La protonterapia e l'attività di ricerca a LNS

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Laboratori Nazionali del Sud

Outline

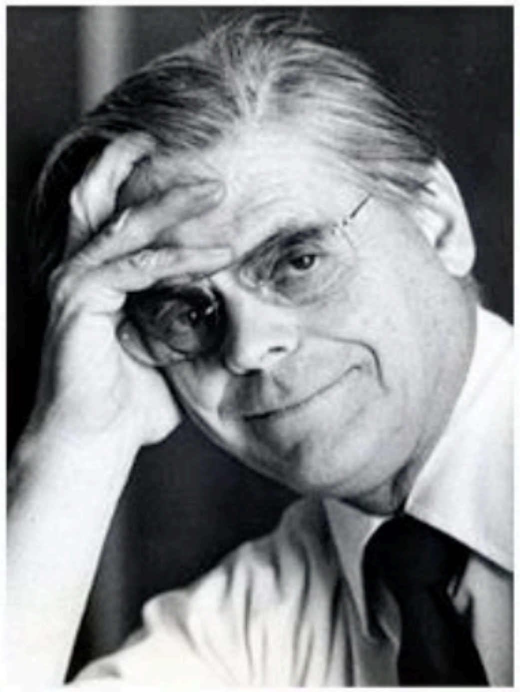
- **Hadrontherapy**
  - **History**
  - **Physical Basics**
  - **Biological Basics**
  - **Hadrontherapy facilities in Italy**

- **CATANA: a passive proton beam line**
  - **Scattering System**
  - **Modulation System**
  - **Monitoring System**
  - **Final Collimator**

- **Some recent activities and R&D @LNS**

History of Hadrontherapy

INFN
Istituto Nazionale di Fisica Nucleare



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.

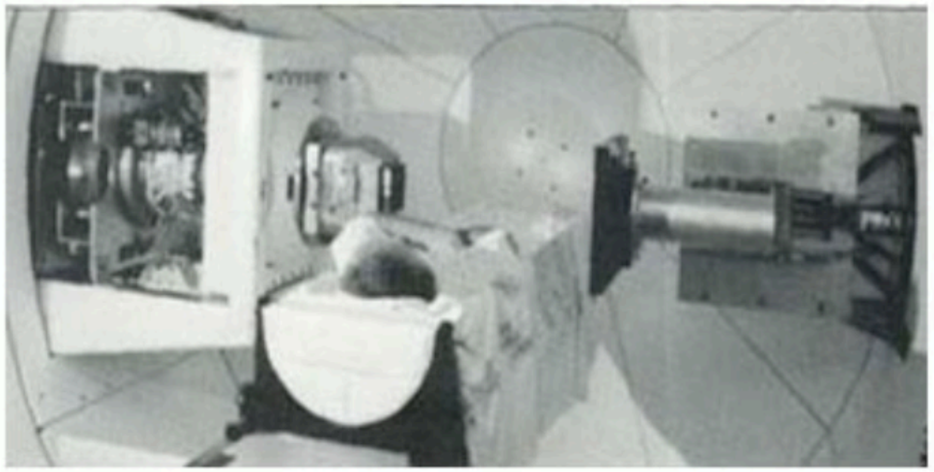
These properties make it possible to irradiate intensely a strictly localized region within the body, with but little skin dose. It will be easy to produce well

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

History of Hadrontherapy

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

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

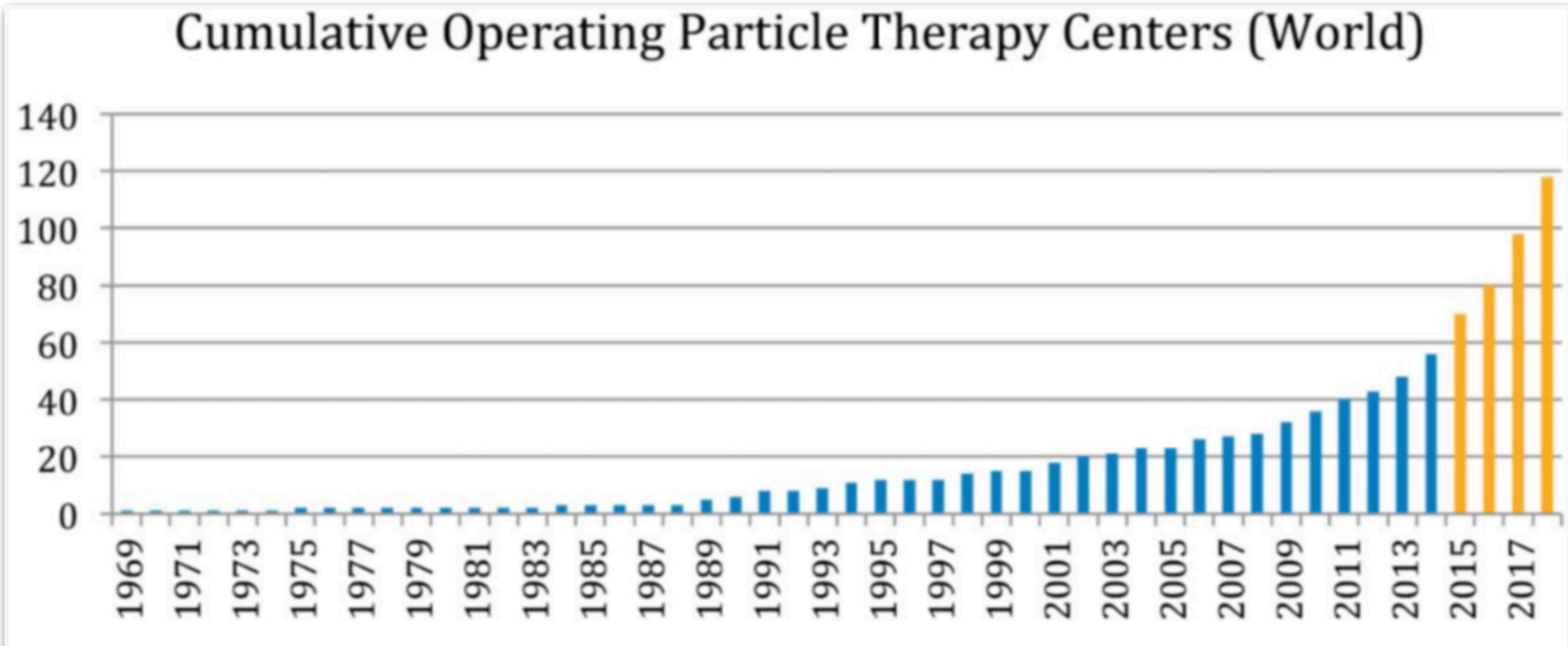


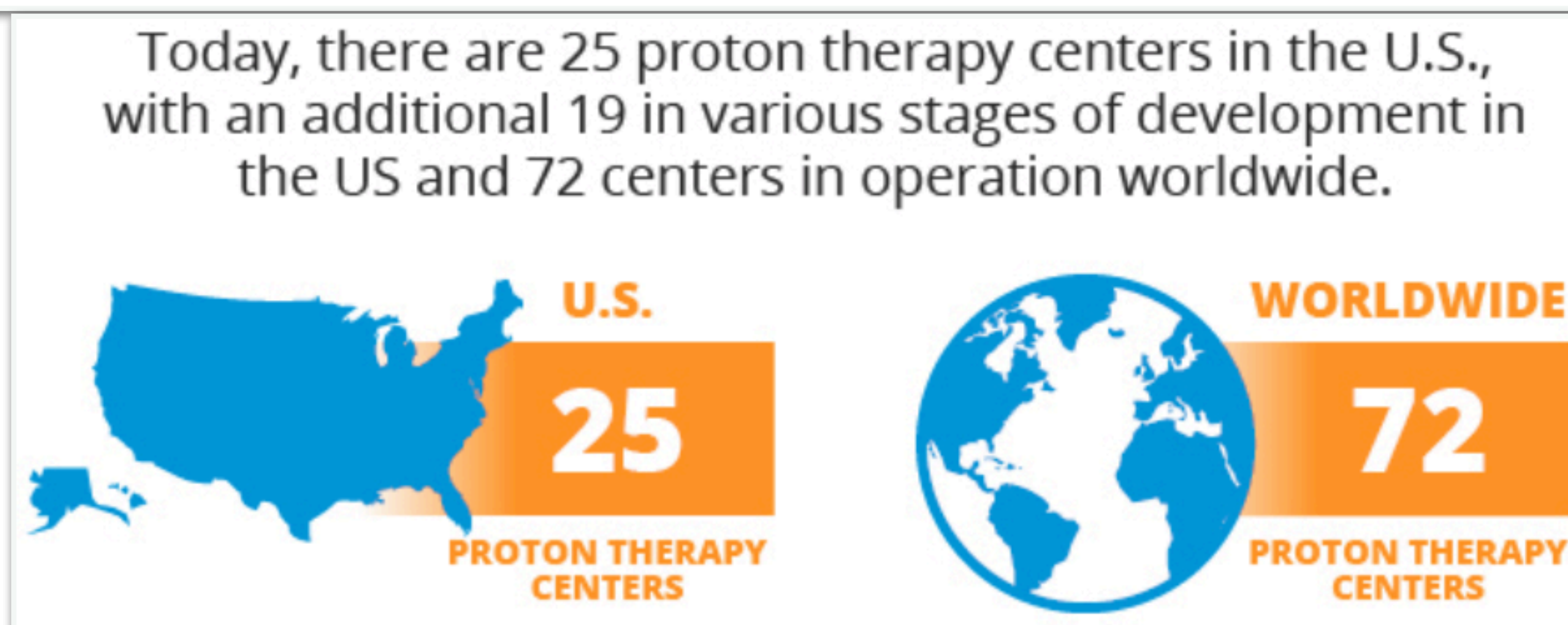
LLUMC (California, USA)

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

Hadrontherapy centers in the world

Particle Therapy Co-Operative Group (PTCOG)





Physical Basics: Beth-Block

[see e.g. PDG 2010]

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

density

$K = 4\pi N_A r_e^2 m_e c^2 = 0.307$ MeV g^{-1} cm^2

$T_{max} = 2m_e c^2\beta^2\gamma^2/(1 + 2\gamma m_e/M + (m_e/M)^2)$
[Max. energy transfer in single collision]

z : Charge of incident particle
M : Mass of incident particle

Z : Charge number of medium
A : Atomic mass of medium

I : Mean excitation energy of medium
δ : Density correction [transv. extension of electric field]

$N_A = 6.022 \cdot 10^{23}$
[Avogardo's number]

$r_e = e^2/4\pi\varepsilon_0 m_e c^2 = 2.8$ fm
[Classical electron radius]

$m_e = 511$ keV
[Electron mass]

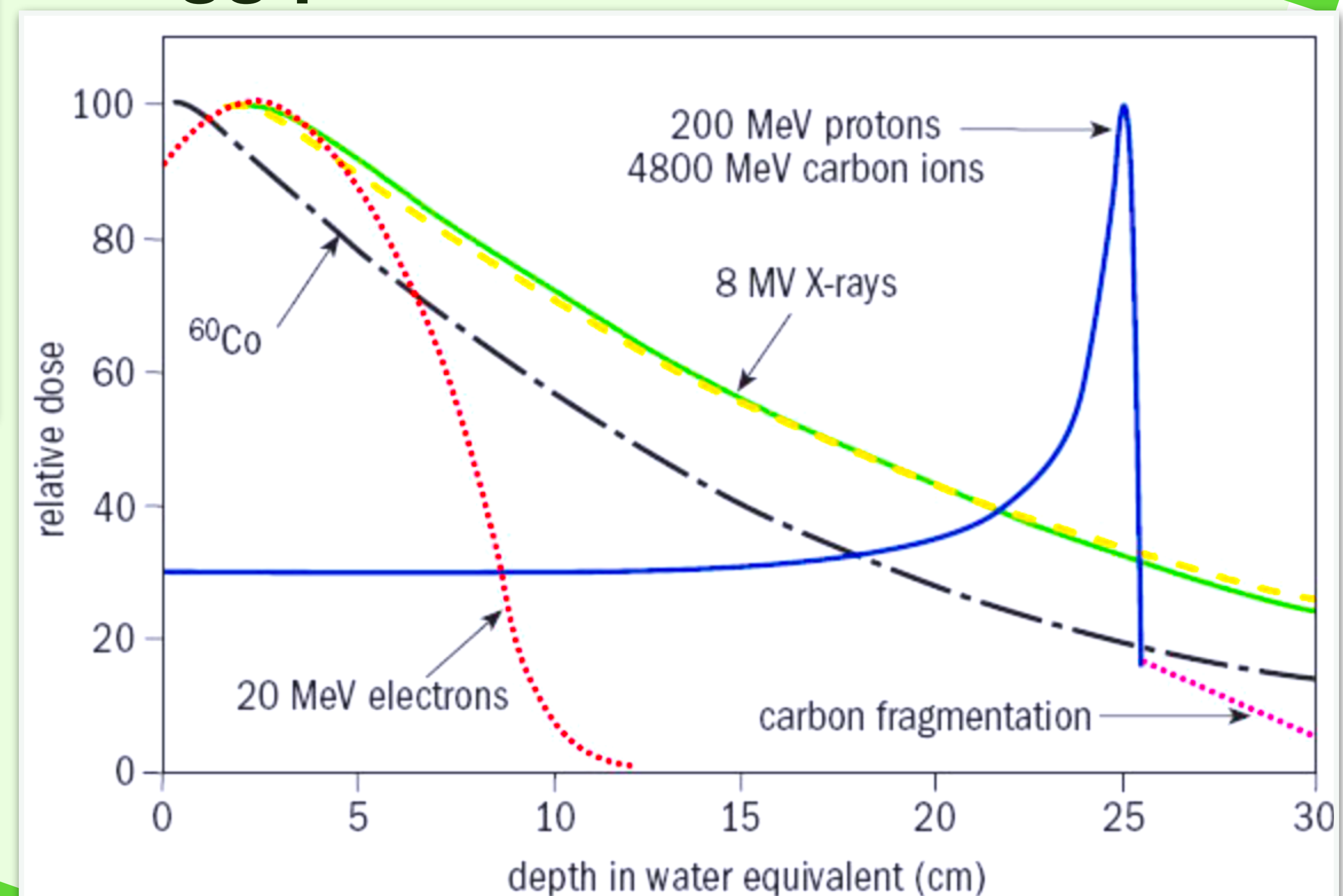
$\beta = v/c$
[Velocity]

$\gamma = (1-\beta^2)^{-2}$
[Lorentz factor]

Validity:
$.05 < \beta\gamma < 500$
$M > m_\mu$

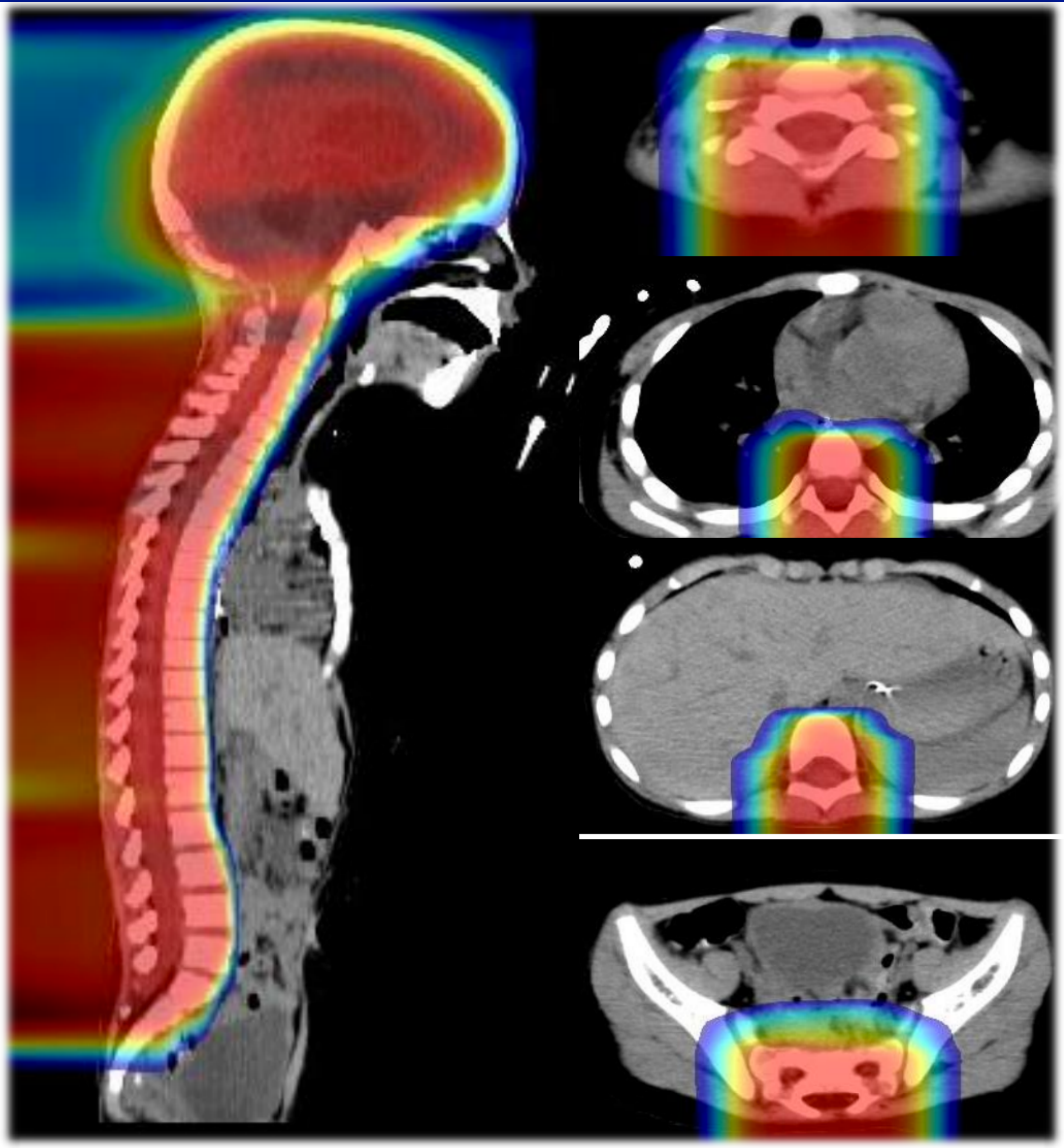
Beth-Block Formula

Bragg peak



Biological Basics: Coventional vs Protontherapy

x-Ray therapy



Protontherapy

Mirabell RA et al.
Potential reduction of the incidence of radiation-induced second cancers by using proton beams in the treatment of pediatric tumor,
Int. Jour. Rad. Onc. Phys. 2002, 54 (3) 824

Biological Basics: Coventional vs Protontherapy

Physical advantages:

- finite range and high inization density;
- lower integral dose;

Clinical advantages:

- treatment of deep-seated, irregular shaped and radioresistant tumors
- small probability of side effects in normal tissue (critical structure)
- proton therapy suitable for pediatric diseases (reduced toxicity)

Pediatric Medulloblastoma: The yearly risk of getting a secondary tumor was estimated to be 8 times greater with X-rays than with proton therapy [2]

Tumor Site	Proton Therapy	X-rays/IMRT
Stomach and esophagus	0%	11%
Colon	0%	7%
Breast	0%	0%
Lung	1%	7%
Thyroid	0%	6%
Bone and connective tissue	1%	2%
Leukemia	3%	5%
All Secondary Cancers	**5%**	**43%**

This chart compares the rates of secondary tumors for a pediatric patient treated for medulloblastoma.

Data shown are from a study that compared treatment plans.

IMRT= intensity modulated radiation therapy (a type of X-ray therapy)

A basic concept: dose

$$D = \frac{dE}{dm} \quad [Gy = J/Kg]$$

$$\downarrow$$

$$D_W(Gy) = \frac{1}{A}(S(E))_W \frac{Q}{e} 1.602 \cdot 10^{-10}$$

Biological Basics: RBE

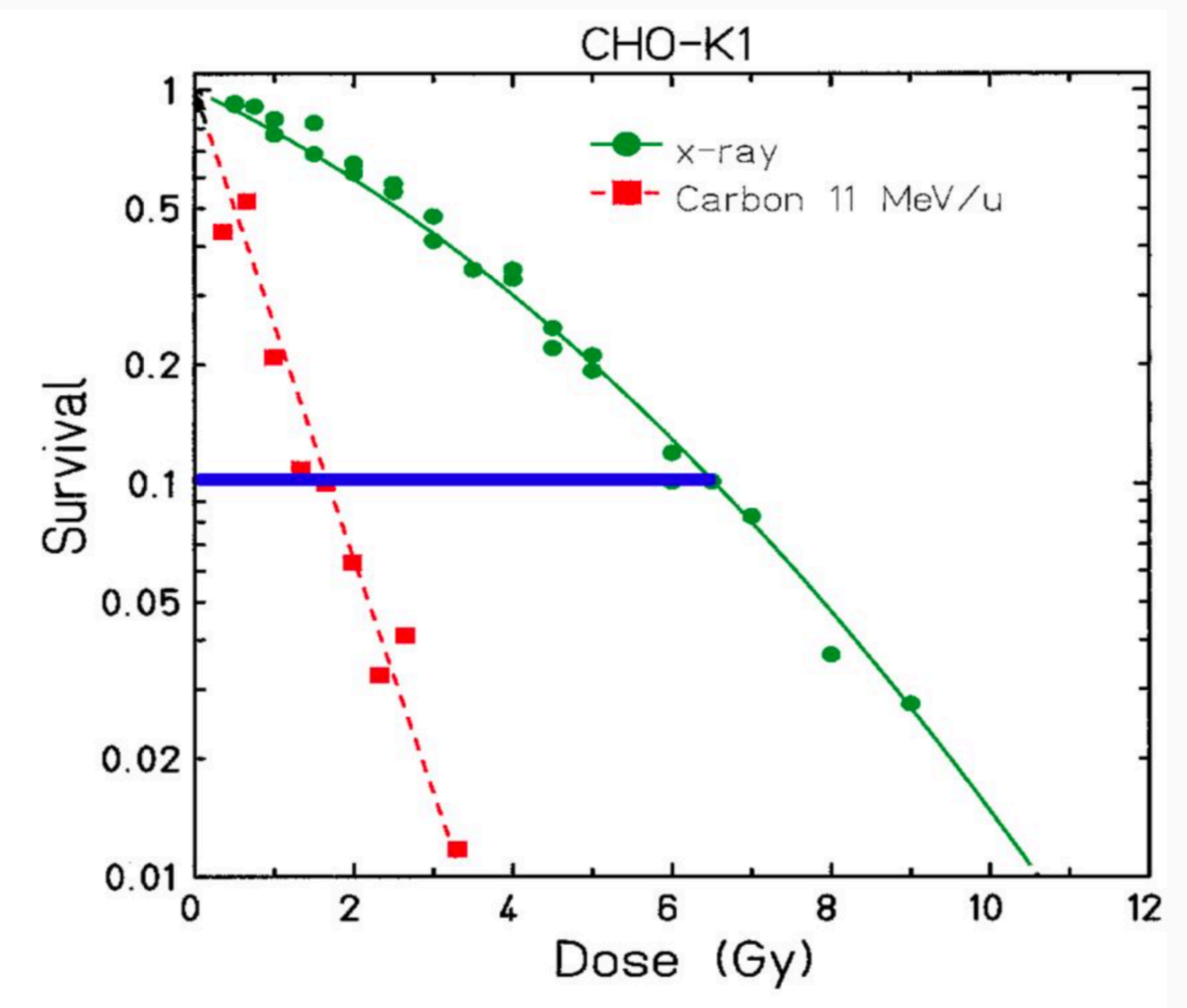
Relative Biological Effectiveness

$$RBE_n = \frac{D_X}{D_{Ion}}\bigg|_{S_X = S_{Ion} = n}$$

RBE-Weighted Dose (RWD):
RWD = *D* x RBE

Protons:
RBE $\sim$ 1.1

Carbon Ions:
RBE $>$ 1



Biological Basics: RBE

Relative Biological Effectiveness

$$RBE_n = \frac{D_X}{D_{Ion}}\Bigg|_{S_X = S_{Ion} = n}$$

RBE-Weighted Dose (RWD):
RWD = *D* x RBE

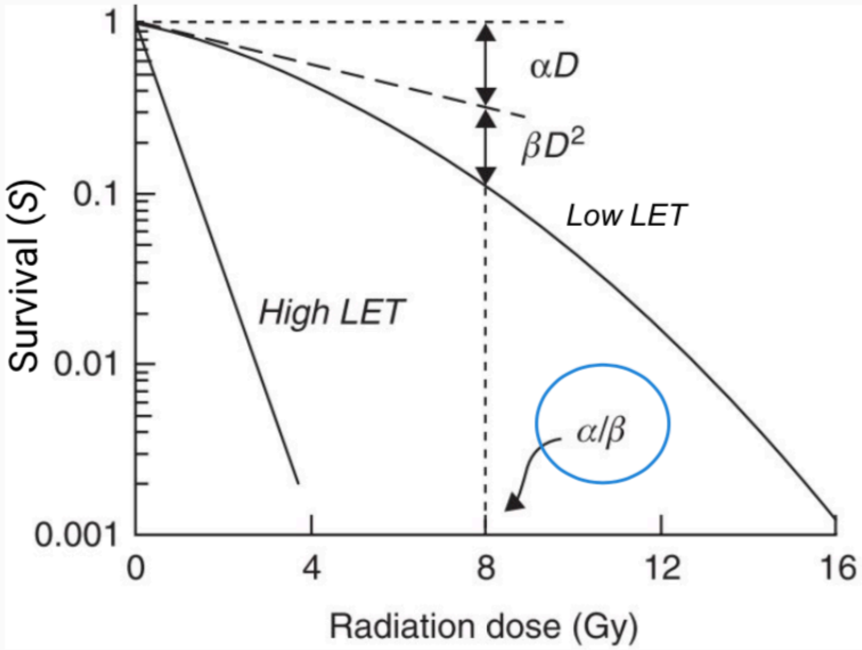
Protons:
$RBE \sim 1.1$

Carbon Ions:
$RBE > 1$

$$-\ln(S) = \alpha D + \beta D^2$$

There are two components of cell killing: one is **proportional to dose** (αD), while the other is **proportional to the square of the dose** (βD^2).

Although we can regard this as based on pure mathematics (i.e. the simplest formula which describes a curve), it has also been possible to attach radiobiological mechanisms.



Physical Parameters
- Dose
- Energy
- Linear Energy Transfer (LET)
- Particle type

Biological Parameters
- Tissue type
- Oxigenation (OER)
- Repair capacity (α_X / β_X)
- Biological endpoint

- "Linear" models (protons)
- Local Effect Model (**LEM**)
- Microdosimetric Kinetic Model (**MKM**)
- Repair-Misrepair-Fixation (**RMF**) Model

Biological Basics: LET

Linear Energy Transfer (LET)

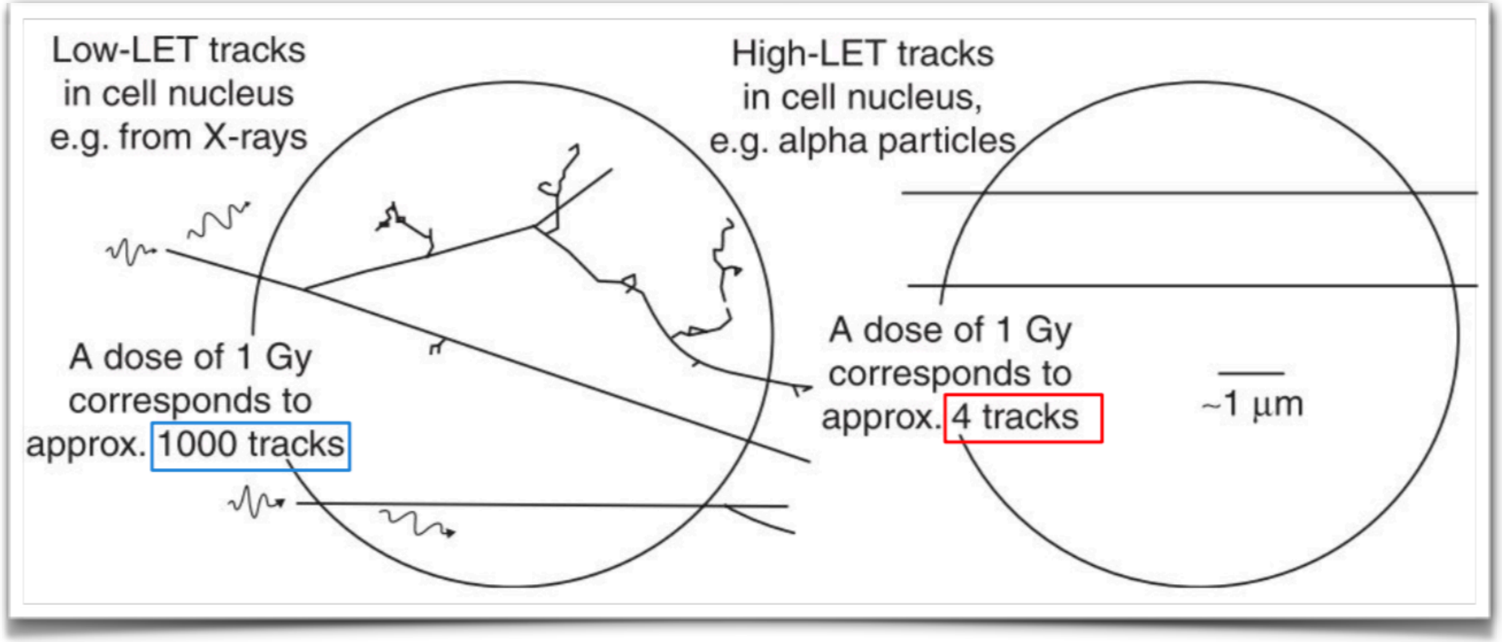
$$LET = \frac{dE}{dl} \quad [\text{keV}/\mu\text{m}]$$

The biological damage is strictly related to the radiation quality

LET -> ionization density -> quality of radiation

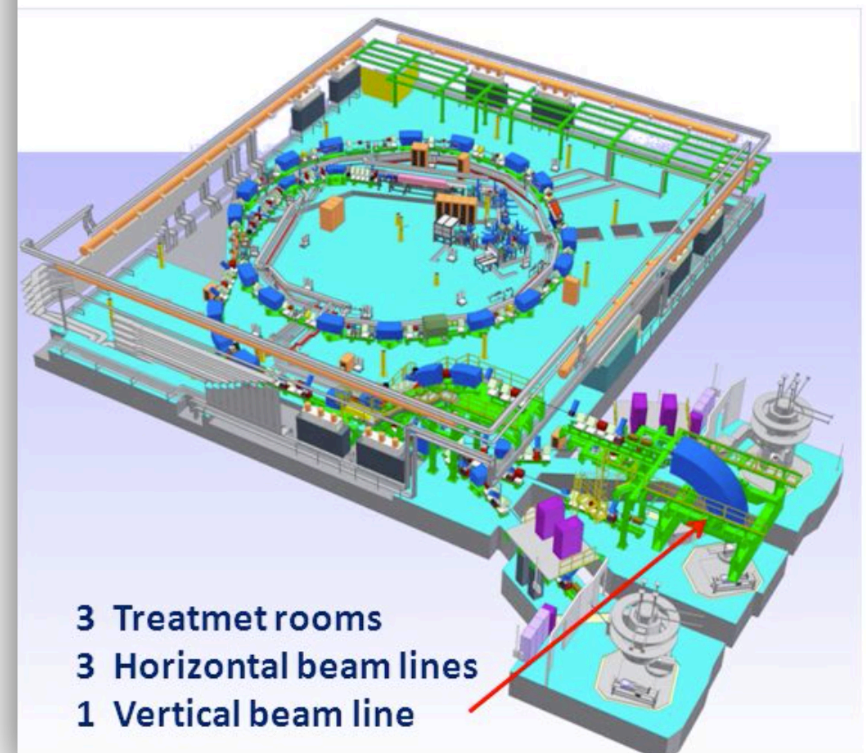
High LET (> 10 keV/µm) -> multiple DNA damages

Hadrons are high LET with respect to photons



Hadrontherapy 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

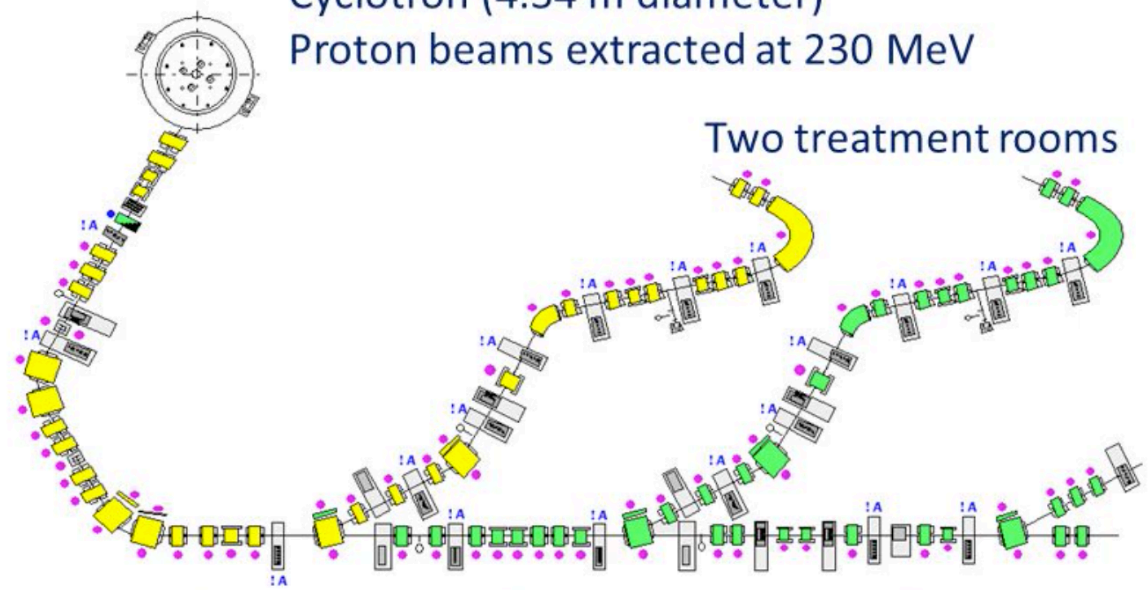
C^{6+} E : [120, 400] MeV/u

Syncrotron
(26 m diameter)

ATreP (Agenzia Provinciale per la Protonterapia) @ Trento

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

Two treatment rooms



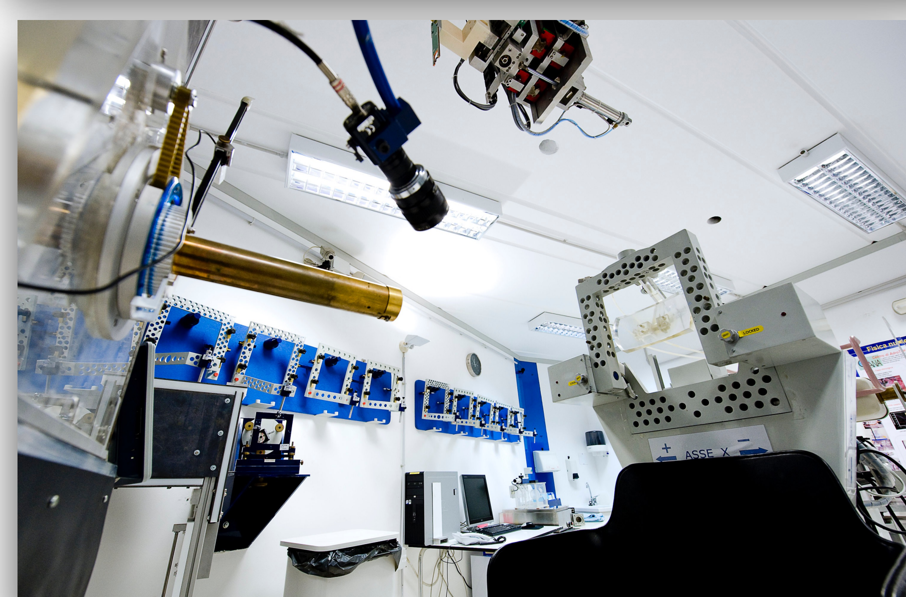
Inaugurated in July 2013, after commissioning it's starting the clinical activity

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

CATANA treatment room

CATANA

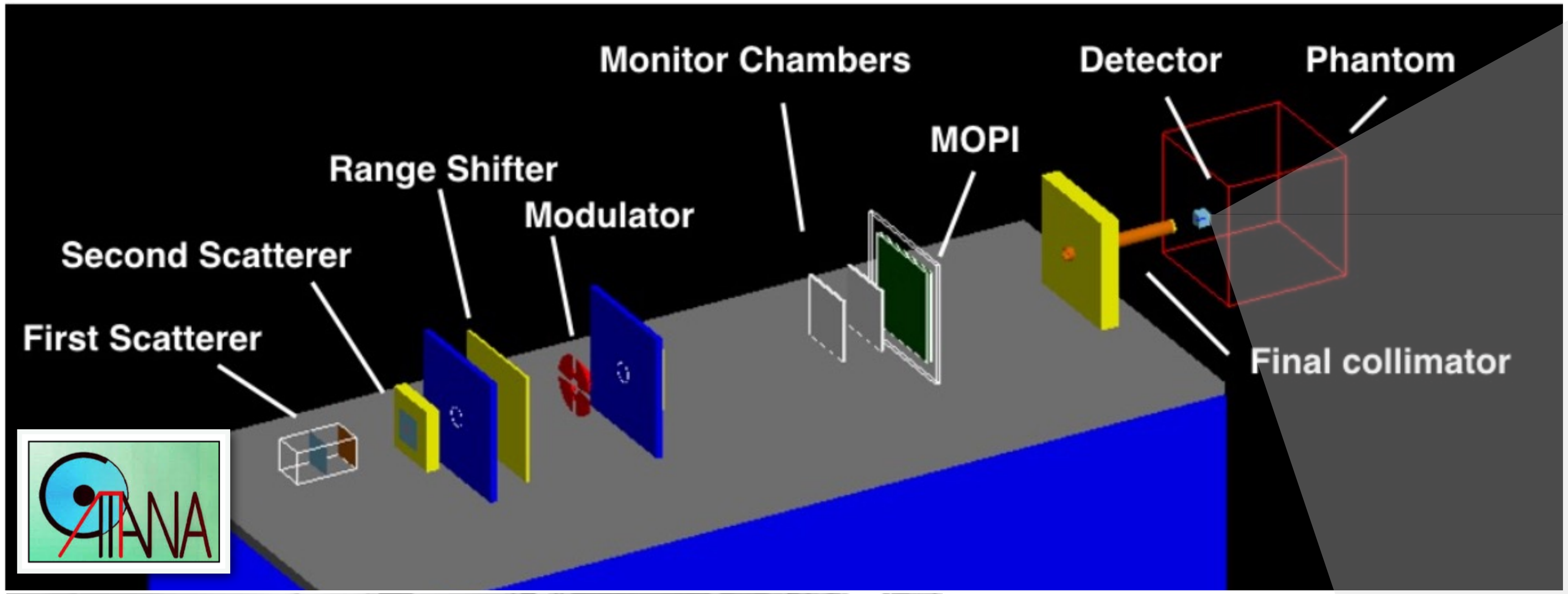
Cuttone et al. EPJ **126** (2011)

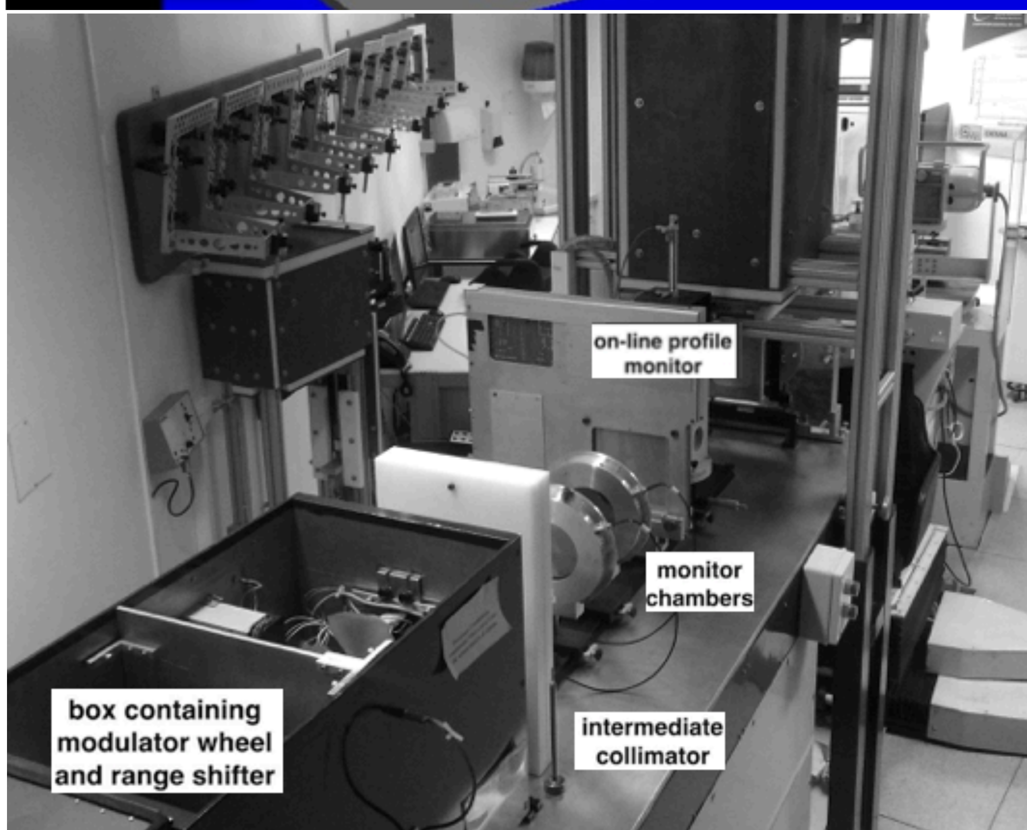


CATANA
Centro di AdroTerapia ed Applicazioni Nucleari Avanzate

- First Italian proton therapy facility
- First Patient treated on March 2002 (about 400 treated)
- passive proton beam line
- 62 MeV of energy

CATANA: a passive proton beam line



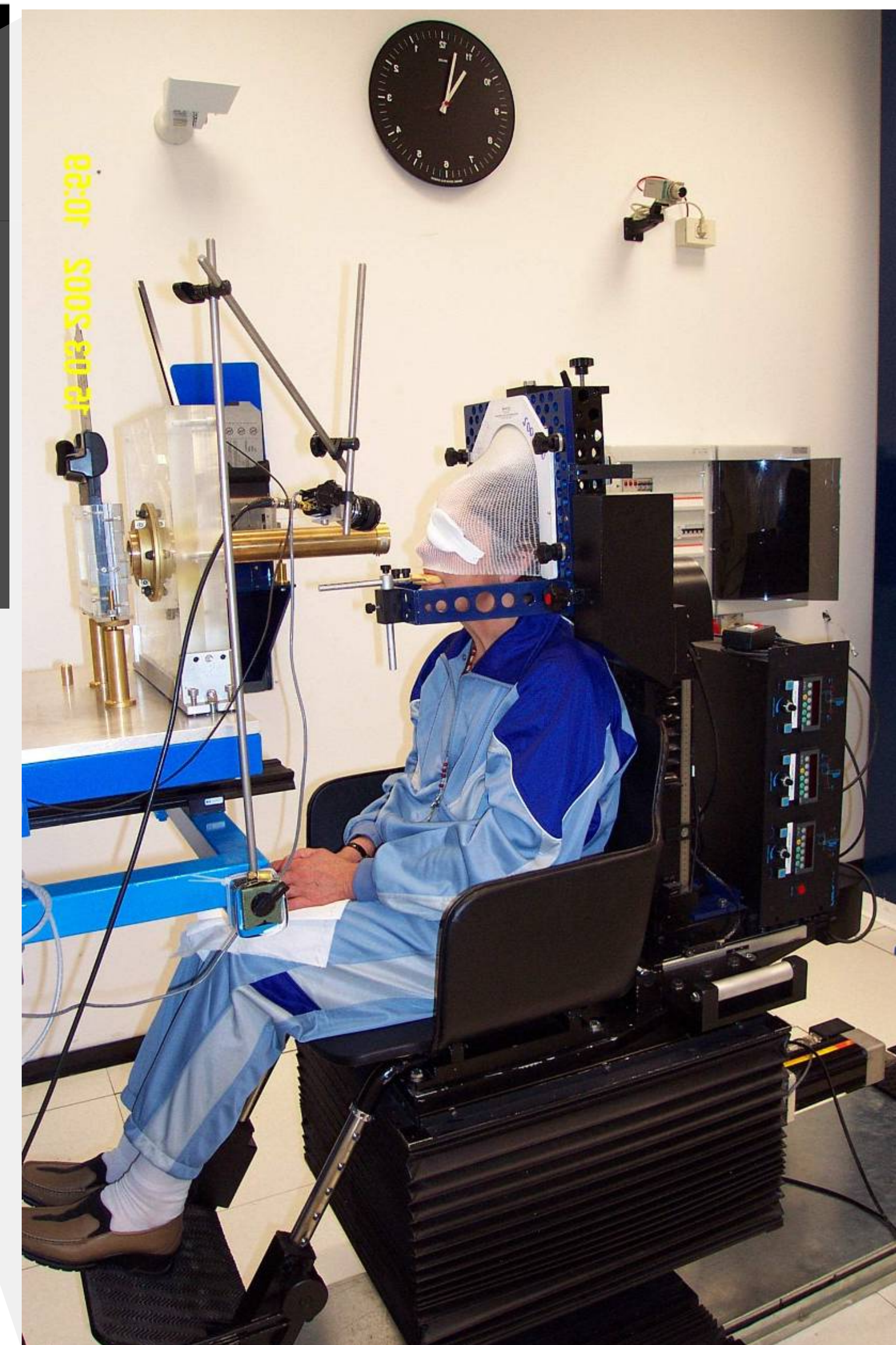


<u>Dose</u>:15 CGE per fraction

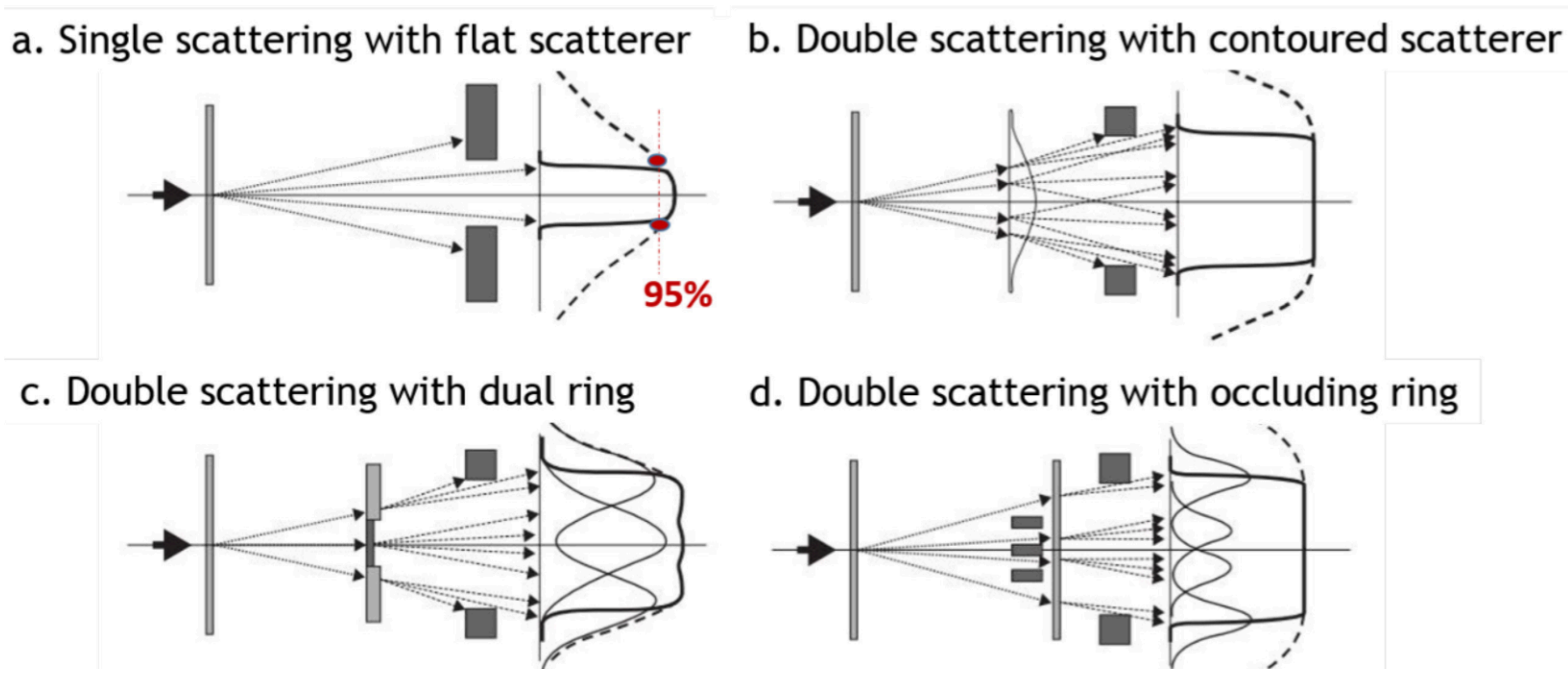
<u>Treatment time</u>: 40-50 sec

<u>Total dose</u>: 60 CGE

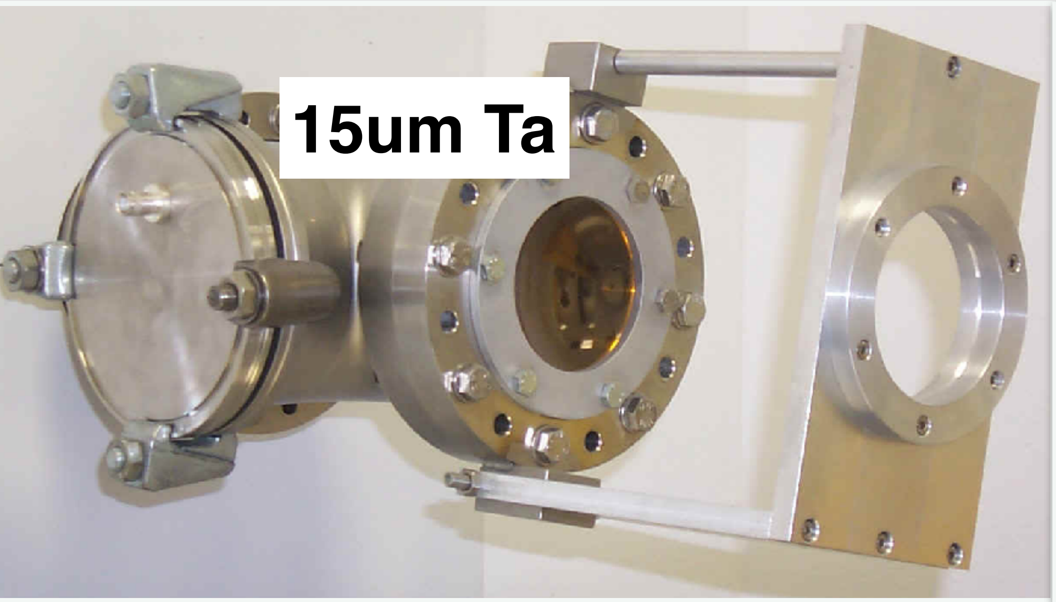
<u>Fractions</u>:4

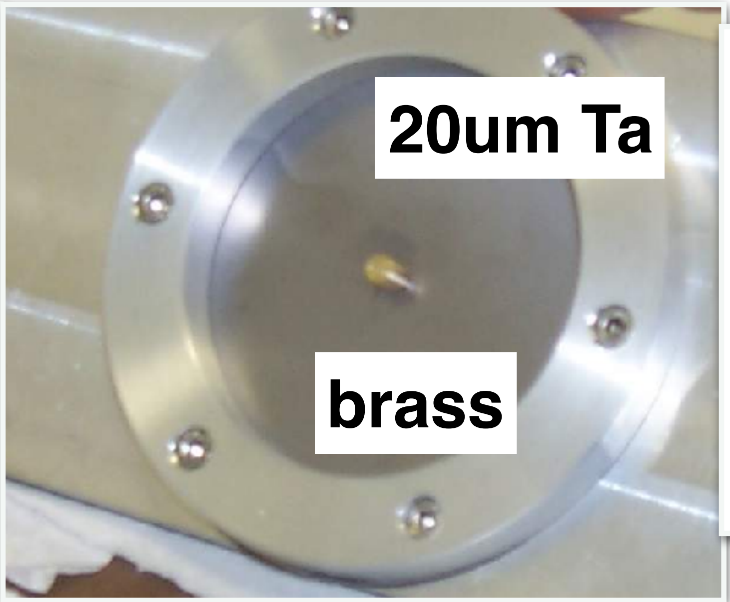


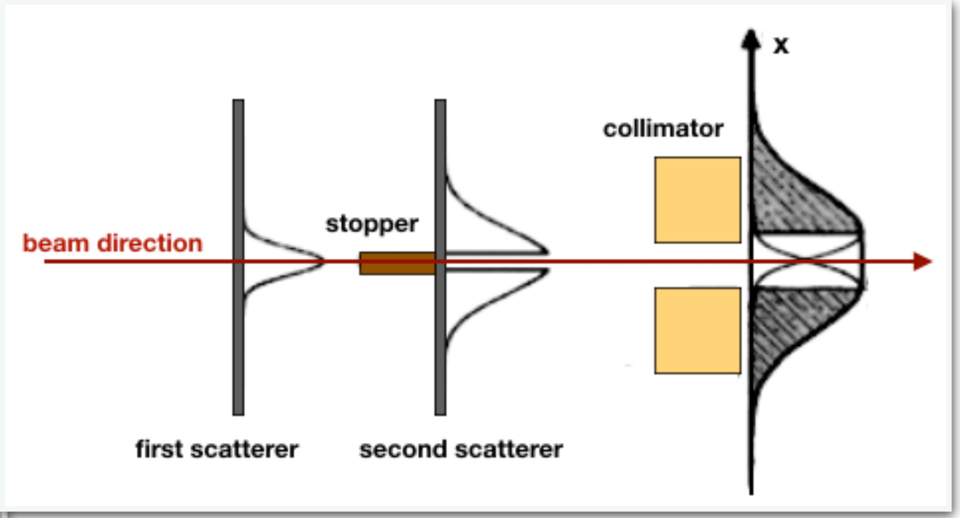
The scattering system



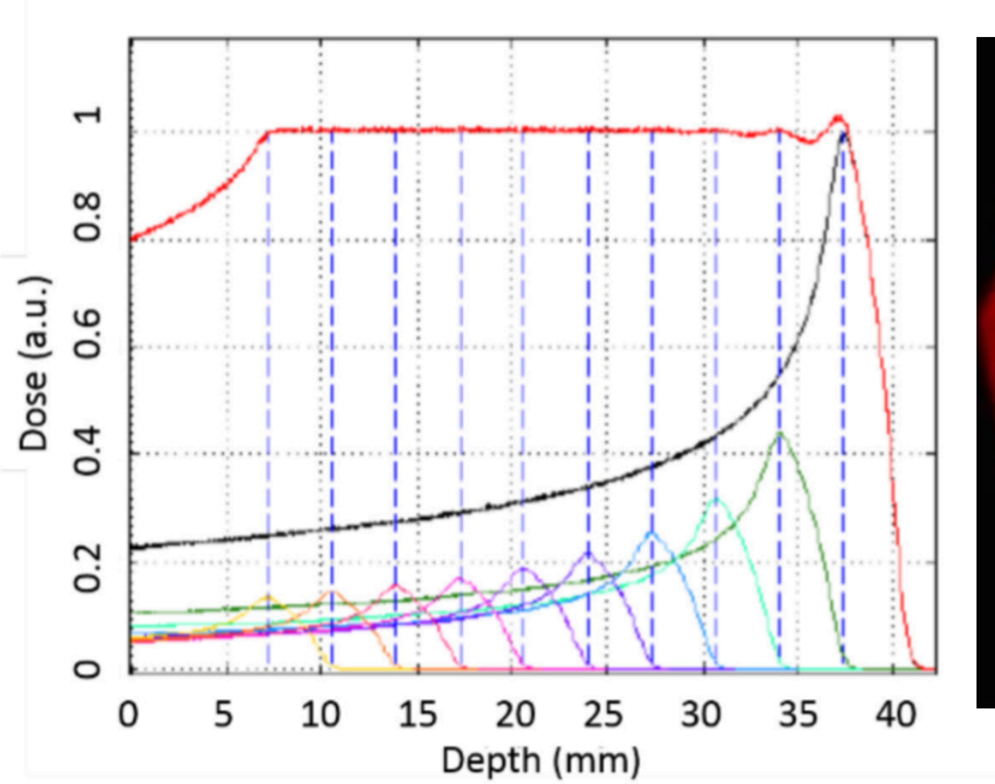
Double Scattering system with one occluding central stopper

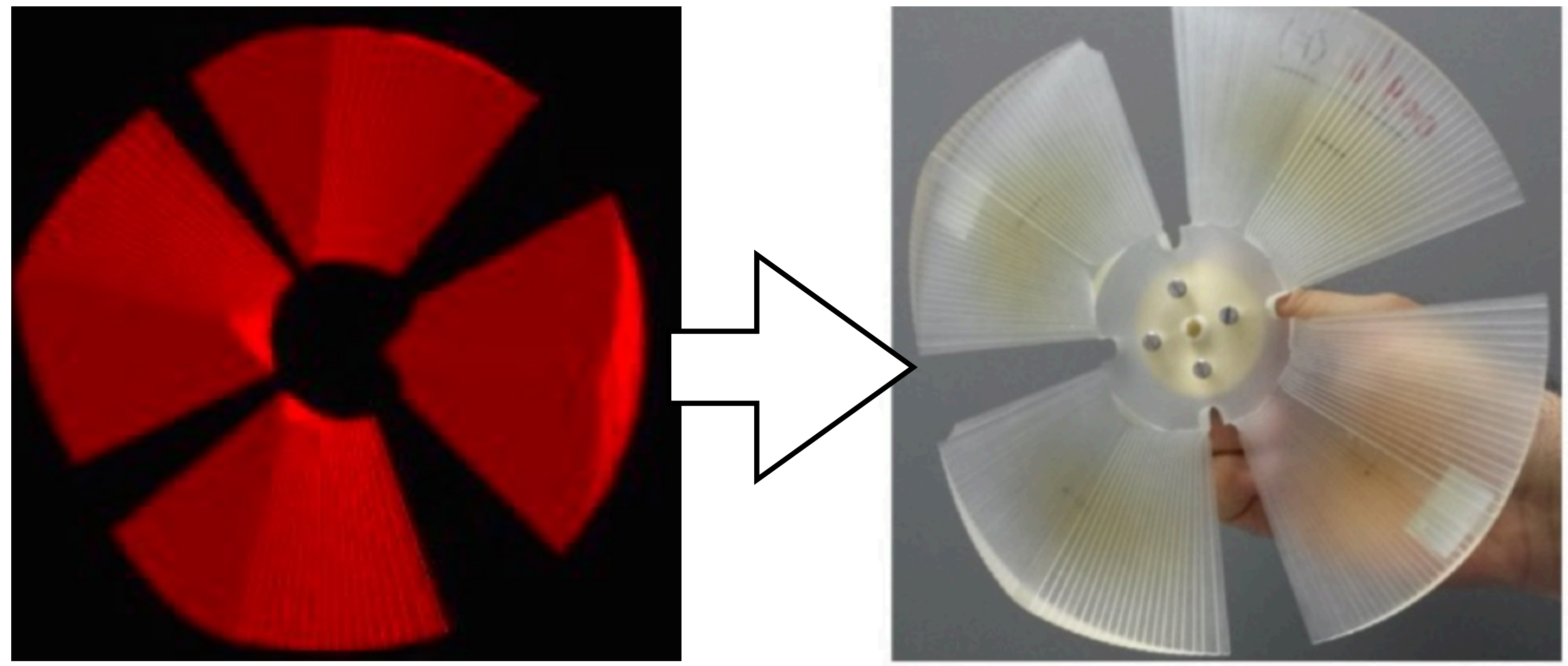






The modulation system





The dose in the SOBP can be expressed as the superimposition of many Bragg curves expressed as:

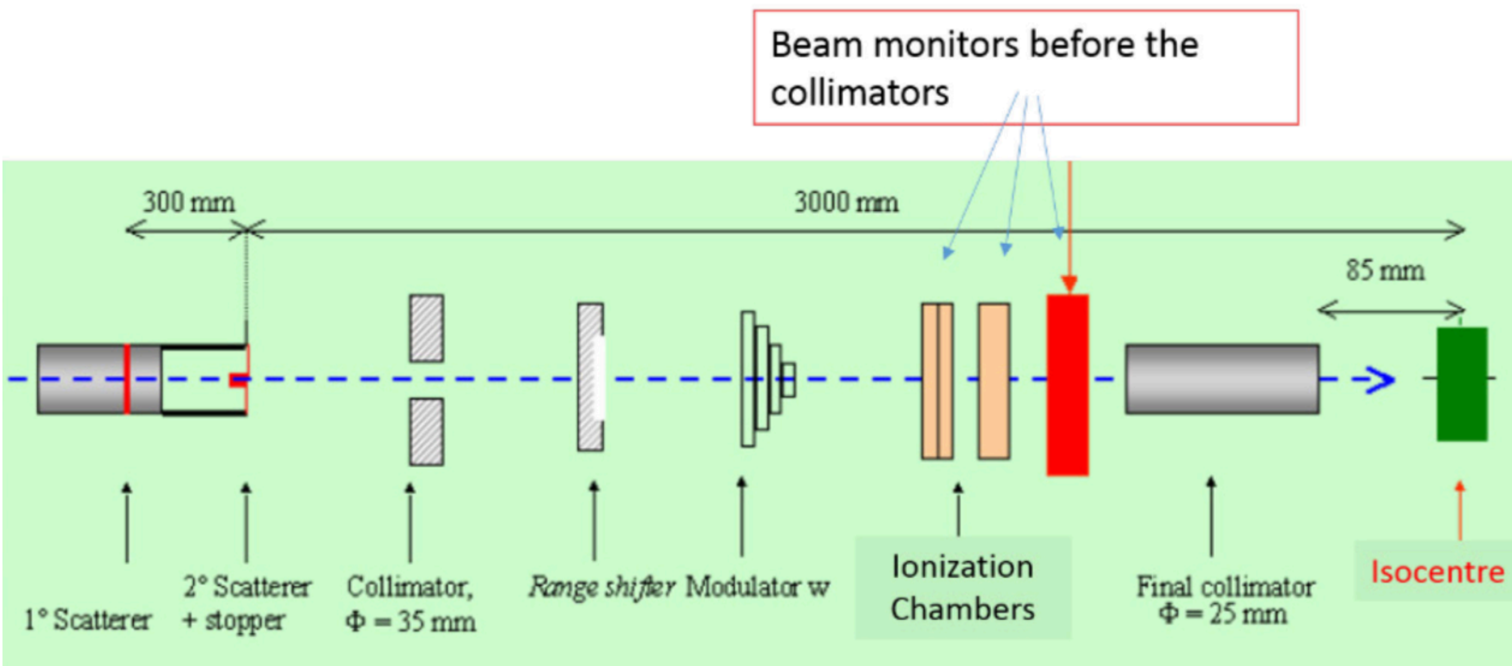
$$D(x,y,z) = \sum_i w_i B_i(x,y,z)$$

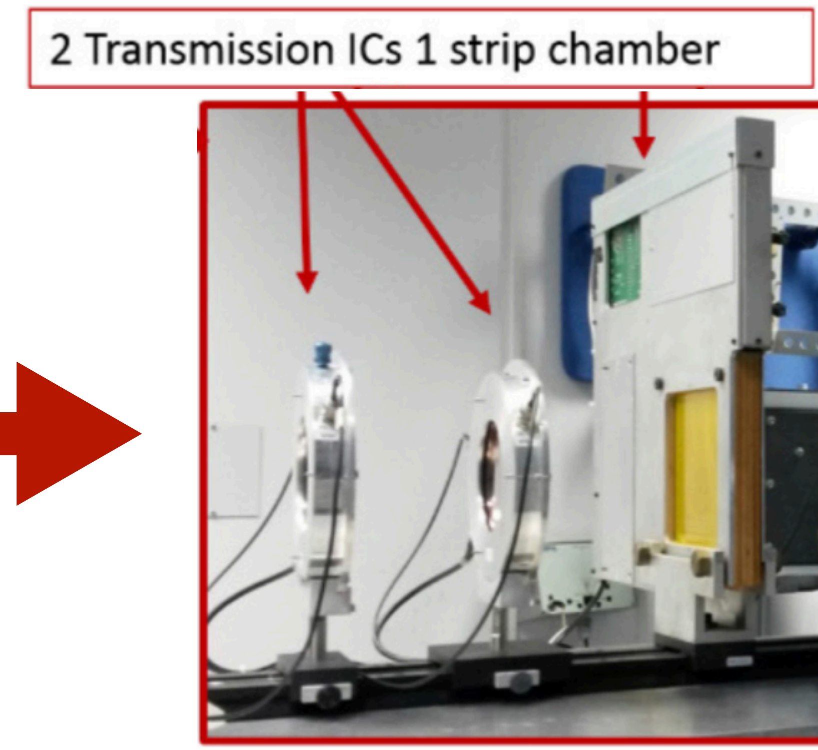
where $B_i(x,y,z)$ is a Bragg curve that can be determined experimentally and analytically; w_i is the optimized weight determining the modulator shape, and accounting for the contribution of each peak i to the final SOBP. The weights can be obtained by the minimization of a cost function, Q, defined as

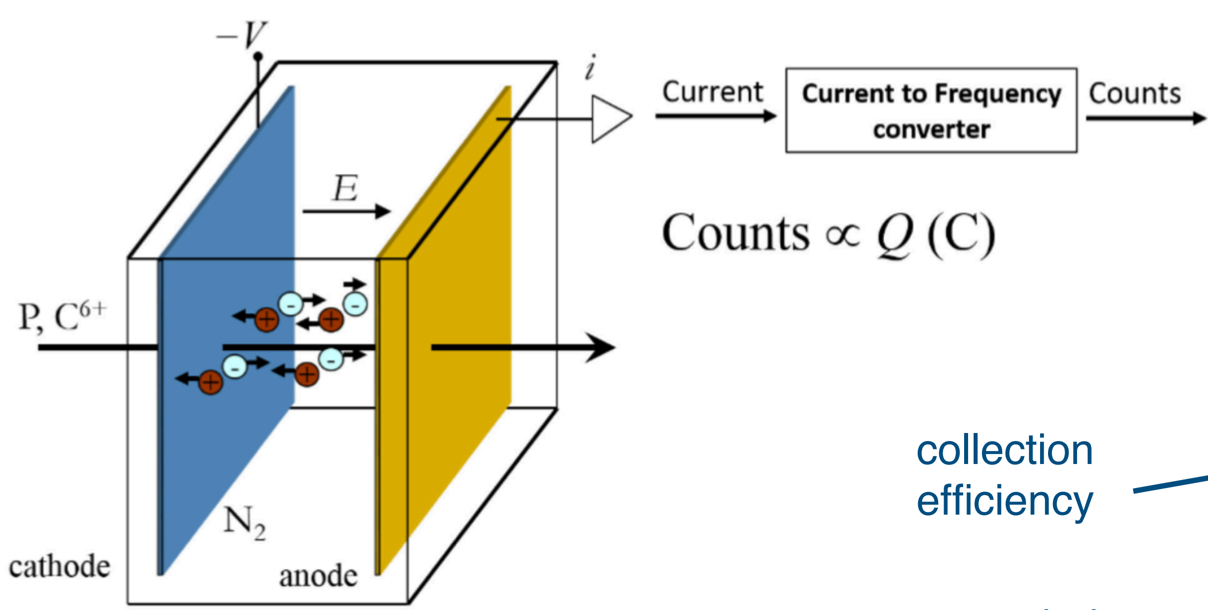
$$Q^2 = [D_p - D(x,y,z)]^2$$

where D_p is the prescribed dose (taken constant to atten the physical dose) and D(x,y,z) is the three-dimensional dose distribution of the Bragg curves, that are assumed to have a well-de ned shape and lateral profile for each depth.

The monitoring system







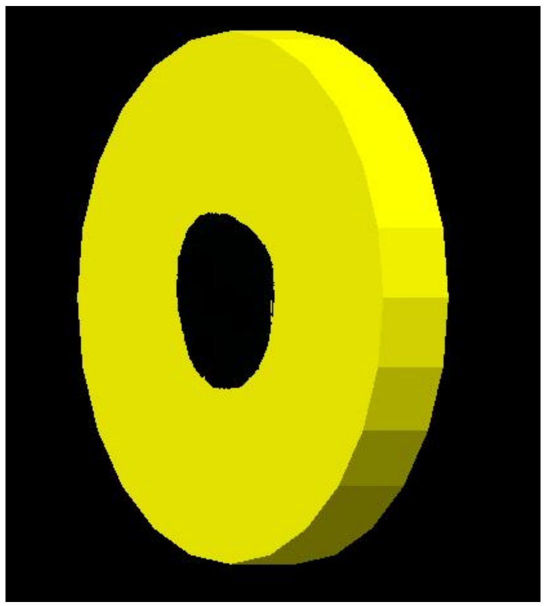
$$\text{Counts} \propto Q\ (\text{C})$$

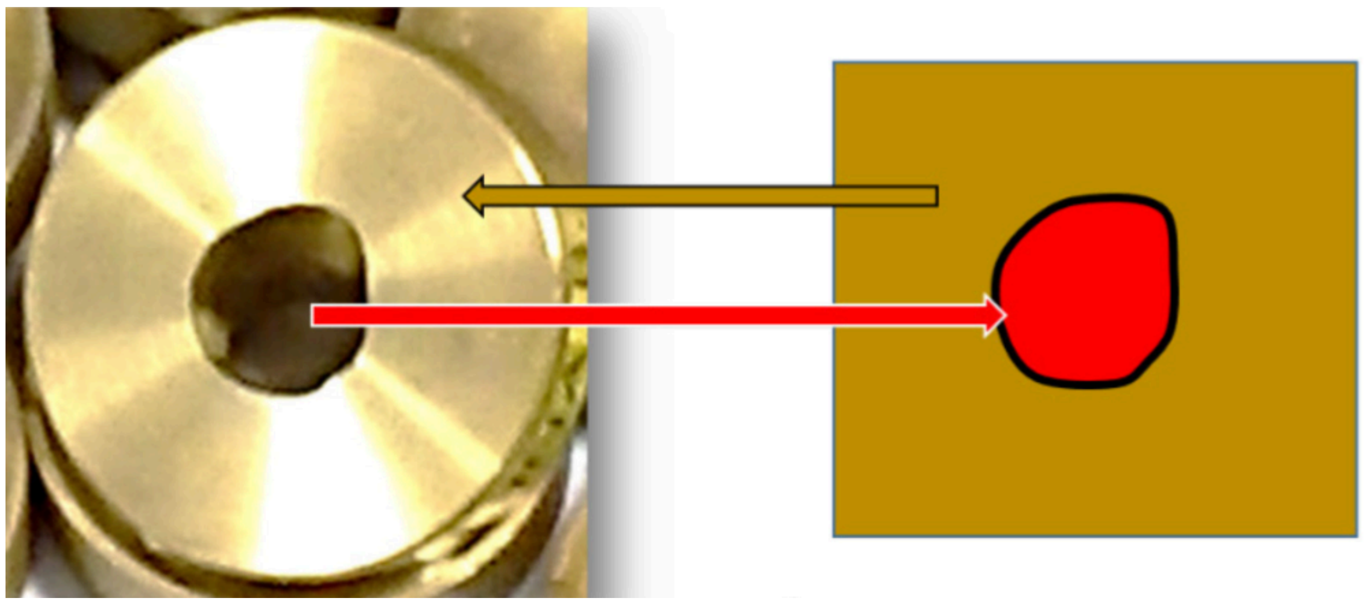
$$i = \varepsilon . \Phi . \frac{\left(\frac{S(E_p)}{\rho}\right)_g . \rho . x}{W(E)}$$

- collection efficiency (ε)
- beam flux (Φ)
- mass electronic stopping power ($S(E_p)/\rho$)
- gas density (ρ)
- mean free path in the gas (x)
- mean energy needed to produce an ion pair for a charged particle of energy *E* ($W(E)$)

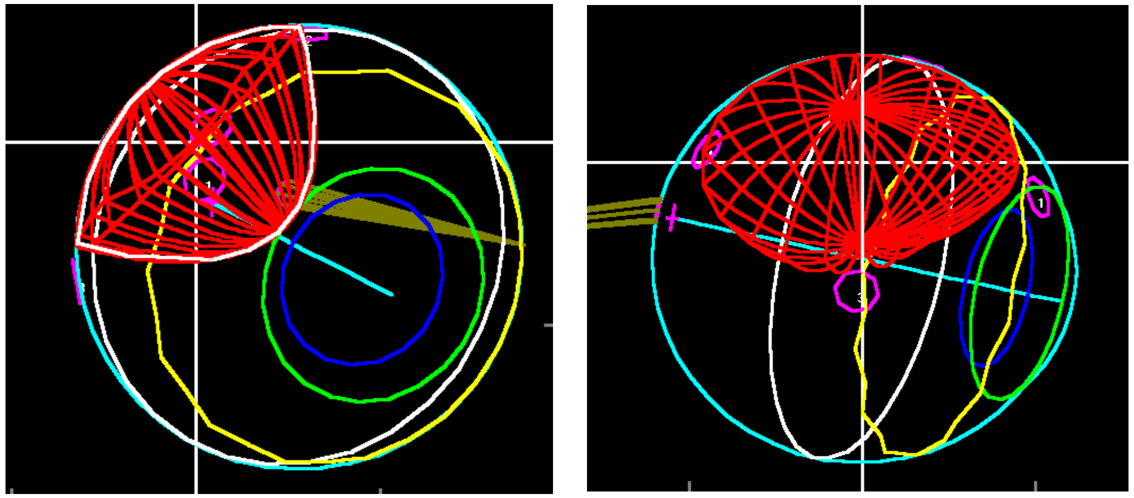
The final collimator system

MC simulation

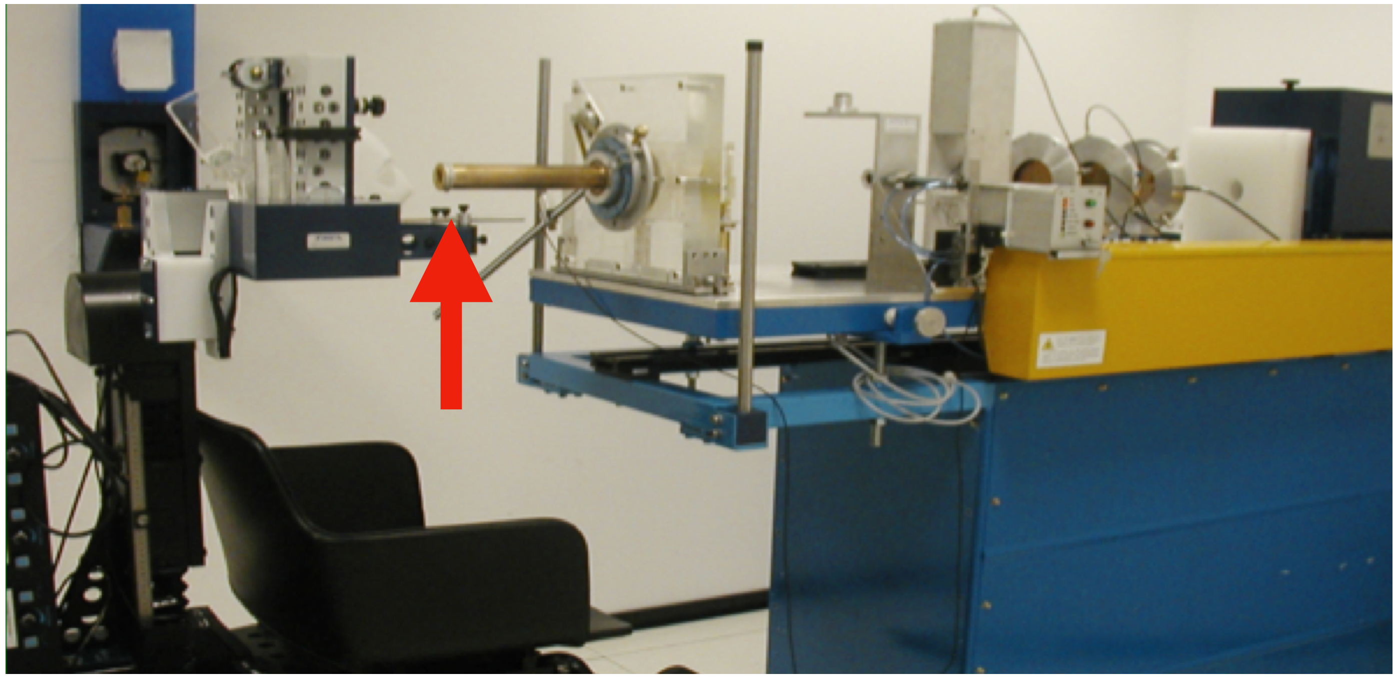




The collimator has a shape dependents by the particular tumour

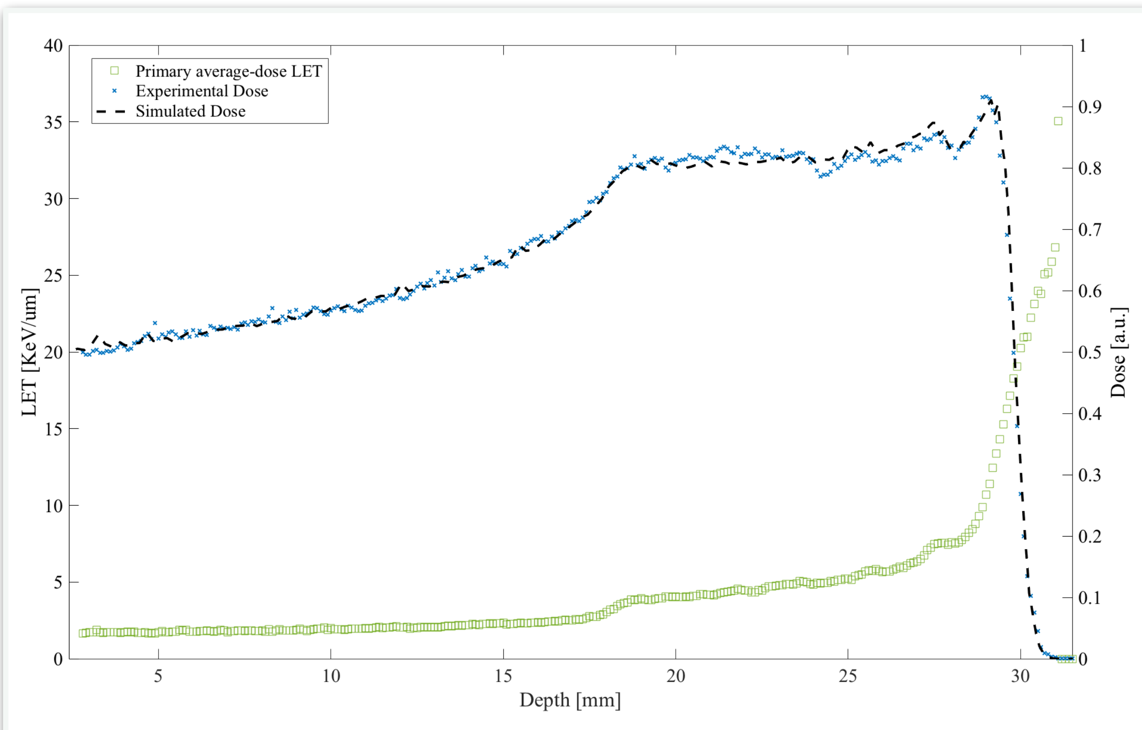


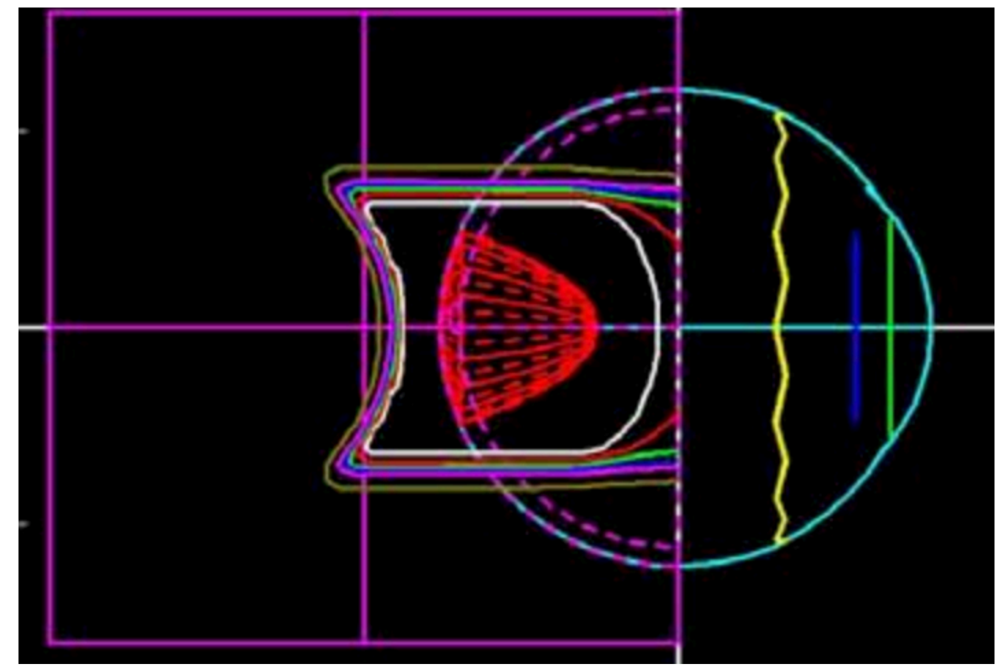
EyePlan - Varian



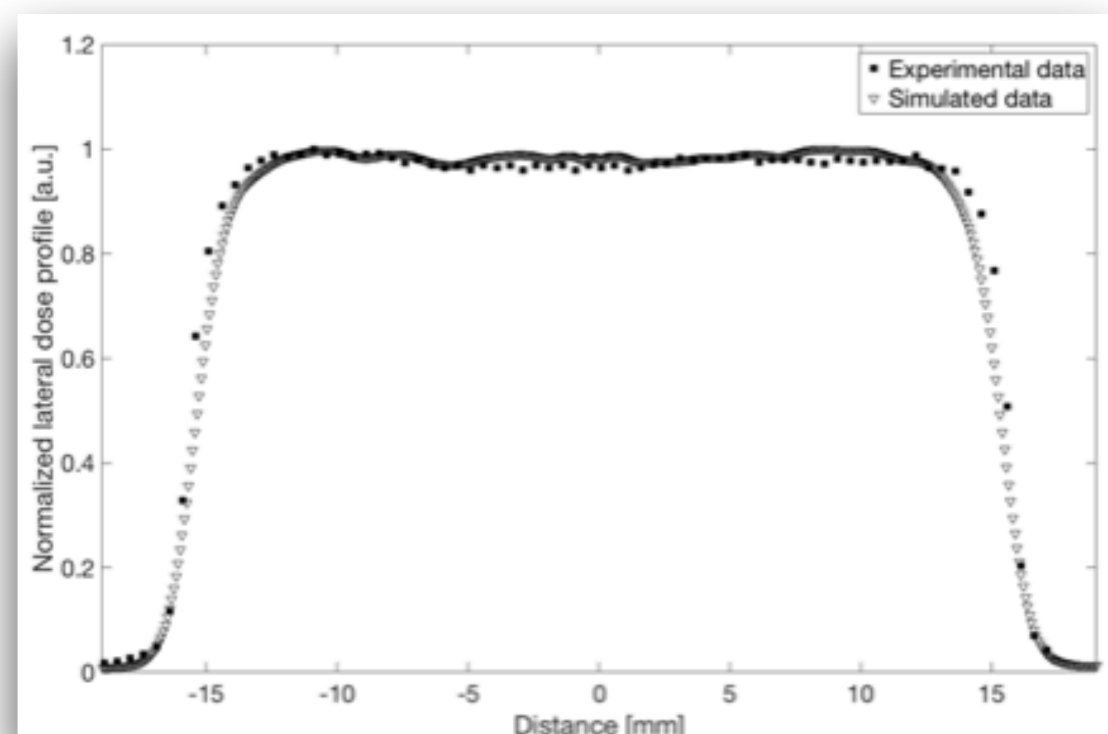
Treatment optimization

Depth-dose distribution





Lateral dose profile distribution



	Field size [mm]	$W_{95\%}$ [mm]	Penumbra [mm]	Homogeneity [%]	Symmetry [%]
Axis Y	20.82	16.64	1.6	2.8	104.3
Axis Z	13.25	9.89	1.5	0.9	101.5

	Advanced Markus [mm]	PTW diode [mm]
95% Prossimal	9.772	9.706
95% Distal	26.203	26.098
Range (90%)	26.380	26.188
Penumbra (80–20%)	0.488	0.629
SOBP width (95–95%)	16.431	16.391
Penumbra (90–10%)	0.799	0.898

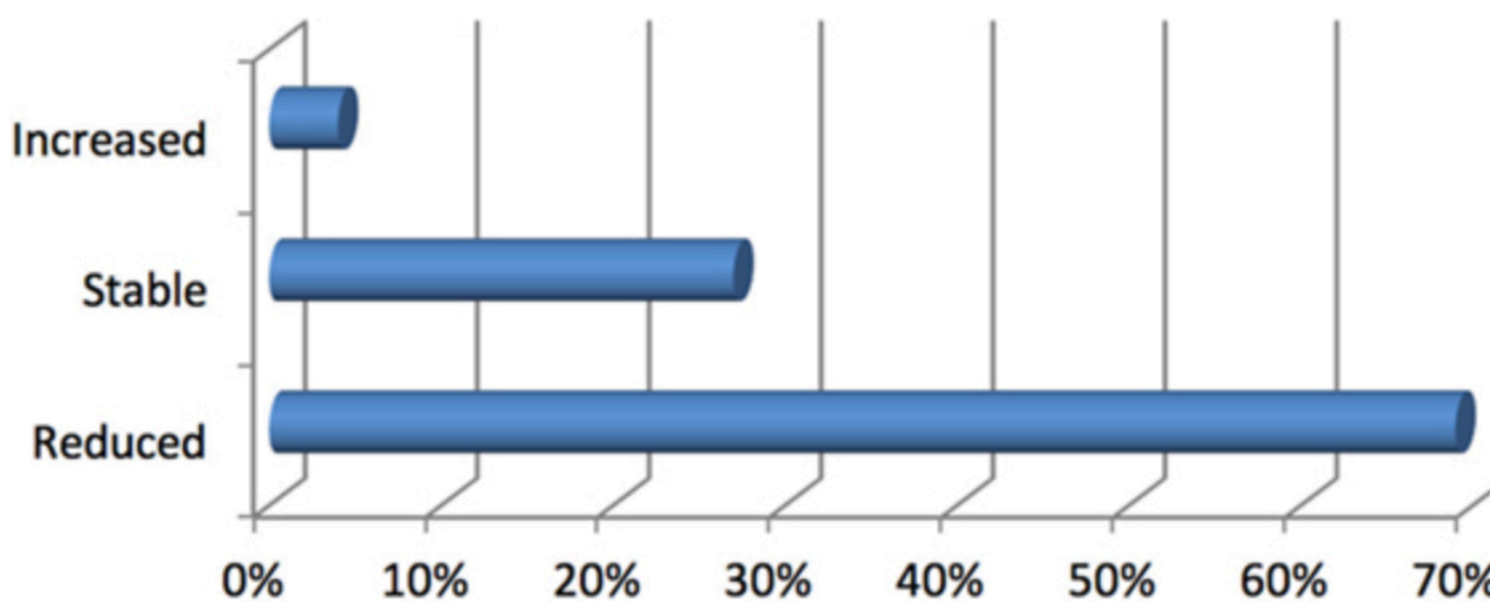
Patient statistics

Patients	
Sex	Male: 176 Female: 118
Age	Range between: 12-88 Median: 59
Diagnosis	Uveal melanoma: 252 pts Conjunctival melanoma: 5 pts Orbital rhabdomyosarcoma: 3 pts Orbital non-Hodgkin lymphoma: 4 pts Conjunctival papilloma: 1 pt Eyelid/periorbital carcinoma: 18 pts Other orbital tumors: 11 pt

Dead patients	4	
	Metastatis	3
	Other	1
Eye retention rate	92,68 %	
TOTAL SURVIVAL	95 %	
LOCAL CONTROL	97 %	

- First Patient treated on March 2002 (about 400 treated)

Tumor thickness



Some recent activities and R&D @LNS

- Monte Carlo simulations and Radiobiological damage extimation
- Beam profiling system
- Proton Boron Capture Therapy
- ELECTRODE

Geant4 - MC

Collaborator Login

GEANT4
A SIMULATION TOOLKIT

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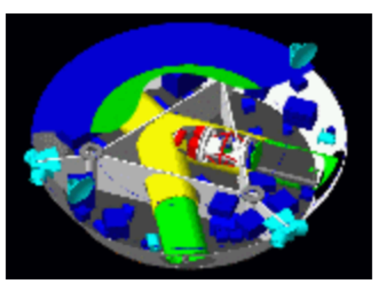
Overview

Geant4 is a toolkit for the simulation of the passage of particles through matter. Its areas of application include high energy, nuclear and accelerator physics, as well as studies in medical and space science. The three main reference papers for Geant4 are published in Nuclear Instruments and Methods in Physics Research A 506 (2003) 250-303, IEEE Transactions on Nuclear Science 53 No. 1 (2006) 270-278 and Nuclear Instruments and Methods in Physics Research A 835 (2016) 186-225.

Applications

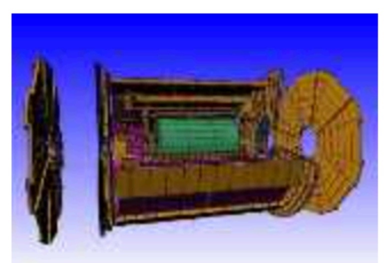
A sampling of applications, technology transfer and other uses of Geant4

User Support



Getting started, guides and information for users and developers

Publications



Validation of Geant4, results from experiments and publications

Collaboration

Who we are: collaborating institutions, members, organization and legal information

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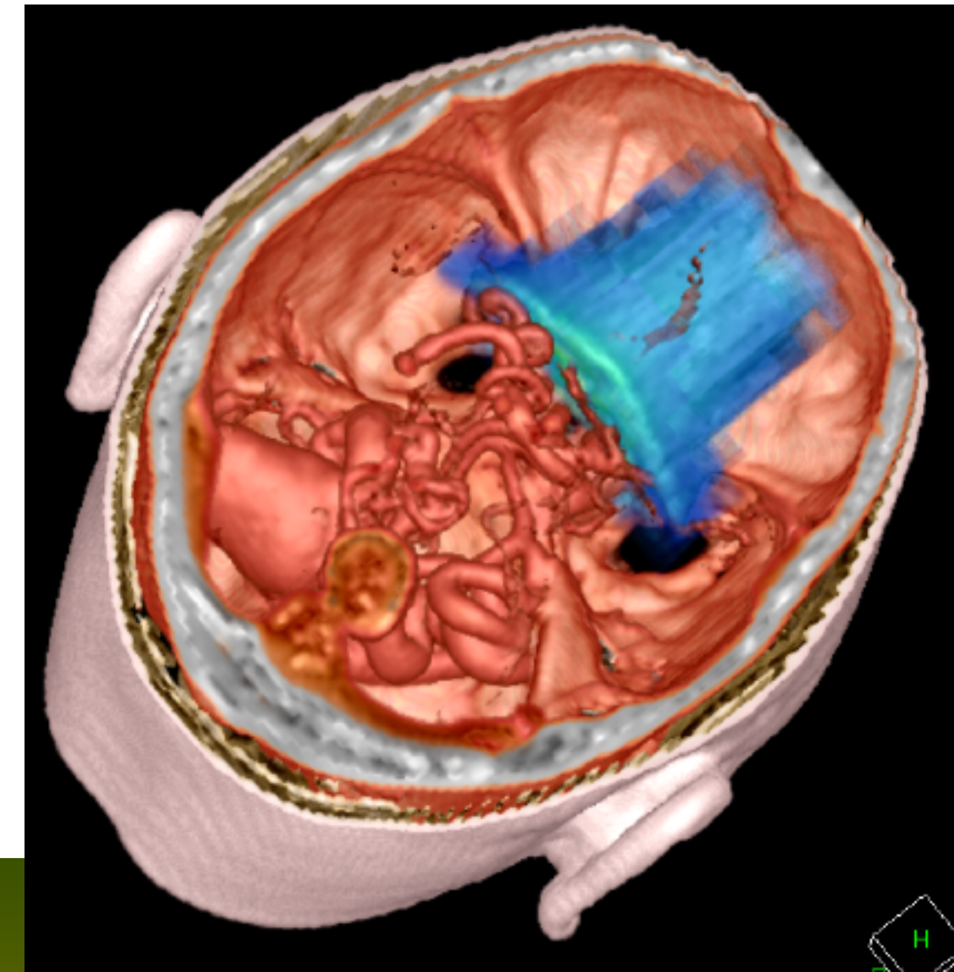
News

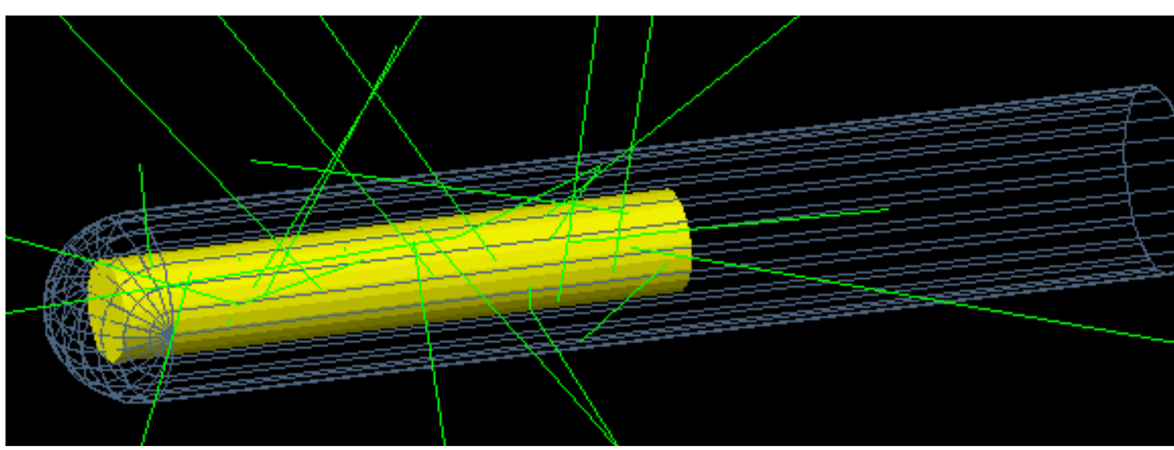
- *29 Jun 2018*
  Release 10.5-BETA is available from the BETA Download area.
- *25 May 2018*
  Patch-02 to **release 10.4** is available from the Download area.
- *12 Mar 2018*
  2018 planned developments
- *20 Oct 2017*
  Patch-03 to release 10.3 is available from the source archive area.

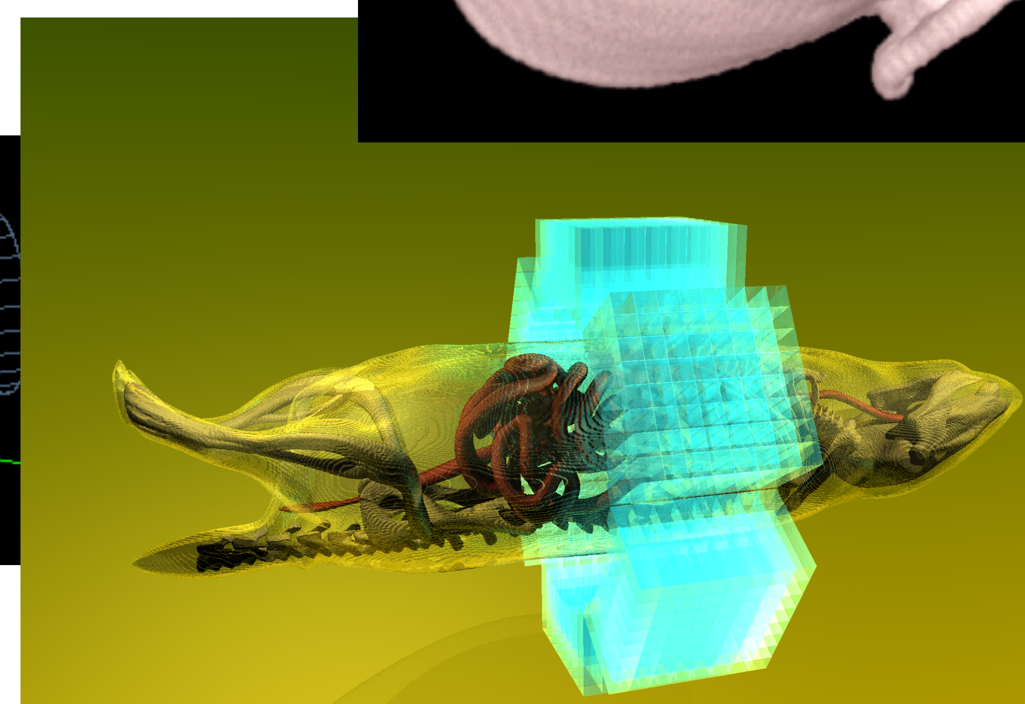
Geant4 - MC

Major use cases

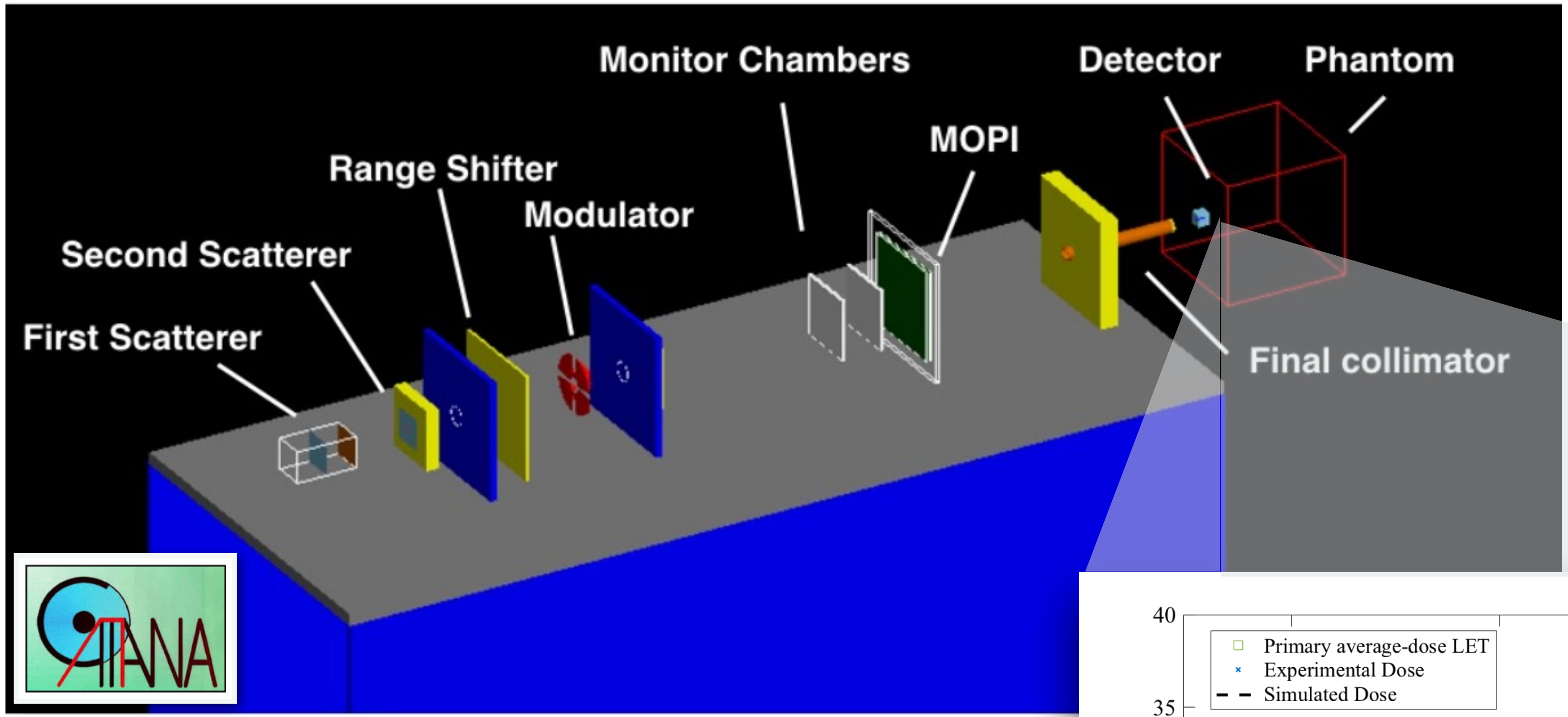
- Beam therapy
- Brachytherapy
- Imaging
- Irradiation study
- Nuclear medicine and radioisotopes

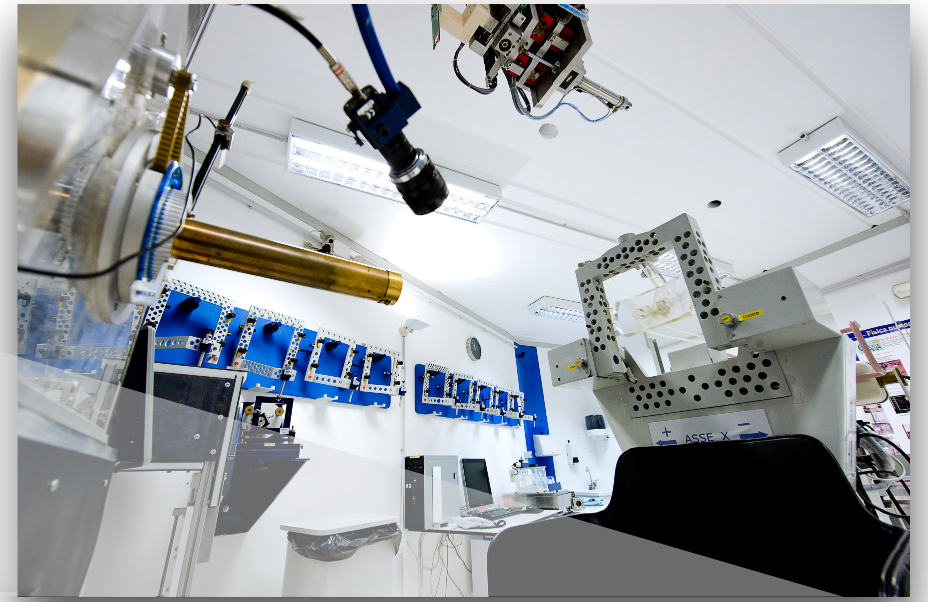


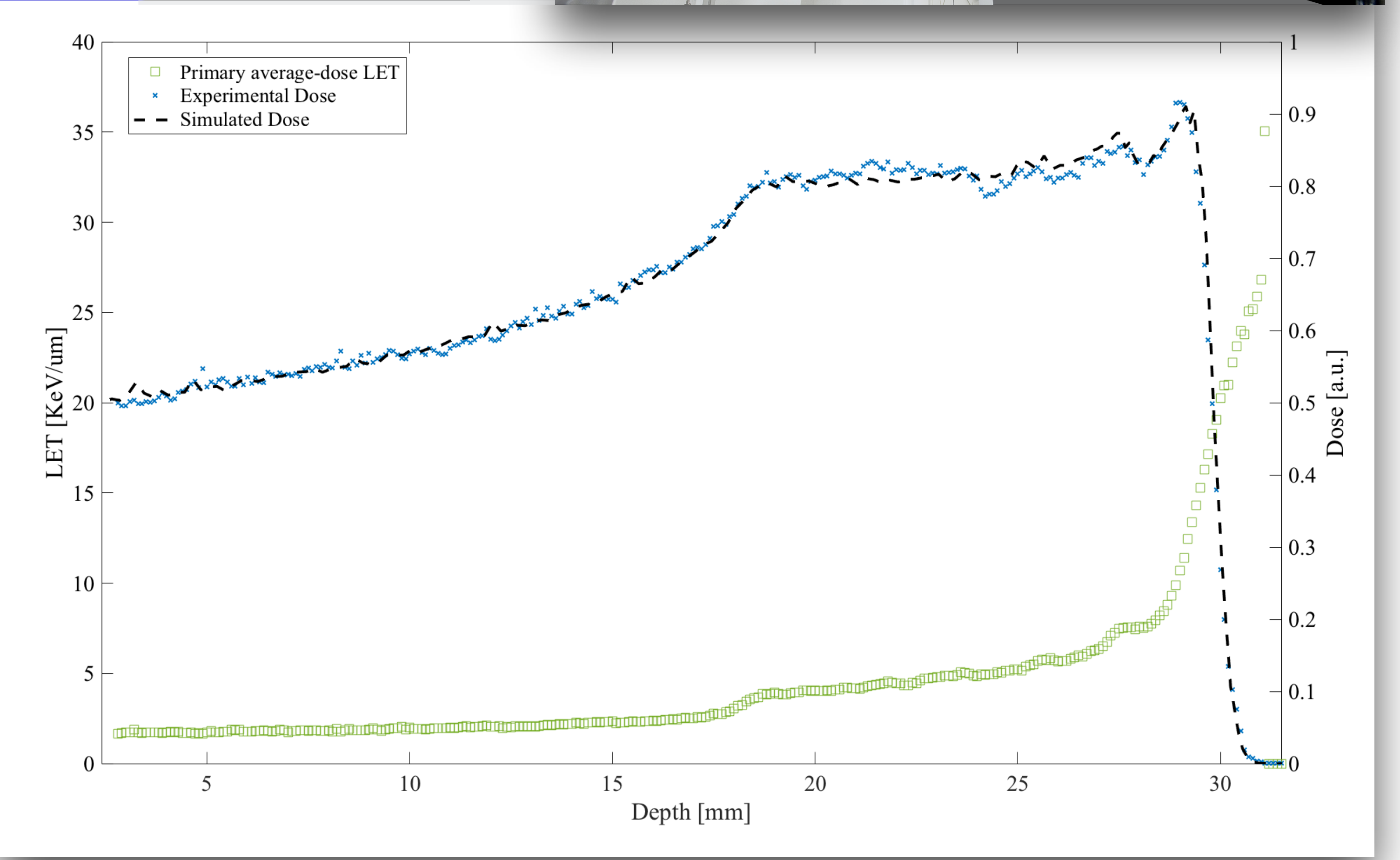


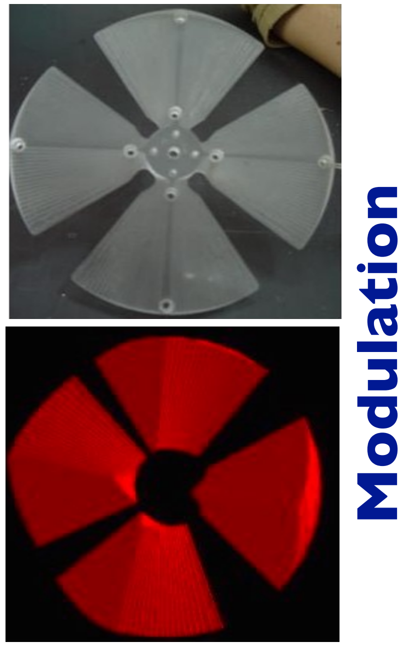


PassiveProtonBeamLine

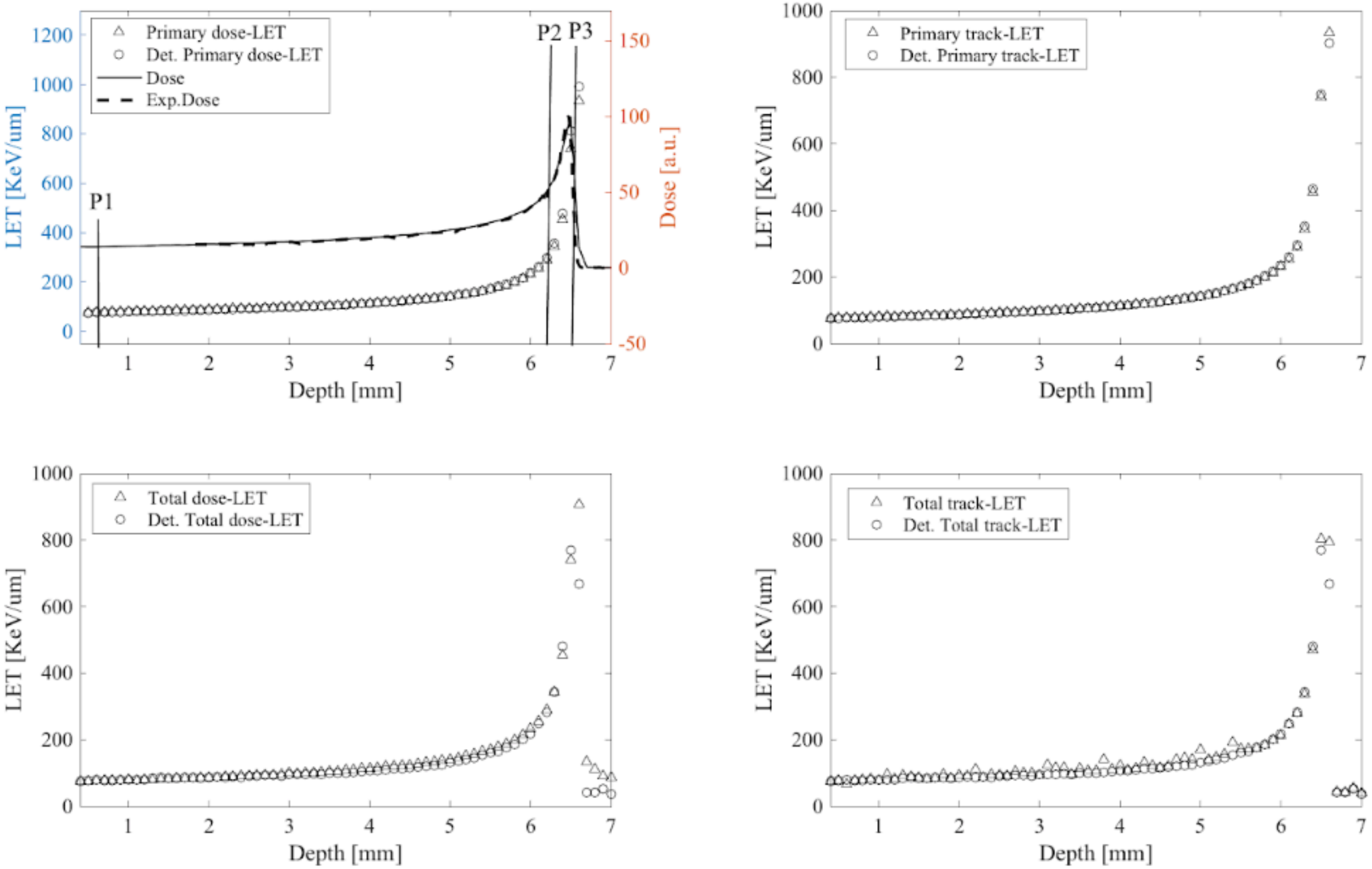








LET calculation



New LET class based on G4EmCalculator:

LET track

$$\bar{L}_T = \frac{\sum_{i=1}^{N} L_i l_i}{\sum_{i=1}^{N} l_i} \qquad \bar{L}_T^{Total} = \frac{\sum_{j=i}^{n} \left[\sum_{i=1}^{N} L_i l_i\right]_j}{\sum_{j=i}^{n} \left[\sum_{i=1}^{N} l_i\right]_j}$$

LET dose

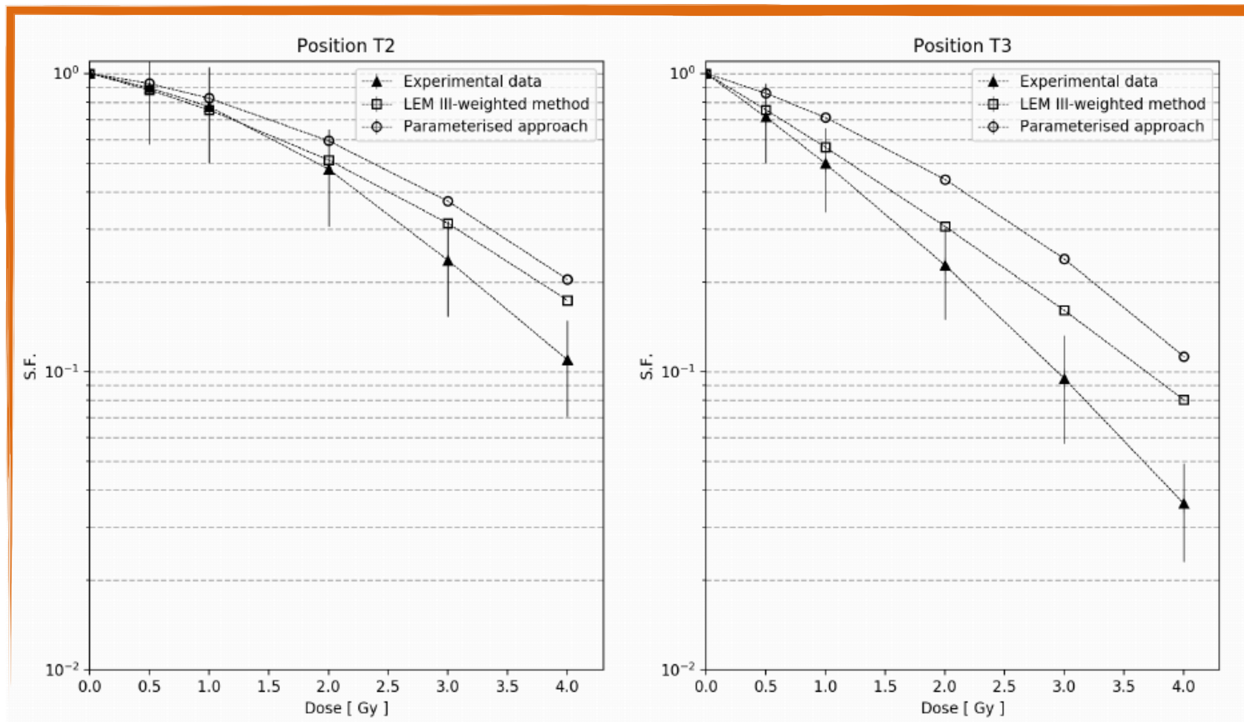
$$\bar{L}_D = \frac{\sum_{i=1}^{N} L_i \varepsilon_i}{\sum_{i=1}^{N} \varepsilon_i} \qquad \bar{L}_D^{Total} = \frac{\sum_{j=i}^{n} \left[\sum_{i=1}^{N} L_i \varepsilon_i\right]_j}{\sum_{j=i}^{n} \left[\sum_{i=1}^{N} \varepsilon_i\right]_j}$$

M.G. Cortes et al."A critical study of different Monte Carlo scoring methods of dose averaged linear-energy- transfer maps calculated in voxelized geometries irradiated with clinical proton beams",Phys. Med. Biol. 60 (2015) 2645-2669

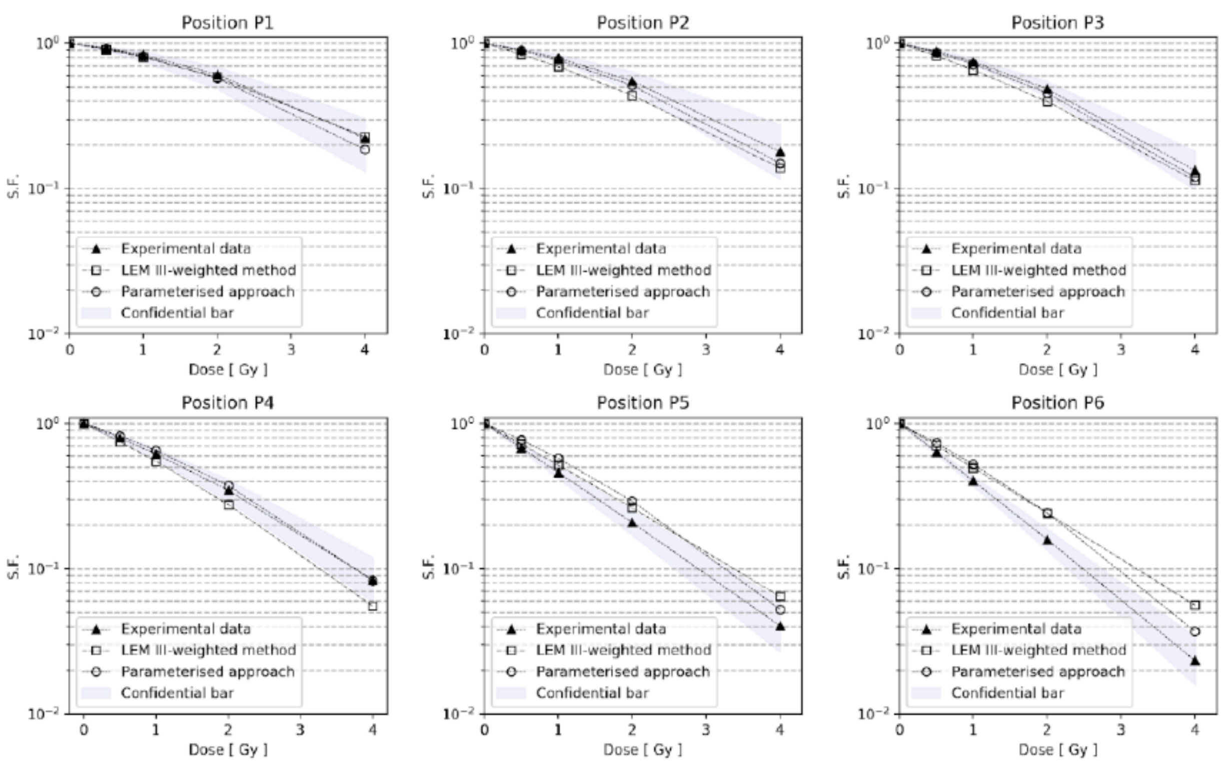
A comparison with experimental data is already ongoing

RBE calculation

DU145

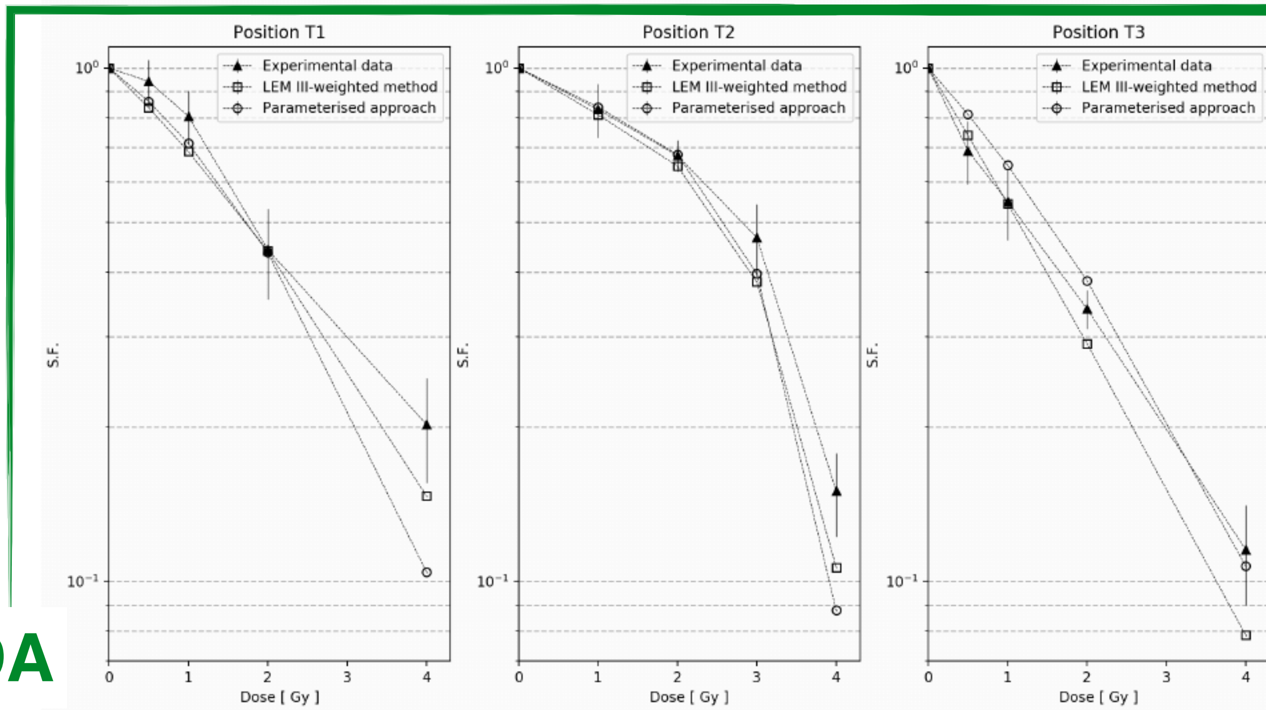


U87

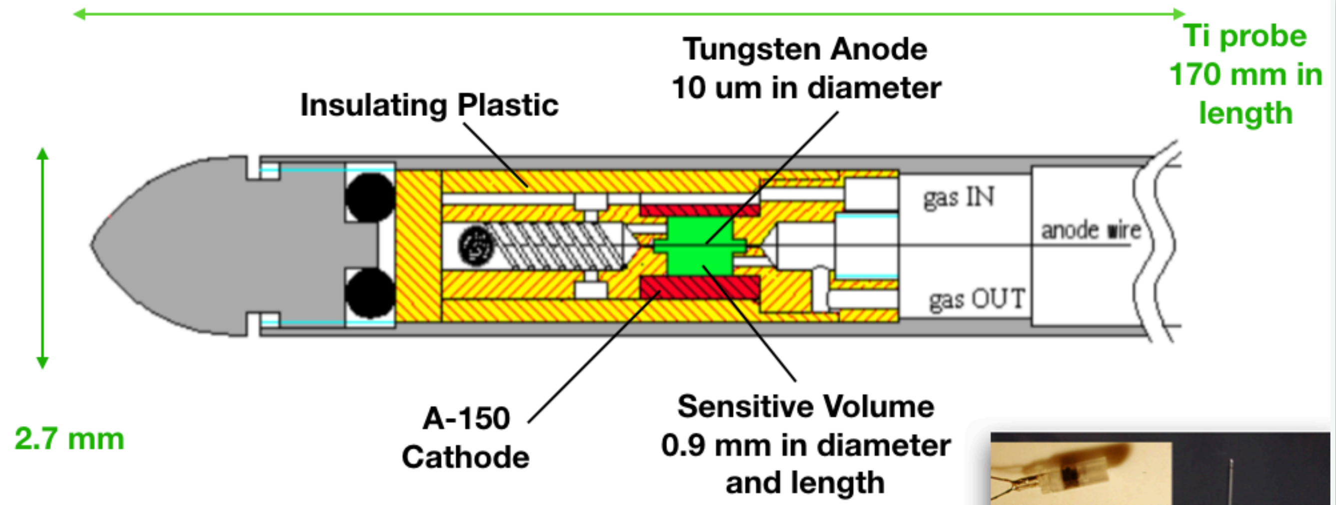


G. Petringa, "Estimation and validation of radibiologically and clinically relebant quantities using Geant4-based Monte Carlo simulations", Physica Medica, Jan 2019

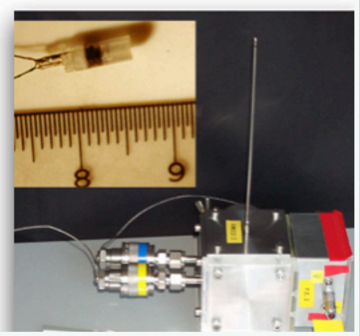
MDA



Microdosimeter detectors



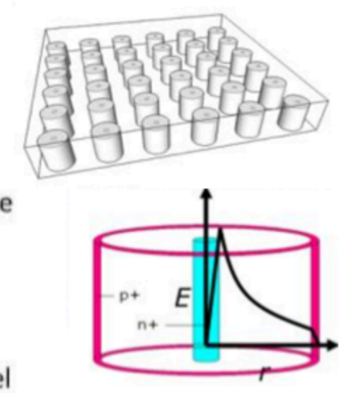
The mini-TEPC has a cylindrical sensitive volume 0.9 mm in diameter and height, surrounded by a 0.35 mm cathode wall, and a 0.2 mm-thick aluminium sleeve for a total external diameter of 2.7 mm. The detector is inserted inside a 160-mm-long aluminium sleeve. The mini-TEPC operates in gas-flow modality and it is filled with propane gas. Individual pulses from the preamplifier are fed into a NIM/CAMAC/PC based data acquisition system for analogue and digital signal processing.

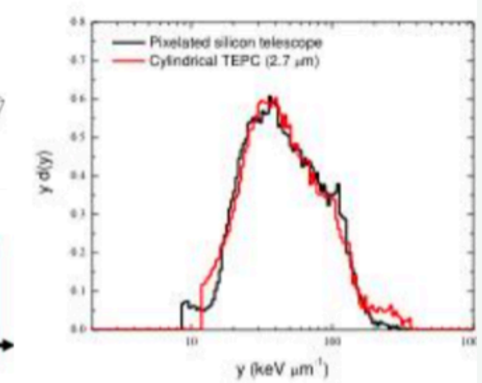


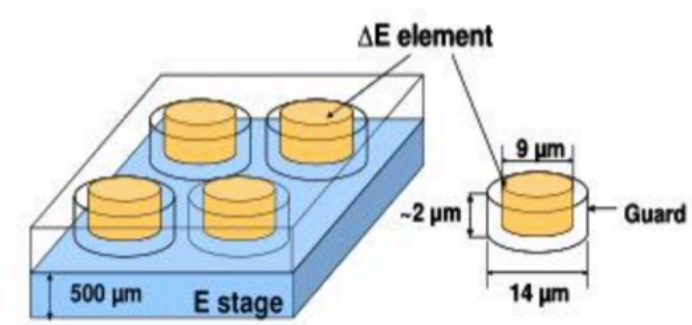
Mini-TEPCs are miniaturized gas-filled proportional counters, simulating tissue volumes of micrometric size and density of $1 g/cm^3$ by means of a tissue-equivalent gas at low pressure.

Silicon detectors →

- ✓ constituted by a matrix of cylindrical ΔE elements (about 2 µm in thickness) and a single residual-energy E stage (500 µm in thickness);
- ✓ the nominal diameter of the ΔE elements is about 9 µm and the width of the pitch separating the elements is about 41 µm.
- ✓ more than 7000 pixels are connected in parallel to give an effective sensitive area of about 0.5 mm^2.
- ✓ minimum detectable energy is limited to about 20 keV by the electronic noise.
- ✓ the ΔE stage acts as a microdosimeter and the E stage plays a fundamental role for assessing the full energy of the recoil-protons, thus allowing to perform a LET-dependent correction for tissue-equivalency.

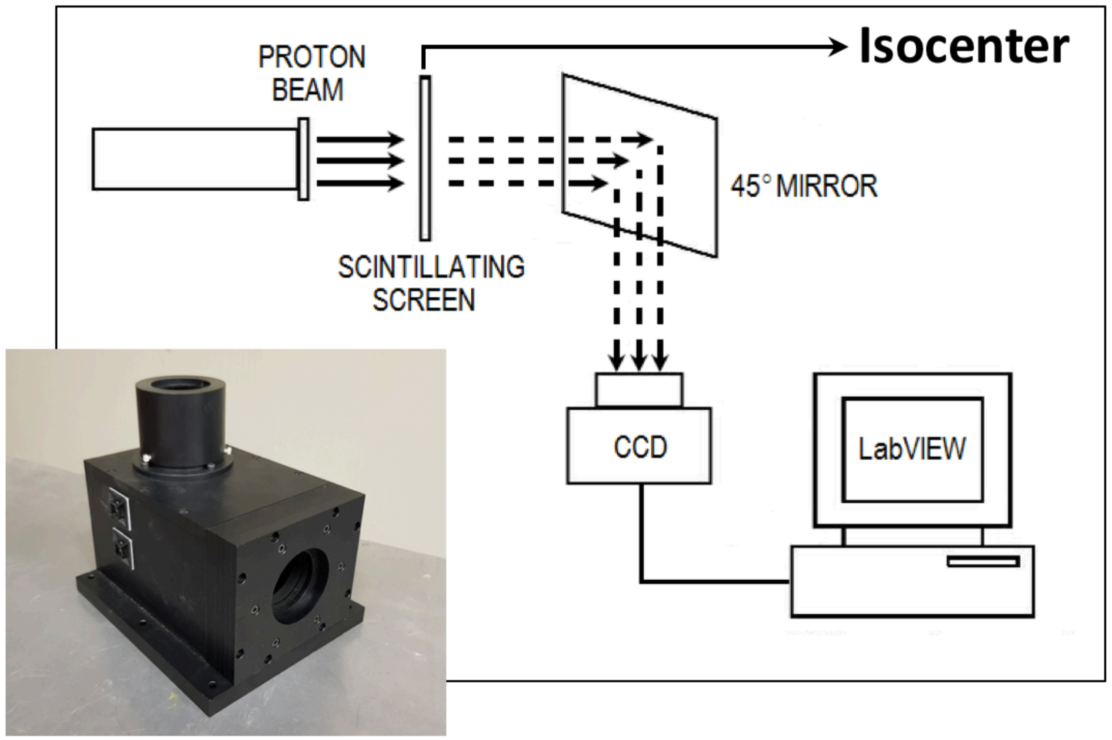






- Monte Carlo simulations and Radiobiological damage extimation
- Beam profiling system
- Proton Boron Capture Therapy
- ELECTRODE

System for on-line beam profiling



Prototype

LabView dedicated software for real-time data acquisition and processing. Suitable MATLAB routines allow for data analysis:

- Radiation field (FWHM)
- Lateral penumbras
- Field Ratio
- Flatness and Asymmetry
- 2-D contour plot

Acquisition and processing time: max 30 sec

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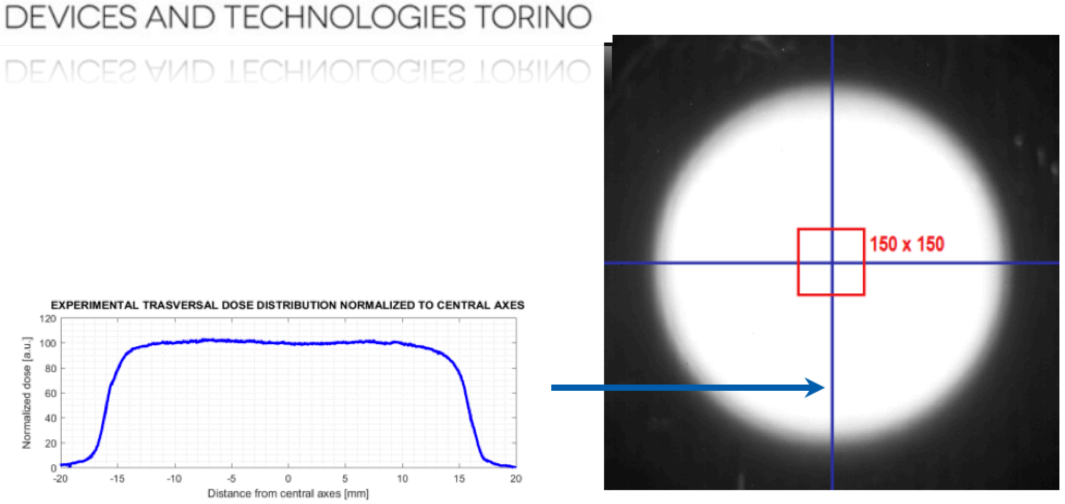
System very preliminary characterization in terms of:

- Response dependence on the dose rate and the number of the acquired frames (ROI)
- Short-term stability



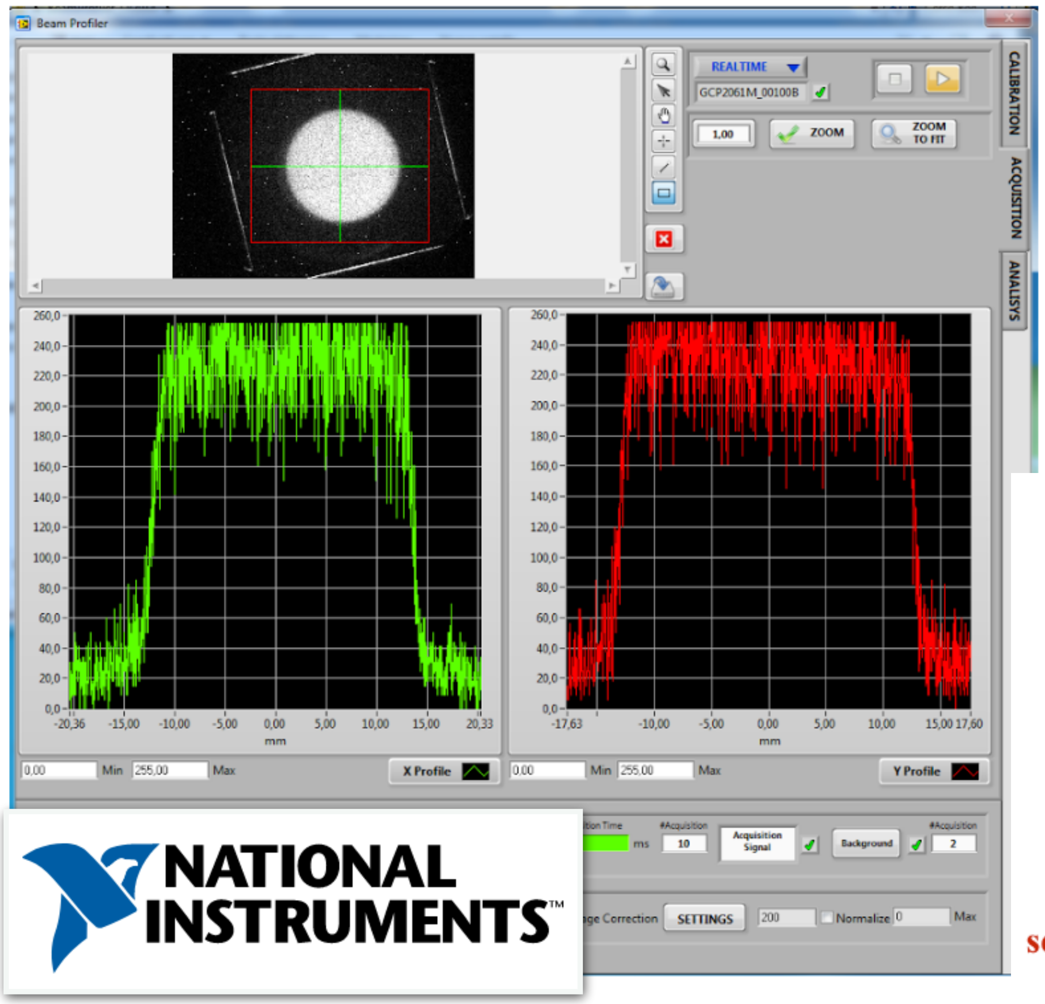
References

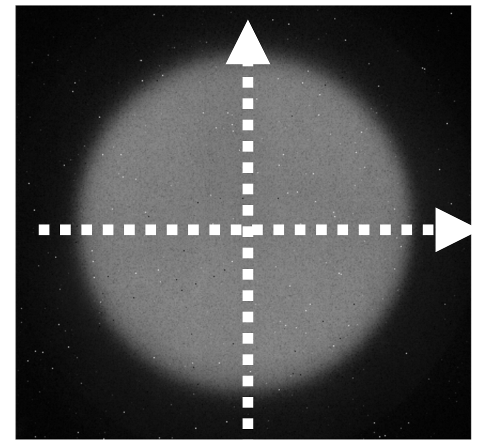
Cirrone G.A.P. et al., A Fast Monitoring system for Radiotherapeutic Proton Beams Based on Scintillating Screens and a CCD camera, IEEE Transaction on Nuclear Science, vol. 51, n. 4, 2003

Cirrone G.A.P. et al., Deep Characterization of o Fast Monitoring System for Radiotherapeutic Proton Beams Based on Scintillating Screens and a CCD camera, IEEE Nuclear Science Symposium, 2004

System for on-line beam profiling

Real time Analysis Software

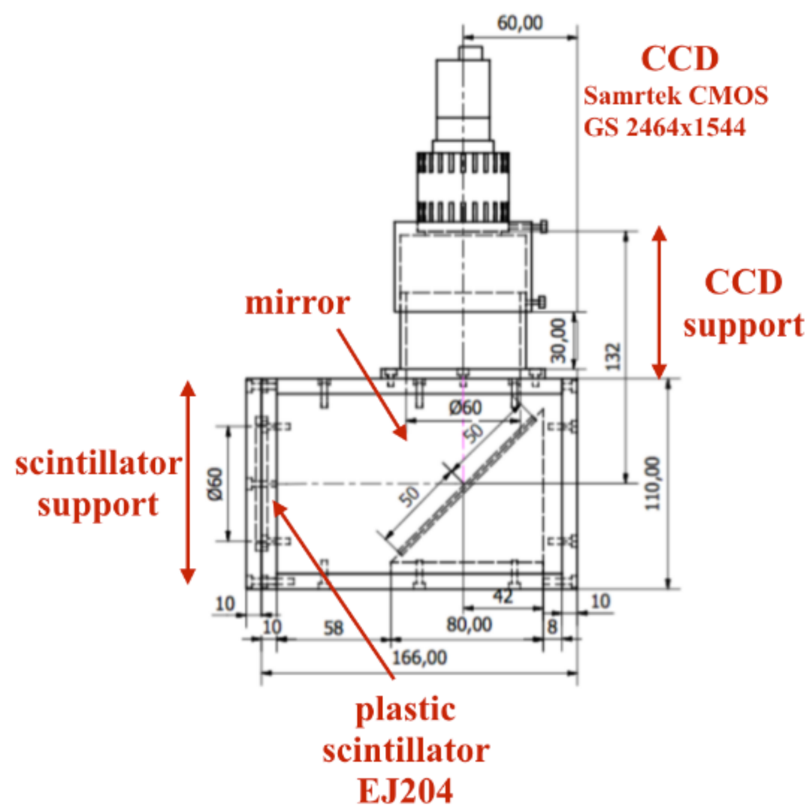


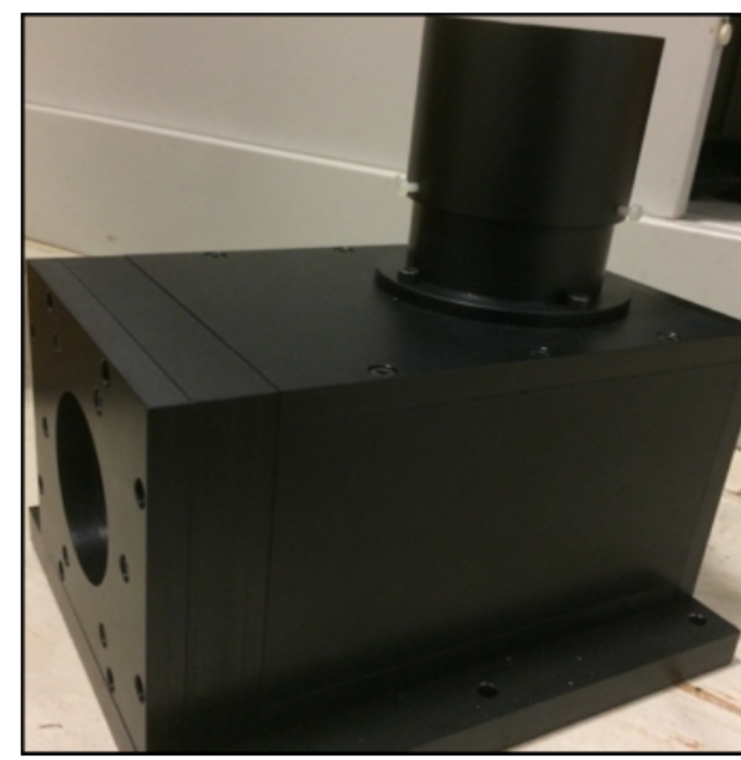


Light-tigh box (166X125X110mm) with supports for scintillators and CCD camera

CCD CMOS GCP2061M (resolution 2064x1544 pixels)

EJ-204 plastic scintillators

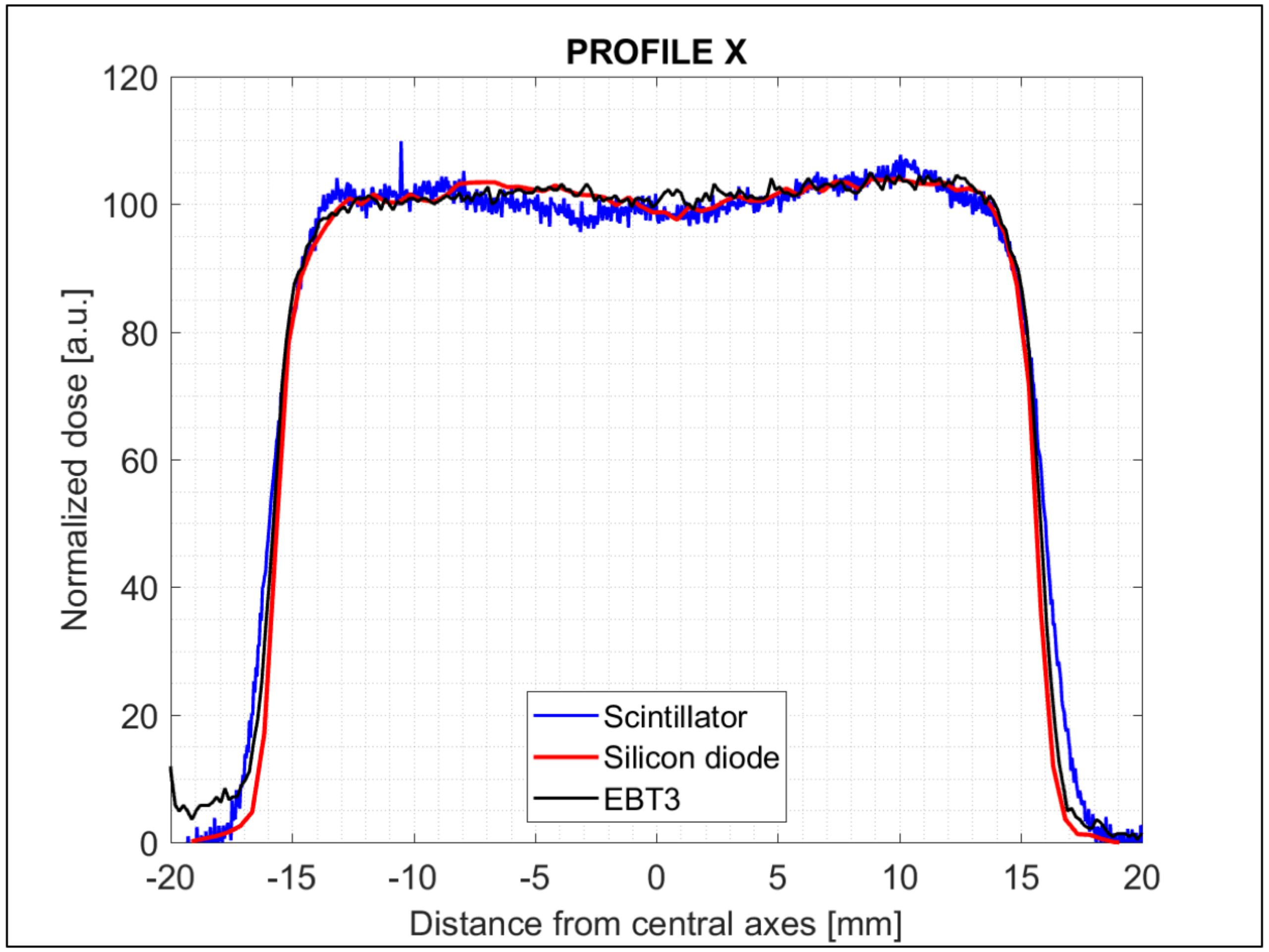




Real time data analysis:

- **Image processing**
- **Spatial Calibration**
- **Filtering**
- **Penumbra calculation**

Characterisation @CATANA



Beam Energy: 62 MeV protons

Position: Isocenter (17 cm from the beam exit)

Collimator diameter: 30 mm

Exposure time: 30 ms

- EBT3 radiochromic film (thickness 0.2 mm)
- Silicon diode
- INFN scintillator-based beam profiling system (thickness 1 mm)

Profile X	EBT3 Radiochromic film	Silicon diode	Scintillator-based system
FWHM [mm]	31.665	31.655	31.970
90/50 Ratio	0.930	0.937	0.921
Left Penumbra [mm]	1.220	1.250	1.575
Right Penumbra [mm]	1.185	1.210	1.530
Flatness [%]	3.802	3.813	4.798
Asymmetry [%]	105.430	105.512	106.502

- Monte Carlo simulations and Radiobiological damage extimation
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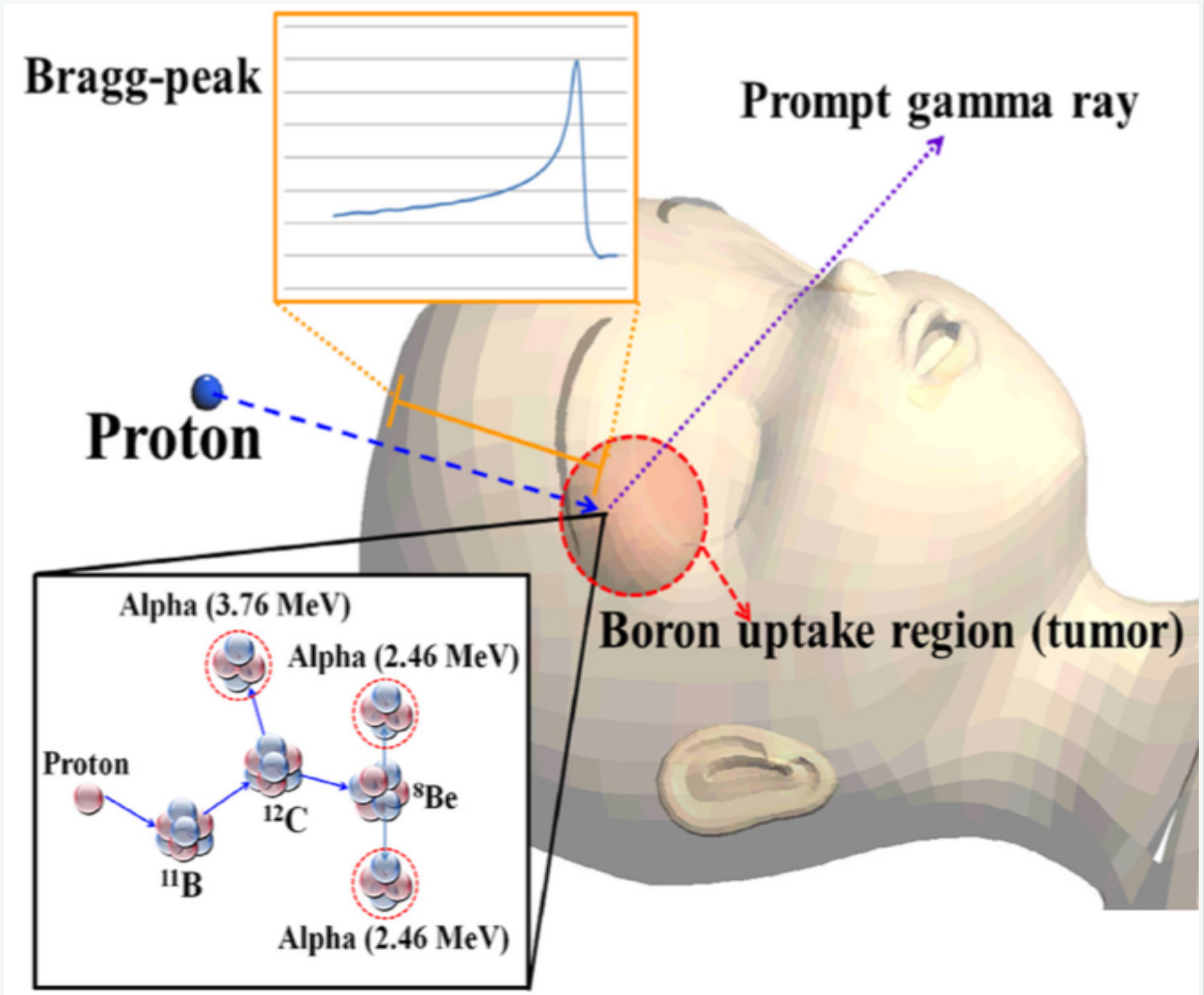
A proton enhancement technique

NEPTUNE

Nuclear process driven Enhancement of Proton Therapy UNravEled



Reaction channels

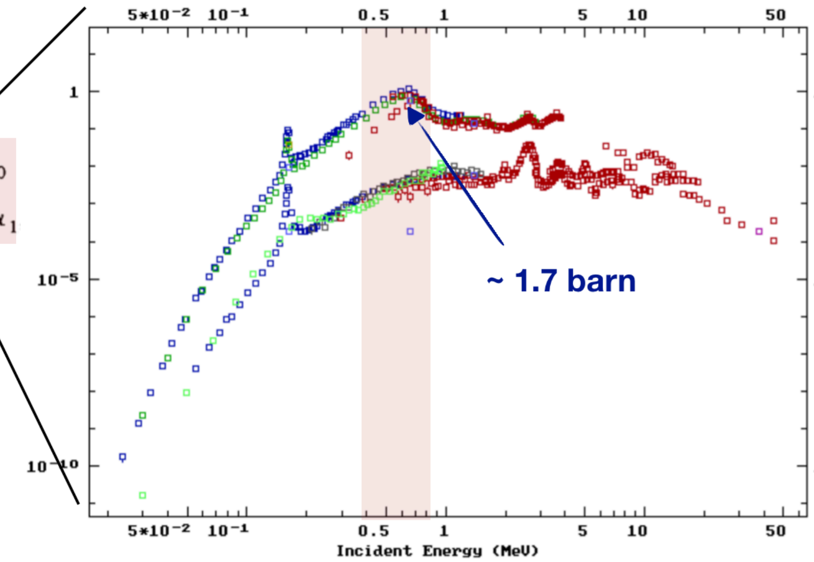
$^{11}B + p \rightarrow {}^{12}C^* \rightarrow {}^{8}B + \alpha_0 \rightarrow \alpha_{01} + \alpha_{02} + \alpha_0$

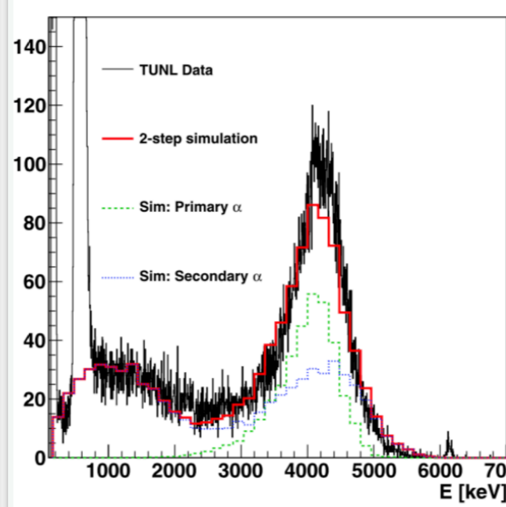
$^{11}B + p \rightarrow {}^{12}C^* \rightarrow {}^{8}B^* + \alpha_1 \rightarrow \alpha_{11} + \alpha_{12} + \alpha_1$

$^{11}B + p \rightarrow {}^{12}C^* \rightarrow \alpha_2 + \alpha_3 + \alpha_4$

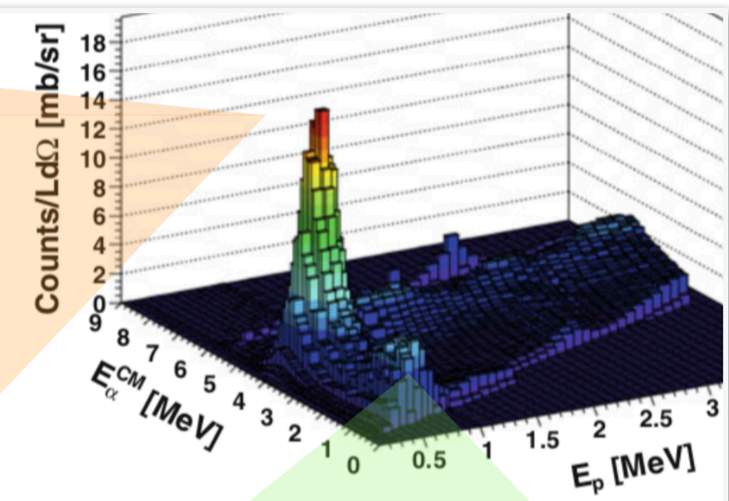
$^{11}B + p \rightarrow {}^{12}C^* \rightarrow {}^{12}C + \gamma$

The reaction exit channels have a maximum cross section of 157 ub for incident proton energy under 1 MeV





M.H.Sikora,H.R.Weller,A new evaluation of the 11B(p,a)aa reaction rates, J. Fusion Energy (2016) 35:538



Resonances

E_p= 0.150 MeV

E_p= 0.675 MeV

E_p= 2.64 MeV

A proton enhancement technique

nature.com > scientific reports > articles > article

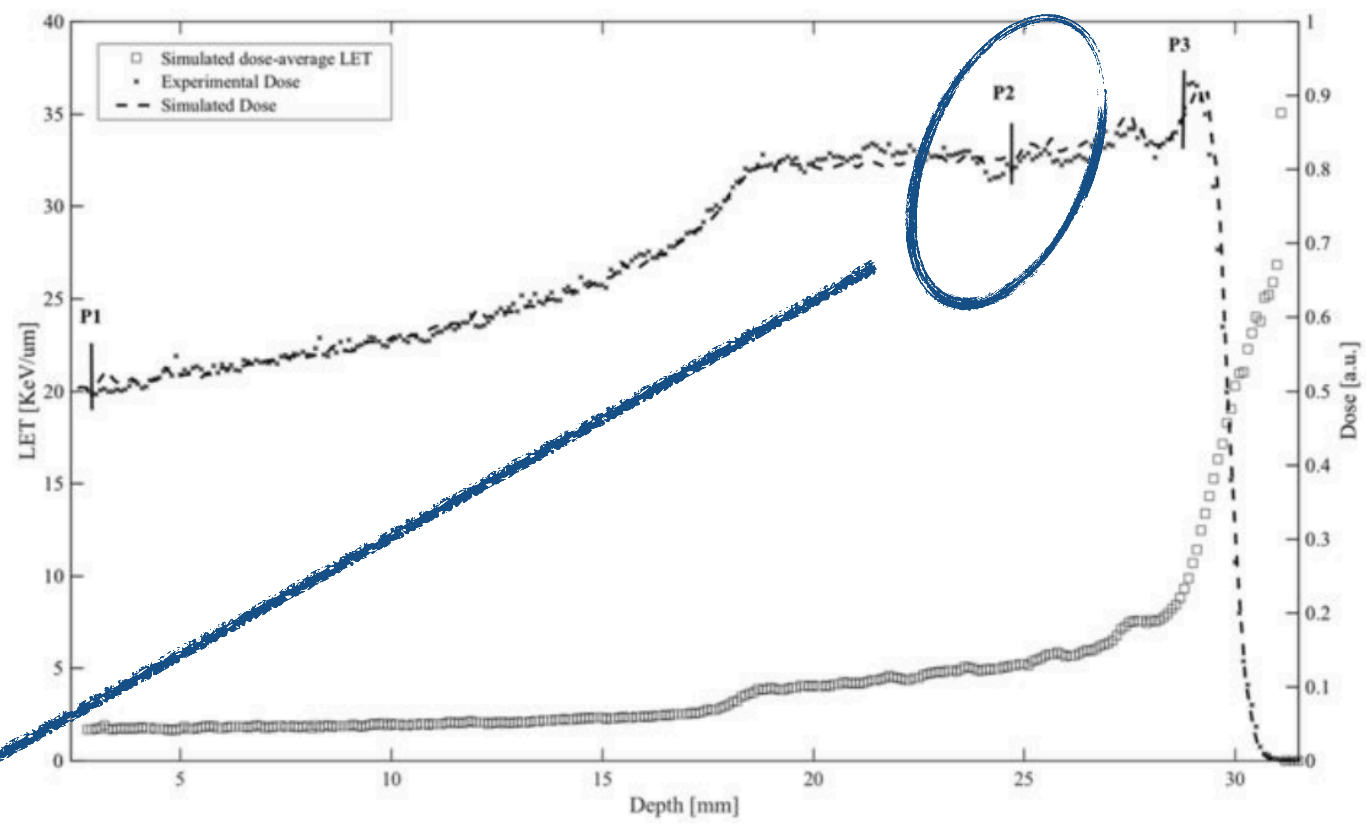
SCIENTIFIC REPORTS

Article | OPEN | Published: 18 January 2018

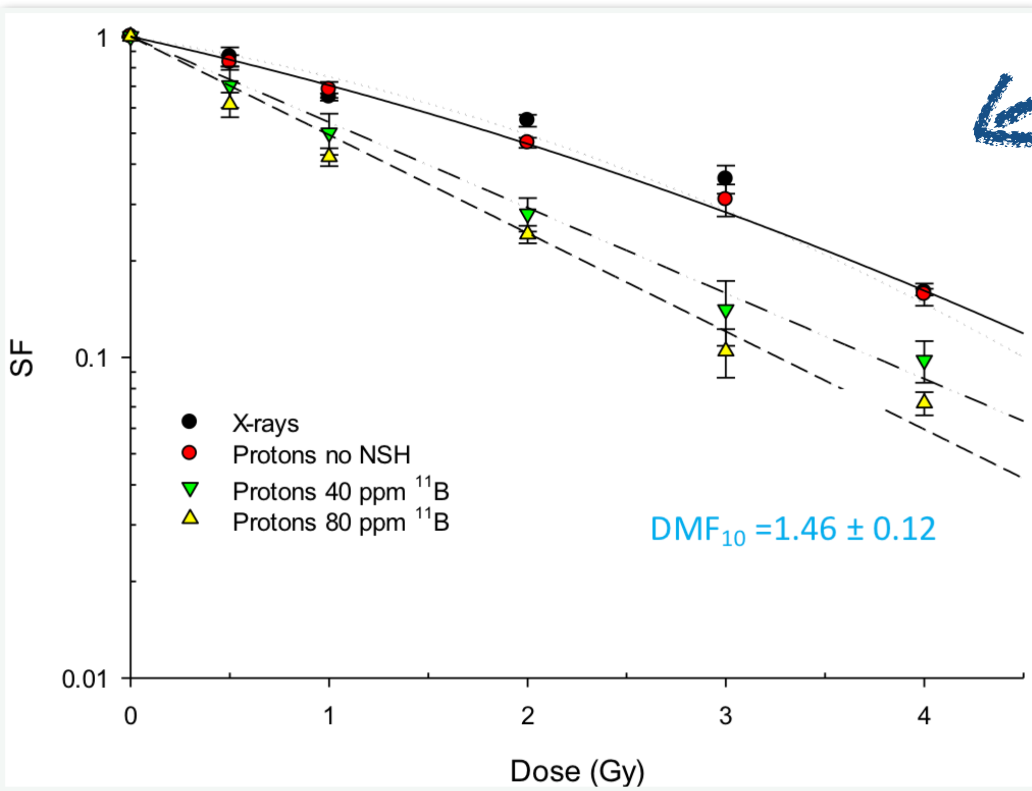
First experimental proof of Proton Boron Capture Therapy (PBCT) to enhance protontherapy effectiveness

G. A. P. Cirrone, L. Manti, D. Margarone, G. Petringa, L. Giuffrida, A. Minopoli, A. Picciotto, G. Russo, F. Cammarata, P. Pisciotta, F. M. Perozziello, F. Romano, V. Marchese, G. Milluzzo, V. Scuderi, G. Cuttone & G. Korn

Scientific Reports **8**, Article number: 1141 (2018) | Download Citation



Irradiation @MID-SOBP



DMF_{10} (RBE_{10})= 1.46 ± 0.12

	α (Gy^{-1})	β (Gy^{-2})
X ray irradiation	0.222 ± 0.062	0.064 ± 0.014
Proton irradiation in the absence of BSH	0.314 ± 0.022	0.035 ± 0.007
Proton irradiation with 40 ppm ^{11}B	0.614 ± 0.069	—
Proton irradiation with 80 ppm ^{11}B	0.705 ± 0.033	—

- Monte Carlo simulations and Radiobiological damage extimation
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- Proton Boron Capture Therapy
- ELECTRODE

A new in-vivo dosimeter

ELECTRODE (**E**xterna**L** non-invasiv**E** approa**C**h for radio**T**he**R**apy d**O**s**E** monitoring)

The idea is based on measure the net charge **unbalance** in a patient undergoing radiotherapy

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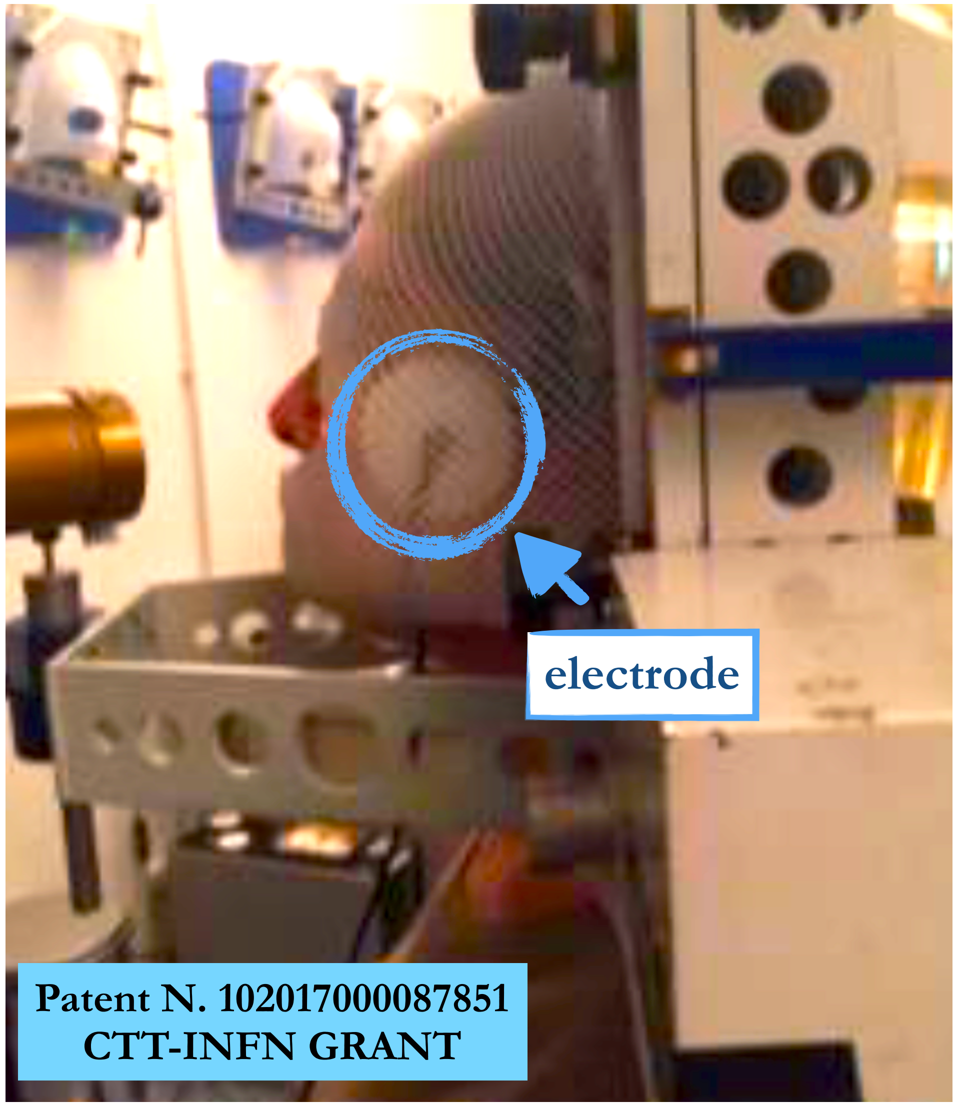
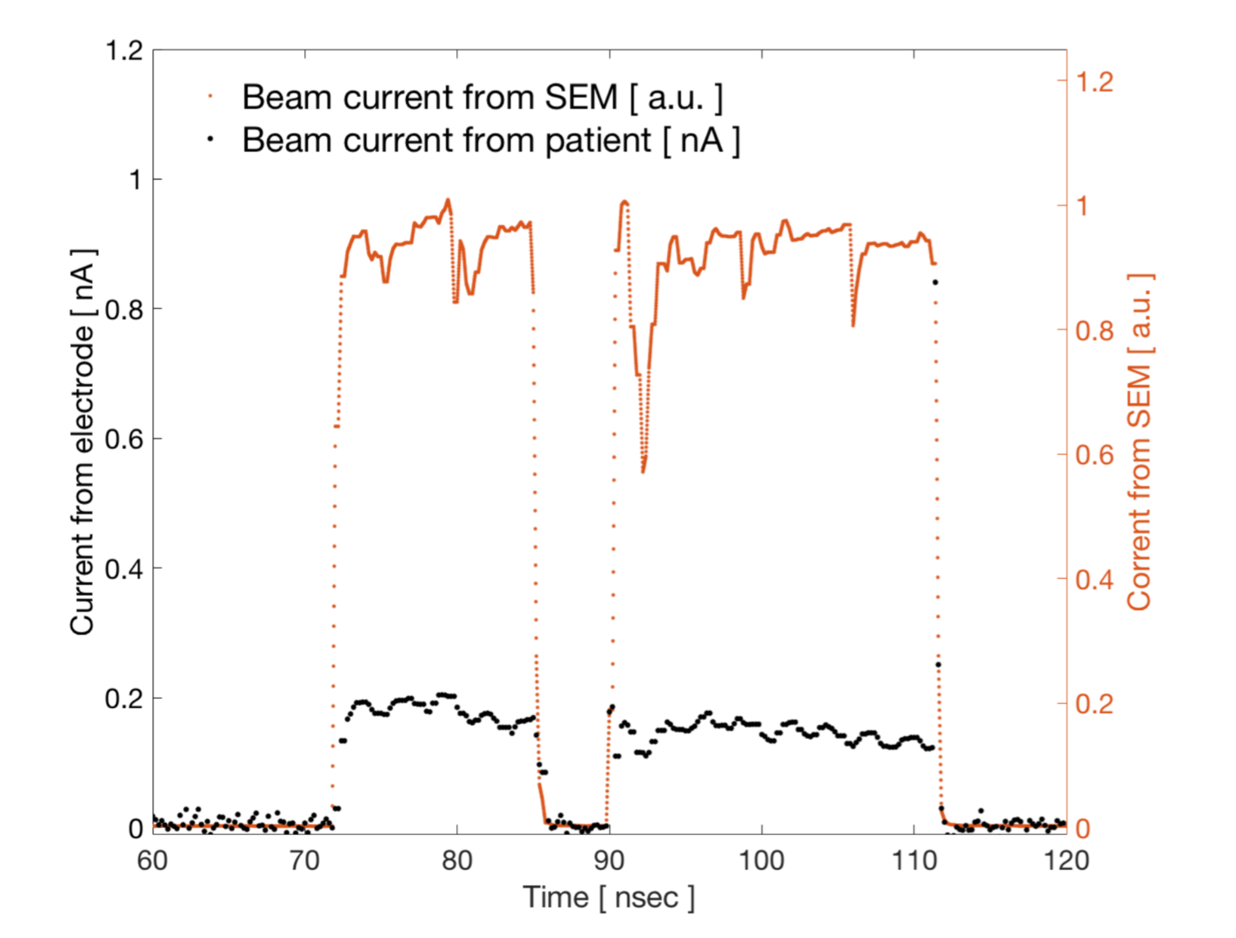
DEVICES AND TECHNOLOGIES TORINO



Adopted configuration during a proton therapy treatment

- on-line treatment monitoring
- not biased
- outside the irradiation field



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Any questions?