
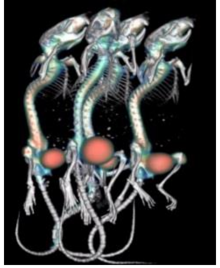
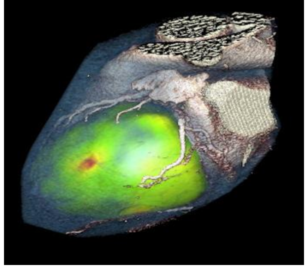
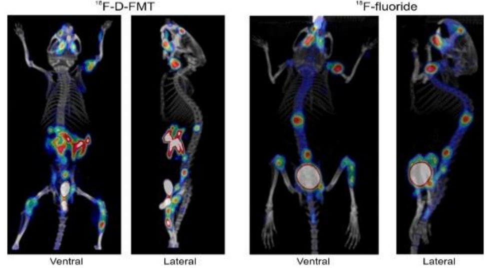

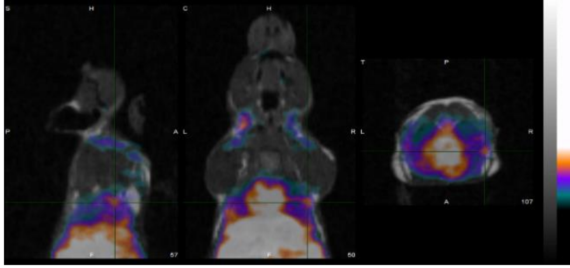

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Preclinical Imaging in Small Laboratory Animals

Instrumentation and Application

Functional Imaging Modalities

PET & SPECT

Sebastian Eigner, M.Sc.

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EVROPSKÁ UNIE
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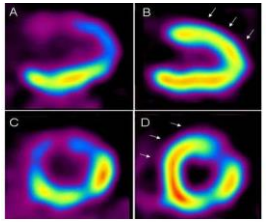
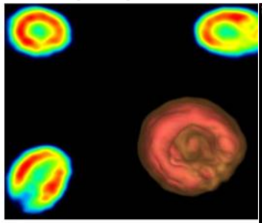
INVESTICE DO VAŠÍ BUDOUCNOSTI

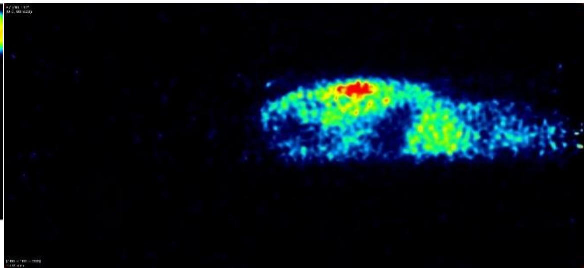
2007–13
OP Výzkum a vývoj pro inovace



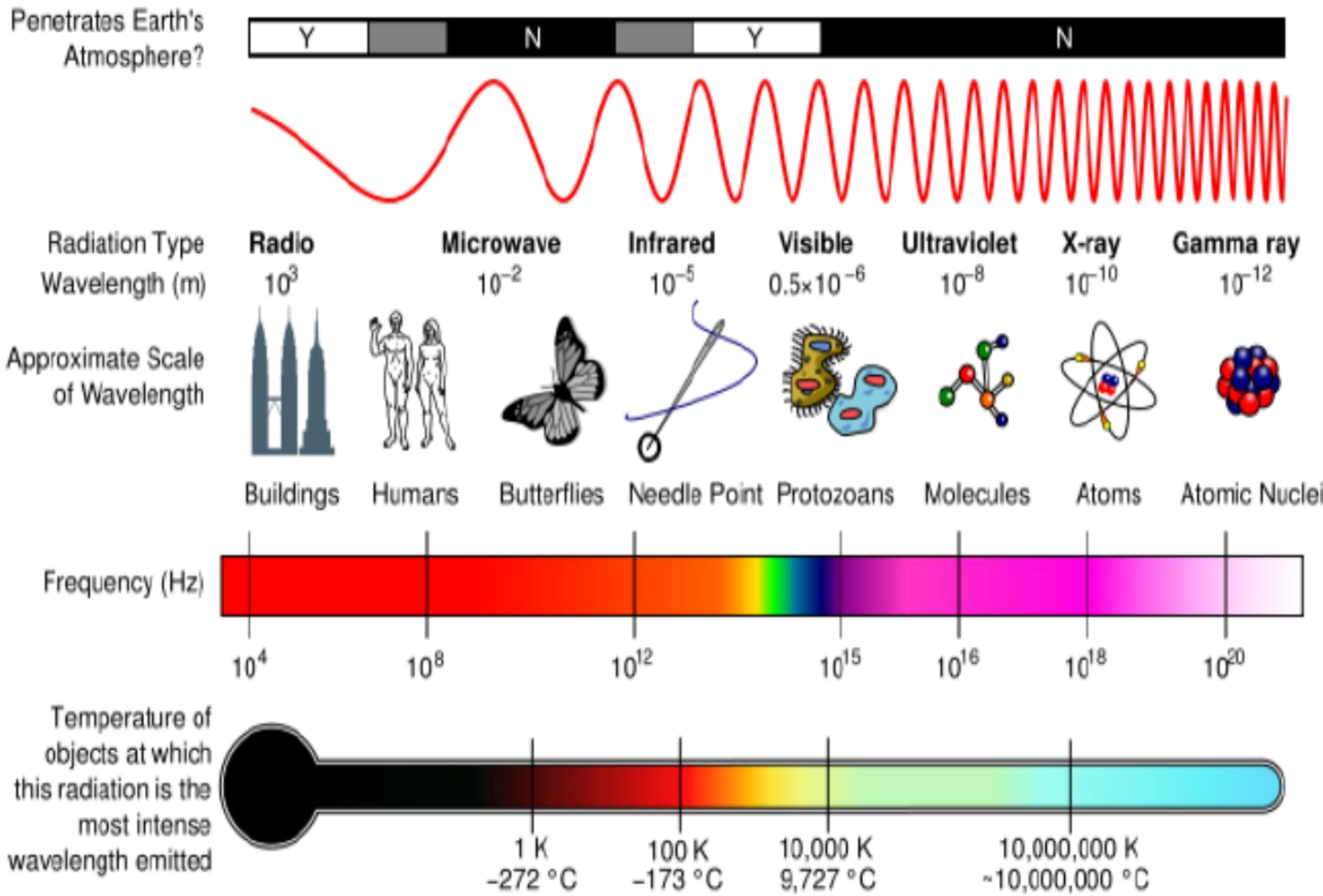
^{18}F-FDG – human heart A



^{18}F-FDG –rat heart B



Radioation



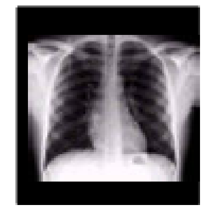
Penetrates Earth's Atmosphere?
Y
N
Y
N
Radiation Type
Wavelength (m)
Radio
10^{3}
Microwave
10^{-2}
Infrared
10^{-5}
Visible
0.5×10^{-6}
Ultraviolet
10^{-8}
X-ray
10^{-10}
Gamma ray
10^{-12}
Approximate Scale of Wavelength
Buildings
Humans
Butterflies
Needle Point
Protozoans
Molecules
Atoms
Atomic Nuclei
Frequency (Hz)
10^{4}
10^{8}
10^{12}
10^{15}
10^{16}
10^{18}
10^{20}
Temperature of objects at which this radiation is the most intense wavelength emitted
1 K
−272 °C
100 K
−173 °C
10,000 K
9,727 °C
10,000,000 K
~10,000,000 °C

Resolution and Sensitivity

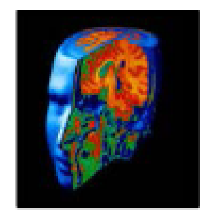
Imaging Method	Spatial resolution	Sensitivity
Ultrasound	50 µm	10^{-3} Mol
CT	50 µm	10^{-3} Mol
MRI	100 µm	10^{-5} Mol
Bioluminescent	1-3 mm (depth!)	10^{-8} Mol
Nuclear*	***> 2 mm***	***10^{-9}-10^{-12} Mol***

* ***P**ositron **E**mission **T**omography - **PET***

S**ingle **P**hoton **E**mission **C**omputed **T**omography - **SPECT



Morphology



Function

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Nuclear Imaging

PET + SPECT

Radioactive Decay

(EC,γ), (β^-,γ), (I.T.,γ)	β^+

one angular view

Projection imaging collimator needed	**Projection imaging** coincidence imaging, no colimator needed

complete set of angular views 0-180°

Single Photon Emission Computed Tomography (SPECT)	**Positron Emission Tomography (PET)**

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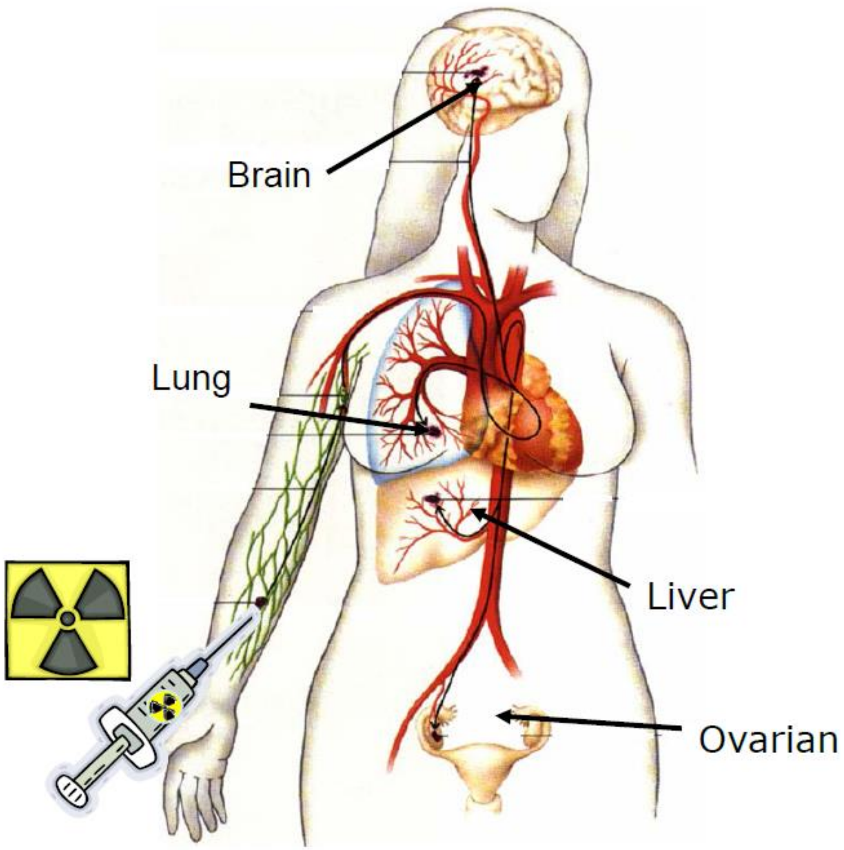
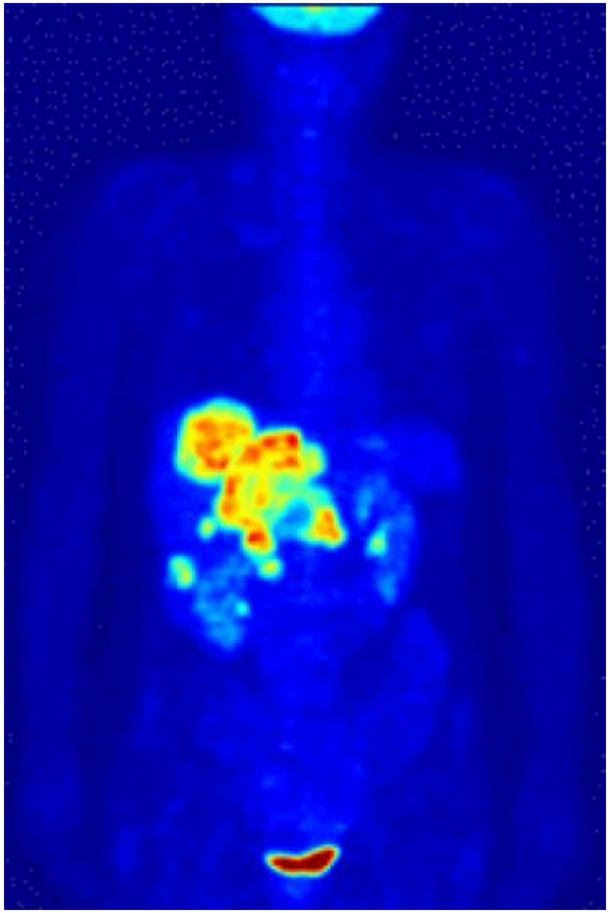
Functional Imaging

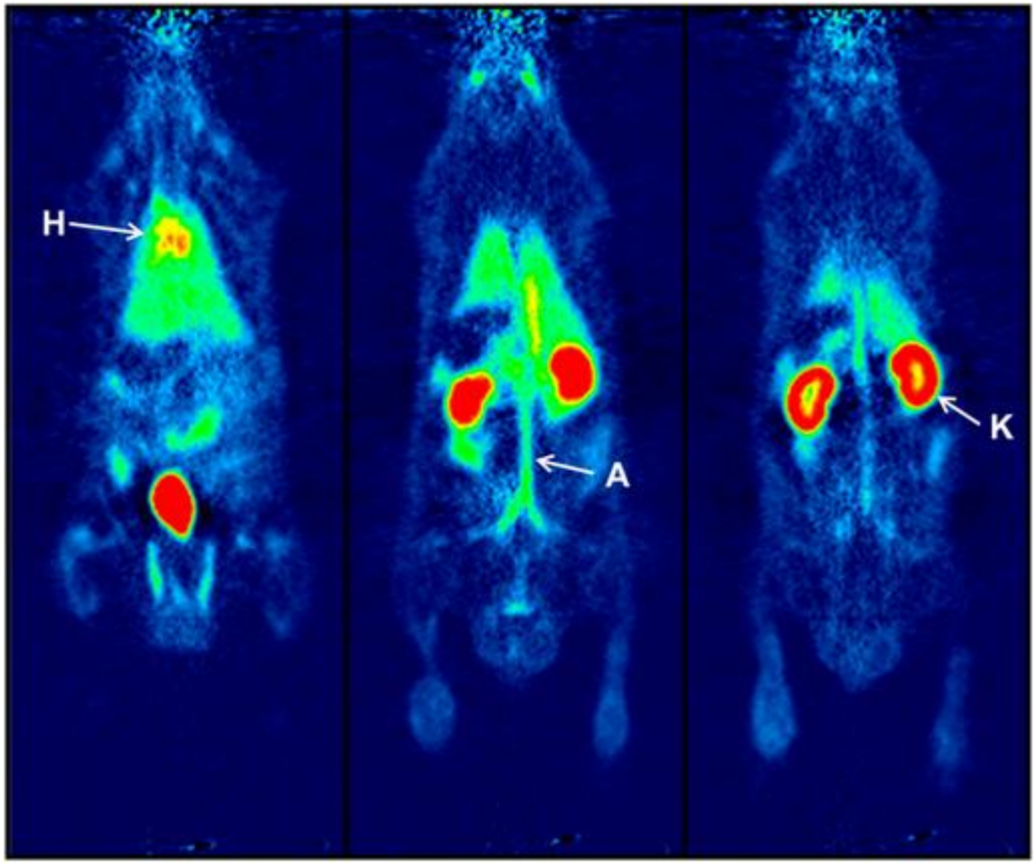
Principles in Nuclear Imaging





Positron Emission Tomography

PET



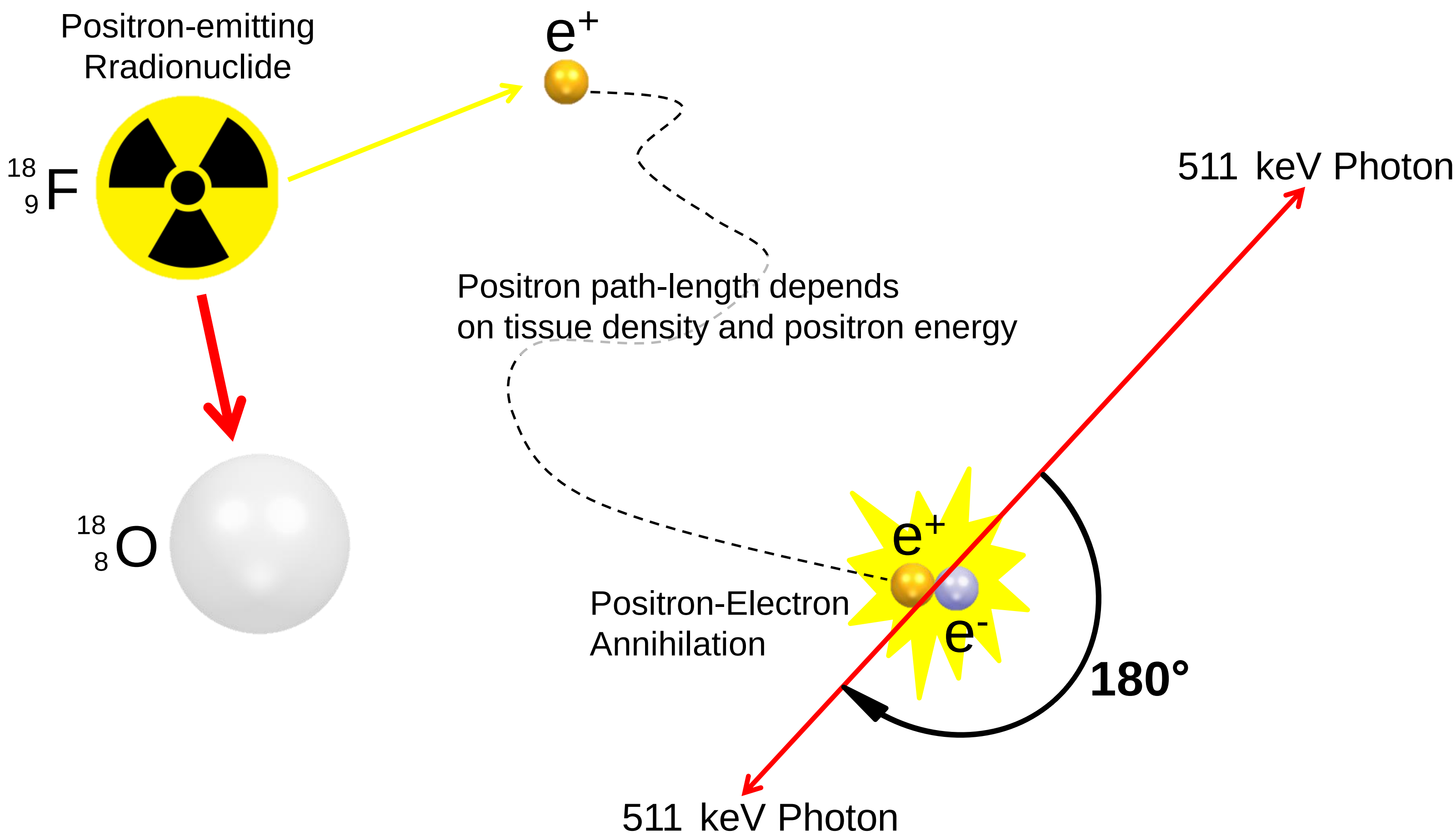
Positron Emission Tomography

in vivo PET imaging

- Tomographic imaging modality
- Functional information
- Non-invasive
- High sensitivity – pmol
- Short lived radioisotopes
- Large variety of labeled compounds
    - Energy metabolism (FDG)
    - Amino acid metabolism (^{18}F and ^{11}C labeled AA)
    - Protein biosynthesis (DOTA conjugated puromycin analogues)
    - Neurotransmitter
    - Receptor imaging (neuro, onco,…)
    - Hemodynamic parameters
    - Gene expression
    - Cell tracking (stem cells)
- 1-2 mm spacial resolution
- 6-10 % sensitivity
- temporal resolution < 0.5 sec
- QUANTIFIABLE

Positron Emission Tomography

Positron – Electron Annihilation



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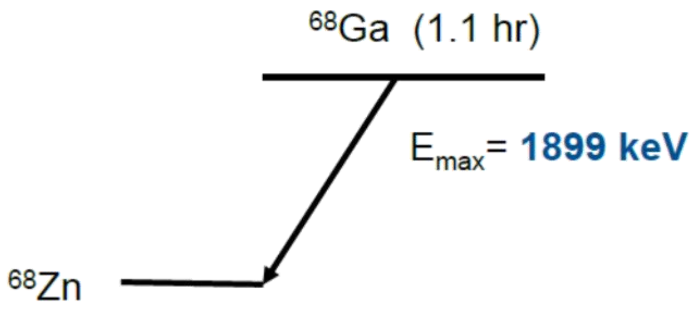
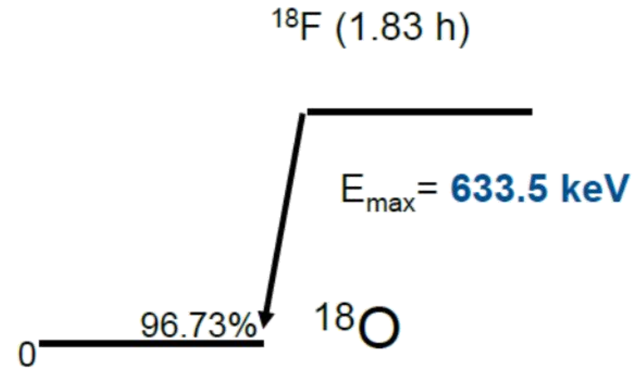
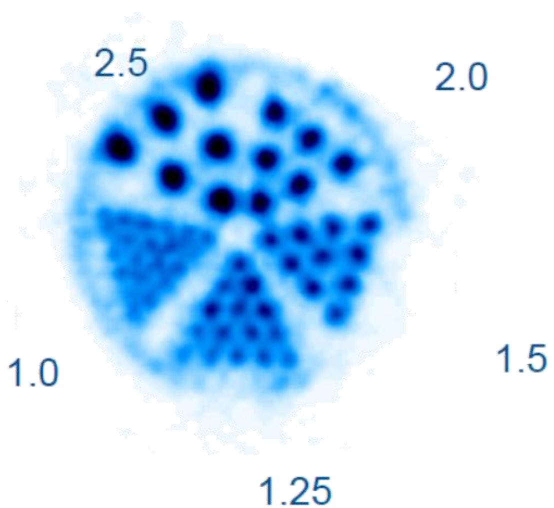
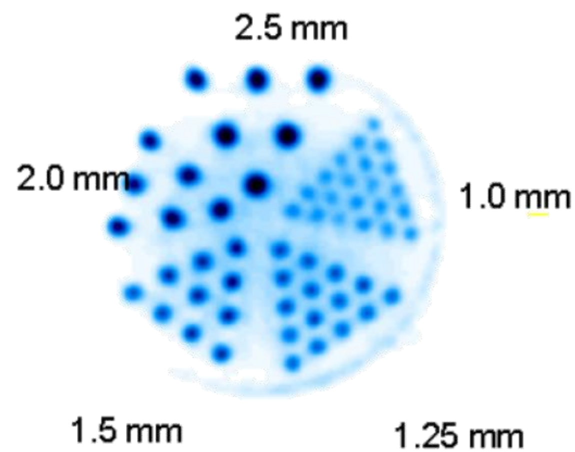
Positron Emission Tomography

Influence of Positron Energy on Resolution









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Positron Emission Tomography

Positron Emitting Radionuclides

Isotope	Halflife	β^+ fraction	Max. Energy	range(mm)	production
C–11	20.4 mins	0.99	0.96 MeV	0.4 mm	cyclotron
N–13	9.96 mins	1.00	1.20 MeV	0.7 mm	cyclotron
O–15	123 secs	1.00	1.74 MeV	1.1 mm	cyclotron
F–18	110 mins	0.97	0.63 MeV	0.3 mm	cyclotron
Cu–62	9.74 mins	0.98	2.93 MeV	2.7 mm	generator
Cu-64	12.7 hours	0.19	0.65 MeV	0.3 mm	cyclotron
Ga–68	68.3 mins	0.88	1.83 MeV	1.2 mm	generator
Br-76	16.1 hours	1.00	1.90 MeV	1.2 mm	cyclotron
Rb–82	78 secs	0.96	3.15 MeV	2.8 mm	generator
I–124	4.18 days	0.22	1.50 MeV	0.9 mm	cyclotron

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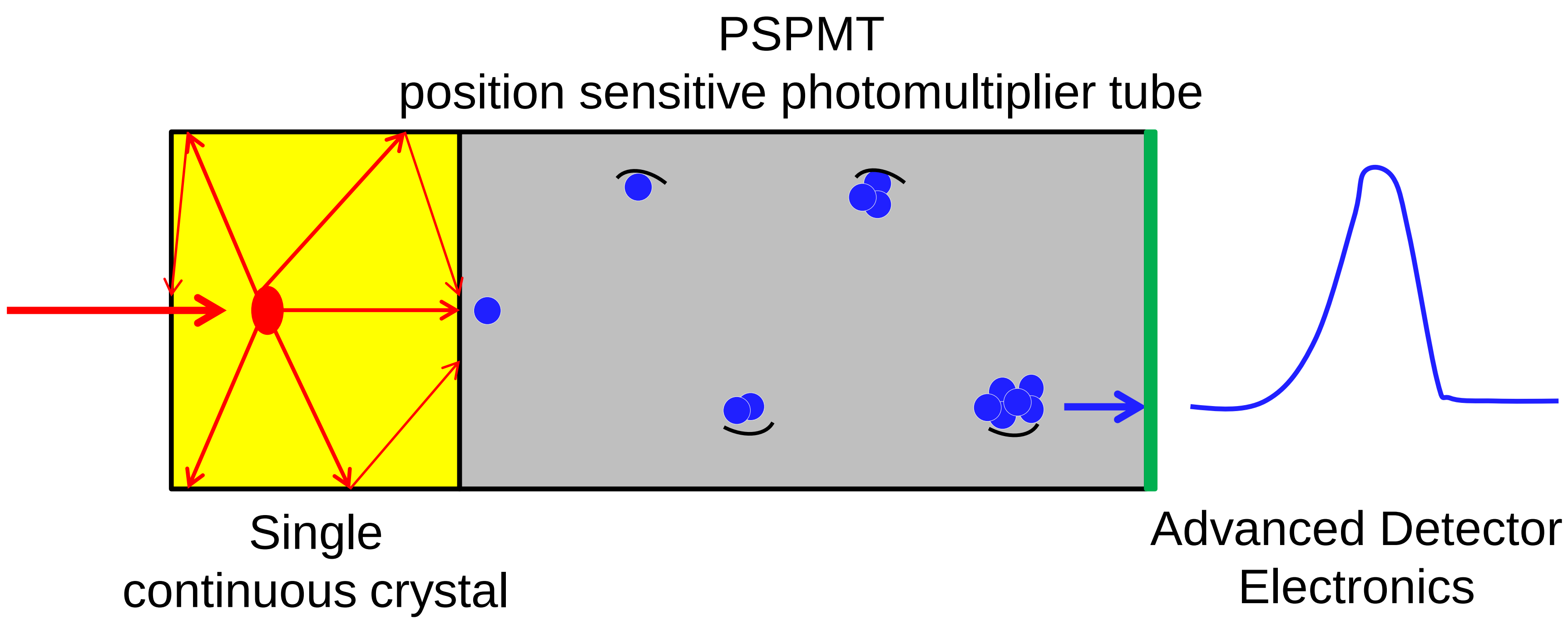
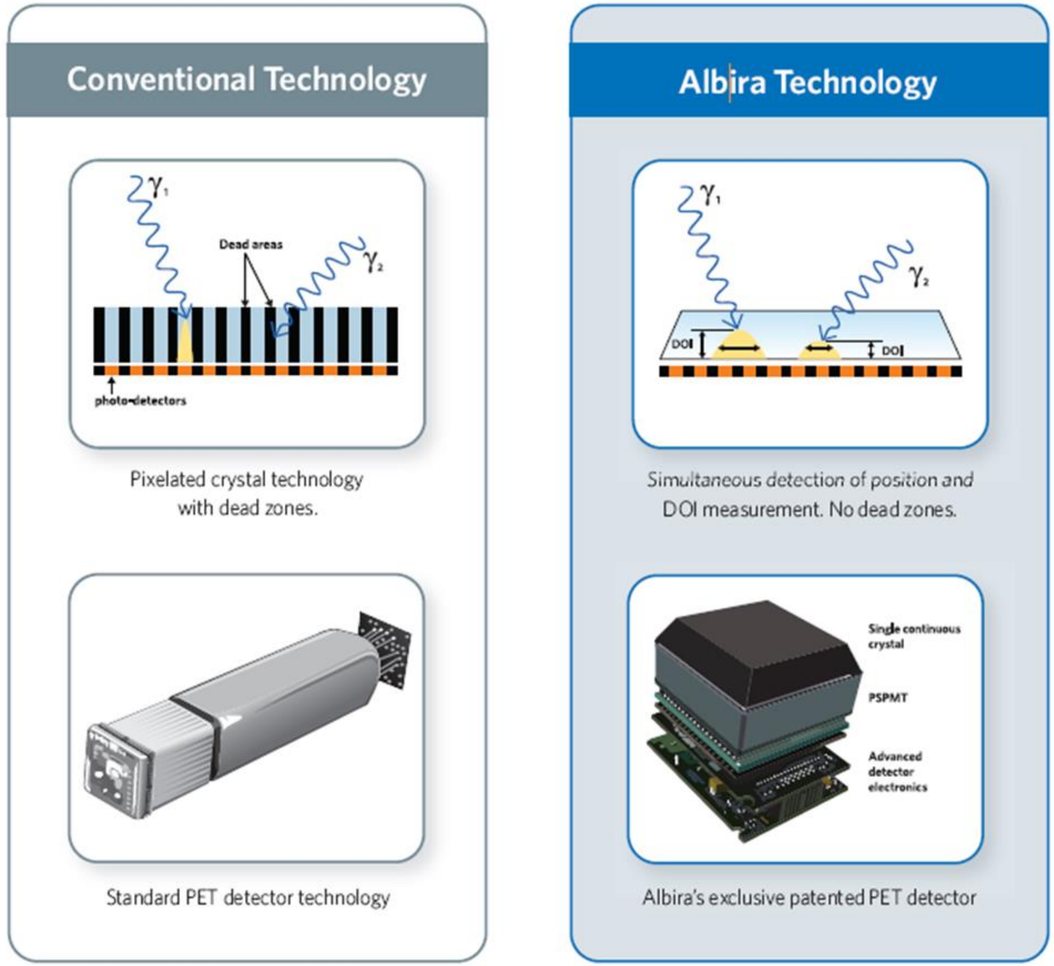
Positron Emission Tomography

ALBIRA ɣ-ray Detector Principle



Positron Emission Tomography

Positron – Electron Annihilation



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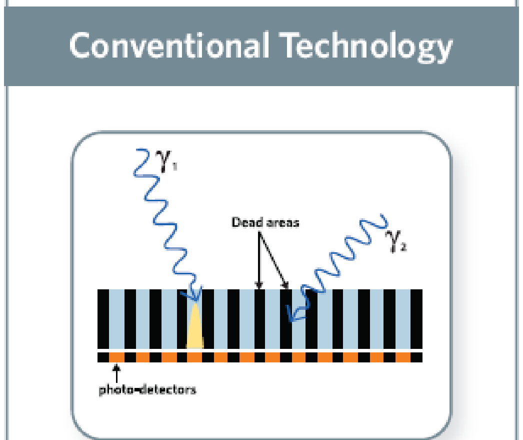
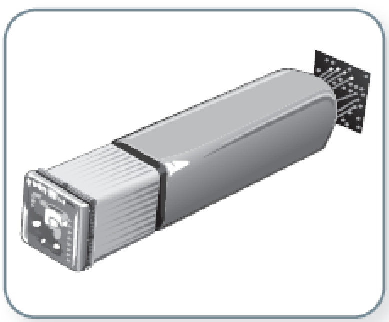
Positron Emission Tomography

Positron – Electron Annihilation



Pixelated crystal technology with dead zones.



Standard PET detector technology

Current technology utilized packed crystals with dead zones

Tighter packing yields more dead zones

Susceptible to the parallax error (ignoring depth and order of interaction)

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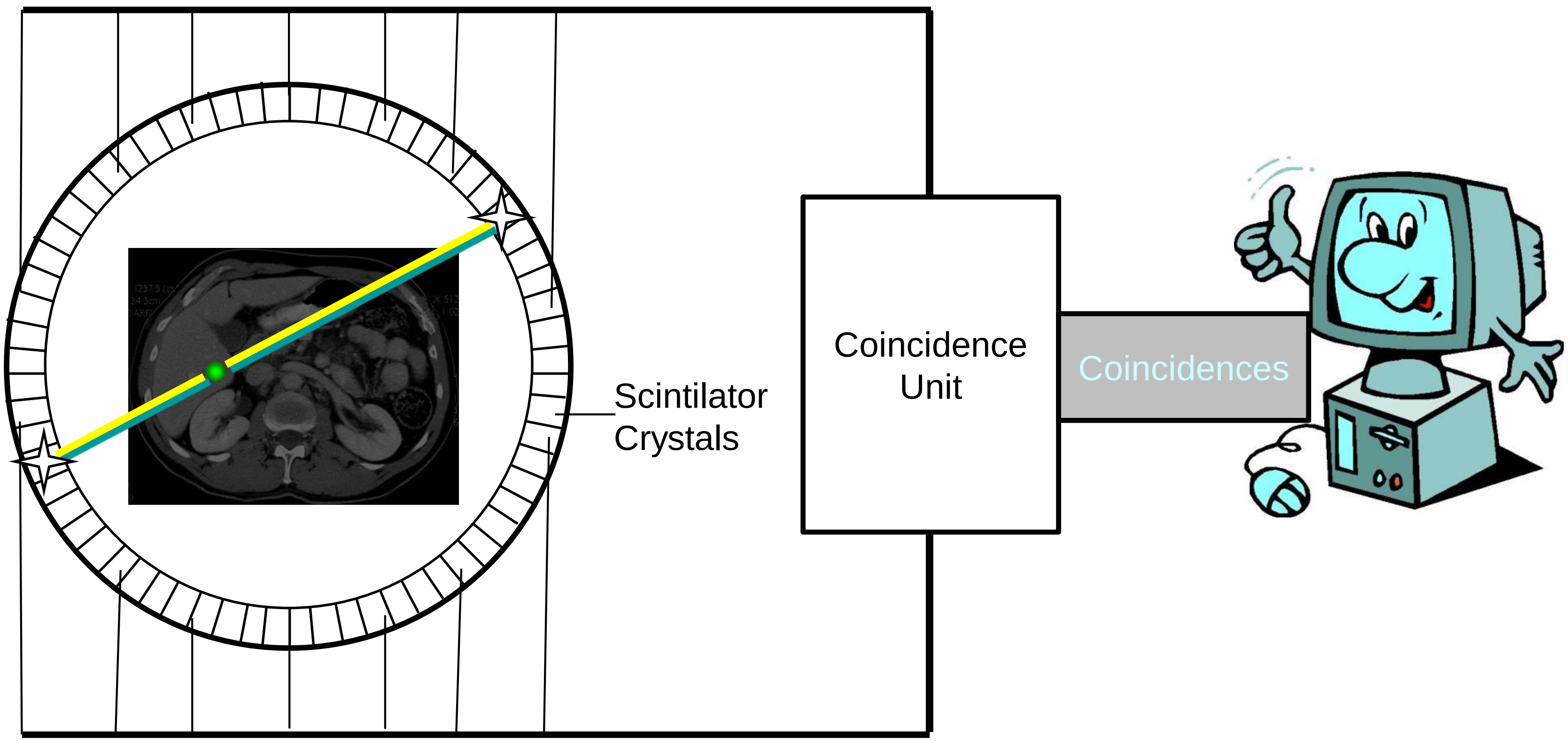
Positron Emission Tomography

Operation of a PET-Scanner



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Positron Emission Tomography

ɣ-ray Detection in a PET system

True Coincidences

both ɣ-rays escape without scatter and interact in detctors

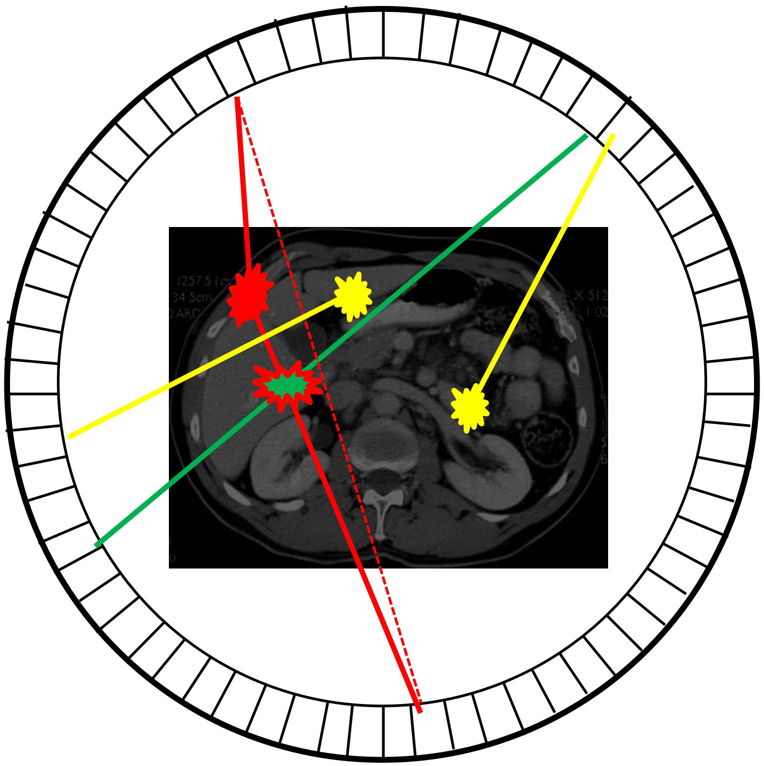
Scatter coincidences

one, or both ɣ-rays scatter in tissue

Random coincidences

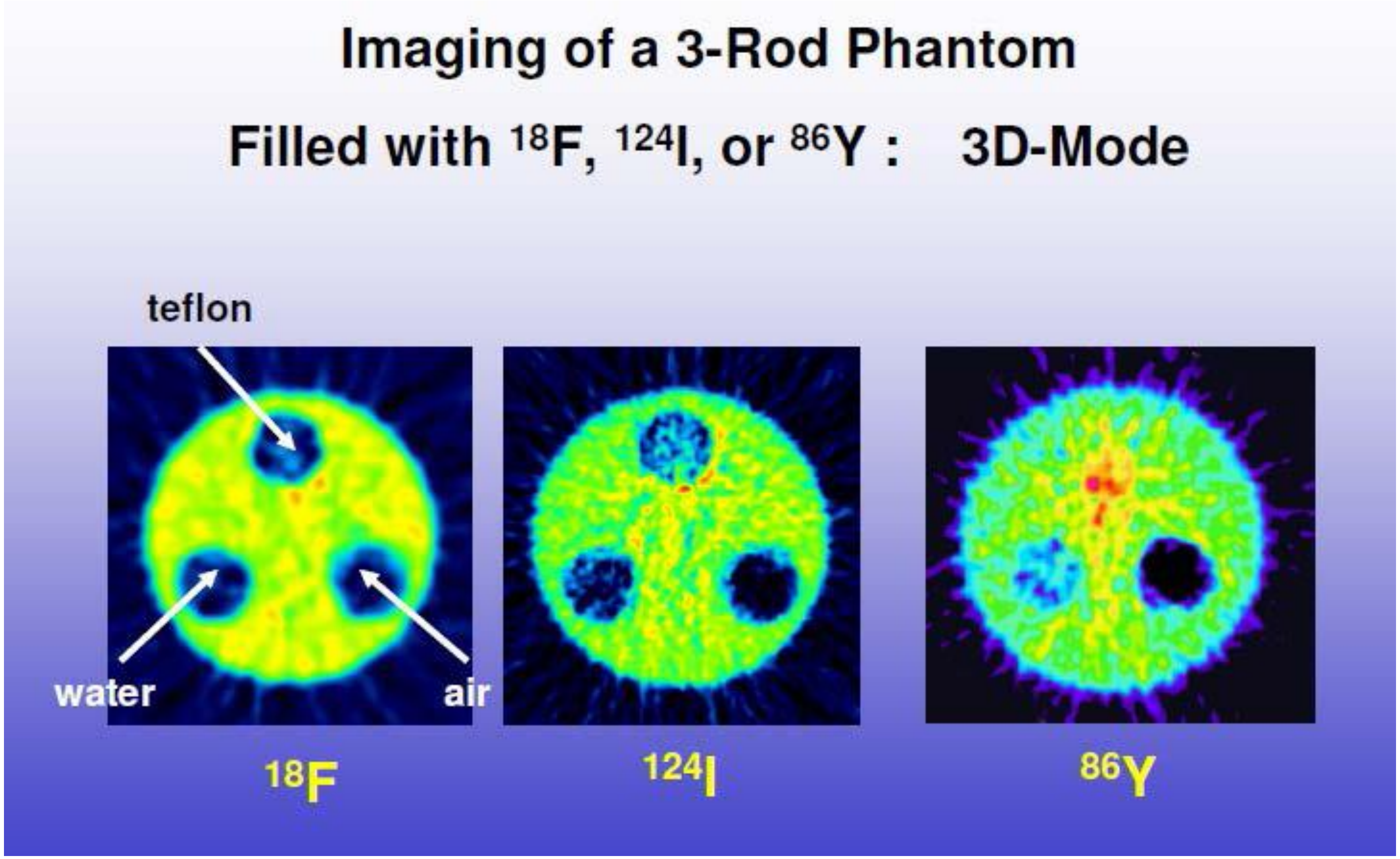
two ɣ-rays from different origins strike the detectors at the same time

(a.k.a. *accidental coincidences*)



Positron Emission Tomography

Scatter Effects



Buchholz et al., Eur J Nucl Med Mol Imaging (2003) 30:716–720

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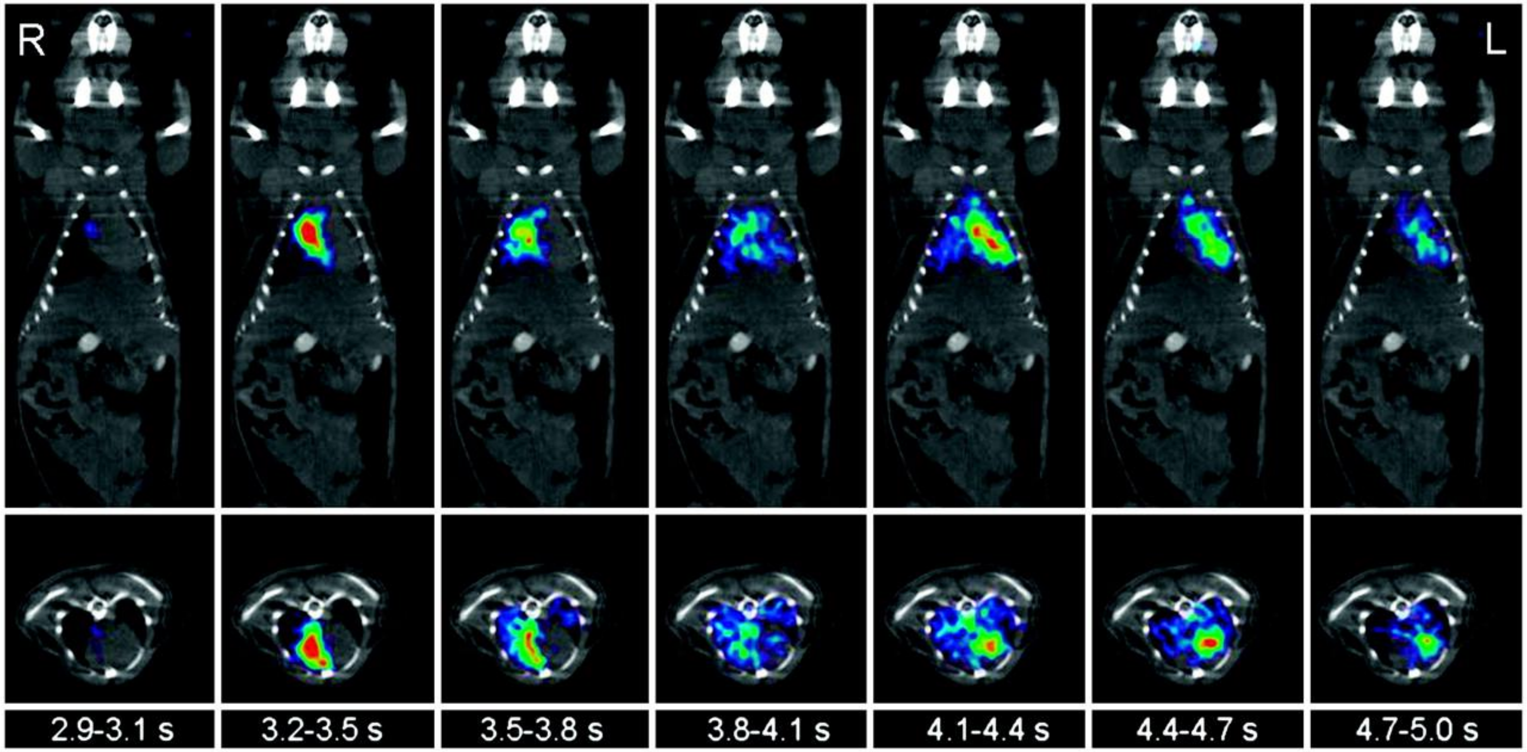
Positron Emission Tomography

Temporal resolution



Consecutive 0.3-s frames show passage of tracer bolus through RV cavity, lungs, and LV chamber of mouse on coronal and transverse slices. Times are those after start of image acquisition / injection. For better anatomic orientation, PET scan is overlaid with coregistered CT scan.

Michael C. Kreissl et al. J Nucl Med 2006;47:974-980

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Positron Emission Tomography

PET Hardware

Scintilators	Light-Detectors	Detectortype
• High stopping power • High light output • Fast scintillator • Small crystal size → High spatial resolution **LSO, LYSO, YAP, etc**.	**Photomultiplier Tubes (PMT)** • Single Channel • Multi Channel **Solid State Detectors** • Avalanche Photo Diodes (APD) • Geiger-Mode APDs Silicon-PMTs	• Single Crystal Coupling • Block Detector • Detectors with DOI capabilities (Phoswitch)

- A full PET system comprises several detector rings summing up to several 1000 to 10.000 individual crystals
- The performance of a PET system as well as physical limitations will be determined by the choice of hardware

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Positron Emission Tomography

Important Scanner Parameters

Energy Resolution

detection limit for measured energy of detected ɣ-rays

Timing Resolution

time variation (inaccuracy) of the system for detection of two single events originating from the same annihilation

Spatial Resolution

smallest object that can be visualized (partial volume effect)

Sensitivity

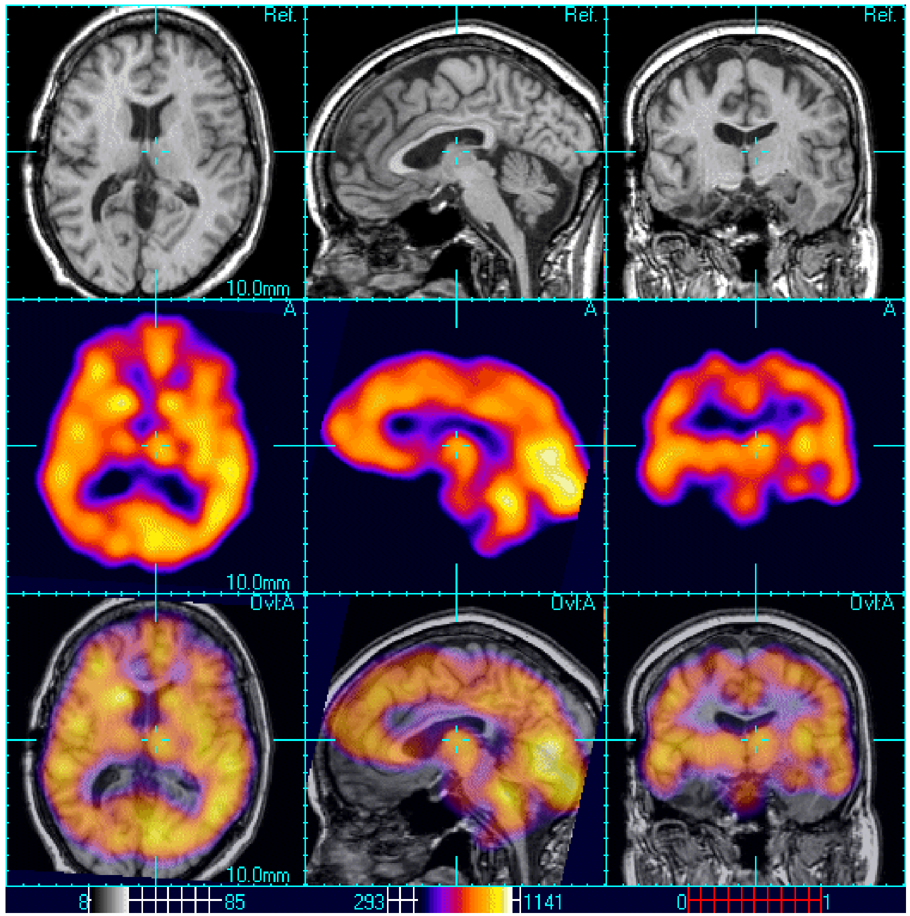
detection limit for radiotracer (isotope) or contrast media

Temporal Resolution

< 0.5 sec. per frame – allows for fast kinetic acquisition (e.g. first pass of tracer through heart)

Single Photon Emission Computed Tomography

SPECT



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Single Photon Emission computed Tomography
SPECT

- Tomographic imaging modality
- Functional information
- Non-invasive
- High sensitivity – nmol (not as good as PET)
- Longer lived radioisotopes than PET
- Large variety of labeled compounds

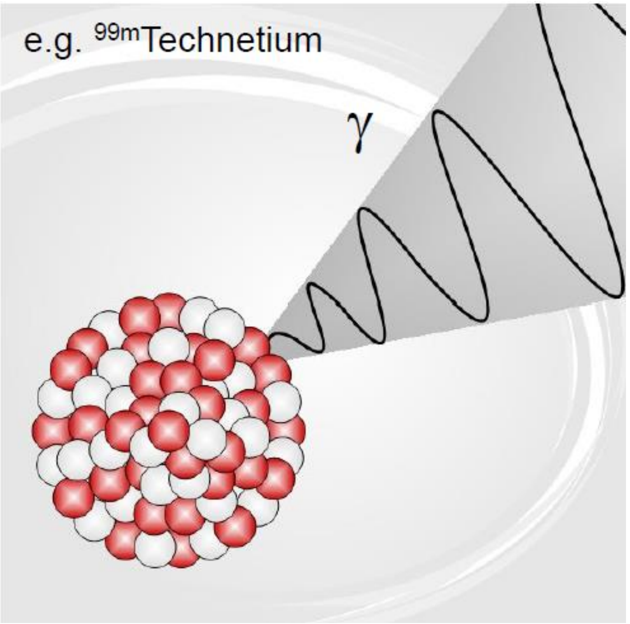
- 0.5-1 mm spatial resolution
- temporal resolution much slower than PET
- Quantification nearly impossible
- temporal resolution > 10 sec.

SPECT

Gamma-Radiation

$^{99m}Tc \Longrightarrow {}^{99}Tc + \gamma$

Nucleus in an excited state decays to ground state



$^{111}In \qquad {}^{111}Cd + \gamma$

Electron capture: Nucleus possesses too many protons but is unable to emit a positron and instead captures an electron

$^{67}Cu \qquad {}^{67}Zn + e^- + \gamma$

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SPECT

Important SPECT Radionuclides

Radionuclide	Main Emission Energy	$T_{1/2}$
^{67}Ga	93, 185 keV	3.3 days
^{99m}Tc	140 keV	6.02 h
^{123}I	159 keV	13.3 h
^{111}In	171, 245 keV	2.8 days
^{201}Tl	135, 167 keV	3.0 days
^{131}I	364 keV	8.2 days

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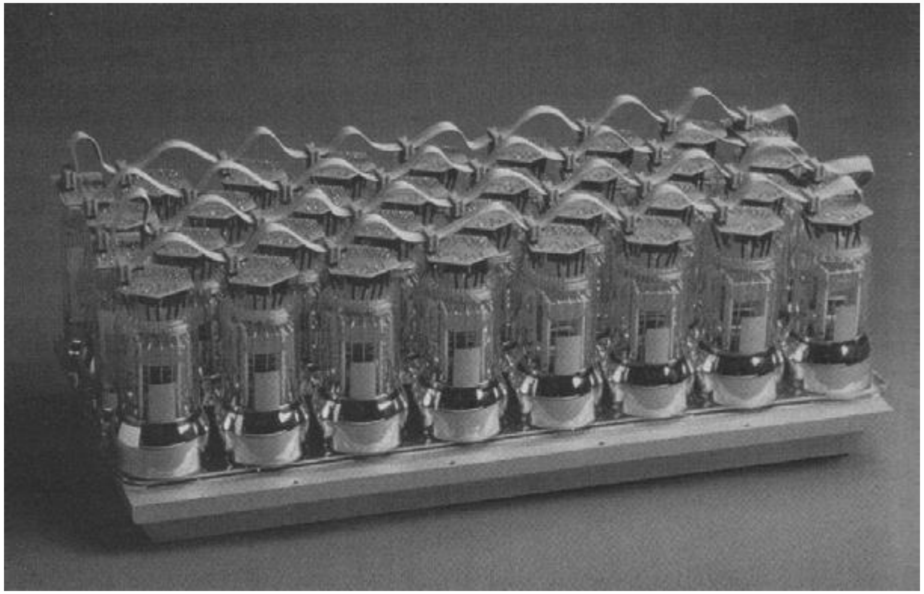
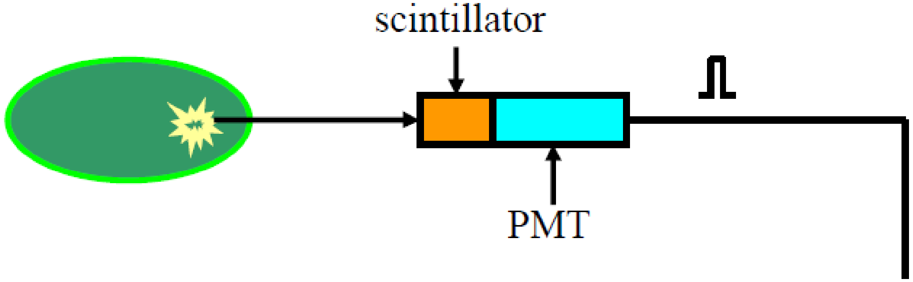
SPECT
Anger Camera

Hal Oscar Anger (1920-2005)



Anger camera (NaI-scintillator and photo multipliers)



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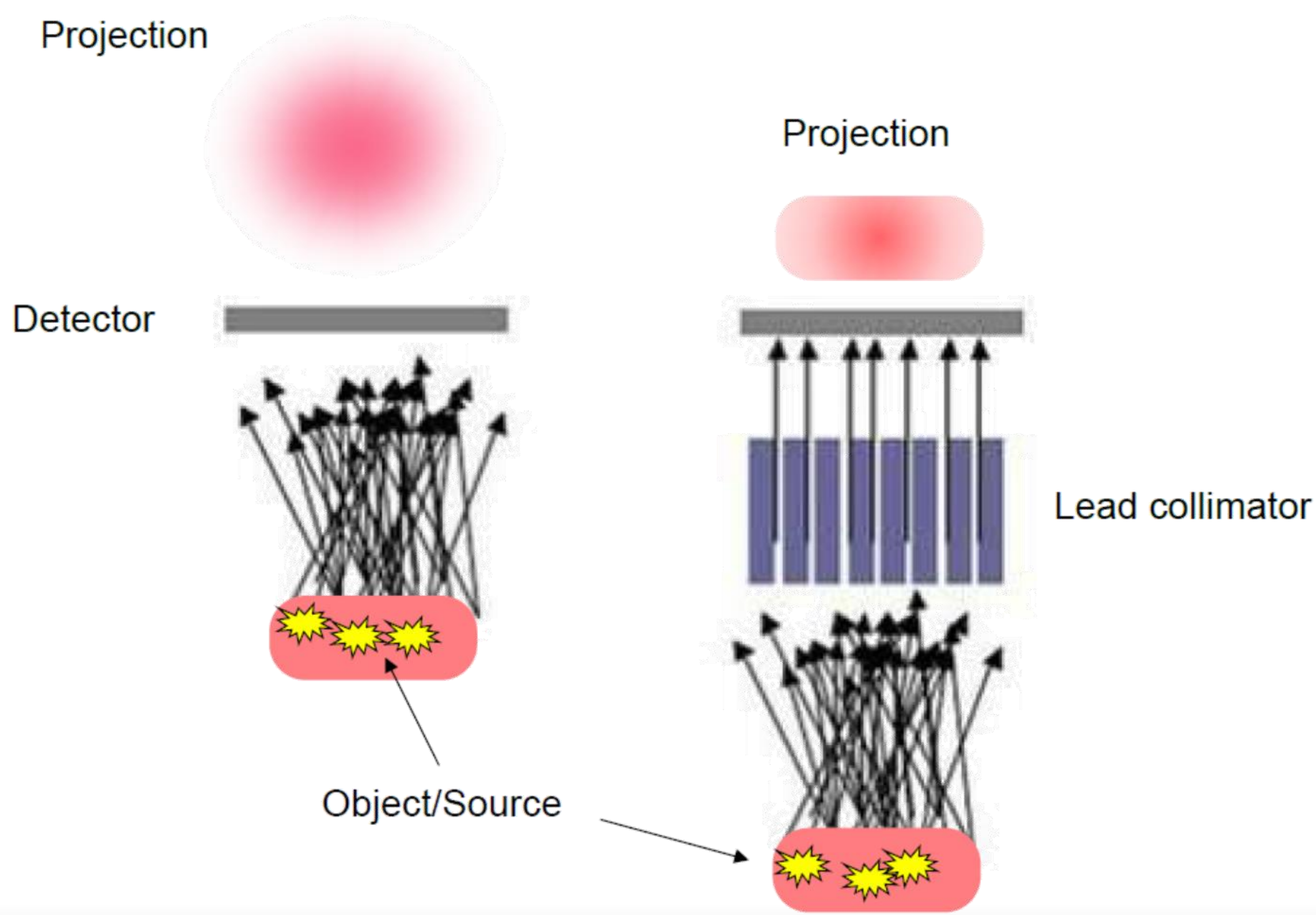
SPECT

Scintillation Material

Scintillator	Density [g/cm^3]	Peak emission [nm]	Decay time [ns]	relative yield*
NaI(Tl)	3.67	415	230	100
CsI	4.51	315	16	4-6
CsF	4.64	390	3-5	5-7
CaF_2(Eu)	3.18	435	940	50
BaF_2	4.88	310	630	16
BGO	7.13	480	300	15-20
$CdWO_4$	7.90	350	28	130
$LaCl_3$(Ce)	3.79	350	28	130
$LaBr_3$(Ce)	5.29	380	16	160
YAP	5.37	347	28	40

*relativ to NaI(Tl)

SPECT
Parallel Hole Collimator



SPECT

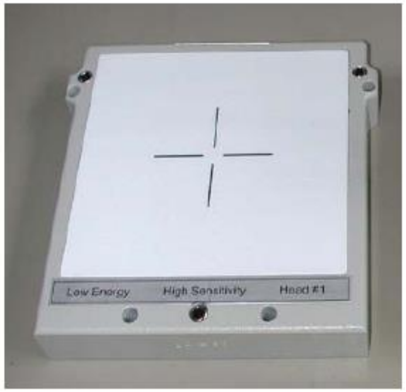
Parallel Hole Collimator

$$R = \frac{d_e * (L + H)}{L}$$

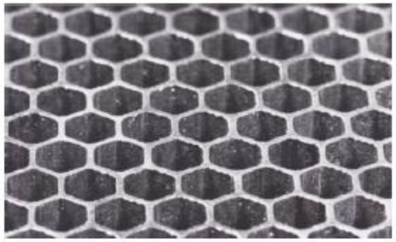
L = length of the holes

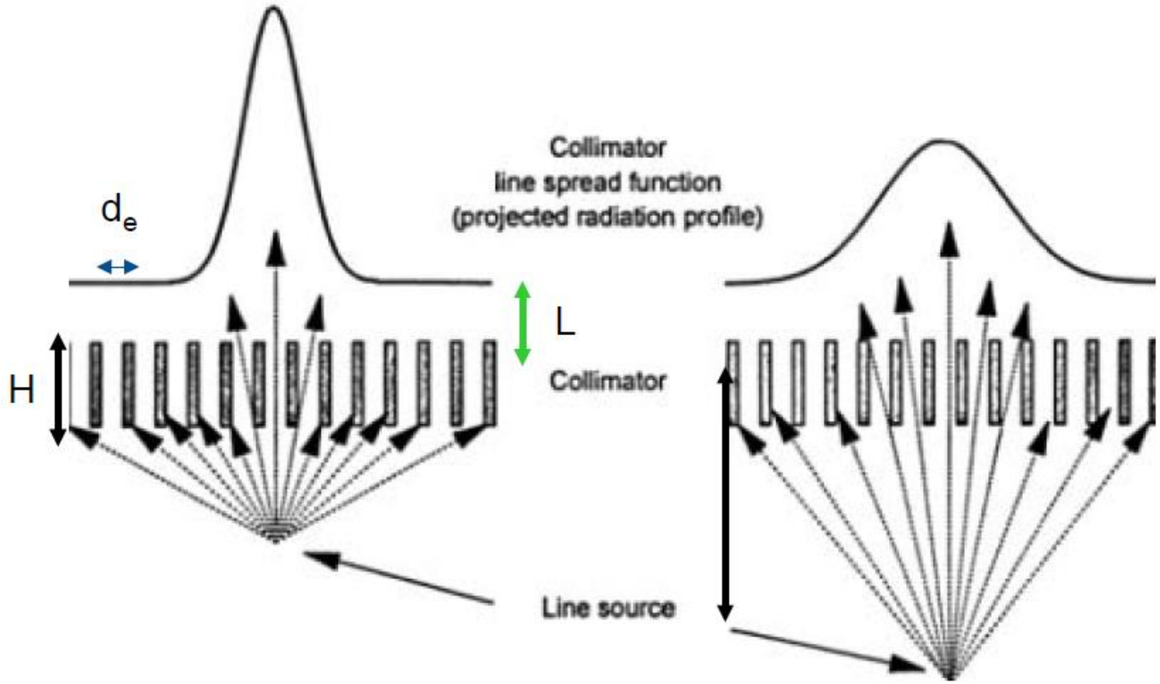
d_e = hole diameter

H = collimator to the source distance



Lead collimator





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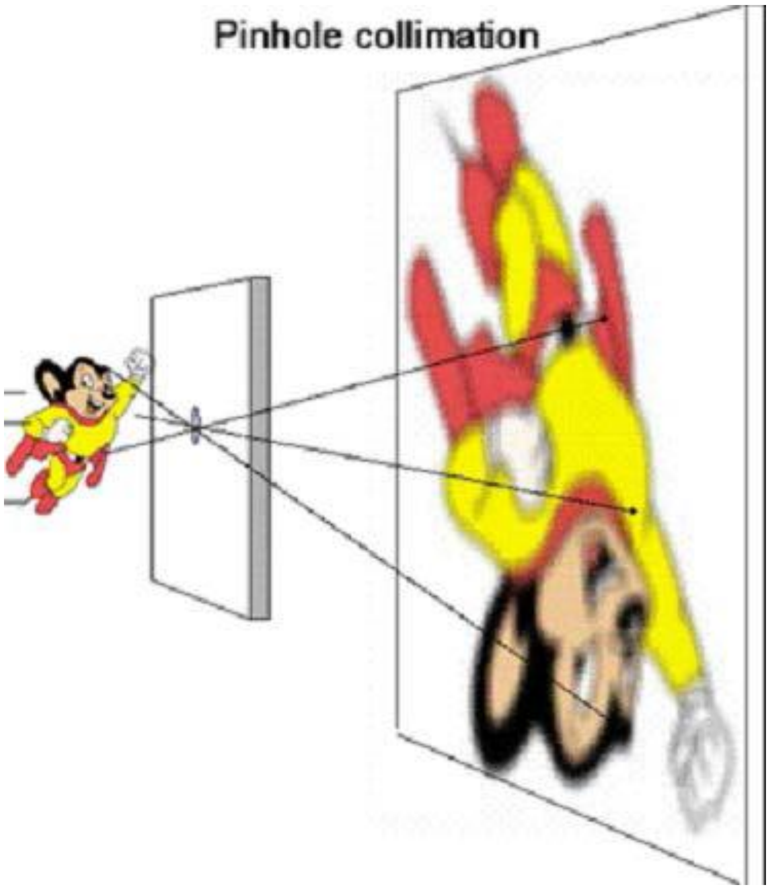
SPECT
Pinhole Collimator

"*Camera Obscura*"

Magnification of the projected object



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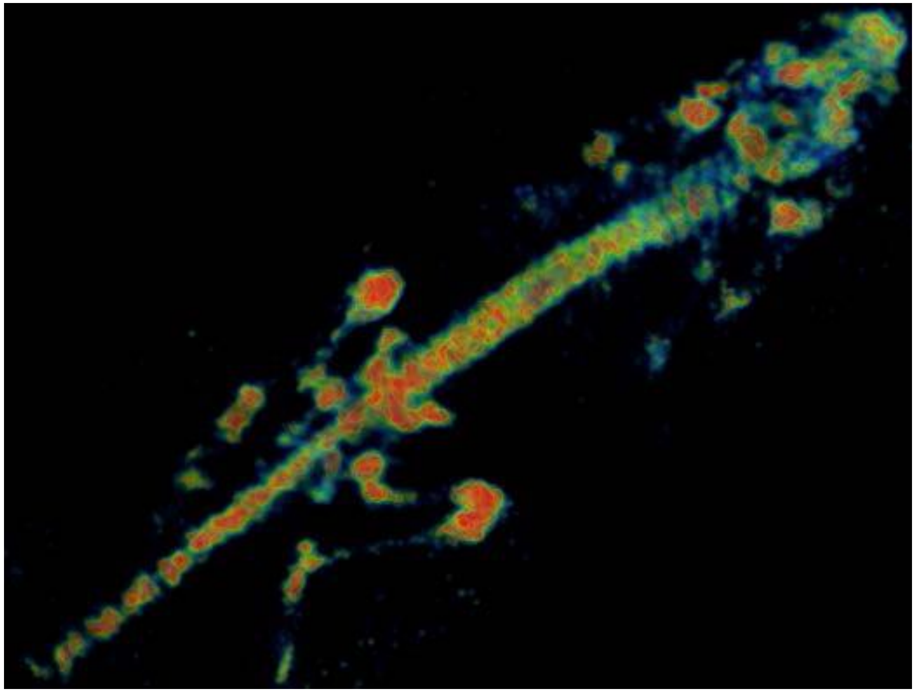
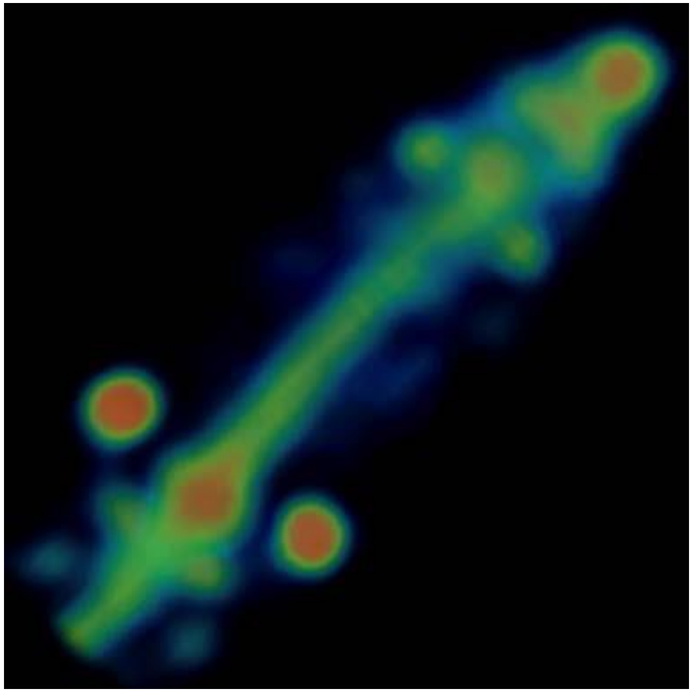
SPECT

Pinhole vs. Parallel Hole Collimator

Pinhole:



Parallel hole:



$^{177}LuCl_3$ bone scan in a normal mouse

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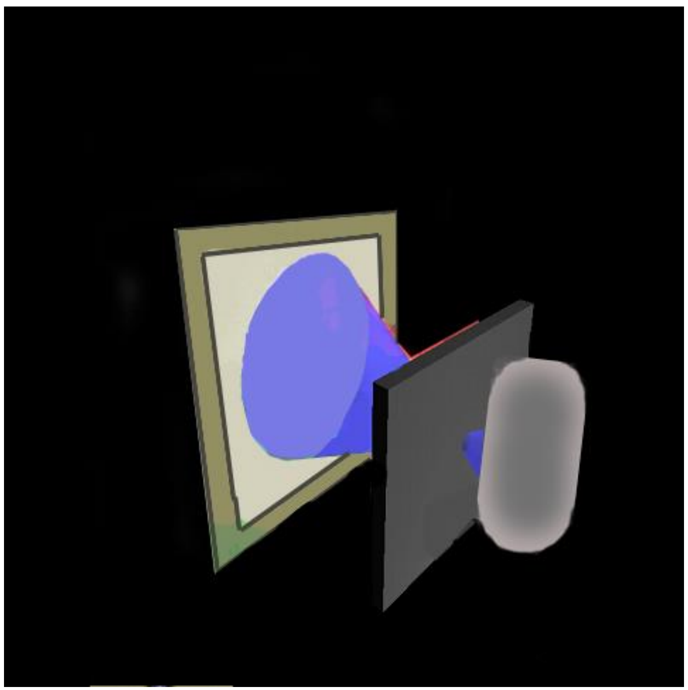
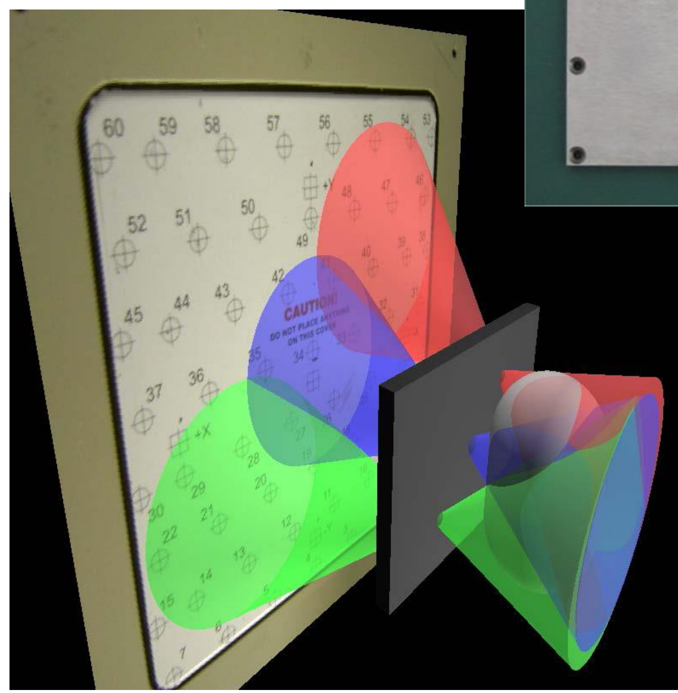
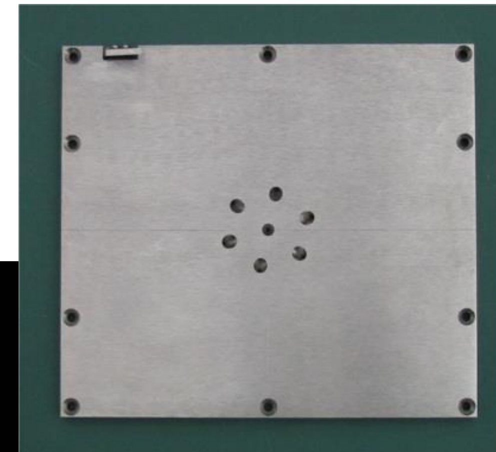
SPECT

Multiple Pinhole Technology

Higher sensitivity and better resolution







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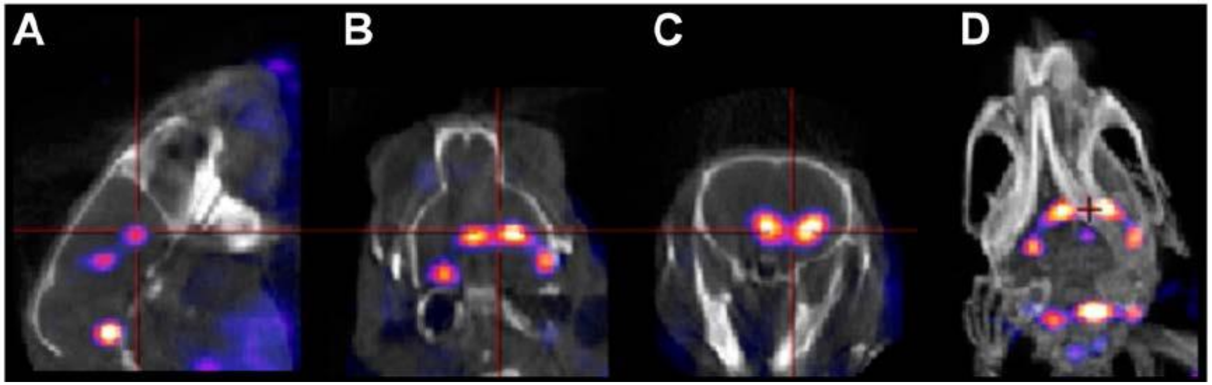
SPECT

Multiple Pinhole Technology - Performance



Choroid Plexus (folate receptor positive organ)

99mTc-Folate (tumor and kidney FR-positiv) female nude mice with human KB-cell tumors, 24 h p.i.

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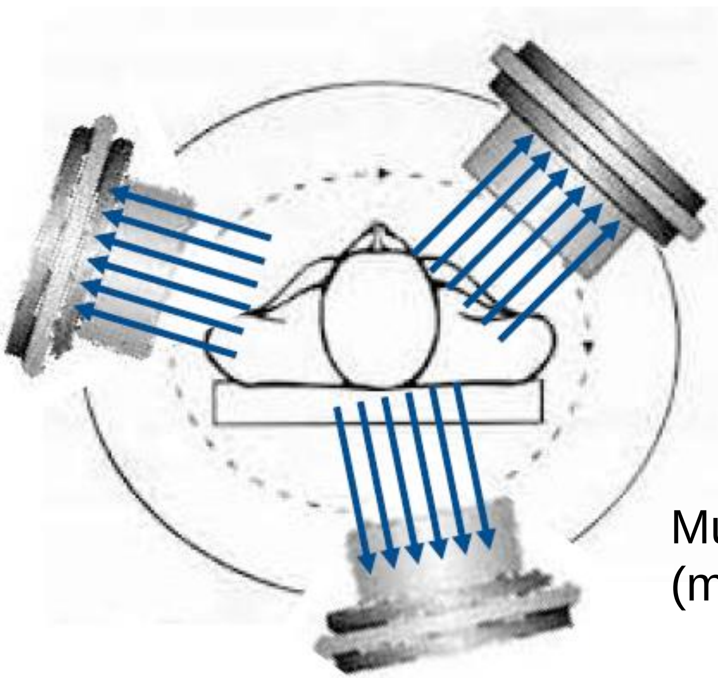
SPECT

Principle of SPECT

- Flat panel *head* used for detection
- Acquisition time depending on:
  - detector, collimator
  - size of the imaging region
  - amount of activity available.



Multiple angle detection
(minimum 2 detectors (180°))

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SPECT

Dual Isotope Imaging

^{99m}Tc-MDP (red-blue) – bone scintigraphy
^{99m}Tc (140.5 keV)

^{123}I (green-yellow) – thyroid imaging
^{123}I (159.0 keV)

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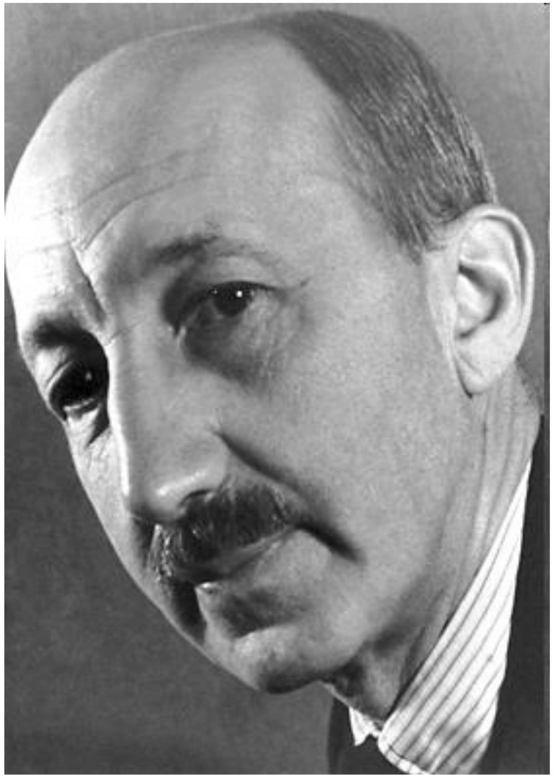
Functional Imaging

Tracer Principle



George de Hevesy (1885-1966);
Nobel Prize for Chemistry in 1943

A radioactive tracer is a chemical compound in which one or more atoms have been replaced by a radioisotope. It is applied in minimal amounts, therefore, it has no pharmacologic effect in vivo. It can also be used to explore the mechanism of bio-/chemical reactions by tracing the path that the radioisotope follows from reactant to product

E.g. 370 MBq of ^{11}C-tracer necessary for a brain scan with ^{11}C-Raclopride (D2-receptor ligand) corresponds to 100 picogram total mass injected.

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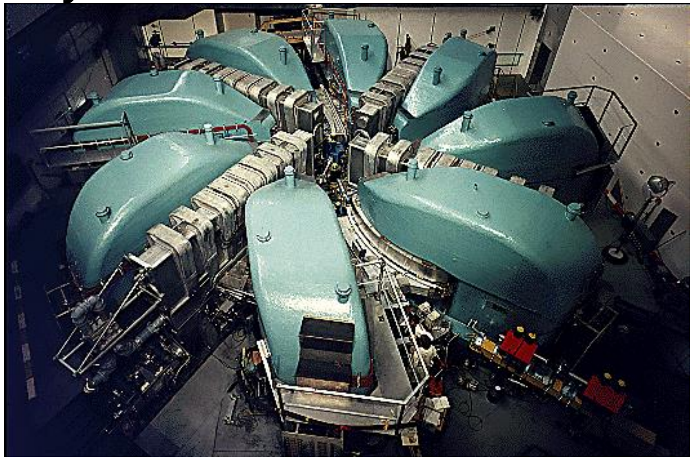
Radiopharmacy

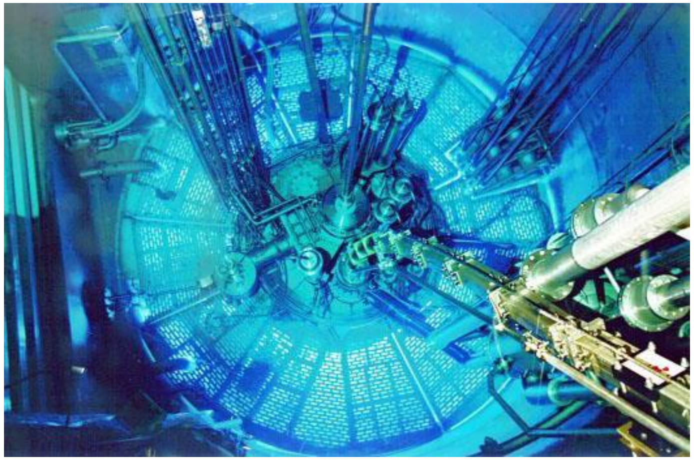
Radionuclide Production

Cyclotron



C-11
N-13
F-18
Cu-64
Cu-67
In-111
1-123

Reactor (neutron bombardment)



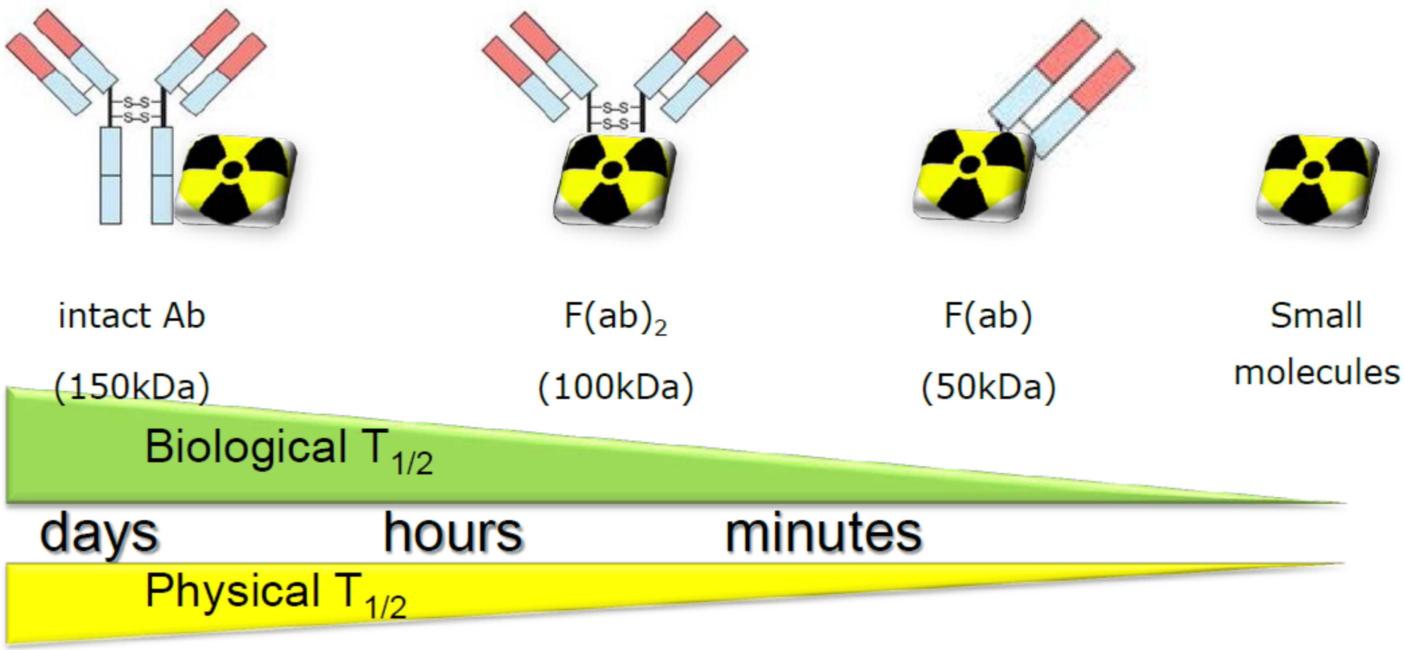
I-131
Sm-153
Ho-166
Lu-177
W-188

Radionuclide generators

Sc-44
Ga-68
Tc-99m
Re-188

Radiopharmacy

Do we need so many radionuclides?



^{89}Zr	3.2 d	^{99m}Tc	6 h	^{11}C	20 min
^{111}In	2.8 d	^{64}Cu	12.7 h	^{18}F	1.9 h
^{67}Ga	3.2 d	^{76}Br	16.3 h	^{68}Ga	1.1 h
^{124}I	4.2 d	^{123}I	13.3 h		

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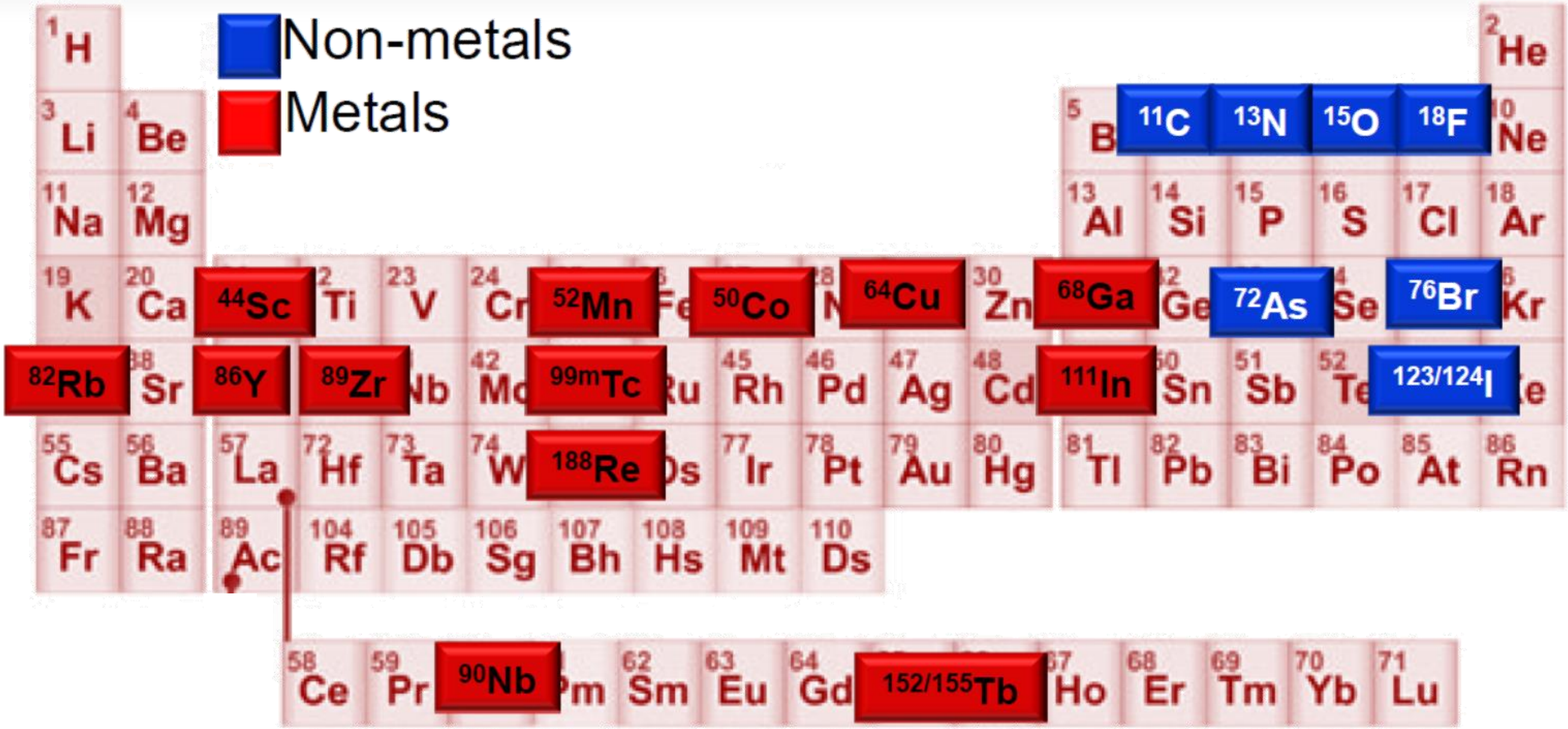
Radiopharmacy

Radionuclides for Diagnosis



- Direct labeling with non-metal radionuclides
- Indirect labeling strategies via bifunctional chelators
- 60 % of suitable radionuclides are metals!

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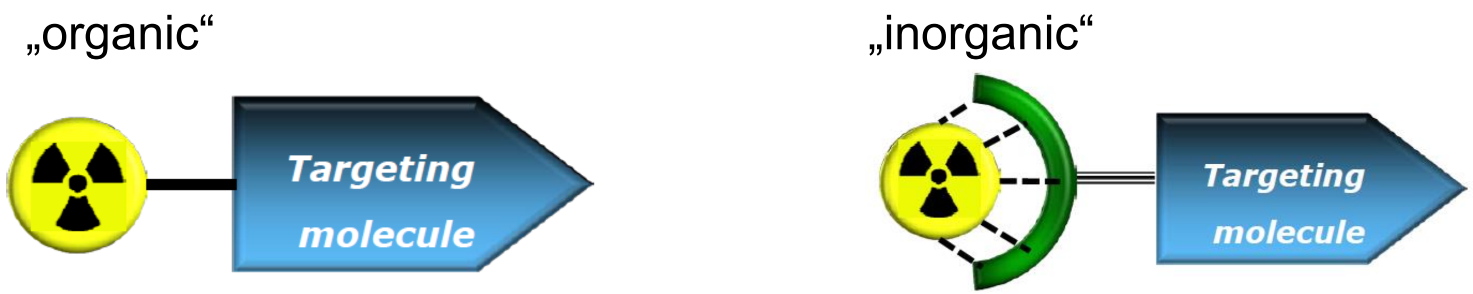
Radiopharmacy

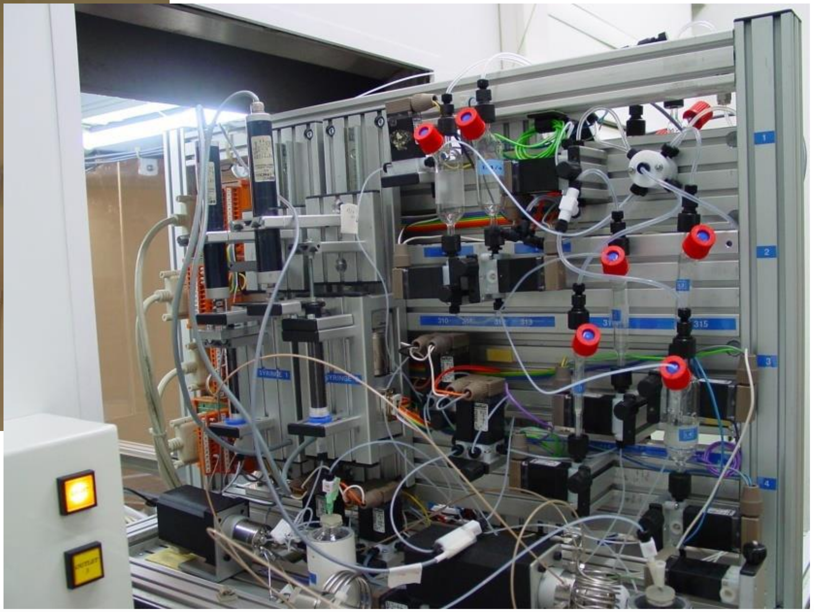
Radiolabeling – Critical Issues of Functionalization



- Labeling yields
- Synthetic steps
- Avoid cross reactivity with other functional groups
- Avoid mixtures of products and formation of isomers
- Optimal pharmacokinetic
- Retention of biological activity and integrity

Radiopharmacy

Radiotracer Production



Thank you for your Attention

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