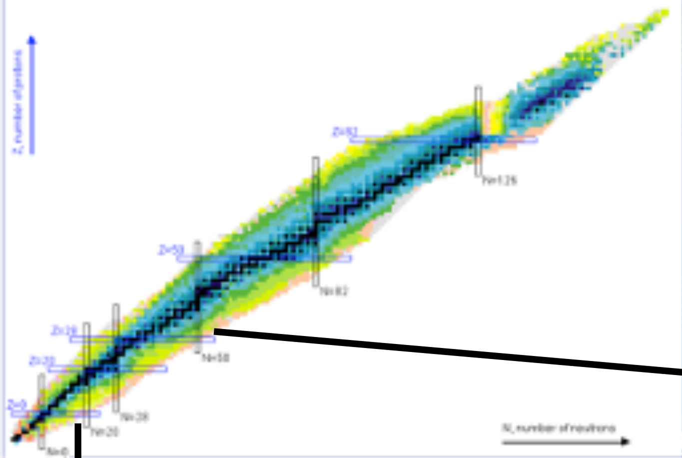
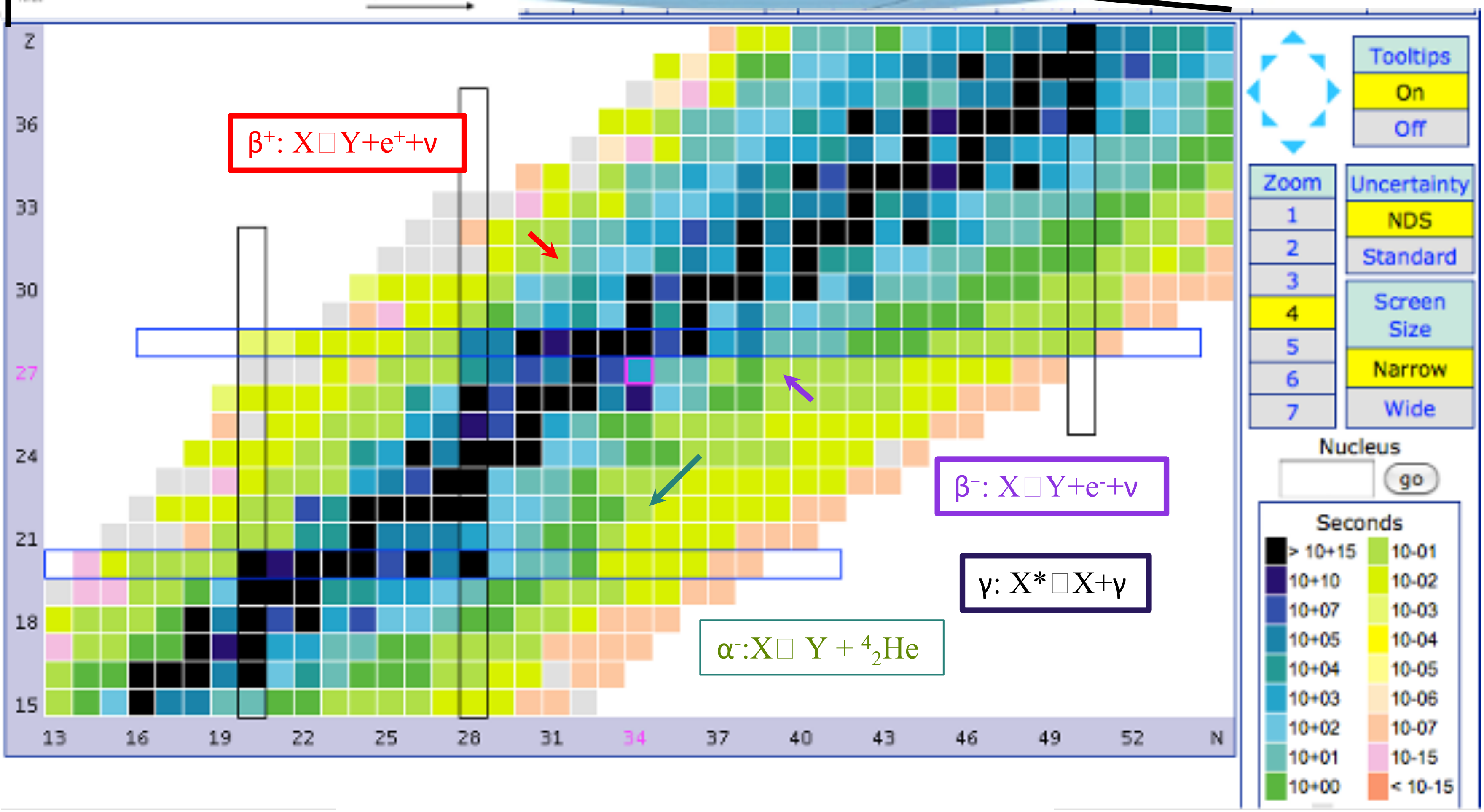
Particle Physics for Leading Edge Medicine

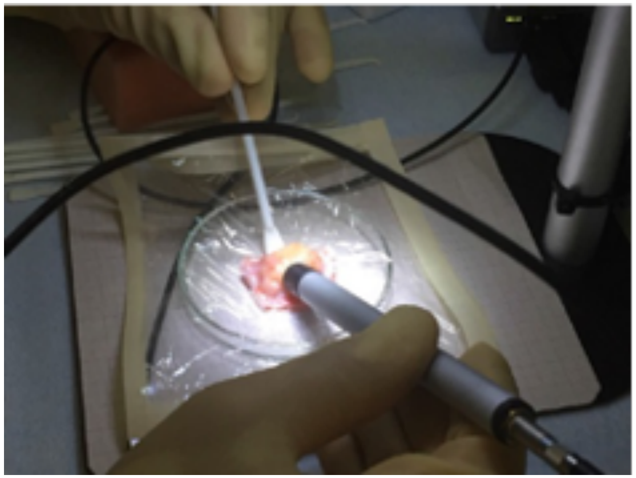
Riccardo Faccini, Univ. «La Sapienza» and INFN Rome

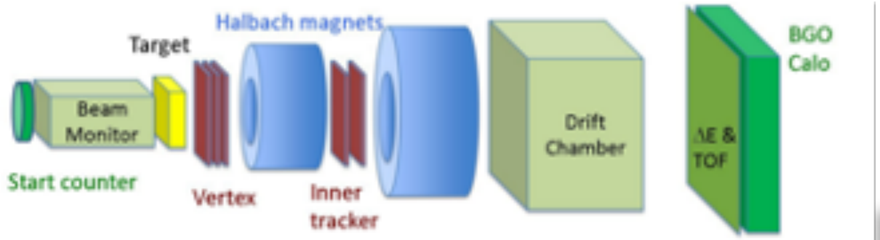
Key ingredients: Nuclear Physics





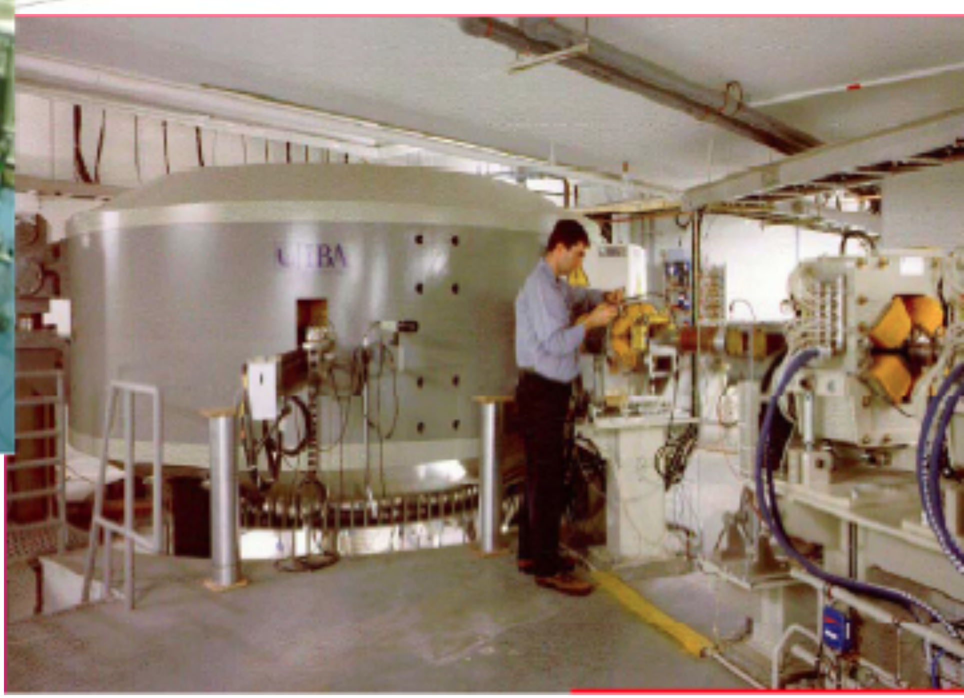
Key Ingredients: detectors





Low Energy Radiation detection

Key Ingredients: accelerators



protons/ions acceleration

- 10-30 MeV for radio-isotopes production
- up to 400 MeV/u for radiotherapy

Key Ingredients: Data Analysis

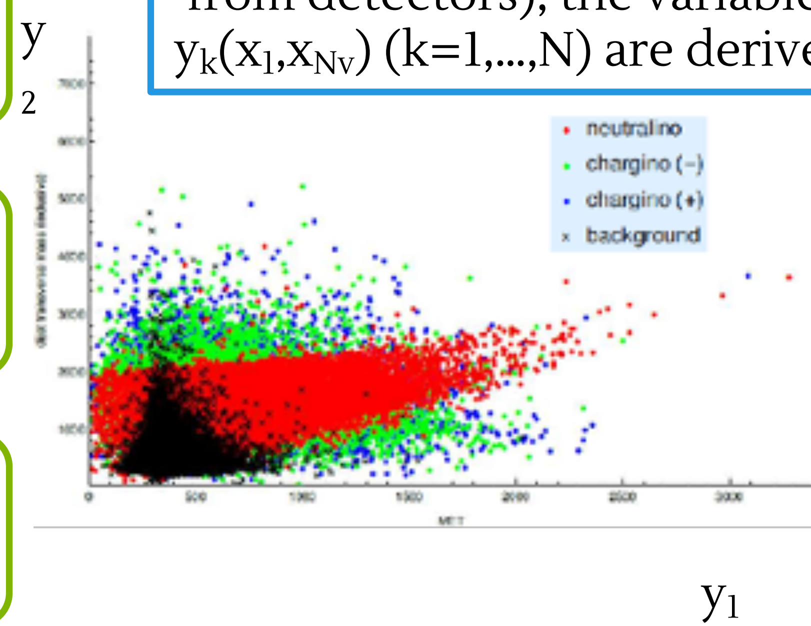
Different Levels of Data Analysis in Particle Physics

Given N_v variables x_i (signals from detectors), the variables $y_k(x_1,x_{N_v})$ ($k=1,\dots,N$) are derived

Analysis
- $y_1 \dots y_N$ are used as discriminators (cuts)

Machine Learning
- $y_1 \dots y_N$ are input to multivariate analysis tools (fisher discriminants, neural networks, ...)

Deep Learning
- The x_i variables are directly input to multilayer neural networks



ARPG

SAPIENZA
UNIVERSITÀ DI ROMA

INFN
Istituto Nazionale di Fisica Nucleare

CENTRO RICERCHE ENRICO FERMI

Applied Radiation Physics Group

NUCLEAR MEDICINE

EX-CHIRONE
(Radio Guided

WIDMAPP
(Targeted Metabolic

RADIO/HADRON THERAPY

FOOT
(RBE in PT)

FRED
(TPS with

MONDO
(Fast Neutron

FRIDA
(FLASH THERAPY)

DOSE PROFILER
(Particle Therapy

ARTIFICIAL INTELLIGENCE IN MEDICINE

ATTRACT-AI
(Radiogenomic

NEPTUNE
(19F-MRI)

MUCCA
(AI explainability)

GENIALE
(Low Energy Nuclear Interactions)

http://arpg-serv.ing2.uniroma1.it/arpg-site/index.php

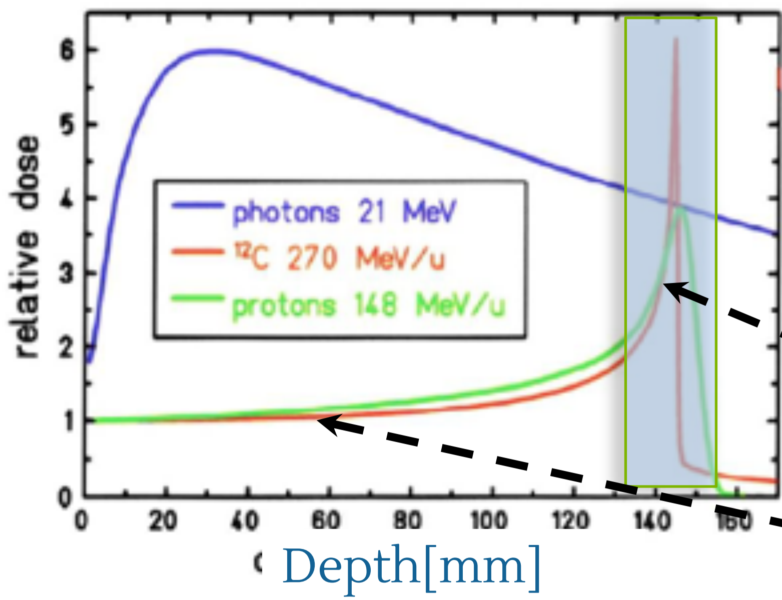
ARPG

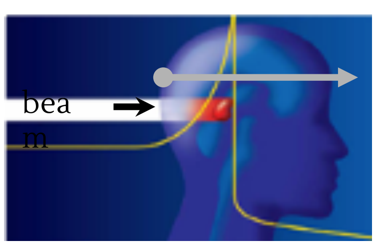
Activity driven by medical input, with involvement of SMEs

RADIO/HADRO THERAPY

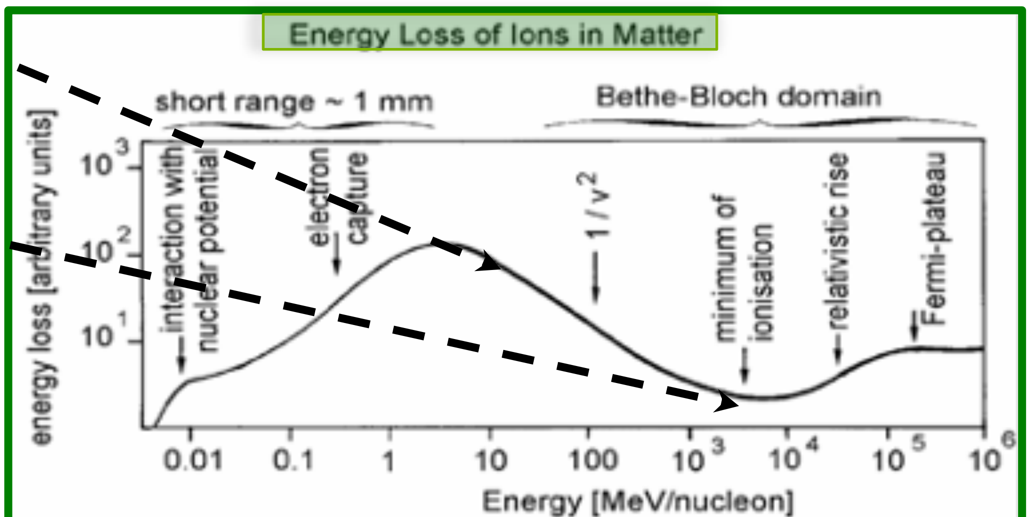
Hadrotherapy

Proton/ion beams on patient



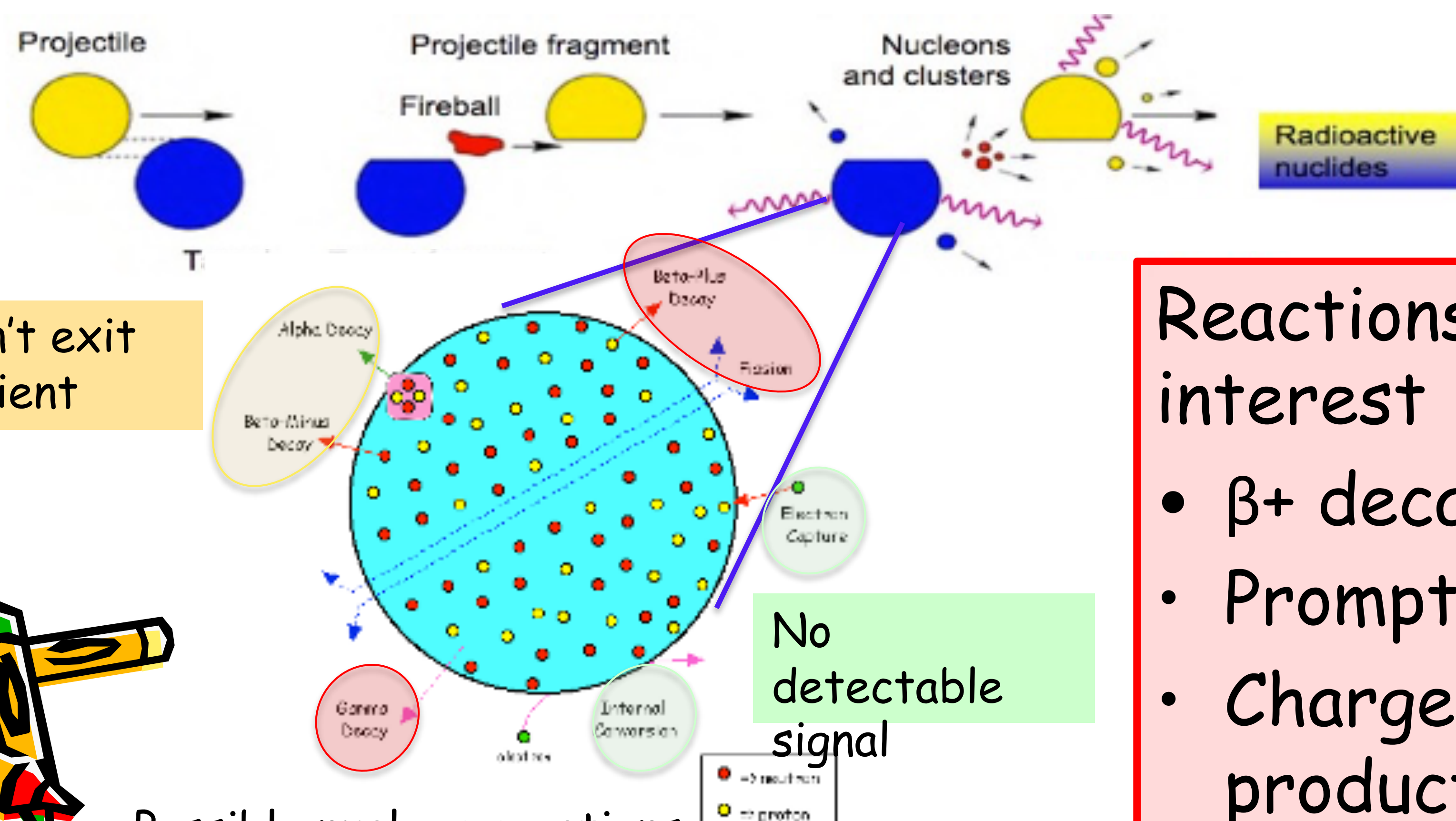


Concentrate release of energy inside tumor due to release of energy in ionization.



WHERE ARE WE AIMING?

Dose profiling based on nuclear reactions between the projectile and the patient

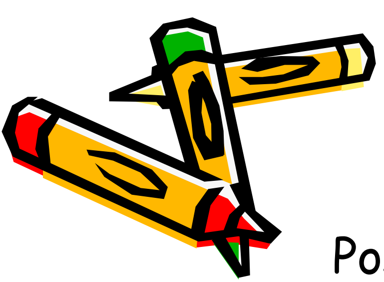


Don't exit patient

No detectable signal

Reactions of interest

- β+ decays
- Prompt γ
- Charged products



Possible nuclear reactions

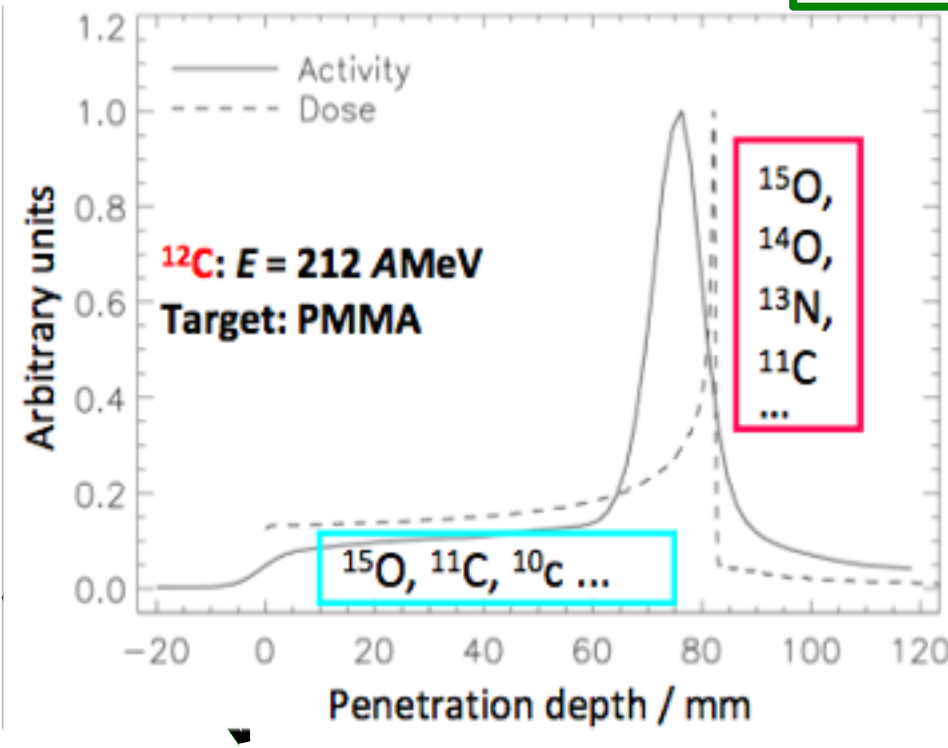
Correlation between activity and dose

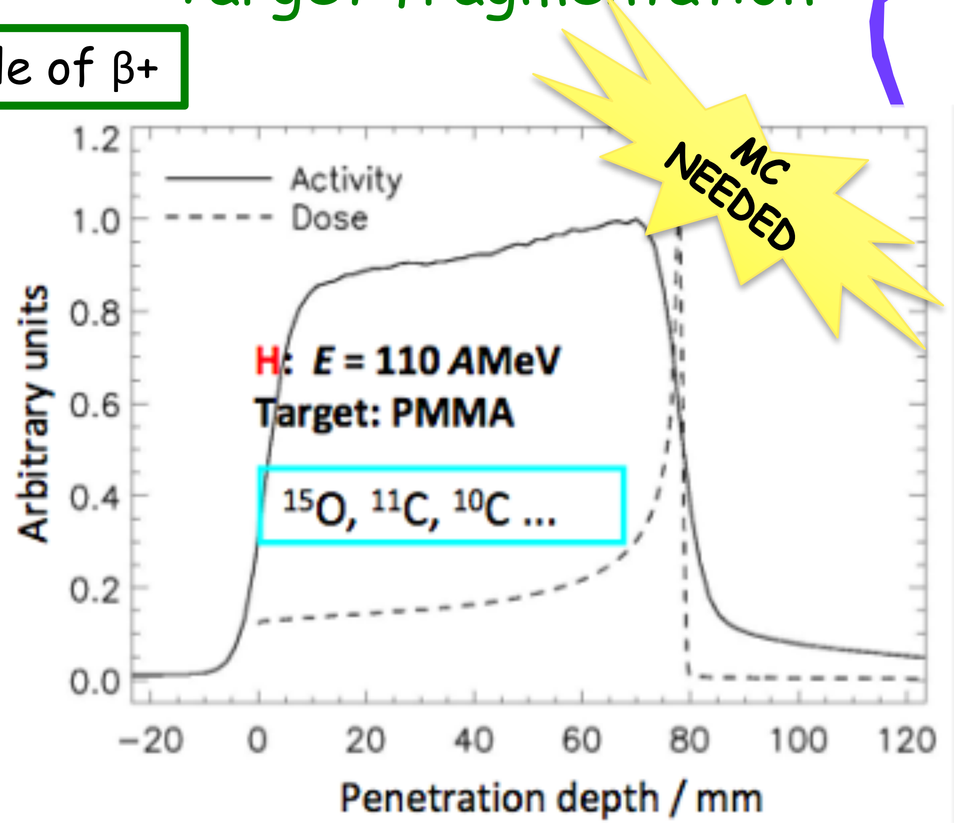
Therapy beam	^{1}H	^{3}He	^{7}Li	^{12}C	^{16}O	Nuclear medicine
Activity density / Bq cm^{-3} Gy^{-1}	6600	5300	3060	1600	1030	$10^4 - 10^5$ Bq cm^{-3}

Projectiles & target fragmentation

Target fragmentation

Example of β+





Details in the talk from Alessio Sarti

The FLASH effect

Recently (starting from 2015, exploding from 2019) the 'fractionation' paradigm has been questioned.

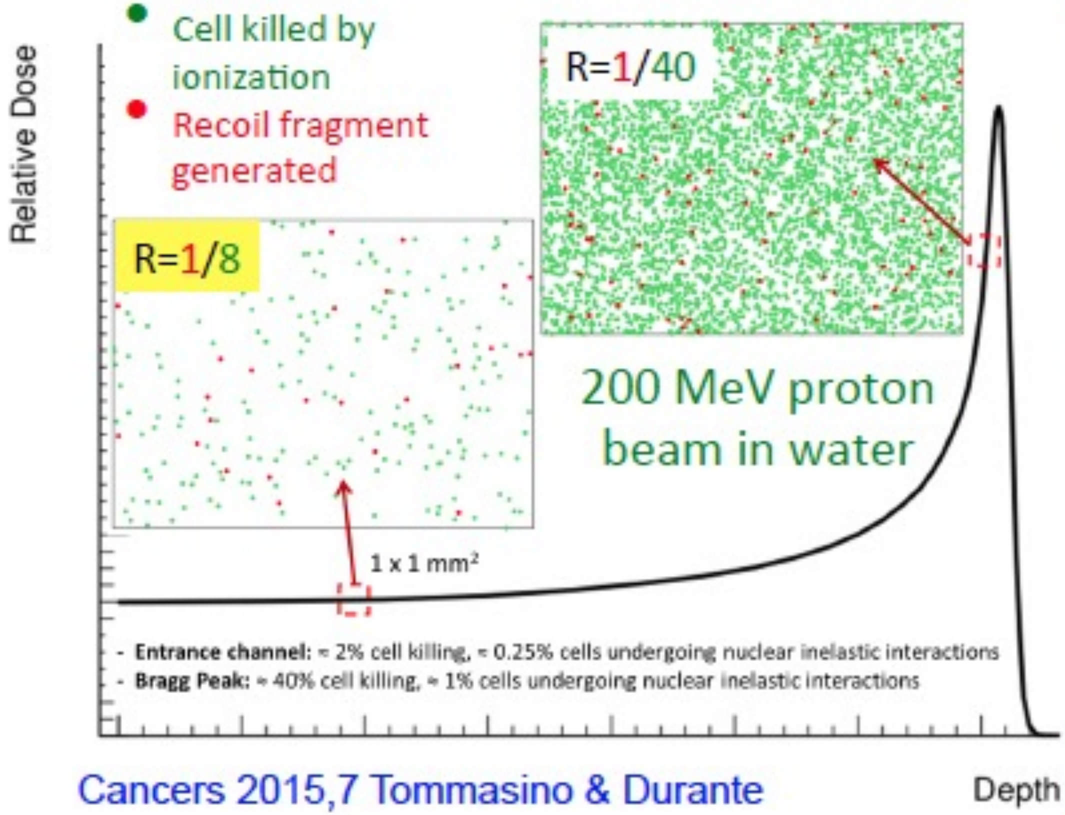
- Before: dose has to be delivered in several fractions, and slowly as the 'healty' tissue has better healing capabilities and can recover in a better way 60 Gy treatments are currently delivered in 30 fractions of 2 Gy that can last more than 1 month!

Oriatron eRT6 5.6-MeV linac located at Lausanne University Hospital → specifically engineered for accelerating electrons in a FLASH mode

- Now: the FLASH revolution overturns that idea. A better sparing can be achieved if high doses and ultra high dose rates (3 orders of magnitude larger wrt conventional irradiation!) are used. Instead of going with 0.1 Gy/s one goes 100 Gy/s!
- Mechanism is yet to be understood... but.. It works!

Target (patient) fragmentation & PT

Target fragmentation in proton therapy: gives contribution also outside the tumor region!

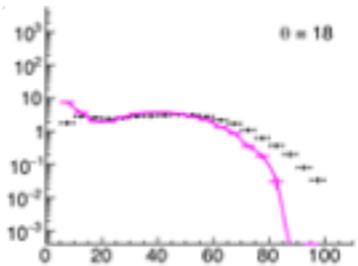


Cancers 2015,7 Tommasino & Durante

About 10% of biological effect in the entrance channel due to secondary fragments (Grun 2013)

Largest contributions of recoil fragments expected from
He, C, Be, O, N
In particular on Normal Tissue Complication Probability
See also :
- Paganetti 2002 PMB
- Grassberger 2011 PMB

Projects on HadronTherapy

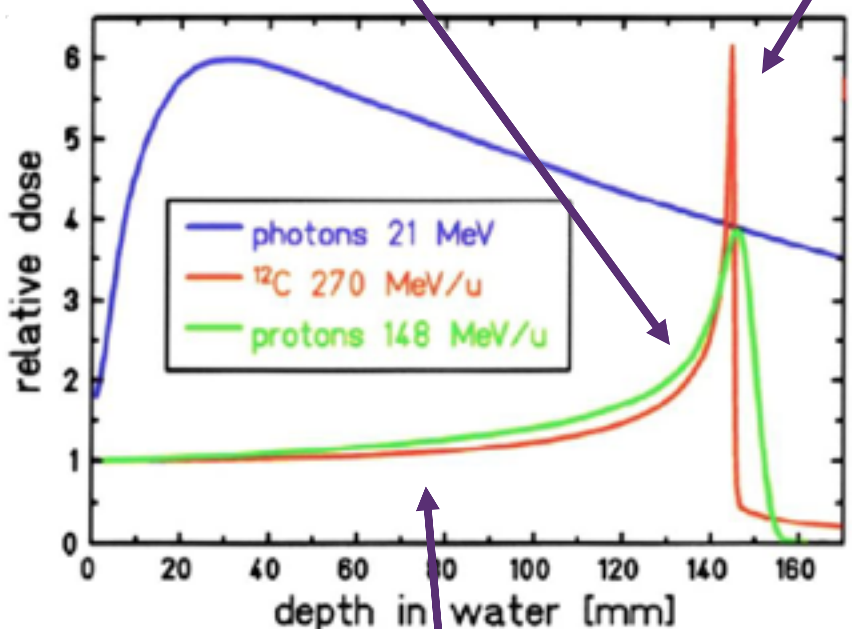


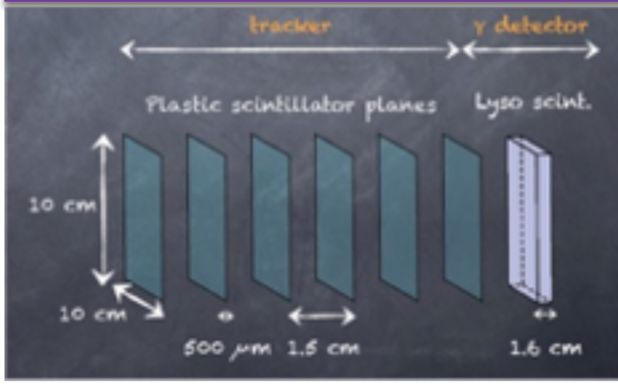
GENIALE

Simulation of low energy nuclear interactions

DOSE PROFILER

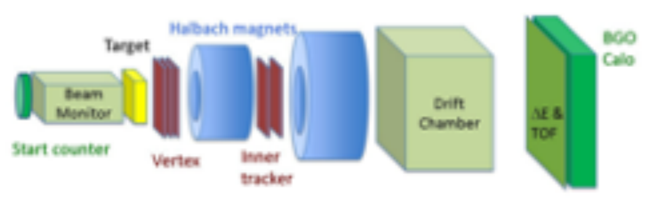
Bragg Peak position estimate





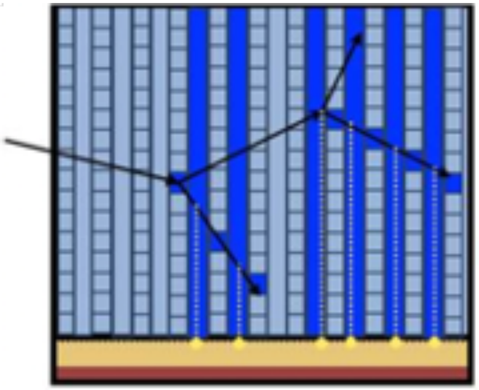
Evalutation of dose on healthy tissues

FOOT



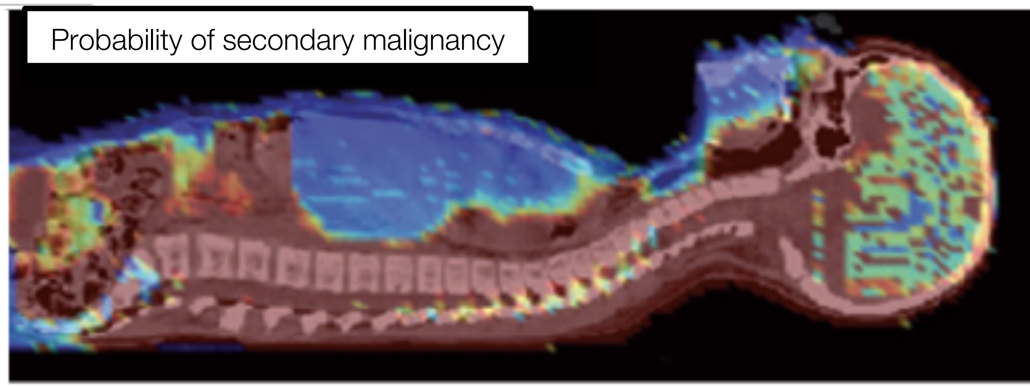
Cross section measurements

Hadrontherapy projects (II)



MONDO

Measurement of neutron production



FRED

Treatment planning systems on GPU

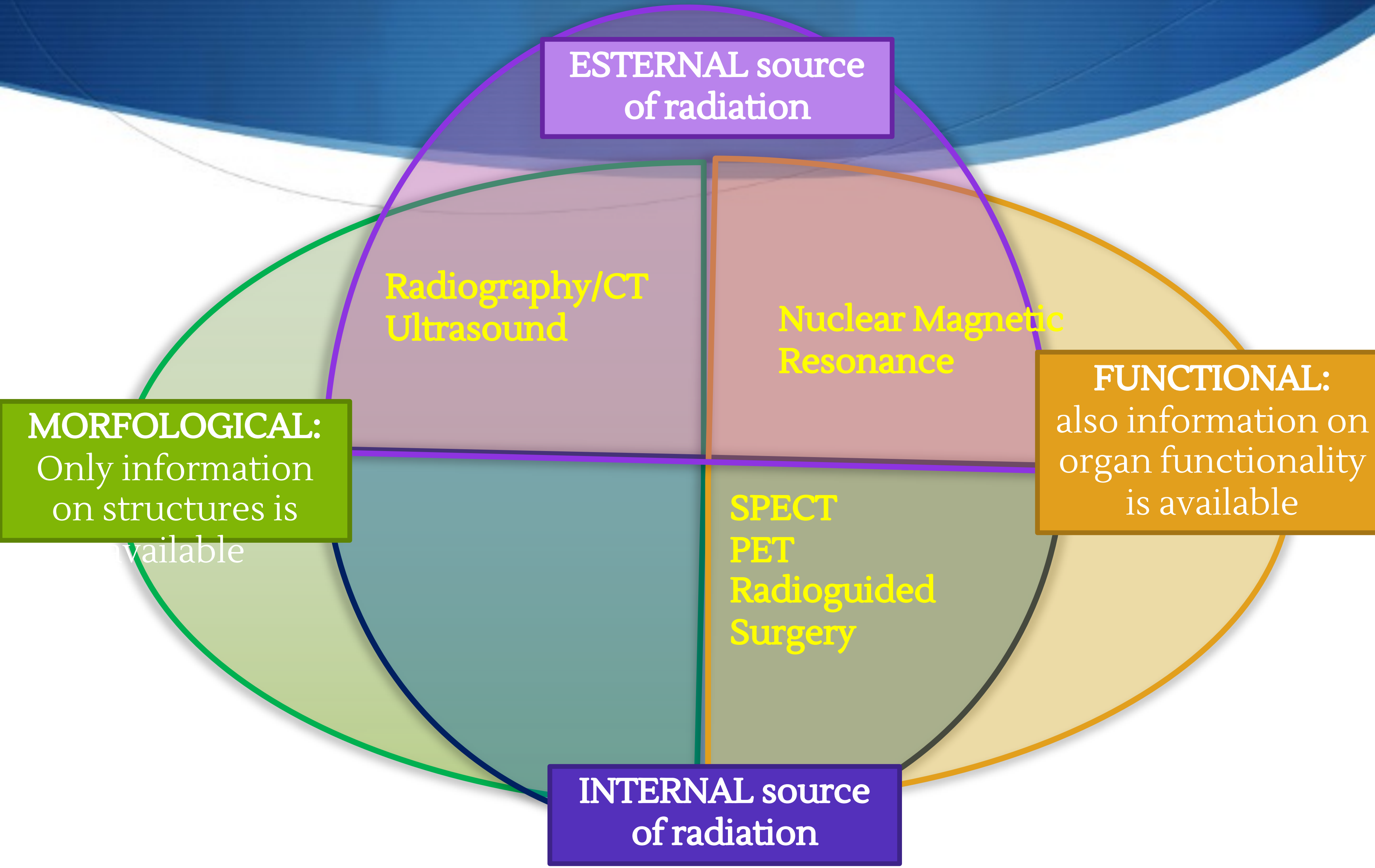
		Threads	primary/s	μs/primary
CPU*	full-MC *	1	0.75 k	1340
	FRED	1	15 k	68
	FRED	16	50 k	20
	FRED	32	80 k	12.5
GPU	FRED	1 GPU[1]	500 k	2
	FRED	2 GPU[2]	2000 k	0.5
	FRED	4 GPU[3]	20000 k	0.05

FRIDA
(FLASH THERAPY)

See talk from A. Sarti

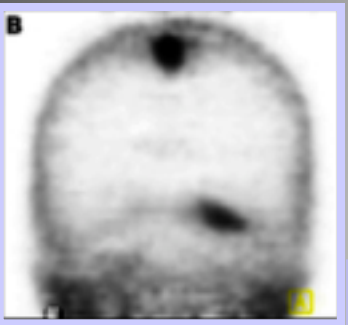
NUCLEAR MEDICINE

DIAGNOSTICS



CHIRONE
(Radio Guided Surgery)

Radio Guided Surgery



PET/SPECT scan to estimate receptivity and background

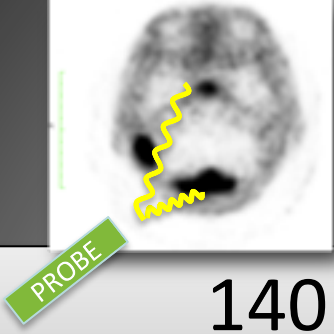
Each tumor requires its own tracer

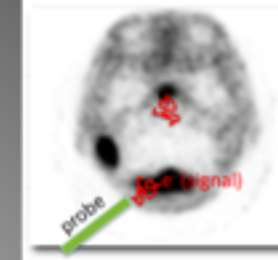
Administration of radio-tracer

During surgery a probe is used to detect residuals/lymphnodes

Probe adjustable to needs

From γ to $e^{+/-}$





140 keV photons

⍰ attenuation in body ~8cm

Long range of gamma's involve:

- exposure of medical personnel
- Background from healthy organs

Difficult to apply in:

- Brain tumors
- Abdominal tumors
- Pediatric tumors

- Use of β^- tracers
  - Detect electrons that travel ~100 times less than γ
  - Tracers with ^{90}Y can be used
  - No background from gamma
- Shorter time to have a response
  - Smaller administered activity
- Smaller and more versatile detector
- reduced effect of nearby healthy tissues
- Reduced dose to medical staff

To the clinical ground

PATENT → COMPANY → ENGINEERING

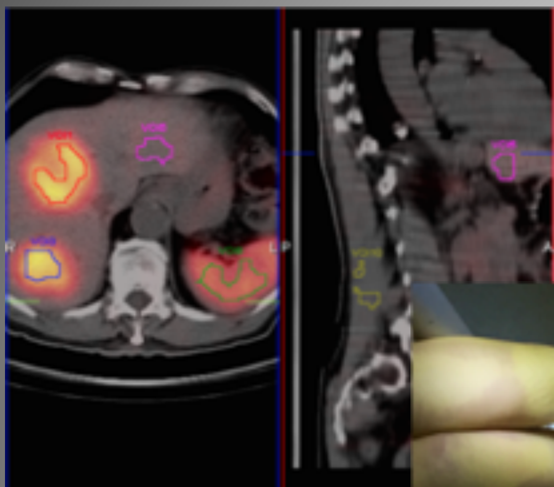
1) Feasibility studies

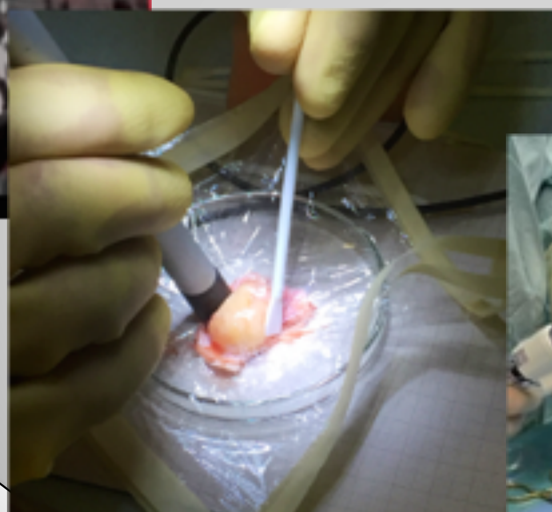
...o tests

(meningio...)

Pro... tests

3) In-vivo tests
(Prostate – Ga 68)
Proposed by clinicians





fruitful and effective collaboration with clinicians!

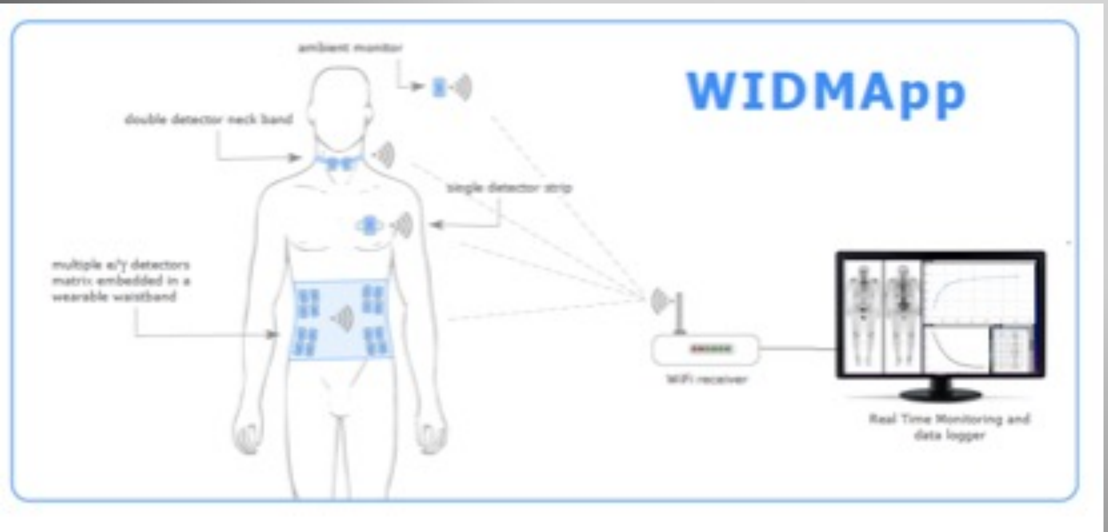
Dosimetry in Target Radio Therapy

Reponding to urgent need of nuclear medicine

- TRT: Injection of radio-tracer that links preferentially with tumor → beta- radiation for therapy
- Need to certify acquired dose on patient-by-patient basis

Development of sensors (evolution of the probe)

MC simulation/data analysis ⍰ proof of principle



WIDMAPP (DOSIMETRI FOR TRT)

Perspectives

Application to other radio-tracers

- explore the ^{18}F fronteer
- MC Studies

Development of **new radiotracers** (with chemists, nuclear physicians, …) and **detectors** to measure bio-distributions in pre-clinical tests

Development of new detectors

- solid state detectors
- new scintillators

ARTIFICIAL INTELLIGENCE IN MEDICINE

Details in talk from C. Mancini Terracciano

AI Applied to Medical Imaging

Aim: help the clinician to take clinical decision based on images (CT, MRI, PET..)

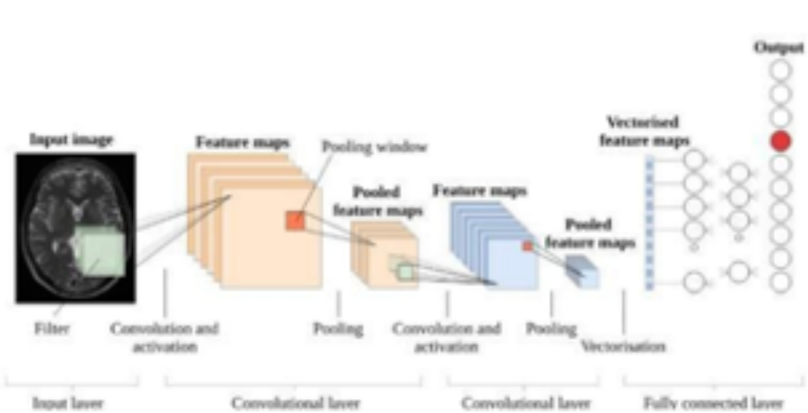
Various **tasks**:

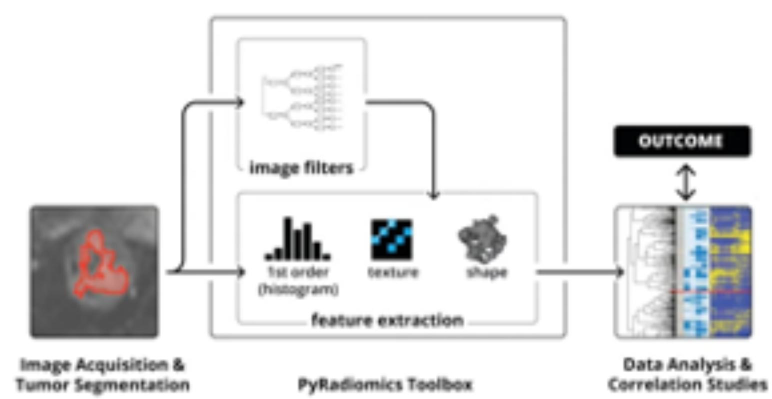
- segmentation of lesion (e.g. tumor)
- tumor staging and re-staging
- prognosis
- evaluation of response to therapy

The image can be directly input to a **Neural Network** that learns a specific task

OR

Radiomic pipeline
=> compute mathematical quantities (features) from the images and then use a AI algorithms to learn the task ..





AI Applied to Medical Imaging

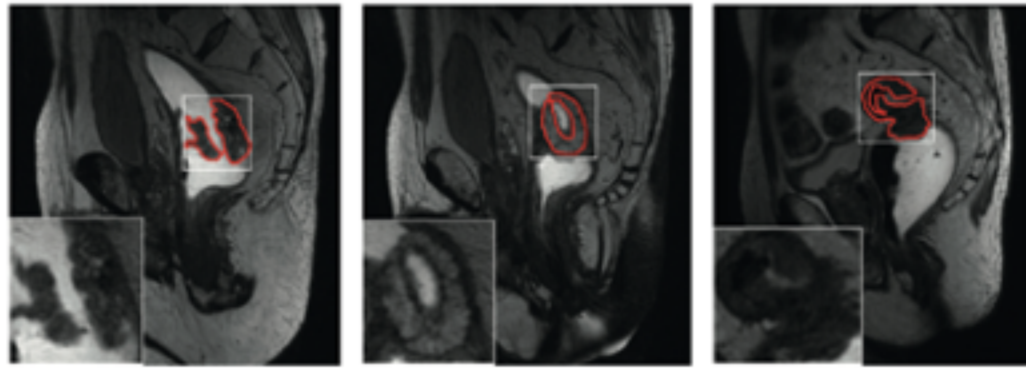
Considerations:

- Physicians are making diffused (ab)use of Artificial intelligence
- Needs a guidance from physicists in terms of:
  - Explainability
  - Assessment of statistical significance
  - Optimization of algorithms
- Besides the technical aspect, the approach of the physicists to the problems and in particular to the analysis of data and search for signals can be a grat contribution

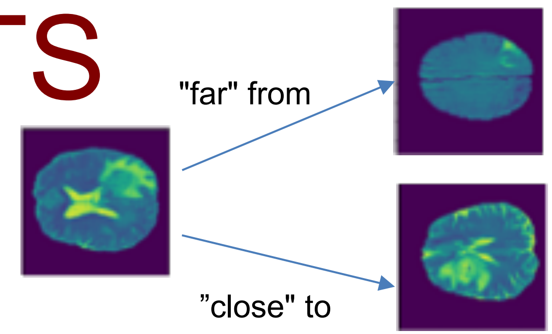
See talk from C. Mancini Terracciano

ATTRACT-AI
(radiogenomics)

AIRC project to develop a **radiogenomic signature** that characterizes colon tumors

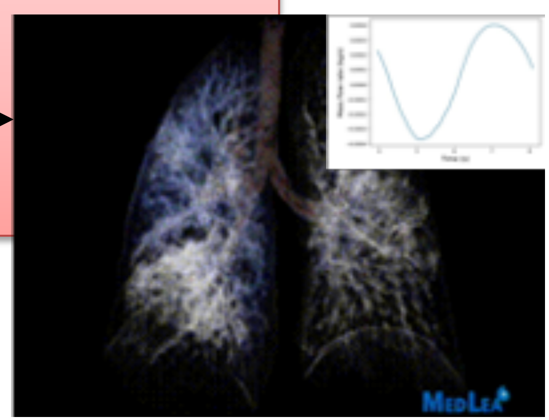


AI PROJECTS



real-time predictions of the patient respiratory condition based on

- CT
- Arterial blood gas
- Biomedical simulations→



AIRC project to develop a **radiogenomic signature** that characterizes colon tumors

MUCCA
(AI explainability)

CORONA
(real time COVID signatures)

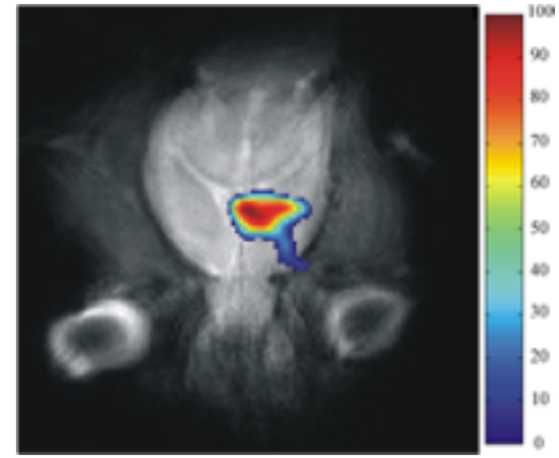
Improving ^{19}F-MRI

^{19}F-MRI currently limited from low SNR ratio

Different strategies:

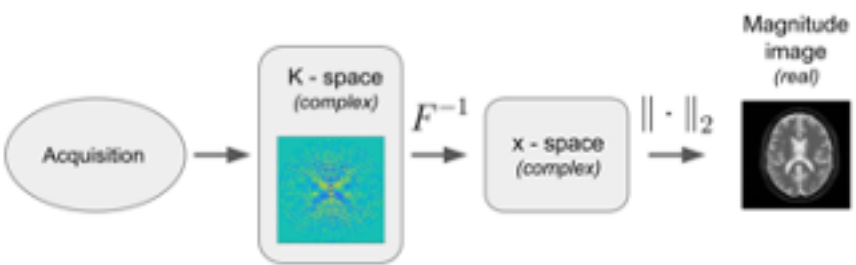
- improve raw signal processing
  - **Software Defined Radio technology**
  - **Development of antella**

^{1}H-MRI + ^{19}F-MRI

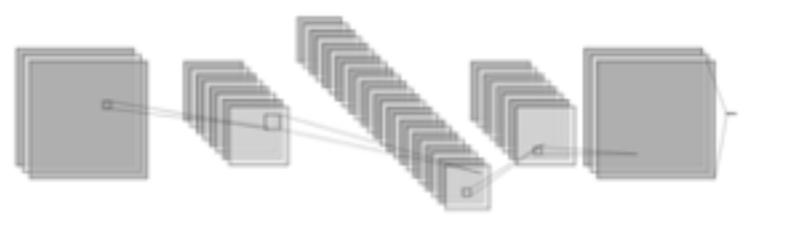


P. Porcari, S. Capuani, E. D'Amore *et al.* 2008 *Phys. Med*. Biol.

- **Deep learning based image analysis**



fully convolutional Architecture



NEPTUNE
(^{19}F MRI)

A LAND WITH BLURRED BORDERS
FINAL REMARKS

Between applied and 'pure' physicists

encourage mixture, which did not take place
Required competences: nuclear physics, detectors, accelerations, data analysis

Between physics and other disciplines

keep being stakeholder driven
Not only medicine (geology, environmental physics, ...)
cultivate our specificity as physicists in particular in education

Between research and Technology Transfer

political/organizational issue
constant and improving help needed (interaction with

Between Technology Transfer and the business of others

spin off, start up
an unfamilar land to be seriously explored

BACKUP

GENIALE
(Low Energy Nuclear Interactions)

- Despite the numerous and relevant application would use it, there is no dedicated model to nuclear interaction below 100 MeV/A in Geant4

- Many papers showed the difficulties of Geant4 in this energy domain:

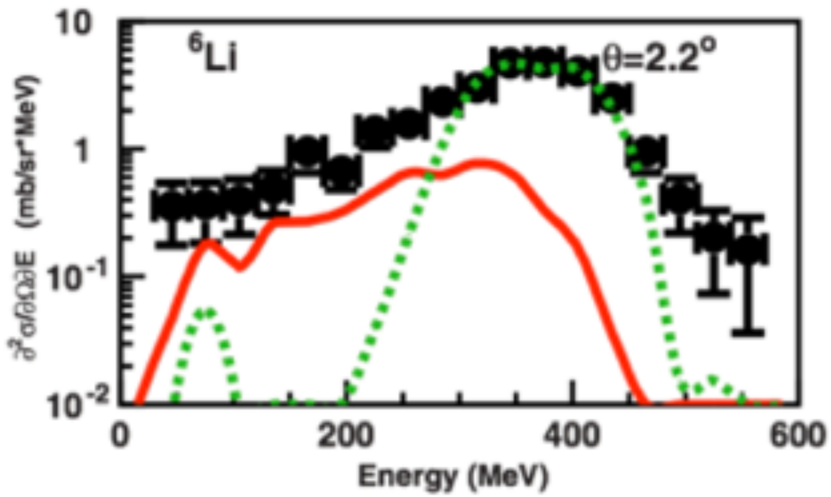
  - Braunn et al. have shown discrepancies up to one order of magnitude in ^{12}C fragmentation at 95 MeV/A on thick PMMA target

  - De Napoli et al. showed discrepancy specially on angular distribution of the secondaries emitted in the interaction of 62 MeV/A ^{12}C on thin carbon target

  - Dudouet et al. found similar results with a 95 MeV/A ^{12}C beam on H, C, O, Al and Ti targets

- **Exp. data**
- **G4-BIC**
- **G4-QMD**

[Plot from De Napoli et al. Phys. Med. Biol., vol. 57, no. 22, pp. 7651–7671, Nov. 2012]



Cross section of the ^{6}Li production at 2.2 degree in a ^{12}C on ^{nat}C reaction at 62 MeV/A.

ATTRACT- AI based Radiogenomics in Colon Tumors

Funded AIRC project in collaboration with Policlinico Umberto I (2021-2025)

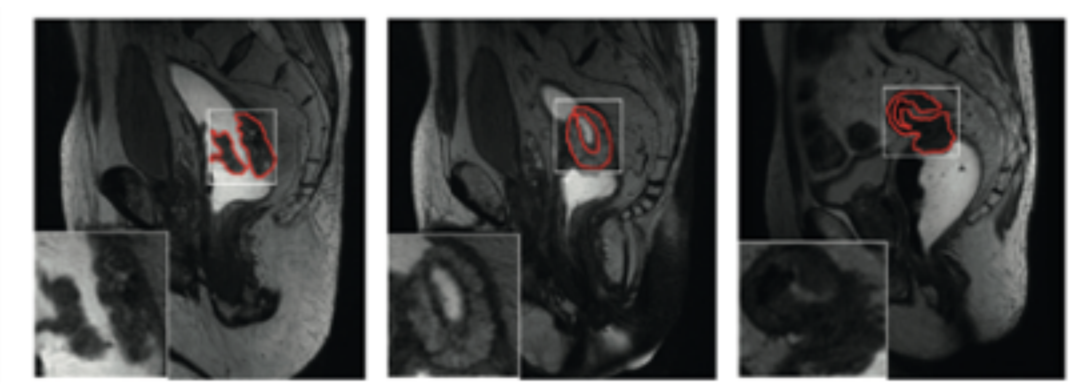
Goal: develop a **radiogenomic signature** that characterize colon tumor =

Radiomic & Machine learning techniques applied to colon CT and genomic data

Steps:

- tumor segmentation with artificial network from CT
- radiomic feature extraction and reduction
- radiogenomic model

300 retrospective annotated cases
200 prospective annotated cases for external validation



ATTRACT-AI
(radiogenomic signature)

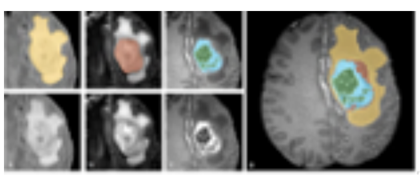
MUCCA- AI Explainability of Medical Imaging

Funded by CHIST-ERA (EU) call "Explainable Artificial Intelligence"

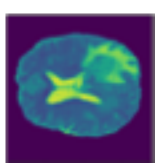
Goal: develop explainable AI algorithms in different fields (Physics Applied to Medicine, High Energy Physics, Physics Applied to Neuroscience)

Explainable AI models for the brain lesion segmentation in publicly available MRI dataset (Unet2D, Resnet 3D)

Brats17

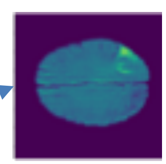


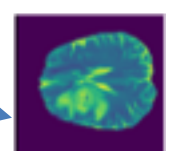
state-of-the-art xAI



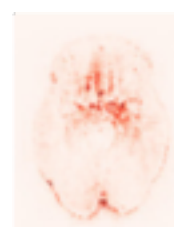
training influence (gradient tracing)

"far" from





saliency maps

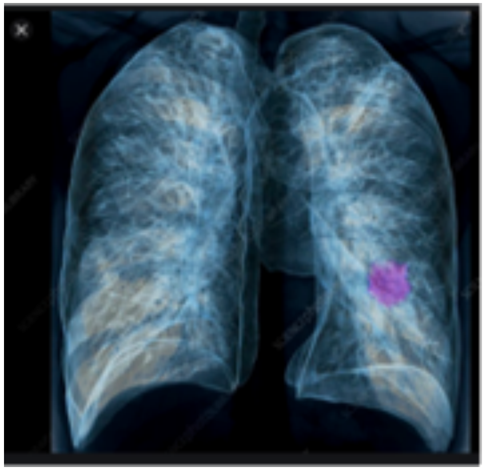


MUCCA
(AI explainability)

CORONA – Prognostic Algorithm for COVID-19

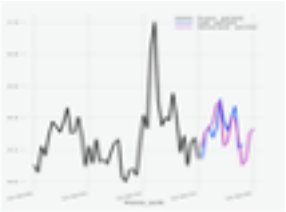
- The goal of the project is to make **real-time predictions of the patient respiratory condition** and functional response at few days using an **AI algorithm** on the basis of:

initial CT

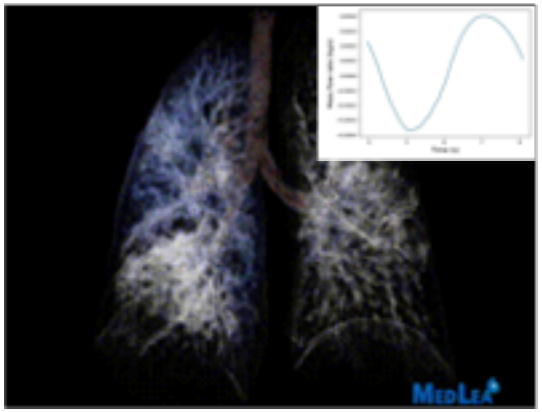


Arterial Blood Gas (ABG) analysis

Time series prediction



biomechanical simulations

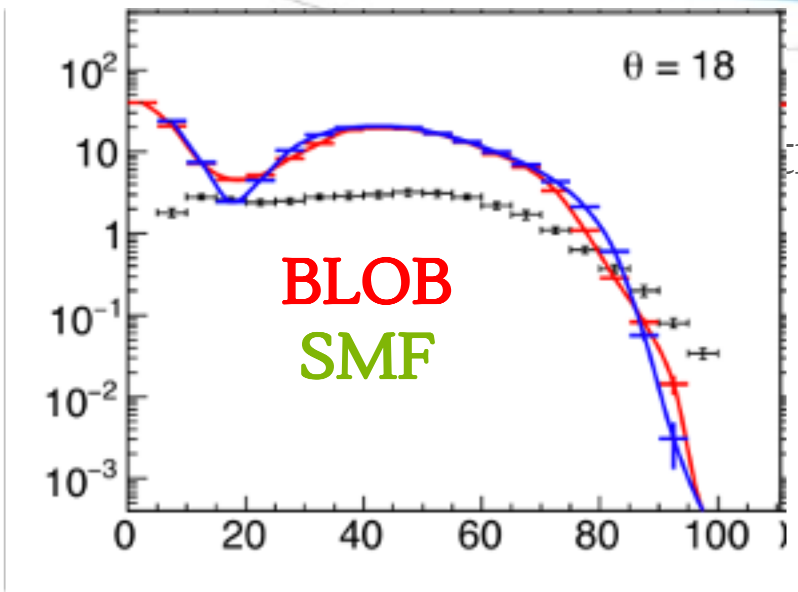


Can be a support to ventilatory management

Collaborative research agreement between INFN, Sapienza, and Medlea srls

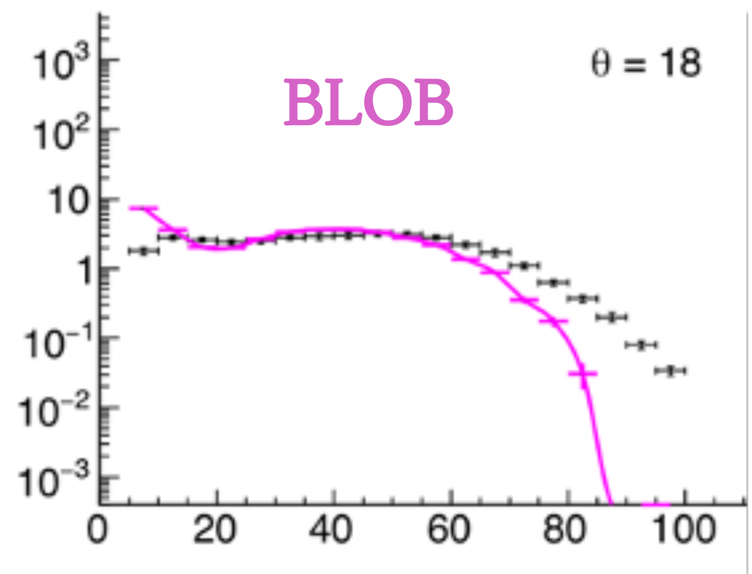
CORONA
(real time COVID signatures)

GENIALE: results



ion

- COALESCENCE
- EXITATION ENERGY CORRECTION



p-> C, p->O scattering @200 MeV

The elastic interaction and the forward Z=1 fragment production (p,d,t) are quite well known. Large uncertainty on large angle Z=1,2 fragments.

Missing data on heavy fragments. Unreliable nuclear models

"Heavy" (A>4) fragment yields and emission energy ~ unknown

Very low energy-short range fragments.

MCs confirm this picture

Nuclear model & MC not reliable

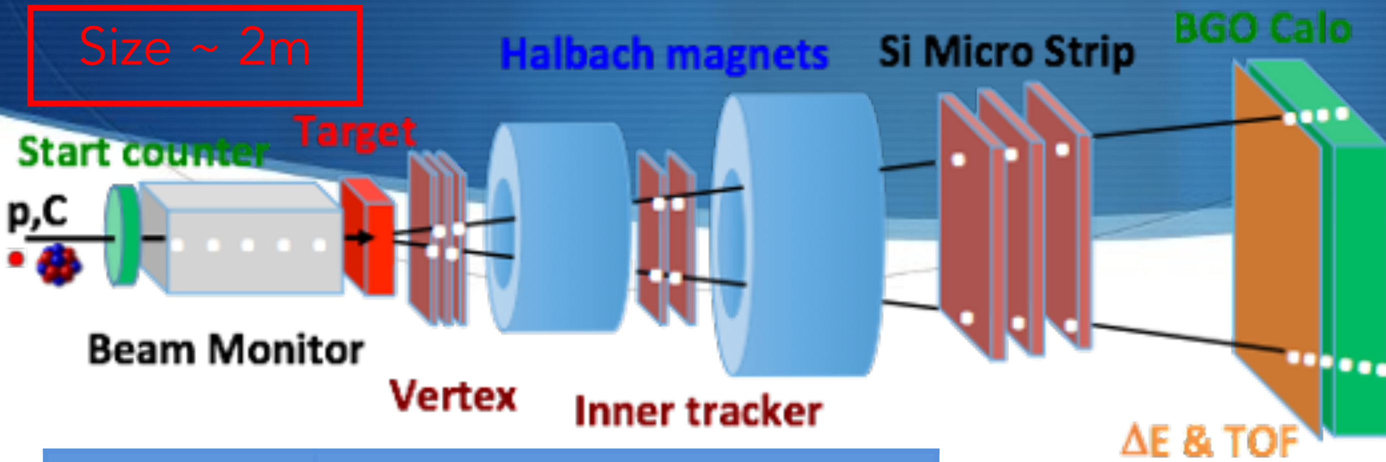
Analitic model results on p->O @200 MeV

Fragment	E (MeV)	LET (keV/µm)	Range (µm)
^{15}O	1.0	983	2.3
^{15}N	1.0	925	2.5
^{14}N	2.0	1137	3.6
^{13}C	3.0	951	5.4
^{12}C	3.8	912	6.2
^{11}C	4.6	878	7.0
^{10}B	5.4	643	9.9
^{8}Be	6.4	400	15.7
^{6}Li	6.8	215	26.7
^{4}He	6.0	77	48.5
^{3}He	4.7	89	38.8
^{2}H	2.5	14	68.9

Cancers 2015,7 Tommasino & Durante

The FOOT setup

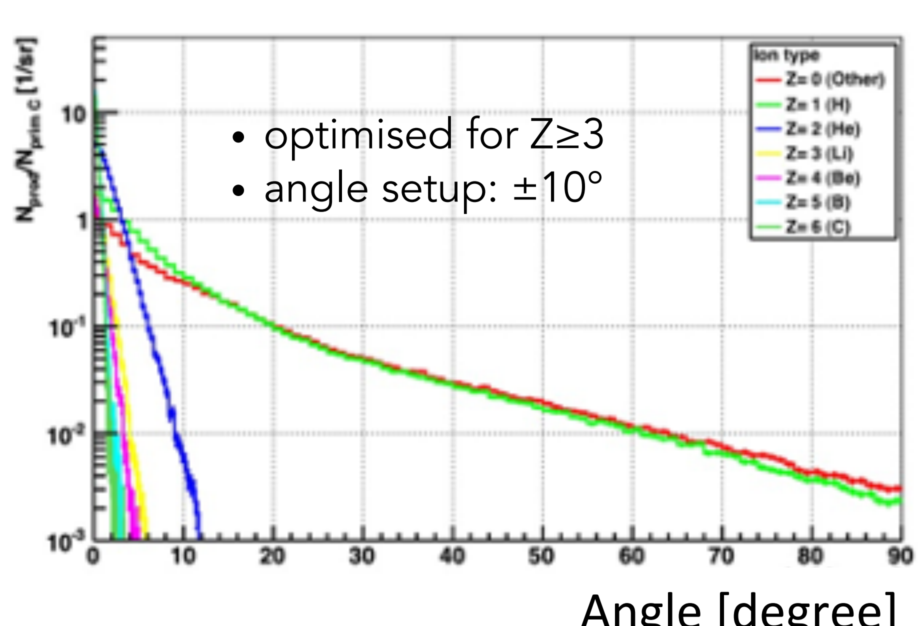
Size ~ 2m



Target performances

- $\Delta p/p$ <3.5%
- Δ_{TOF} <70ps
- $\Delta E_{kin}/E_{kin}$ <2%
- $\Delta(dE)/dE$ ~3%

Sub-detector	Main characteristics
Start counter	plastic scintillator 250 μm
Beam monitor	drift chamber (12 layers of wires)
Target	$C+C_2H_4$ (2 mm)
Vertex	4 layers silicon pixel (20x20 μm)
Magnet	2 permanent dipoles (~ 1 T)
Inner tracker	2 layers silicon pixel (20x20 μm)
Outer tracker	3 layers silicon strip (125 μm pitch)
Scintillator	2 layers of 20 bars (2x40x0.3 μm) [illegible]
[illegible]	[illegible]ystals (2x2x14 μm)



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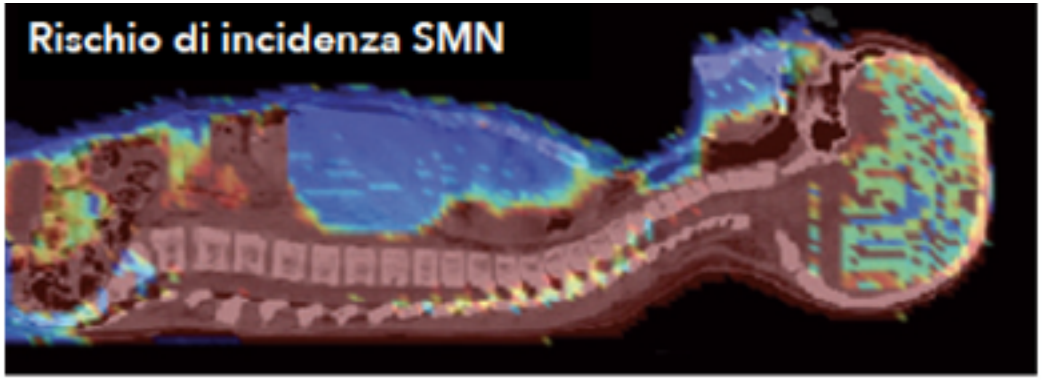
MONDO (Fast Neutron Detection)

Secondary neoplasia in particle therapy

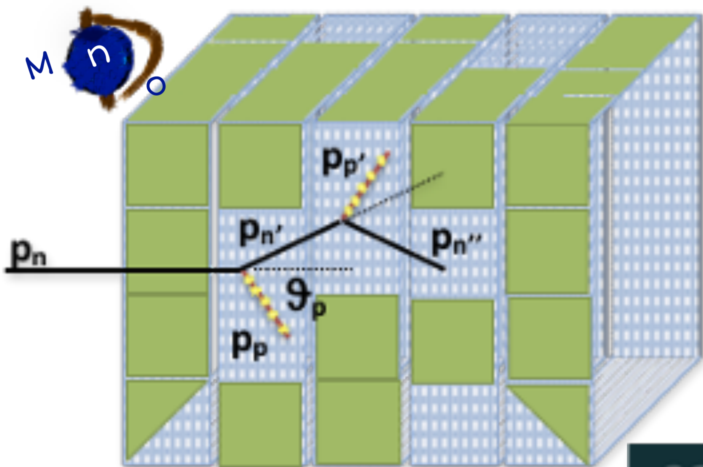


Probability of secondary malignant neoplasia
Uncertainty dominated by fast neutron production

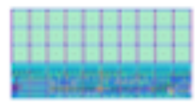
Particularly relevant for paediatric treatments

MONDO

In Particle Therapy (PT) the beam interacts with the patient producing secondary particles. Secondary neutrons can release **additional dose** also far away from the volume under treatment. The incidence (also years after the treatment) of SMNs (**Secondary Malignant Neoplasm**) impacts directly on the quality and life expectation of the patient.



Chip (SBAM)

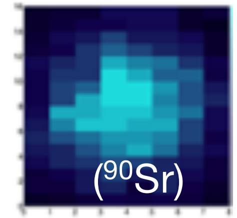


Tile (4x4 chips)

Module Fibre

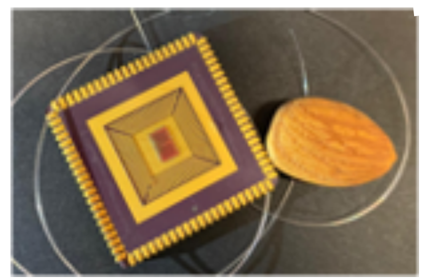
MONDO: 16 x 16 x 20 cm³

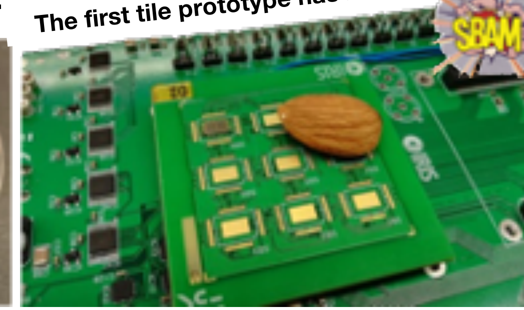
MONDO is a **tracking detector** that exploits double neutron elastic scattering to reconstruct the energy and the direction of the secondary neutrons produced in PT.

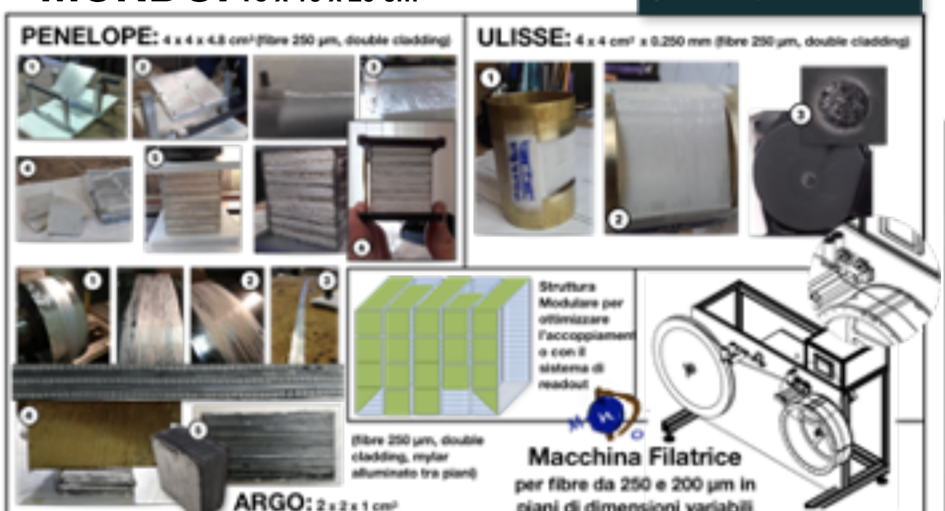


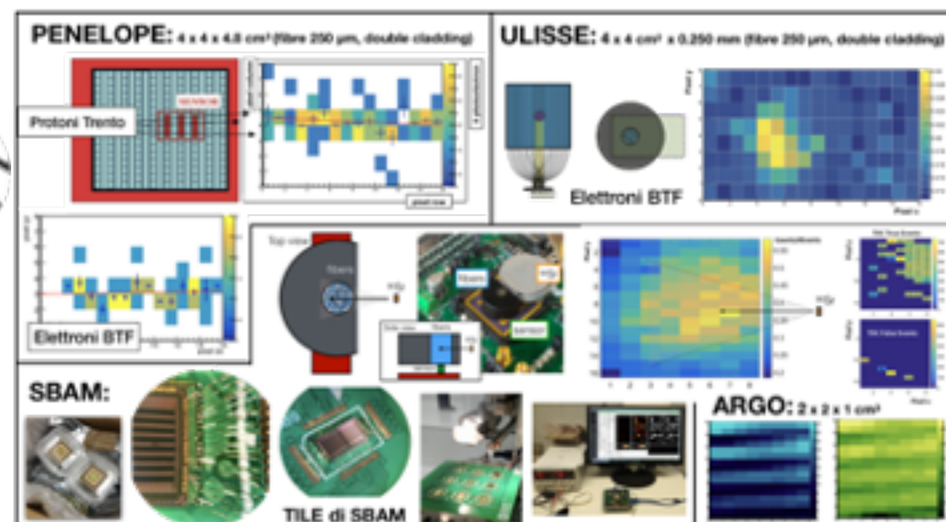
A dedicated readout silicon based system is under development in collaboration with FBK.

The first tile prototype has been produced









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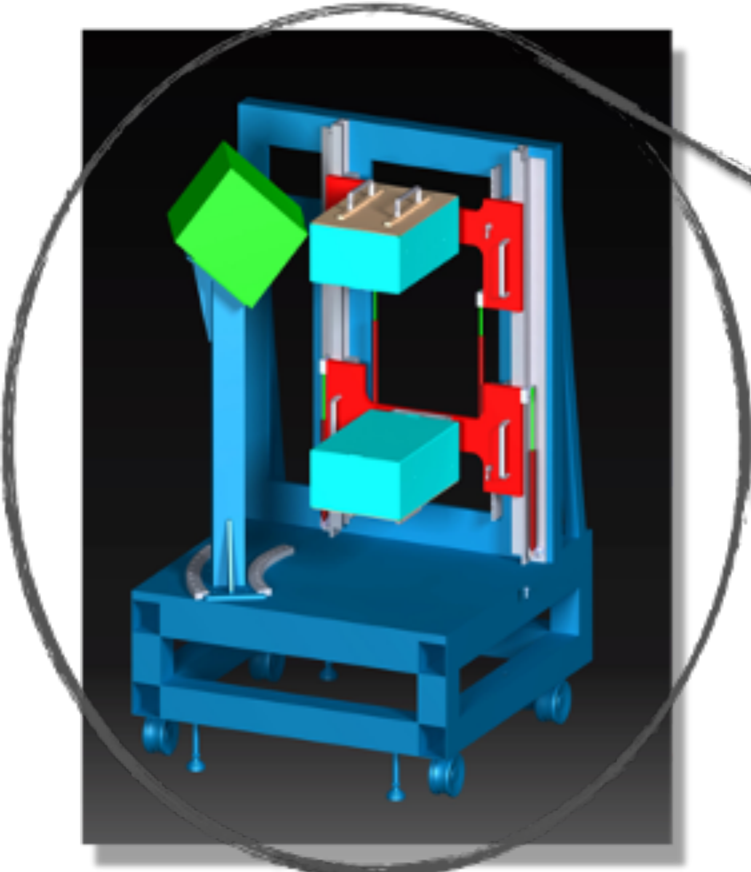
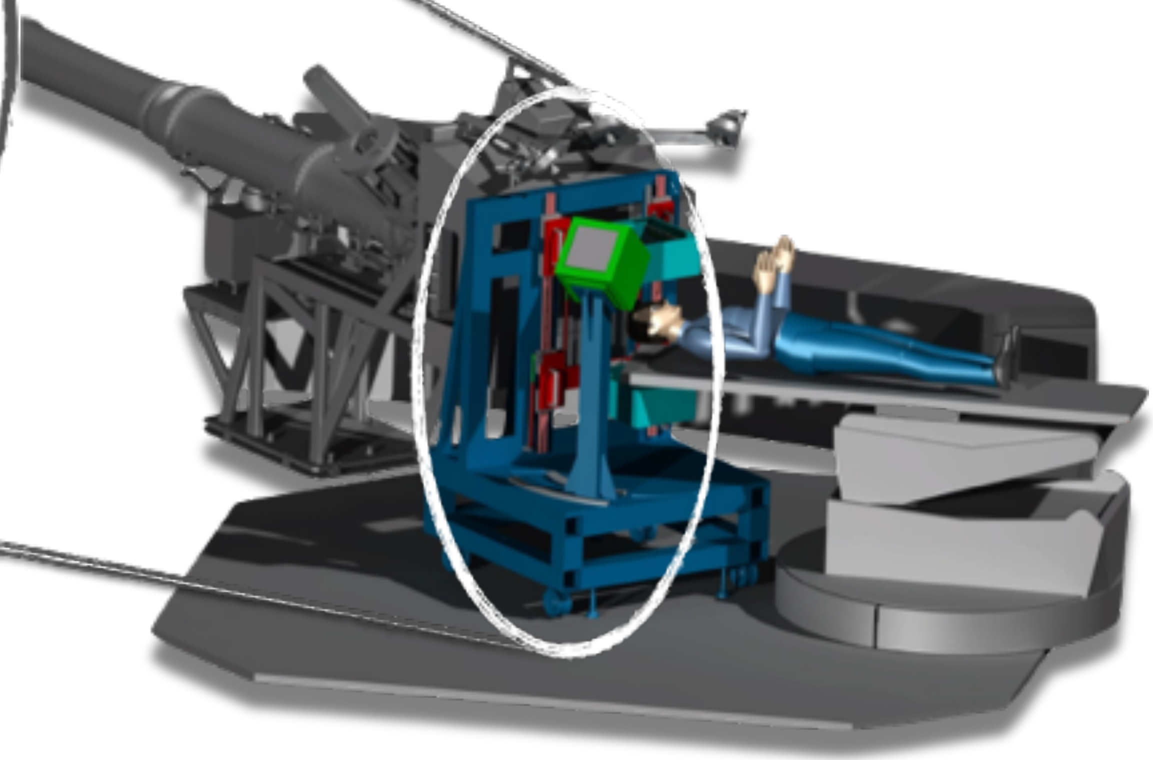
E.Gioscio, et al. "Development of a novel neutron tracker for the characterisation of secondary neutrons emitted in Particle Therapy" under press on NIM A (2019) 162862 doi: https://doi.org/10.1016/j.nima.2019.162862

Range monitor applications



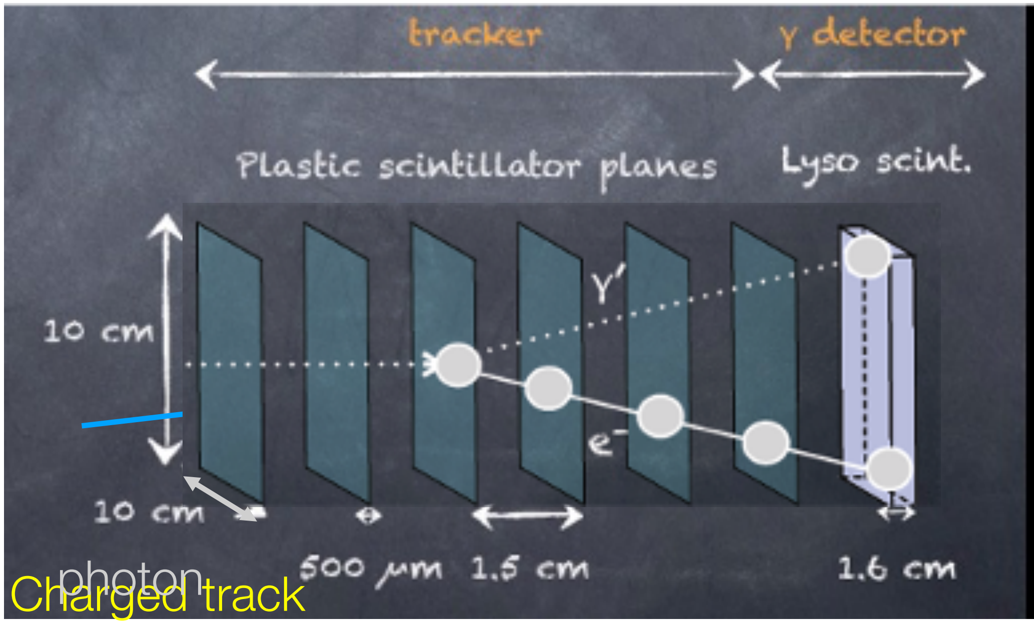
- To exploit the secondary particles detections as an online monitor, a Dose Profiler has been designed (within the INSIDE Italian project) to be deployed in the CNAO treatment center.



Dose Profiler

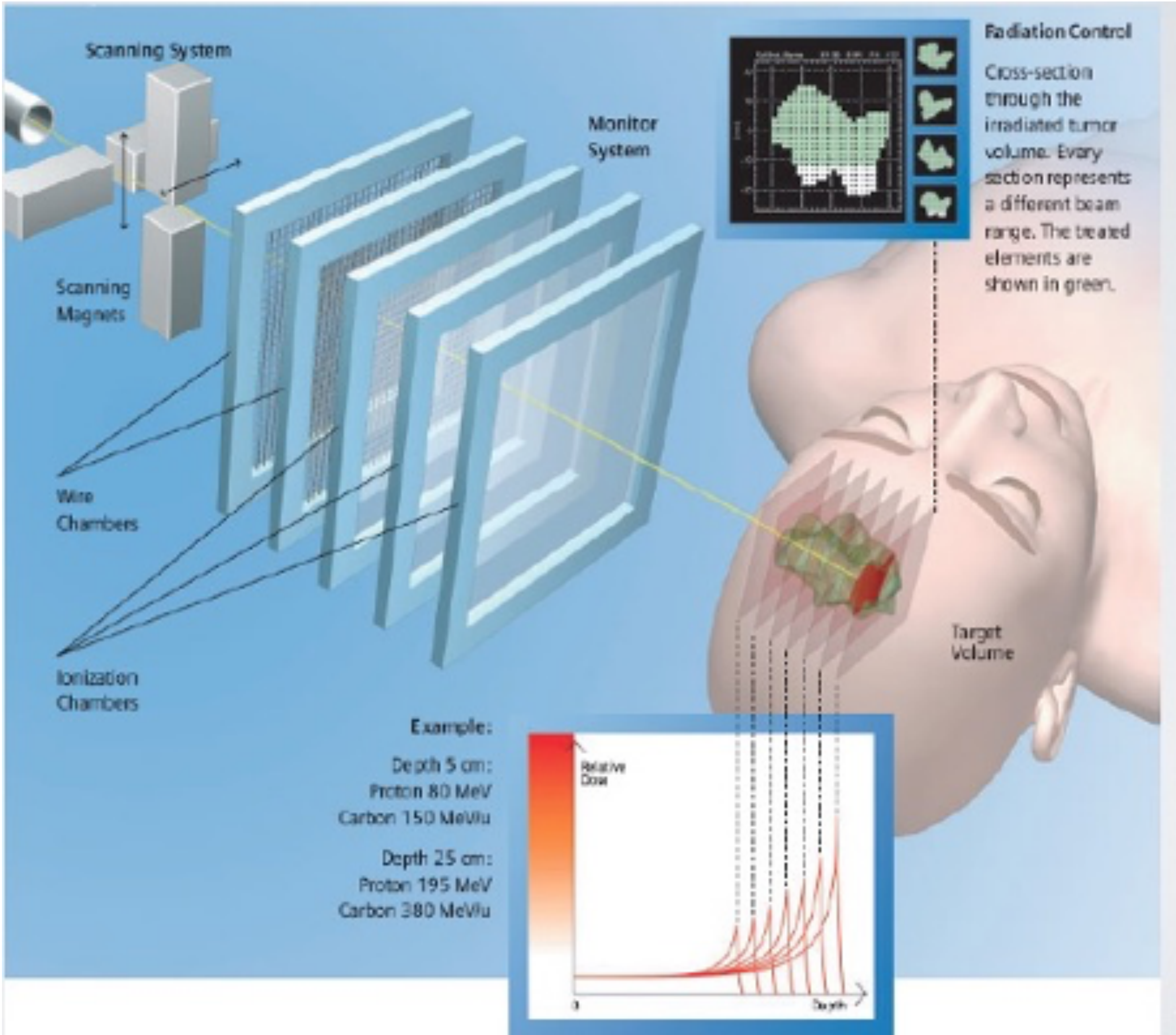
Need a detector to simultaneously measure the rate of:

- charged particles with multilayer for track reconstruction
- single photons with compton camera



Treatment Planning System

From the tumor margin to the beam sequencing ("Raster Scan")



Hardware and Performance

Split algo to parallelize

		Threads	primary/s	$\mu s/primary$
CPU[a]	full-MC *	1	0.75 k	1340
	FRED	1	15 k	68
	FRED	16	50 k	20
	FRED	32	80 k	12.5
GPU	FRED	1 GPU[1]	500 k	2
	FRED	2 GPU[2]	2000 k	0.5
	FRED	4 GPU[3]	20000 k	0.05

Table A1: Computing times for different hardware architectures.

[a] motherboard with two Intel® Xeon E5-2687 8-Core CPU at 3,1GHz

[1] LAPTOP: Apple® MacBook Pro with one AMD® Radeon R9 M370X.

[2] DESKTOP: Apple® Mac Pro with two AMD® FirePro D300.

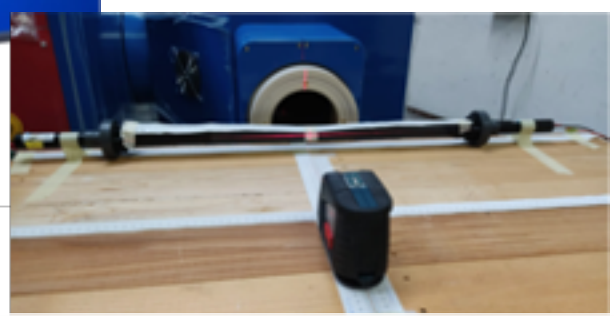
[3] WORKSTATION: Linux box with four NVIDIA® GTX 980.

* FLUKA or Geant4

Monitors for UHDR

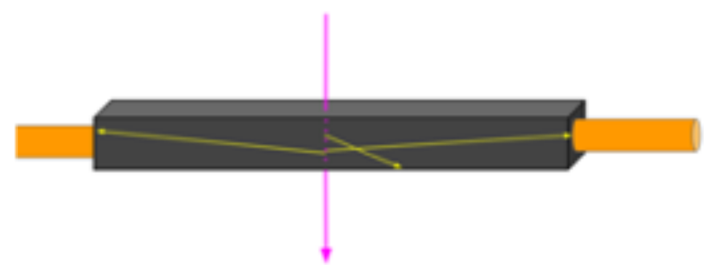
At ultra high dose rates, beams can induce fluorescence in air that could be exploited to measure the beam intensity.

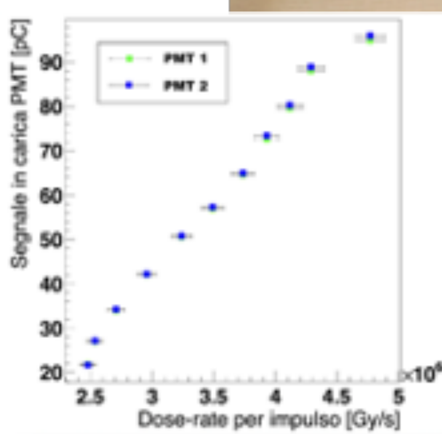
A prototype detector has been built (just to demonstrate the possibility to exploit the effect) and has been tested against an e- beam at FLASH intensities..

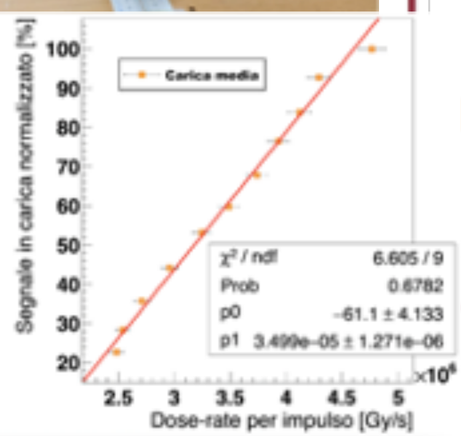


Prototipo di beam monitor (**Tubino**): parallelepipedo lungo 60 cm e con sezione di 4 cm con due PMT ai bordi.

Materiali: rivestimento in **PTFE** (trasparente al fascio), l'interno è in **PVC** (materiale assorbente).





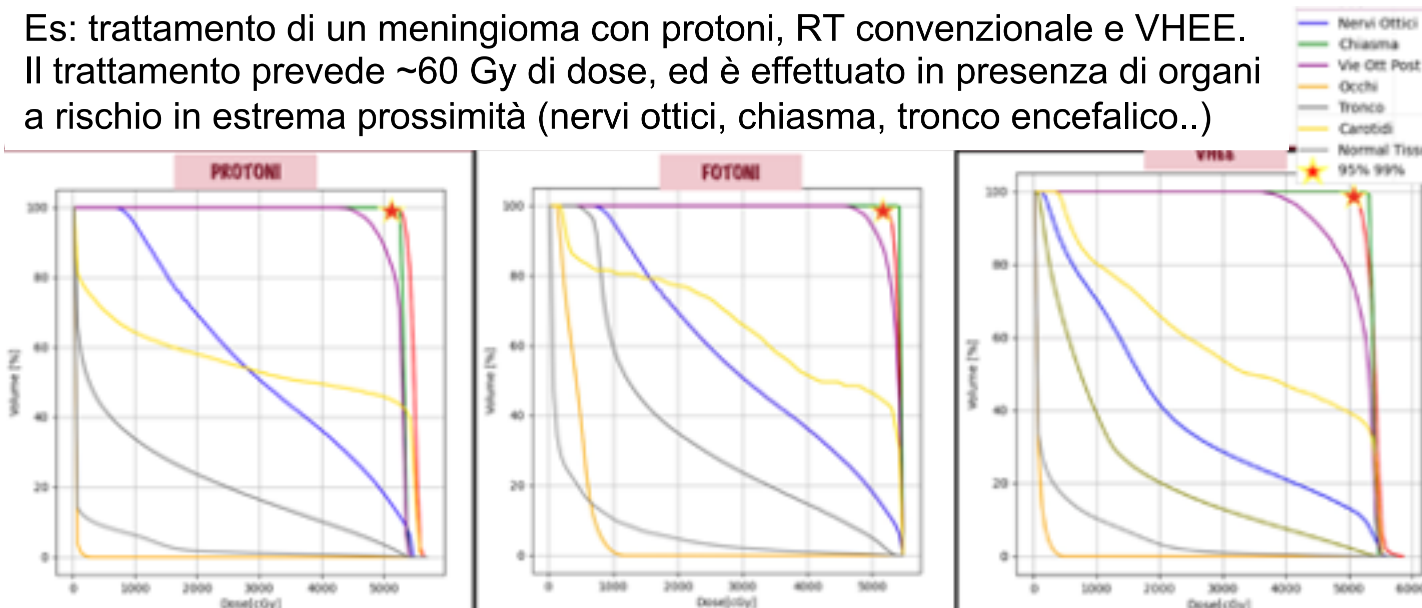


Planning VHEE treatments

FRIDA aim is to explore what Very High Energy Electrons can do (VHEE), for the treatment of deep seated tumors..

Prostate, Head &neck have been alread studied.. **Promising preliminary results have been already obtained..** Other districts can be explored (Pancreatic cancer… Lungs..)

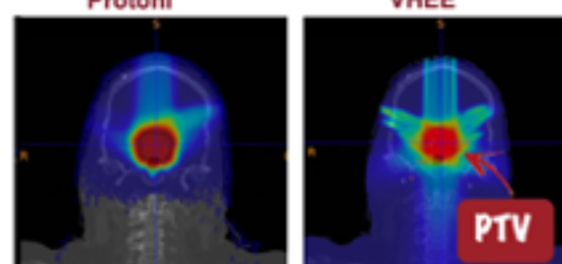
Es: trattamento di un meningioma con protoni, RT convenzionale e VHEE. Il trattamento prevede ~60 Gy di dose, ed è effettuato in presenza di organi a rischio in estrema prossimità (nervi ottici, chiasma, tronco encefalico..)



CONFRONTO TRA I VINCOLI DOSE-VOLUME

Organo		Protoni	Fotoni	VHEE
PTV	$V_{95\%}$	100%	100%	99.44%
	$V_{100\%}$	90.62%	81.60%	67.41%
	$V_{105\%}$	0.01%	0.01%	1.16%
Nervi Ottici	D_{max}	53.52 GyRBE	54.36 GyRBE	55.61 GyRBE
Chiasma	D_{max}	53.60 GyRBE	54.19 GyRBE	54.59 GyRBE
Vie Ottiche Posteriori	D_{max}	53.81 GyRBE	54.30 GyRBE	55.13 GyRBE
Occhi	D_{max}	2.82 GyRBE	12.62 GyRBE	4.76 GyRBE
Tronco Encefalico	D_{max}	54.26 GyRBE	53.61 GyRBE	54.73 GyRBE
Arterie Carotidi	$V_{105\%}$	0.03%	9.17%	0.19%

Protoni VHEE



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