PET Developments and Progress

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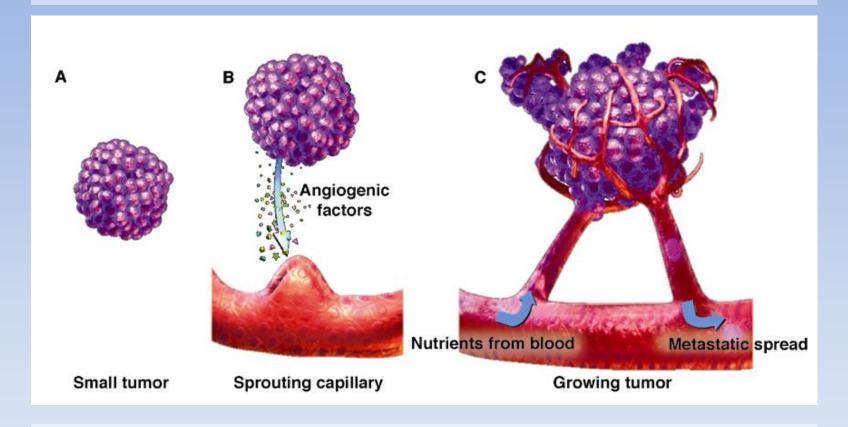
Basics on Positron Emission Tomography

- Metabolism imaging
- Sinogram
- Correcting for detector effects
- Attenuation map
- Quantification

Metabolism imaging

On the metabolism side, cancer cells are very different from normal cells.

They divide much faster and need large amounts of energy to do so.

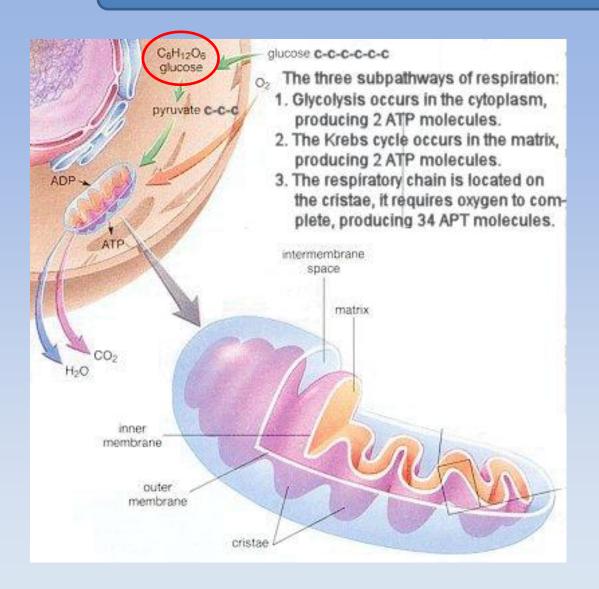


Active tumor = need for energy

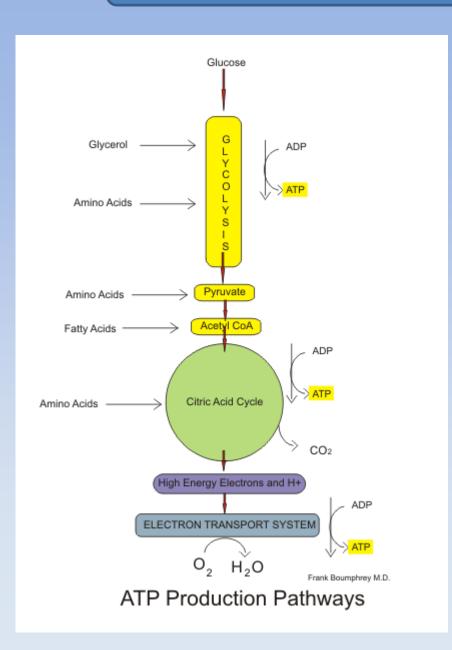
Energy comes from

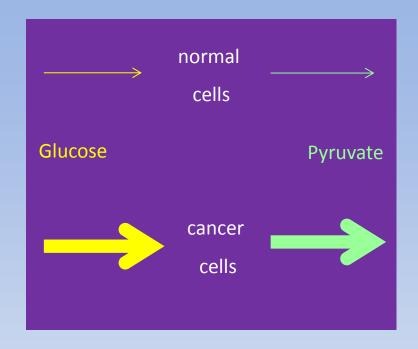
ADP is "recharged" to ATP in the mitochondria

Metabolism imaging

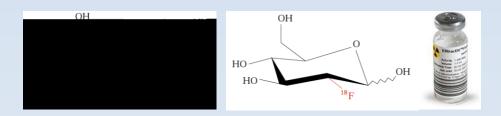


Metabolism imaging

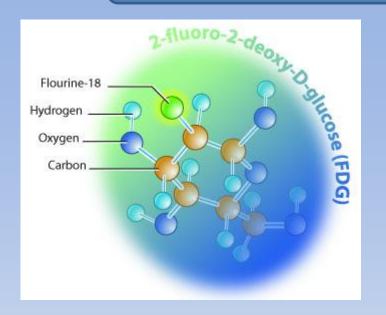




The tracer consists of a molecule analog to glucose associated with a radioactive beta+ emitter.



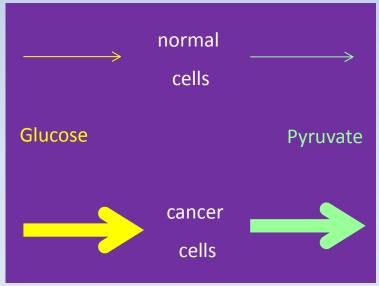
A radiotracer for tumor cells: the 18F-FDG



Because of its slightly different composition, the FDG cannot be metabolized into pyruvate.

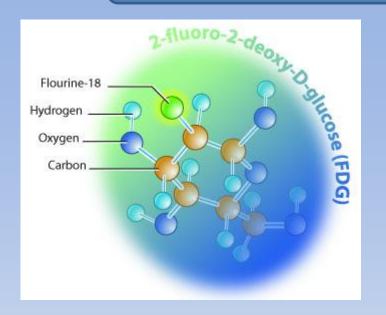
The FDG is absorbed by the cells needing energy as considered as gluco, se but **remains trapped until fluor turns to oxygen**, after the beta decay.

The physiological properties are restored and the FDG can be metabolized. The concentration of FDG is an image of the glucose uptake.





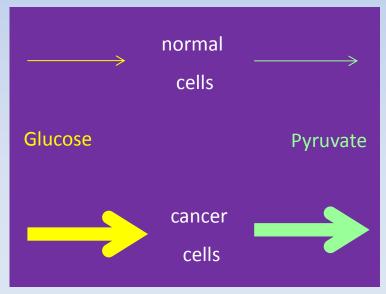
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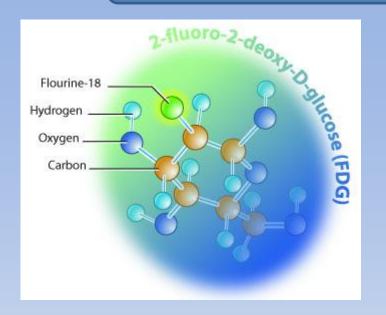
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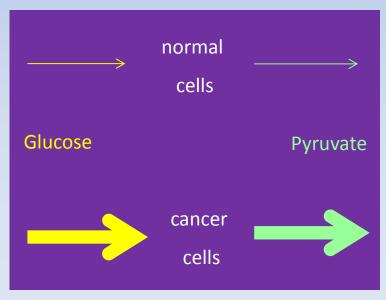
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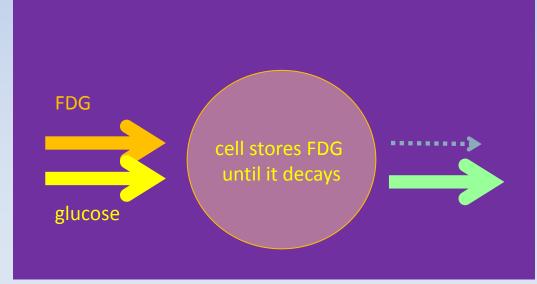


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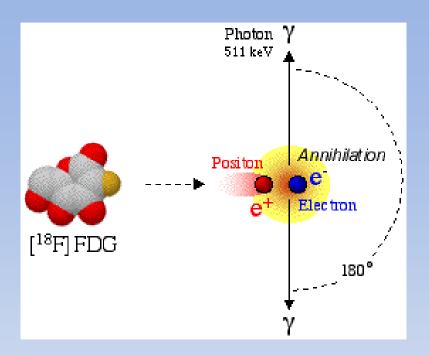
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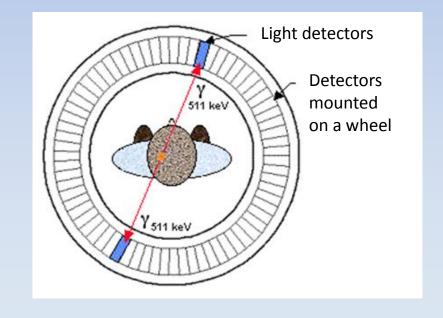


The Positron Emission Tomography

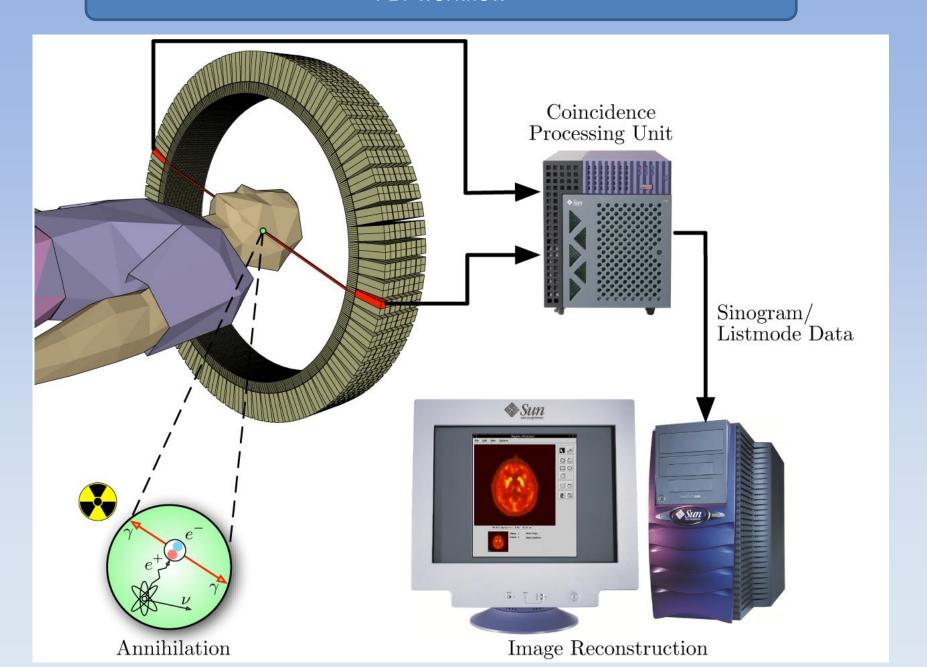


Positron from the fluor 18 nucleus decay losses its energy on a few millimeters in water, then annihilates with a nearby electron (97% of e⁺ annihilations happens at rest). Two 511 keV photons are emitted back to back.

Photon detectors surrounding the patient detects pairs of 511 keV annihilation photons. Data is analyzed and allows to locate the beta+ emitters, where FDG has accumulated.



PET workflow

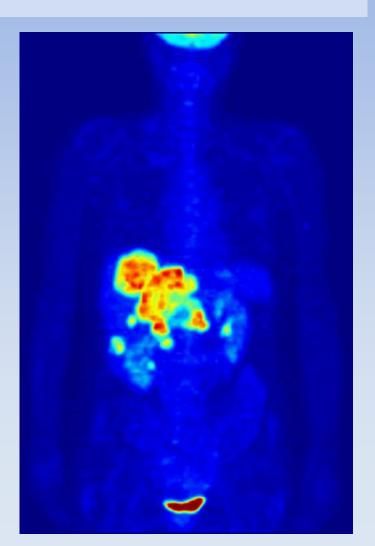


The Positron Emission Tomography

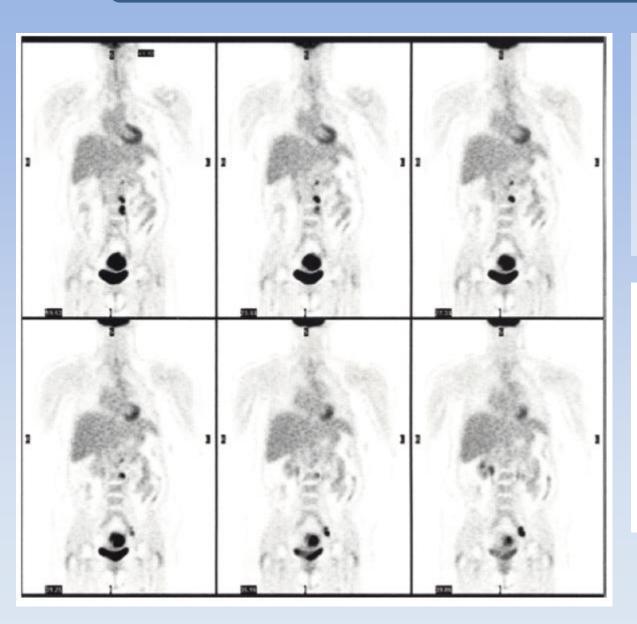
Naïve approach:

Inject patient with specific marker (pure beta+ emitter) and reconstruct images to sign tumors.

| Radiotracers & radiopharmaceuticals | Examples of biomedical applications |
|-------------------------------------|---------------------------------------|
| [¹⁵ O]oxygen | oxygen metabolism |
| [15O]carbon monoxide | blood volume |
| [¹⁵ O]carbon dioxide | blood flow |
| [¹⁵ O]water | blood flow |
| [¹³ N]ammonia | blood flow |
| [¹⁸ F]FDG | glucose metabolism |
| [¹⁸ F]FMISO | hypoxic tissue |
| [¹⁸ F]MPPF | serotonin 5HT _{1A} receptors |
| [¹⁸ F]A85380 | nicotinic acetylcholine receptors |
| [¹⁸ F]FLT | DNA proliferation |
| [¹¹ C]SCH23390 | dopamine DI receptor |
| [¹¹ C]Ro151788 | central benzodiazepine receptor |
| [¹¹ C]PK11195 | peripheral benzodiazepine receptor |
| [¹¹ C]PIB | amyloid plaque: Alzheimer's disease |
| [¹¹ C]AG1478 | EGF receptors |
| [¹¹ C]choline | biosynthesis of phospholipids |



FDG uptake after an injection



Time-lapse Images of 18-FDG Uptake.

Initially, the tracer has high uptake in the cardiac and renal systems.

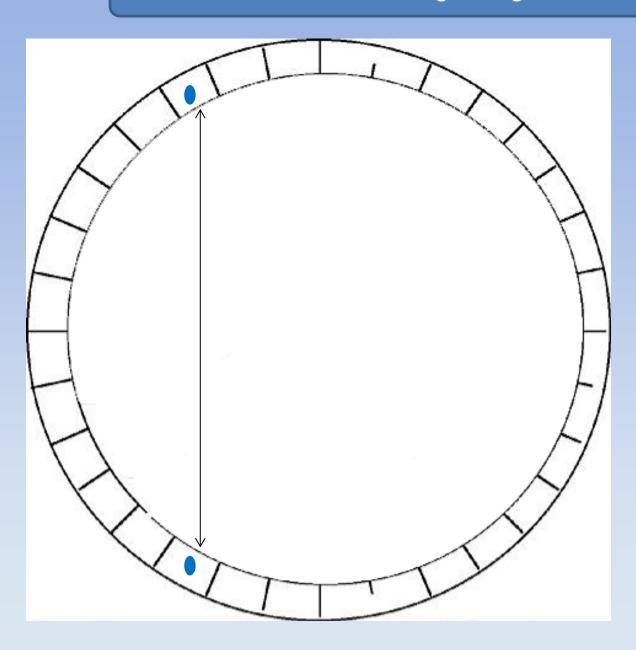
As time goes by, 18-FDG accumulates at the site of the tumor in the lower abdomen.

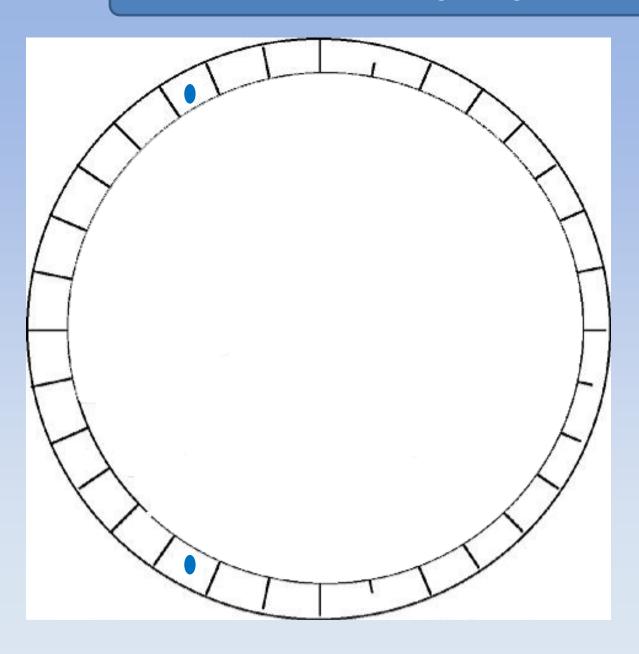
In addition, metabolic imaging detected multiple lymph node metastases along the left iliac and left para-aortic chains. (Driedger)

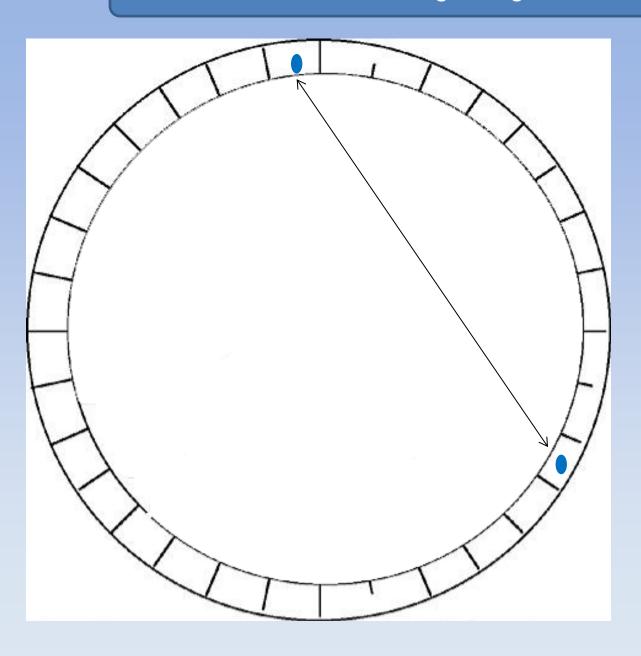
Functional imaging:

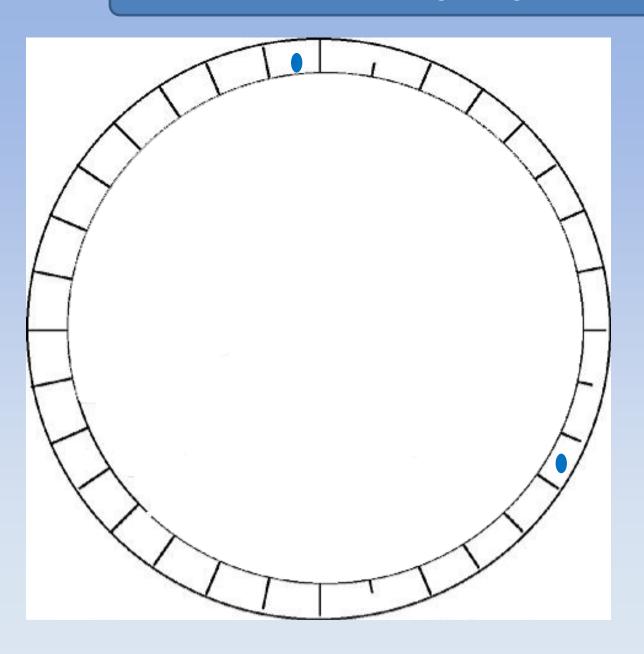
Huge amount of data (>150 Mb per second!!!): can be "projected" on a sinogram or recorded in *listmode*.

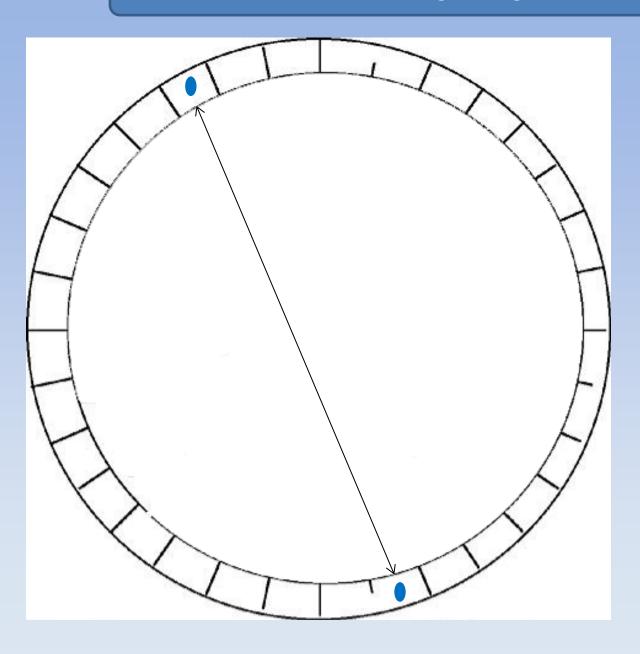
- accumulate data (static image)
- dynamic mode (dynamic images)

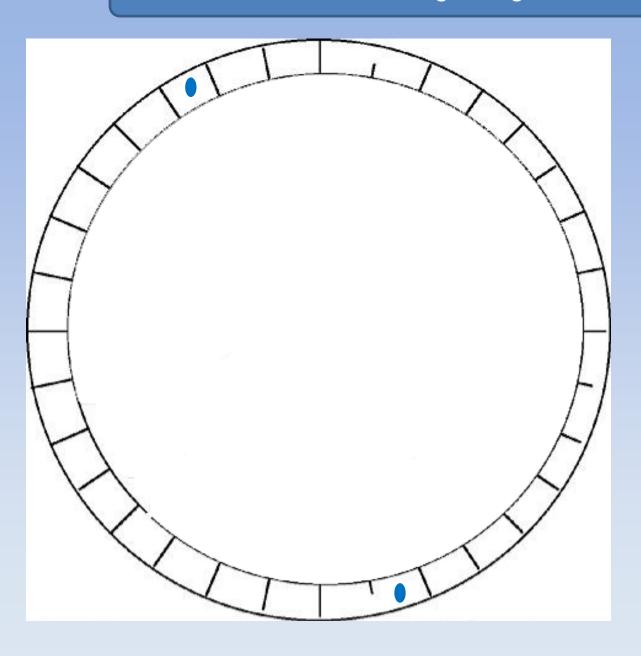


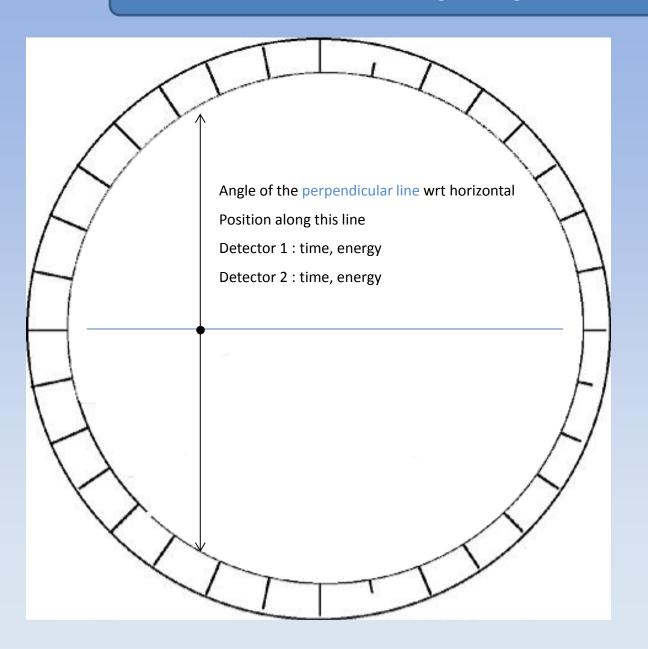


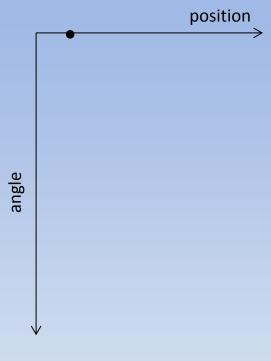


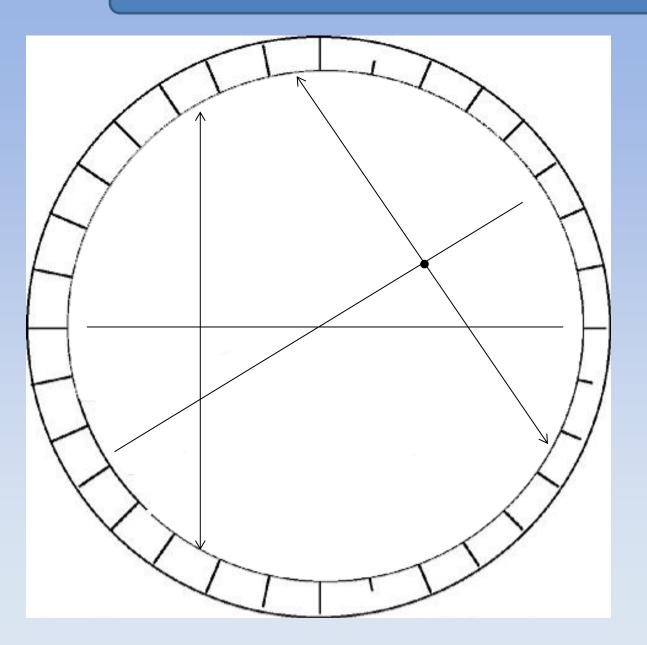


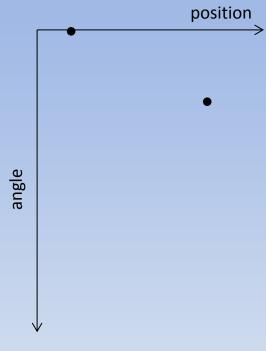


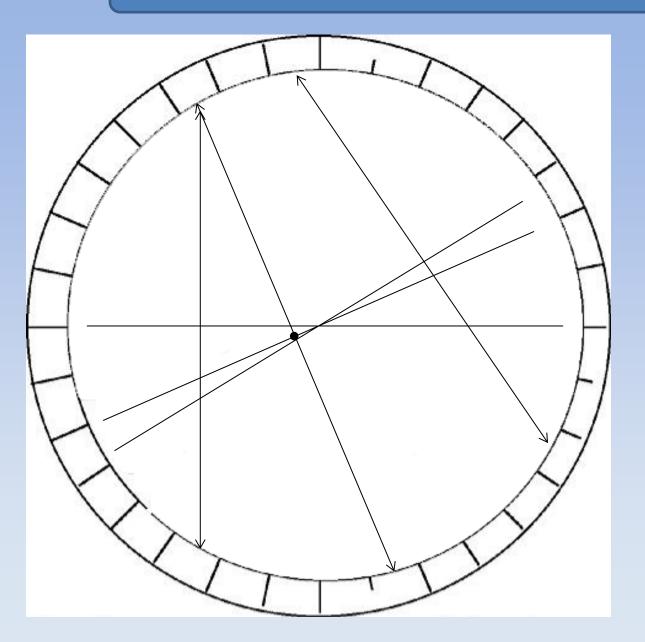


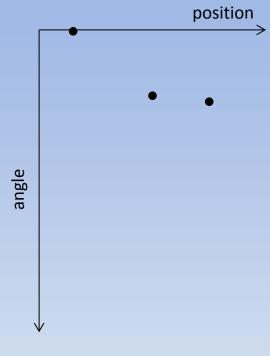


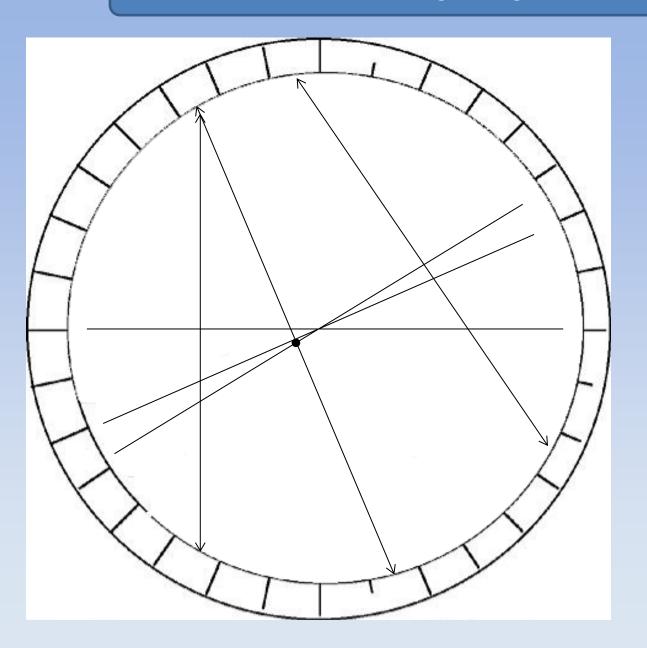


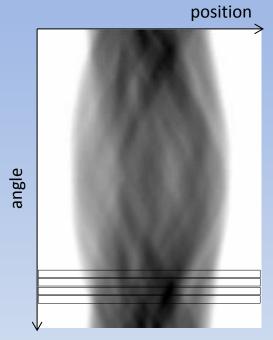










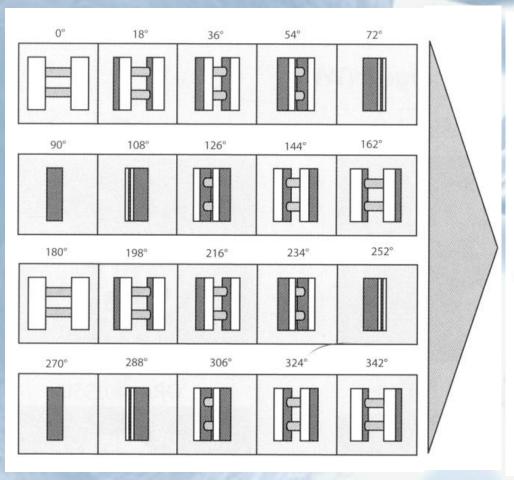


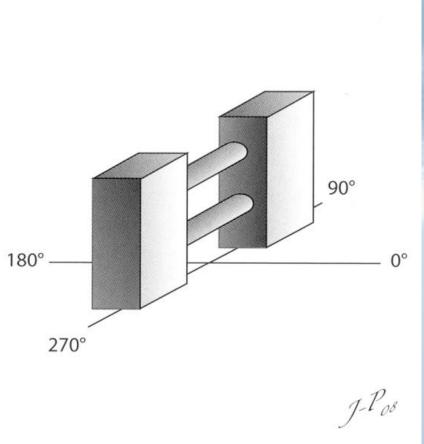
Set of 1D intensities, one for each projection angle



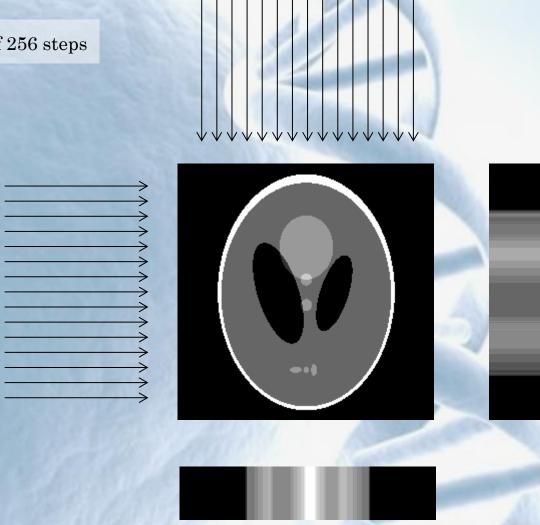
Location of F-18, in 2D

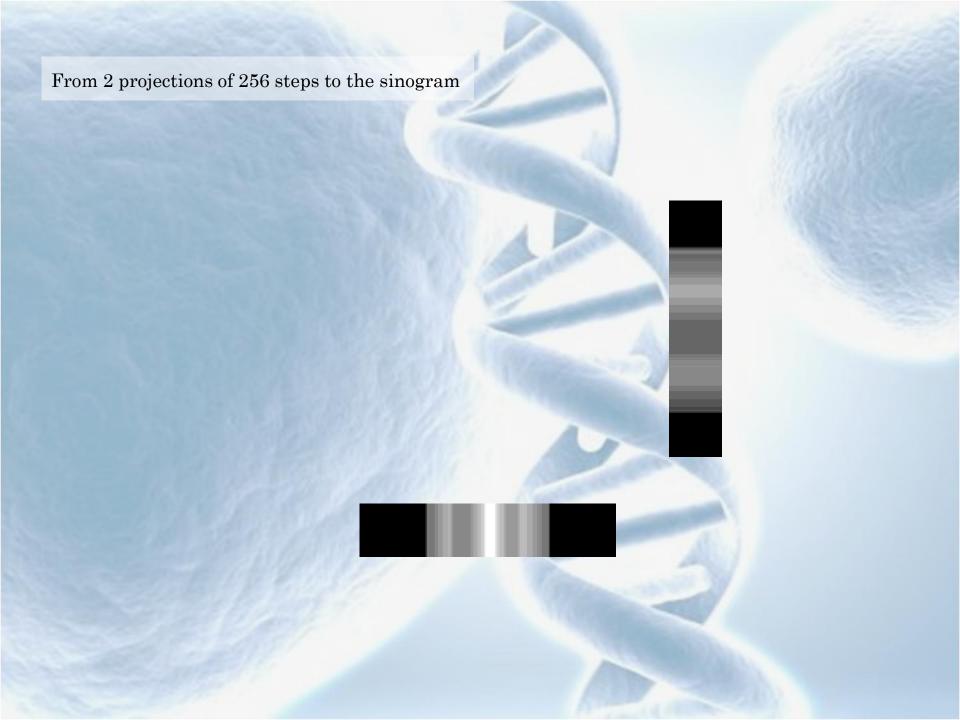
Tomography: how to get an extra dimension (eg: $2D \rightarrow 3D$)?





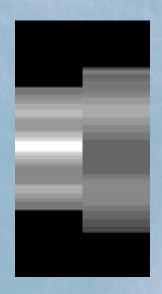
2 projections of 256 steps

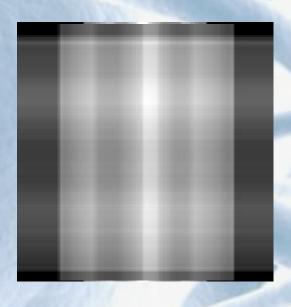


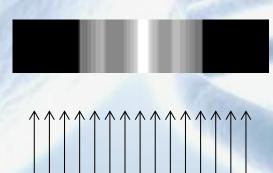


Back propagation of the sinogram with 2 projections







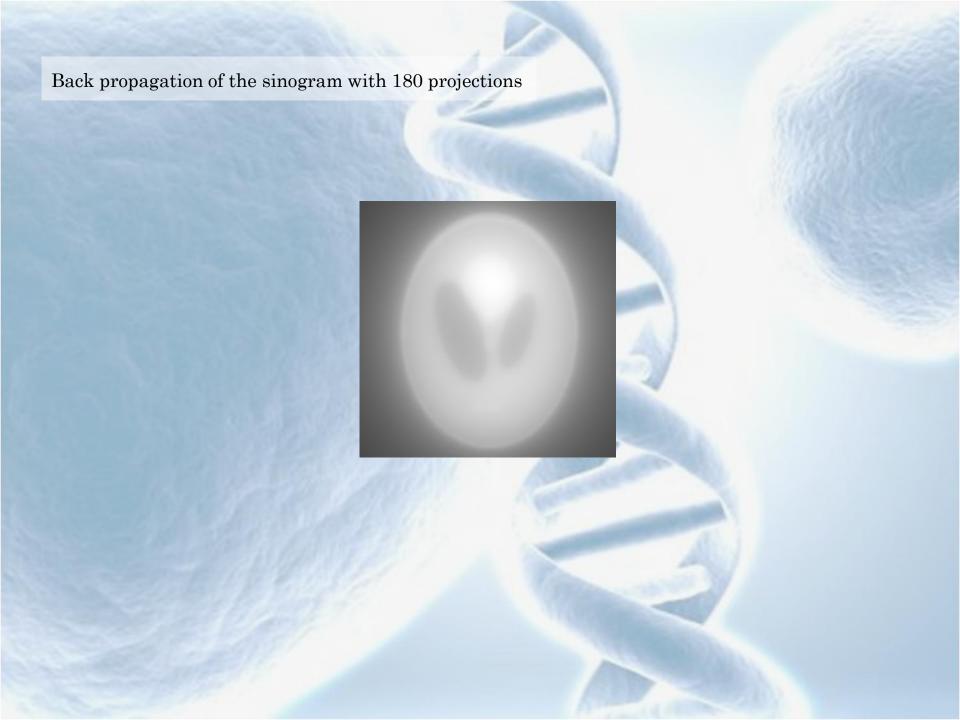


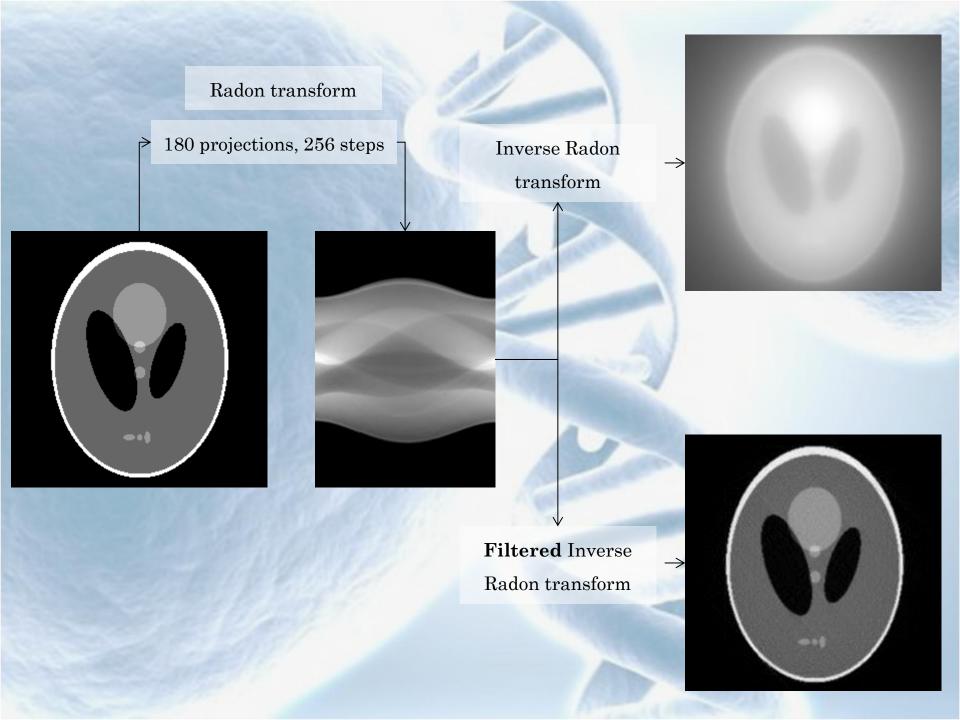


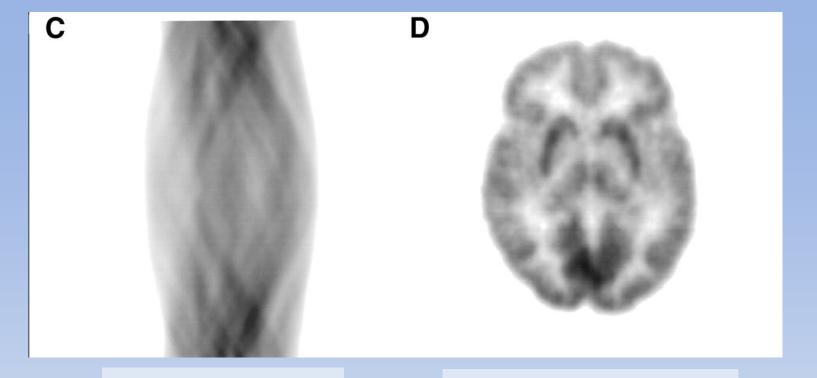
Back propagation of the sinogram with 8 projections

Back propagation of the sinogram with 12 projections







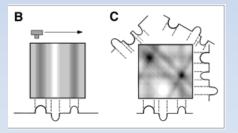


Sinogram (or data in listmode)

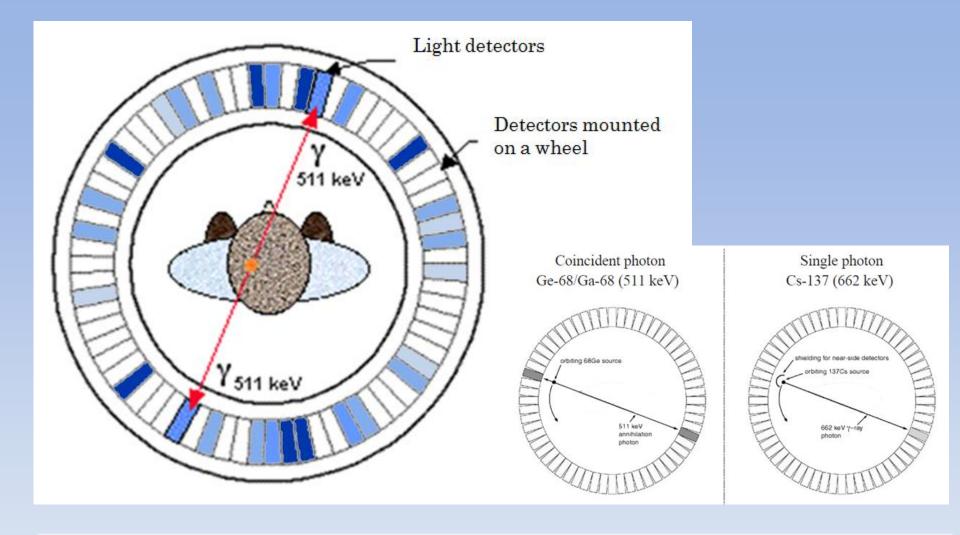
Reconstructed image





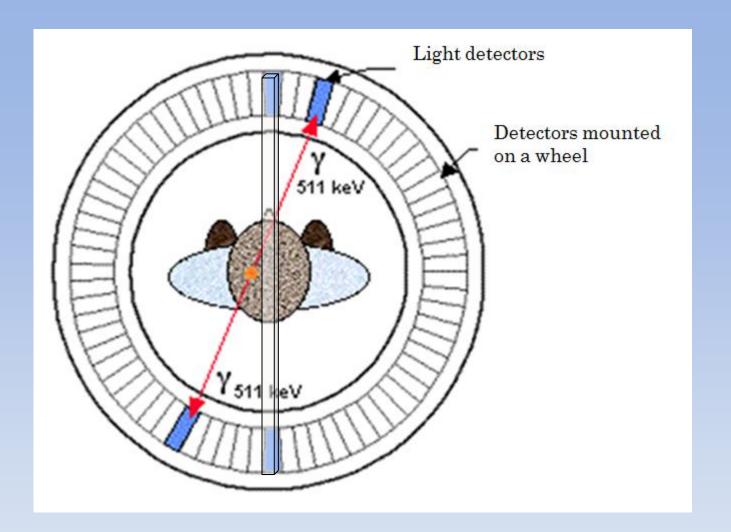


Corrections + Radon inverse transform + filtering + ... or corrections + OSEM 3D (ordered subset expectation maximization)

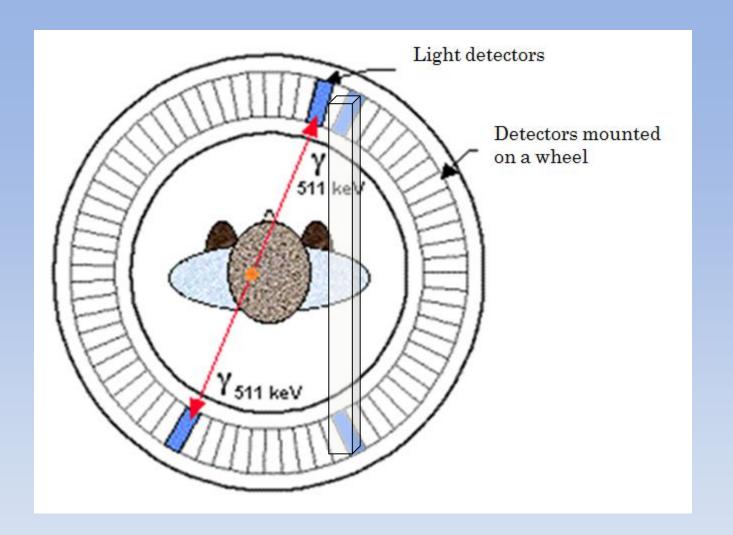


Overall detector response will depend on individual channel gain: need for calibration.

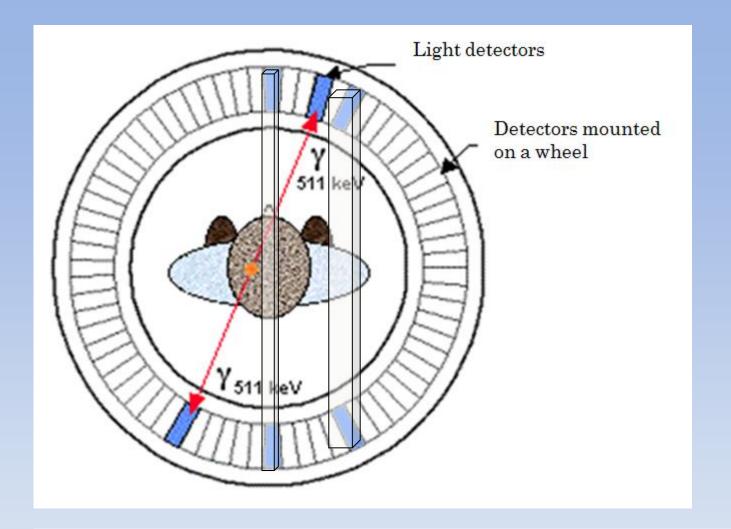
- Blank acquisition (noise)
- Calibration with a gamma emitter (energy close to 511 keV) rotating all around the detector ring



Line of response is indeed a volume of response

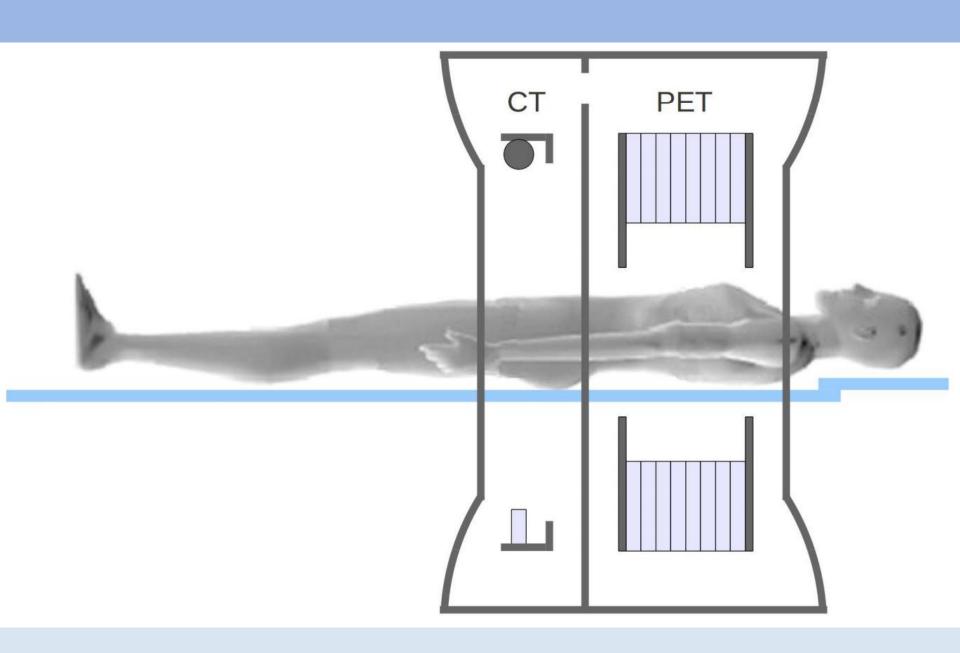


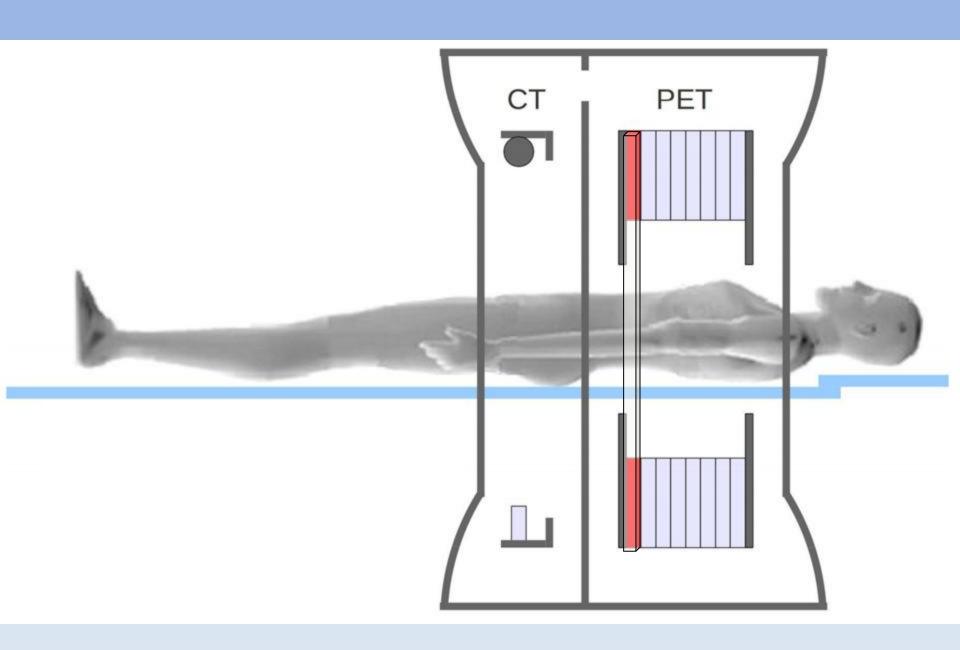
Volume of response depends on the source location w.r.t. the arc structure

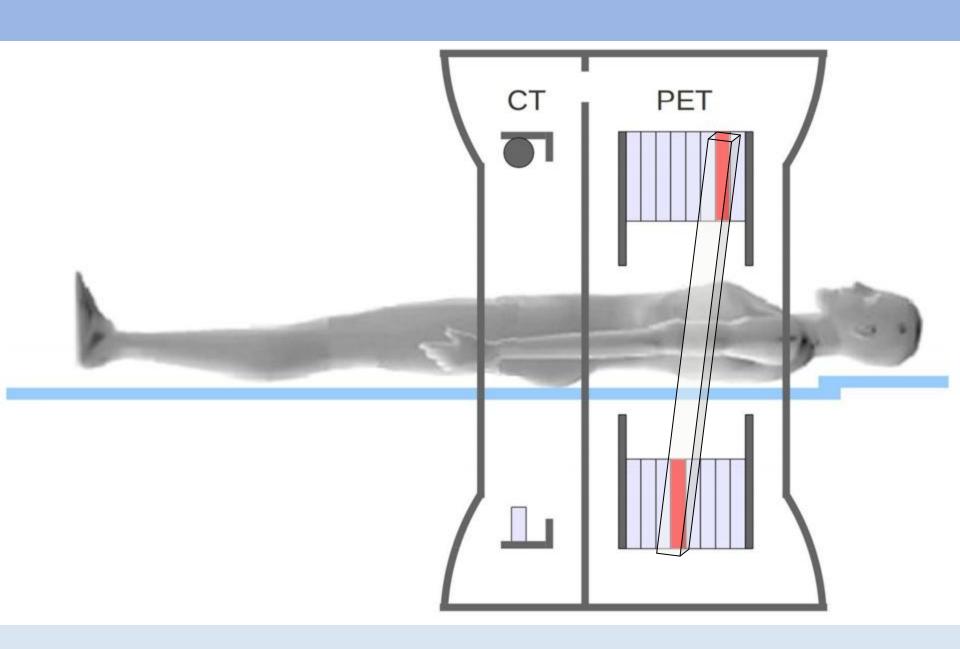


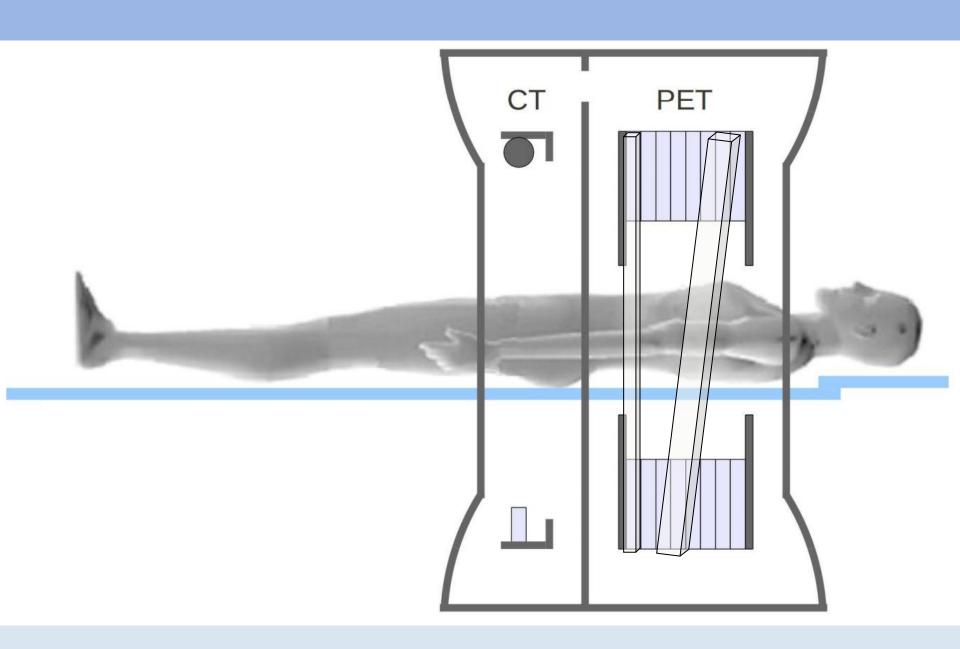
Intensity of response and spatial accuracy will depend on the off-axis position of the emitter

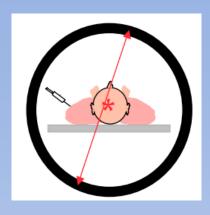
- Geometrical corrections : use Ge-68 to activate all possible LOR situations
- Spatial resolution could be improved by measuring the Depth of Interaction (DOI)



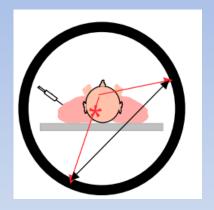












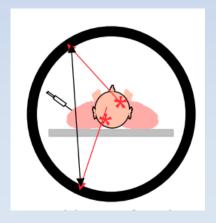
Scattered coincidence: useless information

Bad localization

Decreases contrast

Bias in quantification

Reduced by measuring the photon energy



Random coincidence: useless information

Bad localization

Decreases contrast

Dead time

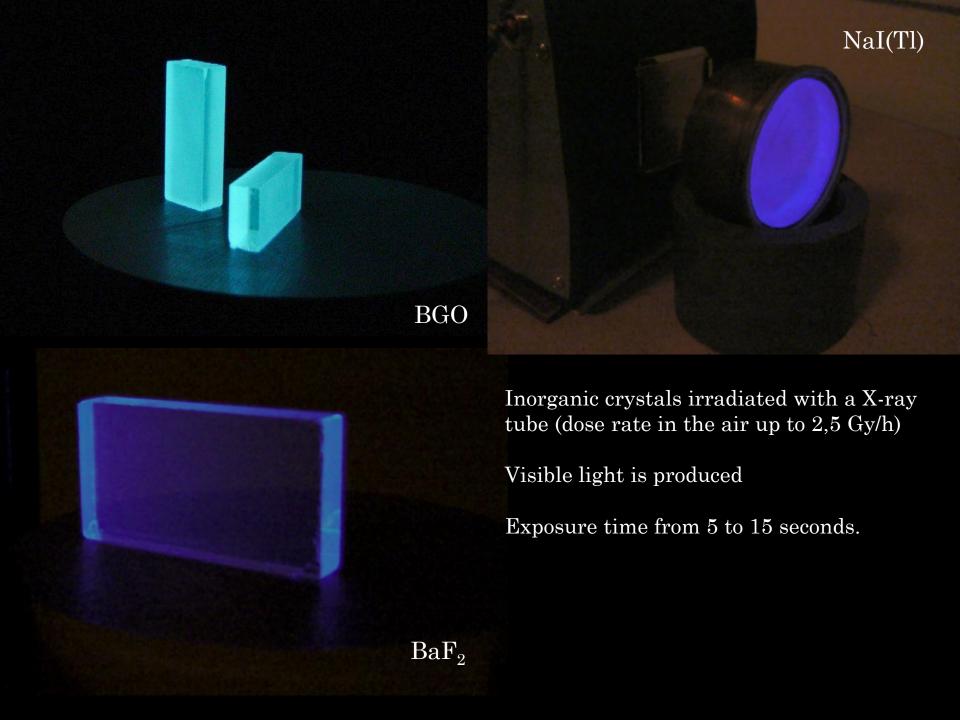
Bias in quantification

Reduced by accurate timing measurement

How to get signal from 511 keV photon interactions?

X photons cannot be directly detected: first need an interaction medium

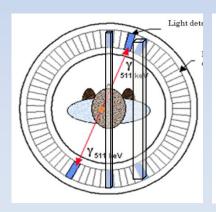
Inorganic scintillators provide visible light that can be detected

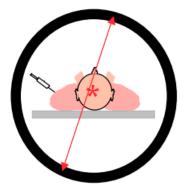


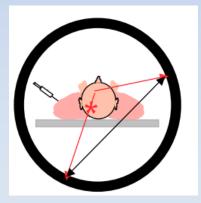
Scintillator: Light production from 511 keV photon interaction

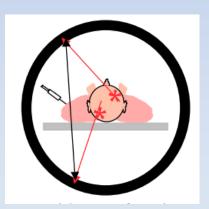
X photons cannot be detected : first need an interaction medium to generate visible photons Specification :

- Photon energy converted in a tiny volume: high stopping power (small X₀)
- Short light pulse: remove random coincidences and decrease dead time
- Good energy resolution : remove scattered events
- Light yield and wavelength matching with visible light detector sensitivity
- Stability versus accumulated dose
- Reasonable price









Scintillator: Light production from 511 keV photon interaction

| | NaI(Tl) | BaF ₂ | BGO | LSO | GSO | LYSO | LaBr ₃ |
|---------------------------------------|---------|------------------|------|------------------|------|------|-------------------|
| Effective atomic no. (Z) | 51 | 54 | 74 | 66 | 59 | 60 | 47 |
| Linear attenuation coeff. (cm^{-1}) | 0.34 | 0.44 | 0.92 | o.8 ₇ | 0.62 | o.86 | 0.47 |
| Density (gm cm ⁻³) | 3.67 | 4.89 | 7.13 | 7.4 | 6.7 | 7.1 | 5.3 |
| Index of refraction | 1.85 | _ | 2.15 | 1.82 | 1.85 | 1.81 | 1.88 |
| Light yield (% NaI(Tl)) | 100 | 5 | 15 | 75 | 30 | 8o | 160 |
| Peak wavelength (nm) | 410 | 220 | 480 | 420 | 430 | 420 | 370 |
| Decay constant (ns) | 230 | 0.8 | 300 | 40 | 65 | 41 | 25 |
| Hydroscopic | Yes | Slight | No | No | No | No | No |

LYSO(Ce) is very similar to LSO(Ce) except that the crystal growing process is slightly different and with less impurities at the end. LYSO properties drift w.r.t. accumulated dose is reduced.

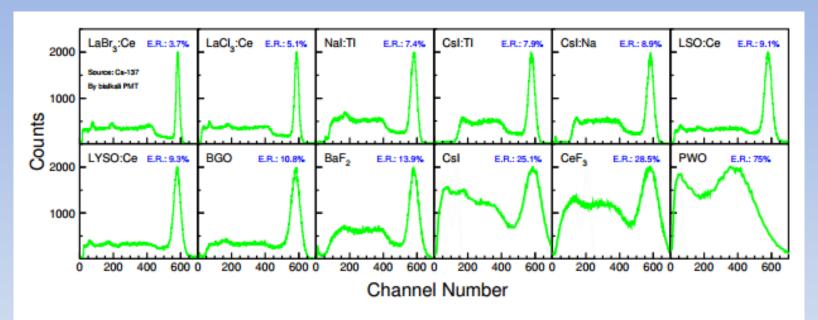
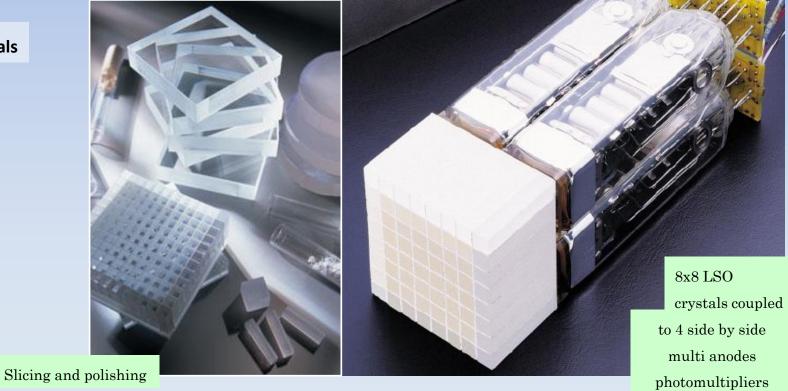


Figure 3. 137 Cs γ -ray pulse hight spectra measured by a Hamamatsu R1306 PMT are shown for twelve crystal samples. The numerical values of the FWHM resolution (E.R.) are also shown in the figure.



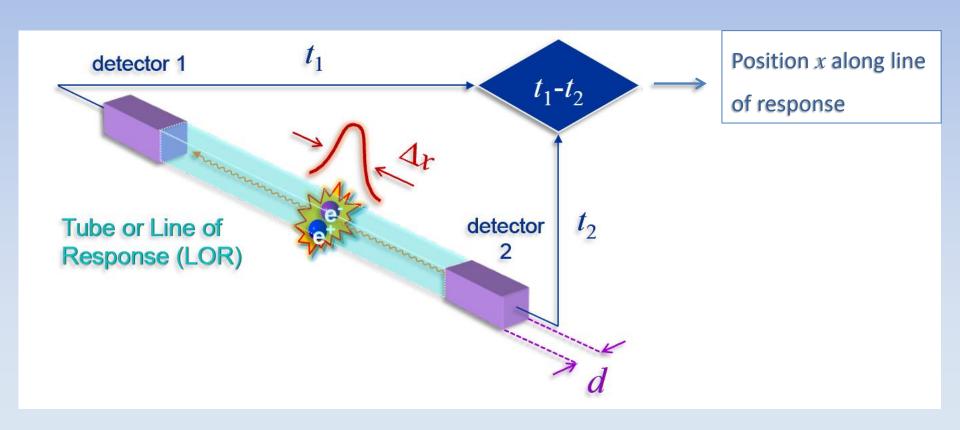
LSO crystals

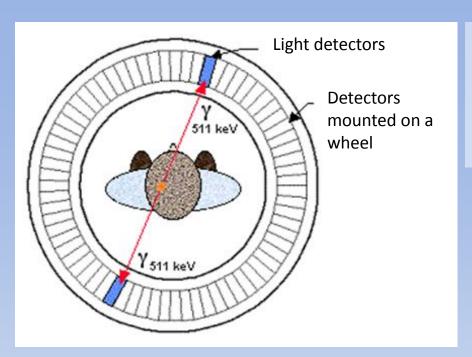


Energy resolution to reject scattered coincidences, timing to reject random coincidences

Could timing also help in image reconstruction?

Introducing Time of Flight

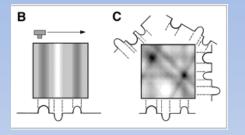


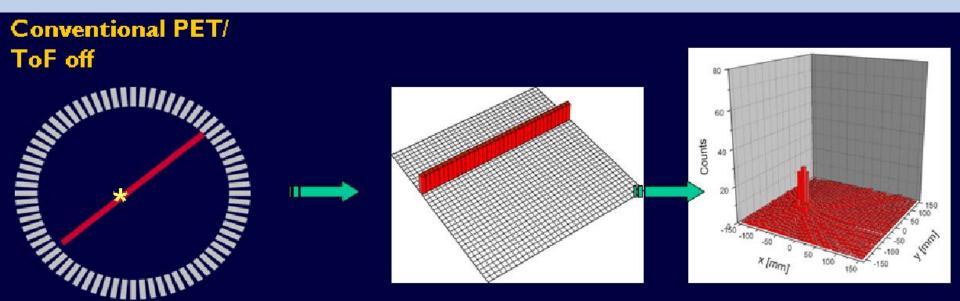


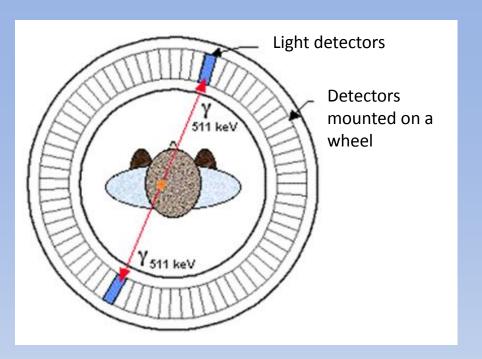
Light detectors are not (yet) fast enough:

the annihilation point cannot be reconstructed...

... only lines of response are

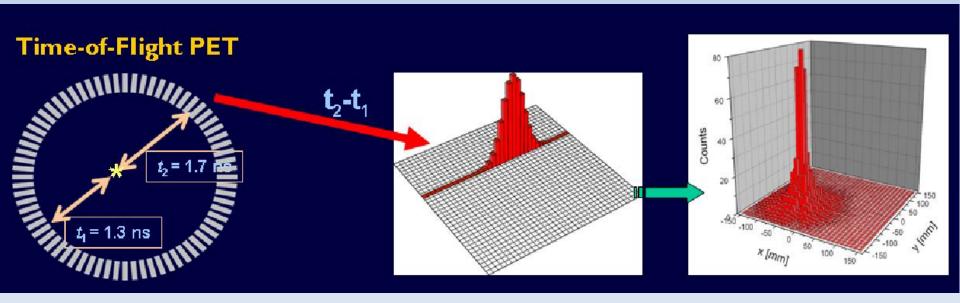






State of the art : resolution down to 500 ps

 $\Delta x = 7.5 \text{ cm}$



Visible light photodetectors

Requirements:

- Wavelength sensitivity in accordance with light from crystals
- High gain & quantum efficiency
- Small rise time
- Low noise
- behavior in magnetic field if used near magnetic devices (MRI)

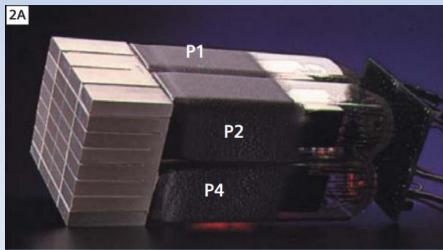
| | PM | APD | SiPM* |
|--------------------------------|-----------------------------------|-----------------------------------|-----------------------------------|
| Gain | 10 ⁴ - 10 ⁶ | 10 ² - 10 ³ | 10 ⁴ - 10 ⁶ |
| Additional preamplifier needed | no | yes | no |
| Multi channels | yes | yes | yes |
| Timing resolution | 300 ps | 1 ns | 190 ps |
| Works in B | no | yes | yes |
| Gain | stable | Gain | dark current, Gain |
| Cost | | | \$\$\$ |

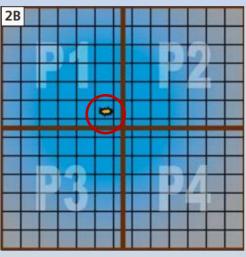
^{*}Geiger Mode APD = Silicon PhotoMultiplier. Large gain, needs quenching after initiating the avalanche

Multi anodes photomultipliers

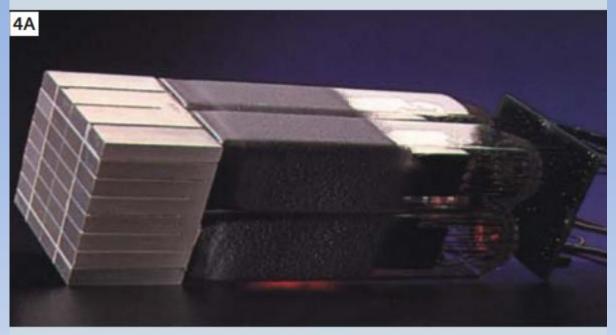


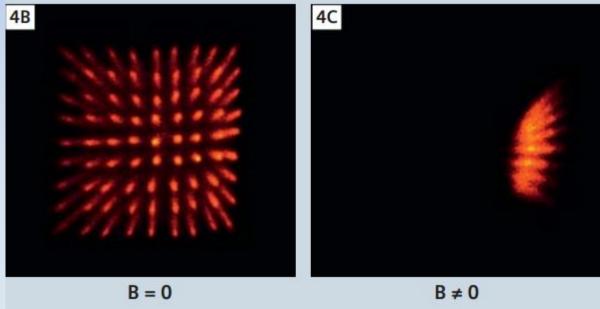
Use Anger weighting algorithm on measured signals: position of interaction of the incoming annihilation photon





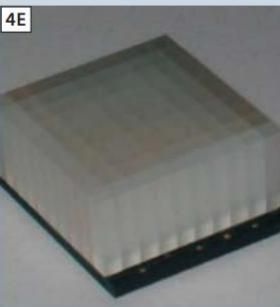
Conventional PET detectors

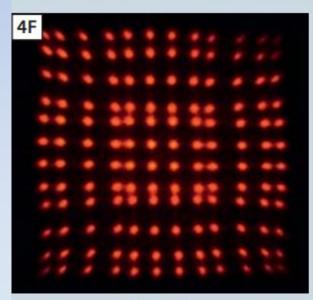


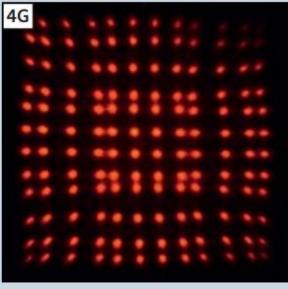


APD-based PET detectors





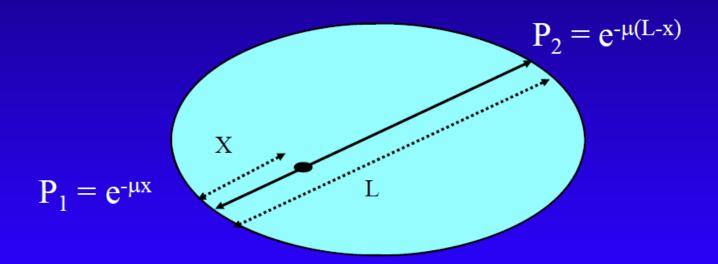




 $B = 0 B \neq 0$

4 Conventional PET detectors (A) are based on scintillation crystals and Anger-logics readout. They work only outside magnetic fields (B). If a PMT is operated inside a magnetic field (B ≠ 0) then the multiplier step is construed and the readout map severely distorted (C). Avalanche photodiodes (APD) based detectors (D, E) are semiconductors that can be operated in magnetic fields, even at ultra-high field strengths (F, G). (Image courtesy of Prof. B. Pichler, University of Tübingen, Germany.)

PET Attenuation Correction

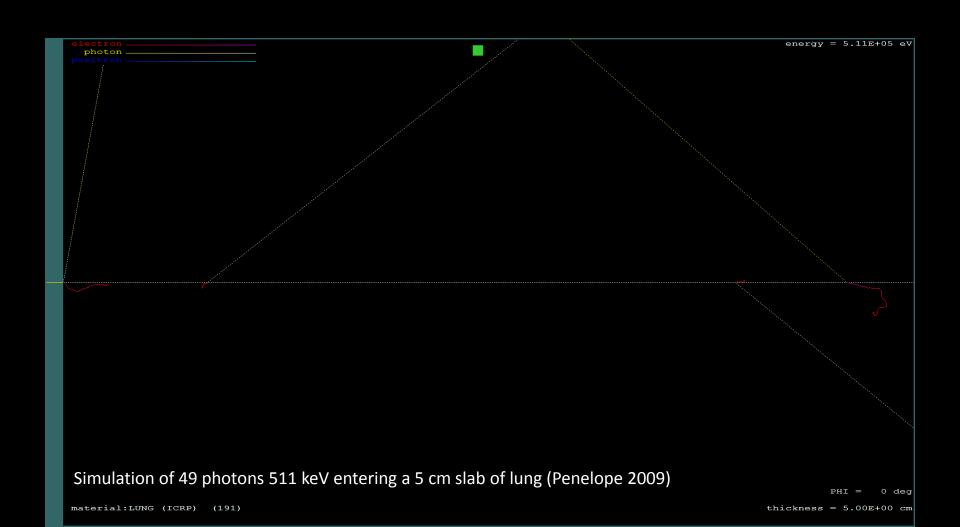


Reconstruction algorithm needs integrated attenuation for each LOR

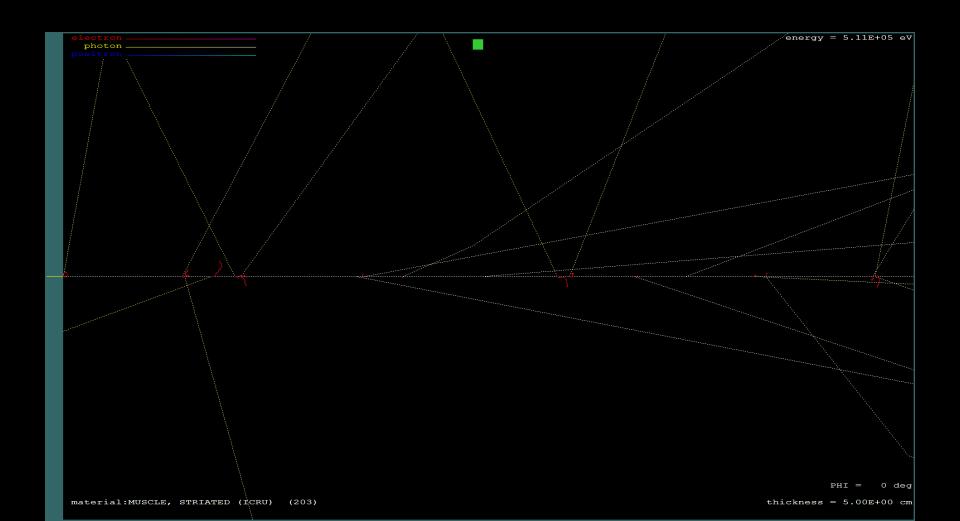
$$P_{\text{TOT}} = P_1 \times P_2$$
$$= e^{-\mu L}$$

Photons do interact with matter: mostly with atomic electrons

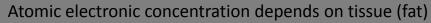
Atomic electronic concentration depends on tissue (lung)

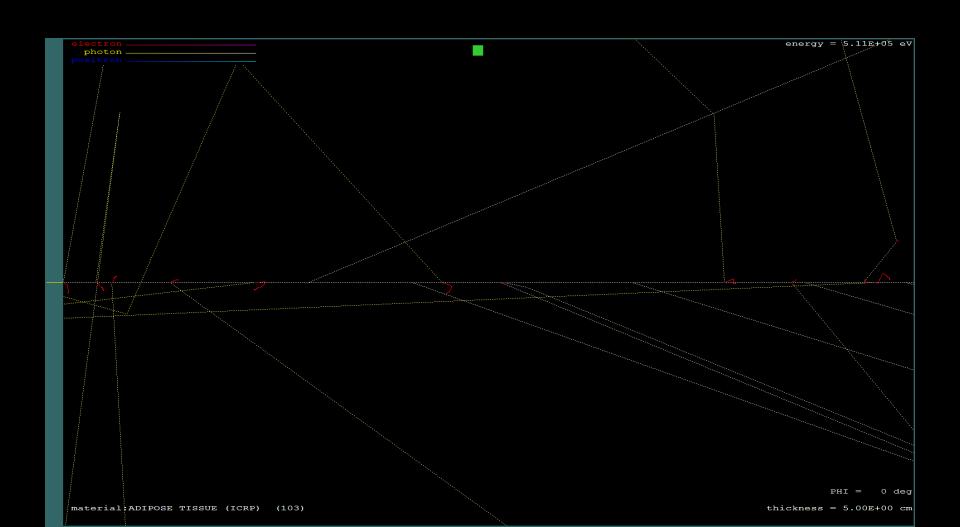


Photons do interact with matter: mostly with atomic electrons Atomic electronic concentration depends on tissue (muscle)



Photons do interact with matter : mostly with atomic electrons



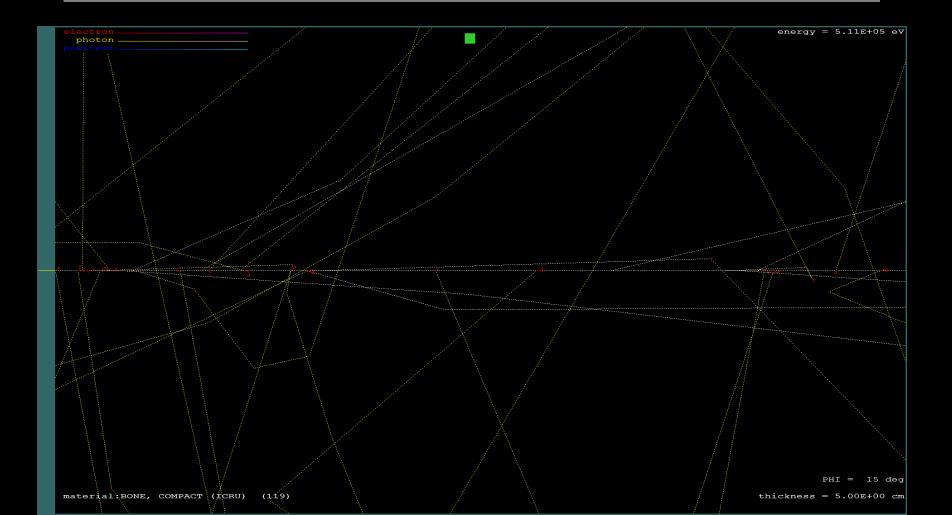


Photons do interact with matter: mostly with atomic electrons

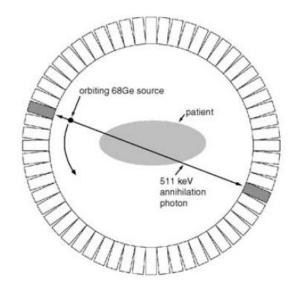
Atomic electronic concentration depends on tissue (bone / fat / muscle / lung, ...)

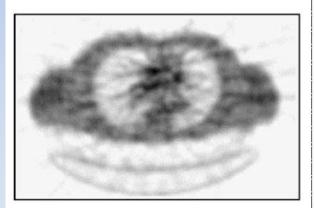
Atomic electronic concentration has to be measured all along the possible path of annihilation photons

= tissue content in terms of electronic concentration has to be determined



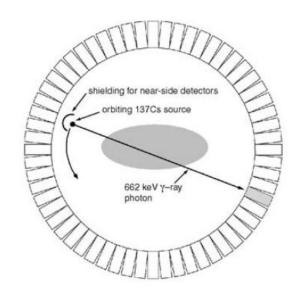
Coincident photon Ge-68/Ga-68 (511 keV)

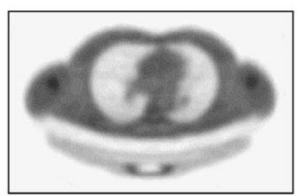




high noise
~12-45 min scan time
no bias
lowest contrast

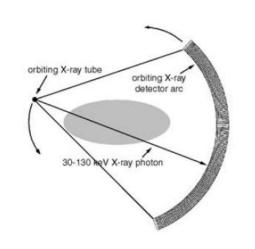
Single photon Cs-137 (662 keV)

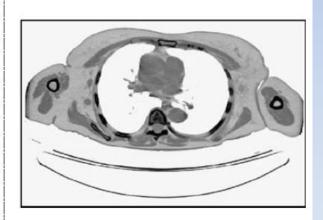




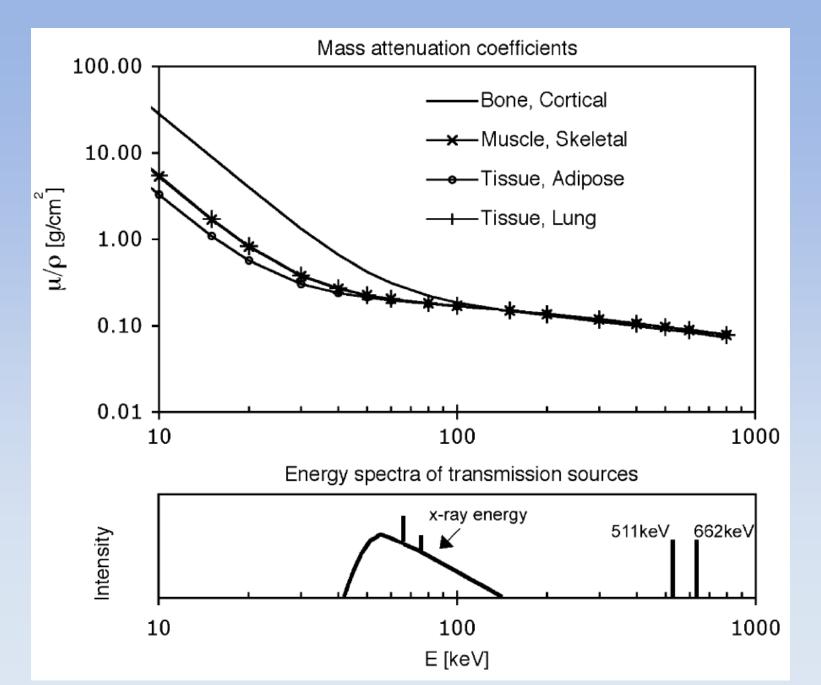
lower noise
~4-20 min scan time
some bias
lower contrast

X-ray (~30-140kVp)





no noise
~20 sec scan time
potential for significant bias
high contrast



Haunsfield Unit scale

The Hounsfield Unit (HU) scale is a linear transformation of the linear attenuation coefficient measurement into one in which the radiodensity of distilled water (at standard pressure and temperature) is defined as zero HU, while the radiodensity of air at STP is defined as - 1000 HU. For a material X with linear attenuation coefficient μ_X , the HU value is therefore given by:

$$HU = \frac{\mu_X - \mu_{water}}{\mu_{water} - \mu_{air}} \times 1000$$

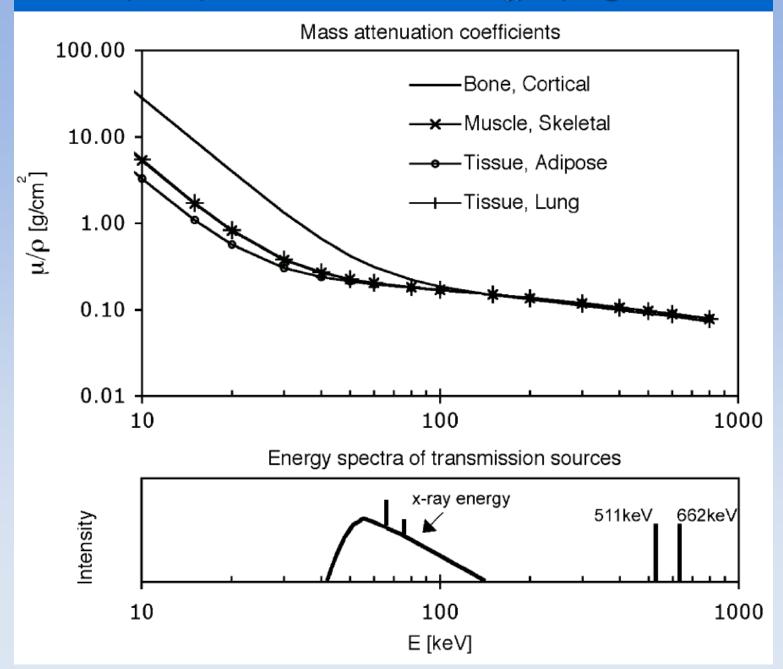
Computed Medical Imaging Nobel Lecture, 8 December 1979 Godfrey N. Hounsfield J Radiol. 1980 Jun-Jul;61(6-7):459-68

where μ_{water} and μ_{air} are the linear attenuation coefficients of water and air, respectively.

HU scale (indicative values)

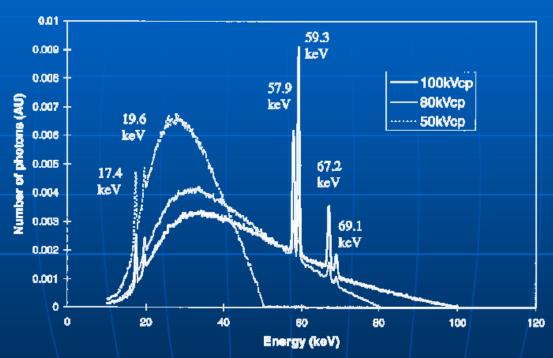
| material | HU value | notes | | | | |
|----------|----------|---|--|--|--|--|
| air | - 1000 | and vacuum as well, for all practical effects | | | | |
| fat | - 100 | | | | | |
| water | 0 | distilled, at STP | | | | |
| muscle | + 40 | | | | | |
| Blood | +40 | | | | | |
| bone | ~ > 400 | spans over a large range, i.e. up to >1200 | | | | |
| aluminum | 2640 | (at 60 KeV) | | | | |

extrapolate μ's measured at the CT energy to μ's @ 511 keV



... unfortunately, real X-ray beams are NOT AT ALL monochromatic!

50, 80 and 100kVcp x-ray spectra



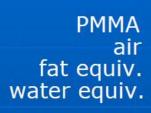
Diagnostic x-ray spectra: A comparison of spectra generated by different computational methods with a measured spectrum M. Bhat, J. Pattison, G. Bibbo, and M. Caon Med. Phys. (1998) 25(1):114-120

Specific CT energy spectrum

Calibrate system to:

- HU(air) = -1000
- HU(water) = 0

test phantom



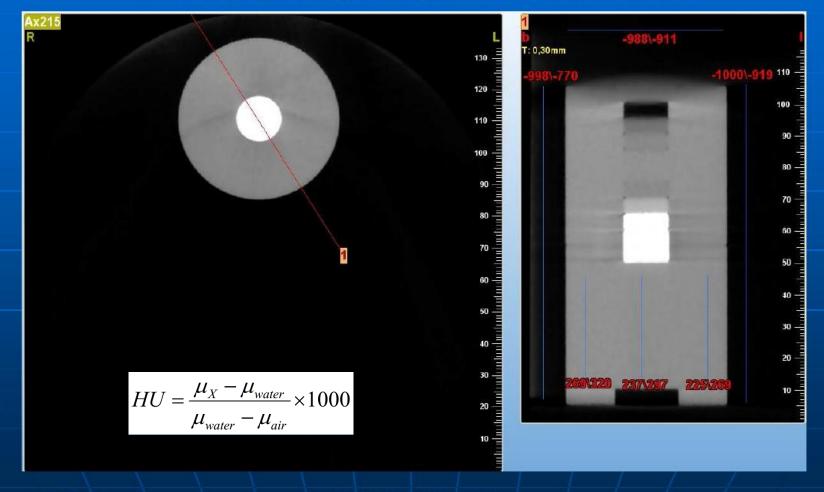
muscle equiv. cancellous bone equiv. cortical bone equiv. aluminum

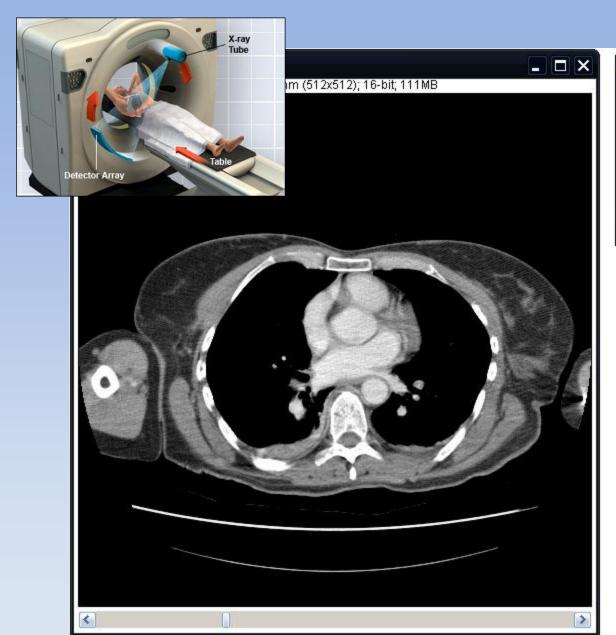
body of phantom: PMMA (polymethylmethacrylate)

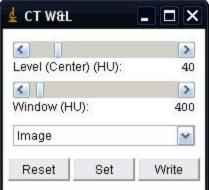
air

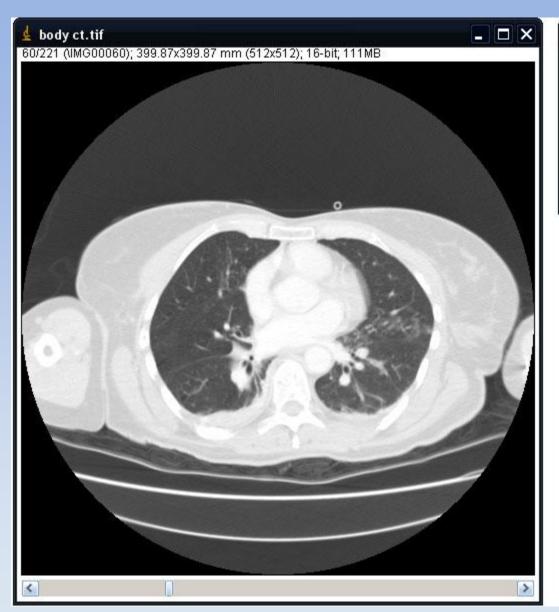
10 cm

measured CT Numbers











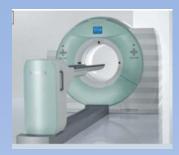
PET calibration

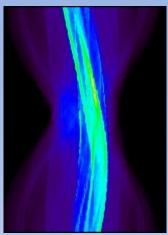
PET acquisition

CT acquisition



EMrecon: An Expectation Maximization Based Image Reconstruction Framework for Emission Tomography Data





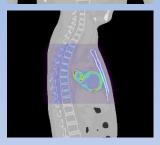




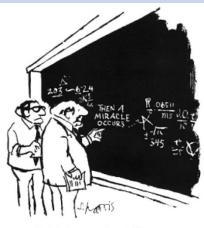
- HU to CT $\mu\mbox{'s}$
- CT μ 's to μ 's @ 511 keV



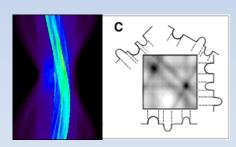




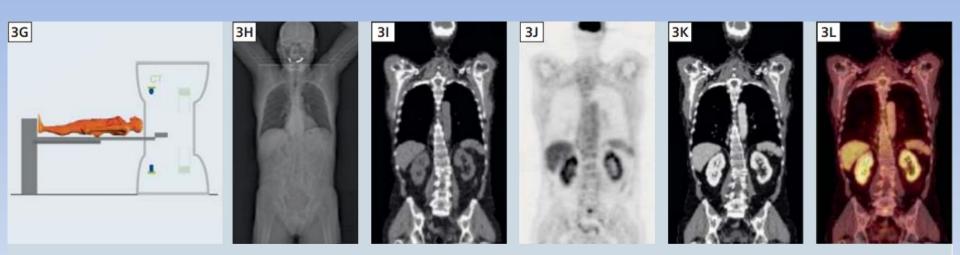
Dose quantification



"I think you should be more explicit here in step two."

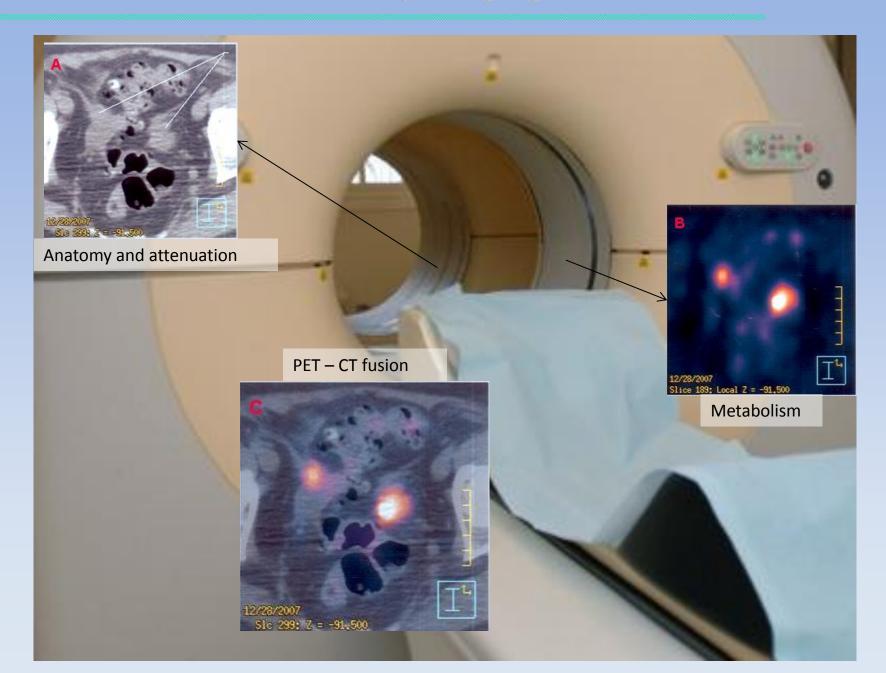


Back propagation algorithm including attenuation map



3G-L Schematic illustration of a standard PET/CT investigation: tracer injection, uptake time and patient positioning (G), topogram and scan range definition (H), CT acquisition for attenuation correction (I), emission scan (J), contrast-enhanced CT scan (K) and image reconstruction/fusion (L).

PET functional & CT anatomy imaging



PET cameras, a status report

- Positron Emission Tomography Products
- Acquisition
- Quantification



Based on material from:

- Etat de l'art sur les caméras TEP, Pierre Malik Koulibaly, Medical Physicist, Centre Antoine Lacassagne, Nice,
 France
- Development of Hybrid Imaging, Uwe Pietrzyk, research center Jülich and University of Wuppertal, Germany

PET/CT Products

Three main suppliers:







And also:





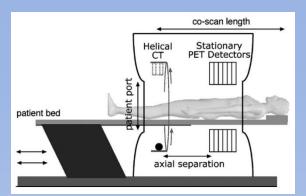


3A–F Current commercial PET/CT systems: (A) Discovery series from General Electrics Healthcare, (B) Gemini series from Philips Healthcare, (C) Biograph mCT from Siemens Healthcare, (D) Acquiduo series from Toshiba Medical Systems, (E) Sceptre series from Hitachi Medical Systems, (F) Anyscan from Mediso (this device can be combined with a SPECT to form a triple-modality imaging system). Variations apply to the individual performance parameters of PET and CT.

| % | Discovery ST, STE, STX | Optima 560 | Discovery 600 | Discovery 610 | Discovery 690 | Discovery 710 | High Level Range |
|----------|---------------------------|---------------|-------------------------|-----------------------------------|---------------------------------------|---------------------------------------|-------------------------------------|
| | | BGO | BGO View Point HD | BGO Time of flight Sharp IR | LYSO Time of flight Sharp IR | LYSO Time of flight Sharp IR | |
| PHILIPS | | Gemini LXL | Gemini TF (Big Bore) | TruFlight Select | Astonish TF | Ingenuity TF | High Level Range |
| РПІ | LIPS | LYSO | LYSO Time of flight | LYSO Time of flight | LYSO Time of flight Astonish TF | LYSO Time of flight Astonish TF | |
| | | | | | | | |
| CIE | ИENS | | Biograph | Biograph TruePoint | Biograph mCT Excel | Biograph mCT | High Level Range ──────────── |

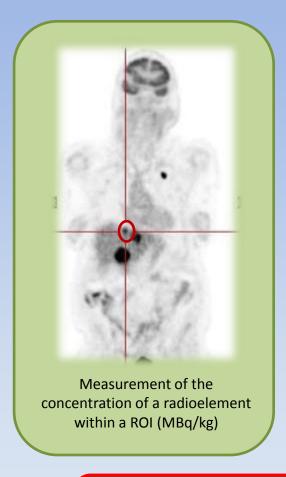
Available acquisition modes

| | Static | Dynamic | Gated |
|----------|----------|----------------------|---|
| | 18F-FDG | 18F-Choline | R 1 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 |
| % | | V | \square |
| PHILIPS | | $\overline{\square}$ | |
| SIEMENS | | V | \square |
| | ✓ | ☑ | |



| TEP module | Discovery 710 | Ingenuity TF | Biograph mCT |
|---------------------------------------|--------------------------------|----------------------------|----------------------------|
| Crystal type | LYSO | LYSO | LSO |
| Crystal size | 4.7 x 6.3 x 30 mm ³ | 4 x 4 x 22 mm ³ | 4 x 4 x 20 mm ³ |
| Number of crystals | 13,824 | 28,336 | 32,448 |
| Patient scan range | 188 cm | 194 cm | 198 cm |
| Patient port | 70 cm | 70 cm | 78 cm |
| Axial field of view | 15.7 cm | 18 cm | 21.6 cm |
| time measurement resolution | 550 ps | 495 ps | 555 ps |
| Coincidence window to accept events | 4.9 ns | 3.8 ns | 4.1 ns |
| Energy window to accept events | 425-650 keV | 440-665 keV | 435-650 keV |
| System sensitivity | 7 cps per kBq | 7.4 cps per kBq | 9.5 cps per kBq |
| Transverse spatial resolution @ 1 cm | 4.9 mm | 4.7 mm | 4.4 mm |
| Transverse spatial resolution @ 10 cm | 6.3 mm | 5.2 mm | 4.9 mm |
| Axial spatial resolution @ 1 cm | 5.6 mm | 4.7 mm | 4.5 mm |
| Axial spatial resolution @ 10 cm | 6.3 mm | 5.2 mm | 5.9 mm |

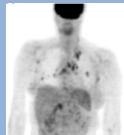
Quantification: extracting a physical value from an image In PET, it could be the uptake value of FDG in a given volume.

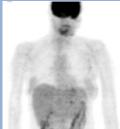


Prognostic: provides information on tumor grade (survival probability)



Therapeutic actions: visible slow down in the glucose uptake is a good indicator of an efficient treatment.





PET images have to be corrected from all distortions

Quantification in PET: Standard Uptake Value (SUV)

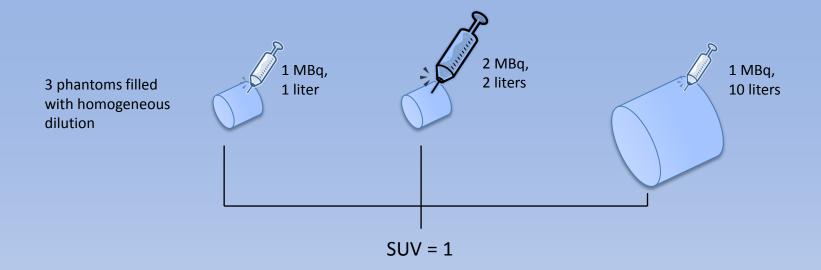
SUV is calculated over a region of interest

It is defined as follows:

SUV =
$$\frac{\text{concentration of radiotracer (kBq/ml)}}{\text{Injected dose (kBq)/patient weight (g)}}$$

SUV is a precious common tool (quoted in all studies), even if not very accurate

- Injected dose is estimated with an accuracy of 5 -10 %
- The patient weight is known to a few percent
- The radiotracer fixation is estimated after many corrections



SUV = 1 indicates an homogenous spread of the radiotracer within the body. Any deviation from this value is a sign of hyper fixation.

Why is quantification so difficult to estimate?

Patient side

- Spatial displacements (patient is moving, breathing, heart beating)
- Compton scattering
- Photon attenuation
- Random coincidences



PET side

- Detectors response non uniform
- Spatial resolution not constant
- Dead time
- Partial volume effect

Isotope decays

Decreasing activity

Reconstruction algorithm

• Bias and nonlinearities

Corrections to reach correct quantification

Patient side

Breathing: triggered acquisition (gating)

Heart beat : gating

Attenuation: HU from CT-map to μ

Compton scattering : estimated then subtracted

Random coincidences : estimated then subtracted

PFT side

Detector uniformity: normalization

Arc geometry: transverse and longitudinal normalization

Dead time : estimate real counting rate

• Spatial resolution not constant : measure the Point Spread Function

Spatial resolution not constant: measure the Depth Of Interaction

Partial volume effect: correction function

Isotope decays

• Decreasing activity: compensate for exponential decrease

Reconstruction algorithm

Bias and nonlinearities:
 algorithm correction

Corrections to reach correct quantification: breathing

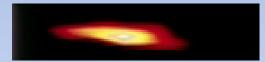
Breathing induces 15-20 times a minute shifts with an amplitude up to 5 cm.

Shifts due to breathing affects many organs, in particular lung and liver

As a consequence, the volume and the intensity of the fixating target will be distorted.



Lung PET image



Tumor displacement



Fixed tumor

Apparent tumor volume increased by 10 to 30 % Intensity of absorbed activity drops by 5% to 100%

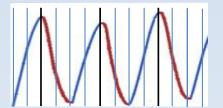
Solution:

Gating technics are adapted to respiratory motion

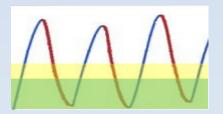
Chest amplitude checked:

- a belt around the patient chest measures the abdominal volume
- the motion of multiple fiducial markers are tracked simultaneously in two-dimensions (in the vertical plane) using a standard video camera.

Time splitting: The motion is split into different phases and images are reconstructed for each phase of the cycle.



Amplitude splitting: images are recorded if the motion lies between adjustable lower and upper limits



Belts for respiratory motion monitoring

PHILIPS



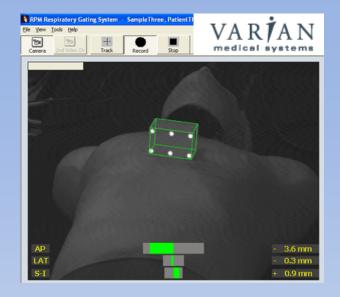
Deformable belt that when placed across the patient's chest/abdomen measures abdomen circumference. It generates a breathing signal corresponding to the expansion and contraction of the abdomen. The breathing signal is fed to the PET/CT system.

SIEMENS ANZAI system









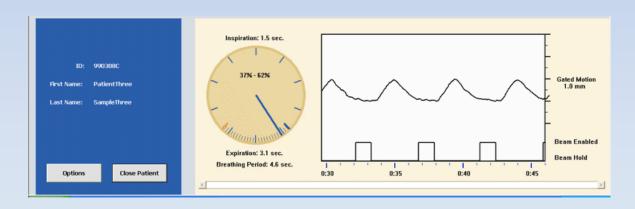
Real-time Position Management (RPM) System:

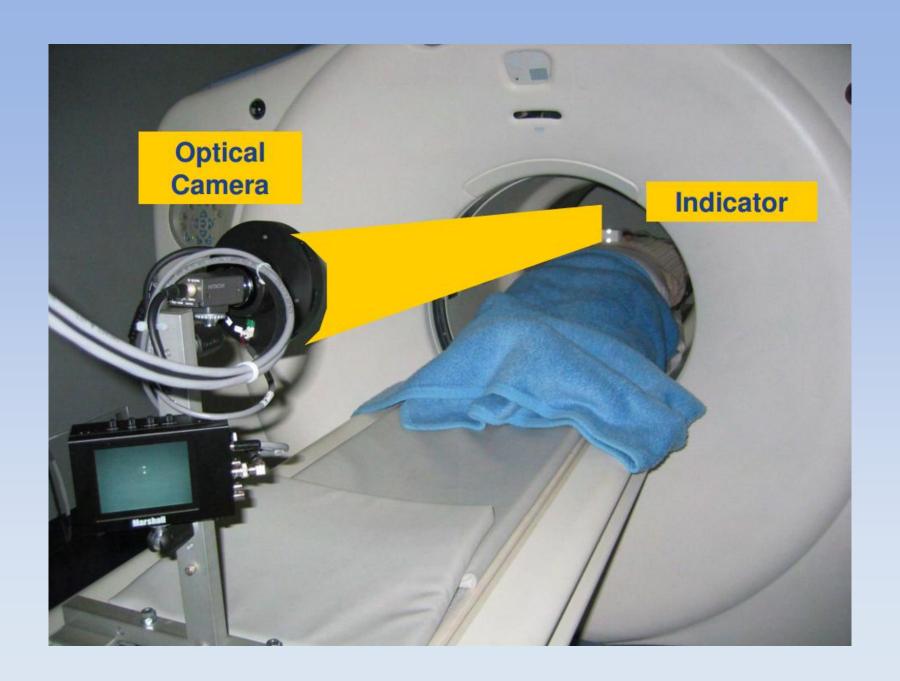
(used in CT / simulator / clinac)

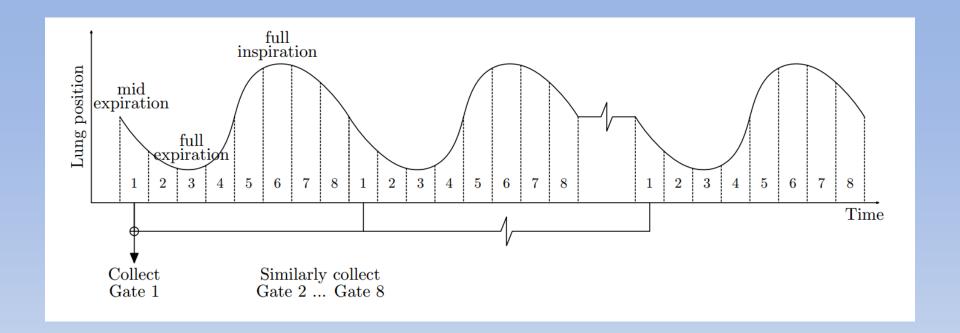
Reflective external marker placed on the abdomen of the chest

Infrared illuminator coupled with a CCD camera
Workstation to process signals and generate triggers
for PET CT acquisition.









Mid expiration triggers a sequence of 8 sub samples, or gates.

Gates created assuming a perfectly periodic breathing motion.

PET data are divided into a number of gates: "motion freeze"

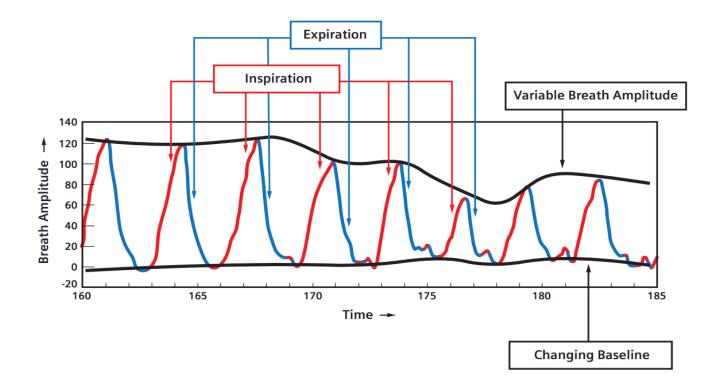
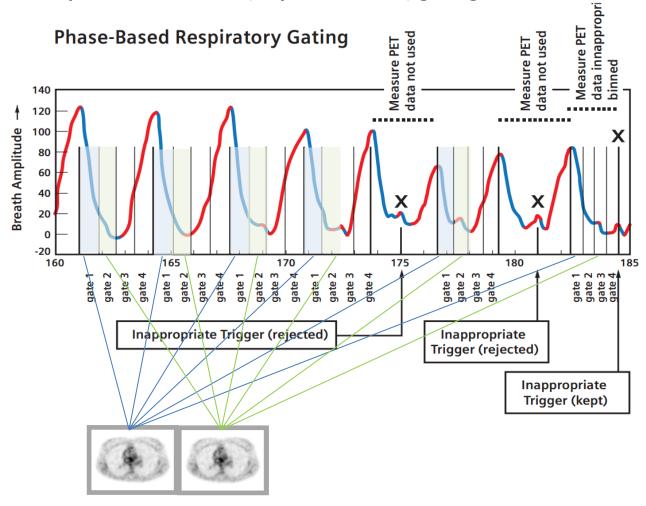


Fig. 1. Respiration signal vs. time in a 25-sec interval.



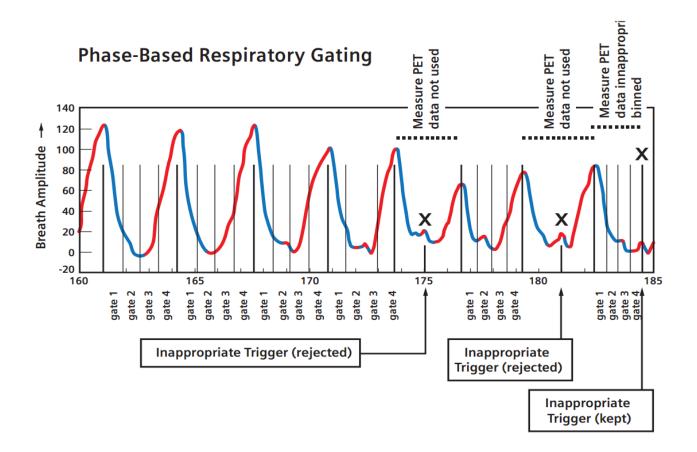
Example of time based (or phase-based) gating



Set parameters at the beginning of the PET session:

- Trigger defined at the max. of respiratory motion (end of inspiration).
- Four gates are defined after the trigger.

Decide online whether or not to keep the data.





Time splitting:

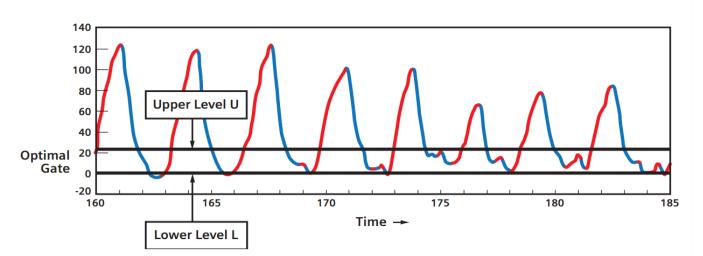
Splitting into different phases reduces the amount of available data: images are noisy.

Bad triggers will reject additional data, making the images noise worse

Some inappropriate triggers are kept, mixing bad data with good data

Example of amplitude based gating

HD•Chest Optimal Respiratory Gating





Amplitude splitting:

SIEMENS HD Chest: acquisition is performed when the amplitude is above a lower level L but below an upper level U.

The user selects the percentage of data that will be kept, which set the value of U when L has been selected.

The data is analyzed at the end of the acquisition. After it has considers all possible L values, the computer determines which one gave the smallest range of respiratory motion. This determines the optimal setting for L and U,

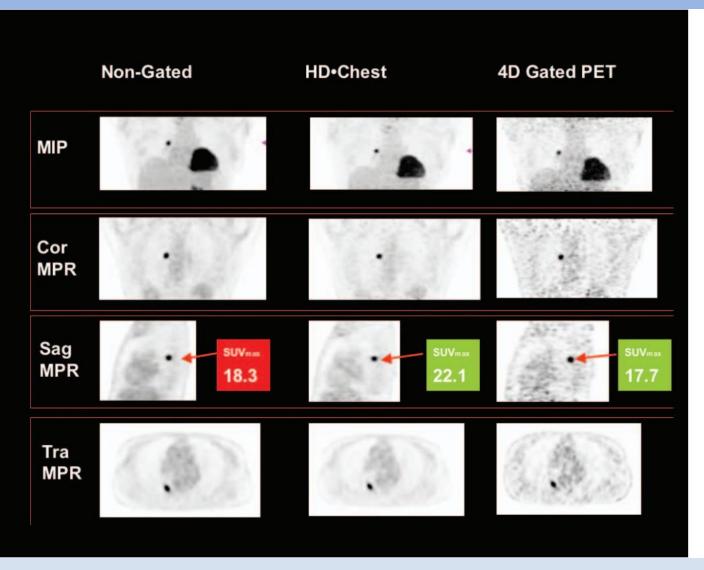


Figure 3. A solitary pulmonary nodule in the posterior aspect of the right upper lobe, showing the improvement in SUV value with HD•Chest. Although the nodule is well delineated in the non-gated PET, respiratory motion related effects make the nodule appear slightly larger on the non-gated compared to the HD•Chest study. The HD•Chest study also shows higher SUV_{max} compared with non-gated PET. (Data courtesy of University of Michigan)

Amplitude splitting: clear improvement in the SUV quality!

Apnea protocols with spirometer are being tested on selected patients (PET : 20 sec. hold x 3 times, CT : one 5s hold). Reduces acquisition time but gives results similar or worse as compared with gated acquisitions.

Conclusion

- PET is evolving rapidly in many aspects (quantification, image quality, PET/CT)
- Mastering its features is a least a ½ full time job for a medical physicist :
 - Commissioning (individual and geometrical efficiencies)
 - Correct from natural organ motions and systematic effects to achieve proper
 SUV quantification :
 - 4D-CT,
 - amplitude based PET acquisition,
 - partial volume correction
- PET, a precious tools in nuclear medicine

