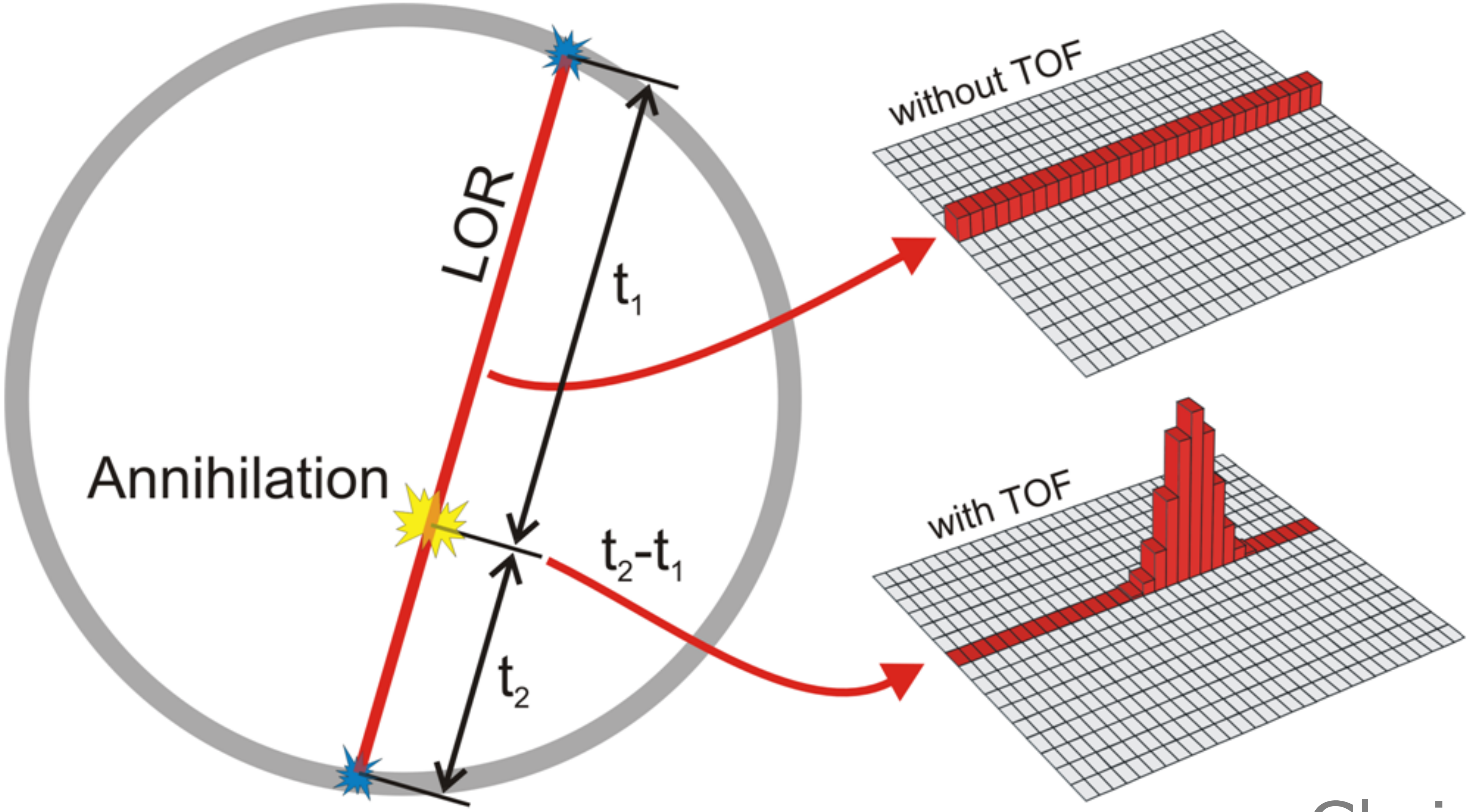
A challenge on the mythic 10 ps frontier for time-of-flight positron emission tomography



Christian MOREL

ASP Online Seminars, October 29 2020

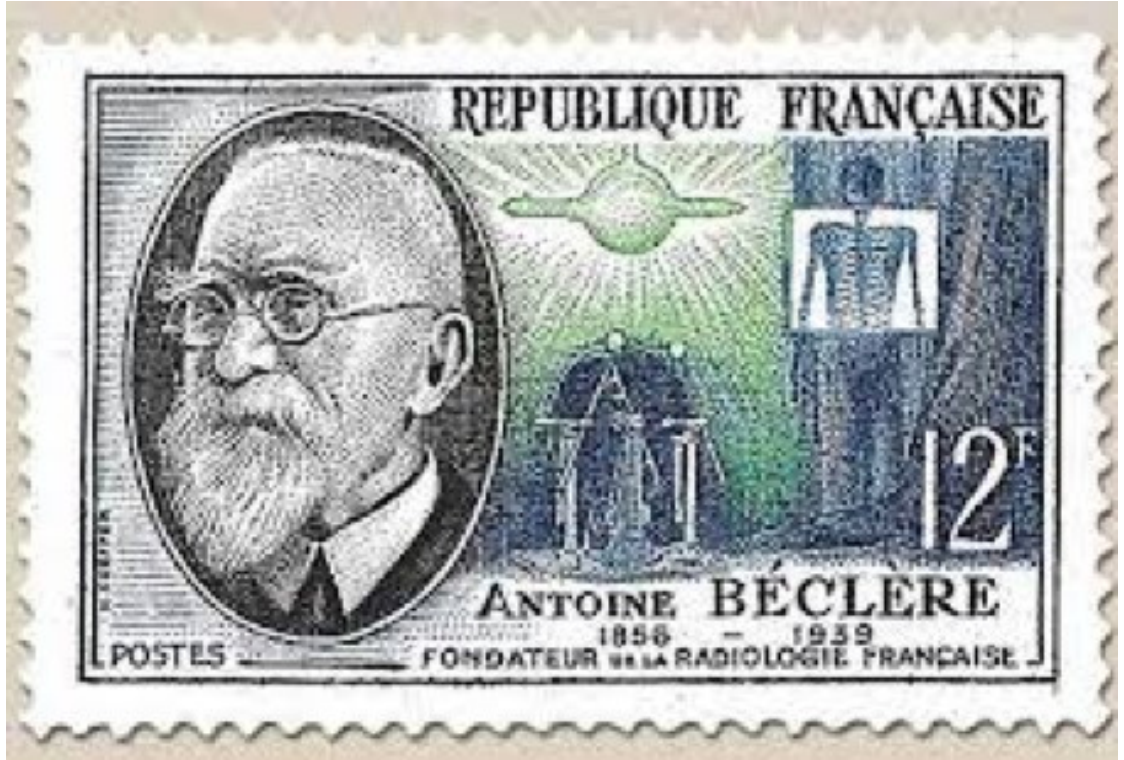
Aix Marseille université
cnrs IN2P3 Les deux infinis
CENTRE DE PHYSIQUE DES PARTICULES DE MARSEILLE CPPM

Discovery of X-rays (1895)

Wilhelm Roentgen (1845-1923)
Nobel Prize in Physics (1901)

22 Dec 1895 – published in the New York Times on 16 Jan 1896

Development of radiology (roentgenology)



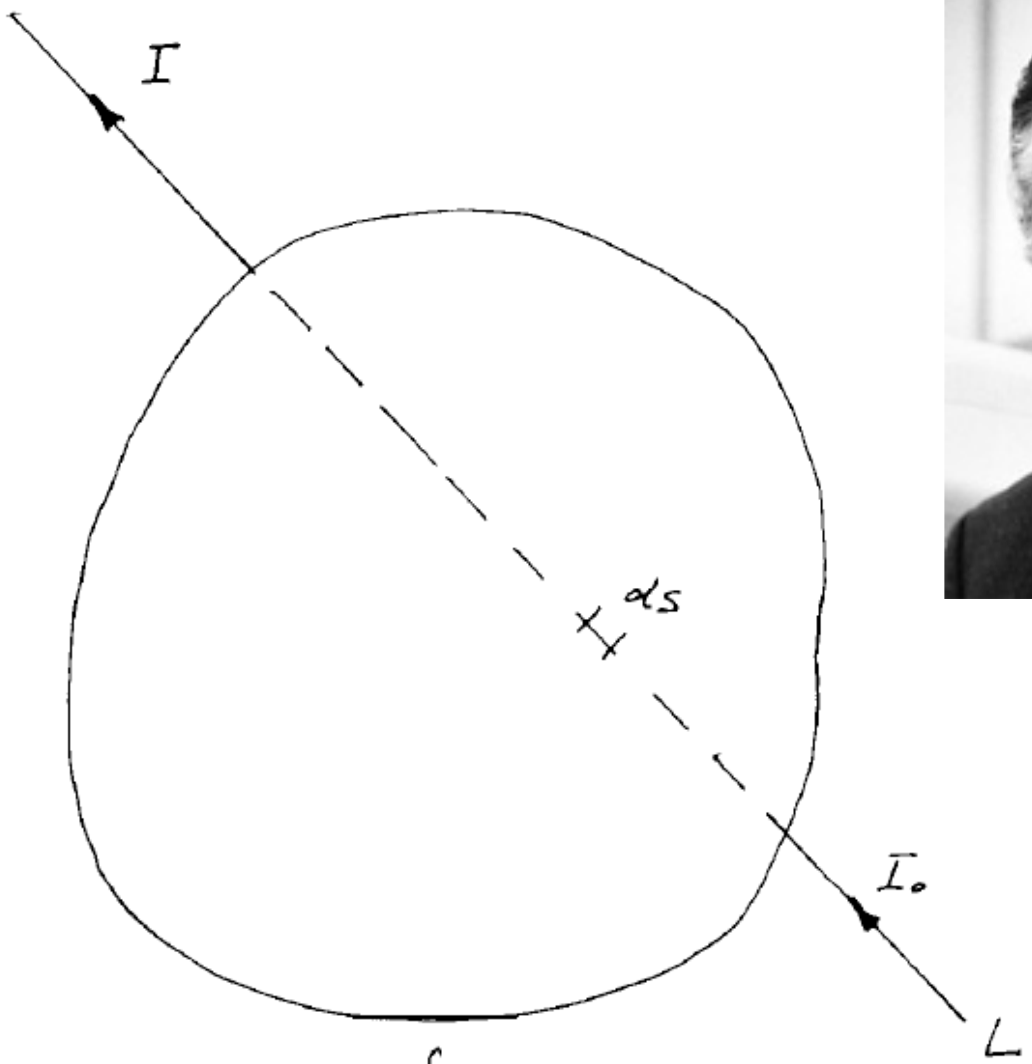
Hôpital Tenon (Paris, 1897)
Antoine Béclère (1858–1939)

Radiological Renault «Petite Curie» (1916)
Marie Curie (1867-1934)

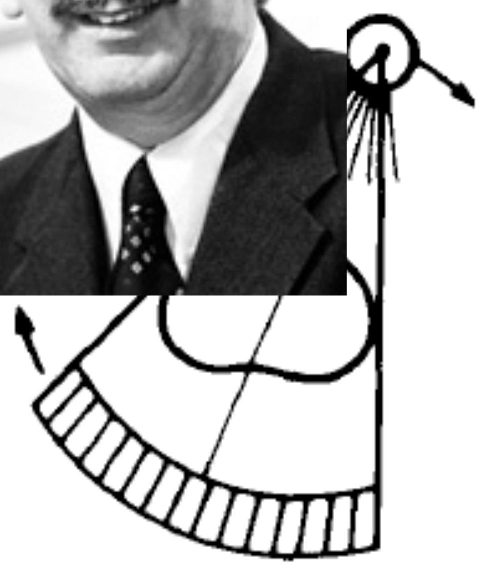
Development of Computerized Tomography (CT)

Rediscovery of the Radon solution for reconstruction from projections (Cape Town, 1963)
Allan McLoed Cormack (1924-1998)

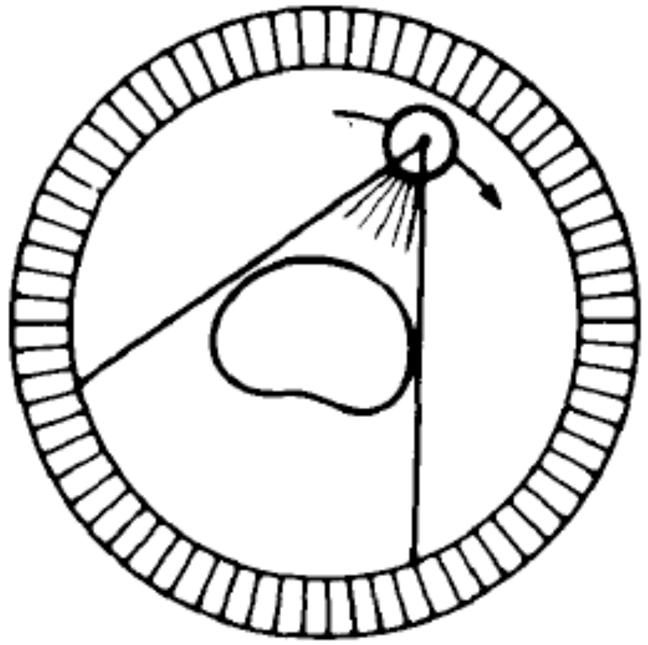
Development of the first CT scanner at EMI (London, 1972)
Sir Godfrey Newbold Hounsfield (1919-2004)



$$I = I_0 \, e^{-\int_L f \, ds}$$



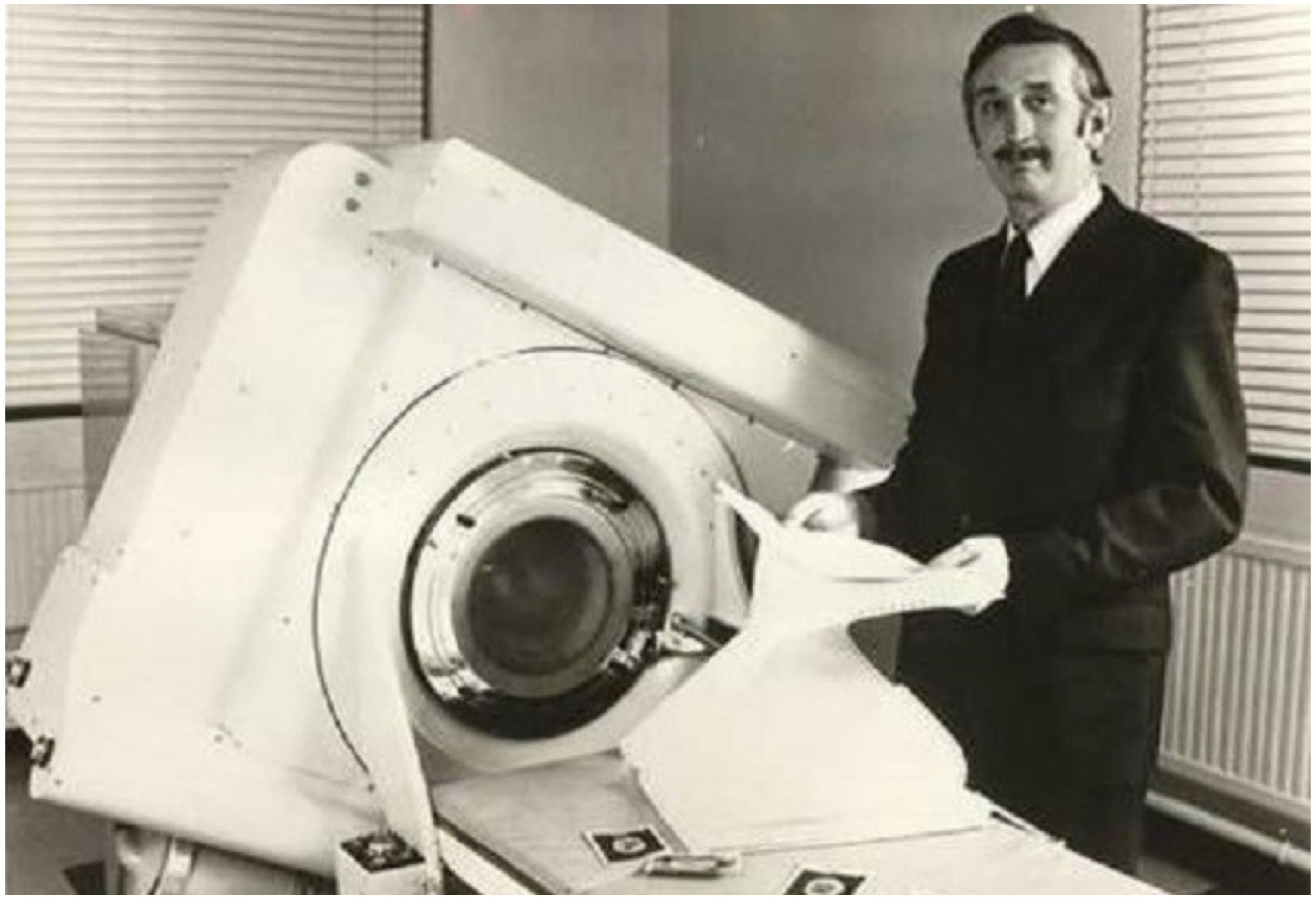
300 detectors
Scan time 2 - 4 seconds

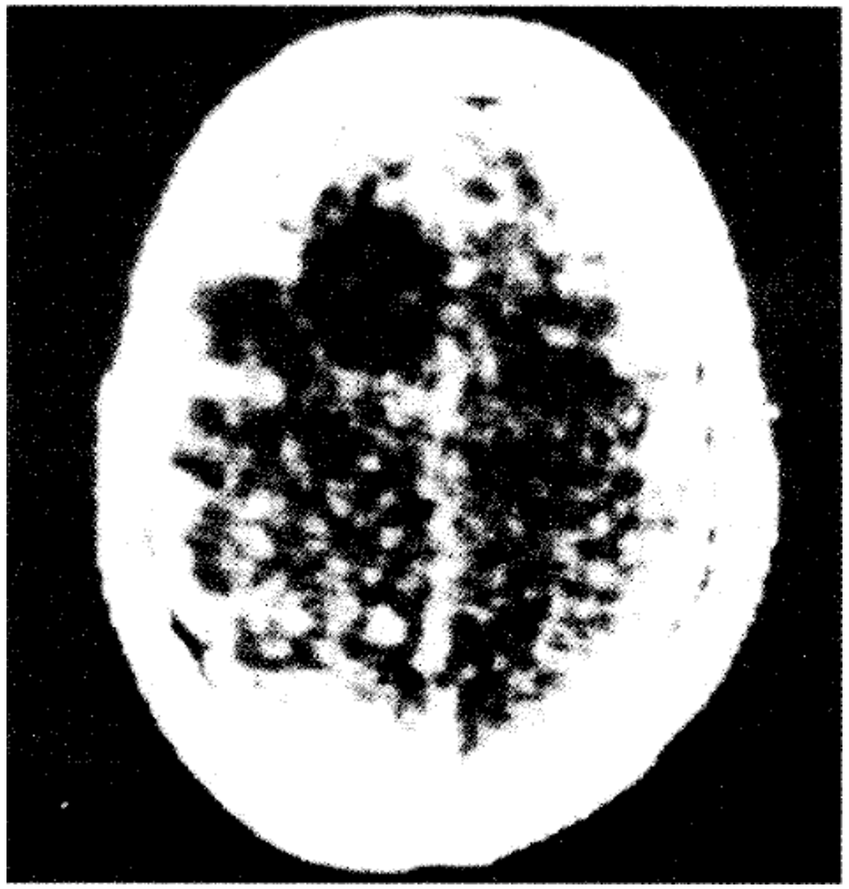


700 stationary detectors
Scan time 2 - 4 seconds

Nobel Prize in Medicine (1979)

Computerized Tomography (CT)

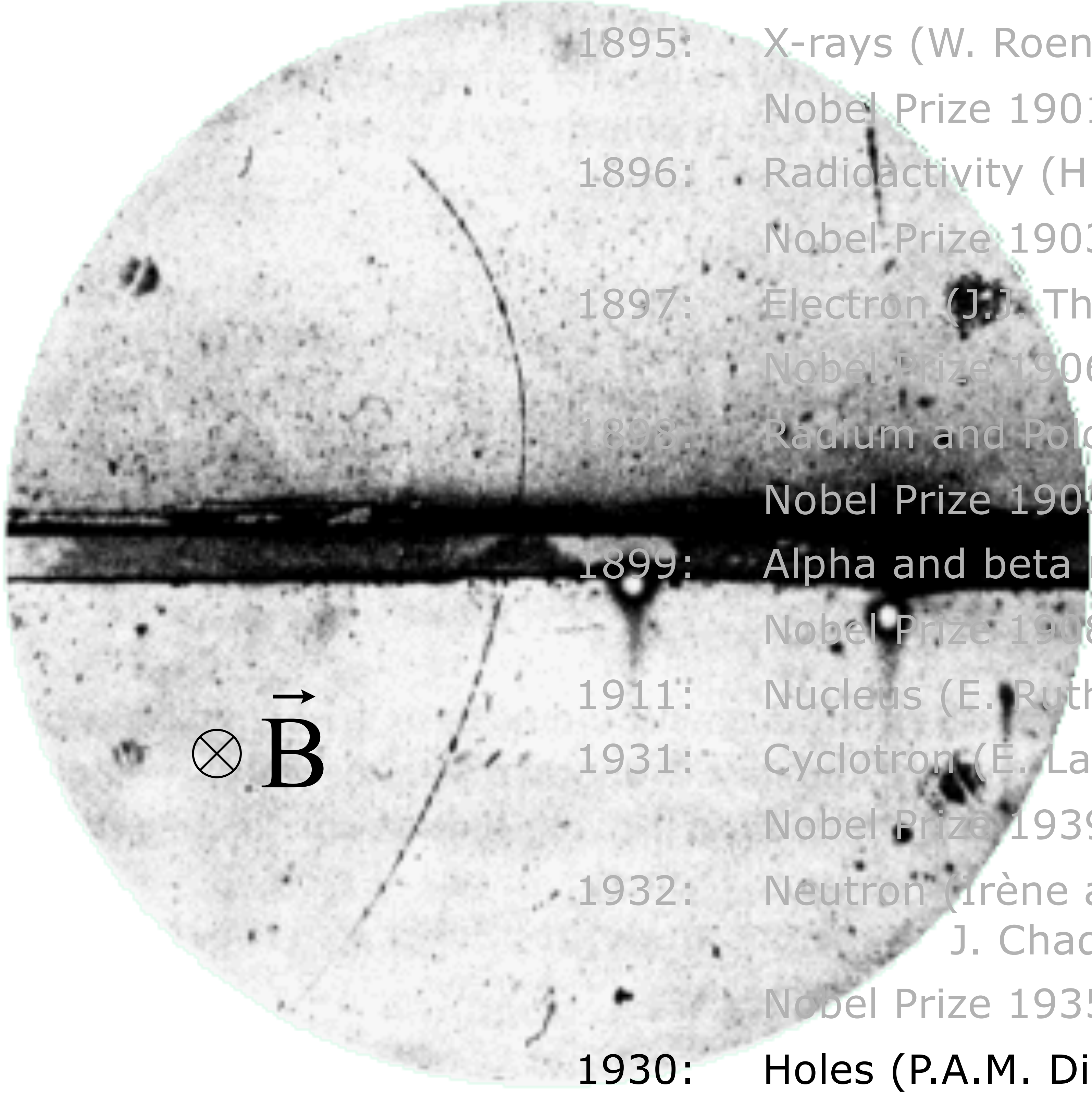




G. Hounsfield, J. Ambrose
(Atkinson Morley Hospital, London, 1/10/1971)

X-ray and neutron radiography

Courtesy: Paul Scherre Institut (PSI)



1895: X-rays (W. Roentgen, Wuerzburg)
Nobel Prize 1901

1896: Radioactivity (H. Becquerel, Paris)
Nobel Prize 1903

1897: Electron (J.J. Thomson, Cambridge)
Nobel Prize 1906

1898: Radium and Polonium (Pierre and Marie Curie, Paris)
Nobel Prize 1903, 1911 (Marie Curie)

1899: Alpha and beta rays (E. Rutherford, Cambridge)
Nobel Prize 1908

1911: Nucleus (E. Rutherford, Cambridge)

1931: Cyclotron (E. Lawrence, Berkeley)
Nobel Prize 1939

1932: Neutron (Irène and Frédéric Joliot-Curie, Paris,
J. Chadwick, Cambridge)
Nobel Prize 1935 (Chadwick)

1930: Holes (P.A.M. Dirac, Cambridge)
Nobel Prize 1933

1932: Positron (C.D. Anderson, Berkeley)
Nobel Prize 1936

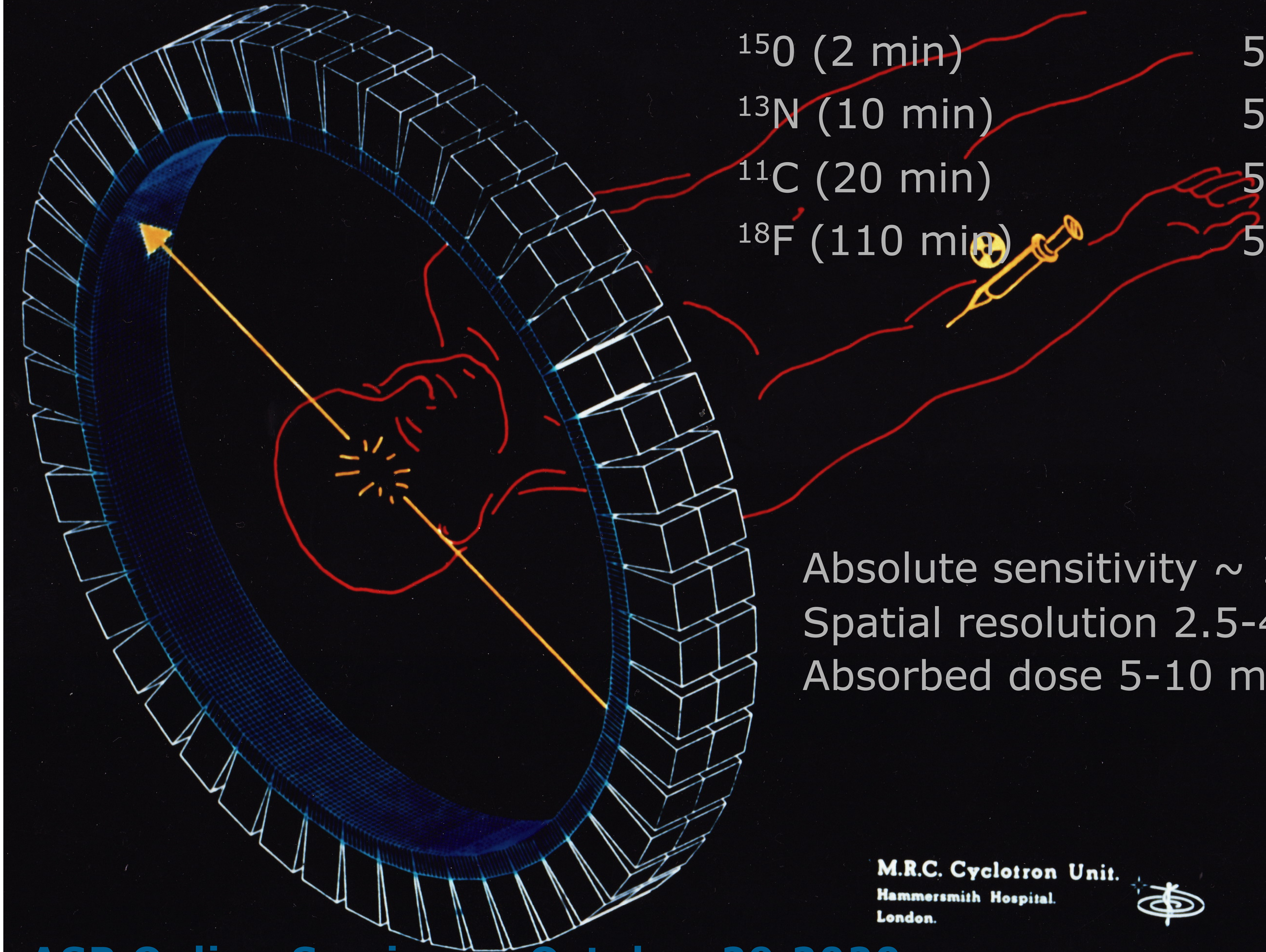
Compton scattering

$$e^- + \gamma \rightarrow e^- + \gamma$$

$$e^- + e^+ \rightarrow \gamma + \gamma$$

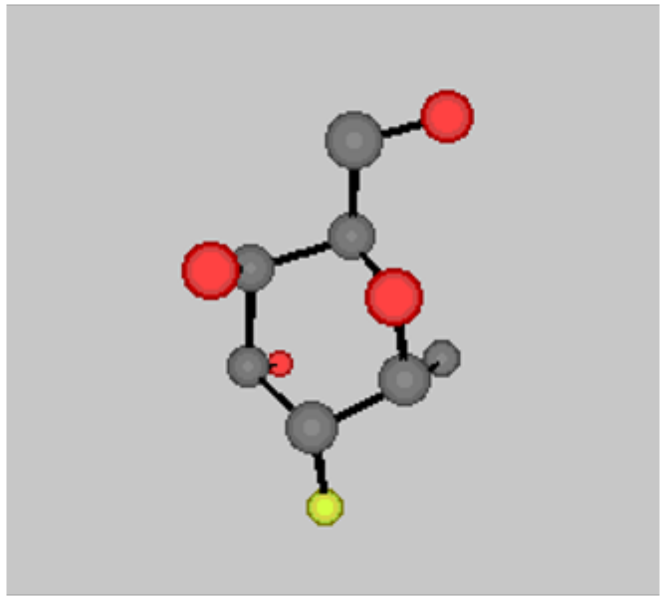
Matter-antimatter annihilation

Positron Emission Tomography (PET)

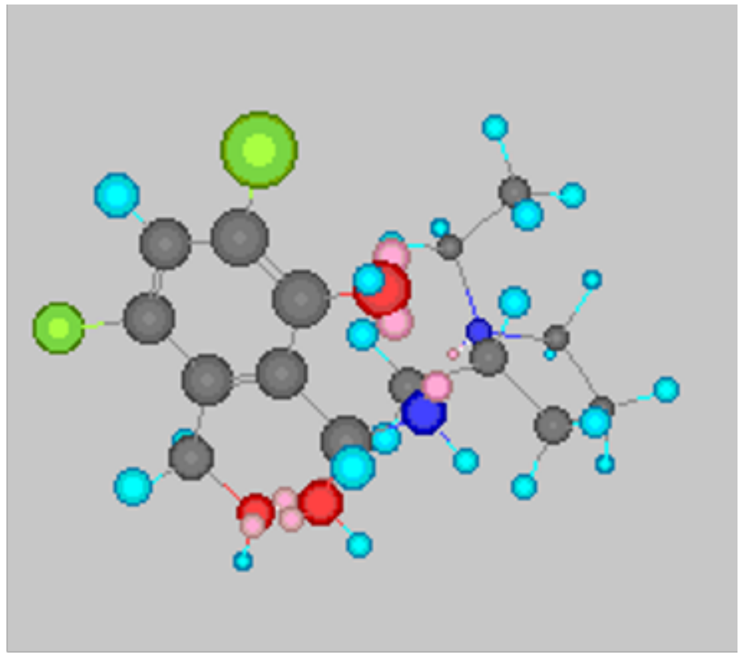


Absolute sensitivity ~ 10^{-2}
Spatial resolution 2.5-4 mm
Absorbed dose 5-10 mSv

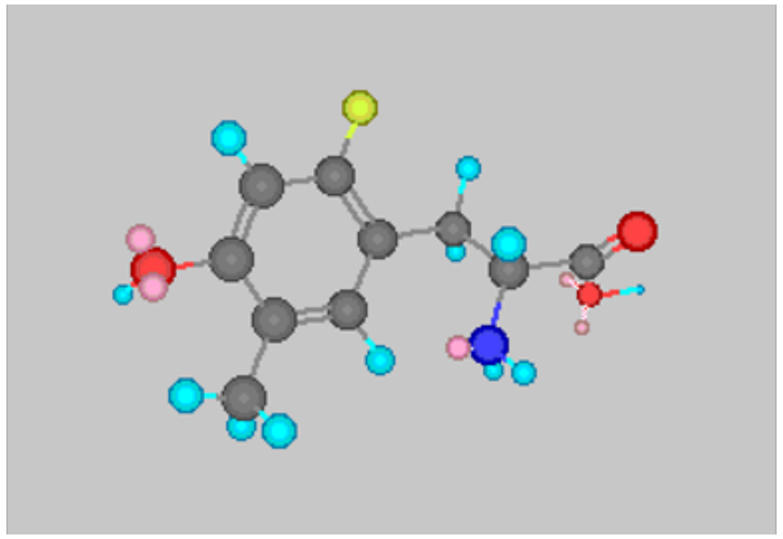
Radio-pharmaceutical labelling



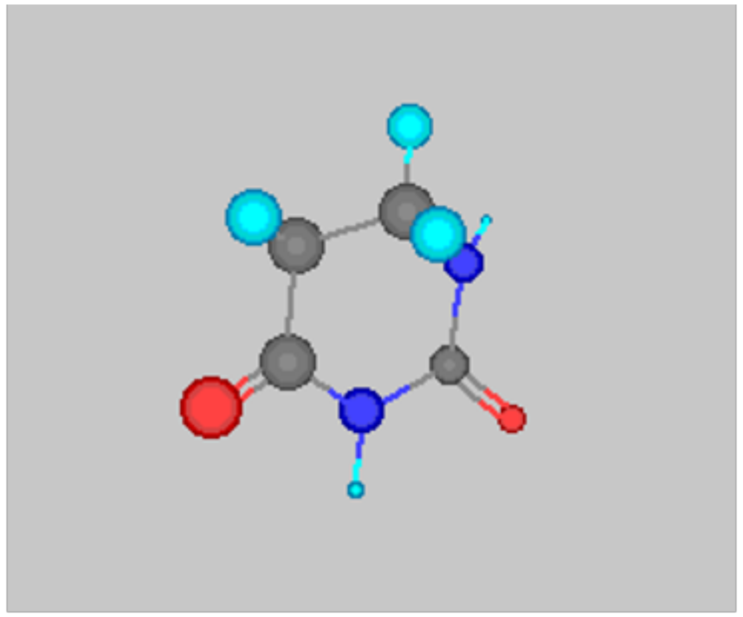
$[^{18}F]$FDG



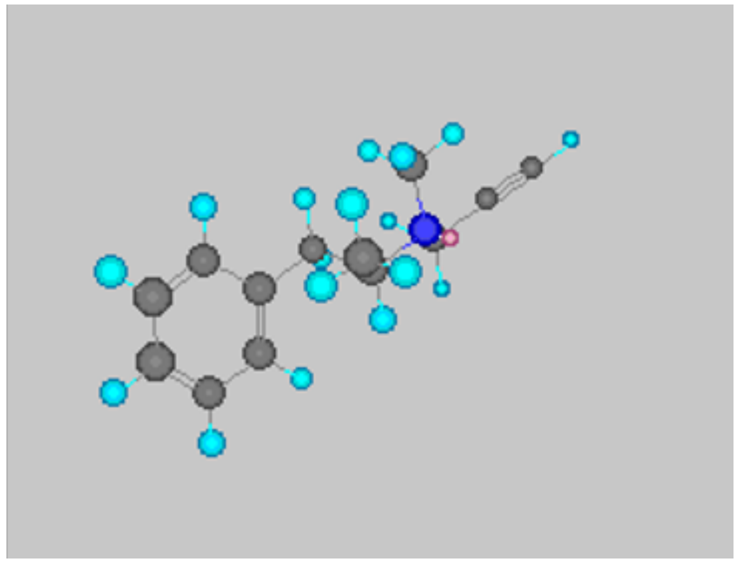
$[^{11}C]$Raclopride



$[^{18}F]$FluoroLDopa

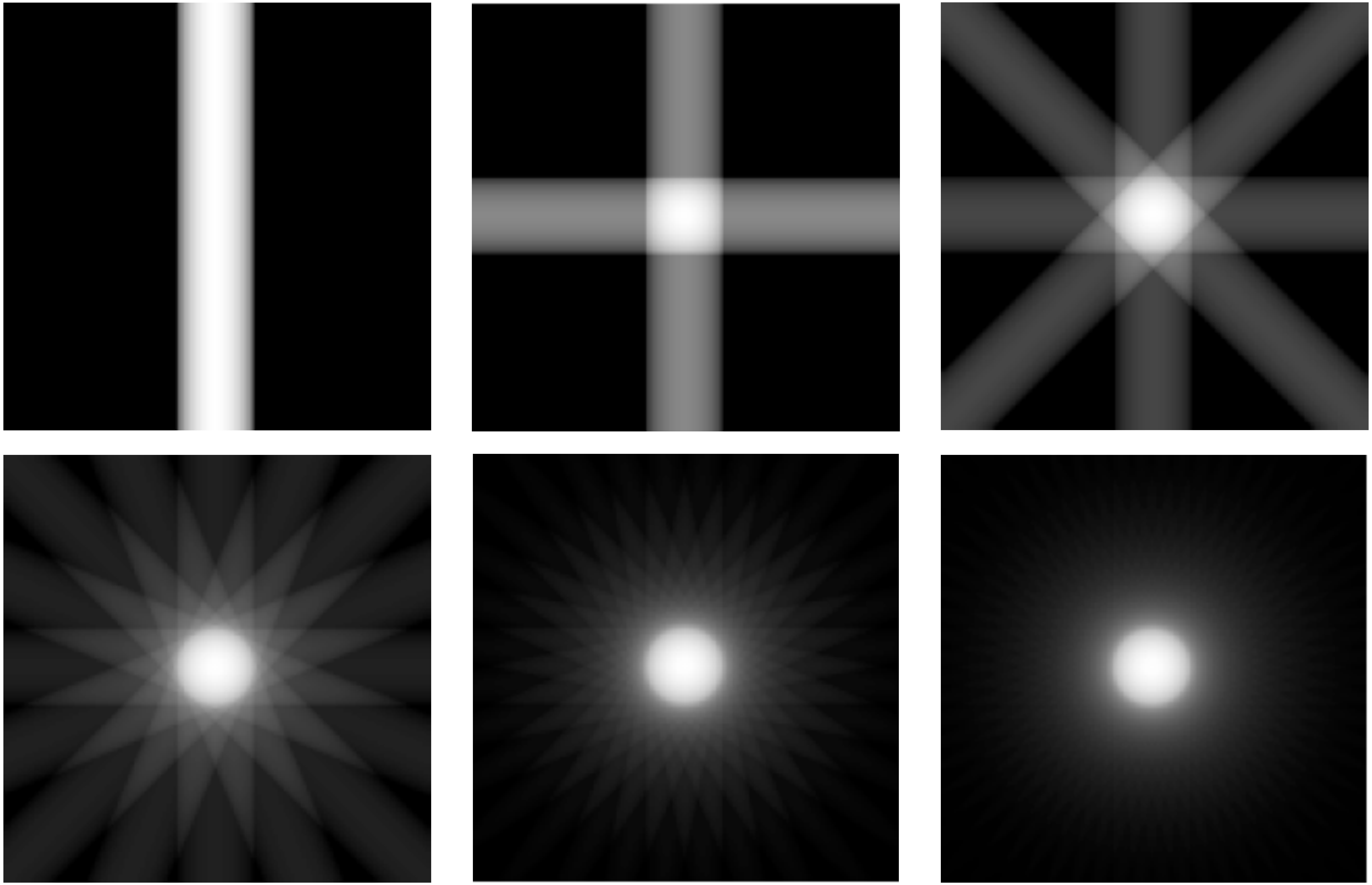


$[^{18}F]$Fluorouracil



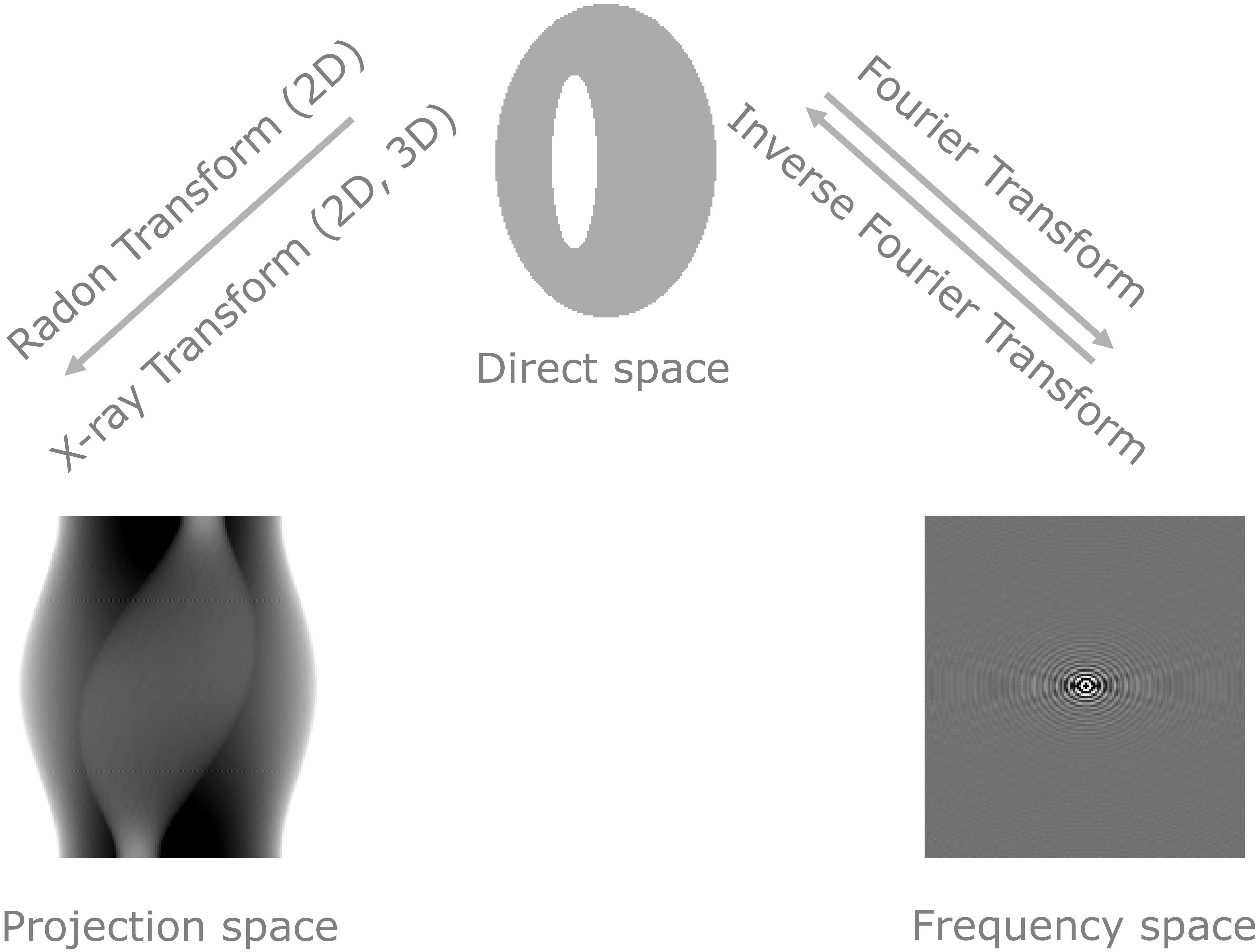
$[^{11}C]$L-deprenyl

Backprojection



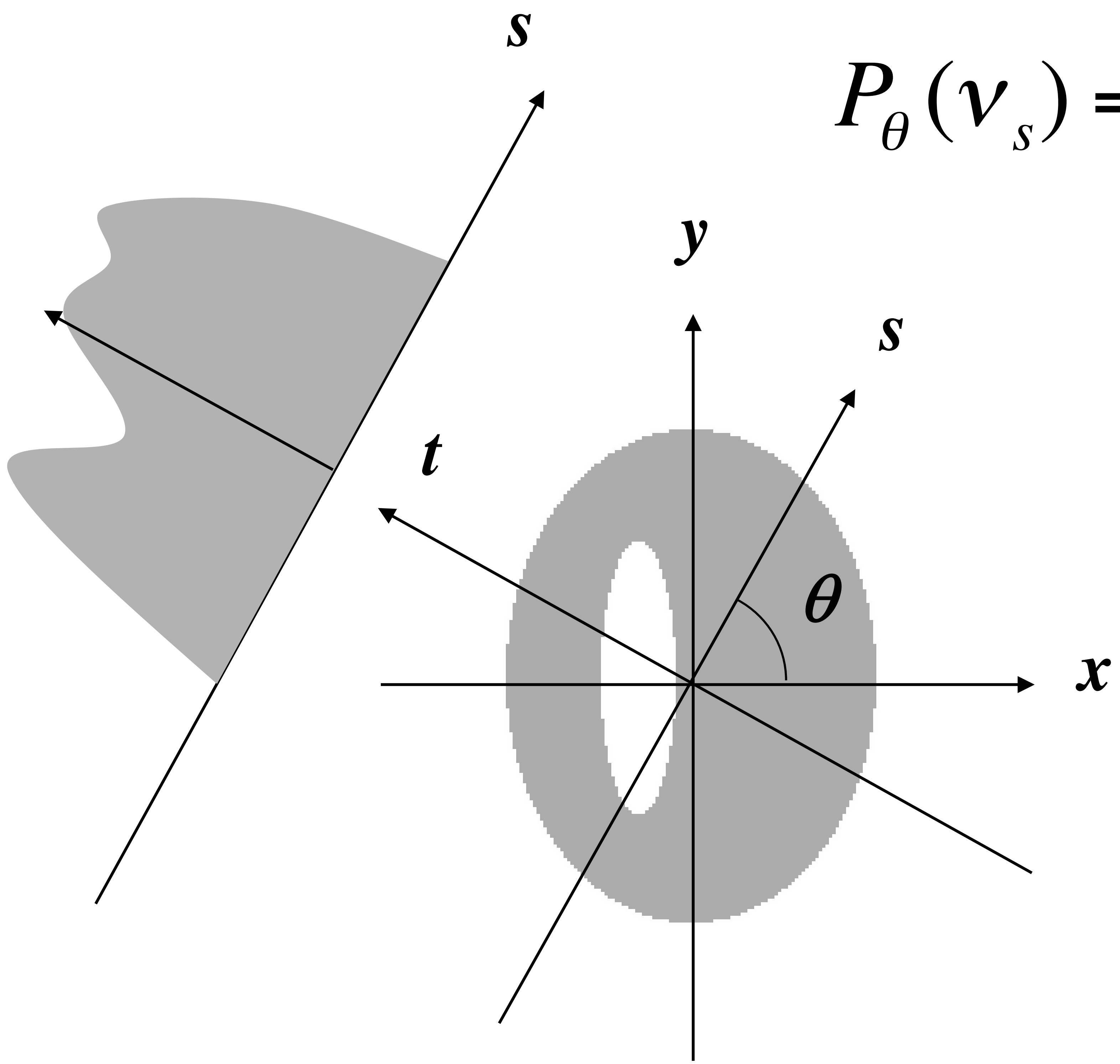
courtesy: S. Valton, Créatis, Lyon

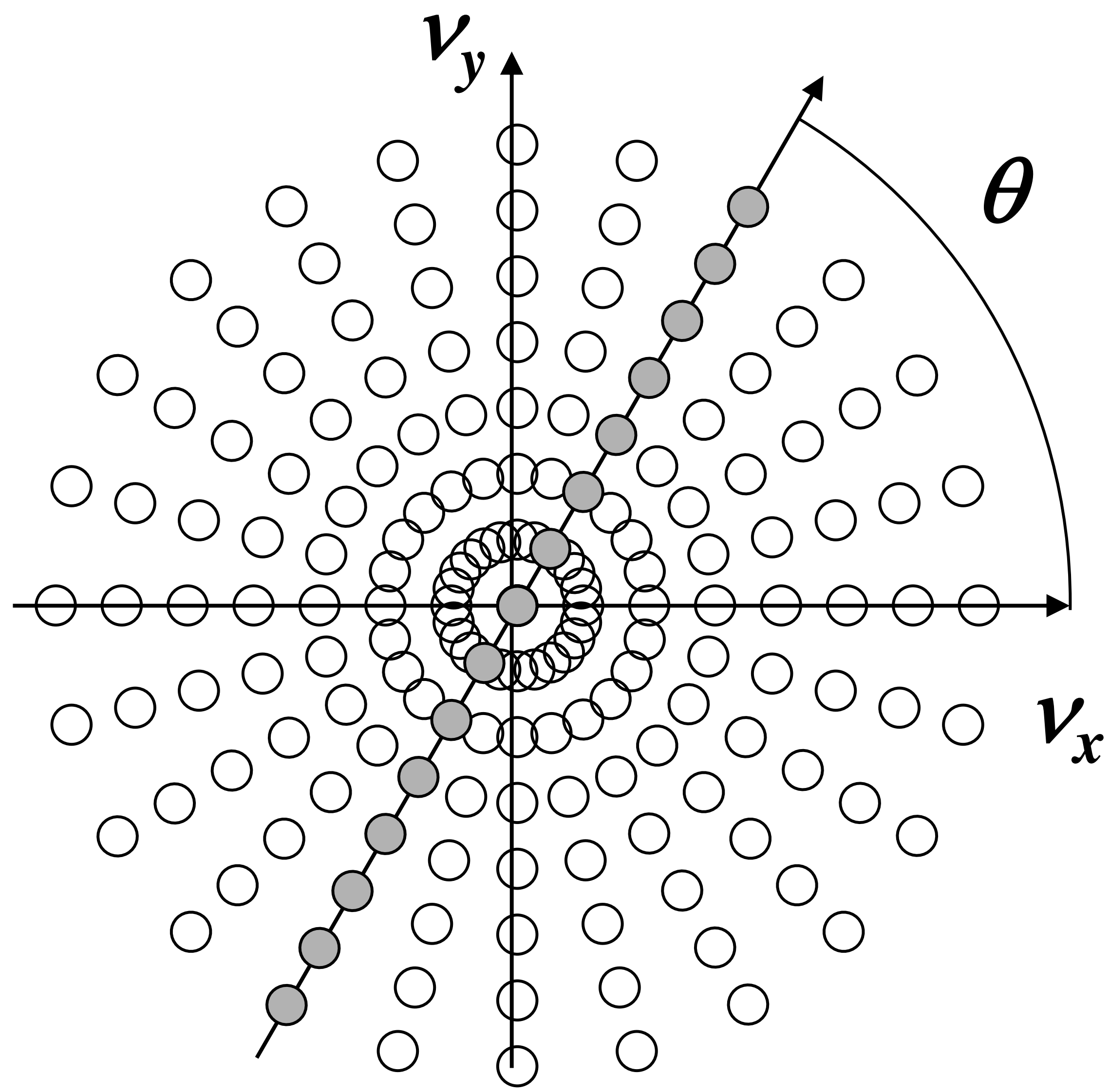
Tomographical reconstruction



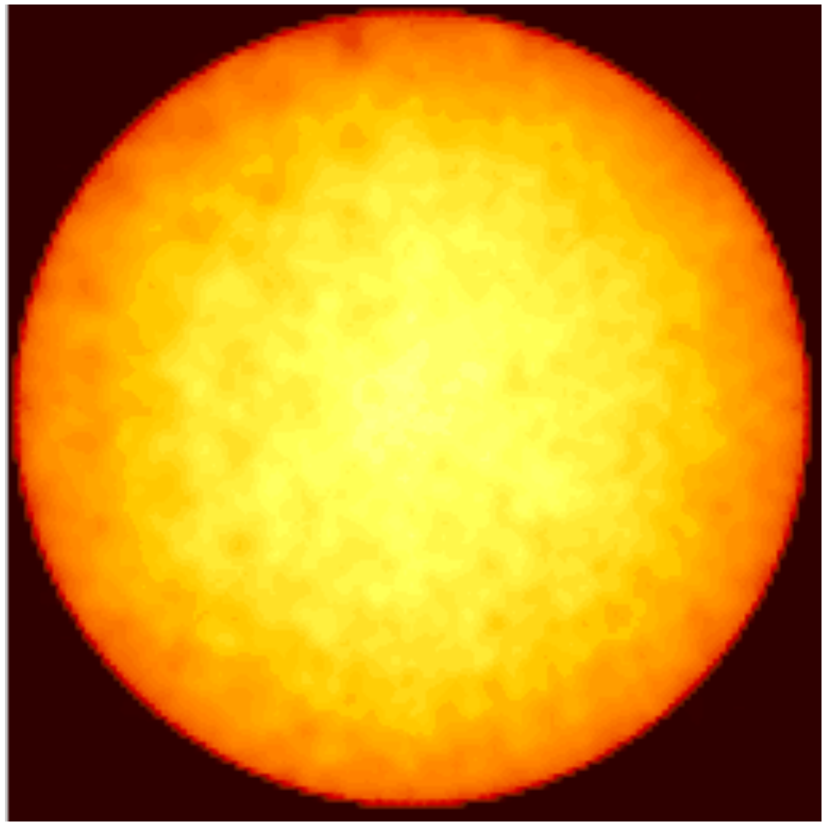
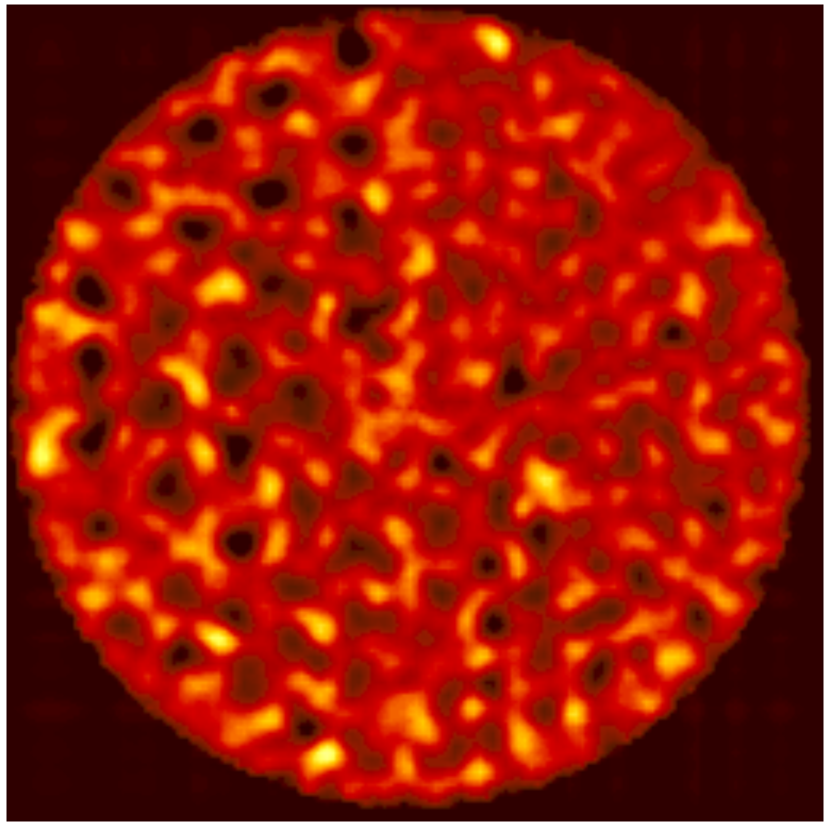
Central slice theorem

$$P_\theta(\nu_s) = F(\nu_s \cos\theta, \nu_s \sin\theta)$$

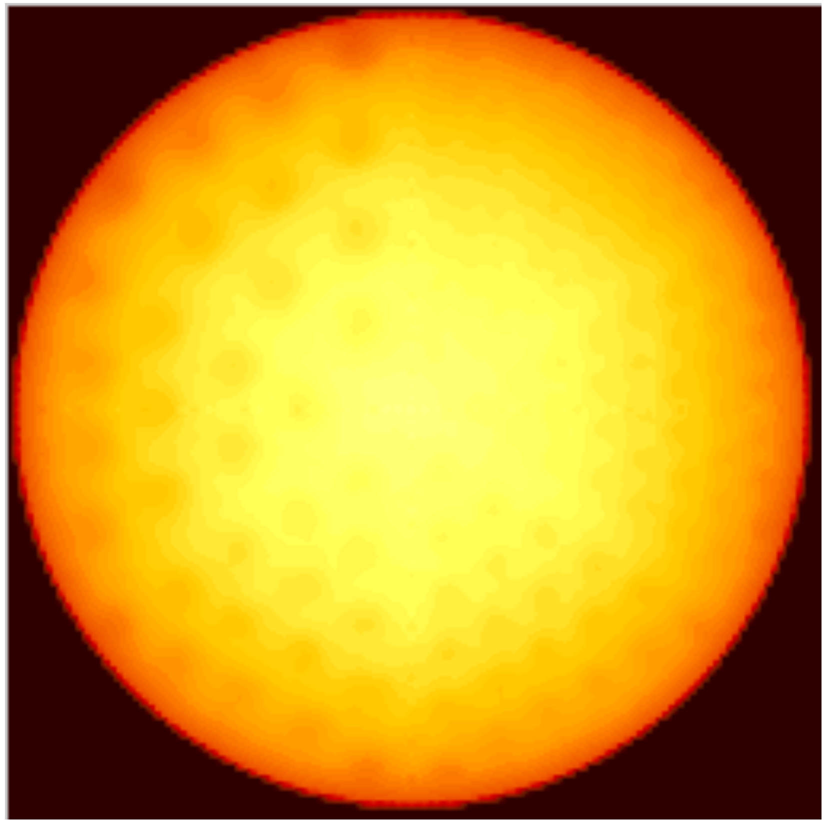
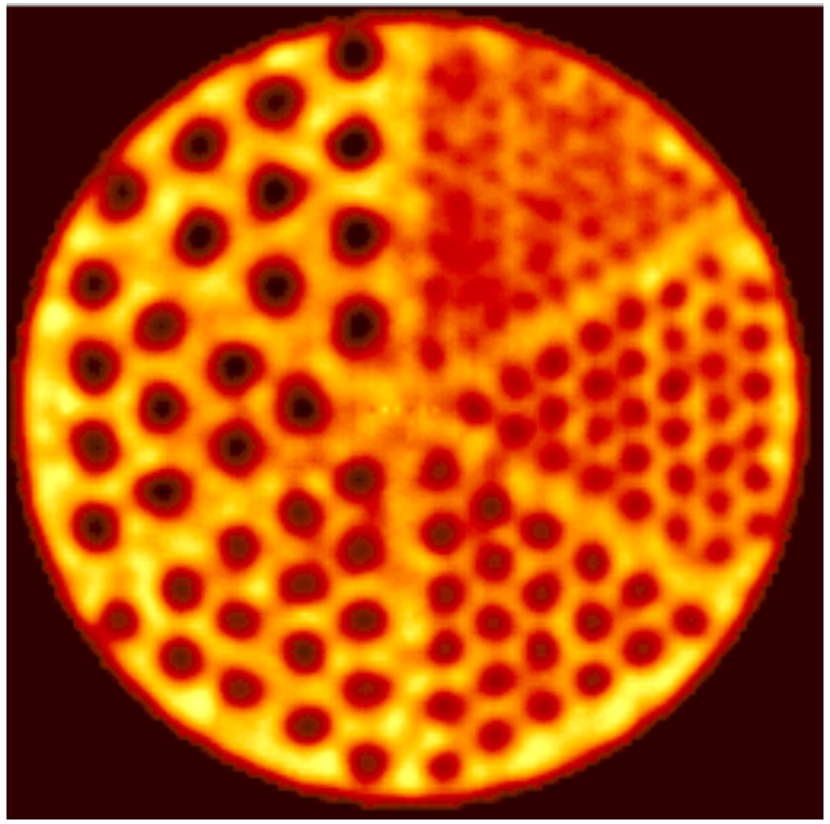




2D reconstruction

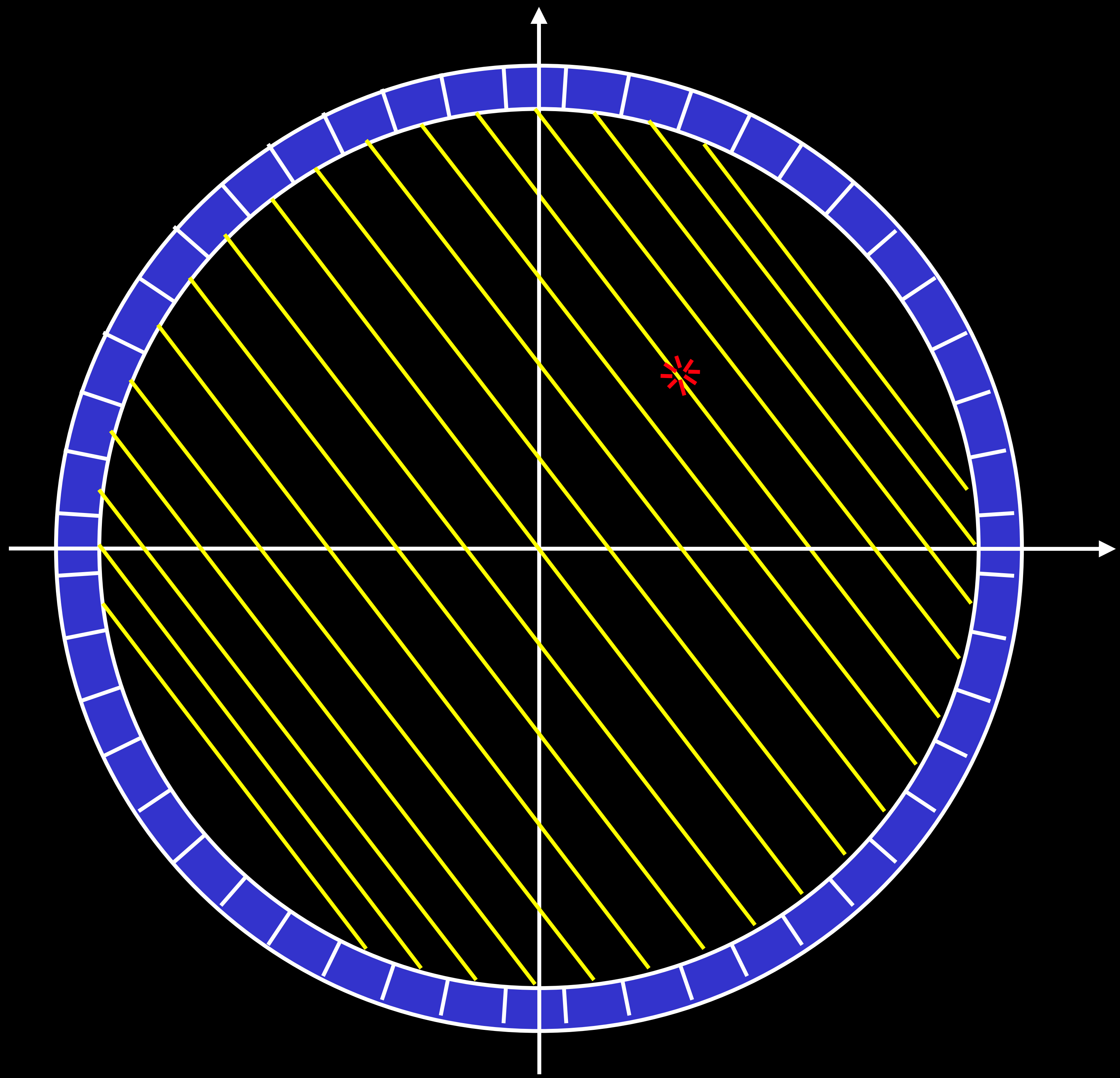



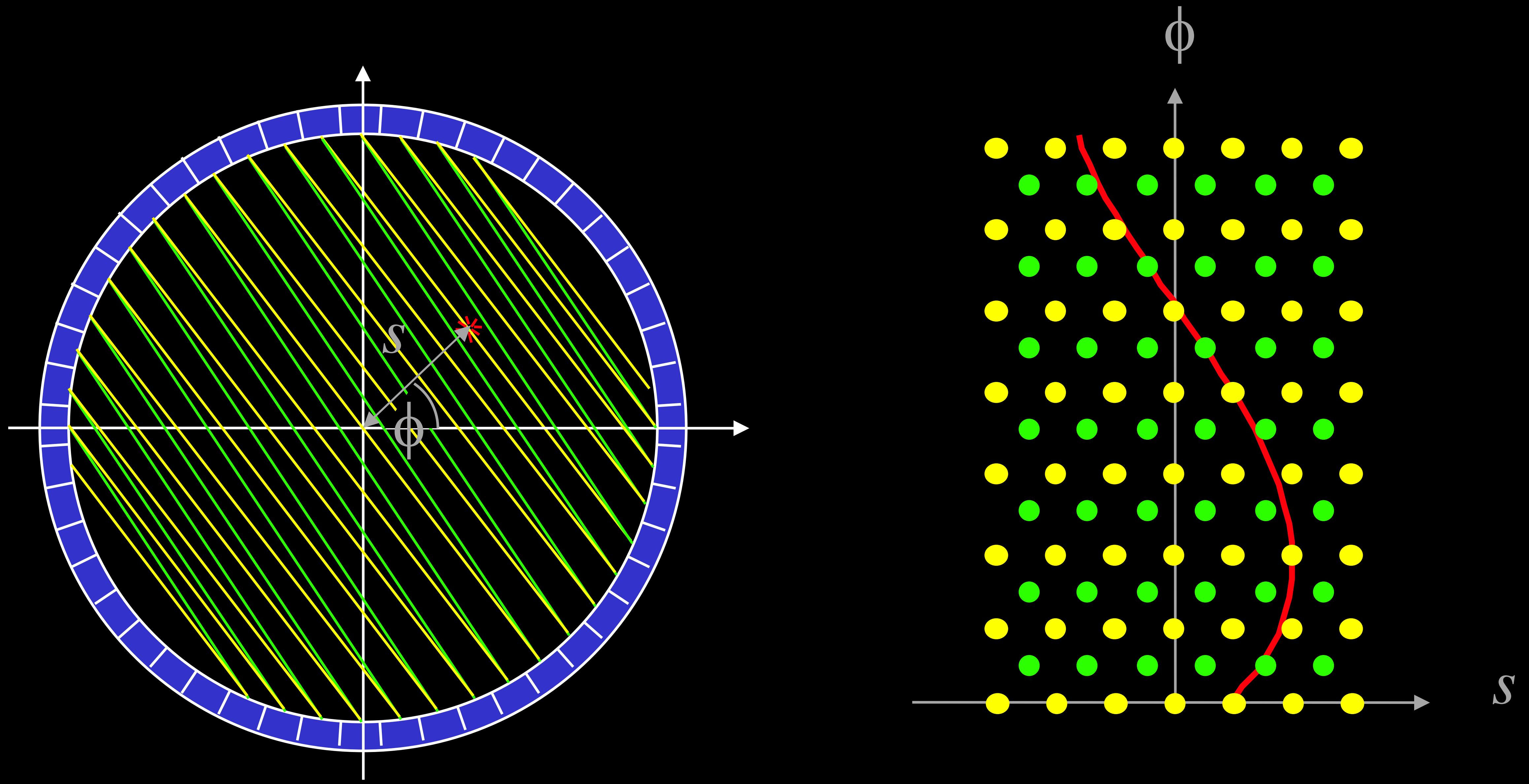
3D Reconstruction

Backprojection

Filtered backprojection

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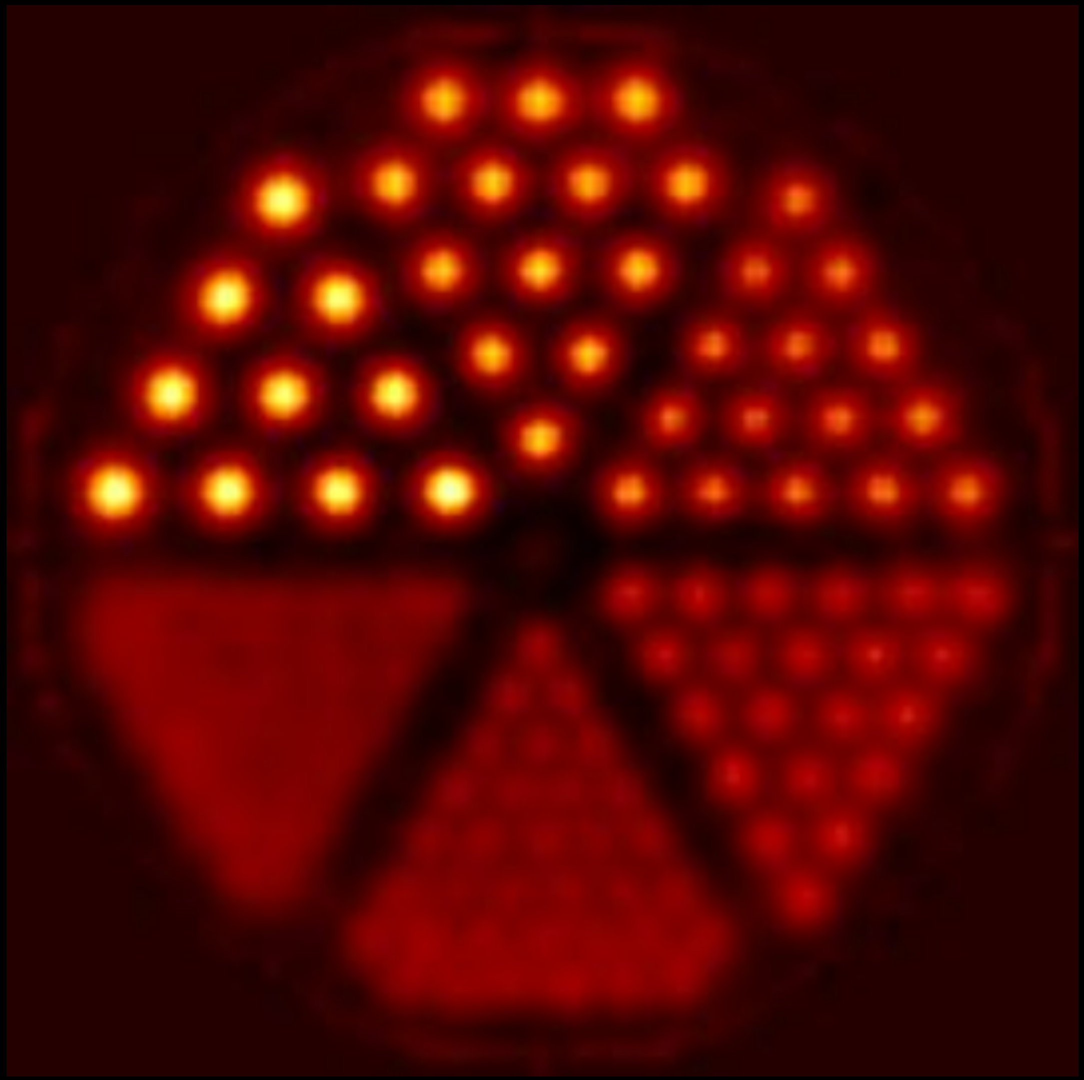
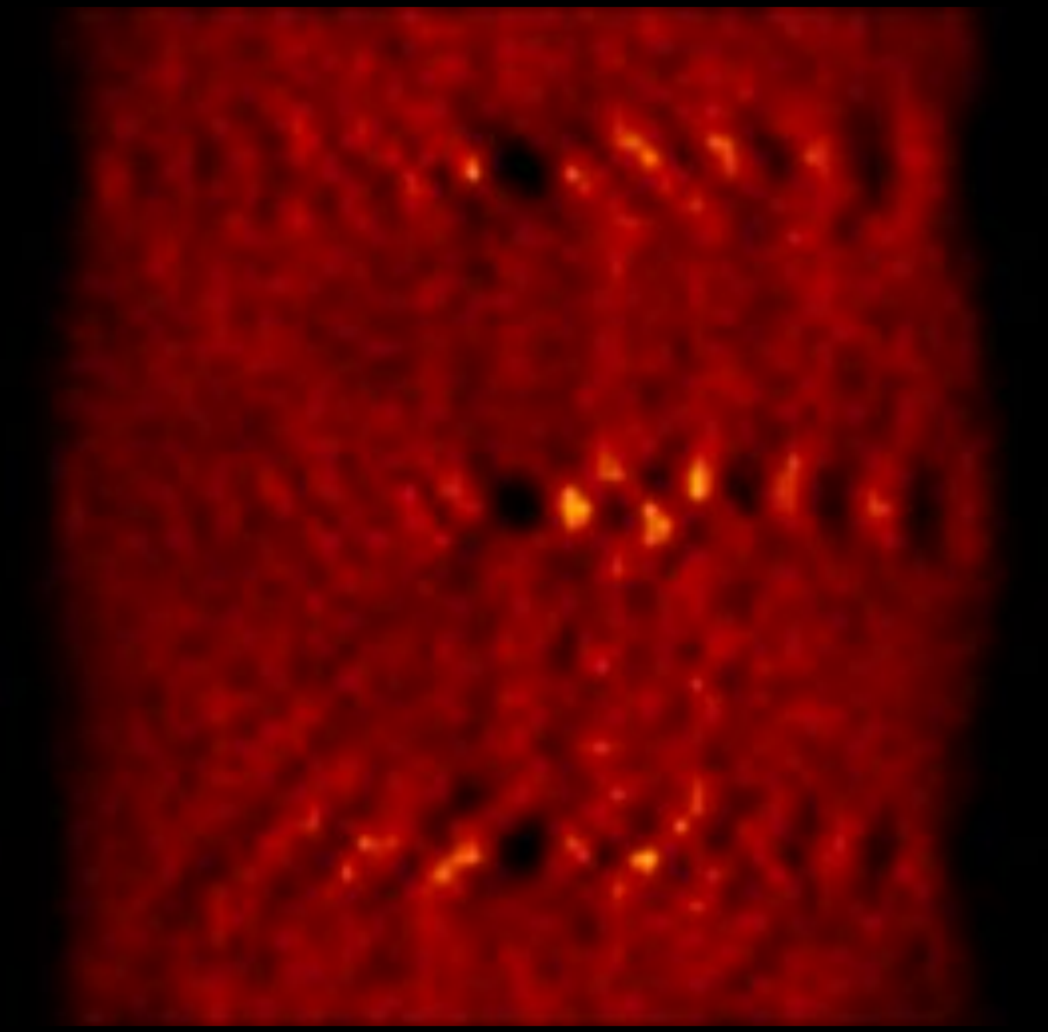
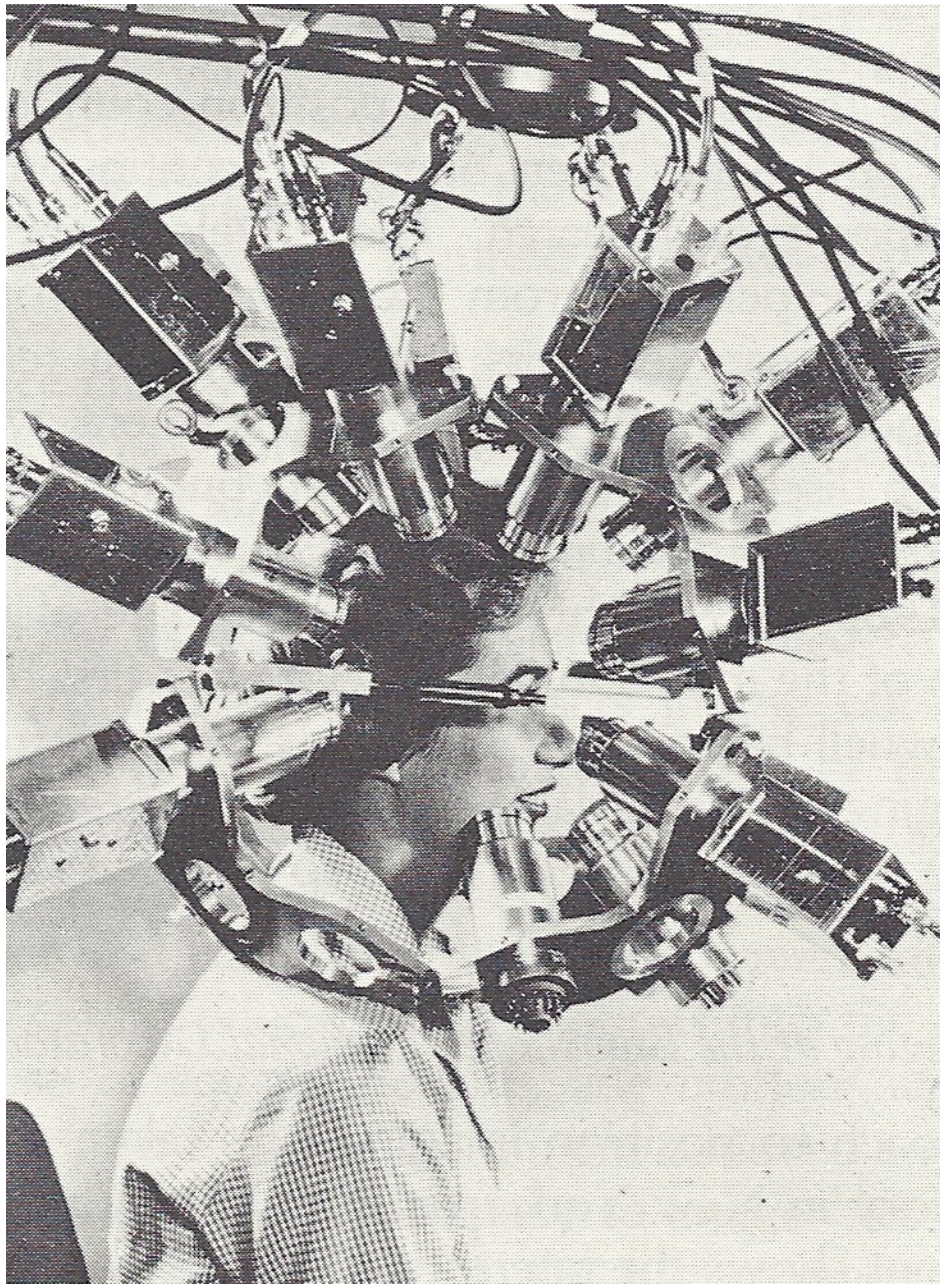
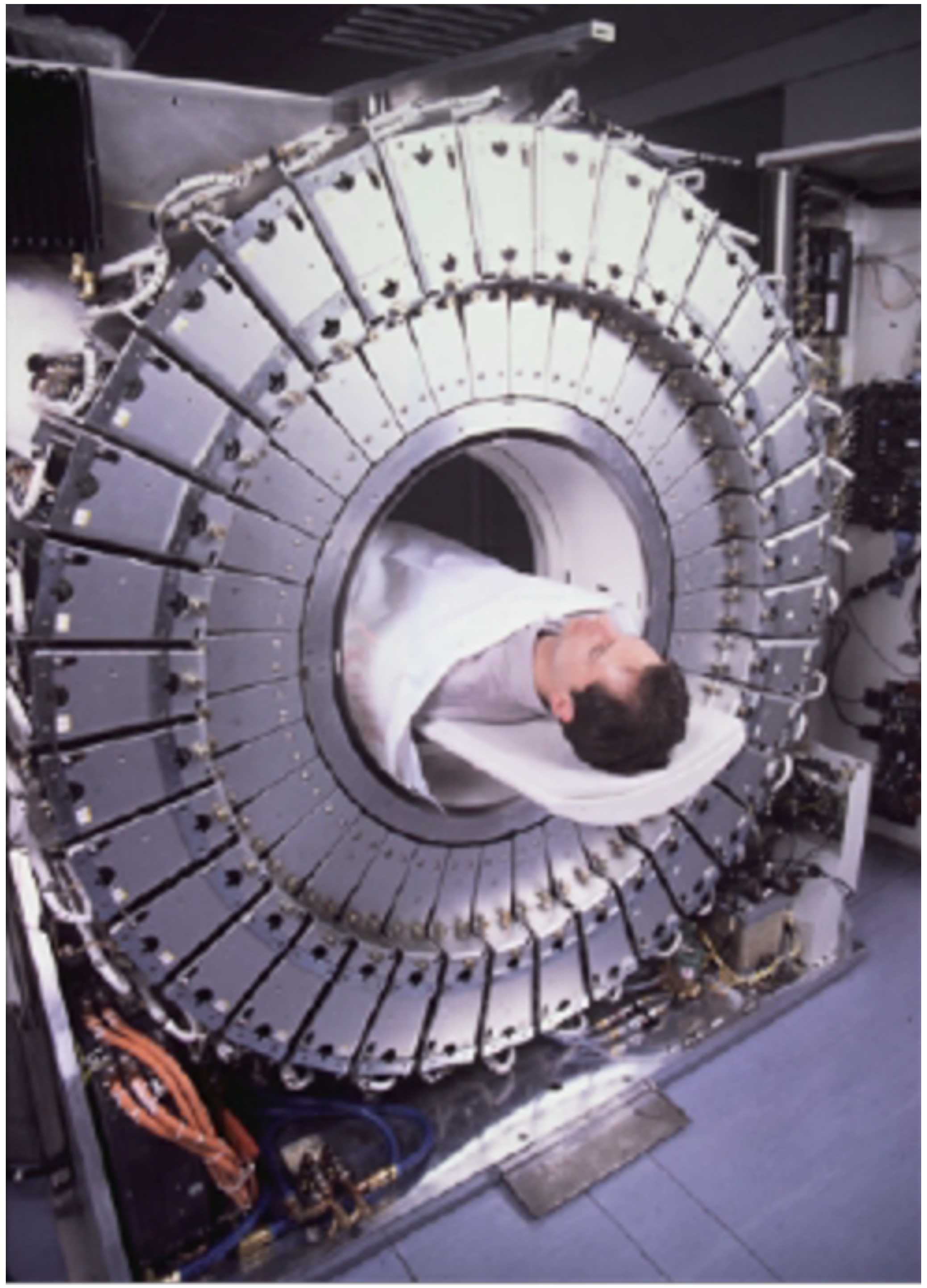




PET instrumentation

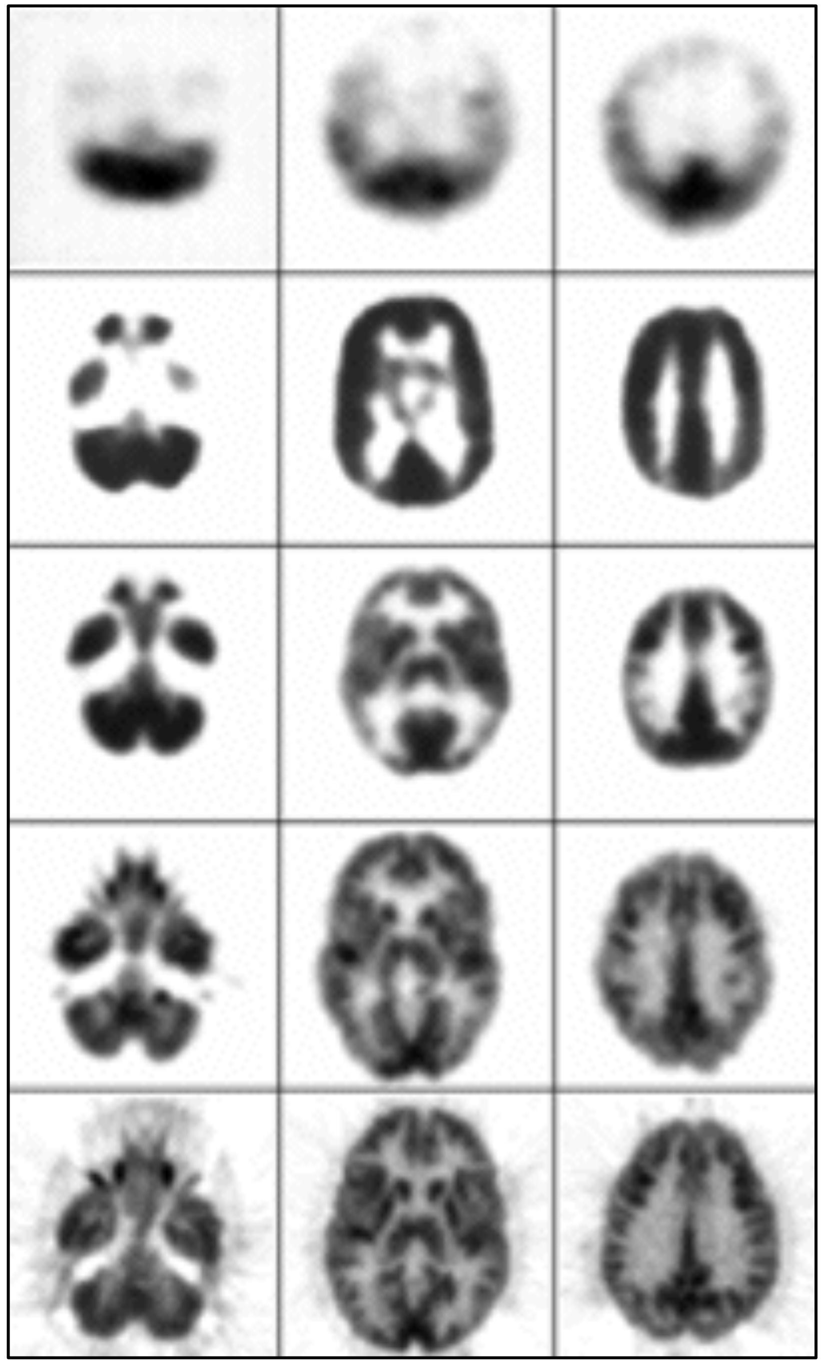


Hair dryer (BNL, 1960)



ECAT EXACT HR+ (CTI, 1995)

Continuous progress in PET instrumentation



PET III 1975

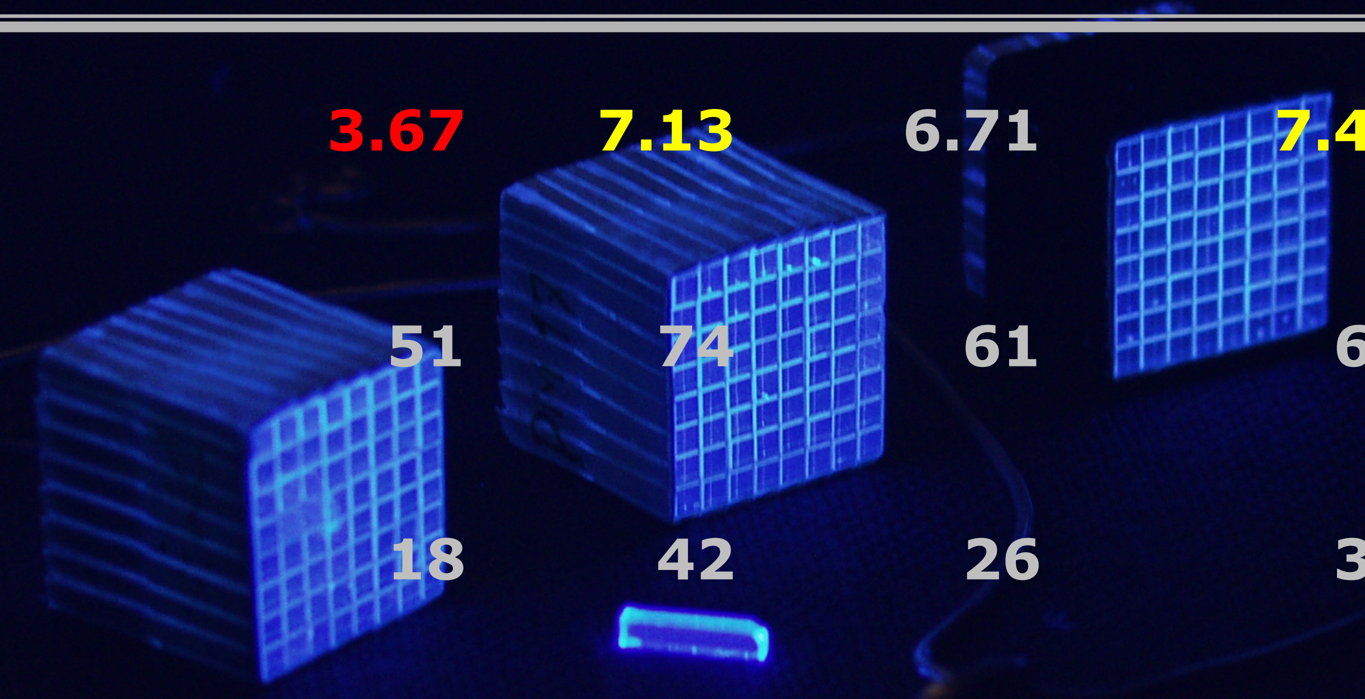
ECAT II 1977

NeuroECAT 1978

ECAT 931 1985

ECAT EXACT HR+ 1995

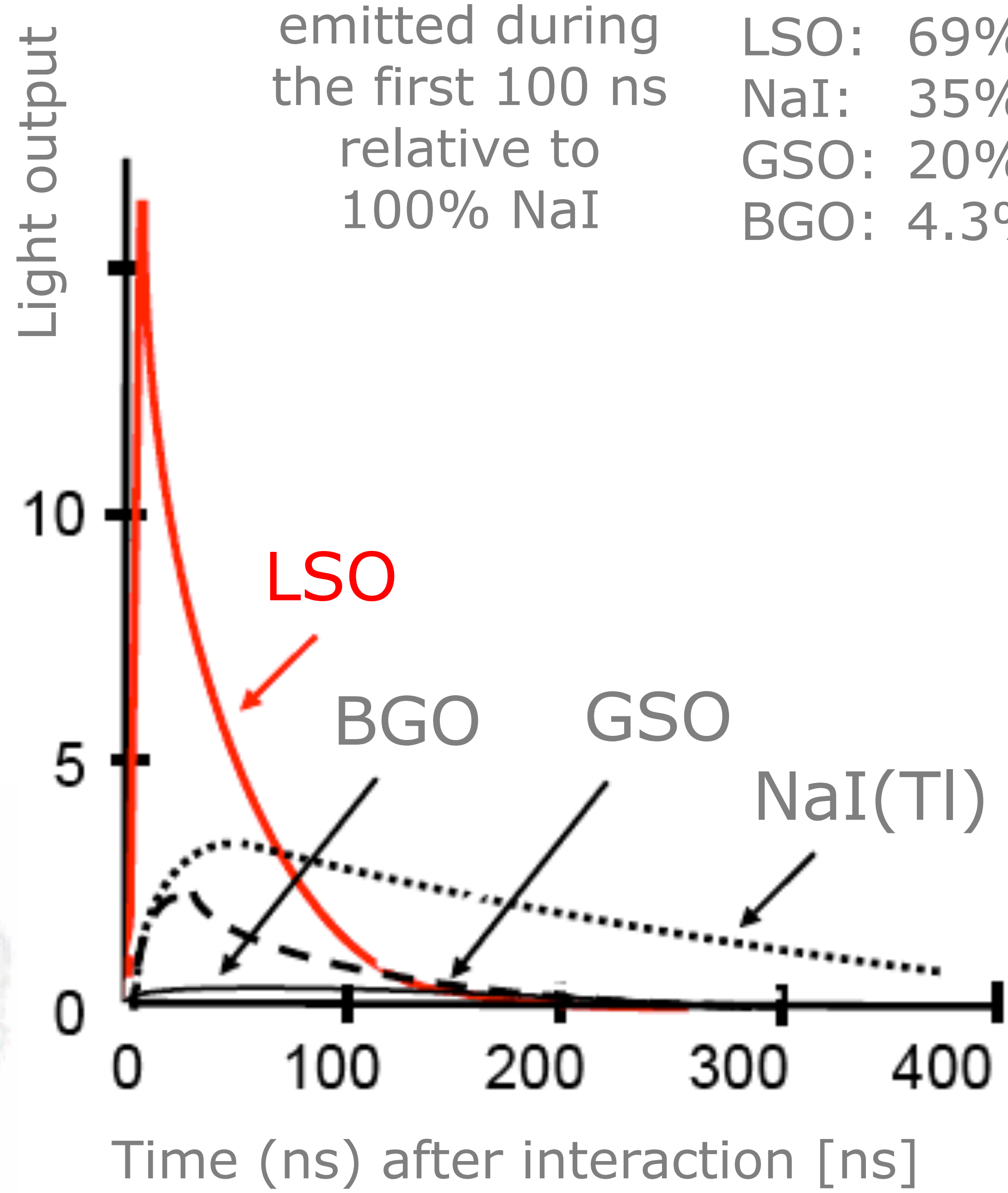
Scintillateurs inorganiques utilisés en TEP



	NaI	BGO	GSO	L(Y)SO	LuAP	$LaBr_3$
Density (g/cm^3)	3.67	7.13	6.71	7.40	8.34	5.3
Effective Z	51	74	61	66	65	52
Photofraction (%)	18	42	26	33	32	14
Decay time (ns)	230	300	30-60	35-45	17	25
Light yield (ph/MeV)	43000	8200	10000	28000	11400	60000
Peak emission (nm)	415	480	430	420	365	370
Refraction index	1.85	2.15	1.85	1.82	1.97	1.9

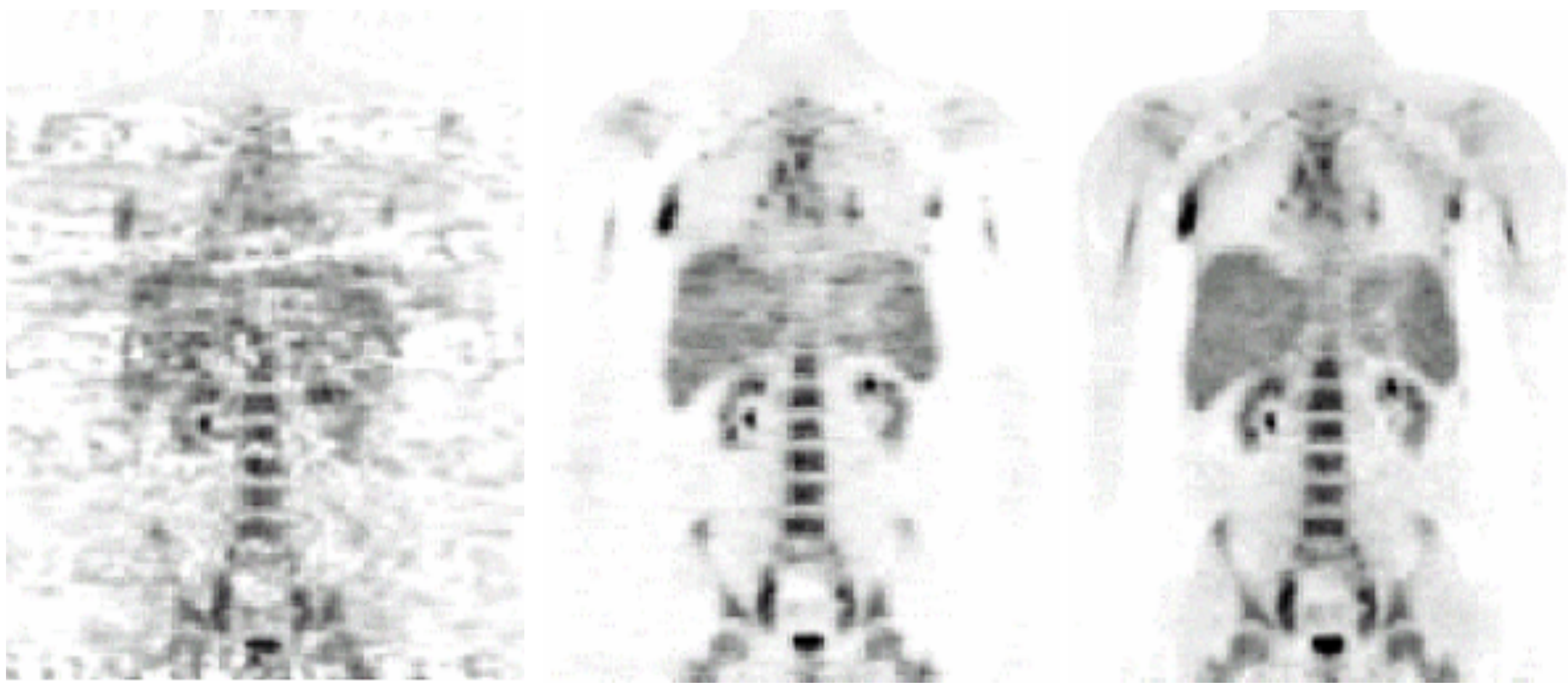
Technical progress in PET

	BGO	LSO	GSO
Dens. [g/cm³]	7.13	7.4	6.7
Z effectif	74	66	61
Decay [ns]	300	35-45	30-60
ph/MeV	8200	28000	10000
% NaI(Tl)	15	75	25



Fraction of light emitted during the first 100 ns relative to 100% NaI

LSO: 69%
NaI: 35%
GSO: 20%
BGO: 4.3%

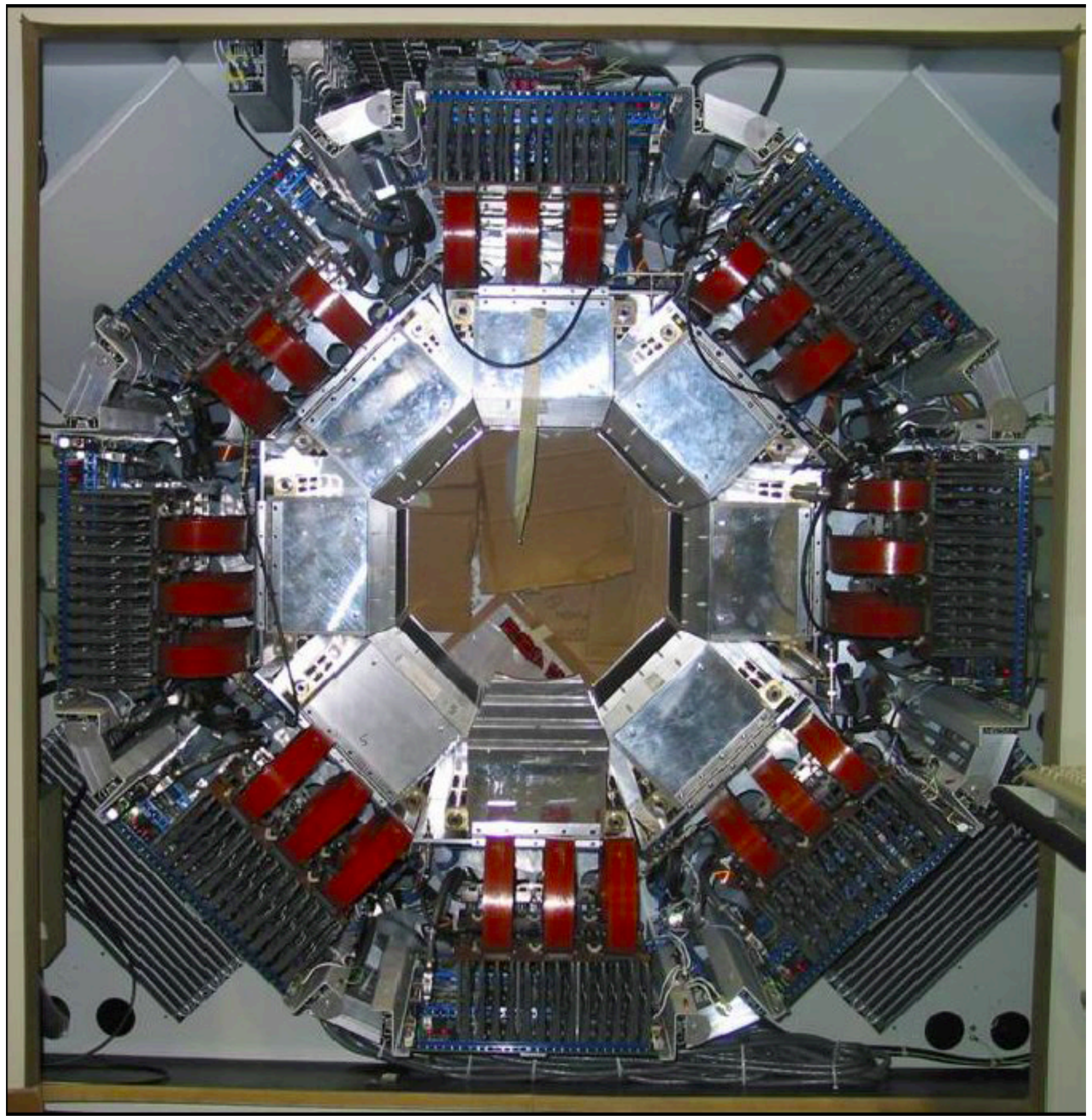


3DRP FORE+OSEM FORE+AWOSEM

courtesy: DW Townsend, UPMC

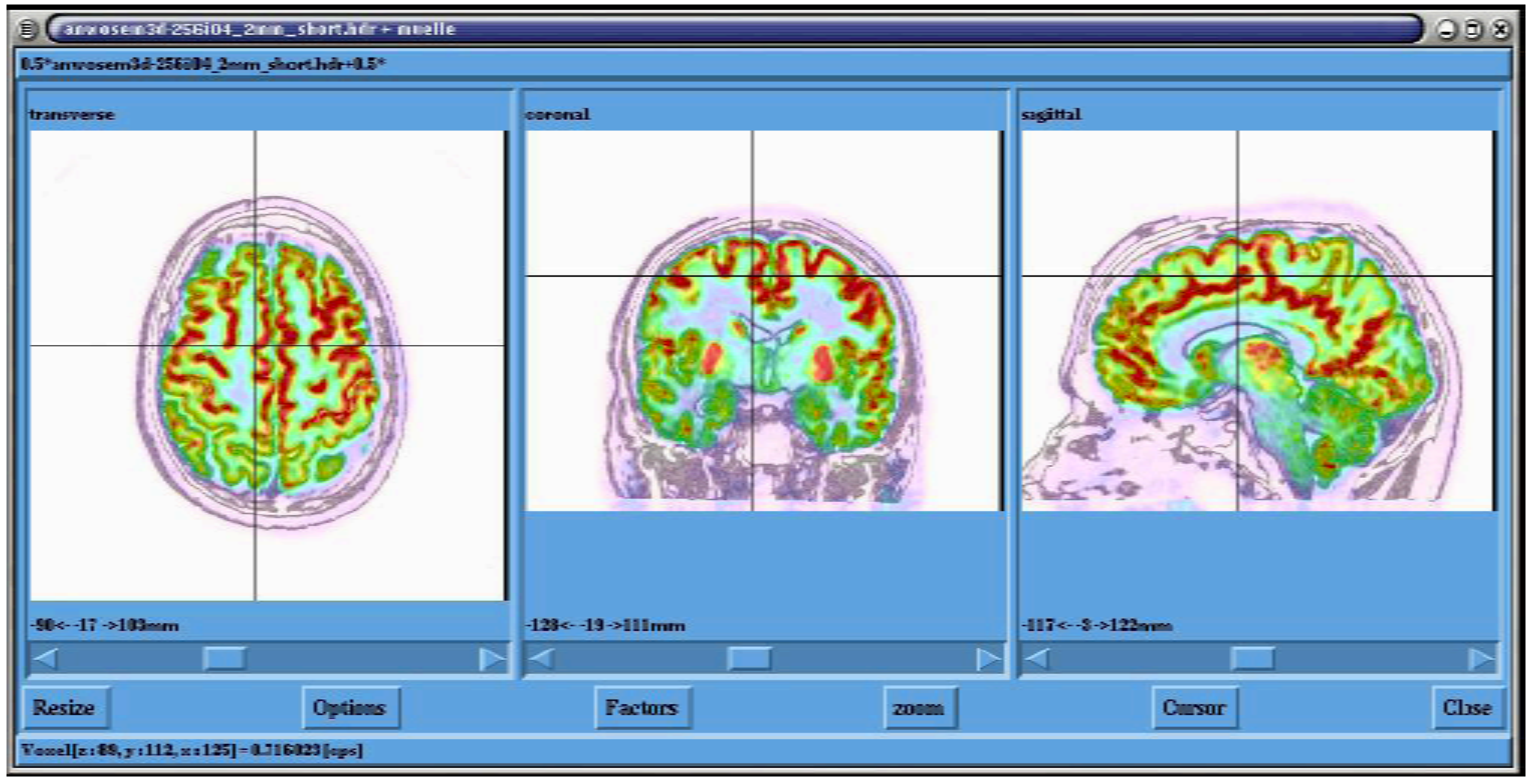
- Detectors
- Data correction
- image reconstruction

High Resolution Research Tomograph (HRRT)



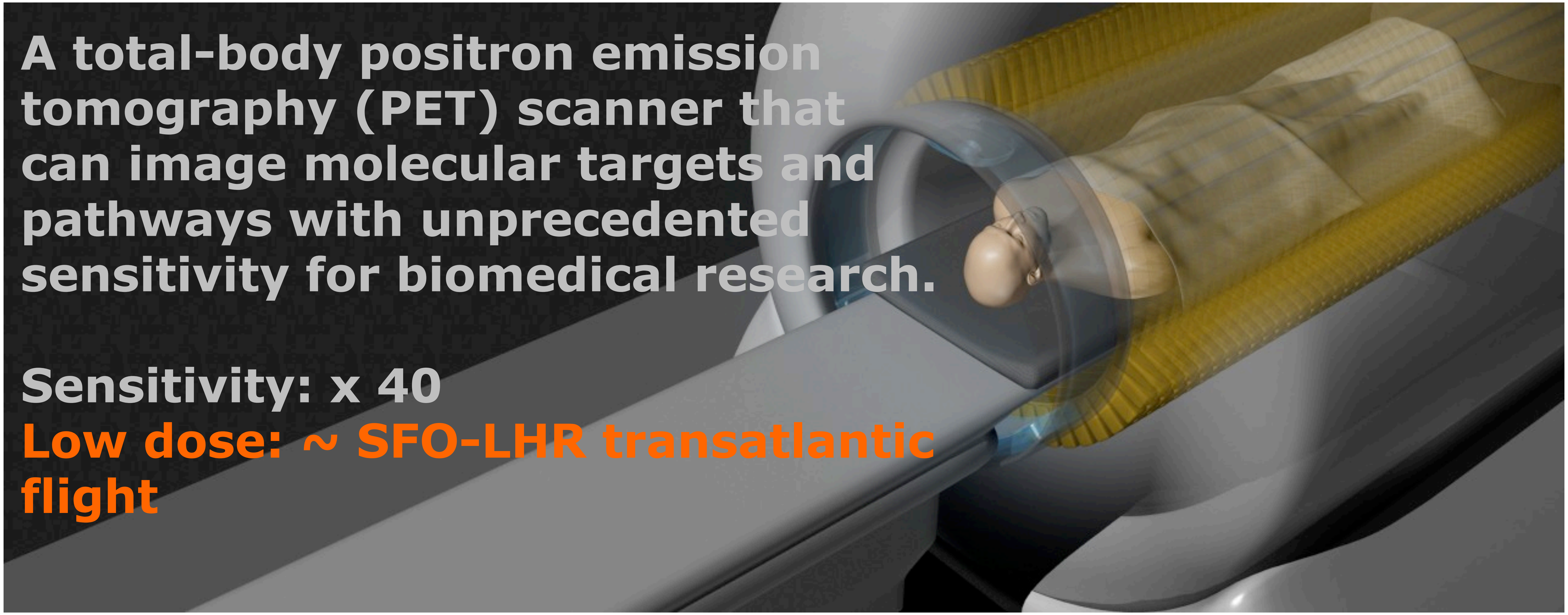
- LSO/GSO phoswich
- 153600 cristaux
- 1120 PMTs

Courtesy: K.Wienhard, Köln



40 min FDG fusionnée avec IRM-T1

EXPLORER



A total-body positron emission tomography (PET) scanner that can image molecular targets and pathways with unprecedented sensitivity for biomedical research.

Sensitivity: x 40

Low dose: ~ SFO-LHR transatlantic flight

UC DAVIS
UNIVERSITY OF CALIFORNIA

Penn
UNIVERSITY of PENNSYLVANIA

BERKELEY LAB

ASP Online Seminars, October 29 2020

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CENTRE DE PHYSIQUE DES PARTICULES DE MARSEILLE CPPM

EXPLORER is Completed!

System:
Ring diameter: 78.6 cm
Transaxial FOV: 68.6 cm
Axial FOV: 194.8 cm

# of crystals: 564,480
crystal blocks: 13,440
of SiPMs: 53,760

EXPLORER

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CENTRE DE PHYSIQUE DES PARTICULES DE MARSEILLE CPPM

EXPLORER First Human Images

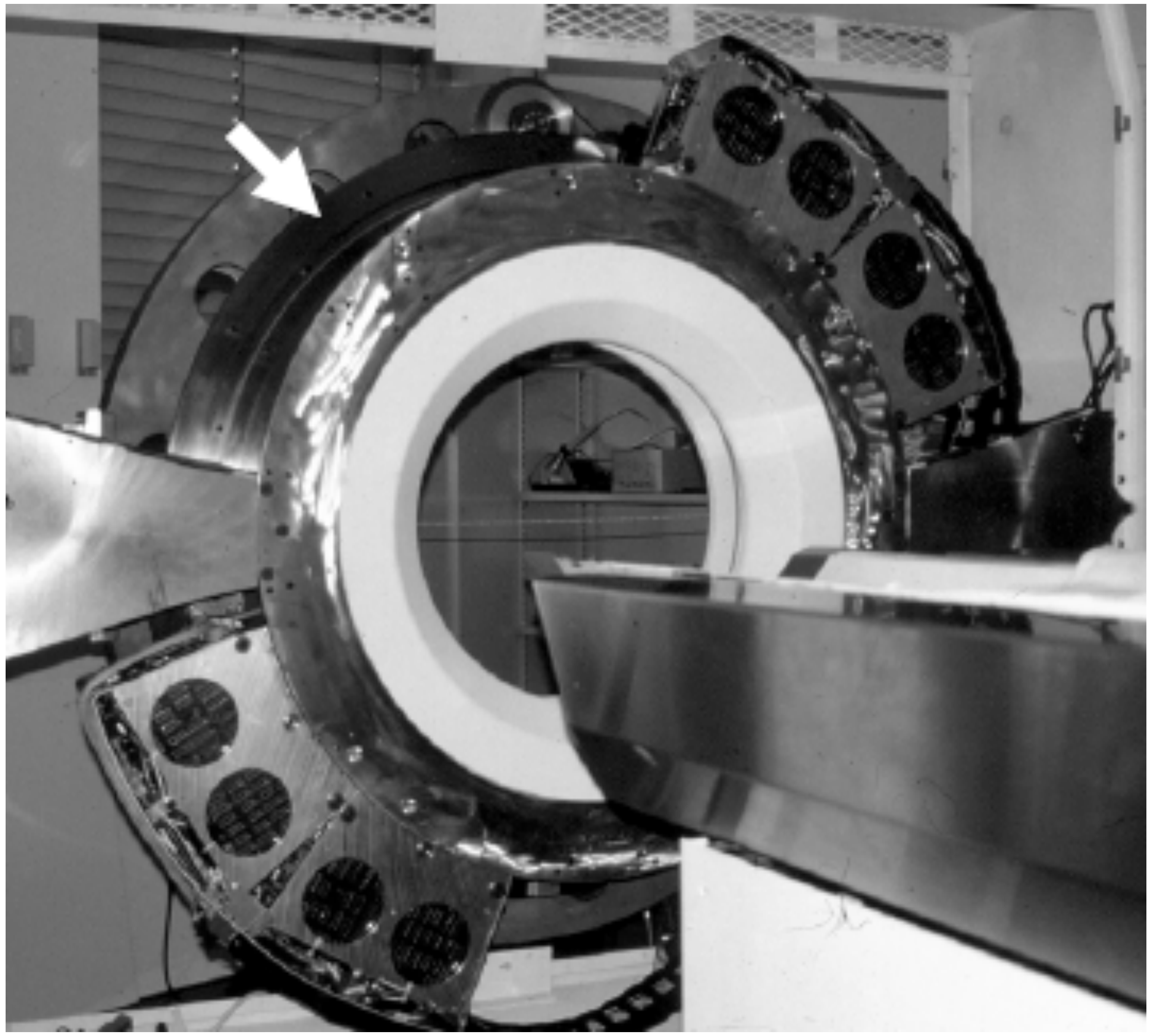
1 min scan, 81 min p.i.

20 min scan, 82 min p.i.

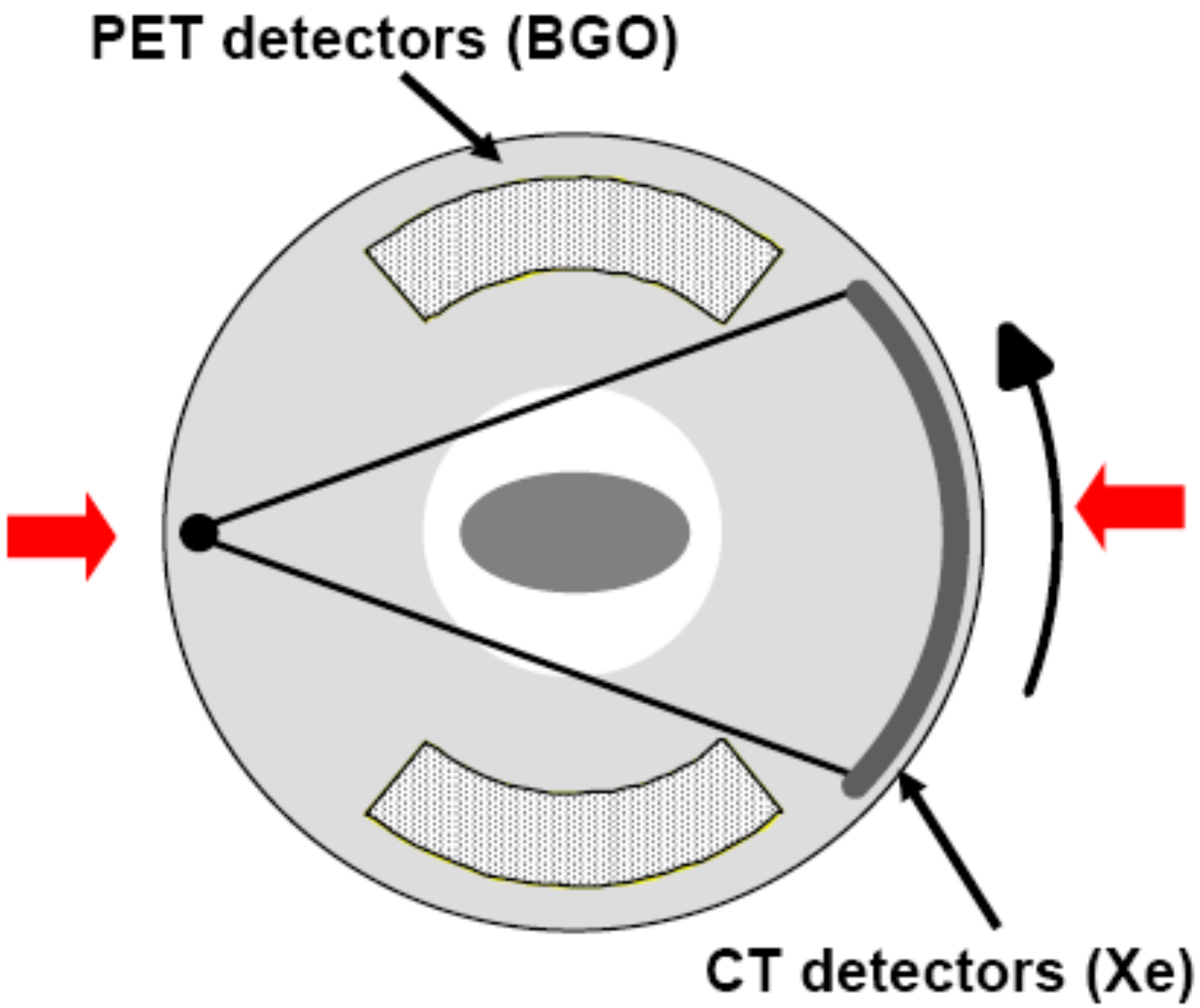
61-yo male, 65 kg; 164 cm; 7.8 mCi injected

courtesy: Zhongshan Hospital, Shanghai

1991: PET/CT concept, D.W. Townsend (HUG)



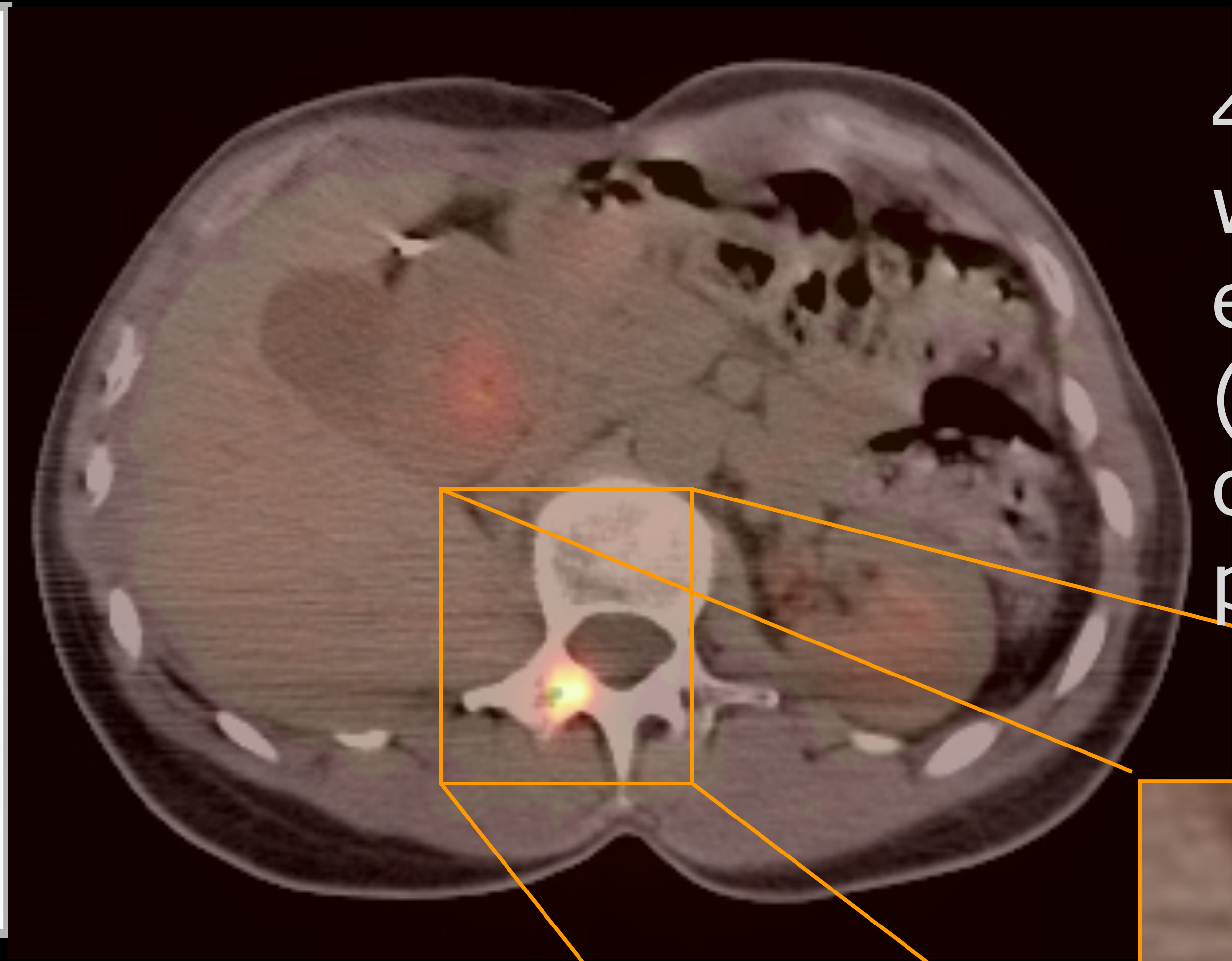
PRT-1



Courtesy: D.W. Townsend, UPMC

CT: 160 mAs; 130 KV_p; pitch 1.6; 5 mm slices

PET: 6.3 mCi FDG; 3 x 10 min; 3.4 mm slices



40 year-old woman with multiple endocrine syndrome (MEN-1) and history of malignant pheochromocytoma

MIBG scan one year ago showed right adrenal lesion; adrenal resected but no tumor found. PET suggested a lesion in the adrenal resection bed but PET/CT showed lesion located in spine.

UPMC, 1998

Courtesy: D.W. Townsend, UPMC

TIME magazine Dec 2000


INVENTORS & INVENTIONS

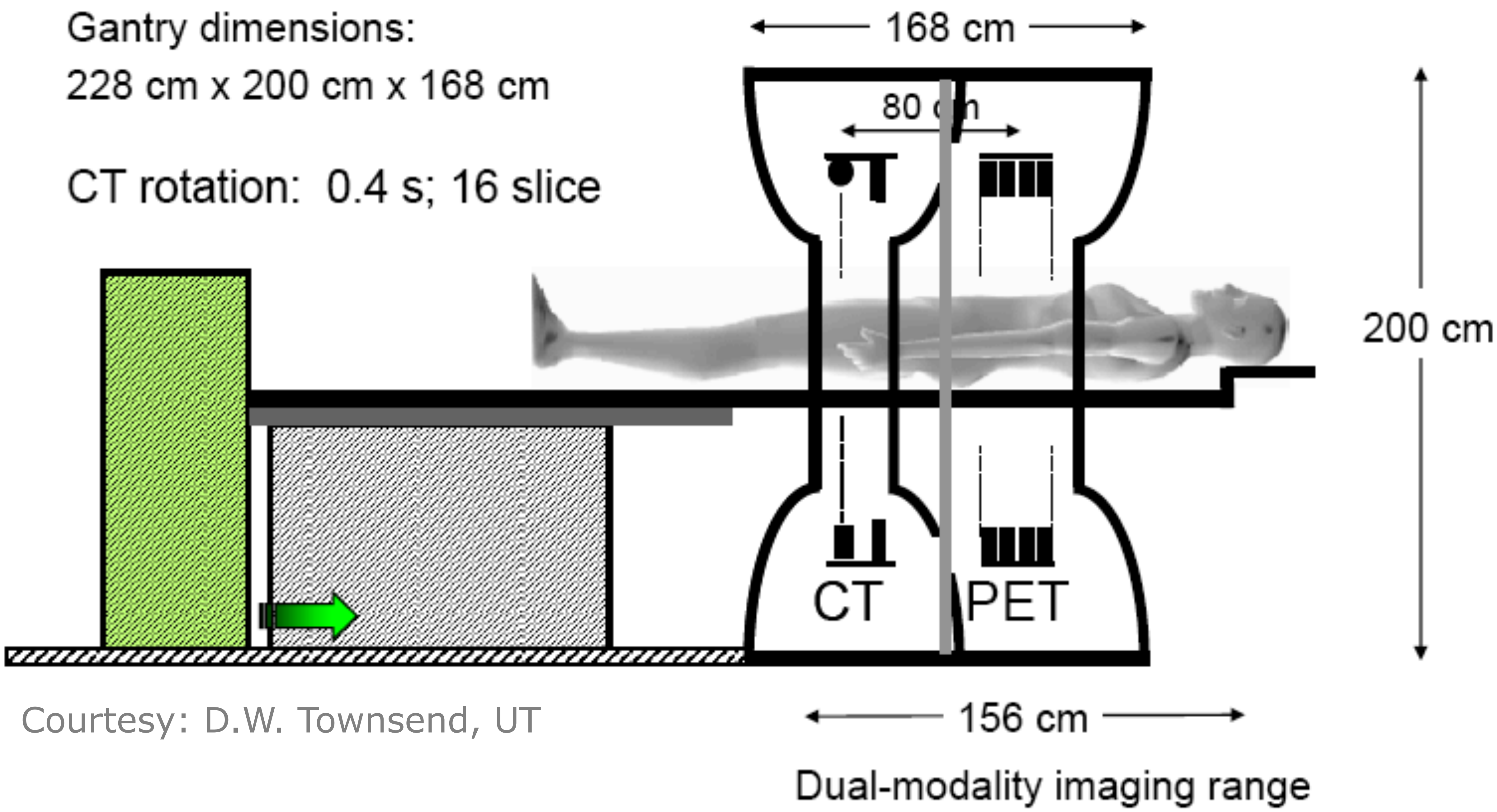
INVENT-ORS & INVENT-IONS

1+1=3

Accidents plus luck: the sum of innovation is greater than its parts

BY JAMES BURKE

Typical design of a PET/CT scanner

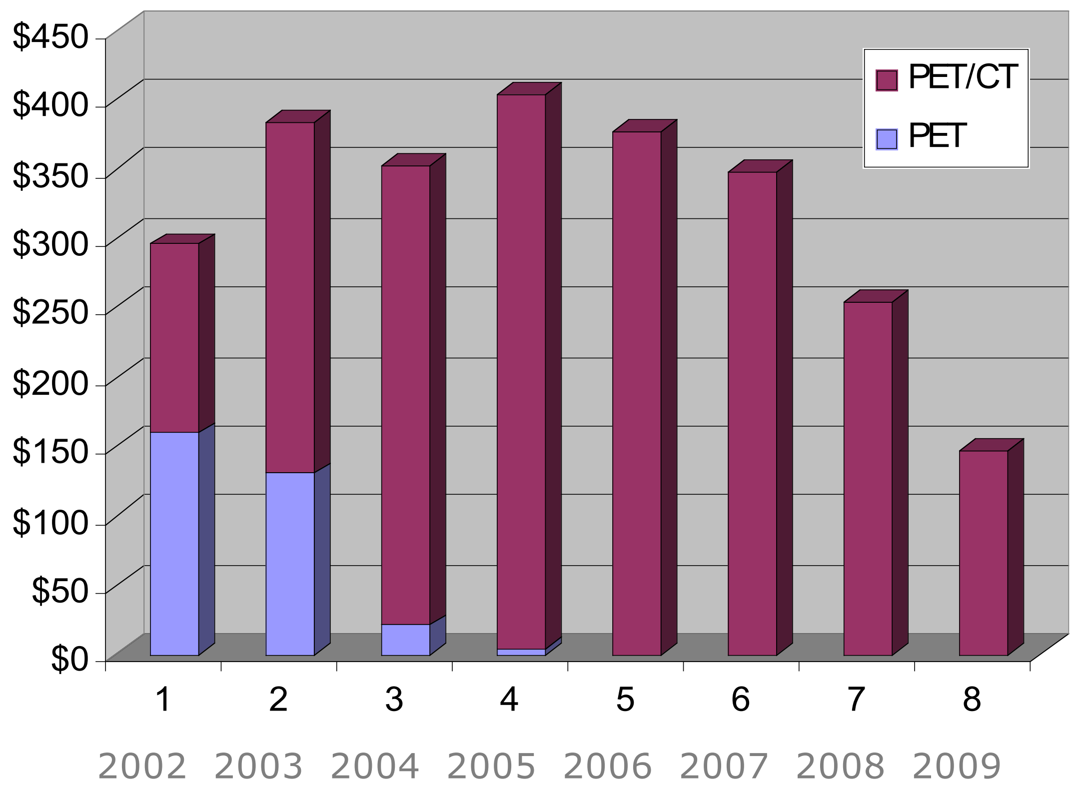


Courtesy: D.W. Townsend, UT

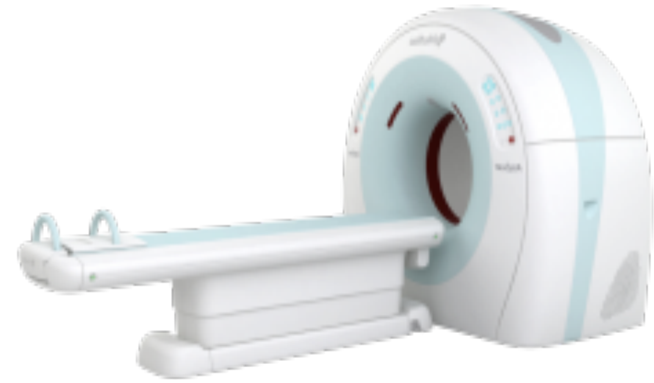
2001 : 1st commercial PET/CT scanner installed in Zurich by GE
2005 : > 650 TEP/TDM scanners installed, 95% PET sales

PET/CT scanners

Discovery IQ, GE



NEMA - US Shipments ($M) TEP/CT



AnyScan, Pozitron Teknik

Gemini, Philips

Celesteion, Toshiba

Biograph, Siemens

uMI 510, United Imaging

SceptreP3, Hitachi

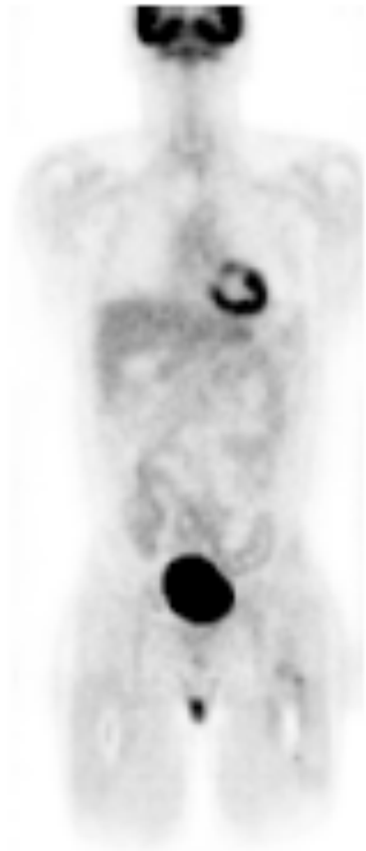
courtesy: D.W. Townsend, UT

Clinical + Preclinical

microPET Focus 220

Mouse
6 MBq FDG

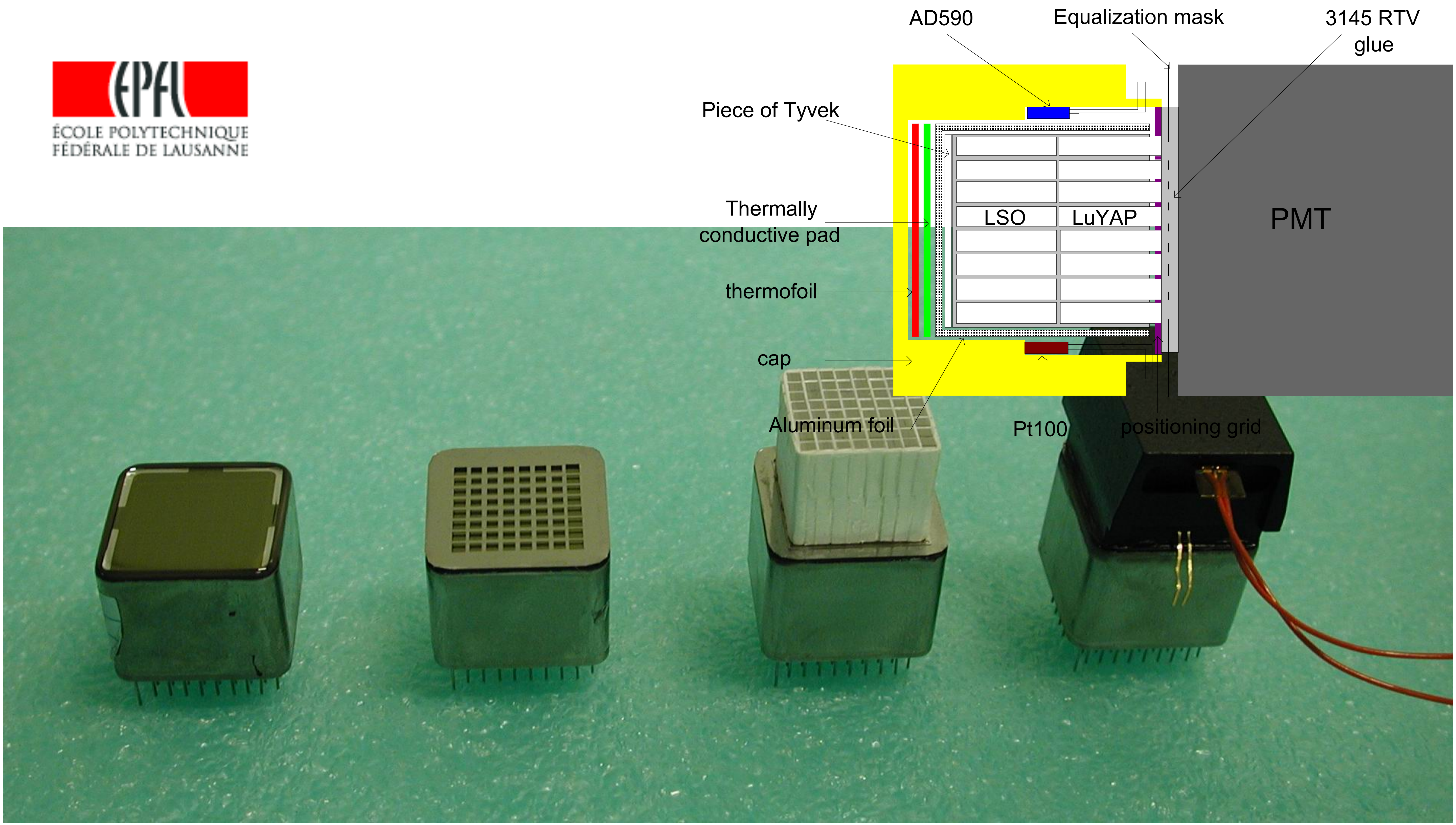
ECAT EXACT HR+



Humain
390 MBq FDG

Phosphor-sandwich (phoswich) detector

ÉCOLE POLYTECHNIQUE FÉDÉRALE DE LAUSANNE



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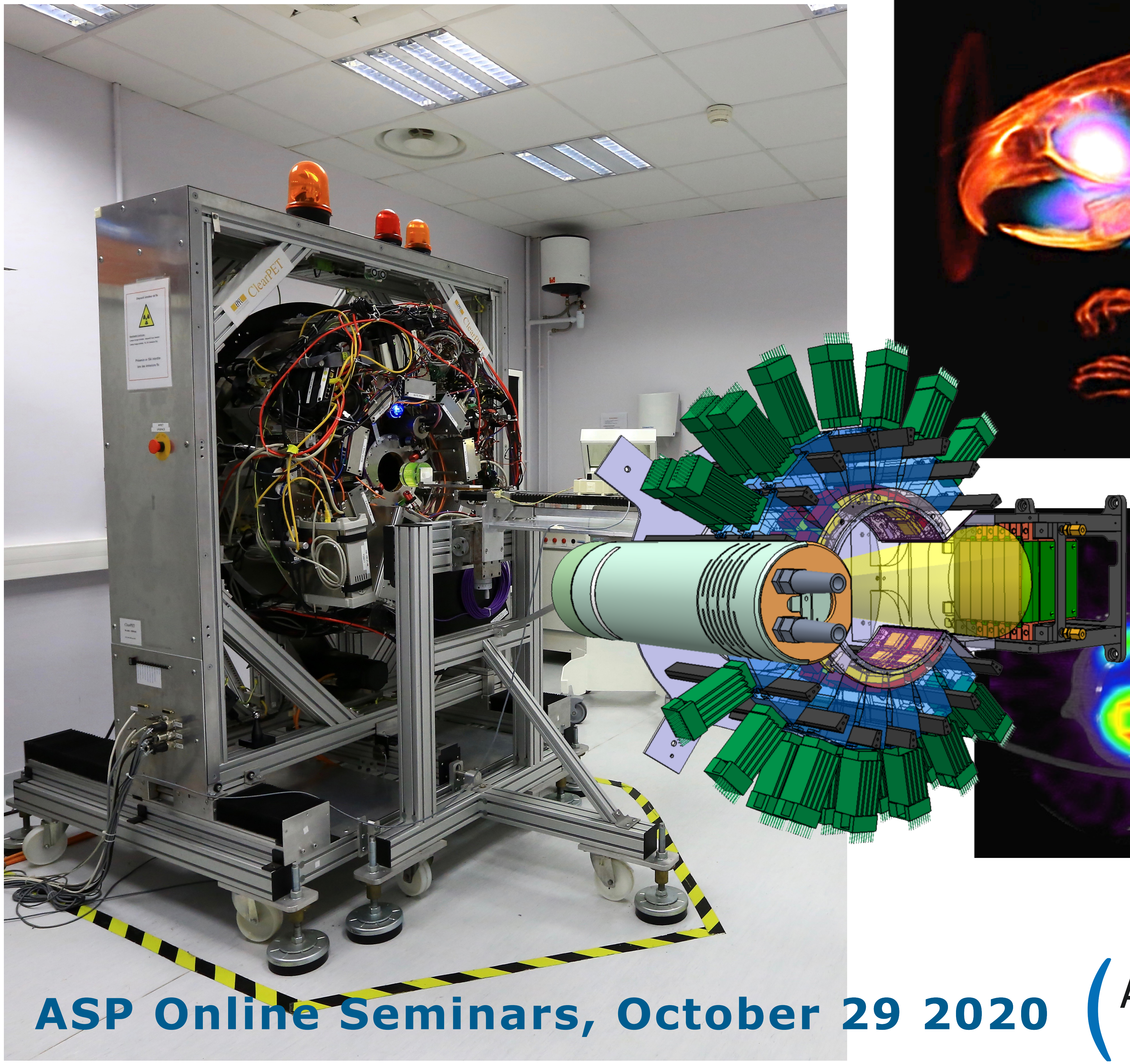
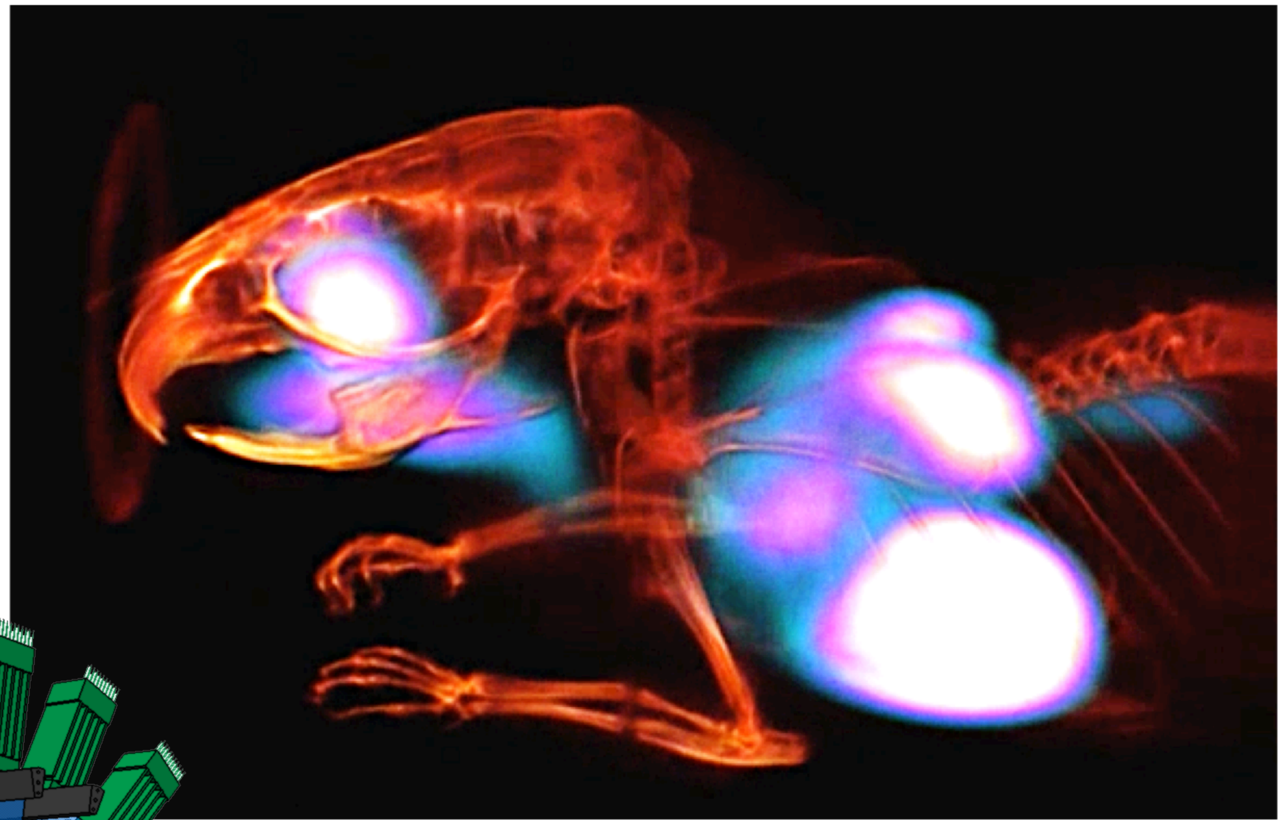
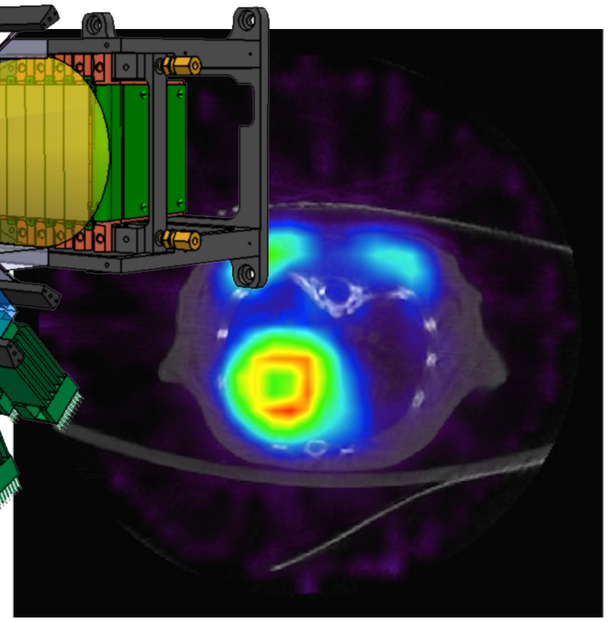
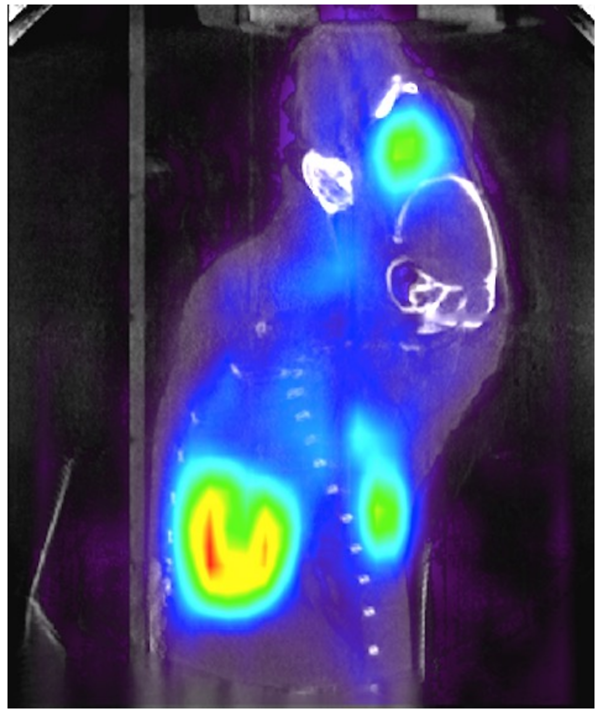
Proof of concept of simultaneous PET/CT

ClearPET/XPAD prototype PET/CT scanner at CPPM









M Hamonet et al., Proc. IEEE NSS/MIC 2016

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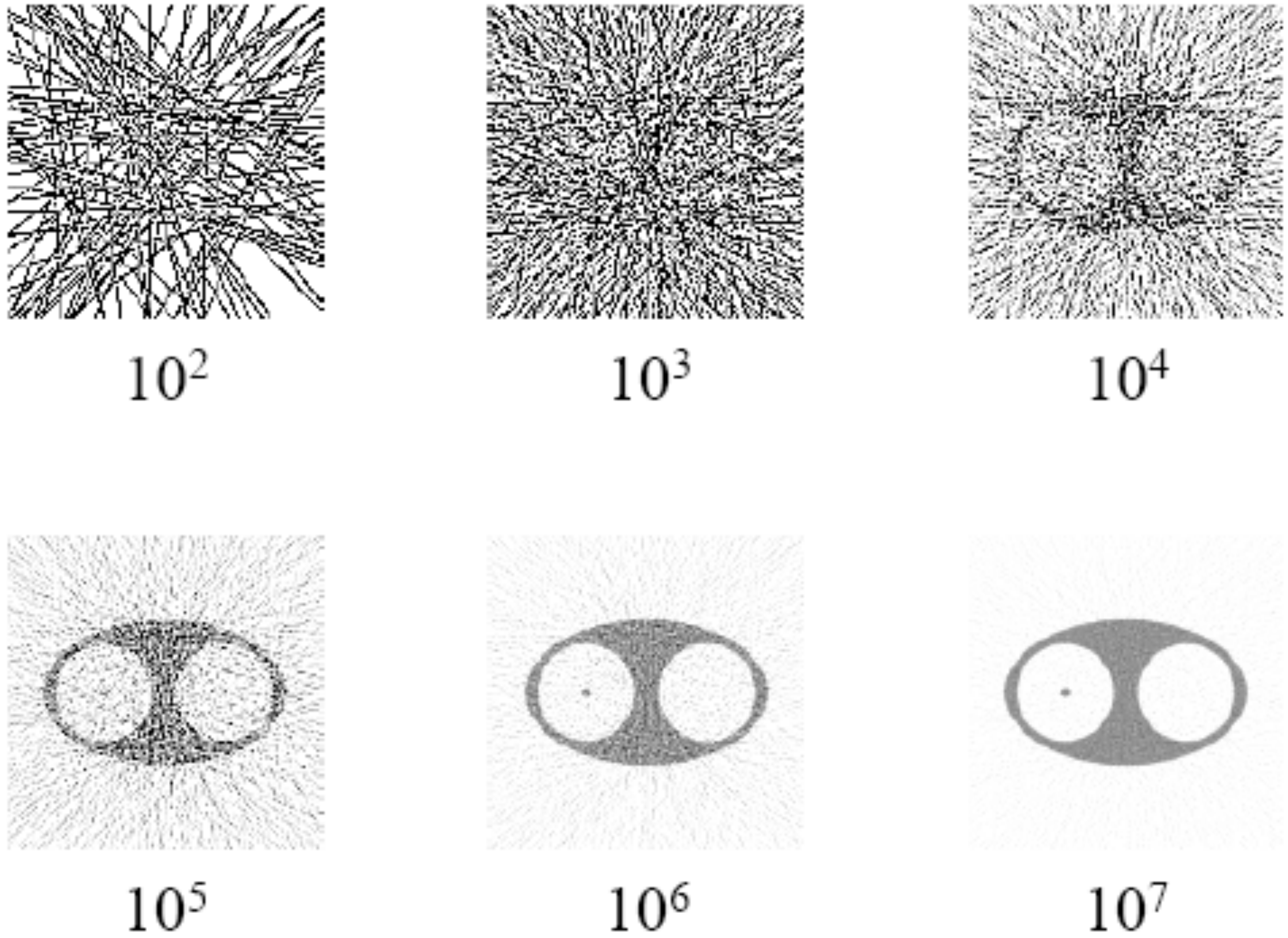
Centre de Physique des Particules de Marseille CPPM

Tomographical reconstruction and counting statistics

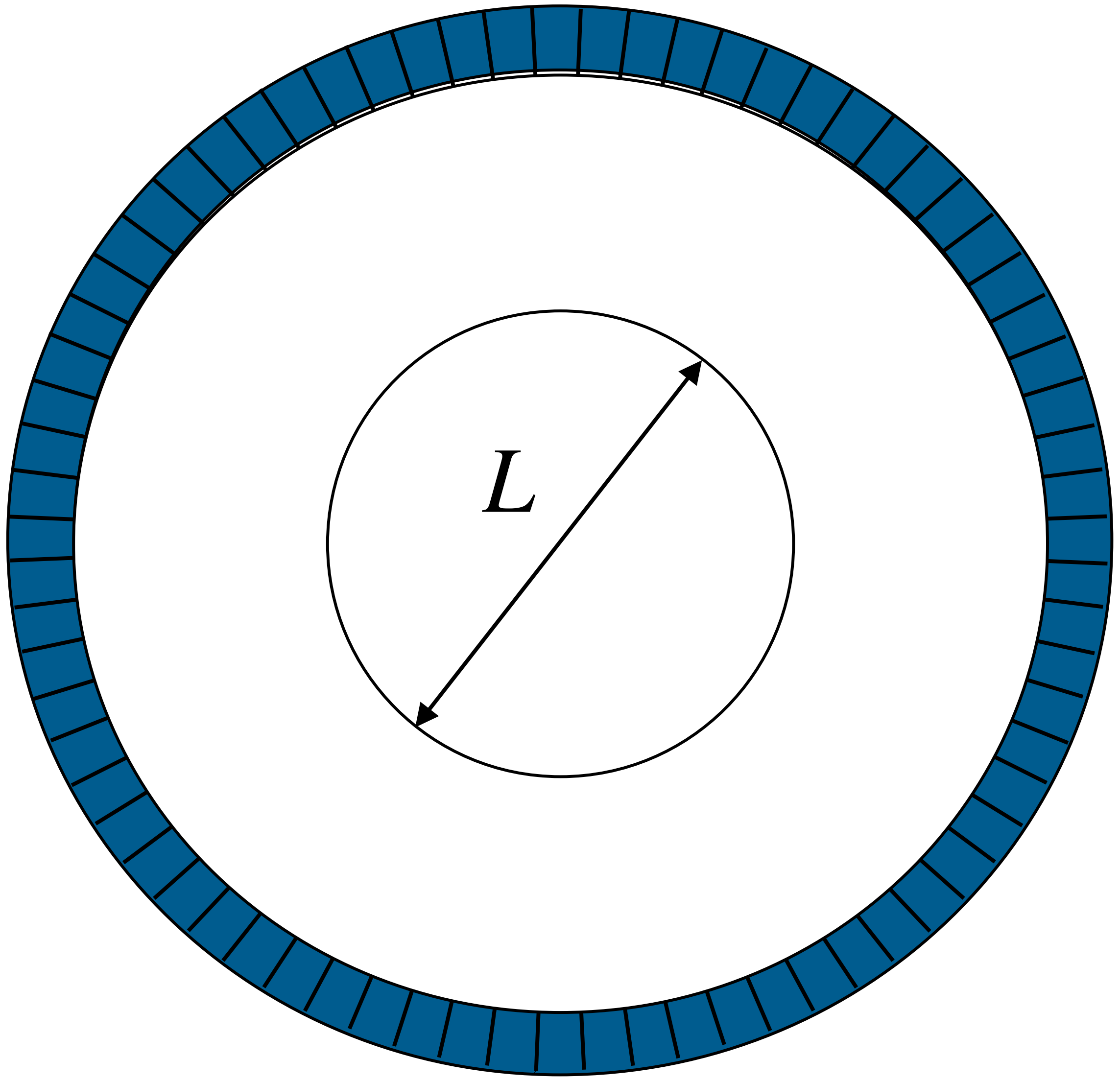


Courtesy: C. Comtat, CEA-SHFJ

Signal-to-noise ratio and counting statistics

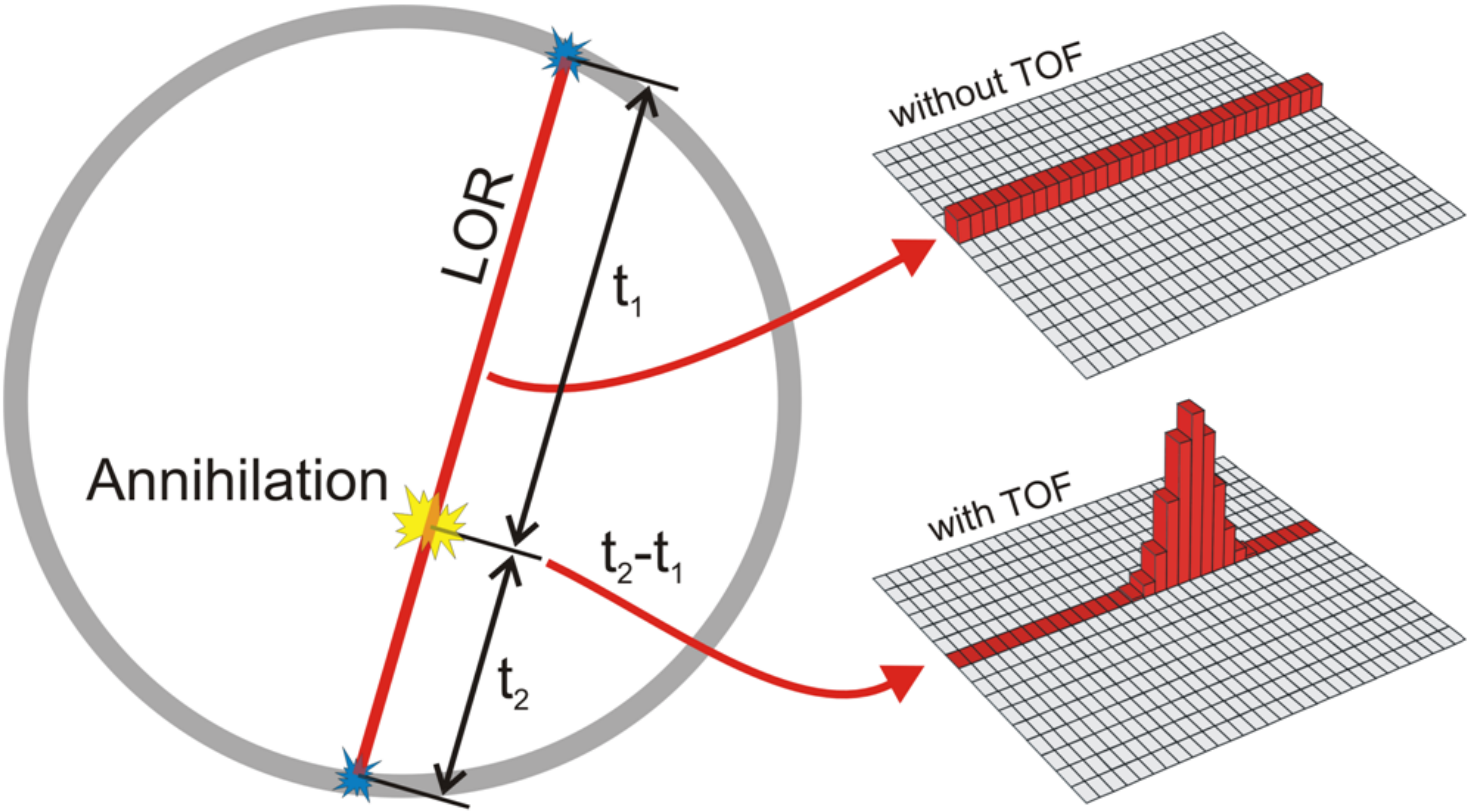
$$\frac{A}{\Delta A} = \sqrt{N_{\beta^+}} \Rightarrow N_{\beta^+} = \left(\frac{A}{\Delta A}\right)^2$$

$$N_{Tot} = \left(\frac{L}{d}\right)^3 \times \left(\frac{A}{\Delta A}\right)^2 \times \left(\frac{L}{d}\right)$$



Improving spatial resolution x 2 ⇒ increasing counting statistics x 16 to get unchanged SNR in the reconstructed image voxels

Time-Of-Flight (TOF)-PET

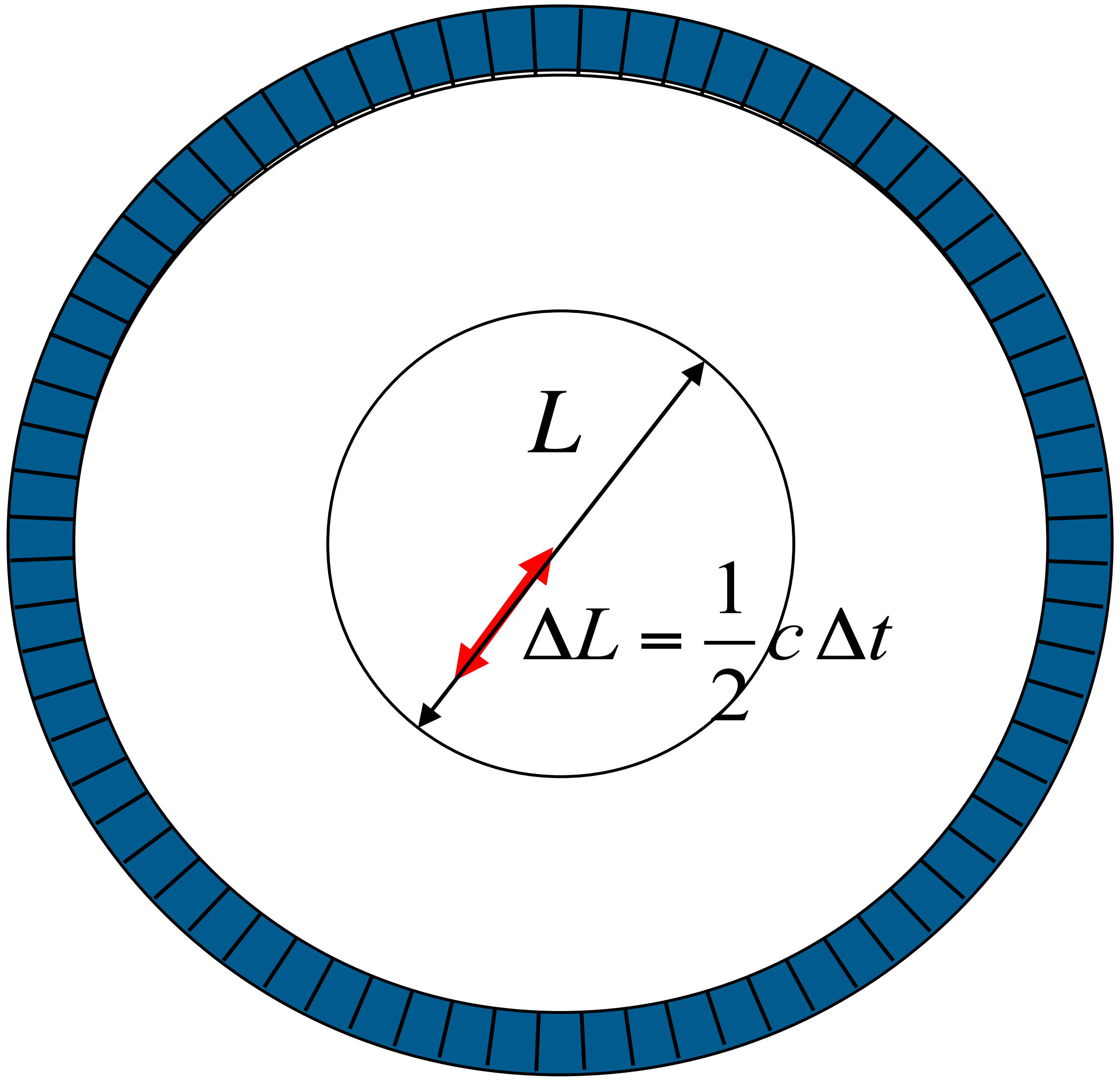


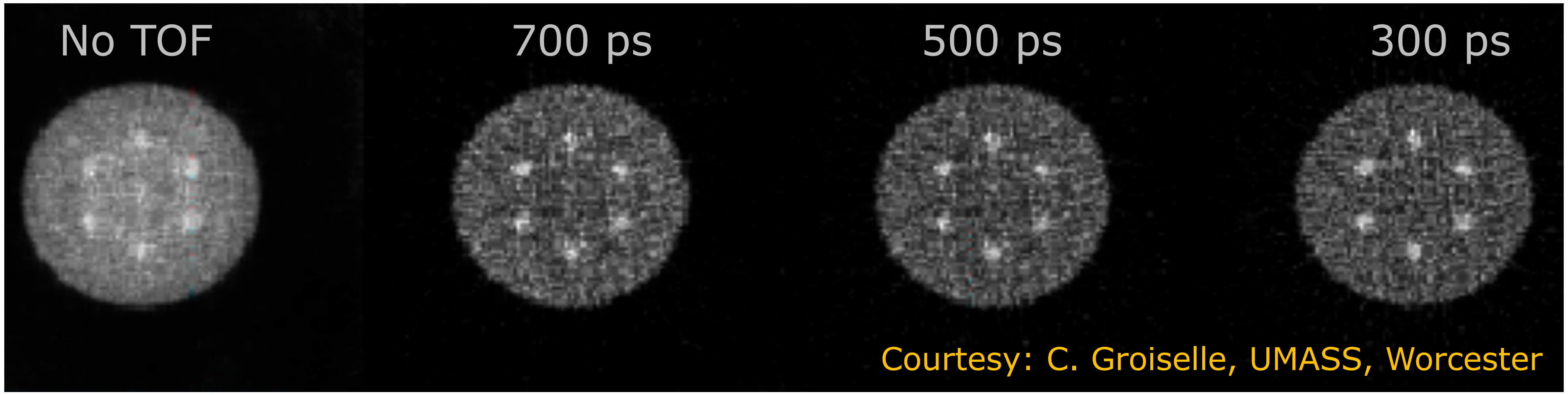
Impact of TOF-PET on image SNR

$$N_{Tot} = \left(\frac{L}{d}\right)^3 \times \left(\frac{A}{\Delta A}\right)^2 \times \left(\frac{L}{d}\right)$$

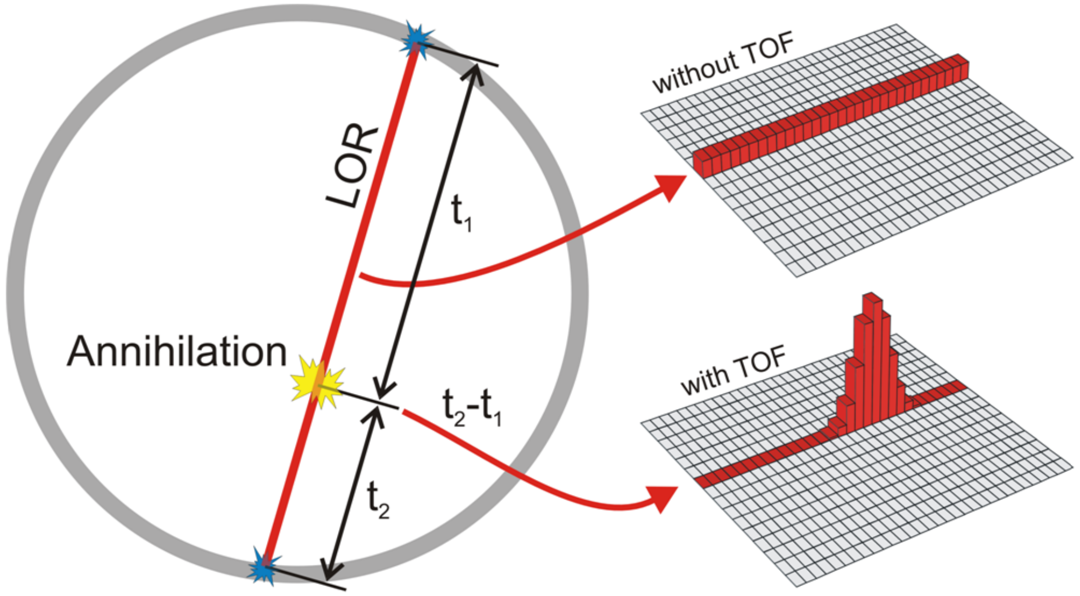
$$N_{ToF} = \left(\frac{L}{d}\right)^3 \times \left(\frac{A}{\Delta A}\right)^2 \times \left(\frac{\Delta L}{d}\right)$$

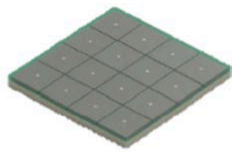
Variance reduction factor $f = \frac{L}{\Delta L} = \frac{2L}{c\Delta t}$



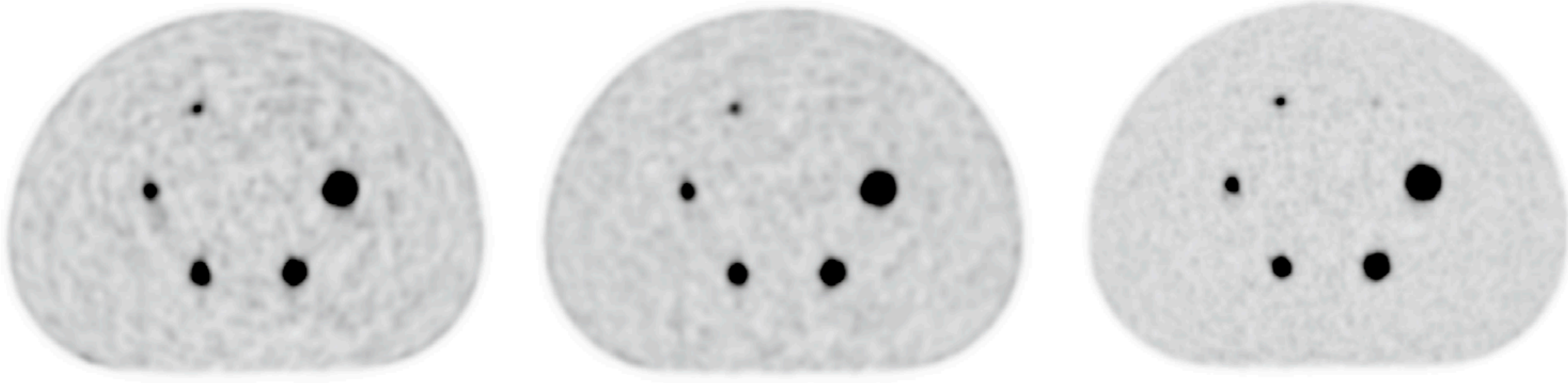


State-of-the-art TOF-PET



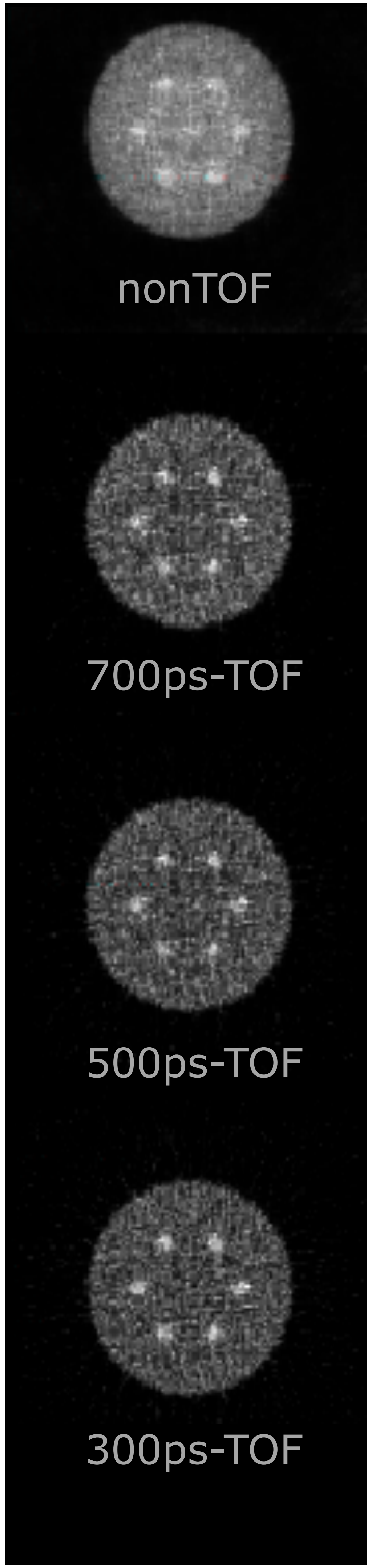


$$\left(\frac{SNR_{TOF}}{SNR_{nonTOF}}\right)^2 = \frac{2D}{c \times CTR}$$



nonTOF   527ps-TOF   210ps-TOF

M. Conti and B. Bendriem, Clin Transl Imaging 7 (2019) 139–147



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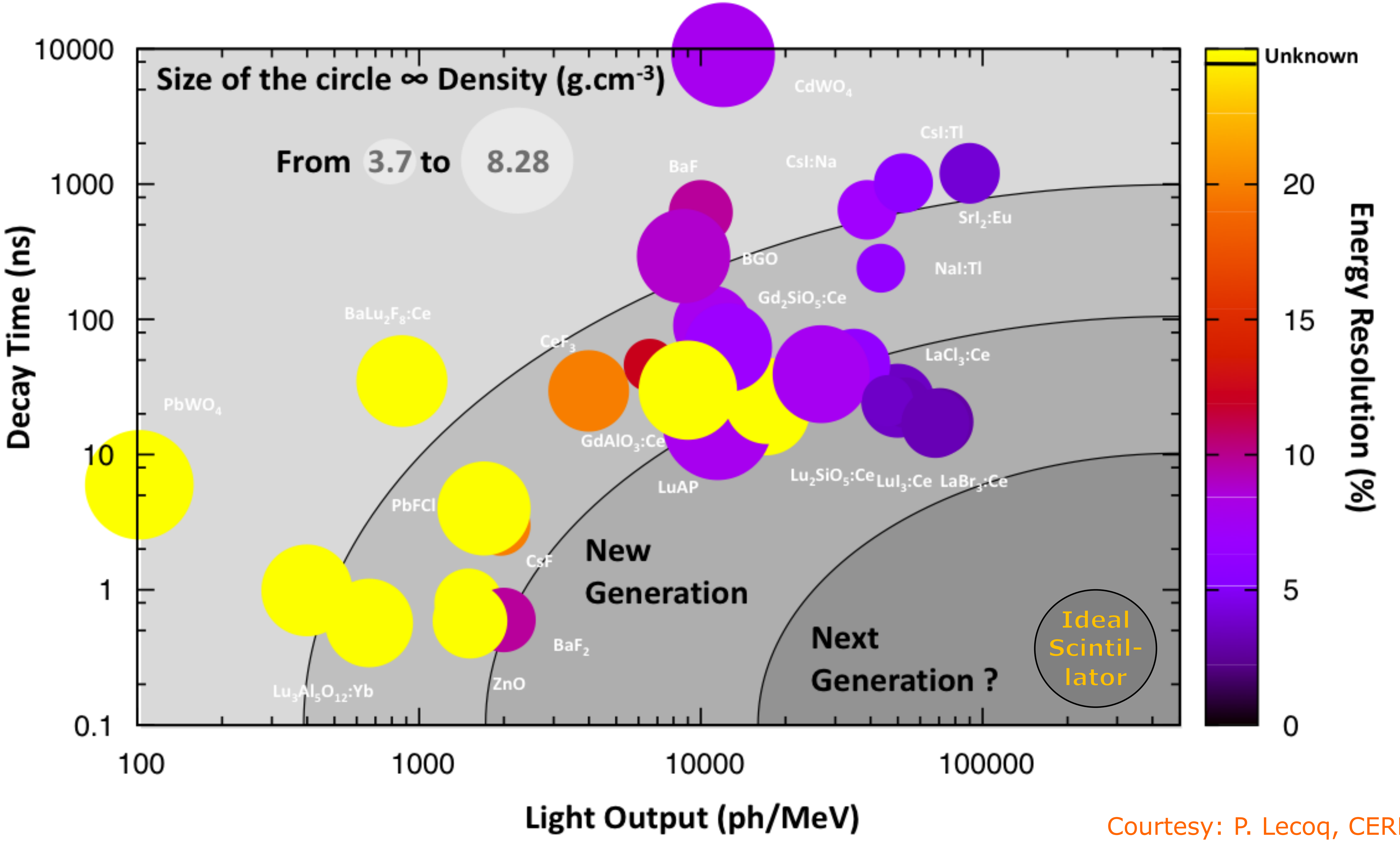
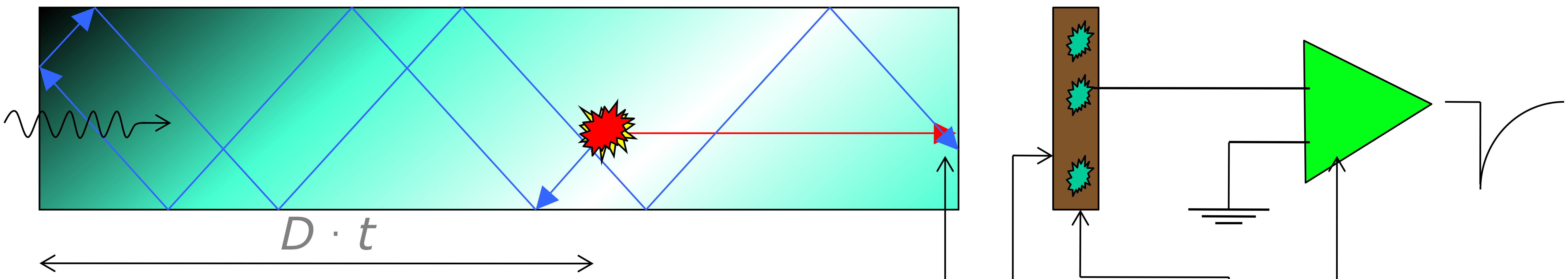
Classification of scintillators



Courtesy: P. Lecoq, CERN

The detection chain

Crystal SiPM electronics



$$t_{kth\ pe} = D \cdot t + t_{k'\ ph} + t_{transit} + t_{SPTR} + t_{TDC}$$

Conversion depth

Scintillation process

Transit time jitter

Single Photon Time Spread

TDC conversion time

Random deletion 1
Absorption
Self-absorption

Random deletion 2
SiPM PDE

Unwanted pulses 1
Dark Count Rate (DCR), crosstalks, afterpulses

Unwanted pulses 2
DCR

Courtesy: P. Lecoq, CERN

The detection chain

From the time of detection $t_{d,i}$ of n optical photons

$$T_d = \{t_{d,1}, t_{d,2}, \ldots, t_{d,n}\}$$

- provides the Fisher information $I_{Td}(\Theta)$ of the gamma ray interaction time Θ
- defines the Cramér-Rao lower bound by minimizing the variance of the time estimator Ξ

$$\mathrm{Var}(\Xi) \geq 1 / I_{Td}(\Theta)$$

Random deletion 2
SiPM PDE

Unwanted pulses 2
DCR

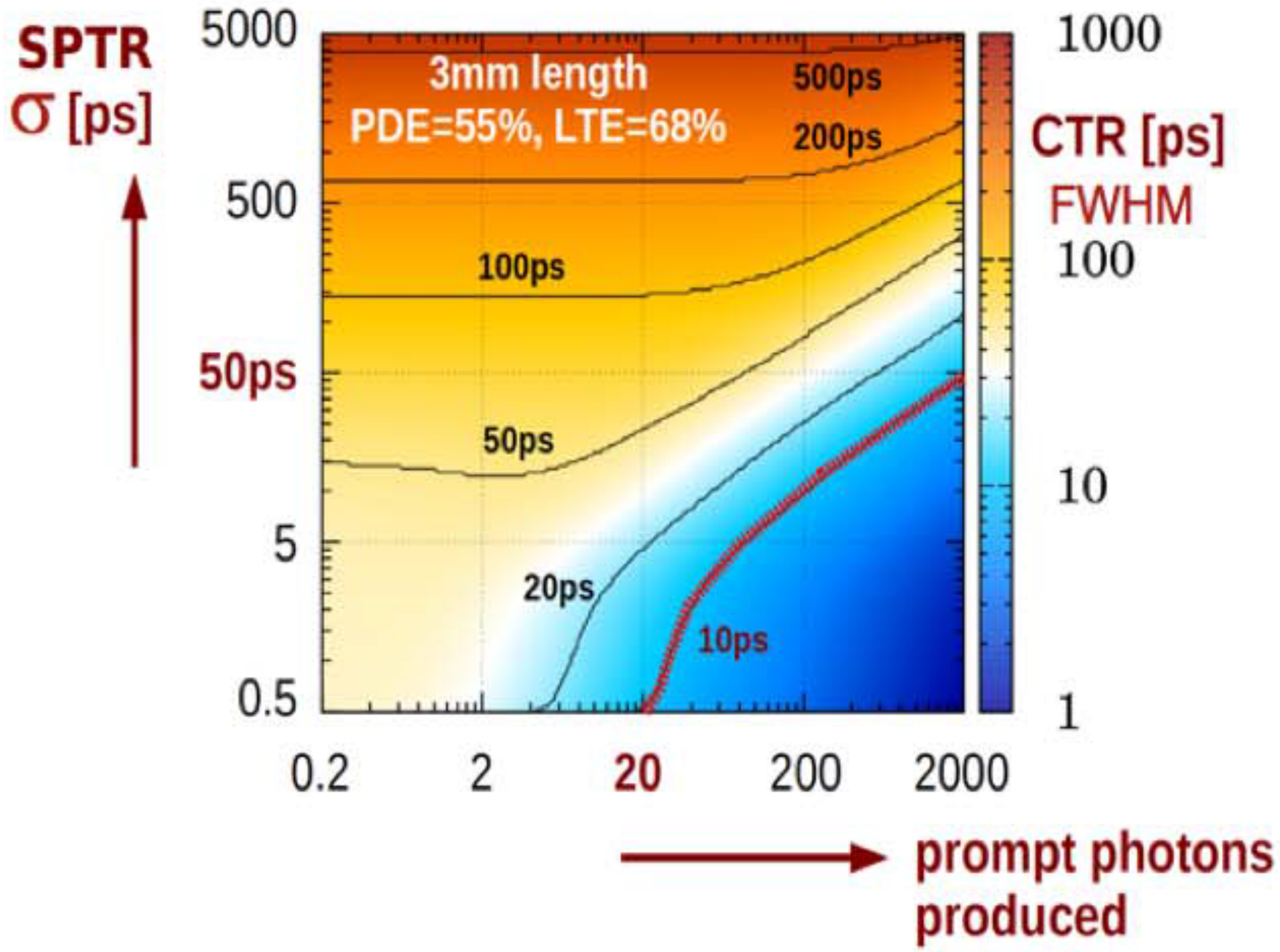
Courtesy: P. Lecoq, CERN

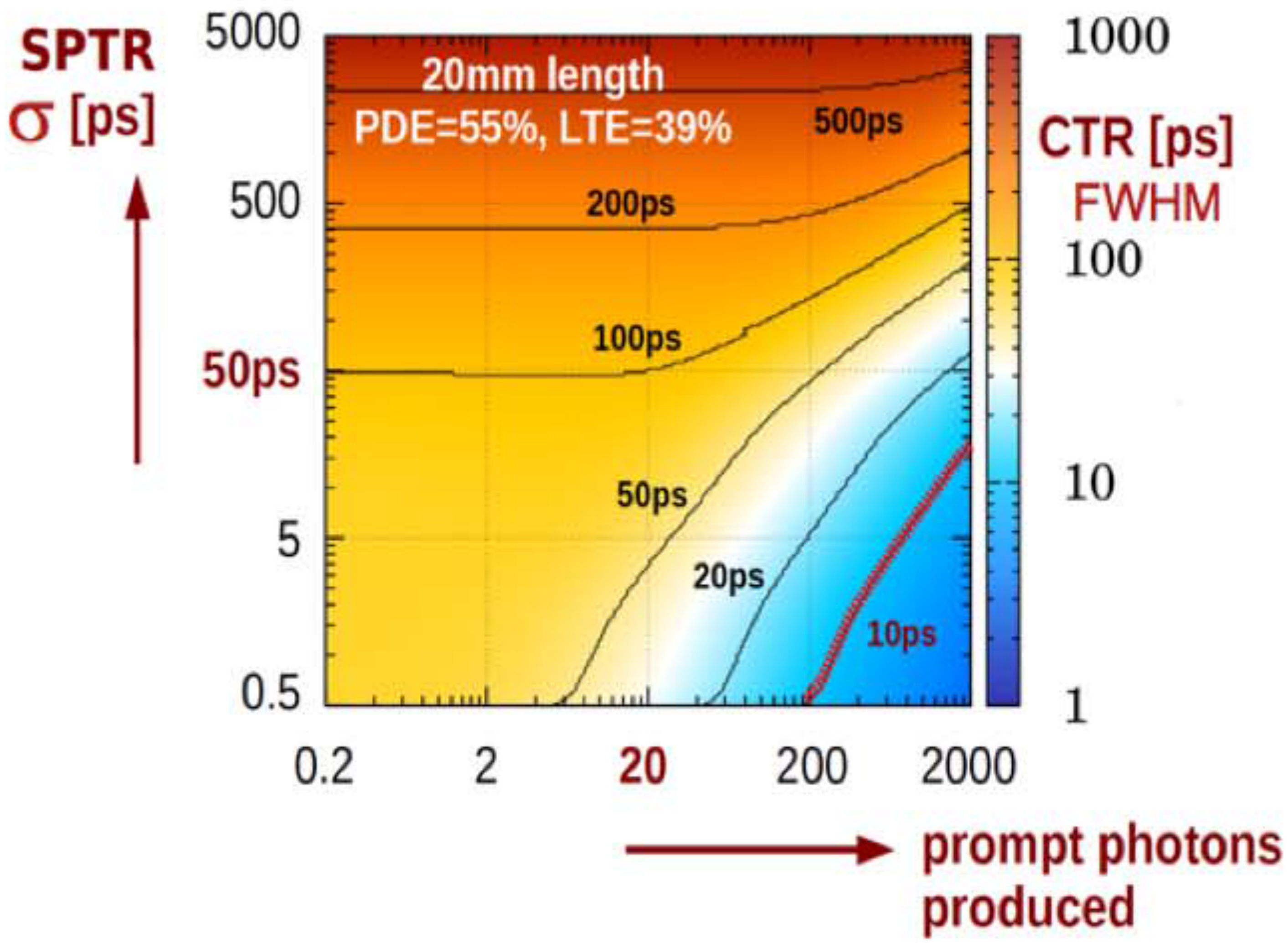
Prompt photons to boost the timing resolution

$$CRT \propto \sqrt{\frac{\tau_r \tau_d}{N_{pe}}} \xrightarrow[\tau_r \div 10]{} \sqrt{\tau_r}$$

Length 3mm | **Length 20mm**

Parameters for LSO: Ce, Ca and Hamamatsu S10931-050P MPPC





Cramér–Rao lower bound calculations for 2 x 2 x 3 mm^3 and 2 x 2 x 20 mm^3 LSO:Ce,Ca scintillator with a SiPM having a PDE of 55%, as a function of the number of additional prompt photons generated

Courtesy:S. Gundacker, CERN

Possible sources of prompt photons (< 1 ns)

Excitons/bi-exciton stable at 300 K (e.g. CdSe CQwells)

Ce^{3+} Activator: 5d-4f
Ca^{2+} & Mg^{2+} co-doping
$\tau_r \sim 20$ ps $\tau_d < 16$ ns

$$\frac{1}{\tau} = \frac{4e^2}{3\hbar c^3}\omega_{21}^3 \left|\vec{r}_{21}\right|^2$$

Hot intraband luminescence
0.1 - 10 ps
(e.g. $PbWO_4$, $CaWO_4$)

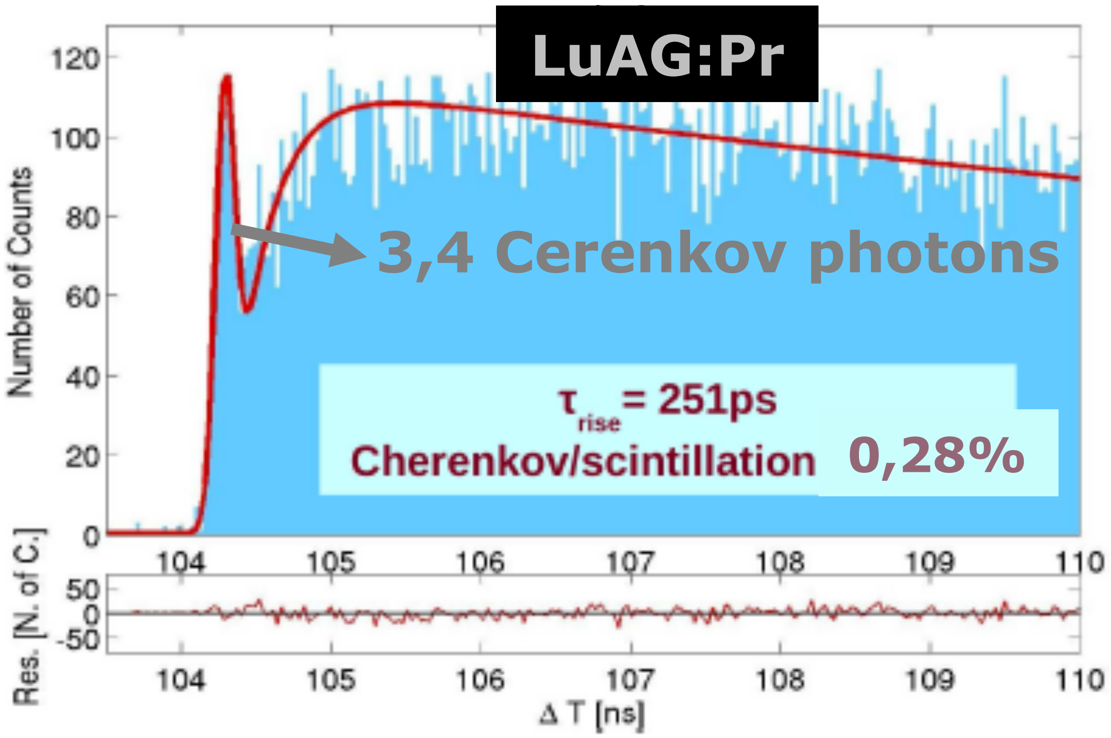
Cross luminescence
<1 ns (e.g. BaF_2)
< 300 nm
low light yield

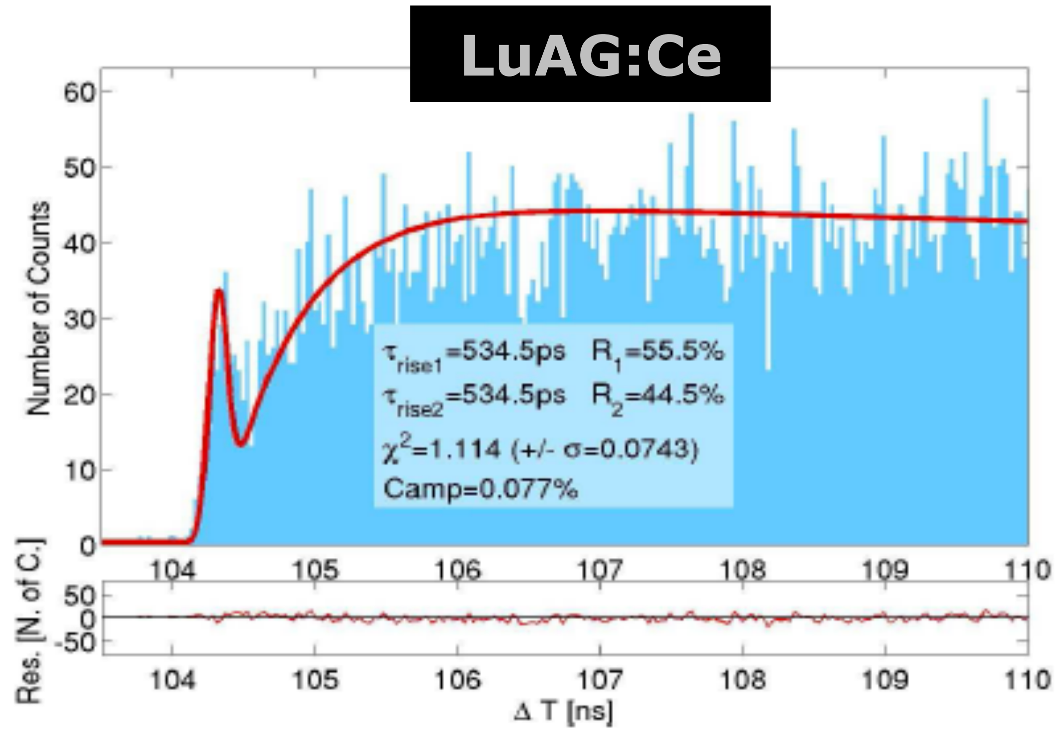
High donor band semiconductors
< 1 ns (e.g. ZnO)
quenched at room temperature

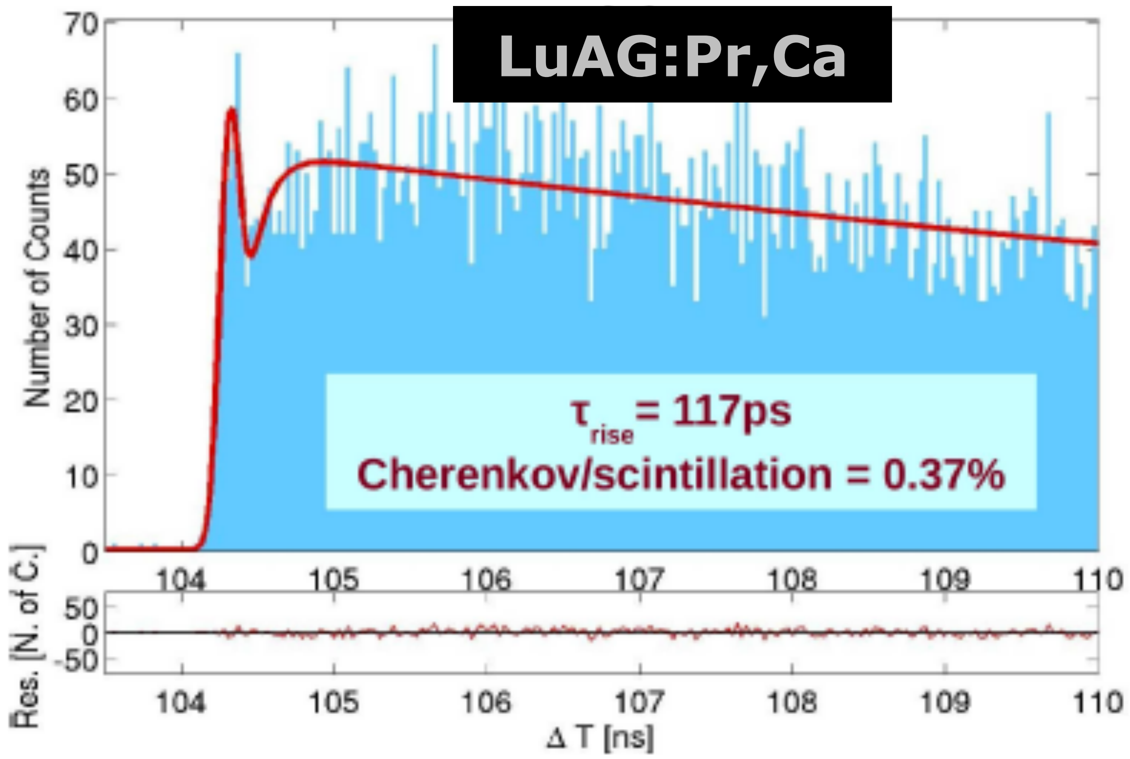
Cherenkov emission
τ ~ 5-10 ps

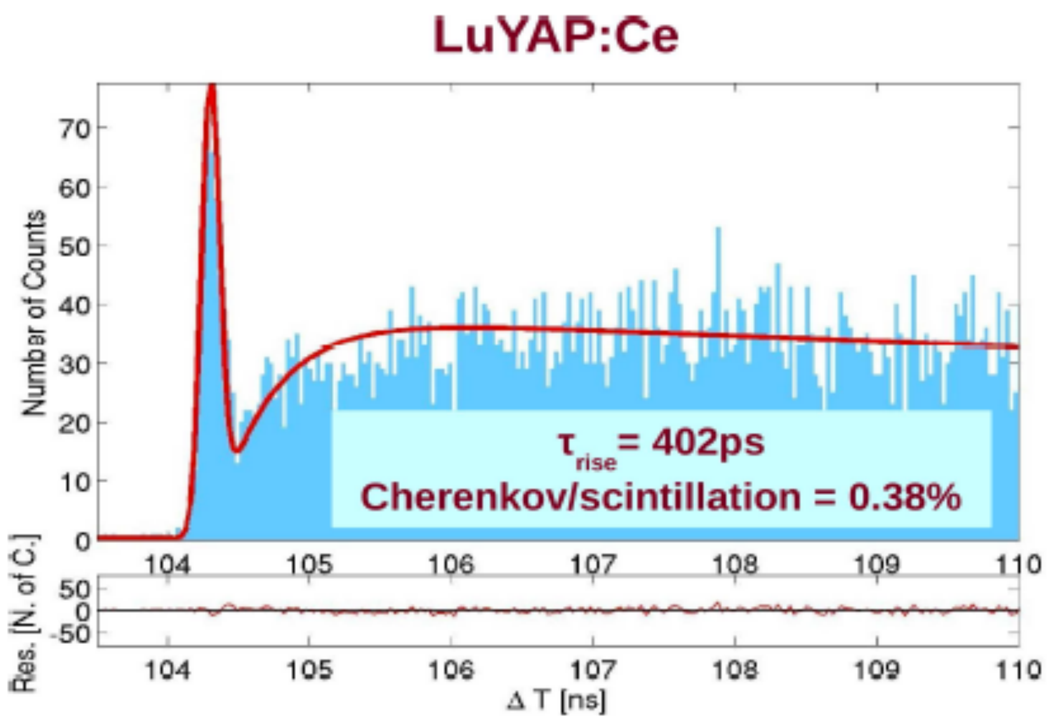
Courtesy: P. Lecoq, CERN

Cherenkov contribution







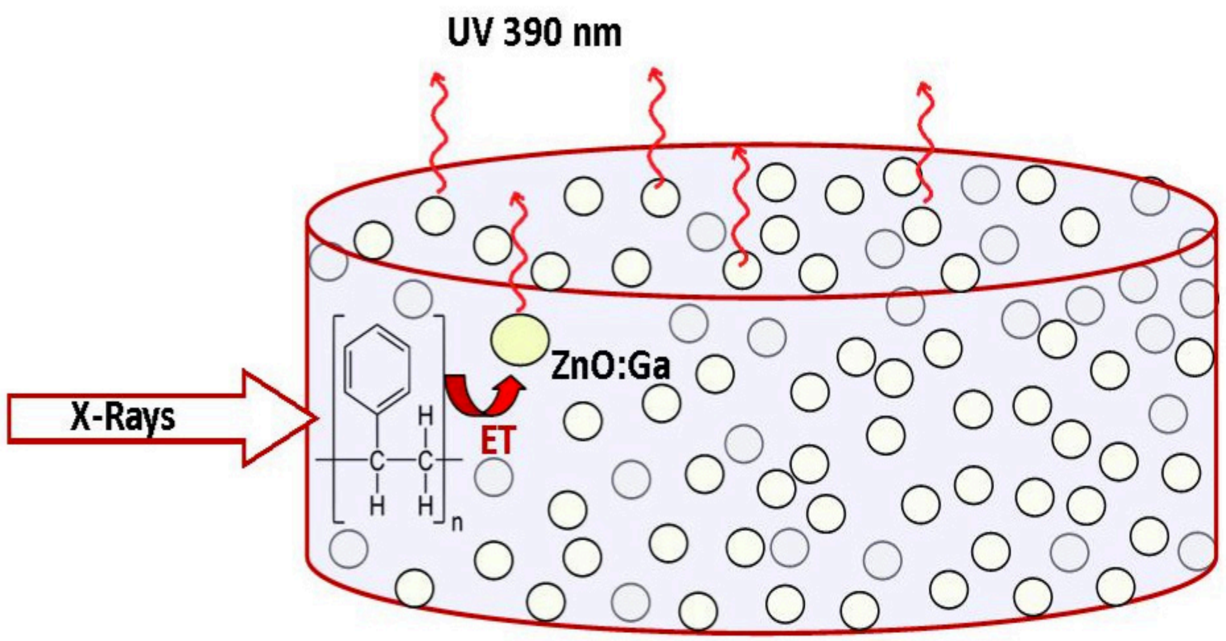


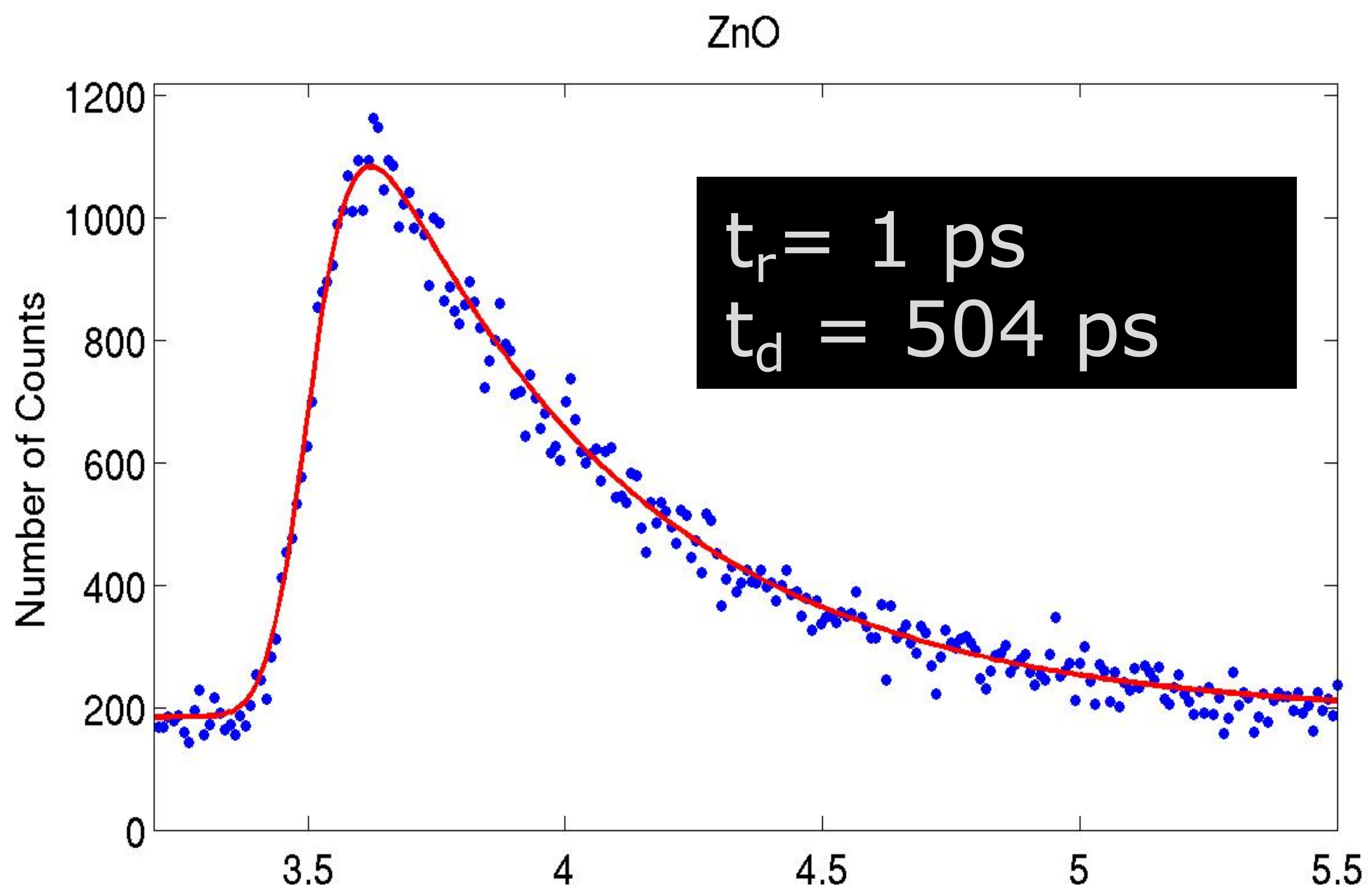
Courtesy: P. Lecoq, CERN

ZnO:Ga polystyrene composite scintillator

Highly luminescent ZnO:Ga nanocrystals 80-100 nm

- Prepared by a photochemical method
- 4000 pe/511 keV in powder (same as LSO)
- Embedded in a polystyrene sheet 10% weigth





Courtesy: R. Martinez Turtos, CERN

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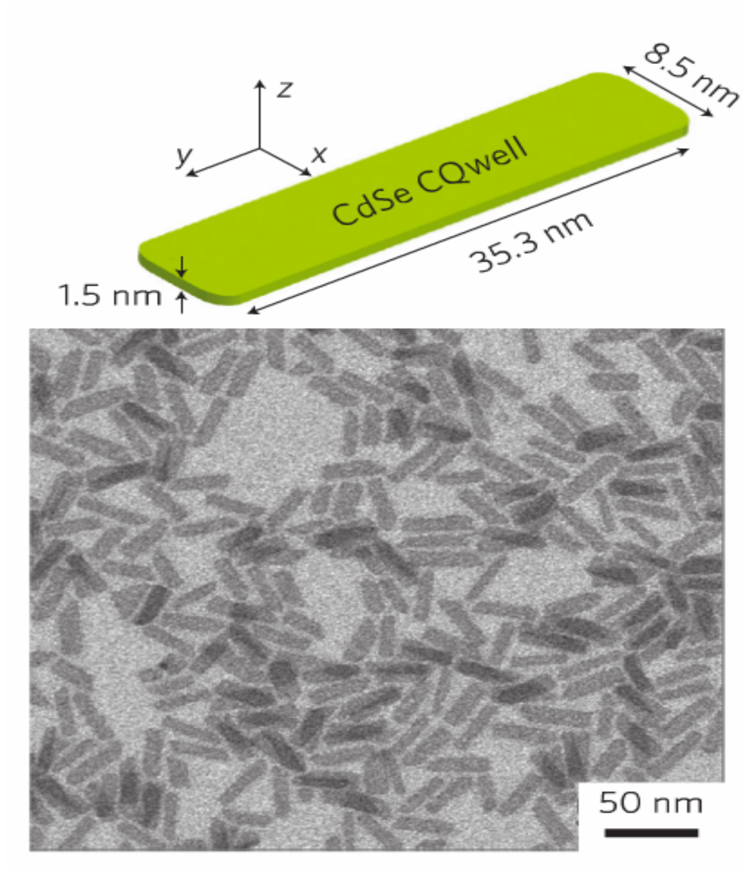
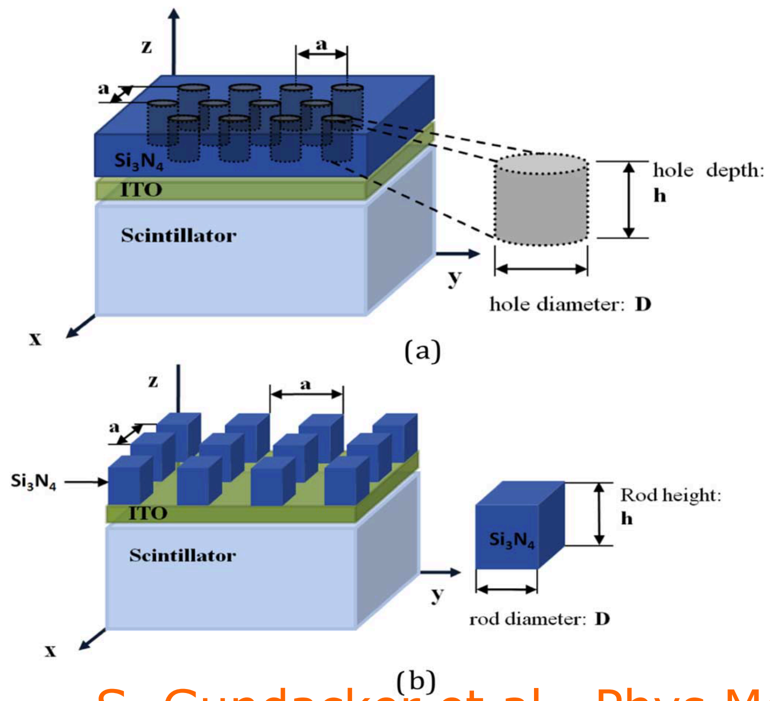
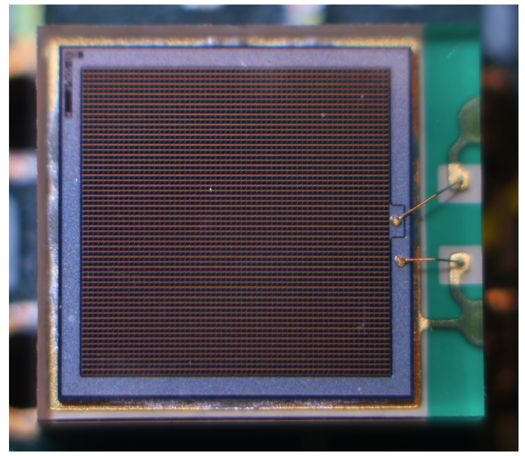
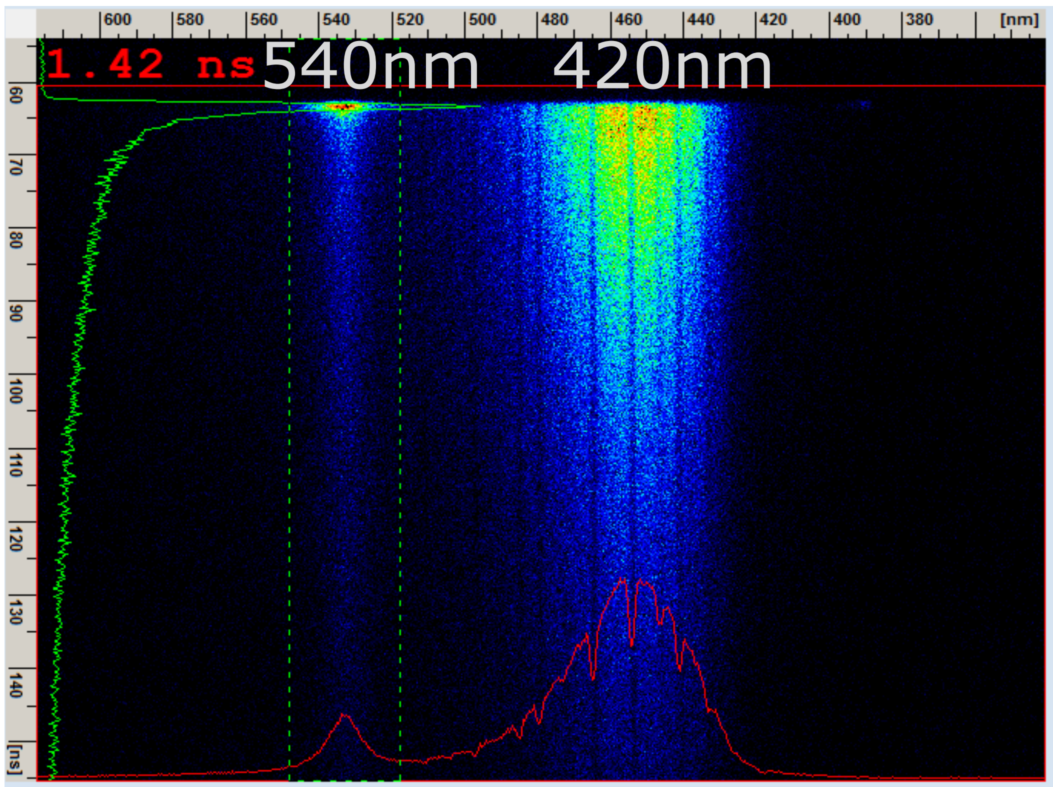
Improving Coincidence Time Resolution (CTR)



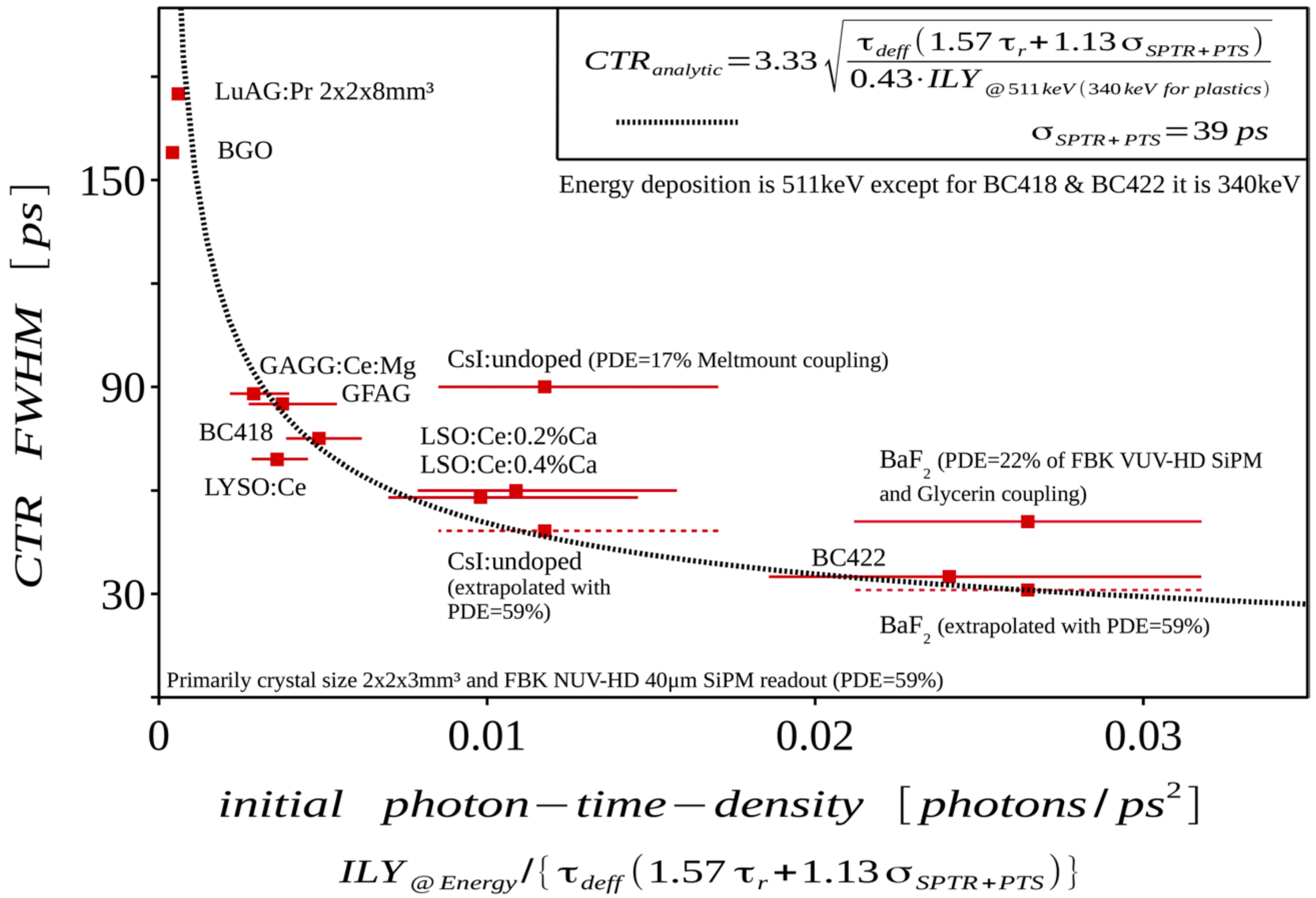
P Lecoq et al. Nucl. Instrum. Meth. A 718 (2013) 569





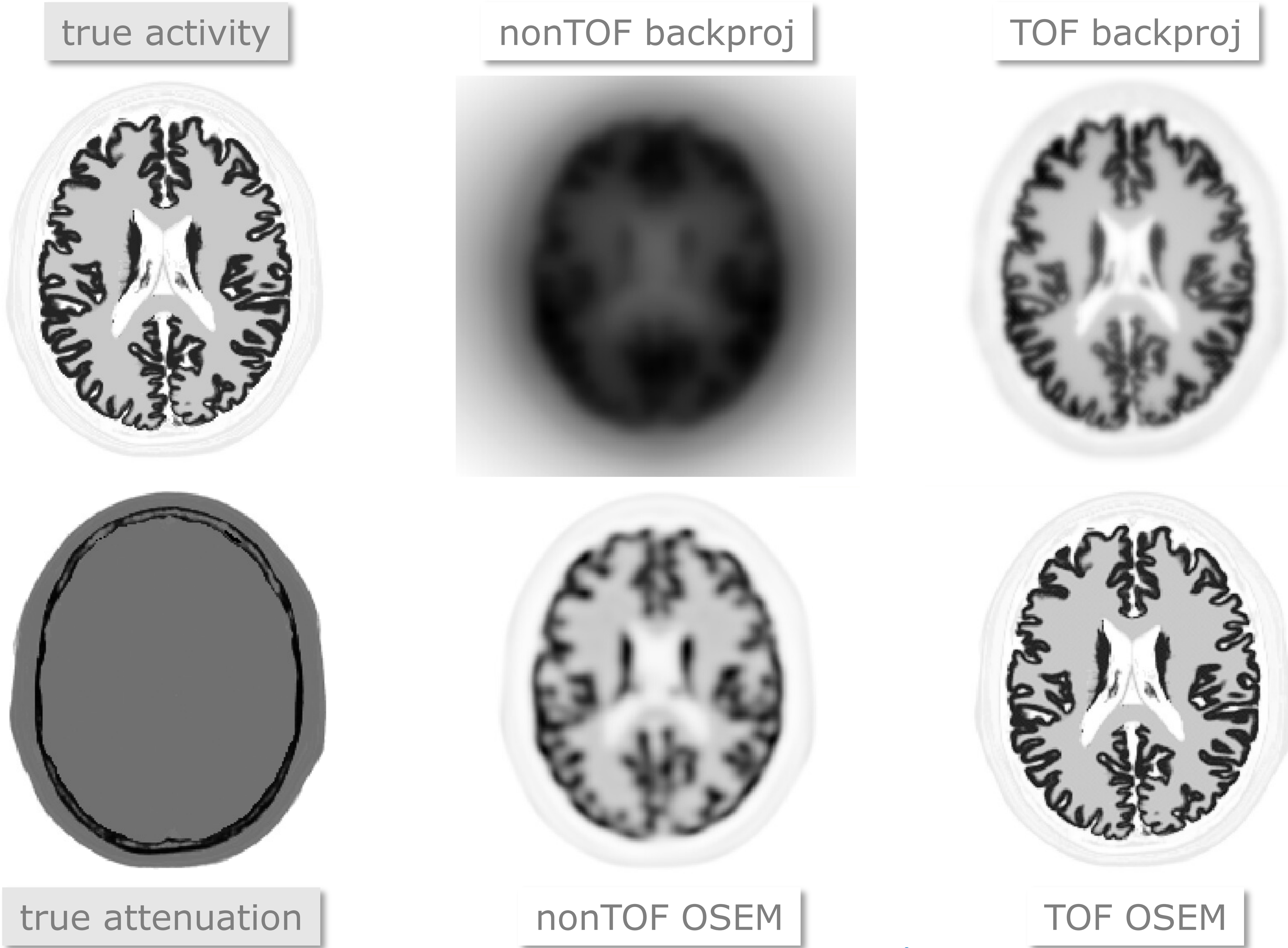


S. Gundacker et al., Phys Med Biol 65 (2020) 025001



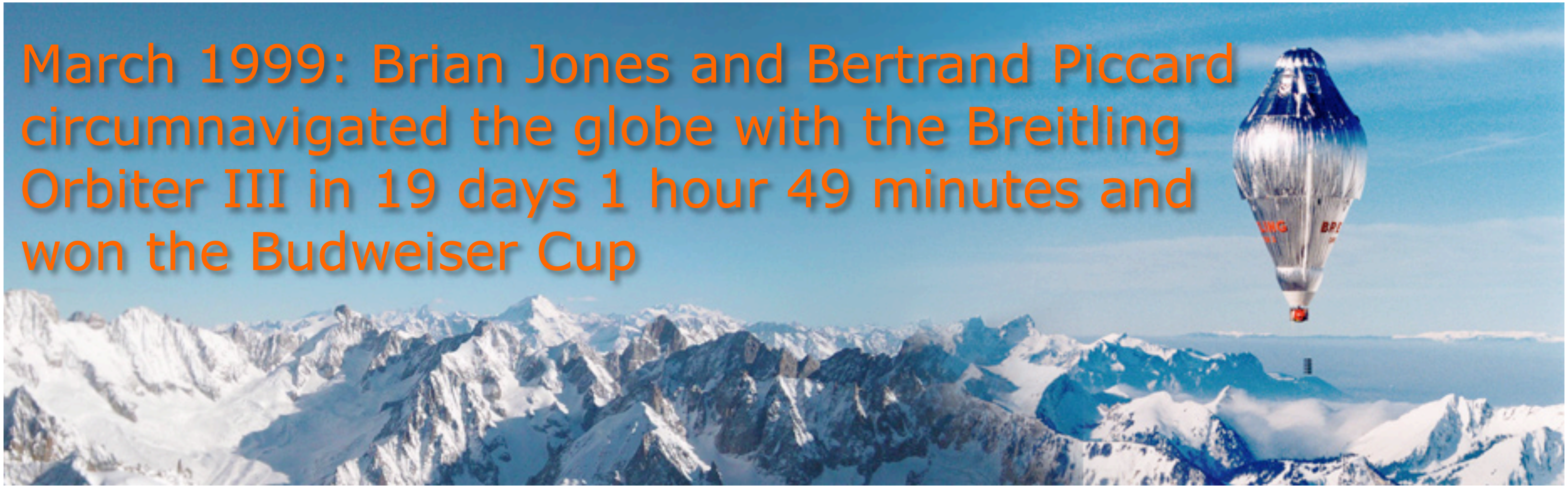
Courtesy: R. Martinez Turtos, CERN

Resolution in TOF-direction: ~1.5 mm ↔ CTR: ~10 ps FWHM
Resolution in detector direction: 5 mm



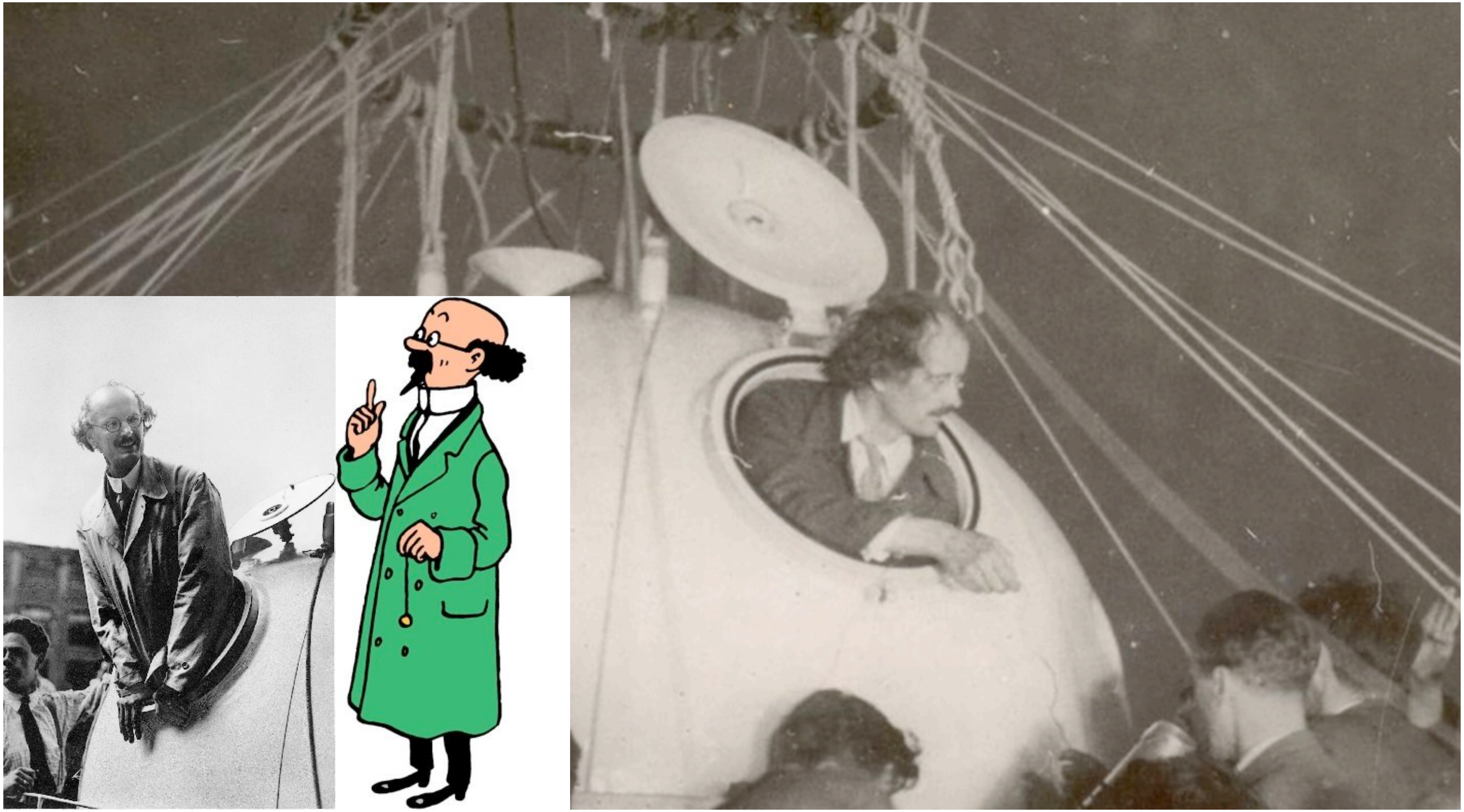
Courtesy: J. Nuyts, Univ Leuven

1992: FAI raised a challenge for the first balloon circumnavigation



This was a clear-cut case to shed light on TOF-PET with CTR < 10 ps FWHM and raise a challenge on reconstruction-less positron tomography

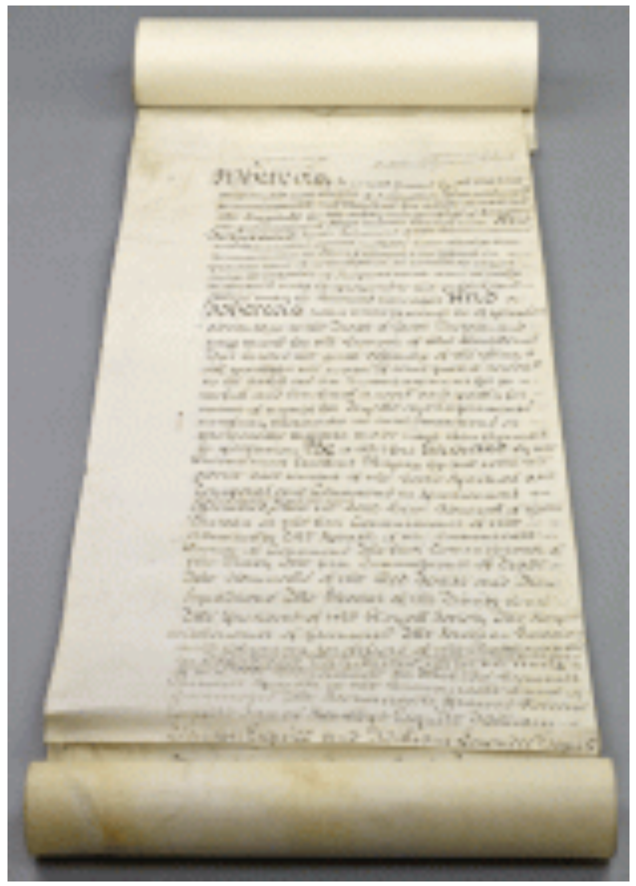
1931: Auguste Piccard performed the first stratospheric balloon flights above 16000 m

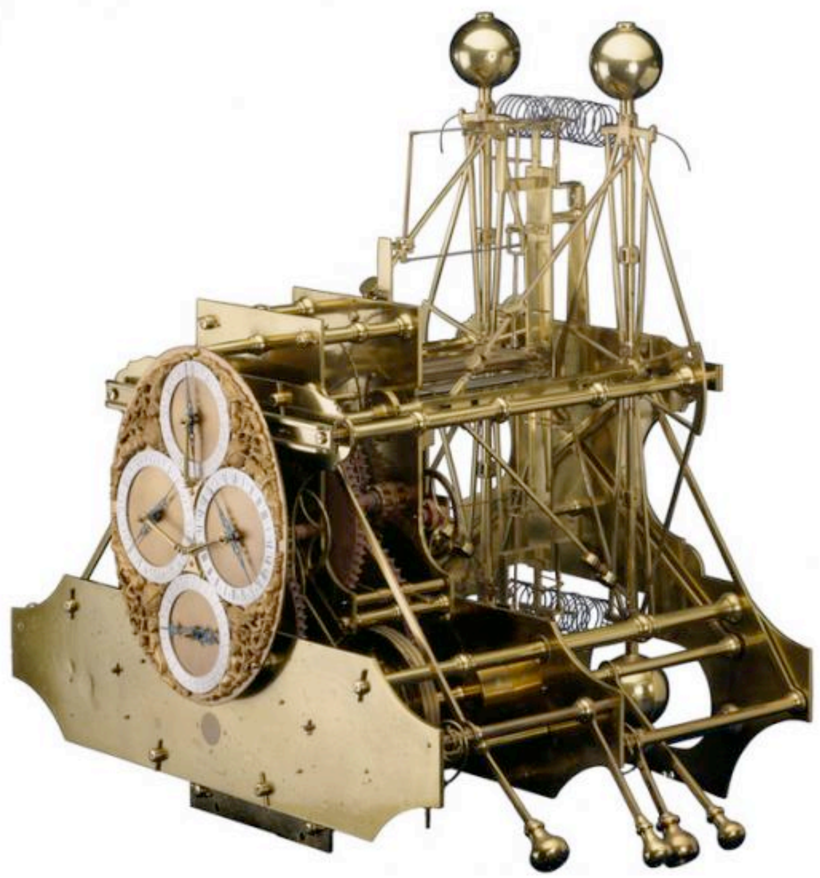


The challenge as a spur on technological R&D

The Longitude Act was enacted by the parliament of the United Kingdom in July 1714 after the shipwreck of the HMS Association on the reefs of Gilstone Ledges during the night of Oct 22 1707, leading to the death of 1400 to 2000 mans.

The Longitude Act established the Longitude **Office in Greenwich** and offered a reward to anybody who would find a simple and practical way to determine precisely the longitude of a ship.





John Harrison's H1 Marine Chronometer

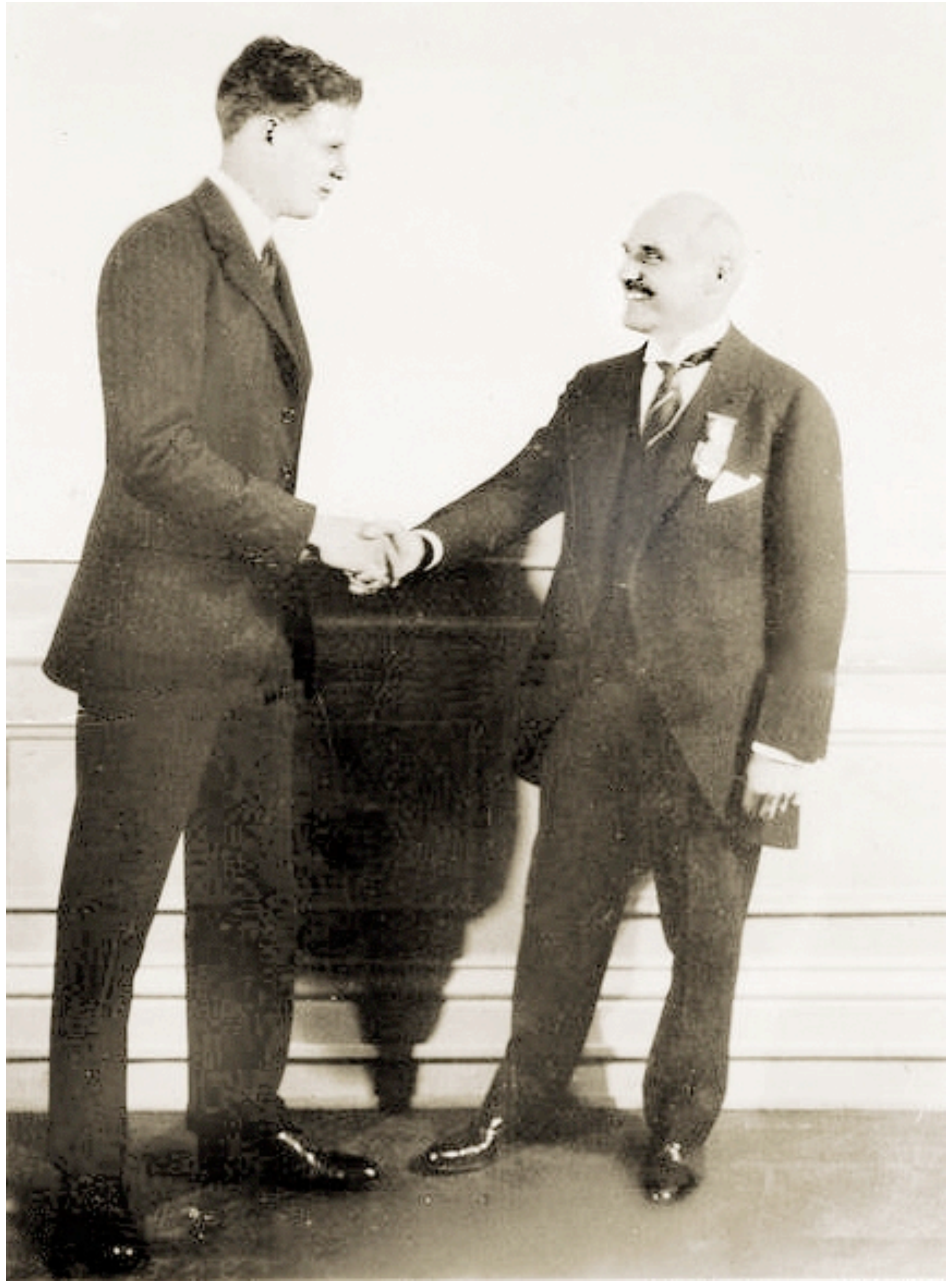
Longitude rewards:

- ✓ **£ 10,000 < 1°**
  (= 110 km on the equator)
- ✓ **£ 15,000 < 40'**
- ✓ **£ 20,000 < 0,5°**

John Harrison received £ 10,000 in 1765 (~1.33 million £ in 2020) for the development of the Marine Chronometer

1919: Raymond Orteig offered a prize of 25,000 US$ to the first aviator who would flight from New York to Paris without stops

The Orteig Prize offer was initially available for 5 years, and then was renewed for another 5 years in 1924



May 1927 : Charles Lindbergh made the first flight from New York to Paris on board of the Spirit of Saint-Louis in 33 h and 30 minutes

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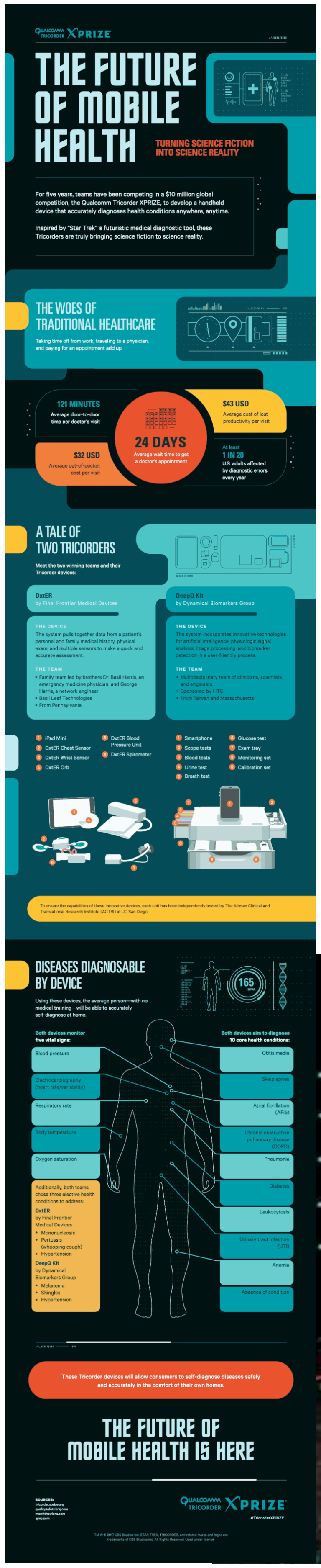

Foundation based in California distributing prices of several millions of dollars for challenges launched in the domains of energy & environment, life sciences, exploration and development

Its slogan is *making the impossible possible*

Elon Musk, James Cameron, Larry Page, Arianna Huffington, Ratan Tata are members of its administration council

2012 : Qualcomm Tricorder XPrize 10 M$

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The 10 ps challenge: a step toward reconstruction-less TOF-PET

The 10 ps challenge:
- a spur on the development of fast timing
- an opportunity to get together
- an incentive to raise funding
- a way to shed light on nuclear instrumentation for medical imaging and beyond

One unique challenge launched for 5 to 10 years and operated by an international organisation with rules issued by the community based on the measurement of CTR combined to sensitivity

Several milestones and prizes:
- 3 years after the launch of the challenge: 1M€ expected for the Flash Gordon Prizes delivered to the 3 best certified achievements
- until the end of the challenge: 1M€ expected for the Leonard McCoy Prize for the first team meeting successfully the specifications of the challenge

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Physics in Medicine & Biology

IPEM Institute of Physics and Engineering in Medicine

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Topical Review

Roadmap toward the 10 ps time-of-flight PET challenge

Paul Lecoq[1], Christian Morel[2], John O Prior[3], Dimitris Visvikis[4], Stefan Gundacker[1,5], Etiennette Auffray[1], Peter Križan[6], Rosana Martinez Turtos[1,21], Dominique Thers[7], Edoardo Charbon[8], Joao Varela[9], Christophe de La Taille[10], Angelo Rivetti[11], Dominique Breton[12], Jean-François Pratte[13], Johan Nuyts[14], Suleman Surti[15], Stefaan Vandenberghe[16], Paul Marsden[17], Katia Parodi[18], Jose Maria Benlloch[19] and Mathieu Benoit[20]

10 ps TOF-PET properties:

- ❑ Better image characteristics
- ❑ Faster image reconstruction
- ❑ Higher effective sensitivity

Advantages:

- ➢ Better lesion detectability
- ➢ Low and ultra-low dose imaging
- ➢ Scan time reduction
- ➢ Longer post-injection observation

Applications:

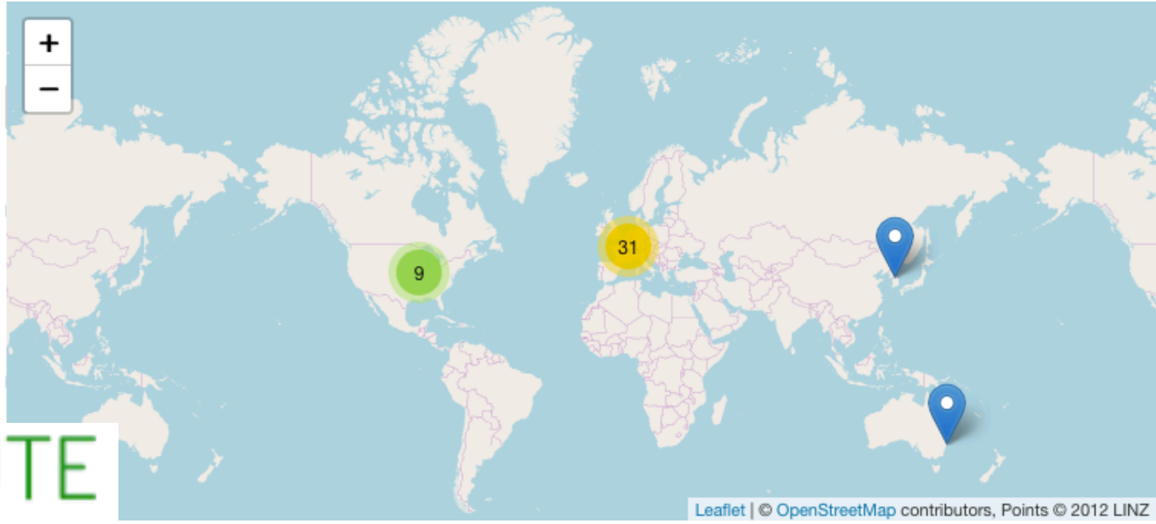
- ✓ Immuno-PET imaging (antibodies imaging)
- ✓ Cell-based therapy imaging
- ✓ Lung cancer screening
- ✓ Infectious disease imaging
- ✓ Foetal imaging research
- ✓ Psychiatric disease imaging and screening

Other fast timing applications (outside of TOF-PET):

- ❖ Compton imaging
- ❖ Protontherapy range monitoring
- ❖ Positron annihilation lifetime spectroscopy (PALS)
- ❖ Light detection and ranging (LIDAR)

The10ps-challenge.org

Scientists



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CRYSTAL CLEAR

SNMMI Value Initiative
SOCIETY OF NUCLEAR MEDICINE & MOLECULAR IMAGING

Companies

PETsys Electronics

Crystal Photonics Inc.

ASP Online Seminars, October 29 2020

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The 10 ps challenge: a step toward reconstruction-less TOF-PET

Thank you

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