Nuclear Instruments and Methods for the Campaign against Cancer

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Outline

- Introduction: a short historical review
- Applications in medical diagnostics
- Applications in conventional cancer radiation therapy
- Hadrontherapy, the new frontier of cancer radiation therapy: Proton and Carbon therapy
- Other tools (Peroperative probes)
- Organisation of Physics-Biology interface activities at IN2P3 in France

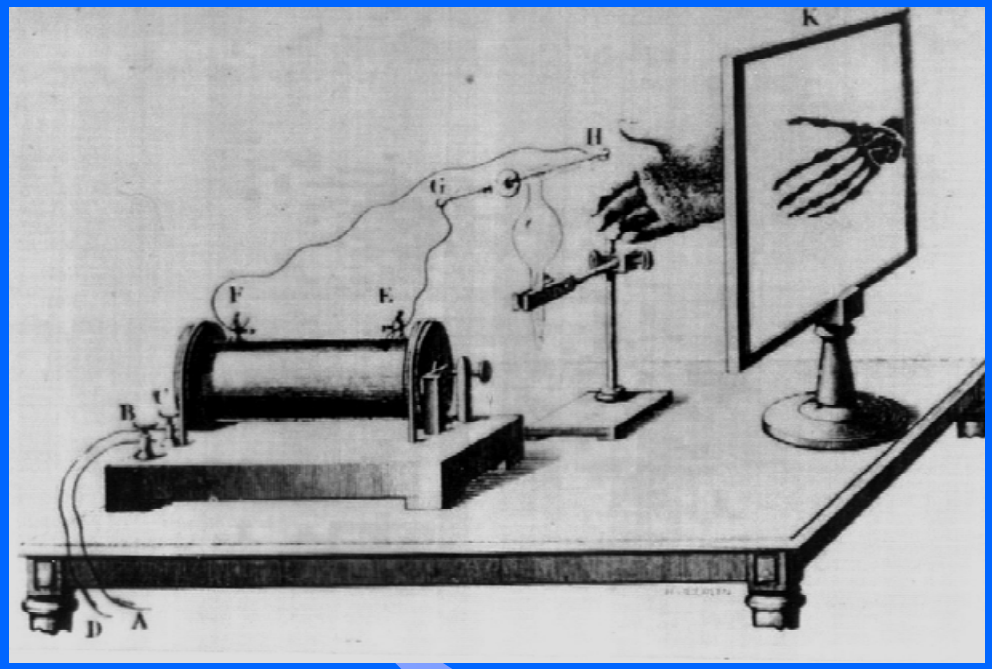
1. Introduction

Fundamental research in nuclear and particle physics and medical applications

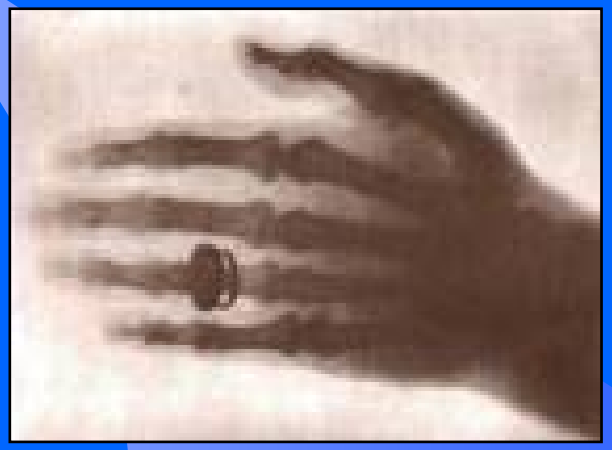
Progress in Health and life sciences had always been strongly correlated to technological developments in physical science, especially in Nuclear and High Energy Physics.

• November 1895 : discovery of X rays

Wilhelm Conrad Röntgen



• December 1895 : first radiography

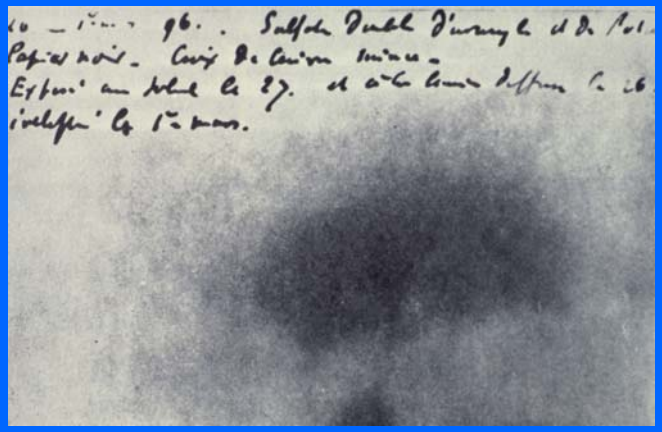


The beginning of modern physics and medical physics

Henri Becquerel
(1852-1908)

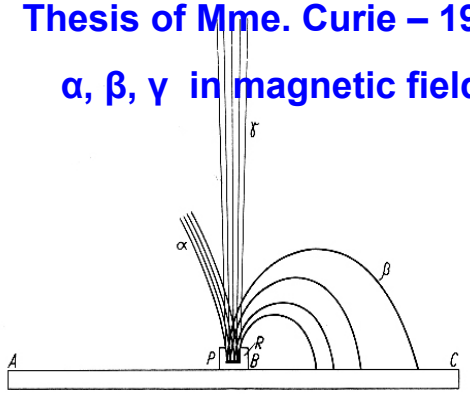
1896:

Discovery of natural radioactivity



Thesis of Mme. Curie – 1904

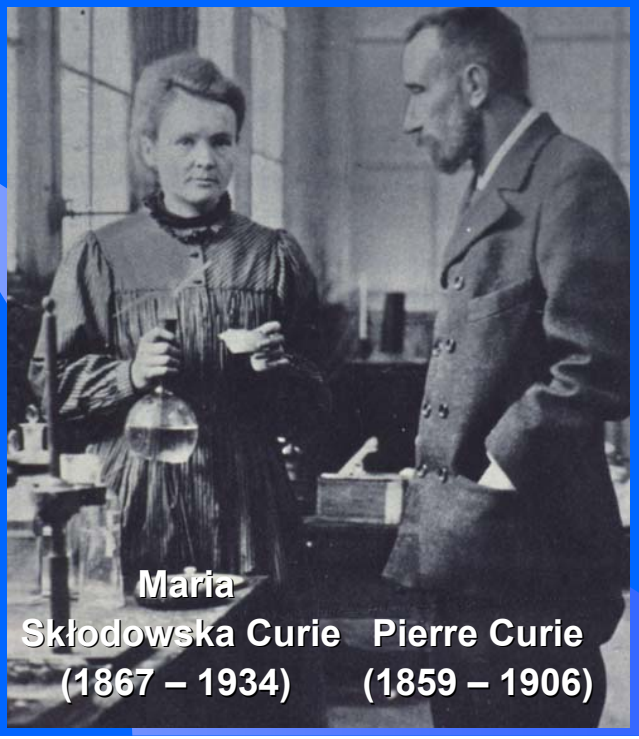
α, β, γ in magnetic field



About one hundred years ago

1898

Discovery of radium

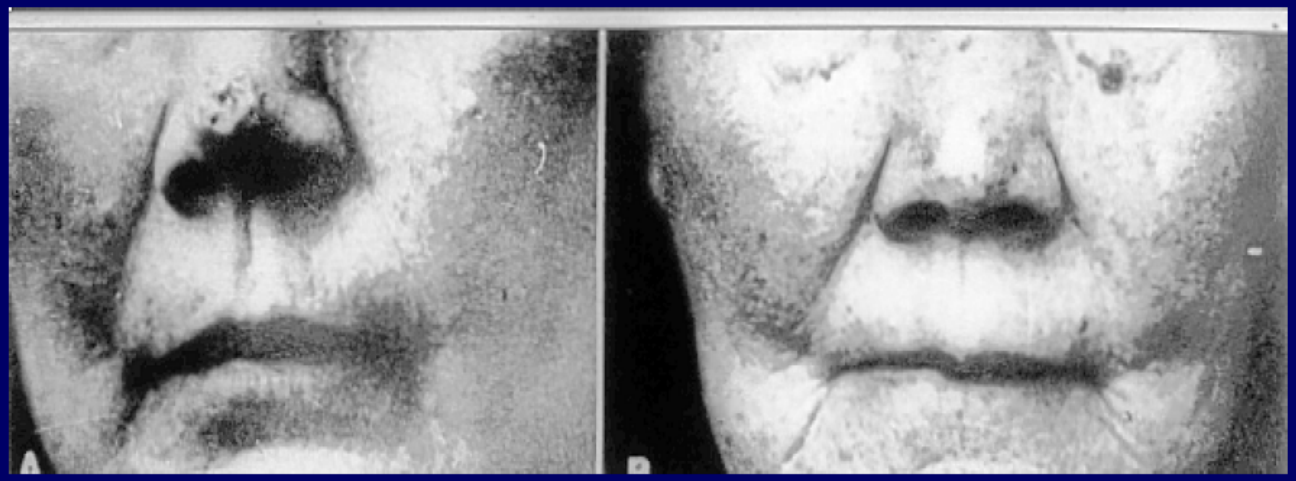


Maria Skłodowska Curie (1867 – 1934)

Pierre Curie (1859 – 1906)

First applications in cancer therapy

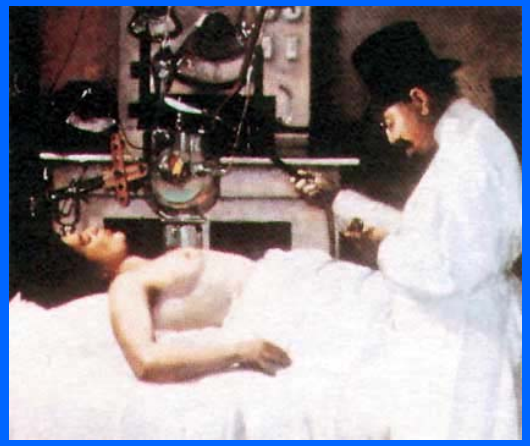
STOCKHOLM



1902 **1912**

Basic concept

Local control of the tumour



1908 : first attempts of skin cancer radiation therapy in France ("*Curiethérapie*")

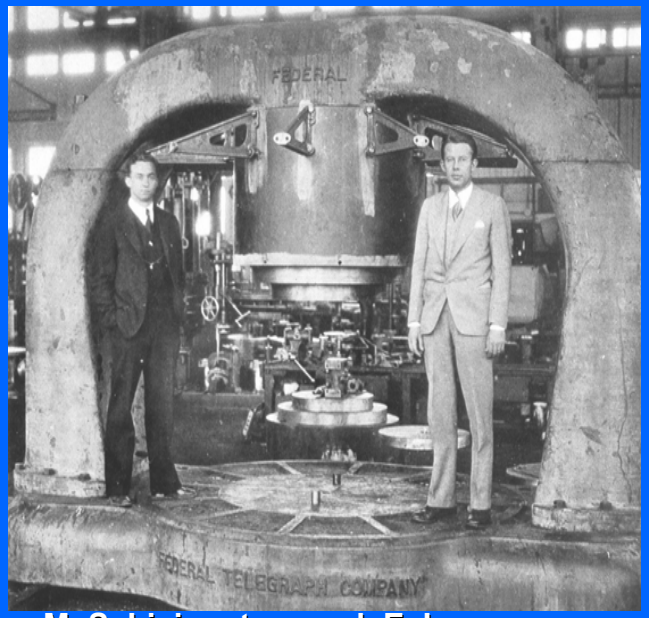
A big step forward…

…in physics and in

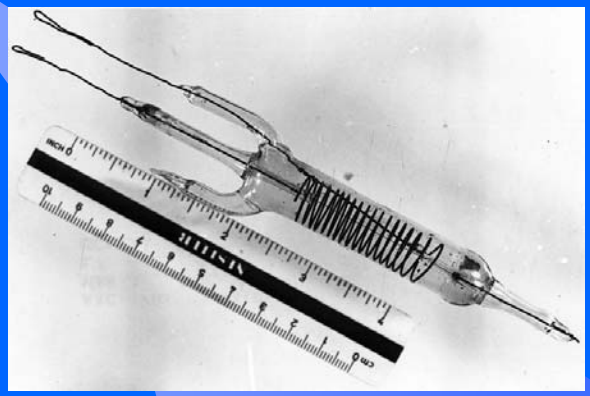
- Medical diagnostics
- Cancer radiation therapy

due to the development of three fundamental tools

- Particle accelerators
- Particle detectors
- Computers



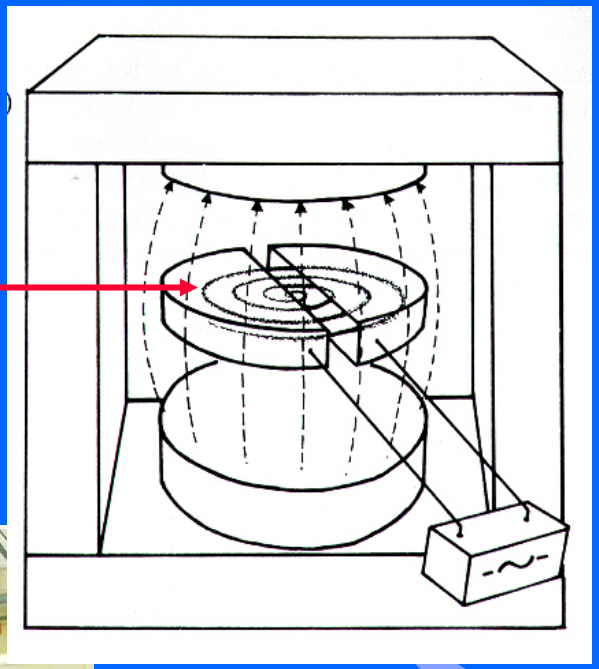
M. S. Livingston and E. Lawrence with the 25 inches cyclotron



Geiger-Müller counter built by E. Fermi and his group in Rome

1930: invention of the cyclotron

Spiral trajectory of an accelerated nucleus



Ernest Lawrence

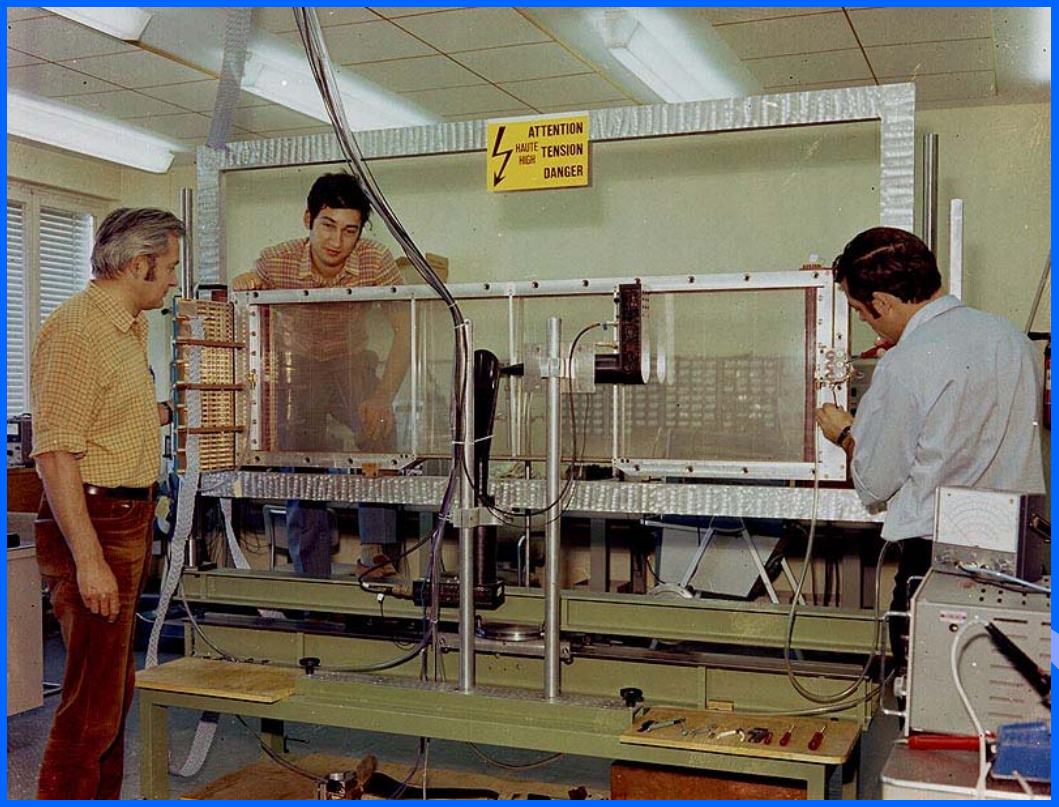
(1901 – 1958)

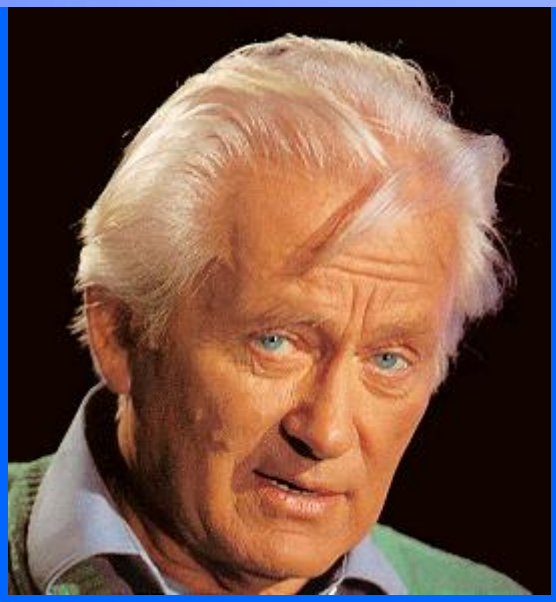
Modern cyclotron

Particle detectors

- They are the “eyes” of particle physicists
- A very impressive development in the last 100 years
  - From the Geiger counter to ATLAS and CMS !
- Crucial in many medical applications

One example: the multiwire proportional chamber





Georges Charpak, CERN physicist since 1959,

Nober prize 1992

- Invented in 1968, launched the era of fully electronic particle detection
- Used for biological research and could eventually replace photographic recording in applied radio-biology
- The increased recording speeds translate into faster scanning and lower body doses in medical diagnostic tools based on radiation or particle beams

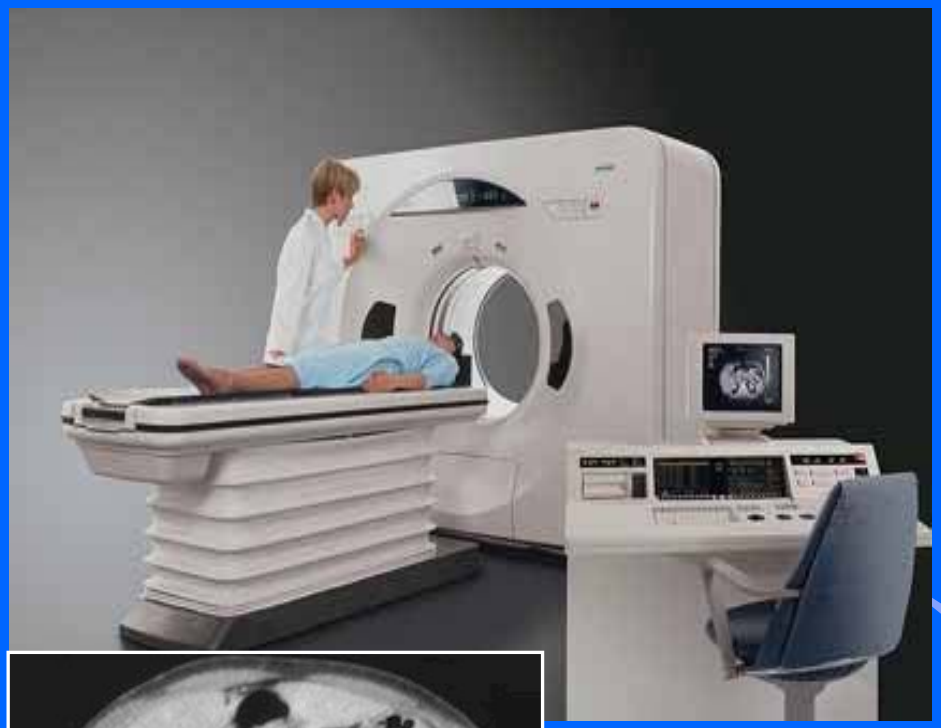
2. Applications in medical diagnostics

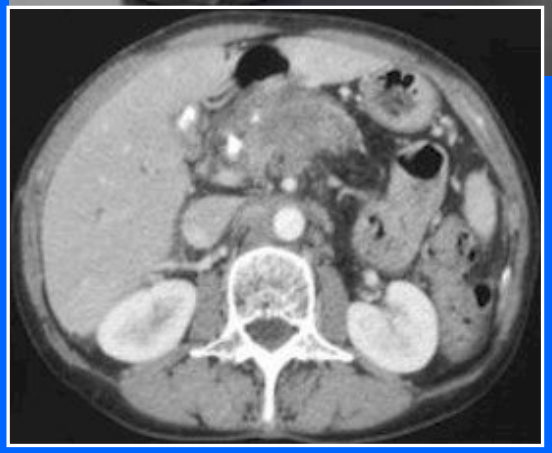
➔ *Medical Imaging systems are more and more powerfull and complex*

➔ *Combining different modality of which nuclear imaging is a major component*

➔ *Early Diagnostics is essential !*

Computer Tomography (CT)



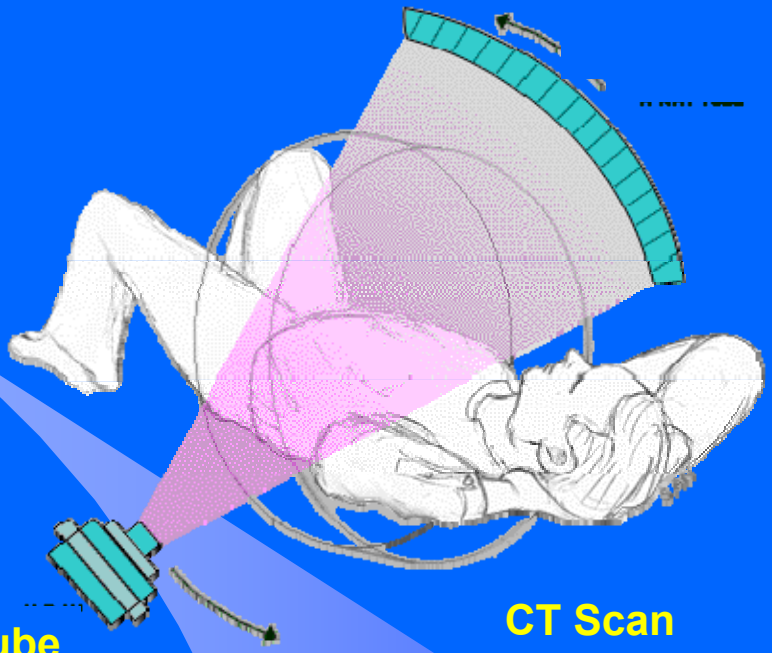


Abdomen

Detectors rotated

Around the patient

with the X ray tube



X ray tube

CT Scan

- Measurement of the electron density
- Information on the morphology

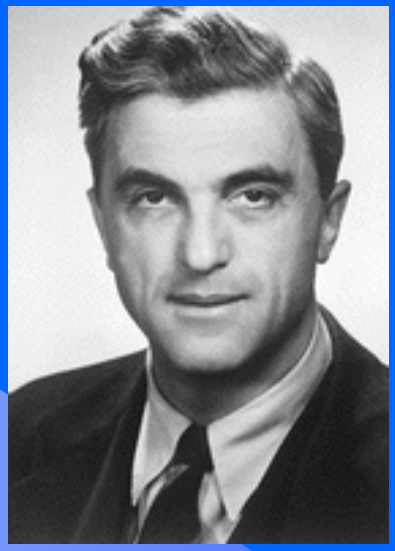
Nuclear Magnetic Resonance Imaging

1938-1945

Felix Bloch and Edward Purcell

discover and study

NMR



MRI was first a spectroscopy technique for chemistry, physics and biology

In the 70ths, interest growed-up for medical application of MRI, and first human imagery was done

In the 80th, technical progress in temporal resolution and in spatial as well so that RMI imagery became one of the most important clinical imagery technique

In 1954 Felix Bloch became the first CERN Director General

MRI : magnetic stuff !!

External magnetic field
$B_0 = 3$ T

Magnetic properties of the NUCLEI

Electromagnetic field B_1 (Radio-frequency or RF)

The nuclear *SPIN* → no radioactivity !!

→ characterized by a spin number *I*
→ *quantum mechanics !!*
→ a nucleus with $I \neq 0$ behaves like a small magnet

The Hydrogen nucleus

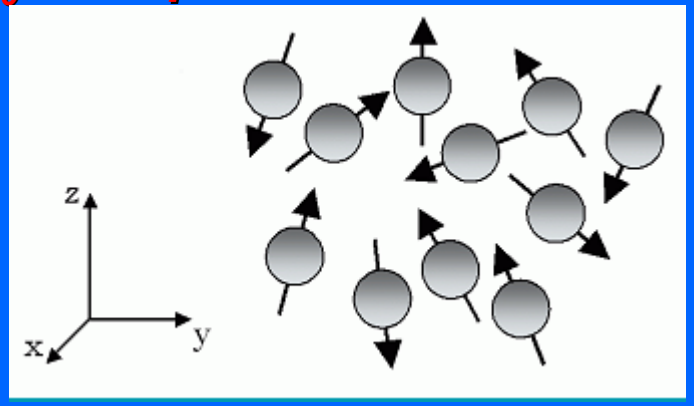
→ the most abundant (~⅔ of the atoms in living tissues)

Behaviour of the nuclei interacting with :

1°) An external magnetic field B_0 ➔ Equilibrium state

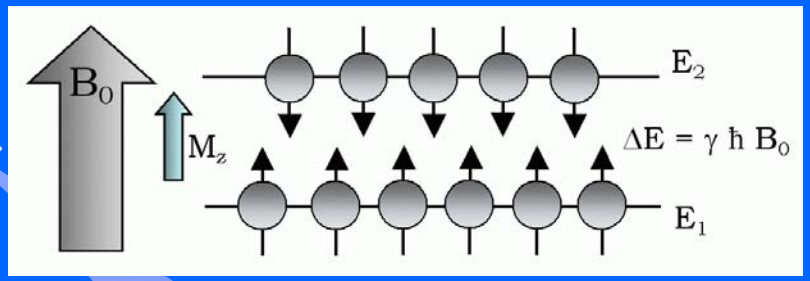
When no magnetic field B_0 is applied

➔ spin orientation is completly random



When a static magnetic field B0 is applied (along axis z)

➔ spins are aligned with the field B_0.



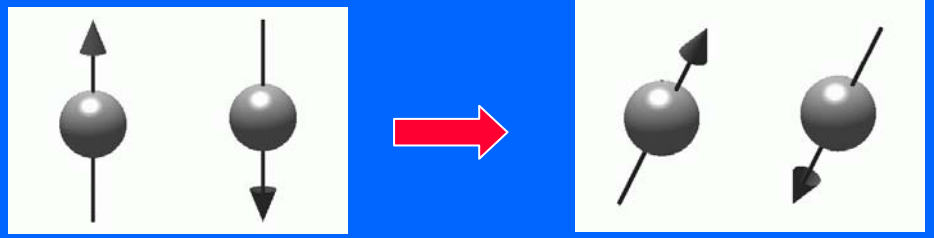
Somme of them have parallel orientation (spin-up), other have antiparralel orientation (spin-down)

The two different orientations correspond to two different energies: E_1 corresponds to spin-up; E_2 corresponds to « spin down ».

➔ difference $\Delta E = E_2 - E_1$ is proportional to the strength of the field B_0.

Number of spins with energy E_1 is larger than number of spins with energy E_2 are so that a macroscopic resultant magnetic field M_z appears parallel to B_0.

Interaction with B_0

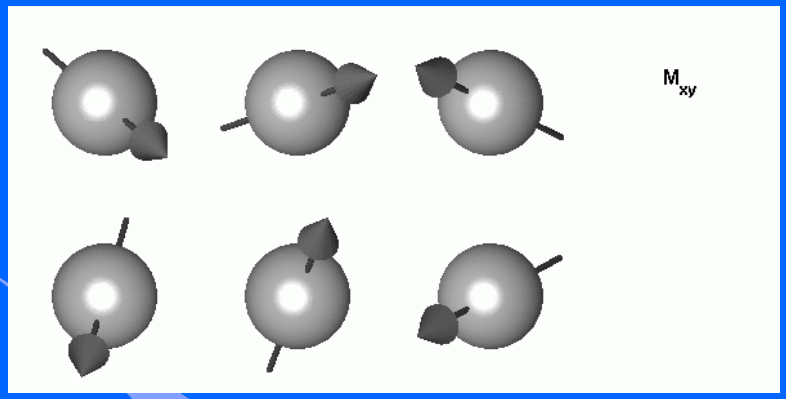


→ Rotation or *precession* about the axis of the magnetic field Bo with frequency :

$$\omega_o = \gamma Bo$$

ω_o = *Larmor frequency*

γ = *gyromagnetic ratio*



At the equilibrium state :

- The rotation is *not in phase*
- no transverse magnetization M_{xy}

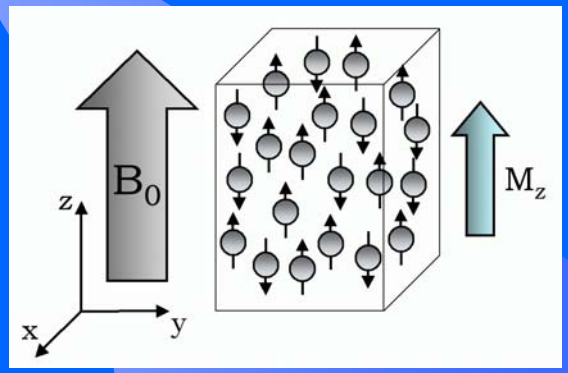
Summary of the equilibrium state :

1. spin orientation « up » > « down »

→ *longitudinal magnetization M_z*

2. precession

→ *no transverse magnetization M_{xy}*

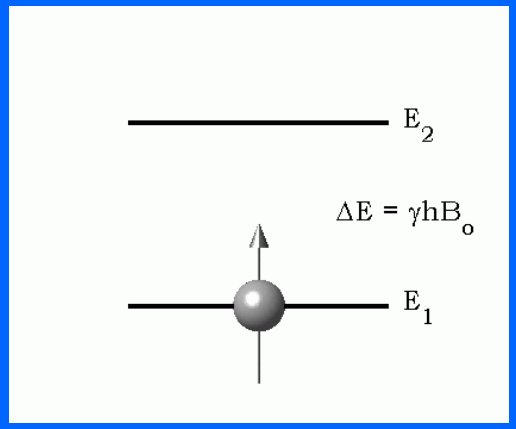


Behaviour of the nuclei interacting with :

2°) An electromagnetic field B_1 (RF) ➔ Disturbance

Resonance phenomenon

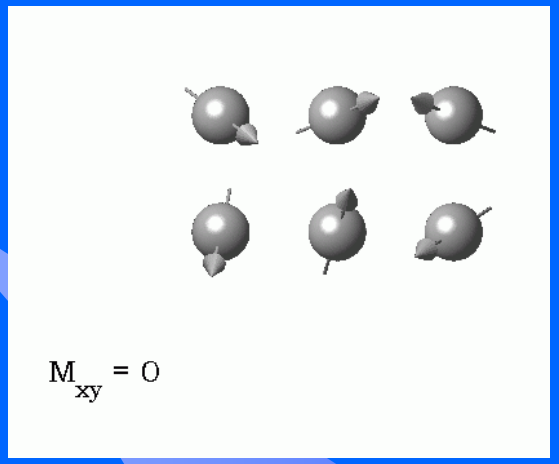
TRANSITIONS



Transitions $E_1 \rightarrow E_2$

$\Rightarrow$ M_z decreases

REPHASING



Phase coherence increases

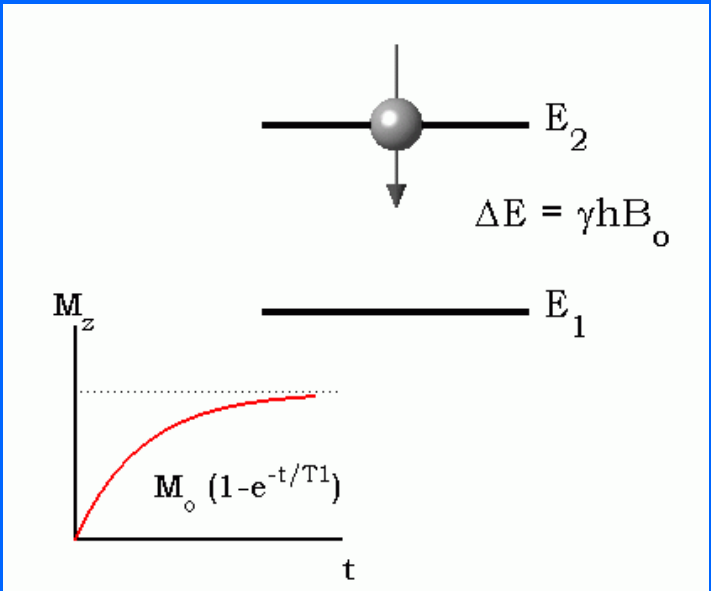
$\Rightarrow$ M_{xy} increases

RF frequency = Larmor frequency = ω_0

Behaviour of the nuclei interacting with :

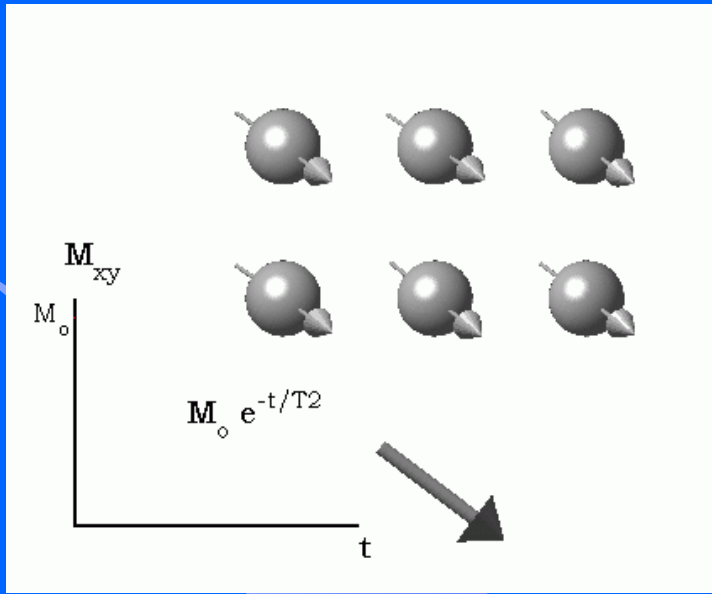
Relaxation ➔ Back to the equilibrium state

TRANSITIONS



Transitions $E_2 \rightarrow E_1$
$\Rightarrow$ M_z increases
$\Rightarrow$ T_1 relaxation

DEPHASING

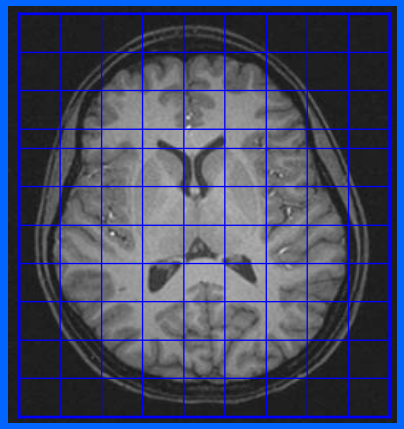


Dephasing
$\Rightarrow$ M_{xy} decreases
$\Rightarrow$ T_2 relaxation

Signal localization

Up to now ➔ the signal received contains information from the entire body !!

Use field gradients along the 3 axis to spatially encode the signal in three steps :



1. Application of a gradient Gz ➔ Slice selection

Resonance Phenomenon ➔ $\omega_{RF} = \omega_0$!!!

Before Gz is applied : all the spins preces with same frequency ωo
➔ all could resonate !!

During application of Gz : the spins precess with $\neq \omega$

➔ only spins with frequency = ω_{RF} resonate

2. Application of a gradient Gx ➔ Frequency-encoding ➔ columns selection

Before Gx is applied : all the spins preces with same Larmor frequency ω_o

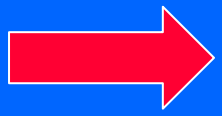
During application of Gx : the spins preces with $\neq$ frequencies
$\Rightarrow$ Fourier Transform of the signal allows discrimination between columns !

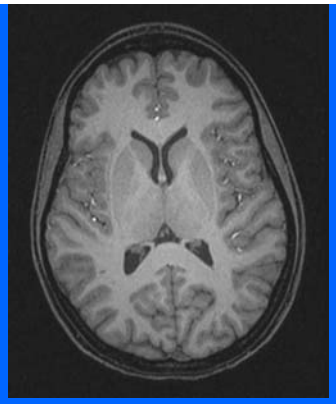
3. Application of a gradient Gy ➔ Phase-encoding ➔ lines selection

After application of Gy : all the spins precess again at same Larmor frequency, but with different phase shifts from line to line…

Contrast in MRI

Grey-level images :





➔ **the intensity of a voxel depends on the intensity of the corresponding signal**

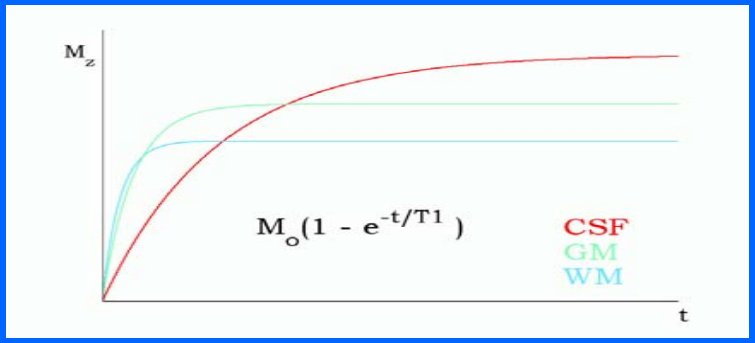
Contrast depends on :

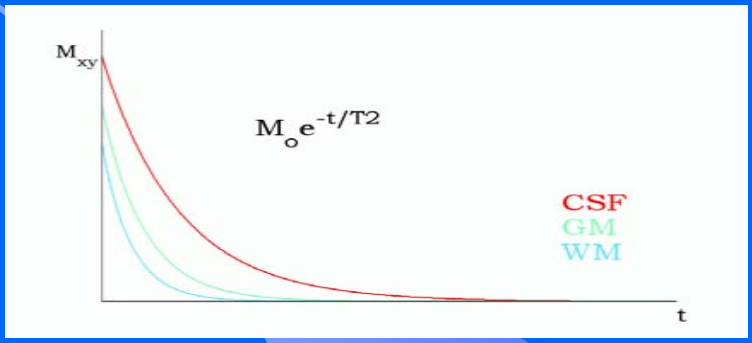
1. tissue properties : T_1, T_2, ρ ➔ user-independent

2. sequence parameters : T_R, T_E, … ➔ user-dependent

T_R = repetition time = time interval between two RF pulses

T_E = echo time = when the acquisition is performed

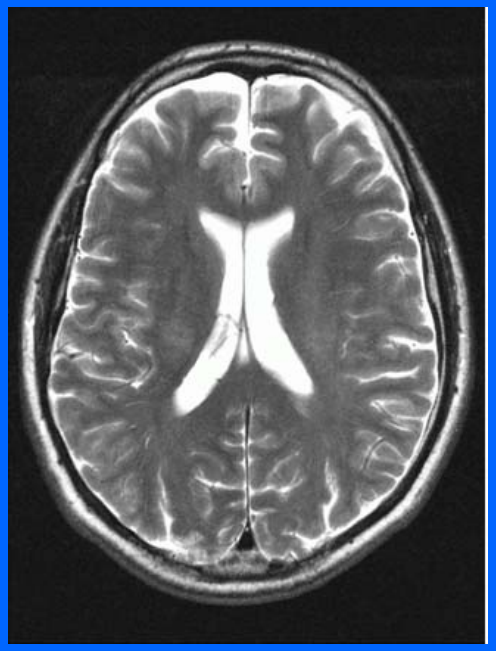




	T_1 (ms)	T_2 (ms)	proton density ρ
WM	500	75	0.65
GM	750	90	0.8
CSF	3000	200	1.0

Contrast in MRI

T2-weighted image : long T_R – long T_E



T_R = 3370 ms

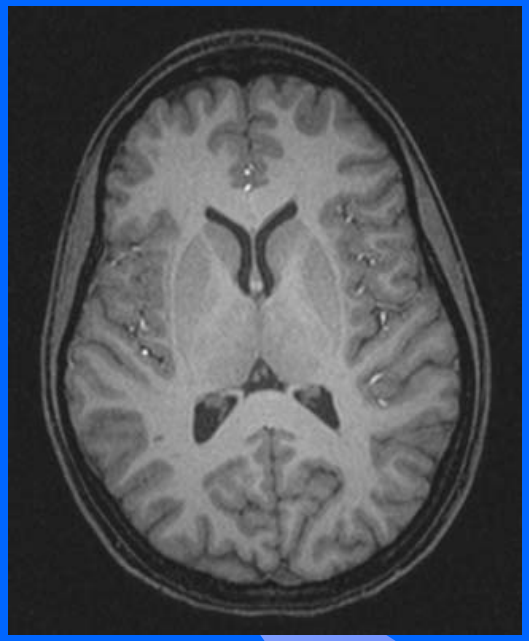
T_E = 112 ms

CSF

GM

WM

T1-weighted image : short T_R – short T_E



T_R ~ 500 ms

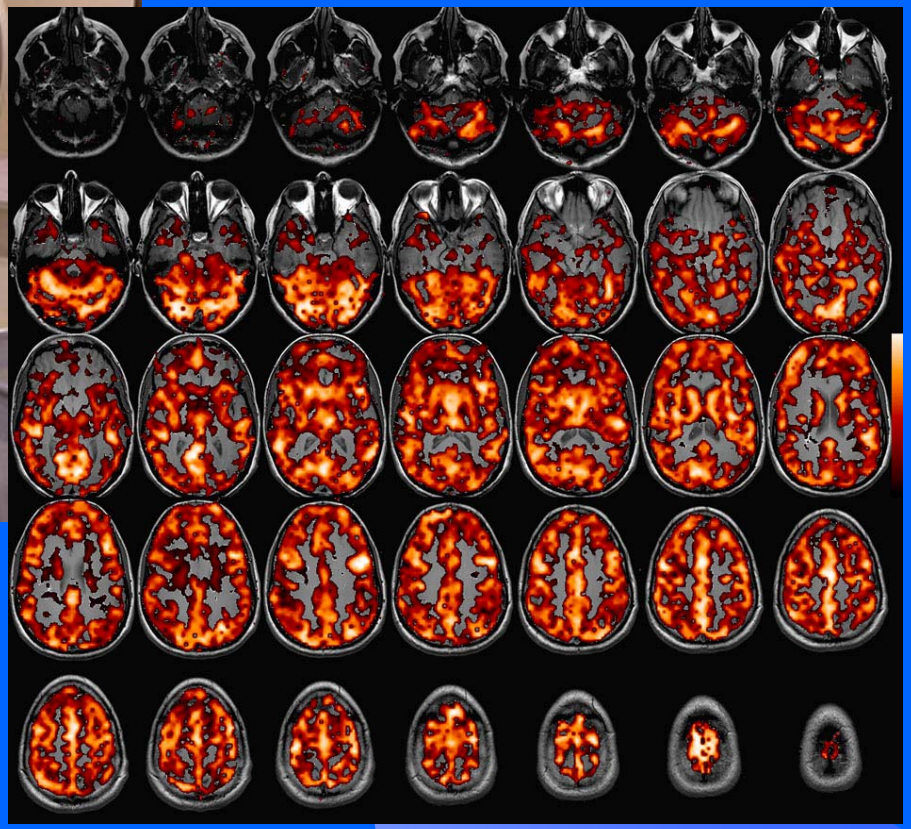
T_E ~ 10 ms

WM

GM

CSF

A MRI scanner



MRI is based on nuclear properties of the nuclei (the spin)

➔ ***morphologic & functional imaging system***

➔ ***But it does not use at all radioactivity***

Instead of nuclear imaging systems that give acces to the metabolism of the organs by the way of radioactive molecules (mainly glucose based molecules)

➔ radioactive molecules are injected into the patient

➔ trapped in the cells that try to metabolize it

➔ Concentration builds up in proportion to the rate of glucose metabolism

➔ Radioactive molecules decay with gamma emission

➔ Tumors have a high rate of glucose metabolism and appear as "hot spots" in images

Gammas are detected by systems using scintillating crystals coupled to photodetectors and front-end electronics

The two main nuclear imaging techniques are :

➔Single Photon Emission Computer Tomography SPECT (using γ)

➔Positron Emission Tomography PET (using β^+)

Combined PET + MRI + CT ?

« Multimodality imaging »

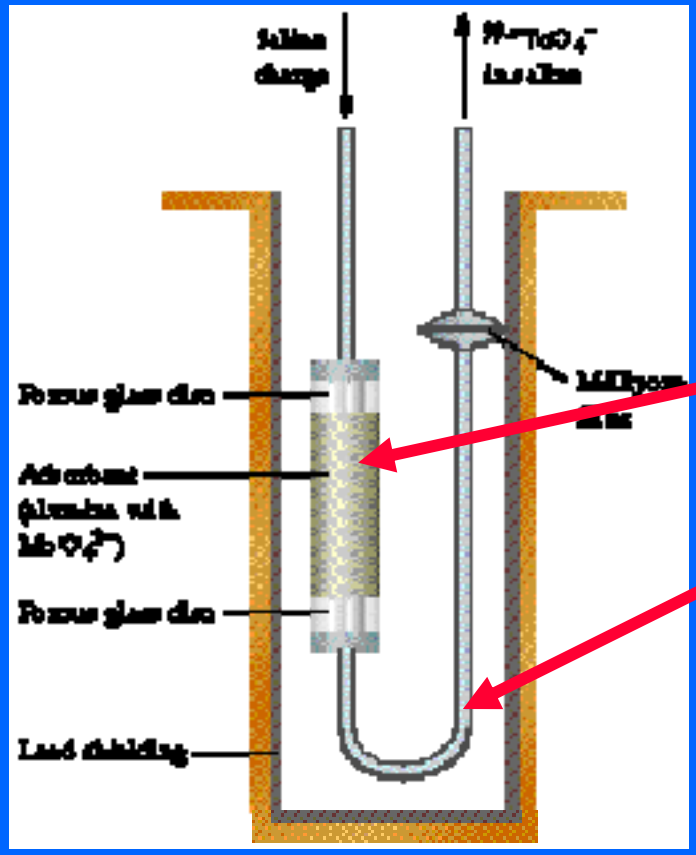
MRI ➔ morphologic & functional images

PET ➔ functional & metabolic images

Fusion of different kind of images

➔ improve clinical diagnostic

SPECT = Single Photon Emission Computer Tomography

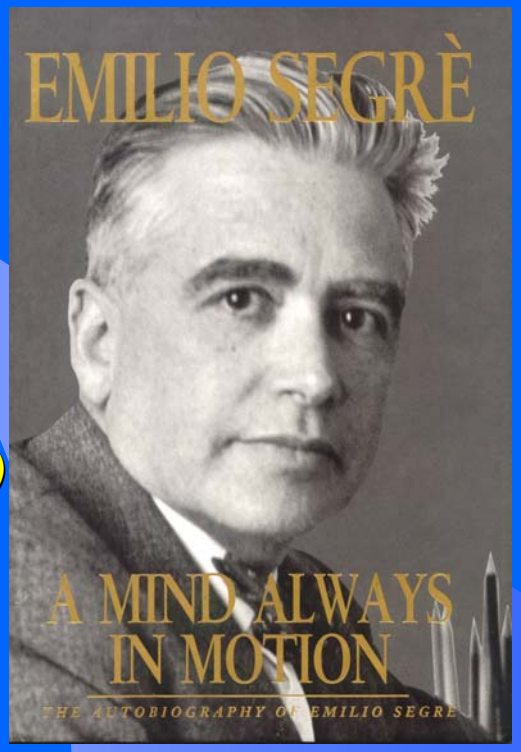


In reactors <u>slow neutrons</u> produce

$^{98}Mo + n = {}^{99}Mo + \gamma$

$^{99}Mo\ (66\ h) = {}^{99m}Tc\ (6\ h) + e^- + \overline{\nu}$

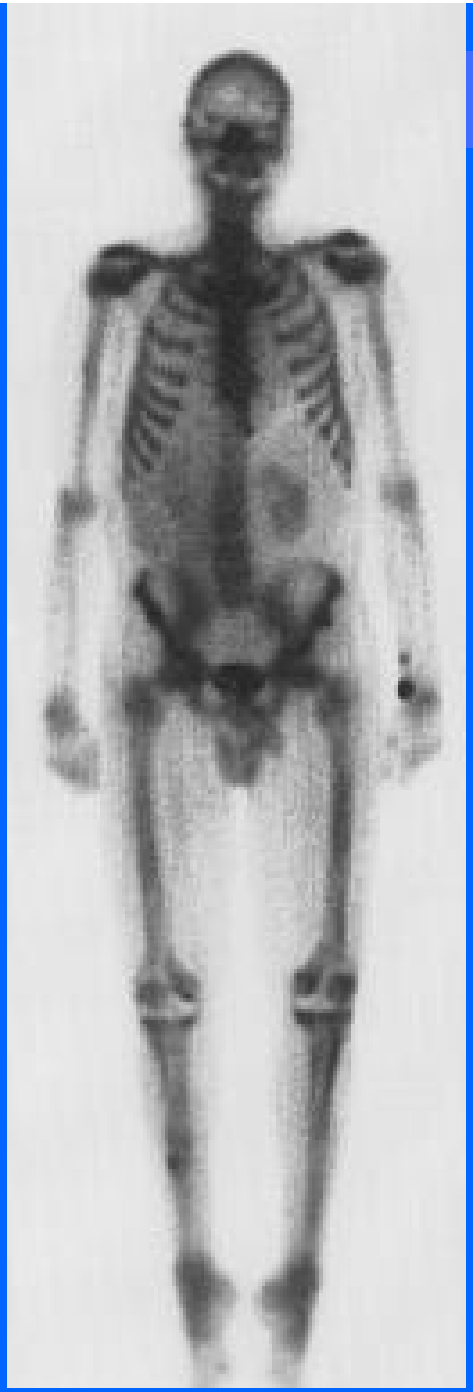
emmission of gamma of 140 keV



Emilio Segrè

1937: Discovery of element 43 "Technetium" ^{97}Tc(2.6 My)

1938: discovery of ^{99m}Tc with E. McMillan

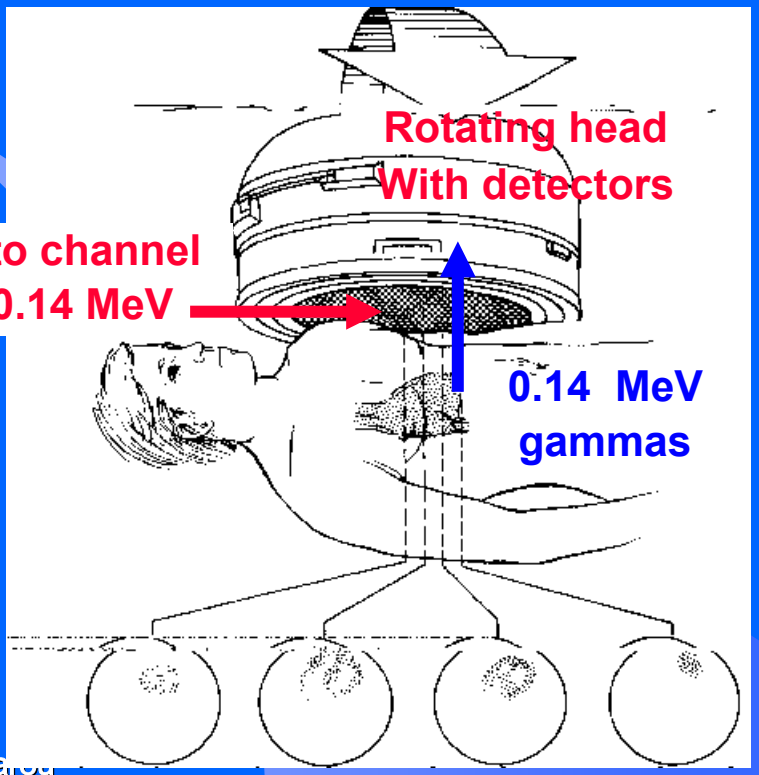


SPECT scanner

85% of all nuclear medicine examinations use technetium

… liver,lung, bones …

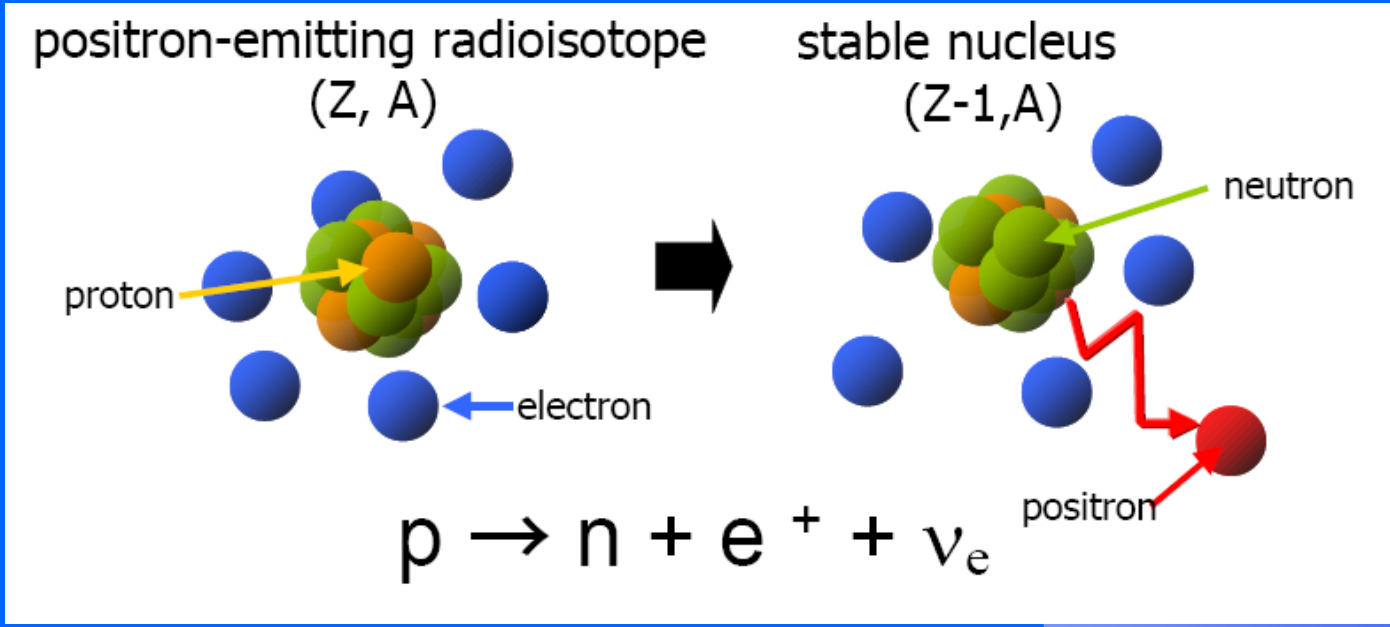
- Measurement of the density the molecules which contain technetium
- Information on morphology and/or metabolism



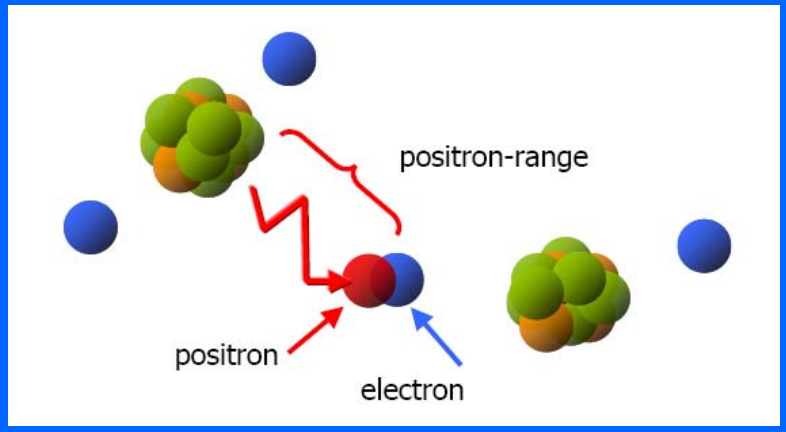
Positron Emission Tomography (PET) How does it work?

β^+ emiting Isotopes → T1/2 :

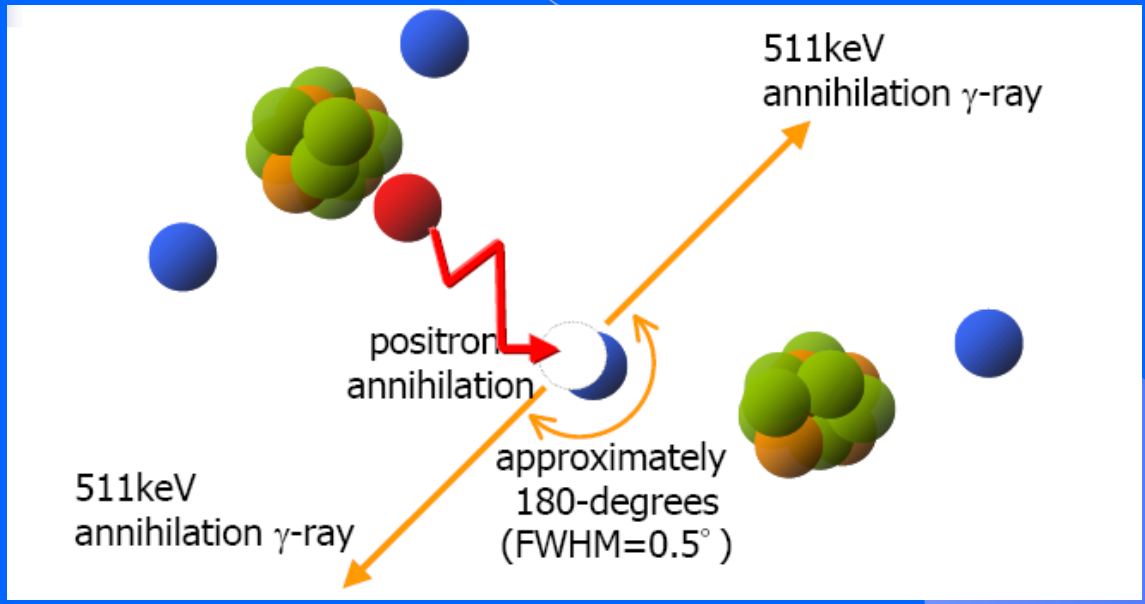
^{18}F	^{15}O	^{11}C	^{13}N
114 min.	2 min.	20 min	10 min



Thermalization of the positron in biological tissu



Positron Annihilation : $e^+e^- \rightarrow \gamma\,\gamma$

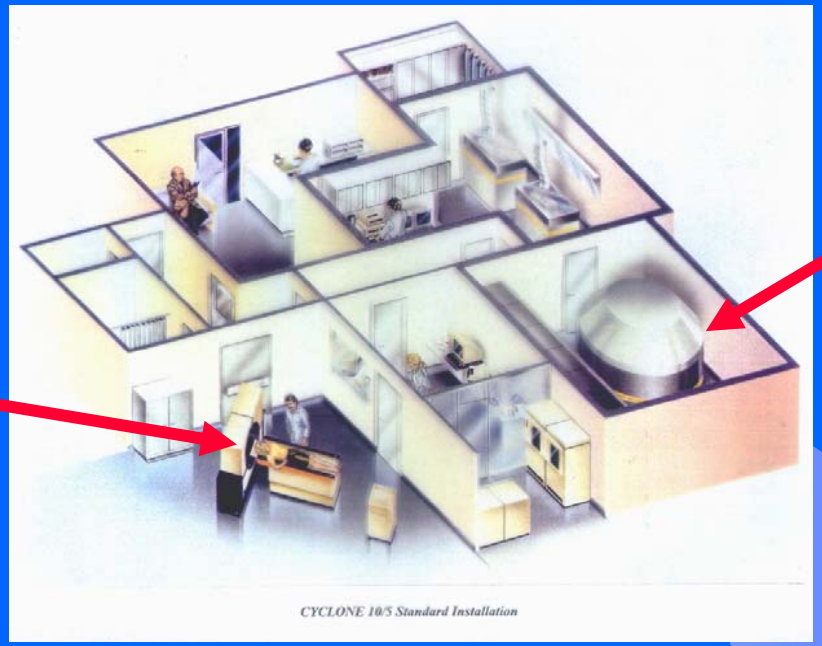


Positron Emission Tomography (PET) How does it work?

These isotopes are produced by proton reaction on stable nuclei using a cyclotron (IBA, Cyclopharma..) ➔ ideal configuration cyclotron should be close of the PET in hospital

General electric

PET tomograph



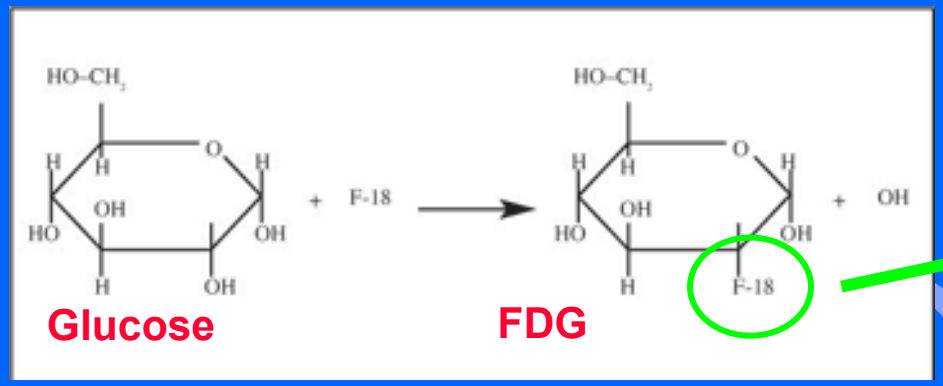
Cyclotron
Protons

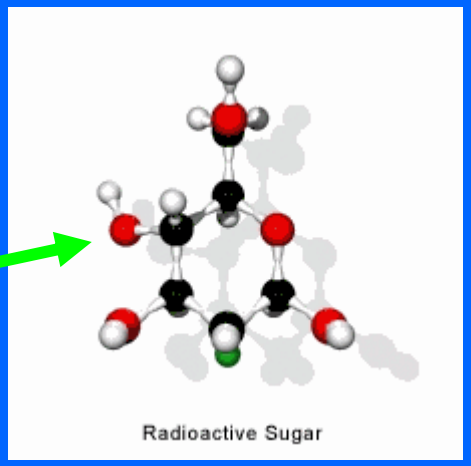
~15 MeV, ~50 μA

IBA

90 % of the radiopharmaceutic molecules used in PET is FluoroDesoxyGlucose with $^{18}F \Rightarrow$ FDG

- $H_2{}^{18}O$ water is bombarded with protons to produce ^{18}F
- Fluoro-Deoxy-D-Glucose (FDG) is synthesized





- FDG is transported to the hospital
- FDG is injected into the patient
- FDG is trapped in the cells that try to metabolize it
- Concentration builds up in proportion to the rate of glucose metabolism

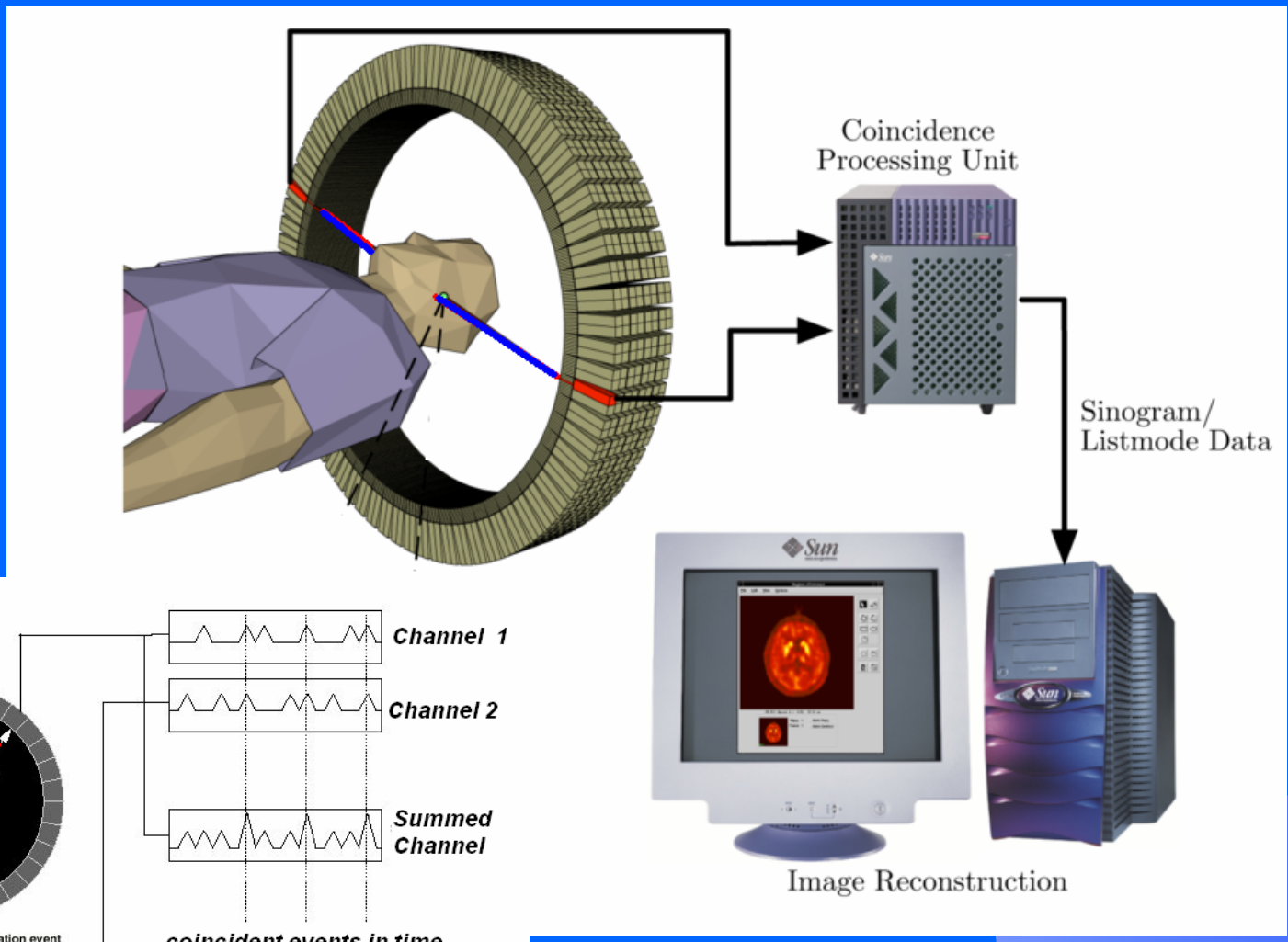
To few FDG production centers !! ➔ bootleneck for PET use in hospital

Active research field at the interface between nuclear physics and chemistry for the production of other kind of radiopharamaceutic

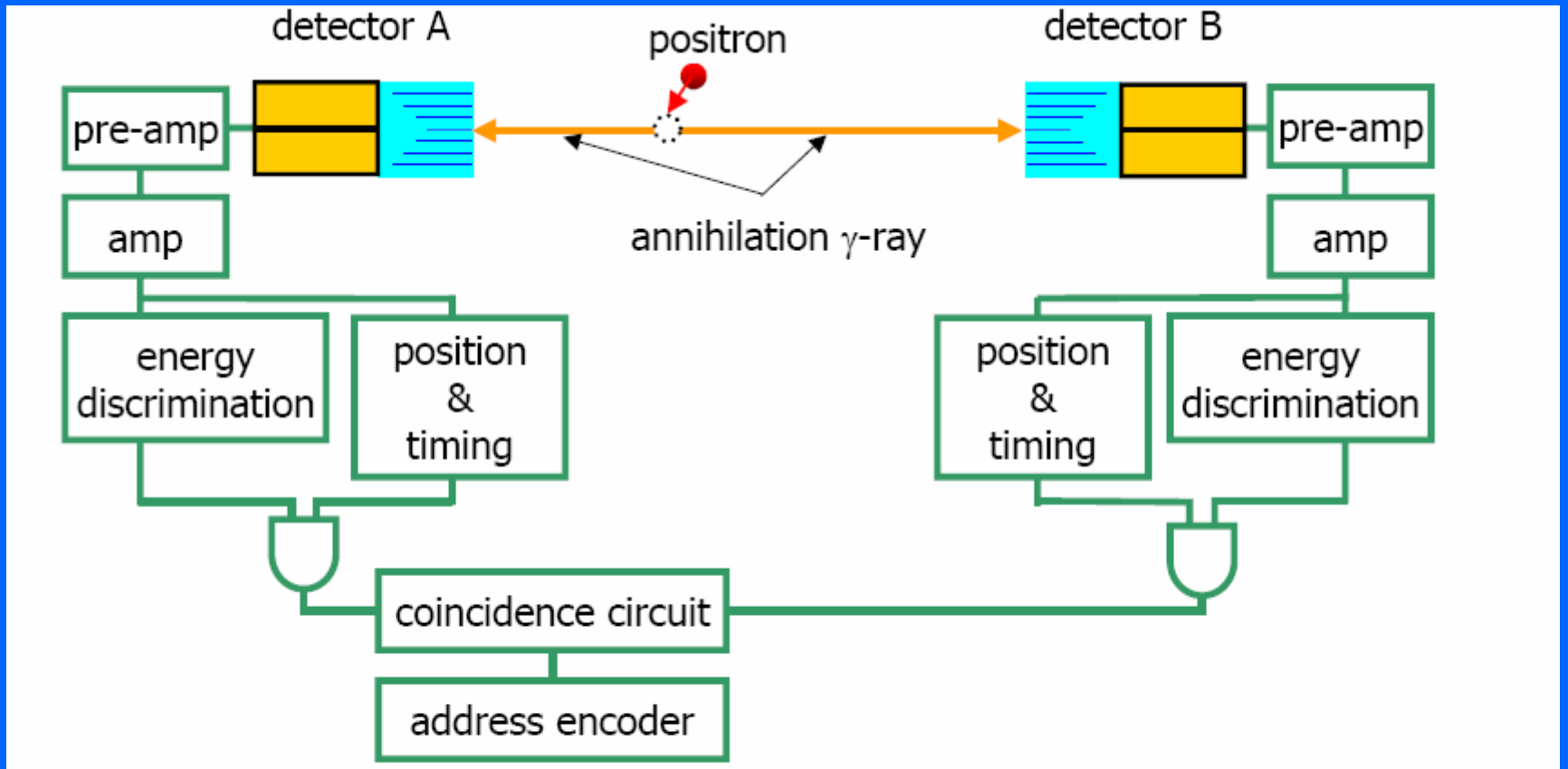
➔Accélérateur pour la Recherche en Radiochimie et Oncologie à Nantes Atlantique (ARRONAX)

Research center for production of innovative radioisotopes
➔ IBA Cyclotron 70 MeV, 750 microamps

One signal event = detection of two 511 keV γ in time coincidence in two back to back detectors



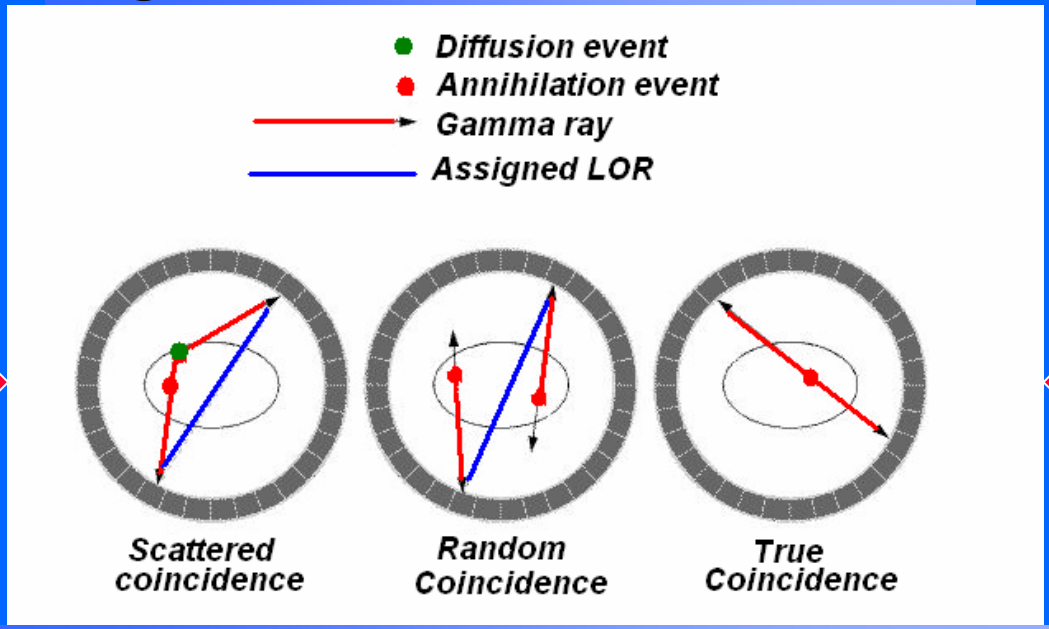
Positron Emission Tomography (PET)= electronic collimation



Coincidence detection determines a unique detection line (LOR: Ligne of response) which is used to forming tomographic images with PET

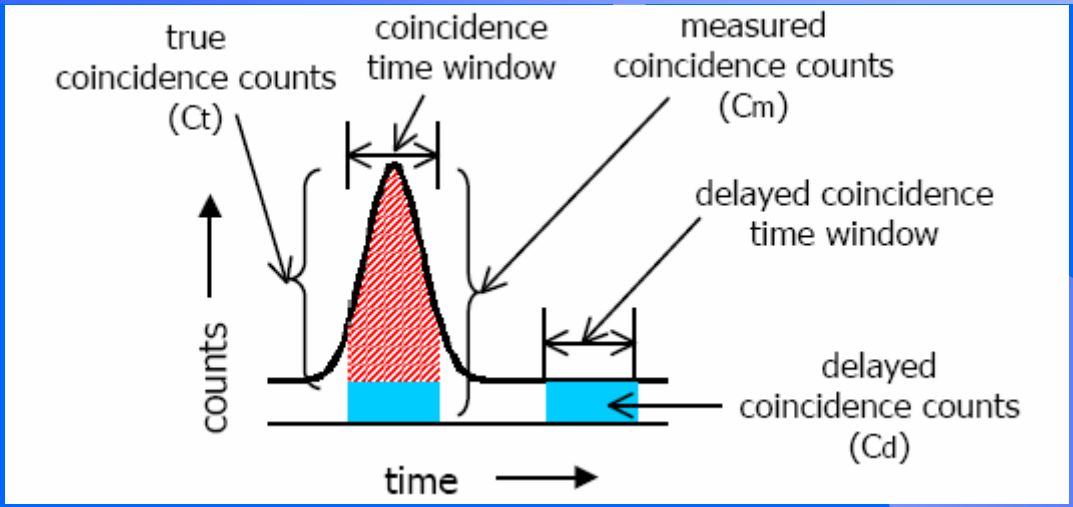
Signal and Noise Events

Random events = Noise



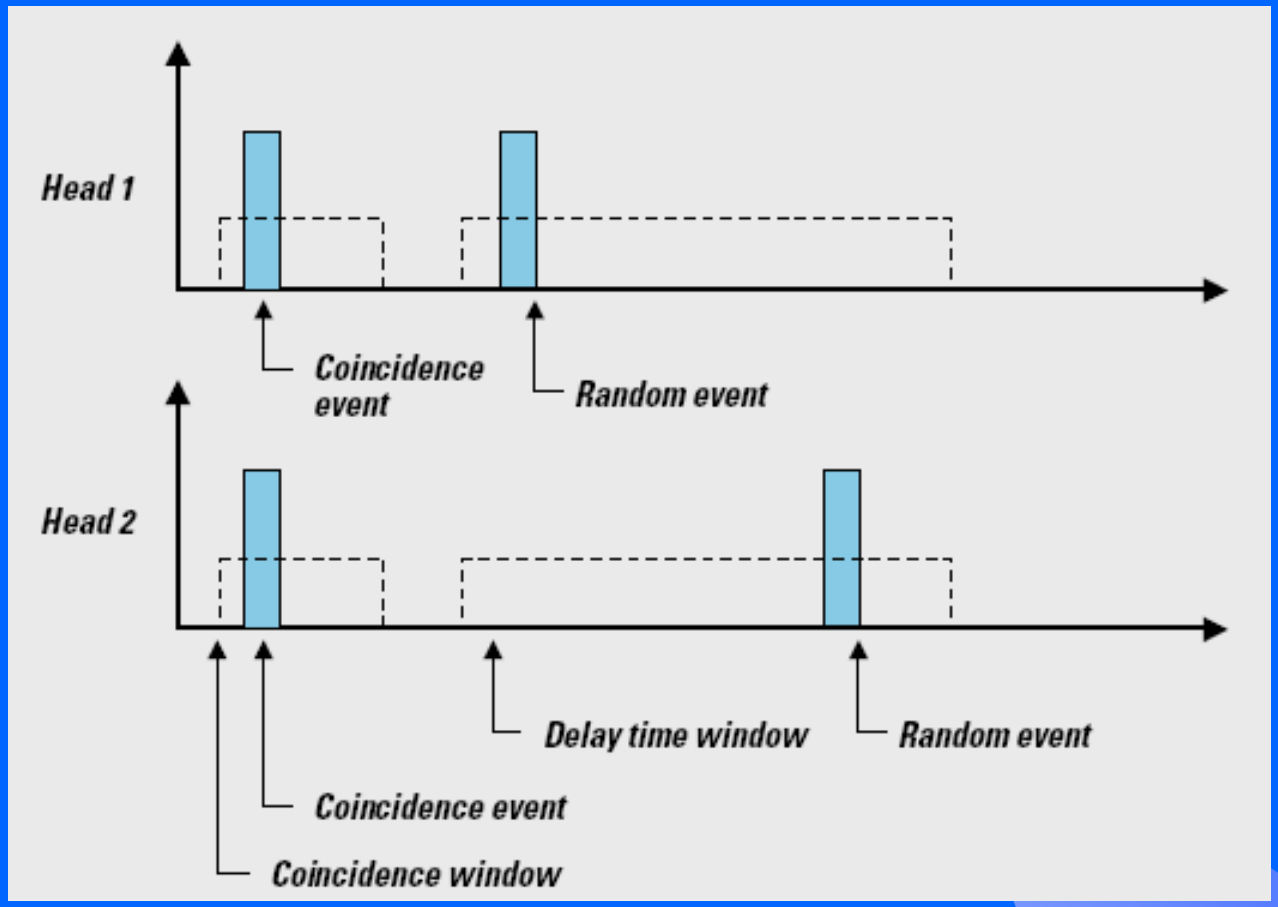
True event = Signal

Noise = Random Coincidence in time

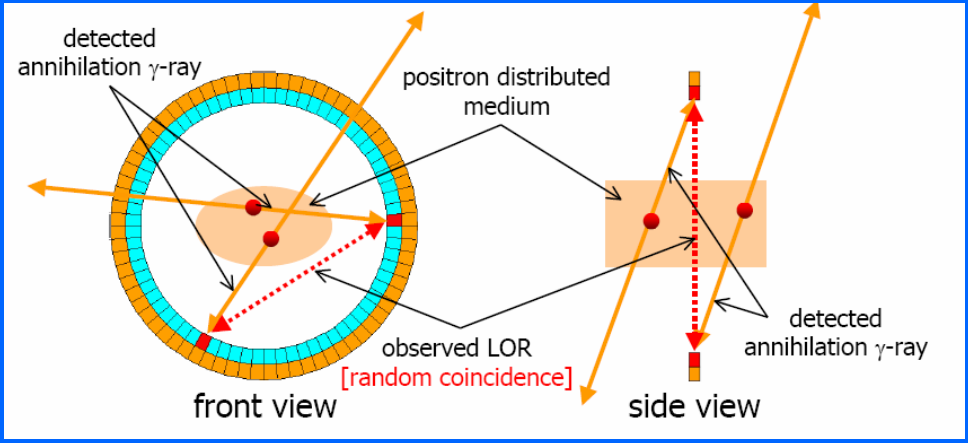


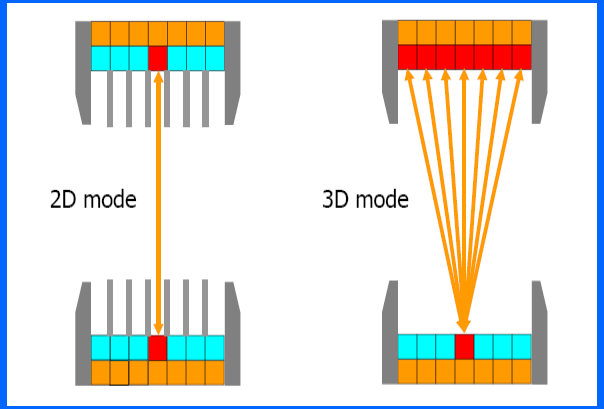
Delayed coincidence method → $Ct = Cm - Cd$

Random Coincidence estimation = delay time window counts

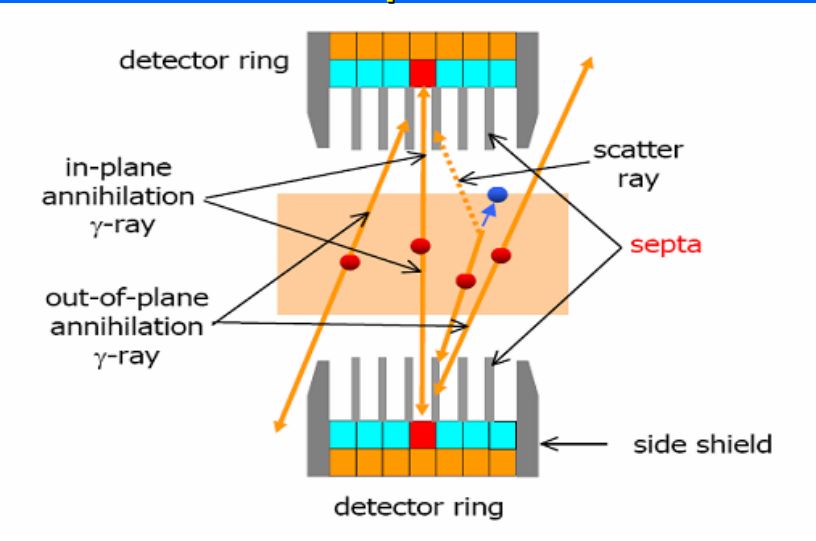


2D (septa) vs. 3D (no septa)



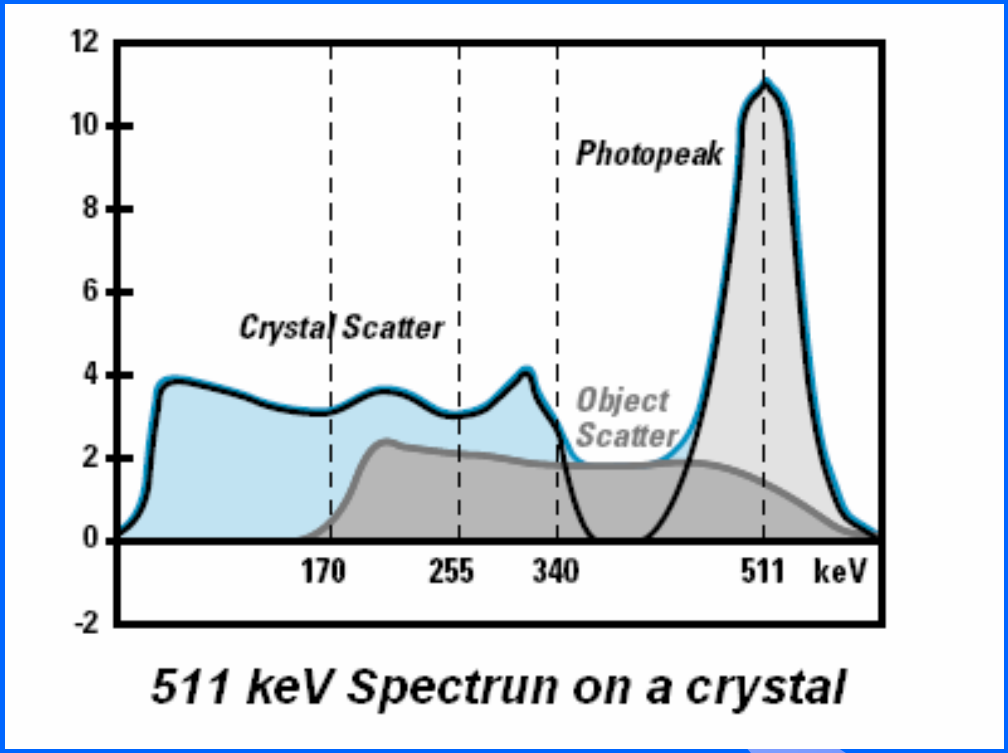


Septa are interring collimators that shield detectors from out-ofplane annihilation γ-rays And scatter rays at a conventional 2D out-of-plane mode scan.



In the 3D-mode scan, septa are retracted for inter-plane coincidence at over all planes. Therefore the system efficiency can be greatly increased. But the retraction of septa increases detection events of out-of-plane annihilation γ-rays and scattered γ-rays.

Energy window selection to cuts scatter events



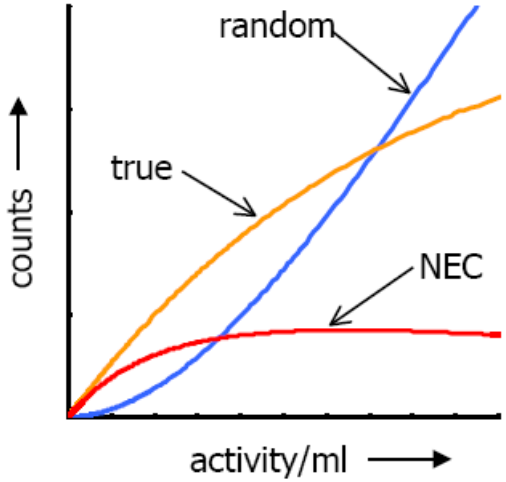
511 keV Spectrun on a crystal

Scatter decreases with high energy threshold but *depends on energy resolution*

Noise Equivalent Counts (NEC)

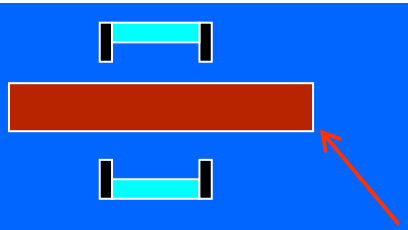
True count rate dose not directly indicate the signal-to-noise ratio in a PET image.

The NEC defines an effective true count rate by accounting for the additional noise from scatter and random events.



$$NEC = T / (1 + S/T + 2R/T)$$

NEC	: noise equivalent count rate
T	: true count rate
S	: scatter count rate
R	: random count rate (delayed coincidence)



70-cm long x 20-cm diameter

NEMA 2001 (body)

HOW A PET IS MADE OF ?

γ

Array of Crystals

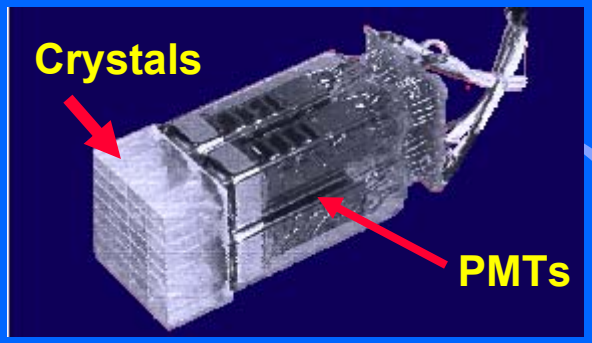
convert gamma incident energy in light (visible photons)

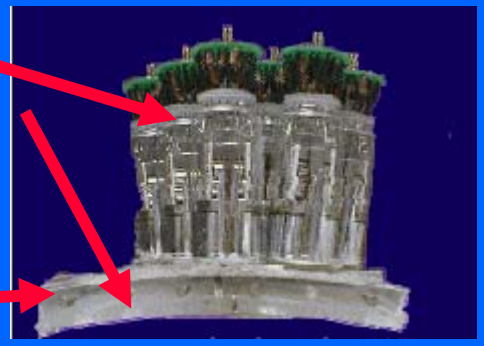
Photodetectors

convert visible photons in electric pulse

Front-end Electronics

transform and convert analogic pulse in numeric data



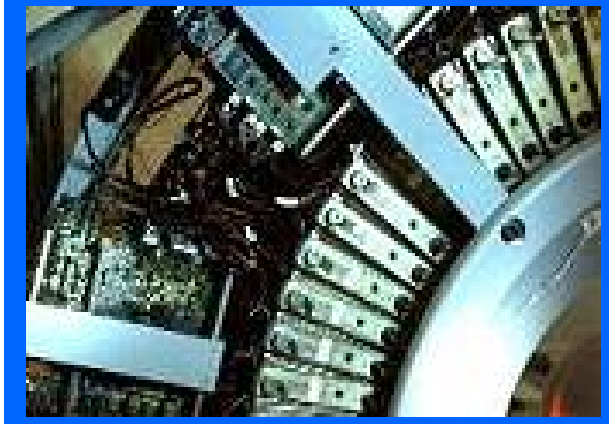


**PMT is magnetic field sensitive*

Cannot be use for PET+MRI

HR+ SIEMENS

32 rings of 576 crystals.
2D/3D.
transversal spatial resolution : 4,5mm
axial resolution : 3,6mm



Small Animals PET

Pharmacology studies use animal models ➔ Smaller PET for Animals

Dedicated small animals multimodal imaging Plateforms

➔Imaging system develloped in laboratory by physical groups but used by biological groups

A very small PET for mouse

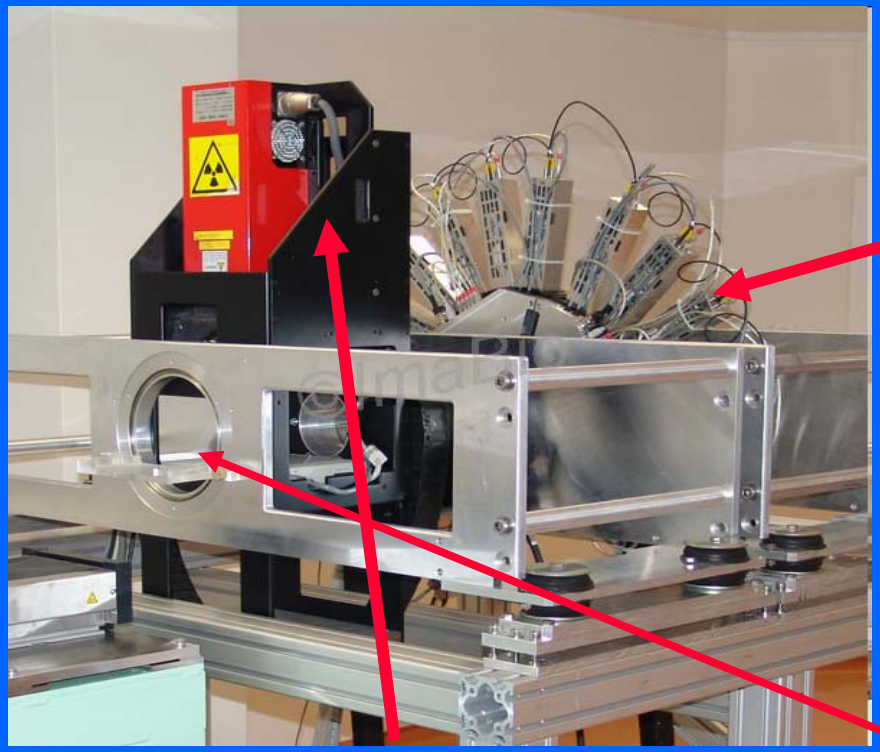
The RatCAP PET in Brookhaven

Examples of multimodal platforms

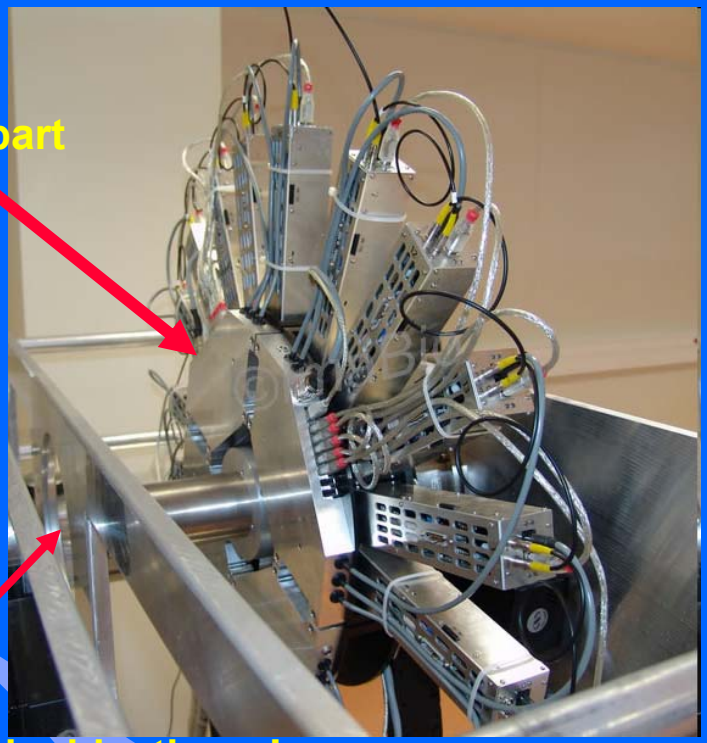
➔ AMISSA platform (μCT/μSPECT/μPET) at IPHC Strasbourg

➔ ImXgam platform (μCT/μPET) at CPPM Marseille

The AMISSA MULTIMODAL PLATFORM (IPHC)



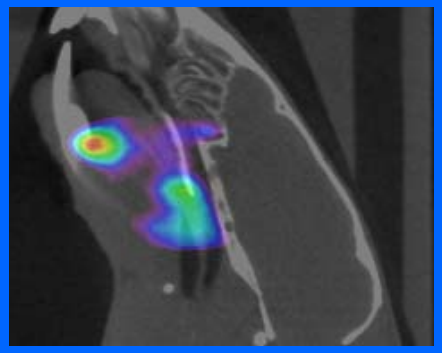
SPECT part

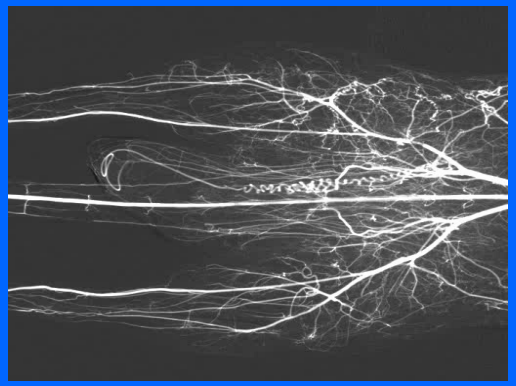


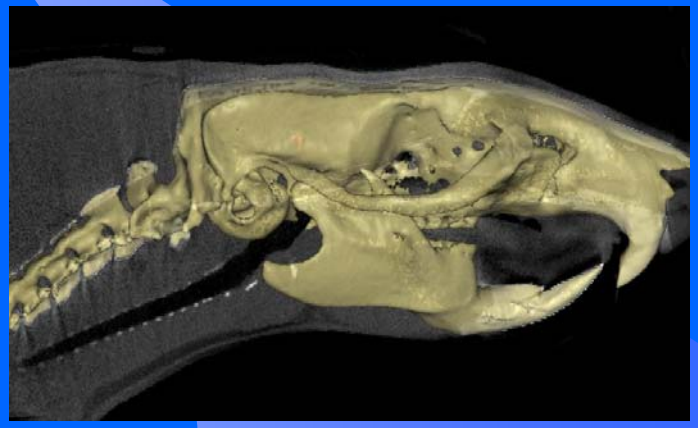
Rotating CT part

The rat should go inside there !

Some Images !

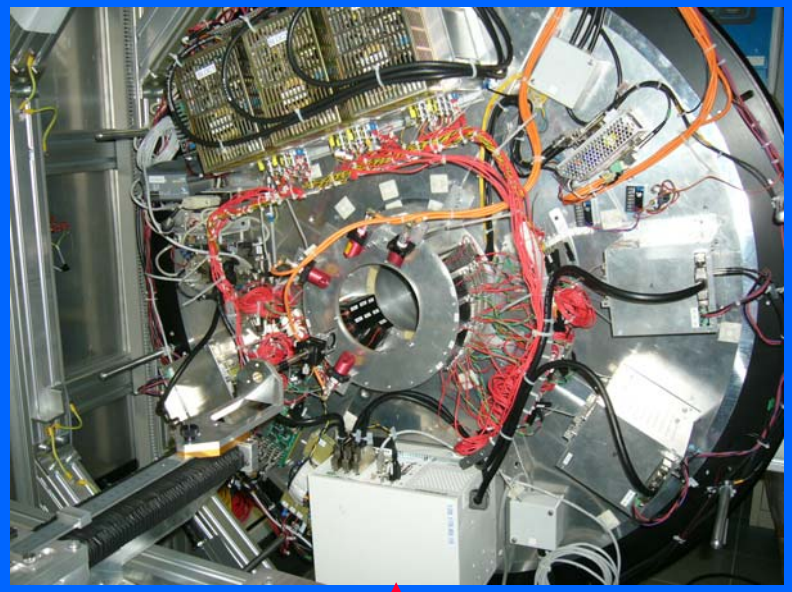




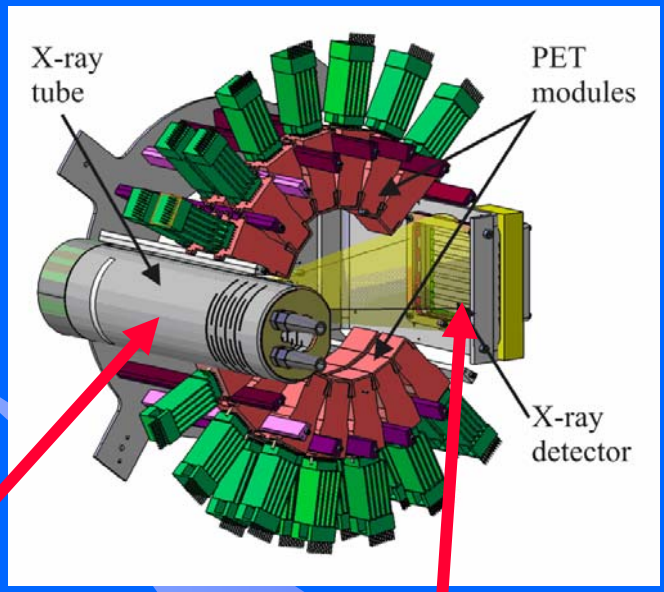


The imXgam MULTIMODAL PLATFORM (CPPM Marseille)

Based on the ClearPET from EPFL Lausanne but modified to achieve simultaneous small animal X-ray CT-scanner based on ultra fast hybrid pixels in collaboration with the Developmental Biology Institute of Marseille-Luminy (IBDML).



The original ClearPET



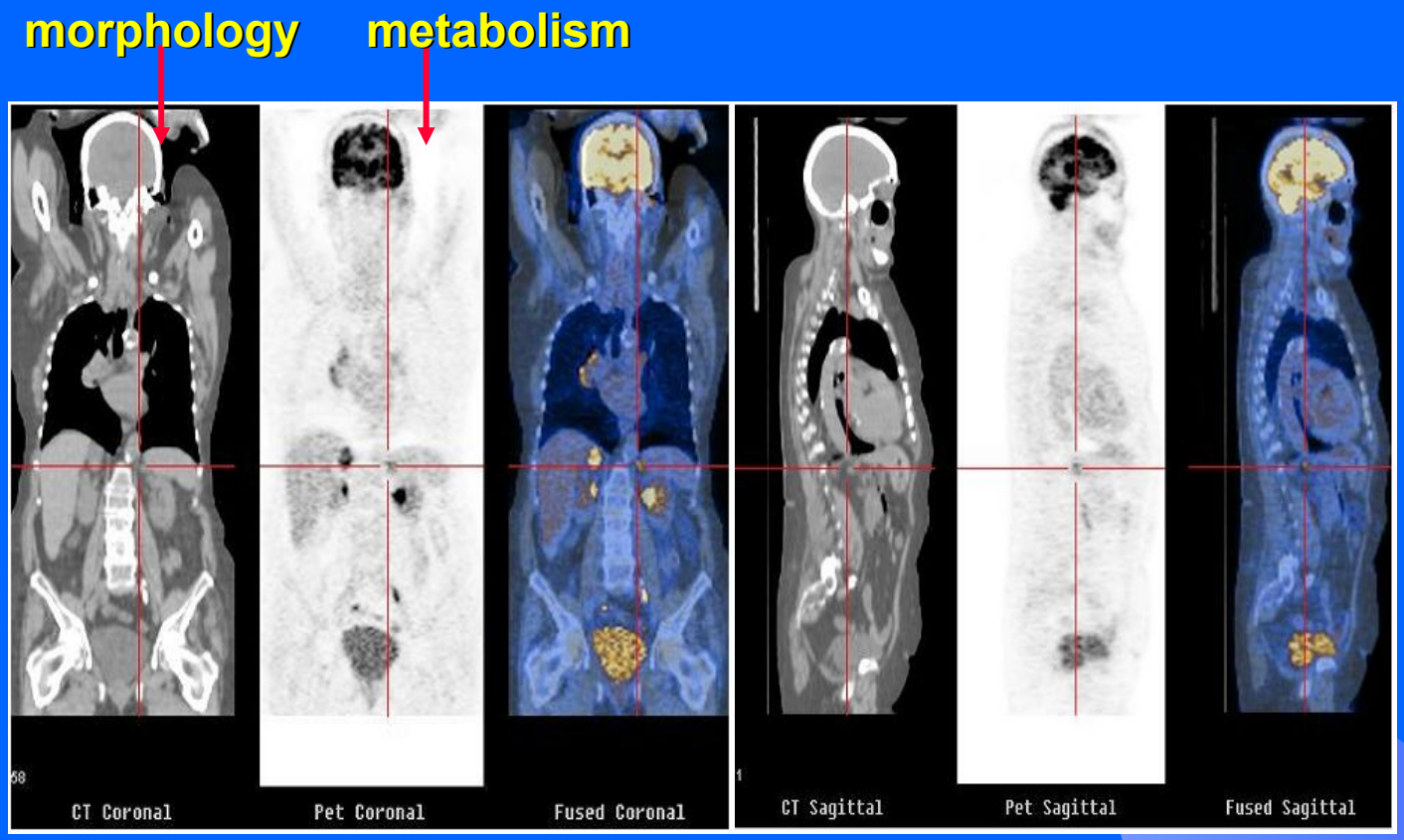
X ray source

Hybrid Pixel detectors (XPAD3)

118×76 mm2 with 130×130 µm2 pixels

How to improve PET imaging

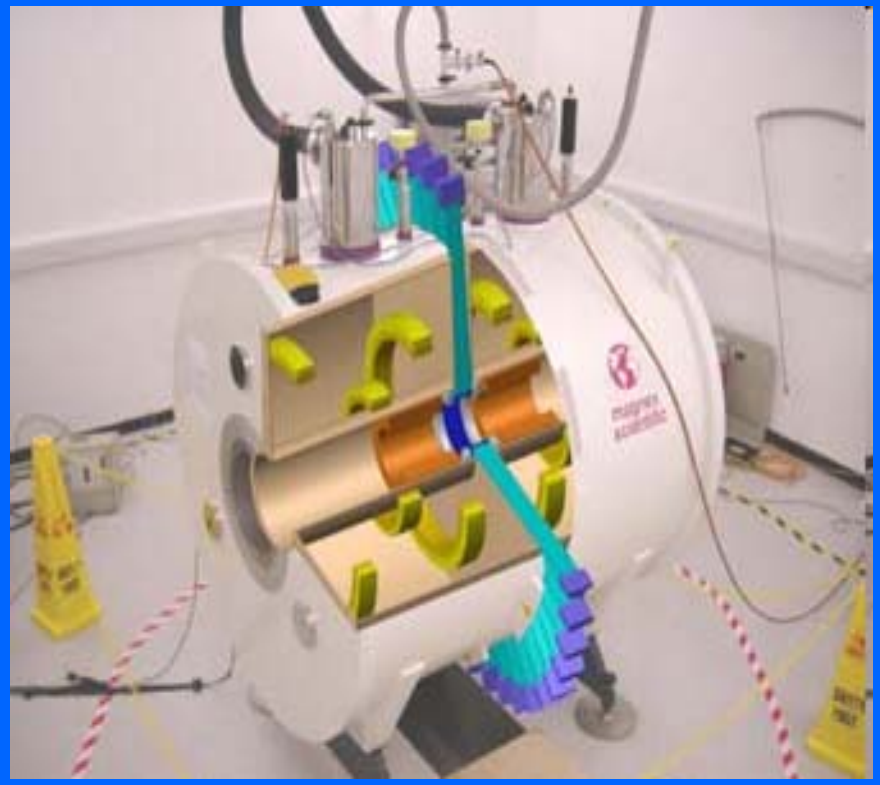
1°) As we already seen in previous slides, extensive use of multimodality imaging ➔ PET+CT is now currently used in hospital



How to improve PET imaging

➔ **PET+MRI is quite difficult**

MRI scanners rely on very strong, very smooth magnetic fields that can easily be disturbed by metallic objects inside the scanner. At the same time, those magnetic fields can seriously affect the detectors and electronics needed for PET scanning

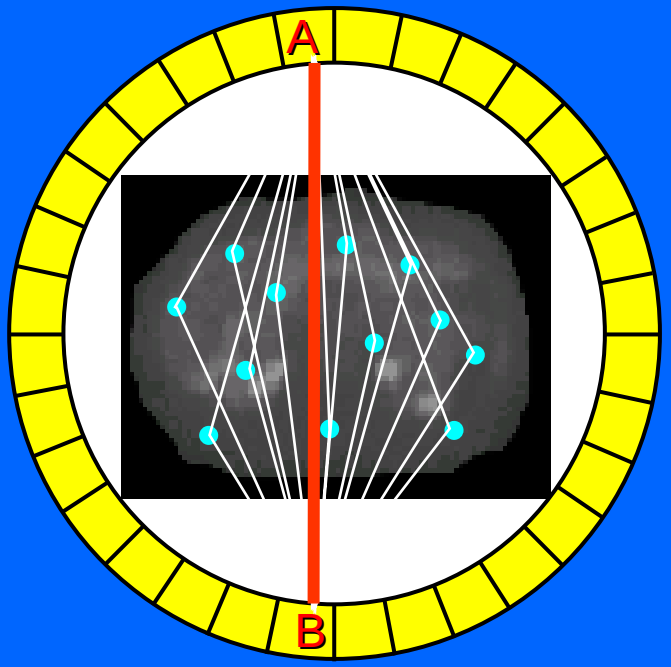


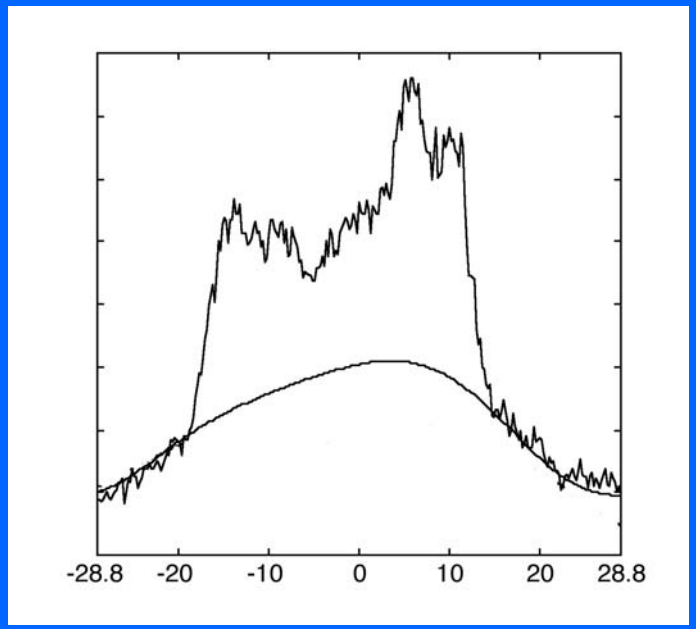
PET+MRI at Cavendish University

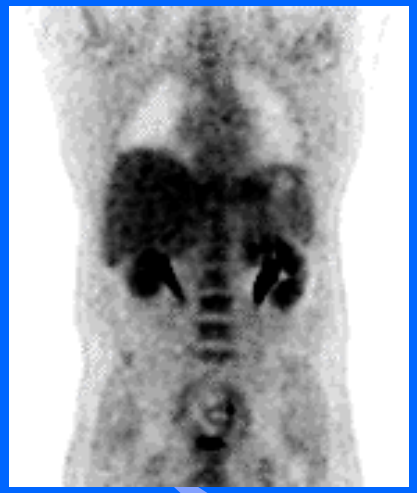
2°) Scatter corrections

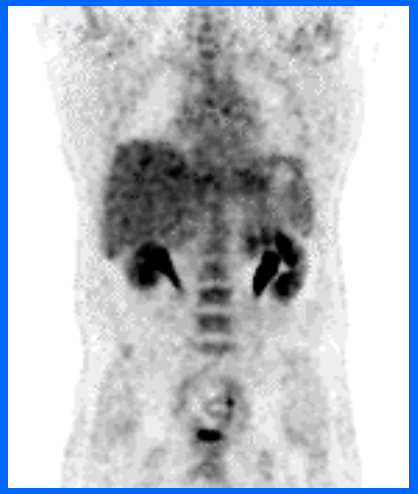
3°) Attenuation corrections

Scatter Correction









Before Scatter correction

After Scatter correction

Single Scatter - Model based correction
Calculate the contribution for an arbitrary scatter point using the Klein-Nishina equation

Attenuation Correction

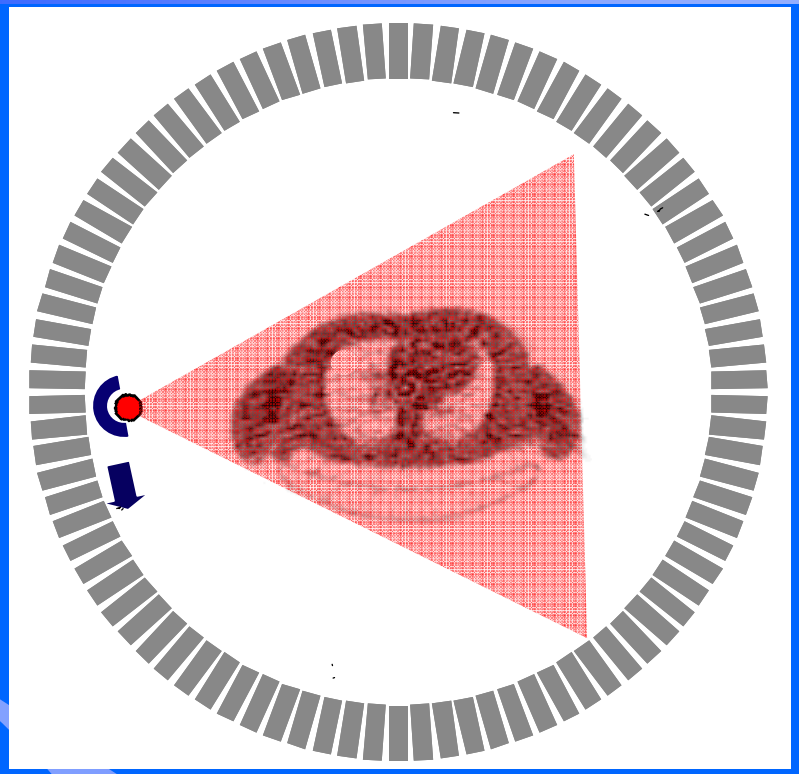
Attenuation correction with radioisotope transmission scan

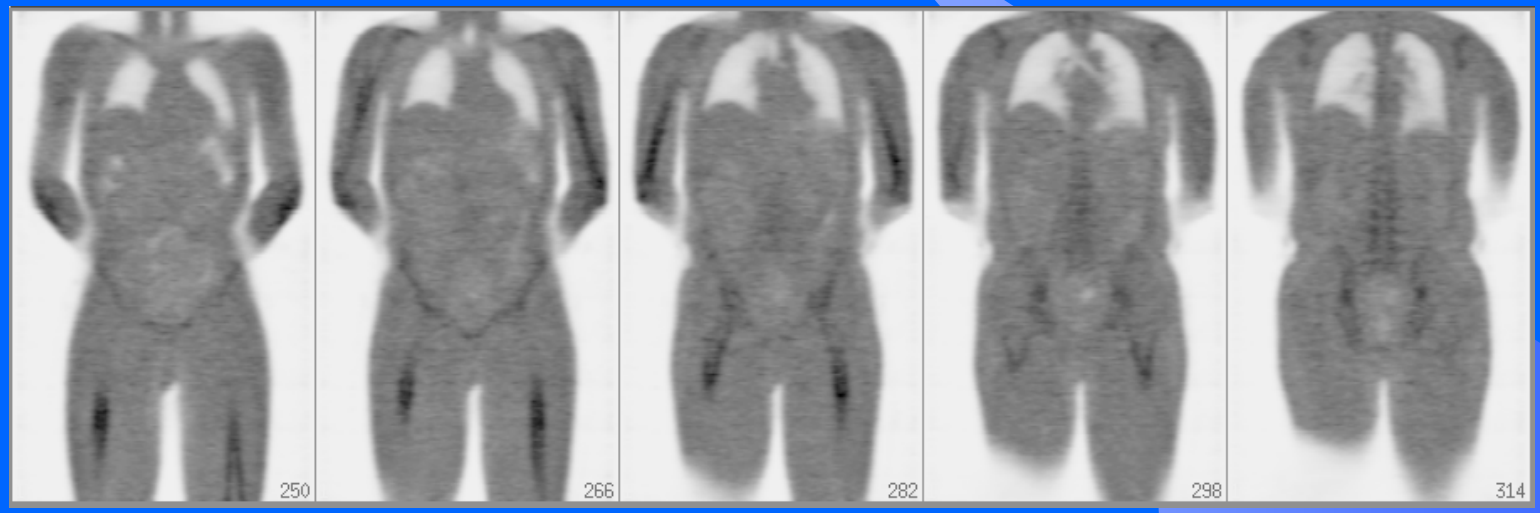
20 mCi ^{137}Cs source - 662 keV

$$A = 1 / e^{-\mu d}$$

d = length of chord through tissue

μ = attenuation coefficient

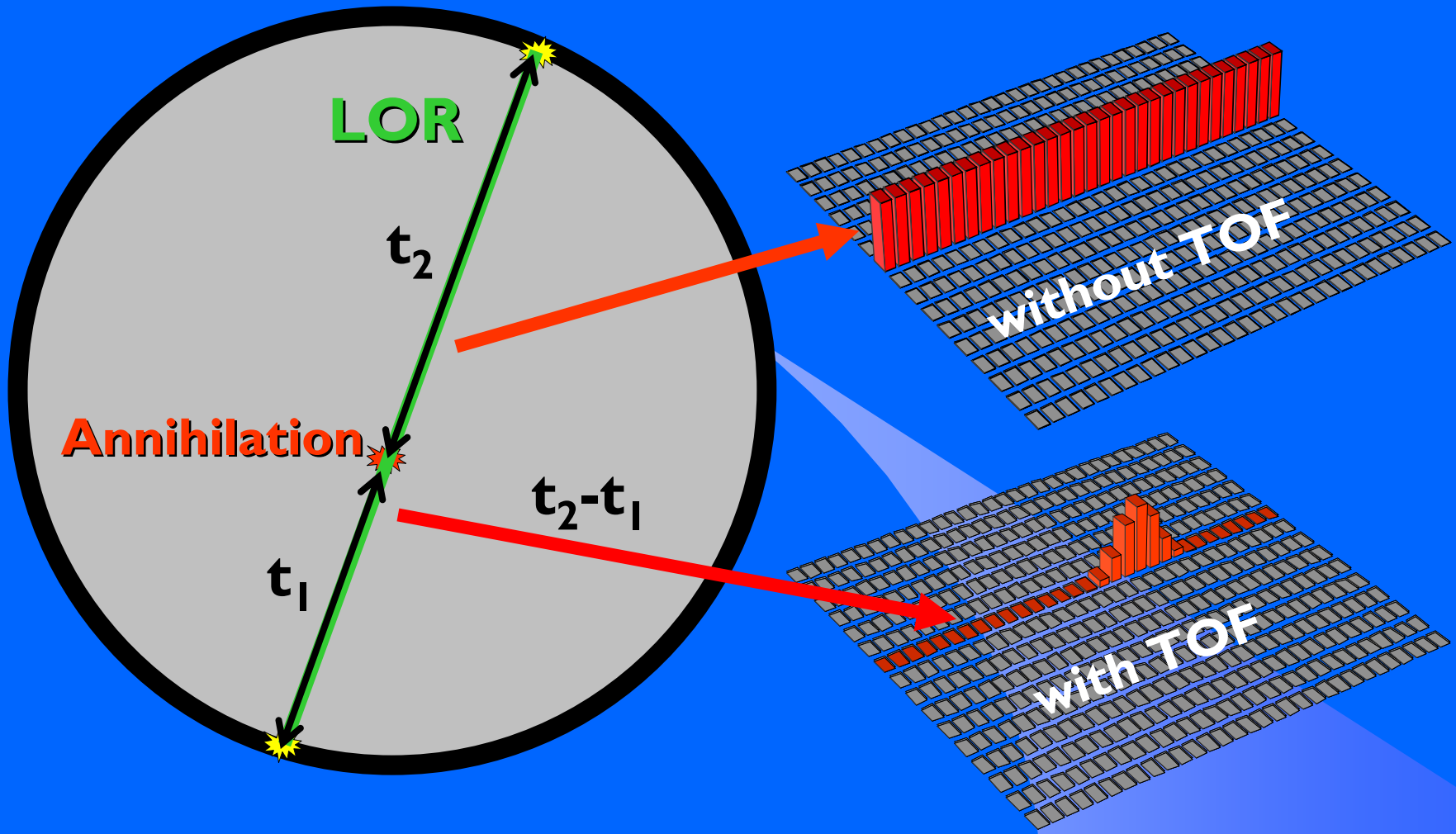




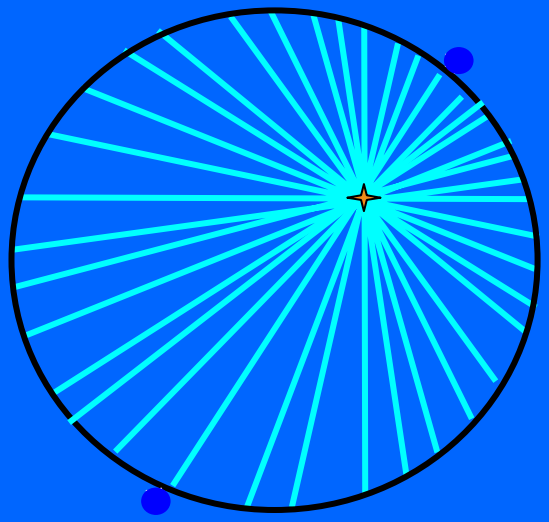
How to improve PET imaging ➔ Time of Flight PET

Basic Concept of Time-of-Flight-PET

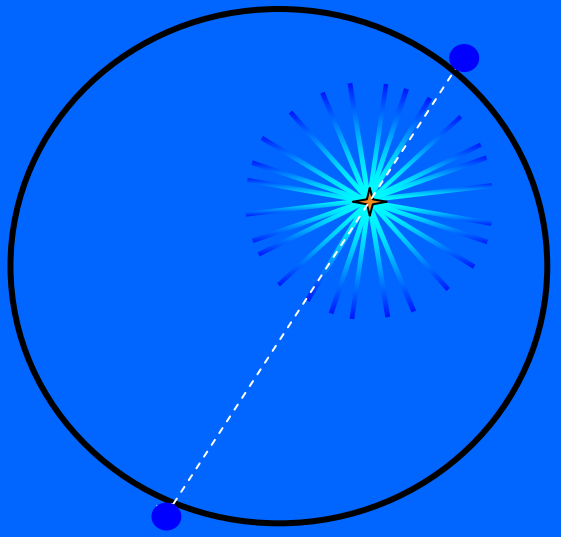
Localization of source along line of response depends on timing resolution Δt



TOF PET vs. Conventional PET



Conventional PET Image Formation



TOF PET Image Formation

More precise localization of annihilation event reduces noise

$$\Delta \text{ sens.} = \frac{D}{\Delta x}$$

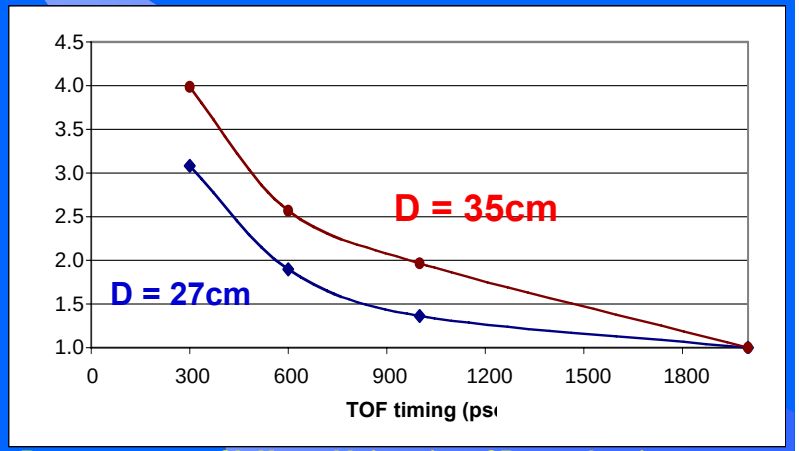
Lesion detectability model using numerical observer and iterative reconstruction

D: Object size

$$\Delta x = c * \Delta t / 2$$

c :Speed of Light

Δt : system timing res.



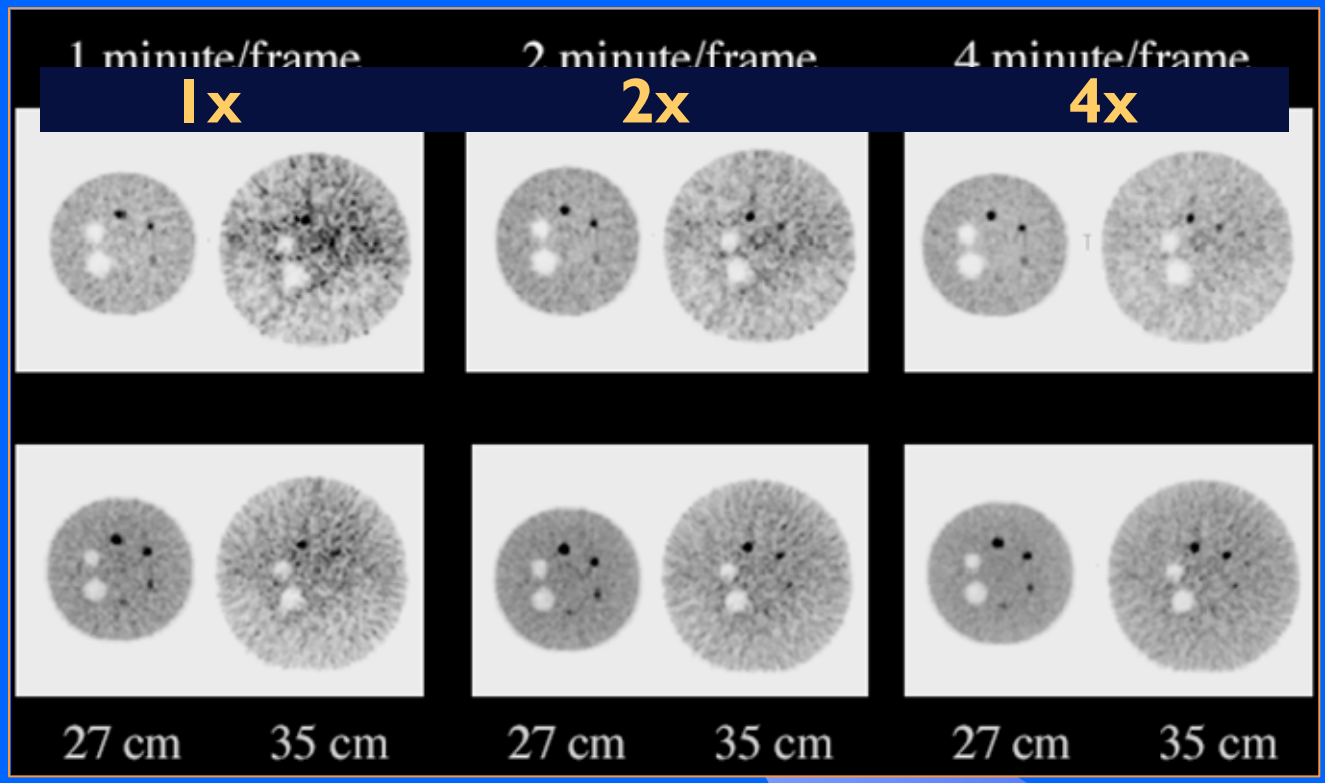
Data courtesy of J. Karp, University of Pennsylvania

Image comparison (phantoms) ToF – non ToF

Imaging Time

Non-Time of Flight

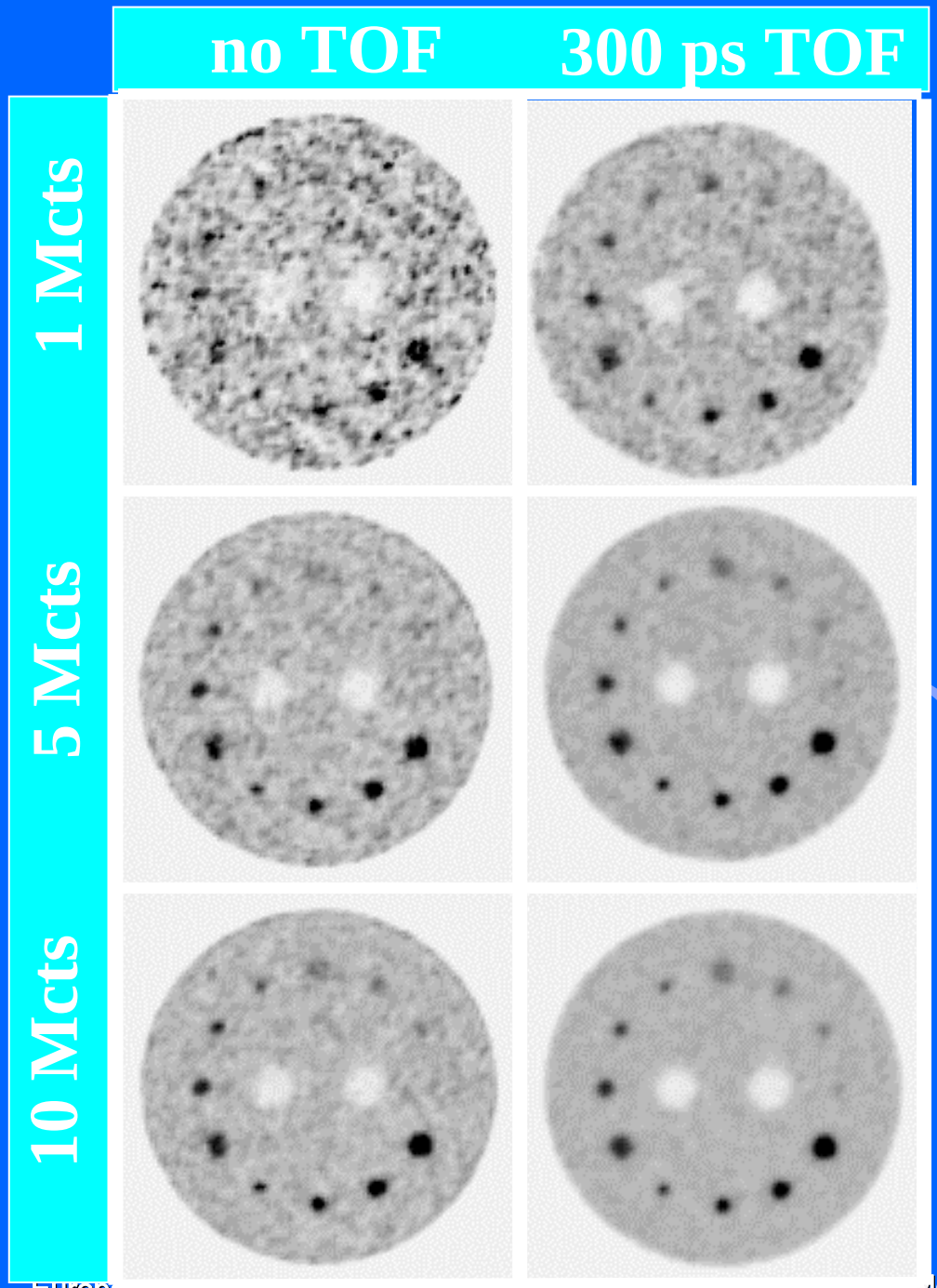
Time of Flight



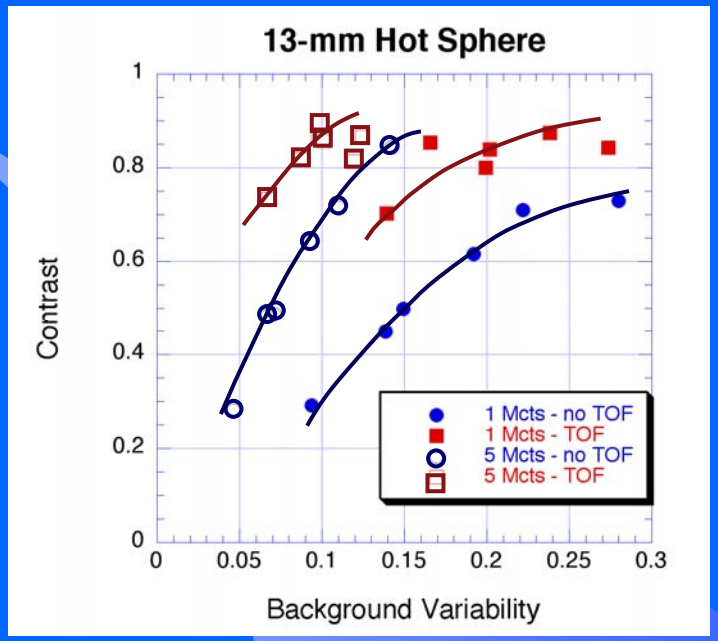
Time of flight reduces noise resulting in higher image quality, shorter scans or lower dose.

Phantom studies (IEC spheres in a 27 cm diameter and 35 cm diameter cylinder)
Data of J. Karp, University of Pennsylvania

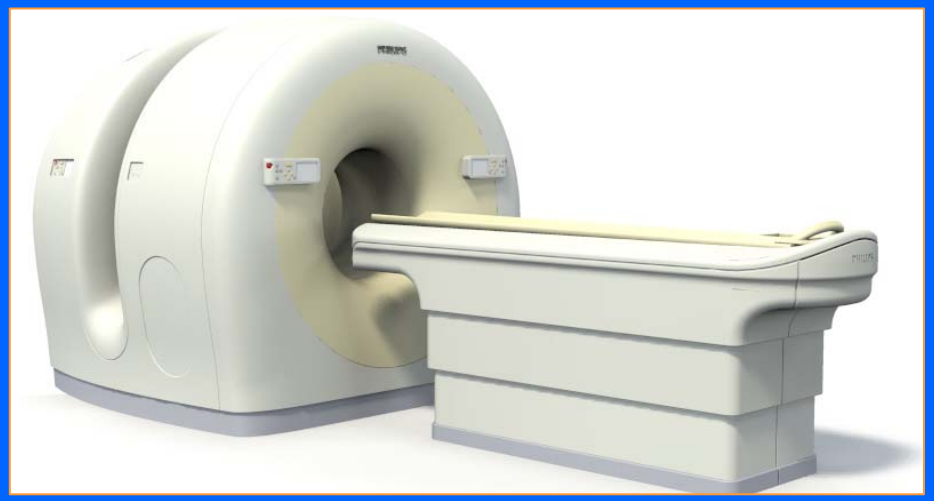
Time-of-Flight : list-mode iterative reconstruction



5Mcts TOF
5Mcts
1Mcts TOF
1Mcts



PHILLIPS GEMINI TF™: *Performance summary*



PET scanner

LYSO : 4 x 4 x 22 mm^3

28,338 crystals, 420 PMT's

crystal gap: 0.75 µm

$2\tau = 4$ ns

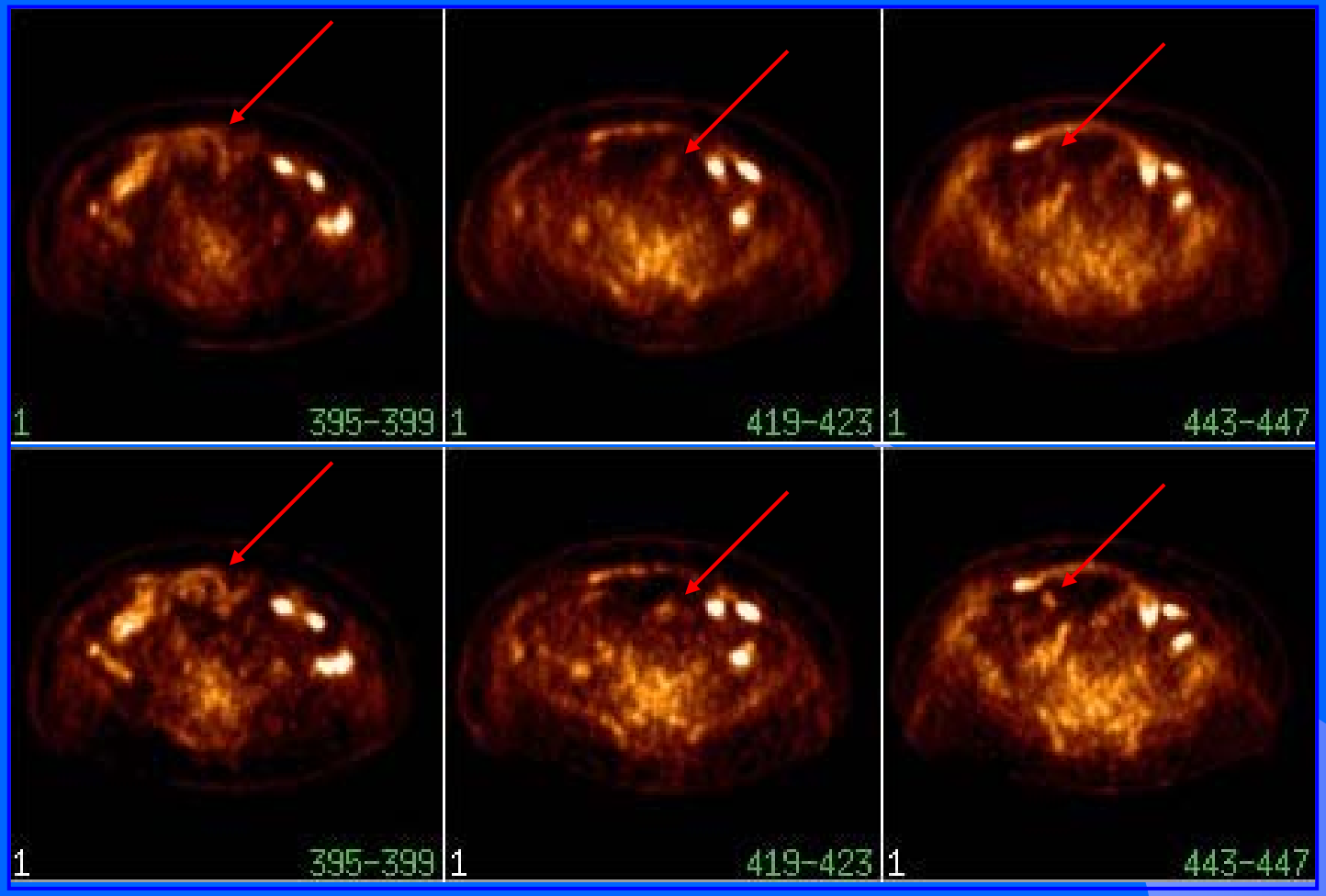
70-cm bore, 18-cm axial FOV

CT scanner

Brilliance™ 16 or 64 slice

	NEMA	LOR-TOF
Spatial resolution @ 1cm off center:		
transaxial (mm)	4.8	4.3*
axial (mm)	5.2	4.2*
Sensitivity (kcps/MBq):	6.6	
Energy resolution (FWHM):	12%	
Scatter fraction @ 440 keV:	29%	
Peak NEC (kcps@mCi/ml):	97@ 0.42	eff. NEC > x 4

TruFlight™: *Clinical Image Quality Improvement*



list-mode non-ToF

list-mode ToF

Data courtesy of J. Karp, University of Pennsylvania

PHILLIPS GEMINI TF™ *in "Val de Grace" hospital (Paris)*
Typical TOF Performance between 450 and 500 ps

➔ To improve TOF resolution, we should go below 200 ps

TOF resolution:

More brilliant and faster crystals (LSO, LaBr3:Ce,????

Fast photodetector (from PMT to SiPM and MCPPMT)

Fast electronic (sampling method ➔ > 1 GHz/s)

Or use different technology like RPC

Crystals

Current Crystal : LSO (orthosilicate of Lutetium doped with cerium

25 000 photon/MeV 40 ns scintillation time

➔Easy to manipulate (not hygroscopic) and relatively ship

➔ Could be improve with Calcium doping

Ca concentration (%)	Light output (photons/MeV)	Decay time (ns)
0.0	30900	43.0
0.1	38800	36.7
0.2	36200	33.3
0.3	32400	31.3
0.4	34800	31.0

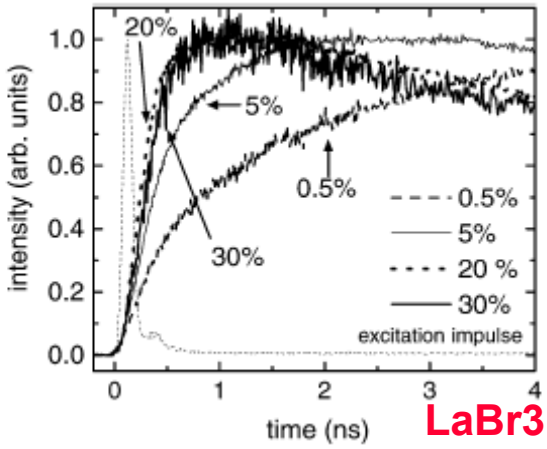
Light output and decay time values are the average of multiple samples.

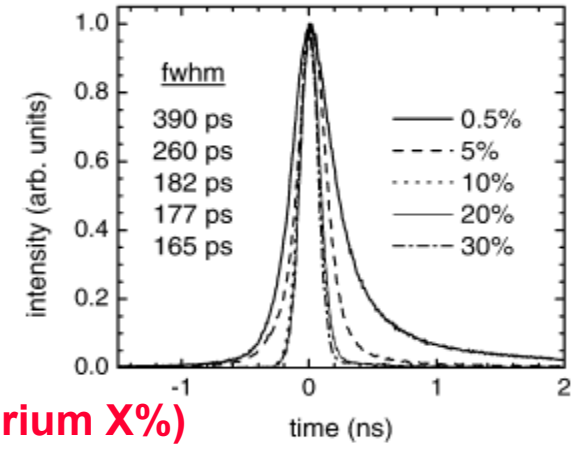
Most efficient Crystal : LaBr3 (Lantanium Bromure doped with cerium

40 000 photon/MeV 15 ns scintillation time

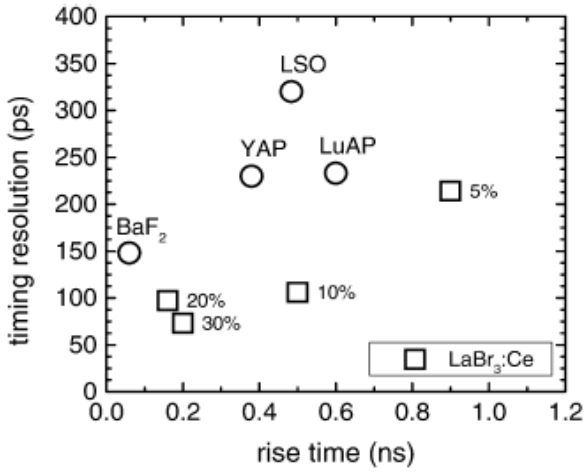
hygroscopic and expansive

Could be improve with Cerium doping

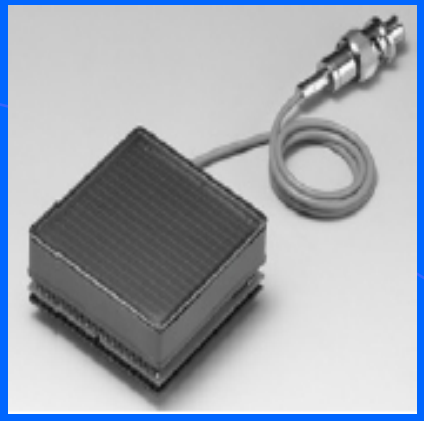


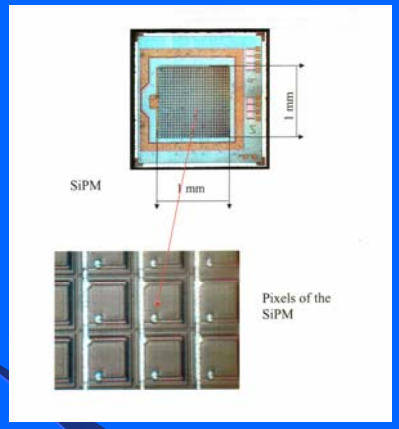


LaBr3 (Cerium X%)



Fast Timing Devices

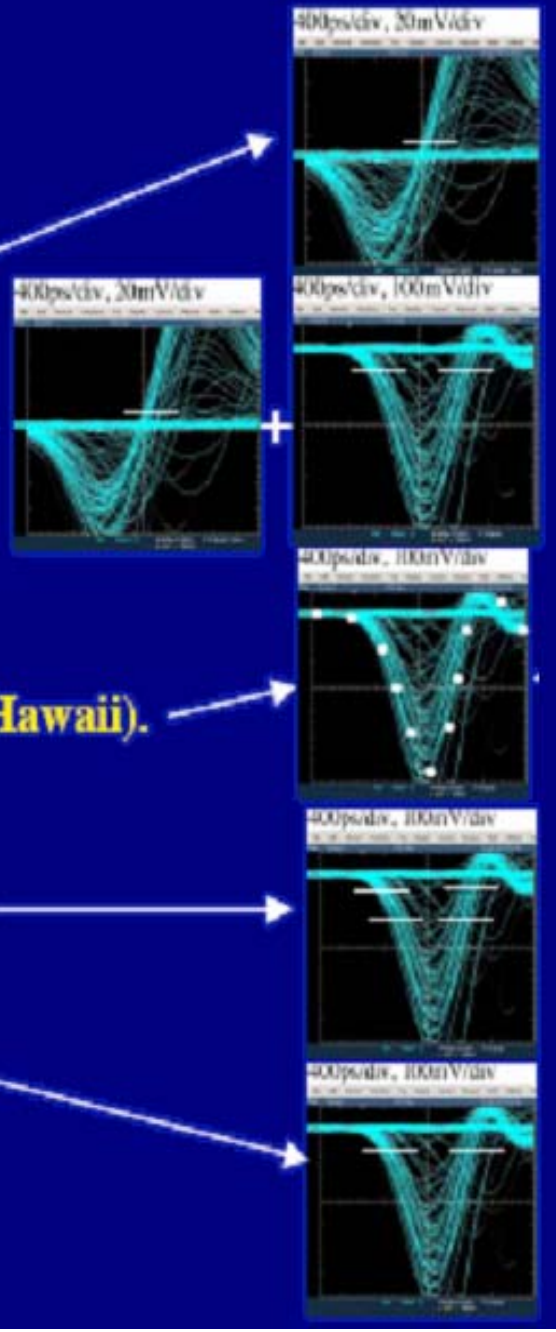




	Multi-anodes PMTs Dynodes	Si-PMTs Quenched Geiger	MicroChannelPlatePMTs Micro-Pores
QE	30%	90%	30%
CE	90%	70%	
Rise-time	**0.5-1ns**	**250ps**	**60-200ps**
TTS (1PE)	150ps	100ps	**20-30ps**
Pixel size	2x2mm2	**50x50mm2**	1.5x1.5mm2
Dark counts	**1-10Hz**	1-10MHz/pixel	1-10 kHz/cm**2**
Dead time	**5ns**	100-500ns	1ms
Magnetic field	no	yes	15kG
Lifetime	-	?	~ Coulomb total charge

Timing strategies

- **Constant-fraction-discriminator (CFD).**
- **CFD + additional pulse height correction.**
  - A slight time-walk as number of photoelectrons corrected by the QTNT + ADC
- **Waveform sampling (a'la Gary Varner's design from U. of Hawaii).**
  - The most powerful timing method.
- **Double-threshold timing on both leading and trailing edges.**
- **Single threshold on both leading and trailing edges.**
  - The most simple.



Alternative technology

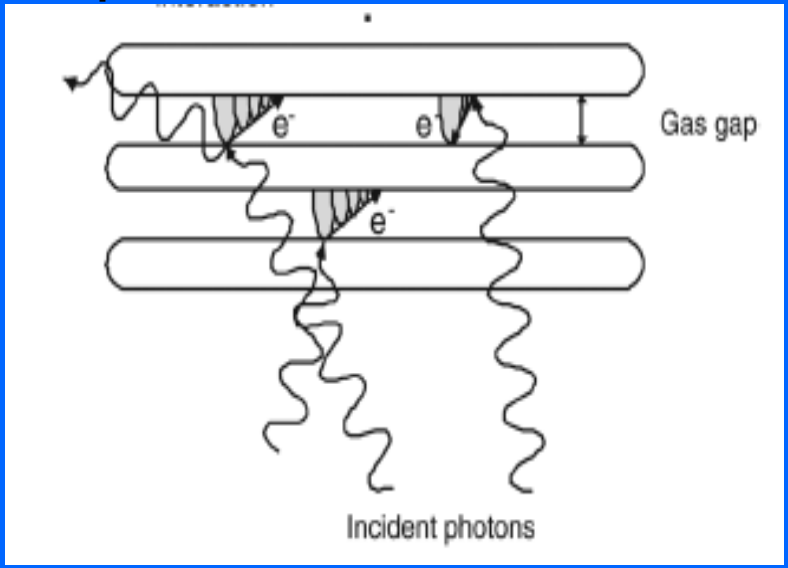
Use of stack of Resistive Plate Chambers (RPC)

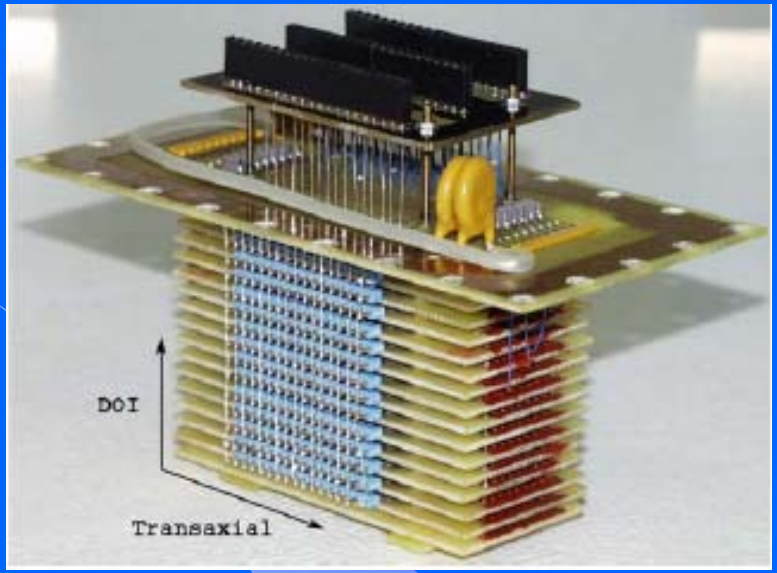
1°) photoconversion of photon to electron

2°) detection of the secondaries produced electron

➔Gazeous detector

➔Absorption of a RPC is limitted ➔ need a stack of detectors





A. Blanco et al NIM 2003 & 2006

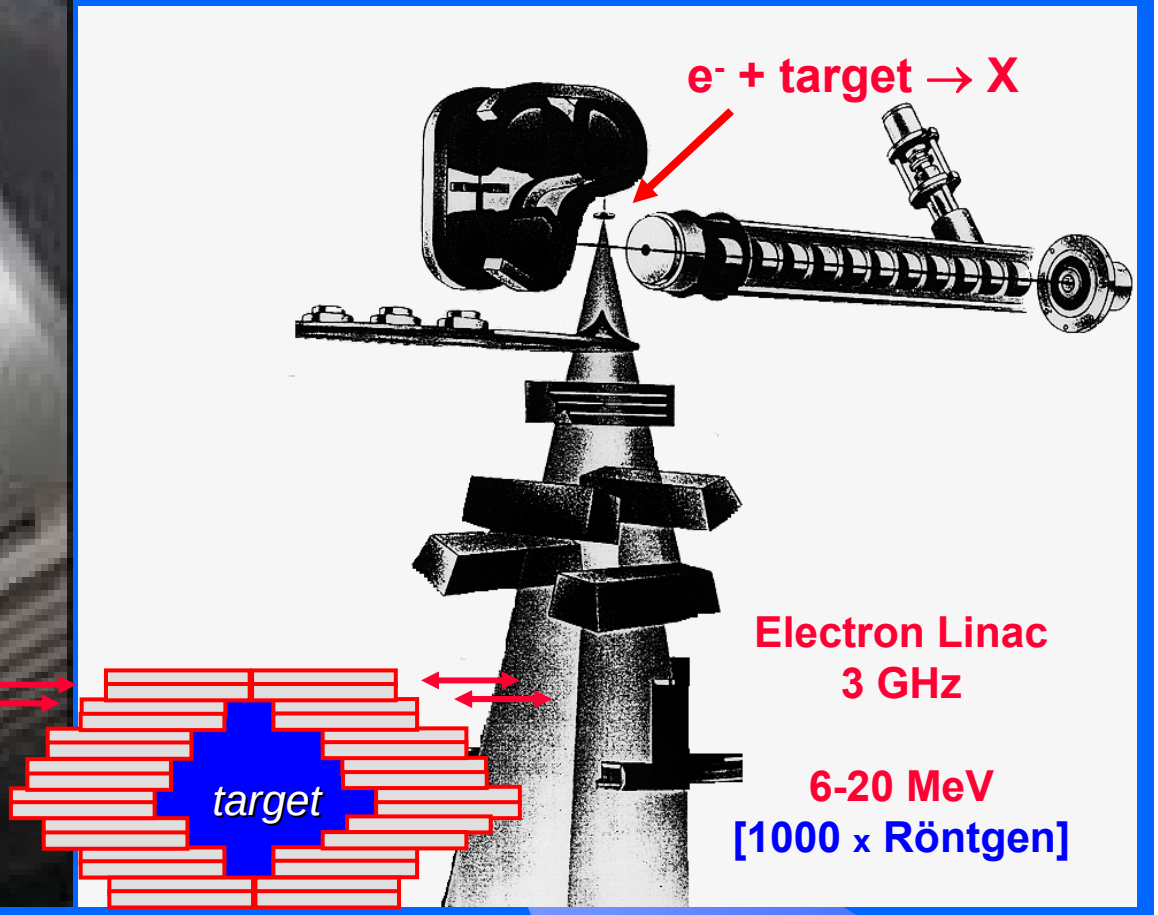
Comparison between different small animal PET parameters and the expected parameters of the RPC-PET

	Quad HIDAC (32 modules) [8]	YAP-PET [2]	MicroPET® II [3]	RPC-PET[a]
Central point absolute sensitivity (cps/kBq)	18[b]	17.3 (∅ = 150 mm)[c]	22.6[d]	9[e]
Image spatial resolution (mm) FWHM	1 mm (uniform)	< 1.8 (uniform)	1.07	⩽ 0.6 (uniform)
Time resolution (ns) FWHM	—	2	3	< 300 ps
Window time (ns)	< 80	< 5	< 10	< 1
FOV (mm)	170 ∅ × 280 (axial)	40 × 40 × 40	160 ∅ × 49 (axial)	150 ∅ × 300 (axial)

WP9 of GDR MI2B: IPHC, LPC Clermont, CPPM, IMNC Orsay
Use of Innovative Developments for High Energy Physics to *go below 200 ps TOF resolution:*

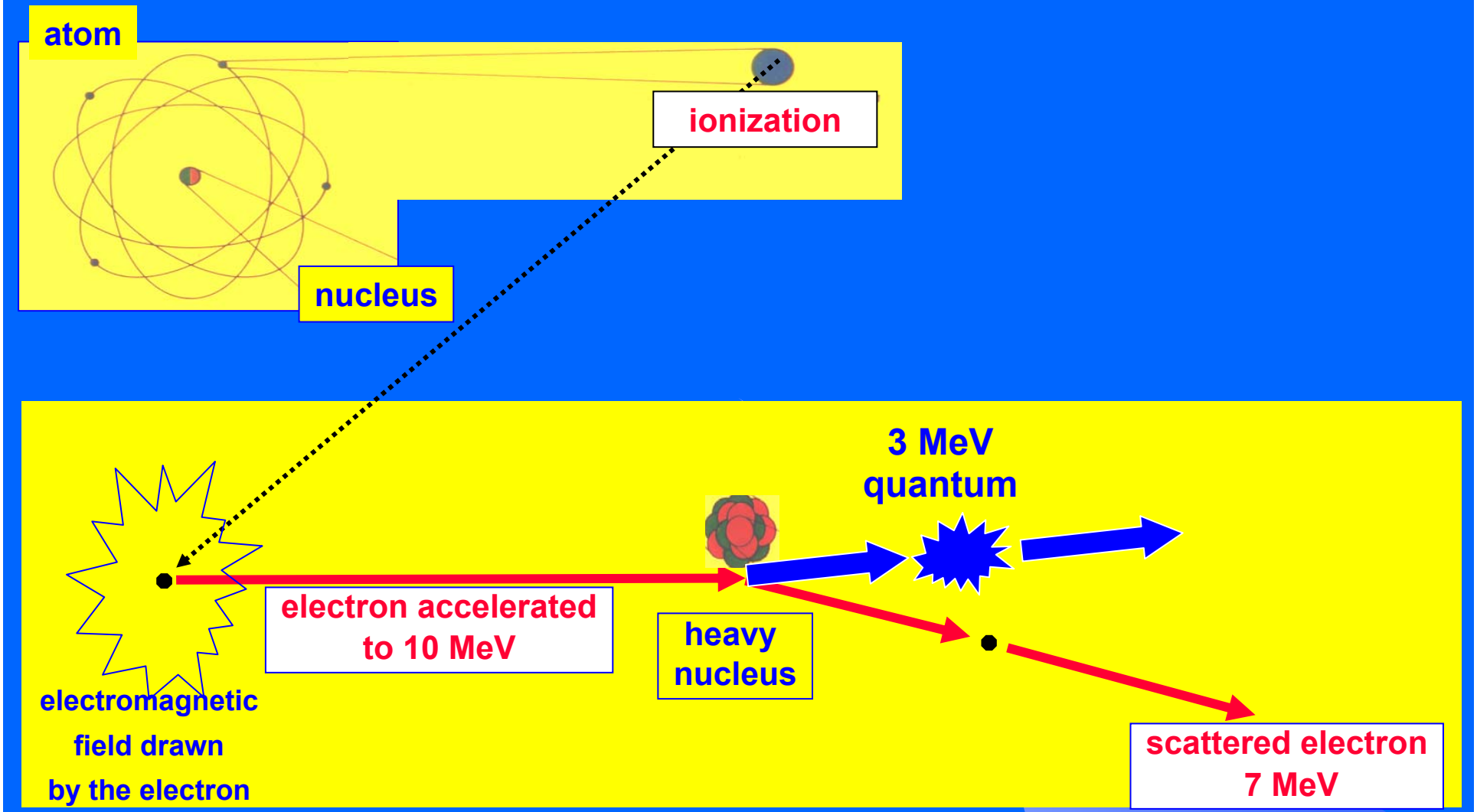
3. Applications in conventional cancer radiation therapy

Radiotherapy with X-rays

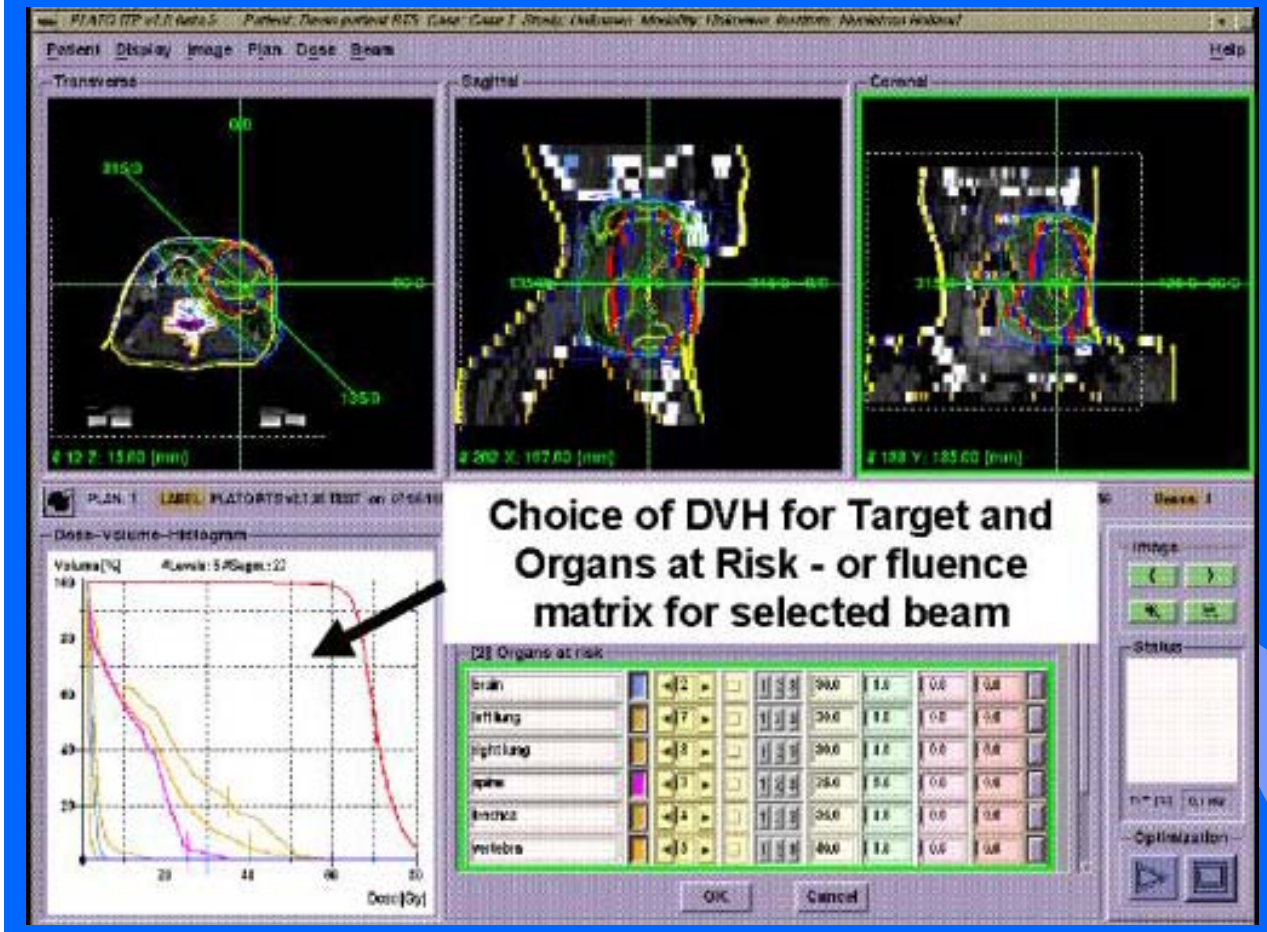


- Electron linacs to produce gamma rays (called X-rays by medical doctors)
- 20'000 patients/year every 10 million inhabitants

Production of X "quanta"

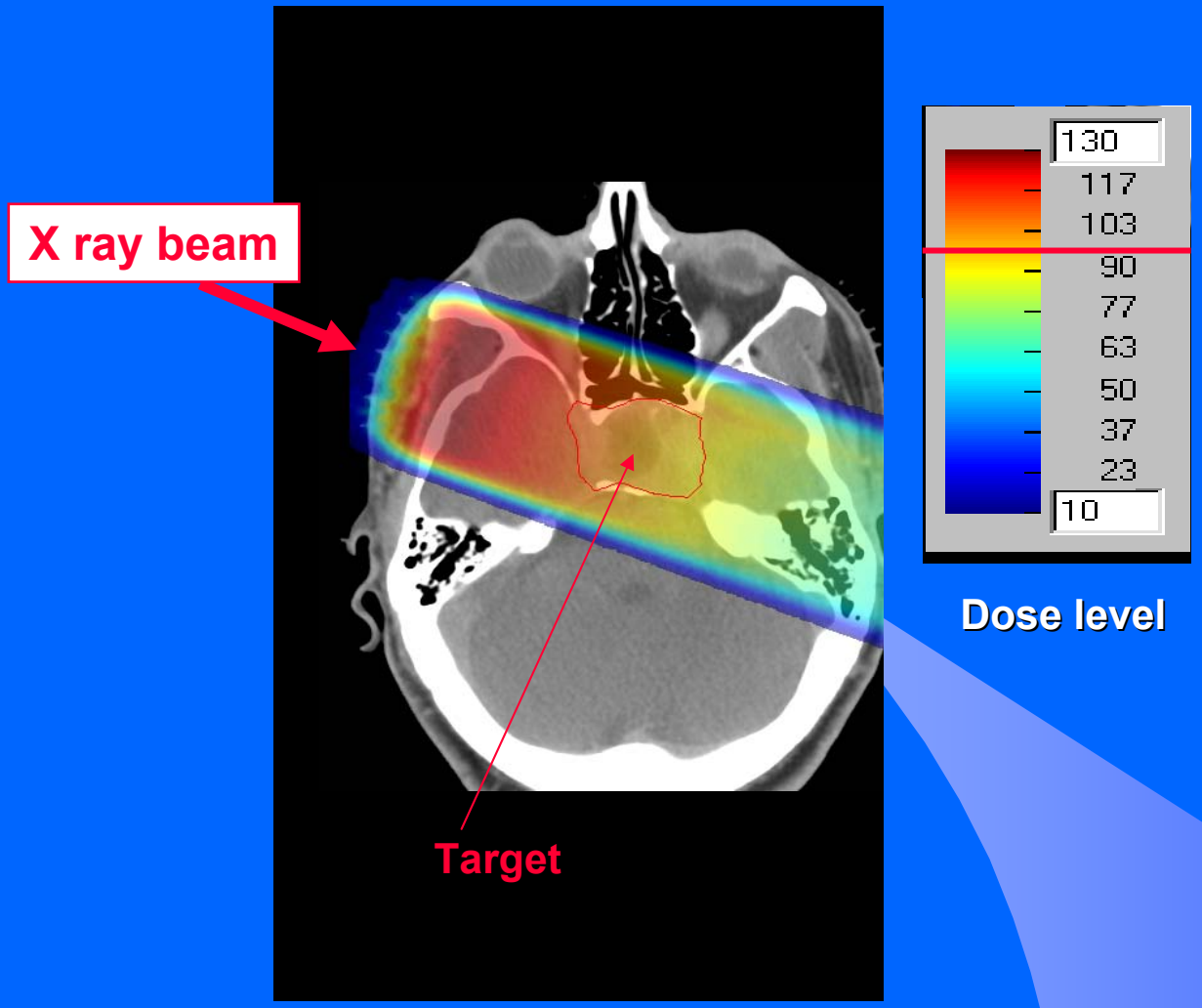


Computerized Treatment Planning System (TPS)



- CT scan data are used to
  - design the volume to be irradiated
  - choose the radiation fields
  - calculate the doses to the target and to healthy tissues
- The dose is given in about 30-40 fractions of about 2 Gray

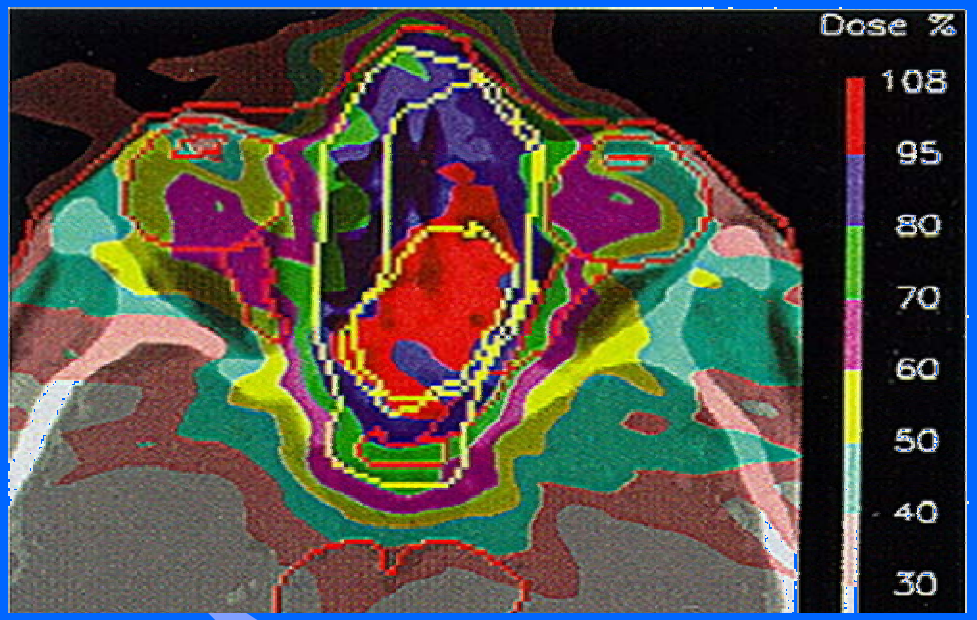
The problem of X ray therapy



The problem of X ray therapy

Solution:

- **Use of many crossed beams**
- **Intensity Modulation Radiation Therapy (IMRT)**

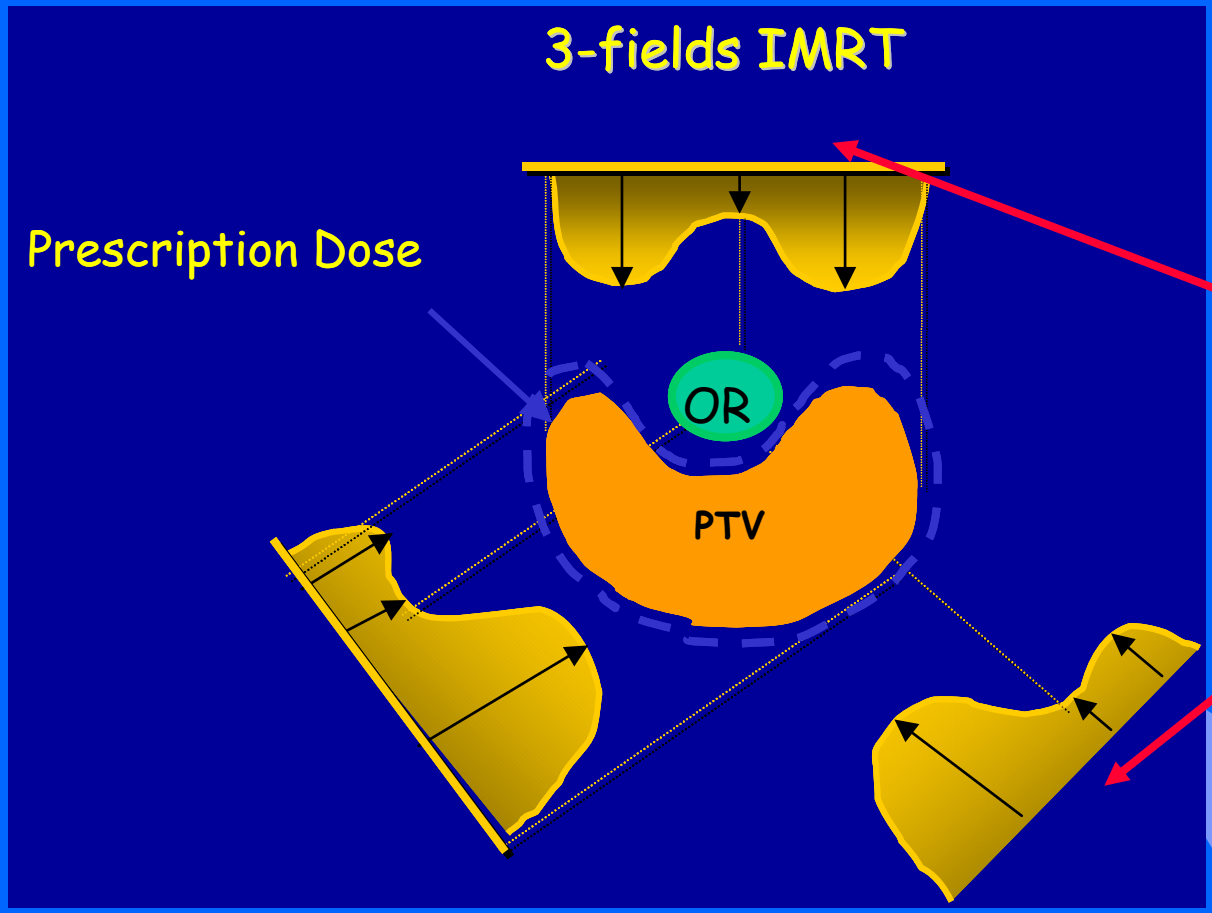


9 different photon beams

The limit is due to the dose given to the healthy tissues!

Especially near organs at risk (OAR)

Multi leaf collimators and IMRT



Multi leaf collimator which moves during irradiation

- It is possible to obtain concave dose volumes
- Time consuming (used for selected cases)

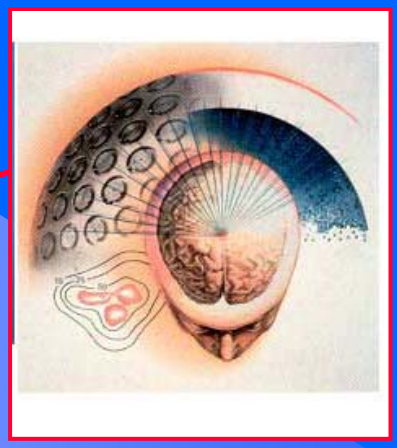
The "gamma knife"

- Proposed in 1967 by Lars Leksell (neurosurgeon) and Borje Larsson (physicist) at Karolinska Institutet, Stockholm
- Treatment of selected brain tumors, arteriovenous malformations and brain dysfunctions
- Small volume diseases (located in the head) treated in one session only ("stereo-tactic radio-surgery")
- Today, more than 30000 patients every year

Lars Leksell poses with his Gamma Knife head frame

The original 1967 Leksell Gamma Knife

Today's Leksell Gamma Knife



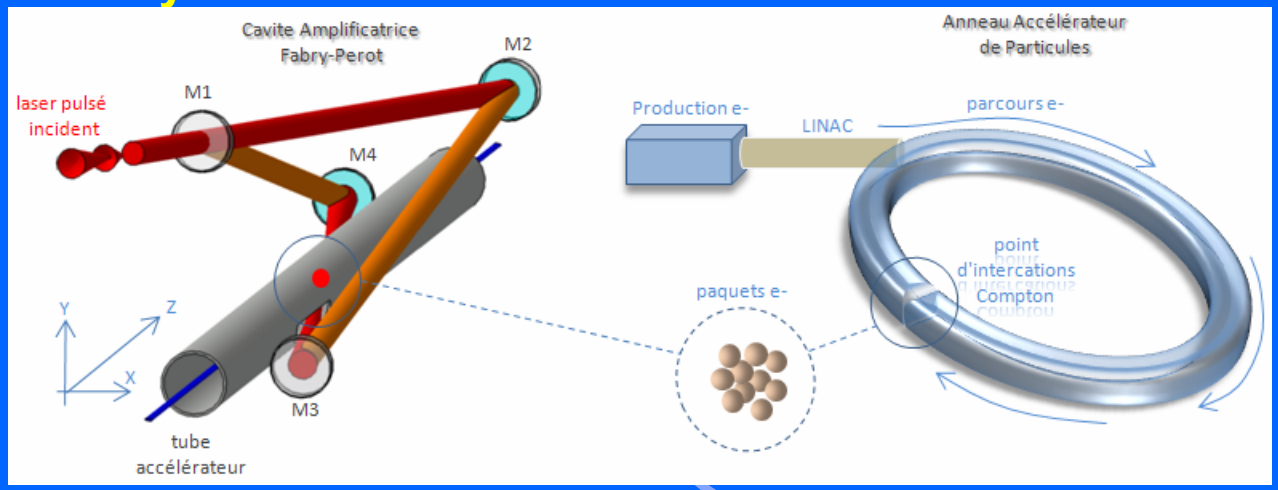
201 ^{60}Co radiation sources

The "cyber-knife"

- **Lightweight 6 MV linear accelerator to produce X-rays mounted on a robotic arm**
- **Use of X-rays taken during treatment to establish the position of the lesion and monitor the treatment**
- **Possibility of multiple fractions**
- **Used to treat small volume tumours (ex . Brain, head & neck, lung, spine, abdomen and pelvis) and lesions throughout the spine**

Intense Monochromatic X-ray source

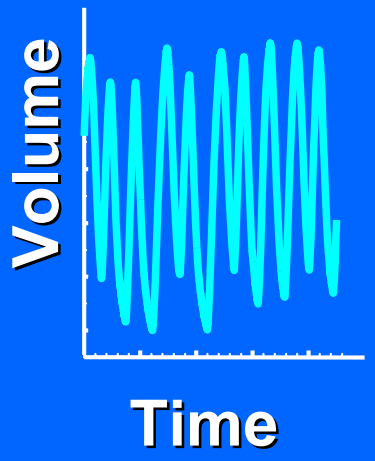
LAL at Orsay in collaboration with CELIA de Bordeaux, Thalès, Institut Gustave Roussy and SOLEIL, initiate the project ThomX to design a very intense monochromatic X ray source ➔ WP1 of GDR MI2B

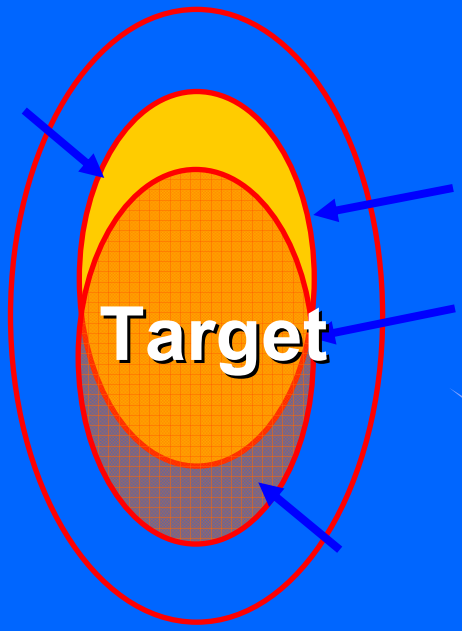


In such an approach, contrast agents (marker) are injected into the patient, targeting tumoral cells. Tumours are irradiated by a quasi-monochromatic X-radiation near the energy of the X absorption peak, in order that the marker's molecules goes to resonant states and have strong local interaction with tumour cells

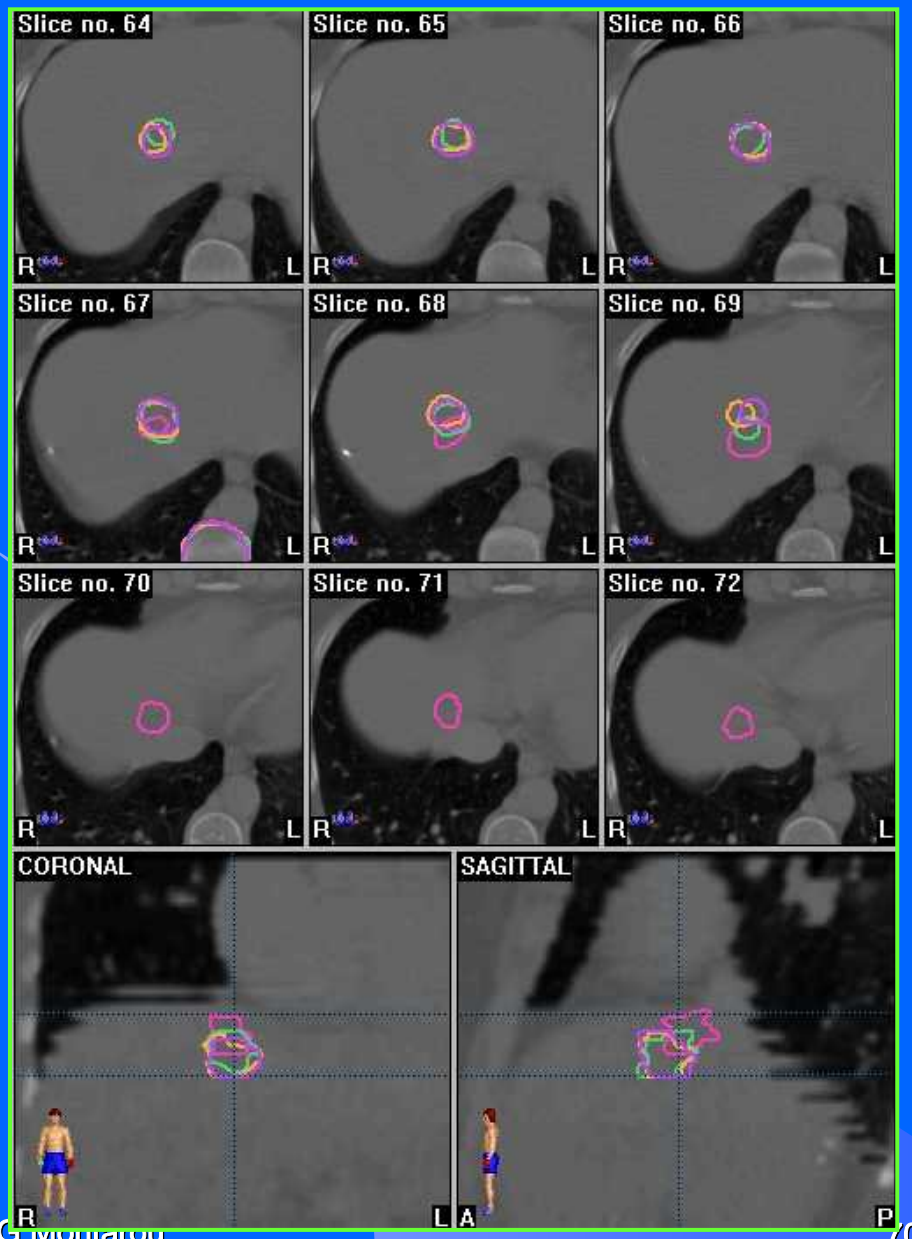
It is also possible by subtracting images performed at energies below and above the Kalpha threshold of the marker (Iodine, Gadolinium, cis-Platinum),to increase spectacularly the visibility of tissues charged with marker's molecules
The use of this property in oncology would make it possible to distinguish tumours of low size, or difficult to distinguish in the middle of an important photonic noise due to the diffusion in biological tissues; the angiographic imagery would be also strongly improved.

The problem of organ motion





Liver CT images

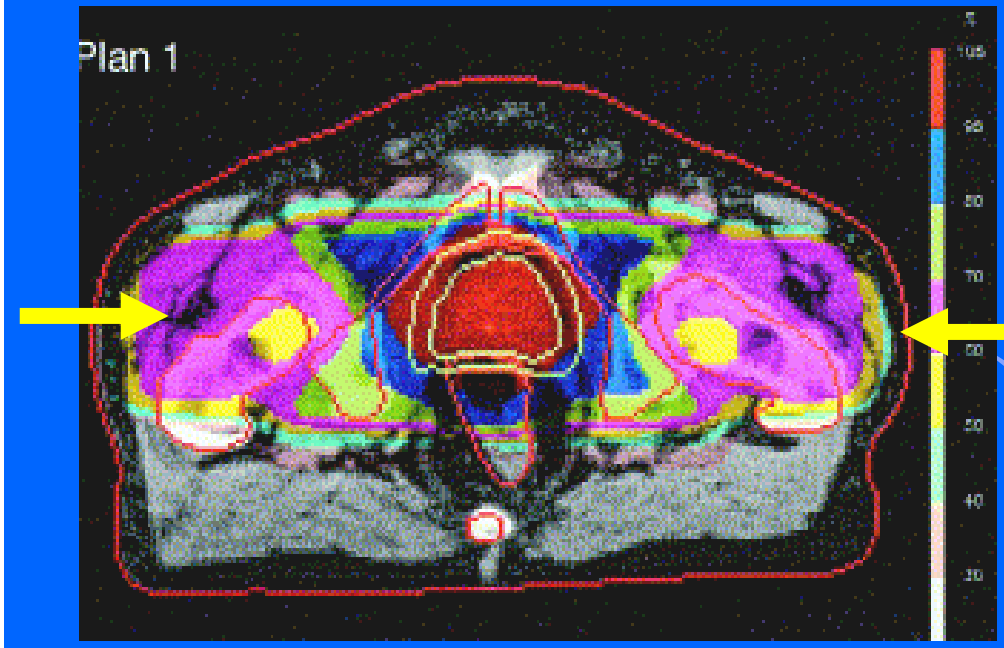


Possible solutions:

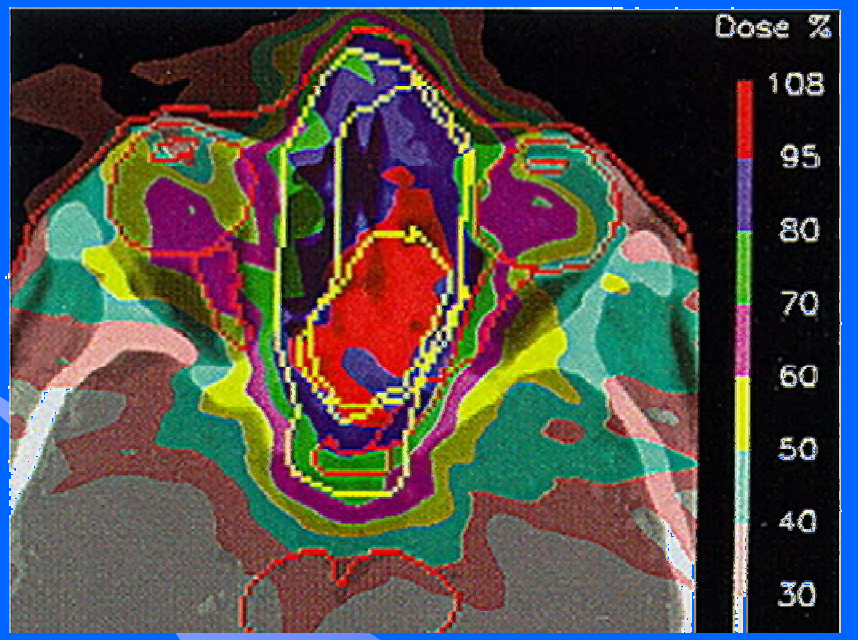
- Respiratory gating
- Image Guided Radiation Therapy (IGRT)

Can we do better ?

2 X ray beams



9 X ray beams (IMRT)



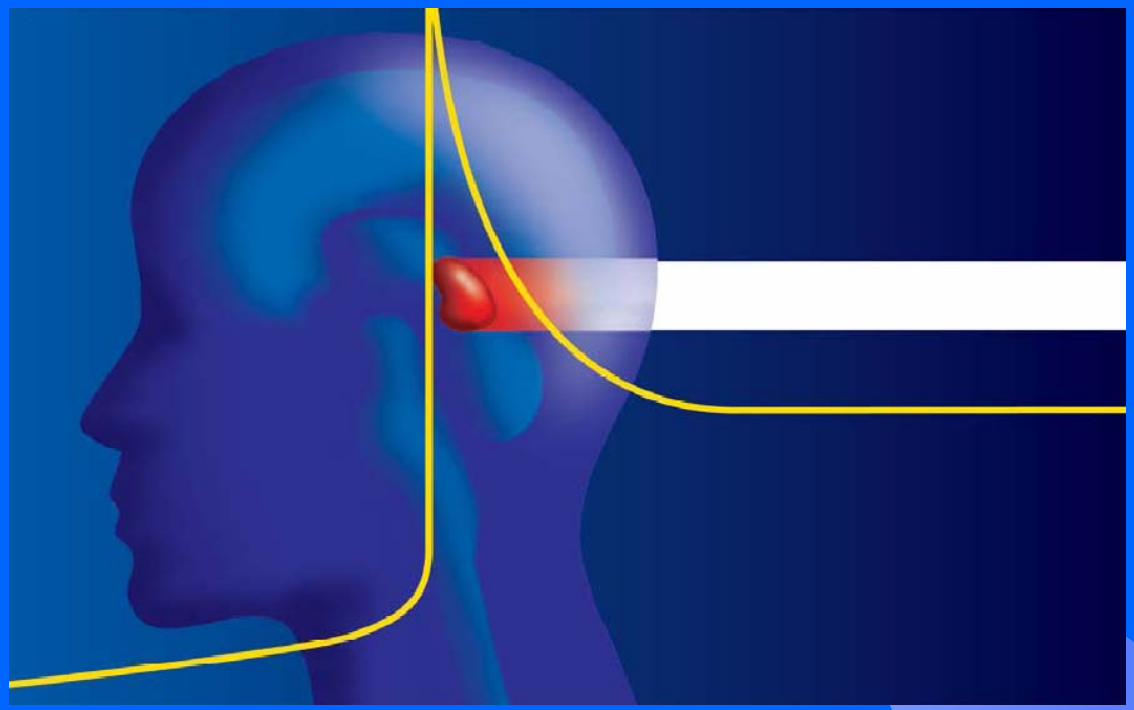
A question for a particle physicist

Are there better radiations to attack the tumour and spare at best the healthy tissues?

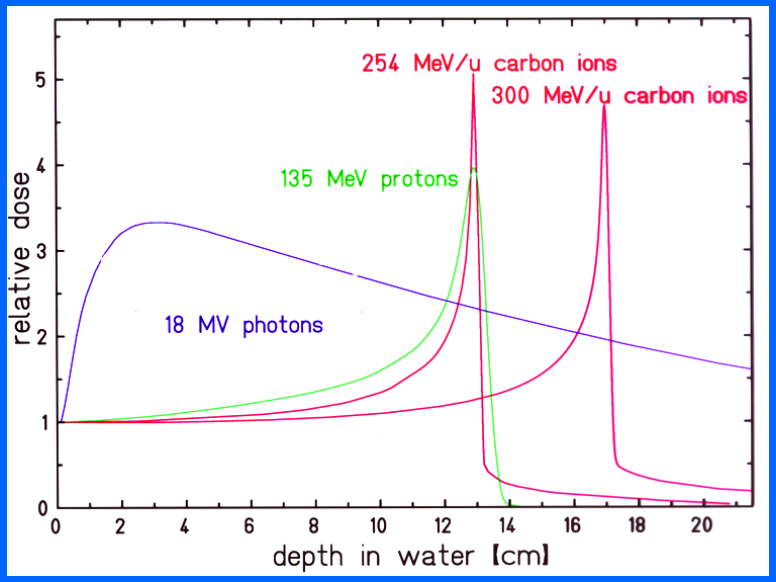
Answer : BEAMS OF CHARGED HADRONS

4.Hadronthetapy

The frontier of cancer radiation therapy



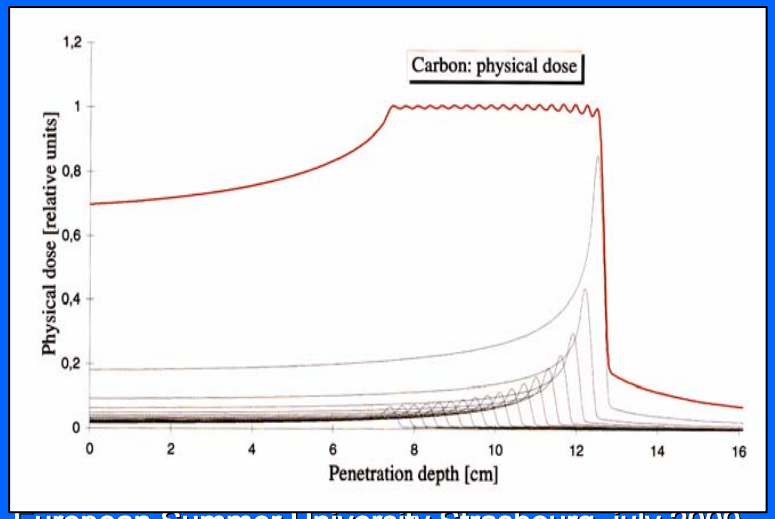
The Bragg peak



Depth dose distribution of various radiation modalities

Depth-dose curve for a single beam of 254 and 300 MeV/u carbon, and 135 MeV proton

Both particles, protons and Carbon ions interaction with matter produces a limited energy release in the first part of their path, where the beam has more energy. When the beam energy decreases, and in the final part of the trajectory there is a sudden and strong energy release with a precise and sharp decrease to zero energy release in a few millimetres. This feature produces the well-known ***Bragg Peak*** in the curve of the relative dose vs. trajectory length.



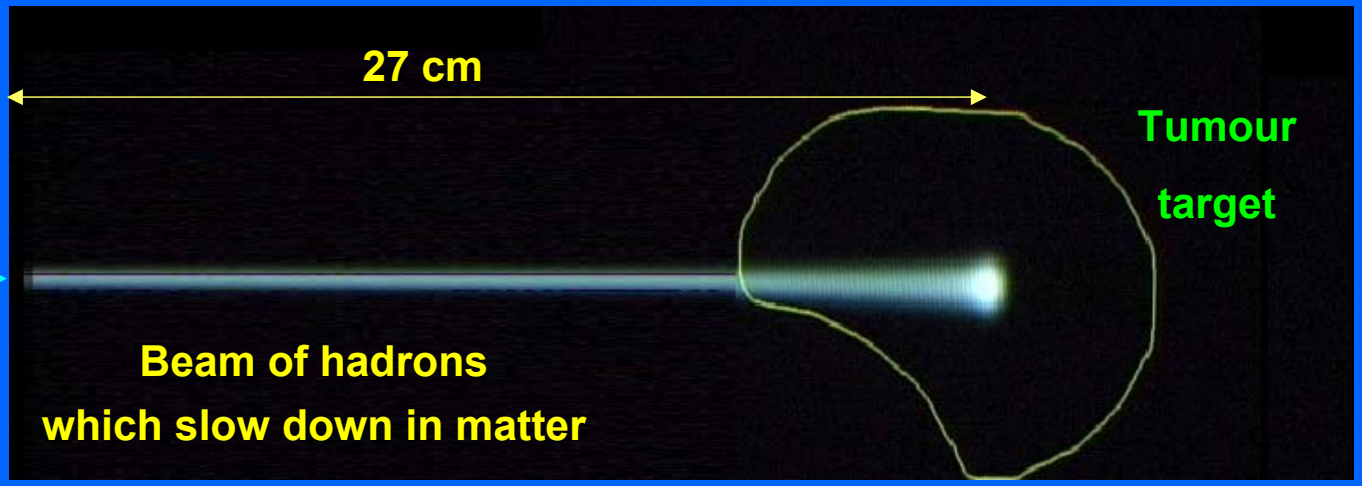
If projectile energy is spread

➔ "Spread out Bragg Peak" (SOBP)

The basic principles of hadrontherapy

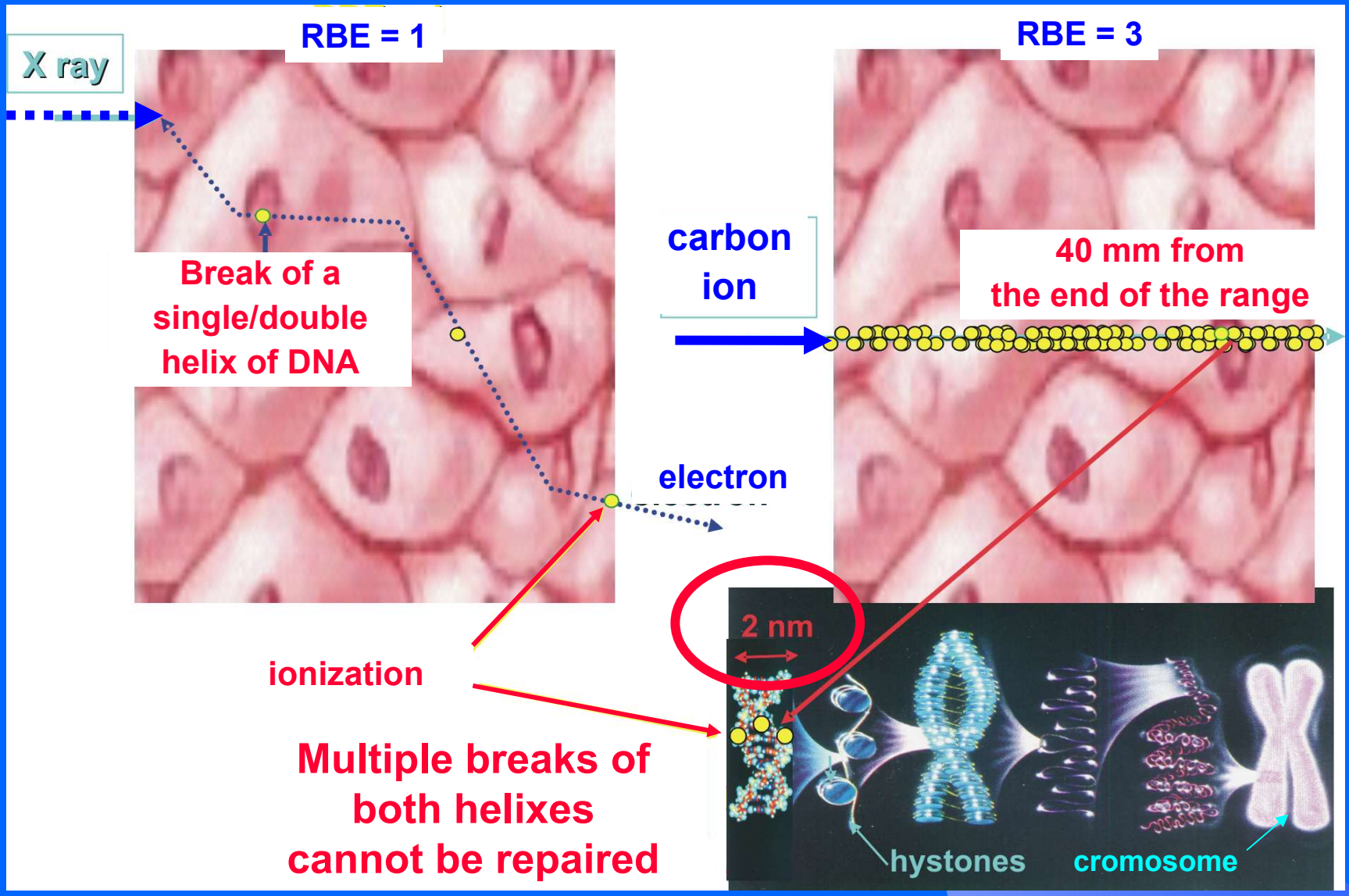
Protons
200 MeV
1 nA

Carbon ions
400 MeV/u
0.1 nA



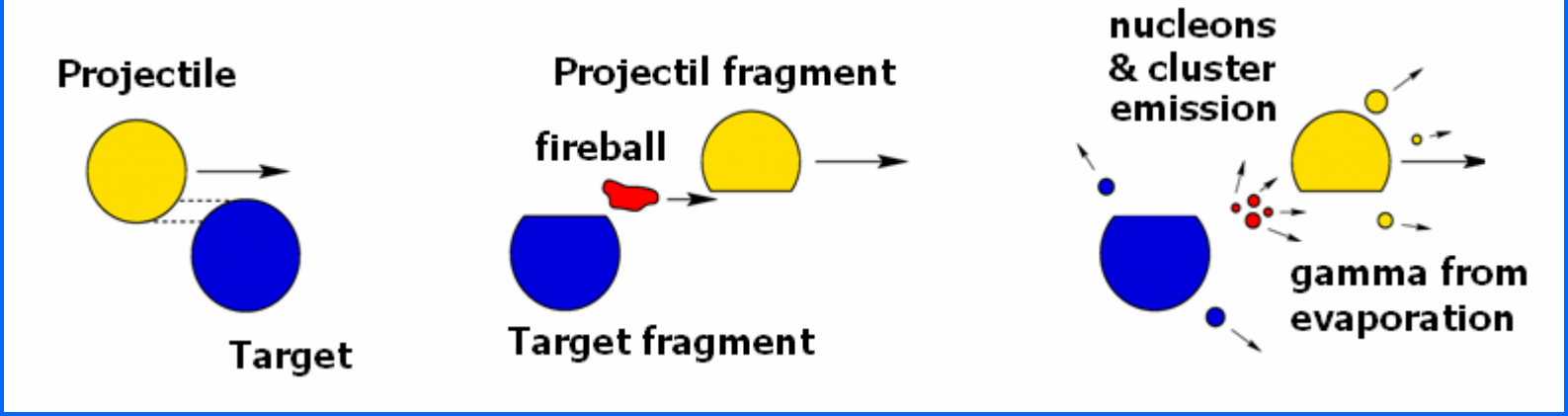
- Bragg peak
  - Better conformity of the dose to the target → healthy tissue sparing
- Hadrons are charged
  - Beam scanning for dose distribution
- Heavy ions
  - Higher biological effectiveness (RBE)

Why ions have a large biological effectiveness?



Ions have high LET (Linear Energy Transfer)

Let's go back to physics...



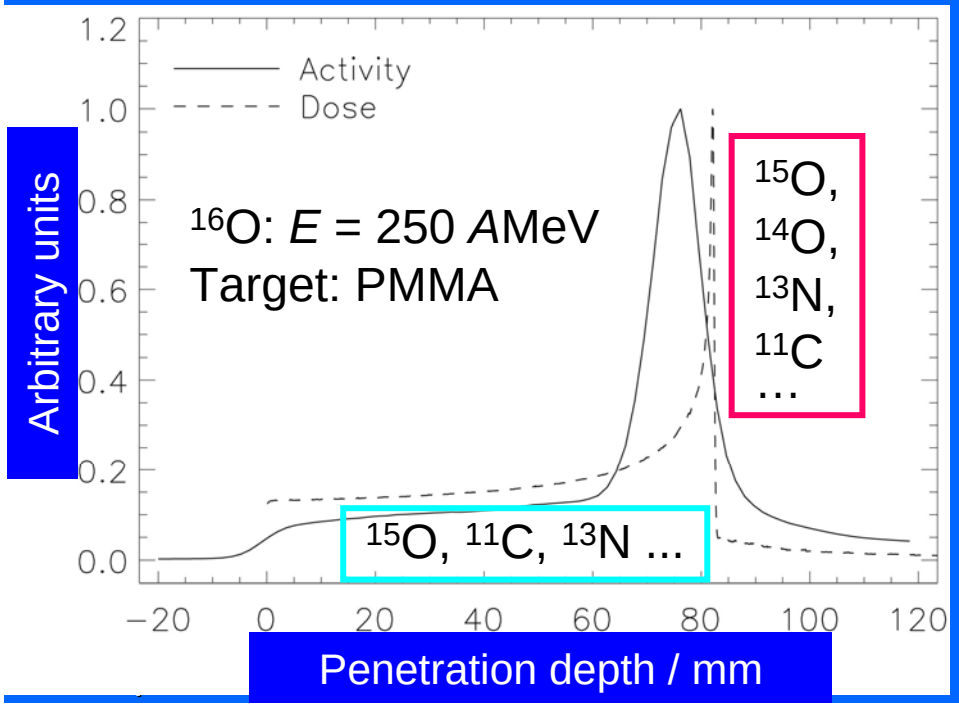
Carbon $Z \geq 6$

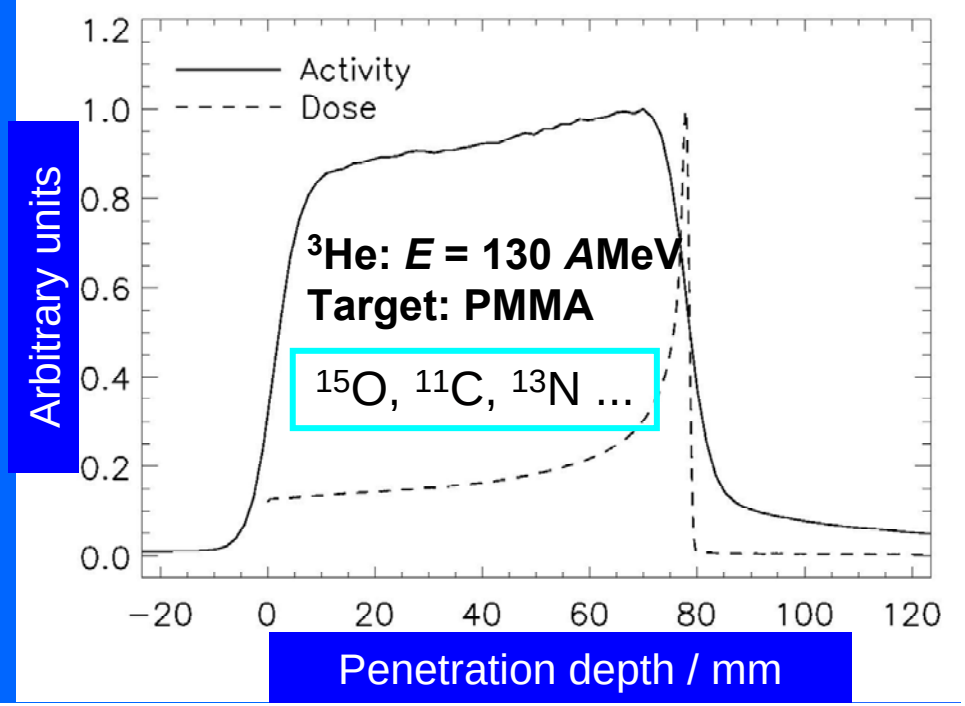
Projectile fragments

Target fragments

$Z < 6$ **Proton**

Target fragments

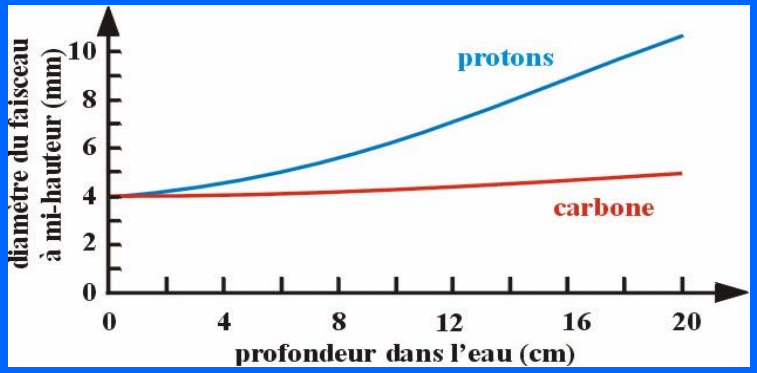




Why carbon is better than proton ?

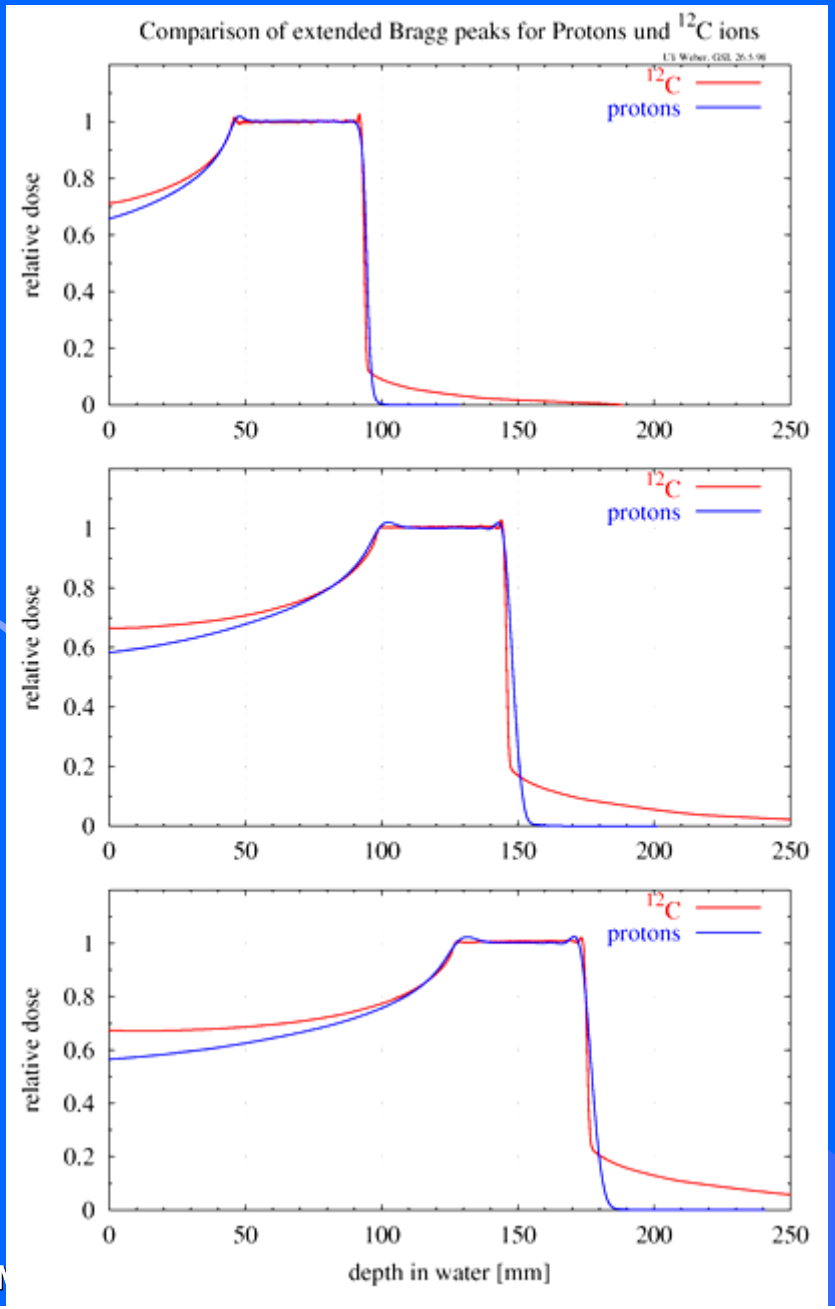
Balistic

➔ **Less lateral scattering for carbon (X, Y)**

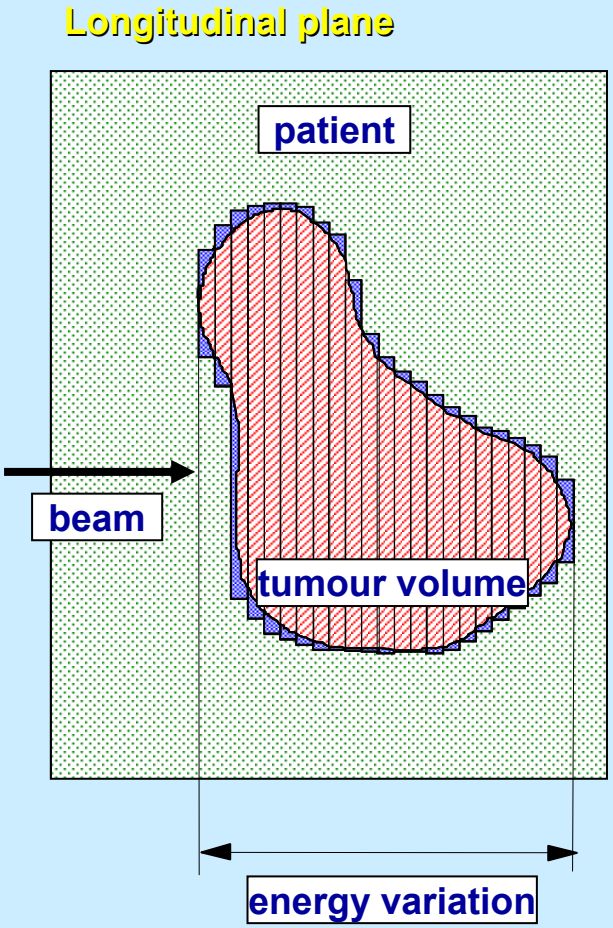


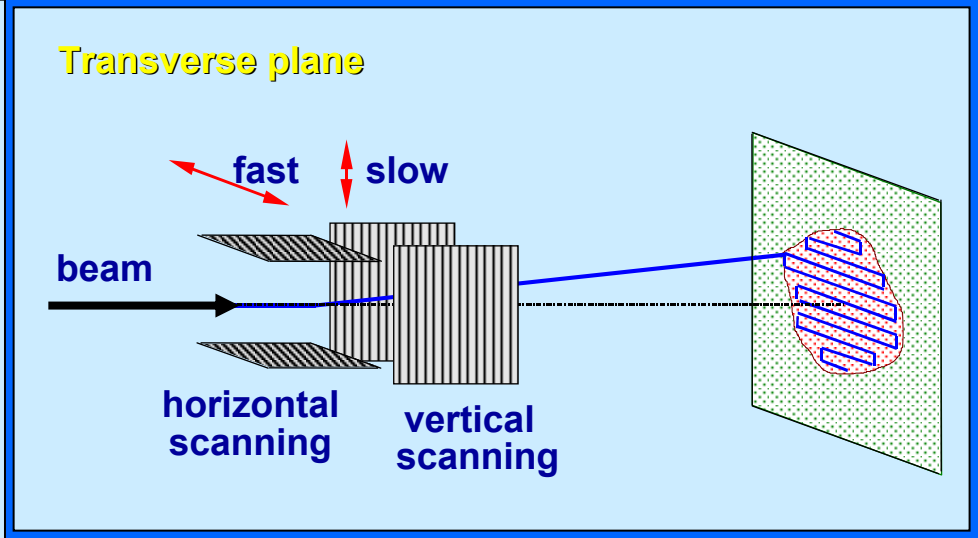
➔ **Lower Tail of dose after Bragg Peak for proton**

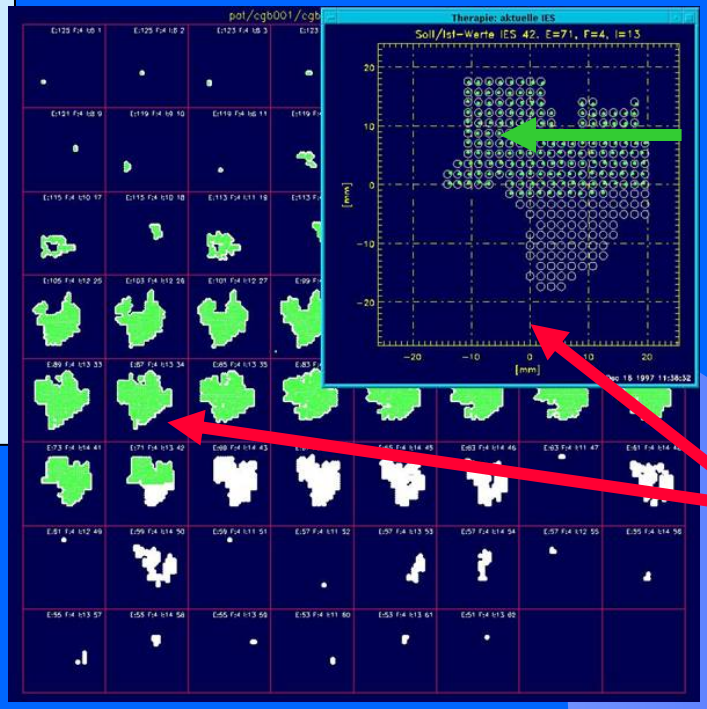
Comparison of dose profiles of protons and carbon



Dose distribution: active scanning





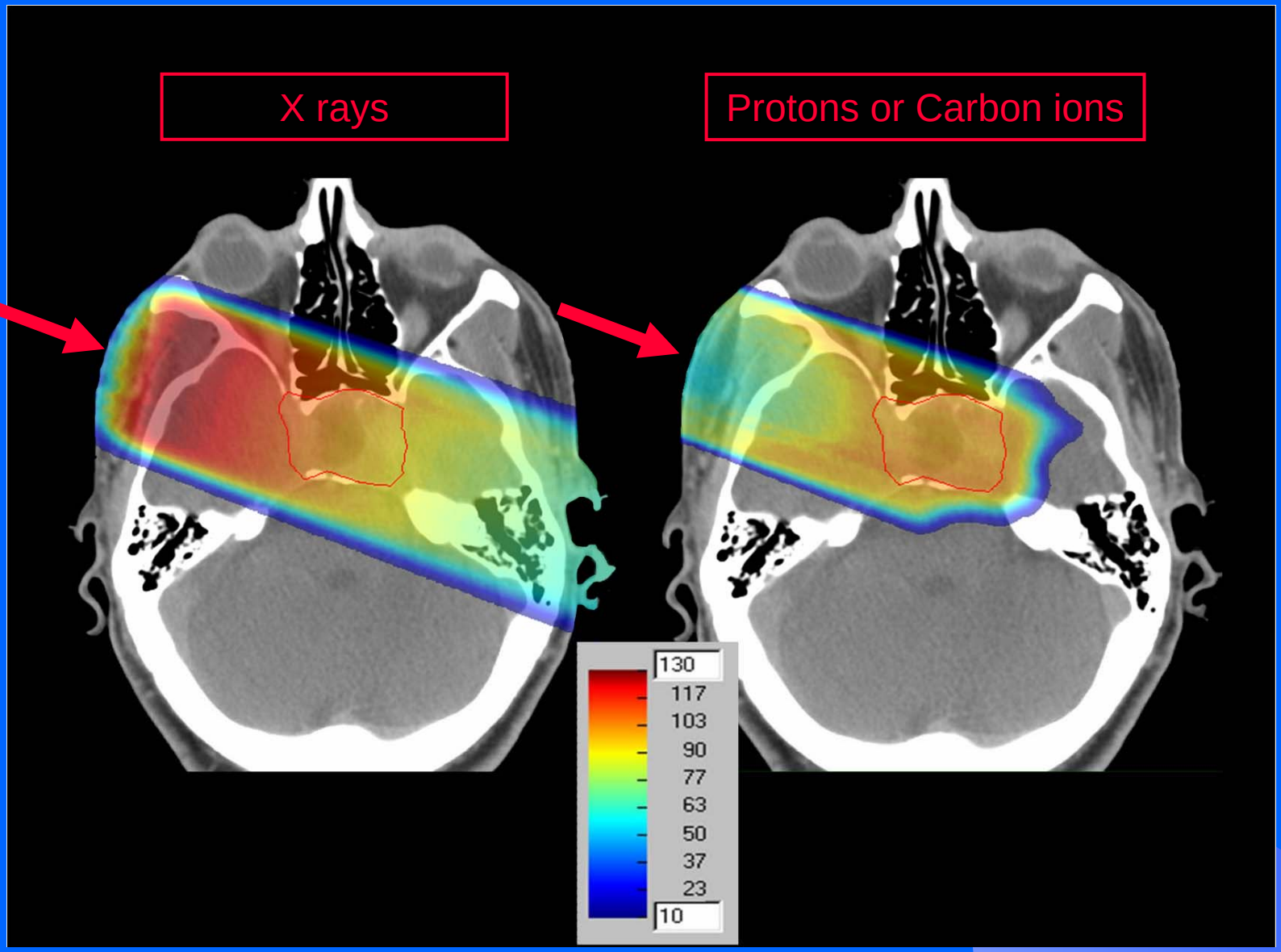


A spot corresponds to a fixed position in x and y
In a slice, where dose is set

A slice in depth corresponds to a fixed energy and a value along the beam axis

New technique developed mainly at GSI and PSI

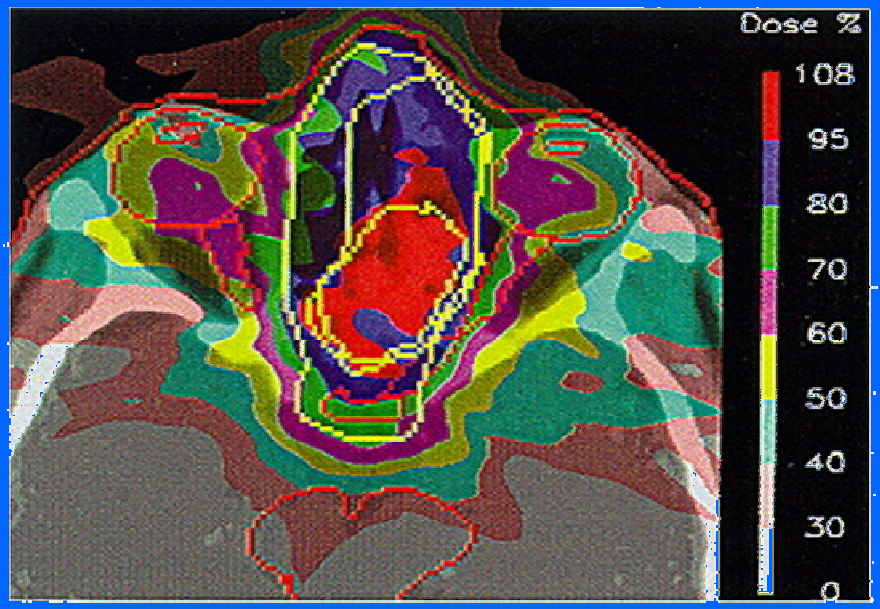
Single beam comparison



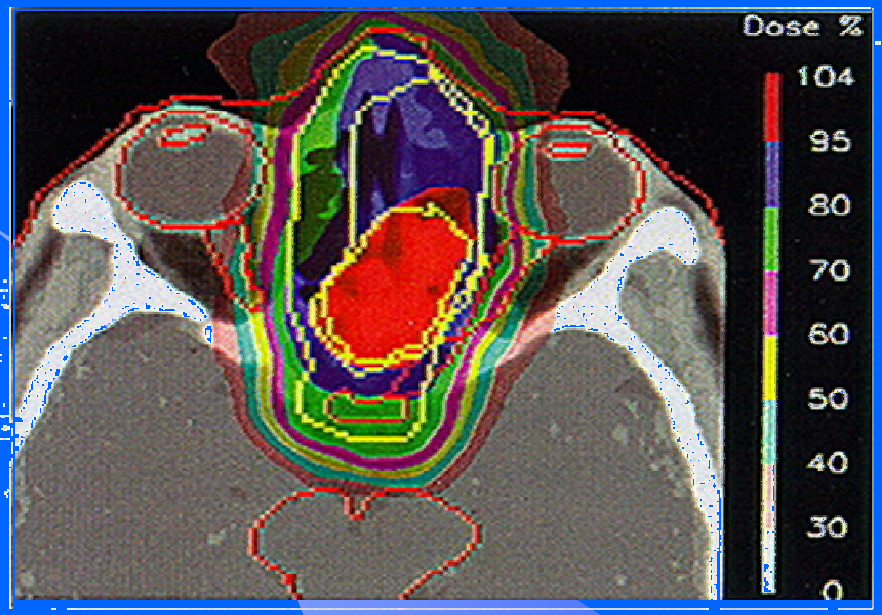
Protons and ions are more precise than X-rays

Tumour between the eyes

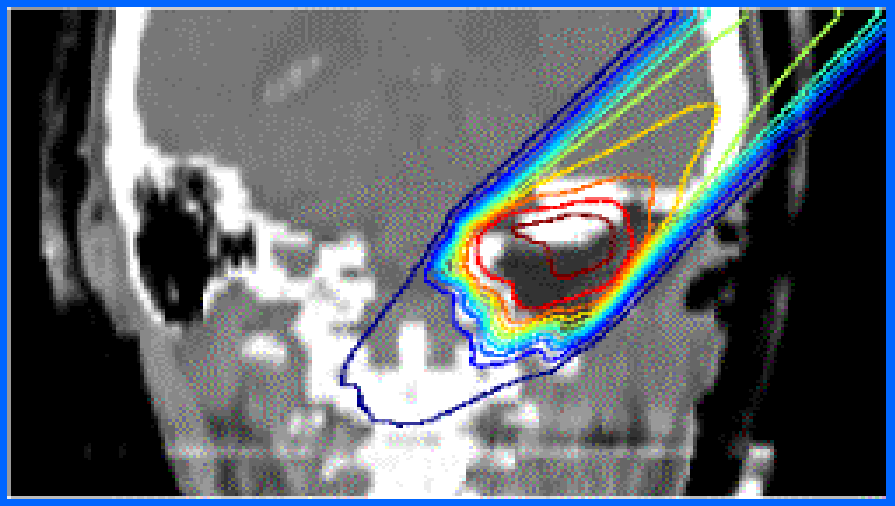
9 X ray beams



1 proton beam

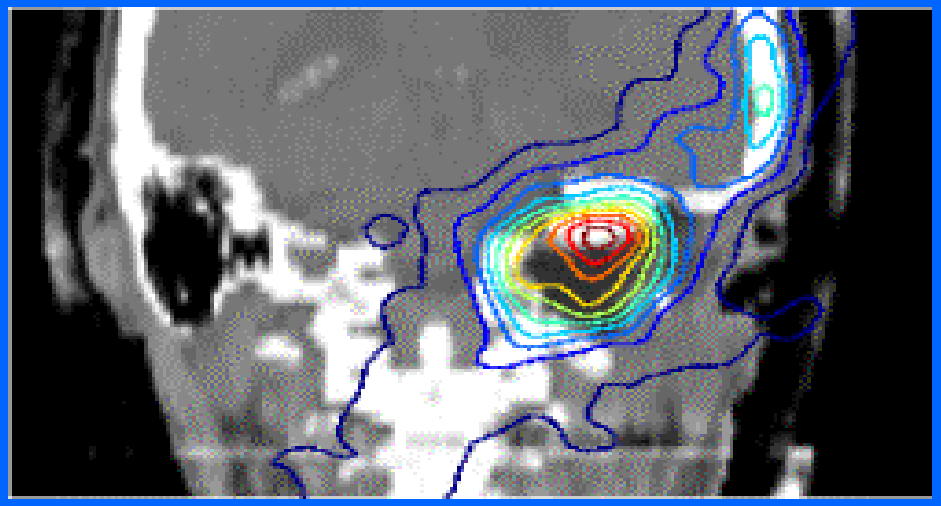


Verifying the position of the irradiation field

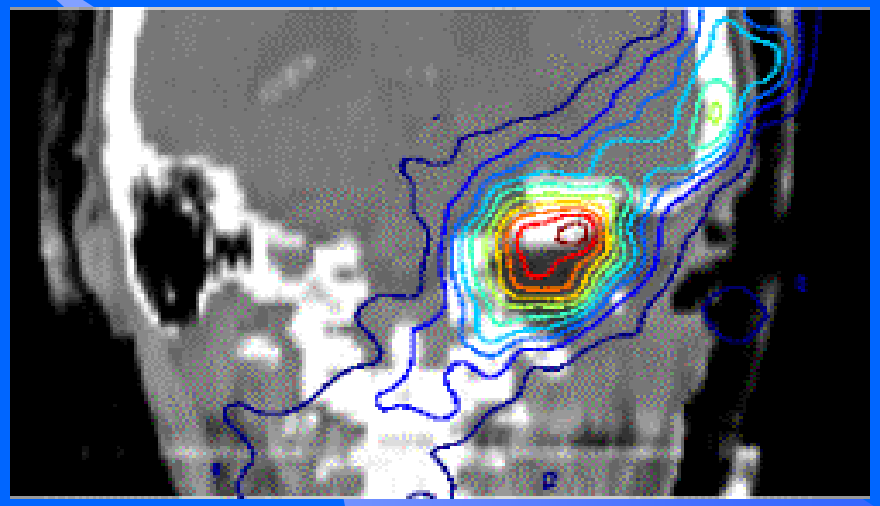


W.Enghardt et al. ,
FZR Dresden

TPS➔dose plan



Dose
Measured



Dose
Simulated

What are the key points in Hadrontherapy ?

To define the treatment (TPS), one should be able to

(1) Know the dose and how it is deposited in the biological tissus

(2) Know what is the biological effect of the dose in the tissus

First item needs to know exactly about all the physical processes that are involved in the reaction of the beam with the medium

- ➔ That means to be able to predict and simulate these reactions
- ➔ Whe should know the differential cross sections of the physical processes
- ➔ These are still not completly measured at such energies

- ➔ Experimental data has been measured at low energy at GANIL (LPC Caen, IPHC, IPNL) WP4 of GDR MI2B

- ➔ Experimental program at higher energy is planned at GSI using already existing expermental set-up (Aladin spectrometer) G Cutonne, LPC Caen, IPHC, CEA, IPNL,GSI

What are the key points in Hadrontherapy ?

First item needs also to CONTROL how and where the dose is deposited in the tissus

➔ That means to be detect physical signals (outgoing particles) with a close correlation to the macroscopic dose in a small volume

➔ Need of a quality control procedure that could be performed in time during the treatment and in beam conditions

Second item needs to know Biological effectiveness of hadron on different kind of cells

➔ That is means to measure the survival curves of these cells as a function of the dose (Gy) ➔ radiobiological experiments at the interface of physics and biology

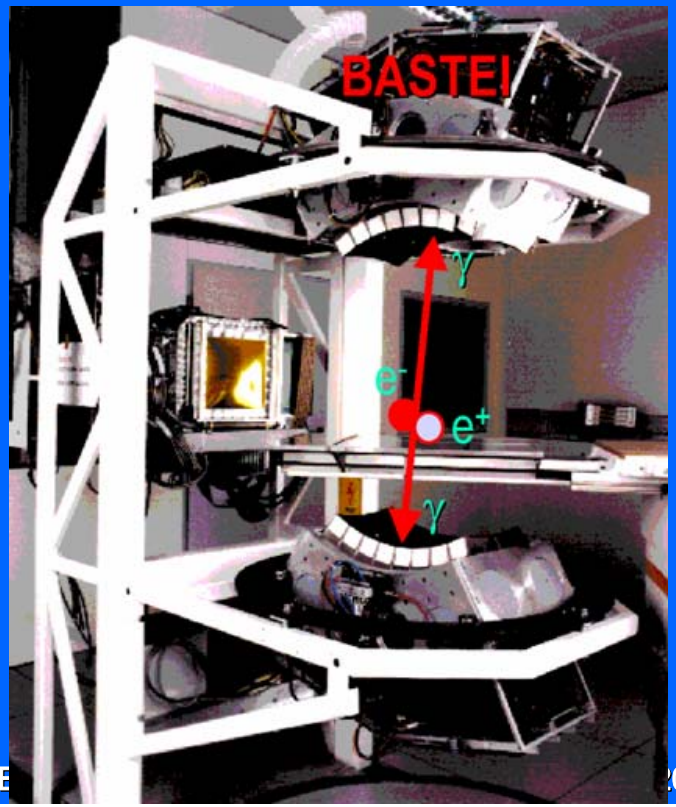
➔ To define Biological models that could be used by doctors to define a specific treatment for each treated patient (LEM model in GSI, M Beuve et al ..)

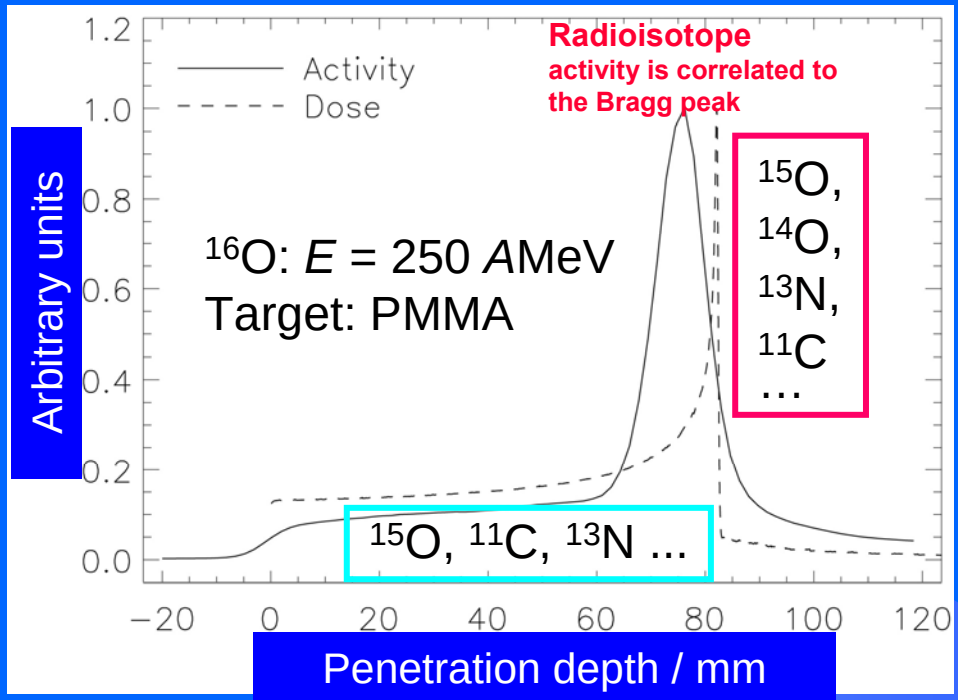
How to Control in situ the Dose ?

Two methods

1. **In beam PET**
2. **Single nuclear photon detection (prompt gammas)**

Special PET close to the patient should be able to detect 511 KeV from decay of radioisotopes produced during beam interaction (mainly ^{11}C)





How to Control in situ the Dose ?

1998 - GSI pilot project (G. Kraft)

200 patients treated with carbon ions

PET on-beam

How to Control in situ the Dose ?

Problems of such a method :

1°) radioisotopes of short half life time ^{11}C (20 min), ^{15}O (2min), ^{10}C (10s)

2°) Low activitity (~10 KiloBq) in comparaison with clinical TEP (250 MegaBq)

3°) need at least tenth of minutes to have sufficient statitics

4°) metabolic washout of the radioisotopes in the body (blood)

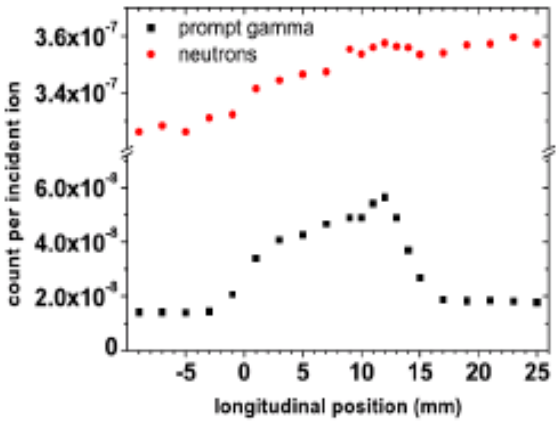
➔ To be efficient In beam PET need TOF resolution less than 200 ps

Other method is to detect nuclear high energy gammas comming from nuclear reaction of the beam ➔ correlation with the range of the projectile

GANIL :

^{13}C @ 73 MeV/u → PMMA

[Testa et al., Appl. Phys. Lett. 2008]



But also many neutrons

➔Gamma should be selected by the experimental set-up

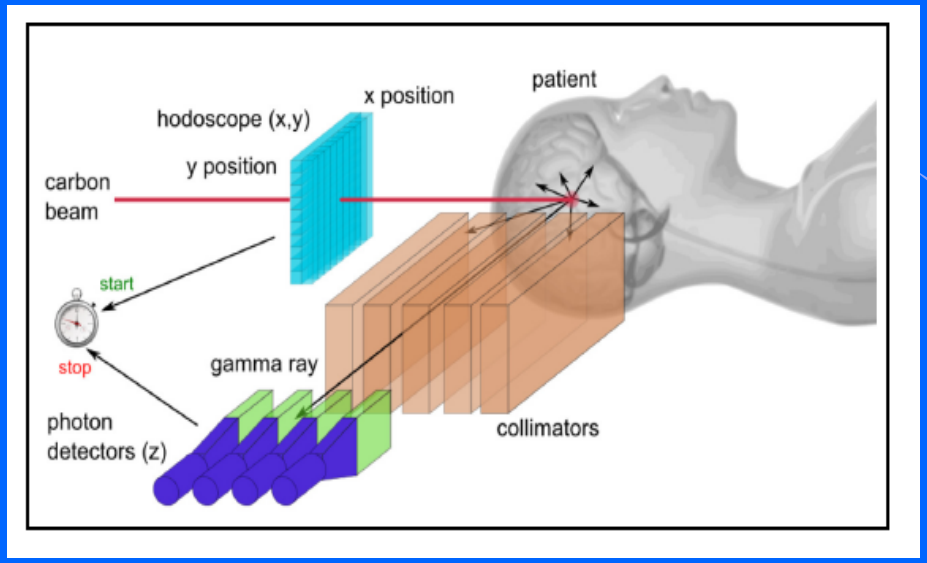
➔Use of TOF

How to Control in situ the Dose ?

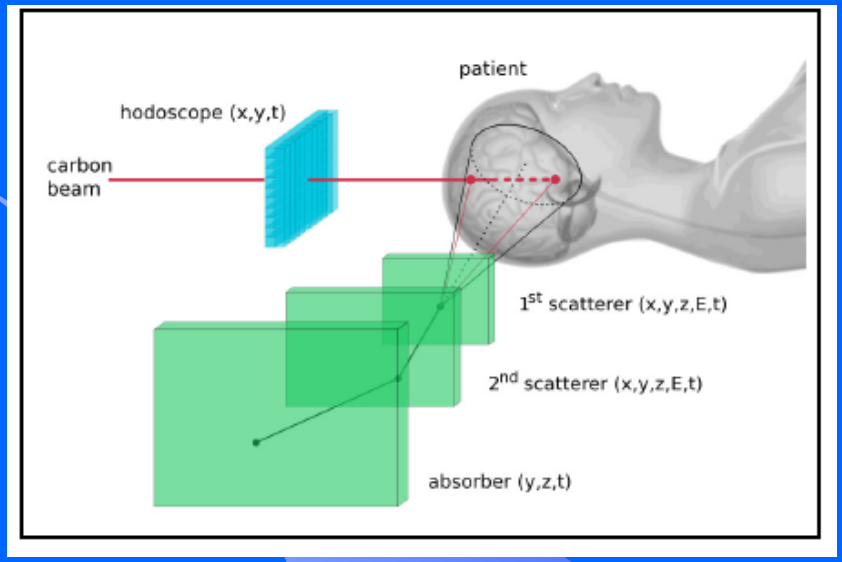
National project GAMHADRON (LPC Clermont; IPNL, CEA/LIST, INSA Lyon) and European Project ENVISION (WP9 of GDR MI2B)

➔ Test and define an experimental setup to detect high energy nuclear gamma

- **SPECT technology (passive collimator)**
- **Compton Camera**



SPECT technology (passive collimator)



Compton Camera

Number of potential patients

X-ray therapy every 10 million inhabitants: 20'000 pts/year

Protontherapy

12% of X-ray patients = 2'400 pts/year

Therapy with Carbon ions for radio-resistant tumours

3% of X-ray patients = 600 pts/year

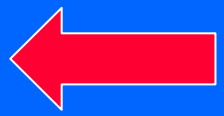
Every 50 M inhabitants

- **Proton-therapy**

5 centres

- **Carbon ion therapy**

1 centre



TOTAL about 3'000 pts/year

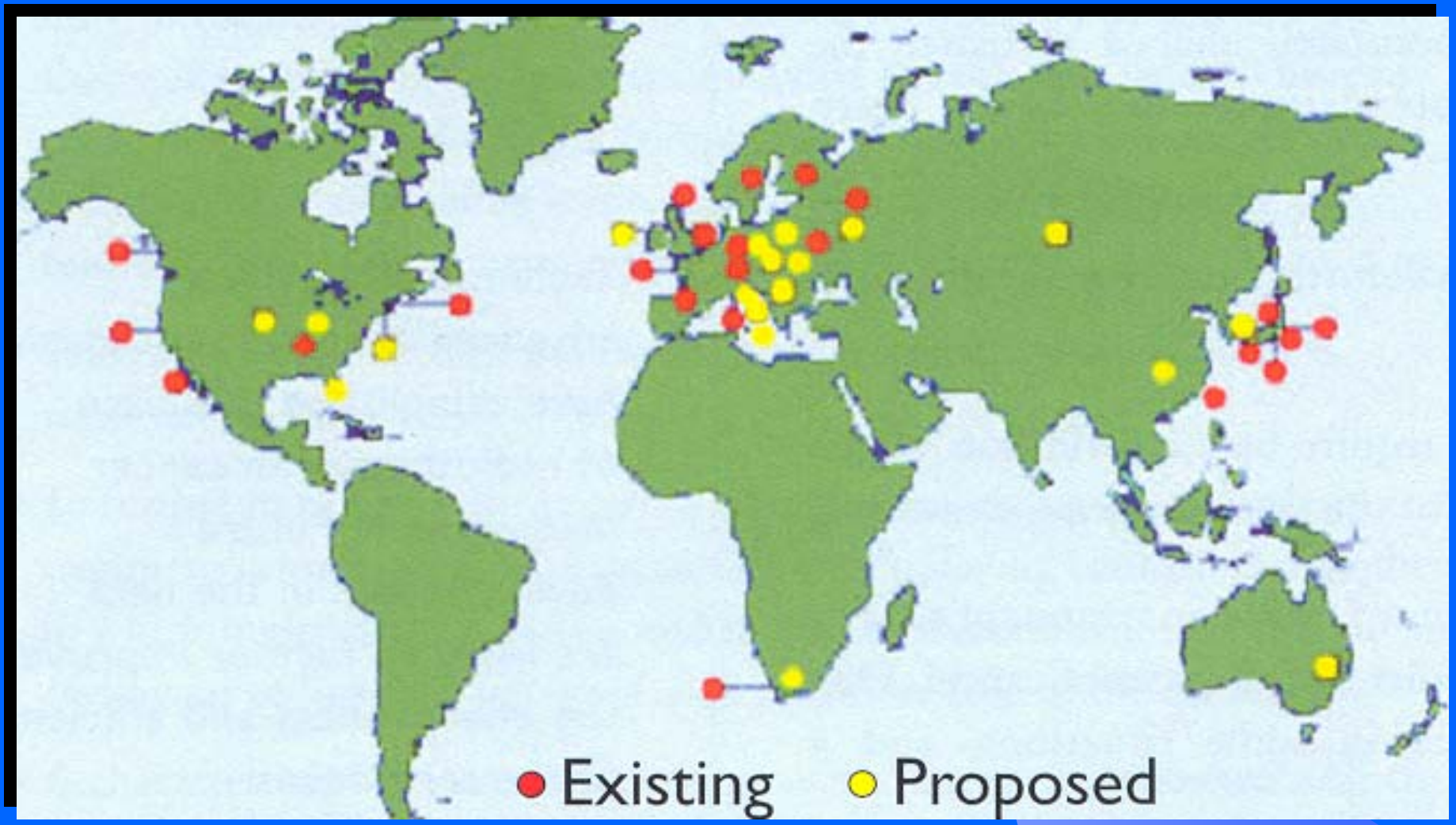
every 10 M

Present and "near" future of hadrontherapy

- **Proton-therapy is "booming"!** *(for more information see PTCOG, www.ptcog.com)*
  - **Laboratory based centres: Orsay, Nice, PSI, INFN-Catania, …**
  - **Hospital based centres: 3 in USA, 4 in Japan and many under construction (USA, Japan, Germany, China, Korea, Italy, …)**
  - **Companies offer "turn-key" centres (cost: 50-60 M Euro)**

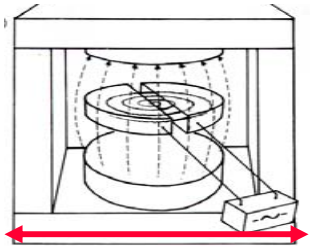
- **Carbon ion therapy**
  - **2 hospital based centres in Japan**
  - **Pilot project at GSI**
  - **3 hospital based centres in Germany (Heidelberg, Marburg, Kiel)**
  - **1 hospital under construction in Italy (CNAO in Pavia)**
  - **2 projects approved (France and Austria)**
  - **European network ENLIGHT**

The map of hadrontherapy

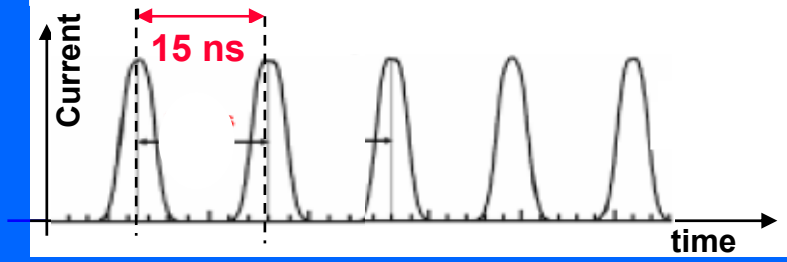


The accelerators used today in protontherapy

CYCLOTRONS (Normal or SC)

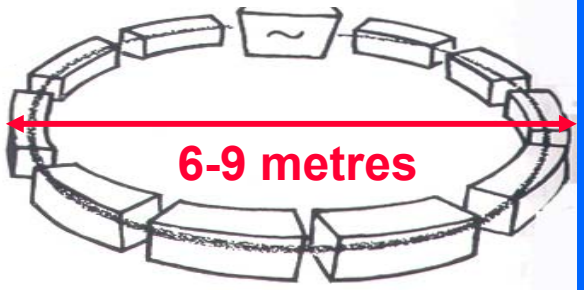


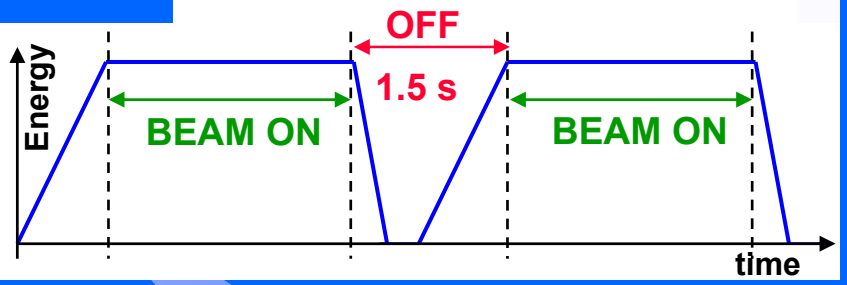
4-5 metres

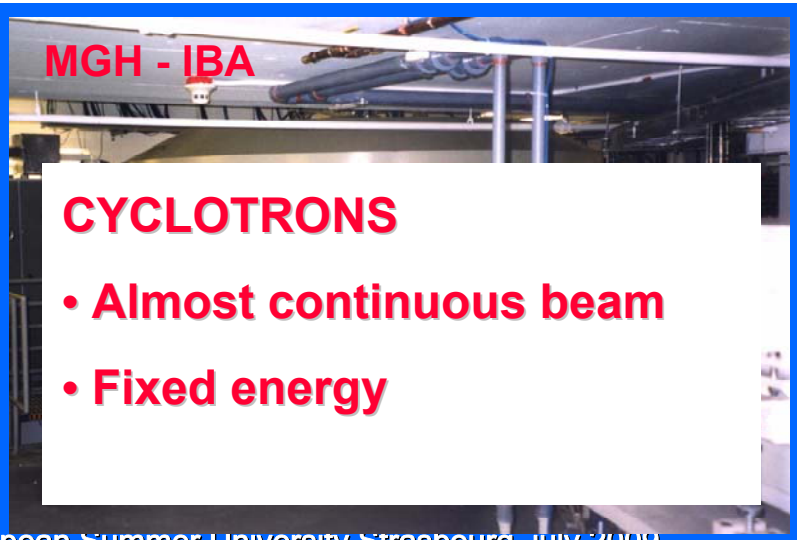


OR

SYNCHROTRONS







CYCLOTRONS

- Almost continuous beam
- Fixed energy

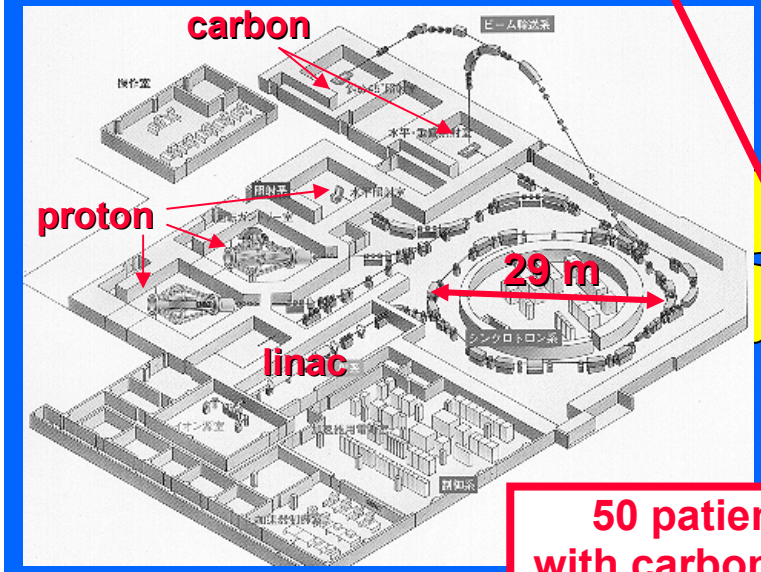
SYNCHROTRONS

- Beam ON and OFF
- Continuous energy

Japan: 4 proton and 2 carbon ion therapy centres

WAKASA BAY PROJECT
by Wakasa-Bay Energy Research Center
Fukui (2002)
protons (≤ 200 MeV) synchrotron
(Hitachi)
1 h beam + 1 v beam + 1 gantry

HYOGO MED CENTRE
Hyogo (2001)
protons (≤ 230 MeV) - He and C ions (≤ 320 MeV/u)
Mitsubishi synchrotron
2 p gantries + 2 fixed p beam + 2 ion rooms



50 patients
with carbon ions

TSUKUBA CENTRE
Ibaraki (2001)
protons (≤ 270 MeV)
synchrotron (Hitachi)
2 gantries
2 beam for research

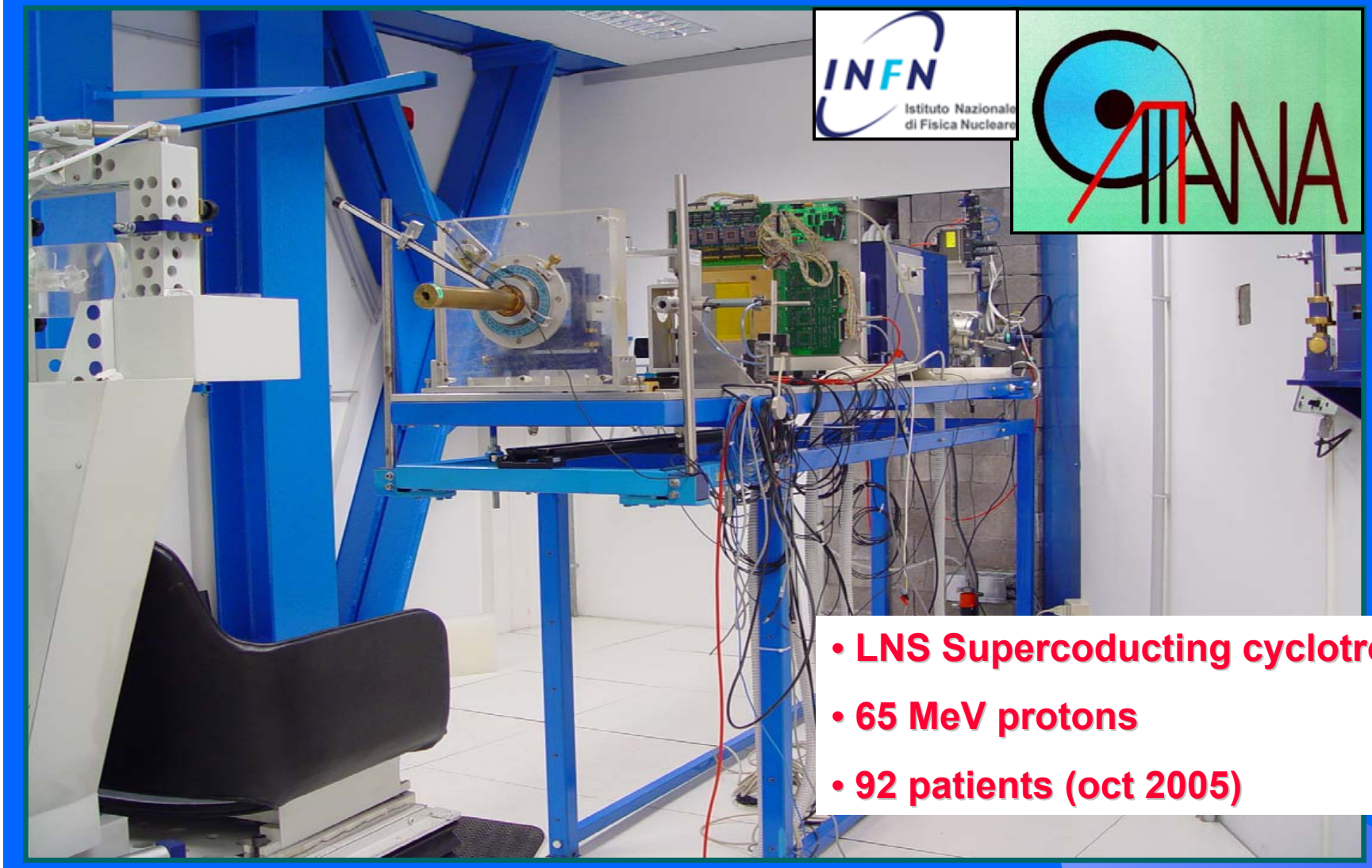
KASHIWA CENTER
Chiba (1998)
protons (≤ 235 MeV)
cyclotron (IBA – SHI)
2 Gantries + 1 hor. beam

HEAVY ION MEDICAL ACCELERATOR
HIMAC of NIRS (1995)
He and C (≤ 430 MeV/u) 2 synchrotrons
2 h beams + 2 v beams

2000 patients
with carbon ions

SHIZUOKA FACILITY
Shizuoka (2002)
Proton synchrotron
2 gantries + 1 h beam

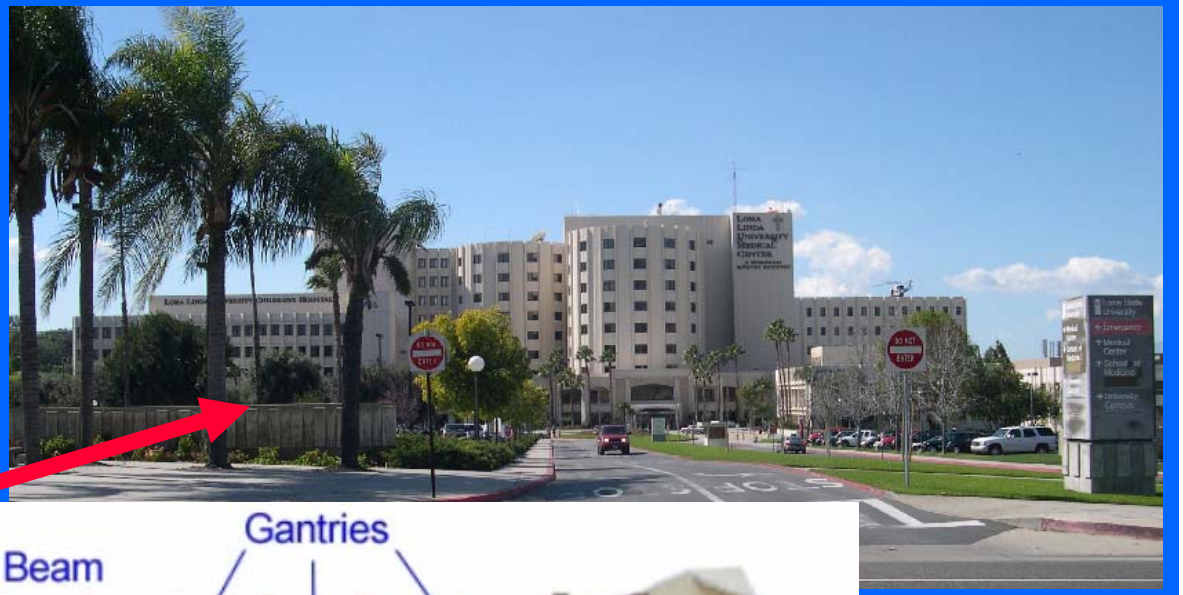
The eye melanoma treatment at INFN-LNS in Catania

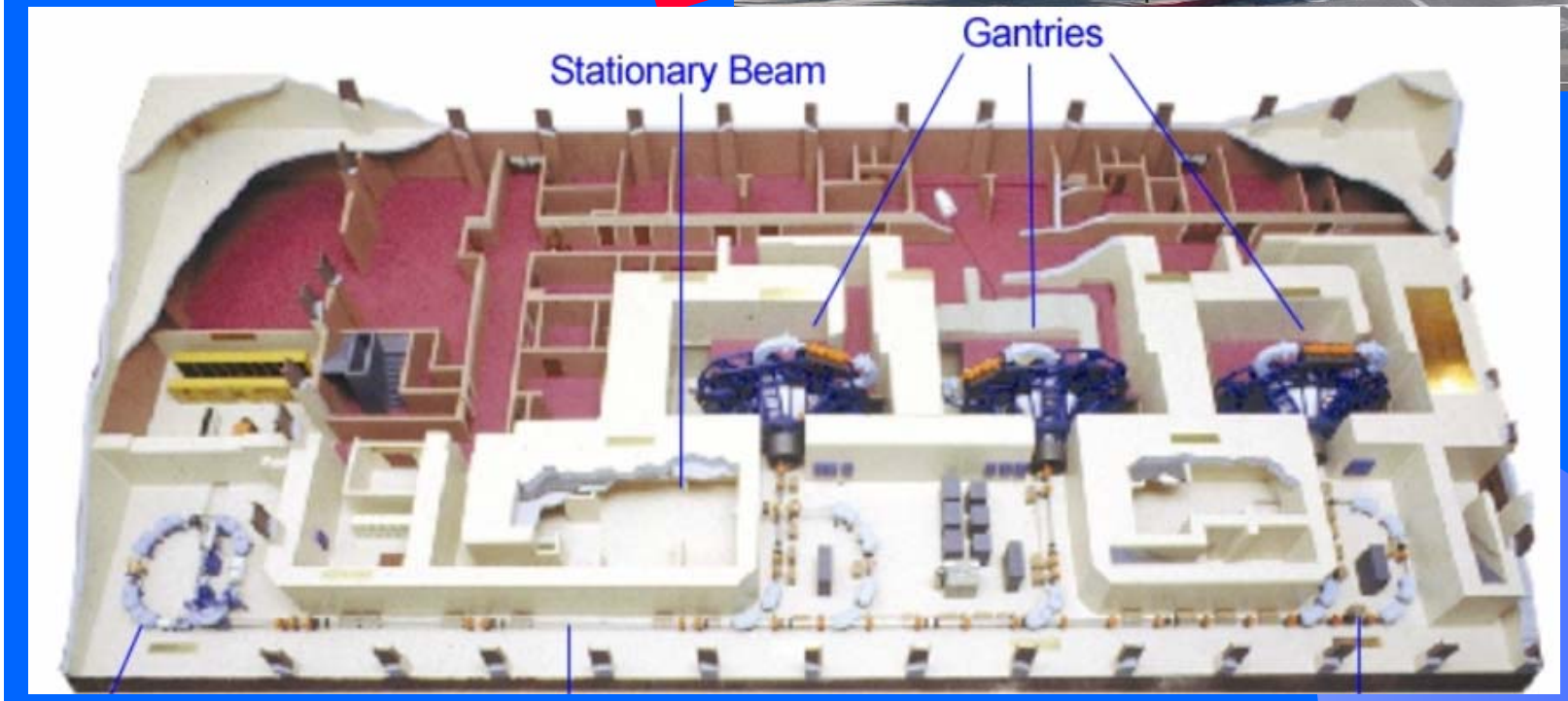


- LNS Supercoducting cyclotron
- 65 MeV protons
- 92 patients (oct 2005)

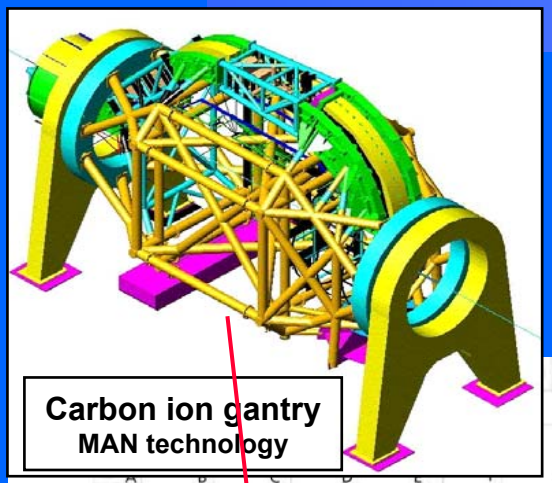
The Loma Linda University Medical Center (USA)

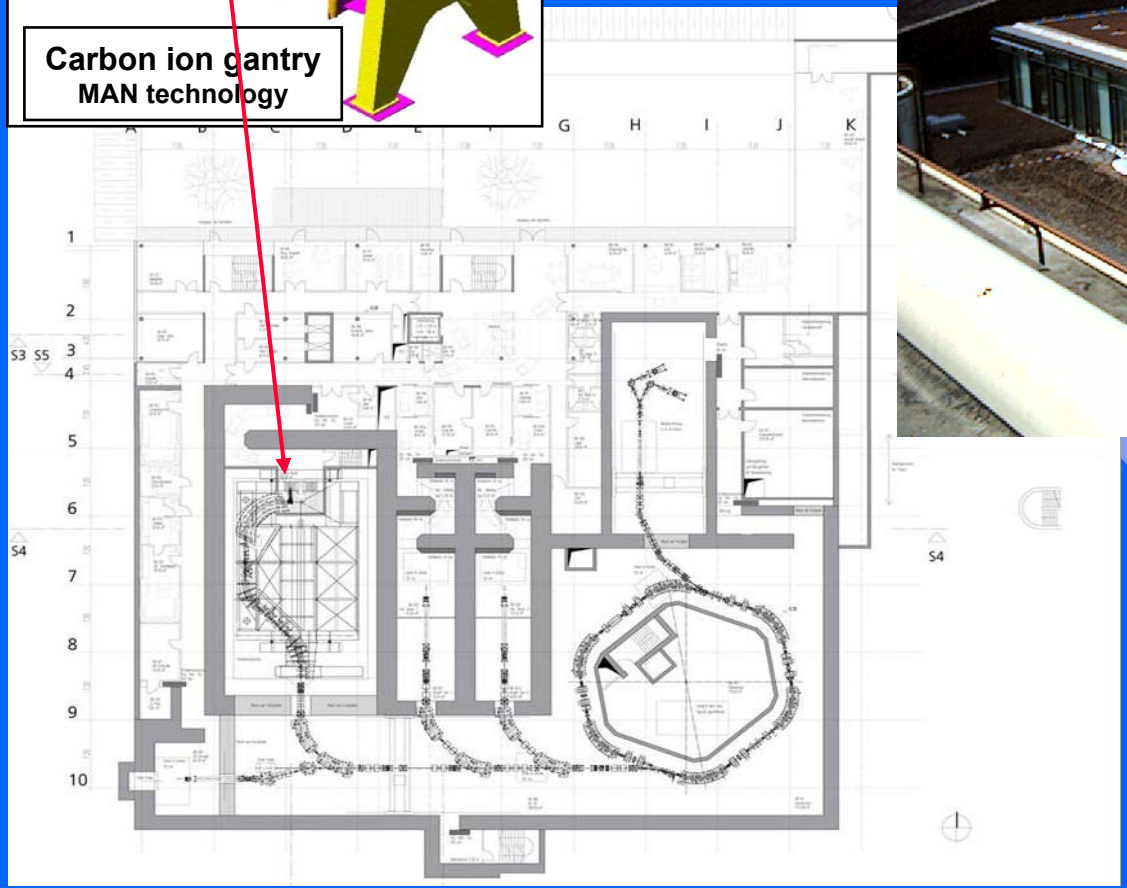
- First hospital-based proton-therapy centre, built in 1993
- ~160/sessions a day
- ~1000 patients/year





HIT – University of Heidelberg





- Hospital based centre
- Project started in 2001
- First patient treatment foreseen in 2007

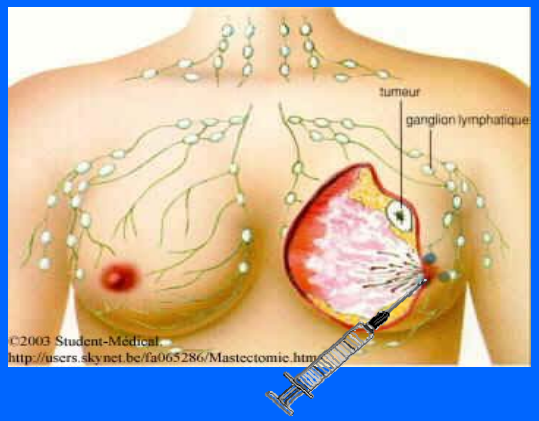
5. Some other examples of application

➔ *Peroperative Probes*
Detection system to help tumor detection during surgery

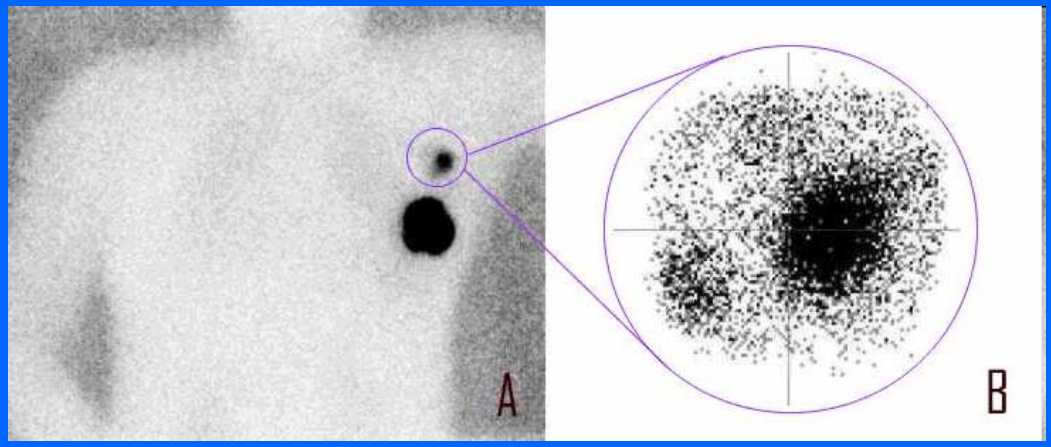
Per Operative Probes

System to help tumour detection during surgery

Sentinel Lymph Node procedure



Use of camera POCI (IMNC Orsay)
Previous and during surgery



Lymphoscintigraphy made with a usual gamma camera (SPECT) And POCI camera

IPHC Per Operative Probe and gamma camera

γ probe

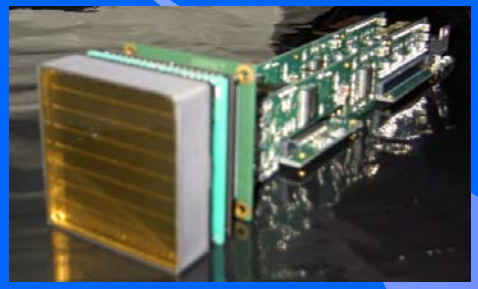
Sentinel Lymph Node procedure

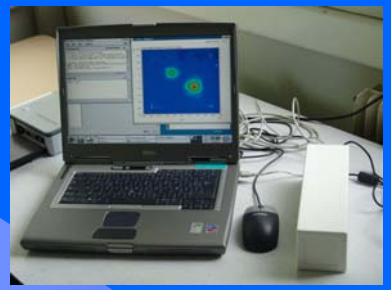
To reinforce before the surgery the diagnostic obtained the day before by lymphoscyntigraphy (γ camera).

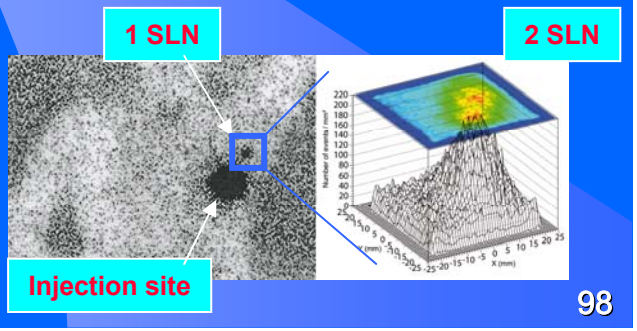
To localize the radioactive lymph node during the surgery (probe & γ camera).

To confirm after the surgery the removal of the all radioactive lymph nodes (γ camera).

γ camera







6. Organisation of medical application activities at the interface between physic and biology at IN2P3

➔ IN2P3 is the institut of French CNRS in charge of Nuclear and High Energy Physics

➔ 17 laboratories ➔ (Institut PluriDisciplinaire Hubert Curien in Strasbourg)

➔ There is a group working at the interface between Life Sciences and Physics in almost each laboratory

➔ MI2B joined Research Group (GDR in French) to help coordination of all these activities as high energy physics project

R&D on TOF PET

Physics Simulation for biology and oncology

Small Animal multimodal imaging platform (Amissa)

Peroperative probes

R&D on TOF PET

Physical data measurements

R&D on Dosimetry

Physics Simulation for Hadrontherapy

Physical data measurements

R&D on monochromatic X ray source

Small Animal multimodal imaging platform (ClearPET)

R&D on TOF PET

Physics Simulation for biology

R&D on hadrontherapy control quality

Physics Simulation for biology and oncology

Radiochemistry for oncology and cardiology (Arronax)

R&D on Liquid Xenon PET

autoradiography

R&D on imaging for neurology and oncology

Peroperative Probes

Physics Simulation for biology and oncology

X ray radiotherapy beam profiler

Radiobiology (microbeam)

Physics Simulation for biology and oncology

Peroperatives probes

Preclinic imaging