Medical Physics Workshop
PET cameras: Principles, use in hospital & ongoing developments

Ohdir, 6-8 September 2015

USE OF PET IN HADRON THERAPY

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USE OF PET IN HADRON THERAPY

- ✓ **PART I: HADRON THERAPY PRINCIPLES**

- ✓ **PART II: ON LINE DOSE MONITORING**

PART I: HADRON THERAPY PRINCIPLES
Outline

- ✓ HISTORY OF HADRON THERAPY
- ✓ PHYSICAL BASICS
- ✓ BIOLOGICAL BASICS
- ✓ FACILITIES AND TREATMENT TECHNIQUES
- ✓ CONCLUSIONS AND FUTURE CHALLENGES

HISTORY OF HADRON THERAPY

The problem: cancer

Cancer figures among the **leading causes of morbidity and mortality worldwide**, with approximately 14 million new cases and 8.2 million cancer related deaths in 2012[1].

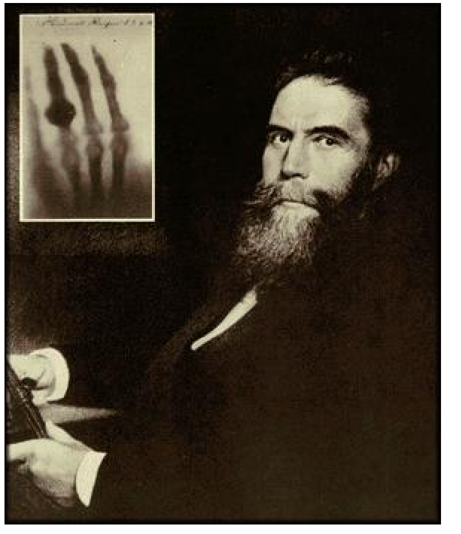
Available therapeutic strategies

- **surgery**: the most successful therapy for well localized tumors (the earlier the diagnosis and the smaller the tumor, the better the chances for a good therapeutic outcome);
- **radiation therapy**: used when the tumor is inoperable but is well localized in a specific region of the body (often in combination with surgery);
- **chemotherapy**: used to eliminate the disease when it's spread in the whole body (with distant metastases).

(1) World Cancer Report 2014, International Agency for Research on Cancer (IARC).

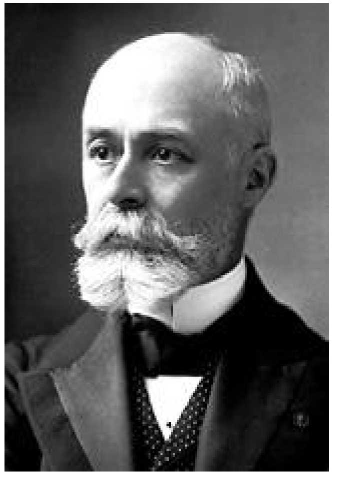
HISTORY OF HADRON THERAPY

1895: discovery of X rays



Wilhelm Roentgen

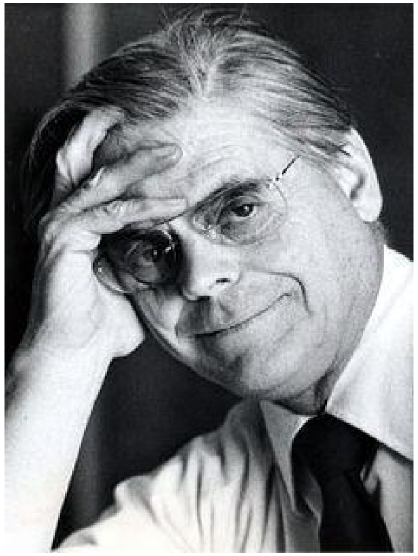
1898: discovery of radioactivity



Henri Becquerel

Pierre and Marie Curie

HISTORY OF HADRON THERAPY



Robert Rathbun Wilson

1946: R. Wilson first proposed a possible therapeutic application of proton and ion beams

R. Wilson, Radiologial use of fast protons, Radiology 47, 487-491, 1946

Radiological Use of Fast Protons

ROBERT R. WILSON

Research Laboratory of Physics, Harvard University

Cambridge, Massachusetts

EXCEPT FOR electrons, the particles which have been accelerated to high energies by machines such as cyclotrons or Van de Graaff generators have not been directly used therapeutically. Rather, the neutrons, gamma rays, or artificial radioactivities produced in various reactions of the primary particles have been applied to medical problems. This has, in large part, been due to the very short penetration in tissue of protons, deuterons per centimeter of path, or specific ionization, and this varies almost inversely with the energy of the proton. Thus the specific ionization or dose is many times less where the proton enters the tissue at high energy than it is in the last centimeter of the path where the ion is brought to rest.

These properties make it possible to irradiate intensely a strictly localized region within the body, with but little skin dose. It will be easy to produce well

1954: first patient treated with deuteron and helium beams at Lawrence Berkeley Laboratory (LBL), California (USA).

HISTORY OF HADRON THERAPY

The first hadron therapy centers operated at the nuclear and subnuclear physics laboratories:

- 1957: Uppsala (Sweden);
- 1961: Massachusetts General Hospital and Harvard Cyclotron Laboratory (USA);
- 1967: Dubna (Russia);
- 1979: Chiba (Japan);
- 1985: Villigen (Switzerland).

<u>1990</u>: the <u>first hospital-based proton therapy facility</u> at *Loma Linda University Medical Center* (LLUMC).

LLUMC (California, USA)

PHYSICAL BASICS

Hadron therapy

Treatment of tumors through external irradiation by means of accelerated hadronic particles:

neutrons, **protons**, pions, antiprotons, helium, lithium, boron, **carbon** and oxygen ions.

Protons and **heavy ions** (particles with mass greater than helium) have **physical properties**, and so **radiobiological effects**, such that:

1.high and conformal dose is delivered to the tumor target;

1.minimazing the irradiation of healthy tissue.

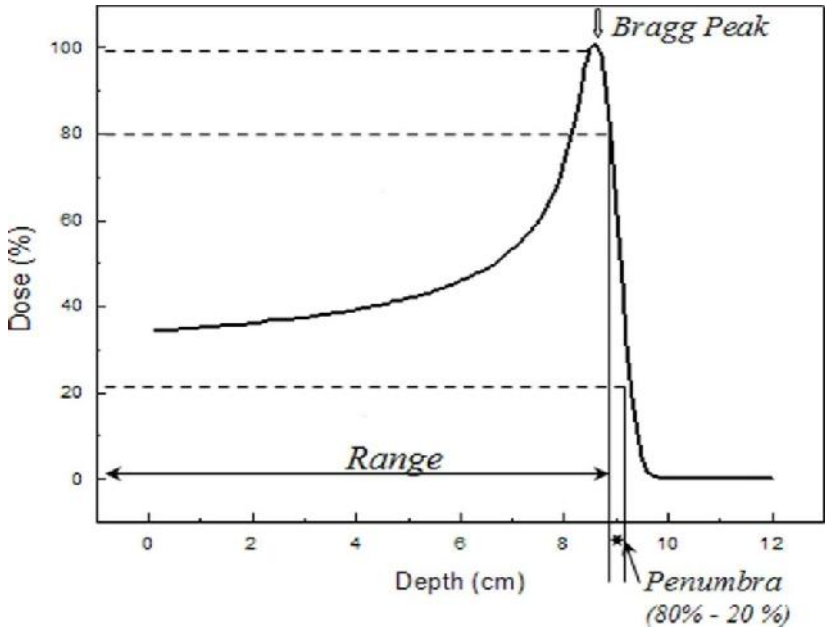
Ideal dose distribution:

- 100% to the target
- 0% to surrounding healthy tissue

PHYSICAL BASICS
Most important physical quantities

<u>Physical absorbed dose</u>: the mean energy dE deposited by ionizing radiation in a mass element dm

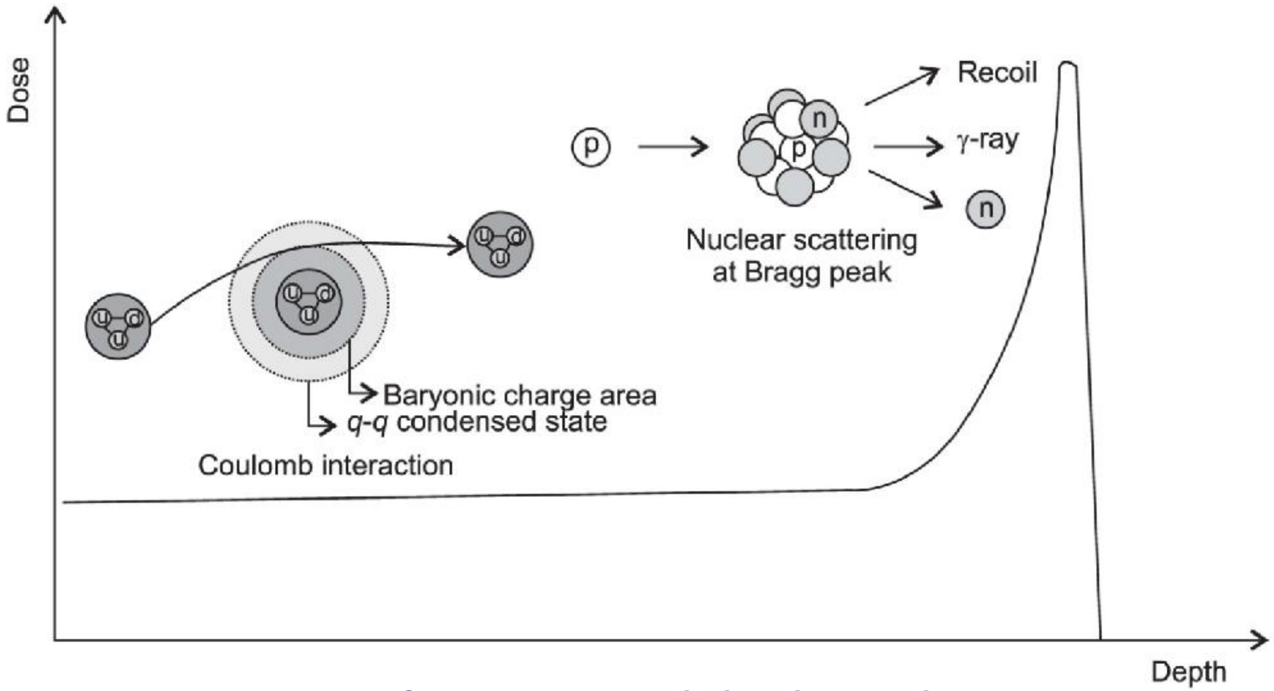
$$\textbf{\textit{Dose}} = \frac{dE}{dm} \quad [Gy = J/kg]$$



<u>Range</u>: penetration depth such that dose absorbed is 80% of peak value.

PHYSICAL BASICS

Interactions of protons with biological matter



Interactions of protons with biological matter

Seo Hyun Park, Jin Oh Kang, *Basis of particle therapy I*: *physis,* Radiat. Onol. J 29(3), 135-146, 2011

PHYSICAL BASICS

Interactions of protons with biological matter

Energy transfer relies mainly on:

➢ **Coulomb interactions** **(Stopping)** with the **outer-shell electrons** of the target atoms **-> excitation and ionization of atoms -> protons slow down - > energy loss** (80 ÷ 90%)

- loss per interaction small **-> continuously slow down**
- secondary electrons have range < 1mm **-> dose absorbed locally**

Energy loss is given by **Bethe-Bloch equation:**

$$-\frac{dE}{dx} = K z^2 \frac{Z}{A} \frac{1}{\beta^2} \left[\frac{1}{2} \ln \frac{2 m_e c^2 \beta^2 \gamma^2 T_{\max}}{I^2} - \beta^2 - \frac{\delta(\beta\gamma)}{2} \right]$$

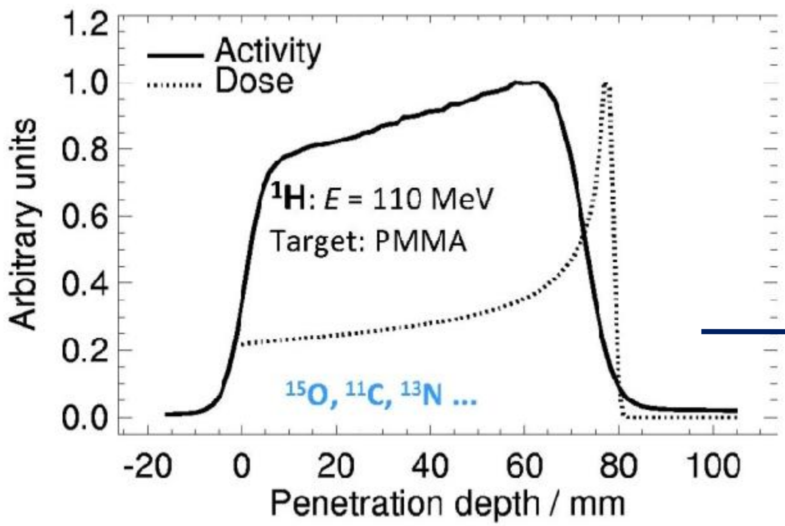
ze	Charge of incident particle	K/A	$4\pi N_A r_e^2 m_e c^2 / A$
Z	Atomic number of absorber	T_{max}	max energy transfer to free electron
A	Atomic mass of absorber	I	Mean excitation energy

PHYSICAL BASICS

Interactions of protons with biological matter

➢ **Nuclear reactions: nonelastic nuclear reactions** with the target nuclei (energy loss 5 ÷ 20%) **->** production of secondaries such as

- protons, α ,recoils nuclei, γ-rays (nuclei excitation), **neutrons -> radiation safety**
- **radioactive isotopes** (**tissue activation**), es. ^{15}O, ^{11}C, ^{13}N **(β^+-emitters)** **->** from isotopes activity 3D **dose verification** with PET/CT (topic of part II)



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

→ **Proton beam @ 110 MeV**

PHYSICAL BASICS

Interactions of protons with biological matter

Angular deflection of hadrons is due to

➢ **Multiple Coulomb Scattering (MCS): elastic Coulomb interactions** with the target nuclei -> superposition of small deflections **-> beam lateral penumbra (important for its effect on organs at risk)**

Proton mass >> electron mass **->** deflections for elastic collisions can be neglected

MCS is well described from Moliére theory

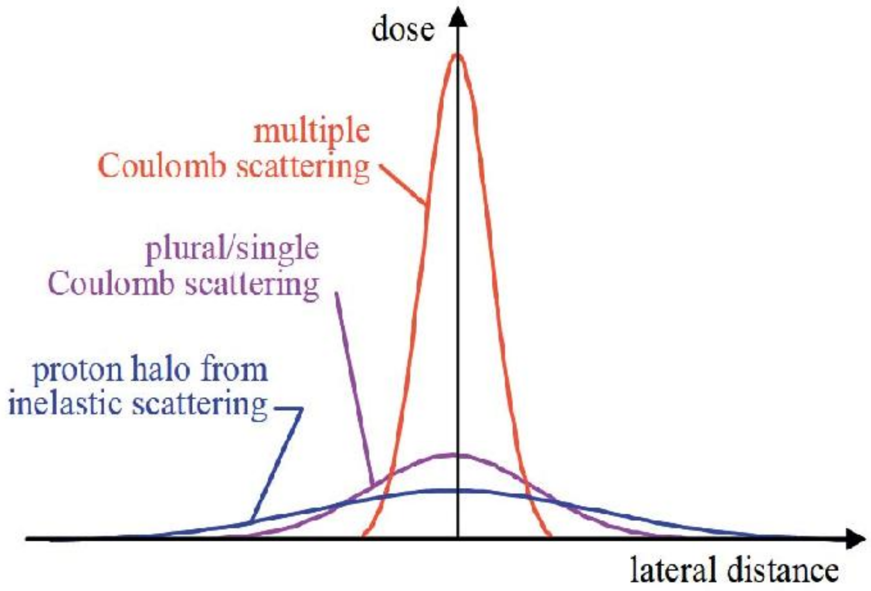
$$\theta_0 = \frac{14.1\ \mathrm{MeV}}{pv} z \sqrt{\frac{L}{L_R}} \left[1 + \frac{1}{9} \log_{10}\left(\frac{L}{L_R}\right)\right]$$

p proton momentum
v proton speed
L target thickness
L_R target radiation length

Lateral scattering can be approximately described with a **Gauss distribution.**

PHYSICAL BASICS

Interactions of protons with biological matter



Proton beam angular spread caused by MCS, scattering at large angle (very rare) and secondary protons production.

Lateral dose falloff (*apparent punumbra*) is of great **clinical importance** because the normal tissues adjacent to the target volume can be exposed to the radiation.

PHYSICAL BASICS

Interactions of carbon ions with biological matter

Due to their heavier mass ions (C-ions) exhibit a sharper lateral dose falloff (small lateral deflection) than protons -> ion beams ideal for the treatment of small target

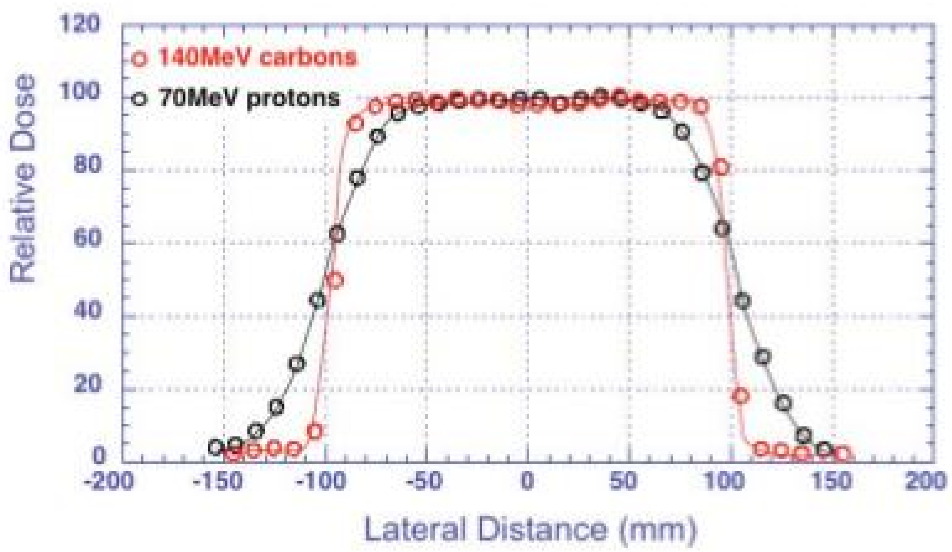


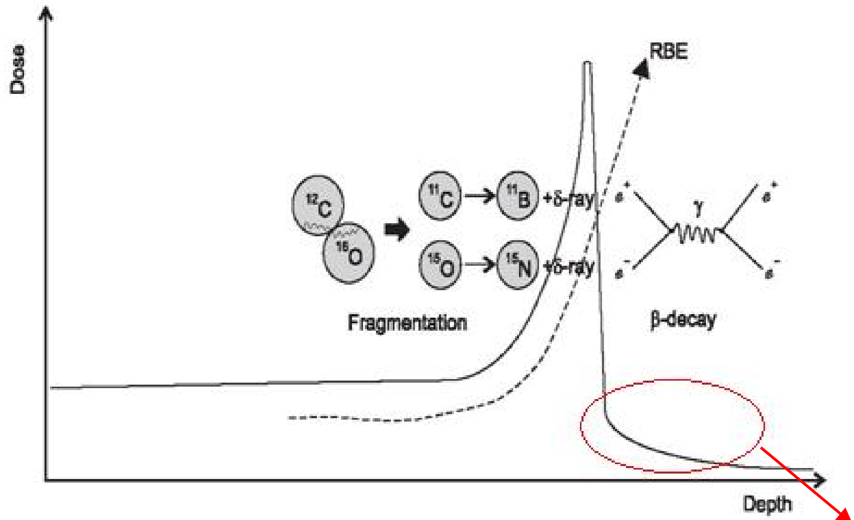
Fig. 4. The penumbra of a carbon beam is much sharper than that of a proton beam of the comparable range. (Based on the paper presented by H. Tsuji, at the 39th meeting of PTCOG, San Francisco, October 2002.)

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

PHYSICAL BASICS

Fragmentation reactions of heavy ions

At energies of several hundreds MeV/u and at large penetration depths the **nuclear reactions** may result in a complete **disintegration of both projectile and target nuclei** (e.g., in central head-on collisions)



Interaction of carbon ions

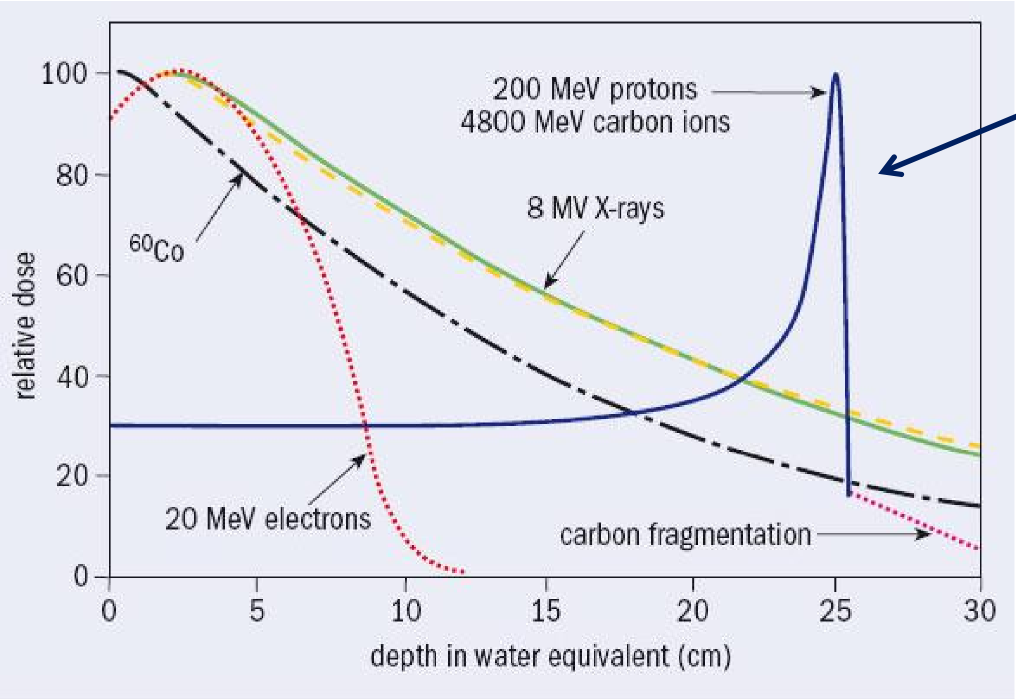
Fragmentation tail

Seo Hyun Park, Jin Oh Kang, *Basis of particle therapy I: physis,* Radiat. Onol. J 29(3), 135-146, 2011

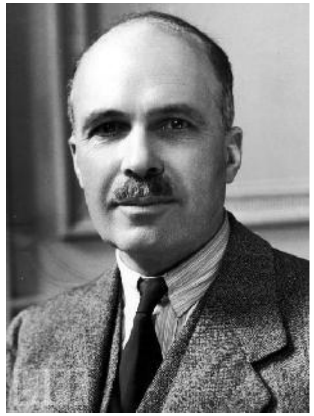
- ✓ Loss of primary beam particles;
- ✓ the secondary fragments move with about the same velocity as the primary ions and have a longer range -> significant **overdose** beyond the actual stopping range -> **side effects and secondary cancer inductions.**

PHYSICAL BASICS

Depth-dose curve



Bragg Peak



William Bragg

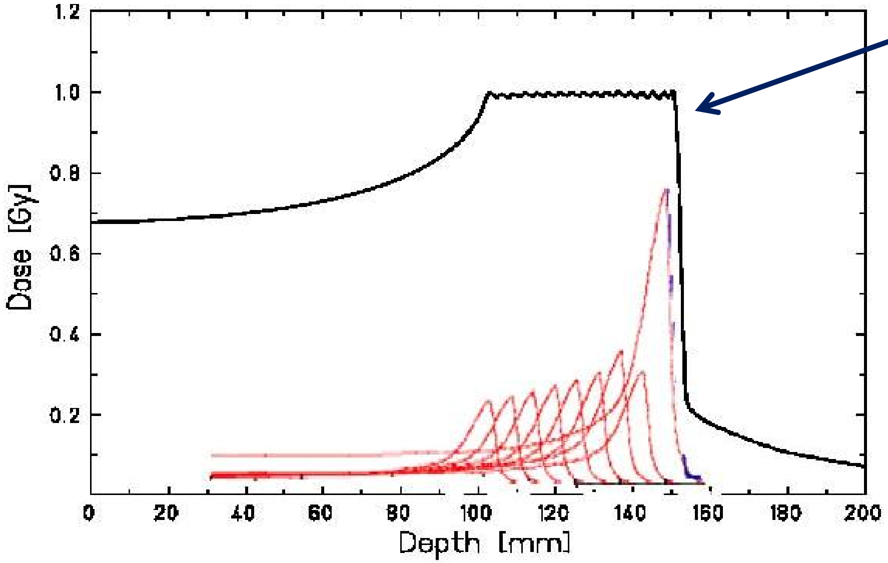
From the **Bethe-Bloch Formula :** $-dE/dx \propto \beta^{-2}$ where $\beta = V/c$

$$-\frac{dE}{dx} \propto V^{-2}$$ ⇒ **the highest dose is released near the end of hadron range giving rise to the "Bragg Peak"**

<u>**Range and dose distribution calculation must be as accurate as possible**</u>

PHYSICAL BASICS

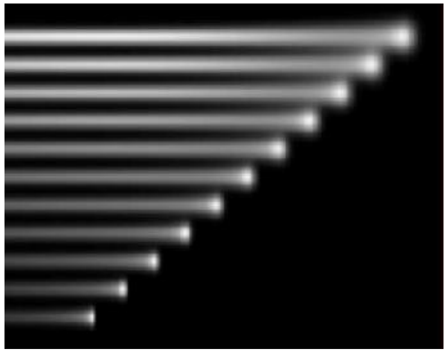
Spread-out of Bragg Peak (SOBP)



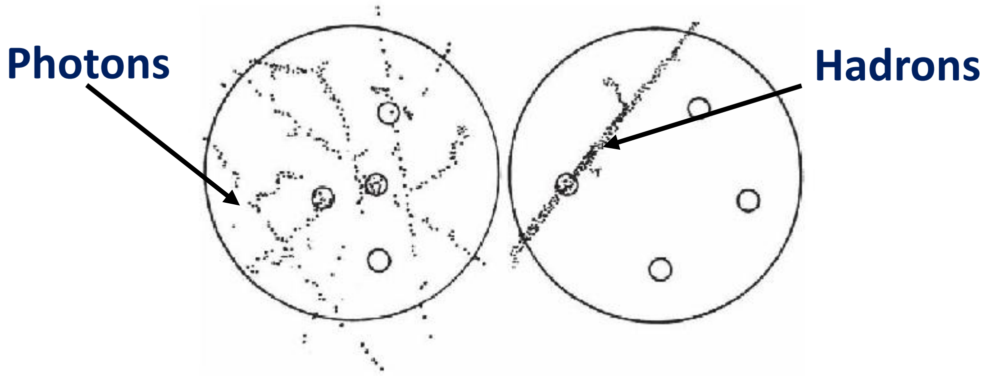
SOBP is the sum of several individual Bragg Peaks at staggered depth.

By modulating the beam energy is possible to cover the whole target volume.

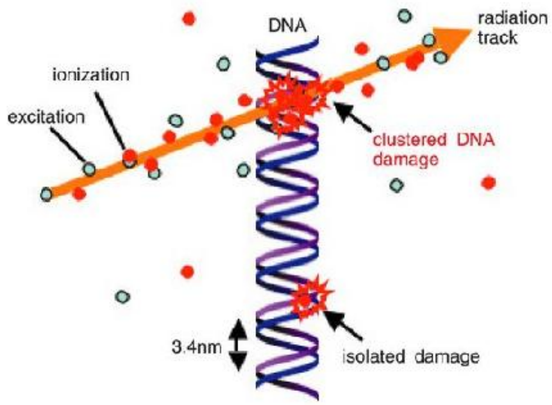
Beam energy modulation



BIOLOGICAL BASICS



Ionization density



Effect on cellular DNA

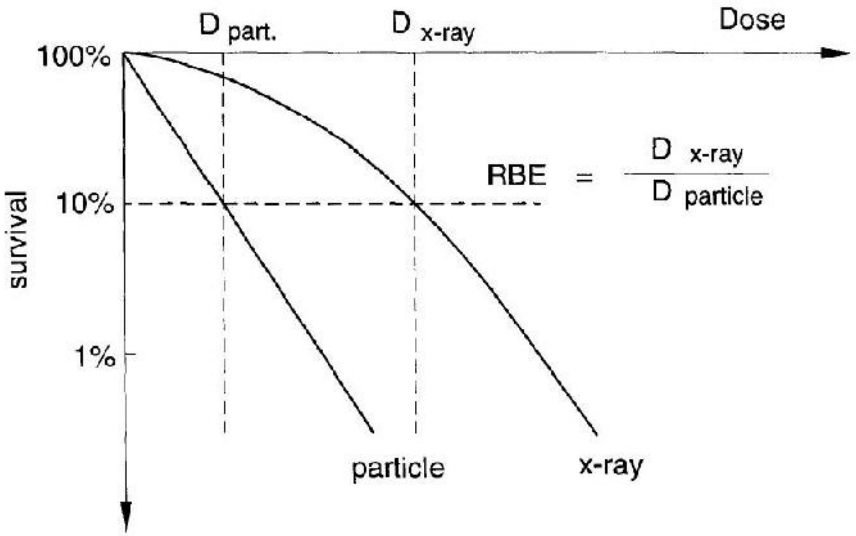
Modern research in particle radiobiology on cellular DNA damage and repair mechanisms now allows an unprecedented insight into the molecular damage induced by fast ions: densely ionising radiation (hadrons) induces a **high fraction of clustered DNA damage**, which is more difficult to repair and triggers a different intra- and inter-cellular signaling cascade compared to sparsely ionising radiation (X-ray).

BIOLOGICAL BASICS

Relative Biological Effectiveness (RBE)

RBE: the ratio of the dose of a reference radiation (typcally X or γ rays) to the dose of radiation in question to produce an identical biological effect (isoeffect)

$$RBE_{iso} = \frac{D_{X\text{-}rays}}{D_{particle}}$$



RBE depens on many factors:

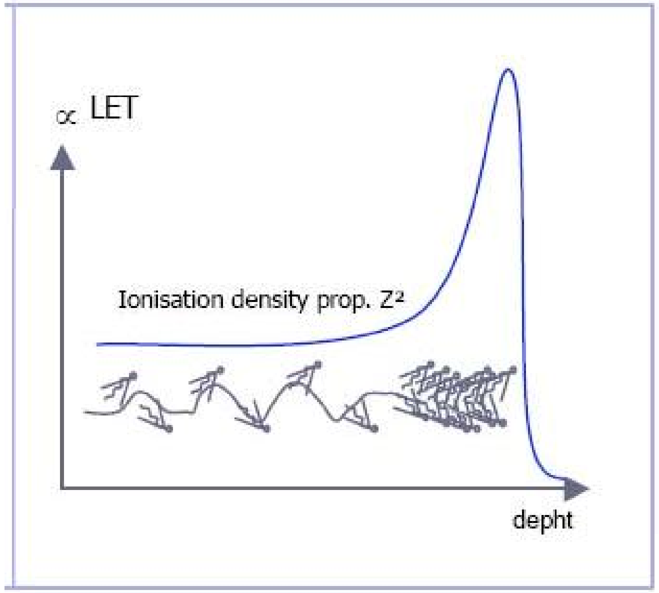
- energy;
- particle type;
- organ dimensions;
- tissue type;
- presence of oxygen.

hadrons more biologically effective than photons: lower dose is required to cause the same biological effect

BIOLOGICAL BASICS

Linear Energy Transfer (LET)

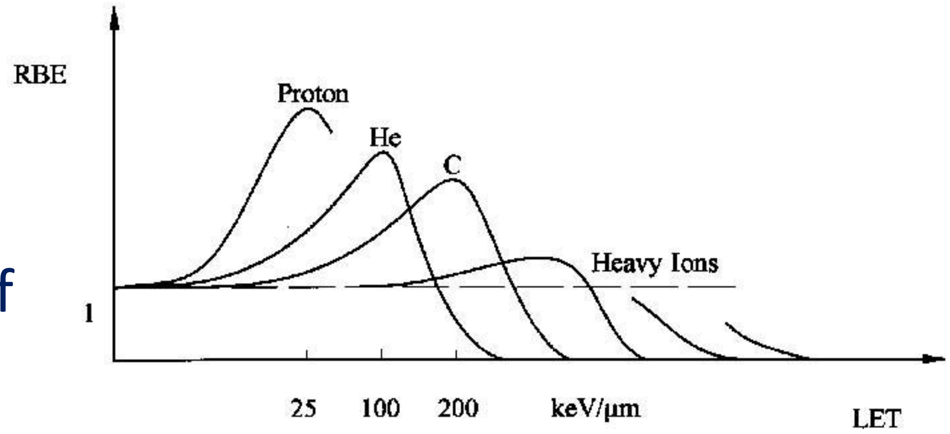
$$LET = \frac{dE}{dl} \quad [\mathrm{keV}/\mu\mathrm{m}]$$



LET **->** ionization density **->** quality of radiation

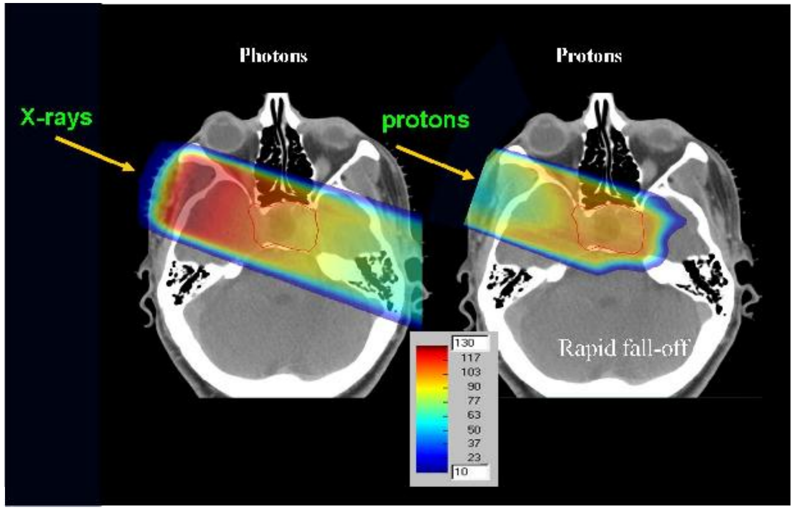
High LET (> 10 keV/µm) **->** multiple DNA damages

Hadrons are high LET with respect to photons



Relationship between RBE and LET as a function of particle type

BIOLOGICAL BASICS
Protons Vs Photons



CT image: dose distribution calculated for proton beams and X-rays.

<u>Physical advantages :</u>

- ✓ **finite range and high ionization density;**
- ✓ **lower integral dose;**
- ✓ **small lateral scattering (larger flexibility).**

<u>Clinical advantages :</u>

- ✓ **treatment of deep-seated, irregular shaped and radio-resistant tumors;**
- ✓ **small probability of side effects in normal tissue (critical structrure);**
- ✓ **<u>proton therapy suitable for pediatric diseases (reduced toxicity)</u>.**

BIOLOGICAL BASICS

Carbon ions Vs protons

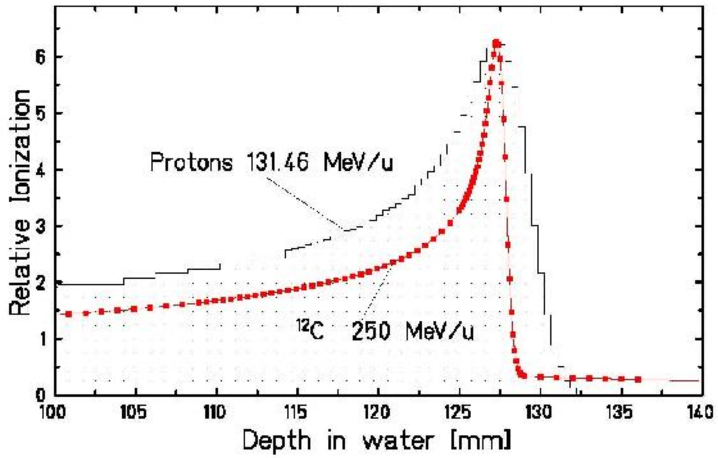
Compared to protons, carbon ions:

I. allow a more precise concentration of the dose in the target volumes with steeper gradients to the normal tissue;

II. higher RBE for tumors which are radio-resistent to the conventional treatment.

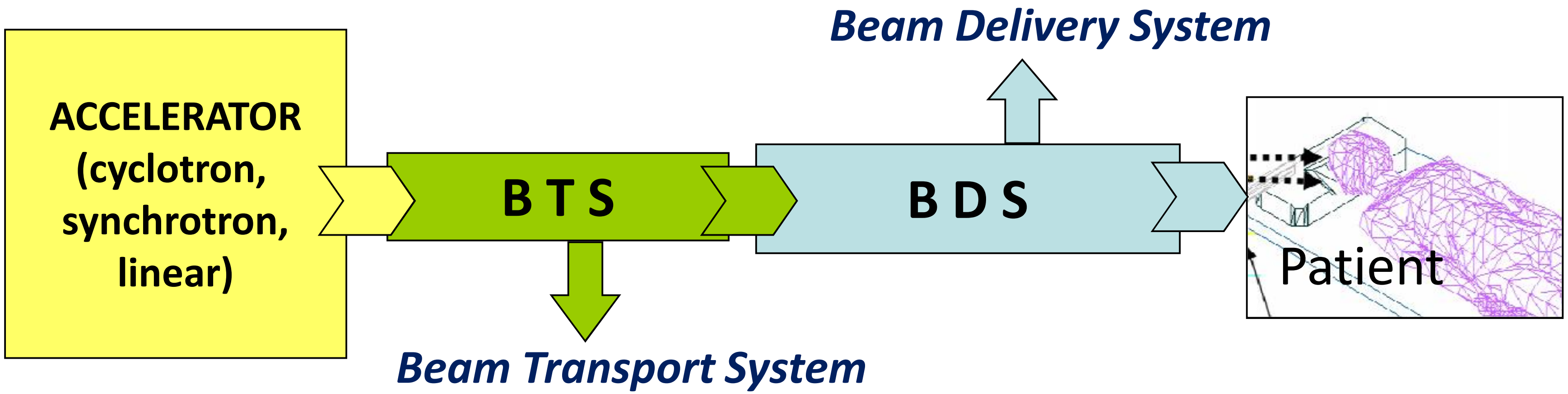
Disadvantage: due to the **nuclear fragmentation**, beyond the Bragg Peak the dose deposition does not decrease to zero -> **overdose**.

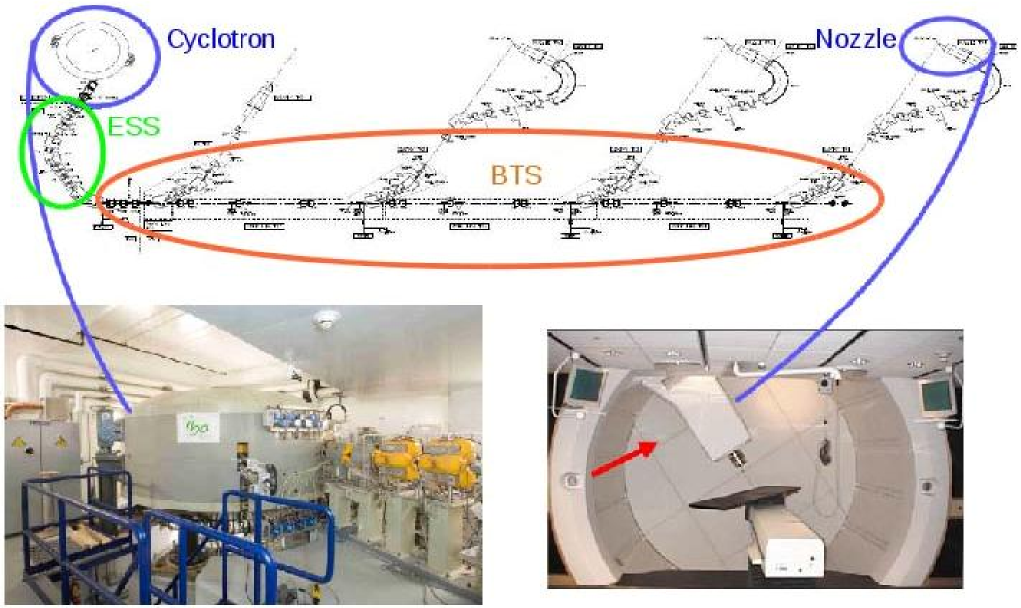
Protons are more widely used than carbon ions



Measured Bragg Peaks of protons and ^{12}C ions having the same mean range in water *(Schardt et al.,2008)*.

FACILITIES AND TREATMENT TECHNIQUES
Main parts of a hadron therapy facility

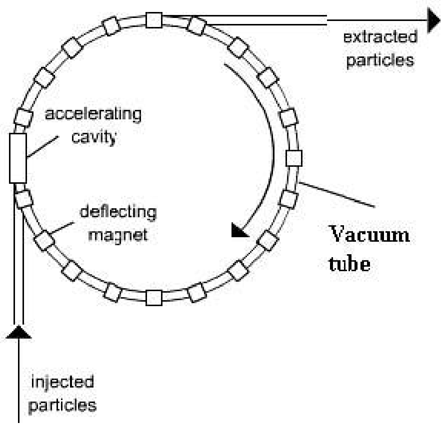




Hadron therapy facility scheme – IBA (Belgium)

FACILITIES AND TREATMENT TECHNIQUES

Particle accelerators



Synchrotron: presents a cycle (spill) that lasts about 2 s, beam is present for about 0,5 s and its energy can be varied from spill to spill without passive elements.

Energy range for therapeutic hadron beams:

- **p: [60, 250] MeV**
- **^{12}C: [120, 400] MeV/u**

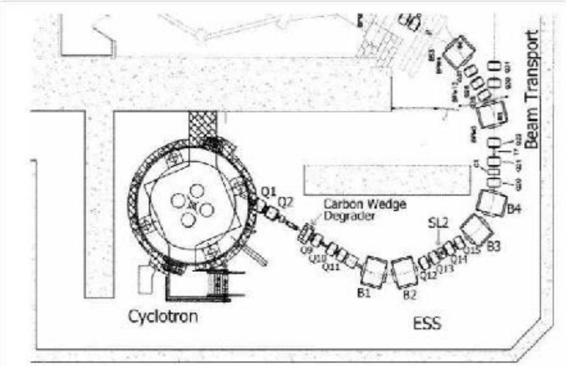
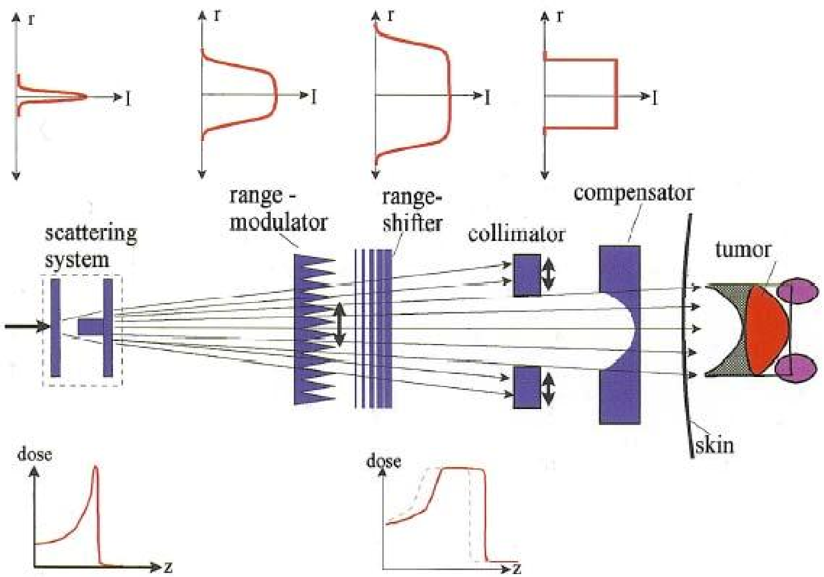


fig. 1. Detail of the Energy Selection System (ESS) showing the location of the carbon energy degrader and the momentum spread limiting slit (SL2).

Cyclotron: high intensity, continuous beam, its energy is fixed and can be degraded with passive absorbers in the Energy Selection System (ESS).

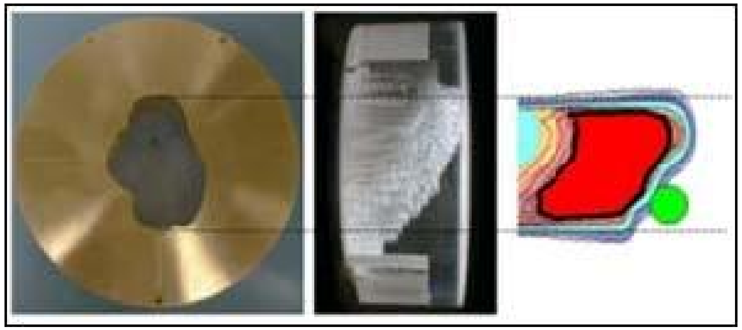
FACILITIES AND TREATMENT TECHNIQUES

Beam Delivery System – Passive Scattering System



Passive Scattering System

Beam is widened and flattened by means of personalized collimators and compensators. Range shifter (rotating wheel with different thickness) is used to irradiate at different penetration depths (SOBP).

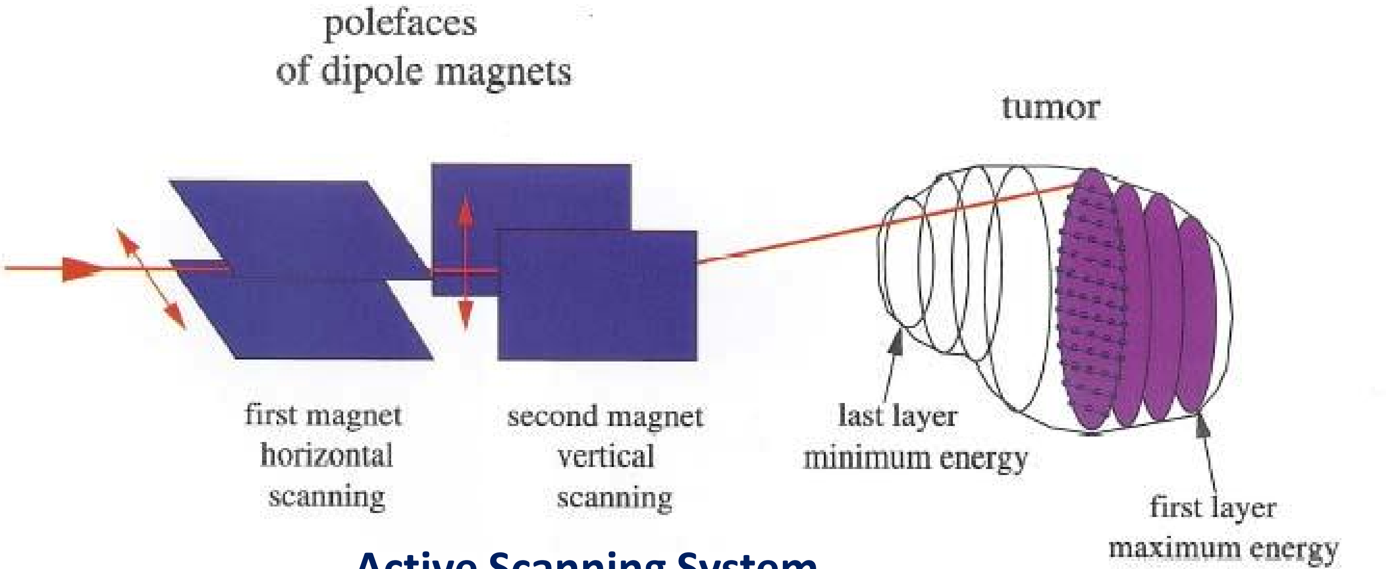


Collimator and compensator

Range Modulator

FACILITIES AND TREATMENT TECHNIQUES

Beam delivery system – Active Scanning System



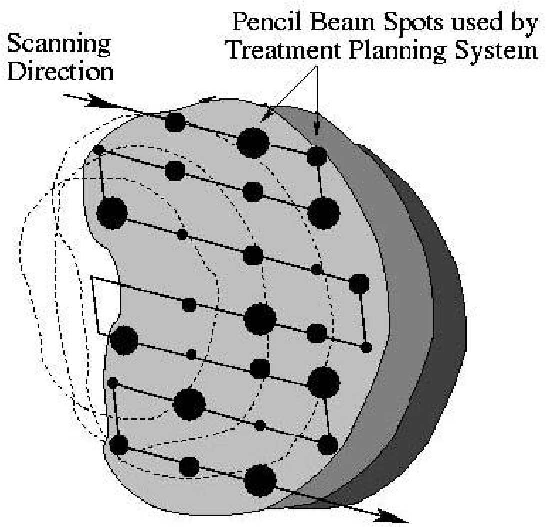
Active Scanning System

✓ Hadrons can be deflected magnetically **->** a narrow mono-energetic **"pencil beam"** can be scanned magnetically across the target volume in a zig-zag pattern in the x-y plane perpendicular to the beam direction (z);

✓ the depth scan is done by means of energy variation.

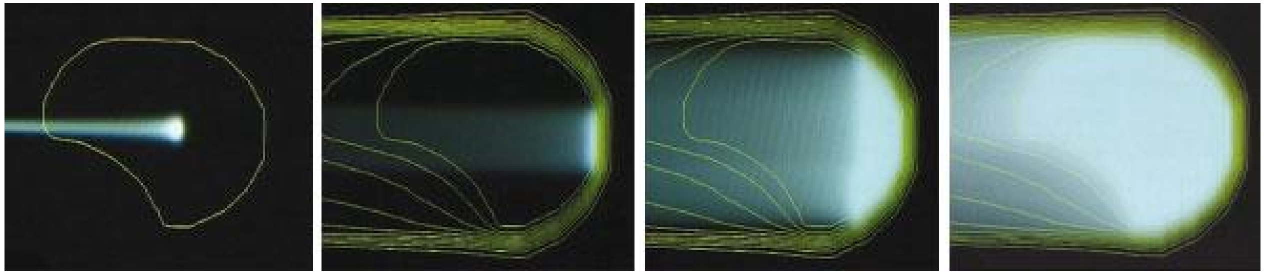
FACILITIES AND TREATMENT TECHNIQUES

Dose delivery system – Active Scanning System



Principle of active beam scanning

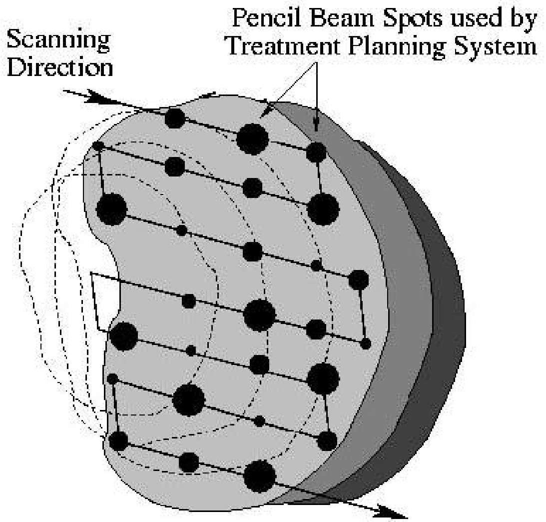
<u>Discrete spot scanning</u>: (developed at **PSI** - Zurich) dose is delivered to a given spot at a static position (constant magnet settings). Then the pencil beam is switched off and the magnet settings are changed to target the next spot, dose is delivered to the next spot, and so forth.



Single beam | **Lateral scanning** | **Scanning in depth** | **3D dose distribution**

FACILITIES AND TREATMENT TECHNIQUES

Dose delivery system – Active Scanning System



Principle of active beam scanning

Raster scanning: (developed at **GSI** - Darmstadt) continuous path, beam does not switch off between two voxels (except two spot are away from each other).

Dynamic spot scanning: beam is scanned fully continuously across the target volume. Intensity modulation can be achieved through a modulation of the output of the source, or the speed of the scan, or both.

FACILITIES AND TREATMENT TECHNIQUES

Active Scanning System vs Passive Scattering System

<u>Advantages of Active Scanning technique</u>:

1. No need of compensators and collimators (dependent on patient anatomy), <u>the beam has less nuclear interactions outside the patient</u>, this means **less neutron contamination and overdose**;

1. <u>great flexibility</u>, arbitrary shapes can be irradiated with a single beam, this allows **better target conformation**.

Disadvantage of Active Scanning technique:

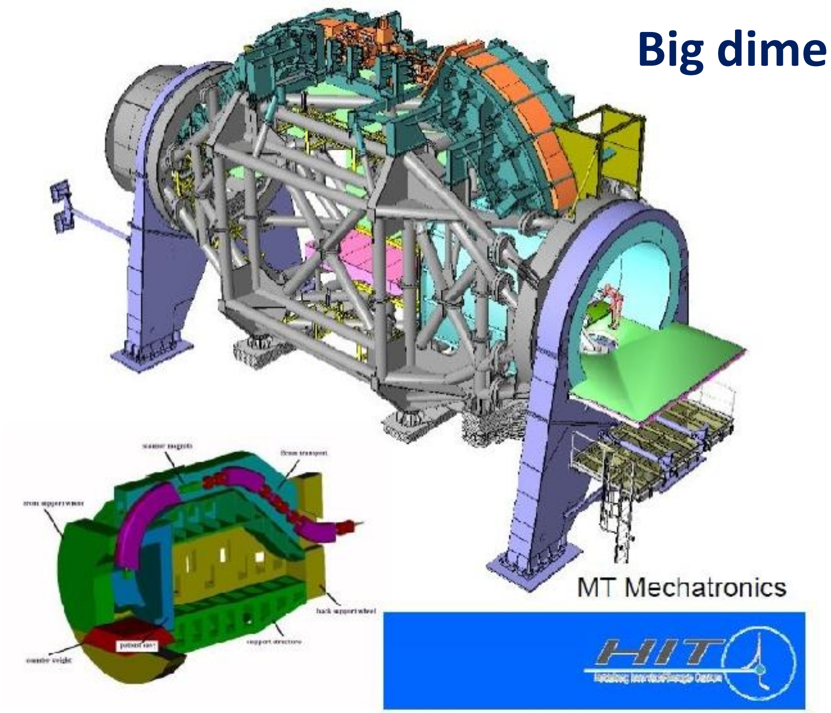
1. Difficulty to treat "*moving organs*" (organs subject to motion due to respiration) such as lung cancer, it is necessary to develop systems to synchronize the beam and the patient's respiration.

FACILITIES AND TREATMENT TECHNIQUES

Gantry and nozzle

Conformal radiation therapy requires target irradiation from any desired angle. The beam is deflected by the magnetic field in the **gantry**. Treatment **nozzle** (final part of the gantry) consists of various components for <u>beam shaping and beam monitoring</u>.

Big dimensions (3,5 m diameter) **-> very expensive**



Gantry at Hidelberg Ion-beam Therapy Center (HIT)

Treatment room at Boston Northeast Proton Therapy Center (NPTC)

FACILITIES AND TREATMENT TECHNIQUES

Disadvantage of hadron therapy: the problem of the cost-effectiveness

Hadron therapy **is useful for treating solid tumors** (also combined with standard radiation therapy, surgery and/or chemotherapy) such as:

- Central nervous system cancers (including chordoma, chondrosarcoma, and malignant meningioma)
- Eye cancer (including uveal melanoma or choroidal melanoma);
- Head and neck cancers (including nasal cavity and paranasal sinus cancer and some nasopharyngeal cancers)
- Lung cancer;
- Liver cancer;
- Prostate cancer;
- Spinal and pelvic sarcomas (cancers that occur in the soft-tissue and bone);
- Noncancerous brain tumors;
- **Pediatric cancers** (only proton therapy for brain, spinal cord and eye tumors);

FACILITIES AND TREATMENT TECHNIQUES

Disadvantage of hadron therapy: the problem of the cost-effectiveness

But **hadron therapy is very expensive -> limited availability**

Large investments for building accelerators, beam transport systems and gantries.

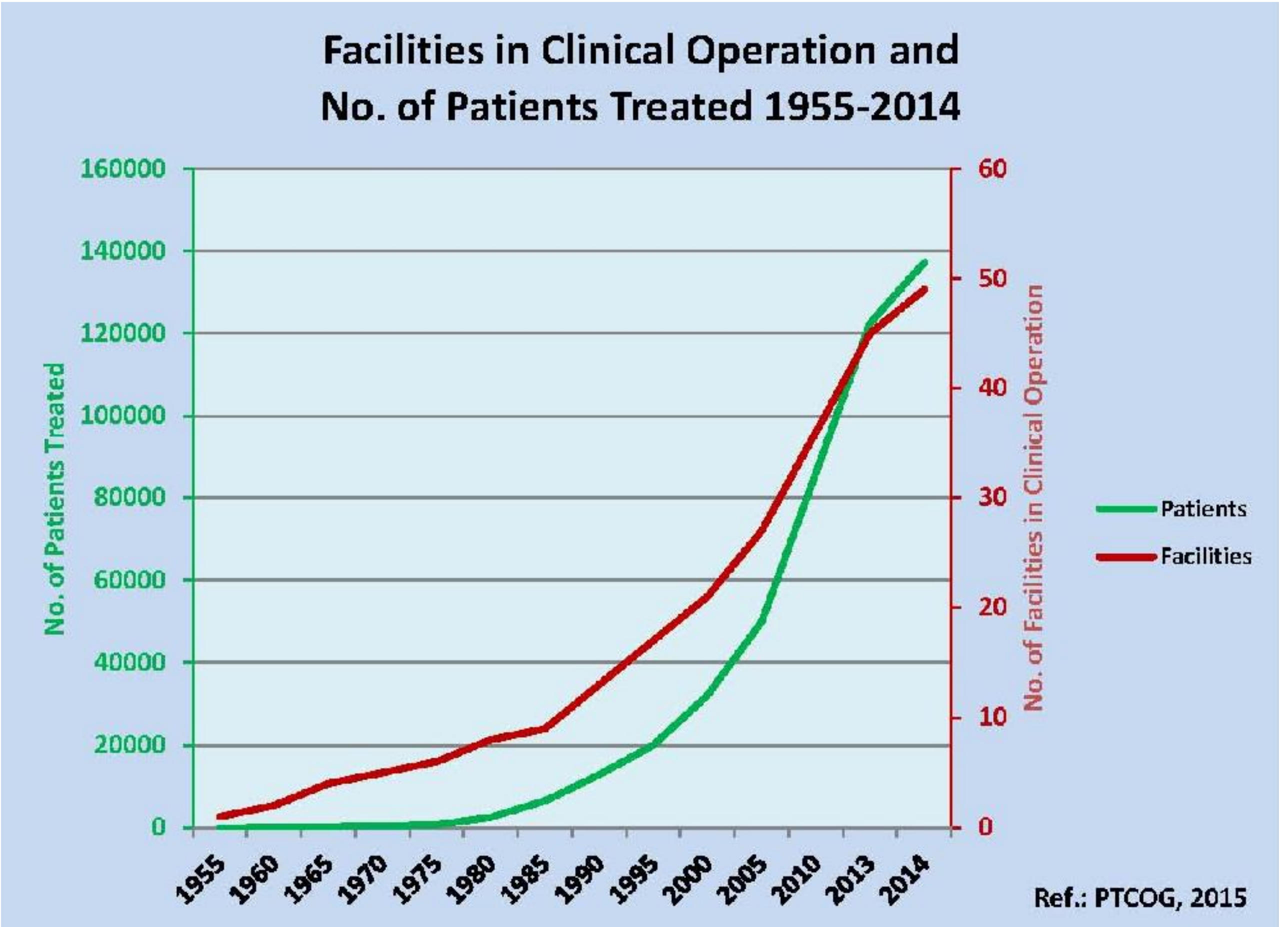
The equipmets of a proton thetrapy center is of the order of **100 M€**, the **operation and tratment/fraction cost** must also be considered.

Limited number of clinical studies, so there is an open discussion:

Are the medical benefits large enough to motivate the high costs?

FACILITIES AND TREATMENT TECHNIQUES

Status of hadron therapy in the world: facilities in operation

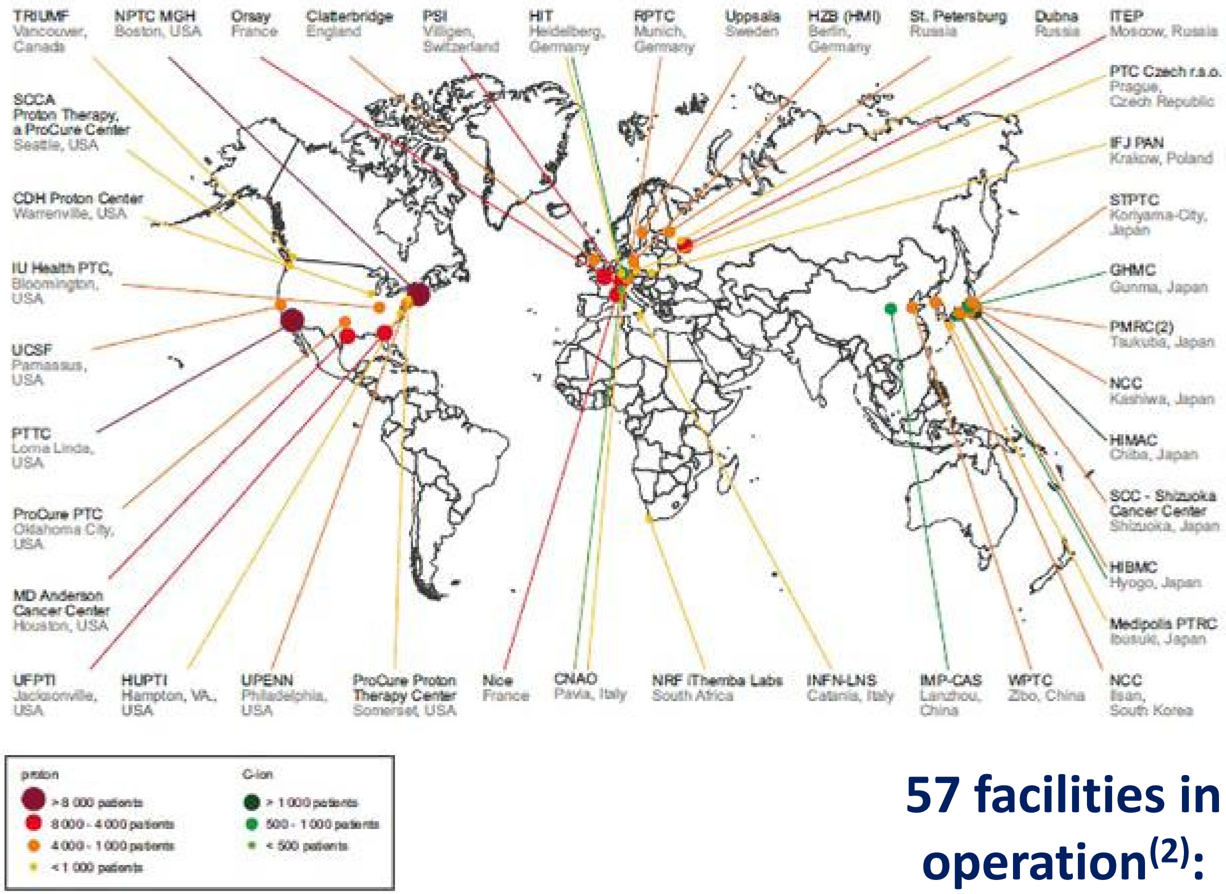


From Eugen B. Hug, 2° Annual PTCOG(2) 2015 – San Diego.

(2) *Particle Therapy Co-Operative Group (PTCOG)* web page: http://www.ptcog.ch/

FACILITIES AND TREATMENT TECHNIQUES

Status of hadron therapy in the world: facilities in operation



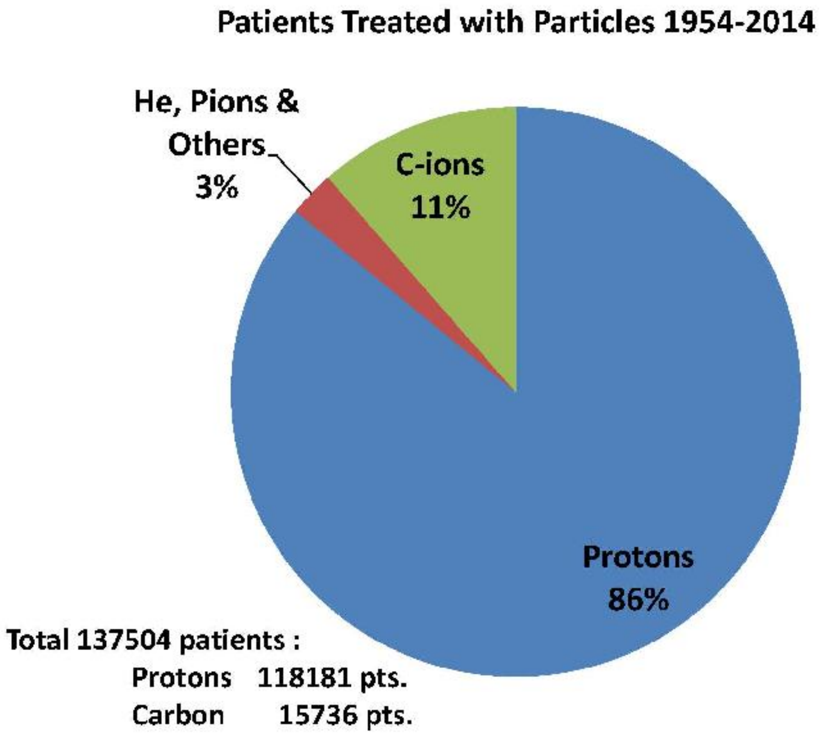
57 facilities in operation(2):
- **49 with p-beam**
- **4 with C-ion + p beam**
- **4 with C-ion beam**

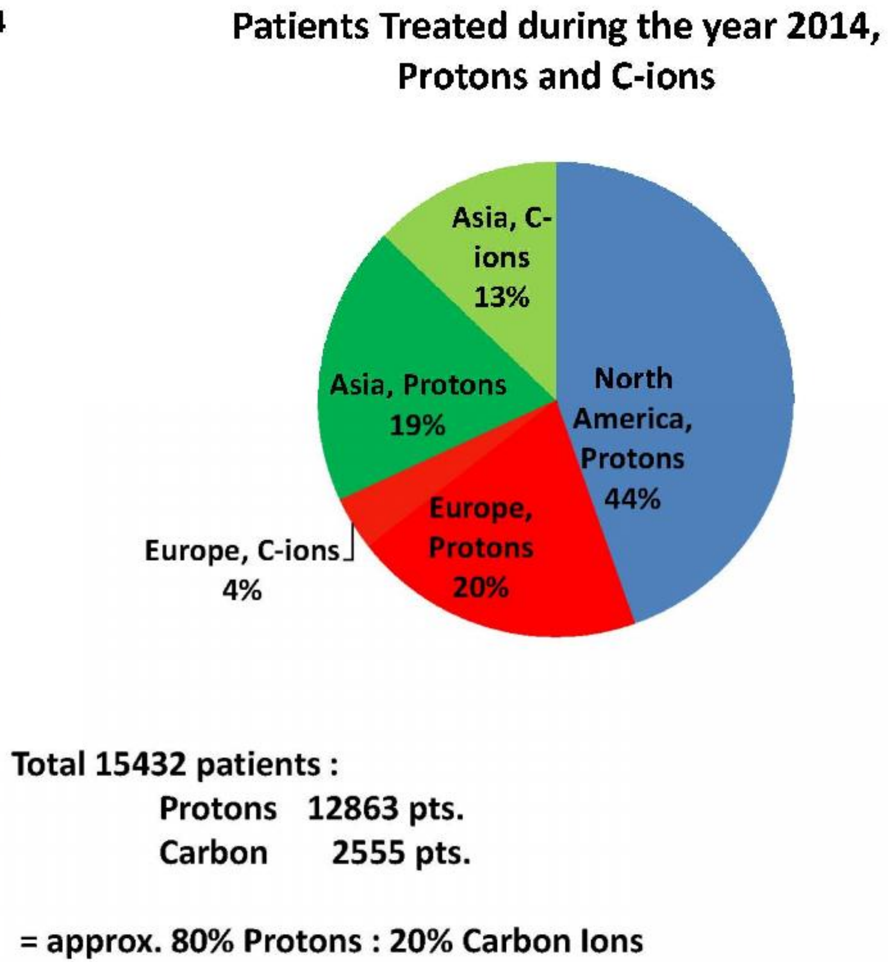
Proton (red-orange) and C-ion (green) centres active worldwide. The size of the spot is proportional to the number of patients treated as indicated in the figure legend.

(2) *Particle Therapy Co-Operative Group (PTCOG)* web page: http://www.ptcog.ch/

FACILITIES AND TREATMENT TECHNIQUES

Status of hadron therapy in the world: patient statistics





From Eugen B. Hug, 2° Annual PTCOG 2015 – San Diego.

FACILITIES AND TREATMENT TECHNIQUES

Status of hadron therapy in the world: facilities under construction

Particle therapy facilities under construction:

COUNTRY	WHO, WHERE	PARTICLE(S)	MAX. ENERGY (MeV) Accelerator type	BEAM DIRECTIONS	NO. OF TREATMENT ROOMS	START OF TREATMENT PLANNED
Austria	MedAUSTRON	p, C-ion	[illegible] synchrotron	[illegible] 1 horiz./fixed beam 1 fixed beam 0 + 90 deg	3	2016
China	[illegible], Lanzhou	C-ion	[illegible] synchrotron	[illegible] fixed beams	4	[illegible]
China	[illegible] Hospital [illegible] University, [illegible]	p	[illegible] synchrotron	2 gantries, 1 horiz. fixed beam	2	2015?
France	Centre Antoine Lacassagne, Nice	p	[illegible] cyclotron	1 gantry	1	[illegible]
India	Apollo Hospitals PTC, Chennai	p	[illegible] cyclotron	2 gantries, 1 horiz. fixed beam	2	[illegible]
Japan	[illegible] Hospital [illegible]	p	[illegible] synchrotron	1 gantry	1	[illegible]
Japan	[illegible] Group [illegible] Proton Therapy Clinic [illegible]	p	[illegible] synchrotron	1 gantry	1	[illegible]
Japan	[illegible] Hospital PTC, [illegible]	p	235 [illegible]	1 gantry	1	[illegible]
Japan	[illegible], Kanagawa Cancer Center, Yokohama	C-ion	430/u synchrotron	4 horiz., 2 vertical beams	4	201[illegible]
Netherlands	HollandPTC, Delft	p	[illegible] cyclotron	2 gantries, 1 horiz. fixed beam	3	2017
Netherlands	UMC Groningen PTC, Groningen	p	[illegible] cyclotron	2 gantries	2	[illegible]
Poland	IFJ PAN, Krakow	p	230 cyclotron	1 gantry	1	2015?
Russia	PMHPTC, Protvino	p	250 synchrotron	1 horiz. fixed beam	1	2015?
Saudi Arabia	King Fahad Medical City PTC, Riyadh	p	250 SC cyclotron	4 gantries	4	2016
Slovak Rep	CMHPTC, Ruzomberok	p	250 synchrotron	1 horiz. fixed beam	1	2015?
South Korea	Samsung Proton Center, Seoul	p	230 cyclotron	2 gantries	2	2015
South Korea	KIRAMS, Busan	C-ion, p	430/u, 230 synchrotron	2 vertical and horiz. fixed beams, 1 horiz. fixed beam	3	2018
Sweden	Skandion Clinic, Uppsala	p	230 cyclotron	2 gantries	2	2015
Taiwan	Chang Gung Memorial Hospital, Taipei	p	235 cyclotron	4 gantries, 1 experimental room	4	2015
Taiwan	National Taiwan University CC, Taipei	p	250 SC cyclotron	2 gantries, 1 experimental room	3	2018
USA	Robert Wood Johnson, New Brunswick, NJ	p	250 SC synchro-cyclotron	1 gantry	1	2015
USA	MD Anderson, Orlando, FL	p	250 SC synchro-cyclotron	1 gantry	1	2015
USA	Oklahoma University, Oklahoma City, OK	p	250 SC synchro-cyclotron	1 gantry	1	2015
USA	McLaren PTC, Flint, MI	p	250/330 synchrotron	3 gantries	3	2015
USA	Maryland Proton Treatment Center, Baltimore, MD	p	250 SC cyclotron	3 gantries, 2 horiz. fixed beams	5	2015
USA	Mayo Clinic Proton Beam Therapy Center, Rochester, MN	p	220 synchrotron	4 gantries	4	2015
USA	Mayo Clinic Proton Beam Therapy Center, Phoenix, AZ	p	220 synchrotron	4 gantries	4	2016
USA	UH Sideman Cancer Center, Case Medical Center, Cleveland, OH	p	250 SC synchro-cyclotron	1 gantry	1	2016
USA	Emory Proton Therapy Center, , Atlanta, GA	p	250 SC cyclotron	3 gantries, 2 horiz. fixed beams	5	2016
USA	Texas Center for Proton Therapy, Irvin, TX	p	230 cyclotron	2 gantries, 1 horiz. fixed beam	3	2016

30 new facilities under construction(2):

- **26 with p-beam**
- **2 with C-ion + p beam**
- **2 with C-ion beam**

(2) *Particle Therapy Co-Operative Group* web page: http://www.ptcog.ch/

FACILITIES AND TREATMENT TECHNIQUES

Status of hadron therapy in the world: facilities in planning stage

Particle therapy facilities in a planning stage:

COUNTRY	WHO, WHERE	PARTICLE	MAX. ENERGY (MeV)	BEAM DIRECTIONS	NO. OF TREATMENT ROOMS	START OF TREATMENT PLANNED
China	SJFH, Beijing	p	230 cyclotron	1 gantry 1 horiz. fixed beam	?	?
Denmark	DCPT Aarhus	p	250 SC cyclotron	3 gantries, 1 horiz. exp. fixed beam	3	2013
France	ARCHADE, Caen	p	230 cyclotron	1 gantry	1	2015
India	Proton Therapy Hospital, Mumbai	p	open	open	?	2017?
Japan	Teishinkai Corporation, Sapporo, Hokkaido	p	230 cyclotron	1 gantry	1	2013
Netherland	APTC Amsterdam	p	open	2 gantries	?	?
Netherland	PTC, Maastricht	p	230 cyclotron	1 gantry	1	?
Russia	Hospital No.63 PTC, Moscow	p	250 synchrotron	open	?	?
Slovak Rep.	CCSR, Bratislava	p	72 cyclotron	1 horiz. fixed beam	1	?
Switzerland	PTC Zürichobersee, Galgenen	p	230 cyclotron	4 gantries, 1 horiz. fixed beam	5	?
Taiwan	National Taiwan University CC, Taipei	p	250 SC cyclotron	2 gantries, 1 horiz. fixed beam	3	2013
United Kingdom	The Christie Proton Therapy Center, Manchester	p	250 SC cyclotron	3 gantries	3	2013
United Kingdom	PTC UCLH, London	p	250 SC cyclotron	3 gantries	3	2013
USA	Proton Institute of New York, NY	p	230 cyclotron	4? gantries	4?	?
USA	Atlantic Health System, New Jersey, NY	p	330 synchrotron	2? gantries	2?	2017?
USA	MGH, Boston, MA	p	330 synchrotron	1 gantry	1	2017?

16 proton beam therapy centers planned(2)

(2) *Particle Therapy Co-Operative Group* web page: http://www.ptcog.ch/

FACILITIES AND TREATMENT TECHNIQUES

Hadron therapy facility in Italy

CATANA (Centro di Adroterapia e Applicazioni Nucleari Avanzate) @ LNS (Laboratori Nazionali del Sud) - Catania

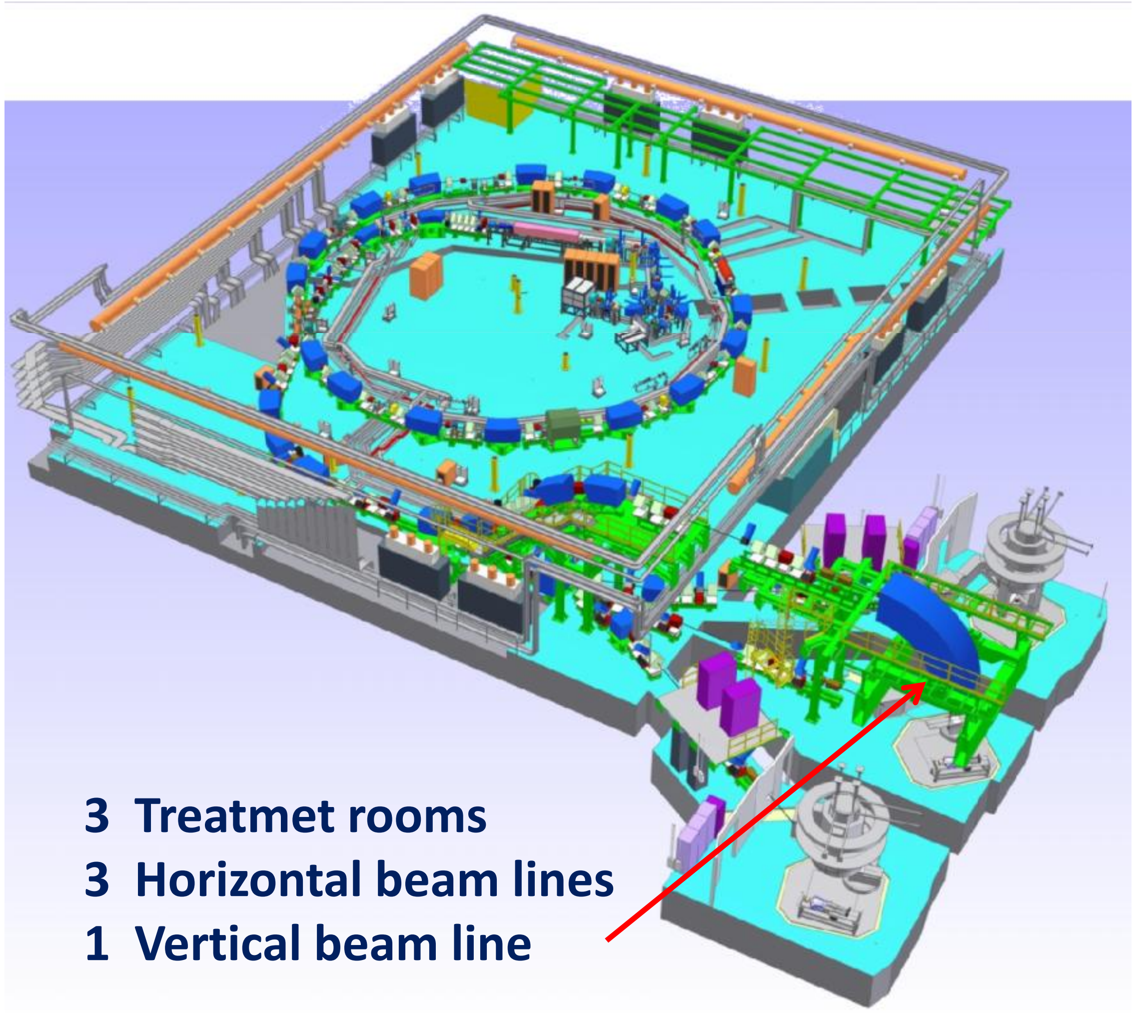
CATANA treatment room

Since 2002 eye tumors are successfully treated with proton beams of 62 MeV produced by a superconducting cyclotron (SC).

FACILITIES AND TREATMENT TECHNIQUES

Hadron therapy facility in Italy

CNAO (Centro Nazionale di Adroterapia Oncologica) @ Pavia



- Treatments with protons started in september 2011
- Treatments with carbon ions started in november 2012

p E : [60, 250] MeV

C^{6+} E : [120, 400] MeV/u

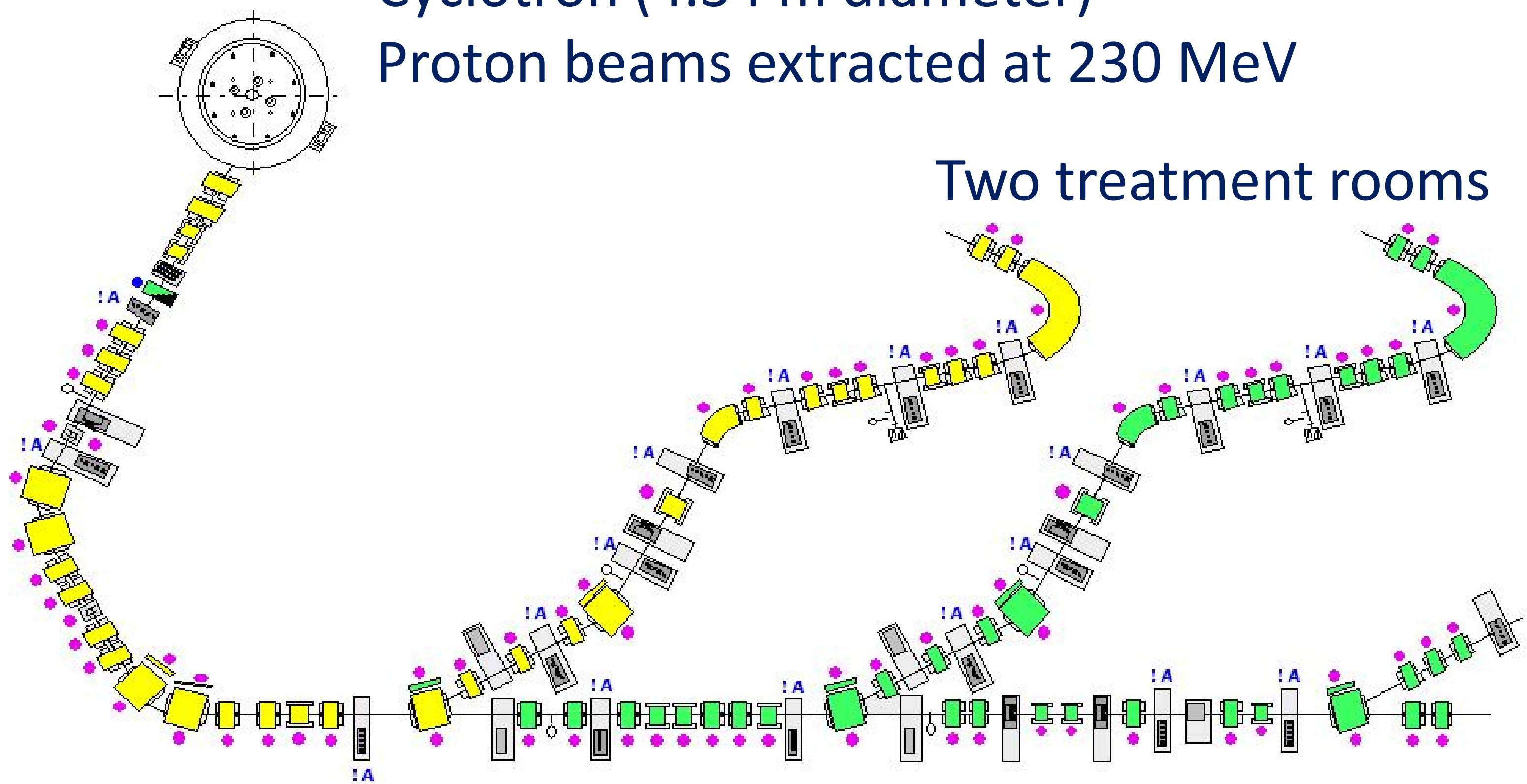
Syncrotron
(26 m diameter)

FACILITIES AND TREATMENT TECHNIQUES
Hadron therapy facility in Italy

ATreP (Agenzia Provinciale per la Protonterapia) @ Trento

Cyclotron (4.34 m diameter)
Proton beams extracted at 230 MeV

Two treatment rooms



Inaugurated in July 2013, after commissioning the clinical activity is started last autumn.

CONCLUSIONS AND FUTURE CHALLENGES

Hadron therapy reperesents an important instrument for the cure of cancer;

it can be considered the direct application of high energy physics research and technologies developed for the experiments;

it’s a multidisciplinary field (medicine, physics, biology, engineering, IT) in continuous evolution;

there is a great collaboration between research and indutrial partners.

CONCLUSIONS AND FUTURE CHALLENGES

R&D in medical physics and radiobiology is focusing on reducing the costs and increasing the benefits of this treatment

to improve carbon ion treatment and introduce new hadrons (helimun ions) by increasing our understanding of the biological response of cells and tissues (in both tumors and normal organs) to irradiation with various ions;

to improve beam delivery techniques and moving organs treatment;

to construct new and less expensive accelerators (LINAC or laser plasma accelerator).

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

Treatment Planning System

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 <u>well-defined range</u> of hadrons is the main advantage of hadron therapy

In order to fully utilize this potential advantage **the range needs to be predicted <u>as accurate as possible</u>** -> 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**.

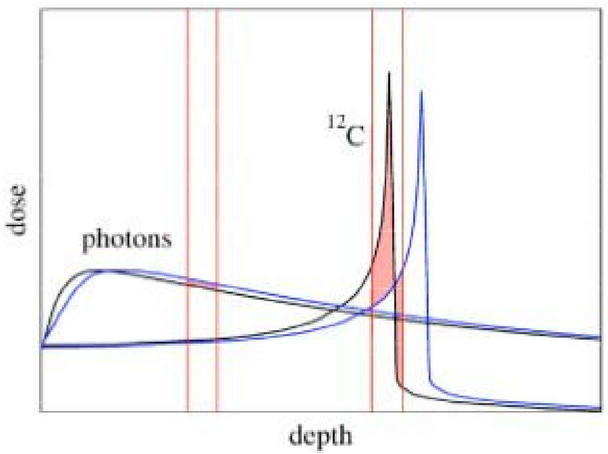


Fig. 12. For photon treatment, an error in target depth, indicated by two red lines at left, results in small dose error (red area). Whereas, for light ions, a similar error in range determination, shown in displaced Bragg peaks, would result in much more severe dose error as indicated by red areas (a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

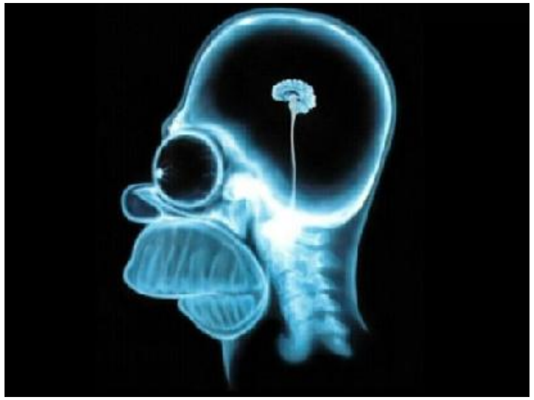
(3) Paganetti H., 2012, "*Range uncertainties in proton therapy and the role of Monte Carlo Simulations*", Phys. Med. Biol., 57:99-117.

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

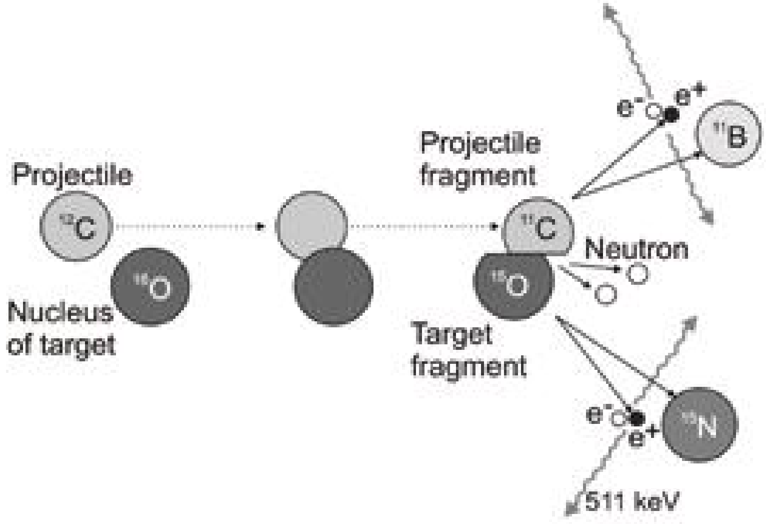
The use of PET imaging for the verification of hadron therapy was first proposed by **Maccabee *et al* in 1969 (@ Lawrence Berekeley Laboratory - California)**: H D Maccabee *et al*, 1969, "*Tissue activation studies with alpha-particle beams*", Phys Med Biol 1969 Vol 14 (213-24).

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).

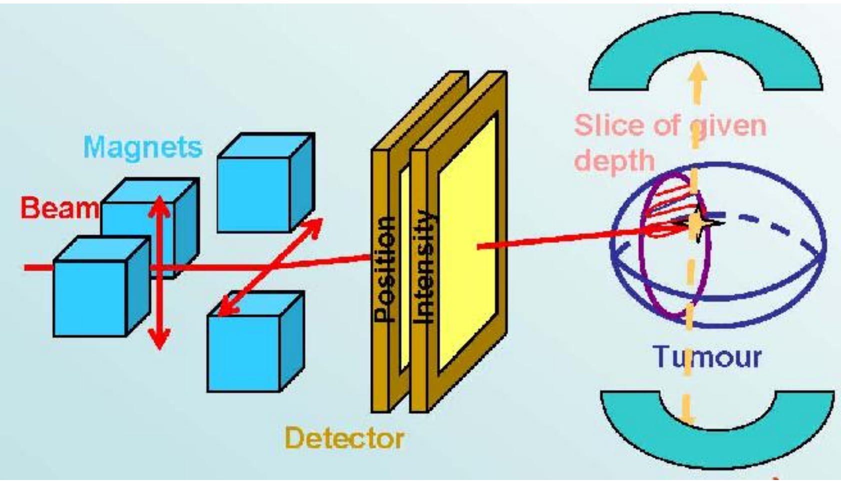
Than various research group **investigated the possibility of particle therapy monitoring by means of PET**, which **is still today the subject of intense studies**.

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 (γ) can be detected in coincidence -> 3D treatment delivery verification

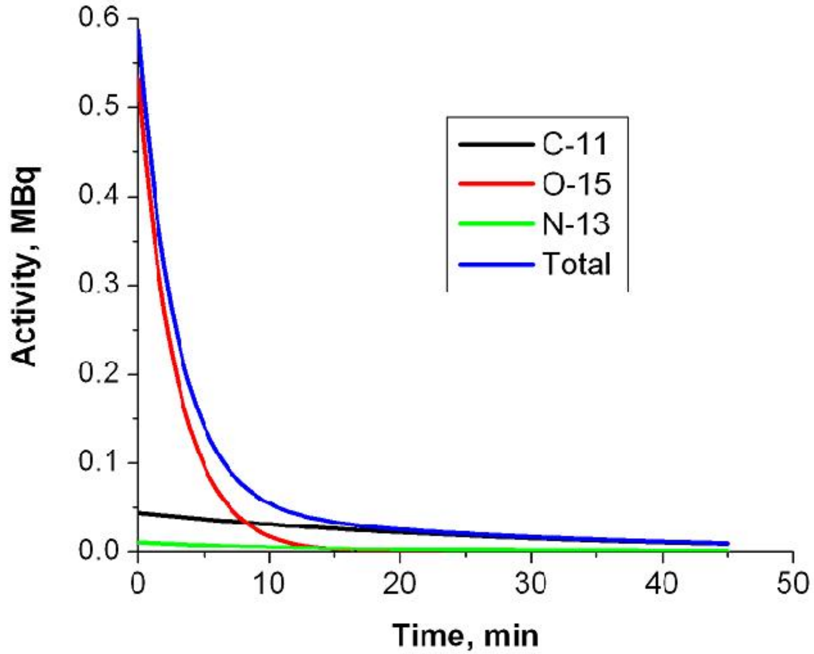
No additional dose cost for the patient

PET IMAGING

Principles of PET imaging in particle therapy

Table 1. 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: $\mathbf{A = A_0 e^{-\lambda t}}$

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.**

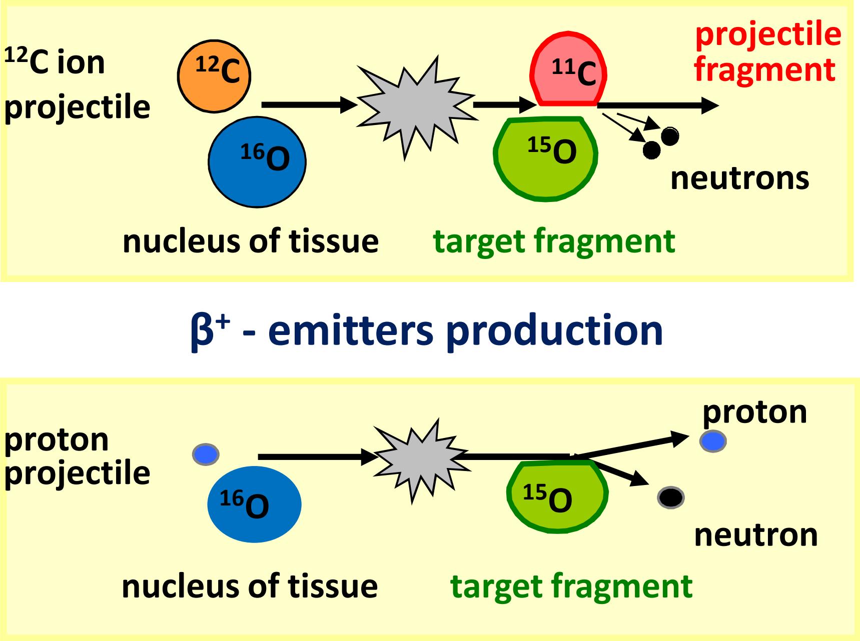
The mix of radionuclide species contributes to the PET signal (^{15}O for 80%) **-> treatment verification via PET is very sensitive to the time course of data acquisition.**

PET IMAGING

Principles of PET imaging in particle therapy

Ion beam inelastic collisions:
projectile and target fragmentation

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



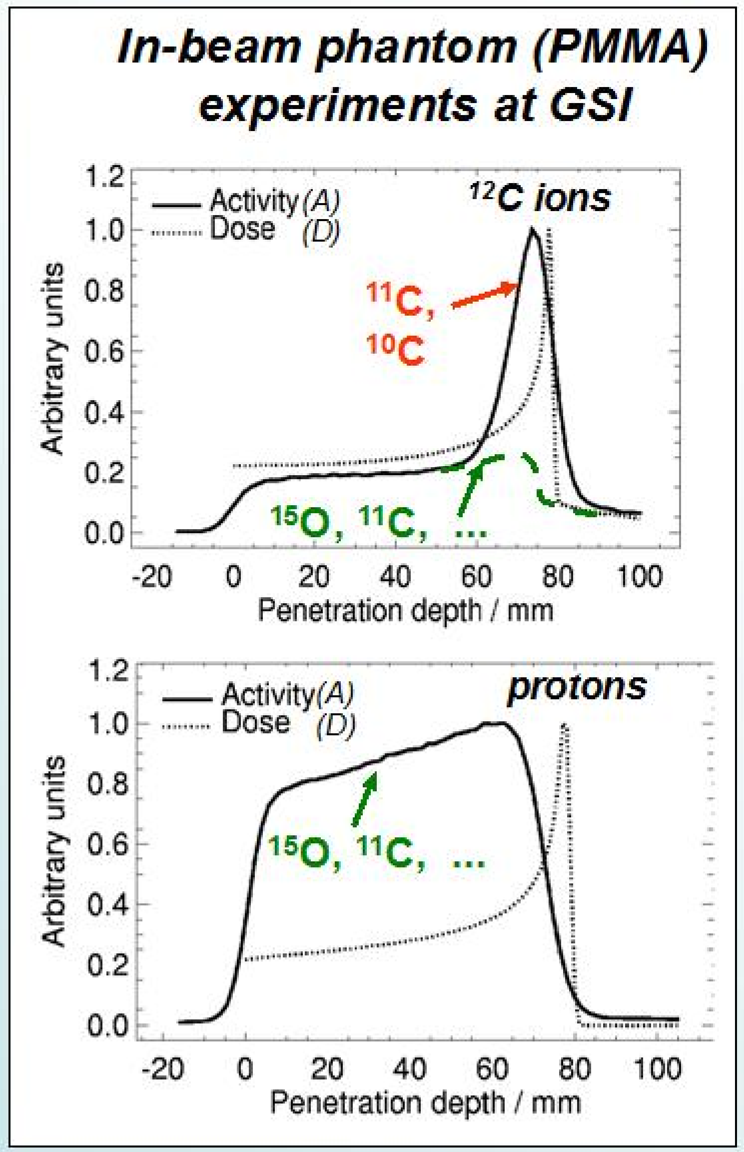
β^+- emitters **yield** dependes on:

- 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 ($\tau_{1/2}$ 2÷10 s)

signal changes over time -> **correction**

PET IMAGING

Principles of PET imaging in particle therapy

PET activity and dose distribution <u>cannot be compared directly:</u>

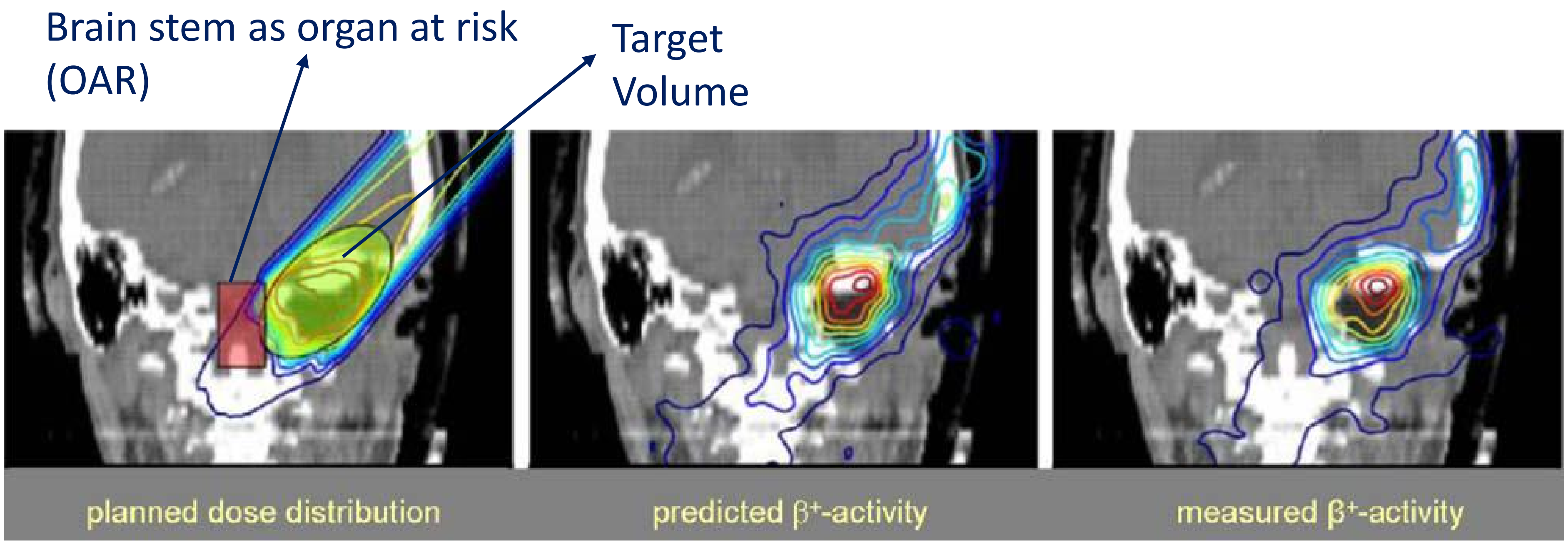
The relation between the induced activity and dose distribution is not straightforward -> PET measurements have to be compared with predicted activity distributions or other reference images.

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**.

PHITS
Particle and Heavy Ion Transport code System

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:

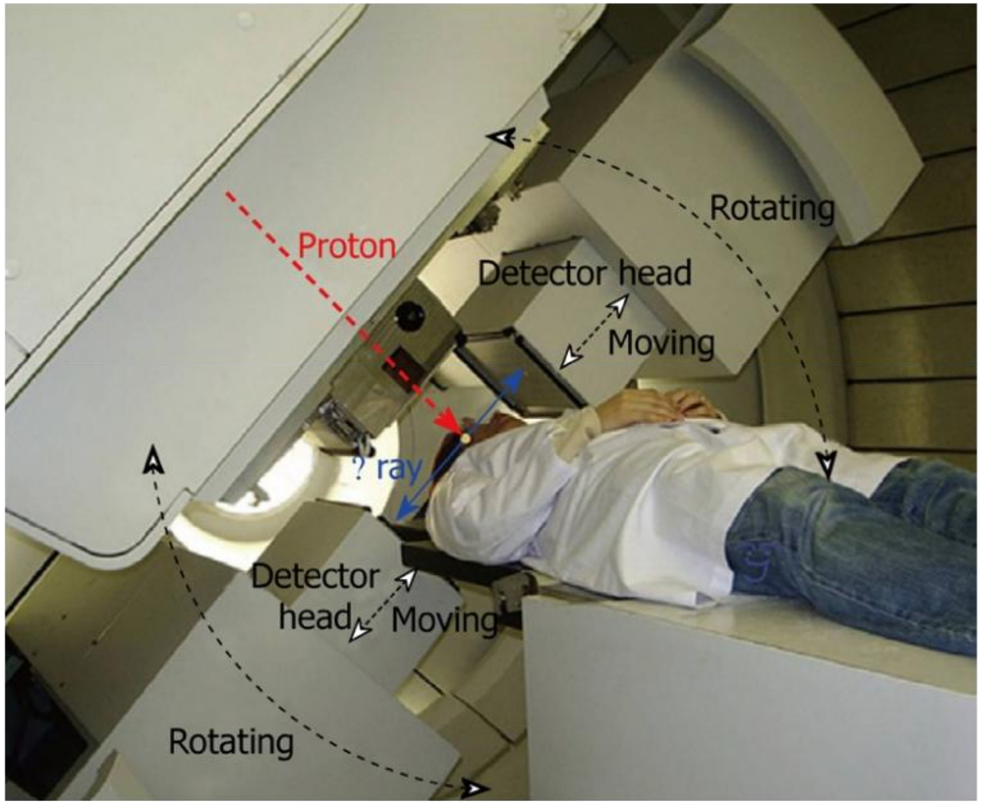
a. In-beam PET: measurement of β^+-activity **during irradiation** by means of a customized PET scanner integrated into the treatment site or directly into the gantry. First prototype used from 1997 to 2008 @ GSI (*Gesellschaft für Schwerionenforschung*) - Darmstadt.

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

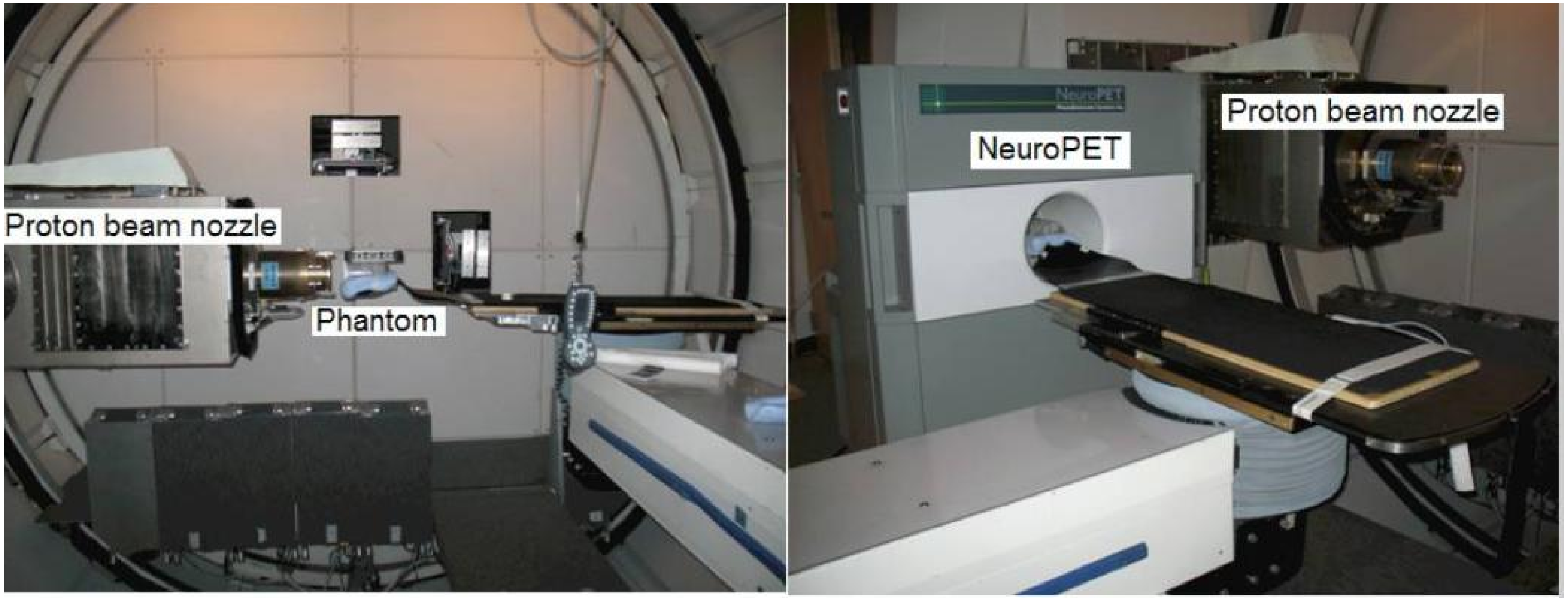


Setup of the on-line PET (**dual-head PET scanner**) system mounted on the rotating proton gantry. The proton beam direction is shown by the red line and the direction of the detected annihilation photons is shown in blue[6].

(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

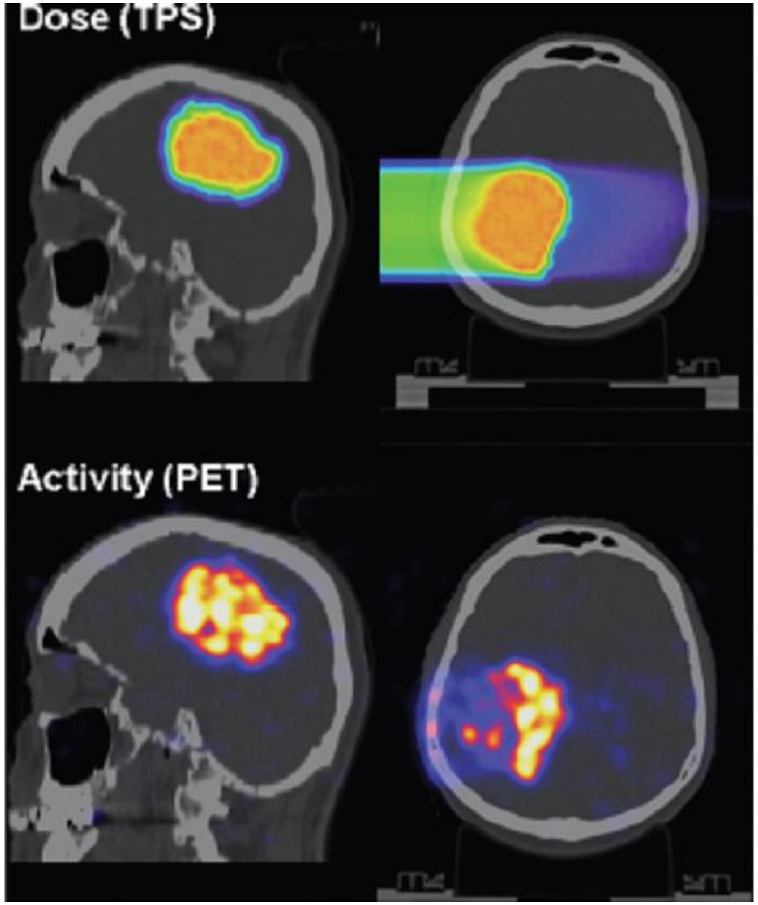
Clinical implementations: off-line PET

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

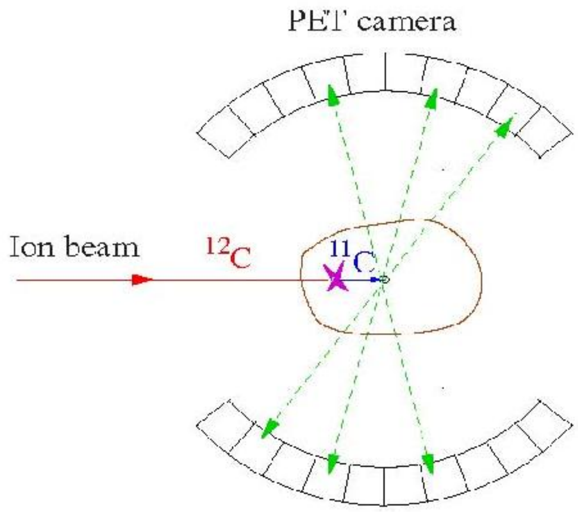
The detection principle of PET-based hadron therapy verification is similar to conventional PET diagnostic, but the **technical implementation** differs since, for particle therapy in-beam monitoring, **PET scanner has to be integrated into the treatment site** -> **double-head system** based on conventional 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;

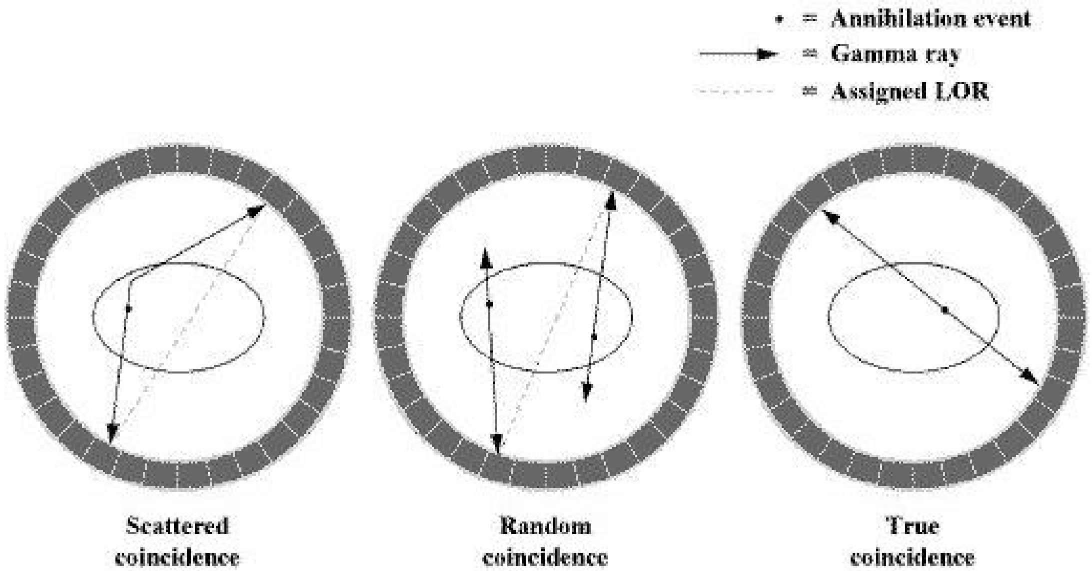
Detector geometry:

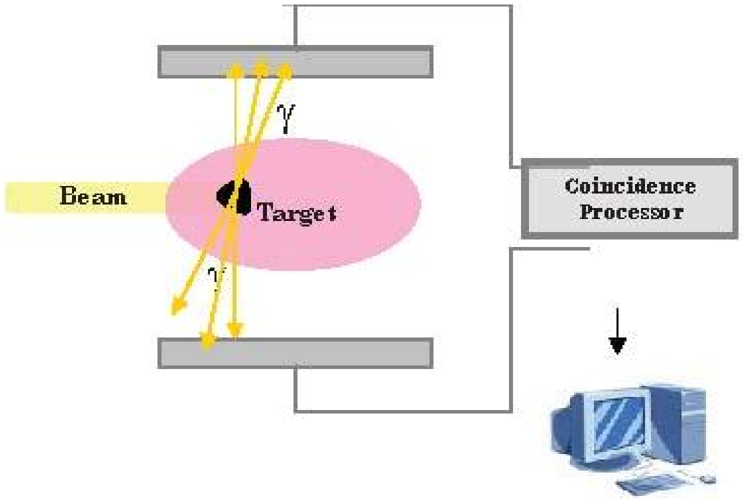
- ✓ Large solid angle;
- ✓ Shift invariant point response function;
- ✓ Ports for the primary beam and the light fragments;

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, <u>the amount of **true coincidences** has to be recovedered from the whole collected data</u> -> **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.

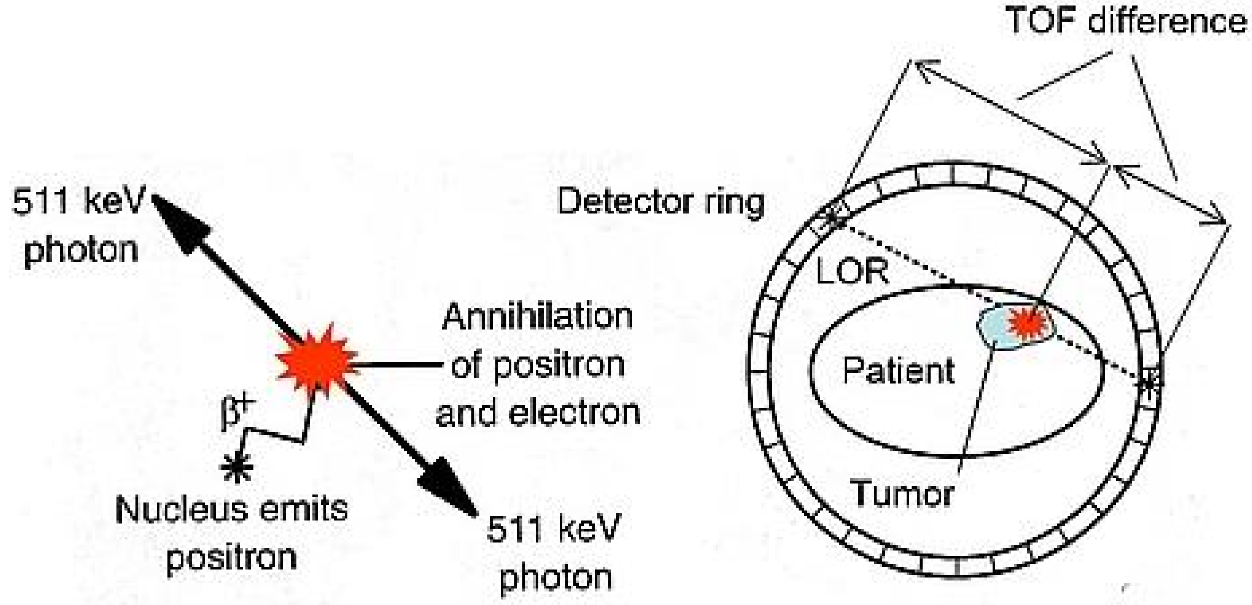
But nowadays, all the existing crystals do not meet all these requirements.

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**).

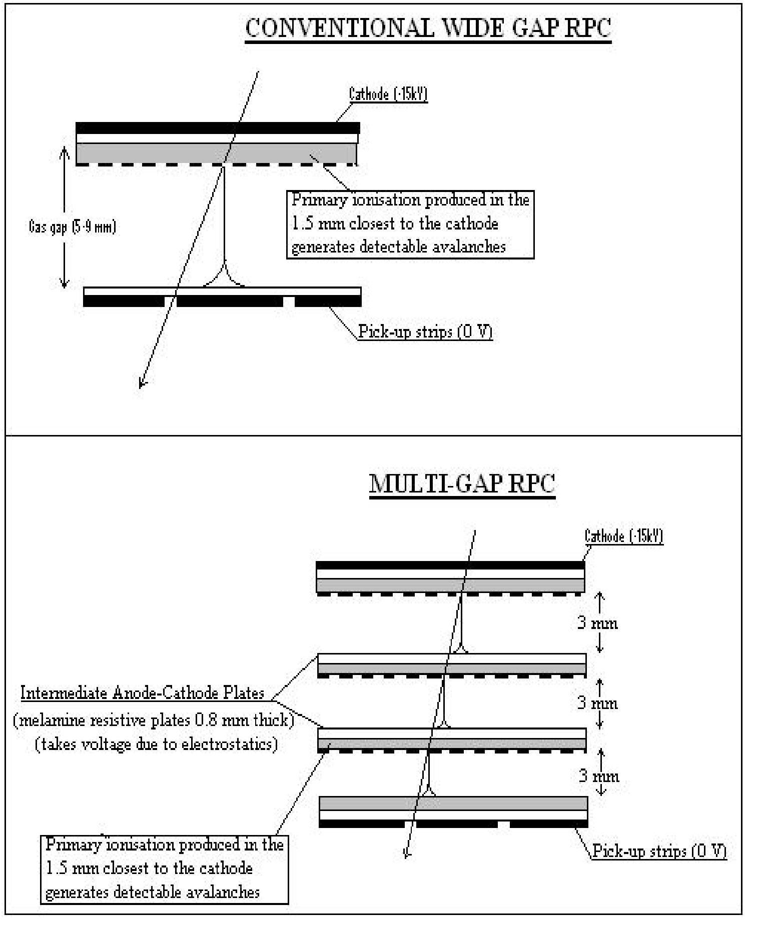
INSIDE (*Innovative Solutions for In-beam Dosimetry in hadrontherapy*) project:
born from the collaboration of Italian Universities and INFN to build a multimodal in-beam dose monitoring system able to detect at the same time, back-to-back gammas from β^+ annihilation and charged secondary particles 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 cm^2 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.



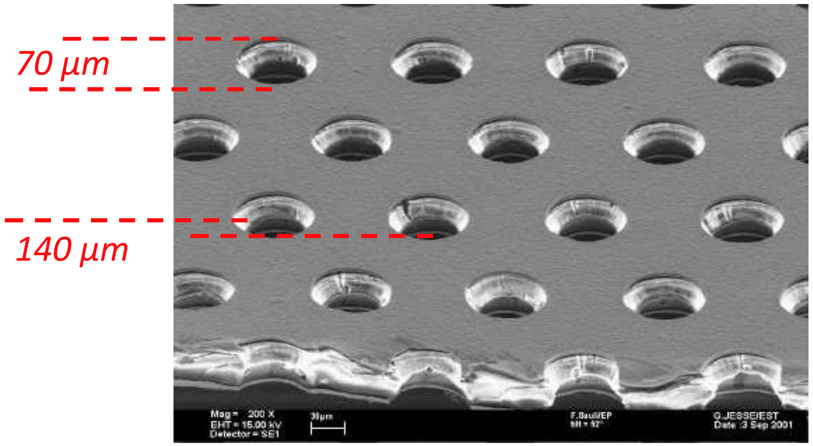
The limit is **the low efficiency** (weak signal induced on the electrodes) but it's can be <u>increased by using a stack of MRPC modules with large surface area</u> (**Watts D. et al," *The use of multi-gap resistive plate chambers for in-beam PET in proton and carbon ion therapy*", 2013, Journal of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

PET ON LINE MONITORING

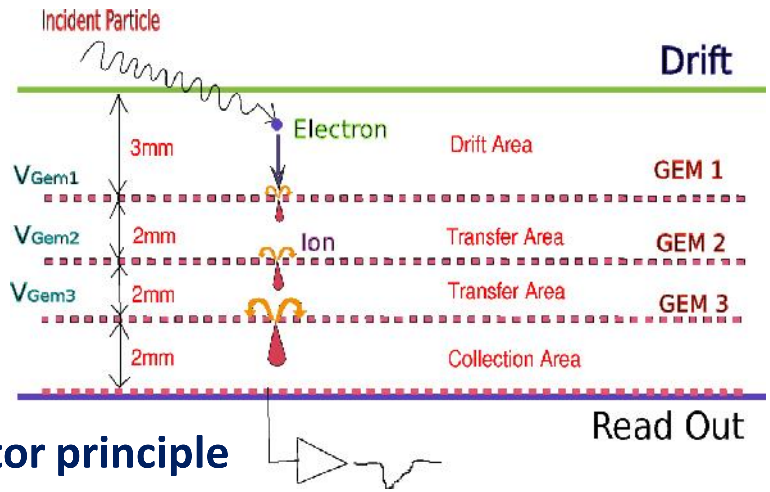
On-going developments

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**.

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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