PART II: ON LINE DOSE MONITORING
Outline

- ✓ Treatment planning
- ✓ Treatment verification
- ✓ PET imaging
- ✓ Monte Carlo Simulations
- ✓ PET on-line monitoring
- ✓ Future developments and outlook

TREATMENT PLANNING

Radiotherapy treatment: a complex procedure that starts with the diagnosis of the cancer disease and ends with the dose delivery.

The dose to be delivery is established with the **treatment planning:**

CT Scan (also CT/PET and CT/MRI) -> patient anatomy (tissue density and target volume)

Radiation beam model

Machine instructions to deliver the treatment (beam energy, beam shape and number of hadrons to be delivered in each beam)

Expected dose distribution in the patient

TREATMENT VERIFICATION
Motivations

The well-defined range of hadrons is the main advantage of hadron therapy

In order to fully utilize this potential advantage **the range needs to be predicted as accurate as possible** -> profound impact on the **actually applied dose distribution** -> **treatment outcome**

Verification of particle therapy is very important to ensure **treatment planning and delivery systems are functioning properly**.

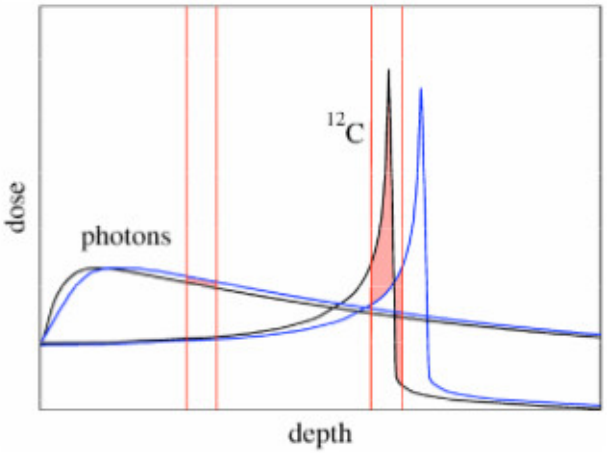


Fig. 12. For photon treatment, an error in target depth, indicated by two red lines at left, results in small dose error (red area). Whereas, for light ions, a similar error in range determination, shown in displaced Bragg peaks, would result in much more severe dose error as indicated by red areas (a big under-dose under the peak, and an overdose beyond the dose falloff region).

Chu W. T., Columbus-Ohio, ICRU-IAEA meeting, 18-20 March 20006

A **range error** could mean:
- a portion of a tumor not receiving any radiation dose at all (**under-shooting**);
- the normal tissue lying distal to the beam receiving a full dose (**over-shooting**).

TREATMENT VERIFICATION

Motivations

Hadron therapy is <u>strongly sensitive to uncertainties</u>

- During **treatment planning process** (systematic errors):

✓ Hounsfield units (HU) conversion method:
CT scan is used to determine stopping powers in dfferent tissues.
CT images have pixel that are Hounsfield units -> related to electron density in tissue.
Conversion error between Hounsfield units and particle stopping power -> errors range up to several mm in bone end soft tissue.

✓ CT artifacts;

✓ CT resolution;

✓ Particle scattering in complex anatomy and density variations (soft tissue-bone);

✓ Presence of metallic implants.

TREATMENT VERIFICATION
Motivations

Hadron therapy is <u>strongly sensitive to uncertainties</u>

- During **treatment** (random errors):

✓ Set-up and positioning errors;

✓ Beam delivery;

✓ Organ motion (breathing) and/or organ deformation (**inter- and intra-fraction target motion**);

✓ Change of anatomical structures (tumors shrinkage);

✓ Change of weights and body shape.

} The whole treatmnet consists of *fractions* spread over several weeks

all sources of uncertainties (order of several mm) must be <u>minimize</u>

TREATMENT VERIFICATION

Motivations

Beam range errors -> dose delivery errors

Source of range uncertainty in the patient	Range uncertainty without Monte Carlo	Range uncertainty with Monte Carlo
Independent of dose calculation		
Measurement uncertainty in water for commissioning	±0.3 mm	±0.3 mm
Compensator design	±0.2 mm	±0.2 mm
Beam reproducibility	±0.2 mm	±0.2 mm
Patient setup	±0.7 mm	±0.7 mm
Dose calculation		
Biology (always positive) ^	+~0.8%	+~0.8%
CT imaging and calibration	±0.5%[a]	±0.5%[a]
CT conversion to tissue (excluding I-values)	±0.5%[b]	±0.2%[g]
CT grid size	±0.3%[c]	±0.3%[c]
Mean excitation energy (I-values) in tissues	±1.5%[d]	±1.5%[d]
Range degradation; complex inhomogeneities	−0.7%[e]	±0.1%
Range degradation; local lateral inhomogeneities *	±2.5%[f]	±0.1%
Total (excluding *, ^)	2.7% + 1.2 mm	2.4% + 1.2 mm
Total (excluding ^)	4.6% + 1.2 mm	2.4% + 1.2 mm

Estimated proton range uncertainties and their sources and the potential of Monte Carlo method for reducing the uncertainty(3).

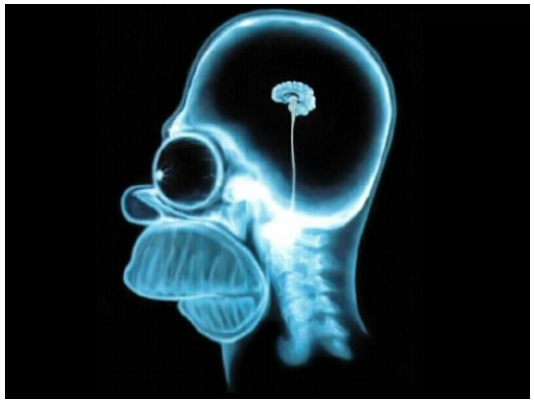
(3) Paganetti H., 2012, "*Range uncertainties in proton therapy and the role of Monte Carlo Simulations*", Phys. Med. Biol., 57:99-117.

TREATMENT VERIFICATION

Imaging and quality assurance

Computed Tomography (CT) / Positron Emission Tomography (PET) essential:

- prior to treatment planning for delineating target volumes and structures of interest;
- to position and immobilize the patient reducing errors;
- on-line and off-line monitoring (*in vivo* 3D dose and/or range verification).



Homer Simpson CT

During commissioning and clinical practice:

- test for mechanical and electrical safety;
- test of beam characteristics (intensity, profile and position must be stable);
- check of tolerances and geometric misalignments;
- shielding for secondary radiation (specially neutrons).

TREATMENT VERIFICATION

Uncertainties could be better understood if *in vivo* and *in situ* range measurement could be done with high precision (about 1 mm)

Hadrons stop completely in the body -> **direct *in vivo* treatment monitoring is very difficult -> the verification has to rely on a "surrogate" signal induced by the therapeutic beam during or shortly after the irradiation**.

Proposed approaches:

I. use of implanted dosimeter -> invasive;

II. MRI (*Magnetic Resonance Imaging*);

III. prompt gamma imaging;

IV. PET (*Positron Emission Tomography*) imaging of hadron induced positron emitters.

Non–invasive

PET IMAGING
Pioneering studies

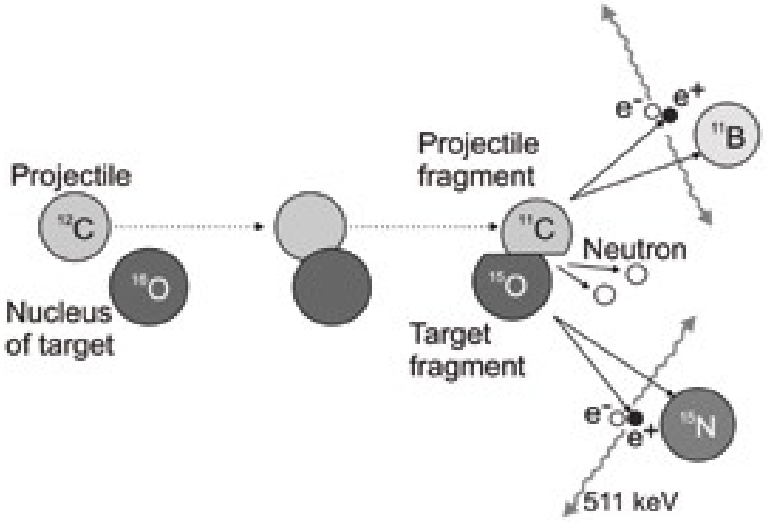
The use of PET imaging for the verification of hadron therapy was first proposed by **Maccabee *et al* in 1969 (@ Lawrence Berekeley Laboratory - California)**: H D Maccabee *et al*, 1969, "*Tissue activation studies with alpha-particle beams*", Phys Med Biol 1969 Vol 14 (213-24).

And later by **Chatterjee et al in 1981**: Chatterjee A et al, "*High energy beams of radioactive nuclei and their biomedical applications*", 1981, Int. J. Radiat. Oncol. Biol. Phys. 7 (503-507).

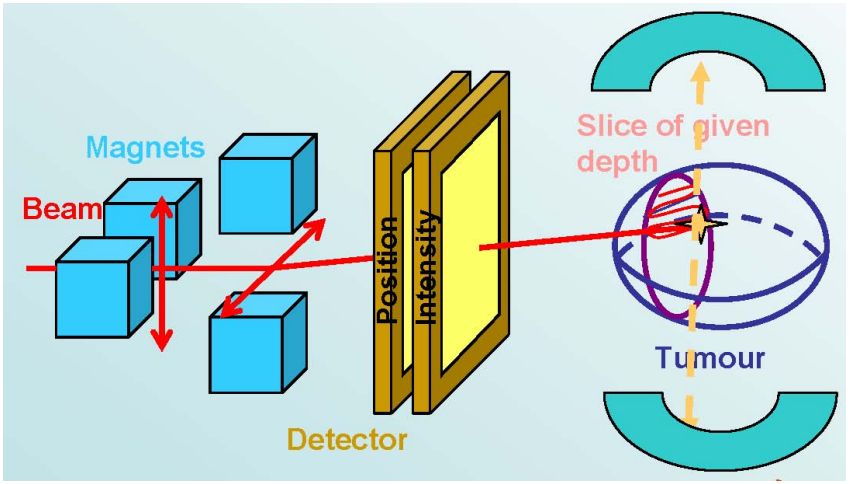
Than various research group **investigated the possibility of particle therapy monitoring by means of PET**, which **is still today the subject of intense studies**.

PET IMAGING

Principles of PET imaging in particle therapy



^{12}C ion (projectile) colliding with an ^{16}O atom of the irradiated tissue.



Positrons annihilation

Inelastic nuclear collitions of hadrons with the atoms of the irradiated tissue -> tissue activation: β^+-emitters prodution -> radioactive dacay -> annihilation of e^+ with the e^- of tissue

By means of a PET scanner the annihilation photons (ɣ) can be detected in coincidence -> 3D treatment delivery verification

No additional dose cost for the patient

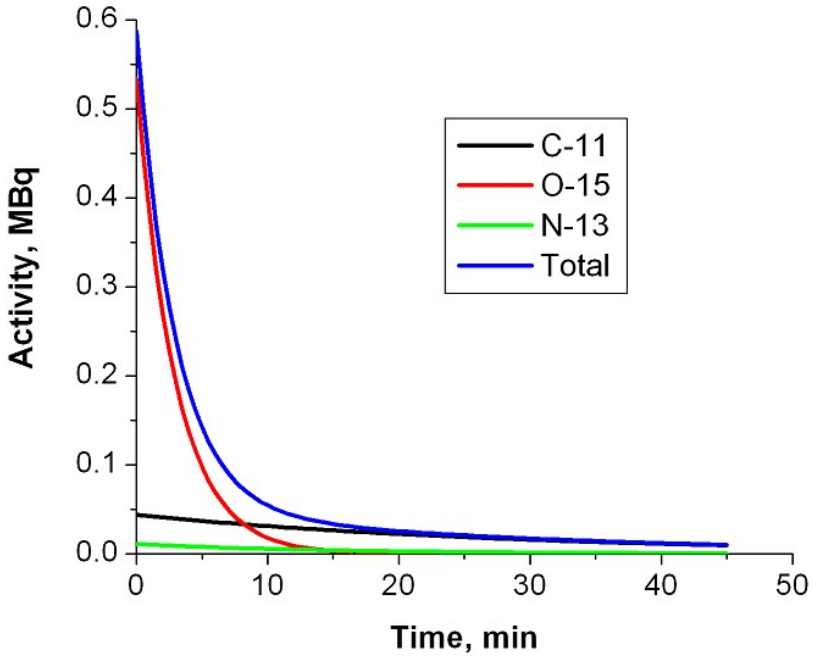
PET IMAGING

Principles of PET imaging in particle therapy

Table I. Major nuclear reaction channels for proton induced positron emitter productions.

Radionuclide	Half live (min)	Nuclear reaction channels / Threshold energies (MeV)
^{15}O	2.037	$^{16}O(p,pn)^{15}O/16.79$
^{11}C	20.385	$^{12}C(p,pn)^{11}C/20.61$, $^{14}N(p,2p2n)^{11}C/3.22$, $^{16}O(p,3p3n)^{11}C/59.64$
^{13}N	9.965	$^{16}O(p,2p2n)^{13}N/5.66$, $^{14}N(p,pn)^{13}N/11.44$
^{30}P	2.498	$^{31}P(p,pn)^{30}P/19.7$
^{38}K	7.636	$^{40}Ca(p,2p2n)^{38}K/21.2$

Major nuclear reaction channels for proton induced positron emitter productions[(4)].



Relative contributions of major radionuclide species as a function of time due to radioactive decay[(4)].

(4) Xuping Zhu, Georges El Fakhri, 2013, "*Proton Therapy Verification with PET Imaging*", Theranostics , 3(10):731-740.

PET IMAGING

Principles of PET imaging in particle therapy

In soft tissues **^{11}C**, **^{13}N** and **^{15}O** are the relevant radionuclide species.

Activity: $A = A_0 e^{-\lambda t}$

Where

A_0: initial Activity of the radioactive material;
λ: decay constant ($\tau_{½}$ half-life -> $\lambda = \ln 2/\tau_{½}$);
t: time.

Short half-life -> high decay constant -> **^{15}O and ^{11}C become the dominant nuclides after a few minutes.**

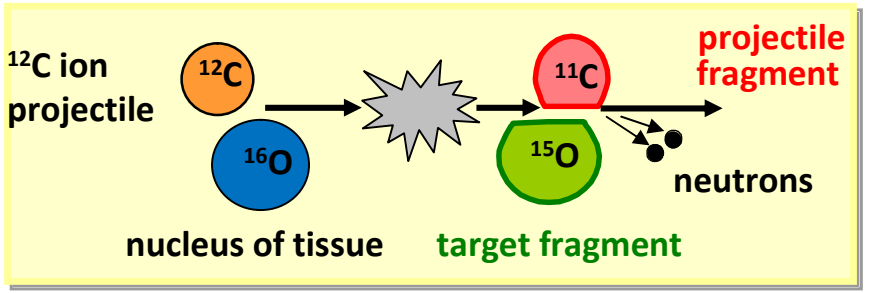
The mix of radionuclide species contributes to the PET signal (^{15}O for 80%) **-> treatment verification via PET is very sensitive to the time course of data acquisition.**

PET IMAGING

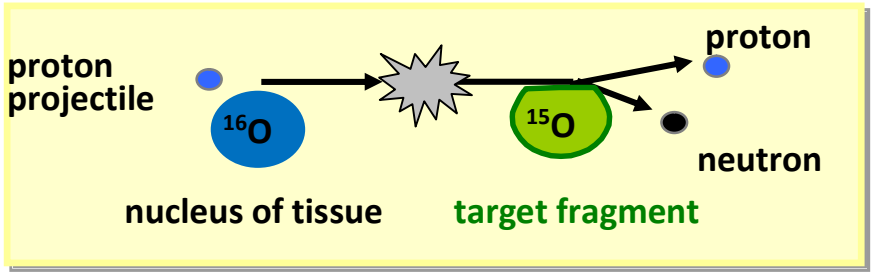
Principles of PET imaging in particle therapy

Ion beam inelastic collisions:
projectile and target fragmentation

Proton beam inelastic collisions**: only target fragmentation**



β⁺ - emitters production



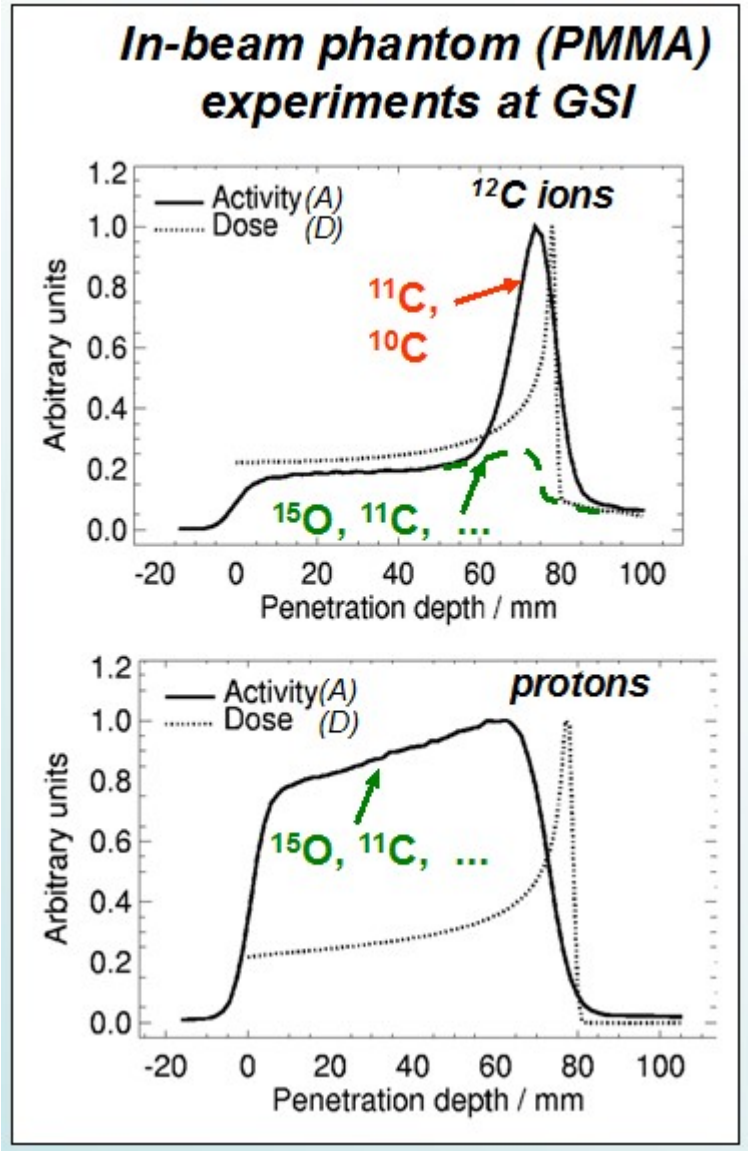
β⁺- emitters **yield** dependes on:

- particle fluence;
- cross section of specific reaction channels (energy dependent);
- density of target nuclei.

The threshold energies for the b⁺-isotopes cause the activity distribution to drop prior to the dose distribution -> Fall-off activity position and dose distribution are shifted against each other

PET IMAGING

Principles of PET imaging in particle therapy



Ion beam: an **activity peak close to the Bragg Peak** can be found (due to projectile fragmentation reactions);

→ **^{12}C ion beam @ 212 MeV**

proton beam: PET activity distribution is completely different from the dose distribution (only target fragmentation reactions).

→ **Proton beam @ 110 MeV**

K. Parodi et al., IEEE MIC CR, 2002

PET IMAGING

Principles of PET imaging in particle therapy

Living body is different from inorganic matter

In vivo **radioisotope distributions can be spread out and carried away from the location of activity production** due to

- complex chemistry processes;
- diffusion;
- physiological processes related to blood flow (perfusion) and fluid components present in the living organ.

biological wash-out effect which is dependent on the organ species, varies between patients, and increases with the delay between treatment and scanning -> biological decay (τ½ 2÷10 s)

signal changes over time -> correction

PET IMAGING

Principles of PET imaging in particle therapy

PET activity and dose distribution cannot be compared directly:

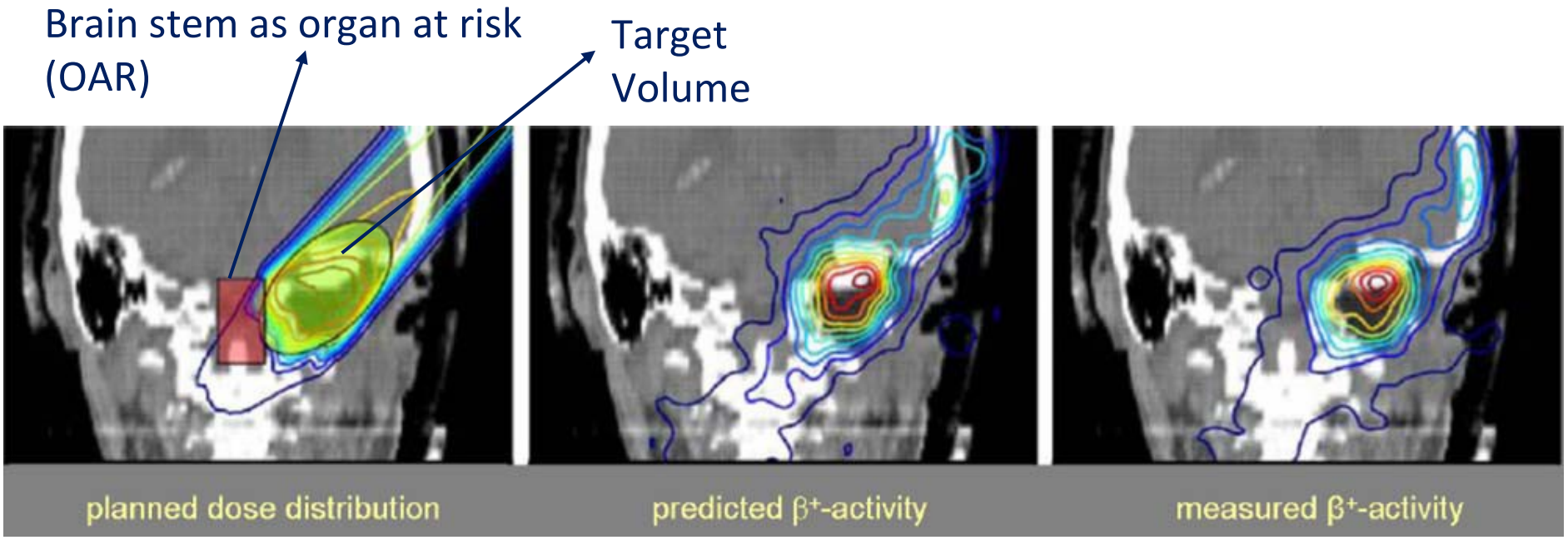
The relation between the induced activity and dose distribution is not straightforward -> PET measurements have to be compared with predicted activity distributions or other reference images.

The method consists in comparing the spatial distribution of the annihilation photons predicted by Monte Carlo (MC) simulations (***in silico* modelling**) based on the treatment plan with the actual PET image.

Analysis of **mismatch between MC simulated and the PET image** (reference) -> **errors detection in dose delivery**

PET IMAGING

Principles of PET imaging in particle therapy



Example of on-line PET monitoring showing the irradiation of a skull base tumor at GSI - Darmstadt[(5)].

(5) Enghardt, W. *et al*, 1999, "*Positron emission tomography for quality assurance of cancer therapy with light ion beams*", Nucl. Phys. A **654,** 1047c–1050c.

MONTE CARLO SIMULATIONS

Monte Carlo method: probabilistic method that allows to solve analytically complex problems, stochastic or deterministic, by means of sampling techniques.

Advantages:

- To reproduce accurately the **interaction of hadrons with biological matter** taking into account the real tissue composition;
- accurate **3D** particle track transport;
- to describe **complex field and geometries** (and interfaces between rather different materials);
- fully detailed description of the **patient anatomy** -> CT image converted into a MC geometry;
- to reproduce the effects caused by the **heterogeneities** (metal implants, fat tissue, …).

MONTE CARLO SIMULATIONS

Patient cannot be the subject of experimentation:

MCS "gold standard" in radiation therapy for:

- ✓ dose distribution prediction;
- ✓ range uncertainties estimation;

} treatment planning validation

- ✓ radiobilogical studies for cell survival experiments;
- ✓ design an commissioning of facilities;
- ✓ **prediction/analysis of in-beam PET application**.

Need to improve **nuclear reaction models** used in the codes on the basis of **experimental data** on radioisotope production in various light materials.

MONTE CARLO SIMULATIONS

Monte Carlo simulations toolkits

Name: **FLUKA (*FLUktuierende KAskade*)**
Provider: INFN/CERN
Short describtion: fully integrated particle physics MC simulation package; has many applications in high energy experimental physics and engineering, shielding, detector and telescope design, cosmic ray studies, dosimetry, **medical physics and radiobiology**.

Name: **MCNPX (*Monte Carlo N-Particle eXtended*)**
Provider: Los Alamos National Laboratory
Short describtion: stands for MC N-Particle eXtended; extends the capabilities of MCNP4C3 to nearly all particle types, to nearly all energies, and to nearly all applications; n, e, g, p...**heavy ions transport**.

Name: **PHITS (*Particle and Heavy Ion Transport code System*)**
Provider: Collaboration of may institutes in Japan and Europe
Short describtion: It can deal with the transport of all particles over wide energy ranges, using several nuclear reaction models and nuclear data libraries. PHITS can support your researches in the fields of accelerator technology, **radiotherapy**, space radiation, and in many other fields which are related to particle and heavy ion transport phenomena.

MONTE CARLO SIMULATIONS

Monte Carlo simulations toolkits

Name: **GEANT4 (*GEometry ANd Tracking*)**
Provider: CERN
Short describtion: toolkit for the simulation of the passage of particles through matter; areas of application include high energy, nuclear and accelerator physics, as well as studies in space and **medical science.**

Name: **GATE (*Geant4 Application for Emission Tomography*)**
Provider: OpenGATE collaboration
Short describtion: advanced **opensource** software dedicated to **numerical simulations in medical imaging and radiotherapy**. It currently supports simulations of Emission Tomography (Positron Emission Tomography - PET and Single Photon Emission Computed Tomography - SPECT), Computed Tomography (CT) and Radiotherapy experiments.

MONTE CARLO SIMULATIONS

Disadvantage

Accurate results require the simulation of a large number of events ($10^6 \div 10^9$ primary particles) -> long execution time and large computational resources

GRID computing: computing infrastructure whose mission is to provide computing resources to store, distribute and analyse the data, making the data equally available to all partners, regardless of their physical location.

Vadapalli R. *et al*, "*Grid-enabled treatment planning for protpn therapy using Monte Carlo Simulations*", Nucl Technol, 2011 July, 175(1): 16–21:
GEANT4 simulations for the transport of 25 $\times 10^6$ protons @ 200 MeV on Grid environment -> **10^3 processor cores would reduce the MC simulation runtime from 18.3 days to ~ 1 h.**

MONTE CARLO SIMULATIONS

Disadvantage

Accurate results require the simulation of a large number of events ($10^6 \div 10^9$ primary particles) -> long execution time and large computational resources

GPU (*Graphics Processing Unit*)-accelerated computing: offers unprecedented application performance by offloading compute-intensive portions of the application to the GPU, while the remainder of the code still runs on the CPU. From a user's perspective, applications simply run significantly faster.

Wan Chan Tseung. H et al, "*A fast GPU-based Monte Carlo simulation of proton transport with detailed modeling of non-elastic interactions*", 2015, Med. Phys. 42:2967-2978:

The calculation time on a NVIDIA GTX680 card of a GEANT4-TOPAS MC simulation is **~ 20 s for 1×10^7 proton histories, instead of 1h**.

PET ON LINE MONITORING

Modalities

For PET imaging clinical implementation three modalities are investigated:

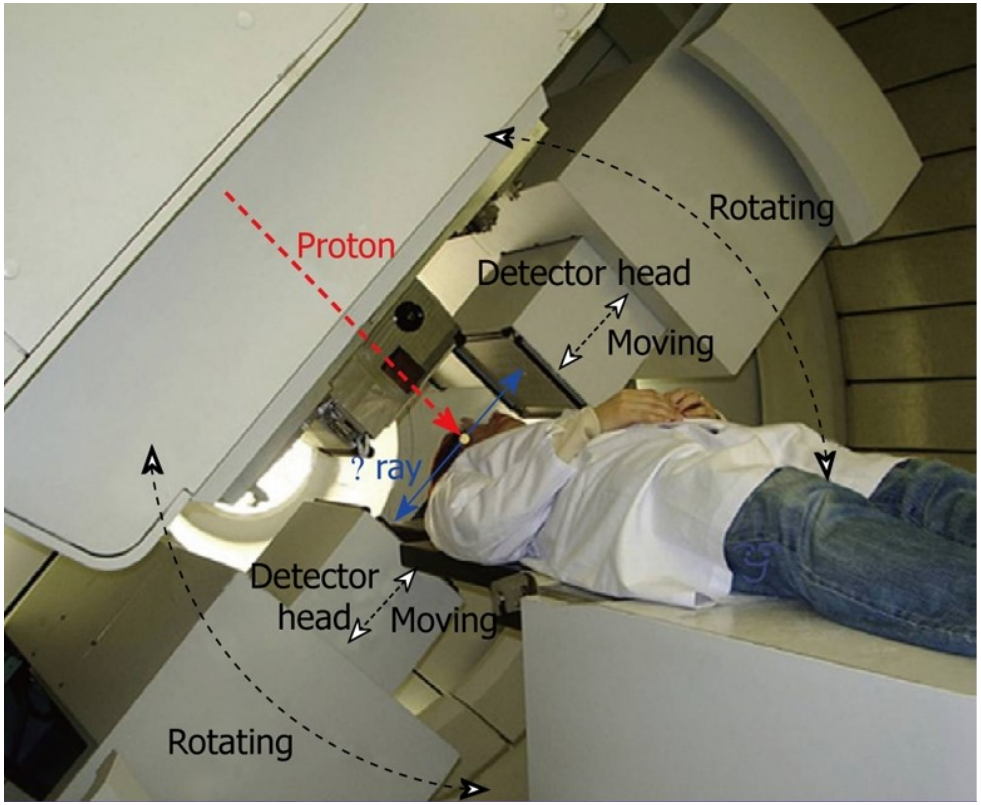
a. In-beam PET: measurement of β^+-activity **during irradiation** by means of a customized PET scanner integrated into the treatment site or directly into the gantry. First prototype used from 1997 to 2008 @ GSI (*Gesellschaft für Schwerionenforschung*) - Darmstadt.

b. In-room PET: the measurement take place **shortly after irradiation** with a PET scanner located in the treatment room. First studies @ MHG (*Massachusetts General Hospital*) - Boston.

c. Off-line PET: the measurement starts with **time delays of several minutes after irraditation,** the patient is transported to a commercial PET system (usually combined with CT). Only the activity of **long half-life** radioisotopes is detected. Currently in use @ HIT (*Heidelberg Ion-Beam Therapy Center)* - Heidelberg.

PET ON LINE MONITORING

Clinical implementations: in-beam PET

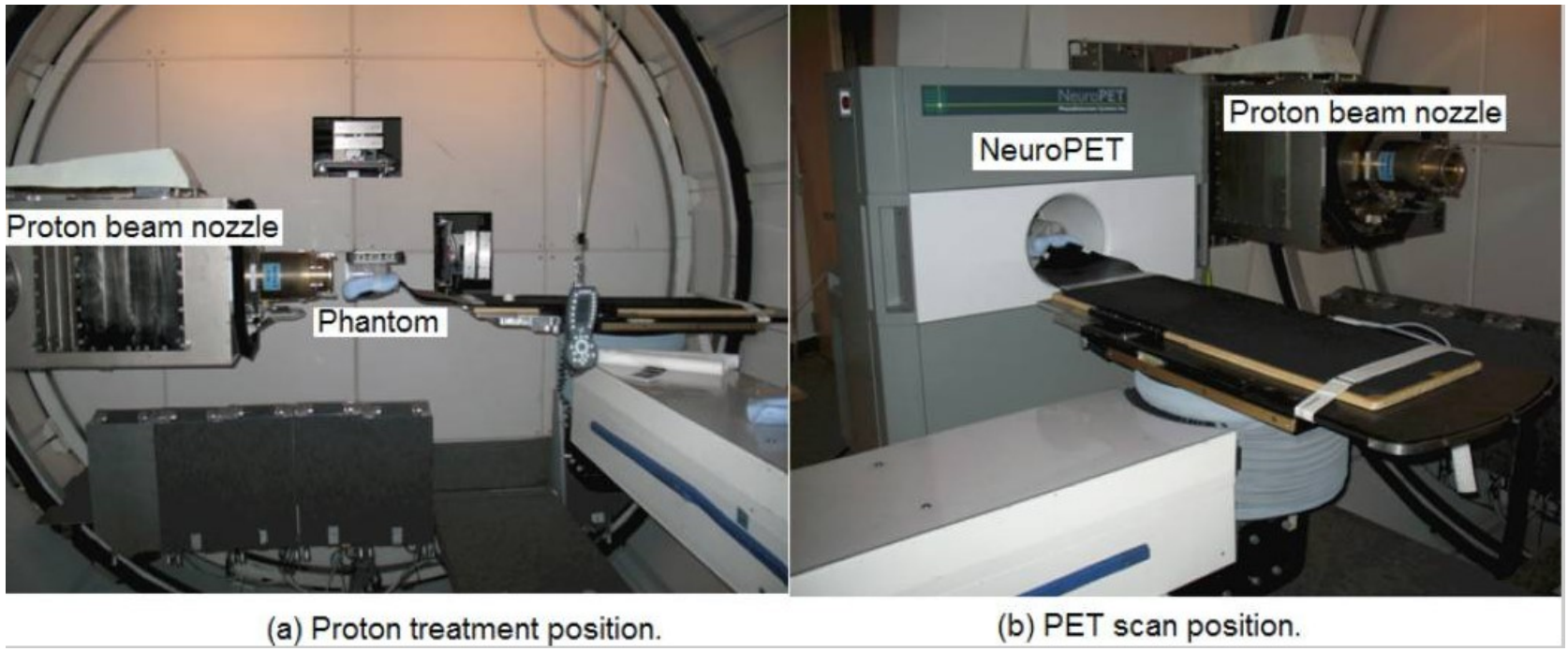


Setup of the on-line PET (**dual-head PET scanner**) system mounted on the rotating proton gantry. The proton beam direction is shown by the red line and the direction of the detected annihilation photons is shown in blue[(6)].

(6) Studenski M. and Xiao Y., *"Proton therapy dosimetry using positron emission tomography",* World J Radiol., 2010, Apr 28, 2(4): 135–142.

PET ON LINE MONITORING

Clinical implementations: in-room PET



(a) Proton treatment position. (b) PET scan position.

Treatment bed in the (a) proton treatment and (b) PET scan positions during an in-room phantom study. After beam delivery, the treatment bed was rotated and moved, and the phantom was inserted directly into the scanner for the PET scan[7].

(7) Zhu X. *et al, "Monitoring proton radiation therapy with in-room PET imaging", Phys Med Biol., 2011 Jul 7, 56(13) :4041-57.*

PET ON LINE MONITORING

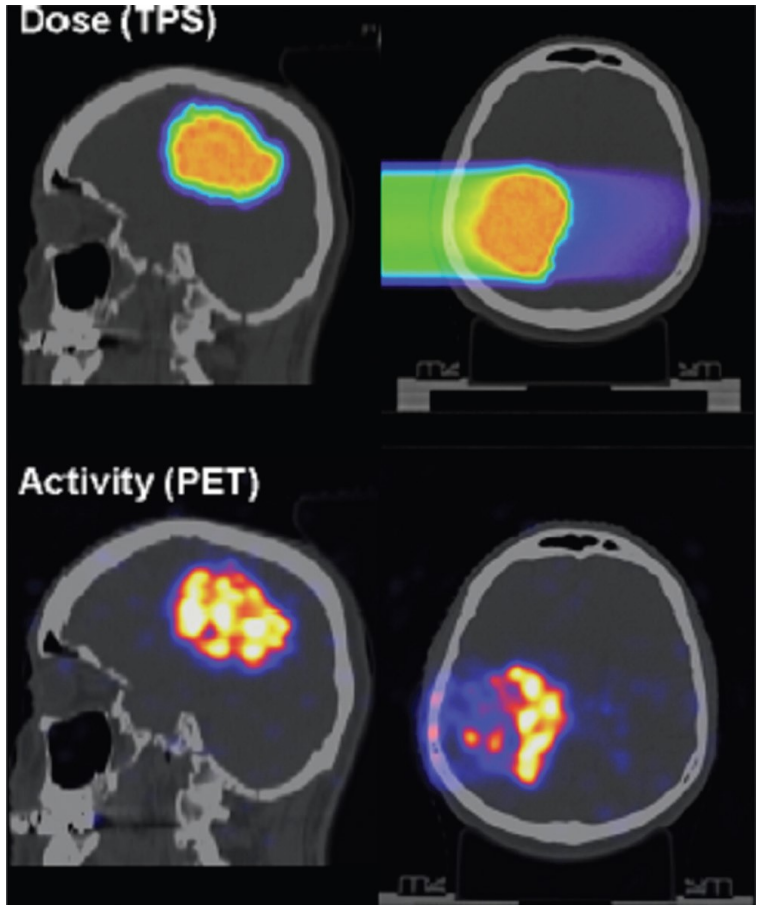
Clinical implementations: off-line PET

Off-line PET, transport between the imaging (PET/CT) and treatment room[(8)].

(8) Parodi K., "*PET monitoring oh hadrontherapy*", Nuclear Medicine Review, 2012, 15, Suppl. C: C37–C42.

PET ON LINE MONITORING

Clinical implementations



Patient treated for a primary brain tumour with a carbon ion boost, (A) **planned dose distribution overlaid onto the planning CT,** undergoing a PET/CT measurement (B) **shortly after scanned ion** irradiation at HIT[8].

(8) Parodi K., "*PET monitoring oh hadrontherapy*", Nuclear Medicine Review, 2012, 15, Suppl. C: C37–C42.

PET ON LINE MONITORING

On line monitoring - requirements

In comparison with off-line PET monitoring, **on-line (in-beam and in-room) PET monitoring minimizes the signal degradation since**:

- requires much **shorter imaging time** since the physical decays available is significantly higher;
- the **influence of biological wash-out is reduced**, as well as the data acquisition time;
- **no patient repositioning** is necessary;
- **real time correction** of the treatment would be possible in case of mismatches between measured and predicted activation distribution.

Anyway for PET on-line monitoring:

- the **available statistics is very low** (positron yield is low);
- the interaction of the therapeutic beam with the patient produce secondary particles -> **high background.**

the highest detection sensitivity is required

$$\text{Sensitivity} = \frac{\text{Number of detected coincidences}}{\text{Number of photon pairs}}$$

PET ON LINE MONITORING

Requirements

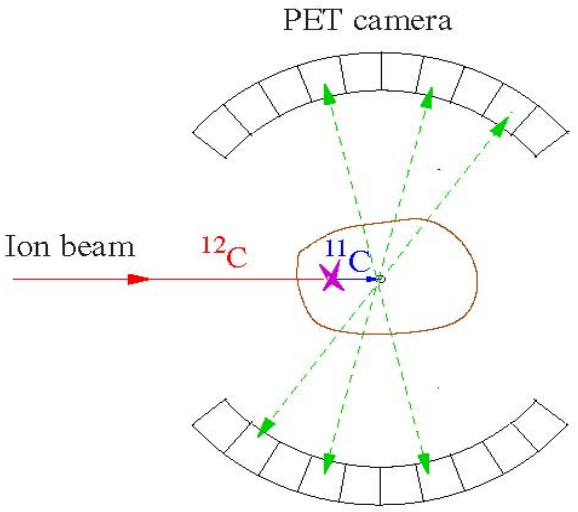
The detection principle of PET-based hadron therapy verification is similar to conventional PET diagnostic, but the **technical implementation** differs since, <u>for particle therapy in-beam monitoring</u>, **PET scanner has to be integrated into the treatment site** -> **double-head system** based on conventional PET (and not a full ring):

- protection of the scanner by the therapeutic beam;
- possibility to position and handle the patient;
- free access to medical staff;
- detector rotation around the central beam.

The two detector heads operate in coincidence.

Dual head geometry -> **limited angual field of view (FOV) -> reduction of sensitivity**

DAQ system needs syncronization with the beam delivery and rejection of unwanted background



PET camera schema

PET ON LINE MONITORING

Requirements

Detector technology:

- ✓ High signal-to-noise ratio;
- ✓ High detector efficiency;
- ✓ Moderate spatial resolution $\Delta x \leq 5$ mm;

Detector geometry:

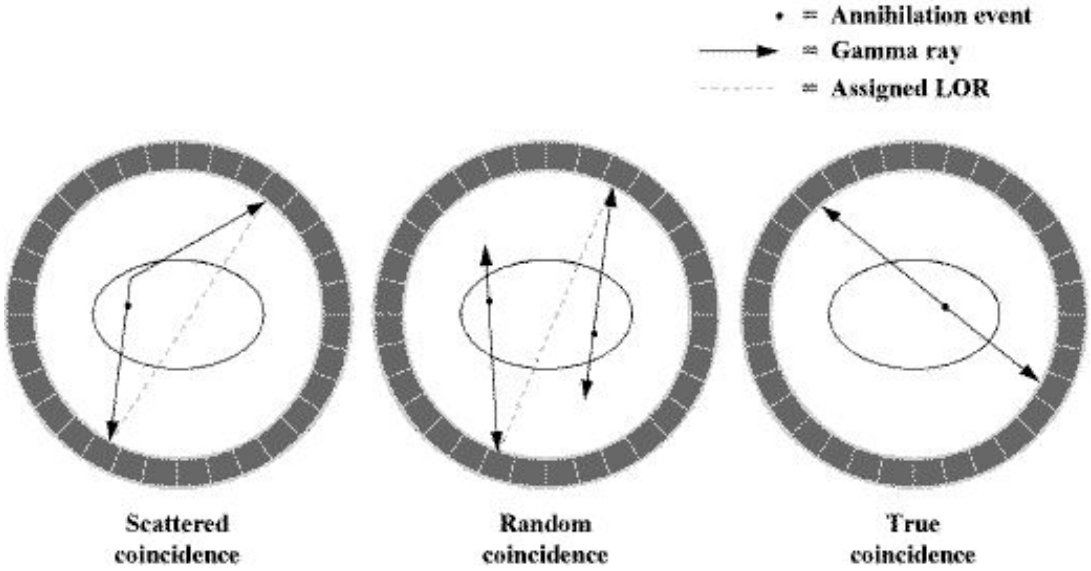
- ✓ Large solid angle;
- ✓ Shift invariant point response function;
- ✓ Ports for the primary beam and the light fragments;

Position control Data acquisition:

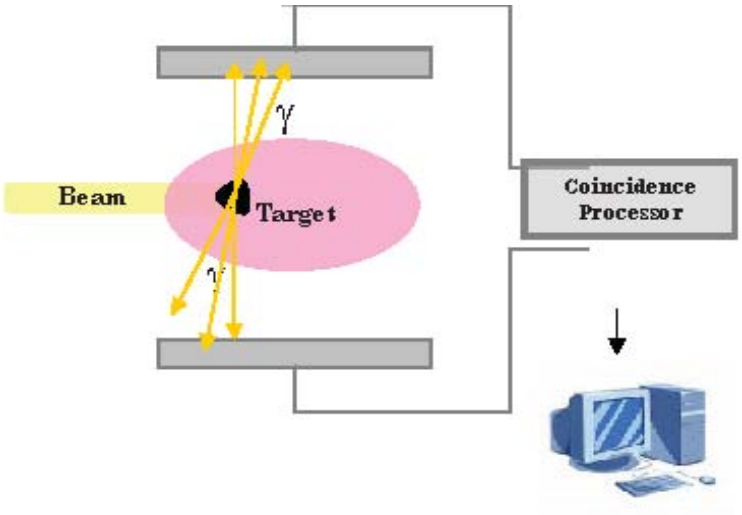
- ✓ Coupled with beam delivery control;
- ✓ Rather slow (≈ 105 cps).

PET ON LINE MONITORING

Requirements



Schematic illustration of scattered (left), random (middle) and true (right) coincidence events in PET acquisition.



Schematic PET imaging process.

For a reliable reconstruction of β^+-activity distribution underlying the measured signal, the amount of **true coincidences** has to be recovedered from the whole collected data -> **proper corrections for random and scattered coincidences**.

Detector system

- **Energy resolution** -> **discrimination of scattered events**
- **Short decay constant** -> good coincidence timing -> **random suppression**

PET ON LINE MONITORING

In-bam PET: the state of the art

First experimental prototype of PET system was implemented in 1979 at LBL: a one-dimentional camera of 48 **NaI(Tl)** detectors, called **PEBA-I** (*Positron Emission Beam Analyzer*) followed after 1982 by a high-accuracy and high-sensitivity camera**, PEBA-II**, made of two opposite heads of detectors, with 64 scintillator block detectors of bismuth germanate (**BGO**) each (size of the detector heads of 10×10 cm^2).

First clinical use of in-beam PET camera:

- At GSI with a system of two detector heads (42×21 cm^2) with detector blocks of **BGO**;

- At HIMAC (*Heavy Ion Medical Accelerator in Chiba* - Japan) with a camera consisting of a pair of **Anger-type** scintillation detectors;

- At NCCHE (*National Cancer Center Hospital East* - Kashiwa) with a PET system mounted on a rotating gantry port and consisting of two opposing detector heads of a planar positron imaging system with **BGO** scintillators and a FOV of 15,6×16,7 cm^2).

PET ON LINE MONITORING

In-bam PET: the state of the art

Ideal scintillators for the **high resolution and high speed PET** should have the **main properties** such as:

a. high stopping power;

b. high light output;

c. fast decay time.

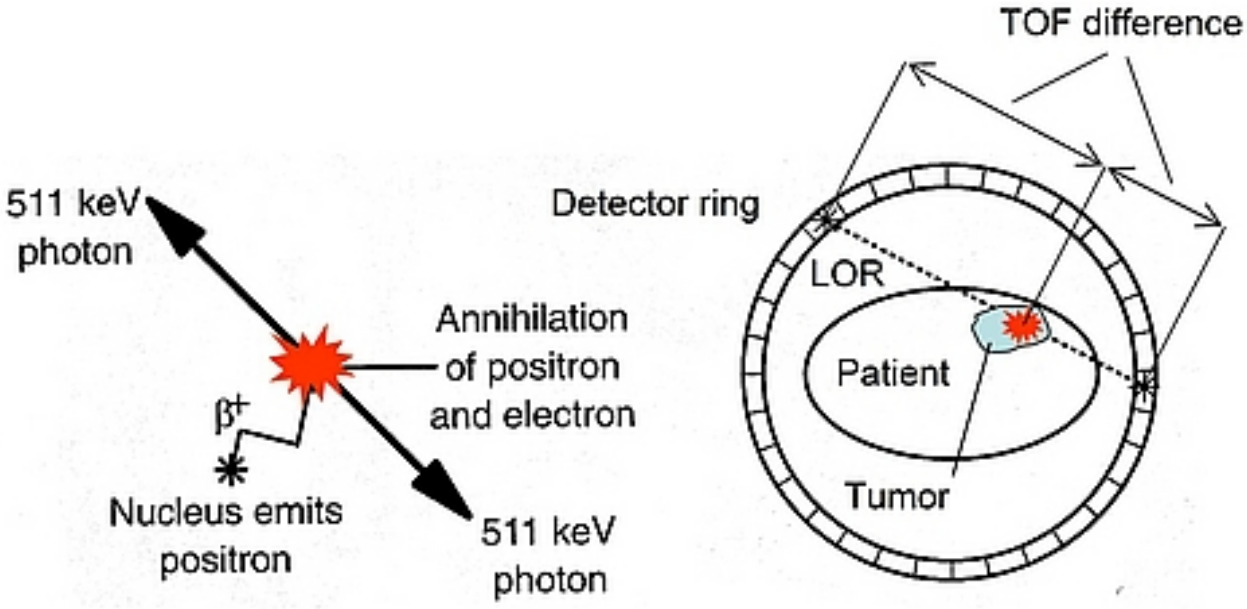
But nowadays, all the existing crystals do not meet all these requirements.

Currently, the most widely used scintillation crystal for PET is **BGO**, which has high stopping power.

However, BGO crystals have a **long decay time (~ 300 ns)** -> this limits its application in high speed PET especially in Time of Flight (TOF) PET.

PET ON LINE MONITORING

In-beam PET: the state of the art



Principle of TOF-PET

Many research groups are investigating **ultra fast TOF techniques** with **timing resolution less than 200 ps**, which enable **almost artefact-free and real-time images**.

Fast scintillator crystals: **LSO** (cerium doped lutetium oxyorthosilicate, Lu_2SiO_5), **LYSO** (cerium doped lutetium yttrium oxyorthosilicate, $Lu2_{(1-x)}Y2_xSiO_5$) and **$LaBr_3$**:

These last surpass BGO on **energy resolution, light output and decay time and resemble BGO in stopping power** (LYSO cheaper than LSO, less amount of expensive Lu_2O_3 required).

PET ON LINE MONITORING

In-bem PET: the state of the art

CATANA (INFN, Catania – Italy): in-beam PET which consists of two 10 cm×10 cm detector heads. Each detector is composed of four scintillating matrices of 23×23 **LYSO** crystals. The crystal size is 1,9 mm×1,9mm×16 mm (**Sportelli G. *et al, "First full-beam PET acquisitions in proton therapy with a modular dual-head dedicated system*", 2014, Phys. Med. Biol., 59:43-60**).

INSIDE (*Innovative Solutions for In-beam Dosimetry in hadrontherapy*) project: born from the collaboration of Italian Universities and INFN to build a multimodal in-beam dose monitoring system able to detect at the same time, back-to-back gammas from β^+ annihilation and charged secondary particles with kinetic energy higher than 30 MeV (prompt photons with energies higher than 1 MeV can be exploited as well). The monitor will be made up of **2 planar of 10×20 cm² PET heads** (made of 2×4 detection modules, each module composed of a pixelated **LYSO** matrix 16×16 pixels of 3×3 mm^2 crystals, pitch 3:1 mm) for back-to-back gammas detection and of a 20×20 cm^2 dual-mode dose profiler made of 3 sub-detectors: a tracker, an absorber and a calorimeter (**Marafini M. *et al*, "*The INSIDE Pro ject: Innovative Solutions for In-Beam Dosimetry in Hadrontherapy*", Pro ceedings of the I I Symp osium on Positron Emission Tomography, Kraków, Septemb er 21-24, 2014**).

PET ON LINE MONITORING

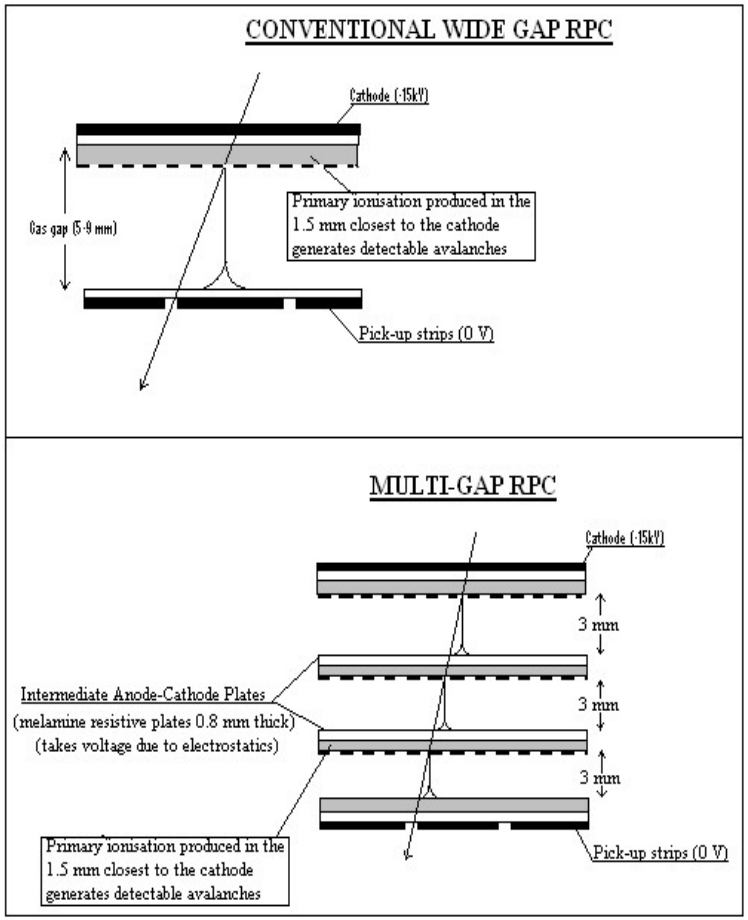
On-going developments

In addition to fast scintillator crystals, researchers are also investigating **alternative detection concepts** for TOF-PET scanners, which offer **high sensitivity, excellent timing resolution and are very cheap to produce in large areas**.

Multi-gap RPC (*Resistive Plate Chamber*): already used in high energy physics expetiments, have

- a very low cost;
- an excellent timing resolution (20 ps) at FWHM (*Full Width at Half Maximum*);
- sub-millimeter spatial resolution.

The limit is **the low efficiency** (weak signal induced on the electrodes) but it's can be increased by using a stack of MRPC modules with large surface area (**Watts D. *et al," The use of multi-gap resistive plate chambers for in-beam PET in proton and carbon ion therapy",* 2013, Journal of Radiation Research, 2013, 54:136-142**).



PET ON LINE MONITORING

On-going developments

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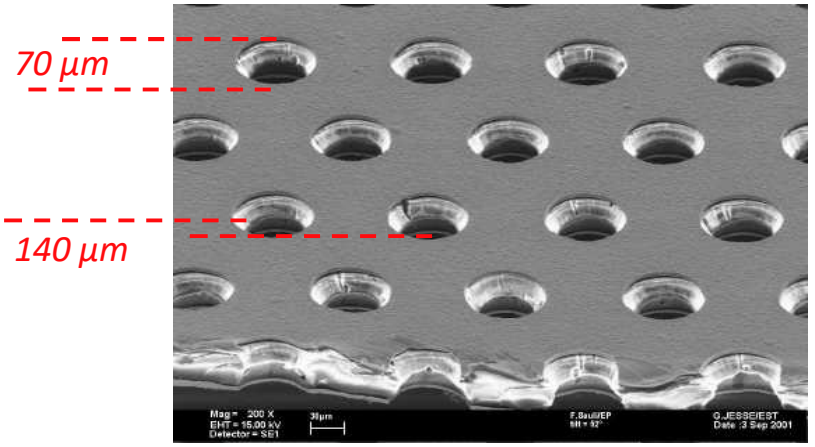
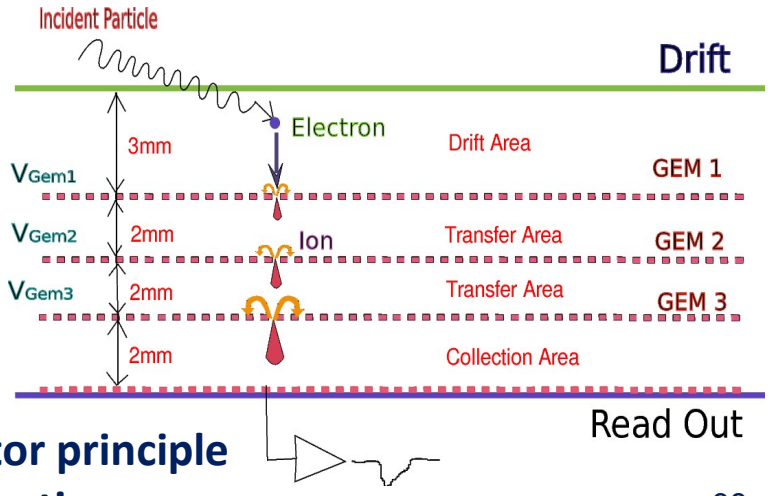
GEM foil



GEM (*Gas Electron Multiplier*) systems offering **high sensitivity and excellent position resolution** may foster the development of efficient monitoring systems exploiting secondary prompt radiation. As for MRPC, low detection efficiency could be compensated by an increase of the axial FOV (their low cost permitting a full body coverage). Researches are on going on this subject in different teams.



GEM detector principle of operation

FUTURE DEVELOPMENTS AND OUTLOOK

The full potential of hadron therapy needs to precisely monitor and control dose delivery and range uncertainties *in vivo,* since **real-time correction of the treatment can improve the therapeutic outcome**.

On-line PET imaging is a promising and **noninvasive** method for determining beam range and dose released to the patient from particle therapy treatment with a **millimiter precision**.

The final goal is to enable direct, **event-by event reconstruction** of the activity measured during patient irradiation, **with minimal degradation of image quality** despite the limited-angle geometry.

FUTURE DEVELOPMENTS AND OUTLOOK

More research activity and investigations are necessary for

- improvement of the knowledge of **reaction cross sections**;

- feasibility studies of PET for *moving organs,* in particular for **time-resolved 4D PET imaging**;

- application of PET for various **other ions** interesting for hadron therapy.

***In vivo* range verification will stay a "hot topic" in the particle therapy community in the next future…**

THANKS FOR YOUR ATTENTION

"Physics is beutiful and useful"

(Ugo Amaldi)

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