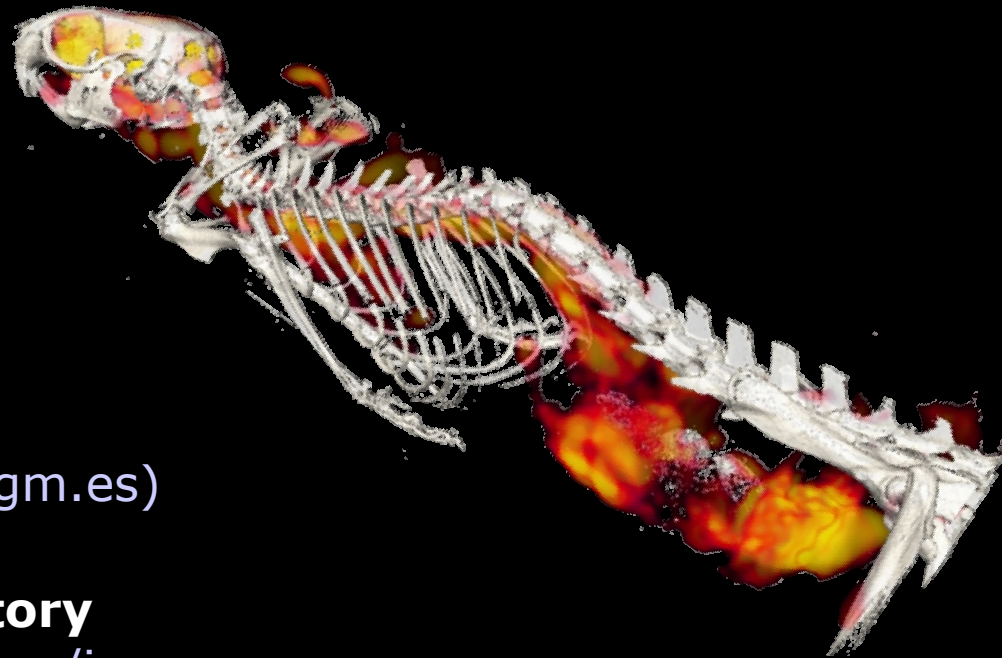


**Small animal PET/CT:
in vivo molecular imaging for
preclinical applications**



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<http://www.hggm.es/image>
Unidad de Medicina y Cirugía experimental.
Hospital Universitario Gregorio Marañón, Madrid, Spain.

- Introduction
- Positron Emission Tomography
- X-ray CT
- Multimodality
 - Registration
 - Hybrid equipment

- Structural
 - MRI (structural)
 - Ultrasound
 - X-ray CT
- Functional
 - MRI (functional)
 - Optical Imaging
 - Nuclear imaging

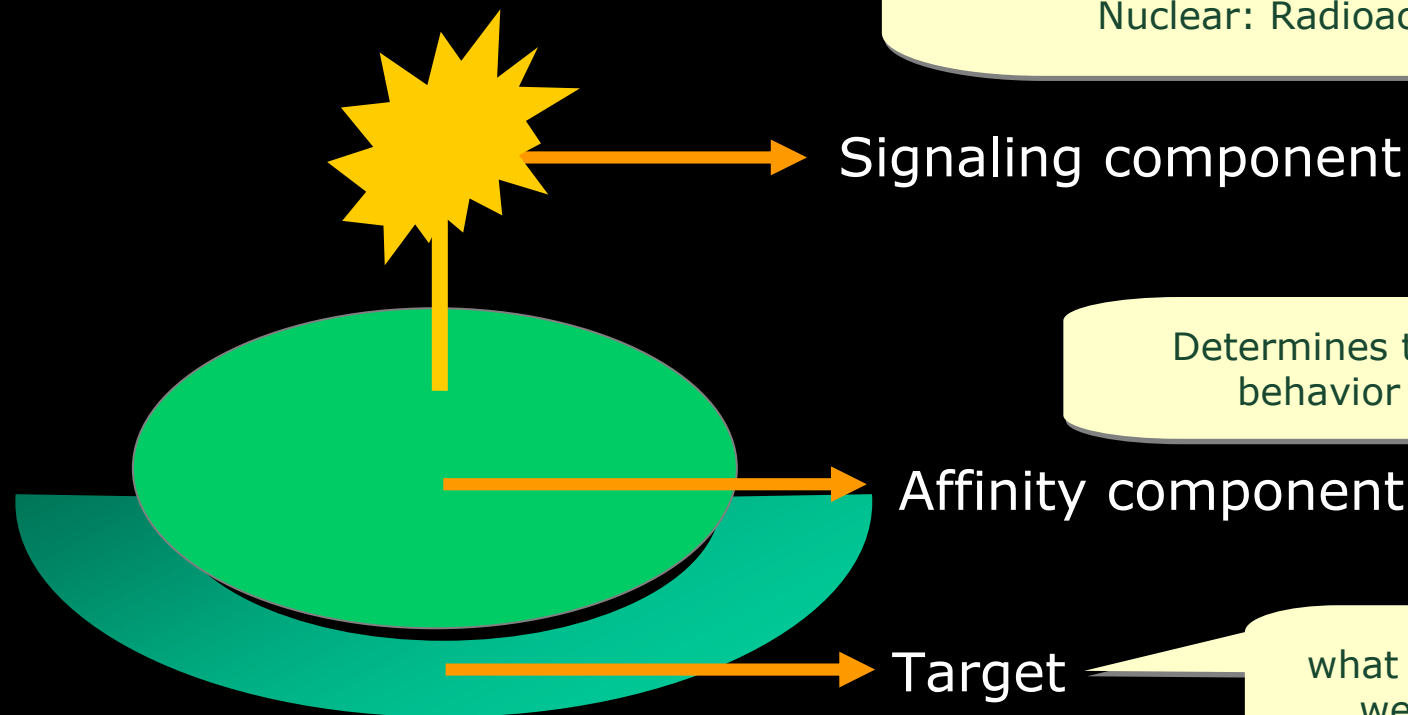
All of them can be useful for ‘Molecular Imaging’

Remote registration and measurement of biological processes at a molecular level, *in vivo*, and without interfering with the system under study

Molecular Imaging Probes

- Molecular probe (tracer):
 - Labeled compound
 - Incorporated to biochemical pathways
 - Detectable from outside
 - Trace concentration: does not

Determines the imaging modality
MRI: Paramagnetic elements (particles)
Optical: Fluorescent / luminiscent compounds
Nuclear: Radioactive element

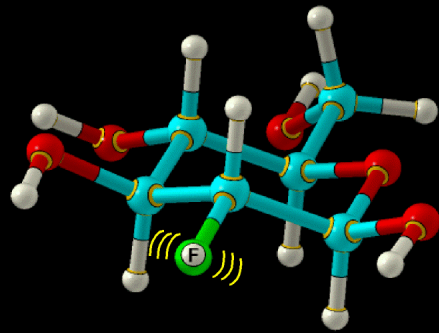


Determines the biological behavior (binding)

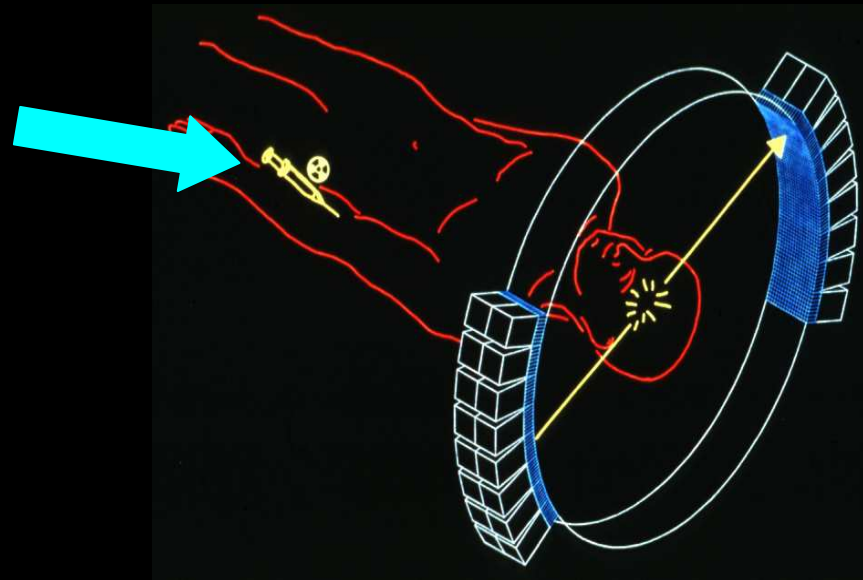
what biological process we want to study?

Nuclear Imaging

- Detection of radiation
 - Radio-active material attached to a biologically active molecule
 - Administered orally or intravenously
- **Contrast:** Concentration of radiotracer



Radiotracer
(^{18}F FDG: FDG molecule with a positron emitting F atom)



Tomograph

J. Clark

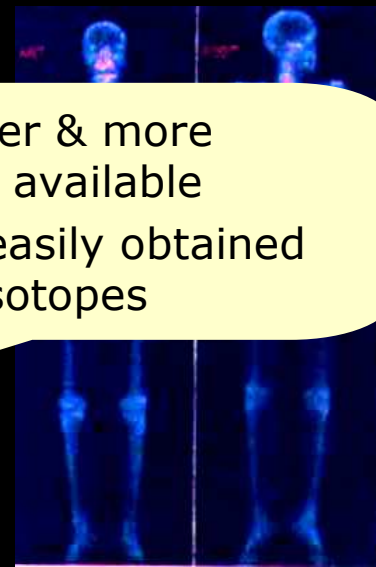
Nuclear Imaging Techniques

- Scintigraphy: Planar

- SPECT (*Single Photon Emission Computed Tomography*)

- Isotopes: ^{99}Tc , ^{201}Tl , ^{67}Ga , ^{111}In , ^{123}I

- Cheaper & more widely available
- More easily obtained radioisotopes

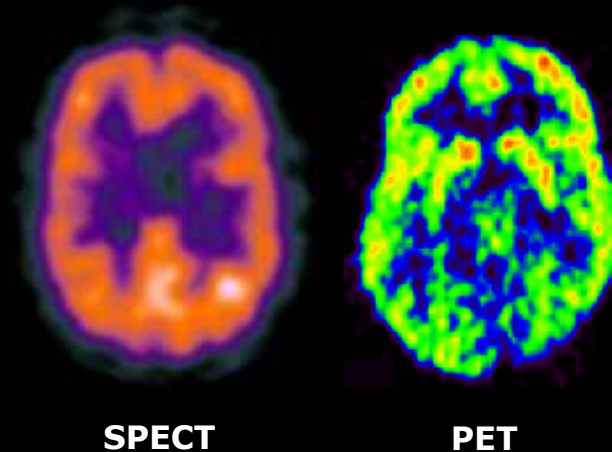


^{99}Tc MDP Bone scintigraphy

- PET (*Positron Emission Tomography*)

- Isotopes: ^{18}F (~H), ^{13}N , ^{15}O , ^{11}C

“Organic” atoms: endogenous compounds (or analogues)



SPECT

PET

Nuclear Imaging: PET

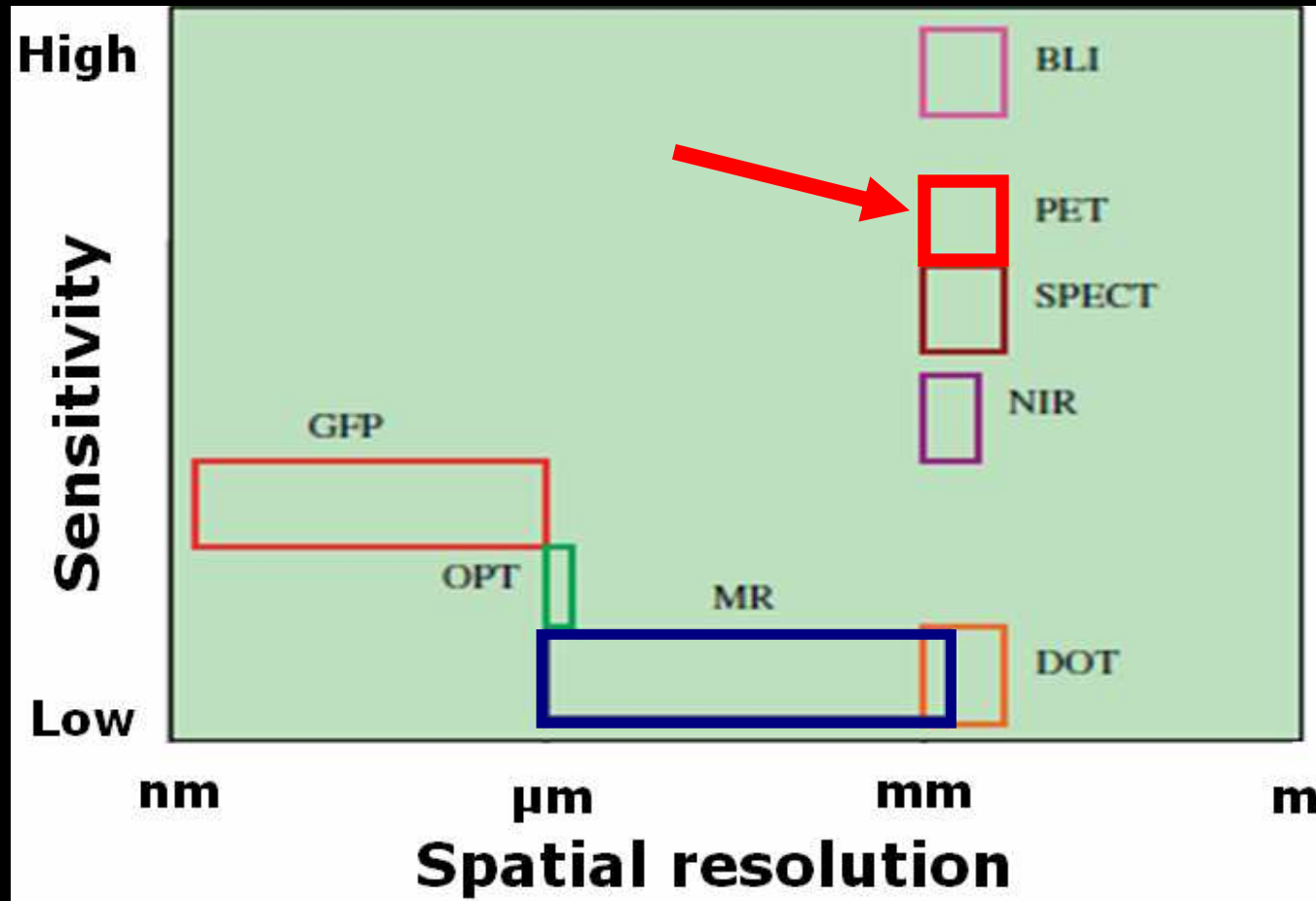
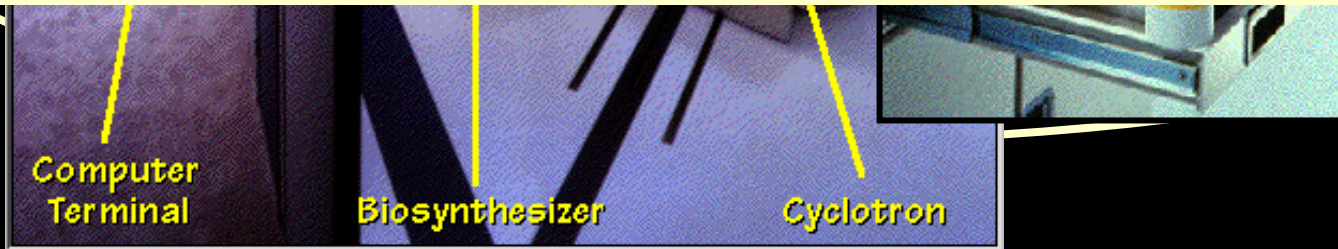


Figure from P. J. Cassidy, 2005

Workflow of a PET Experiment



Expensive and complicated!



Image

**PET Data
Acquisition**

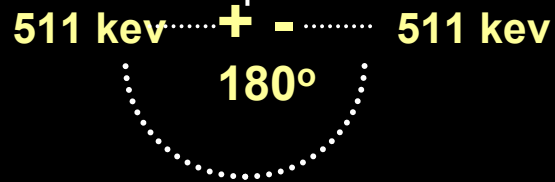
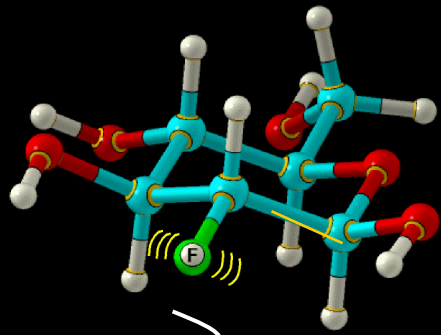
**Inject
Radiotracer**



Example: ^{18}F FDG

Radiotracer

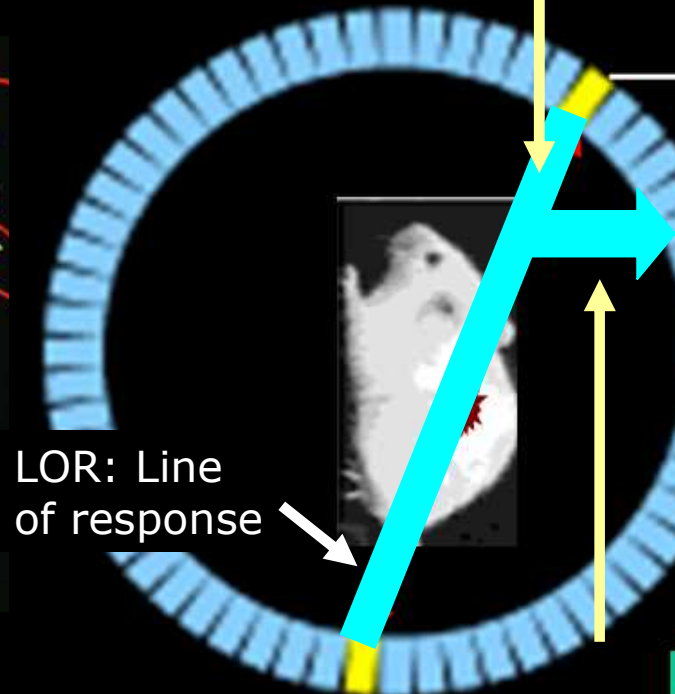
(^{18}F FDG: FDG molecule with a positron emitting F atom)



Electronic collimation



Data Corrections



Ovary cancer with Pulmonar metastasis

Reconstruction algorithms

Coincidence circuit

- **Analytical techniques** (\sim MRI)
 - + **Fast**
 - Based on an idealized mathematical model
 - Simplified physics
- **Iterative techniques**
 - + Models of data acquisition physics and noise
 - + Better SNR
 - + Other geometries (“missing” data)
 - + Side information (MRI or CT boundaries)
 - **High computational cost**

Iterative Methods: Idea

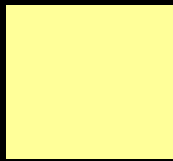
We have:

Measured
projection data

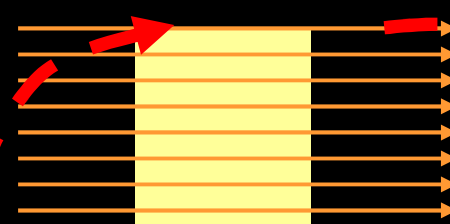
+

System model

0. First estimate



1. Project the estimate



Simulated
projection data

2. Comparison with measured data
medidos

Measured
proj. data

Simulated
proj. data

3. Backproject the error to correct
previous estimate

Error

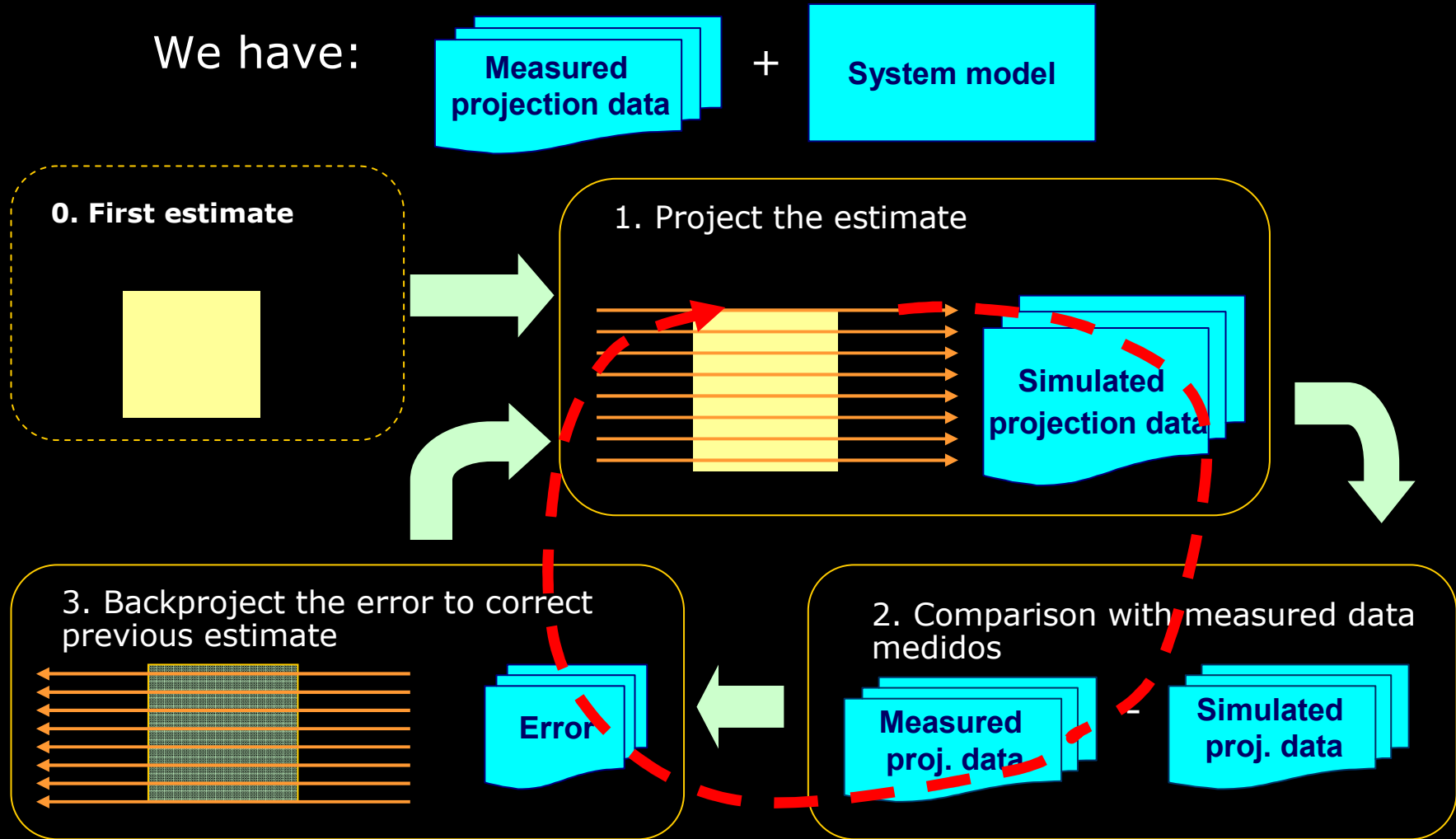
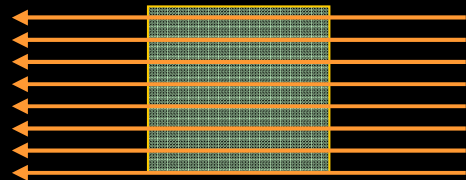
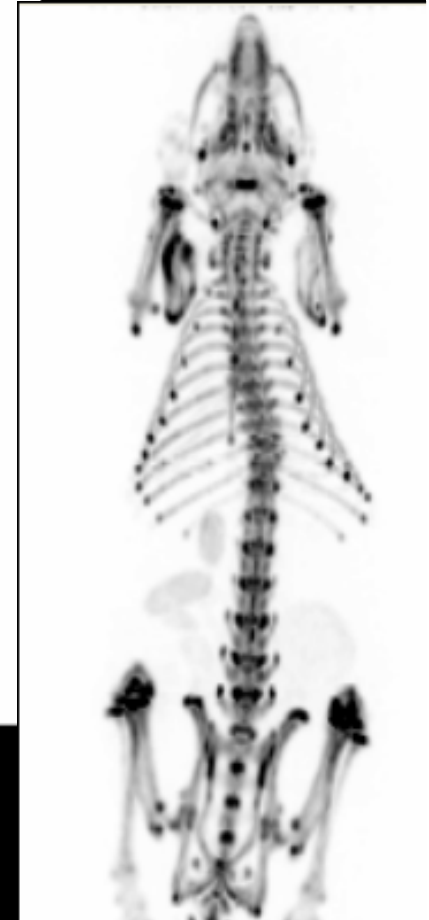


Image Reconstruction

- **Analytical techniques** (\sim MRI)
 - + **Fast**
 - Based on an idealized mathematical model
 - Simplified physics
- **Iterative techniques**
 - + Models of data acquisition physics and noise
 - + Better SNR
 - + Other geometries ("missing" data)
 - + Side information (MRI or CT boundaries)
 - **High computational cost**



FBP



3D OSEM

PET applications

Brain image: Drug Abuse Study

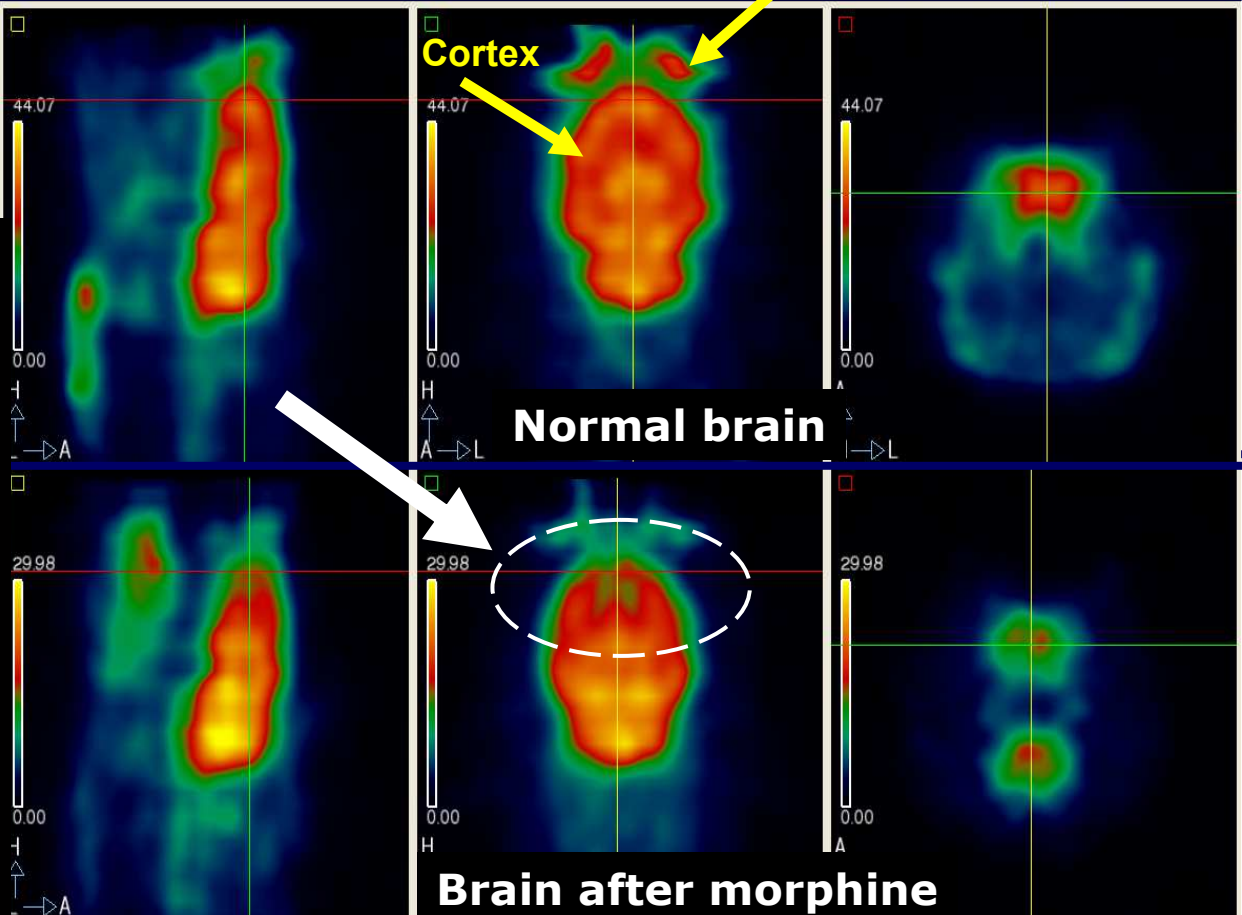


Harderian Glands

Cortex

Normal brain

Brain after morphine

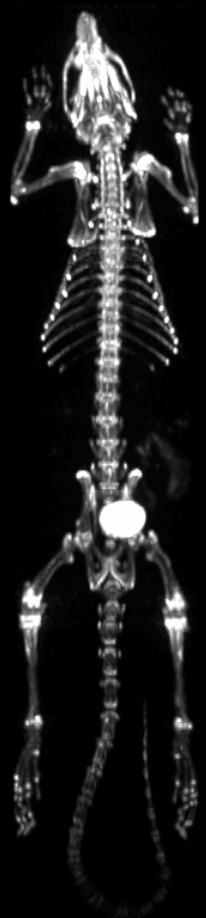


Bone Image: 18-F Fluoride

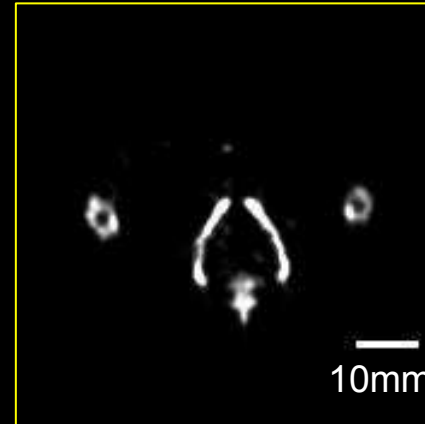
X-Ray



PET MIP(Coronal)



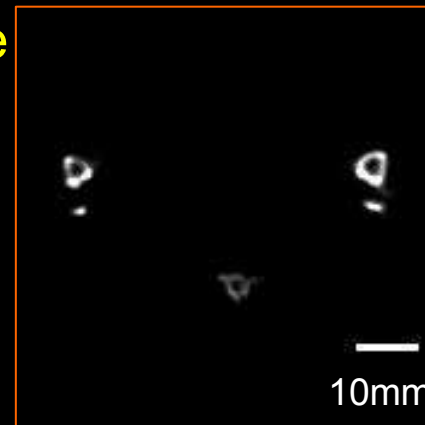
PET (Axial slice)



Medullary cavity

— Femoral bone

— Tibial bone

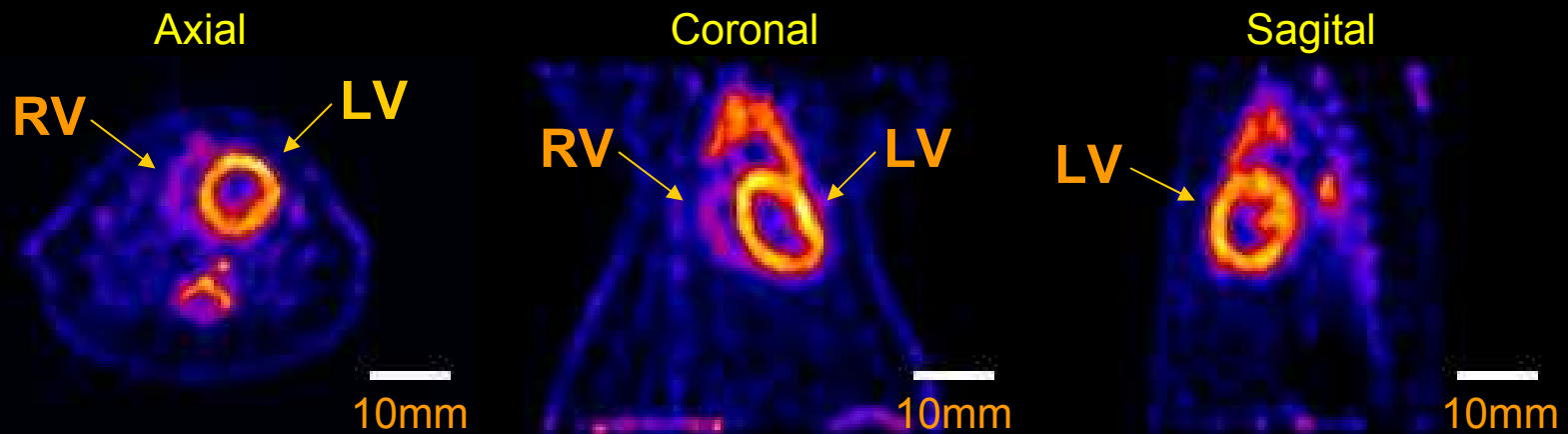


-Triangular shape
-Medullary cavity
-Fibulas!!!

eXplore Vista-CT System, 3D OSEM

Courtesy of Dr. M. Wada, Nihon Medi-Physics Co. (Tokyo, Japan)

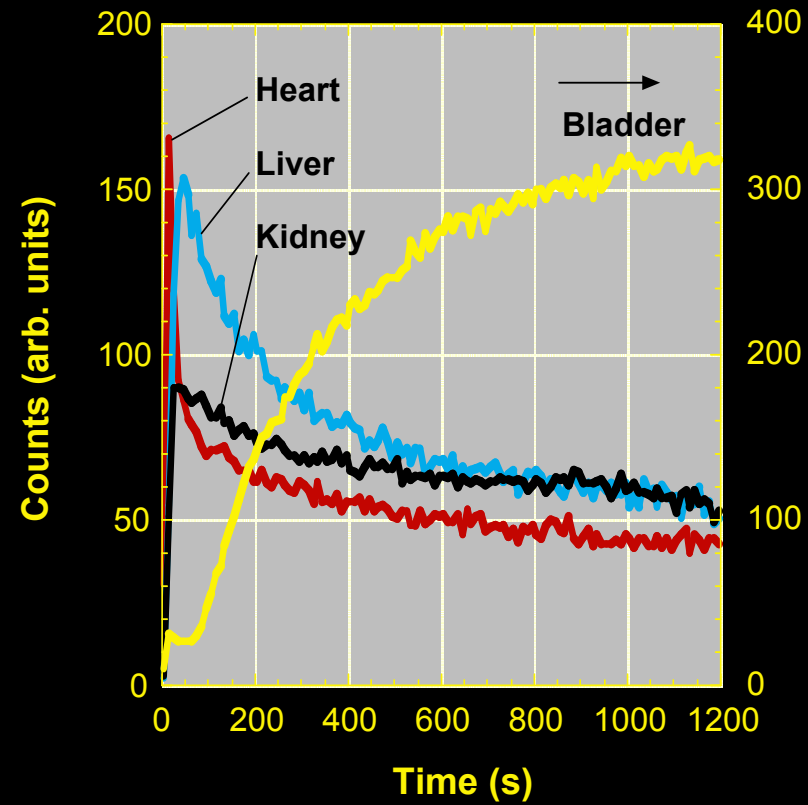
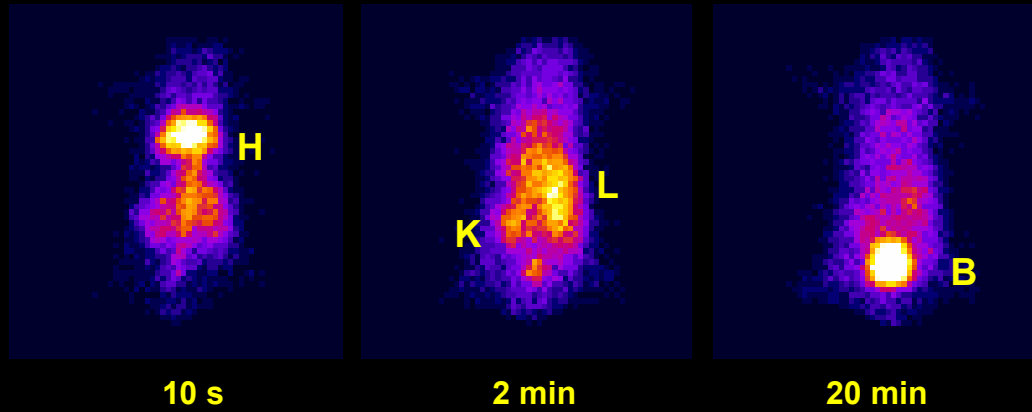
eXplore Vista-CT System



Courtesy of Dr. M. Wada, Nihon Medi-Physics Co. (Tokyo, Japan)

- Ischemic heart disease (perfusion, viability, hypoxia)
- Heart failure

Dynamic Imaging: ^{18}F FDG mouse



How to Take the Decision

- A lot of theoretical considerations

- Good sensitivity: nM (more than MRI: mM)
- Quantitative (MRI?)
- Medium resolution (worse than MRI)
- Many molecular probes
 - **^{18}F (109 min)**
 - FDG (metabolism), FLT (DNA replication), FMISO (hypoxia), F-choline
 - **^{13}N (10 min)**
 - Ammonia (NH_3): Blood flow
 - **^{15}O (2 min)**
 - Water and CO_2 : Blood flow
 - O_2 : O consumption
 - **^{11}C (20 min)**
 - Choline (prostate tumor)
 - Thymidine (DNA replication)
 - Amino acids, methionine
 - Tyrosine

- Expensive (like MRI)
- Complex instrumentation and processing (like MRI)
- Ionizing radiation
- No activatable probes
- Not so many molecular probes available in practice
 - PET: Cyclotron + biosynthesis modules

How to Take the Decision

- A lot of theoretical considerations
- In practice ...
 - What do I have available at my center?
 - What do have my friends?
 - Am I going to get technical support?
 - Can I afford it?

- Structural

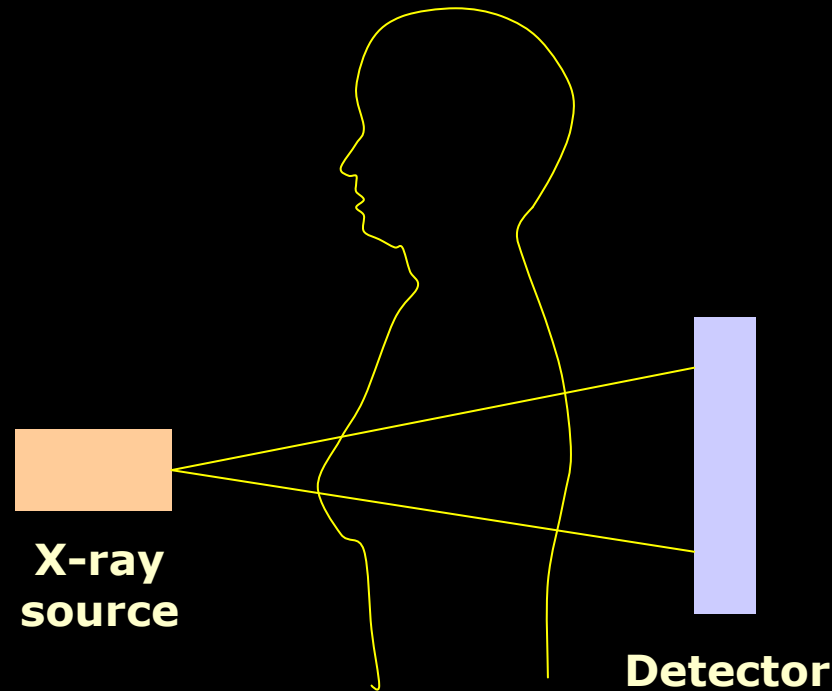
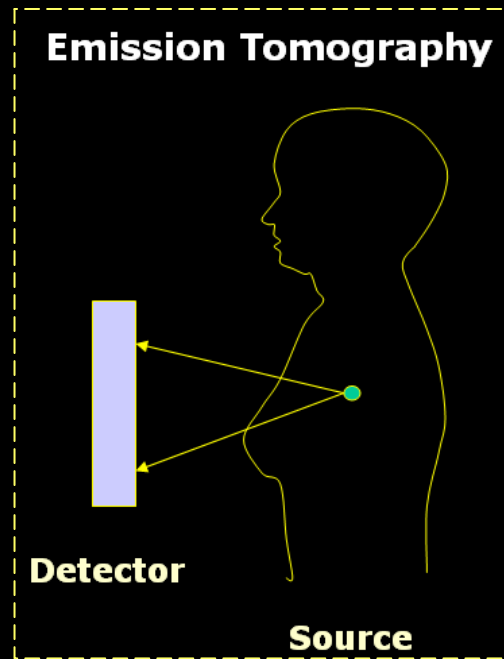
- MRI (structural)
- Ultrasound
- X-ray CT

- Functional

- MRI (functional)
- Optical Imaging
- Nuclear imaging

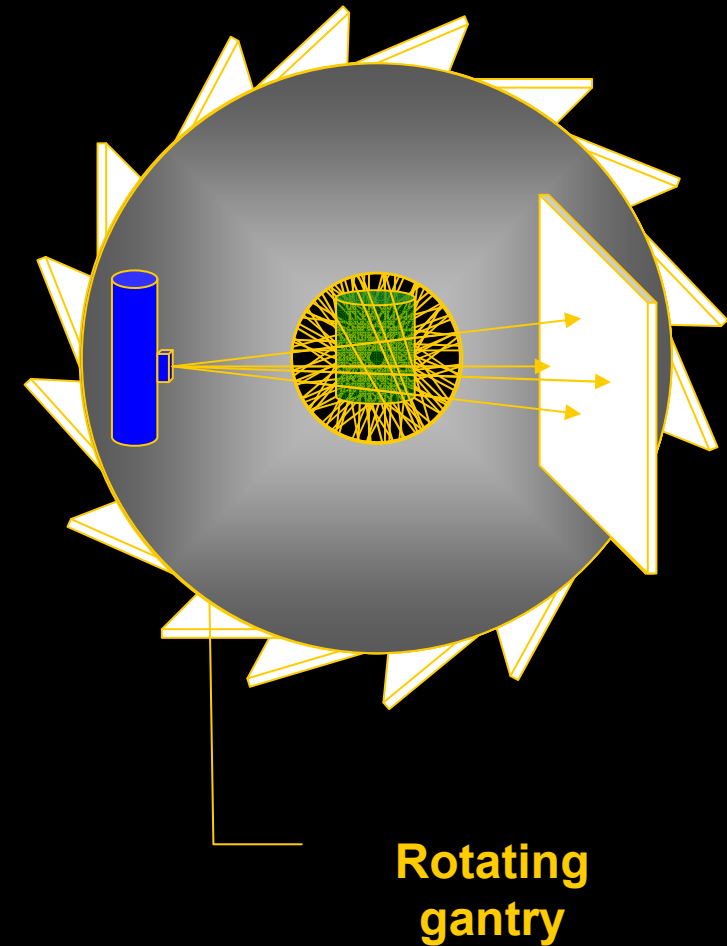
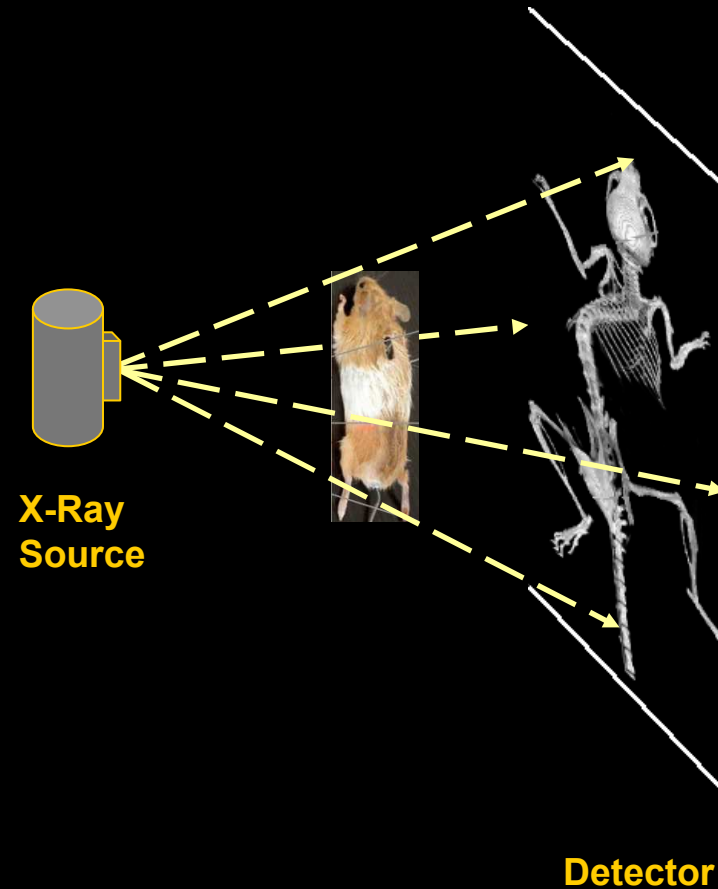
All of them can be useful for 'Molecular Imaging'

X-ray CT: Transmission Tomography



- **Contrast:** attenuation capacity to X-rays, related to **tissue density**

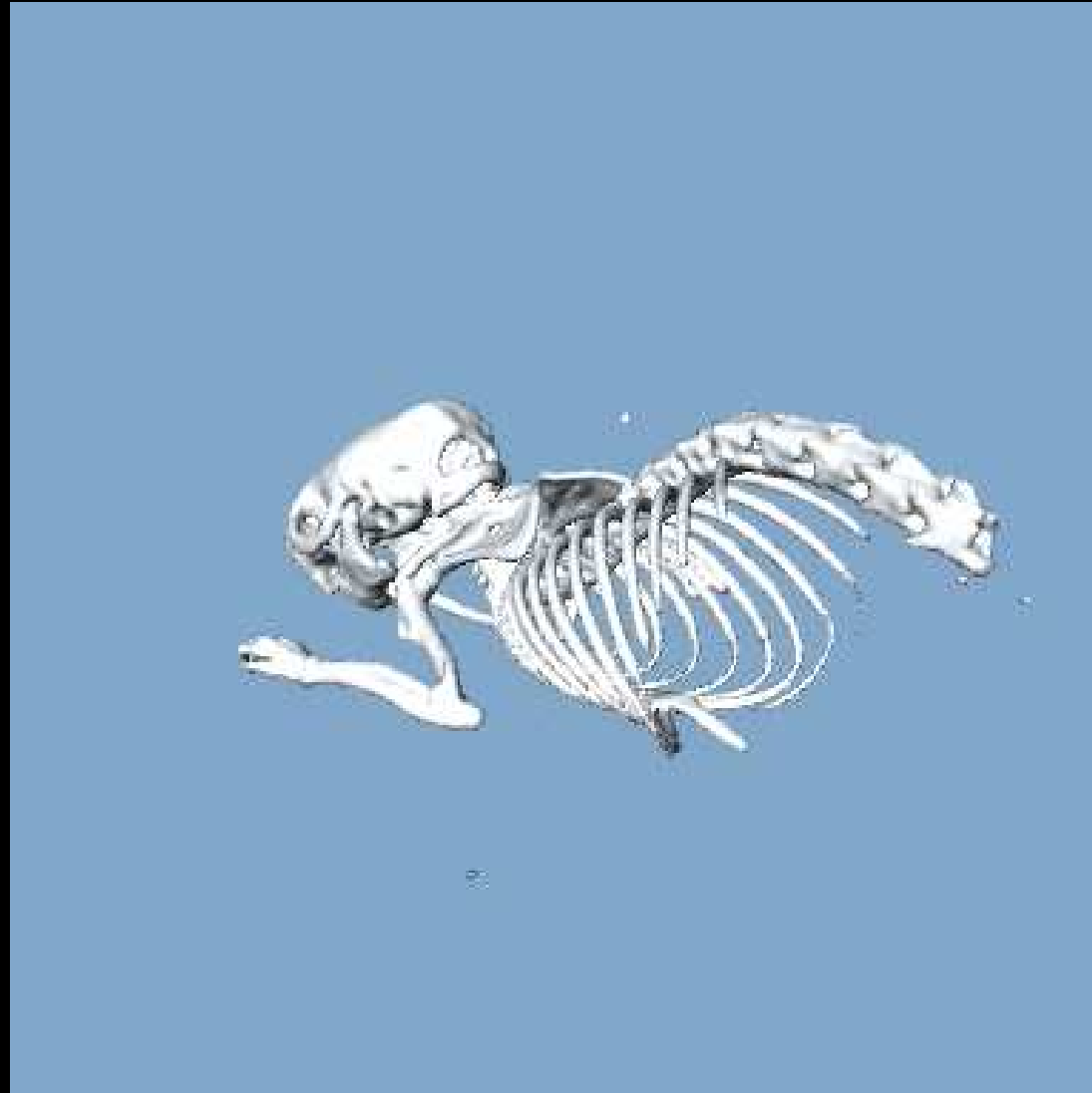
Cone-beam geometry



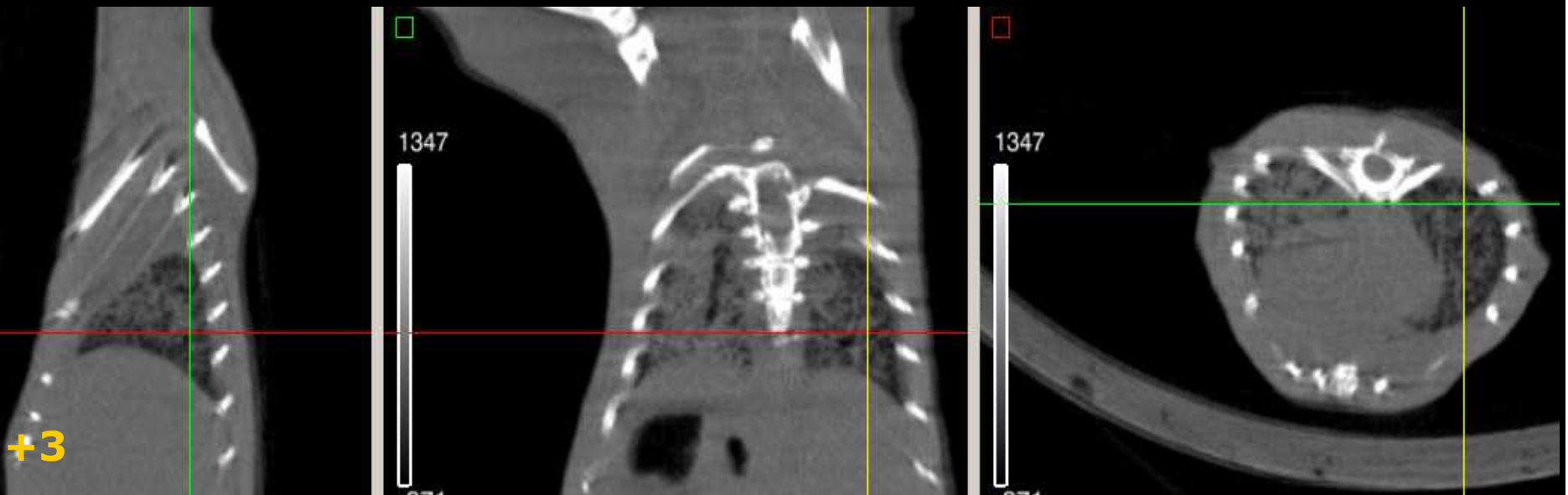
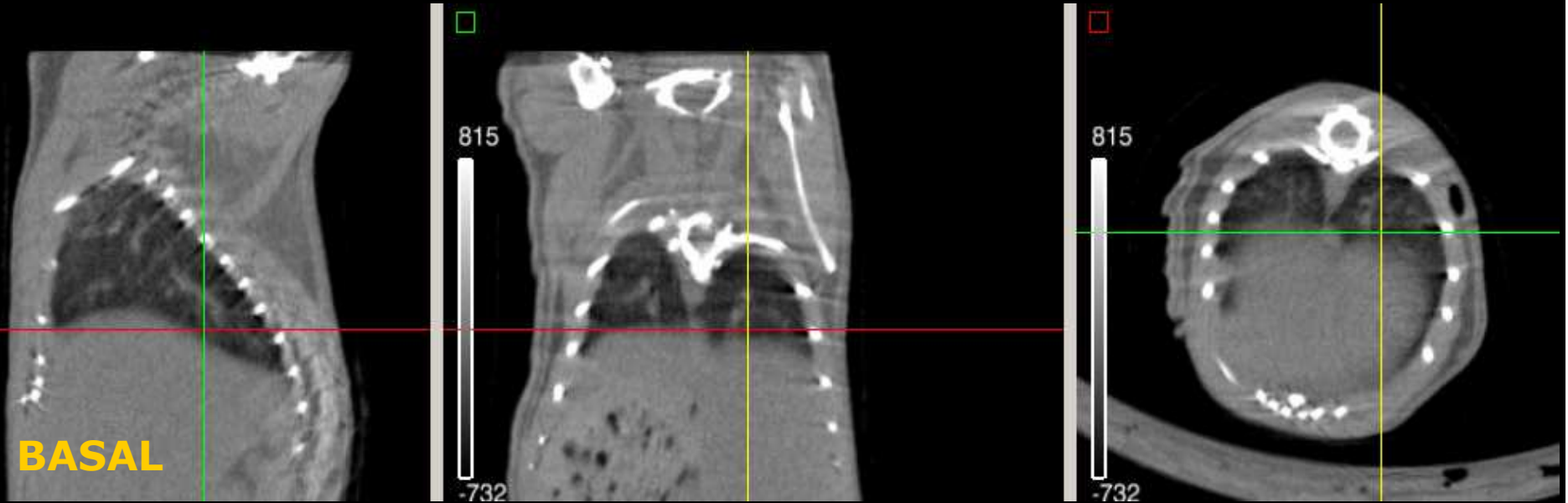
Projections are corrected and reconstructed usually by FDK (analytical algorithm)

X-ray CT applications

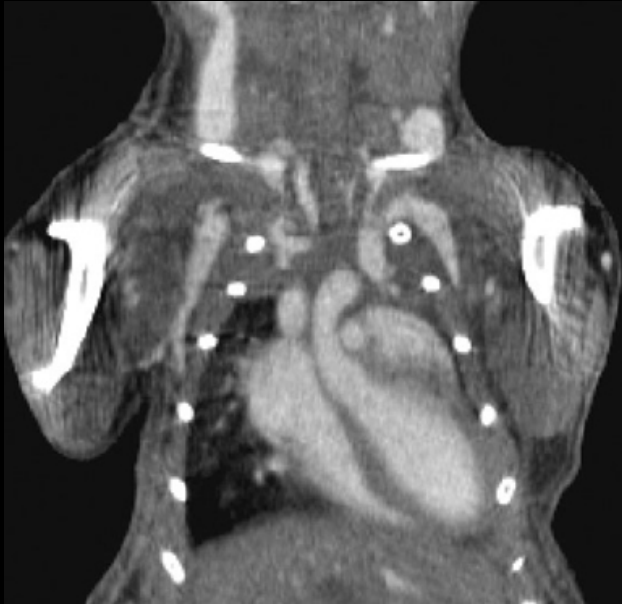
Bone Image



Lung: Study of Aspergillosis



'Molecular': CT Contrast Agents

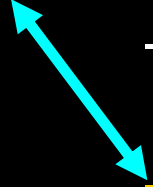


FENESTRA contrast agent, Alerion Biomedical Inc.



IOPAMIRO 300 contrast agent,
Bracco Industria Chimica

CT pros and cons

- + **High resolution (μm)**
 - + Simple to use
 - + Good contrast air-bone-soft tissues
 - Limited contrast for soft tissues
 - Perfusion hardly available for rodents (hardware)
 - **Ionizing radiation**
- 

- In mice:
 - Therapeutical effect in tumors: 0.01~0.2 Gy
 - Affects: 1~2 Gy
 - LD 50/30: 5~7.5 Gy
 - **Typical CT in mice: 0.1~1Gy/exam!!**

$$\text{dose} \approx (\text{resolution})^{-4}$$

Imaging Modalities

- Structural

- MRI (structural)
- Ultrasound
- X-ray CT

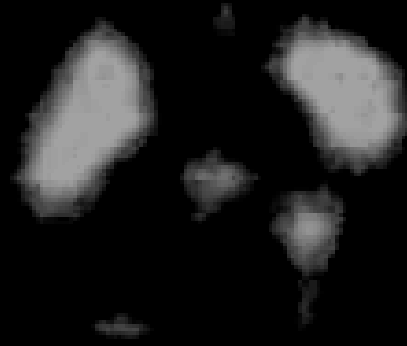
- Functional

- MRI (functional)
- Optical Imaging
- Nuclear imaging

Multimodality

Advantages of Multimodality

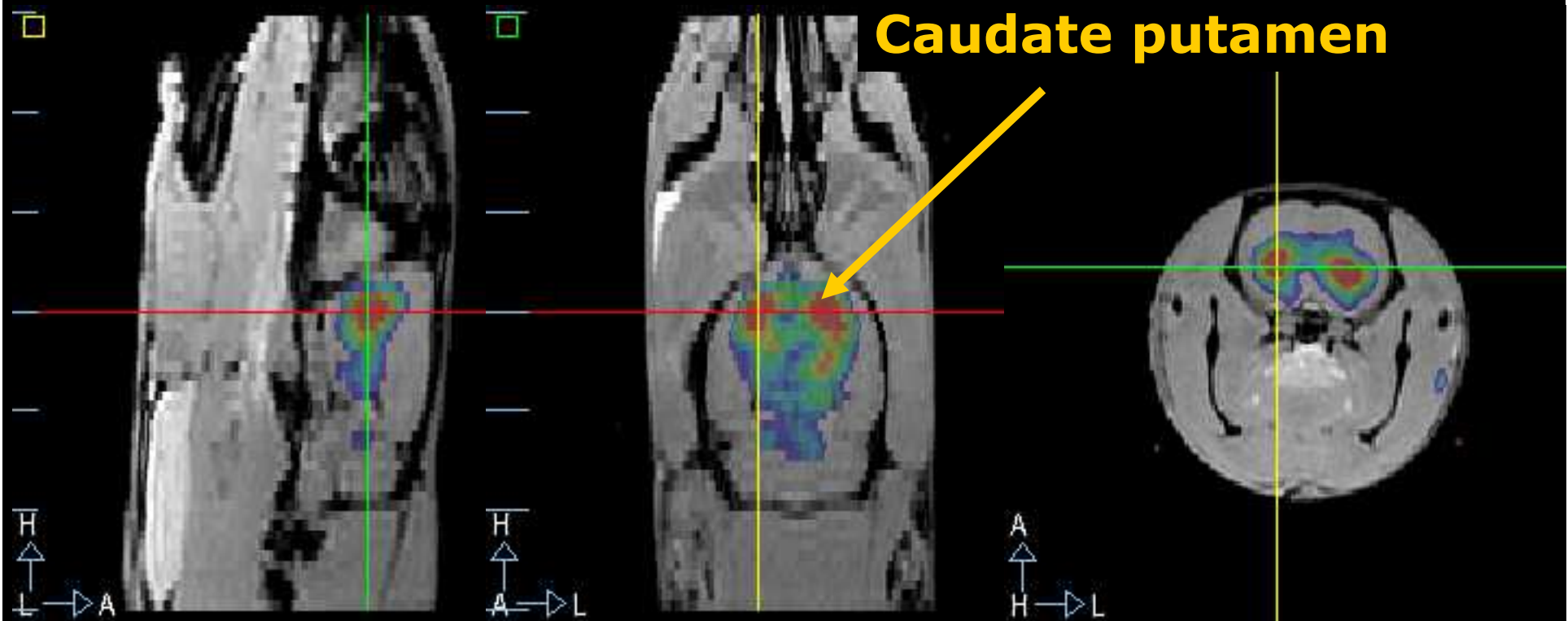
- Anatomical template
 - In tracers with ↑ ↑ specificity



What are we looking at?

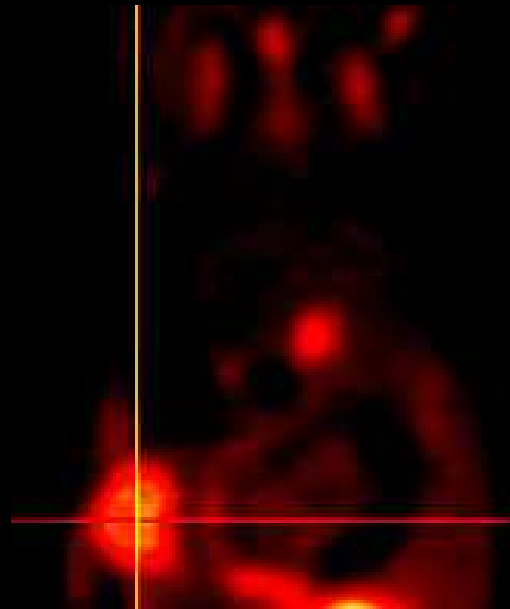
Anatomical Template

- Anatomical template
 - In targets with ↑↑ specificity



Advantages of Multimodality

- Anatomical template
 - In tracers with ↑ ↑ specificity
 - And also with ↓ ↓ specificity !



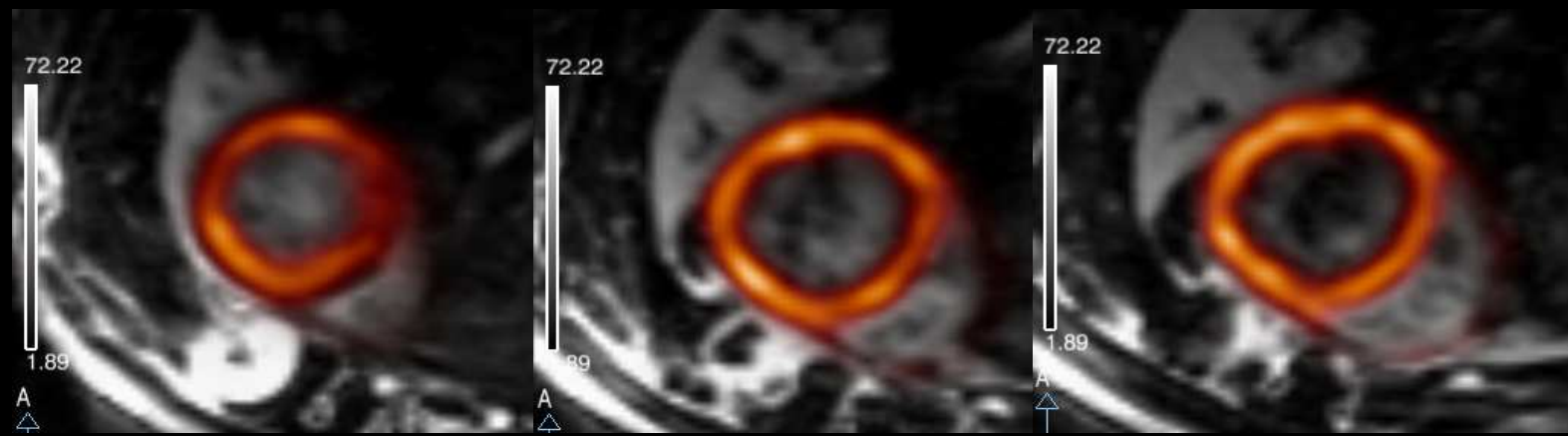
Advantages of Multimodality

- Anatomical template
 - In targets with ↑ ↑ specificity
 - And also with ↓ ↓ specificity!
- Improve the image quality
 - Corrections: Attenuation, Scatter, Partial volume, ...
 - Help in the reconstruction
- Complementary information

Complementary Information

Fused MRI - PET

Control
(SHAM)

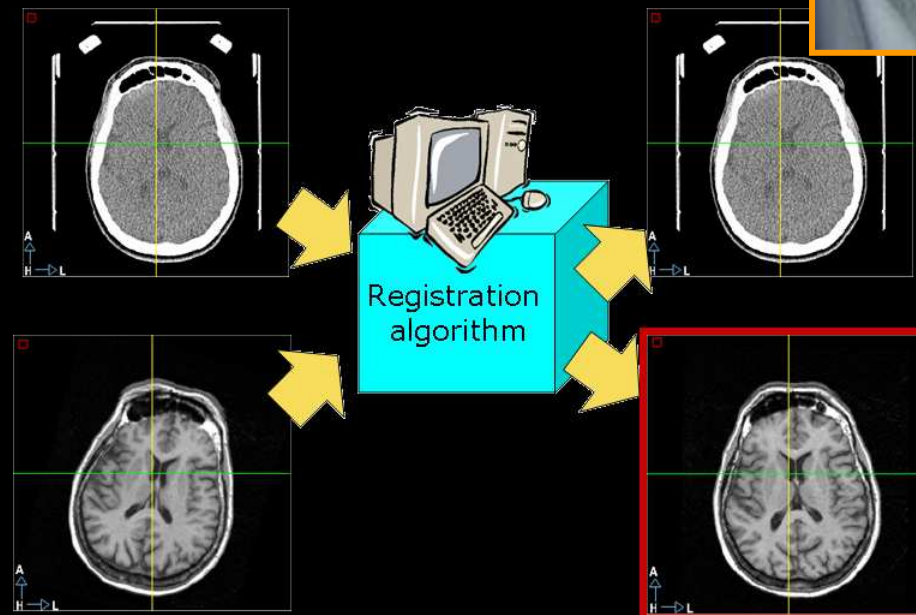


IM



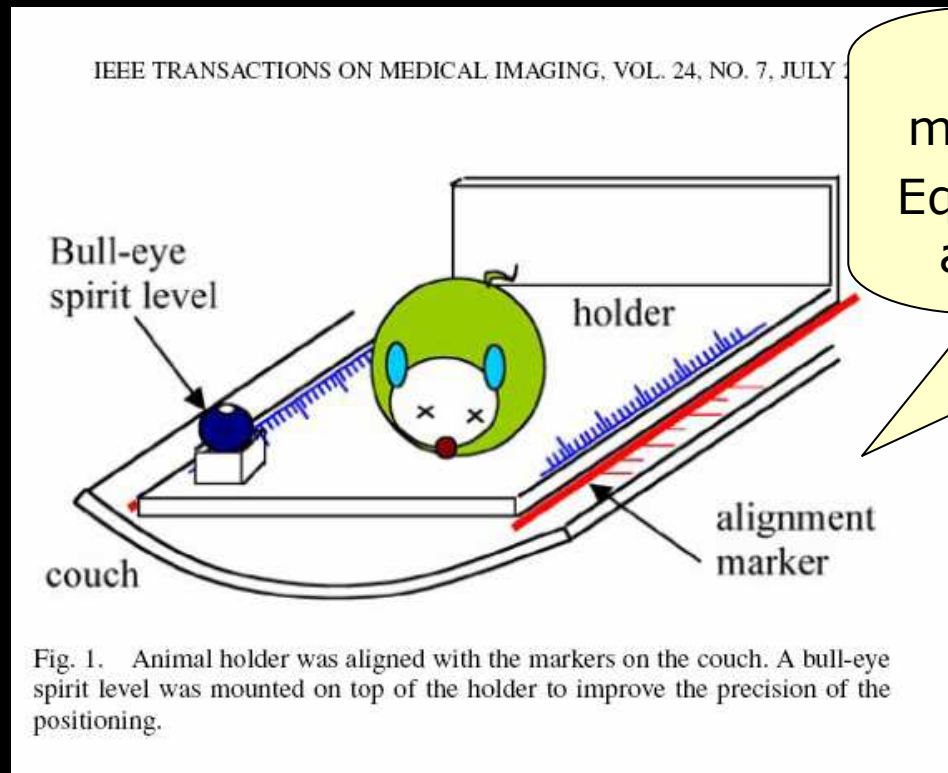
How to Fuse Data?

- “Soft”: registration algorithms
 - No much done in small-animal
 - Extrinsic: based on external markers
 - Intrinsic: based on the content of the



Extrinsic Registration

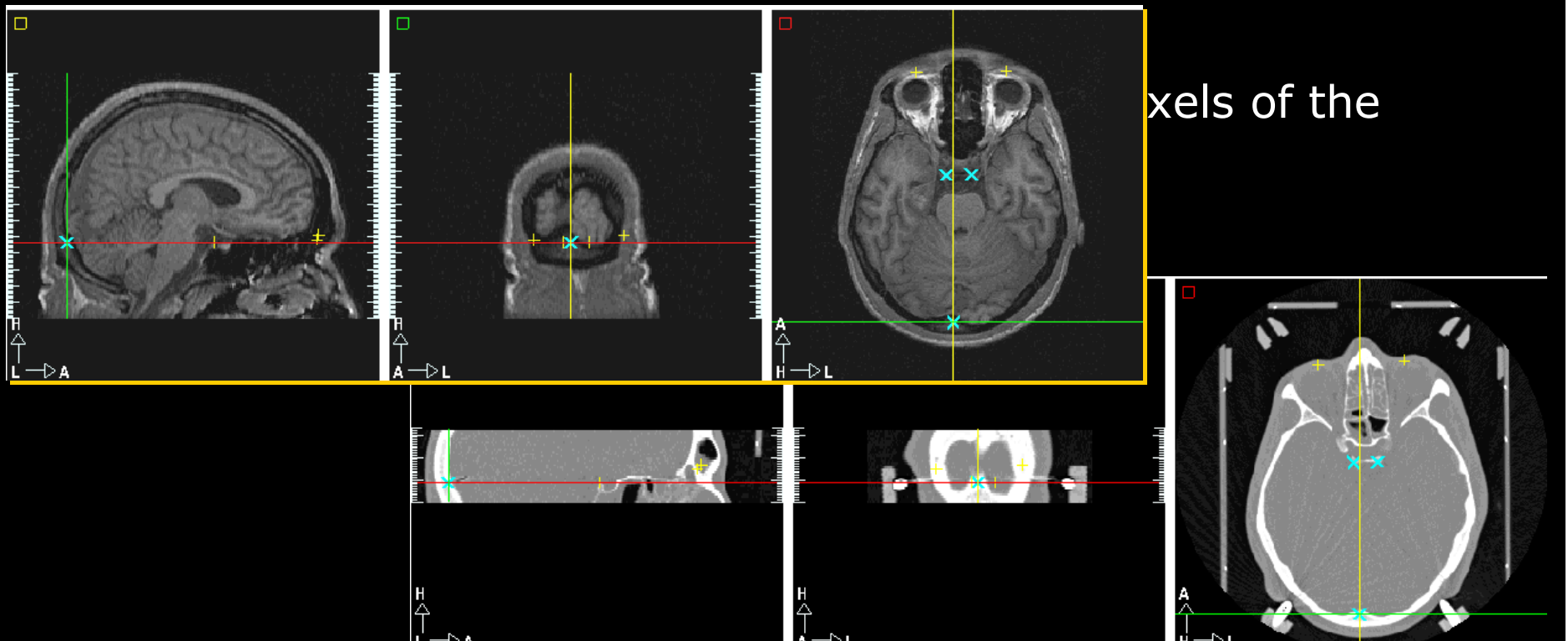
- With external markers (requires previous preparation)
 - Example: Special bed in repeatable position, so as the geometrical transformation is known



The animal should not move between acquisitions
Equipment customization to adapt the calibrated bed

Intrinsic Registration

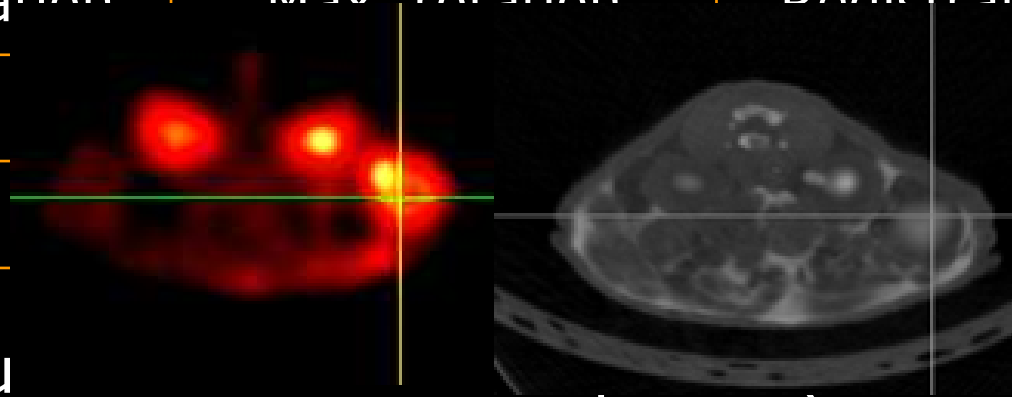
- Intrinsic registration: based on the image content
 - *A priori* decision not required
- Many algorithms
 - Anatomical points (CT, MRI but... NM?)



Difficulties of Automatic Registration

- Dependence on
 - Algorithm parameters
 - Initial position (*'capture range'*)

Max. translation	Max. rotation	Registration OK
10 mm		ases
20 mm		ases



– Manu
based)

– Preprocess (segmentation) to eliminate
the bed

- “Soft”: registration algorithms
- “Hard”: hybrid equipment
 - PET - CT
 - SPECT – CT
 - *PET - MRI*

Multimodality: MRI vs. CT

MRI

- Good contrast
- Difficult to use
- Slow
- Difficult integration
- Expensive
- Non ionizing

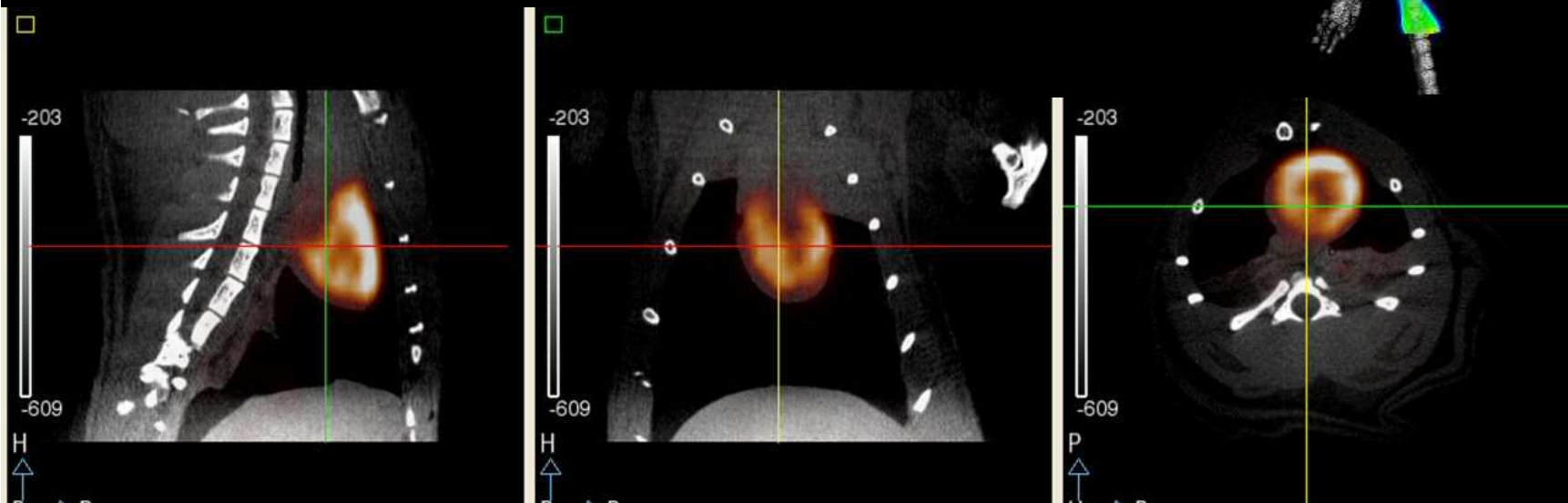
CT

- Low contrast soft tissue
- Easy
- Fast
- Easy to integrate with NM
- Less expensive
- Ionizing radiation

- X-ray CT: anatomical modality preferred for small animal

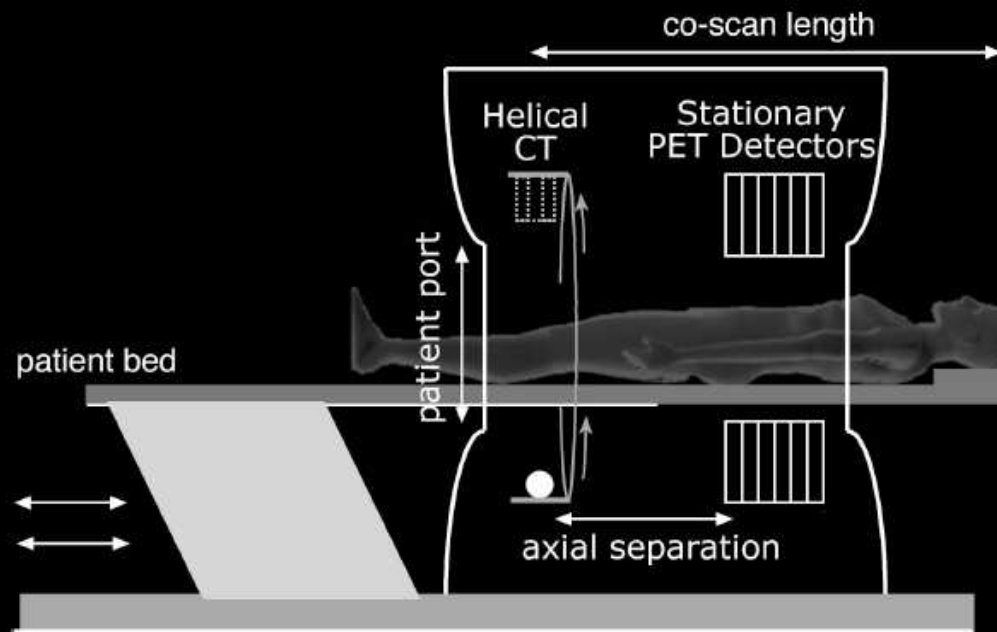
PET/CT in the Same Machine

- Unquestionable clinical interest nowadays
- Even greater in research?

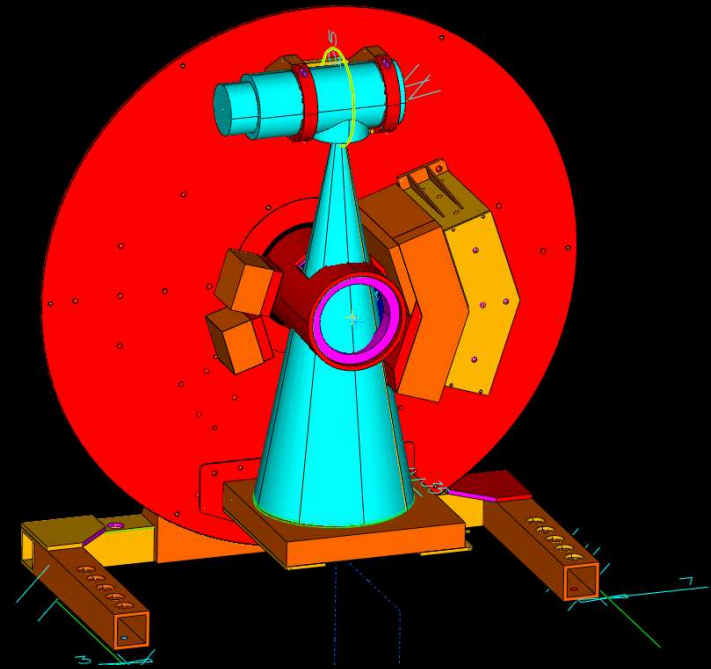


PET/CT in the Same Machine

- Aligned PET and CT are obtained (almost) simultaneously
- First PET/CT (1998) funded by NCI-NIH;

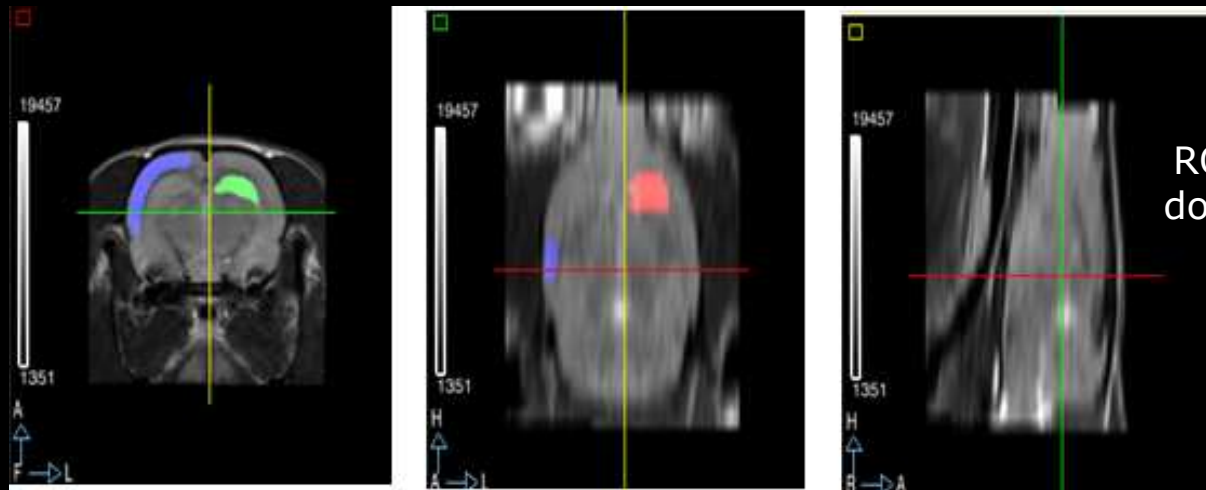


Courtesy of Paul Kinahan



VrPET/CT, Lage et al., 2009

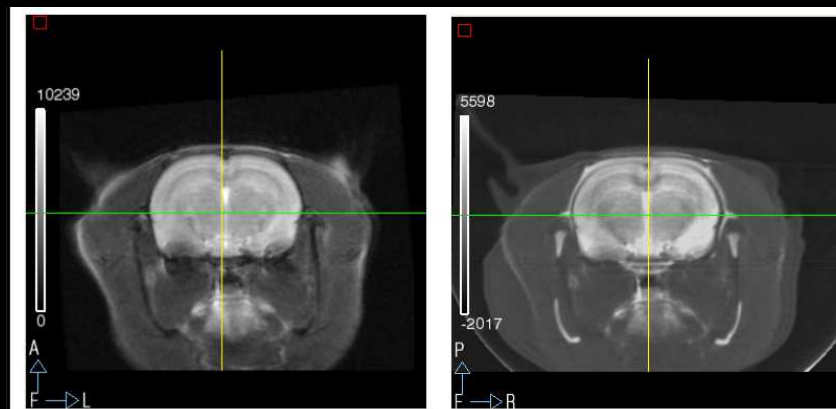
Example MRI – PET/CT



ROIs on MRI: cortex (blue),
dorsal hippocampus (green),
caudate-putamen (red)

MRI (T2)

Fused MRI-CT



PET
analysis

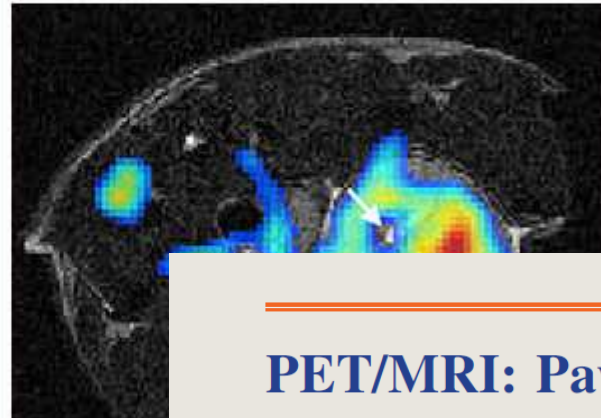
And What About PET/MRI?

Wednesday, March 26, 2008

UC Davis Develops First Combined PET/MRI Tomograph

Filed under: [Radiology](#)

Scientists at UC Davis overcame difficult technical problems and succeeded in building the world's first combined PET/MRI scanner. The two imaging modalities are naturally complementary, as MRI provides information about tissue structure while PET is a functional modality that informs about biological processes.



- Complicated integration (low quality PET)
- Expensive
- Application?

FOCUS ON MOLECULAR IMAGING

PET/MRI: Paving the Way for the Next

Idea: MRI + PET/CT

Multimodality imaging and, more specifically, the combination of PET and CT has matured into an important diagnostic tool. During the same period, concepts for PET scanners integrated into an MR tomograph have emerged. The excellent soft-tissue contrast of MRI and the multifunctional imaging options it offers, such as spectroscopy, functional MRI, and arterial spin labeling, complement the molecular information of PET. The development of a fully integrated PET/MRI system is technologically challenging. It requires not only significant modifications of the PET detector to make it compact and insensitive to magnetic fields but also a major redesign of the MRI hardware.

a clinically viable tool was the introduction of combined PET/CT in 1998 by David Townsend and Ronald Nutt (3-5). Nevertheless, many physicians of that time remained skeptical about the advantages of this dual-modality imaging system over stand-alone PET and CT.

Clinical MRI evolved toward higher fields, faster imaging sequences, and whole-body imaging capabilities. Especially for brain imaging, 3-T MRI is now the standard. Novel coil concepts combined with parallel acquisition techniques helped shorten examination times while maintaining high imaging quality (6).

Thank You!



<http://www.hggm.es/image>