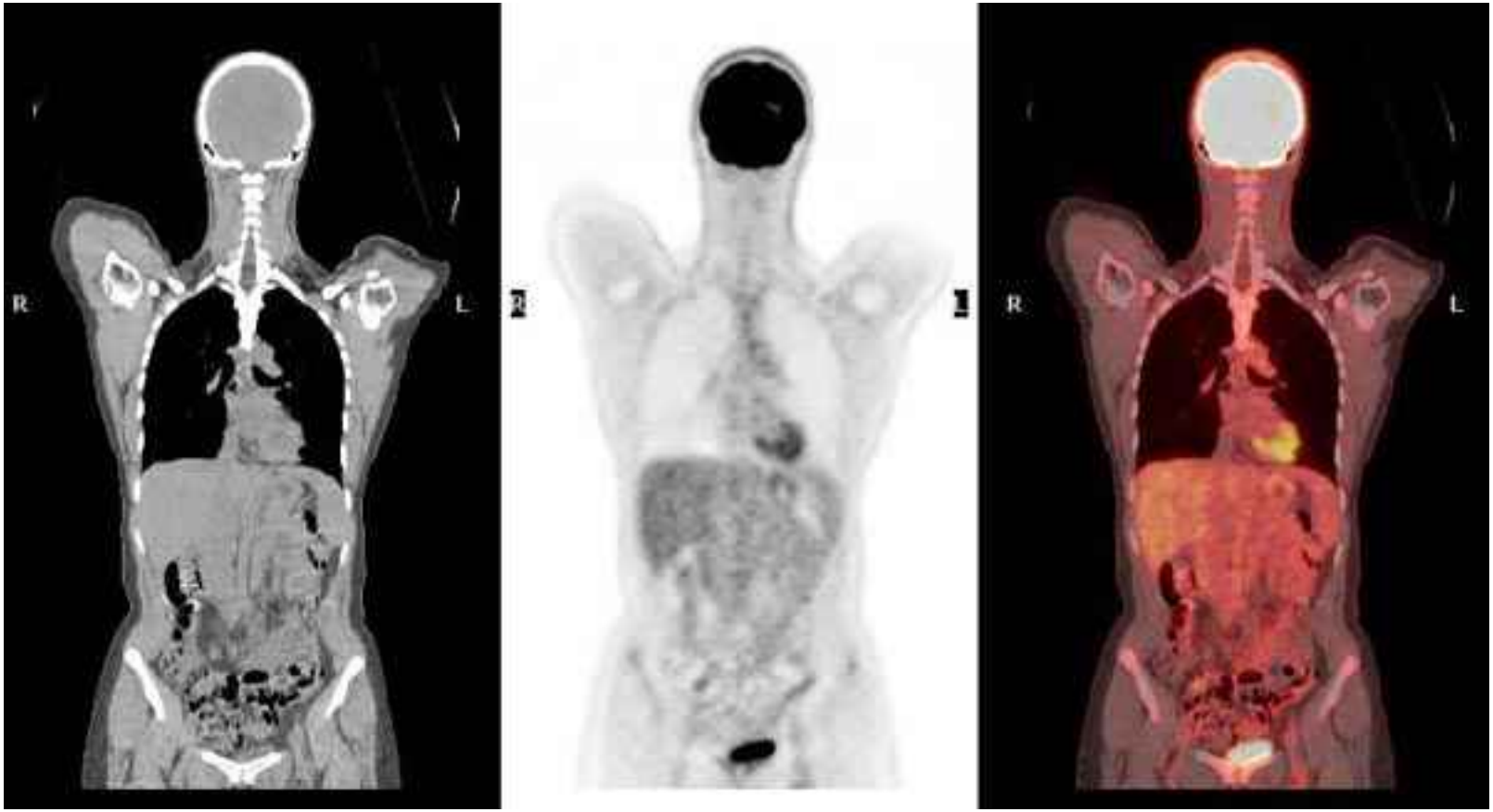


functional

structural

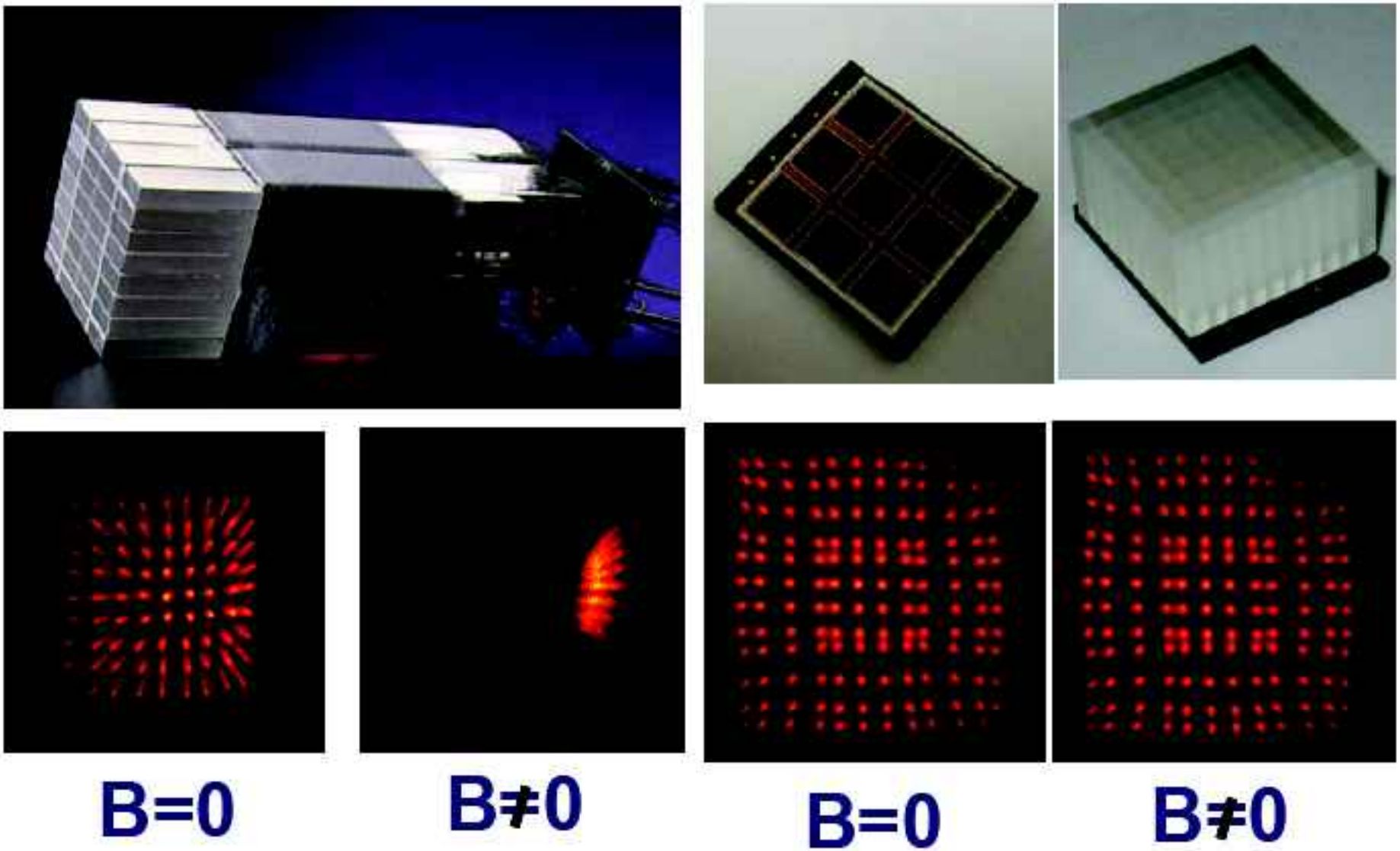
functional and structural

Multimodality



PET-MR

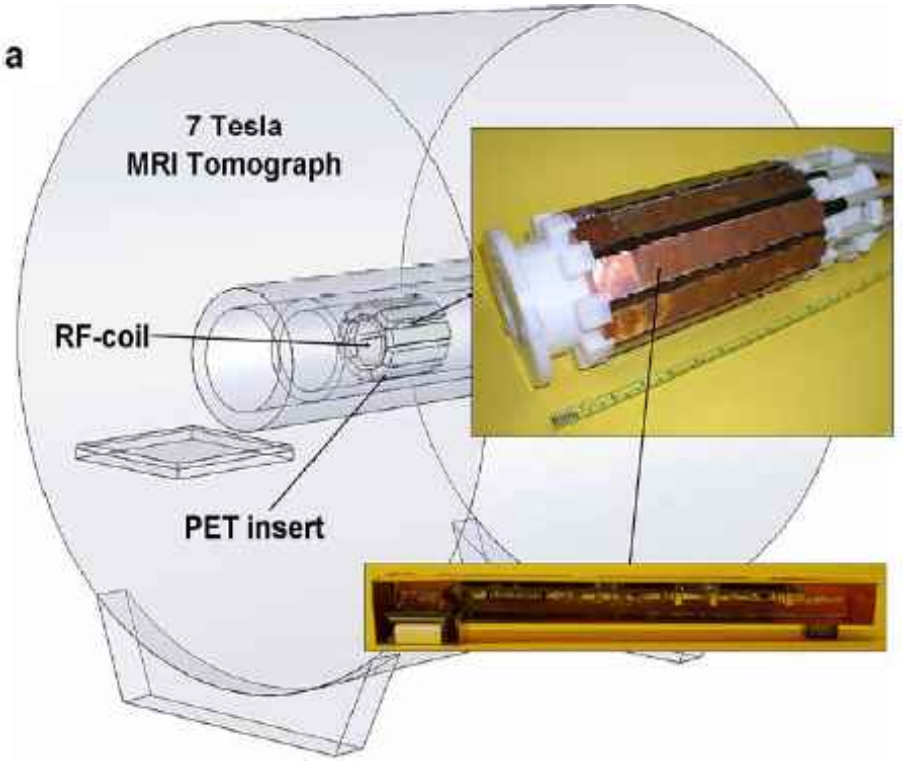
- PET-MR: problems due to PMT sensitivity to magnetic fields



PET-MR

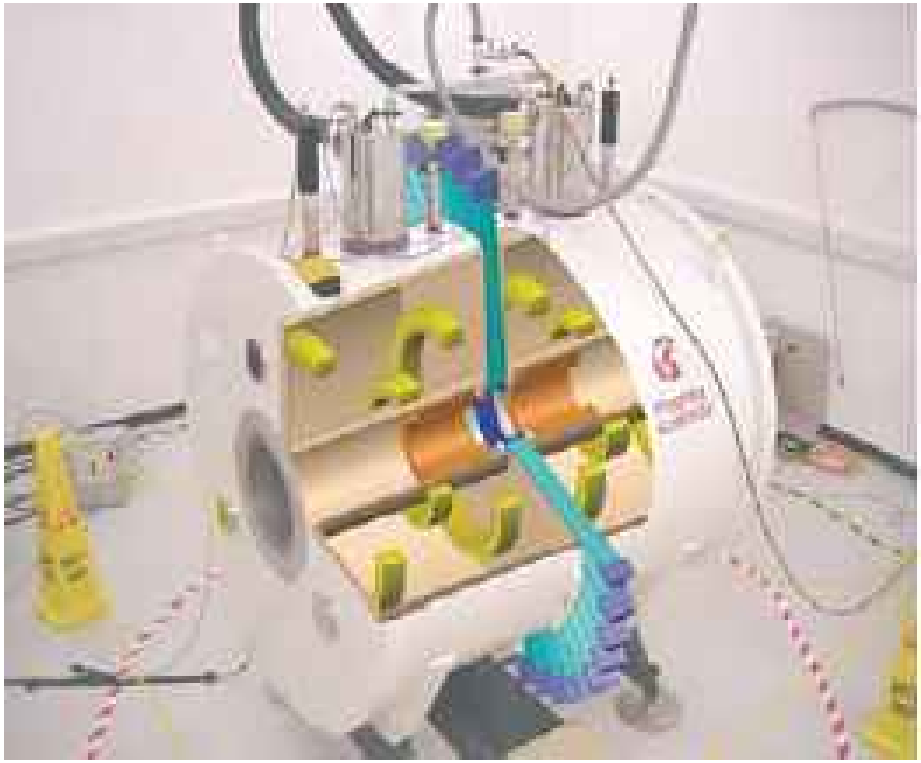
- First, small animal systems.

APDs



B.J. Pichler et al. J. Nucl Med 2006 Apr;47(4):639-47.

PMTs+ light guides



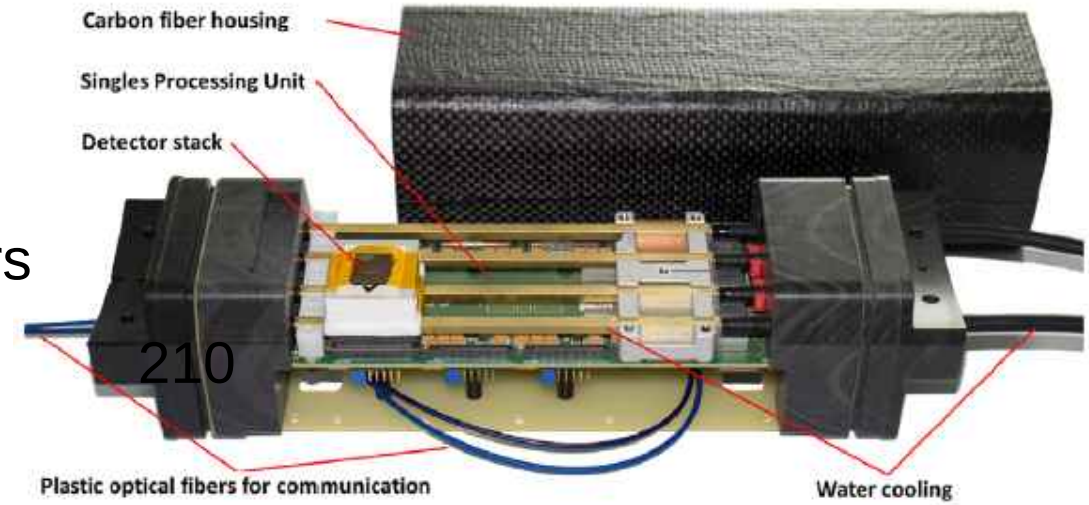
R.C. Hawkes et al.
Tech. Cand. Res. Treat. 9 (1) 2010.

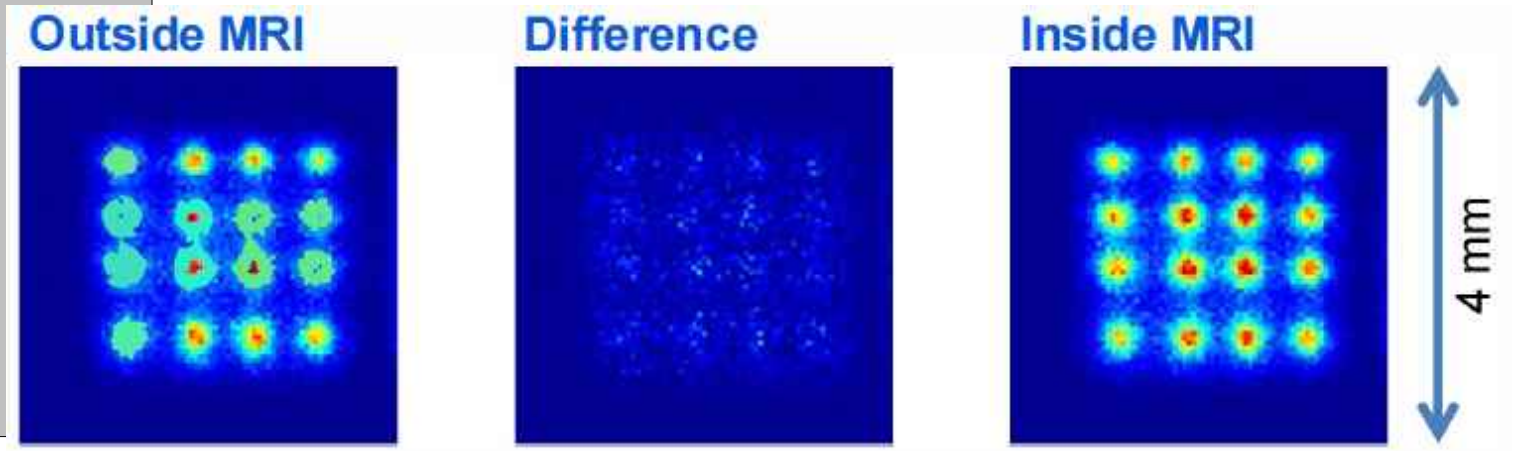
PET-MR

- Currrently preclinical and clinical commercial systems available (Siemens Biograph mMR- APDs, GE SIGNA - SiPMs)
- Advantages over PET-CT:
  - Simultaneous acquisition
  - no radiation
  - Better soft tissue contrast
- Also some drawbacks: attenuation correction is more complex.
- No evidence of clinical advantage yet.
- Still, growing interest in the field.
- Dedicated inserts (brain, breast) under development:
  - Brain: FP7 projects TRIMAGE and MINDVIEW for brain.
  - Breast: H2020 HYPMED
- Few SPECT/MR systems.

PET-MR

- Detector stack:
  - LYSO scintillator array : 30 x 30 pixels of with 1 mm pitch and 12 mm length
  - DSiPM
  - cooling system
- Module: up to 6 detectors
- Ring: 10 modules. 210 mm diameter





Dueppenbecker et al. 2012 IEEENSS MIC Conf Rec. M18-3

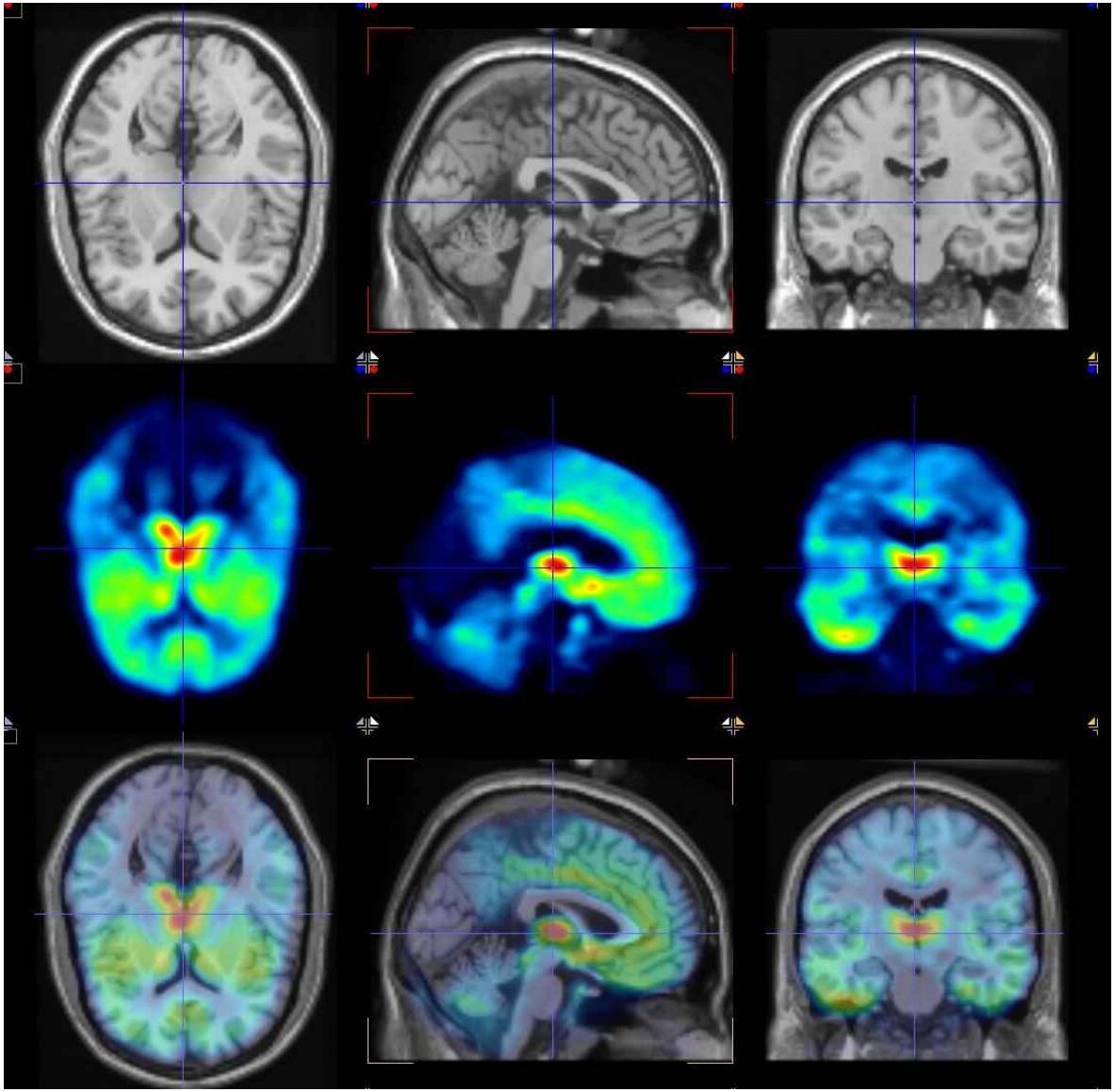
Wehner et al. NIMA 734, 2014

Multimodality

RM
structural

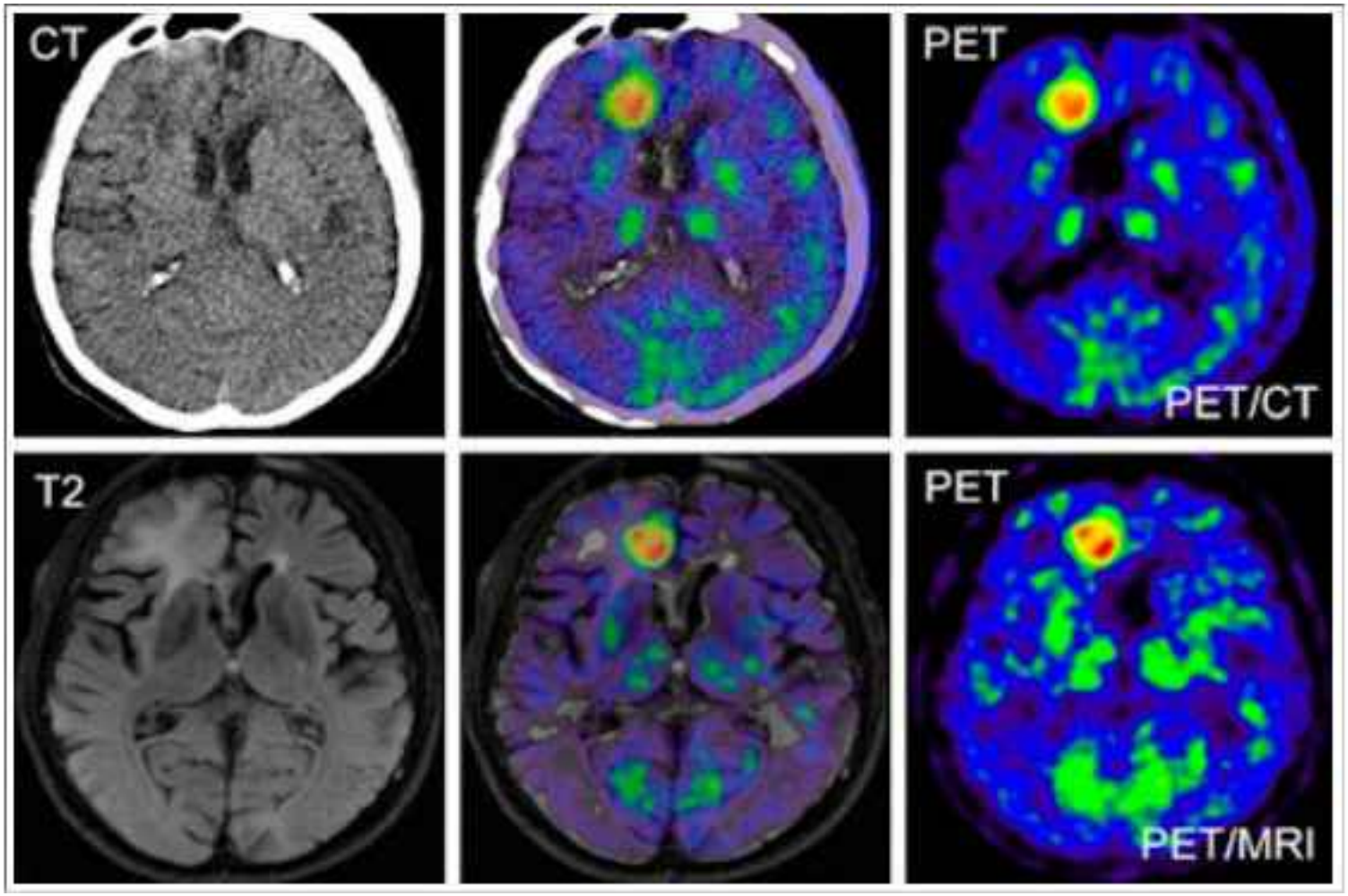
PET
functional

RM + PET
functional
and
structural



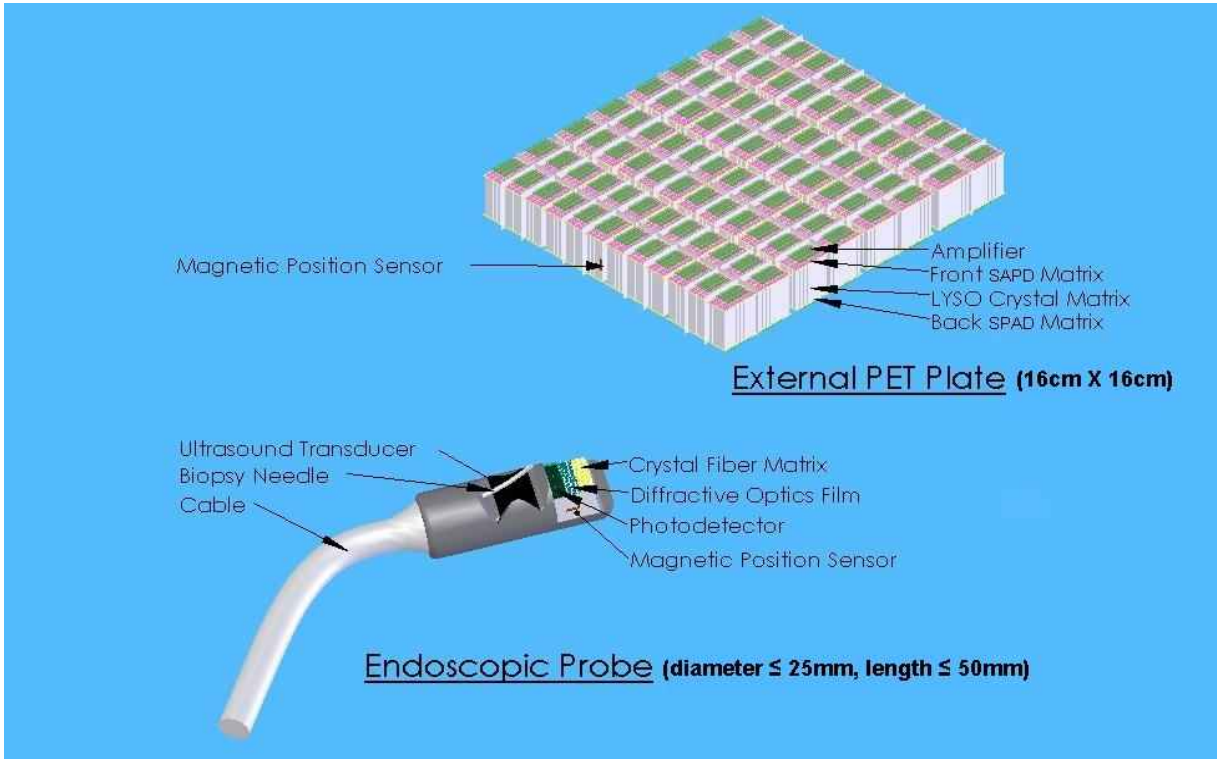
PET-MR

- PET-CT vs PET-MR.



Compact, fast, multimodal

- ENDO TOFPET-US: endoscopic probe for pancreatic and prostatic cancer.
- PET probe in coincidence with an external system. Aims:
  - 1 mm spatial resolution
  - High sensitivity
  - Coincidence timing resolution 200 ps.

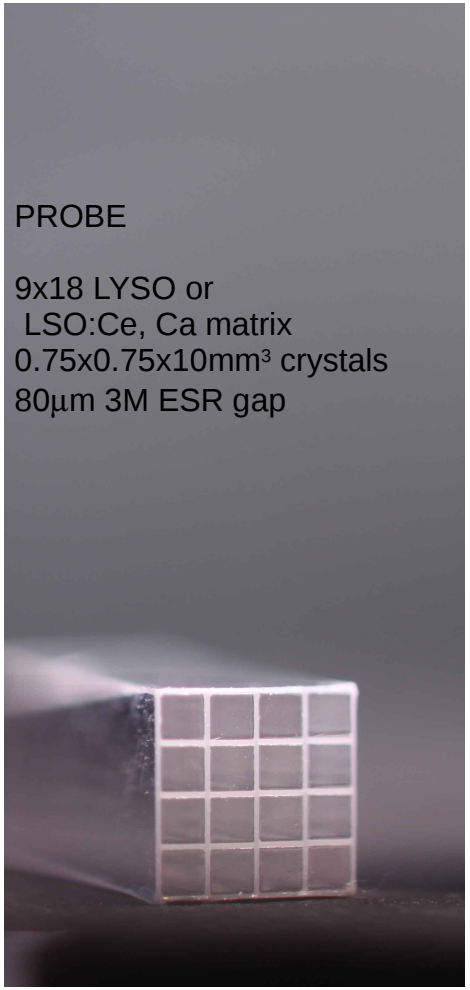


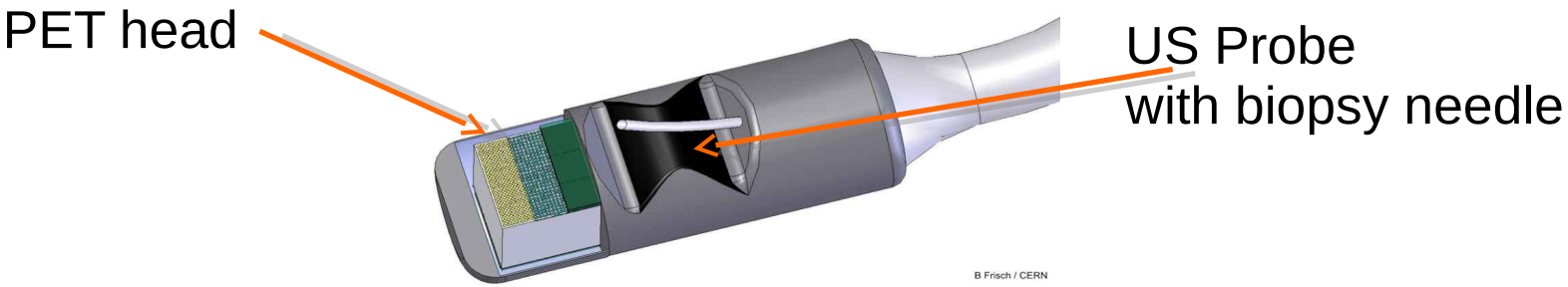
Pictures courtesy of Paul Lecoq

https://endotofpet-us.web.cern.ch/endotofpet-us/

Compact, fast, multimodal

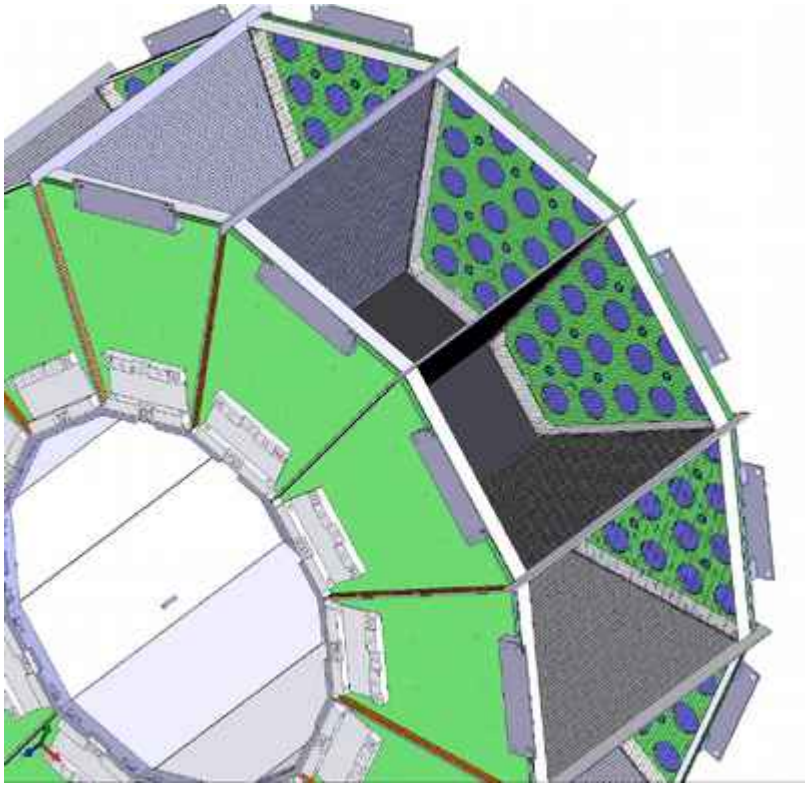
- Probe:
  - Pixellated crystals 0.75x0.75x10mm^3
  - DSiPMs developed at TU Delft
  - US system
  - Tracking sensor.
- Coincidence timing resolution better than 240 ps FWHM achieved





LXe PET - small animal

- 12 modules: LXe TPC with LAAPDs.
- Improved energy resolution.
- Sub-mm spatial resolution
- High sensitivity
- Compton event reconstruction.
- Timing resolution: 1 ns FWHM.



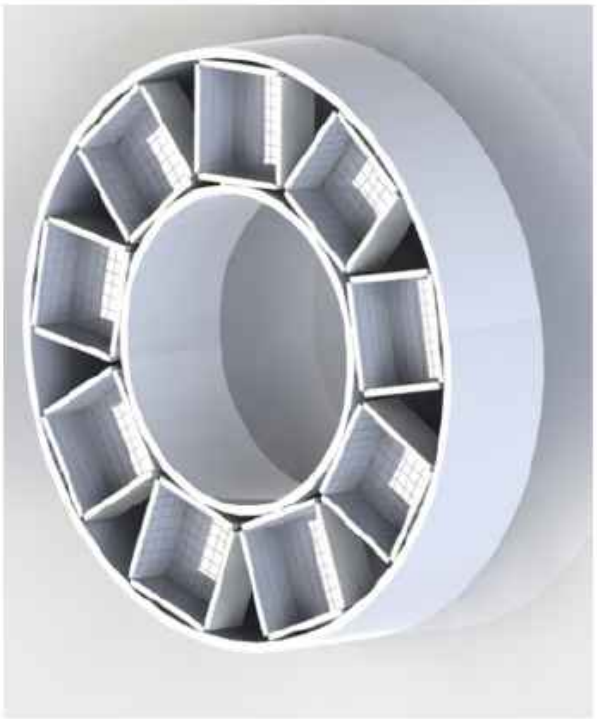
A. Miceli et al. Proc SPIE 2012.

P. Amaudruz et al.

PETALO

- LXe + SiPMs- UV sensitive or TPB-coated.
- Made of Liquid Xenon scintillating cells.
- Energy resolution of 5% FWHM. Spatial resolution 3D – 3 mm.
- CRT in the range of 100-200 ps.
- high-sensitivity, MR compatible.

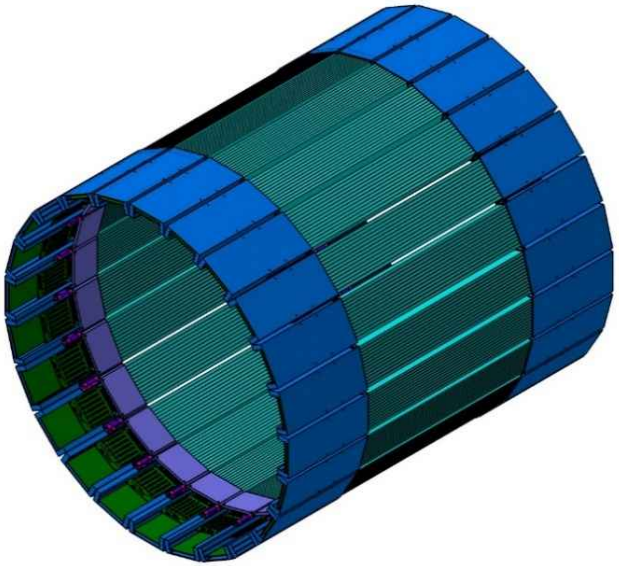
J.M. Benlloch Rodriguez.
Master thesis 2014-2015.



Brain prototype

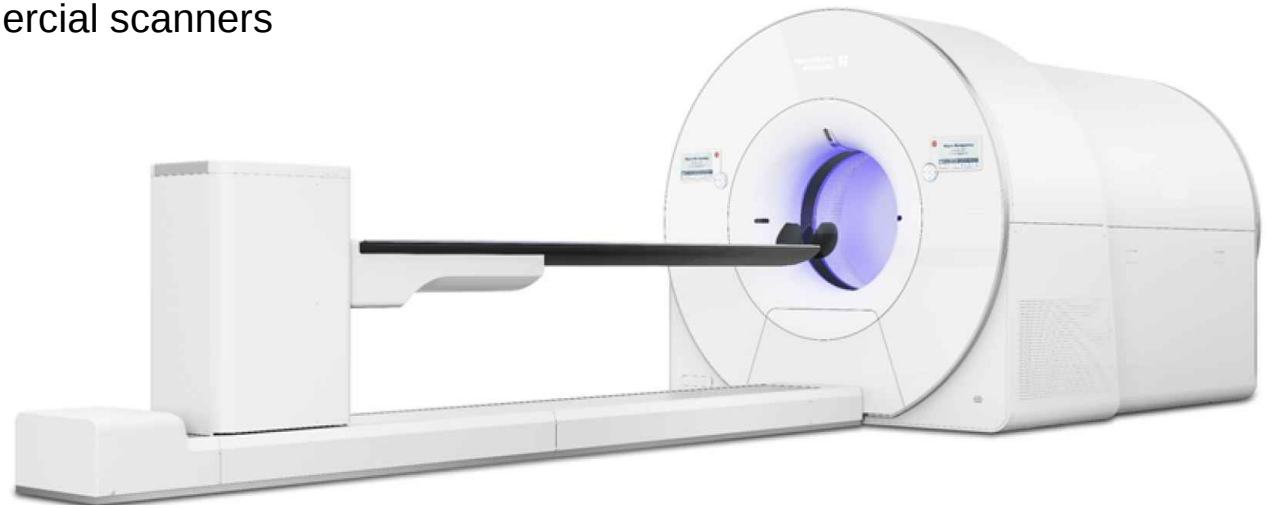
Total body PET

- JPET: plastic scintillators



- EXPLORER

Sensitivity 40-fold higher than current commercial scanners



Outline

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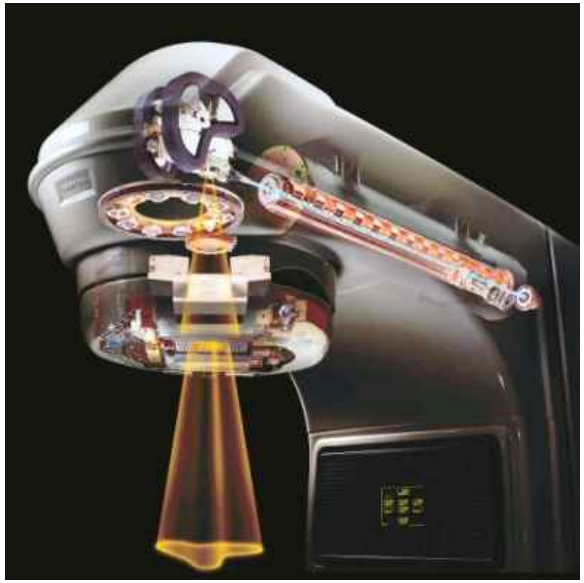
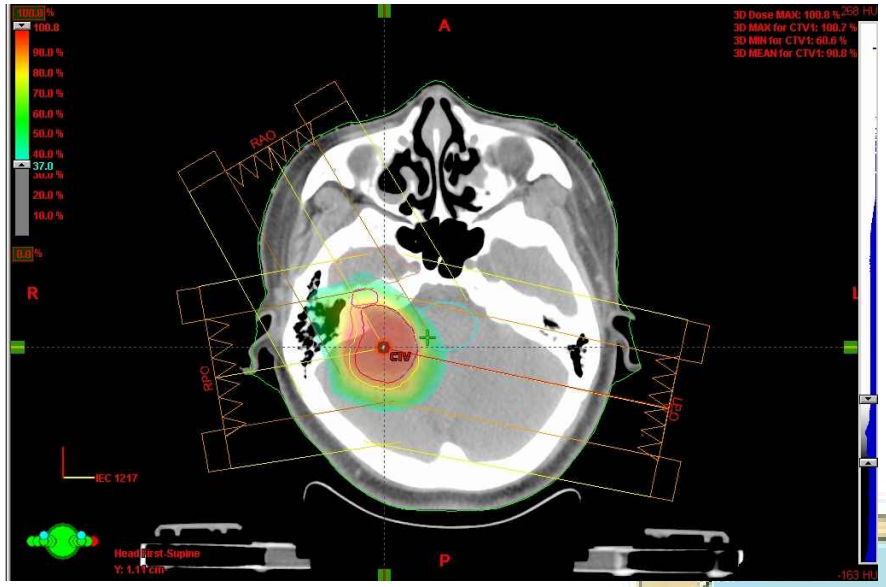
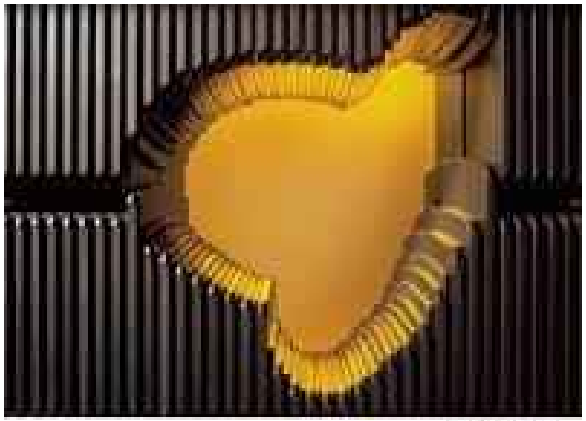
- Overview of status, trends and some recent developments in detectors for nuclear imaging, with emphasis in SiPMs.
  - Single photon imaging / SPECT / Compton imaging.
  - Positron Emission Tomography (PET).
- Detectors for therapy.
- Bioluminescence imaging.
- Cherenkov imaging.

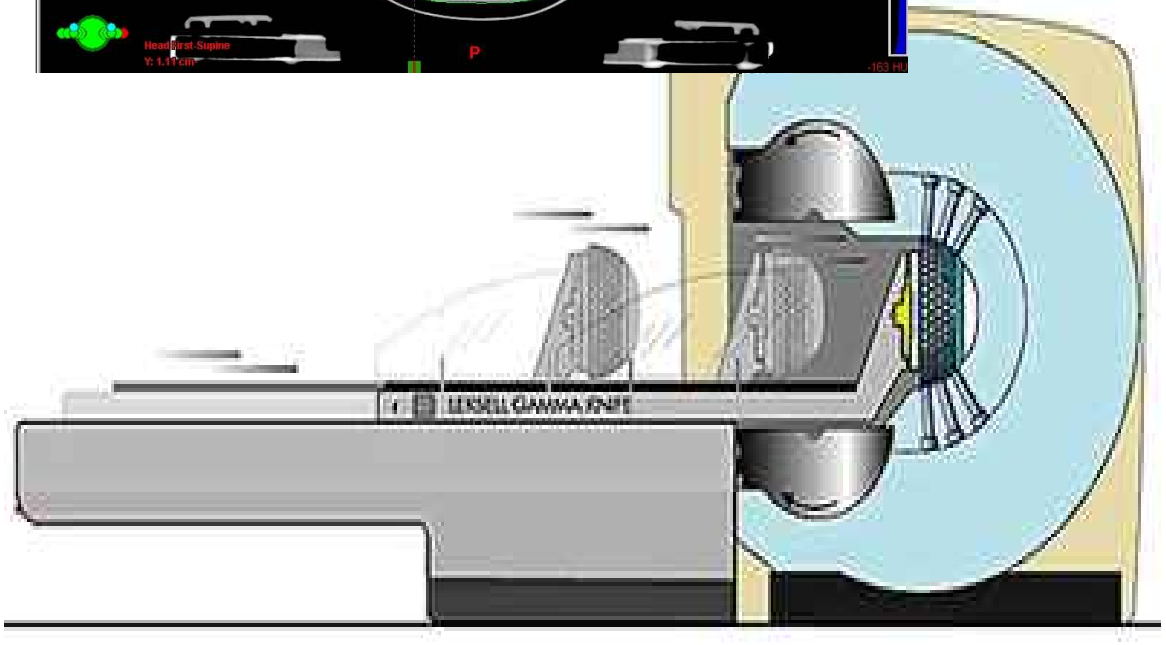
Radiotherapy

- External radiotherapy: Co-60 units or accelerators



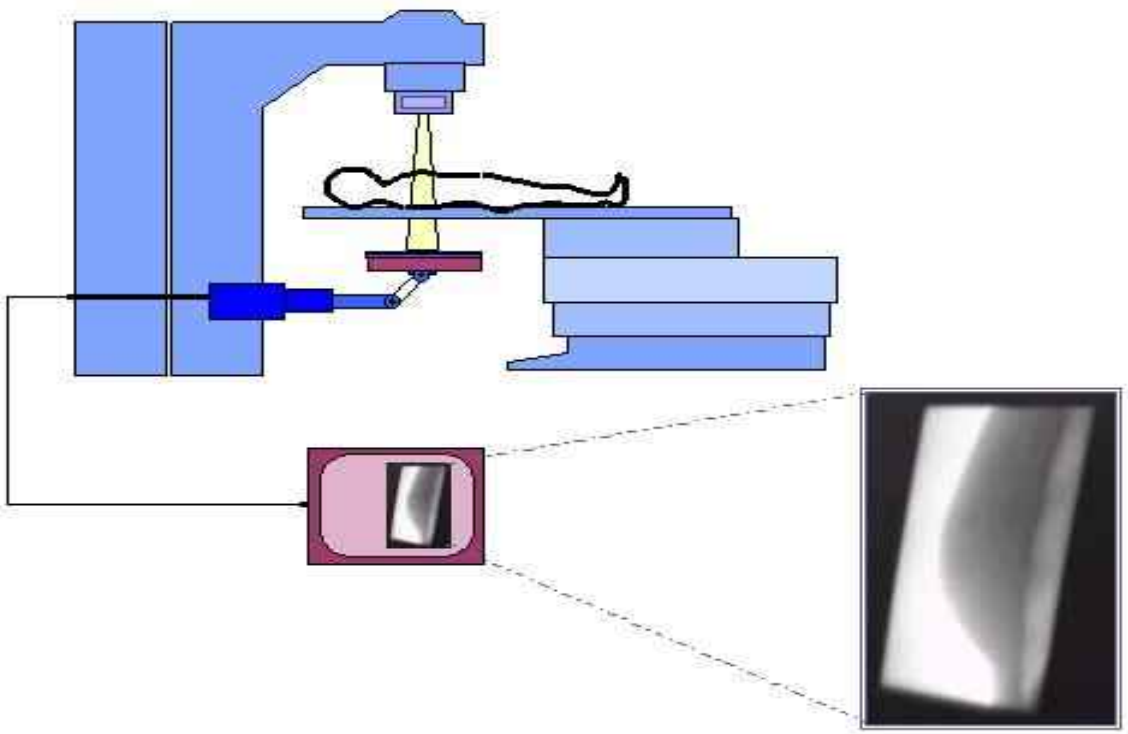






Dose deposition monitoring in radiotherapy

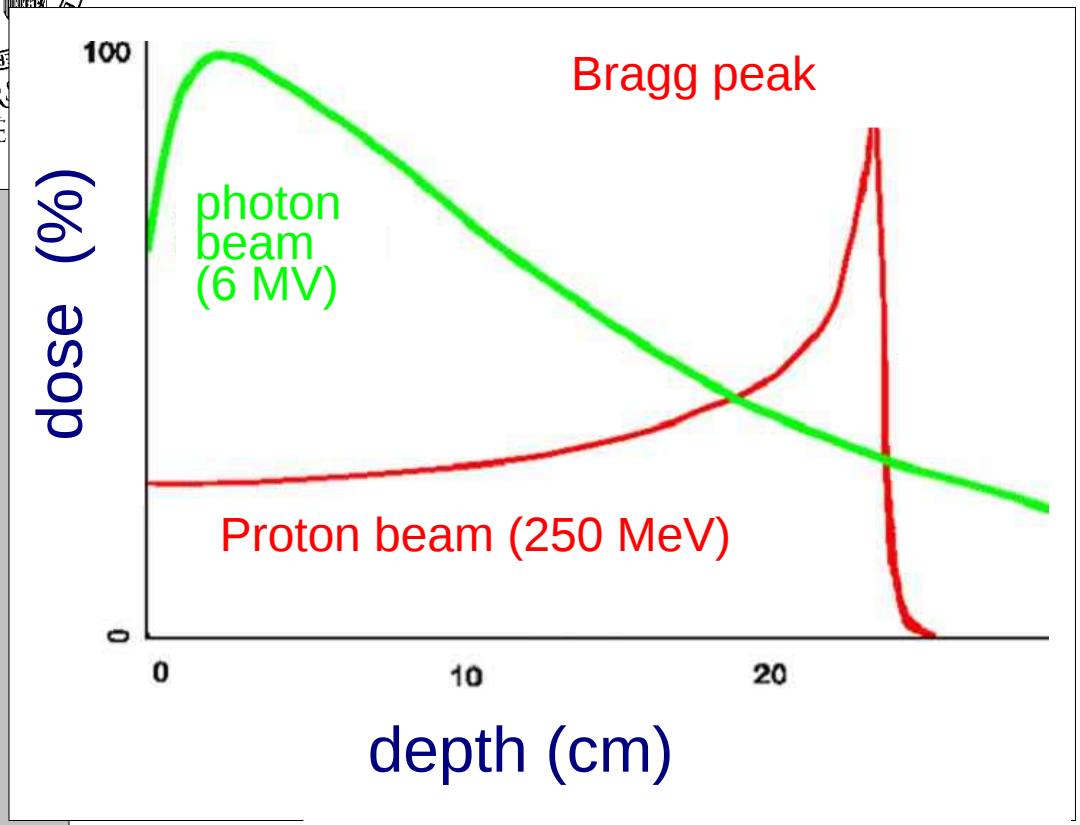
- Detectors to verify correct patient positioning and dose
- Portal radiography (low quality) → EPID: electronic portal imaging devices verify patient position measuring exiting radiation.
  - Mount on the linear accelerator
  - Real time, digital feedback to user

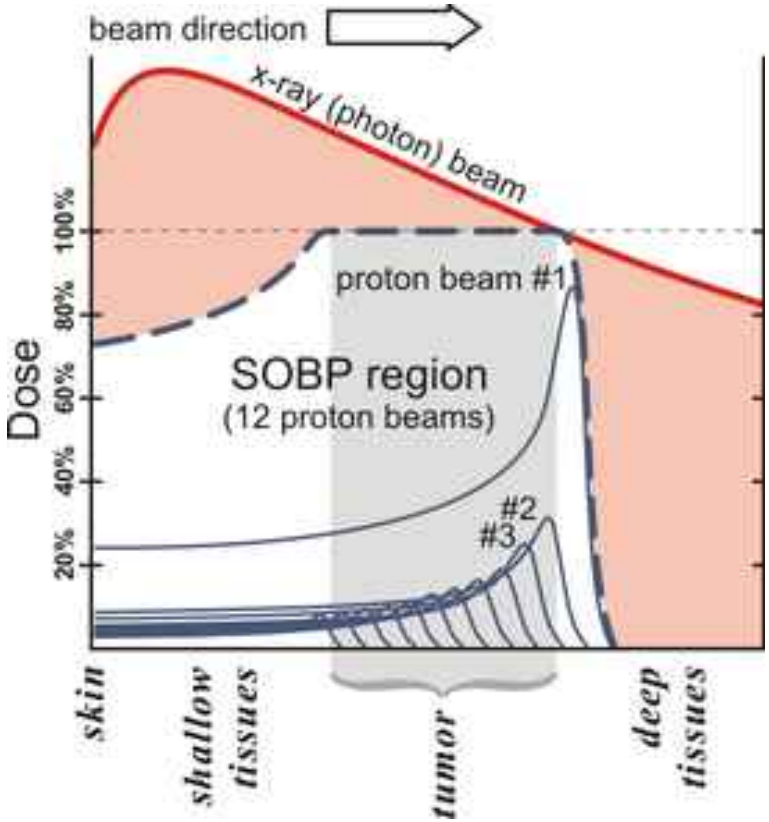


- Fluoroscopy (video)
- Ionization chamber systems
- Flat panel- low efficiency for higher energies.
- Direct detection with amorphous selenium and gaseous amplification.

Hadron therapy

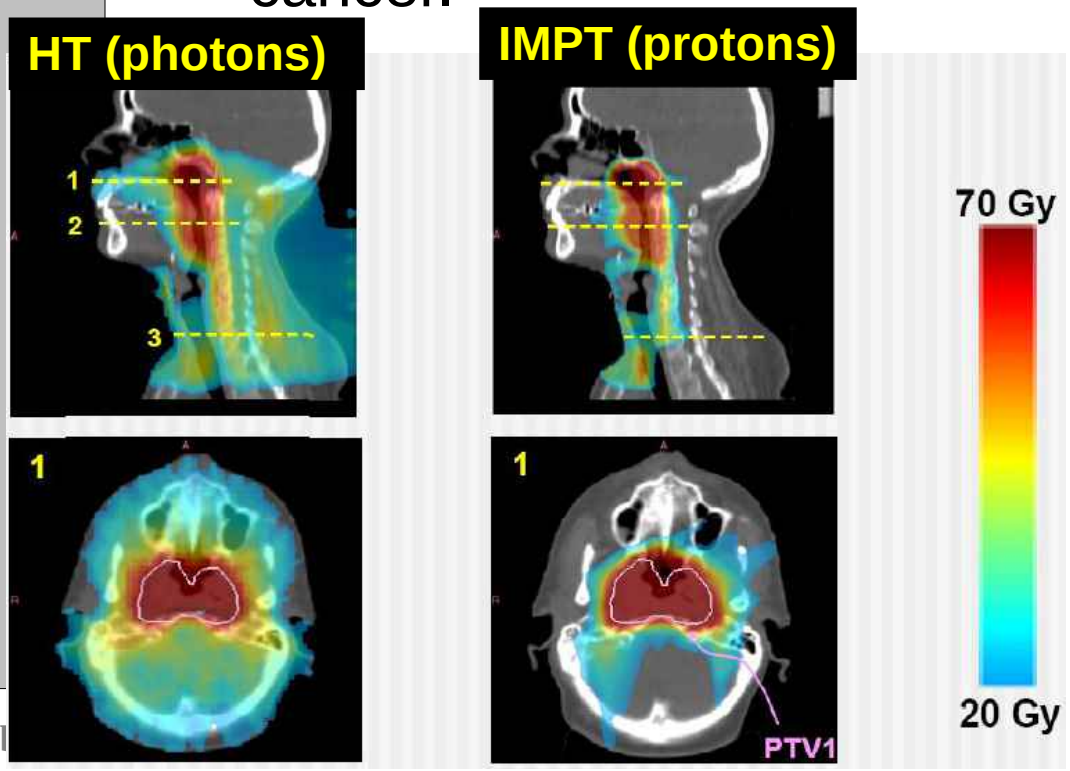
- Hadron therapy: charged particles (protons or Carbon ions), precise delivery of radiation dose (Bragg peak).
- Reduce the dose to healthy tissue.

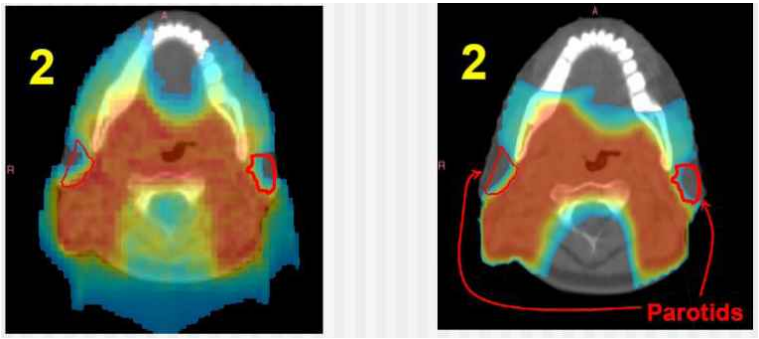




Hadron therapy

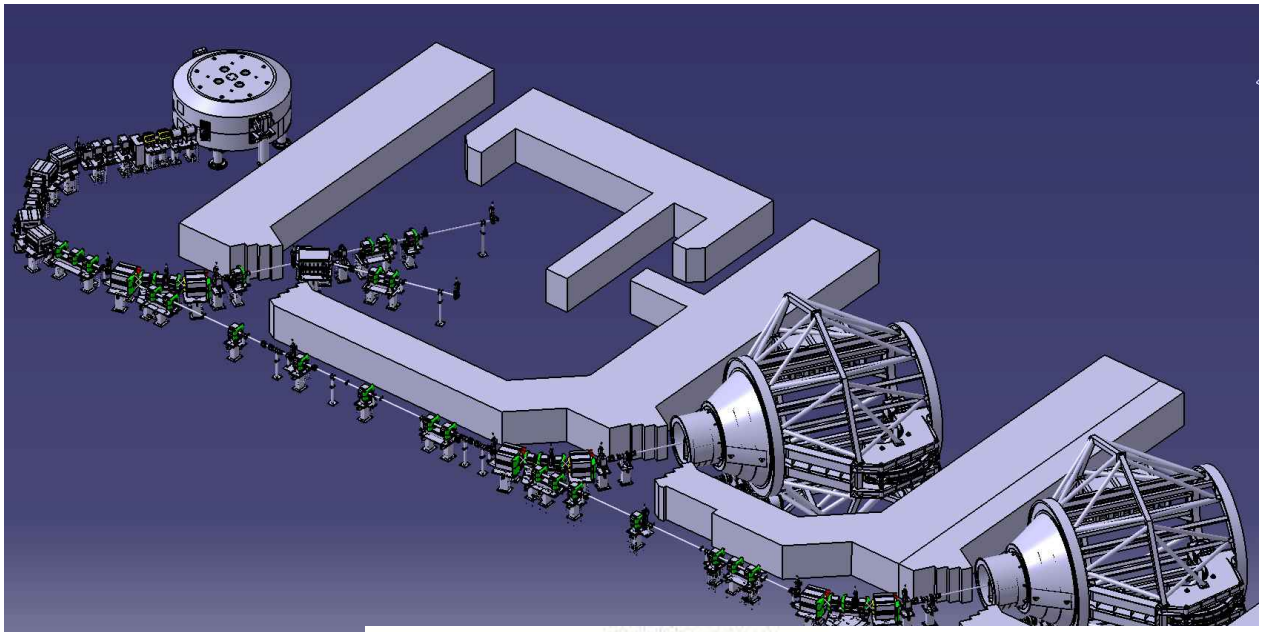
- Large benefit over conventional radiation therapies in some cases (ocular tumours, children, organs at risk, radioresistant tumours).
- Higher relative biological effectiveness (RBE) than photons
- Precise delivery to tumour area => increase of cure rates and reduction of side and long term effects and secondary cancer.

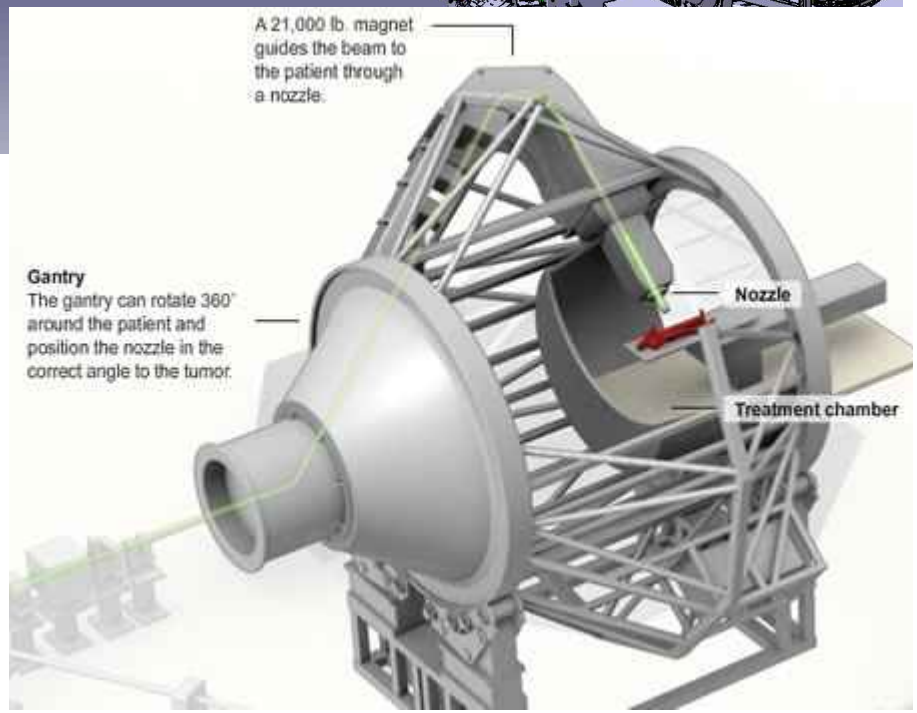




L. Widesott et al.
IJROBP 72(2):589, 2008

Centres



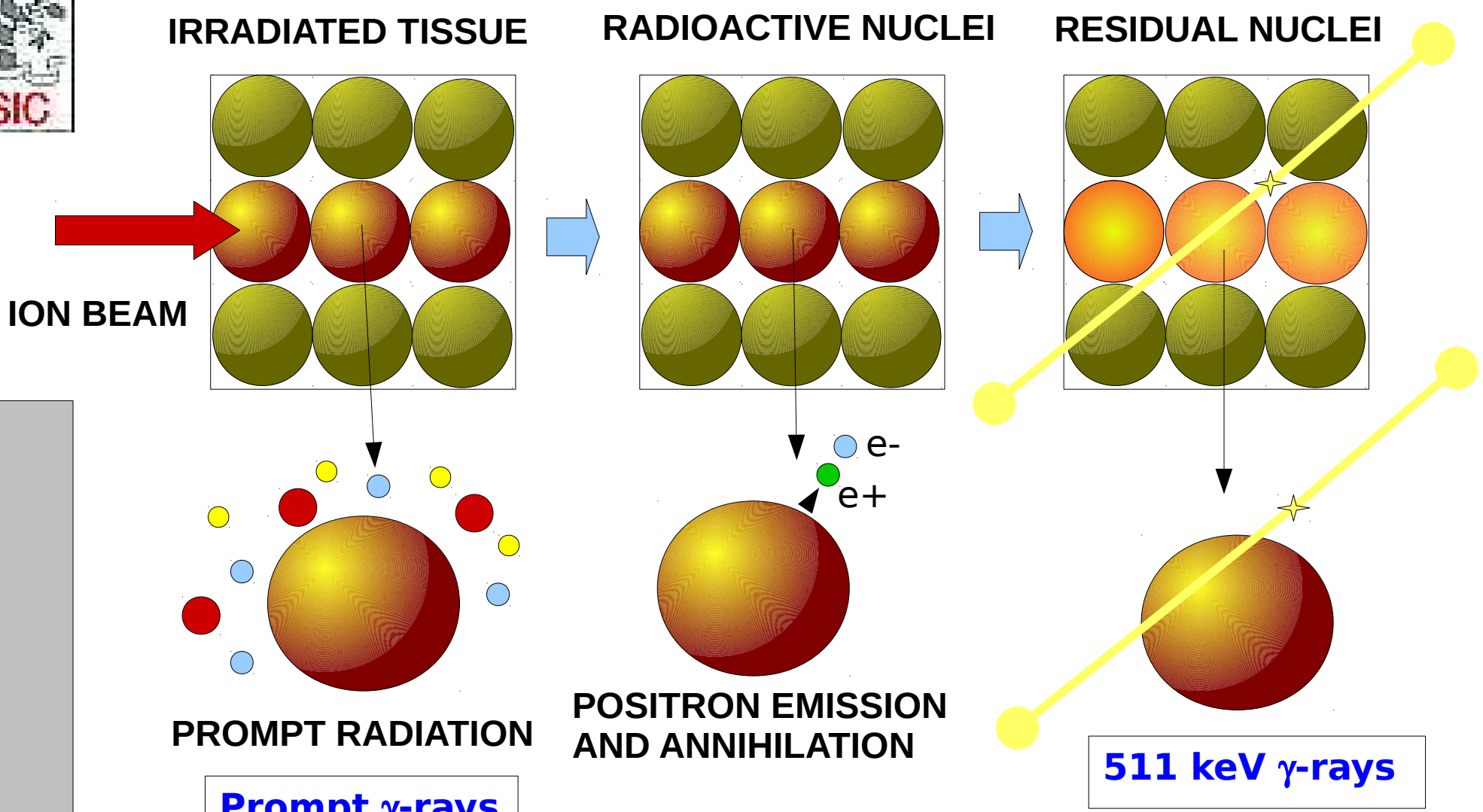

A 21,000 lb. magnet guides the beam to the patient through a nozzle.
Gantry
The gantry can rotate 360° around the patient and position the nozzle in the correct angle to the tumor.
Nozzle
Treatment chamber

Dose monitoring in hadron therapy

- PROBLEM: the dose administered can not be directly measured (as done in conventional radiotherapy).
- Secondary particles emitted during treatment can be used for monitoring the dose delivery.

- An accurate monitoring system is essential:
  - To verify dose delivery and correct for treatment deviations.
  - To reduce safety margins.

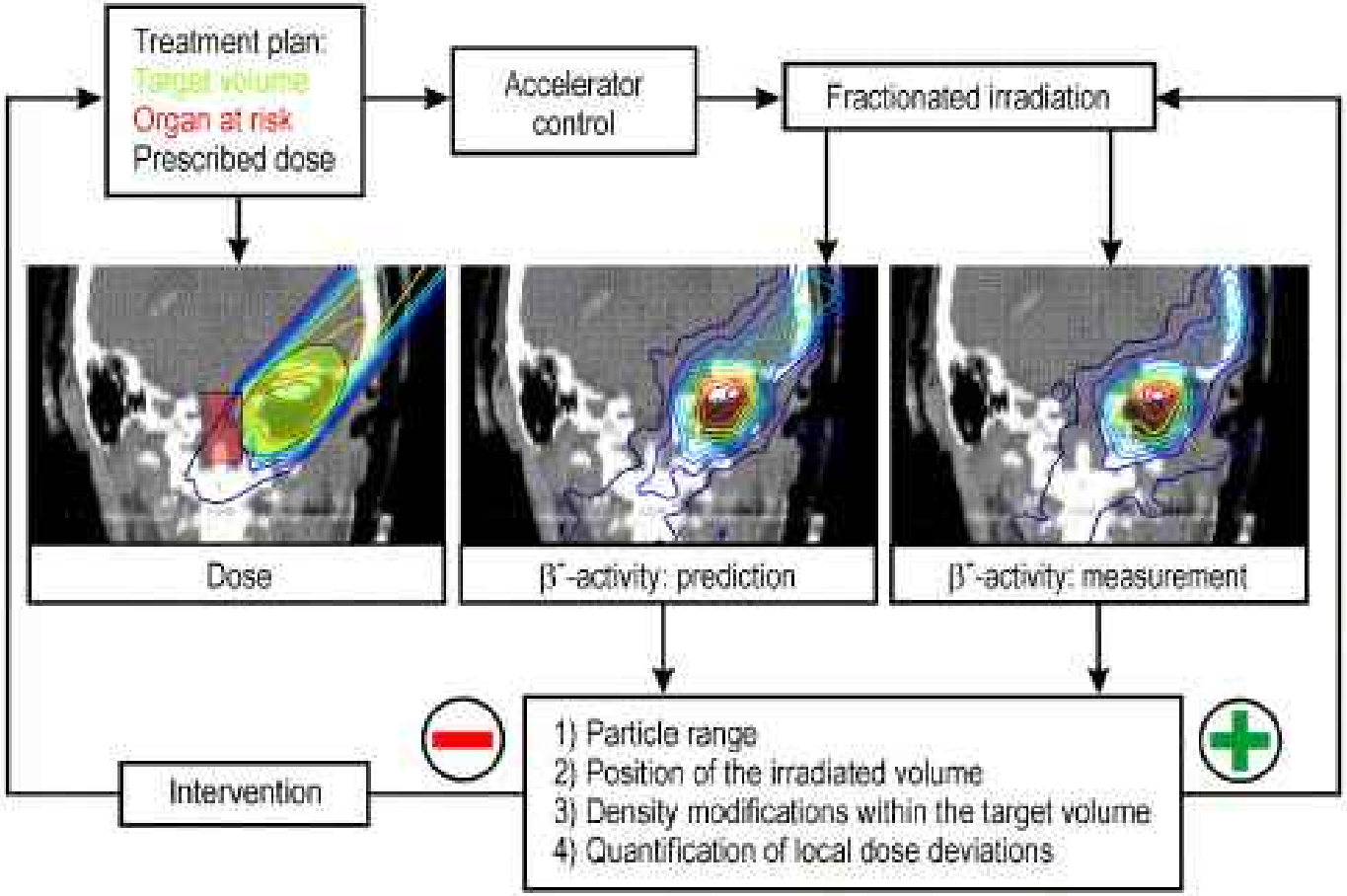
Dose monitoring in hadron therapy



Prompt γ-rays
***E* ~ 1-15 MeV**

Dose monitoring in hadron therapy

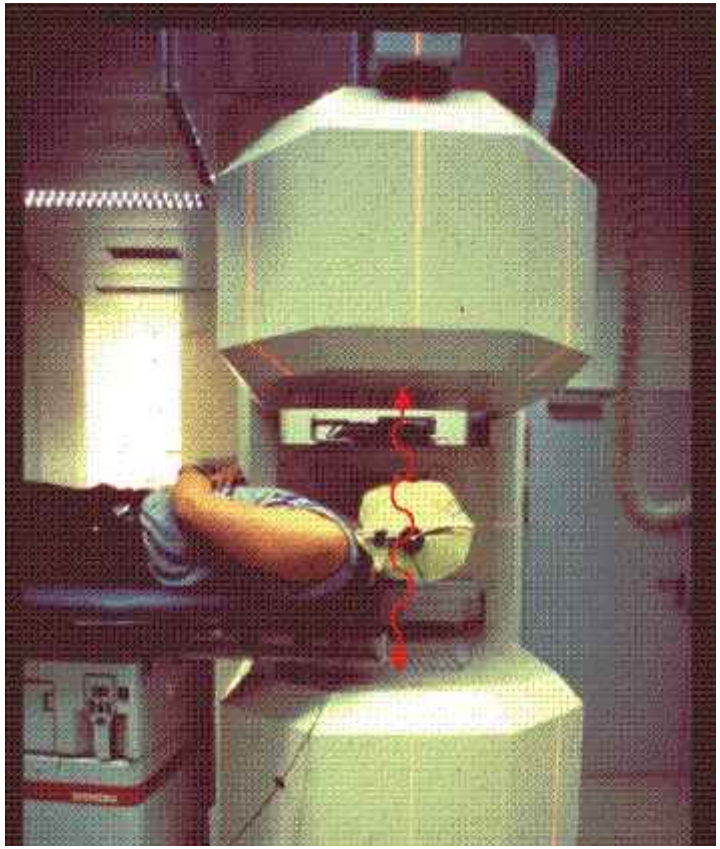
- Positron Emission Tomography (PET) + MC currently employed.



•Dose verification: comparison of dose planned and estimated from detected β+ activity.

PET for treatment monitoring

- Irradiated tissue nuclei become positron emitters (O, C).
- In-beam, in-room, offline

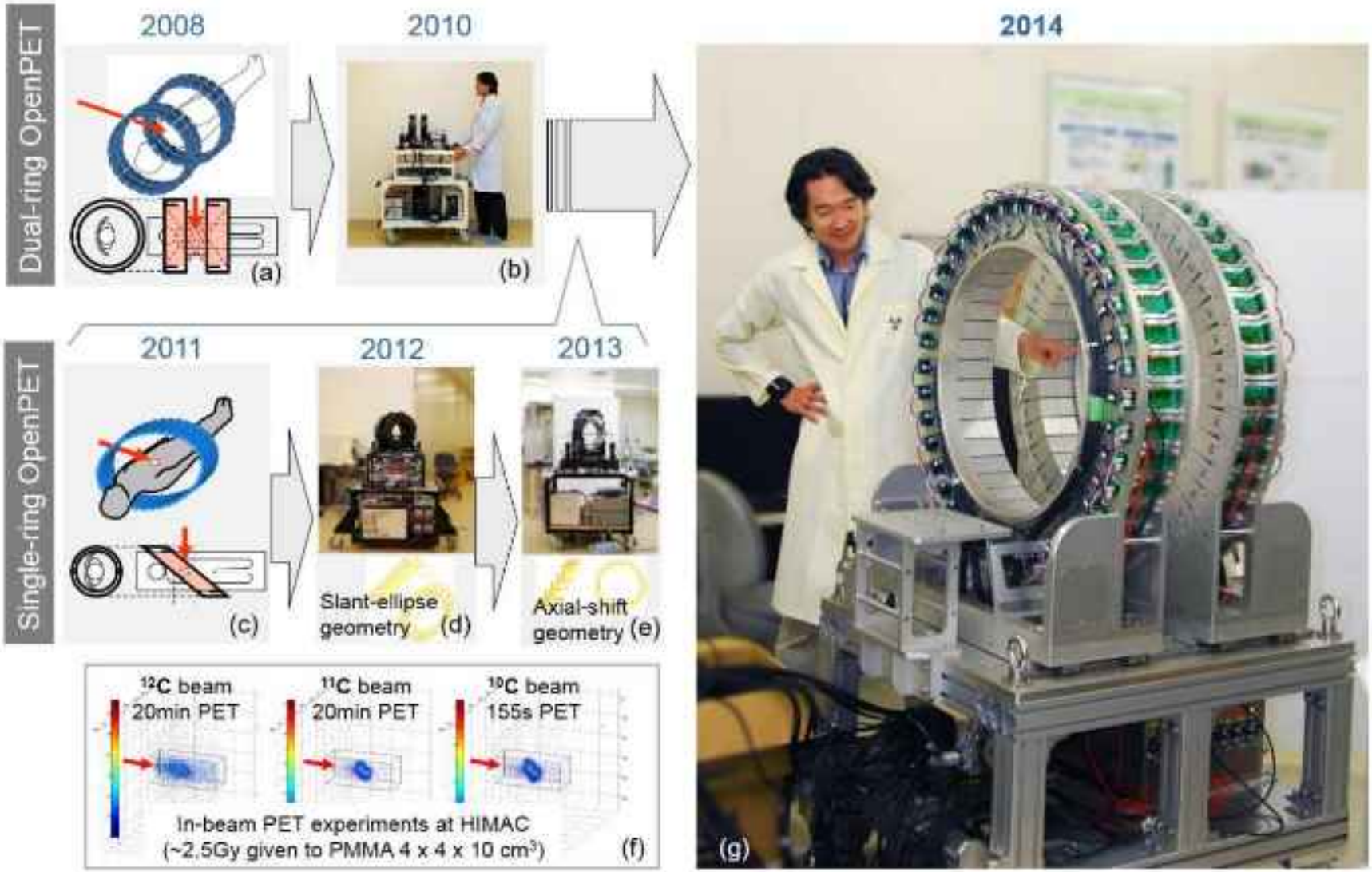


- In-beam -> gaps. Improved results with TOF-PET
- Many groups working on such systems.

PET for treatment monitoring

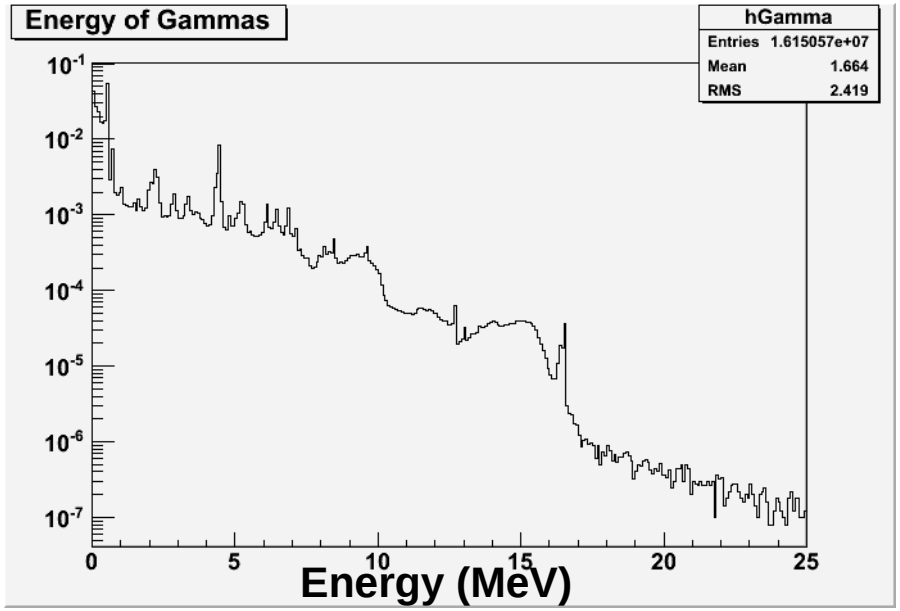
- Limitations:
  - Positron production does not follow irradiation immediately
  - Biological washout- activity carried away by metabolic processes
  - Low amount of β+ activity induced- low efficiency
  - Difficult online studies – in-beam -> partial ring
  - Photons produce significant background
- Attempted solutions:
  - Fast transfer to PET and accurate biological models.
  - In-beam TOF-PET.
  - Short lived isotopes.

PET for treatment monitoring



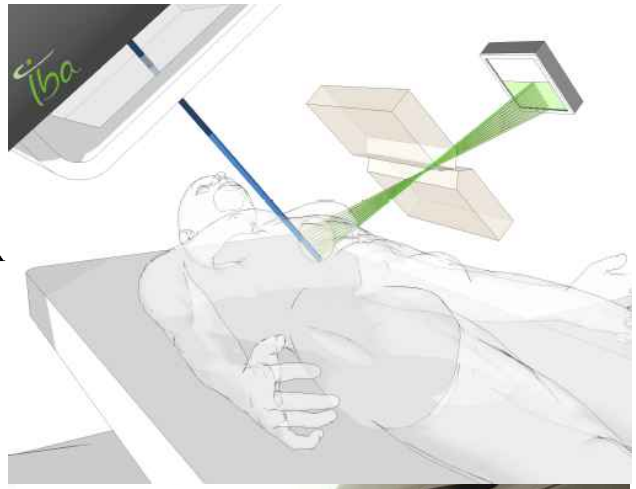
Treatment monitoring in hadron therapy

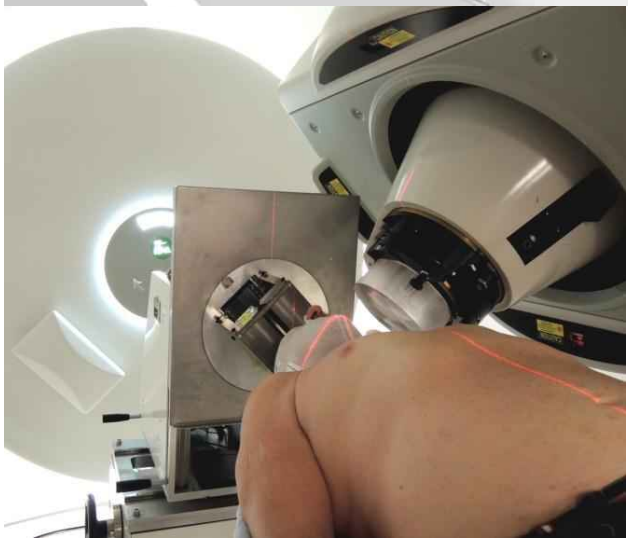
- Alternative: Prompt gammas also emitted from nuclei excited during therapy and can be used for this purpose.
  - Emission ~ns after irradiation.
  - ~ 7 times more particles/cGy
- Emitted in a continuous energy spectrum with energies of MeV.

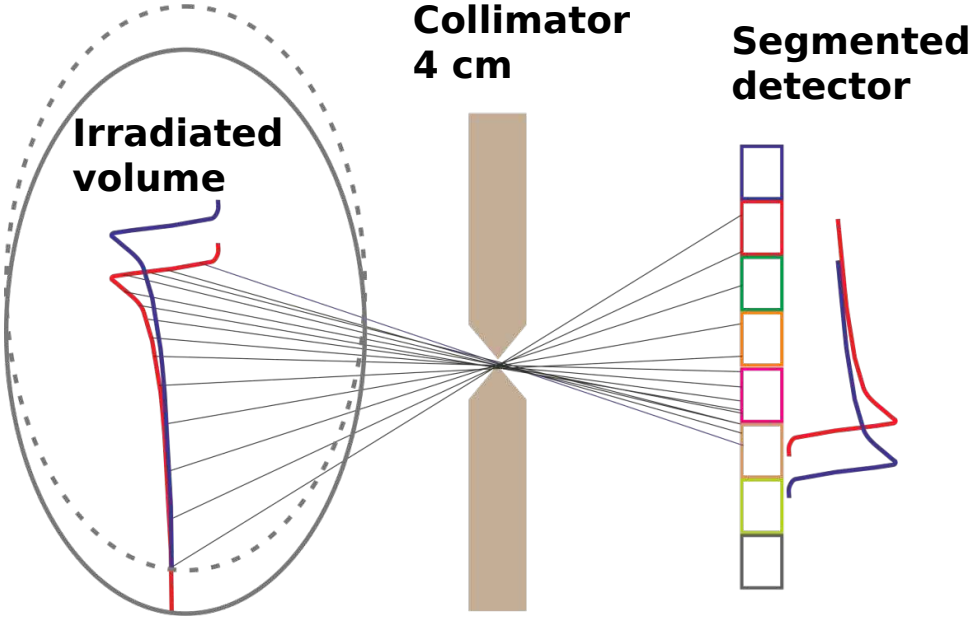


Collimated systems

- Conventional gamma cameras not suited for such high energies.
- Dedicated collimated cameras.







LYSO

$20 \times 0.8 \times 0.32\ cm^3$

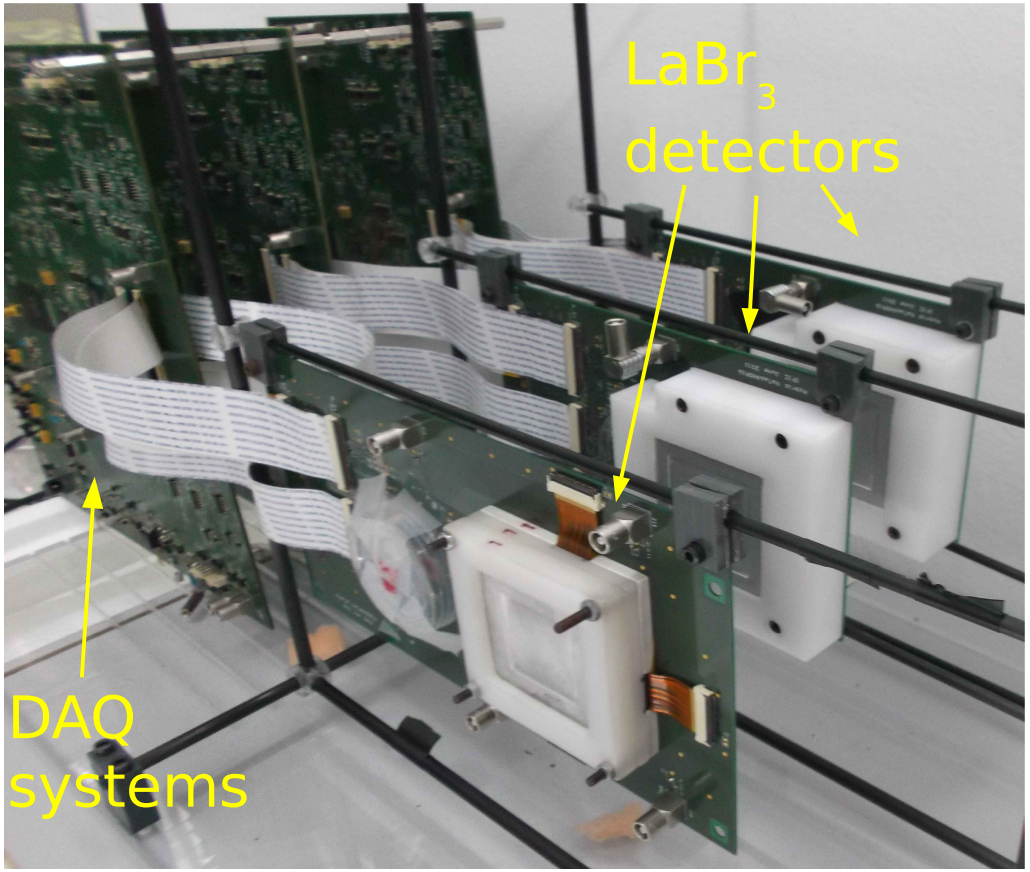
Beam

J. Smeets et al.: Phys. Med Biol. 57 (2012) 3371

2 mm range variations observed

Compton cameras in HT

- Three-plane Compton telescope with LaBr3 monolithic crystals coupled to SiPMs.

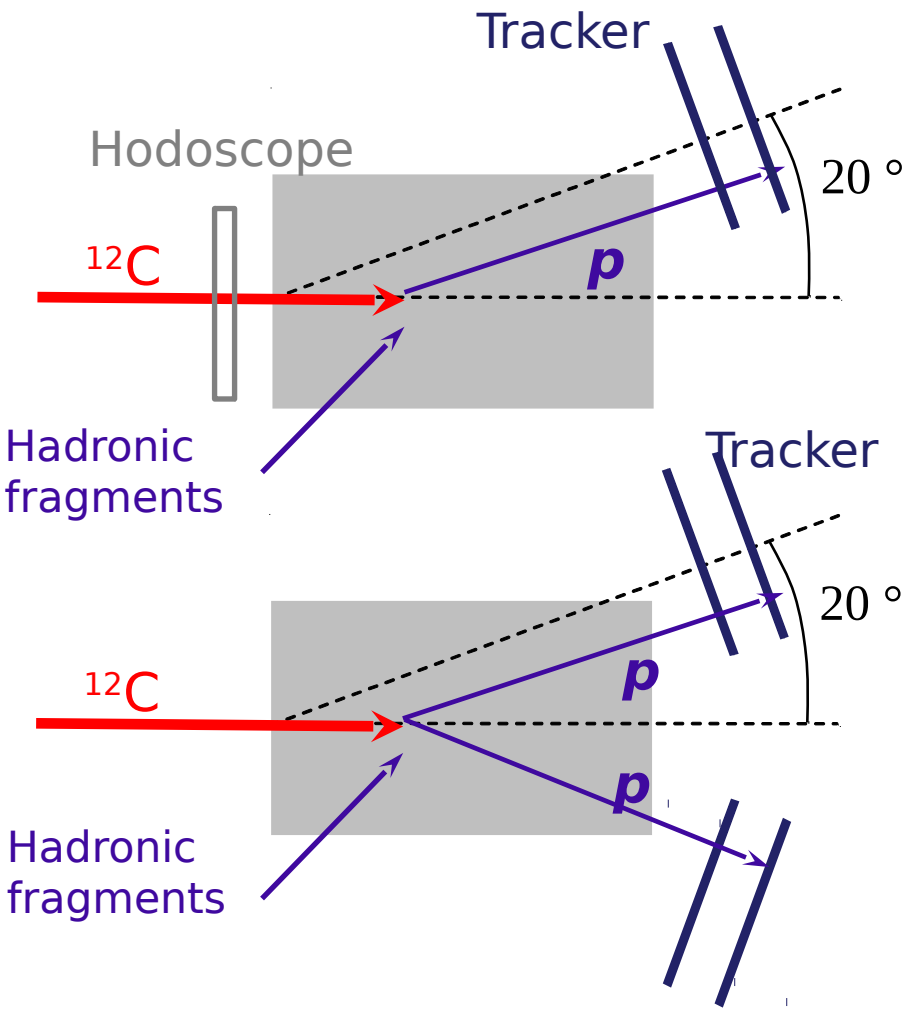


E Muñoz et al. Phys. Med. Biol, 2017.

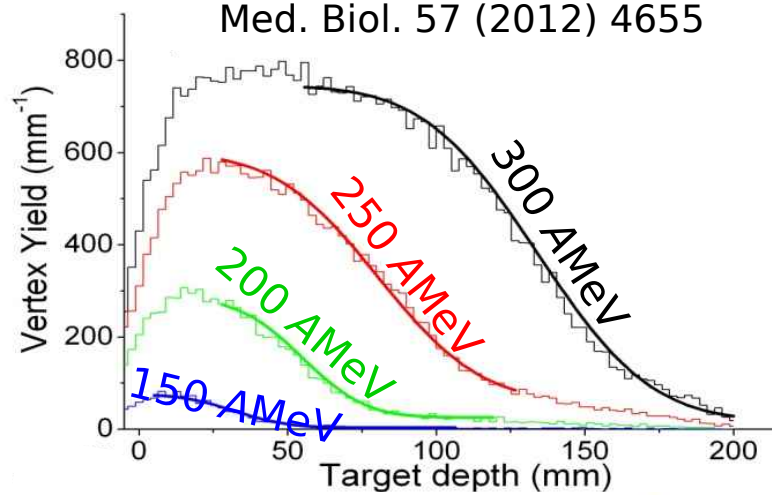
P. Solevi et al. Phys. Med. Biol. 61 (2016), 14, 5149-5165

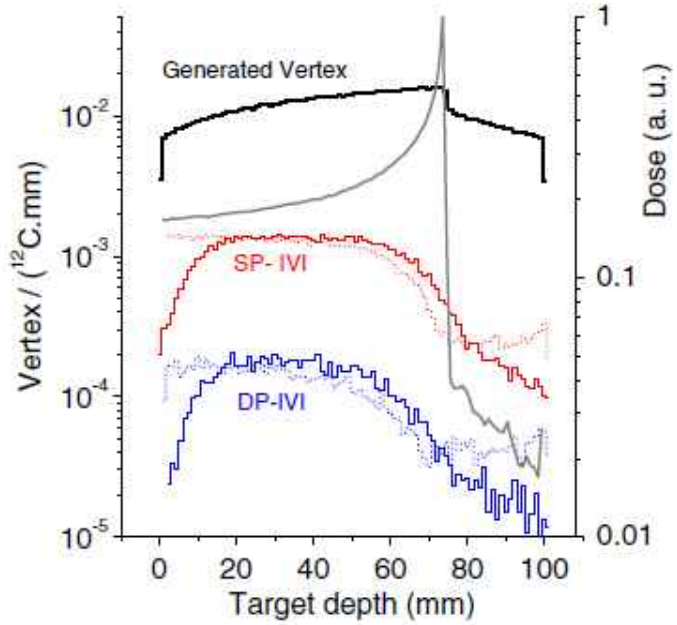
Other with SiPMs

- Interaction Vertex Imaging with scintillating fibers
- Proton CT- scintillating tiles



P Henriquet et al., Phys. Med. Biol. 57 (2012) 4655





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- Bioluminescence imaging.
- Cherenkov imaging.

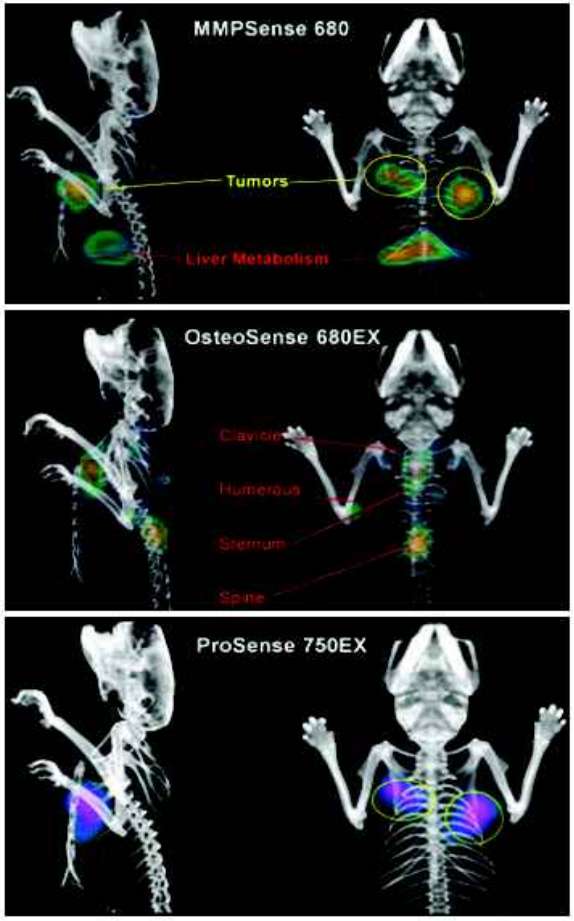
Imaging in the optical range

- Radiation in the optical range emitted through different mechanisms: bioluminescence, fluorescence, fosforescence, cherenkov imaging.
- Luminescence: excitation of electrons to a higher energy state, and return to lower state emitting light (fluorescence or photoluminescence- electromagnetic radiation, thermoluminescence, chemiluminescence, radioluminescence, electroluminescence...).
  - Bioluminescence: chemical reactions in living organisms (cells/tissues/organs).
  - Fosforescence: delayed luminescence or 'afterglow': electron trapped for a while.
  - Optically stimulated luminescence: triggered by visible or infrared light (fosforescence, since it is delayed).

Imaging in the optical range

- Employed in vitro/in vivo, cells, tissues, organs, animals, plants, humans, spontaneous/induced/estimulated.
- Mostly CCDs, PMTs in some applications.
- Different imaging techniques combined.
- Non-invasive.
- Non-ionizing.
- Low cost.
- Low light levels.
- Low penetration.

IVIS Spectrum

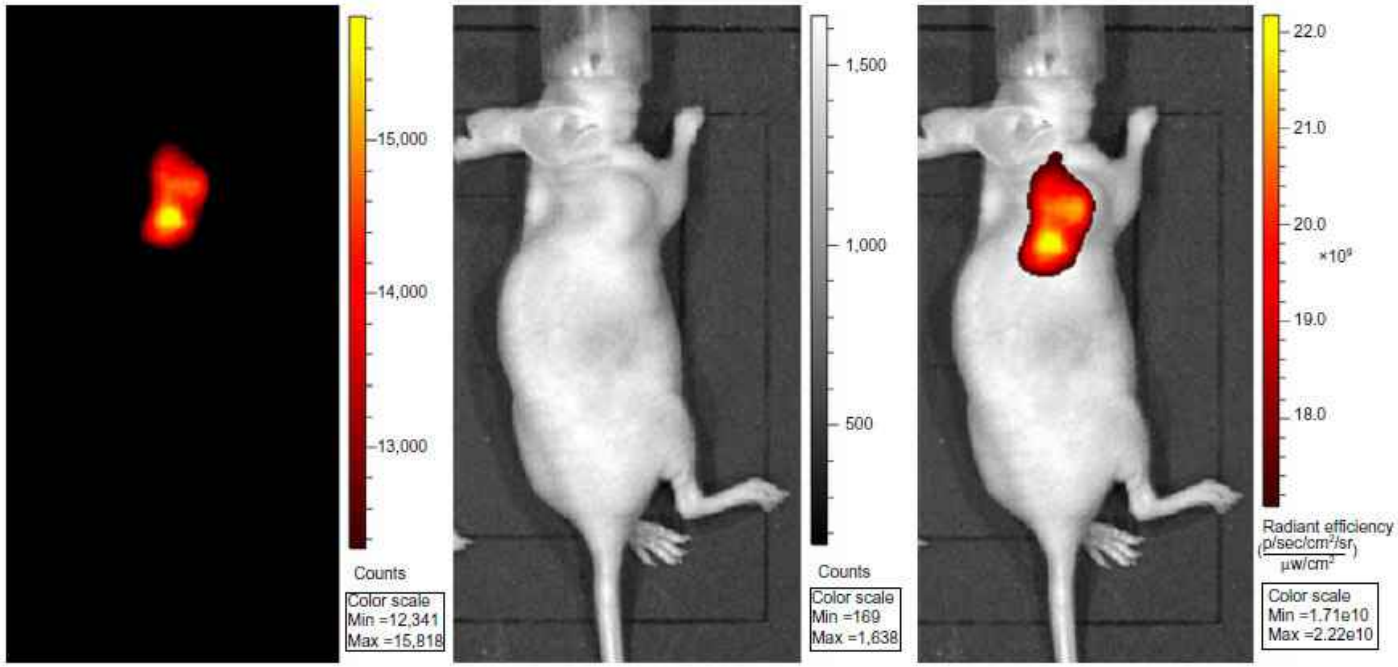


3D coregistration of fluorescence signal from various imaging reagents (MMPSense 680, OsteoSense 680EX, ProSense 750EX) with microCT

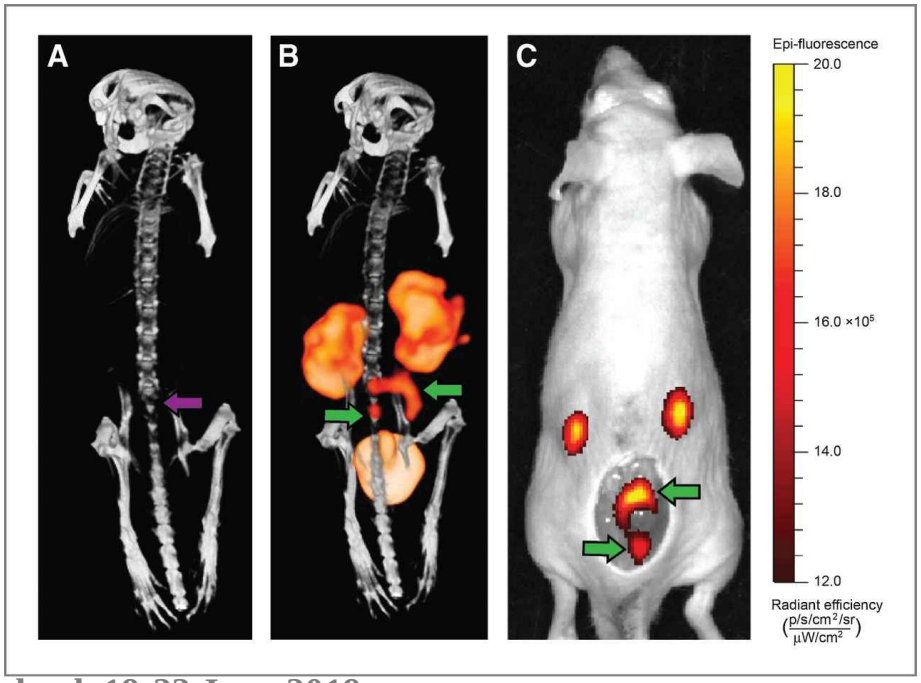
Imaging in the optical range

- Optical dyes (isosulfan blue) and fluorescent probes (fluorescein, indocyanine green) - widely used in preclinical/clinical applications
  - Sentinel nodes.
  - To determine tumour burden and margins and aid in intraoperative removal.
- Bioluminescence: tool for molecular imaging of small laboratory animals.
  - Allows study of ongoing biological processes in vivo.
  - Real-time analysis of disease processes at the molecular level in living organisms.
  - Monitor progression of infection, tumour growth and metastasis, transplantation, toxicology, viral infections and gene therapy.
  - Firefly lucyferase most common marker in tumour cells.

Imaging in the optical range



Combined with other imaging modalities: eg. optical / microCT.



Cherenkov imaging

R. Tamura et al.
Seminars in Nuclear Medicine, 2018

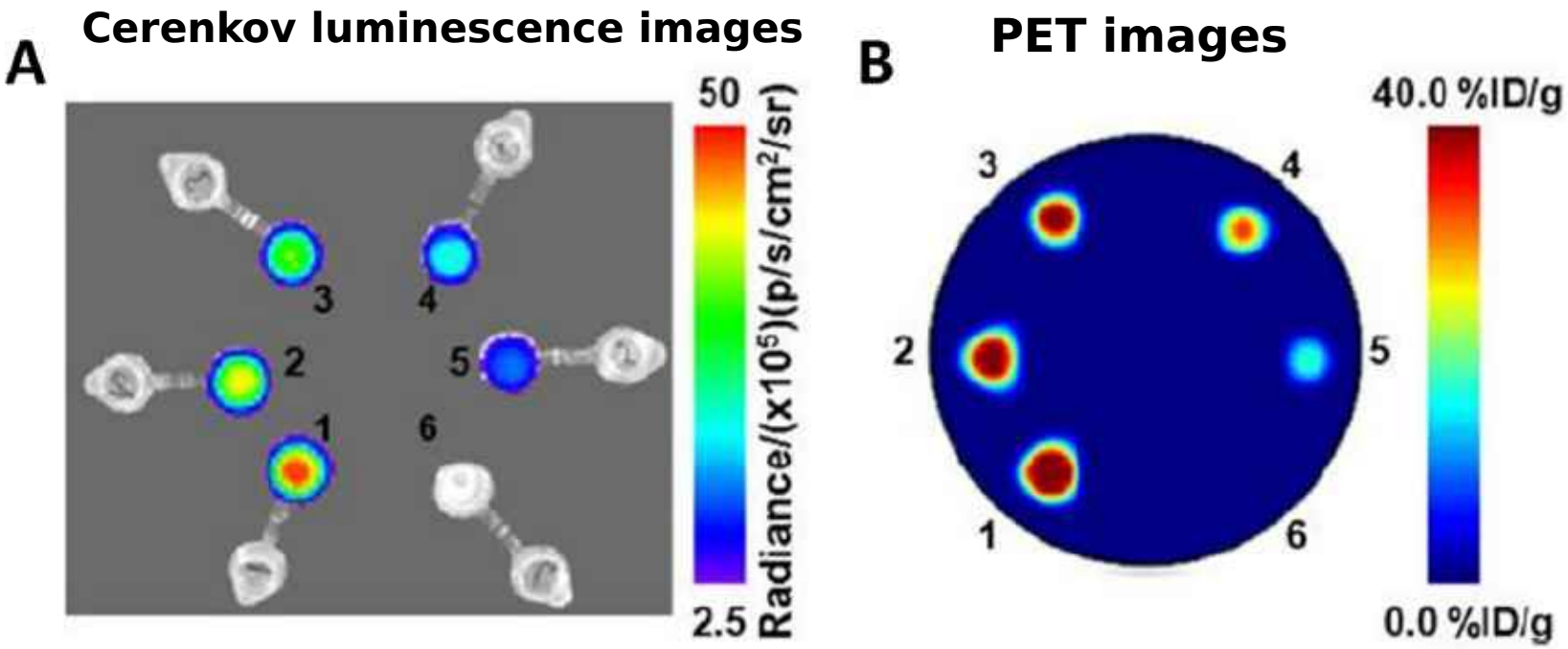
- Cherenkov luminescence (CL) first applied to biomedical imaging in 2009 => Cherenkov luminescence imaging (CLI).
- CL from 18F-FDG can be imaged with optical instrumentation => Multimodal system with PET.
- Other CL emitters: Cu-64, Zr-89, Y-90, Ga-68, I-124, I-131, Lu-177, Ac-225.
- Similar detection systems than those for bioluminescence.
- Possible thanks to instrumentation advances in CCDs:
  - Back-thinned - UV sensitive,
  - back-illuminated and cooled - increased sensitivity and reduced thermal noise.
- IVIS system and commercial and custom made CCD setups.
  - IVIS system adapted- cooled back-thinned CCD, 2.7x2.7 cm2, detecting ~ 100 phot/s/cm2/sr- 4 filters.
  - Newer versions cover 400-860 nm in 20 nm step and FOV 16-506 cm2.

Cherenkov imaging

- Limitations:
  - Photon fluxes are several orders of magnitude lower than traditional fluorescence or bioluminescence: 1.32 photons per F-18, 33.9 photons per Ga-68. (=> for kBq-GBq activity- 10^3-10^5 photons /sec emitted).
  - Long scanning time => possible low image quality due to movements.
  - Limited duration of imaging due to radionuclide half-life.
  - Limited depth: OK for small animals, limited for humans => (near) surface or endoscopic imaging.
- Light enhancement by means of nanoparticles. Wavelength shift form UV/blue to longer wavelengths.
  - SCIFI: Secondary Cherenkov Induced Fluorescence Imaging => 6x larger S/N than fluorescence.
  - CRET: Cherenkov Radiation Energy Transfer.

Cherenkov imaging

- Good for preclinical imaging- organs close to surface. 2-5 min/image.
- Clinical:
  - First in 2009. Cooled electron multiplying CCD (down to -80ºC).
  - Darkness is necessary- complicated.



R. Tamura et al. Semin Nucl Med, 2018 adapted from Ruggiero et al. J Nucl Med, 2010.

Cherenkov imaging

- Clinical applications:
  - Surface or lymph nodes below the skin.
  - Surgery to reach area to be imaged.
  - Endoscope to reach deep organs.
- Examples of use:
  - Sentinel lymph node mapping and biopsy with F-18 FDG - identification of hot spots better than with gammas.
  - Identification of tumour margins in intraoperative imaging instead of fluorescence imaging.
  - Thyroid uptake
  - Colorectal tumours with endoscope.
- CL can also be induced by external beams with a LINAC beam=> visualization of the beam path with fosforescent probes.
- Possible use for proton therapy- observed for 60MeV proton beams from indirect interactions.

Cherenkov imaging

- Total skin electron beam therapy in cutaneous lymphomas.
- Ionization chambers, diodes, TLDs and radiochromic films are limited to point or small region measurements.

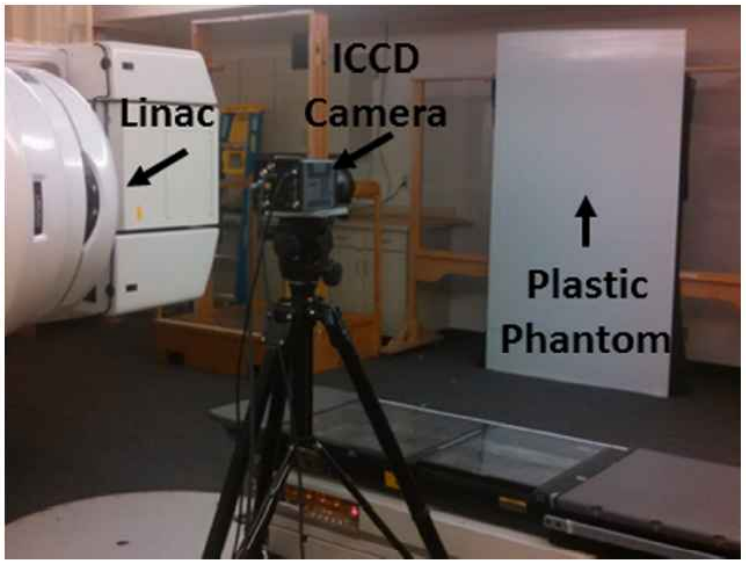


FIG. 1. Experimental setup for rapid TSET optimization using Cherenkov imaging.

J. M. Andreozzi et al.
Med. Phys. 43 (2), 2016

Conclusions

- Significant advances are being made in different areas of medical imaging that contribute to a better and more accurate diagnosis.
- The development of new detectors / photodetectors / associated electronics and transfer of knowledge from other areas is essential.
- Different applications impose different detector requirements => There is room for improvement in many aspects.

Acknowledgements

- Ministerio de Economía, Industria y Competitividad (FPA2014-53599 -R and FPA2017-85622-R).
- Centro de Excelencia Severo Ochoa (SEV-2014-0398).
- Agencia Valenciana de Innovación.
- Ramón y Cajal Programme.

Thank you! Questions?